Diverse and Opposing Roles of IL-27 in Immunity

Zoë Fonseca-Kelly[2], Abdolmohamad Rostami[2] and Denise C. Fitzgerald*[,1]

[1]*Centre for Infection and Immunity, Queen's University Belfast, Northern Ireland*

[2]*Dept. of Neurology, Thomas Jefferson University, Philadelphia, USA*

Abstract: IL-27 was originally thought to play a pro-inflammatory role in immunity, however it is now clear that IL-27 also exerts potent anti-inflammatory effects. Here, we discuss some of the key studies that have elucidated the diverse and apparently paradoxical roles of IL-27. While IL-27 can promote early Th1 development there is evidence of suppressive effects in later phases of Th1 responses. IL-27 exerts a direct inhibitory effect in Th2 immunity by blocking Th2 cell differentiation. The role of IL-27 in Th17 immune responses is also complex as it seems that while IL-27 can block early Th17 development, fully differentiated Th17 cells may become resistant to the inhibitory effects of IL-27. In the field of cancer biology, IL-27 has been shown to have anti-tumourigenic effects however it acts *via* both immunogenic and non-immunogenic mechanisms. Collectively, the studies discussed in this review have demonstrated multiple biological functions and mechanisms of action of IL-27.

Keywords: IL-27, T cell, tumour, autoimmune disease.

INTRODUCTION

IL-27 is a heterodimeric cytokine composed of two subunits namely p28 and Epstein Barr Virus-induced gene 3 (EBI-3) [1]. It has recently been shown that EBI-3 is also a component of the novel heterodimeric cytokine IL-35 which shares its other subunit, p35, with IL-12 [2]. Thus it is recognised that there is a high degree of subunit promiscuity between these cytokines. Thus, it was originally thought that such cytokines would have similar functions and while there is a degree of overlap in certain aspects of their bioactivity, there are also many distinct roles for each individual cytokine. It has been shown that activated antigen presenting cells are the main source of IL-27, however, other cell types including endothelial cells, neutrophils, NKT cells and astrocytes also produce IL-27 [3-8]. Whereas murine p28 can be secreted, human p28 requires EBI-3 for secretion and thus, concomitant expression of both EBI-3 and p28 within the same cell appears to be required for optimal human IL-27 production [1]. Interestingly, it was recently shown in a murine colon carcinoma cell line, that murine p28 monomer inhibits the biological function of IL-27 [9].

Many Toll-like receptor (TLR) signalling pathways induce IL-27 expression including TLR2, TLR3, TLR4 and TLR9 and both MyD88 and TRIF have been identified as important signalling molecules in IL-27 expression. At the transcriptional level, binding sites for NFκB and IRF3 have been identified in the p28 promoter and NFκB can also induce EBI-3 expression [1, 10-15].

IL-27 signals *via* the IL-27 receptor (IL-27R) which is a heterodimer of the signalling IL-6 receptor called gp130 and WSX-1 (also known as T cell cytokine receptor, TCCR) [16]. IL-27R is expressed on a range of cell types including T cells, monocytes, dendritic cells (DCs), mast cells, hepatocytes, endothelial cells, neurons, B and NK cells [16-19]. Thus, a wide range of cell types can be responsive to IL-27 which confers multiple functions to this cytokine. In addition, IL-27R ligation induces activation of a range of signalling pathways which can be cell-specific. Each of STAT1, 3, 4 and 5 have been shown to exert functional cellular responses to IL-27R ligation in several settings [10, 17, 20].

IL-27 IN HELPER T CELL RESPONSES

T Helper 1 (Th1)

Much of the research on IL-27 has focused on its function in adaptive immunity and in particular, its effect on helper T cells. Early work showed a supportive role for IL-27 in Th1 mediated immunity. Mechanisms underlying this phenomenon included induction of the Th1-assocciated transcription factor, T-bet, and upregulation of IL-12Rβ2 expression by naïve T cells [10, 21]. This renders naïve T cells responsive to IL-12 which has long since been known to drive IFN-γ expression and Th1 immunity. Rather than solely driving Th1 development, IL-27 was shown to synergise with IL-12 to promote Th1 development [1]. However, IL-27 can also exert an inhibitory effect on Th1 cells, particularly in the later phases of inflammatory responses. We have observed significant suppression of T cell IFN-γ expression by IL-27 (unpublished observations) and Yoshimura and colleagues also reported IL-27-mediated inhibition of IFN-γ expression by fully differentiated Th1 cells [22]. These findings may explain in part, apparently differing findings in Th1 mediated *in vivo* models. In addition, several groups have reported that IL-27 inhibits IL-2 production. Villarino *et al*. reported enhanced IL-2 expression by IL-27R-deficient cells and that exogenous IL-27 suppressed IL-2 production by wildtype cells [50]. Owaki *et al.* went on to show that this effect was mediated by SOCS3 [49]. As IL-2 plays an important role in the growth and survival of Th1 cells, this may

