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The Common Leukemic Fusions in Pathogenesis and in Treatment Response in Acute Myeloid Leukemia

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Abstract: Chromosomal abnormalities are the most common alterations in acute myeloid leukemia (AML). Among those abnormalities, chromosomal translocations that produce the oncogenic fusion proteins have been frequently observed in different subtypes of AML. Although molecular mechanisms underlying the consequences of the oncogenic transformation resulted from the fusion proteins have been extensively studied, little is known about the molecular events cooperative with the oncogenic fusion proteins in the pathogenesis of leukemia and the cellular mechanisms with regard to the predictive roles of the fusions in treatment response. In this article, we will present an overview of the important aspects of AML-associated fusion proteins and their regulated transcriptional networks in pathogenesis and prognosis of AML. We will also discuss the recent findings pertaining to the functional link between the oncogenic fusions and response of leukemic cells to the treatment. Understanding the regulation of AML-associated fusions and their association with disease characteristics, patient outcome and treatment response will be of fundamental importance for predicting the effectiveness of the treatment and design the specific therapeutic strategies.

Keywords: Acute myeloid leukemia, chromosome translocations, leukemic fusion proteins, transcriptional factors, treatment response.

INTRODUCTION

Hematopoiesis is a complicated multistage process that involves the differentiation and maturation of different blood cell types. Thus, to terminally differentiate and mature, cells have to pass through hierarchy of successive developmental stages [1, 2]. In each stage, the regulatory genes for hematopoiesis are either activated or silenced in a cell type-specific or lineage-specific manner to ensure a precise fine-tuning of the process [3-7]. The disruption of this regulatory process may result in different types of blood disorders. Acute myeloid leukemia (AML) is one of the major blood disorders that are associated with disruption of the regulatory processes.

AML is characterized by accumulation of cells at the early stages of the differentiation process [8-10]. This is mostly attributed to dysfunctional regulatory transcription factors, resulting in aberrant gene expression and function [7, 9]. Dysfunction of the regulatory transcription factors in turn results in blocking of the passage of cells through a given developmental stage depending on the subtype of the disease [7]. Thus, AML is a heterogenous disease, which comprises multiple subtypes [11, 12]. The subtypes are classified according to the FAB classification system. The subtypes are denoted as M0-M7 [2, 4, 10, 13]. The grouping is made based on the degree of granulocytic maturation (M1, M2, M3) or monocytic differentiation (M4 & M5) or presence of large number of erythroblasts (M6) or magakaryoblasts (M7) [10, 13]. The individual subtypes of this heterogenous disease can be identified using multiple methods such as cellular morphology, cytochemistry, immunophenotypes and molecular analysis [14]. For instance, in the most common forms of leukemia, acute promyelocytic leukemia (APL), and acute myeloid leukemia, the differentiation process is blocked at a promyelocyte stage [15], and early myeloid stage [16], respectively. The blocked cells regain a self-renewal capacity and continue to proliferate and overpopulate the bone marrow. The prognosis of leukemia varies in patients depending on ages of the patients. Combination of age, cytogenetics, and white blood cell count (WBC) is a good prognostic factor. Young age tends to be associated with favorable prognosis, while old age is associated with poor prognosis [13, 17]. Cytochemical staining for example is helpful in differentiating AML from ALL as well as identifying subtypes of AML [14]. On the other hand, the specific karyotype is age-independent predictor of the treatment outcome. For example, the t(8; 21), inv(16) and t(15; 17) are indicators of favorable prognosis while, deletion or loss of chromosome 5 or 7 or both is associated with poor prognosis [13]. Multiple parameters have been taken into consideration for accurate diagnosis and better choice of treatment regimens. Genome-wide studies in search of complex genetic alterations and identification of possible novel markers have provided novel tools for the diagnosis and treatment of AML [16].

In AML, the underlying genetic or epigenetic events lead to disruption of this delicate regulatory mechanism affecting multiple cellular processes and regulatory pathways, especially the stage-specific regulations [6, 16]. A large number of diverse translocations have been described. The most frequent are the t(8; 21), t(15; 17), inv(16) which

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together with their variants, account for approximately 40% of all AMLs [7]. These translocations produce the AML1/ETO, PML/RARα, CBFCBFα & CBFβ/SMMHC fusion proteins, respectively [18] and the RARα [15]. These transcription factors are among the most important regulatory proteins that contribute to the normal differentiation and maturation of hematopoietic cells.

