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REVIEW

Interleukin-27: Biological Properties and Clinical Application

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Abstract Interleukin (IL)-27 is a novel cytokine secreted by stimulated antigen-presenting cells. Initial studies on the biology of IL-27 provided evidence for its role in the initiation of T_H1 responses; however, subsequent work has indicated that IL-27 has broad inhibitory effects on T_H1, T_H2, and T_H17 subsets of T cells as well as the expansion of inducible regulatory T cells. The involvement of IL-27 in the regulation of angiogenesis and antiviral response has also recently been reported. The aim of this review is to highlight the potential areas of IL-27 clinical application, especially the management of neoplastic and viral diseases as well as autoimmune disorders, including rheumatoid arthritis and multiple sclerosis. The review will also serve to elaborate on the molecular mechanisms involved in the expression of this cytokine and signaling from the IL-27 receptor.

Keywords IL-27 · Cancer · Multiple sclerosis · Rheumatoid arthritis · HIV · Immunotherapy

Introduction

Cytokines, including interleukins, play a major role in the induction and limitation of inflammation. Depending on the local balance between particular cytokines, helper $CD4^+$ lymphocytes, key regulators of inflammatory response, differentiate toward one of several specialized phenotypes: T_H1, T_H2, the recently recognized T_H17, or one of several regulatory sub-populations.

Interleukin (IL)-27, a member of the same family as IL-12 and IL-23, has been associated mainly with the differentiation of T_H1 lymphocytes, enhancement of the cellular type immune response, and the reciprocal inhibition of T_H2 humoral immune reactions (Lucas et al. 2003). Soon it turned out that IL-27 may also influence other cells, including T_H17 lymphocytes, B lymphocytes, and NK cells (Batten et al. 2006; Diveu et al. 2009; Larousserie et al. 2006; Stumhofer et al. 2006). The latest studies assign new capabilities to IL-27: stimulation of hematopoiesis, enhancement of antigen presentation by antigen-presenting cells (APCs), inhibition of angiogenesis, and inhibition of HIV replication. Although the IL-27 receptor was initially thought to be expressed only by hematopoietic cells, new cell populations, including stem cells, vascular endothelium, and keratinocytes, have been found to be sensitive to IL-27 (Feng et al. 2008; Fitzgerald et al. 2007; Kanda and Watanabe 2008; Shimizu et al. 2006).

Hence this recently discovered protein may play a major role in the coordination of numerous immunological mechanisms. Further understanding of IL-27 function may pave the way for introducing IL-27 in several treatment schemes, especially in cancer, rheumatoid arthritis, and multiple sclerosis. In this short review we would like to summarize current knowledge concerning IL-27, pinpointing areas where recombinant IL-27 could possibly find a niche in the pharmaceutical market.

IL-27 and its Receptor

IL-27 is secreted as a heterodimer consisting of the Epstein-Barr-induced gene 3 product (EBI3) and p28.

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IL-27 shares a similar structural makeup with other members of the IL-12 family, with p28 being a four-helical cytokine and EBI3 structurally resembling a soluble cytokine receptor (Pflanz et al. 2002). Compared with other IL-12-related cytokines, IL-27 differs in that its subunits are not covalently linked. Expression of EBI3 has been found in obligatory APCs, including dendritic cells (DCs) and macrophages, as well as in activated vascular endothelium, syncytiotrophoblasts, and intestinal epithelium (Coulomb-L'Hermine et al. 2007; Maaser et al. 2004). EBI3, secreted readily by itself, also forms an alternative biologically active heterodimer with IL-12p35, forming IL-35 (Collison et al. 2007). Early studies suggested that p28 is not secreted unless it is coexpressed with EBI3. However, forced expression of p28 revealed that it is also secreted as a monomer. According to Shimozato et al., monomeric p28 acts as an inhibitor of IL-27 signaling, thus allowing for tight regulation of IL-27 activity (Shimozato et al. 2009). p28 was also recently found to form a novel, as yet unnamed, cytokine as a complex with cytokine-like factor-1 (Crabé et al. 2009).

