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Mini review

The biology of interleukin-27 reveals unique pro- and anti-inflammatory functions in immunity

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ABSTRACT

Interleukin (IL)-27 is a multifaceted heterodimeric cytokine with pronounced pro- and anti-inflammatory as well as immunoregulatory functions. It consists of the two subunits p28/IL-30 and Epstein Bar virus-induced protein 3 (EBI3). EBI3 functions as a soluble α-receptor, and IL-27 can therefore directly activate its target cells through a heterodimer of glycoprotein 130 (gp130) and WSX-1. Being a heterodimeric cytokine that signals through gp130, IL-27 is either grouped into the IL-6 or the IL-12 family of cytokines. Originally identified as an IL-12-like cytokine that induces proliferation of CD4+ T cells and production of IFN-γ more than ten years ago, subsequent research revealed a much broader role of IL-27 in inflammation, cancer development and regulation and differentiation of immune cells. In this review, we summarize the current biochemical and molecular knowledge about the signal transduction of IL-27. Based on this, we highlight functional overlaps and plasticity with other cytokines and cytokine receptors of the IL-6/IL-12 superfamily, and describe the important role of IL-27 with regard to the differentiation of T cells, infections and cancer development. We further discuss IL-27 as a therapeutic target and how specific blockade of this cytokine could be achieved.

1. Introduction

Interleukin-27 (IL-27) is a heterodimeric cytokine that because of structural properties and shared receptors belongs to the IL-6/IL-12 superfamily of cytokines. It is composed by the two subunits p28 (IL-27a, IL-30) and EBI3 (Epstein-barr virus-induced gene 3, IL-27b) [1]. The α-subunit p28 is a four-helical bundle cytokine like the other members of the IL-6-family, and EBI3 is the soluble α-receptor that consists of two fibronectin-like domains [2] (Fig. 1).

The receptor complex that transduces the signal of IL-27 is composed of gp130 and WSX-1 which form a heterodimer on the cell surface that activates predominantly the Jak/STAT pathway but also PI3K/Akt and MAPK signaling (Fig. 1). In contrast to the pro-inflammatory actions of IL-6 through gp130, IL-27 was initially described to have immunoregulatory functions. This was based on the finding that IL-27 induces the secretion of IL-10 and limits inflammatory responses in the context of infection. Although IL-27 is an inducer of IFN-γ expression, which is part of its pro-inflammatory actions, lack of WSX-1 in mice does not alter IFN-γ-mediated immunity, but induces an immune hyperactivity in response to a parasitic infection revealing a non-redundant immunoregulatory function of IL-27 [3] (see Section 5). Together with IL-12, IL-27 can promote the IFN-γ-induced Th1 response and on the other hand it induces IL-10 producing, forkhead box transcription factor p3-positive (Foxp3+) regulatory T cells (Tr1 cells), limits IL-2 production and reverses the IL-23 mediated lineage commitment of Th17 cells [4–7] (see Section 4). These unique properties show that categorizing this cytokine as pro- or anti-inflammatory is rather simplistic and does not cope with the complex interactions in the cytokine network.

Because of the nature of the heterodimer it is not trivial to discriminate between IL-27 related or independent functions of the two subunits. The soluble α-receptor EBI3 can also bind p35 and have agonistic functions as IL-35 and p28 is known to be secreted in the absence of EBI3 in complex with CLF-1 and to exert functions through binding to the IL-6R [8–10].

Thus, we dissect the biology of IL-27 and its individual subunits in terms of inflammation, infection and cancer, and discuss opportunities and potential pitfalls when studying IL-27 *in vivo*.