Great efforts have been made in treating leukemia to improve the clinical remission and disease-free survival. However, it is important to eliminate the unnecessary side effects that are usually associated with chemotherapy treatment and to improve specificity of drugs. Further, it remains to be investigated in detail whether the leukemic fusions are associated with leukemic subtypes and treatment response.

THE AML1

The core binding factors are a small family of transcription factors CBF comprising a DNA binding CBFα subunit and a non-DNA binding CBFβ subunit. The gene encoding CBFα subunit, AML1 (also known as Runx1, CBFA2, and PEBPA2A), together with the gene encoding CBFβ subunit are essential for hematopoiesis and are frequently fused with other genes to produce fusion genes in human leukemias [4, 19-23]. The gene for AML1, is located in 21q22, while the gene for CBFβ, is located on 16q22 [4, 24, 25-30]. AML1 is the part that contains a DNA-binding and a *trans*-activation domain, while the CBFβ does not contain any known DNA-binding or a *trans*-activation domain [4, 21, 26, 31, 32]. However, it is believed that the CBFβ subunit strengthens the binding of the AML1 [31, 33]. Furthermore, the CBFβ is believed to stabilize the AML1 by protecting it from ubiquitin-mediated degradation [21, 33]. Disruption in each subunit will result in total loss of function of the CBF. Since both subunits are equally important for the function of the CBF, knock-in of the AML1-fusion gene exerts similar phenotype as a AML1 knockout [4, 28]. This notion is supported by the fact that disruption of the CBFβ results in similar phenotype as the disruption of the AML1 [4, 30, 34, 35].

The CBF plays critical roles in lineage commitment of myeloid progenitors and terminal differentiation of hematopoietic cells [31, 36]. Many myeloid-specific regulatory genes have cis-acting binding sites for AML1, and activation of these genes are believed to be critical for the normal granulocyte development [3]. When the function of the CBF is affected by leukemogenesis, the development of the granulocytes is also affected [37]. Although the CBFβ is ubiquitously expressed, its function is not well-studied [38]. However, knockout of either AML1 or CBFβ in mice results in embryonic lethality [18, 22, 39-42]. It is not clear whether AML1 or CBFβ contributes to fetal hematopoiesis through additional pathways. Identification of the upstream actors or downstream targets of the AML1 might be helpful in designing disease-specific therapeutic methodologies.

THE AML1 FUSIONS IN LEUKEMIA

The most commonly t(8;21), t(12;21), and t(3;21) for AML1 generate fusions that are frequently observed in M1 and M2 subtypes of myeloid leukemia [26, 30]. The chromosomal translocation t(8;21) represents significant portion of the M2 subtype of AML [19, 43-45]. This translocation fuses AML1 (RUNX1) to ETO creating a novel hybrid AML1/ETO gene [24, 46-53]. The AML1-ETO interacts with other transcriptional factors act as repressors such as N-CoR, mSin3A and HDACs through its ETO part [9, 33, 37]. Thus, the fusion protein exhibits dominant negative effect over the wild type AML1 inhibiting transcription of the normally AML1-regulated genes that are essential for hematopoiesis [43, 51, 54-56]. Biological features of the fusion AML1-ETO is the disruption of hematopoiesis including the hypergranulation and strong myeloperoxidase-positivity of hematopoietic cells [31, 57, 58].

TREATMENT RESPONSE IN PATIENTS WITH AML1-ETO

Choice of appropriate regimens for treatment of leukemias is mainly based on accurate diagnosis. The major treatment choice is the classical chemotherapy [10]. The M2 AML responds well to high dose cytarabine exhibiting high remission rate and long disease-free survival [57]. Particularly, the AML1/ETO is serving as a paradigm for the M2 subtype of AML due partly to its high percentage of incidence that constitutes about 40% the M2 subtype [43, 58]. Patients who harbor AML1/ETO fusion have favorable prognosis. Patients presenting AML1/ETO normally do not directly require bone marrow transplantation, and thus the transplantation related complications may be avoided in these patients [2]. However, high dose cytarabine is associated with multiple side effects such as cardiovascular and central nervous system damages.