Increased expression of IL-27 has been associated with granulomatous diseases such as tuberculosis, sarcoidosis, and Crohn's disease (Larousserie et al. 2004). Upregulation of IL-27 has also been noted in mouse models of uveitis and multiple sclerosis as well as at sites of inflammation during infection by *Trichuris muris*, *Toxoplasma gondii*, and *Leyshmania mayor* (Stumhofer et al. 2006; Yoshida et al. 2001). IL-27 is also abundantly expressed in placenta throughout normal pregnancy (Coulomb-L'Hermine et al. 2007), although its function there has not yet been described.

IL-27 receptor, like IL-27, is a heterodimer. It is composed of the T-cell cytokine receptor TCCR, also known as WSX-1 or IL-27Rα, and the protein gp130, a signal-transducing chain that is utilized by several other cytokines, including IL-6, IL-11, ciliary neurotrophic factor, and leukemia inhibitory factor. IL-27 is capable of binding to TCCR/WSX-1 in the absence of gp130, although both subunits are required for signal transduction (Pflanz et al. 2004). Ligation of IL-27 receptor activates the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway. JAK proteins associate with the intracellular domains of gp130 and WSX-1 and become activated by phosphorylation upon IL-27 binding. Subsequently, JAKs phosphorylate STAT transcription factors, allowing them to form dimers and translocate to the nucleus, where they induce the transcription of effector genes. Specifically, IL-27 has been shown to activate JAK1, JAK2, TYK2, STAT1, STAT3, STAT4, and STAT5 proteins, with STAT1 and STAT3 as apparent direct targets of IL-27 (Miyazaki et al. 2005; Owaki et al. 2006a; Villarino et al. 2006). IL-27 receptor is expressed by hematopoietic stem cells of all lymphoid and myeloid lineages as well as by vascular endothelium (Shimizu et al. 2006) and keratinocytes (Kanda and Watanabe 2008).

Regulation of IL-27 Expression

APCs, which serve as a bridge between the innate and the adaptive immune systems, are the main source of IL-27 (Pflanz et al. 2002; Wirtz et al. 2005). Thanks to pattern-recognition receptors, including Toll-like receptors (TLRs), APCs can detect pathogens and activate the adaptive immune system by upregulation of costimulatory molecules and secretion of cytokines. TLR agonists induce the expressions of IL-12 and IL-23 in APCs. Likewise, expression of both IL-27 subunits was upregulated upon APC stimulation with poly(I:C), lipopolysaccharide (LPS), and CpG-DNA, which are agonists of TLR3, TLR4, and TLR9, respectively (Pflanz et al. 2002; Pirhonen et al. 2007; Remoli et al. 2007; Schuetze et al. 2005). TLR2 (Wirtz et al. 2005) agonists have little effect on IL-27 expression.

The TLR-associated adapter protein MyD88 and the nuclear factor (NF)-κB family of transcription factors have been found to play a vital role in the induction of IL-12 expression in response to TLR stimulation. Similarly, in the case of IL-27, expression of EBI3 and p28 could not be induced upon TLR4 stimulation in MyD88-deficient DCs (Wirtz et al. 2005) and macrophages (Liu et al. 2007), respectively. In addition to MyD88, other adapter proteins, such as TRIF 9, which is associated with TLR3 and TLR4, take part in signal transduction from TLR receptors. Bone marrow-derived DCs from $Trif^{-/-}$ mice stimulated with LPS are unable to upregulate p28 and EBI3 gene expression (Molle et al. 2007). Apart from TLR agonists, expression of IL-27 subunits can also be upregulated by host-derived inflammatory stimuli such as IL-1β or CD40 ligation in a MyD88-dependent manner (Schnurr et al. 2005; Wirtz et al. 2005).

Until now, several transcription factors have been identified that directly activate IL-28 and EBI3 expression. NF-κB p50 and p65 are required for EBI3 expression (Wirtz et al. 2005), while another NF-κB transcription factor, c-Rel, is partially dispensable for p28 transcription (Liu et al. 2007). Both p50 and p65 bind to the EBI3 promoter. Moreover, p50-deficient DCs stimulated with LPS do not upregulate EBI3. In addition to MyD88 and NF-κB, recruitment of PU.1 transcription factor and interferon regulatory factors (IRF1 and 3) are required for EBI3 and p28 gene promoter activation, respectively (Liu et al. 2004; Molle et al. 2007; Wirtz et al. 2005).

TRIF, mentioned above, is known to activate the transcription factor IRF3. Consistent with that finding, IRF3-deficient DCs express a lower level of p28 (Molle et al.

