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WSX-1 and Glycoprotein 130 Constitute a Signal-Transducing Receptor for IL-27


The recently discovered cytokine IL-27 belongs to the IL-6/IL-12 family of cytokines and induced proliferation of naive CD4+ T cells and the generation of a Th1-type adaptive immune response. Although binding of IL-27 to the cytokine receptor WSX-1 was demonstrated, this interaction proved insufficient to mediate cellular effects. Hence, IL-27 was believed to form a heteromeric signaling receptor complex with WSX-1 and another, yet to be identified, cytokine receptor subunit. In this study, we describe that WSX-1 together with gp130 constitutes a functional signal-transducing receptor for IL-27. We show that neither of the two subunits itself is sufficient to mediate IL-27-induced signal transduction, but that the combination of both is required for this event. Expression analysis of WSX-1 and gp130 by quantitative PCR suggests that IL-27 might have a variety of cellular targets besides naive CD4+ T cells: we demonstrate gene induction of a subset of inflammatory cytokines in primary human mast cells and monocytes in response to IL-27 stimulation. Thus, IL-27 not only contributes to the development of an adaptive immune response through its action on CD4+ T cells, it also directly acts on cells of the innate immune system. The Journal of Immunology, 2004, 172: 2225–2231.

In the absence of an adaptive immune response, bacterial infections can be a lethal threat to the host, because innate immunity can only limit, but not fully eradicate the pathogen. A Th1-type adaptive immune response is necessary to clear these infections. Efficient orchestration of a Th1 immune response to bacterial infections requires permanent communication between cells of the innate and cells of the adaptive immune system, APCs, and T cells. This communication is achieved via two prominent mechanisms, cell-cell contacts and cytokines. Besides using cell-cell contacts such as peptide-MHC/TCR-, B7/CD28-type interactions, and others, APCs also communicate with T cells via production of Th1-favoring cytokines, such as IL-27, IL-12, IL-18, and IL-23 (1, 2). Availability of the respectively specific receptors on the cell surface determines responsiveness of a given cell to the various cytokines. The recently discovered IL-27 belongs to the IL-6/IL-12 structural family of cytokines. Functional IL-27 is a heterodimer consisting of two protein subunits encoded by two different genes: p28 and EBI3, in which p28 is believed to have a four-helix bundle cytokine-like topology and EBI3 resembles the soluble cytokine receptor-like molecules. In vitro, IL-27 has profound biological effects in costimulation of human and mouse naive CD4+ T cells; these involve proliferation and IFN-γ production in synergy with IL-12 (3). The cytokine receptor WSX-1 (or alternatively T cell cytokine receptor (TCCR)2 has been proposed to be a receptor for IL-27, because complex formation between WSX-1 and IL-27 was demonstrated in vitro (3). WSX-1 is expressed in lymphocytes, including naive T cells (4, 5). Moreover, WSX-1/TCCR-deficient mice show an impaired Th1 response (5, 6), which might support the idea of a functional relationship between IL-27 and WSX-1 at least on naive CD4+ T cells. However, despite binding of IL-27 to WSX-1, this receptor proved insufficient to mediate cellular responses to IL-27 (3). In an attempt to identify the complete functional receptor complex for IL-27, we paired various cytokine receptors with WSX-1. Only the combination of WSX-1 with gp130 leads to signal transduction in response to IL-27, and neither receptor chain alone is sufficient independent of the other. An anti-human gp130 (hgp130) mAb was used to specifically block IL-27 signaling in a human NK cell line and IL-27-mediated proliferation in naive CD4+ T cells. We propose that IL-27 engages a heterodimeric receptor complex composed of WSX-1 and gp130 to mediate its cellular effects. Expression analysis for WSX-1 and gp130 on a large panel of cDNA libraries using quantitative PCR suggests that both receptors are coexpressed in a number of different cell types. Thus, IL-27 might have biological effects on a variety of cellular targets, including cells from the innate and adaptive immune system. In line with this hypothesis, we demonstrate that IL-27 triggers STAT activation and gene transcription of a subset of inflammatory cytokines in primary human mast cells and in human monocytes.

Materials and Methods

Cytokines

Recombinant hIL-6/soluble hIL-6Rα (shIL-6Rα), hIL-2, mouse IL-2 (mIL-2), and mIL-3 were purchased from R&D Systems (Minneapolis, MN). Recombinant human and mouse IL-27 fusion proteins were prepared, as described (3).

