Supplementary Material

Supplemental File 1: BH3 Motifs of Known BH3-Containing Proteins Identified

BH3 motif: $\Phi_1\Sigma XX\Phi_2XX\Phi_3\Sigma'DZ\Phi_4\Gamma$

Φ_1: ACGILMFPWVYET
Φ_2: **L**
Φ_3: ACGILMFPWVYETS
Φ_4: ACGILMFPWVYET
Σ: GASCV
Σ': GASC
X: random amino acid
D: conserved **D**
Z: DEKQLSW
Γ: NDSTCGHYEV

The numbering scheme below uses the heptad convention of S. Dutta *et al.* (J. Mol. Biol. 398:747-762, 2010).

2------3---4-
defgabcdefgab

Pro-apoptotic (BH3-only)
YGRE**L**RRMS**D**EFV BAD (does not bind MCL-1)
IGAQ**L**RRMA**D**DLN BBC3/PUMA
IAQE**L**RRIG**D**EFN BCL2L11/BIM
IAGR**L**RMLG**D**QFN BCL2L15/BFK
IARK**L**QCIA**D**QFH BMF
IARH**L**AQVG**D**SMD BID
LALR**L**ACIG**D**EMD BIK
TAAR**L**KALG**D**ELH HRK
CATQ**L**RRFG**D**KLN PMAIP1/NOXA (specifically binds MCL-1)

Pro-apoptotic (multidomain)
VGRQ**L**AIIG**D**DIN BAK
LSEC**L**KRIG**D**ELD BAX
IVEL**L**KYSG**D**QLE BCL2L14/BCL-G
VCAV**L**LRLG**D**ELE BOK

Autophagy (BH3-only/BH3-like)
LSRR**L**KVTG**D**LFD BECN1
EKAE**L**LQGG**D**LLR BNIP1 (not identified)
VESI**L**KKNS**D**WIW BNIP3 (not identified)
EVEA**L**KKSA**D**WVS BNIP3L/NIX

Novel (BH3-like)
VGQL**L**QDMG**D**DVY HUWE1/MULE (HECT E3 ubiquitin ligase binds MCL-1)
AVHS**L**SRIG**D**ELY RAD9A (pro-apoptotic/DNA damage checkpoint)

Supplemental File 2: Annotated List of BH3-Containing Protein Candidates

Genes in the CCDS dataset (http://www.ncbi.nlm.nih.gov/projects/CCDS/CcdsBrowse.cgi) whose encoded proteins contain a sequence corresponding to a consensus BH3 motif, $\Phi_1\Sigma XX\Phi_2XX\Phi_3\Sigma'DZ\Phi_4\Gamma$, are listed where:

Φ_1: ACGILMFPWVYET

Φ_2: L

Φ_3: ACGILMFPWVYETS

Φ_4: ACGILMFPWVYET

Σ: GASCV

Σ': GASC

X: random amino acid

D: conserved D

Z: DEKQLSW

Γ: NDSTCGHYEV

A total of 214 genes were identified including 17 encoding known BH3-containing proteins (pages 2-4). Different CCDS IDs for the same gene represent transcript variants.

For 111 candidates (pages 5-38), predicted binding to BCL2L1/BCL-xL and MCL-1 is indicated based on a position-specific scoring matrix (PSSM) derived by S. Dutta *et al.* (J. Mol. Biol. 398:747-762, 2010). The PSSM predictions were developed from binding analyses using peptide arrays and yeast surface display libraries in which the effects of hundreds of point mutations were assessed in the background of a peptide corresponding to the BH3 region of BCL2L11/BIM. The candidates are listed in the descending order of their binding affinity scores for BCL2L1/BCL-xL.

In those cases where a prediction is not possible because at least one of the amino acids in the motif is not contained in the PSSM matrix (86 genes), no score is given. These candidates are listed alphabetically (pages 39-61).

Amino acids within the BH3-like motif that are predicted to contribute to an α-helical conformation are indicated by 'H'.

Genes highlighted in **RED** are discussed in the text.

Known BH3-Containing Proteins Identified (listed in alphabetical order)

(17 genes)

Gene: BAD
CCDS ID: 8065.1|Hs37.1|chr11
Amino acids: 110--122, BH3-like sequence: YGRELRRMSDEFV
Helix containing: HHHHHHHHHHHHH

Gene: BAK1
CCDS ID: 4781.1|Hs37.1|chr6
Amino acids: 74--86, BH3-like sequence: VGRQLAIIGDDIN
Helix containing: HHHH---------
Affinity score for BCL-xL: -0.443697
Affinity score for MCL-1: 0.360124

Gene: BAX
CCDS ID: 12742.1|Hs37.1|chr19
Amino acids: 59--71, BH3-like sequence: LSECLKRIGDELD
CCDS ID: 12744.1|Hs37.1|chr19
Amino acids: 59--71, BH3-like sequence: LSECLKRIGDELD
CCDS ID: 12745.1|Hs37.1|chr19
Amino acids: 59--71, BH3-like sequence: LSECLKRIGDELD
Helix containing: HHHHHHHHHHHHH-

Gene: BBC3/PUMA
CCDS ID: 12697.1|Hs37.1|chr19
Amino acids: 137--149, BH3-like sequence: IGAQLRRMADDLN
CCDS ID: 46130.1|Hs37.1|chr19
Amino acids: 75--87, BH3-like sequence: IGAQLRRMADDLN
Helix containing: HHHHHHHHHHHHH

Gene: BCL2L11/BIM
CCDS ID: 2089.1|Hs37.1|chr2
Amino acids: 148--160, BH3-like sequence: IAQELRRIGDEFN
CCDS ID: 42731.1|Hs37.1|chr2
Amino acids: 88--100, BH3-like sequence: IAQELRRIGDEFN
Helix containing: HHHHHHHHHHHHH
Affinity score for BCL-xL: -0.075721
Affinity score for MCL-1: -0.022094

Gene: BCL2L14/BCL-G
CCDS ID: 8645.1|Hs37.1|chr12

Amino acids: 212--224, BH3-like sequence: IVELLKYSGDQLE
CCDS ID: 8646.1|Hs37.1|chr12
Amino acids: 212--224, BH3-like sequence: IVELLKYSGDQLE
Helix containing: HHHHHHH-HHHHH
Affinity score for BCL-xL: -2.215662
Affinity score for MCL-1: -2.278435

Gene: BCL2L15/BFK
CCDS ID: 30809.1|Hs37.1|chr1
Amino acids: 53--65, BH3-like sequence: IAGRLRMLGDQFN
Helix containing: HHHHHHHHHH----

Gene: BECN1
CCDS ID: 11441.1|Hs37.1|chr17
Amino acids: 112--124, BH3-like sequence: LSRRLKVTGDLFD
Helix containing: HHHHHHH---HHH
Affinity score for BCL-xL: -1.045758
Affinity score for MCL-1: -2.371902

Gene: BID
CCDS ID: 13747.1|Hs37.1|chr22
Amino acids: 132--144, BH3-like sequence: IARHLAQVGDSMD
CCDS ID: 13748.1|Hs37.1|chr22
Amino acids: 86--98, BH3-like sequence: IARHLAQVGDSMD
Helix containing: HHHHHHHH-----

Gene: BIK
CCDS ID: 14044.1|Hs37.1|chr22
Amino acids: 57--69, BH3-like sequence: LALRLACIGDEMD
Helix containing: HHHHHHH------

Gene: BMF
CCDS ID: 10052.1|Hs37.1|chr15
Amino acids: 133--145, BH3-like sequence: IARKLQCIADQFH
Helix containing: HHHHHHHHHHHHH

Gene: BNIP3L
CCDS ID: 6050.1|Hs37.1|chr8
Amino acids: 130--142, BH3-like sequence: EVEALKKSADWVS
Helix containing: HHHHHHHH-----
Affinity score for BCL-xL: -2.504385
Affinity score for MCL-1: -3.083545
Also known as: NIX; BNIP3a

Gene: BOK
CCDS ID: 2550.1|Hs37.1|chr2
Amino acids: 66--78, BH3-like sequence: VCAVLLRLGDELE
Helix containing: HHHHHHH---HHH

Gene: HRK
CCDS ID: 9181.1|Hs37.1|chr12
Amino acids: 33--45, BH3-like sequence: TAARLKALGDELH
Helix containing: HHHHHHHHH--HHH
Affinity score for BCL-xL: -0.557902
Affinity score for MCL-1: -1.329452

Gene: HUWE1 (HECT E3 ubiquitin ligase family)
CCDS ID: 35301.1|Hs37.1|chrX
Amino acids: 1976--1988, BH3-like sequence: VGQLLQDMGDDVY
Helix containing: HHHHHHHHH--HHH
Also known as MULE; Ib772; LASU1; UREB1; HECTH9; ARF-BP1; HSPC272; KIAA0312

Gene: PMAIP1 (phorbol-12-myristate-13-acetate-induced protein 1)/NOXA
CCDS ID: 11975.1|Hs37.1|chr18
Amino acids: 25--37, BH3-like sequence: CATQLRRFGDKLN
Helix containing: HHHHHHHHH--HHH

Gene: RAD9A
CCDS ID: 8159.1|Hs37.1|chr11
Amino acids: 16--28, BH3-like sequence: AVHSLSRIGDELY
Helix containing: HHHHHHH------
Affinity score for BCL-xL: -1.911070
Affinity score for MCL-1: -0.625989

Genes with PSSM Affinity Scores (ranked in descending order according to predicted BCL-X_L binding affinity with respect to known BH3-containing proteins)

(111 candidates)

Gene: BCL2L11/BIM

CCDS ID: 2089.1|Hs37.1|chr2

Amino acids: 148--160, BH3-like sequence: IAQELRRIGDEFN

CCDS ID: 42731.1|Hs37.1|chr2

Amino acids: 88--100, BH3-like sequence: IAQELRRIGDEFN

Helix containing: HHHHHHHHHHHHH

Affinity score for BCL-xL: -0.075721

Affinity score for MCL-1: -0.022094

Gene: **BAK1**

CCDS ID: 4781.1|Hs37.1|chr6

Amino acids: 74--86, BH3-like sequence: VGRQLAIIGDDIN

Helix containing: HHHH---------

Affinity score for BCL-xL: -0.443697

Affinity score for MCL-1: 0.360124

Gene: SPIRE1 (spire homolog 1)

CCDS ID: 32790.2|Hs37.1|chr18

Amino acids: 94--106, BH3-like sequence: GAVTLAPAADDAG

CCDS ID: 45829.1|Hs37.1|chr18

Amino acids: 94--106, BH3-like sequence: GAVTLAPAADDAG (not conserved)

Helix containing: ----------

Affinity score for BCL-xL: -0.500616

Affinity score for MCL-1: -2.006571

Also known as MGC150621, MGC150622, Spir-1

Spire proteins, such as SPIRE1, are highly conserved between species. They belong to the family of Wiskott-Aldrich homology region-2 (WH2) proteins, which are involved in actin organization

Identification of a short Spir interaction sequence at the C-terminal end of formin subgroup proteins. Pechlivanis M, *et al.* J Biol Chem, 2009 Sep 11. PMID: 19605360.

Analysis of the function of Spire in actin assembly and its synergy with formin and profilin. Bosch M, Le KH, Bugyi B, Correia JJ, Renault L, Carlier MF. Mol Cell. 2007 Nov 30;28(4):555-68.

Targeted proteomic analysis of 14-3-3 sigma, a p53 effector commonly silenced in cancer. Benzinger A, Muster N, Koch HB, Yates JR 3rd, Hermeking H. Mol Cell Proteomics. 2005 Jun;4(6):785-95.

Gene: **HRK**

CCDS ID: 9181.1|Hs37.1|chr12

Amino acids: 33--45, BH3-like sequence: TAARLKALGDELH

Helix containing: HHHHHHHH--HHH

Affinity score for BCL-xL: -0.557902

Affinity score for MCL-1: -1.329452

Gene: CARNS1 (carnosine synthase 1)

CCDS ID: 44658.1|Hs37.1|chr11

Amino acids: 362--374, BH3-like sequence: AAPRLGPAADEAV

Helix containing: H------HHHHHH

Affinity score for BCL-xL: -0.865164

Affinity score for MCL-1: -2.005403

CARNS1 (EC 6.3.2.11), a member of the ATP-grasp family of ATPases, catalyzes the formation of carnosine (beta-alanyl-L-histidine) and homocarnosine (gamma-aminobutyryl-L-histidine), which are found mainly in skeletal muscle and the central nervous system, respectively (Drozak *et al*., 2010).

Gene: CHAF1B [chromatin assembly factor 1, subunit B (p60)]

CCDS ID: 13644.1|Hs37.1|chr21

Amino acids: 77--89, BH3-like sequence: TGEILASGGDDAV

Helix containing: ----------

Conserved in chimp, mouse and rat

Affinity score for BCL-xL: -1.045217

Affinity score for MCL-1: -1.899133

Also known as CAF1; MPP7; CAF-1; CAF1A; CAF1P60; CAF-IP60; MPHOSPH7

Chromatin assembly factor I (CAF-I) is required for the assembly of histone octamers onto newly-replicated DNA. CAF-I is composed of three protein subunits, p50, p60, and p150. The protein encoded by this gene corresponds to the p60 subunit and is required for chromatin assembly after replication. The encoded protein is differentially phosphorylated in a cell cycle-dependent manner. In addition, it is normally found in the nucleus except during mitosis, when it is released into the cytoplasm. This protein is a member of the WD-repeat HIR1 family and may also be involved in DNA repair

Overexpression of CAF-1/p60, on histological and/or cytological samples, characterizes malignant salivary gland tumours with aggressive behaviour Title: The proliferation marker Chromatin Assembly Factor-1 is of clinical value in predicting the biological behaviour of salivary gland tumours.

CAF-1 is a proliferation marker in various malignant tumours with prognostic value in renal, endometrial and cervical carcinomas, which supports the value of CAF-1 as a clinical marker of cancer progression. Title: Clinical significance and prognostic value of chromatin assembly factor-1 overexpression in human solid tumours.

Chromatin Assembly Factor-1/p60 may have a role in progression and metastasis of melanoma Title: Overexpression of Chromatin Assembly Factor-1/p60 helps to predict the prognosis of melanoma patients.

The histone H3K9 methyltransferase SetDB1 associates with the specific heterochromatin protein 1alpha (HP1alpha)-chromatin assembly factor 1 (CAF1) chaperone complex. Title: The HP1alpha-CAF1-SetDB1-containing complex provides H3K9me1 for Suv39-mediated K9me3 in pericentric heterochromatin.

overexpression of CAF-1/p60 characterized prostatic cancers with a worse prognosis Title: Overexpression of chromatin assembly factor-1 (CAF-1) p60 is predictive of adverse behaviour of prostatic cancer.

These data identify chromatin assembly factor 1 as an essential factor not only for S-phase-specific chromatin assembly but also for proliferating cell viability.

Gene: **BECN1**

CCDS ID: 11441.1|Hs37.1|chr17

Amino acids: 112--124, BH3-like sequence: LSRRLKVTGDLFD

Helix containing: HHHHHHH---HHH

Affinity score for BCL-xL: -1.045758

Affinity score for MCL-1: -2.371902

Gene: KRT20 (cytokeratin 20)

CCDS ID: 11379.1|Hs37.1|chr17

Amino acids: 55--67, BH3-like sequence: YGSDLTGGGDLFV

Helix containing: ----------

Affinity score for BCL-xL: -1.130182

Affinity score for MCL-1: -2.337438

Gene: CASP1

CCDS ID: 8330.1|Hs37.1|chr11

Amino acids: 83--95, BH3-like sequence: LAGTLGLSADQTS Helix containing: ----------

Affinity score for BCL-xL: -1.171087

Affinity score for MCL-1: -2.600238

Gene: FOLH1B (folate hydrolase 1B)

CCDS ID: 8286.1|Hs37.1|chr11

Amino acids: 292--304, BH3-like sequence: YAVVLRKYADKIY

Helix containing: HHHHHHHHHHHHH

Affinity score for BCL-xL: -1.218388

Affinity score for MCL-1: -2.319926

Also known as PSM; GCP3; FOLH2; FOLHP; PSMAL; GCPIII; PSMA-LIKE

See all (7) citations in PubMed

This CCDS ID was withdrawn because the gene may be a pseudogene.

Gene: FOLH1 [Folate hydrolase (prostate-specific membrane antigen) 1]

CCDS ID: 7946.1|Hs37.1|chr11

Amino acids: 600--612, BH3-like sequence: YAVVLRKYADKIY

CCDS ID: 31493.1|Hs37.1|chr11

Amino acids: 600--612, BH3-like sequence: YAVVLRKYADKIY

Helix containing: HHHHHHHHHHH--

Affinity score for BCL-xL: -1.218388

Affinity score for MCL-1: -2.319926

Also known as: PSM; FGCP; FOLH; GCP2; PSMA; mGCP; GCPII; NAALAD1; NAALAdase

This gene encodes a type II transmembrane glycoprotein belonging to the M28 peptidase family. The protein acts as a glutamate carboxypeptidase on different alternative substrates, including the nutrient folate and the neuropeptide N-acetyl-l-aspartyl-l-glutamate and is expressed in a number of tissues such as prostate, central and peripheral nervous system and kidney. A mutation in this gene may be associated with impaired intestinal absorption of dietary folates, resulting in low blood folate levels and consequent hyperhomocysteinemia. Expression of this protein in the brain may be involved in a number of pathological conditions associated with glutamate excitotoxicity. In the prostate the protein is up-regulated in cancerous cells and is used as an effective diagnostic and prognostic indicator of prostate cancer.

See all (105) citations in PubMed

Gene: GBP6 (guanylate binding protein family, member 6)

CCDS ID: 723.1|Hs37.1|chr1

Amino acids: 593--605, BH3-like sequence: IARTLDNLADELT

Helix containing: HHHHHHHHHHHHH

Affinity score for BCL-xL: -1.307408

Affinity score for MCL-1: -2.092260

Also known as: FLJ39135; DKFZp686G0786

A family of IFN-gamma-inducible 65-kD GTPases protects against bacterial infection. Kim BH, Shenoy AR, Kumar P, Das R, Tiwari S, MacMicking JD. Science. 2011 May 6;332(6030):717-21. Immune interferon gamma (IFN- γ) is essential for mammalian host defense against intracellular pathogens. IFN-g induces nearly 2000 host genes, yet few have any assigned function. Here, we examined a complete mouse 65-kilodalton (kD) guanylate-binding protein (Gbp) gene family as part of a 43-member IFN-g–inducible guanosine triphosphatase (GTPase) superfamily in mouse and human genomes. Family-wide loss-of-function analysis found that at least four Gbps—Gbp1, Gbp6, Gbp7, and Gbp10—conferred cell-autonomous immunity to listerial or mycobacterial infection within macrophages and gene-deficient animals. These Gbps solicited host defense proteins, including the phagocyte oxidase, antimicrobial peptides, and autophagy effectors, to kill intracellular bacteria. Thus, specific 65-kD Gbps coordinate a potent oxidative and vesicular trafficking program to protect the host from infection.

Guanylate-binding protein (GBP), N-terminal domain. Guanylate-binding proteins (GBPs) define a group of proteins that are synthesized after activation of the cell by interferons. The biochemical properties of GBPs are clearly different from those of Ras-like and heterotrimeric GTP-binding proteins. They bind guanine nucleotides with lowAffinity (micromolar range), are stable in their absence and have a high turnover GTPase. In addition to binding GDP/GTP, they have the unique ability to bind GMP with equalAffinity and hydrolyze GTP not only to GDP, but also to GMP. Furthermore, two unique regions around the base and the phosphate-binding areas, the guanine and the phosphate caps, respectively, give the nucleotide-binding site a unique appearance not found in the canonical GTP-binding proteins. The phosphate cap, which constitutes the region analogous to switch I, completely shields the phosphate-binding site from solvent such that a potential GTPase-activating protein (GAP) cannot approach.

In silico genomic analysis of the human and murine guanylate-binding protein (GBP) gene clusters. Olszewski MA, Gray J, Vestal DJ. J Interferon Cytokine Res. 2006 May;26(5):328-52. The guanylate-binding proteins (GBPs) were among the first interferon (IFN)-stimulated genes (ISGs) discovered, but until recently, little was known about their functions and even less about the composition of the gene family. Analysis of the promoter of human GBP-1 contributed significantly toward the understanding of Jak-Stat signaling and the delineation of the IFN-gamma activation site (GAS) and IFN-stimulated response element (ISRE) promoter elements. In this study, we have examined the genomic arrangement and composition of the GBPs in both mouse and humans. There are seven GBP paralogs in humans and at least one pseudogene, all of which are located in a cluster of genes on chromosome 1. Five of the six MuGBPs and a GBP pseudogene are clustered in a syntenic region on chromosome 3. The sixth MuGBP, MuGBP-4, and three GBP pseudogenes are located on chromosome 5. As might be expected, the GBPs share similar genomic organizations of introns and exons. Five of the MuGBPs had previously been shown to be coordinately induced by IFNs, and as expected, all of the MuGBPs have GAS and ISRE elements in their promoters. Interestingly, not all of the HuGBPs have GAS and ISRE elements, suggesting that not all GBPs are IFN responsive in humans.

See all (11) citations in PubMed

Gene: RBM17 (RNA binding motif protein 17)

CCDS ID: 7077.1|Hs37.1|chr10

Amino acids: 89--101, BH3-like sequence: AGEVLIPLADEYD

Helix containing: ----------

Affinity score for BCL-xL: -1.338146

Affinity score for MCL-1: -2.599471

This gene encodes an RNA binding protein. The encoded protein is part of the spliceosome complex and functions in the second catalytic step of mRNA splicing. Alternatively spliced transcript variants have been described. Related pseudogenes exist on chromosomes 9 and 15.

Nat Struct Mol Biol. 2007 Jul;14(7):620-9. Epub 2007 Jun 24. U2AF-homology motif interactions are required for alternative splicing regulation by SPF45. Corsini L, Bonnal S, Basquin J, Hothorn M, Scheffzek K, Valcárcel J, Sattler M. The U2AF-homology motif (UHM) mediates protein-protein interactions between factors involved in constitutive RNA splicing. Here we report that the splicing factor SPF45 regulates alternative splicing of the apoptosis regulatory gene FAS (also called CD95). The SPF45 UHM is necessary for this activity and binds UHM-ligand motifs (ULMs) present in the 3' splice site-recognizing factors U2AF65, SF1 and SF3b155. We describe a 2.1-A crystal structure of SPF45-UHM in complex with a ULM peptide from SF3b155. Features distinct from those of previously described UHM-ULM structures allowed the design of mutations in the SPF45 UHM that selectively impair binding to individual ULMs. Splicing assays using the ULM-selective SPF45 variants demonstrate that individual UHM-ULM interactions are required for FAS splicing regulation by SPF45 *in vivo*. Our data suggest that networks of UHM-ULM interactions are involved in regulating alternative splicing.

Gene: ERCC4 (excision repair cross-complementing rodent repair deficiency, complementation group 4)

CCDS ID: 32390.1|Hs37.1|chr16

Amino acids: 825--837, BH3-like sequence: AATALAITADSET

Helix containing: HHHHHHHHH-----

Affinity score for BCL-xL: -1.342363

Affinity score for MCL-1: -2.406380

The protein encoded by this gene forms a complex with ERCC1 and is involved in the 5' incision made during nucleotide excision repair. This complex is a structure specific DNA repair endonuclease that interacts with EME1. Defects in this gene are a cause of xeroderma pigmentosum complementation group F (XP-F), or xeroderma pigmentosum VI (XP6).

c-Myc degradation induced by DNA damage results in apoptosis of CHO cells.

Jiang MR, Li YC, Yang Y, Wu JR. Oncogene. 2003 May 22;22(21):3252-9.

Although tripchlorolide (TC), a compound purified from a Chinese herb Tripterygium Wilfordii Hook, has been demonstrated to be a potent antitumor agent, its mechanisms of action are unknown. The present study shows that TC induces apoptosis of Chinese Hamster Ovary (CHO) cells. Most strikingly, TC was particularly potent in inducing apoptosis of the UV41 mutant CHO cells, which are deficient in the ERCC4 gene encoding a nucleotide excision repair protein. TC caused a higher level of DNA damage in UV41 cells than those in the wild-type CHO cells or EM9 cells, which are deficient in single-strand break repair. These results provided a critical link between apoptotic hypersensitivity and DNA damage in defective nucleotide excision repair pathway of UV41 cells by TC treatment. Further analysis showed that degradation of the c-Myc protein in TC-treated UV41 cells was much stronger than those in the wild-type CHOAA8 and the EM9. A proteasome inhibitor, MG132, reduced both the degradation of c-Myc and apoptosis in TC-treated UV41 cells. Expression of exogenous c-Myc also inhibited apoptosis of TC-treated UV41 cells. These results indicate that c-Myc degradation induced by DNA damage in the presence of TC contributes to induction of apoptosis of UV41 cells.

Gene: IL16

CCDS ID: 10317.1|Hs37.1|chr15

Amino acids: 423--435, BH3-like sequence: LGFSLAGGADLEN

CCDS ID: 42069.1|Hs37.1|chr15

Amino acids: 1124--1136, BH3-like sequence: LGFSLAGGADLEN

Helix containing: ----------

Affinity score for BCL-xL: -1.346787

Affinity score for MCL-1: -3.132325

Gene: FNIP2 (folliculin interacting protein 2)

CCDS ID: 47155.1|Hs37.1|chr4

Amino acids: 809--821, BH3-like sequence: IAGQLSHAADLGT

Helix containing: HHHHHHHHHHH---

Conserved in chimp

Affinity score for BCL-xL: -1.368490

Affinity score for MCL-1: -2.779178

Also known as FNIPL; MAPO1; KIAA1450

GO:0008630 DNA damage response, signal transduction resulting in induction of apoptosis

Network organization of the human autophagy system. Behrends C, Sowa ME, Gygi SP, Harper JW. Nature. 2010 Jul 1;466(7302):68-76. PMID: 20562859 [FNIP1 is linked to ULK1 (unc-51-like kinase 1) in autophagy via AMPK]

Identification and characterization of a novel folliculin-interacting protein FNIP2. Hasumi H, *et al.* Gene, 2008 May 31. PMID: 18403135. [The identification and characterization of a novel FNIP1 homolog FNIP2 that also interacts with FLCN and AMPK, is reported.] Birt-Hogg-Dube' syndrome characterized by increased risk for renal neoplasia is caused by germline mutations in the BHD/FLCN gene encoding a novel tumor suppressor protein, folliculin (FLCN*), which interacts with FNIP1 and 5'-AMP-activated protein kinase(AMPK). Here we report the identification and characterization of a novel FNIP1 homolog FNIP2 that also interacts with FLCN and AMPK. C-terminally-deleted FLCN mutants, similar to those produced by naturally-occurring germline mutations in BHD patients, were unable to bind FNIP2. These data taken together with our previous results that demonstrated FNIP1 binding to the C-terminus of FLCN suggest that FLCN tumor suppressor function may be facilitated by interactions with both FNIP1 and FNIP2 through its C-terminus. Furthermore, we demonstrate that FNIP1 and FNIP2 are able to form homo- or heteromeric multimers suggesting that they may function independently or cooperatively with FLCN. Differential expression of FNIP1 and FNIP2 transcripts in some normal tissues may indicate tissue specificity for these homologs. Interestingly FNIP1 and FNIP2 were oppositely expressed in human clear cell renal cell carcinoma (RCC), and coordinately expressed in chromophobe RCC and oncocytoma, suggesting their differential function in different histologic variants of RCC.

*Mutations in FLCN are associated with Birt-Hogg-Dube syndrome, which is characterized by fibrofolliculomas, renal tumors, lung cysts, and pneumothorax.

Interaction of folliculin (Birt-Hogg-Dubé gene product) with a novel Fnip1-like (FnipL/Fnip2) protein. Takagi Y, *et al.* Oncogene. 2008 Sep 11; 27(40): 5339-47.

Birt-Hogg-Dubé (BHD) syndrome is characterized by the development of pneumothorax, hair folliculomas and renal tumors and the responsible BHD gene is thought to be a tumor suppressor. The function of folliculin (Flcn), encoded by BHD, is totally unknown, although its interaction with Fnip1 has been reported. In this study, we identified a novel protein binding to Flcn, which is highly homologous to Fnip1, and which we named FnipL (recently reported in an independent study as Fnip2). The interaction between FnipL/Fnip2 and Flcn may be mediated mainly by the C-terminal domains of each protein as is the case for the Flcn-Fnip1 interaction. FnipL/Fnip2 and Flcn were located together in the cytoplasm in a reticular pattern, although solely expressed Flcn was found mainly in the nucleus. Cytoplasmic retention of Flcn was canceled with C-terminal truncation of FnipL/Fnip2, suggesting that FnipL/Fnip2 regulates Flcn distribution through their complex formation. By the employment of siRNA, we observed a decrease in S6K1 phosphorylation in the BHD-suppressed cell. We also observed a decrease in S6K1 phosphorylation in FNIP1- and, to a lesser extent, in FNIPL/FNIP2-suppressed cells. These results suggest that Flcn-FnipL/Fnip2 and Flcn-Fnip1 complexes positively regulate S6K1 phosphorylation and that FnipL/Fnip2 provides an important clue to elucidating the function of Flcn and the pathogenesis of BHD.

See all (6) citations in PubMed

Phosphorylation of ULK1 (hATG1) by AMP-activated protein kinase connects energy sensing to mitophagy. Egan DF, *et al.* Science, 2011 Jan 28. PMID: 21205641.

AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. Kim J, *et al.* Nat Cell Biol, 2011 Feb. PMID: 21258367.