2007). IRF activation also leads to the upregulation of interferon (IFN)-β expression. IFN-β as well as IFN-α and IFN-γ were found to upregulate p28 expression in DCs; however, in IRF3 knockouts, exogenous IFN is insufficient for restoration of p28 expression to the level observed in wild-type DCs (Pirhonen et al. 2007; Remoli et al. 2007). Upregulation of the IL-12 subunit p35 by IFN-γ requires another IFN regulatory factor, IRF1. Similarly, both IRF1 and IRF3 were shown to bind to p28 promoter (Liu et al. 2004; Molle et al. 2007). Moreover, p28 expression in macrophages stimulated with IFN-γ is completely abrogated by IRF1 knockout (Lapenta et al. 2006; Liu et al. 2003). The current knowledge of the transcriptional regulation of IL-27 is summarized in Fig. 1.

IL-27 Promotes Cell-Mediated Immune Reactions

IL-27 promotes T_H1 polarization of $CD4^+$ lymphocytes in vitro. IL-27, acting through STAT1, induces the expression of transcription factor T-bet, which is crucial for the transcription of T_H1-related genes (Fig. 2). T-bet enhances the expressions of IFN-γ and the IL-12β receptor subunit. IL-12 signaling enables lymphocytes to maintain T_H1 polarization. (Kamiya et al. 2004; Pflanz et al. 2002). Induction of T-bet expression by IL-27 can also occur in a STAT1-independent fashion: IL-27 induces the expression of growth arrest and DNA damage-inducible 45γ gene (GADD45γ). Its product, in turn, enhances T-bet expression through MAPK p38 (Owaki et al. 2006b).

As in the case of $CD4^+$ lymphocytes, IL-27 induces the activation of STAT1, STAT3, STAT4, and STAT5 and the expressions of T-bet and IL-12Rβ in $CD8^+$ lymphocytes (Mayer et al. 2008; Neufert et al. 2007; Owaki et al. 2006a; Villarino et al. 2006). Additionally, in $CD8^+$ lymphocytes, IL-27 augments the expression of the transcription factor eomesodermin, crucial for developing cytotoxic activity. Indeed, it was recently reported (Morishima et al. 2005) that lymphocytes incubated in the presence of IL-27 show higher levels of the key proteins granzyme B and perforin, with concomitant higher cytotoxic activity. IL-27 also influences the migration of $CD8^+$ lymphocytes, probably by upregulation of chemokine CXCL9 and CXCL10 expression (Shimizu et al. 2006). In mice challenged with neuroblastoma, a dramatic increase in $CD8^+$ lymphocyte infiltration was noted in IL-27-transfected versus wild-type neuroblastoma tumors (Salcedo et al. 2004).

Taken together, these data suggest a key role of IL-27 in the initiation of the cellular-type immunological response, with STAT1-dependent induction of T-bet expression being the most important molecular event.

IL-27 Limits Inflammatory Reactions

IL-27 Induces Tr1 Regulatory Lymphocytes and Limits T_H1 Responses

Host control of parasitic infections with *Leishmania donovani*, *Trypanosoma cruzi*, or *Toxoplasma gondii*