Antibodies

The anti-hgp130 mAb B-T2 was a kind gift of the Institute of Biochemistry, Rheinische-Westfälische Technische Hochschule Aachen (Aachen, Germany). The anti-hWSX-1 polyclonal Ab was purchased from USBiological (Swampscott, MA). Abs against STAT1 and STAT3 were from Transduction Laboratories (Lexington, KY), and total STAT3 was from Santa Cruz Biotechnology (Santa Cruz, CA).

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2 Abbreviations used in this paper: TCCR, T cell cytokine receptor; h, human; m, mouse; OSM, oncostatin; s, soluble.
Cells and cell lines

Mouse myeloid precursor Ba/F3 cells and the human leukemic NK cell line (NKL) were cultured in RPMI 1640/10% FCS in the presence of mIL-3 (5 ng/ml) or hIL-2 (5 ng/ml), respectively. The mouse fibroblast cell line NIH3T3 was cultured in DMEM/10% FCS. Naive human primary CD4+ T cells were obtained and cultured, as described (3). Freshly isolated human cord blood was separated into mononuclear leukocytes by standard Ficoll/Hypaque centrifugation. Cord blood mononuclear cells were cultured in Yssel’s media (Gemini Bioproducts, Woodland, CA) supplemented with 2% human serum, 100 ng/ml stem cell factor, and 50 ng/ml IL-6. Cultures were maintained for 7–8 wk with weekly medium exchange. At 8 wk, the cultures were further supplemented with 1 ng/ml IL-4 and 10 μg/ml human IgE. At 9–10 wk, the cultures were harvested and residual myeloid cells were removed by magnetic bead depletion of CD15-, CD11b- (positive) adherent cells, according to the manufacturer’s instruction. The following primers were used: hgp130-forward (f), CTGGGGCAATATGA-3’, hgp130-reverse (r), 5’-TGTGCACCTGGGCAATATGA-3’; hWSX-1-f, 5’-CTTGGAGGAGTGTGA-3’; hWSX-1-r, 5’-CCTTCATGTTCTTGGACCAGC-3’; and mWSX-1-r, 5’-GGC-3’.

Proteins

Expression of gp130 sensitizes Ba/F3 cells to IL-27

Results

Expression of gp130 sensitizes Ba/F3 cells to IL-27

The structural family of IL-6/IL-12 signal-transducing cytokine receptors currently comprises the following type I transmembrane proteins: WSX-1, G-CSFR, IL-12Rβ1, IL-12Rβ2, IL-23R, gp130, LIFR, oncostatin (OSM)Rβ, and gp130-like monocyte receptor. The only receptor in this family that appears to be endogenously expressed on Ba/F3 cells is WSX-1, although not at high levels. Retroviral expression constructs were generated for the above cytokine receptors, and these were introduced into the IL-3-dependent murine pre-B cell line Ba/F3. We next tested whether any particular receptor would allow signal transduction in response to IL-27 in these cells if combined with endogenous WSX-1. It has previously been shown that IL-27 signaling in naive CD4+ T cells and other cells leads to activation and phosphorylation of STAT1 and STAT3 (10, 11). Therefore, STAT activation was chosen as readout in these experiments. The only receptor among the above candidates that scored in permitting IL-27-dependent signal transduction when expressed in the mouse pre-B cell line Ba/F3 cells was gp130. Due to lack of commercially available anti-mWSX-1 mAbs for FACS staining, we initially determined receptor mRNA levels by quantitative PCR. Parental Ba/F3 cells do not express gp130 mRNA, but they do express WSX-1 (Fig. 1A). Stimulation of parental cells with IL-6/sIL-6R did not lead to any detectable activation of STAT1 (Fig. 1B), indicating that there was indeed no functional gp130 expressed on these cells. IL-27 also failed to induce STATs in parental Ba/F3 cells. Even in cells overexpressing WSX-1, IL-27 stimulation did not activate signal transduction (3). After expression of the gp130 receptor, Ba/F3 cells become sensitive to both IL-6/sIL-6R and IL-27-induced tyrosine phosphorylation of STAT1 (Fig. 1B). Activation of STAT3 was also examined with similar results (data not shown).