The ULK1 complex controls early steps in autophagosome formation, and are regulated by nutrient availability via mTOR. The PIK3C3–BECN1 (beclin) vacuolar protein sorting complex controls production of phosphoinositide signals that facilitate assembly of the incipient autophagosome.

The Beclin 1 network regulates autophagy and apoptosis. Kang R, *et al.* Cell Death Differ. 2011 Apr;18(4):571-80. Epub 2011 Feb 11. Beclin 1, the mammalian orthologue of yeast Atg6, has a central role in autophagy, a process of programmed cell survival, which is increased during periods of cell stress and extinguished during the cell cycle. It interacts with several cofactors [Atg14L, UVRAG, Bif-1 (Bax-interacting factor 1), Rubicon, Ambra1, HMGB1, nPIST, VMP1, SLAM, IP(3)R, PINK and survivin] to regulate the lipid kinase Vps-34 protein and promote formation of Beclin 1-Vps34-Vps15 core complexes, thereby inducing autophagy. In contrast, the BH3 domain of Beclin 1 is bound to, and inhibited by Bcl-2 or Bcl-XL. This interaction can be disrupted by phosphorylation of Bcl-2 and Beclin 1, or ubiquitination of Beclin 1. Interestingly, caspase-mediated cleavage of Beclin 1 promotes crosstalk between apoptosis and autophagy. Beclin 1 dysfunction has been implicated in many disorders, including cancer and neurodegeneration. Here, we summarize new findings regarding the organization and function of the Beclin 1 network in cellular homeostasis, focusing on the cross-regulation between apoptosis and autophagy.

MCL-1 is a stress sensor that regulates autophagy in a developmentally regulated manner. Germain M, *et al.* EMBO J. 2011 Jan 19;30(2):395-407. Apoptosis has an important role during development to regulate cell number. In differentiated cells, however, activation of autophagy has a critical role by enabling cells to remain functional following stress. In this study, we show that the antiapoptotic BCL-2 homologue MCL-1 has a key role in controlling both processes in a developmentally regulated manner. Specifically, MCL-1 degradation is an early event not only following induction of apoptosis, but also under nutrient deprivation conditions where MCL-1 levels regulate activation of autophagy. Furthermore, deletion of MCL-1 in cortical neurons of transgenic mice activates a robust autophagic response. This autophagic response can, however, be converted to apoptosis by either reducing the levels of the autophagy regulator Beclin-1, or by a concomitant activation of BAX. Our results define a pathway whereby MCL-1 has a key role in determining cell fate, by coordinately regulating apoptosis and autophagy.

Bif-1 regulates Atg9 trafficking by mediating the fission of Golgi membranes during autophagy. Takahashi Y, *et al.* Autophagy. 2011 Jan;7(1):61-73. Epub 2011 Jan 1. Atg9 is a transmembrane protein essential for autophagy which cycles between the Golgi network, late endosomes and LC3-positive autophagosomes in mammalian cells during starvation through a mechanism that is dependent on ULK1 and requires the activity of the class III phosphatidylinositol-3-kinase (PI3KC3). In this study, we demonstrate that the N-BAR-containing protein, Bif-1 (Bax-interacting factor), is required for Atg9 trafficking and the fission of Golgi membranes during the induction of autophagy. Upon starvation, Atg9-positive membranes undergo continuous tubulation and fragmentation to produce cytoplasmic punctate structures that are positive for Rab5, Atg16L (see below) and LC3. Loss of Bif-1 or inhibition of the PI3KC3 complex II suppresses starvation-induced fission of Golgi membranes and peripheral cytoplasmic redistribution of Atg9. Moreover, Bif-1 mutants, which lack the functional regions of the N-BAR domain that are responsible for membrane binding and/or bending activity, fail to restore the fission of Golgi membranes as well as the formation of Atg9 foci and autophagosomes in Bif-1-deficient cells starved of nutrients. Taken together, these findings suggest that Bif-1 acts as a critical regulator of Atg9 puncta formation presumably by mediating Golgi fission for autophagosome biogenesis during starvation.

See all (39) citations in PubMed

Gene: KCNK2 (potassium channel, subfamily K, member 2)

CCDS ID: 31024.1|Hs37.1|chr1

Amino acids: 170--182, BH3-like sequence: FGFLLAGVGDQLG

CCDS ID: 41466.1|Hs37.1|chr1

Amino acids: 181--193, BH3-like sequence: FGFLLAGVGDQLG

CCDS ID: 41467.1|Hs37.1|chr1

Amino acids: 185--197, BH3-like sequence: FGFLLAGVGDQLG

Helix containing: HHHHHHH---HHH

Affinity score for BCL-xL: -1.370564

Affinity score for MCL-1: -1.706071

Gene: KCNK10 (potassium channel, subfamily K, member 10)

CCDS ID: 9880.1|Hs37.1|chr14

Amino acids: 195--207, BH3-like sequence: FGFLLAGIGDQLG

CCDS ID: 9881.1|Hs37.1|chr14

Amino acids: 200--212, BH3-like sequence: FGFLLAGIGDQLG

CCDS ID: 9882.1|Hs37.1|chr14

Amino acids: 200--212, BH3-like sequence: FGFLLAGIGDQLG

Helix containing: HHHHHHHHH--HHH

Affinity score for BCL-xL: -1.370564

Affinity score for MCL-1: -1.297135

Gene: NOX4 (NADPH oxidase 4)

CCDS ID: 8285.1|Hs37.1|chr11

Amino acids: 367--379, BH3-like sequence: FGVHLKIVGDWTE

CCDS ID: 44695.1|Hs37.1|chr11

Amino acids: 367--379, BH3-like sequence: FGVHLKIVGDWTE

CCDS ID: 44696.1|Hs37.1|chr11

Amino acids: 343--355, BH3-like sequence: FGVHLKIVGDWTE

Helix containing: ----------HHH

Affinity score for BCL-xL: -1.414678

Affinity score for MCL-1: -1.959737

Gene: DCHS1 (dachsous 1)

CCDS ID: 7771.1|Hs37.1|chr11

Amino acids: 2187--2199, BH3-like sequence: EGPLLQVEADDLD

Helix containing: ----------

Affinity score for BCL-xL: -1.435438

Affinity score for MCL-1: -3.021913

This gene is a member of the cadherin superfamily whose members encode calcium-dependent cell-cell adhesion molecules. The encoded protein has a signal peptide, 27 cadherin repeat domains and a unique cytoplasmic region. This particular cadherin family member is expressed in fibroblasts but not in melanocytes or keratinocytes. The cell-cell adhesion of fibroblasts is thought to be necessary for wound healing

Gene: AVEN (apoptosis, caspase activation inhibitor)

CCDS ID: 10030.1|Hs37.1|chr15

Amino acids: 141--153, BH3-like sequence: FSVLLSSAGDSFS

Helix containing: ----------HH

Affinity score for BCL-xL: -1.463450

Affinity score for MCL-1: -1.936553

Also known as PDCD12 (programmed cell death 12)

BH3 motif evolutionarily conserved except for zebrafish (and Drosophila)

Aven-dependent activation of ATM following DNA damage. Guo JY, Yamada A, Kajino T, Wu JQ, Tang W, Freel CD, Feng J, Chau BN, Wang MZ, Margolis SS, Yoo HY, Wang XF, Dunphy WG, Irusta PM, Hardwick JM, Kornbluth S. Curr Biol.

2008 Jul 8;18(13):933-42. BH3-containing **RAD9A** is involved in DNA damage and the G2/M checkpoint; AVEN is a multifunctional protein that is also involved in this pathway (activator of ATM).

Aven blocks DNA damage-induced apoptosis by stabilising Bcl-xL. Kutuk O, Temel SG, Tolunay S, Basaga H. Eur J Cancer. 2010 Sep;46(13):2494-505. Epub 2010 Jul 7. AVEN functions as anti-apoptotic protein and it does so by binding to and enhancing the stability of BCLXL. **(Of note, enforced Aven expression did not affect the stability of Mcl-1 and Bcl-2 proteins.)**

Aven, a novel inhibitor of caspase activation, binds Bcl-xL and Apaf-1. Chau BN, Cheng EH, Kerr DA, Hardwick JM. Mol Cell. 2000 Jul;6(1):31-40. Chau *et al.* (2000) reported that AVEN binding to BCLXL involved both the **BH4*** and BH1 domains. The BH1 domain is part of the hydrophobic groove that binds BH3 motifs, suggesting a BH3-mediated interaction.

Bcl-2 and Bax interact via the BH1-3 groove-BH3 motif interface and a novel interface involving the **BH4*** motif. Ding J, Zhang Z, Roberts GJ, Falcone M, Miao Y, Shao Y, Zhang XC, Andrews DW, Lin J. J Biol Chem. 2010 Sep 10;285(37):28749-63.

According to Moroy *et al.* (2009) [Molecular basis for Bcl-2 homology 3 domain recognition in the Bcl-2 protein family: identification of conserved hot spot interactions. Moroy G, Martin E, Dejaegere A, Stote RH. J Biol Chem. 2009 Jun 26;284(26):17499-511.], N136 of BCLXL forms a hydrogen bond with a carboxylate group of the conserved D in the BH3 motif. Mutation of N136 to I eliminates this and leads to loss of a stabilizing interaction. One of the BCLXL mutants that Chau *et al.* (2000) used that disrupted the BCLXL-AVEN interaction (BCLXL mutant 7) has the N136I mutation (V135A/N136I/W137L). Consistent with this speculation, the Drosophila ortholog of AVEN does not contain a conserved BH3 motif (Zou *et al.*, 2011). There is conservation this region between dAVEN and other AVEN orthologs -- referred to as region II in Fig. 1 -- but the critical L and D residues are not conserved (nor is a F that AVEN shares with BIM and BAD and which apparently makes a significant hydrophobic contribution to the BCLXL interaction). As predicted, dAVEN does not interact with Drosophila BCL2 family members. [Identification of dAven, a Drosophila melanogaster ortholog of the cell cycle regulator Aven. Zou S, Chang J, Lafever L, Tang W, Johnson EL, Hu J, Wilk R, Krause HM, Drummond-Barbosa D, Irusta PM. Cell Cycle. 2011 Mar 15;10(6):989-98. Epub 2011 Mar 15.]

A working hypothesis is that human AVEN (and most AVEN orthologs) is a multifunctional protein that modulates decisions of cell-cycle arrest and apoptosis during the DNA damage response, depending on the extent of damage.

AVEN also shows similarity to BIK (sensitizer BH3-only protein localized to ER) (by Multalin, T-COFFEE and CLUSTAL): BH3 domains other than Bim and Bid can directly activate Bax/Bak. Du H, Wolf J, Schafer B, Moldoveanu T, Chipuk JE, Kuwana T. J Biol Chem. 2011 Jan 7;286(1):491-501. … Our *in vitro* data show that Bim, Bid, Bmf, Puma, and the Noxa/Bad combination all inhibit both types of pro-survival proteins [BCL2/BCLXL vs MCL-1/BCL2A1] as well as directly activate Bax/Bak. Therefore, they are capable of inducing cytochrome c release from mitochondria, as well as apoptosis in cells lacking Bim and Bid. Hrk and **Bik BH3** also elicit weak direct activation, but **only inhibit Bcl-xL-type anti-apoptotic proteins**, which is likely the reason why they fail to trigger cytochrome c release in these cells.

Gene: HIP1R (Huntingtin interacting protein 1 related)

CCDS ID: 31922.1|Hs37.1|chr12

Amino acids: 882--894, BH3-like sequence: GATQLVEAADKVV

Helix containing: -HHHHHHHHHHHHH

Affinity score for BCL-xL: -1.536100

Affinity score for MCL-1: -2.089553

Also known as HIP3; HIP12; ILWEQ; FLJ14000; FLJ27022; KIAA0655; MGC47513

BH3 motif in cow; mouse and rat have conservative changes that match consensus

HIP1R is a multi-domain protein that regulates clathrin-mediated endocytosis and actin assembly. The related HIP1 protein was previously shown to have transforming function due to alterations in receptor trafficking. HIP1R was found to interact with BCL2L10 (human Diva or BCL-B), a member of the BCL2 family that can either function as a pro- or anti-apoptotic protein.

Ectopic expression induced apoptosis and augmented BCL2L10 association with caspase 9. Deletion of both an N-terminal domain as well as a C-terminal domain containing the putative BH3 motif disrupted binding to BCL2L10. What is also noteworthy is that it had been identified in a proteomic screen for proteins that interact with dynein light chain LC8. LC8 is a component of the motor complexes that transport molecules and organelles within the cell. One of their roles is to sequester BH3-only proteins to regulate their activity; in particular, LC8 binds BIM. I didn't find an LC8-binding motif in HIP1R, so it could be an indirect interaction but interesting nonetheless.

HIP1R interacts with a member of Bcl-2 family, BCL2L10, and induces BAK-dependent cell death. Kim JH, *et al.* Cell Physiol Biochem, 2009. PMID: 19255499. The Bcl-2 family members are evolutionally conserved and crucial regulators of apoptosis. BCL2L10 (human Diva or BCL-B) is a member of the Bcl-2 family that has contradictory functions in apoptosis. In the present study, we identified the Huntington-interacting protein 1-related (HIP1R) protein following a search for Diva-interacting proteins using the yeast two-hybrid system. HIP1R is a multi-domain protein that regulates the clathrin-mediated endocytic machinery and actin assembly in cells. Interaction of endogenous proteins of BCL2L10 and HIP1R in 293T cells was determined by immunoprecipitation, and their direct association was confirmed by the Far-Western analysis. The deletion of both the AP180-homology (ANTH) and F-actin-binding the talin-HIP1/R/Sla2p actin-tethering C-terminal homology (THATCH) domains (the latter containing the putative BH3 motif) of HIP1R greatly compromised its binding ability to BCL2L10. Ectopic expression of HIP1R resulted in moderate cell death of 293T cells in conjunction with the dissipation of mitochondrial membrane potential and caspase 9 activation. A member of proapoptotic Bcl-2 family, BAK, was required for HIP1R to induce cell death, while BAX was dispensable. In addition, BCL2L10 was associated with endogenous caspase 9, and their binding was augmented by HIP1R overexpression. Thus, this study provided the previously unknown function of HIP1R involved in the intrinsic cell death pathway and further explored possible mechanisms by which HIP1R induces cell death.

Actin binding by Hip1 (huntingtin-interacting protein 1) and Hip1R (Hip1-related protein) is regulated by clathrin light chain. Wilbur JD, *et al.* J Biol Chem, 2008 Nov 21. PMID: 18790740.

HIP1 and HIP1r stabilize receptor tyrosine kinases and bind 3-phosphoinositides via epsin N-terminal homology domains.

J Biol Chem. 2004 Apr 2;279(14):14294-306. Epub 2004 Jan 19. Hyun TS, Rao DS, Saint-Dic D, Michael LE, Kumar PD, Bradley SV, Mizukami IF, Oravecz-Wilson KI, Ross TS. Huntingtin-interacting protein 1-related (HIP1r) is the only known mammalian relative of huntingtin-interacting protein 1 (HIP1), a protein that transforms fibroblasts via undefined mechanisms. Here we demonstrate that both HIP1r and HIP1 bind inositol lipids via their epsin N-terminal homology (ENTH) domains. In contrast to other ENTH domain-containing proteins, lipid binding is preferential to the 3-phosphate-containing inositol lipids, phosphatidylinositol 3,4-bisphosphate and phosphatidylinositol 3,5-bisphosphate. Furthermore, the HIP1r ENTH domain, like that of HIP1, is necessary for lipid binding, and **expression of an ENTH domain-deletion mutant, HIP1r/deltaE, induces apoptosis**. Consistent with the ability of HIP1r and HIP1 to affect cell survival, full-length HIP1 and HIP1r stabilize pools of growth factor receptors by prolonging their half-life following ligand-induced endocytosis. Although HIP1r and HIP1 display only a partially overlapping pattern of protein interactions, these data suggest that both proteins share a functional homology by binding 3-phosphorylated inositol lipids and stabilizing receptor tyrosine kinases in a fashion that may contribute to their ability to alter cell growth and survival.

Aberrant Huntingtin interacting protein 1 in lymphoid malignancies. Cancer Res. 2007 Sep 15;67(18):8923-31. Bradley SV, Smith MR, Hyun TS, Lucas PC, Li L, Antonuk D, Joshi I, Jin F, Ross TS. Huntingtin interacting protein 1 (HIP1) is an inositol lipid, clathrin, and actin binding protein that is overexpressed in a variety of epithelial malignancies. Here, we report for the first time that HIP1 is elevated in non-Hodgkin's and Hodgkin's lymphomas and that patients with lymphoid malignancies frequently had anti-HIP1 antibodies in their serum. Moreover, p53-deficient mice with B-cell lymphomas were 13 times more likely to have anti-HIP1 antibodies in their serum than control mice. Furthermore, transgenic overexpression of **HIP1** was associated with the development of lymphoid neoplasms. The HIP1 protein was induced by activation of the nuclear factor-kappaB pathway, which is frequently activated in lymphoid malignancies. These data identify HIP1 as a new marker of lymphoid malignancies that contributes to the transformation of lymphoid cells *in vivo*.

Huntingtin interacting protein 1 modulates the transcriptional activity of nuclear hormone receptors. J Cell Biol. 2005 Jul 18;170(2):191-200. Mills IG, Gaughan L, Robson C, Ross T, McCracken S, Kelly J, Neal DE. Internalization of activated receptors regulates signaling, and endocytic adaptor proteins are well-characterized in clathrin-mediated uptake. One of these adaptor proteins, huntingtin interacting protein 1 (HIP1), induces cellular transformation and is overexpressed in some prostate cancers. We have discovered that HIP1 associates with the androgen receptor through a central coiled coil domain and is recruited to DNA response elements upon androgen stimulation. HIP1 is a novel androgen receptor regulator, significantly repressing transcription when knocked down using a silencing RNA approach and activating transcription when overexpressed. We have also identified a functional nuclear localization signal at the COOH terminus of HIP1, which contributes to the nuclear

translocation of the protein. In conclusion, we have discovered that HIP1 is a nucleocytoplasmic protein capable of associating with membranes and DNA response elements and regulating transcription.

Gene: PCSK1N (Proprotein convertase subtilisin/kexin type 1 inhibitor)

CCDS ID: 14307.1|Hs37.1|chrX

Amino acids: 199--211, BH3-like sequence: LGRILAGSADSEG

Helix containing: HHHHH--------

Affinity score for BCL-xL: -1.581036

Affinity score for MCL-1: -3.173674

Gene: FMN2

CCDS ID: 31069.2|Hs37.1|chr1

Amino acids: 475--487, BH3-like sequence: LAAGLSRSADWTE

Helix containing: ----------HHH

Affinity score for BCL-xL: -1.599881

Affinity score for MCL-1: -3.318132

Formin homology (FH) domain proteins (see FMN1; MIM 136535) play a role in cytoskeletal organization and/or establishment of cell polarity

Gene: ANKFY1 (ankyrin repeat and FYVE domain containing 1)

CCDS ID: 42236.1|Hs37.1|chr17

Amino acids: 51--63, BH3-like sequence: ISRLLAIVADLYE

CCDS ID: 45581.1|Hs37.1|chr17

Amino acids: 51--63, BH3-like sequence: ISRLLAIVADLYE

Helix containing: HHHHHHHHHHHHHH

Affinity score for BCL-xL: -1.617083

Affinity score for MCL-1: -2.869232

CCDS ID: 42236.1|Hs37.1|chr17

Amino acids: 530--542, BH3-like sequence: EAASLTSLADSVH

Helix containing: HHH-HHHHHHHHH

Affinity score for BCL-xL: -1.665669

Affinity score for MCL-1: -1.774740

Also known as: ANKHZN; ZFYVE14 (see also ZFYVE9); KIAA1255; DKFZp686M19106

FYVE; FYVE domain; Zinc-binding domain; targets proteins to membrane lipids via interaction with phosphatidylinositol-3-phosphate, PI3P; present in Fab1, YOTB, Vac1, and EEA1;

This gene encodes a cytoplasmic protein that contains a coiled-coil structure and a BTB/POZ domain at its N-terminus, ankyrin repeats in the middle portion, and a FYVE-finger motif at its C-terminus. This protein belongs to a subgroup of double zinc finger proteins which may be involved in vesicle or protein transport. Alternative splicing has been observed at this locus and two variants, each encoding a distinct isoform, have been identified;

Linked to **ATG16L1** via MAP1LC3B (microtubule-associated protein 1 light chain 3 beta)

Note: Bim is associated LC8 cytoplasmic dynein light chain and thereby sequestered to the microtubule-associated dynein motor complex

Network organization of the human autophagy system. Behrends C, Sowa ME, Gygi SP, Harper JW. Nature. 2010 Jul 1;466(7302):68-76. PMID: 20562859

See all (14) citations in PubMed

Gene: EXOSC10 (exosome component 10)

CCDS ID: 126.1|Hs37.1|chr1

Amino acids: 49--61, BH3-like sequence: ASGGLPQFGDEYD

CCDS ID: 30584.1|Hs37.1|chr1

Amino acids: 49--61, BH3-like sequence: ASGGLPQFGDEYD

Helix containing: ----------

Affinity score for BCL-xL: -1.636118

Affinity score for MCL-1: -1.910471

Direct binding of CoREST1 to SUMO-2/3 contributes to gene-specific repression by the LSD1/CoREST1/HDAC complex. Ouyang J, *et al.* Mol Cell, 2009 Apr 24. PMID: 19394292.

Gene: C19orf55

CCDS ID: 46056.1|Hs37.1|chr19

Amino acids: 90--102, BH3-like sequence: PAPTLIDSGDSVV

Helix containing: ---------HHHH

Affinity score for BCL-xL: -1.648420

Affinity score for MCL-1: -1.693487

Gene: KCNH2 (potassium voltage-gated channel, subfamily H)

CCDS ID: 5910.1|Hs37.1|chr7

Amino acids: 765--777, BH3-like sequence: PGDTLVHAGDLLT

CCDS ID: 5911.1|Hs37.1|chr7

Amino acids: 425--437, BH3-like sequence: PGDTLVHAGDLLT

CCDS ID: 47747.1|Hs37.1|chr7

Amino acids: 765--777, BH3-like sequence: PGDTLVHAGDLLT

Helix containing: -------HHHHHHH

Affinity score for BCL-xL: -1.675702

Affinity score for MCL-1: -1.985377

Gene: LDHAL6A (lactate dehydrogenase A-like 6A)

CCDS ID: 7841.1|Hs37.1|chr11

Amino acids: 37--49, BH3-like sequence: ISILLKGLSDELV

Helix containing: HHHHHH-------

Affinity score for BCL-xL: -1.682110

Affinity score for MCL-1: -2.103689

Gene: SNTG2 (syntrophin, gamma 2)

CCDS ID: 46220.1|Hs37.1|chr2

Amino acids: 137--149, BH3-like sequence: VVHLLRNAGDEVT

Helix containing: HHHHHHH------

Affinity score for BCL-xL: -1.686039

Affinity score for MCL-1: -0.760945

This gene encodes a protein belonging to the syntrophin family. Syntrophins are cytoplasmic peripheral membrane proteins that bind to components of mechanosenstive sodium channels and the extreme carboxy-terminal domain of dystrophin and dystrophin-related proteins. The PDZ domain of this protein product interacts with a protein component of a mechanosensitive sodium channel that affects channel gating. Absence or reduction of this protein product has been associated with Duchenne muscular dystrophy. There is evidence of alternative splicing yet the full-length nature of these variants has not been described

Gene: SV2B (Synaptic vesicle glycoprotein 2B)

CCDS ID: 10370.1|Hs37.1|chr15

Amino acids: 161--173, BH3-like sequence: GAFILGGLADKLG

Helix containing: HHHHHHHHHHHHH-

Affinity score for BCL-xL: -1.700499

Affinity score for MCL-1: -2.800690

Also known as: FLJ30413; FLJ42732; HsT19680; KIAA0735

Interacts with SYT1 (synaptotagmin 1): synaptotagmins are integral membrane proteins of synaptic vesicles thought to serve as Ca(2+) sensors in the process of vesicular trafficking and exocytosis. Calcium binding to synaptotagmin-1 participates in triggering neurotransmitter release at the synapse (Fernandez-Chacon *et al*., 2001 [PubMed 11242035]). SYT1 interacts with Nemo

See all (16) citations in PubMed

Gene: SRCAP

CCDS ID: 10689.2|Hs37.1|chr16

Amino acids: 72--84, BH3-like sequence: EGFSLSQAADLAN

Helix containing: ----HHHHHHHHH

Affinity score for BCL-xL: -1.707452

Affinity score for MCL-1: -2.832623

The chromatin remodeling factor SRCAP modulates expression of prostate specific antigen and cellular proliferation in prostate cancer cells. Slupianek A, *et al.* J Cell Physiol, 2010 Aug. PMID: 20432434.

Gene: SRPK1 (SRSF protein kinase 1)

CCDS ID: 47415.1|Hs37.1|chr6

Amino acids: 65--77, BH3-like sequence: GGYHLVKIGDLFN

Helix containing: ----------

Affinity score for BCL-xL: -1.732101

Affinity score for MCL-1: -1.956460

This gene encodes a serine/arginine protein kinase specific for the SR (serine/arginine-rich domain) family of splicing factors. The protein localizes to the nucleus and the cytoplasm. It is thought to play a role in regulation of both constitutive and alternative splicing by regulating intracellular localization of splicing factors. Alternative splicing of this gene results in multiple transcript variants. Additional alternatively spliced transcript variants have been described for this gene, but their full length nature have not been determined.

Gene: FRMD8 (FERM domain containing 8)

CCDS ID: 8102.1|Hs37.1|chr11

Amino acids: 29--41, BH3-like sequence: AADVLVYLADDTV

Helix containing: HHHHHHHHHH----

Affinity score for BCL-xL: -1.738792

Affinity score for MCL-1: -2.506685

Also known as: FKSG44; FLJ32216; FLJ90369; MGC31785

FERM_3 domain (involved in linking cytoplasmic proteins to membrane)

Interacts with Nemo

Expanding the substantial interactome of NEMO using protein microarrays. Fenner BJ, *et al.* PLoS One, 2010 Jan 20. PMID: 20098747.

No other publications

*Gene: SCD (stearoyl-CoA desaturase (delta-9-desaturase)

CCDS ID: 7493.1|Hs37.1|chr10

Amino acids: 24--36, BH3-like sequence: PSRVLQNGGDKLE

Helix containing: --HHH--------

Affinity score for BCL-xL: -1.778109

Affinity score for MCL-1: -2.179053

Gene: NME3 (non-metastatic cells 3)

CCDS ID: 10443.1|Hs37.1|chr16

Amino acids: 129--141, BH3-like sequence: VGKNLIHGSDSVE

Helix containing: ----------HH

Affinity score for BCL-xL: -1.814345

Affinity score for MCL-1: -2.193497

Also known as NDPKC; NDPK-C; NM23H3; DR-nm23; NM23-H3 (related to NM23-H1 = NME1; NM23-H2 = NME2); KIAA0516; c371H6.2

BH3 motif in chimp; but L not evolutionarily conserved in other species, perhaps aliphatic V could substitute

Human and rat NME2 paralogs of NME3 induce apoptosis and associate with BCL2L10 (they were not detected because of conservative substitution of L with hydrophobic I)

Nme protein family evolutionary history, a vertebrate perspective. Desvignes T, Pontarotti P, Fauvel C, Bobe J. BMC Evol Biol. 2009 Oct 23;9:256.

Neuroblastoma specific effects of DR-nm23 and its mutant forms on differentiation and apoptosis. Cell Death Differ. 2000 Sep;7(9):843-50. Negroni A, Venturelli D, Tanno B, Amendola R, Ransac S, Cesi V, Calabretta B, Raschellà G. DR-nm23 belongs to a gene family which includes nm23-H1, originally identified as a candidate metastasis suppressor gene. Nm23 genes are expressed in different tumor types where their levels have been alternatively associated with reduced or increased metastatic potential. Nm23-H1, -H2, DR-nm23 and nm23-H4 all possess NDP kinase activity. Overexpression of DR-nm23 inhibits differentiation and promotes apoptosis in hematopoietic cells. By contrast, it induces morphological and biochemical changes associated with neural differentiation in neuroblastoma cells. In this study, we show that mutations in the catalytic domain and in the serine 61 phosphorylation site, possibly required for protein-protein interactions, impair the ability of DR-nm23 to induce neural differentiation. Moreover, *neuroblastoma cells overexpressing wild-type or mutant DR-nm23 are less sensitive to apoptosis triggered by serum withdrawal*. By subcellular fractionation, wild-type and mutant DR-nm23 localize in the cytoplasm and prevalently in the mitochondrial fraction. In co-immunoprecipitation experiments, wild-type DR-nm23 binds other members of nm23 family, but mutations in the catalytic and in the RGD domains and in serine 61 inhibit the formation of hetero-multimers. Thus, the integrity of the NDP kinase activity and the presence of a serine residue in position 61 seem

essential for the ability of DR-nm23 to trigger differentiation and to bind other Nm23 proteins, but not for the *anti-apoptotic* effect in neuroblastoma cells. These studies underline the tissue specificity of the biological effects induced by DR-nm23 expression.