*Address correspondence to this author at the Centre for Infection and Immunity, Queen's University Belfast, Whitla Medical Building, 97 Lisburn Road, Belfast, BT9 7BL, Northern Ireland; Tel: +4428 9097 2193; Fax: +4428 9097 5839; E-mail: d.fitzgerald@qub.ac.uk

1876-8946/10

represent one of the mechanisms through which IL-27 can exert a suppressive effect on Th1 responses.

IL-27R-deficient mice have shown that IL-27 signalling was not absolutely required for generating Th1 responses as demonstrated by significant Th1-mediated inflammation in these mice. In fact, regulation of such inflammatory responses was impaired in these mice leading to significant host immunopathology. Comparison of wildtype and IL-27R-deficient mice infected with *Mycobacterium tuberculosis* showed greater lethality in the latter genotype despite increased bacterial clearance mediated by IFN-γ producing helper T cells. This presents a paradigm of sufficient Th1 mediated inflammation to eradicate the pathogen but a lack of resolution of inflammation leading to immune-mediated host pathology [23]. In a model of *Toxoplasma gondii* infection, IL-27R-deficiency lead to lethality associated with uncontrolled inflammation [24]. Similarly Rosas *et al*. demonstrated that $CD4^+$ T cell-mediated hepatic immunopathology developed in IL-27R-deficient mice infected with *Leishmania donovani* which was also associated with efficient eradication of the pathogen [25]. These studies suggest that IL-27 plays an inhibitory role at some point in Th1-mediated inflammation that serves to protect the host from excessive immunopathology. In theory, this constraint on Th1 cells could also impair the ability of the immune system to clear pathogenic organisms. However this has not been directly shown in *in vivo* models to date.

In models of autoimmune disease IL-27 has also been shown to exert dichotomous influences on Th1 cells. In the case of dextran sulfate sodium-induced colitis, IL-27R-deficiency resulted in less severe clinical disease with lower levels of IFN-γ compared to wildtype mice suggesting a pro-inflammatory role for IL-27 in this model [26]. Villarino *et al*. also observed that IL-27R-deficent mice exhibited delayed onset of colitis, associated with inhibited Th1 responses [27]. This would also suggest a role for IL-27 signalling in autoimmune pathology driven by Th1-mediated inflammation. However this study was in a model of concurrent IL-10-deficiency (*il27ra*$^{-/-}$ crossed with *il10*$^{-/-}$ mice) and IL-27 signalling was not absolutely required for autoimmune pathology as these mice eventually developed disease [27]. Distinct models of arthritis have shown pro- and anti- inflammatory effects of IL-27. Deficiency of the IL-27R resulted in less severe clinical disease and a delay in disease onset in the proteoglycan-induced model of arthritis compared to wildtype controls. Decreased IFN-γ – producing T cells and overall IFN-γ secretion was reported in this model while the frequency of IL-4- and IL-17-expressing cells did not differ between phenotypes [28]. In contrast, administration of IL-27 at the onset phase of disease ameliorated collagen-induced arthritis [29]. These somewhat conflicting findings may be due to differences in disease pathogenesis between the models employed, the difference in targeting of the IL-27 signalling system (complete signalling deficiency in the absence of IL-27R compared to exogenous IL-27 administration) or perhaps is reflective of the divergent roles of IL-27 at different phases of Th1 immune responses.

That IL-27 may initially support Th1 immunity, but later dampen this inflammatory response, can be explained in part by the expansion of IL-10-producing Th1 cells by IL-27 [30, 31]. As IL-10 is a potent anti-inflammatory cytokine, its expression by Th1 cells as a result of IL-27 bioactivity confers immunoregulatory properties to these cells that are generally perceived as inflammatory. We have reported an IL-10-dependent anti-inflammatory effect of IL-27 in a Th1-driven model of experimental autoimmune encephalomyelitis (EAE). Using IL-12 to polarise myelin-reactive T cells toward a Th1 phenotype, we showed that a combination of IL-12+IL-27 resulted in significantly less severe disease than IL-12 alone. This suppressive effect of IL-27 was not evident in IL-$10^{-/-}$ cells demonstrating that IL-10 was required for the anti-inflammatory effects of IL-27 in Th1-mediated EAE [30]. As cells were exposed to IL-27 after *in vivo* differentiation, these data are consistent with the theory that IL-27 can inhibit differentiated Th1 cells.