Leukemia Related to the Inv(16)

Inv(16) for CBFβ is a result of a pericentric inversion of chromosome 16 [4, 24-30, 59-61]. This inversion results in fusion of the CBFβ in frame to a myosin heavy chain gene (MYH11), which is located on the short arm (16p13) of the chromosome [4, 30, 59]. This chromosomal abnormality creates a novel hybrid gene (CBFβ/MYH11), which is expressed to produce a CBFβ/SMMHC chimeric protein [4, 24, 62, 63]. The chimeric protein is composed of the first 165 amino acids of CBFβ and a half part of SMMHC including its coiled-coil domain [26, 32, 62, 64]. The chimeric protein is still able to heterodimerize with AML1 [65, 66]. In fact, it has been reported that CBFβ/SMMHC binds to AML1 more avidly and with altered stochiometry [32]. This translocation is exclusively associated with the M4eo subtype of AML [24, 50, 59, 62, 67-70]. The M4eo is associated with abnormal eosinophils [12, 25, 26, 30, 59, 67, 70]. The M4eo exhibits similar response to chemotherapy as that of the M2 subtype [40]. Similar to the AML1-ETO fusion, the CBFβ/SMMHC protein exerts dominant negative effect on the wild type AML1 [4, 27, 30, 32, 35, 64, 71, 72]. The CBFβ/SMMHC can sequester the AML1 into nonfunctional complex thus acting as an inhibitor of the CBF [73, 74]. Furthermore, the dominant inhibitory function of the CBFβ/SMMHC is partly attributed to sequesteration of the AML1 in the cytoplasm [26, 28, 36, 75]. Mice chimeras that express CBFβ/SMMHC exhibit a phenotype similar to AML1 or CBFβ null mice [28, 63, 72, 73], and these observations emphasize that the inv(16) most likely exploit

similar biochemical mechanisms that are exploited by the other CBF leukemias to establish its effects.

Leukemia Related to the t(3; 21)

This chromosomal translocation is relatively rare and it is tightly associated with chemotherapy-related myelodysplastic syndrome (MDS) and chronic myelogenous leukemia (CML) [4, 21, 76]. This translocation fuses AML1 to EPA, MDS1 or EVI1, depending on the location of the breakpoint within chromosome 3, because all the three genes are located within the same region of the long arm of the chromosome [21, 50, 77]. In any case, transcription of the fusion gene is driven by AML1 promoter [78]. The t(3; 21) may be induced by the chemotherapeutic agents including topoisomerase II inhibitors in patients [21]. EAP is a highly expressed small nuclear proteins related to Epstein-Barr virus small RNA [21]. MDS1 encodes for small RNA of unknown function, while EVI1 gene encodes a zinc finger transcription factor that seems to be involved in transactivation of some genes [21, 78-80] such as *c-Fos* [21]. In summary, all the AML1-fusion products disrupt the normal function of the AML1, resulting in similar overall disease characteristics of the AML [4, 27].

TREATMENT RESPONSE IN PATIENTS WITH CBF FUSIONS

The CBF leukemias are responsive to the standard chemotherapy regimens such as the combination of anthracyclines and cytarabine (Ara-C) [57]. The intention of induction therapy is to achieve a clinical remission [10]. Once clinical remission is achieved, it is followed by postremission therapy which can be categorized as consolidation therapy or maintenance therapy. The purpose of consolidation therapy is to eradicate residual leukemic cells [10], while maintenance therapy is to preventing relapse. However most of the chemotherapeutic agents are not specific to the leukemic cells. They also attack the normal cells that are actively dividing. Such cells include the skin cells, immune cells, hair follicles, and cells of gastrointestinal lining. Therefore, the reversible side effects include skin rush, hair loss, nausea, vomiting, diarrhea, and poor appetite are frequently associated with the treatment. The irreversible side effects may further include permanent organ damage and introduction of secondary malignancies. Thus, although chemotherapy is effective for treatment of leukemia, it is an urgent need for develop novel treatment agents that can minimize the side-effects.