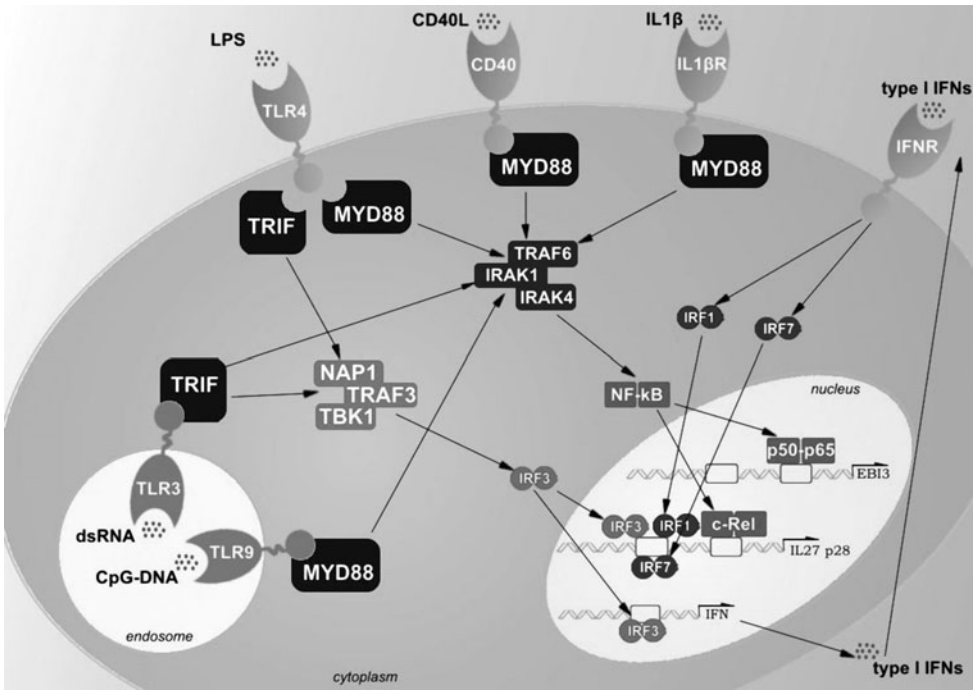
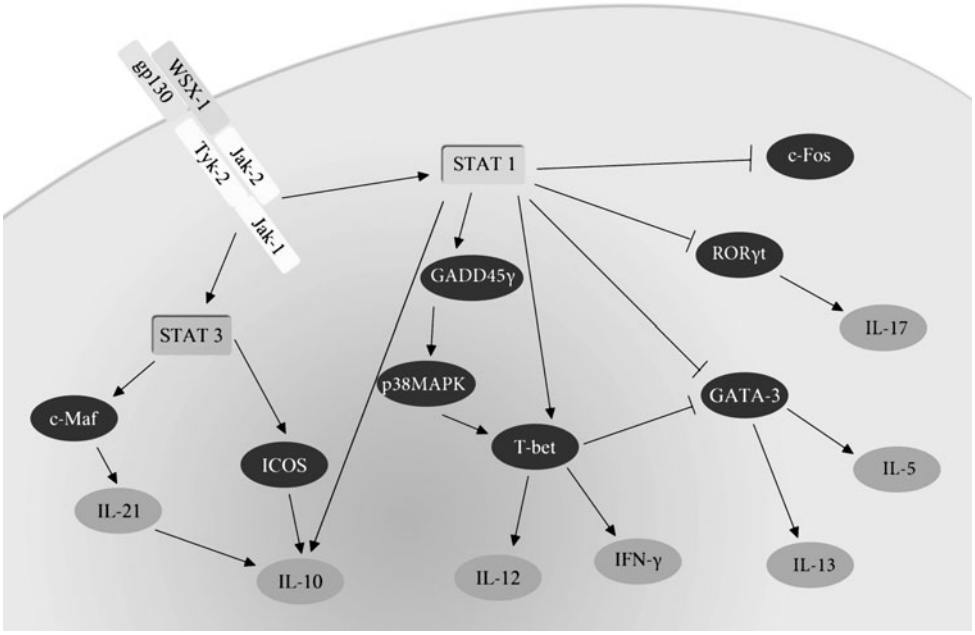


Fig. 1 Transcriptional regulation of IL-27 expression

Fig. 2 IL-27 signaling pathway



depends mainly on T_H1 lymphocytes. Paradoxically, while IL-27 has T_H1 stimulatory capacity in vitro, mice with a genetic Wsx-1 deficiency eliminate these parasites better than wild-type mice, although they suffer from secondary lethal pathologies resulting from an exacerbated inflammatory reaction (Rosas et al. 2006). Also in the case of *Mycobacterium tuberculosis*, Wsx-$1^{-/-}$ mice eliminate the bacilli faster than wild-type mice. However, the excessive inflammatory response, resulting in more intensive lung tissue infiltration and fibrosis, eventually increases mortality (Pearl et al. 2004; Hölscher et al. 2005).

These observations suggested that IL-27 not only induces T_H1 lymphocyte differentiation, but can at the same time suppress them, preventing excessive inflammation. The phenotype of Wsx-$1^{-/-}$ mice shares several similarities with the phenotype of mice lacking IL-10, a cytokine responsible for suppressing T_H1 cytokine production. In fact, Wsx-1 knockout mice produce much less IL-10 than the wild-type.