Th2

In contrast to apparently paradoxical effects of IL-27 on Th1 responses, the inhibitory effect of IL-27 on other helper T cell subsets is clearer. IL-27 abrogates Th2 development by blocking the Th2-associated transcription factor GATA-3 in a STAT1-mediated manner [32]. *In vivo*, the inhibitory

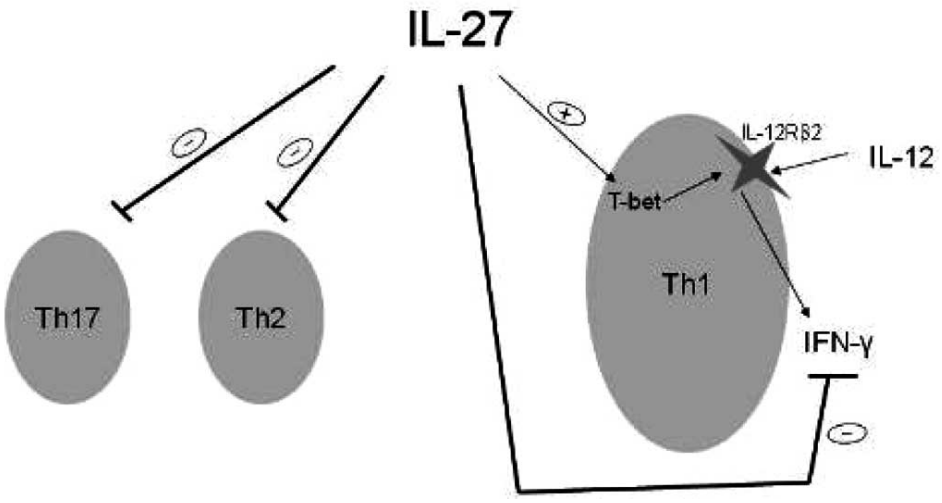

Fig. (1). Multiple effects of IL-27 on helper T cell subsets. IL-27 has direct suppressive (-) effects on Th17 and Th2 cells. However, IL-27 can both support (+) the development of Th1 cells and also inhibit (-) the function of these cells.

effect of IL-27 on Th2 immunity has been shown in both infectious and autoimmune murine models.

Artis and colleagues reported that IL-27R-deficient mice infected with *Trichuris muris* cleared the pathogen more efficiently than wildtype controls demonstrating that IL-27 signalling has an inhibitory effect in this model. Helminth clearance was mediated by Th2 immunity and neutralization of IL-4 resulted in greater larval burden and reduced IL-4 and IL-13 expression by antigen specific cells [17]. In autoimmune models IL-27 has also been shown to suppress Th2 responses. Yoshimoto *et al.* reported suppression of OVA-induced airway hyper-responsiveness by exogenous IL-27 administration which resulted in an inhibition of Th2 cell development and cytokine production [32]. More recently, Fujita and colleagues demonstrated that IL-27 produced by iNKT cells mediated suppression of Th2-associated allergic inflammation by alpha-GalCer [8].

In a model of spontaneous glomerulonephritis, IL-27R-deficiency caused a shift in the Th1:Th2 balance and resulted in a Th2-mediated immunopathology similar to human membranous glomerulonephritis [33]. This observation was a phenotypic switch in the helper T cell profile from Th1 towards Th2 which may be due to both the early supportive role of IL-27 in Th1 cell development as well as the inhibitory effect on Th2 development.

Th17

In terms of Th17-driven inflammatory responses, several groups have shown that IL-27 has an inhibitory effect on Th17 cells both *in vitro* and *in vivo* [3, 7, 34-37]. IL-27 blocks the expression of the Th17 transcription factors RORC and RORγt/RORα in human and mouse $CD4^+$ cells respectively [37, 38] in a STAT1-mediated manner. Interestingly, however, it would appear that once fully differentiated, Th17 cells become resistant to suppression by IL-27 [37].

The first evidence of IL-27 constraining Th17 cells in an infectious setting was shown in a murine model of *T. gondii* infection. Stumhofer *et al.* used a modified, non-lethal model of chronic infection to show greater severity of Th17-driven encephalitis in IL-27R-deficient mice than wildtype controls [7]. Similarly, in an autoimmune model of encephalomyelitis IL-27R-deficiency was shown to confer more severe clinical disease associated with enhanced Th17 cell infiltration into the CNS of mice immunized to develop EAE [35]. Amadi-Obi *et al.* also suggested that IL-27 inhibited Th17-mediated autoimmune pathology in experimental autoimmune uveoretinitis [34]. We have shown that exogenous administration of IL-27 prior to disease onset suppressed clinical disease in murine EAE. This was associated with reduced infiltration of Th17 cells and indeed Th1 cells into the CNS [3].