Overexpression of DR-nm23, a protein encoded by a member of the nm23 gene family, inhibits granulocyte differentiation and induces apoptosis in 32Dc13 myeloid cells. Proc Natl Acad Sci U S A. 1995 Aug 1;92(16):7435-9. Venturelli D, Martinez R, Melotti P, Casella I, Peschle C, Cucco C, Spampinato G, Darzynkiewicz Z, Calabretta B. Chronic myelogenous leukemia evolves in two clinically distinct stages: a chronic and a blast crisis phase. The molecular changes associated with chronic phase to blast crisis transition are largely unknown. We have identified a cDNA clone, DR-nm23, differentially expressed in a blast-crisis cDNA library, which has approximately 70% sequence similarity to the putative metastatic suppressor genes, nm23-H1 (**NME1**) and nm23-H2 (**NME2**). The deduced amino acid sequence similarity to the proteins encoded by these two latter genes is approximately 65% and includes domains and amino acid residues (the leucine zipper-like and the RGD domain, a serine and a histidine residue in the NH2- and in the COOH-terminal portion of the protein, respectively) postulated to be important for nm23 function. DR-nm23 mRNA is preferentially expressed at early stages of myeloid differentiation of highly purified CD34+ cells. Its constitutive expression in the myeloid precursor 32Dc13 cell line, which is growth-factor dependent for both proliferation and differentiation, results in inhibition of granulocytic differentiation induced by granulocyte colony-stimulating factor and *causes apoptotic cell death*. These results are consistent with a role for DR-nm23 in normal hematopoiesis and raise the possibility that its overexpression contributes to differentiation arrest, a feature of blastic transformation in chronic myelogenous leukemia.

The nucleoside diphosphate kinase activity of DRnm23 is not required for inhibition of differentiation and induction of apoptosis in 32Dcl3 myeloid precursor cells. Exp Cell Res. 2000 Jun 15;257(2):265-71. Venturelli D, Cesi V, Ransac S, Engelhard A, Perrotti D, Calabretta B. DRnm23 belongs to a multigene family which includes nm23-H1, the first bona fide metastasis suppressor gene, nm23-H2, nm23-H4, and nm23-H5. Like nm23-H1, nm23-H2, and nm23-H4, DRnm23 possesses nucleoside diphosphate kinase (NDPK) activity. Upon overexpression in myeloid precursor 32Dcl3 cells, DRnm23 inhibits granulocytic differentiation and promotes apoptosis. Two specific mutants of DRnm23 (H134Q and **S136P**), at residues required for the NDPK activity, inhibit differentiation and promote apoptosis of 32Dcl3 cells. By contrast, substitution of serine 61 with proline (S61P) or deletion of the RGD domain (DeltaRGD) abrogates the effects of wild-type DRnm23. Like wild-type DRnm23, all four mutants show a predominantly mitochondrial subcellular localization. These studies indicate that the enzymatic activity of DRnm23 is not required for the effects observed in 32Dcl3 cells. Moreover, the inability of the S61P and DeltaRGD DRnm23 mutants to inhibit differentiation and promote apoptosis may be due to defective protein-protein interactions at the mitochondria, the predominant site of DRnm23 subcellular localization

NM23-H2 (**NME2**) involves in negative regulation of Diva and Bcl2L10 in apoptosis signaling. Biochem Biophys Res Commun. 2007 Jul 20;359(1):76-82. Epub 2007 May 24. Kang Y, Lee DC, Han J, Yoon S, Won M, Yeom JH, Seong MJ, Ko JJ, Lee KA, Lee K, Bae J.

The Bcl-2 family members are evolutionally conserved and crucial regulators of apoptosis. Diva (Boo), an ortholog of Bcl2L10 or Bcl-B, is a member of the Bcl-2 family that has contradictory functions in apoptosis. To understand the signaling mechanisms of Diva, we searched for proteins that interact with Diva using the yeast two-hybrid system. We identified a nucleoside diphosphate kinase isoform, NM23-H2. Here, we show that Diva bound to NM23-H2 in cells in which the transmembrane domain of Diva was required, and both proteins were colocalized in cytoplasm. Of interest, Diva protein level was significantly down-regulated by NM23-H2 as knock down of NM23-H2 restored Diva expression. Overexpression of NM23-H2 induced apoptosis, and the depletion of NM23-H2 led to the increase of Diva's apoptotic activity. Thus, these results indicate the existence of a previously undiscovered mechanism by which NM23-H2 involves in the regulation of Diva-mediated apoptosis.

Gene: IDUA (iduronidase, alpha-L-)

CCDS ID: 3343.1|Hs37.1|chr4

Amino acids: 214--226, BH3-like sequence: PALRLGGPGDSFH

Helix containing: HHHH---------

Affinity score for BCL-xL: -1.830636

Affinity score for MCL-1: -2.156936

Gene: SORT1 (sortilin 1)

CCDS ID: 798.1|Hs37.1|chr1

Amino acids: 110--122, BH3-like sequence: GSVSLSWVGDSTG

Helix containing: ----------

Affinity score for BCL-xL: -1.831957

Affinity score for MCL-1: -1.535474

This gene encodes a protein that is a multi-ligand type-1 receptor with similarity to the yeast carboxypeptidase Y sorting receptor Vps10 protein. The encoded protein, a trans-Golgi network (TGN) transmembrane protein, binds a number of unrelated ligands that participate in a wide range of cellular processes; however, it lacks the typical features of a signalling receptor. In the TGN, furin mediates the activation of the mature binding form. The encoded protein consists of a large luminal domain, a single transmembrane segment and short C-terminal cytoplasmic tail. The luminal domain contains a cysteine-rich region similar to two corresponding segments in the yeast Vps10p; the cytoplasmic tail is similar to the corresponding segment of the cation-independent mannose 6-phosphate receptor and the tail also interacts with the VHS domains of GGA (Golgi-associated, gamma-adaptin homologous, ARF-interacting) proteins.

Gene: JAK3

CCDS ID: 12366.1|Hs37.1|chr19

Amino acids: 698--710, BH3-like sequence: EAQTLSLEADKWG

Helix containing: HHHHH-HHH----

Affinity score for BCL-xL: -1.842870

Affinity score for MCL-1: -3.165740

Gene: ARMC9 [Armadillo repeat containing 9] armadillo/beta-catenin-like repeats

CCDS ID: 2484.1|Hs37.1|chr2

Amino acids: 500--512, BH3-like sequence: AGLVLKVLSDLLG

Helix containing: HHHHHHHHHHHH-

Affinity score for BCL-xL: -1.853793

Affinity score for MCL-1: -2.693842

Also known as ARM; FLJ12584; KU-MEL-1

See all (14) citations in PubMed

Gene: ING1 (inhibitor of growth family, member 1)

CCDS ID: 9517.1|Hs37.1|chr13

Amino acids: 11--23, BH3-like sequence: PAERLVAEADEGG

Helix containing: HHHHHHHHHH---

Affinity score for BCL-xL: -1.896417

Affinity score for MCL-1: -3.431967

Also known as p33; p47 isoform identified; p33ING1; p24ING1c; p33ING1b; p47ING1a; ING1

This gene encodes a tumor suppressor protein that can induce cell growth arrest and apoptosis. The encoded protein is a nuclear protein that physically interacts with the tumor suppressor protein TP53 and is a component of the p53 signaling pathway. Reduced expression and rearrangement of this gene have been detected in various cancers. Multiple alternatively spliced transcript variants encoding distinct isoforms have been reported.

The p53 tumor suppressor is stabilized by inhibitor of growth 1 (ING1) by blocking polyubiquitination. Thalappilly S, Feng X, Pastyryeva S, Suzuki K, Muruve D, Larocque D, Richard S, Truss M, von Deimling A, Riabowol K, Tallen G. PLoS One. 2011;6(6):e21065. Epub 2011 Jun 22. The INhibitor of Growth tumor suppressors (ING1-ING5) affect aging, apoptosis, DNA repair and tumorigenesis. Plant homeodomains (PHD) of ING proteins bind histones in a methylation-sensitive manner to

regulate chromatin structure. ING1 and ING2 contain a polybasic region (PBR) adjacent to their PHDs that binds stress-inducible phosphatidylinositol monophosphate (PtIn-MP) signaling lipids to activate these INGs. ING1 induces apoptosis independently of p53 but other studies suggest proapoptotic interdependence of ING1 and p53 leaving their functional relationship unclear. Here we identify a novel ubiquitin-binding domain (UBD) that overlaps with the PBR of ING1 and shows similarity to previously described UBDs involved in DNA damage responses. The ING1 UBD binds ubiquitin with high affinity (K(d)~100 nM) and ubiquitin competes with PtIn-MPs for ING1 binding. ING1 expression stabilized wild-type, but not mutant p53 in an MDM2-independent manner and knockdown of endogenous ING1 depressed p53 levels in a transcription-independent manner. ING1 stabilized unmodified and six multimonoubiquitinated forms of wild-type p53 that were also seen upon DNA damage, but not p53 mutants lacking the six known sites of ubiquitination. We also find that ING1 physically interacts with herpesvirus-associated ubiquitin-specific protease (HAUSP), a p53 and MDM2 deubiquitinase (DUB), and knockdown of HAUSP blocks the ability of ING1 to stabilize p53. These data link lipid stress signaling to ubiquitin-mediated proteasomal degradation through the PBR/UBD of ING1 and further indicate that ING1 stabilizes p53 by inhibiting polyubiquitination of multimonoubiquitinated forms via interaction with and colocalization of the HAUSP-deubiquitinase with p53.

Mouse ING1 homologue, a protein interacting with A1, enhances cell death and is inhibited by A1 in mammary epithelial cells.

Ha S, Lee S, Chung M, Choi Y. Cancer Res. 2002 Mar 1;62(5):1275-8. We cloned mouse ING1 homologue (mINGh), an A1/Bfl-1-interacting protein, from mouse mammary glands using a yeast two-hybrid assay and unexpectedly found four splicing variants of mINGh by reverse transcription-PCR assay and sequence analysis. The alternative splicing variants were mINGh-S, mINGh-M, mINGh-L, and mINGh-L2 encoding 171, 248, 166, and 227 amino acids, respectively. Cell death of HC11 cells, induced by serum starvation, was enhanced by mINGhs, and the action of mINGhs was inhibited by A1 protein. These results indicate that A1 can inhibit cell death not only via the well known pathway related to the Bcl-2 family but also through direct interaction with mINGh in mammary epithelial cells. **(but this isoform does not have PAERLVAEADEGG)**

ING1 isoforms differentially affect apoptosis in a cell age-dependent manner. Vieyra D, Toyama T, Hara Y, Boland D, Johnston R, Riabowol K. Cancer Res. 2002 Aug 1;62(15):4445-52. Recently, several novel human ING1 isoforms have been cloned. However, the biochemical functions and the involvement of these proteins in apoptosis remain uncharacterized. We have examined the apoptotic effects and biochemical functions of the two major human ING1 isoforms p47(ING1a) **isoform D** and p33(ING1b) in young and senescent human diploid fibroblasts induced to enter into apoptosis by diverse treatments. We have found that ING1 displayed isoform-, stimulus- and cell age-dependent apoptotic properties. We present evidence indicating that ING1 proteins bind to chromatin and are regulated in a manner related to their apoptotic properties. In agreement with previous reports, we have found that only young but not senescent fibroblasts were able to enter into apoptosis induced by growth factor deprivation. This effect was accompanied by up-regulation of endogenous p33(ING1b). Ectopic up-regulation of p33(ING1b), **but not p47(ING1a)**, also induced apoptosis and sensitized young but not senescent cells to UV irradiation and hydrogen peroxide-mediated apoptosis. Cotransfection of p33(ING1b) and the tumor suppressor p53 increased the percentage of apoptotic cells yielded by either of these two proteins alone, in agreement with data from tumor cell models. Finally, we found that the chromatin bindingAffinity of p33(ING1b) was increased in senescent cells, which were resistant to apoptosis. Together, these data support the idea that the apoptotic functions of ING1 may be exerted by chromatin-related functions that are subject to cell age-dependent mechanisms of regulation.

Gene: **RAD9A**

CCDS ID: 8159.1|Hs37.1|chr11

Amino acids: 16--28, BH3-like sequence: AVHSLSRIGDELY

Helix containing: HHHHHHH------

Affinity score for BCL-xL: -1.911070

Affinity score for MCL-1: -0.625989

Gene: HDDC3 (HD domain containing 3)

CCDS ID: 10366.1|Hs37.1|chr15

Amino acids: 113--125, BH3-like sequence: PGAKLVKLADKLY

Helix containing: --HHHHHHHHHHH

Affinity score for BCL-xL: -1.915282

Affinity score for MCL-1: -2.797730

A metazoan ortholog of SpoT hydrolyzes ppGpp and functions in starvation responses. Sun D, *et al*. Nat Struct Mol Biol, 2010 Oct. PMID: 20818390.

Gene: MESDC1 (mesoderm development candidate 1)

CCDS ID: 10316.1|Hs37.1|chr15

Amino acids: 108--120, BH3-like sequence: AGDSLVELGDLVV

Helix containing: HHHHHHHHH-----

Affinity score for BCL-xL: -1.929549

Affinity score for MCL-1: -1.324373

Modulation of LRP6-mediated Wnt signaling by molecular chaperone Mesd. Li Y, *et al*. FEBS Lett, 2006 Oct 2. PMID: 16989816.

Gene: HLCS [holocarboxylase synthetase (biotin-(proprionyl-CoA-carboxylase (ATP-hydrolysing)) ligase]

CCDS ID: 13647.1|Hs37.1|chr21

Amino acids: 135--147, BH3-like sequence: YSSSLESVADETS

Helix containing: ----HHHH-----

Affinity score for BCL-xL: -1.963116

Affinity score for MCL-1: -2.573727

This gene encodes an enzyme that catalyzes the binding of biotin to carboxylases and histones. The protein plays an important role in gluconeogenesis, fatty acid synthesis and branched chain amino acid catabolism

Gene: SIRT7

CCDS ID: 11792.1|Hs37.1|chr17

Amino acids: 47--59, BH3-like sequence: EGRLLAESADLVT

Helix containing: H--HHHHHHHHHH

Affinity score for BCL-xL: -1.967381

Affinity score for MCL-1: -3.262900

This gene encodes a member of the sirtuin family of proteins, homologs to the yeast Sir2 protein. Members of the sirtuin family are characterized by a sirtuin core domain and grouped into four classes. The functions of human sirtuins have not yet been determined; however, yeast sirtuin proteins are known to regulate epigenetic gene silencing and suppress recombination of rDNA. Studies suggest that the human sirtuins may function as intracellular regulatory proteins with mono-ADP-ribosyltransferase activity.

Gene: VCAM1

CCDS ID: 773.1|Hs37.1|chr1

Amino acids: 32--44, BH3-like sequence: ESRYLAQIGDSVS

CCDS ID: 774.1|Hs37.1|chr1

Amino acids: 32--44, BH3-like sequence: ESRYLAQIGDSVS

Helix containing: --HHHH-------

Affinity score for BCL-xL: -1.969247

Affinity score for MCL-1: -0.786909

This gene is a member of the Ig superfamily and encodes a cell surface sialoglycoprotein expressed by cytokine-activated endothelium. This type I membrane protein mediates leukocyte-endothelial cell adhesion and signal transduction, and may play a role in the development of artherosclerosis and rheumatoid arthritis. Three alternatively spliced transcripts encoding different isoforms have been described for this gene.

Gene: EMILIN3 (elastin microfibril interfacer 3)

CCDS ID: 13316.1|Hs37.1|chr20

Amino acids: 594--606, BH3-like sequence: VSKSLTGLSDSVS

Helix containing: -HHHH------HH

Affinity score for BCL-xL: -1.979289

Affinity score for MCL-1: -1.096959

Also known as EMILIN5; C20orf130; dJ620E11.4; DKFZp434A2410

Conserved domain: SMC_prok_B; chromosome segregation protein SMC, common bacterial type

Network organization of the human autophagy system. Behrends C, *et al.* Nature, 2010 Jul 1. PMID: 20562859.

Gene: APOB (apolipoprotein B)

CCDS ID: 1703.1|Hs37.1|chr2

Amino acids: 351--363, BH3-like sequence: LVTELRGLSDEAV

Helix containing: HHHHHH---HHHH

Affinity score for BCL-xL: -1.997699

Affinity score for MCL-1: -1.353764

Gene: NID2 (nidogen 2; osteonidogen)

CCDS ID: 9706.1|Hs37.1|chr14

Amino acids: 43--55, BH3-like sequence: WGDQLLQEGDDES

Helix containing: HHHHHH-------

Affinity score for BCL-xL: -2.014125

Affinity score for MCL-1: -2.043779

This gene encodes a member of the nidogen family of basement membrane proteins. This protein is a cell-adhesion protein that binds collagens I and IV and laminin and may be involved in maintaining the structure of the basement membrane.

Gene: ETF1 (eukaryotic translation termination factor 1)

CCDS ID: 4207.1|Hs37.1|chr5

Amino acids: 208--220, BH3-like sequence: TAVQLFISGDKVN

Helix containing: HHHHH--------

Affinity score for BCL-xL: -2.022899

Affinity score for MCL-1: -1.986198

Also known as ERF; RF1; ERF1; TB3-1; D5S1995; SUP45L1; MGC111066

Three distinct peptides from the N domain of translation termination factor eRF1 surround stop codon in the ribosome. Bulygin KN, *et al.* RNA, 2010 Oct. PMID: 20688868.

Gene: BZW2 (basic leucine zipper and W2 domains 2)

CCDS ID: 5362.1|Hs37.1|chr7

Amino acids: 34--46, BH3-like sequence: LVQGLNEAGDDLE

Helix containing: HHHHHHHH--HHH

Affinity score for BCL-xL: -2.024455

Affinity score for MCL-1: -1.229774

Also known as MST017; HSPC028; MSTP017; renamed eIF5-mimic protein 1 (5MP1) by Singh *et al*.

Conserved Domains: Contains a W2 domain found at the C-terminus of several translation initiation factors (eIF4-gamma/eIF5/eIF2-epsilon).

BH3 motif conserved in chimp, dog, cow, mouse and rat

Mechanisms of translational regulation by a human eIF5-mimic protein. [BZW2 = eIF5-mimic protein 1 (5MP1)]. Singh CR, Watanabe R, Zhou D, Jennings MD, Fukao A, Lee B, Ikeda Y, Chiorini JA, Campbell SG, Ashe MP, Fujiwara T, Wek RC, Pavitt GD, Asano K. Nucleic Acids Res. 2011 Jul 10. [Epub ahead of print]

Combined analysis of murine and human microarrays and ChIP analysis reveals genes associated with the ability of MYC to maintain tumorigenesis. Wu CH, Sahoo D, Arvanitis C, Bradon N, Dill DL, Felsher DW. PLoS Genet. 2008 Jun 6;4(6):e1000090.

In vitro nuclear interactome of the HIV-1 Tat protein. Gautier VW, *et al*. Retrovirology, 2009 May 19. PMID: 19454010.

Gene: SVIL (supervillin)

CCDS ID: 7163.1|Hs37.1|chr10

Amino acids: 120--132, BH3-like sequence: YGLTLDPEADSEY

CCDS ID: 7164.1|Hs37.1|chr10

Amino acids: 120--132, BH3-like sequence: YGLTLDPEADSEY

Helix containing: H---------HHH

Affinity score for BCL-xL: -2.033877

Affinity score for MCL-1: -3.281905

This gene encodes a bipartite protein with distinct amino- and carboxy-terminal domains. The amino-terminus contains nuclear localization signals and the carboxy-terminus contains numerous consecutive sequences with extensive similarity to proteins in the gelsolin family of actin-binding proteins, which cap, nucleate, and/or sever actin filaments. The gene product is tightly associated with both actin filaments and plasma membranes, suggesting a role as a high-affinity link between the actin cytoskeleton and the membrane. The encoded protein appears to aid in both myosin II assembly during cell spreading and disassembly of focal adhesions.

Gene: PLD3 (phospholipase D3)

CCDS ID: 33027.1|Hs37.1|chr19

Amino acids: 472--484, BH3-like sequence: YSHDLDTSADSVG

Helix containing: --------HHHHH

Affinity score for BCL-xL: -2.073518

Affinity score for MCL-1: -2.709979

Gene: C7orf59

CCDS ID: 34702.1|Hs37.1|chr7

Amino acids: 23--35, BH3-like sequence: EGAVLASSGDLEN

Helix containing: ----------

Affinity score for BCL-xL: -2.075721

Affinity score for MCL-1: -2.669140

Gene: SLC38A10

CCDS ID: 42397.1|Hs37.1|chr17

Amino acids: 931--943, BH3-like sequence: VSRDLGLAADLPG

Helix containing: ----------

Affinity score for BCL-xL: -2.079375

Affinity score for MCL-1: -2.876237

Putative sodium-coupled neutral amino acid transporter 10

Gene: BOP1 (block of proliferation 1)

CCDS ID: 6418.1|Hs37.1|chr8

Amino acids: 424--436, BH3-like sequence: GGQWLVSGSDDGS

Helix containing: ----------

Affinity score for BCL-xL: -2.107398

Affinity score for MCL-1: -3.564523

Block of proliferation 1 (BOP1) plays an oncogenic role in hepatocellular carcinoma by promoting epithelial-to-mesenchymal transition. Chung KY, Cheng IK, Ching AK, Chu JH, Lai PB, Wong N. Hepatology. 2011 Jul;54(1):307-18. doi: 10.1002/hep.24372. Genomic amplification of regional chromosome 8q24 is a common event in human cancers. In hepatocellular carcinoma (HCC), a highly aggressive malignancy that is rapidly fatal, recurrent 8q24 gains can be detected in >50% of cases. In this study, attempts to resolve the 8q24 region by way of array comparative genomic hybridization for affected genes in HCC revealed distinctive gains of block of proliferation 1 (BOP1). Gene expression evaluation in an independent cohort of primary HCC (n = 65) revealed frequent BOP1 up-regulation in tumors compared with adjacent nontumoral liver (84.6%; P < 0.0001). Significant associations could also be drawn between increased expressions of BOP1 and advance HCC staging (P = 0.004), microvascular invasion (P = 0.006), and shorter disease-free survival of patients (P = 0.02). Examination of expression of C-MYC, a well-known oncogene located in proximity to BOP1, in the same series of primary HCC cases did not suggest strong clinicopathologic associations. Functional investigations by small interfering RNA-mediated suppression of BOP1 in HCC cell lines indicated significant inhibition on cell invasion (P < 0.005) and migration (P < 0.05). Overexpression of BOP1 in the immortalized hepatocyte cell line L02 showed increase cellular invasiveness and cell migratory rate (P < 0.0001). In both gene knockdown and ectopic expression assays, BOP1 did not exert an effect on cell viability and proliferation. Evident regression of the epithelial-mesenchymal transition (EMT) phenotype was readily identified in BOP1 knockdown cells, whereas up-regulation of epithelial markers (E-cadherin, cytokeratin 18, and γ-catenin) and down-regulation of mesenchymal markers (fibronectin and vimentin) were seen. A corresponding augmentation of EMT was indicated from the ectopic expression of BOP1 in L02. In addition, BOP1 could stimulate actin stress fiber assembly and RhoA activation. Conclusion: Our findings underline an important role for BOP1 in HCC invasiveness and metastasis potentials through inducing EMT and promoting actin cytoskeleton remodeling.

Deregulation of the BOP1 pathway contributes to chromosomal instability in colorectal tumorigenesis.

Gene: CHMP4A (chromatin modifying protein 4A)

CCDS ID: 9619.1|Hs37.1|chr14

Amino acids: 216--228, BH3-like sequence: LAQELLNVGDKEE

Helix containing: HHHHHH-------

Affinity score for BCL-xL: -2.113509

Affinity score for MCL-1: -1.471857

CHMP4A belongs to the chromatin-modifying protein/charged multivesicular body protein (CHMP) family. These proteins are components of ESCRT-III (endosomal sorting complex required for transport III), a complex involved in degradation of surface receptor proteins and formation of endocytic multivesicular bodies (MVBs). Some CHMPs have both nuclear and

cytoplasmic/vesicular distributions, and one such CHMP, CHMP1A (MIM 164010), is required for both MVB formation and regulation of cell cycle progression (Tsang *et al*., 2006 [PubMed 16730941]).

High-throughput screening identifies CHMP4A associated with hypoxia-inducible factor 1. Shi T, *et al.* Life Sci, 2010 Nov 20. PMID: 20888838.

Gene: DUSP2 (dual specificity phosphatase 2)

CCDS ID: 2016.1|Hs37.1|chr2

Amino acids: 147--159, BH3-like sequence: PAPALPPTGDKTS

Helix containing: ----------

Affinity score for BCL-xL: -2.156099

Affinity score for MCL-1: -2.530620

The protein encoded by this gene is a member of the dual specificity protein phosphatase subfamily. These phosphatases inactivate their target kinases by dephosphorylating both the phosphoserine/threonine and phosphotyrosine residues. They negatively regulate members of the mitogen-activated protein (MAP) kinase superfamily (MAPK/ERK, SAPK/JNK, p38), which are associated with cellular proliferation and differentiation. Different members of the family of dual specificity phosphatases show distinct substrate specificities for various MAP kinases, different tissue distribution and subcellular localization, and different modes of inducibility of their expression by extracellular stimuli.

Gene: CLINT1 (clathrin interactor 1)

CCDS ID: 47330.1|Hs37.1|chr5

Amino acids: 197--209, BH3-like sequence: FSDKLGELSDKIG

Helix containing: --HHH----HHH-

Affinity score for BCL-xL: -2.166740

Affinity score for MCL-1: -1.572745

Also known as ENTH; EPN4; EPNR; CLINT; FLJ46753; KIAA0171; CLINT1

This gene encodes a protein with similarity to the epsin family of endocytic adapter proteins. The encoded protein interacts with clathrin, the adapter protein AP-1 and phosphoinositides. This protein may be involved in the formation of clathrin coated vesicles and trafficking between the trans-Golgi network and endosomes. Mutations in this gene are associated with a susceptibility to schizophrenia and psychotic disorders. Alternate splicing results in multiple transcript variants.

Network organization of the human autophagy system. Behrends C, *et al.* Nature, 2010 Jul 1. PMID: 20562859.

Gene: ZNF831

CCDS ID: 42894.1|Hs37.1|chr20

Amino acids: 209--221, BH3-like sequence: AGGGLLEEGDKAG

Helix containing: ----------

Affinity score for BCL-xL: -2.170767

Affinity score for MCL-1: -2.131589

Gene: BCL2L14/BCL-G

CCDS ID: 8645.1|Hs37.1|chr12

CCDS ID: 8646.1|Hs37.1|chr12

Amino acids: 212--224, BH3-like sequence: IVELLKYSGDQLE

Helix containing: HHHHHHH-HHHHH

Affinity score for BCL-xL: -2.215662

Affinity score for MCL-1: -2.278435

Gene: PCDHB8 (protocadherin beta 8)

CCDS ID: 4250.1|Hs37.1|chr5

Amino acids: 278--290, BH3-like sequence: ISYSLFQASDEIS

Helix containing: ---------HHHH

Affinity score for BCL-xL: -2.231950

Affinity score for MCL-1: -1.726823

This gene is a member of the protocadherin beta gene cluster, one of three related gene clusters tandemly linked on chromosome five. The extracellular domains interact in a homophilic manner to specify differential cell-cell connections

Gene: PLAC1L

CCDS ID: 7979.1|Hs37.1|chr11

Amino acids: 40--52, BH3-like sequence: ESRNLYIFADELH

Helix containing: -------HHHHHHH

Affinity score for BCL-xL: -2.254548

Affinity score for MCL-1: -3.195322

PLAC1, a trophoblast-specific cell surface protein, is expressed in a range of human tumors and elicits spontaneous antibody responses. Silva WA Jr, Gnjatic S, Ritter E, Chua R, Cohen T, Hsu M, Jungbluth AA, Altorki NK, Chen YT, Old LJ, Simpson AJ, Caballero OL. Cancer Immun. 2007 Nov 6;7:18.

Gene: TACC2 (transforming, acidic coiled-coil containing protein 2)

CCDS ID: 7626.1|Hs37.1|chr10

Amino acids: 1939--1951, BH3-like sequence: PAKDLSRSSDSEE

Helix containing: HHH--------HH

Affinity score for BCL-xL: -2.304868

Affinity score for MCL-1: -2.394001

Transforming acidic coiled-coil proteins are a conserved family of centrosome- and microtubule-interacting proteins that are implicated in cancer. This gene encodes a protein that concentrates at centrosomes throughout the cell cycle. This gene lies within a chromosomal region associated with tumorigenesis. Expression of this gene is induced by erythropoietin and is thought to affect the progression of breast tumors.