Expression of WSX-1 sensitizes NIH3T3 cells to IL-27

On the basis of our experiments in Ba/F3 cells, we could not fully exclude the possibility that gp130 by itself was sufficient to mediate IL-27-induced STAT activation. To address this, we searched for a retrovirally infectable cell line that would express high levels of gp130, but only negligible levels of WSX-1. FACS analysis of the mouse fibroblast cell line NIH3T3 showed that these cells express substantial amounts of gp130 on the cell surface (data not shown). Because no anti-mWSX-1 mAb for a direct detection of the surface-expressed receptor is commercially available, we analyzed mRNA levels for both gp130 and WSX-1 in NIH3T3 cells by quantitative PCR. We found that gp130 mRNA was about three orders of magnitude more abundant compared with WSX-1 in NIH3T3 cells.
these cells (Fig. 2A). Moreover, stimulation of parental NIH3T3 cells with IL-27 did not lead to any detectable level of STAT activation, whereas stimulation with IL-6/sIL-6R did (Fig. 2B). This implies that NIH3T3 cells express functional gp130, but gp130 alone is insufficient to mediate IL-27 signaling. Thus, the NIH3T3 cells were reconstituted with WSX-1. They were infected...

**FIGURE 2.** NIH3T3 cells expressing WSX-1 are sensitive to IL-27. A, Total mRNA was isolated from NIH3T3 cells and analyzed for expression of WSX-1 and gp130 using quantitative PCR. The indicated mRNA levels for both receptors are relative to ubiquitin, which was used as a reference gene. B, NIH3T3 cells were stably transfected with WSX-1 or a control receptor or were left untransfected; they were stimulated with saturating concentrations of IL-6/sIL-6R or IL-27; or were left unstimulated. Tyrosine phosphorylation of STAT1 and STAT3 as readout for cytokine receptor activation in response to the various factors was determined using pY-STAT-specific Abs. A representative of three experiments is shown.

**FIGURE 3.** An anti-hgp130 mAb blocks IL-27-mediated cellular effects. A, NKL cells were preincubated in the presence or absence of either the anti-hgp130 mAb B-T2 or an isotype control mAb. Each mAb was used at 10,000, 500, and 25 ng/ml concentrations, from left to right, as indicated. Cells were then stimulated with saturating amounts of IL-27 or were left unstimulated. Tyrosine phosphorylation of STAT1 and STAT3 as a readout for receptor activation in response to IL-27 was determined using pY-STAT-specific Abs. B, FACS-purified naive human T cells were incubated with saturating concentrations of IL-27, agonistic anti-CD3 and anti-CD28 Abs, and neutralizing anti-IL-2 Ab in the absence and presence of titrated amounts of the anti-gp130 mAb B-T2 or an isotype control mAb. IL-27-dependent proliferation was measured by thymidine incorporation. Data points shown represent means and SD from triplicate experiments.
with a retroviral vector encoding flag-tagged mWSX-1, a control receptor, or were left untransfected and then stimulated with IL-27. Whereas parental cells or cells that had received the control receptor remained unresponsive to IL-27, WSX-1-expressing NIH3T3 cells showed IL-27-dependent tyrosine phosphorylation of STAT1 and STAT3 (Fig. 2B). Stimulation with IL-2 had no effect on the WSX-1-positive cells, indicating that the observed cytokine sensitivity was specific for IL-27 (data not shown). In all cases, stimulation with IL-6/sIL-6R induced STAT1 and STAT3 activation, indicating that functional gp130 is sufficient for IL-6, but not for IL-27 signal transduction in NIH3T3 cells.

An anti-hgp130 mAb blocks IL-27-mediated cellular effects

The human leukemic NK cell line NKL is sensitive to IL-27, as measured by induction of tyrosine phosphorylation of STAT1 and STAT3 (10). As a signaling event upstream of STAT activation, the cytoplasmic region of gp130 is tyrosine phosphorylated in response to IL-27 stimulation (data not shown). To confirm the role of gp130 in IL-27-dependent signal transduction, we attempted to block IL-27 responses using the anti-hgp130 mAb B-T2 (12). Incubation of the human leukemic NK cell line NKL with this Ab before IL-27 stimulation blocked STAT1 and STAT3 tyrosine phosphorylation in a B-T2-dose-dependent manner, while an isotype control Ab had no effect (Fig. 3A). IL-2-induced STAT activation was not affected by the B-T2 Ab in the same assay (data not shown). Because STAT activation assays are considered short-term readout experiments with stimulations typically lasting only 10–20 min, we also wanted to confirm our findings in a long-term readout experiment. Purified naive CD4+ T cells have been shown to proliferate in response to IL-27 costimulation (3). Therefore, we

![FIGURE 4. Cellular distribution of mRNA expression for WSX-1 and gp130. Various human cDNA libraries were screened for mRNA expression of WSX-1 and gp130 using quantitative PCR. Levels shown are relative to ubiquitin, which was used as a reference gene in this experiment. □, Represent gp130; ■, WSX-1.](image-url)
investigated the role of this Ab in a proliferation assay. The anti-hgp130 mAb B-T2 dose dependently inhibits IL-27-mediated proliferation of sorted naive CD4+ T cells, whereas an isotype control Ab has no effect (Fig. 3B). These data strongly support the concept that gp130 is a part of the functional IL-27R.