IL-27 was recently shown to induce the differentiation of Tr1 cells, a subset of T cells that have strong immunosuppressive properties and predominantly produce IL-10 (Awasthi et al. 2007; Batten et al. 2008). Stumhofer et al. have shown that IL-27-treated T cells produce IL-10 in a STAT1- and STAT3-dependent manner. IL-27 induces a transcription factor, c-Maf, to transactivate IL-21 (Stumhofer et al. 2007). Because IL-27 induces not only IL-21 production, but also the expression of IL-21 receptor, IL-21 seem to act as an autocrine growth/differentiation factor for all Tr1 cells (Xu et al. 2009). Loss of IL-21 signaling in T cells from IL-21R-deficient cells results in significant inhibition of the IL-27-driven generation of Tr1 cells and IL-10 cytokine production. IL-27 is also a potent inducer of the costimulatory receptor ICOS which, together with c-Maf and IL-21, promotes the expression of IL-10. IL-27 can augment IL-10 expression only for a very short time. In contrast to IL-27 alone, simultaneous stimulation by IL-27 and transforming growth factor (TGF)-β causes a long-lasting production of IL-10 by T lymphocytes (Awasthi et al. 2007), which could possibly be explained by TGF-β-induced sustained STAT3 activation and consequent c-Maf expression (Xu et al. 2009).

Suppression of T_H2 Lymphocytes by IL-27

IL-27-mediated activation of STAT1 and T-bet suppresses transcription factor GATA-3 in T cells (Lucas et al. 2003). GATA-3 is a marker transcription factor that is expressed by T_H2-polarized T lymphocytes. In fact, Wsx-$1^{-/-}$ TGF mice show evidence of enhanced T_H2 responses and control infestation with *Trichuris muris* larvae much faster than wild-type mice, and this correlates with T_H2-type cytokine production (Artis et al. 2004). Together, these data suggest that IL-27 can inhibit T_H2 cell differentiation. Accordingly, IL-27 has been found to suppress GATA-3 expression and induce T-bet expression even in polarized T_H2 cells (Yoshimoto et al. 2007). IL-27 inhibited the production of IL-5 and IL-13 in polarized T_H2 cells in a dose-dependent manner (Yoshimoto et al. 2007).

Miyazaki et al. found that the phenotype of induced experimental asthma, in which T_H2 cytokines are central

modulators of the pathology, was exacerbated in Wsx-1-deficient mice (Miyazaki et al. 2005). When challenged with allergen, Wsx-$1^{-/-}$ mice showed increased serum levels of IgE and T_H2 cytokines, airway hyperresponsiveness (AHR) with hyperplasia of goblet cells, and increased pulmonary eosinophil infiltration compared with wild-type mice (Miyazaki et al. 2005). Interestingly, 946A→G polymorphism in p28 seems to be associated with susceptibility to asthma in humans (Chae et al. 2007). Conversely, nasally administered IL-27 dose-dependently diminished AHR, airway eosinophilic inflammation, and goblet cell hyperplasia in antigen-challenged mice (Yoshimoto et al. 2007). IL-13 is suggested to play a critical role in AHR, airway eosinophilia, and mucus oversecretion. Since IL-27 was shown to diminish the IL-13 level in the lung dose-dependently (Yoshimoto et al. 2007), IL-27 administration might become an important therapeutic approach in allergic asthma and further studies are necessary to explore this promising therapeutic modality.

IL-27 Suppresses T_H17 Helper Lymphocytes

Helper T_H17 lymphocytes, which produce the effector cytokine IL-17 as well as IL-22, tumor necrosis factor-α, and granulocyte–macrophage colony stimulating factor, are associated with the antimicrobial immunological response. Increased numbers of T_H17 lymphocytes, and IL-17 secretion by them, are noted in patients with auto-immunological disorders such as rheumatoid arthritis and multiple sclerosis. IL-17 is central to the pathology observed in murine models of those diseases, i.e. collagen-induced arthritis (CIA) and experimental autoimmune encephalitis (EAE) (Graber et al. 2008; Shahrara et al. 2008).

IL-27 suppresses the T_H17 key transcription factor RORγt (Yang et al. 2008) and thus inhibits expression of IL-17 by T cells. Accordingly, mice deficient in either the IL-27 Ebi3 subunit or IL-27 receptor Wsx-1 have increased levels of IL-17 (Batten et al. 2006; Yang et al. 2008). As a consequence, Wsx-$1^{-/-}$ mice are more susceptible to EAE compared with wild-type mice (Batten et al. 2006).