Gene: KCNC1 (potassium voltage-gated channel, Shaw-related subfamily, member 1)

CCDS ID: 7827.1|Hs37.1|chr11

Amino acids: 123--135, BH3-like sequence: GGAPLDNSADDAD

CCDS ID: 44547.1|Hs37.1|chr11

Amino acids: 123--135, BH3-like sequence: GGAPLDNSADDAD

Helix containing: ----------

Affinity score for BCL-xL: -2.351211

Affinity score for MCL-1: -3.693693

Gene: MYH9 (Myosin, heavy chain 9, non-muscle)

CCDS ID: 13927.1|Hs37.1|chr22

Amino acids: 596--608, BH3-like sequence: IATLLHQSSDKFV

Helix containing: HHHHHHH--HHHH

Affinity score for BCL-xL: -2.398114

Affinity score for MCL-1: -3.176221

Gene: OMA1 [OMA1 homolog, zinc metallopeptidase (S. cerevisiae)]

CCDS ID: 608.1|Hs37.1|chr1

Amino acids: 387--399, BH3-like sequence: YSRKLEAEADKIG

Helix containing: --HHHHHHHHHHH

Affinity score for BCL-xL: -2.401319

Affinity score for MCL-1: -3.030800

Also known as DAB1; MPRP-1; YKR087C; ZMPOMA1; FLJ33782; 2010001O09Rik

Nuclear-encoded mitochondrial protease

Inducible proteolytic inactivation of OPA1 mediated by the OMA1 protease in mammalian cells. Head B, Griparic L, Amiri M, Gandre-Babbe S, van der Bliek AM. J Cell Biol. 2009 Dec 28;187(7):959-66.The mammalian mitochondrial inner membrane fusion protein OPA1 is controlled by complex patterns of alternative splicing and proteolysis. A subset of OPA1 isoforms is constitutively cleaved by YME1L. Other isoforms are not cleaved by YME1L, but they are cleaved when mitochondria lose membrane potential or adenosine triphosphate. In this study, we show that this inducible cleavage is mediated by a zinc metalloprotease called OMA1. We find that OMA1 small interfering RNA inhibits inducible cleavage, helps retain fusion competence, and slows the onset of apoptosis, showing that OMA1 controls OPA1 cleavage and function. We also find that OMA1 is normally cleaved from 60 to 40 kD by another as of yet unidentified protease. Loss of membrane potential causes 60-kD protein to accumulate, suggesting that OMA1 is attenuated by proteolytic degradation. We conclude that a proteolytic cascade controls OPA1. Inducible cleavage provides a mechanism for quality control because proteolytic inactivation of OPA1 promotes selective removal of defective mitochondrial fragments by preventing their fusion with the mitochondrial network.

OPA1 processing reconstituted in yeast depends on the subunit composition of the m-AAA protease in mitochondria. Duvezin-Caubet S, Koppen M, Wagener J, Zick M, Israel L, Bernacchia A, Jagasia R, Rugarli EI, Imhof A, Neupert W, Langer T, Reichert AS. Mol Biol Cell. 2007 Sep;18(9):3582-90

Identification of a human cDNA sequence which encodes a novel membrane-associated protein containing a zinc metalloprotease motif. Bao YC, Tsuruga H, Hirai M, Yasuda K, Yokoi N, Kitamura T, Kumagai H. DNA Res. 2003 Jun 30;10(3): 123-8

See all (6) citations in PubMed

Gene: NEUROG2

CCDS ID: 3698.1|Hs37.1|chr4

Amino acids: 197--209, BH3-like sequence: ASAALSSSGDSPS

Helix containing: ----------

Affinity score for BCL-xL: -2.407865

Affinity score for MCL-1: -2.691715

Gene: SM11 (SNRPB small nuclear ribonucleoprotein polypeptides B and B1)

CCDS ID: 4342.1|Hs37.1|chr5

Amino acids: 20--32, BH3-like sequence: PSPRLDVSSDSFD

Helix containing: ----------

Affinity score for BCL-xL: -2.495978

Affinity score for MCL-1: -3.139968

Gene: BNIP3L/NIX

CCDS ID: 6050.1|Hs37.1|chr8

Amino acids: 130--142, BH3-like sequence: EVEALKKSADWVS

Helix containing: HHHHHHHHH-----

Affinity score for BCL-xL: -2.504385

Affinity score for MCL-1: -3.083545

Gene: VGF (nerve growth factor inducible)

CCDS ID: 5712.1|Hs37.1|chr7

Amino acids: 458--470, BH3-like sequence: LSTKLHLPADDVV

Helix containing: HHHH--------H

Affinity score for BCL-xL: -2.529178

Affinity score for MCL-1: -2.719224

An inducer of VGF protects cells against ER stress-induced cell death and prolongs survival in the mutant SOD1 animal models of familial ALS. Shimazawa M, *et al.* PLoS One, 2010 Dec 9. PMID: 21151573.

Gene: NFE2L2 [nuclear factor (erythroid-derived 2)-like]

CCDS ID: 42782.1|Hs37.1|chr2

Amino acids: 366--378, BH3-like sequence: YGDTLLGLSDSEV

CCDS ID: 46457.1|Hs37.1|chr2

Amino acids: 350--362, BH3-like sequence: YGDTLLGLSDSEV

CCDS ID: 46458.1|Hs37.1|chr2

Amino acids: 343--355, BH3-like sequence: YGDTLLGLSDSEV

Helix containing: ----------HH

Affinity score for BCL-xL: -2.540187

Affinity score for MCL-1: -2.541371

Also known as: NRF2

NFE2 (MIM 601490), NFE2L1 (MIM 163260), and NFE2L2 comprise a family of human genes encoding basic leucine zipper (bZIP) transcription factors. They share highly conserved regions that are distinct from other bZIP families, such as JUN (MIM 165160) and FOS (MIM 164810), although remaining regions have diverged considerably from each other (Chan *et al*., 1995 [PubMed 7868116]).

Oncogene-induced Nrf2 transcription promotes ROS detoxification and tumorigenesis. DeNicola GM, Karreth FA, Humpton TJ, Gopinathan A, Wei C, Frese K, Mangal D, Yu KH, Yeo CJ, Calhoun ES, Scrimieri F, Winter JM, Hruban RH, Iacobuzio-Donahue C, Kern SE, Blair IA, Tuveson DA. Nature. 2011 Jul 6;475(7354):106-9. Reactive oxygen species (ROS) are mutagenic and may thereby promote cancer. Normally, ROS levels are tightly controlled by an inducible antioxidant program that responds to cellular stressors and is predominantly regulated by the transcription factor Nrf2 (also known as Nfe2l2) and its repressor protein Keap1 (refs 2-5). In contrast to the acute physiological regulation of Nrf2, in neoplasia there is evidence for increased basal activation of Nrf2. Indeed, somatic mutations that disrupt the Nrf2-Keap1 interaction to stabilize Nrf2 and increase the constitutive transcription of Nrf2 target genes were recently identified, indicating that enhanced ROS detoxification and additional Nrf2 functions may in fact be pro-tumorigenic. Here, we investigated ROS metabolism in primary murine cells following the expression of endogenous oncogenic alleles of Kras, Braf and Myc, and found that ROS are actively suppressed

by these oncogenes. K-Ras(G12D), B-Raf(V619E) and Myc(ERT2) each increased the transcription of Nrf2 to stably elevate the basal Nrf2 antioxidant program and thereby lower intracellular ROS and confer a more reduced intracellular environment. Oncogene-directed increased expression of Nrf2 is a new mechanism for the activation of the Nrf2 antioxidant program, and is evident in primary cells and tissues of mice expressing K-Ras(G12D) and B-Raf(V619E), and in human pancreatic cancer. Furthermore, genetic targeting of the Nrf2 pathway impairs K-Ras(G12D)-induced proliferation and tumorigenesis *in vivo*. Thus, the Nrf2 antioxidant and cellular detoxification program represents a previously unappreciated mediator of oncogenesis.

The cytoprotective role of the Keap1-Nrf2 pathway. Baird L, Dinkova-Kostova AT. Arch Toxicol. 2011 Apr;85(4):241-72. An elaborate network of highly inducible proteins protects aerobic cells against the cumulative damaging effects of reactive oxygen intermediates and toxic electrophiles, which are the major causes of neoplastic and chronic degenerative diseases. These cytoprotective proteins share common transcriptional regulation, through the Keap1-Nrf2 pathway, which can be activated by various exogenous and endogenous small molecules (inducers). Inducers chemically react with critical cysteine residues of the sensor protein Keap1, leading to stabilisation and nuclear translocation of transcription factor Nrf2, and ultimately to coordinate enhanced expression of genes coding for cytoprotective proteins. In addition, inducers inhibit pro-inflammatory responses, and there is a linear correlation spanning more than six orders of magnitude of concentrations between inducer and anti-inflammatory activity. Genetic deletion of transcription factor Nrf2 renders cells and animals much more sensitive to the damaging effects of electrophiles, oxidants and inflammatory agents in comparison with their wild-type counterparts. Conversely, activation of the Keap1-Nrf2 pathway allows survival and adaptation under various conditions of stress and has protective effects in many animal models. Cross-talks with other signalling pathways broadens the role of the Keap1-Nrf2 pathway in determining the fate of the cell, impacting fundamental biological processes such as proliferation, apoptosis, angiogenesis and metastasis.

Molecular mechanisms of the Keap1–Nrf2 pathway in stress response and cancer evolution. Taguchi K, Motohashi H, Yamamoto M. Genes Cells. 2011 Feb;16(2):123-40. Review. The Keap1–Nrf2 regulatory pathway plays a central role in the protection of cells against oxidative and xenobiotic damage. Under unstressed conditions, Nrf2 is constantly ubiquitinated by the Cul3–Keap1 ubiquitin E3 ligase complex and rapidly degraded in proteasomes. Upon exposure to electrophilic and oxidative stresses, reactive cysteine residues of Keap1 become modified, leading to a decline in the E3 ligase activity, stabilization of Nrf2 and robust induction of a battery of cytoprotective genes. Biochemical and structural analyses have revealed that the intact Keap1 homodimer forms a cherry-bob structure in which one molecule of Nrf2 associates with two molecules of Keap1 by using two binding sites within the Neh2 domain of Nrf2. This two-site binding appears critical for Nrf2 ubiquitination. In many human cancers, missense mutations in KEAP1 and NRF2 genes have been identified. These mutations disrupt the Keap1–Nrf2 complex activity involved in ubiquitination and degradation of Nrf2 and result in constitutive activation of Nrf2. Elevated expression of Nrf2 target genes confers advantages in terms of stress resistance and cell proliferation in normal and cancer cells. Discovery and development of selective Nrf2 inhibitors should make a critical contribution to improved cancer therapy.

Gene: C17orf76

CCDS ID: 11178.2|Hs37.1|chr17

Amino acids: 30--42, BH3-like sequence: WASLLLRAGDKAG

CCDS ID: 45620.1|Hs37.1|chr17

Amino acids: 30--42, BH3-like sequence: WASLLLRAGDKAG

Helix containing: HHHHHHH------

Affinity score for BCL-xL: -2.561100

Affinity score for MCL-1: -2.538560

Gene: SLC39A7 (solute carrier family 39 (zinc transporter), member 7)

CCDS ID: 43453.1|Hs37.1|chr6

Amino acids: 317--329, BH3-like sequence: VSGYLNLAADLAH

Helix containing: ---HHHHHHHHHH

Affinity score for BCL-xL: -2.567390

Affinity score for MCL-1: -2.836083

ZIP7 releases zinc from the endoplasmic reticulum and might be required for tyrosine kinase activation.

Gene: SPEG (SPEG complex locus)

CCDS ID: 42824.1|Hs37.1|chr2

Amino acids: 1914--1926, BH3-like sequence: PSGGLSSSSDSEE

Helix containing: ----------HH

Affinity score for BCL-xL: -2.578915

Affinity score for MCL-1: -2.642643

This gene encodes a protein with similarity to members of the myosin light chain kinase family. This protein family is required for myocyte cytoskeletal development. Studies in mouse have determined that a lack of this protein affected myocardial development. Multiple alternatively spliced transcript variants have been reported for this gene, but the full-length nature of only two variants that encode different protein isoforms has been defined

Gene: KLHL18 (kelch-like 18)

CCDS ID: 33749.1|Hs37.1|chr3

Amino acids: 292--304, BH3-like sequence: AVGGLNSAGDSLN

Helix containing: ----------

Affinity score for BCL-xL: -2.592127

Affinity score for MCL-1: -1.355628

BTB protein, dKLHL18/CG3571, serves as an adaptor subunit for a dCul3 ubiquitin ligase complex. Fujiyama-Nakamura S, *et al.* Genes Cells, 2009 Aug. PMID: 19624754.

Fork head controls the timing and tissue selectivity of steroid-induced developmental cell death. Cao C, *et al.* J Cell Biol, 2007 Mar 12. PMID: 17339378.

Gene: KDM3B [Lysine (K)-specific demethylase 3B]

CCDS ID: 34242.1|Hs37.1|chr5

Amino acids: 1218--1230, BH3-like sequence: PSSALHWLADLAT

Helix containing: --HHHHHHHHHHH

Affinity score for BCL-xL: -2.670204

Affinity score for MCL-1: -3.109367

Also known as: 5qNCA; NET22; C5orf7; JMJD1B; KIAA1082; KDM3B

A novel nuclear protein, 5qNCA (LOC51780) is a candidate for the myeloid leukemia tumor suppressor gene on chromosome 5 band q31. Hu Z, Gomes I, Horrigan SK, Kravarusic J, Mar B, Arbieva Z, Chyna B, Fulton N, Edassery S, Raza A, Westbrook CA. Oncogene. 2001 Oct 18; 20(47): 6946-54. Interstitial deletion or loss of chromosome 5, del(5q) or -5, is a frequent finding in myeloid leukemias and myelodysplasias, suggesting the presence of a tumor suppressor gene within the deleted region. In our search for this gene, we identified a candidate, 5qNCA (LOC51780), which lies within a consistently-deleted segment of 5q31. 5qNCA expresses a 7.2-kb transcript with a 5286-bp open reading frame which is present at high levels in heart, skeletal muscle, kidney, placenta, and liver as well as CD34+ cells and AML cell lines. 5qNCA encodes a 191-kD nuclear protein which contains a highly-conserved C-terminus containing a zinc finger with the unique spacing Cys-X2-Cys-X7-His-X2-Cys-X2-Cys-X4-Cys-X2-Cys and a jmjC domain, which is often found in proteins that regulate chromatin remodeling. Expression of 5qNCA in a del(5q) cell line results in suppression of clonogenic growth. Preliminary sequence results in AML and MDS samples and cell lines has revealed a possible mutation in the KG-1 cell line resulting in a THR to ALA substitution that has not been found in over 100 normal alleles to date. We propose 5qNCA is a good candidate for the del(5q) tumor suppressor gene based on its predicted function and growth suppressive activities, and suggest that further mutational and functional study of this interesting gene is warranted.

The JmjC domain belongs to the Cupin superfamily. JmjC-domain proteins may be protein hydroxylases that catalyse a novel histone modification.

A domain family that is part of the cupin metalloenzyme superfamily. Probable enzymes, but of unknown functions, that regulate chromatin reorganisation processes. See all (17) citations in PubMed

Gene: GRAMD4 (GRAM domain containing 4)

CCDS ID: 33672.1|Hs37.1|chr22

Amino acids: 218--230, BH3-like sequence: FVKNLSALSDWYS

Helix containing: HHHHHHHHHH-HHH

Affinity score for BCL-xL: -2.725898

Affinity score for MCL-1: -2.457586

Also known as **DIP** (death inducing protein)

BH3 motif evolutionarily conserved except for zebrafish

GRAMD4 mimics p53 and mediates the apoptotic function of p73 at mitochondria. John K, Alla V, Meier C, Pützer BM. Cell Death Differ. 2011 May;18(5):874-86. Epub 2010 Dec 3. p73, a member of the p53 family, shares high sequence homology with p53 and shows many p53-like properties: it binds to p53-DNA target sites, transactivates p53-responsive genes and induces cell cycle arrest and apoptosis. Apart from this transcription-dependent effect, less is known about the downstream mechanism(s) by which p73 controls cell fate at the mitochondria. We have previously identified GRAMD4 (alias KIAA0767 or Death-Inducing-Protein) as a novel p53-independent pro-apoptotic target of E2F1, which localizes to mitochondria. In this study, we found that p73-induced apoptosis is mediated by GRAMD4 expression and translocation to the mitochondria. We showed that **this protein physically interacts with Bcl-2**, promotes Bax mitochondrial relocalization and oligomerization, and is highly efficient in inducing mitochondrial membrane permeabilization with release of cytochrome c and Smac. Overexpression of p73α and p73β isoforms, but not p53, leads to direct GRAMD4 promoter transactivation. In addition, GRAMD4 induces changes in Bcl-2 and Bax protein levels. GRAMD4 transcription is activated in response to cisplatin (cDDP) in a manner dependent on endogenous p73. Using solid tumor xenografts, ectopic expression of GRAMD4 together with cDDP resulted in enhanced cancer killing. Our findings demonstrate that p73 is able to trigger apoptosis via the mitochondrial pathway by a new mechanism using pro-apoptotic GRAMD4 as mediator, and strongly support its p53-like function. … Mapping by SMART database searches to predict putative interaction sites between both proteins revealed **a Bcl-like domain for GRAMD4 encompassing amino acids 92-176** [putative BH3 motif 218--230]. As demonstrated in lanes 4 and 5 of Figure 7a (right), deletion of this Bcl-2 homology (BH) domain clearly disrupts the interaction of GRAMD4 with endogenous (lane 2) and ectopically expressed Bcl-2 protein (lane 3).

A novel mitochondrial protein DIP mediates E2F1-induced apoptosis independently of p53. Stanelle J, Tu-Rapp H, Pützer BM.

Cell Death Differ. 2005 Apr;12(4):347-57. The transcription factor E2F1 does not only induce cell proliferation but also shows the strongest proapoptotic effect of all E2F family members as part of an antitumor safeguard mechanism. We have recently identified KIAA0767 as a novel p53-independent target of E2F1. Here, we investigated the biological function of interaction. Overexpression studies of KIAA0767, termed D(eath)-I(nducing)-P(rotein), revealed its strong proapoptotic effect. DIP greatly reduced cell viability in several *in vitro* systems accompanied by typical apoptotic features such as caspase-3 activation and cleavage of poly(ADP-ribose)-polymerase. Endogenous DIP levels increased following E2F1 activation. Yet, inhibition of endogenous DIP function by small interfering RNA rescued p53-negative cells from E2F1-induced apoptosis, indicating that DIP is an essential mediator of the p53-independent E2F1 death pathway. Localization studies showed that DIP localizes to the mitochondria, where endogenous DIP is upregulated following E2F1 induction. These results provide new insights to the incompletely understood regulatory mechanisms of E2F1-induced apoptosis.

Gene: NOP14 [NOP14 nucleolar protein homolog (yeast)]

CCDS ID: 33945.1|Hs37.1|chr4

Amino acids: 474--486, BH3-like sequence: FGFLLEYVGDLAT

Helix containing: HHHHHHHHHHH--

Affinity score for BCL-xL: -2.809019

Affinity score for MCL-1: -2.669477

Also known as: NOL14; C4orf9; RES425; RES4-25

Novel stress-responsive genes EMG1 and NOP14 encode conserved, interacting proteins required for 40S ribosome biogenesis. Liu PC, *et al.* Mol Biol Cell, 2001 Nov. PMID: 11694595. Under stressful conditions organisms adjust the synthesis, processing, and trafficking of molecules to allow survival from and recovery after stress. In baker's yeast Saccharomyces cerevisiae, the cellular production of ribosomes is tightly matched with environmental conditions and nutrient availability through coordinate transcriptional regulation of genes involved in ribosome biogenesis. On the basis of stress-responsive gene expression and functional studies, we have identified a novel, evolutionarily conserved gene, EMG1, that has similar stress-responsive gene expression patterns as ribosomal protein genes and is required for the biogenesis of the 40S ribosomal subunit. The Emg1 protein is distributed throughout the cell; however, its nuclear localization depends on physical interaction with a newly characterized nucleolar protein, Nop14. Yeast depleted of Nop14 or harboring a temperature-sensitive allele of emg1 have selectively reduced levels of the 20S pre-rRNA and mature18S rRNA and diminished cellular levels of the 40S ribosomal subunit. Neither Emg1 nor Nop14 contain any characterized functional motifs; however, isolation and functional analyses of mammalian orthologues of Emg1 and Nop14 suggest that these proteins are functionally conserved among eukaryotes. We conclude that Emg1 and Nop14 are novel proteins whose interaction is required for the maturation of the 18S rRNA and for 40S ribosome production.

Gene: LMLN [Leishmanolysin-like (metallopeptidase M8 family)]

CCDS ID: 3332.1|Hs37.1|chr3

Amino acids: 309--321, BH3-like sequence: YSLGLYQWSDKVV

CCDS ID: 46988.1|Hs37.1|chr3

Gene: LMLN 89782 CC+

Amino acids: 309--321, BH3-like sequence: YSLGLYQWSDKVV

Helix containing: ---------HHHH

Affinity score for BCL-xL: -2.817854

Affinity score for MCL-1: -2.856715

This gene encodes a zinc-metallopeptidase. The encoded protein may play a role in cell migration and invasion. Studies of a similar protein in Drosophila indicate a potential role in mitotic progression. Alternatively spliced transcript variants have been described

Gene: PRMT5 (protein arginine methyltransferase 5)

CCDS ID: 9579.1|Hs37.1|chr14

Amino acids: 202--214, BH3-like sequence: IAVALEIGADLPS

CCDS ID: 41922.1|Hs37.1|chr14

Amino acids: 185--197, BH3-like sequence: IAVALEIGADLPS

Helix containing: HHHHHHH------

Affinity score for BCL-xL: -2.820448

Affinity score for MCL-1: -4.282818

Protein Arginine Methyltransferase 5 Accelerates Tumor Growth by Arginine Methylation of the Tumor Suppressor Programmed Cell Death 4. Powers MA, Fay MM, Factor RE, Welm AL, Ullman KS. Cancer Res. 2011 Aug 9. [Epub ahead of print]

A role for the arginine methylation of Rad9 in checkpoint control and cellular sensitivity to DNA damage. He W, Ma X, Yang X, Zhao Y, Qiu J, Hang H. Nucleic Acids Res. 2011 Jun;39(11):4719-27.

Increased PRMT5 activity mediates key events associated with cyclin D1-dependent neoplastic growth, including CUL4 repression, CDT1 overexpression, and DNA rereplication.

PRMT5 regulates Golgi apparatus structure through methylation of the golgin GM130. Zhou Z, Sun X, Zou Z, Sun L, Zhang T, Guo S, Wen Y, Liu L, Wang Y, Qin J, Li L, Gong W, Bao S. Cell Res. 2010 Sep;20(9):1023-33.

Gene: PODXL

CCDS ID: 34755.1|Hs37.1|chr7

Amino acids: 246--258, BH3-like sequence: AGLELLTSGDLPT

Helix containing: H----------

Affinity score for BCL-xL: -2.838033

Affinity score for MCL-1: -3.009856

This gene encodes a member of the sialomucin protein family. The encoded protein was originally identified as an important component of glomerular podocytes. Podocytes are highly differentiated epithelial cells with interdigitating foot processes covering the outer aspect of the glomerular basement membrane. Other biological activities of the encoded protein include: binding in a membrane protein complex with Na+/H+ exchanger regulatory factor to intracellular cytoskeletal elements, playing a role in hematopoetic cell differentiation, and being expressed in vascular endothelium cells and binding to L-selectin

Podocalyxin EBP50 ezrin molecular complex enhances the metastatic potential of renal cell carcinoma through recruiting Rac1 guanine nucleotide exchange factor ARHGEF7. Hsu YH, *et al.* Am J Pathol, 2010 Jun. PMID: 20395446.

Results suggest that human podocalyxin enhances the adherence of cells to immobilized ligands and to vascular endothelial cells through a mechanism(s) dependent on the activity of integrins.

Gene: CREB3

CCDS ID: 6588.1|Hs37.1|chr9

Amino acids: 13--25, BH3-like sequence: LAFLLEESGDLGT

Helix containing: HHHHHHHH-----

Affinity score for BCL-xL: -2.858237

Affinity score for MCL-1: -3.623853

Also known as: LZIP; LUMAN; MGC15333; MGC19782

This gene encodes a transcription factor that is a member of the leucine zipper family of DNA binding proteins. This protein binds to the cAMP-response element and regulates cell proliferation. The protein interacts with host cell factor C1, which also associates with the herpes simplex virus (HSV) protein VP16 that induces transcription of HSV immediate-early genes. This protein and VP16 both bind to the same site on host cell factor C1. It is thought that the interaction between this protein and host cell factor C1 plays a role in the establishment of latency during HSV infection. This protein also plays a role in leukocyte migration, tumor suppression, and endoplasmic reticulum stress-associated protein degradation. Additional transcript variants have been identified, but their biological validity has not been determined.

Interacts with BNIP2 by proteomic screen (BNIP2 does not contain BH3 motif)

CREB3 subfamily transcription factors are not created equal: Recent insights from global analyses and animal models. Chan CP, Kok KH, Jin DY. Cell Biosci. 2011 Feb 17;1(1):6. The CREB3 subfamily of membrane-bound bZIP transcription factors has five members in mammals known as CREB3 and CREB3L1-L4. One current model suggests that CREB3 subfamily transcription factors are similar to ATF6 in regulated intramembrane proteolysis and transcriptional activation. Particularly, they were all thought to be proteolytically activated in response to endoplasmic reticulum (ER) stress to stimulate genes that are involved in unfolded protein response (UPR). Although the physiological inducers of their proteolytic activation remain to be identified, recent findings from microarray analyses, RNAi screens and gene knockouts not only demonstrated their critical roles in regulating development, metabolism, secretion, survival and tumorigenesis, but also revealed cell type-specific patterns in the activation of their target genes. Members of the CREB3 subfamily show differential activity despite their structural similarity. The spectrum of their biological function expands beyond ER stress and UPR. Further analyses are required to elucidate the mechanism of their proteolytic activation and the molecular basis of their target recognition.

Identification of the BCL2/adenovirus E1B-19K protein-interacting protein 2 (BNIP-2) as a granzyme B target during human natural killer cell-mediated killing. Biochem J. 2010 Oct 11;431(3):423-31. Scott GB, Bowles PA, Wilson EB, Meade JL, Low BC, Davison A, Blair GE, Cook GP. Cytotoxic lymphocytes eliminate infected cells and tumours via the perforin-mediated delivery of pro-apoptotic serine proteases known as granzymes. Granzyme B triggers apoptosis via the cleavage of a repertoire of cellular proteins, leading to caspase activation and mitochondrial depolarization. A simple bioinformatics strategy identified a candidate granzyme B cleavage site in the widely expressed BNIP-2 (BCL2/adenovirus E1B-19K protein-interacting protein 2). Granzyme B cleaved recombinant BNIP-2 *in vitro* and endogenous BNIP-2 was cleaved during the NK (natural killer) cell-mediated killing of tumour cells. Cleavage required the site identified in the bioinformatics screen and was caspase-independent. Expression of either full-length BNIP-2 or a truncated molecule mimicking the granzyme B cleaved form was pro-apoptotic and led to the caspase-dependent cleavage of BNIP-2 at a site distinct from granzyme B cleavage. Inhibition of BNIP-2 expression did not affect the susceptibility to NK cell-mediated killing. Furthermore, target cells in which BID (BH3-interacting domain death agonist) expression was inhibited also remained highly susceptible to NK cell-mediated killing, revealing redundancy in the pro-apoptotic response to human cytotoxic lymphocytes. Such redundancy reduces the opportunity for escape from apoptosis induction and maximizes the chances of immune-mediated clearance of infected cells or tumour cells.

Luman/CREB3 induces transcription of the endoplasmic reticulum (ER) stress response protein Herp through an ER stress response element. Liang G, Audas TE, Li Y, Cockram GP, Dean JD, Martyn AC, Kokame K, Lu R. Mol Cell Biol. 2006 Nov;26(21):7999-8010. Luman/CREB3 (also called LZIP) is an endoplasmic reticulum (ER) membrane-bound transcription factor which is believed to undergo regulated intramembrane proteolysis in response to cellular cues. We previously found that Luman activates transcription from the unfolded protein response element. Here we report the identification of Herp, a gene involved in ER stress-associated protein degradation (ERAD), as a direct target of Luman. We found that Luman was transcriptionally induced and proteolytically activated by the ER stress inducer thaspsigargin. Overexpression of Luman activated transcription of cellular Herp via ER stress response element II (ERSE-II; ATTGG-N-CCACG) in the promoter region. Mutagenesis studies and chromatin immunoprecipitation assays showed that Luman physically associates with the Herp promoter, specifically the second half-site (CCACG) of ERSE-II. Luman was also necessary for the full activation of Herp during the ER stress response, since Luman small interfering RNA knockdown or functional repression by a dominant negative mutant attenuated Herp gene expression. Like Herp, overexpression of Luman protected cells against ER stress-induced apoptosis. With Luman structurally similar to ATF6 but resembling XBP1 in DNA-binding specificities, we propose that Luman is a novel factor that plays a role in ERAD and a converging point for various signaling pathways channeling through the ER.

Gene: FLNB (filamin B, beta)

CCDS ID: 2885.1|Hs37.1|chr3

Amino acids: 1164--1176, BH3-like sequence: GALGLEAVSDSGT

Helix containing: ----------

Affinity score for BCL-xL: -2.876566

Affinity score for MCL-1: -3.001304

BH3 motif evolutionarily conserved in chimp and dog; cow, mouse and rat have conservative changes that match consensus except for C-cap

The filamins: organizers of cell structure and function. Nakamura F, Stossel TP, Hartwig JH. Cell Adh Migr. 2011 Mar-Apr;5(2):160-9. Filamin A (FLNa), the first non-muscle actin filament cross-linking protein, was identified in 1975. Thirty five years of FLNa research has revealed its structure in great detail, discovered its isoforms (FLNb and c), and identified over 90 binding partners including channels, receptors, intracellular signaling molecules, and even transcription factors. Due to this diversity, mutations in human FLN genes result in a wide range of anomalies with moderate to lethal consequences. This review focuses on the structure and functions of FLNa in cell migration and adhesion.

Filamin B serves as a molecular scaffold for type I interferon-induced c-Jun NH2-terminal kinase signaling pathway. Jeon YJ, Choi JS, Lee JY, Yu KR, Ka SH, Cho Y, Choi EJ, Baek SH, Seol JH, Park D, Bang OS, Chung CH. Mol Biol Cell. 2008 Dec;19(12):5116-30.