WSX-1 and gp130 are coexpressed in many cell types

The above data indicate that coexpression of WSX-1 and gp130 is required to sensitize cells to IL-27. To date, naive CD4+ T cells and NK cells are the only cell types shown to be sensitive to IL-27 stimulation (3). To identify additional cellular targets of this cytokine, we investigated levels of mRNA encoding both WSX-1 and gp130 on a large panel of human cDNA libraries. Surprisingly, the two receptors show varying, but relevant levels of coexpression in a number of different cell types, including monocytes, dendritic cells, T and B lymphocytes, NK cells, mast cells, and endothelial cells (Fig. 4). Highest mRNA expression for gp130 is found on mesangial cells and microvascular endothelial cells, whereas maximal levels of WSX-1 message are detected in T cell libraries and the erythroleukemic cell line TF1.

IL-27 stimulates transcription of genes encoding a distinct subset of proinflammatory cytokines in primary human mast cells

Because mRNA analysis for both receptors WSX-1 and gp130 indicated coexpression on a number of cells, including mast cells, we investigated the effects of IL-27 stimulation on primary human mast cells obtained from cord blood. Increasing evidence suggests that mast cells can play an active role in the innate immune response against bacteria, which appears to be at least in part independent of degranulation (13, 14). It is not yet known whether secretion of proinflammatory cytokines does inevitably require direct exposure of mast cells to bacterial products or whether this event could alternatively be triggered through an indirect mechanism involving soluble mediators. Because IL-27 is believed to be among the earliest cytokines released by APCs in response to bacterial challenge, this cytokine potentially could be a candidate for an indirect activation mechanism of mast cells. As a first approach, the presence of a functional receptor complex for IL-27 on mast cells was verified performing a STAT activation experiment; stimulation with IL-27 leads to tyrosine phosphorylation of STAT3 (Fig. 5A). Sensitivity of primary human mast cells to IL-27, as evident by STAT activation, led us to search for possible IL-27 target genes. We were particularly interested to analyze expression of proinflammatory cytokines of the IL-1 and TNF families. Stimulation with IL-27 for 2 h led to up-regulation of mRNA expression of IL-1α, IL-1β, IL-18, TNF-α, OX40, receptor activator of NF-κB ligand, a proliferation-inducing ligand, B lymphocyte stimulator, and T cell-expressed activating specific receptor ligand, while lymphotoxin-α, lymphotoxin-β, CD40 ligand, and CD27 ligand essentially remained unchanged (Fig. 5B). Whereas IL-18 mRNA was only slightly enhanced, IL-1β, APRIL, and BLYS expression increased ~2-fold. In contrast, mRNA expression of IL-1α, OX40, TNF-α, TEASRL, and RANKL was up-regulated >5-fold. With the experiment limited to a 2-h time period, indirect effects involving protein intermediates seem unlikely, although they cannot entirely be excluded. IL-27 stimulation had no effect on FcεR-dependent degranulation or production of IL-8 (data not shown).

IL-27 mediates autocrine activation of STATs and induces inflammatory cytokine mRNA expression in primary human monocytes

Coexpression of WSX-1 and gp130 was also found on monocytes (Fig. 4). Because monocytes produce IL-27, as well as IL-12 and IL-23, in response to bacterial challenge, this finding suggested that monocytes can also respond to IL-27. Primary human monocytes, isolated from buffy coat, were stimulated with IL-27, and tyrosine phosphorylation of both STAT1 and STAT3 was shown evident by STAT activation, led us to search for possible IL-27 target genes. We were particularly interested to analyze expression of proinflammatory cytokines of the IL-1 and TNF families. Stimulation with IL-27 for 2 h led to up-regulation of mRNA expression of IL-1α, IL-1β, TNF-α, OX40, receptor activator of NF-κB ligand, a proliferation-inducing ligand, B lymphocyte stimulator, and T cell-expressed activating specific receptor ligand, while lymphotoxin-α, lymphotoxin-β, CD40 ligand, and CD27 ligand essentially remained unchanged (Fig. 5B). Whereas IL-18 mRNA was only slightly enhanced, IL-1β, APRIL, and BLYS expression increased ~2-fold. In contrast, mRNA expression of IL-1α, OX40, TNF-α, TEASRL, and RANKL was up-regulated >5-fold. With the experiment limited to a 2-h time period, indirect effects involving protein intermediates seem unlikely, although they cannot entirely be excluded. IL-27 stimulation had no effect on FcεR-dependent degranulation or production of IL-8 (data not shown).