We have also shown that exogenous IL-27 inhibits the encephalitogenicity of proteolipid peptide $(PLP)_{139-151}$ - reactive Th17 cells that have been primed with IL-23 for 10 days *in vitro* [3]. However, more recent studies in our laboratory have produced apparently conflicting data to suggest that IL-27 does not inhibit the encephalitogenicity of IL-23-driven Th17 cells. Using the 2D2 mouse model, naïve myelin oligodendrocyte glycoprotein$(MOG)_{35-55}$-specific Th17 cells were differentiated *in vitro* using TGF-β+IL-6 and in a subsequent activation with antigen, cells were treated with IL-23 alone or IL-23+IL-27. Purified $CD4^+$ cells were then transferred to irradiated, naïve recipient mice. There was no

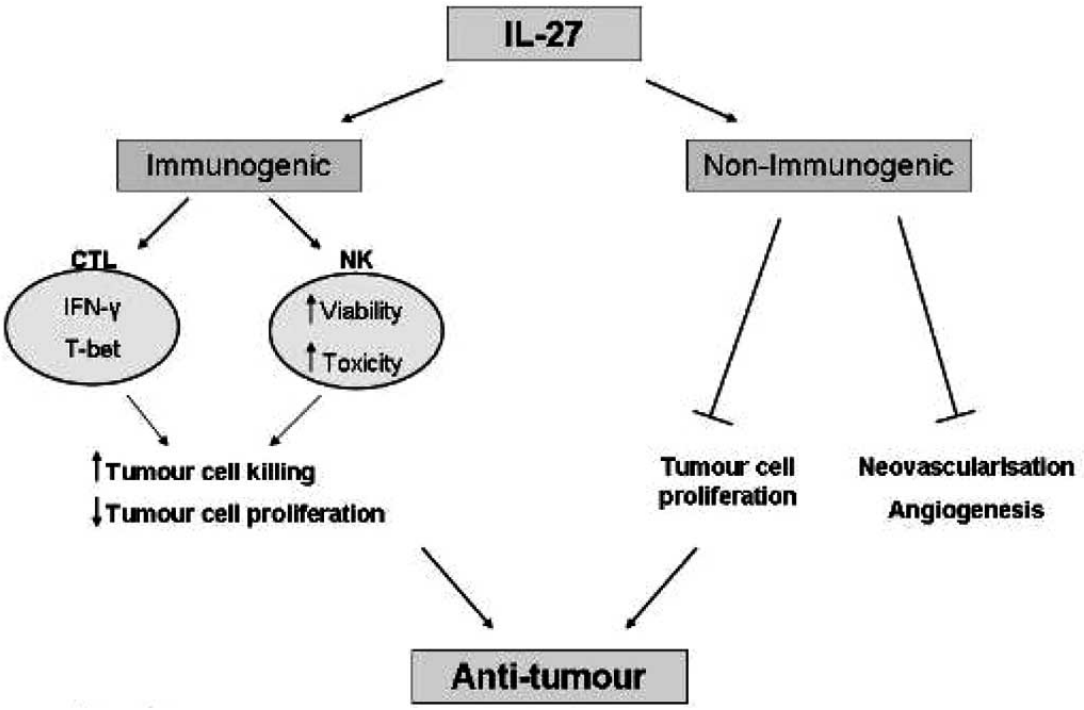

Fig. (2). Multiple anti-tumour effects of IL-27. Immunogenic mechanisms of action: Inhibition of tumour cell proliferation by IL-27 is mediated through CD8+ CTL cells and IFN-γ and dependant on T-bet. IL-27 also increases viability and toxicity of NK cells resulting in the death of tumour cells. Non-immunogenic mechanisms of action: IL-27 directly acts on tumour cells to inhibit tumour cell proliferation, neovascularisation and angiogenesis.

significant difference in clinical disease between groups and only mild suppression of IL-17 expression by IL-27 was observed [37].