Type I interferons (IFNs) activate Janus tyrosine kinase-signal transducer and activator of transcription pathway for exerting pleiotropic biological effects, including antiviral, antiproliferative, and immunomodulatory responses. Here, we demonstrate that filamin B functions as a scaffold that links between activated Rac1 and a c-Jun NH(2)-terminal kinase (JNK) cascade module for mediating type I IFN signaling. Filamin B interacted with Rac1, mitogen-activated protein kinase kinase kinase 1, mitogen-activated protein kinase kinase 4, and JNK. Filamin B markedly enhanced IFNalpha-dependent Rac1 activation and

the sequential activation of the JNK cascade members. Complementation assays using M2 melanoma cells revealed that filamin B, but not filamin A, is required for IFNalpha-dependent activation of JNK. Furthermore, **filamin B promoted IFNalpha-induced apoptosis**, whereas short hairpin RNA-mediated knockdown of filamin B prevented it. These results establish a novel function of filamin B as a molecular scaffold in the JNK signaling pathway for type I IFN-induced apoptosis, thus providing the biological basis for antitumor and antiviral functions of type I IFNs.

FLNB-Related Disorders. Robertson S. In: Pagon RA, Bird TD, Dolan CR, Stephens K, editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-. 2008 Oct 10.

Gene: POLE2

CCDS ID: 32073.1|Hs37.1|chr14

Amino acids: 473--485, BH3-like sequence: PVPDLLVIADKYD

Helix containing: ----------

Affinity score for BCL-xL: -2.917927

Affinity score for MCL-1: -2.149910

Mutations/polymorphisms in the 55 kDa subunit of DNA polymerase epsilon in human colorectal cancer. Zhou Q, *et al.* Cancer Genomics Proteomics, 2009 Nov-Dec. PMID: 20065316.

Gene: DIS3L (DIS3 mitotic control homolog)

CCDS ID: 10214.1|Hs37.1|chr15

Amino acids: 327--339, BH3-like sequence: FVRVLGRIGDLEG

CCDS ID: 45286.1|Hs37.1|chr15

Amino acids: 410--422, BH3-like sequence: FVRVLGRIGDLEG

Helix containing: ----------

Affinity score for BCL-xL: -2.921053

Affinity score for MCL-1: -1.653900

Dis3-like 1: a novel exoribonuclease associated with the human exosome. Staals RH, *et al.* EMBO J, 2010 Jul 21. 29(14):2342-57. PMID: 20531389. The eukaryotic RNA exosome is a ribonucleolytic complex involved in RNA processing and turnover. It consists of a nine-subunit catalytically inert core that serves a structural function and participates in substrate recognition. Best defined in Saccharomyces cerevisiae, enzymatic activity comes from the associated subunits Dis3p (Rrp44p) and Rrp6p. The former is a nuclear and cytoplasmic RNase II/R-like enzyme, which possesses both processive exo- and endonuclease activities, whereas the latter is a distributive RNase D-like nuclear exonuclease. Although the exosome core is highly conserved, identity and arrangements of its catalytic subunits in different vertebrates remain elusive. Here, we demonstrate the association of two different Dis3p homologs--hDIS3 and hDIS3L--with the human exosome core. Interestingly, these factors display markedly different intracellular localizations: hDIS3 is mainly nuclear, whereas hDIS3L is strictly cytoplasmic. This compartmental distribution reflects the substrate preferences of the complex *in vivo*. Both hDIS3 and hDIS3L are active exonucleases; however, only hDIS3 has retained endonucleolytic activity. Our data suggest that three different ribonucleases can serve as catalytic subunits for the exosome in human cells.

Gene: FAM189B

CCDS ID: 1103.1|Hs37.1|chr1

Amino acids: 327--339, BH3-like sequence: GSLVLSAIGDLPG

CCDS ID: 1104.1|Hs37.1|chr1

Amino acids: 231--243, BH3-like sequence: GSLVLSAIGDLPG

Helix containing: --HHHH-------

Affinity score for BCL-xL: -2.921862

Affinity score for MCL-1: -2.667901

Gene: C15orf59

CCDS ID: 32289.1|Hs37.1|chr15

Amino acids: 5--17, BH3-like sequence: GAPDLGQPSDDPS

Helix containing: ----------

Affinity score for BCL-xL: -2.934937

Affinity score for MCL-1: -3.016056

Gene: HOXA10

CCDS ID: 5410.2|Hs37.1|chr7

Amino acids: 61--73, BH3-like sequence: GGVYLPPAADLPY

Helix containing: ----------

Affinity score for BCL-xL: -3.000257

Affinity score for MCL-1: -4.755663

Gene: HTT (Huntingtin)

CCDS ID: 43206.1|Hs37.1|chr4

Amino acids: 2700--2712, BH3-like sequence: VVRSLLVVSDLFT

Helix containing: HHHH---------

Affinity score for BCL-xL: -3.033553

Affinity score for MCL-1: -2.565225

Interacts with CASP1, p53 AND CBP

Mutant huntingtin binds the mitochondrial fission GTPase dynamin-related protein-1 and increases its enzymatic activity. Song W, *et al*. Nat Med. 2011 Mar; 17(3): 377-82. PMID: 21336284. Huntington's disease is an inherited and incurable neurodegenerative disorder caused by an abnormal polyglutamine (polyQ) expansion in huntingtin (encoded by HTT). PolyQ length determines disease onset and severity, with a longer expansion causing earlier onset. The mechanisms of mutant huntingtin-mediated neurotoxicity remain unclear; however, mitochondrial dysfunction is a key event in Huntington's disease pathogenesis. Here we tested whether mutant huntingtin impairs the mitochondrial fission-fusion balance and thereby causes neuronal injury. We show that mutant huntingtin triggers mitochondrial fragmentation in rat neurons and fibroblasts of individuals with Huntington's disease *in vitro* and in a mouse model of Huntington's disease *in vivo* before the presence of neurological deficits and huntingtin aggregates. Mutant huntingtin abnormally interacts with the mitochondrial fission GTPase dynamin-related protein-1 (DRP1) in mice and humans with Huntington's disease, which, in turn, stimulates its enzymatic activity. Mutant huntingtin-mediated mitochondrial fragmentation, defects in anterograde and retrograde mitochondrial transport and neuronal cell death are all rescued by reducing DRP1 GTPase activity with the dominant-negative DRP1 K38A mutant. Thus, DRP1 might represent a new therapeutic target to combat neurodegeneration in Huntington's disease.

Mutant Huntingtin induces activation of the Bcl-2/adenovirus E1B 19-kDa interacting protein (BNip3). Sassone J, *et al.* Cell Death Dis. 2010; 1: e7. PMID: 21364626. Huntington's disease (HD) is a neurodegenerative disorder characterized by progressive neuronal death in the basal ganglia and cortex. Although increasing evidence supports a pivotal role of mitochondrial dysfunction in the death of patients' neurons, the molecular bases for mitochondrial impairment have not been elucidated. We provide the first evidence of an abnormal activation of the Bcl-2/adenovirus E1B 19-kDa interacting protein 3 (BNip3) in cells expressing mutant Huntingtin. In this study, we show an abnormal accumulation and dimerization of BNip3 in the mitochondria extracted from human HD muscle cells, HD model cell cultures and brain tissues from HD model mice. Importantly, we have shown that blocking BNip3 expression and dimerization restores normal mitochondrial potential in human HD muscle cells. Our data shed light on the molecular mechanisms underlying mitochondrial dysfunction in HD and point to BNip3 as a new potential target for neuroprotective therapy in HD.

The Huntington's disease protein interacts with p53 and CREB-binding protein and represses transcription. Steffan JS, Kazantsev A, Spasic-Boskovic O, Greenwald M, Zhu YZ, Gohler H, Wanker EE, Bates GP, Housman DE, Thompson LM. Proc Natl Acad Sci USA. 2000 Jun 6; 97(12): 6763-8. Huntington's Disease (HD) is caused by an expansion of a polyglutamine tract within the huntingtin (htt) protein. Pathogenesis in HD appears to include the cytoplasmic cleavage of htt and release of an amino-terminal fragment capable of nuclear localization. We have investigated potential consequences to nuclear function of a pathogenic amino-terminal region of htt (httex1p) including aggregation, protein-protein interactions, and transcription. httex1p was found to coaggregate with p53 in inclusions generated in cell culture and to interact with p53 *in vitro* and in cell culture. Expanded httex1p represses transcription of the p53-regulated promoters, p21(WAF1/CIP1) and MDR-1. httex1p was also found to interact *in vitro* with CREB-binding protein (CBP) and mSin3a, and CBP to localize to neuronal intranuclear inclusions in a transgenic mouse model of HD. These results raise the possibility that expanded repeat htt causes aberrant transcriptional regulation through its interaction with cellular transcription factors which may result in neuronal dysfunction and cell death in HD.

Gene: VIL1

CCDS ID: 2417.1|Hs37.1|chr2

Amino acids: 251--263, BH3-like sequence: AALKLYHVSDSEG

Helix containing: HHHHH--------

Affinity score for BCL-xL: -3.044967

Affinity score for MCL-1: -2.990888

This gene encodes a member of a family of calcium-regulated actin-binding proteins. This protein represents a dominant part of the brush border cytoskeleton which functions in the capping, severing, and bundling of actin filaments. Two mRNAs of 2.7 kb and 3.5 kb have been observed; they result from utilization of alternate poly-adenylation signals present in the terminal exon.

Gene: UBR4 (ubiquitin protein ligase E3 component n-recognin 4)

CCDS ID: 189.1|Hs37.1|chr1

Amino acids: 3395--3407, BH3-like sequence: LVNQLNKFADKET

Helix containing: HHHHHHH---HHH

Affinity score for BCL-xL: -3.055083

Affinity score for MCL-1: -2.374085

Also known as: p600; ZUBR1; RBAF600; FLJ41863; KIAA0462; KIAA1307; RP5-1126H10.1

Putative zinc finger in N-recognin (UBR box); This region is found in E3 ubiquitin ligases that recognize N-recognins

PHA03018 super family[cl14486], hypothetical protein; Provisional

Compare with MCL-1-binding BH3 protein HUWE1 (HECT E3 ubiquitin ligase family)

The protein encoded by this gene is an E3 ubiquitin-protein ligase that interacts with the retinoblastoma-associated protein in the nucleus and with calcium-bound calmodulin in the cytoplasm. The encoded protein appears to be a cytoskeletal component in the cytoplasm and part of the chromatin scaffold in the nucleus. In addition, this protein is a target of the human papillomavirus type 16 E7 oncoprotein. [provided by RefSeq]

p600, a unique protein required for membrane morphogenesis and cell survival. Nakatani Y *et al.* Proc Natl Acad Sci USA. 2005 Oct 18; 102(42): 15093-8. Epub 2005 Oct 7. Erratum in: Proc Natl Acad Sci USA. 2005 Dec 6; 102(49): 17882.

Association of the human papillomavirus type 16 E7 oncoprotein with the 600-kDa retinoblastoma protein-associated factor, p600. Huh KW *et al.* Proc Natl Acad Sci U S A. 2005 Aug 9;102(32):11492-7. Epub 2005 Aug 1.

A family of mammalian E3 ubiquitin ligases that contain the UBR box motif and recognize N-degrons. Tasaki T *et al*., Mol Cell Biol. 2005 Aug; 25(16): 7120-36.

See all (13) citations in PubMed

Gene: METTL10 (Methyltransferase like 10)

CCDS ID: 31307.1|Hs37.1|chr10

Amino acids: 262--274, BH3-like sequence: AGLELLGSSDSPT

Helix containing: HHHHH--------

Affinity score for BCL-xL: -3.091711

Affinity score for MCL-1: -3.239530

Gene: GRM7 (glutamate receptor, metabotropic 7)

CCDS ID: 43042.1|Hs37.1|chr3

Amino acids: 305--317, BH3-like sequence: VGHFLWVGSDSWG

Helix containing: ----------

Affinity score for BCL-xL: -3.110038

Affinity score for MCL-1: -3.512354

L-glutamate is the major excitatory neurotransmitter in the central nervous system, and it activates both ionotropic and metabotropic glutamate receptors. Glutamatergic neurotransmission is involved in most aspects of normal brain function and can be perturbed in many neuropathologic conditions. The metabotropic glutamate receptors are a family of G protein-coupled receptors that have been divided into three groups on the basis of sequence homology, putative signal transduction mechanisms, and pharmacologic properties. Group I includes GRM1 and GRM5, and these receptors have been shown to activate phospholipase C. Group II includes GRM2 and GRM3, while Group III includes GRM4, **GRM6** (see below), GRM7 and GRM8. Group II and III receptors are linked to the inhibition of the cyclic AMP cascade but differ in their agonist selectivities. Multiple transcript variants encoding different isoforms have been found for this gene.

Gene: ASTN1

CCDS ID: 1319.1|Hs37.1|chr1

Amino acids: 339--351, BH3-like sequence: GSAFLNPEGDSGT

CCDS ID: 44280.1|Hs37.1|chr1

Amino acids: 339--351, BH3-like sequence: GSAFLNPEGDSGT

Helix containing: ----------

Affinity score for BCL-xL: -3.160792

Affinity score for MCL-1: -3.081868

Astrotactin is a neuronal adhesion molecule required for glial-guided migration of young postmitotic neuroblasts in cortical regions of developing brain, including cerebrum, hippocampus, cerebellum, and olfactory bulb (Fink *et al*., 1995).

Gene: GRM6 (glutamate receptor, metabotropic 6)

CCDS ID: 4442.1|Hs37.1|chr5

Amino acids: 298--310, BH3-like sequence: TGHFLWVGSDSWG

Helix containing: ----------

Affinity score for BCL-xL: -3.165555

Affinity score for MCL-1: -3.649031

L-glutamate is the major excitatory neurotransmitter in the central nervous system, and it activates both ionotropic and metabotropic glutamate receptors. Glutamatergic neurotransmission is involved in most aspects of normal brain function and can be perturbed in many neuropathologic conditions. The metabotropic glutamate receptors are a family of G protein-coupled receptors that have been divided into three groups on the basis of sequence homology, putative signal transduction mechanisms, and pharmacologic properties. Group I includes GRM1 and GRM5, and these receptors have been shown to activate phospholipase C. Group II includes GRM2 and GRM3, while Group III includes GRM4, GRM6, **GRM7** (see above) and GRM8. Group II and III receptors are linked to the inhibition of the cyclic AMP cascade but differ in their agonist selectivities. Multiple transcript variants encoding different isoforms have been found for this gene.

Gene: C12orf53

CCDS ID: 44818.1|Hs37.1|chr12

Amino acids: 235--247, BH3-like sequence: GVTVLGAFGDSPT

Helix containing: ----------

Affinity score for BCL-xL: -3.210179

Affinity score for MCL-1: -2.646389

Gene: RABGAP1L (RAB GTPase activating protein 1-like)

CCDS ID: 1314.1|Hs37.1|chr1

Amino acids: 456--468, BH3-like sequence: EVVSLQRESDKEE

Helix containing: ----------

Affinity score for BCL-xL: -3.226388

Affinity score for MCL-1: -2.492923

Network organization of the human autophagy system. Behrends C, *et al.* Nature, 2010 Jul 1. PMID: 20562859.

Gene: EZH1 (enhancer of zeste homolog 1)

CCDS ID: 32659.1|Hs37.1|chr17

Amino acids: 179--191, BH3-like sequence: LVDALNQYSDEEE

Helix containing: HHHHHH----HHH

Affinity score for BCL-xL: -3.236147

Affinity score for MCL-1: -2.036516

Ezh1 and Ezh2 maintain repressive chromatin through different mechanisms. Margueron R, *et al.* Mol Cell, 2008 Nov 21. PMID: 19026781.

Gene: CNGA1 (cyclic nucleotide gated channel alpha 1)

CCDS ID: 47050.1|Hs37.1|chr4

Amino acids: 47--59, BH3-like sequence: AGLELLISSDLPT

Helix containing: H----------

Affinity score for BCL-xL: -3.306555

Affinity score for MCL-1: -3.649704

Gene: PEX26 (peroxisomal biogenesis factor 26)

CCDS ID: 13750.1|Hs37.1|chr22

Amino acids: 34--46, BH3-like sequence: AVDLLEEAADLLV

Helix containing: HHHHHHHHHHHHH

Affinity score for BCL-xL: -3.366041

Affinity score for MCL-1: -3.500627

Also known as: FLJ20695; PEX26M1T; Pex26pM1T

This gene belongs to the peroxin-26 gene family. It is probably required for protein import into peroxisomes. It anchors PEX1 and PEX6 to peroxisome membranes, possibly to form heteromeric AAA ATPase complexes required for the import of proteins into peroxisomes. Defects in this gene are the cause of peroxisome biogenesis disorder complementation group 8 (PBD-CG8).

PBD refers to a group of peroxisomal disorders arising from a failure of protein import into the peroxisomal membrane or matrix. The PBD group is comprised of four disorders: Zellweger syndrome (ZWS), neonatal adrenoleukodystrophy (NALD), infantile Refsum disease (IRD), and classical rhizomelic chondrodysplasia punctata (RCDP). Alternatively spliced transcript variants have been identified for this gene.

Interacts with SUFU, a negative regulator of the hedgehog signaling pathway. See all (17) citations in PubMed

Gene: SLC4A4

CCDS ID: 3549.1|Hs37.1|chr4

Amino acids: 210--222, BH3-like sequence: TSSSLNDISDKPE

CCDS ID: 43236.1|Hs37.1|chr4

Amino acids: 254--266, BH3-like sequence: TSSSLNDISDKPE

CCDS ID: 47071.1|Hs37.1|chr4

Amino acids: 254--266, BH3-like sequence: TSSSLNDISDKPE

Helix containing: ----------H

Affinity score for BCL-xL: -3.382275

Affinity score for MCL-1: -2.238126

CCDS ID: 43236.1|Hs37.1|chr4

Amino acids: 10--22, BH3-like sequence: GASFLKHVCDEEE

CCDS ID: 47071.1|Hs37.1|chr4

Amino acids: 10--22, BH3-like sequence: GASFLKHVCDEEE

Helix containing: -HHHHHH---HHH

This gene encodes a sodium bicarbonate cotransporter (NBC) involved in the regulation of bicarbonate secretion and absorption and intracellular pH. Mutations in this gene are associated with proximal renal tubular acidosis

Gene: MED12 (Mediator complex)

CCDS ID: 43970.1|Hs37.1|chrX

Amino acids: 904--916, BH3-like sequence: EAELLLKSSDLVG

Helix containing: HHHHHHHH-----

Affinity score for BCL-xL: -3.394510

Affinity score for MCL-1: -3.470509

The initiation of transcription is controlled in part by a large protein assembly known as the preinitiation complex. A component of this preinitiation complex is a 1.2 MDa protein aggregate called Mediator. This Mediator component binds with a CDK8 subcomplex which contains the protein encoded by this gene, mediator complex subunit 12 (MED12), along with MED13, CDK8 kinase, and cyclin C. The CDK8 subcomplex modulates Mediator-polymerase II interactions and thereby regulates transcription initiation and reinitation rates. The MED12 protein is essential for activating CDK8 kinase. Defects in this gene cause X-linked Opitz-Kaveggia syndrome, also known as FG syndrome, and Lujan-Fryns syndrome.

Gene: SETD5

CCDS ID: 46741.1|Hs37.1|chr3

Amino acids: 1345--1357, BH3-like sequence: ASPTLQGPSDSPT

Helix containing: ----------

Affinity score for BCL-xL: -3.399553

Affinity score for MCL-1: -3.121006

Interacts with TRAF2: The protein encoded by this gene is a member of the TNF receptor associated factor (TRAF) protein family. TRAF proteins associate with, and mediate the signal transduction from members of the TNF receptor superfamily. This protein directly interacts with TNF receptors, and forms a heterodimeric complex with TRAF1. This protein is required for TNF-alpha-mediated activation of MAPK8/JNK and NF-kappaB. The protein complex formed by this protein and TRAF1 interacts with the inhibitor-of-apoptosis proteins (IAPs), and functions as a mediator of the anti-apoptotic signals from TNF receptors. The interaction of this protein with TRADD, a TNF receptor associated apoptotic signal transducer, ensures the recruitment of IAPs for the direct inhibition of caspase activation. BIRC2/c-IAP1, an apoptosis inhibitor possessing ubiquitin ligase activity, can unbiquitinate and induce the degradation of this protein, and thus potentiate TNF-induced apoptosis.

Interaction of the TNFR-receptor associated factor TRAF1 with I-kappa B kinase-2 and TRAF2 indicates a regulatory function for NF-kappa B signaling. Sughra K, *et al.* PLoS One, 2010 Sep 13. PMID: 20856938.

Roles of TRAF2 and TRAF3 in Epstein-Barr virus latent membrane protein 1-induced alternative NF-kappaB activation. Song YJ, *et al.* Virus Genes, 2010 Oct. PMID: 20585848.

Interacts with DPPA2: ECSA/DPPA2 is an embryo-cancer antigen that is coexpressed with cancer-testis antigens in non-small cell lung cancer. John T, *et al.* Clin Cancer Res, 2008 Jun 1. PMID: 18519755.

Differential expression of the embryo/cancer gene ECSA(DPPA2), the cancer/testis gene BORIS and the pluripotency structural gene OCT4, in human preimplantation development. Monk M, *et al.* Mol Hum Reprod, 2008 Jun. PMID: 18467432.

Gene: LAIR1 (Leukocyte-associated immunoglobulin-like receptor 1)

CCDS ID: 12891.1|Hs37.1|chr19

Amino acids: 213--225, BH3-like sequence: AVDVLERTADKAT

CCDS ID: 12892.1|Hs37.1|chr19

Amino acids: 196--208, BH3-like sequence: AVDVLERTADKAT

Helix containing: HHHHHHHHH-HHH

Affinity score for BCL-xL: -3.454361

Affinity score for MCL-1: -3.191226

Gene: PHF3 (PHD finger protein 3)

CCDS ID: 4966.1|Hs37.1|chr6

Amino acids: 281--293, BH3-like sequence: VGSPLFKFSDKEE

Helix containing: ----------HH

Affinity score for BCL-xL: -3.460262

Affinity score for MCL-1: -3.303309

Gene: FAM111A (family with sequence similarity 111, member A)

CCDS ID: 7973.1|Hs37.1|chr11

Amino acids: 346--358, BH3-like sequence: VVKLLVRLSDSVG

Helix containing: ----------

Affinity score for BCL-xL: -3.468462

Affinity score for MCL-1: -2.084251

Gene: ERAL1

CCDS ID: 11244.1|Hs37.1|chr17

Amino acids: 199--211, BH3-like sequence: LVVVLVDVSDKWT

Helix containing: ----------HHH

Affinity score for BCL-xL: -3.484149

Affinity score for MCL-1: -2.973849

Human ERAL1 is a mitochondrial RNA chaperone involved in the assembly of the 28S small mitochondrial ribosomal subunit. Dennerlein S, *et al.* Biochem J, 2010 Aug 27. PMID: 20604745.

Gene: PLCZ1 (phospholipase C, zeta 1)

CCDS ID: 8680.1|Hs37.1|chr12

Amino acids: 175--187, BH3-like sequence: VSDQLLGPSDLWG

Helix containing: ---------HHHH

Affinity score for BCL-xL: -3.663701

Affinity score for MCL-1: -3.347620

Gene: TMEM41A

CCDS ID: 3271.1|Hs37.1|chr3

Amino acids: 38--50, BH3-like sequence: GGRSLWFPSDLAE

Helix containing: ---------HHHH

Affinity score for BCL-xL: -3.740551

Affinity score for MCL-1: -3.469766

Gene: TSNAX

CCDS ID: 1596.1|Hs37.1|chr1

Amino acids: 184--196, BH3-like sequence: PVDYLLGVADLTG

Helix containing: -------HHHHHHH

Affinity score for BCL-xL: -3.758370

Affinity score for MCL-1: -3.493869

This gene encodes a protein which specifically interacts with translin, a DNA-binding protein that binds consensus sequences at breakpoint junctions of chromosomal translocations. The encoded protein contains bipartite nuclear targeting sequences that may provide nuclear transport for translin, which lacks any nuclear targeting motifs.

Gene: TANC1 (tetratricopeptide repeat, ankyrin repeat and coiled-coil containing 1)

CCDS ID: 42766.1|Hs37.1|chr2

Amino acids: 30--42, BH3-like sequence: PVLHLDHSADSPV

Helix containing: ----------

Affinity score for BCL-xL: -3.788018

Affinity score for MCL-1: -4.125162

MINK is a Rap2 effector for phosphorylation of the postsynaptic scaffold protein TANC1. Nonaka H, Takei K, Umikawa M, Oshiro M, Kuninaka K, Bayarjargal M, Asato T, Yamashiro Y, Uechi Y, Endo S, Suzuki T, Kariya K. Biochem Biophys Res Commun. 2008 Dec 12; 377(2): 573-8. Epub 2008 Oct 18.

Gene: REPS1 (RALBP1 associated Eps domain containing 1 signaling adaptor)

CCDS ID: 5193.2|Hs37.1|chr6

Amino acids: 481--493, BH3-like sequence: TSPLLVKPSDLLE

CCDS ID: 47488.1|Hs37.1|chr6

Amino acids: 454--466, BH3-like sequence: TSPLLVKPSDLLE

Helix containing: ---------HHHH

Affinity score for BCL-xL: -3.804575

Affinity score for MCL-1: -3.821844

Doxorubicin transport by RALBP1 and ABCG2 in lung and breast cancer. Singhal SS, *et al.* Int J Oncol, 2007 Mar. PMID: 17273774.

RALBP1/RLIP76 mediates multidrug resistance. Drake KJ, *et al.* Int J Oncol, 2007 Jan. PMID: 17143522.

Gene: SLC25A13

CCDS ID: 5645.1|Hs37.1|chr7

Amino acids: 268--280, BH3-like sequence: EVDILFQLADLYE

Helix containing: HHHHHHHHHHHHH-

Affinity score for BCL-xL: -3.827502

Affinity score for MCL-1: -4.164170

Gene: TMEM215

CCDS ID: 6530.1|Hs37.1|chr9

Amino acids: 91--103, BH3-like sequence: VVELLRTPSDLES

Helix containing: ----------

Affinity score for BCL-xL: -4.076880

Affinity score for MCL-1: -3.316658

Gene: TGFB1

CCDS ID: 33031.1|Hs37.1|chr19

Amino acids: 182--194, BH3-like sequence: LSNRLLAPSDSPE

Helix containing: HHHH---------

Affinity score for BCL-xL: -4.150832

Affinity score for MCL-1: -4.072426

Genes without PSSM Affinity Scores (listed in alphabetical order)

(86 candidates)

Gene: AADACL3 (arylacetamide deacetylase-like 3)

CCDS ID: 41252.1|Hs37.1|chr1

Amino acids: 7--19, BH3-like sequence: ICSRLCKESDSVV

CCDS ID: 41253.1|Hs37.1|chr1

Amino acids: 77--89, BH3-like sequence: ICSRLCKESDSVV

Helix containing: HHHHH--------

Gene: ANGPTL5 (angiopoietin-like 5)

CCDS ID: 8312.1|Hs37.1|chr11

Amino acids: 209--221, BH3-like sequence: WCDYLDGFGDLLG

Helix containing: HHHHHHHHHHHHH

Fibrinogen-related domains (FReDs); C terminal globular domain of fibrinogen. Fibrinogen is involved in blood clotting, being activated by thrombin to assemble into fibrin clots. The N-termini of 2 times 3 chains come together to form a globular arrangement called the disulfide knot. The C termini of fibrinogen chains end in globular domains, which are not completely equivalent. C terminal globular domains of the gamma chains (C-gamma) dimerize and bind to the GPR motif of the N-terminal domain of the alpha chain, while the GHR motif of N-terminal domain of the beta chain binds to the C terminal globular domains of another beta chain (C-beta), which leads to lattice formation.

Identification of a novel human angiopoietin-like gene expressed mainly in heart. Zeng L, *et al.* J Hum Genet, 2003. PMID: 12624729. The angiopoietins are an important family of growth factors specific for vascular endothelium. Most of them bind to the TIE2 receptor and are related to regulation of angiogenesis. During large-scale DNA sequencing of the human fetal brain cDNA library, we cloned a novel human angiopoietin-like cDNA and termed it human angiopoietin-like 5 (ANGPTL5). Like other members of the angiopoietin family, ANGPTL5-deduced protein also has an N-terminal cleavable signal peptide, a predicted coiled-coil domain, and a fibrinogen-like domain. The search against the human genome database indicated that ANGPTL5 maps to 11q22. Expression analysis of ANGPTL5 shows that it is mainly expressed in adult human heart.

Gene: ANKMY1 (ankyrin repeat and MYND domain containing 1)

CCDS ID: 2535.1|Hs37.1|chr2

Amino acids: 505--517, BH3-like sequence: LGSALCVACDLTY

CCDS ID: 2536.1|Hs37.1|chr2

Amino acids: 729--741, BH3-like sequence: LGSALCVACDLTY

Helix containing: --HHH-------H

Gene: AP2A2 (adaptor-related protein complex 2, alpha 2 subunit)

CCDS ID: 44512.1|Hs37.1|chr11

Amino acids: 178--190, BH3-like sequence: TSPDLVPMGDWTS

Helix containing: ----------H

Also known as HIP9; HYPJ; ADTAB; CLAPA2

HM1.24 is internalized from lipid rafts by clathrin-mediated endocytosis through interaction with alpha-adaptin. Masuyama N, *et al.* J Biol Chem, 2009 Jun 5. PMID: 19359243.

aPKC-mediated phosphorylation regulates asymmetric membrane localization of the cell fate determinant Numb. Smith CA, *et al.* EMBO J, 2007 Jan 24. PMID: 17203073.