THE RETINOIC ACID RECEPTOR α (RAR α)

Within the steroid/thyroid nuclear receptors, the subfamily of the retinoic acid receptors is composed of RARs and RXRs, each consisting of different isotypes (α, β, and γ) and each isotype is encoded by different genes [81, 82]. All of the RAR family members (RARα, β, and γ) are activated by retinoic acids (RAs) [82]. The RARα is a ligand-activated nuclear transcription factor [68, 81, 83, 84]. Retinoid-induced RARα regulate various cellular processes form embryonic development to maintenance of homeostasis and induction of cell death in adults [85, 82]. RARα functions as a heterodimer and its heterodimeric partner is the RXRα [83, 86]. In the absence of the ligands, the RARα/RXRα heterodimers are believed to function as transcriptional inhibitors. The binding of the ligands coverts these transcriptional inhibitors into transcriptional activators, possibly by inducing conformational changes. The activated RARs in general bind to the response elements within the promoter regions of the RARα-regulated genes and induce gene expression, in general [83, 87]. Since the RARs are pleiotropic, treatment of multipotent cells such as FDCP mixA4 with erythropoietin results in inhibition of RARα and commitment of the cells into erythroid lineage, while treatment with G-CSF results in upregulation of expression of RARα resulting in commitment of the cells into myeloid lineage [84, 88]. Lines of evidence strengthen the notion that the AR/RARα signaling is necessary for neutrophil maturation. Transgenic mice harboring a mutation within ligand-binding domain of RARα exhibit increased immature neutrophil cell count suggesting the importance of RARα in neutrophil maturation [83]. The RARα pathway also plays very important roles driving the pluripotent hematopoietic cells along the granulocytic lineage [88-90].

RARα ASSOCIATED FUSIONS IN SUBTYPES OF ACUTE MYELOID LEUKEMIA

The APL is a subtype of AML with a differentiation blockage at a promyelocytic stage of myeloid cell maturation [81, 91, 92]. Thus, the APL is characterized by expansion or proliferation of the myeloid lineage blocked at a promyelocyte stage of differentiation [10, 92-94]. This group of disease is generally categorized as a FAB M3 subtype of the AML, while the t(15;17) is the most representative of the group. The unique cytogenetic abnormalities that are tightly associated with APL are the chromosomal translocations that target RARα [81, 95]. The genetic abnormalities underlying the initiation or the progression or the manifestation of APL include the chromosomal translocations t(15;17)(q22;q21), t(11;17)(q23;q21), t(11;17)(q13;q21), t(5;17)(q35;q21) and der(17) [83]. These reciprocal chromosomal translocations fuse RARα to different partners such as PML, PLZF, NuMA, NPM, and STAT5b respectively [15, 81, 96-98].

The leukemia that is cytogenetically characterized as having the t(15;17) chromosomal translocation is categorized as the M3 subtype of AML, which is also known as APL [89, 98-102]. The t(15;17)(q22;q21) is the most common form of the chromosomal translocations that target RARα, and seems to be responsible for transformed phenotype of APL [12, 15, 68, 81, 83, 88, 91]. This chromosomal translocation represents over 95% clinically relevant APL cases [1, 27, 83]. The PML/RARα may disrupt the normal function of RARα and PML [24, 98]. APL that harbors PML/RARα fusion respond well to the current therapeutic regimens and exhibit favorable prognosis [101, 102].

The t(11;17)(q23;q21) is also clinically relevant accounting for about 0.8% of APL cases [83]. This translocation fuses PLZF in frame to RARα creating a disease-specific hybrid gene (PLZF/RARα) [83, 103]. PLZF is a zinc finger transcription factor which seems to be expressed during early stage of hematopoietic cell development [83, 104]. PLZF may play important roles in maintenance or survival of early progenitor cells. PZLF is also known to regulate some powerful regulatory genes such as *c-myc*, cyclin A2. Therefore, PZLF may have direct or

indirect tumor-suppressor activity that is disrupted by the chromosomal translocation. Unlike the PML/RARα containing cells, the PLZF/RARα containing cells do not respond to ATRA [81, 98].

The t(5;21)(q35;q21) only represents less than 0.5% of the clinically relevant APL cases [83]. This translocation fuses NPM in frame with RARα again creating a disease-specific hybrid gene [83]. The NPM/RARα fusion protein is believed to disrupt the normal function of RARα [83]. NPM is a nuclear phosphoprotein that is ubiquitously expressed [83, 105]. Its main function is believed to be transportation of ribosomal materials between the nucleolus and the cytoplasm [83]. NPM is also a target of other chromosomal translocations [83], implying involvement of the protein in important regulatory processes. This protein is also implicated in regulation of p53, because it was found directly binding and stabilizing p53 in the events such as cellular stresses that induce expression of p53 [83, 105]. The APL cells that harbor the t(5;17)(q35;q21) have favorable prognosis because they respond well to ATRA treatment [81, 83].