While it is too early to definitively explain these apparently opposing findings, several differences between the models used suggest interesting possibilities. The MOG_{35-55} model involved transfer of purified $CD4^+$ cells whereas total cells were transferred in $PLP_{139-151}$ model suggesting that effects of IL-27 on non-$CD4^+$ cells may mediate disease suppression. Alternatively, the duration of culture with IL-23 ± IL-27 may affect the sensitivity of Th17 cells to IL-27; the MOG model involved a 3-day exposure whereas the PLP model involved a 10-day exposure to IL-23 ± IL-27. It is also possible that the difference in the differentiation conditions of naïve $CD4^+$ cells confers differential susceptibility of Th17 cells to suppression by IL-27; the MOG_{35-55} model utilized *in vitro* differentiation of $CD4^+$ cells with antigen, TGF-β+IL-6 whereas the $PLP_{139-151}$ model induced Th17 differentiation *in vivo* by immunization of animals with antigen in Complete Freunds' Adjuvant [3, 37]. These studies highlight some tantalizing unanswered questions in IL-27 biology and served to expand further the multitude of effects of IL-27 in immunity.

Th17 cells play an important role in the pathogenesis of EAE and other groups have also demonstrated a regulatory role of IL-27 in EAE. In a murine model of Type I Interferon receptor deficiency (*ifnar*$^{-/-}$), Guo and colleagues demonstrated enhanced disease severity compared to wildtype controls which was ameliorated by exogenous IL-27 treatment [37, 39]. Shinohara *et al.* made similar observations in this murine model at that time. However this group uncovered a novel mechanism of osteopontin-I-induced IL-27 expression which reduced the severity of clinical disease [40].

T Regulatory Cells (Treg)

IL-27 also plays an important role in the development of T regulatory (Treg) cells. Neufert *et al.* demonstrated that IL-27 inhibited TGF-β-induced Treg cells by almost 50% in an *in vitro* setting in a STAT-1-independent manner [36]. Huber *et al.* also demonstrated the suppressive effect of IL-27 on Tregs. Using transient siRNA, this group showed that the suppressive effect was partially *via* STAT-3 signaling [48]. Furthermore, Pot *et al.* demonstrated that IL-27 promotes the differentiation of IL-10-producing Tr1 cells which have potent immunomodulatory functions. This was shown to be *via* the induction of c-Maf, IL-21 and ICOS. IL-2 is an important cytokine in the development and function of iTregs. As discussed earlier, IL-27 has a potent inhibitory effect on IL-2 production by T cells. Neufert *et al*. addressed whether suppression of IL-2 by IL-27 was responsible for the inhibitory effect of IL-27 on Tregs. However, exogenous IL-2 could not protect Tregs from the suppressive effect of IL-27 and thus, this is likely not the primary mechanism of Treg suppression by IL-27 [36].

ANTI-TUMOUR EFFECTS OF IL-27

The field of cancer biology has also interrogated biological functions of IL-27. While published studies generally agree on the anti-tumour effect of IL-27, there are striking differences in the mechanisms through which IL-27 exerts this effect. In 2004, Hisada and colleagues first demonstrated potent anti-tumour effects of IL-27 *in vivo* with the use of a murine model of colon carcinoma. Transduction of C26 cells with IL-27 cDNA resulted in significant inhibition of tumour growth and tumour-specific protective immunity when mice were challenged with parent C26 tumour. Mechanistically, tumour inhibition was mediated by CD8+ cytotoxic T lymphocytes (CTL) and IFN-γ and was dependent on the transcription factor, T-bet, but independent of STAT4 signalling [41]. Salcedo *et al.* observed similar IFN-γ and CTL- mediated inhibition of tumour growth in a neuroblastoma model transduced with IL-27 [42]. This group later demonstrated that combined IL-2 and IL-27 therapy inhibited neuroblastoma metastases in a $CD8^+$ T cell dependent manner and this combination was particularly effective in bone marrow metastases [43].

However, the mechanisms by which IL-27 inhibits tumourogenesis are not limited to $CD8^+$ T cells. Matsui *et al.* showed an anti-tumour effect of IL-27 in a squamous cell carcinoma model which in general is not susceptible to NK cell cytotoxicity. However delivery of the IL-27 gene correlated with the presence of tumour-specific antibodies in sera which conferred susceptibility of tumour cells to NK cell cytotoxicity [44]. While the importance of IL-27 in the development of anti-tumour immunity has been demonstrated in several models, Shinozaki and colleagues recently highlighted an important example of opposing effects of IL-27 in this regard. As expected, mice that lacked IL-27 responsiveness (IL-27R-deficient) that were inoculated with B16 melanoma cells displayed enhanced tumour growth coupled with reduced tumour specific CTLs. Transfer of wildtype DCs did not rescue this phenotype however, injection of DCs from IL-27R-deficient mice resulted in tumour specific CTL expansion and inhibition of tumour growth. Importantly, the most effective combination of anti-tumourigenic cells was wildtype CTLs with IL-27R-deficient DCs which suggests that IL-27 directly acts on CTLs and actually inhibits the activity of DCs in anti-tumour immunity [45].