Gene: APLNR (apelin receptor)

CCDS ID: 7950.1|Hs37.1|chr11

Amino acids: 163--175, BH3-like sequence: PVMVLRTTGDLEN

Helix containing: ----------

This gene encodes a member of the G protein-coupled receptor gene family. The encoded protein is related to the angiotensin receptor, but is actually an apelin receptor that inhibits adenylate cyclase activity and plays a counter-regulatory role against the pressure action of angiotensin II by exerting hypertensive effect. It functions in the cardiovascular and central nervous systems, in glucose metabolism, in embryonic and tumor angiogenesis and as a human immunodeficiency virus (HIV-1) coreceptor

Gene: ATF6B (activating transcription factor 6 beta)

CCDS ID: 4737.1|Hs37.1|chr6

Amino acids: 129--141, BH3-like sequence: LAPPLCLLGDDPT

CCDS ID: 47408.1|Hs37.1|chr6

Amino acids: 126--138, BH3-like sequence: LAPPLCLLGDDPT

Helix containing: ----------

Also known as G13; CREBL1; CREB-RP; FLJ10066

BH3 motif evolutionarily conserved except for zebrafish

Contains a leucine zipper: LrrenaaLrrrleaLlaenseL

The protein encoded by this gene is a transcription factor in the unfolded protein response (UPR) pathway during ER stress. Either as a homodimer or as a heterodimer with ATF6-alpha, the encoded protein binds to the ER stress response element, interacting with nuclear transcription factor Y to activate UPR target genes. The protein is normally found in the membrane of the endoplasmic reticulum; however, under ER stress, the N-terminal cytoplasmic domain is cleaved from the rest of the protein and translocates to the nucleus.

N-glycosylation of ATF6beta is essential for its proteolytic cleavage and transcriptional repressor function to ATF6alpha. Guan D, *et al.* J Cell Biochem, 2009 Nov 1. PMID: 19693772.

Opposing roles for ATF6alpha and ATF6beta in endoplasmic reticulum stress response gene induction. Thuerauf DJ, Morrison L, Glembotski CC. J Biol Chem. 2004 May 14; 279(20): 21078-84. The endoplasmic reticulum (ER) transmembrane proteins, ATF6alpha and ATF6beta, are cleaved in response to ER stress, which can be induced by tunicamycin. The resulting N-terminal fragments of both ATF6 isoforms, which have conserved basic leucine-zipper and DNA binding domains but divergent transcriptional activation domains, translocate to the nucleus where they bind to ER stress-response elements (ERSE) in ER stress-response genes (ERSRG), such as GRP78. Although it is known that ATF6alpha is a potent activator of ERSRGs, the transcriptional potency and functions of ATF6beta remain to be explored. Accordingly, N-terminal fragments of each ATF6 isoform (N-ATF6alpha and N-ATF6beta) were overexpressed in HeLa cells and the effects on GRP78 induction were assessed. When expressed at similar levels, N-ATF6alpha conferred approximately 200-fold greater GRP78 promoter activation than N-ATF6beta. Because ER stress activates nuclear translocation of both ATF6alpha and beta and because both bind to ERSEs, the effect of co-expressing them on GRP78 induction was assessed. Surprisingly, N-ATF6beta inhibited N-ATF6alpha-mediated GRP78 promoter activation in a dominant-negative manner. Moreover, N-ATF6beta inhibited TN-mediated GRP78 promoter activation, which requires endogenous ATF6alpha. ATF6 isoform-specific small inhibitory RNAs were used to show that, as expected, endogenous ATF6alpha was required for maximal ERSRG induction; however, endogenous ATF6beta moderated ERSRG induction. These results indicate that compared with ATF6alpha, ATF6beta is a very poor activator of ERSRG induction and it represses ATF6alpha-mediated ERSRG induction. Thus, ATF6beta may serve as a transcriptional repressor functioning in part to regulate the strength and duration of ATF6alpha-mediated ERSRG activation during the ER stress response.

The anti-apoptotic role of the unfolded protein response in Bcr-Abl-positive leukemia cells. Tanimura A, Yujiri T, Tanaka Y, Hatanaka M, Mitani N, Nakamura Y, Mori K, Tanizawa Y. Leuk Res. 2009 Jul;33(7):924-8. Epub 2009 Feb 23. To define the role of the unfolded protein response (UPR) in leukemogenesis, we investigated UPR activation in the cells expressing the representative oncogene Bcr-Abl (B-A). The expression of UPR-related proteins and mRNAs, namely, X-box-binding protein (XBP1) and glucose-regulated protein 78 (GRP78) was increased in B-A. UPR inhibition using inositol-requiring enzyme 1alpha (IRE1alpha) or activating transcription factor 6 (ATF6) dominant-negative mutants diminished the ability of Bcr-Abl to protect the cells from etoposide- and imatinib-induced apoptosis. We also noted that the expression of UPR-related genes in primary leukemia cells from Philadelphia chromosome (Ph)-positive cells was higher than that in the control by quantitative RT-PCR assay. Thus, our results suggested that UPR is a downstream target of Bcr-Abl and plays an anti-apoptotic role in Ph-positive leukemia cells.

Identification of the G13 (cAMP-response-element-binding protein-related protein) gene product related to activating transcription factor 6 as a transcriptional activator of the mammalian unfolded protein response. Haze K, Okada T, Yoshida H, Yanagi H, Yura T, Negishi M, Mori K. Biochem J. 2001 Apr 1; 355(Pt 1): 19-28.

Gene: ATG16L1 (ATG16 autophagy related 16-like 1 (S. cerevisiae))

CCDS ID: 2502.2|Hs37.1|chr2

Amino acids: 131--143, BH3-like sequence: IAECLQTISDLET

CCDS ID: 2503.2|Hs37.1|chr2

Amino acids: 131--143, BH3-like sequence: IAECLQTISDLET

Helix containing: HHHHHHHHHHHHH

Also known as: IBD10; WDR30; APG16L; ATG16A; ATG16L; FLJ00045; FLJ10035; FLJ10828; FLJ22677

Autophagy gene, interacts with Nemo (FLJ22677)

BH3 motif evolutionarily conserved except for chicken and zebrafish

The protein encoded by this gene is part of a large protein complex that is necessary for autophagy, the major process by which intracellular components are targeted to lysosomes for degradation. Defects in this gene are a cause of susceptibility to inflammatory bowel disease type 10 (IBD10) Crohn's disease. Several transcript variants encoding different isoforms have been found for this gene.

Network organization of the human autophagy system. Behrends C, Sowa ME, Gygi SP, Harper JW. Nature. 2010 Jul 1; 466(7302): 68-76. PMID: 20562859

A physical and functional map of the human TNF-alpha/NF-kappa B signal transduction pathway. Bouwmeester T *et al.* Nat Cell Biol. 2004 Feb;6(2):97-105. (**FLJ22677**)

Plasma membrane contributes to the formation of pre-autophagosomal structures. Ravikumar B, Moreau K, Jahreiss L, Puri C, Rubinsztein DC. Nat Cell Biol. 2010 Aug; 12(8): 747-57.

Golgi-resident small GTPase Rab33B interacts with Atg16L and modulates autophagosome formation. Itoh T, Fujita N, Kanno E, Yamamoto A, Yoshimori T, Fukuda M. Mol Biol Cell. 2008 Jul; 19(7): 2916-25. Epub 2008 Apr 30.

See all (79) citations in PubMed

Gene: ATP6AP2 (ATPase, H+ transporting, lysosomal accessory protein 2)

CCDS ID: 14252.1|Hs37.1|chrX

Amino acids: 240--252, BH3-like sequence: LVDALQKFADDMY

Helix containing: HHHHHHHHHHHHH

Also known as: M8-9; MRXE; XMRE; HT028; ELDF10; ATP6IP2; MSTP009; APT6M8-9; ATP6M8-9; MGC99577;

This gene encodes a protein that is associated with adenosine triphosphatases (ATPases). Proton-translocating ATPases have fundamental roles in energy conservation, secondary active transport, acidification of intracellular compartments, and cellular pH homeostasis. There are three classes of ATPases- F, P, and V. The vacuolar (V-type) ATPases have a transmembrane

proton-conducting sector and an extramembrane catalytic sector. The encoded protein has been found associated with the transmembrane sector of the V-type ATPases.

Prorenin engages the (pro)renin (ATP6AP2) receptor like renin and both ligand activities are unopposed by aliskiren. Schefe JH, Neumann C, Goebel M, Danser J, Kirsch S, Gust R, Kintscher U, Unger T, Funke-Kaiser H. J Hypertens. 2008 Sep;26(9):1787-94. This is the first report demonstrating equal ligand activities of both, renin and prorenin, on the (pro)renin receptor - promyelocytic zinc finger protein-phosphatidylinositol-3 kinase-p85alpha pathway.

See all (23) citations in PubMed

Gene: BACH2 (BTB and CNC homology 1, basic leucine zipper transcription factor 2)

CCDS ID: 5026.1|Hs37.1|chr6

Amino acids: 287--299, BH3-like sequence: ESITLCLSGDEPD

Helix containing: ----------

BACH2 may be partially responsible for regulation of BCL2 expression from the t(14;18)(q21;q34) translocation

Title: High levels of BACH2 associated with lower levels of BCL2 transcript abundance in t(14;18)(q21;q34) translocation positive non-Hodgkin's lymphoma.

reporter assays demonstrated that Bach2 and Bcl6 cooperate to repress Prdm1 through its intron enhancer region

Gene: BTAF1 (BTAF1 RNA polymerase II, B-TFIID transcription factor-associated)

CCDS ID: 7419.1|Hs37.1|chr10

Amino acids: 1188--1200, BH3-like sequence: VVPVLGRMSDQTD

Helix containing: ----------H

Gene: C9orf79

CCDS ID: 6676.1|Hs37.1|chr9

Amino acids: 1167--1179, BH3-like sequence: PCALLWKGGDSPG

Helix containing: ----------

Gene: C19orf28

CCDS ID: 42463.1|Hs37.1|chr19

Amino acids: 383--395, BH3-like sequence: LVTSLAMTADLIG

CCDS ID: 42464.1|Hs37.1|chr19

Amino acids: 383--395, BH3-like sequence: LVTSLAMTADLIG

CCDS ID: 42465.1|Hs37.1|chr19

Amino acids: 383--395, BH3-like sequence: LVTSLAMTADLIG

Helix containing: HHHHHHHHHHHH-

Also known as: PP3501; MGC20700;

MelB domain; Na+/melibiose symporter and related transporters [Carbohydrate transport and metabolism]

Gene: CACNA1G (calcium channel, voltage-dependent, T type, alpha 1G subunit)

CCDS ID: 45738.1|Hs37.1|chr17

Amino acids: 1492--1504, BH3-like sequence: TGPCLVIPADSGG

Helix containing: ----------

Voltage-activated calcium channels can be distinguished based on their voltage-dependence, deactivation, and single-channel conductance. See MIM 601011. Low-voltage-activated calcium channels are referred to as 'T' type because their currents are both transient, owing to fast inactivation, and tiny, owing to small conductance. T-type channels are thought to be involved in pacemaker activity, low-threshold calcium spikes, neuronal oscillations and resonance, and rebound burst firing.

Gene: CASP3

CCDS ID: 3836.1|Hs37.1|chr4

Amino acids: 219--231, BH3-like sequence: LCAMLKQYADKLE

Helix containing: HHHHHHHHHHHHH

Gene: CCDC47 (coiled-coil domain containing 47)

CCDS ID: 11643.1|Hs37.1|chr17

Amino acids: 317--329, BH3-like sequence: MVHFLTHYADKIE

Helix containing: HHHHHHHHH-----

Network organization of the human autophagy system. Behrends C, *et al*. Nature, 2010 Jul 1. PMID: 20562859.

Gene: CHD2 (chromodomain helicase DNA binding protein 2)

CCDS ID: 10374.2|Hs37.1|chr15

Amino acids: 1513--1525, BH3-like sequence: IAECLKAYSDQEH

Helix containing: HHHHHHH---HHH

The CHD family of proteins is characterized by the presence of chromo (chromatin organization modifier) domains and SNF2-related helicase/ATPase domains. CHD genes alter gene expression possibly by modification of chromatin structure thus altering access of the transcriptional apparatus to its chromosomal DNA template.

Role of chromodomain helicase DNA-binding protein 2 in DNA damage response signaling and tumorigenesis. Nagarajan P, Onami TM, Rajagopalan S, Kania S, Donnell R, Venkatachalam S. Oncogene. 2009 Feb 26; 28(8): 1053-62. Epub 2009 Jan 12.

Gene: CNTNAP3 (contactin associated protein-like 3)

CCDS ID: 6616.1|Hs37.1|chr9

Amino acids: 512--524, BH3-like sequence: GCLRLITIGDKAV

Helix containing: ----------

The protein encoded by this gene belongs to the NCP family of cell-recognition molecules. This family represents a distinct subgroup of the neurexins. NCP proteins mediate neuron-glial interactions in vertebrates and glial-glial contact in invertebrates

Gene: CR1L (complement component (3b/4b) receptor 1-like)

CCDS ID: 44310.1|Hs37.1|chr1

Amino acids: 24--36, BH3-like sequence: LVLLLSSFSDQCN

Helix containing: HHHHHH-------

Gene: DCLK1

CCDS ID: 9354.1|Hs37.1|chr13

Amino acids: 463--475, BH3-like sequence: LVMELVKGGDLFD

Helix containing: ----------

Also known as CL1; DCLK; CLICK1; DCDC3A; DCAMKL1; KIAA0369; DCLK1

BH3 motif conserved in chimp, dog, mouse and chicken

This gene encodes a member of the protein kinase superfamily and the doublecortin family. The protein encoded by this gene contains two N-terminal doublecortin domains, which bind microtubules and regulate microtubule polymerization, a C-terminal serine/threonine protein kinase domain, which shows substantial homology to Ca2+/calmodulin-dependent protein kinase, and a serine/proline-rich domain in between the doublecortin and the protein kinase domains, which mediates multiple protein-protein interactions. The microtubule-polymerizing activity of the encoded protein is independent of its protein kinase activity. The encoded protein is involved in several different cellular processes, including neuronal migration, retrograde transport, neuronal apoptosis and neurogenesis. This gene is up-regulated by brain-derived neurotrophic factor and associated with memory and general cognitive abilities. Multiple transcript variants generated by two alternative promoter usage and alternative splicing have been reported, but the full-length nature and biological validity of some variants have not been defined. These variants encode different isoforms, which are differentially expressed and have different kinase activities. (See DCLK2 below)

Silencing of the microtubule-associated proteins doublecortin-like and doublecortin-like kinase-long induces apoptosis in neuroblastoma cells. Verissimo CS, *et al.* Endocr Relat Cancer, 2010 Jun. PMID: 20228126.

Gene: DCLK2 (doublecortin-like kinase 2)

CCDS ID: 34076.1|Hs37.1|chr4

Amino acids: 467--479, BH3-like sequence: LVMELVKGGDLFD

CCDS ID: 47142.1|Hs37.1|chr4

Amino acids: 466--478, BH3-like sequence: LVMELVKGGDLFD

Helix containing: HHHHHH-------

This gene encodes a member of the protein kinase superfamily and the doublecortin family. The protein encoded by this gene contains two N-terminal doublecortin domains, which bind microtubules and regulate microtubule polymerization, a C-terminal serine/threonine protein kinase domain, which shows substantial homology to Ca^{2+}/calmodulin-dependent protein kinase, and a serine/proline-rich domain in between the doublecortin and the protein kinase domains, which mediates multiple protein-protein interactions. The microtubule-polymerizing activity of the encoded protein is independent of its protein kinase activity. (See DCLK1 above)

Gene: **DFNA5 (deafness, autosomal dominant 5) isoform b**

CCDS ID: 5389.1|Hs37.1|chr7

Amino acids: 416--428, BH3-like sequence: LCHLLRALSDDGV

CCDS ID: 47563.1|Hs37.1|chr7

Amino acids: 252--264, BH3-like sequence: LCHLLRALSDDGV

Helix containing: HHHHHHHHH-----

Also known as ICERE-1 (inversely correlated with estrogen receptor expression)

BH3 motif conserved in chimp (mouse and rat have conservative changes that match consensus)

Apoptosis in acquired and genetic hearing impairment: The programmed death of the hair cell. Op de Beeck K, Schacht J, Van Camp G. Hear Res. 2011 Jul 18. [Epub ahead of print] Apoptosis is an important physiological process. Normally, a healthy cell maintains a delicate balance between pro- and anti-apoptotic factors, allowing it to live and proliferate. It is thus not surprising that disturbance of this delicate balance may result in disease. It is a well known fact that apoptosis also contributes to several acquired forms of hearing impairment. Noise-induced hearing loss is the result of prolonged exposure to excessive noise, triggering apoptosis in terminally differentiated sensory hair cells. Moreover, hearing loss caused by the use of therapeutic drugs such as aminoglycoside antibiotics and cisplatin potentially may result in the activation of apoptosis in sensory hair cells leading to hearing loss due to the "ototoxicity" of the drugs. Finally, apoptosis is a key contributor to the development of presbycusis, age-related hearing loss. Recently, several mutations in apoptosis genes were identified as the cause of monogenic hearing impairment. These genes are TJP2, **DFNA5** and MSRB3. This implies that apoptosis not only contributes to the pathology of acquired forms of hearing impairment, but also to genetic hearing impairment as well. We believe that these genes constitute a

new functional class within the hearing loss field. Here, the contribution of apoptosis in the pathology of both acquired and genetic hearing impairment is reviewed.

The DFNA5 gene, responsible for hearing loss and involved in cancer, encodes a novel apoptosis-inducing protein. Eur J Hum Genet. 2011 Apr 27. [Epub ahead of print] de Beeck KO, Van Camp G, Thys S, Cools N, Callebaut I, Vrijens K, Van Nassauw L, Van Tendeloo VF, Timmermans JP, Van Laer L. DFNA5 was first identified as a gene causing autosomal dominant hearing loss (HL). Different mutations have been found, all exerting a highly specific gain-of-function effect, in which skipping of exon 8 causes the HL. Later reports revealed the involvement of the gene in different types of cancer. Epigenetic silencing of DFNA5 in a large percentage of gastric, colorectal and breast tumors and p53-dependent transcriptional activity have been reported, concluding that DFNA5 acts as a tumor suppressor gene in different frequent types of cancer. Despite these data, the molecular function of DFNA5 has not been investigated properly. Previous transfection studies with mutant DFNA5 in yeast and in mammalian cells showed a toxic effect of the mutant protein, which was not seen after transfection of the wild-type protein. Here, we demonstrate that DFNA5 is composed of two domains, separated by a hinge region. The first region induces apoptosis when transfected in HEK293T cells, **the second region masks and probably regulates this apoptosis inducing capability**. Moreover, the involvement of DFNA5 in apoptosis-related pathways in a physiological setting was demonstrated through gene expression microarray analysis using Dfna5 knockout mice. In view of its important role in carcinogenesis, this finding is expected to lead to new insights on the role of apoptosis in many types of cancer. In addition, it provides a new line of evidence supporting an important role for apoptosis in monogenic and complex forms of HL.European Journal of Human Genetics advance online publication, 27 April 2011; doi:10.1038/ejhg.2011.63.

In CEM cells the autosomal deafness gene dfna5 is regulated by glucocorticoids and forskolin. J Steroid Biochem Mol Biol. 2007 Oct;107(1-2):15-21. Epub 2007 May 24. Webb MS, Miller AL, Thompson EB. Certain mutations of the dfna5 gene result in a form of autosomal deafness that holds special interest because its phenotype resembles the hearing loss often seen during aging. Little is known of the function or regulation of dfna5 or its encoded protein. However dfna5 has recently been shown to be induced by p53. It also is epigenetically repressed in gastric cancer. We have discovered that dfna5 can be induced by glucocorticoids (GCs) and that this regulation is influenced by crosstalk with the protein kinase A (PKA) system. We show that GCs induce dfna5 mRNA and that its expression appears to be repressed in the basal state. Induction of dfna5 mRNA correlates with GC-dependent apoptosis of CEM cells, though dfna5 expression alone is not sufficient for apoptosis.

DFNA5 (ICERE-1) contributes to acquired etoposide resistance in melanoma cells. FEBS Lett. 2001 Apr 6;494(1-2):54-9. Lage H, Helmbach H, Grottke C, Dietel M, Schadendorf D. Resistance to drug treatment is a common observation in malignant melanoma. In order to analyze alterations in mRNA expression profiles associated with drug resistance in melanoma cells we previously established a panel of various drug-resistant cell variants derived from the human melanoma line MeWo and compared the mRNA expression profiles by a differential display technique. By that approach it could be demonstrated that the expression level of a mRNA encoded by a gene found to be mutated in non-syndromic hearing impairment, DFNA5 (ICERE-1), was distinctly decreased in the 33-fold etoposide-resistant melanoma cell line MeWo ETO 1. To evaluate the hypothesis that a decrease in DFNA5 mRNA expression level contributes to the acquired etoposide resistance phenotype exhibited by MeWo ETO 1 cells, this drug-resistant line was stably transfected with the DFNA5-encoding cDNA. Transfected clones showed a 30-35% reduced etoposide susceptibility by comparing the IC(25), IC(50) and IC(75) values of these clones with those displayed by the non-transfected, etoposide-resistant melanoma cell line MeWo ETO 1 and controls. Furthermore, etoposide exposure of stable DFNA5 transfectants resulted in an increase of caspase-3-mediated apoptotic events in DFNA5-transfected clones in comparison to MeWo ETO 1 cells and controls. The data therefore demonstrate that a decrease in DNFA5 mRNA expression level is associated with an increased etoposide resistance in melanoma cells due to an elevated cellular susceptibility to trigger a caspase-3-depending signal pathway leading to programmed cell death.

The potential role of DFNA5, a hearing impairment gene, in p53-mediated cellular response to DNA damage. J Hum Genet. 2006; 51(8): 652-64. Epub 2006 Aug 2. Masuda Y, Futamura M, Kamino H, Nakamura Y, Kitamura N, Ohnishi S, Miyamoto Y, Ichikawa H, Ohta T, Ohki M, Kiyono T, Egami H, Baba H, Arakawa H. The tumor suppressor p53 plays a crucial role in the cellular response to DNA damage by transcriptional activation of numerous downstream genes. Although a considerable number of p53 target genes have been reported, the precise mechanism of p53-regulated tumor suppression still remains to be elucidated. Here, we report a novel role of the DFNA5 gene in p53-mediated etoposide-induced cell death. The DFNA5 gene has been previously reported to be responsible for autosomal-dominant, nonsyndromic hearing impairment. The expression of the DFNA5 gene was strongly induced by exogenous and endogenous p53. The chromatin immunoprecipitation assay indicated that a potential p53-binding sequence is located in intron 1 of the DFNA5 gene. Furthermore, the reporter gene assay revealed that the sequence displays p53-dependent transcriptional activity. The ectopic expression of DFNA5 enhanced etoposide-induced cell death in the presence of p53; however, it was inhibited in the absence of p53. Finally, the expression of DFNA5 mRNA was remarkably induced by gamma-ray irradiation in the colon of p53(+/+) mice but not in that of p53(-/-) mice. These results suggest that DFNA5 plays a role in the p53-regulated cellular response to genotoxic stress probably by cooperating with p53.

Identification of DFNA5 as a target of epigenetic inactivation in gastric cancer. Cancer Sci. 2007 Jan; 98(1):88-95.

Akino K, Toyota M, Suzuki H, Imai T, Maruyama R, Kusano M, Nishikawa N, Watanabe Y, Sasaki Y, Abe T, Yamamoto E, Tarasawa I, Sonoda T, Mori M, Imai K, Shinomura Y, Tokino T. Epigenetic gene inactivation plays a key role in the development of various types of cancer. Using methylated CpG island amplification coupled with representational difference analysis to identify genes inactivated by DNA methylation in gastric cancer, we identified seven DNA fragments corresponding to the 5' CpG islands of the affected genes. One of the clones recovered was identical to the 5' flanking region of DFNA5, a gene previously shown to be associated with deafness and induced by DNA damage. Further analysis revealed that DFNA5 is expressed in normal tissues but is down-regulated in gastric cancer cell lines due to methylation of the region around its transcription start site. Treating gastric cancer cells that lacked DFNA5 expression with a methyltransferase inhibitor, 5-aza-2'-deoxycytidine, restored the gene's expression. Methylation of DFNA5 was detected in 50% of primary gastric tumors, and was correlated with positivity for Epstein-Barr virus and the absence of metastasis. Moreover, introduction of exogenous DFNA5 into silenced cells suppressed colony formation. Taken together, these data suggest that the silencing of DFNA5 occurs frequently in gastric cancer and may play a key role in development and progression of the disease.

Characterization of a gene that is inversely correlated with estrogen receptor expression (ICERE-1) in breast carcinomas. Eur J Biochem. 1998 Feb 15; 252(1): 169-77.

Thompson DA, Weigel RJ. Differential display was used to compare patterns of gene expression in two estrogen receptor (ER)-positive breast carcinoma cell lines (MCF7 and T-47D) and two ER-negative breast carcinoma cell lines (MDA-MB-231 and HBL-100). A 377-bp fragment was identified that was overexpressed in the ER-negative cell lines. Sequence analysis of this clone and comparison with the GenBank/EMBL databases indicated that it did not match any genes published previously. The expression pattern of this gene was inversely correlated with the expression of ER and has been termed ICERE-1 (inversely correlated with estrogen receptor expression). A longer clone of ICERE-1 was isolated from a MDA-MB-231 cDNA library and sequence analysis indicated that this 2168-bp cDNA contained an ORF encoding a protein of 234 amino acids that bears little similarity with any previously described protein sequence. Northern blot analysis of a panel of breast cancer cell lines demonstrated that an ICERE-1 mRNA of approximately 2.2 kb was abundantly expressed in the ER-negative breast carcinoma cell lines, MDA-MB-231 and HBL-100, and the ER-negative cell lines. HEC-1-B, HeLa, and 293. Expression of ICERE-1 was absent or minimal in the ER-positive breast carcinoma cell lines MCF7, T-47D, MDA-MB-361, ZR-75-1, BT-474 and BT-20. Reverse transcription/PCR was used to examine ICERE-1 expression in 29 primary breast carcinomas, 15 of which had been designated as ER positive and 14 as ER negative by immunohistochemistry. The expression level of ICERE-1 was significantly lower ($P < 0.001$) in the ER-positive tumors compared with the ER-negative tumors. The pattern of expression of ICERE-1 indicates that this gene may be involved in tumor biology specific to hormonally unresponsive breast cancers.

Gene: DNAH2 (dynein, axonemal, heavy chain 2)

CCDS ID: 32551.1|Hs37.1|chr17

Amino acids: 3463--3475, BH3-like sequence: GGRLLMRIGDKEV

Helix containing: H----------

Gene: DNAH10 (dynein, axonemal, heavy chain 10)

CCDS ID: 9255.2|Hs37.1|chr12

Amino acids: 4440--4452, BH3-like sequence: MGVGLVFEADLFT

Helix containing: ----------HHH

Dyneins are microtubule-associated motor protein complexes composed of several heavy, light, and intermediate chains. The axonemal dyneins, found in cilia and flagella, are components of the outer and inner dynein arms attached to the peripheral microtubule doublets. DNAH10 is an inner arm dynein heavy chain

Gene: DYNC1H1 (dynein, cytoplasmic 1, heavy chain 1)

CCDS ID: 9966.1|Hs37.1|chr14

Amino acids: 2655--2667, BH3-like sequence: LGKWLVLFCDEIN

Helix containing: ----------

Gene: DYNC2H1 (dynein, cytoplasmic 2, heavy chain 1)

CCDS ID: 44717.1|Hs37.1|chr11

Amino acids: 2561--2573, BH3-like sequence: GSDILDNMSDSFY

Helix containing: -HHHHH-------

Gene: FBXO30

CCDS ID: 5208.1|Hs37.1|chr6

Amino acids: 427--439, BH3-like sequence: TAALLFCLGDSPG

Helix containing: HHHHHHHHH-----

Results suggest that D6S1581 is highly associated with nasopharyngeal carcinoma, and there may be one or more NPC associated genes near D6S1581, including FBXO30. Title: [Studies on the relationship between D6S1581, a high frequency allele imbalance locus, and genetic susceptibility to nasopharyngeal carcinoma].

Gene: FGD2 (FYVE, RhoGEF and PH domain containing 2) (related to MCF2)

CCDS ID: 4829.1|Hs37.1|chr6

Amino acids: 547--559, BH3-like sequence: MCSFLQLIGDKWG

Helix containing: HHHHHHHHHH----

FYVE, RhoGEF and PH domain containing 2

Also known as ZFYVE4; FLJ00048; FLJ40929; MGC71330

FYVE, RhoGEF and PH domain containing 2

double zinc finger (FYVE domain)

BH3 motif evolutionarily conserved in chimp; dog, mouse and cow have conservative changes that match consensus

Homology to MCF2/DBL (NME1 interacts with DBL)

FGD2, a CDC42-specific exchange factor expressed by antigen-presenting cells, localizes to early endosomes and active membrane ruffles. J Biol Chem. 2008 Dec 5; 283(49): 34002-12. Epub 2008 Oct 6. Huber C, Mårtensson A, Bokoch GM, Nemazee D, Gavin AL. Members of the Fgd (faciogenital dysplasia) gene family encode a group of critical guanine nucleotide exchange factors (GEFs), which, by specifically activating Cdc42, control cytoskeleton-dependent membrane rearrangements. In its first characterization, we find that FGD2 is expressed in antigen-presenting cells, including B lymphocytes, macrophages, and dendritic cells. In the B lymphocyte lineage, FGD2 levels change with developmental stage. In both mature splenic B cells and immature bone marrow B cells, FGD2 expression is suppressed upon activation through the B cell antigen receptor. FGD2 has a complex intracellular localization, with concentrations found in membrane ruffles and early endosomes. Although endosomal localization of FGD2 is dependent on a conserved FYVE domain, its C-terminal pleckstrin homology domain mediates recruitment to membrane ruffles. FGD2 overexpression promotes the activation of Cdc42 and leads to elevated JNK1 activity in a Cdc42- but not Rac1-dependent fashion. These findings are consistent with a role of FGD2 in leukocyte signaling and vesicle trafficking in cells specialized to present antigen in the immune system.