FIGURE 5. IL-27 triggers expression of a subset of inflammatory cytokines in primary human mast cells. A, Primary human mast cells were stimulated with IL-6/sIL-6Rα or IL-27, and tyrosine phosphorylation was assessed using a pY-STAT3-specific Ab. B, Primary human mast cells were stimulated with IL-27 for 2 h or were left unstimulated; total RNA was prepared from both cell populations; and quantitative PCR was performed to determine mRNA levels for the indicated cytokines. Ubiquitin and water were used as controls. Data were plotted as relative change of mRNA level in stimulated vs unstimulated cells.
target genes in these primary human monocytes. In contrast to mast cells, up-regulation of proinflammatory cytokine mRNA in monocytes after IL-27 stimulation was not as immediate and more restricted. Early up-regulation after 2 h could be detected for IL-1β and to some extent TNF-α mRNA; at later time points, up-regulation of these two genes becomes more prominent. Interestingly, IL-12p35 and IL-18 mRNAs after 2 and 6 h did not show differences compared with control, but ~10-fold up-regulation for these genes was observed after 24 h. Up-regulation is restricted to these proinflammatory cytokines, as all other genes essentially remained unchanged (Fig. 6B).

Discussion

The recently discovered cytokine IL-27 has been proposed to play a role in the early phase of the Th1 commitment process of naive CD4⁺ T cells in response to pathogen challenge (3, 10). IL-27 also acts as a proliferation and clonal expansion factor for Ag-specific naive T cells (3). However, the cytokine receptor components mediating cellular effects of IL-27 have not been well defined. In this study, we have demonstrated that in addition to WSX-1, the cytokine receptor gp130 is necessary to mediate signal transduction in response to IL-27. Previous reports show that IL-27 induces STAT1 and STAT3 phosphorylation in naive CD4⁺ T cells (10, 11). Identification of gp130 as part of the receptor complex for IL-27 strongly supports this finding; both STAT1 and in particular STAT3 are known to be tyrosine phosphorylated in response to gp130 engagement. As a consequence of ligand binding, cytokine receptors in this family typically are phosphorylated by receptor-associated kinases on defined tyrosine-based motifs in the cytoplasmic region of the receptor. These phosphorylated tyrosine-based motifs in turn serve as docking sites for the Src homology 2 domains of STAT proteins, which subsequently will be tyrosine phosphorylated themselves. Tyrosine phosphorylation of STATs is a requirement for nuclear translocation and transcriptional activity (15). The only tyrosine-based phosphorylation motif in the cytoplasmic domain of WSX-1 is GYEKHF. This sequence closely resembles the STAT motif found in the cytoplasmic region of IFN-γR (GYDKPH), which strongly and selectively activates tyrosine phosphorylation of STAT1 (16). Because gp130 activation leads to strong activation of STAT3 and relatively weaker activation of STAT1 (17), it might be expected that in the IL-27R complex WSX-1 mostly contributes to STAT1 tyrosine phosphorylation and gp130 to STAT3 tyrosine phosphorylation.

Remarkably, the finding that gp130 is part of the IL-27R complex extends the number of cytokines that use this promiscuous receptor as a signal transducer to a total of eight: IL-6, IL-11, LIF, OSM, ciliary neurotrophic factor, CT-1, cardiotoxin-like cytokine, and IL-27. The cytokines IL-6 and IL-11 use gp130/gp130 homodimers for signaling. In contrast, LIF, OSM, CTNF, CT-1, and CLC use heterodimers gp130/LIFR; alternatively, OSM can signal through gp130/OSMRβ. IL-27 appears to be unique among cytokines using gp130 because it engages a heterodimeric receptor gp130/WSX-1 that to date is exclusive; we did not obtain evidence that any cytokine other than IL-27 can signal via this receptor complex. Interestingly, the neutralizing anti-gp130 mAb B-T2, which neutralizes IL-6 and IL-11 bioactivity (12), was shown to target a gp130 epitope located in the N-terminal Ig-like domain of the receptor (18, 19); thus, it can be expected that this domain of gp130 is essential for IL-27-mediated cellular responses.