Further diversity in the anti-tumour effects of IL-27 is evident in studies that have shown non-immunological mechanisms of tumour inhibition. Shimuzu and colleagues investigated the efficacy of IL-27 in inhibiting tumour growth in a poorly immunogenic model of melanoma. Using B16F10 cells they showed anti-tumourigenic and anti-metastatic effects of IL-27 however this effect was preserved in the absence of IFN-γ and also partially in NOD/SCID mice suggesting novel mechanisms of action. Indeed this study went on to demonstrate anti-angiogenic actions directly affecting endothelial cells which was in part due to IP-10 induction [46]. In 2008 Yoshimoto *et al.* identified a direct anti-proliferative effect of IL-27, *via* STAT1 signalling, in the B16F10 model of melanoma which was translated to human melanoma cells [47].

Collectively, these studies demonstrate multiple roles of IL-27 in anti-tumourogenicity which encompass immune-mediated, vascular and direct anti-proliferative mechanisms.

In conclusion, the field of IL-27 biology has elucidated surprising and apparently paradoxical functions for IL-27, particularly in *in vivo* models. However, it is likely that, as with many other cytokines, the biological function of IL-27 is greatly influenced by the microenvironment as well as the global immune status of the organism. Clearly much data has

demonstrated a supportive role for IL-27 in the development of Th1 responses, in several *in vivo* models. That IL-27 can also inhibit Th1 immune responses in certain settings is perplexing and warrants further investigation. Several other importance questions remain to be addressed in the field of IL-27 biology. In particular, it is unclear how and when fully differentiated helper Th17 cells become partially or fully resistant to suppression by IL-27. What are the molecular mechanisms underlying this transition? Importantly in the context of therapeutic applications of IL-27, is this phenomenon reversible? Answering these questions will help to progress towards a unifying model that may explain the apparent paradoxical roles of IL-27 in inflammation.

REFERENCES

[1] Pflanz S, Timans JC, Cheung J, *et al*. IL-27, a heterodimeric cytokine composed of EBI3 and p28 protein, induces proliferation of naive CD4(+) T cells. Immunity 2002; 16: 779-90.

[2] Niedbala W, Wei XQ, Cai B, *et al.* IL-35 is a novel cytokine with therapeutic effects against collagen-induced arthritis through the expansion of regulatory T cells and suppression of Th17 cells. Eur J Immunol 2007; 37: 3021-9.

[3] Fitzgerald DC, Ciric B, Touil T, *et al*. Suppressive effect of IL-27 on encephalitogenic Th17 cells and the effector phase of experimental autoimmune encephalomyelitis. J Immunol 2007; 179: 3268-75.

[4] Li J, Gran B, Zhang GX, Rostami A, Kamoun M. IL-27 subunits and its receptor (WSX-1) mRNAs are markedly up-regulated in inflammatory cells in the CNS during experimental autoimmune encephalomyelitis. J Neurol Sci 2005; 232: 3-9.

[5] Smits HH, van Beelen AJ, Hessle C, *et al.* Commensal Gram-negative bacteria prime human dendritic cells for enhanced IL-23 and IL-27 expression and enhanced Th1 development. Eur J Immunol 2004; 34: 1371-80.

[6] Sonobe Y, Yawata I, Kawanokuchi J, *et al.* Production of IL-27 and other IL-12 family cytokines by microglia and their subpopulations. Brain Res 2005; 1040: 202-7.

[7] Stumhofer JS, Laurence A, Wilson EH, *et al.* Interleukin 27 negatively regulates the development of interleukin 17-producing T helper cells during chronic inflammation of the central nervous system. Nat Immunol 2006; 7: 937-45.

[8] Fujita H, Teng A, Nozawa R, *et al.* Production of both IL-27 and IFN-gamma after the treatment with a ligand for invariant NK T cells is responsible for the suppression of Th2 response and allergic inflammation in a mouse experimental asthma model. J Immunol 2009; 183: 254-60.

[9] Shimozato O, Sato A, Kawamura K, *et al.* The secreted form of p28 subunit of interleukin (IL)-27 inhibits biological functions of IL-27 and suppresses anti-allogeneic immune responses. Immunology 2009; 128: e816-25.

[10] Hibbert L, Pflanz S, De Waal Malefyt R, Kastelein RA. IL-27 and IFN-alpha signal *via* Stat1 and Stat3 and induce T-Bet and IL-12Rbeta2 in naive T cells. J Interferon Cytokine Res 2003; 23: 513-22.