Gene: GPR126 (G protein-coupled receptor 126)

CCDS ID: 47489.1|Hs37.1|chr6

Amino acids: 364--376, BH3-like sequence: PAAELASCADLGT

CCDS ID: 47490.1|Hs37.1|chr6

Amino acids: 364--376, BH3-like sequence: PAAELASCADLGT

CCDS ID: 47491.1|Hs37.1|chr6

Amino acids: 364--376, BH3-like sequence: PAAELASCADLGT

Helix containing: -HHHHHHHHHH--

Gene: GREB1 (growth regulation by estrogen in breast cancer 1)

CCDS ID: 42655.1|Hs37.1|chr2

Amino acids: 1871--1883, BH3-like sequence: FSGLLLYLCDSFV

Helix containing: HHHHHHHHHHHHH

Also known as: KIAA057

This gene is an estrogen-responsive gene that is an early response gene in the estrogen receptor-regulated pathway. It is thought to play an important role in hormone-responsive tissues and cancer.

GREB1 is a novel androgen-regulated gene required for prostate cancer growth. Rae JM, Johnson MD, Cordero KE, Scheys JO, Larios JM, Gottardis MM, Pienta KJ, Lippman ME. Prostate. 2006 Jun 1;66(8):886-94.

GREB 1 is a critical regulator of hormone dependent breast cancer growth. Rae JM, Johnson MD, Scheys JO, Cordero KE, Larios JM, Lippman ME. Breast Cancer Res Treat. 2005 Jul;92(2):141-9.

See all (12) citations in PubMed

Gene: GREB1L (growth regulation by estrogen in breast cancer-like)

CCDS ID: 45836.1|Hs37.1|chr18

Amino acids: 1178--1190, BH3-like sequence: AGETLKQECDSLG

Helix containing: --HHHHHHHHHH--

Amino acids: 1846--1858, BH3-like sequence: FSGLLLYLCDSFV

Helix containing: HHHHHHHHHHHHH-

Also known as C18orf6; KIAA1772;

Transcriptome characterization elucidates signaling networks that control human ES cell growth and differentiation. Brandenberger R, *et al.* Nat Biotechnol, 2004 Jun. PMID: 15146197. Human embryonic stem (hES) cells hold promise for generating an unlimited supply of cells for replacement therapies. To characterize hES cells at the molecular level, we obtained 148,453 expressed sequence tags (ESTs) from undifferentiated hES cells and three differentiated derivative subpopulations. Over 32,000 different transcripts expressed in hES cells were identified, of which more than 16,000 do not match closely any gene in the UniGene public database. Queries to this EST database revealed 532 significantly upregulated and 140 significantly downregulated genes in undifferentiated hES cells. These data highlight changes in the transcriptional network that occur when hES cells differentiate. Among the differentially regulated genes are several components of signaling pathways and transcriptional regulators that likely play key roles in hES cell growth and differentiation. The genomic data presented here may facilitate the derivation of clinically useful cell types from hES cells.

Gene: HDAC3

CCDS ID: 4264.1|Hs37.1|chr5

Amino acids: 250--262, BH3-like sequence: TCIVLQCGADSLG

Helix containing: ----------

Gene: HEATR5B (HEAT repeat containing 5B)

CCDS ID: 33181.1|Hs37.1|chr2

Amino acids: 1692--1704, BH3-like sequence: ACTVLGEGGDSGG

Helix containing: HHHHH--------

Gene: HECTD1 (HECT domain containing 1)

CCDS ID: 41939.1|Hs37.1|chr14

Amino acids: 475--487, BH3-like sequence: VVAILQSPGDWMC

Helix containing: ----------

Defining the human deubiquitinating enzyme interaction landscape. Sowa ME, Bennett EJ, Gygi SP, Harper JW. Cell. 2009 Jul 23;138(2):389-403. Epub 2009 Jul 16.

Proteomic, functional, and domain-based analysis of *in vivo* 14-3-3 binding proteins involved in cytoskeletal regulation and cellular organization. Jin J, Smith FD, Stark C, Wells CD, Fawcett JP, Kulkarni S, Metalnikov P, O'Donnell P, Taylor P, Taylor L, Zougman A, Woodgett JR, Langeberg LK, Scott JD, Pawson T. Curr Biol. 2004 Aug 24;14(16):1436-50.

Gene: HEXDC (hexosaminidase (glycosyl hydrolase family 20, catalytic domain) containing)

CCDS ID: 42402.1|Hs37.1|chr17

Amino acids: 139--151, BH3-like sequence: GAQRLHIGCDEVY

Helix containing: ----------

Mammalian cells contain a second nucleocytoplasmic hexosaminidase. Gutternigg M, *et al.* Biochem J, 2009 Apr 1. PMID: 19040401.

Gene: INTS8 (integrator complex subunit 8)

CCDS ID: 34925.1|Hs37.1|chr8

Amino acids: 308--320, BH3-like sequence: ACDVLVPSSDSTS

Helix containing: H----------

INTS8 is a subunit of the Integrator complex, which associates with the C-terminal domain of RNA polymerase II large subunit (POLR2A; MIM 180660) and mediates 3-prime end processing of small nuclear RNAs U1 (RNU1; MIM 180680) and U2 (RNU2; MIM 180690)

Gene: KDM5B (lysine (K)-specific demethylase 5B)

CCDS ID: 30974.1|Hs37.1|chr1

Amino acids: 1489--1501, BH3-like sequence: AVSCLQPEGDEVD

Helix containing: ----------

Histone demethylase JARID1B/KDM5B is a corepressor of TIEG1/KLF10. Kim J, *et al.* Biochem Biophys Res Commun, 2010 Oct 22. PMID: 20863814.

PARP-1 regulates chromatin structure and transcription through a KDM5B-dependent pathway. Krishnakumar R, *et al.* Mol Cell, 2010 Sep 10. PMID: 20832725.

A temporarily distinct subpopulation of slow-cycling melanoma cells is required for continuous tumor growth. Roesch A, *et al.* Cell, 2010 May 14. PMID: 20478252.

The flexible loop L1 of the H3K4 demethylase JARID1B ARID domain has a crucial role in DNA-binding activity. Yao W, *et al.* Biochem Biophys Res Commun, 2010 May 28. PMID: 20403335.

Overexpression of the JmjC histone demethylase KDM5B in human carcinogenesis: involvement in the proliferation of cancer cells through the E2F/RB pathway. Hayami S, *et al.* Mol Cancer, 2010 Mar 13. PMID: 20226085.

Gene: KIAA0174

CCDS ID: 10905.1|Hs37.1|chr16

Amino acids: 113--125, BH3-like sequence: EVAELKIVADQLC

Helix containing: HHHHHHHHHHHHH

Also known as: IST1; MGC117220

SPG20 protein spartin is recruited to midbodies by ESCRT-III protein Ist1 and participates in cytokinesis. Renvoisé B, *et al.* Mol Biol Cell, 2010 Oct 1. PMID: 20719964.

Calpain 7, a mammalian ortholog of yeast Cpl1/Rim13 and fungal PalB, is an atypical calpain that lacks a penta-EF-hand domain. Previously, we reported that a region containing a tandem repeat of microtubule-interacting and transport (MIT) domains in calpain 7 interacts with a subset of endosomal sorting complex required for transport (ESCRT)-III-related proteins, suggesting involvement of calpain 7 in the ESCRT system. Although yeast and fungal calpains are thought to be involved in alkaline adaptation via limited proteolysis of specific transcription factors, proteolytic activity of calpain 7 has not been demonstrated yet. In this study, we investigated the interaction between calpain 7 and a newly reported ESCRT-III family member, increased sodium tolerance-1 (IST1), which possesses two different types of MIT-interacting motifs (MIM1 and MIM2). We found that glutathione-S-transferase (GST)-fused tandem MIT domains of calpain 7 (calpain 7MIT) pulled down FLAG-tagged IST1 expressed in HEK293T cells. Coimmunoprecipitation assays with various deletion or point mutants of epitope-tagged calpain 7 and IST1 revealed that both repetitive MIT domains and MIMs are required for efficient interaction. Direct MIT-MIM binding was confirmed by a pulldown experiment with GST-fused IST1 MIM and purified recombinant calpain 7MIT. Furthermore, we found that the GST-MIM protein enhances the autolysis of purified Strep-tagged monomeric green fluorescent protein (mGFP)-fused calpain 7 (mGFP-calpain 7-Strep). The autolysis was almost completely abolished by 10 mmN-ethylmaleimide but only partially inhibited by 1 mm leupeptin or E-64. The putative catalytic Cys290-substituted mutant (mGFP-calpain 7(C290S)-Strep) showed no autolytic activity. These results demonstrate for the first time that human calpain 7 is proteolytically active, and imply that calpain 7 is activated in the ESCRT system.

See all (17) citations in PubMed

Gene: KIAA1210

CCDS ID: 48156.1|Hs37.1|chrX

Amino acids: 141--153, BH3-like sequence: MAESLSEISDSLD

Helix containing: HHHHHHHHHH--HH

Gene: LAMA5 (laminin, alpha 5)

CCDS ID: 33502.1|Hs37.1|chr20

Amino acids: 591--603, BH3-like sequence: PAGTLPEGCDEAG

Helix containing: --------HHHHH

Gene: LRRC52 (leucine rich repeat containing 52)

CCDS ID: 30930.1|Hs37.1|chr1

Amino acids: 69--81, BH3-like sequence: PAMHLGLLSDLVY

Helix containing: HHHHHHHH-----

Gene: MCF2 [MCF.2 cell line derived transforming sequence (also known as DBL oncogene; ARHGEF21)]

CCDS ID: 14667.1|Hs37.1|chrX

Amino acids: 57--69, BH3-like sequence: PVVMLSSVSDLLT

CCDS ID: 48175.1|Hs37.1|chrX

Amino acids: 117--129, BH3-like sequence: PVVMLSSVSDLLT

Helix containing: -------HHHHHH

Linked to p75NTR, NME1 (NM23-H1 is related to NME3); FGD2 is related to DBL

BH3 motif evolutionarily conserved except for zebrafish

The oncogenic protein encoded by this gene is a guanine nucleotide exchange factor (GEF) that exerts control over some members of the Rho family of small GTPases. Several transcript variants encoding different isoforms have been found for this gene. These isoforms exhibit different expression patterns and varying levels of GEF activity.

The suppressor of metastasis Nm23-H1 interacts with the Cdc42 Rho family member and the pleckstrin homology domain of oncoprotein Dbl-1 to suppress cell migration. Murakami M, *et al.* Cancer Biol Ther, 2008 May. PMID: 18728402.

Nm23-H1 modulates the activity of the guanine exchange factor Dbl-1. Murakami M, *et al.* Int J Cancer, 2008 Aug 1. PMID: 18470881.

Identification of a novel blocker of IkappaBalpha kinase activation that enhances apoptosis and inhibits proliferation and invasion by suppressing nuclear factor-kappaB. Sung B, Pandey MK, Nakajima Y, Nishida H, Konishi T, Chaturvedi MM, Aggarwal BB. Mol Cancer Ther. 2008 Jan;7(1):191-201. 3,4-dihydroxybenzalacetone (DBL) is a polyphenol derived from the medicinal plant Chaga [Inonotus obliquus (persoon) Pilat]. Although Chaga is used in Russia folk medicine to treat tumors, very little is known about its mechanism of action. Because most genes involved in inflammation, antiapoptosis, and cell proliferation are regulated by the transcription factor nuclear factor-kappaB (NF-kappaB), we postulated that DBL activity is mediated via modulation of the NF-kappaB activation pathway. We investigated the effects of DBL on NF-kappaB activation by electrophoretic mobility shift assay and on NF-kappaB-regulated gene expression by Western blot analysis. We found that DBL suppressed NF-kappaB activation by a wide variety of inflammatory agents, including tumor necrosis factor (TNF), interleukin-1beta, epidermal growth factor, okadaic acid, phorbol 12-myristate 13-acetate, and lipopolysaccharide. The suppression was not cell type specific and inhibited both inducible and constitutive NF-kappaB activation. DBL did not interfere with the binding of NF-kappaB to DNA but rather inhibited IkappaBalpha kinase activity, IkappaBalpha phosphorylation and degradation, p65 phosphorylation, and translocation. DBL also suppressed the expression of TNF-induced and NF-kappaB-regulated proliferative, antiapoptotic, and metastatic gene products. These effects correlated with enhancement of TNF-induced apoptosis and suppression of TNF-induced invasion. Together, our results indicate that DBL inhibits NF-kappaB activation and NF-kappaB-regulated gene expression, which may explain the ability of DBL to enhance apoptosis and inhibit invasion.

Gene: MEGF8 (multiple EGF-like-domains 8)

CCDS ID: 12604.2|Hs37.1|chr19

Amino acids: 784--796, BH3-like sequence: YSSCLGCLADQGC

Helix containing: -HHHHHHH-----

Also known as SBP1; EGFL4; C19orf49; FLJ22365; MGC120684; MGC138147

SP1 is present in reduced levels in several cancer types as compared with normal tissues, and lower levels are associated with poor clinical prognosis.

Gene: MEI1 (meiosis inhibitor 1)

CCDS ID: 46718.1|Hs37.1|chr22

Amino acids: 543--555, BH3-like sequence: FSEFLLSACDSLC

Helix containing: HHHHHHHHHHH--

Also known as MGC40042

Claimed to be expressed mainly in the testis although other expression seen in EST profiles;

Required for vertebrate meiosis

Putative transcription coactivator

Gene: MIPEP (Mitochondrial intermediate peptidase)

CCDS ID: 9303.1|Hs37.1|chr13

Amino acids: 111--123, BH3-like sequence: LSDSLCRVADLAD

Helix containing: --HHHHHHHHHHH

Also known as: MIP; HMIP

The product of this gene performs the final step in processing a specific class of nuclear-encoded proteins targeted to the mitochondrial matrix or inner membrane. This protein is primarily involved in the maturation of oxidative phosphorylation (OXPHOS)-related proteins. This gene may contribute to the functional effects of frataxin deficiency and the clinical manifestations of Friedreich ataxia.

See all (9) citations in PubMed

Gene: MN1 [meningioma (disrupted in balanced translocation) 1]

CCDS ID: 4027.1|Hs37.1|chr5

Amino acids: 592--604, BH3-like sequence: PVVRLPRACDSAE

CCDS ID: 47234.1|Hs37.1|chr5

Amino acids: 539--551, BH3-like sequence: PVVRLPRACDSAE

Helix containing: ----------HHH

Also known as MGCR; MGCR1; MGCR1-PEN; dJ353E16.2

Cell of Origin in AML: Susceptibility to MN1-Induced Transformation Is Regulated by the MEIS1/AbdB-like HOX Protein Complex. Heuser M *et al.* Cancer Cell. 2011 Jul 12;20(1):39-52.

1. high MN1 levels are important for the growth of leukemic cells, and that increased MN1 expression can synergize with MLL-ENL and probably other transforming fusion genes in leukemia induction.
2. Data demonstrate that MN1 overexpression correlates with progression from MDS to sAML and therefore might be involved in the pathogenesis of sAML
3. Down-regulation of CEBPA activity contributes to MN1-modulated proliferation and impaired myeloid differentiation of hematopoietic cells.
4. MN1 expression independently predicts outcome in cytogenetically normal acute myeloid leukemia
5. Observational study of gene-disease association. (HuGE Navigator)
6. Title: Coeliac disease-associated risk variants in TNFAIP3 and REL implicate altered NF-kappaB signalling.
7. MN1 and MN1-TEL interfere with the ATRA pathway and this might explain the differentiation block in leukemias in which these genes are involved.
8. role of MN1 in myeloid leukemia [review]
9. MN1 is a unique oncogene in hematopoiesis that both promotes proliferation/self-renewal and blocks differentiation, and may become useful as a predictive marker in AML treatment.
10. Title: MN1 overexpression induces acute myeloid leukemia in mice and predicts ATRA resistance in patients with AML.
11. MN1 overexpression is associated with the development of inv(16) acute myeloid leukemia

Gene: MS4A7 (membrane-spanning 4-domains, subfamily A, member 7)

CCDS ID: 7985.1|Hs37.1|chr11

Amino acids: 128--140, BH3-like sequence: AGAGLFLLADSMV

CCDS ID: 7986.1|Hs37.1|chr11

Amino acids: 83--95, BH3-like sequence: AGAGLFLLADSMV

Helix containing: HHHHHHHHHHHHH

Also known as: CFFM4; MS4A8; 4SPAN2; CD20L4; MGC22368

This gene encodes a member of the membrane-spanning 4A gene family, members of which are characterized by common structural features and similar intron/exon splice boundaries and display unique expression patterns in hematopoietic cells and nonlymphoid tissues. This family member is associated with mature cellular function in the monocytic lineage, and it may be a component of a receptor complex involved in signal transduction. This gene is localized to 11q12, in a cluster of other family members. At least four alternatively spliced transcript variants encoding two distinct isoforms have been observed.

See all (11) citations in PubMed

Gene: MYCBPAP (MYCBP associated protein)

CCDS ID: 32680.2|Hs37.1|chr17

Amino acids: 959--971, BH3-like sequence: LVTDLMVLADELS

Helix containing: HHHHHHHHHH---

Also known as AMAP1; AMAP-1; DKFZp434N1415

Interacts with Casp4 and MYCBP (AMY-1); conflicting reports as to whether it is testis-specific

IRES-mediated translational control of AMAP1 expression during differentiation of monocyte U937 cells. Miyata M, *et al.* Cell Cycle, 2008 Oct. PMID: 18843202. Global control of mRNA translation plays key roles in cell regulation, including growth, differentiation and apoptosis. Human monocyte-like U937 cells differentiate into macrophage-like cells upon 12-O-tetradecanoylphorbol-13-acetate (TPA) treatment, a process which is known to be accompanied with a large decrease in general protein synthesis. Here, we found that protein levels of AMAP1 (also called ASAP1 or DDEF1), a GTPase-activating protein for Arf GTPases, increase several fold during U937 cell differentiation. This increase was not accompanied with a notable increase in the AMAP1 gene transcript, nor seemed to be due to 5'-Cap-dependent mRNA translational activities in differentiated U937 cells. We identified the 5'-untranslated region (5'-UTR) of AMAP1 mRNA, and found that this 5'-UTR exhibits significant internal ribosome entry site (IRES)-dependent translational activity in differentiated U937 cells, but not in undifferentiated cells. Our results indicate that monocyte differentiation involves enhancement of IRES activity, by which protein levels of AMAP1 are primarily upregulated.

AMAP-1, a novel testis-specific AMY-1-binding protein, is differentially expressed during the course of spermatogenesis. Yukitake H, Furusawa M, Taira T, Iguchi-Ariga SM, Ariga H. Biochim Biophys Acta. 2002 Aug 19;1577(1):126-32. AMY-1 has been identified by us as a c-Myc-binding protein and was found to stimulate c-Myc transcription activity. AMY-1 was also found to be associated with AKAP84/149 in the mitochondria in somatic cells and sperm, suggesting that it plays a role in spermatogenesis. To access the molecular function of AMY-1, a two-hybrid screening of cDNAs encoding AMY-1-binding proteins was carried out with AMY-1 as a bait using a human testis cDNA library, and a clone encoding a novel protein, AMAP-1, was obtained. The amap-1 gene was mapped at human chromosome 17q21. AMY-1 was found to bind to and be colocalized with AMAP-1 in human 293T and HeLa cells. AMAP-1 was found to be specifically expressed in the testis and expressed post-meiotically in the testis, as was AMY-1. These results suggest that both AMAP-1 and AMY-1 play roles in spermatogenesis.

Gene: MYOM1 (myomesin 1, 185kDa)

CCDS ID: 45823.1|Hs37.1|chr18

Amino acids: 1056--1068, BH3-like sequence: GVISLNFECDKMT

CCDS ID: 45824.1|Hs37.1|chr18

Amino acids: 1152--1164, BH3-like sequence: GVISLNFECDKMT

Helix containing: ----------

The giant protein titin, together with its associated proteins, interconnects the major structure of sarcomeres, the M bands and Z discs. The C-terminal end of the titin string extends into the M line, where it binds tightly to M-band constituents of apparent molecular masses of 190 kD (myomesin 1) and 165 kD (myomesin 2). This protein, myomesin 1, like myomesin 2, titin, and other myofibrillar proteins contains structural modules with strong homology to either fibronectin type III (motif I) or immunoglobulin C2 (motif II) domains. Myomesin 1 and myomesin 2 each have a unique N-terminal region followed by 12 modules of motif I or motif II, in the arrangement II-II-I-I-I-I-I-II-II-II-II-II. The two proteins share 50% sequence identity in this repeat-containing region. The head structure formed by these 2 proteins on one end of the titin string extends into the center

of the M band. The integrating structure of the sarcomere arises from muscle-specific members of the superfamily of immunoglobulin-like proteins.

Gene: NEK11 (NIMA (never in mitosis gene a)- related kinase 11)

CCDS ID: 3069.1|Hs37.1|chr3

Amino acids: 178--190, BH3-like sequence: VSRLLMGSCDLAT

CCDS ID: 46915.1|Hs37.1|chr3

Amino acids: 178--190, BH3-like sequence: VSRLLMGSCDLAT

Helix containing: ---------HHHH

Gene: NEK11

This gene encodes a member of the never in mitosis gene A family of kinases. The encoded protein localizes to the nucleoli, and may function with NEK2A in the S-phase checkpoint. The encoded protein appears to play roles in DNA replication and response to genotoxic stress. Alternatively spliced transcript variants have been described.

NEK11: linking CHK1 and CDC25A in DNA damage checkpoint signaling. Sørensen CS, *et al.* Cell Cycle, 2010 Feb 1. PMID: 20090422.

NEK11 regulates CDC25A degradation and the IR-induced G2/M checkpoint. Melixetian M, *et al.* Nat Cell Biol, 2009 Oct. PMID: 19734889.

Gene: NRN1L (Neuritin 1-like)

CCDS ID: 10850.1|Hs37.1|chr16

Amino acids: 49--61, BH3-like sequence: FAECLIRLGDSMG

Helix containing: HHHHHHHHH-----

Also known as UNQ2446; MGC118990; MGC118993; **cpg15-2** (mouse)

Neurite growth and survival

cpg15 and cpg15-2 constitute a family of activity-regulated ligands expressed differentially in the nervous system to promote neurite growth and neuronal survival. Fujino T, Wu Z, Lin WC, Phillips MA, Nedivi E. J Comp Neurol. 2008 Apr 10;507(5):1831-45. Many ligands that affect nervous system development are members of gene families that function together to coordinate the assembly of complex neural circuits. cpg15/neuritin encodes an extracellular ligand that promotes neurite growth, neuronal survival, and synaptic maturation. Here we identify cpg15-2 as the only paralogue of cpg15 in the mouse and human genome. Both genes are expressed predominantly in the nervous system, where their expression is regulated by activity. cpg15-2 expression increases by more than twofold in response to kainate-induced seizures and nearly fourfold in the visual cortex in response to 24 hours of light exposure following dark adaptation. cpg15 and cpg15-2 diverge in their spatial and temporal expression profiles. cpg15-2 mRNA is most abundant in the retina and the olfactory bulb, as opposed to the cerebral cortex and the hippocampus for cpg15. In the retina, they differ in their cell-type specificity. cpg15 is expressed in retinal ganglion cells, whereas cpg15-2 is predominantly in bipolar cells. Developmentally, onset of cpg15-2 expression is delayed compared with cpg15 expression. CPG15-2 is glycosylphosphatidylinositol (GPI) anchored to the cell membrane and, like CPG15, can be released in a soluble-secreted form, but with lower efficiency. CPG15 and CPG15-2 were found to form homodimers and heterodimers with each other. In hippocampal explants and dissociated cultures, CPG15 and CPG15-2 promote neurite growth and neuronal survival with similar efficacy. Our findings suggest that CPG15 and CPG15-2 perform similar cellular functions but may play distinct roles *in vivo* through their cell-type- and tissue-specific transcriptional regulation.

Gene: NUDT22 [Nudix (nucleoside diphosphate linked moiety X)-type motif 22]

CCDS ID: 8061.1|Hs37.1|chr11

Amino acids: 183--195, BH3-like sequence: FSSVLQEICDEVN

Helix containing: HHHHHHHHHHHH--

Also known as: MGC13045 (related to NUDT1/nudix/MTH1)

MutT homolog-1 (MTH1) is a member of the Nudix hydrolase superfamily. MTH1, the mammalian counterpart of MutT, hydrolyzes oxidized purine nucleoside triphosphates, such as 8-oxo-dGTP and 2-hydroxy-ATP, to monophosphates, thereby preventing the incorporation of such oxygen radicals during replication. This is an important step in the repair mechanism in genomic and mitochondrial DNA. Like other members of the Nudix family, it requires a divalent cation, such as Mg2+ or Mn2+, for activity, and contain the Nudix motif, a highly conserved 23-residue block (GX5EX7REUXEEXGU, where U = I, L or V), that functions as a metal binding and catalytic site. MTH1 is predominantly localized in the cytoplasm and mitochondria. Structurally, this enzyme adopts a similar fold to MutT despite low sequence similarity outside the conserved nudix motif. The most distinctive structural difference between MutT and MTH1 is the presence of a beta-hairpin, which is absent in MutT. This results in a much deeper and narrower substrate binding pocket. Mechanistically, MTH1 contains dual specificity for nucleotides that contain 2-OH-adenine bases and those that contain 8-oxo-guanine bases.

Cell cycle arrest induced by hydrogen peroxide is associated with modulation of oxidative stress related genes in breast cancer cells. Chua PJ, Yip GW, Bay BH. Exp Biol Med (Maywood). 2009 Sep;234(9):1086-94. Depending on the amounts present, reactive oxygen species can exert either beneficial or deleterious effect to cells. In the present study, we observed a decrease in cell viability concomitant with an increase of malondialdehyde concentration in hydrogen peroxide (H(2)O(2))-treated MCF-7 breast cancer cells. There was also a concurrent G1/S phase cell cycle arrest with increased apoptosis in H(2)O(2)-treated cells. Analysis of 84 oxidative stress related genes showed that five genes were significantly and differentially regulated, namely, Cytoglobin (CYGB), Forkhead box M1 (FOXM1), NADPH oxidase (NOX5), Nudix (nucleoside diphosphate linked moiety X)-type motif 1 (NUDT1) and Selenoprotein P1 (SEPP1) genes with H(2)O(2) treatment. It would seem that oxidative stress induces cell cycle arrest in the breast cancer by modulation of these genes. Manipulation of these genes, in particular FOXM1, a proliferation-specific gene associated with human malignancies, could stifle cancer progression and enhance the therapeutic efficacy of drugs which exert their effects by oxidative stress.

hMTH1 depletion promotes oxidative-stress-induced apoptosis through a Noxa- and caspase-3/7-mediated signaling pathway. Youn CK, *et al.* DNA Repair (Amst), 2008 Nov 1. PMID: 18708163. Although the accumulation of 8-oxo-dGTP in DNA is associated with apoptotic cell death and mutagenesis, little is known about the exact mechanism of hMTH1-mediated suppression of oxidative-stress-induced cell death. Therefore, we investigated the regulation of DNA-damage-related apoptosis induced by oxidative stress using control and hMTH1 knockdown cells. Small interfering RNA (siRNA) was used to suppress hMTH1 expression in p53-proficient GM00637 and H460 cells, resulting in a significant increase in apoptotic cell death after H(2)O(2) exposure; however, p53-null, hMTH1-deficient H1299 cells did not exhibit H(2)O(2)-induced apoptosis. In addition, hMTH1-deficient GM00637 and H460 cells showed increased caspase-3/7 activity, cleaved caspase-8, and Noxa expression, and gamma-H2AX formation in response to H(2)O(2). In contrast, the caspase inhibitors, p53-siRNA, and Noxa-siRNA suppressed H(2)O(2)-induced cell death. Moreover, in 8-week (long-term) cultured H460 and H1299 cells, hMTH1 suppression increased cell death, Noxa expression, and gamma-H2AX after H(2)O(2) exposure, compared to 3-week (short-term) cultured cells. These data indicate that hMTH1 plays an important role in protecting cells against H(2)O(2)-induced apoptosis via a Noxa- and caspase-3/7-mediated signaling pathway, thus conferring a survival advantage through the inhibition of oxidative-stress-induced DNA damage.