IL-27 cannot inhibit IL-17A production after the initiation of the T_H17 program since, as presented by Diveau et al. (Diveu et al. 2009), addition of IL-27 to IL-23-activated $CD62L^{low}$ and $CD44^{high}$ effector T cells did not modify the amounts of IL-17. Accordingly, IL-27 did not change the level of the RORγt protein in committed T_H17 cells. On these activated T cells, IL-27 did, however, increase the amounts of IL-10, thus regulating the pathogenicity of T_H17 cells in EAE (Diveu et al. 2009), possibly through induction of the transcription factor c-Maf, which directly transactivates IL-10 gene expression through binding to the IL-10 promoter (Xu et al. 2009).

Pleiotropic Effects of IL-27

IL-27 Modulates Antigen Presentation

IL-27 was recently shown to upregulate MHC molecules in several cell subsets (Feng et al. 2007; Feng et al. 2008; Kamiya et al. 2004; Salcedo et al. 2004). CIITA is a critical transcriptional activator that coordinately regulates the expression of the majority of genes involved in antigen processing and presentation. CIITA promoter depends on IRF1 and STAT1, otherwise known to be upregulated by IL-27. IL-27 induces STAT1-dependent IRF1 upregulation and subsequent upregulation of CIITA transcripts (Feng et al. 2007).

As shown by Feng et al., IL-27-treated THP-1 human acute monocytic leukemia cells displayed increased levels of HLA-A, B, C, b2 m, and TAP-1 transcripts. IL-27 thus not only induces HLA I heavy-chain expression, but also induces genes involved in antigen processing and the assembly of MHC class I molecules (Feng et al. 2008). Salcedo et al. found four to fivefold upregulation of class I MHC in the TBJ neuroblastoma cell line (Salcedo et al. 2004). Slight but constant upregulation of MHC I has also been reported on naïve $CD4^+$ lymphocytes (Kamiya et al. 2004).

Effective presentation of antigens requires the expression of co-stimulatory and adhesion molecules such as CD80, CD86, and CD54. IL-27 increased the surface expressions of these molecules by THP-1 cells (Feng et al. 2008). IL-27 also upregulates MHC class II expression. IL-27 induces the expressions of HLA-DRA, HLA-DP, and HLA-PQ as well as the accessory molecules Ii, HLA-DO, and HLA-DM on the THP-1 monocytic cell line in a dose-dependent manner (Feng et al. 2008). Protein Ii is crucial for the proper trafficking of class II molecules to the peptide-loading compartment, while DM plays a critical role in stable binding by class II molecules.

Taken together, this data suggest that IL-27 promotes antigen presentation; however, the majority of the data was obtained from cell lines and further studies are needed to confirm these findings in primary cells, especially DCs.

IL-27 Inhibits Angiogenesis

Microarray experiments conducted by Feng et al. (Feng et al. 2007) showed that IL-27 is capable of inducing the expression of IFN-γ-inducing protein (IP-10/CXCL10) and a monokine induced by IFN-γ (MIG/CXCL9). Both molecules were previously reported to inhibit tumor growth and metastasis through their antiangiogenic effects. In human umbilical vein endothelial cells, IL-27 induced the upregulation of CXCL9 and CXCL10 by 10- and nearly 60-fold, respectively (Feng et al. 2007). Shimizu et al.

demonstrated that mice injected with B16F10 malignant melanoma cells transfected with IL-27 genes had lower vascular endothelial growth factor levels and greatly reduced vasculature in lung metastasis compared with animals injected with B16F10 cells that did not express IL-27 (Shimizu et al. 2006). Moreover, treatment with anti-IP-10 antibody partially but significantly abrogated the antitumor effect of IL-27.

These results clearly indicate that IL-27 acts as an inhibitor of angiogenesis. This may be of clinical importance since in normal tissues only a small percentage of vascular endothelial cells is positive for CXCR3, which is a receptor for IL-27-induced CXCL10, whereas the frequency of CXCR3-positive cells in neoplastic tissues is much higher than in normal ones. IL-27 could conceivably be used as a tumor-specific inhibitor of angiogenesis; however, this needs experimental confirmation.