[11] Liu J, Guan X, Ma X. Regulation of IL-27 p28 gene expression in macrophages through MyD88- and interferon-gamma-mediated pathways. J Exp Med 2007; 204: 141-52.

[12] Molle C, Nguyen M, Flamand V. IL-27 synthesis induced by TLR ligation critically depends on IFN regulatory factor 3. J Immunol 2007; 178: 7607-15.

[13] Redecke V, Hacker H, Datta SK, *et al.* Cutting edge: activation of Toll-like receptor 2 induces a Th2 immune response and promotes experimental asthma. J Immunol 2004; 172: 2739-43.

[14] Wirtz S, Becker C, Fantini MC, *et al.* EBV-induced gene 3 transcription is induced by TLR signaling in primary dendritic cells *via* NF-kappa B activation. J Immunol 2005; 174: 2814-24.

[15] Schuetze N, Schoeneberger S, Mueller U, *et al*. IL-12 family members: differential kinetics of their TLR4-mediated induction by Salmonella enteritidis and the impact of IL-10 in bone marrow-derived macrophages. Int Immunol 2005; 17: 649-59.

[16] Pflanz S, Hibbert L, Mattson J, *et al*. WSX-1 and glycoprotein 130 constitute a signal-transducing receptor for IL-27. J Immunol 2004; 172: 2225-31.

[17] Artis D, Villarino A, Silverman M, *et al*. The IL-27 receptor (WSX-1) is an inhibitor of innate and adaptive elements of type 2 immunity. J Immunol 2004; 173: 5626-34.

[18] Bender H, Wiesinger MY, Nordhoff C, *et al.* Interleukin-27 displays interferon-gamma-like functions in human hepatoma cells and hepatocytes. Hepatology 2009; 50: 585-91.

[19] Hashimoto Y, Kurita M, Aiso S, Nishimoto I, Matsuoka M. Humanin inhibits neuronal cell death by interacting with a cytokine receptor complex or complexes involving CNTF receptor alpha/WSX-1/gp130. Mol Biol Cell 2009; 20: 2864-73.

[20] Takeda A, Hamano S, Yamanaka A, *et al.* Cutting edge: role of IL-27/WSX-1 signaling for induction of T-bet through activation of STAT1 during initial Th1 commitment. J Immunol 2003; 170: 4886-90.

[21] Kamiya S, Owaki T, Morishima N, *et al.* An indispensable role for STAT1 in IL-27-induced T-bet expression but not proliferation of naive CD4+ T cells. J Immunol 2004; 173: 3871-7.

[22] Yoshimura T, Takeda A, Hamano S, *et al.* Two-sided roles of IL-27: induction of Th1 differentiation on naive CD4+ T cells versus suppression of proinflammatory cytokine production including IL-23-induced IL-17 on activated CD4+ T cells partially through STAT3-dependent mechanism. J Immunol 2006; 177: 5377-85.

[23] Holscher C, Holscher A, Ruckerl D, *et al*. The IL-27 receptor chain WSX-1 differentially regulates antibacterial immunity and survival during experimental tuberculosis. J Immunol 2005; 174: 3534-3544.

[24] Villarino A, Hibbert L, Lieberman L, *et al.* The IL-27R (WSX-1) is required to suppress T cell hyperactivity during infection. Immunity 2003;19: 645-55.

[25] Rosas LE, Satoskar AA, Roth KM, *et al.* Interleukin-27R (WSX-1/T-cell cytokine receptor) gene-deficient mice display enhanced resistance to leishmania donovani infection but develop severe liver immunopathology. Am J Pathol 2006; 168: 158-69.

[26] Honda K, Nakamura K, Matsui N, *et al.* T helper 1-inducing property of IL-27/WSX-1 signaling is required for the induction of experimental colitis. Inflamm Bowel Dis 2005; 11: 1044-52.

[27] Villarino AV, Artis D, Bezbradica JS, *et al*. IL-27R deficiency delays the onset of colitis and protects from helminth-induced pathology in a model of chronic IBD. Int Immunol 2008; 20: 739-52.

[28] Cao Y, Doodes PD, Glant TT, Finnegan A. IL-27 induces a Th1 immune response and susceptibility to experimental arthritis. J Immunol 2008; 180: 922-30.

[29] Niedbala W, Cai B, Wei X, *et al.* Interleukin 27 attenuates collagen-induced arthritis. Ann Rheum Dis 2008; 67: 1474-9.

[30] Fitzgerald DC, Zhang GX, El-Behi M, *et al.* Suppression of autoimmune inflammation of the central nervous system by interleukin 10 secreted by interleukin 27-stimulated T cells. Nat Immunol 2007; 8: 1372-9.