The t(11;17)(q13;q21) is a rare chromosomal translocation that fuses NuMA to RARα [83]. This translocation also exhibit favorable prognosis because it is sensitivity to ATRA [83]. NuMA seems to have important roles in mitosis, specifically in formation of spindle asters, and in re-formation of daughter nuclei [83, 106], and microtubule assembly [107]. Like the other RARα partners, RARα-NuMA disrupts the normal function of RARα and may lead to the leukemogenesis [81, 83].

In der (17) chromosomal abnormality, an interstitial deletion spanning a 3Mb DNA region on the long arm of chromosome 17 results in the fusion of *STAT4b* with RARα [83]. This event is very rare and its response to therapeutic regimens has not been determined. The *STAT5b* belongs to a family of transcription factors that are involved in multiple cellular processes and their aberrant expression is implicated in many cancer types including leukemia [83]. *STAT5b* is widely expressed including in hematopoietic progenitors [83]. Like the other RARα partners, this protein heterodimerizes with its coiled-coil motif. Disruption of the normal function of RARα as well as that of *STAT5b* could contribute to the leukemogenesis, although the function of *STAT5b* is not known.

TREATMENT RESPONSE IN PATIENTS WITH RARA FUSIONS

The most studied and better understood mechanism exploited by the fusion proteins is to recruit the transcriptional corepressors to the RARα regulated gene promoters, thus preventing RARα to activate its targeting genes that are important for hematopoiesis [33, 108]. It has been established that RARα and AML1 interacts with corepressors including N-CoR, mSin3A and HDACs [4, 21, 51, 109-112]. The classical treatment of APL is the intensive chemotherapy. Overall, APL exhibits favorable prognosis due to its sensitivity to treatment in general [113]. During the last 15 years, ATRA has become the mainstay of the treatment of APL [86, 96, 114]. Although a physiological concentration of ATRA is not effective, a pharmacological concentration of ATRA causes terminal differentiation of leukemic cells, and results in long term survival in APL patients [86, 88, 115, 116]. Furthermore, simultaneous administration of chemotherapy and ATRA has improved the remission rate and significant reduction of relapse risk [10, 97]. This combination therapy is more effective than either chemotherapy or ATRA alone and improved an overall survival rate [10, 97]. Although the mechanism of action of ATRA is not clear, it is believed that ATRA forces the APL cells into neutrophil-like differentiation [81, 84, 85, 88], which ultimately leads to apoptosis [81]. ATRA acts through the RARα signaling pathway [82, 84]. ATRA is also is believed to be involved in interferon signaling pathways because induction of interferon regulatory factor-1 (IRF-1) has been observed during ATRA treatment, and IRF-1 induces expression of interferons, which ultimately lead to apoptosis and cell death [84]. Most recently, use of an old medicine, As_2O_3, in APL has proven useful because it induces apoptosis in APL cells that are resistant to ATRA [81]. Furthermore, As_2O_3 has proven itself to be effective to treat the APL patients at disease recurrence [97].

Although positive results have been achieved in treating APL, significant problems remain to be solved. For instance, APL is linked to bleeding diathesis which occurs during early stage of the treatment. The bleeding seems to occur due to disseminated intravascular coagulation and excessive fibrinolysis [81]. Severe coagulation that can lead to hemorrhagic complications has become clinical feature of the disease [97]. The coagulopathy is usually triggered or more exacerbated by chemotherapy leading to high induction death rate at 10%, meanwhile increased awareness has resulted in better supportive care that resulted in decreased induction death [97]. The side effects including fever, respiratory distress, pleural or pericardial effusion and interstitial lung infiltration usually occur during the first month of treatment and occasionally immediately after administration of the first dose of ATRA [81]. These side effects are so serious that if left untreated, they can lead to hypoxia, respiratory failure and ultimate death [81]. Other common and reversible side effects associated with ATRA treatment are headache, dry skin and mucosal membrane [81]. Hence, better treatment methods and regimens that eliminate the unnecessary side effects that affect the quality of life of the patients are urgently needed.