Therapeutic Potential of IL-27

IL-27 as an Antitumor Agent

The ability to polarize T lymphocytes towards cytotoxic activity with concomitant enhancement of MHC expression on tumor cells could be a rationale for using IL-27 in the therapy of solid tumors. Initial results obtained in murine models gave some promising results.

As mentioned previously, IL-27 induced the expression of class I MHC in TBJ neuroblastoma cells. In the case of TBJ, as well as Colon 26 colon cancer cells and GL26 glioma cells, tumor growth inhibition was associated with the cytotoxic activity of MHC I-dependent $CD8^+$ lymphocytes. Depletion of $CD8^+$ lymphocytes greatly diminished the antitumor effect of IL-27 on those tumors in vivo (Chiyo et al. 2005; Hisada et al. 2004; Salcedo et al. 2004; Yuan et al. 2005). It seems that enhancement of antigen presentation lies behind the observed antitumor activity of IL-27 (Chiyo et al. 2005; Hisada et al. 2004; Oniki et al. 2006; Salcedo et al. 2004; Shimizu et al. 2006; Wesa et al. 2007; Yuan et al. 2005).

In the case of B10F16 melanoma, however, the inhibitory effect of IL-27 was only slightly diminished by $CD8^+$ lymphocyte depletion, which is in line with the fact that B10F16 melanoma cells have a very low MHC I expression; additionally, they do not have a functional IL-27 receptor. On the other hand, the effects of IL-27 could be partially abolished by administration of antibodies against the anti-angiogenic chemokine IP-10 (Shimizu et al. 2006). Therefore, in poorly immunogenic tumors, the inhibitory properties of IL-27 seem to depend on inhibition of angiogenesis. As reported by Shimizu et al., IL-27-transduced tumors have lower microvessel density and grow more slowly than the parental tumor (Shimizu et al. 2006). What is important, IL-27-mediated suppression of neoangiogenesis affected not only parental tumors, but also metastases, reducing their number by 98%.

Notwithstanding controversies concerning the roles of regulatory T cells and T_H17 lymphocytes in the tumor microenvironment, there is evidence suggesting that increased numbers of these cells in the tumor stroma actually promote tumor progression (Kryczek et al. 2007; Zhang et al. 2008). Therefore the capability of IL-27 to block those lineages may add to its antitumor properties.

Last but not least, Yoshimoto et al. observed direct antiproliferative effects of IL-27 on several WSX-1-positive human melanoma lines (Yoshimoto et al. 2008). Therefore, IL-27 can inhibit tumor progression by several mechanisms simultaneously, regardless of tumor immunogenicity, potentially making it a valuable therapeutic tool in poorly immunogenic tumors. Importantly, IL-27 inhibits the growth of both primary and metastatic tumors. By virtue of that fact, IL-27 could find application in the therapy of advanced tumors. Therefore, in the opinion of the authors, there is a place for IL-27 as an adjuvant in the treatment of a broad range of solid tumors. Administration of IL-27 for human neuroblastoma is especially promising given the results of extensive animal studies showing complete tumor regression and long-term survival in mice bearing widely metastatic neuroblastoma tumors (Salcedo et al. 2009). Most of the research in this area has been conducted on animal models; however, a recent study by Tassi et al. confirmed IL-27's capability to revert the Th2 polarization of in vivo primed lymphocytes from pancreatic cancer patients (Tassi et al. 2009). The study also showed IL-27-dependent enhancement of preexisting antigen-specific T_H1 responses.

IL-27 in the Therapy of Autoimmune Disorders

Due to its anti-inflammatory properties, especially inhibition of IL-17 expression, IL-27 could be thought of as a potential therapeutic agent against autoimmune disorders. Indeed there is evidence that IL-27 could be applied in the treatment of multiple sclerosis and rheumatoid arthritis. IL-27 has been shown to play a suppressive role in EAE, a murine model of multiple sclerosis, as demonstrated by exacerbated disease in Wsx-1-deficient mice (Batten et al. 2006). In a recent report, Fitzgerald et al. investigated whether exogenous IL-27 could reduce the severity of EAE in mice (Fitzgerald et al. 2007). When delivered s.c. by osmotic pump, IL-27 reduced central nervous system inflammatory infiltration and T_H17 lymphocyte numbers. In vitro IL-27 significantly inhibited IL-17 production by myelin-reactive T cells. Incubation with IL-27 strongly suppressed the ability of encephalitogenic lymph node and

spleen cells to transfer EAE. This is in line with a study by Wang et al. on the prevention of adoptive transfer of EAE by bone marrow stromal cell (BMSC) treatment (Wang et al. 2008). Neutralization of IL-27 resulted in abrogation of the BMSC effect.