Although mice lacking individual members of the gp130-dependent cytokine family typically display only relatively mild phenotypes, gp130-deficient mice show embryonic lethality. However, conditional gp130-deficient or gp130-mutant animals have been generated to evaluate the collective role of this cytokine family (20–22). The diverse phenotypes reported in these animals have revealed widespread importance of gp130 in numerous neurologic, cardiac, hemopoietic, immunological, hepatic, and pulmonary processes in vivo. Some of the phenotypes were only revealed in gp130-deficient animals and not in any of the available mutant mice lacking individual components of the gp130-cytokine system. Characterization of IL-27 as a new member of gp130-dependent cytokine family suggests that some effects observed as a consequence of gp130 deficiency are at least in part caused by the abolished IL-27 responsiveness. These effects might be revealed by careful comparison between WSX-1/ITCCR-deficient animals and conditional gp130-deficient animals.

We cannot fully exclude the possibility that a gp130/WSX-1 receptor heterodimer might not be sufficient and additional plasma membrane-associated molecules might contribute to IL-27 signal transduction. However, in the IL-6/IL-12 family of cytokine receptors, engagement of factors other than the signal-transducing receptors as a prerequisite for cytokine signaling has not been reported, and we did not obtain any experimental evidence that would support this possibility.

IL-27 is a member of a small family of potent immune regulatory cytokines that includes, besides IL-27, IL-12 and IL-23 (1, 3, 23). All three cytokines are produced by activated APCs of the
monocyte/macrophage/dendritic cell lineage. Identification of the complete IL-27 signal-transducing receptor complex has allowed us to search for cells that coexpress both receptors and thus can potentially respond to IL-27 stimulation. Unlike the receptors for IL-12 and IL-23, expression of the receptor subunits of IL-27 appears much less restricted; WSX-1 and gp130 are coexpressed on a variety of cells and tissues. This observation indicates that IL-27, besides specifically acting on naive CD4+ T cells and NK cells (3), can be expected to have additional immune regulatory functions. We report activity of IL-27 on two additional cell types, human primary mast cells and human monocytes.

Human mast cells respond to IL-27 through STAT activation, leading to increased expression of a subset of inflammatory cytokines (Fig. 5). Interestingly, secretion of these inflammatory cytokines occurs in the absence of a general degranulation response, indicating cytokine-specific rather than generic mast cell-activating activity. Mast cells are well recognized as key mediators of allergic reactions triggered by the release of inflammatory cytokines, histamines, and arachidonic acid metabolites through degranulation and are not primarily known for their role in propagation of bacterial products through Toll-like receptors (14, 24).

Primary mast cells and human monocytes.

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The finding that IL-27 directly regulates expression of proinflammatory cytokines in mast cells points to a possible role of this cytokine in mast cell biology.

Coexpression of the two IL-27R components WSX-1 and gp130 was also found on monocytes (Fig. 4). Because activated monocytes produce IL-27, as well as its close relatives IL-12 and IL-23, an immediate consequence would be IL-27-dependent autocrine stimulation. Tyrosine phosphorylation of STAT1 and STAT3 was shown in response to IL-27 stimulation (Fig. 6A). This implies that IL-27 can stimulate monocytes in an autocrine manner. Analysis of the target genes downstream of IL-27 signaling in human primary monocytes indicates that IL-27 induces inflammatory cytokines in these cells. In particular, IL-27 significantly induced the expression of IL-18 mRNA, a cytokine that, in combination with IL-12 (25), plays a key role in the induction of IFN-γ by activated CD4+ T cells. This suggests that IL-27 not only synergizes directly with IL-12 in the production of IFN-γ, but can also indirectly enhance immune responses via induction of IL-18 in activated monocytes. Because IL-18 up-regulation is seen after 24 h, it remains to be investigated whether IL-27 directly triggers IL-18 mRNA or whether unidentified intermediates contribute.

The IL-27R WSX-1 and gp130 are present on a variety of immune cells involved in both innate and adaptive defense mechanisms. WSX-1/gp130 double-positive cells include NK cells, dendritic cells, monocytes, mast cells, and B and T cells, and functional consequences of IL-27 stimulation have already been demonstrated for several of these cell types. In conclusion, these data indicate an active role of IL-27 as a regulator in the coordination of innate as well as adaptive immune responses.

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