THE COMMON CHARACTERISTICS OF THE CBF AND RARα, ASSOCIATED-FUSION PROTEINS AND NOVEL THERAPEUTIC APPROACHES

Remarkably, despite the structural and functional divergences among the fusion partners of the CBF and the RARα, the fusion proteins exploit similar, if not identical biochemical mechanisms to exert their dominant inhibitory efforts. The recruitment of corepressors and HDACs accompanied by some epigenetic changes such as hypermethylation of the promoters result in effective inhibition of gene expression [97]. It has been established that the AML1/ETO chimeric protein interacts with corepressors including N-CoR, mSin3A and HDACs [4, 21, 51, 109-111]. The ETO part of the chimeric protein is responsible for the recruitment of the corepressors [4, 43, 54, 113]. The RARα/fusion proteins also recruit corepressors and HADC-complexes in order to repress the genes that are normally activated by RARα [83, 110]. In deed, it has been

demonstrated that the RARα fusion proteins recruits N-CoR and HDAC3 [108]. The PML/RARα fusion protein in particular recruits N-CoR/Sin3/HDAC1 complex to RARα-target promoter regions and inhibits transcription [68]. These unifying themes of the diverse subtypes of leukemia may offer the opportunity for designing a single treatment agent that can specifically target the leukemic cells and improve therapeutic efficacy compared to the classical chemotherapy. The CBF leukemias and the RARα-targeting APL all exploit similar biochemical mechanisms including recruitment of HDACs to the promoter region of the genes that play crucial roles in hematopoiesis [33]. Usage of HDAC inhibitors is underway in research laboratories and shows some promising results [117]. For instance, treatment of leukemia cell lines with valproic acid (VPA) has shown encouraging results [117]. VPA is known to selectively inhibit some HDACs. Treatment of cell lines that harbor AML1/ETO with VPA resulted in inhibition of the recruitment of HDACs by AML1/ETO and induced histone hyperacetylation, which resulted in re-expression of the AML1/ETO repressed genes [117]. HDAC inhibitors are not as dangerous as chemotherapy because they exert their therapeutic effects at the epigenetic level, and therefore can offer milder yet effective treatment choice.

Molecular and gene targeting therapeutic approaches have been tested. Specific protein redirection as a transcriptional therapy approach for t(8;21) has been attempted [118]. In another study, overexpression of the domains of the fusion proteins that recruit corepressors has been attempted in cell lines that harbor the leukemic fusion genes [119]. In the protein redirection approach, it was intended to remove the fusion proteins such as the AML1/ETO form the AML1-regulated gene promoters. Epigenetic therapy combined with some molecular targeting methodologies might offer safer and more effective therapeutic choice in the future.

FUTURE PERSPECTIVE

Genome-wide studies have allowed identification and further classification of risk groups and subtypes of AML. Gene-expression profiling allows a comprehensive classification of AML that includes previously identified genetically defined subgroups and a novel cluster with an adverse prognosis [120]. A unique cluster with a distinctive gene-expression signature included cases of AML with a poor treatment outcome has been identified [121]. The biological and prognostic heterogeneity of CBF-AML subtypes, including gene mutation and gene expression profiles as well as molecular response to therapy needed to be further studied. The future studies to address the heterogeneity and sub-risk group of CBF-AML will help to design a unique predefined strategy to treat these patients. Prognostic significance of microRNA expression signatures associated with, for example, CEBPA mutations in cytogenetically normal acute myeloid leukemia with high-risk molecular features have been investigated [122]. More comprehensive gene-expression signature-based and microRNA expression-based classifiers are needed for predicting outcome for individual patients with greater accuracy in the future diagnostics. This information is likely to have a major impact on the clinical management of in selection of appropriate treatment, since many of the identified genetic alterations already constitute or will potentially become targets for specific therapeutic intervention. The molecular effects induced by chemotherapeutic agents such as panobinostat and doxorubicin have been investigated by analyzing gene expression, cell cycle, apoptosis and signaling pathways. Analyses of gene expression profiles identified many genes whose expression was exclusively affected by the combination of panobinostat and doxorubicin [123]. Molecular cytology and pathology will have a great future impact on the precise classification of subtypes of leukemia and define the risk groups for diagnostics and prognostics and treatment respond. These novel approaches will help clinicians to design unique strategies to treat individual patients and to minimize the side-effects.

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