IL-27 was also proven to attenuate the severity of CIA, which is a murine model of human rheumatoid arthritis (Niedbala et al. 2008). Elevated levels of IL-17 have been reported in CIA and IL-17 neutralization prevents bone destruction (Kelchtermans et al. 2009). Administration of IL-27 profoundly reduced symptoms of CIA, including cellular infiltration in the joints, synovial hyperplasia, and joint erosion (Niedbala et al. 2008). The treatment decreased serum levels of IL-6 and collagen-specific IgG2a. Spleen and lymph node lymphocytes from the IL-27-treated mice produced significantly less IFN-γ and IL-17 compared with the cells from control mice when cultured with collagen in vitro. Animal studies on the CIA model of arthritis seem to correlate with the findings of Furukawa et al. that IL-27 inhibits the expressions of c-Fos and calcineurin-dependent 1 NFAT, which are indispensable transcription factors for osteoclastogenesis, resulting in dose-dependent inhibition of osteoclastogenesis (Furukawa et al. 2009). Human IL-27 also repressed bone resorption by osteoclasts on a dentine slice.

All these data show a high therapeutic potential of IL-27 in rheumatoid arthritis, especially taking into account the feasibility of local, intra-articular, administration of recombinant IL-27. It is imaginable that IL-27 could also find application in the treatment of psoriasis vulgaris, since in psoriatic lesions, as compared with skin without lesions, there are increased numbers of T_H17 cells producing IL-17 (Kryczek et al. 2008).

IL-27 as an Antiviral Agent

Recent reports suggest that IL-27 could possibly be used as an antiviral therapeutic agent. Fakruddin et al. demonstrated that IL-27 is a potent inhibitor of HIV-1 replication (Fakruddin et al. 2007). In peripheral blood mononuclear cells (PBMCs) treated with human papilloma virus-like particles (VLPs), IL-27 expression was upregulated 14- and 6-fold as measured by real-time PCR and ELISA, respectively. Soluble factors secreted by VLP-treated PBMCs potently inhibit HIV-1 replication, and IL-27 depletion strongly reduced this inhibition. In another paper, Lapenta et al. reported that increased presentation of HIV-1 antigens by IFN-α-treated DCs is associated with IL-27 upregulation (Lapenta et al. 2006).

In an experimental set-up by Fakruddin et al., recombinant IL-27 inhibited HIV-1 replication in $CD4^+$ T lymphocytes, PBMCs, and macrophages (Fakruddin et al. 2007). A recent study by Greenwell-Wild et al. provides a possible explanation to this phenomenon (Greenwell-Wild et al. 2009). IL-27 induces type I interferons which in turn induce APOBEC cytidine deaminases, molecules known to disrupt the viral life cycle. IL-27 also induces other IFN-regulated genes with antiviral activity such as guanylate binding protein GBP2 and myxovirus resistance MxA (Bender et al. 2009).

With respect to these reports, one can imagine the use of recombinant IL-27 in the therapy of viral diseases, especially AIDS. Although the antiviral activity of IL-27 depends on type I IFNs, IL-27-induced IFN-α may function in an autocrine or paracrine manner at a lower concentration than systemically administered IFN-α. Conceivably, by use of IL-27 the side effects of IFN-α administration could be circumvented (Greenwell-Wild et al. 2009).

Concluding Remarks

Major advances in understanding the biology of IL-27 have been achieved since its discovery. While the majority of the literature has focused on the effects of IL-27 on T cells, the IL-27 receptor complex is expressed by a number of innate immune cells, hematopoietic stem cells, vascular endothelium, and keratinocytes. Since polymorphisms in the p28 gene seem to be associated with asthma and chronic obstructive pulmonary disease, it would be interesting to examine the exact role of IL-27 in these pathologies and explore the potential of IL-27 administration or depletion in the their treatment. IL-27 definitely shows promise as an anticancer, antiviral, and anti-inflammatory agent with apparent low toxicity risk, as observed in animal and in vitro models.

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