Gene: OGT

[O-linked N-acetylglucosamine (GlcNAc) transferase (UDP-N acetylglucosamine:polypeptide-N-acetylglucosaminyl transferase)]

CCDS ID: 14414.1|Hs37.1|chrX

Amino acids: 469--481, BH3-like sequence: LAHCLQIVCDWTD

CCDS ID: 35502.1|Hs37.1|chrX

Amino acids: 459--471, BH3-like sequence: LAHCLQIVCDWTD

Helix containing: HHHHHHHHH----

Also known as: FLJ23071, HRNT1, MGC22921, O-GLCNAC

Structure of human O-GlcNAc transferase and its complex with a peptide substrate. Lazarus MB, Nam Y, Jiang J, Sliz P, Walker S. Nature. 2011 Jan 27;469(7331):564-7. OGT The essential mammalian enzyme O-linked β-N-acetylglucosamine transferase (O-GlcNAc transferase, here OGT) couples metabolic status to the regulation of a wide variety of cellular signalling pathways by acting as a nutrient sensor. We report here two crystal structures of human OGT, as a binary complex with UDP (2.8 Angstrom resolution) and as a ternary complex with UDP and a peptide substrate (1.95 Angstrom). The structures provide clues to the enzyme mechanism, show how OGT recognizes target peptide sequences, and reveal the fold of the unique domain between the two halves of the catalytic region. This information will accelerate the rational design of biological experiments to

investigate OGT's functions; it will also help the design of inhibitors for use as cellular probes and help to assess its potential as a therapeutic target.

See all (61) citations in PubMed

Gene: OLR1 [Oxidized low density lipoprotein (lectin-like) receptor 1]

CCDS ID: 8618.1|Hs37.1|chr12

Amino acids: 56--68, BH3-like sequence: LGMQLSQVSDLLT

Helix containing: ---HHHHHHHHHH

Also known as: LOX1; LOXIN; SLOX1; CLEC8A; SCARE1

This gene encodes a low density lipoprotein receptor that belongs to the C-type lectin superfamily. This gene is regulated through the cyclic AMP signaling pathway. The encoded protein binds, internalizes and degrades oxidized low-density lipoprotein. This protein may be involved in the regulation of Fas-induced apoptosis.

Extracellular HSP70 binding to surface receptors present on antigen presenting cells and endothelial/epithelial cells. Thériault JR, Mambula SS, Sawamura T, Stevenson MA, Calderwood SK. FEBS Lett. 2005 Mar 28;579(9):1951-60. Extracellular HSP70 has been found to participate in both innate and adaptive immune responses. However, little is known about the molecular mechanisms that mediate this process. Previous reports suggest that HSP70 interacts with antigen presenting cells (APC) through a plethora of surface receptors. In this study, we have examined the relative binding of potential HSP70 receptors and found highAffinity binding to LOX-1 but not other structures with a role in HSP70-APC interactions such as LRP/CD91, CD40, TLR2, TLR4 or another c-type lectin family member (DC-SIGN) closely related to LOX-1. In addition to APC, HSP70 can avidly bind to non-APC cell lines, especially those from epithelial or endothelial background.

See all (140) citations in PubMed

Gene: OTOF (otoferlin)

CCDS ID: 1724.1|Hs37.1|chr2

Amino acids: 305--317, BH3-like sequence: FAKPLVKMADEAY

CCDS ID: 1725.1|Hs37.1|chr2

Amino acids: 1052--1064, BH3-like sequence: FAKPLVKMADEAY

CCDS ID: 1726.1|Hs37.1|chr2

Amino acids: 305--317, BH3-like sequence: FAKPLVKMADEAY

CCDS ID: 46241.1|Hs37.1|chr2

Amino acids: 362--374, BH3-like sequence: FAKPLVKMADEAY

Helix containing: H-HHHHHHHHHH-

Also known as AUNB1; DFNB6; DFNB9; NSRD9; FER1L2; OTOF

Mutations in this gene are a cause of neurosensory nonsyndromic recessive deafness, DFNB9. The short form of the encoded protein has 3 C2 domains, a single carboxy-terminal transmembrane domain found also in the C. elegans spermatogenesis factor FER-1 and human dysferlin, while the long form has 6 C2 domains. The homology suggests that this protein may be involved in vesicle membrane fusion.

Gene: PAPPA2 (pappalysin 2)

CCDS ID: 41438.1|Hs37.1|chr1

Amino acids: 1120--1132, BH3-like sequence: VSERLGEECDDGD

Helix containing: ----------

This gene encodes a member of the pappalysin family of metzincin metalloproteinases. The encoded protein cleaves insulin-like growth factor-binding protein 5 and is thought to be a local regulator of insulin-like growth factor (IGF) bioavailability

Gene: PDS5A (regulator of cohesion maintenance, homolog A)

CCDS ID: 47045.1|Hs37.1|chr4

Amino acids: 864--876, BH3-like sequence: LSAMLVSEGDLTE

CCDS ID: 47046.1|Hs37.1|chr4

Amino acids: 824--836, BH3-like sequence: LSAMLVSEGDLTE

Helix containing: HHHHHH------H

The cohesin-interacting protein, precocious dissociation of sisters 5A/sister chromatid cohesion protein 112, is up-regulated in human astrocytic tumors. Hagemann C, *et al.* Int J Mol Med, 2011 Jan. PMID: 21069257.

Cohesin acetylation speeds the replication fork. Terret ME, *et al.* Nature, 2009 Nov 12. PMID: 19907496.

Cohesin promotes the repair of ionizing radiation-induced DNA double-strand breaks in replicated chromatin. Bauerschmidt C, *et al.* Nucleic Acids Res, 2010 Jan. PMID: 19906707.

Gene: PEX11G (peroxisomal biogenesis factor 11 gamma)

CCDS ID: 12178.1|Hs37.1|chr19

Amino acids: 91--103, BH3-like sequence: CVSVLGNLADQLY

Helix containing: -HHHHHHHHHHH-

PEX11 family members are membrane elongation factors that coordinate peroxisome proliferation and maintenance. Koch J, *et al.* J Cell Sci, 2010 Oct 1. PMID: 20826455.

Gene: PIGM (phosphatidylinositol glycan anchor biosynthesis, class M)

CCDS ID: 1192.1|Hs37.1|chr1

Amino acids: 94--106, BH3-like sequence: FGKFLFISCDLLT

Helix containing: HHHHH---HHHHH

This gene encodes a transmembrane protein that is located in the endoplasmic reticulum and is involved in GPI-anchor biosynthesis. The glycosylphosphatidylinositol (GPI)-anchor is a glycolipid which contains three mannose molecules in its core backbone. The GPI-anchor is found on many blood cells and serves to anchor proteins to the cell surface. This gene encodes a mannosyltransferase, GPI-MT-I, that transfers the first mannose to GPI on the lumenal side of the endoplasmic reticulum.

Gene: PIKFYVE (phosphoinositide kinase, FYVE finger containing)

CCDS ID: 2382.1|Hs37.1|chr2

Amino acids: 229--241, BH3-like sequence: IGEDLNALSDSAC

CCDS ID: 33368.1|Hs37.1|chr2

Amino acids: 132--144, BH3-like sequence: IGEDLNALSDSAC

Helix containing: HHHHHHHHH-----

Also known as CFD; FAB1; PIP5K; PIP5K3; FLJ37746; KIAA0981; MGC40423

Regulation of PIP5K activity by Arf6 and its physiological significance. Funakoshi Y, *et al.* J Cell Physiol, 2011 Apr. PMID: 20945365.

Gene: PRDM7 (PR domain containing 7)

CCDS ID: 45557.1|Hs37.1|chr16

Amino acids: 350--362, BH3-like sequence: GCELLVWSGDEYG

Helix containing: ----------

The protein encoded by this gene is a transcription factor of the PR-domain protein family. It contains a PR-domain and multiple zinc finger motifs. Transcription factors of the PR-domain family are known to be involved in cell differentiation and tumorigenesis

Evolutionary analysis suggests that human PRDM7 and PRDM9 genes, a pair of close paralogs corresponding to a single mouse gene Prdm9, were generated by a recent gene duplication event after the divergence of the ancestors of human and mouse. Title: Genome-wide survey and developmental expression mapping of zebrafish SET domain-containing genes.

Gene: PRDM9 (PR domain containing 9

CCDS ID: 43307.1|Hs37.1|chr5

Amino acids: 350--362, BH3-like sequence: GCELLVWYGDEYG

Helix containing: ----------

The PR domain is a protein-protein interaction module of about 100 amino acids. PR domain-containing proteins, such as PRDM9, are often involved in transcriptional regulation

Prdm9 controls activation of mammalian recombination hotspots. Parvanov ED, *et al.* Science, 2010 Feb 12. PMID: 20044538.

Gene: PROSC (proline synthetase co-transcribed homolog (bacterial))

CCDS ID: 6096.1|Hs37.1|chr8

Amino acids: 208--220, BH3-like sequence: LCKKLNIPADQVE

Helix containing: HHHH---------

Gene: RANGAP1

CCDS ID: 14012.1|Hs37.1|chr22

Amino acids: 350--362, BH3-like sequence: MAKVLASLSDDED

Helix containing: HHHHHHH----HH

RanGAP1, is a homodimeric 65-kD polypeptide that specifically induces the GTPase activity of RAN, but not of RAS by over 1,000-fold. RanGAP1 is the immediate antagonist of RCC1, a regulator molecule that keeps RAN in the active, GTP-bound state. The RANGAP1 gene encodes a 587-amino acid polypeptide. The sequence is unrelated to that of GTPase activators for other RAS-related proteins, but is 88% identical to Fug1, the murine homolog of yeast Rna1p. RanGAP1 and RCC1 control RAN-dependent transport between the nucleus and cytoplasm. RanGAP1 is a key regulator of the RAN GTP/GDP cycle.

Gene: SAMM50

CCDS ID: 14055.1|Hs37.1|chr22

Amino acids: 319--331, BH3-like sequence: WGGMLVPIGDKPS

Helix containing: ----------

SAMM50 is a component of the sorting and assembly machinery (SAM) complex of the outer mitochondrial membrane. The SAM complex has a role in integrating beta-barrel proteins into the outer mitochondrial membrane

Gene: SCGB2A1 (Secretoglobin, family 2A, member 1)

CCDS ID: 8016.1|Hs37.1|chr11

Amino acids: 10--22, BH3-like sequence: AALLLHCYADSGC

Helix containing: HHHHHHHHHH-HH

Also known as: CFFM4; MS4A8; 4SPAN2; CD20L4; MGC22368

Secreted biomarker breast cancer: This gene encodes a member of the membrane-spanning 4A gene family, members of which are characterized by common structural features and similar intron/exon splice boundaries and display unique expression patterns in hematopoietic cells and nonlymphoid tissues. This family member is associated with mature cellular function in the monocytic lineage, and it may be a component of a receptor complex involved in signal transduction.

See all (11) citations in PubMed

Gene: SEH1L (SEH1-like)

CCDS ID: 32791.1|Hs37.1|chr18

Amino acids: 289--301, BH3-like sequence: TGTVLASSGDDGC

CCDS ID: 45832.1|Hs37.1|chr18

Amino acids: 289--301, BH3-like sequence: TGTVLASSGDDGC

Helix containing: ----------

The protein encoded by this gene is part of a nuclear pore complex, Nup107-160. This protein contains WD repeats and shares 34% amino acid identity with yeast Seh1 and 30% identity with yeast Sec13. All constituents of the Nup107-160 complex, including this protein, specifically localize to kinetochores in mitosis.

Interacts with BECN1

Network organization of the human autophagy system. Behrends C, Sowa ME, Gygi SP, Harper JW. Nature. 2010 Jul 1;466(7302):68-76. PMID: 20562859

Gene: SLC30A7 / ZNT7 [Solute carrier family 30 (zinc transporter), member 7]

CCDS ID: 776.1|Hs37.1|chr1

Amino acids: 58--70, BH3-like sequence: WSNCLGLISDSFH

Helix containing: HHHHHHHHH-----

Also known as: DKFZp686M0368, ZNT7, ZnT-7, ZnTL2

Nuclear encoded mitochondrial gene; neuronal cell death through reduced ZNT3 expression

Intracellular zinc homeostasis in leukocyte subsets is regulated by different expression of zinc exporters ZnT-1 to ZnT-9. Overbeck S, Uciechowski P, Ackland ML, Ford D, Rink L. J Leukoc Biol. 2008 Feb;83(2):368-80. We found that hZnT-5, hZnT-6, and hZnT-7 in Raji as well as hZnT-6 and hZnT-7 in THP-1 are up-regulated in response to cellular zinc depletion. Those zinc exporters are all localized in the Golgi network, and this type of regulation explains the observed zinc increase in both cell types after up-regulation of their expression during zinc deficiency and, subsequently, high zinc exposure.

See all (17) citations in PubMed

Gene: SLC35D3 (solute carrier family 35, member D3)

CCDS ID: 34544.1|Hs37.1|chr6

Amino acids: 141--153, BH3-like sequence: CGAALAGAGDLTG

Helix containing: HHHHHH-------

Gene: ST14 (suppression of tumorigenicity 14)

CCDS ID: 8487.1|Hs37.1|chr11

Amino acids: 500--512, BH3-like sequence: FCKPLFWVCDSVN

Helix containing: ----------

The protein encoded by this gene is an epithelial-derived, integral membrane serine protease. This protease forms a complex with the Kunitz-type serine protease inhibitor, HAI-1, and is found to be activated by sphingosine 1-phosphate. This protease has been shown to cleave and activate hepatocyte growth factor/scattering factor, and urokinase plasminogen activator, which suggest the function of this protease as an epithelial membrane activator for other proteases and latent growth factors. The expression of this protease has been associated with breast, colon, prostate, and ovarian tumors, which implicates its role in cancer invasion, and metastasis.

Gene: SYNE1 (Spectrin repeat containing, nuclear envelope 1)

CCDS ID: 5235.1|Hs37.1|chr6

Amino acids: 670--682, BH3-like sequence: AGNFLIETCDEMV

CCDS ID: 5236.1|Hs37.1|chr6

Amino acids: 663--675, BH3-like sequence: AGNFLIETCDEMV

Helix containing: H-HHHHHHHHHHH

Also known as: 8B; CPG2; ARCA1; EDMD4; MYNE1; SCAR8; C6orf98; FLJ30878; FLJ41140; KIAA0796; KIAA1262; KIAA1756; dJ45H2.2; DKFZp781J13156

This gene encodes a spectrin repeat containing protein expressed in skeletal and smooth muscle, and peripheral blood lymphocytes, that localizes to the nuclear membrane. Mutations in this gene have been associated with autosomal recessive spinocerebellar ataxia 8, also referred to as autosomal recessive cerebellar ataxia type 1 or recessive ataxia of Beauce.

Actomyosin tension exerted on the nucleus through nesprin-1 connections influences endothelial cell adhesion, migration, and cyclic strain-induced reorientation. Chancellor TJ, Lee J, Thodeti CK, Lele T. Biophys J. 2010 Jul 7;99(1):115-23. Endothelial cell polarization and directional migration is required for angiogenesis. Polarization and motility requires not only local cytoskeletal remodeling but also the motion of intracellular organelles such as the nucleus. However, the physiological significance of nuclear positioning in the endothelial cell has remained largely unexplored. Here, we show that siRNA knockdown of nesprin-1, a protein present in the linker of nucleus to cytoskeleton complex, abolished the reorientation of endothelial cells in response to cyclic strain. Confocal imaging revealed that the nuclear height is substantially increased in nesprin-1 depleted cells, similar to myosin inhibited cells. Nesprin-1 depletion increased the number of focal adhesions and substrate traction while decreasing the speed of cell migration; however, there was no detectable change in nonmuscle myosin II activity in nesprin-1 deficient cells. Together, these results are consistent with a model in which the nucleus balances a portion of the actomyosin tension in the cell. In the absence of nesprin-1, actomyosin tension is balanced by the substrate, leading to abnormal adhesion, migration, and cyclic strain-induced reorientation.

Spectrin repeats, found in several proteins involved in cytoskeletal structure; Calponin homology domain; actin-binding domain

The KASH (for Klarsicht/ANC-1/Syne-1 homology) or KLS domain is a highly hydrophobic nuclear envelope localisation domain of approximately 60 amino acids comprising an 20-amino-acid transmembrane region and a 30-35-residue C-terminal region that lies between the inner and the outer nuclear membranes.

Smc, Chromosome segregation ATPases

SMC_prok_B (structural maintenance of chromosomes) proteins bind DNA and act in organizing and segregating chromosomes for partition

See all (42) citations in PubMed

Gene: TBC1D10B (TBC1 domain family, member 10B)

CCDS ID: 10676.2|Hs37.1|chr16

Amino acids: 276--288, BH3-like sequence: MSGTLESLADDVS

Helix containing: H--HHHHHH--HH

Small G proteins of the RAB family (see MIM 179508) function in intracellular vesicle trafficking by switching from the GTP-bound state to the GDP-bound state with the assistance of guanine nucleotide exchange factors (GEFs; see MIM 609700) and GTPase-activating proteins (GAPs). TBC1D10B functions as a GAP for several proteins of the Rab family

Gene: TBL1XR1 (transducin (beta)-like 1 X-linked receptor 1)

CCDS ID: 46961.1|Hs37.1|chr3

Amino acids: 360--372, BH3-like sequence: TGNLLASCSDDMT

Helix containing: ----------

Also known as F-box-like/WD repeat-containing protein; C21; DC42; IRA1; TBLR1; FLJ12894

Ski co-repressor complexes maintain the basal repressed state of the TGF-beta target gene, SMAD7, via HDAC3 and PRMT5. Tabata T, *et al.* Genes Cells, 2009 Jan. PMID: 19032343.

The complex genomic profile of ETV6-RUNX1 positive acute lymphoblastic leukemia highlights a recurrent deletion of TBL1XR1. Parker H, *et al.* Genes Chromosomes Cancer, 2008 Dec. PMID: 18767146.

TBL1 and TBLR1 phosphorylation on regulated gene promoters overcomes dual CtBP and NCoR/SMRT transcriptional repression checkpoints. Perissi V, *et al.* Mol Cell, 2008 Mar 28. PMID: 18374649.

Histone deacetylase 3 localizes to the mitotic spindle and is required for kinetochore-microtubule attachment. Ishii S, *et al.* Proc Natl Acad Sci U S A, 2008 Mar 18. PMID: 18326024.

Gene: TMEM194A

CCDS ID: 44927.1|Hs37.1|chr12

Amino acids: 169--181, BH3-like sequence: LGLMLFFCGDLLS

Helix containing: HHHHHHHHHHHHH-

Also known as TMEM194; KIAA0286; DKFZp686N1768;

Contains DUF2215 region (uncharacterized conserved protein)

This entry is the central 200 residues of a family of proteins conserved from worms to humans. The function is unknown.

Gene: TMEM214

CCDS ID: 46242.1|Hs37.1|chr2

Amino acids: 535--547, BH3-like sequence: CASHLAWFGDSLT

CCDS ID: 42664.1|Hs37.1|chr2

Amino acids: 580--592, BH3-like sequence: CASHLAWFGDSLT

Helix containing: HHHHHHHHH-HHH

Also known as: FLJ20254; FLJ39682

Interacts with LSM1 homolog, U6 small nuclear RNA associated: A protein interaction framework for human mRNA degradation. Lehner B, *et al.* Genome Res, 2004 Jul. PMID: 15231747.

Contains DUF2359 region (uncharacterized conserved protein)

This is a 450 amino acid region of a family of proteins conserved from insects to humans. The mouse protein, Q8BM55, is annotated as being a putative Vitamin K-dependent carboxylation gamma-carboxyglutamic (GLA) domain containing protein, but this could not be confirmed. The function is not known.

Gene: UBA7 (ubiquitin-like modifier activating enzyme 7)

CCDS ID: 2805.1|Hs37.1|chr3

Amino acids: 990--1002, BH3-like sequence: LVLELSCEGDDED

Helix containing: ----------

Also known as D8; UBE2; UBA1B; UBE1L; MGC12713

This gene encodes a member of the E1 ubiquitin-activating enzyme family. The encoded enzyme is a retinoid target that triggers promyelocytic leukemia (PML)/retinoic acid receptor alpha (RARalpha) degradation and apoptosis in acute promyelocytic leukemia, where it is involved in the conjugation of the ubiquitin-like interferon-stimulated gene 15 protein.

UBE1L causes lung cancer growth suppression by targeting cyclin D1. Feng Q, *et al.* Mol Cancer Ther, 2008 Dec. PMID: 19074853.

UBE1L is a retinoid target that triggers PML/RARalpha degradation and apoptosis in acute promyelocytic leukemia. Kitareewan S, Pitha-Rowe I, Sekula D, Lowrey CH, Nemeth MJ, Golub TR, Freemantle SJ, Dmitrovsky E. Proc Natl Acad Sci U S A. 2002 Mar 19;99(6):3806-11. Epub 2002 Mar 12.

Association of human fas (CD95) with a ubiquitin-conjugating enzyme (UBC-FAP). Wright DA, Futcher B, Ghosh P, Geha RS. J Biol Chem. 1996 Dec 6;271(49):31037-43.

Gene: UPK3A (uroplakin 3A)

CCDS ID: 14064.1|Hs37.1|chr22

Amino acids: 103--115, BH3-like sequence: VAFDLIPCSDLPS

Helix containing: ----------

This gene encodes a member of the uroplakin family, a group of transmembrane proteins that form complexes on the apical surface of the bladder epithelium.

Differentiation-induced uroplakin III expression promotes urothelial cell death in response to uropathogenic E. coli. Thumbikat P, *et al.* Microbes Infect, 2009 Jan. PMID: 19007907.

Gene: VPS53 (vacuolar protein sorting 53 homolog (S. cerevisiae))

CCDS ID: 10995.1|Hs37.1|chr17

Amino acids: 435--447, BH3-like sequence: GGAVLPSCADLFV

CCDS ID: 45558.1|Hs37.1|chr17

Amino acids: 464--476, BH3-like sequence: GGAVLPSCADLFV

Helix containing: ------HHHHHHH

Also known as PP13624, FLJ10979, FLJ41112, FLJ61757; MGC39512, hVps53L, pp13624

This gene encodes a protein with sequence similarity to the yeast Vps53p protein. Vps53p is involved in retrograde vesicle trafficking in late Golgi.

Structure of a C-terminal fragment of its Vps53 subunit suggests similarity of Golgi-associated retrograde protein (GARP) complex to a family of tethering complexes. Vasan N, Hutagalung A, Novick P, Reinisch KM. Proc Natl Acad Sci U S A. 2010 Aug 10;107(32):14176-81.

A genome-wide screen in Saccharomyces cerevisiae reveals pathways affected by arsenic toxicity. Zhou X, Arita A, Ellen TP, Liu X, Bai J, Rooney JP, Kurtz AD, Klein CB, Dai W, Begley TJ, Costa M. Genomics. 2009 Nov;94(5):294-307. Epub 2009 Jul 22 (Mutant confers arsenic sensitivity)

Gene: WDR41 (WD repeat domain 41)

CCDS ID: 4038.1|Hs37.1|chr5

Amino acids: 391--403, BH3-like sequence: TSCSLELIGDLIG

Helix containing: ----HHHHHHHHH-

Gene: WISP2 (WNT1 inducible signaling pathway protein 2)

CCDS ID: 13336.1|Hs37.1|chr20

Amino acids: 56--68, BH3-like sequence: CARRLGEPCDQLH

Helix containing: ----------

Also known as:CCN5; CT58; CTGF-L

This gene encodes a member of the WNT1 inducible signaling pathway (WISP) protein subfamily, which belongs to the connective tissue growth factor (CTGF) family. WNT1 is a member of a family of cysteine-rich, glycosylated signaling proteins that mediate diverse developmental processes. The CTGF family members are characterized by four conserved cysteine-rich domains: insulin-like growth factor-binding domain, von Willebrand factor type C module, thrombospondin domain and C-terminal cystine knot-like (CT) domain. The encoded protein lacks the CT domain which is implicated in dimerization and heparin binding. It is 72% identical to the mouse protein at the amino acid level. This gene may be downstream in the WNT1 signaling pathway that is relevant to malignant transformation. Its expression in colon tumors is reduced while the other two WISP members are overexpressed in colon tumors. It is expressed at high levels in bone tissue, and may play an important role in modulating bone turnover.

CCN5, a novel transcriptional repressor of the transforming growth factor β signaling pathway. Sabbah M, *et al.* Mol Cell Biol, 2011 Apr. PMID: 21262769.

Gene: ZBTB22 (zinc finger and BTB domain containing 22)

CCDS ID: 4775.1|Hs37.1|chr6

Amino acids: 253--265, BH3-like sequence: TSGKLLLEADELC

Helix containing: -HHHHHHHHHHH-

Also known as fru; BING1; ZNF297; ZBTB22A; ZNF297A; fruitless; ZBTB22

The zinc finger protein ZNF297B interacts with BDP1, a subunit of TFIIIB. Schoenen F, Wirth B. J. Biol Chem. 2006 Mar;387(3):277-84.

Gene: ZBTB45 (zinc finger and BTB domain containing 45)

CCDS ID: 12984.1|Hs37.1|chr19

Amino acids: 241--253, BH3-like sequence: AAGFLTAAADSAC

Helix containing: HHHHHHHHHHHH-

Also known as: ZNF499; FLJ14486; DKFZp547H249

Interacts with MED31 (mediator complex subunit 31). The Mediator is a multiprotein coactivator required for activation of RNA polymerase II transcription by DNA binding transactivators.

See all (16) citations for MED31 in PubMed

Gene: ZFYVE9 (zinc finger, FYVE domain containing 9)

CCDS ID: 563.1|Hs37.1|chr1

Amino acids: 470--482, BH3-like sequence: AANYLSNGCDSYG

CCDS ID: 564.1|Hs37.1|chr1

Amino acids: 470--482, BH3-like sequence: AANYLSNGCDSYG

CCDS ID: 565.1|Hs37.1|chr1

Amino acids: 470--482, BH3-like sequence: AANYLSNGCDSYG

Helix containing: HHHHHH-------

This gene encodes a double zinc finger (FYVE domain) protein that interacts directly with SMAD2 and SMAD3, and is involved in Alzheimer's disease. SMAD proteins transmit signals from transmembrane serine/threonine kinase receptors to the nucleus. The FYVE domain has been identified in a number of unrelated signaling molecules. This protein functions to recruit SMAD2 to the transforming growth factor-beta receptor. The FYVE domain is required to maintain the normal localization of this protein but is not involved in mediating interaction with SMADs. The C-terminal domain of this protein interacts with the TGFB receptor. This protein is a component of the TGFB pathway that brings the SMAD substrate to the receptor.

Gene: ZIC3 (zinc finger protein of the cerebellum 3)

CCDS ID: 14663.1|Hs37.1|chrX

Amino acids: 33--45, BH3-like sequence: AGMGLNPFGDSTH

Helix containing: ----------HHH

This gene encodes a member of the ZIC family of C2H2-type zinc finger proteins. This nuclear protein probably functions as a transcription factor in early stages of left-right body axis formation. Mutations in this gene cause X-linked visceral heterotaxy, which includes congenital heart disease and left-right axis defects in organs.

Gene: ZMYM5 (Zinc finger, MYM-type 5)

CCDS ID: 31942.1|Hs37.1|chr13

Amino acids: 24--36, BH3-like sequence: MATSLMDIGDSFG

CCDS ID: 31943.1|Hs37.1|chr13

Amino acids: 24--36, BH3-like sequence: MATSLMDIGDSFG

CCDS ID: 45015.1|Hs37.1|chr13

Amino acids: 24--36, BH3-like sequence: MATSLMDIGDSFG

Helix containing: HHHHHHHHH-----

Also known as: RP11-61K9.1, HSPC050, MYM, ZNF198L1, ZNF237

Transcriptional regulation of the presenilin-1 gene controls gamma-secretase activity. Lee S, Das HK. Front Biosci (Elite Ed). 2010 Jan 1;2:22-35. Inhibition of basal JNK activity by JNK inhibitor SP600125 or JNK1siRNA repressed presenilin-1 (PS1) expression in SK-N-SH cells by augmenting the level of p53, a repressor of the PS1 gene (1). We now showed that repression of PS1 transcription by JNK inhibitor SP600125 inhibited gamma-secretase mediated processing of amyloid precursor protein (APP) resulting in the accumulation of C99 fragment and the reduction of secreted Abeta40 level without altering the

expression of nicastrin (NCT). Co-treatment of cells with SP600125 and p53 inhibitor, pifithrin-alpha, partially nullified the suppressive effects of SP610025 on PS1 expression and secreted Abeta40 level. Suppression of JNK1 by JNK1siRNA also decreased Abeta40 level. Furthermore, overexpression of the repressors p53, ZNF237 and CHD3 of the PS1 gene also suppressed the processing of APP through repression of PS1 transcription by deacetylation of histone at the PS1 promoter. Transcriptional activator Ets2 increased PS1 protein and secreted Abeta40 levels without affecting the expression of NCT by activating PS1 transcription via hyper-acetylation of histone at the PS1 promoter. Therefore, regulation of PS1 transcription modulates gamma-secretase activity.

Analysis of transcriptional modulation of the presenilin 1 gene promoter by ZNF237, a candidate binding partner of the Ets transcription factor ERM. Pastorcic M, Das HK. Brain Res. 2007 Jan 12;1128(1):21-32.

Gene: ZNF318

CCDS ID: 4895.2|Hs37.1|chr6

Amino acids: 507--519, BH3-like sequence: FSRILSMLADSTS

Helix containing: HHHHHHHHH----

Also known as TZF; ZFP318; FLJ21852; HRIHFB2436

Opposite effects of alternative TZF spliced variants on androgen receptor. Tao RH, *et al.* Biochem Biophys Res Commun, 2006 Mar 10. PMID: 16446156.

A zinc finger protein TZF is a novel corepressor of androgen receptor. Ishizuka M, *et al.* Biochem Biophys Res Commun, 2005 Jun 17. PMID: 15882980