[31] Stumhofer JS, Silver JS, Laurence A, *et al.* Interleukins 27 and 6 induce STAT3-mediated T cell production of interleukin 10. Nat Immunol 2007; 8: 1363-71.

[32] Yoshimoto T, Yoshimoto T, Yasuda K, Mizuguchi J, Nakanishi K. IL-27 suppresses Th2 cell development and Th2 cytokines production from polarized Th2 cells: a novel therapeutic way for Th2-mediated allergic inflammation. J Immunol 2007; 179: 4415-23.

[33] Shimizu S, Sugiyama N, Masutani K, *et al*. Membranous glomerulonephritis development with Th2-type immune deviations in MRL/lpr mice deficient for IL-27 receptor (WSX-1). J Immunol 2005; 175: 7185-92.

[34] Amadi-Obi A, Yu CR, Liu X, *et al.* TH17 cells contribute to uveitis and scleritis and are expanded by IL-2 and inhibited by IL-27/STAT1. Nat Med 2007; 13: 711-8.

[35] Batten M, Li J, Yi S, *et al.* Interleukin 27 limits autoimmune encephalomyelitis by suppressing the development of interleukin 17-producing T cells. Nat Immunol 2006; 7: 929-36.

[36] Neufert C, Becker C, Wirtz S, *et al*. IL-27 controls the development of inducible regulatory T cells and Th17 cells *via* differential effects on STAT1. Eur J Immunol 2007; 37: 1809-16.

[37] El-Behi M, Ciric B, Yu S, *et al*. Differential Effect of IL-27 on Developing versus Committed Th17 Cells. J Immunol 2009; 183(8): 4957 - 67.

[38] Diveu C, McGeachy MJ, Boniface K, *et al.* IL-27 blocks RORc expression to inhibit lineage commitment of Th17 cells. J Immunol 2009; 182: 5748-56.

[39] Guo B, Chang EY, Cheng G. The type I IFN induction pathway constrains Th17-mediated autoimmune inflammation in mice. J Clin Invest 2008; 118: 1680-90.

[40] Shinohara ML, Kim JH, Garcia VA, Cantor H. Engagement of the type I interferon receptor on dendritic cells inhibits T helper 17 cell development: role of intracellular osteopontin. Immunity 2008; 29: 68-78.

[41] Hisada M, Kamiya S, Fujita K, *et al.* Potent antitumor activity of interleukin-27. Cancer Res 2004; 64: 1152-6.

[42] Salcedo R, Stauffer JK, Lincoln E, *et al.* IL-27 mediates complete regression of orthotopic primary and metastatic murine neuroblastoma tumors: role for CD8+ T cells. J Immunol 2004; 173: 7170-82.

[43] Salcedo R, Hixon JA, Stauffer JK, *et al.* Immunologic and therapeutic synergy of IL-27 and IL-2: enhancement of T cell sensitization, tumor-specific CTL reactivity and complete regression of disseminated neuroblastoma metastases in the liver and bone marrow. J Immunol 2009; 182: 4328-38.

[44] Matsui M, Kishida T, Nakano H, *et al.* Interleukin-27 activates natural killer cells and suppresses NK-resistant head and neck squamous cell carcinoma through inducing antibody-dependent cellular cytotoxicity. Cancer Res 2009; 69: 2523-30.

[45] Shinozaki Y, Wang S, Miyazaki Y, *et al.* Tumor-specific cytotoxic T cell generation and dendritic cell function are differentially regulated by interleukin 27 during development of anti-tumor immunity. Int J Cancer 2009; 124: 1372-8.

[46] Shimizu M, Shimamura M, Owaki T, *et al.* Antiangiogenic and antitumor activities of IL-27. J Immunol 2006; 176: 7317-24.

[47] Yoshimoto T, Morishima N, Mizoguchi I, *et al.* Antiproliferative activity of IL-27 on melanoma. J Immunol 2008; 180: 6527-35.

[48] Huber M, Steinwald V, Guralnik A, *et al.* IL-27 inhibits the development of regulator T cells *via* STAT3. Int Immunol 2008; 20: 223-34.

[49] Owaki T, Asakawa M, Morishima N, *et al.* STAT3 is indispensable to IL-27-mediated cell proliferation but not to IL-27 induced Th1 differentiation and suppression of proinflammatory cytokine production. J Immunol 2008; 180: 2903-11.

[50] Villarino AV, Stumhofer JS, Saris CJ, *et al.* IL-27 limits IL-2 production during Th1 differentiation. J Immunol 2006; 176: 237-47.

Received: November 04, 2009 Revised: December 12, 2009 Accepted: December 16, 2009