2. Expression of interleukin-27 and its receptors

Although p28 is poorly secreted when expressed in the absence of EBI3, the transcription of both subunits is independently

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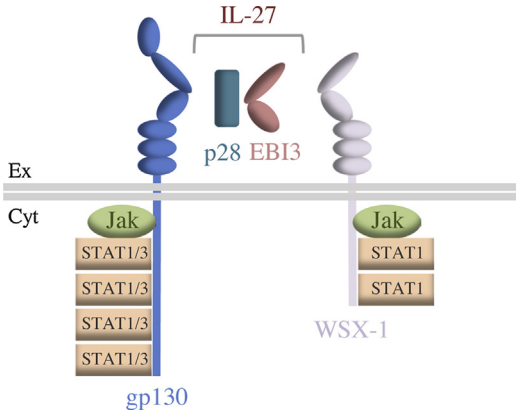

Fig. 1. *Interleukin-27 and its receptor complex.* IL-27 is composed of the subunits p28 and EBI3 and induces the formation of the receptor complex consisting of gp130 and WSX-1. These β-receptor chains are associated with Janus kinases (Jaks) that upon activation phosphorylate the cytoplasmic tyrosine residues of the β-receptors and the associating STAT transcription factors. Ex: extracellular space, Cyt: cytosol.

regulated. In humans *IL27A* is located on chromosome 16 whereas *IL27B* is located on chromosome 19.

The primary source of p28 and EBI3 are cells of the myeloid lineage mainly monocytes and activated dendritic cell [1]. The IL-27p28 mRNA is not detectable under steady state conditions, but is upregulated in murine splenocytes after infection [3]. Recently, it was shown that especially plasmacytoid dendritic cells (pDCs) from the liver express detectable amounts of mRNA for IL-27p28 without infection and that the protein levels are higher than in pDCs from the spleen. Also here it was shown that the expression levels of the subunit p28 are strongly regulated whereas transcript and protein levels of EBI3 are comparable and constitutively present in various cell types [11].

LPS-induced endotoxic shock in mice strongly increases p28 levels, which originate mainly from macrophages residing in the spleen and to a lesser extent in the lung. This elevated expression is reversed by IL-10 in a STAT3-dependent manner, revealing a negative feedback mechanism for IL-27 induced IL-10 production [12]. Furthermore, upregulation of both EBI3 as well as p28 occur during T cell activation with low but detectable levels in both naïve and memory CD4+ T cells and also in B cells [13].

The receptor complex for IL-27 consists of the two subunits gp130, which is ubiquitiously expressed and the main signal transducing β-receptor of the IL-6 family, and WSX-1, which has few known functions apart from IL-27 signaling. As gp130, WSX-1 is a type I transmembrane protein that activates the Jak/STAT signaling pathway upon ligand binding and receptor complex formation. WSX-1 is expressed in low levels on naïve and higher levels on effector and memory T cells which renders them the main targets of IL-27 actions [14].

Apart from this canonical receptor complex both cytokine subunits are also described to activate other receptors. Cross-talk between the actions of the many cytokines takes place on various levels. Through different subunit pairing especially in the IL-12 family EBI3 as well as p28 are used by different cytokines. EBI3 can form the cytokine IL-35 by binding the IL-12 subunit p35 [15,16], although the interaction site seems to be very unconventional in the context of this cytokine family [17]. For p28 it was shown that the site II binding to the cytokine binding module (CBM) of different cytokine β-receptors is depending on the bound α-receptor, in this case EBI3 or the IL-6R, which results in the activation of a gp130/WSX-1 heterodimer by IL-27 and the activation of a gp130 homodimer by p28 through the IL-6R [10]. All these data suggest that the binding surfaces of the subunits and the receptors reveal a high plasticity and depend on the different interaction partners and complexes in which the cytokines occur (reviewed in [18], Fig. 2).

3. Signal transduction and cross-talk of IL-27

The main signal transducing receptor of the IL-6 family of cytokines is gp130, which is constitutively interacting with kinases of the Janus family namely, Jak1, Jak2 and Tyk2. Concerning the signaling of IL-6-type cytokines only Jak1 has non-redundant functions and loss of Jak1 cannot be compensated by the other two kinases [19,20]. WSX-1 appears to have the same box 1 motif that mediates the interaction with the Jak kinases in the cytoplasmic portion of the receptor. Ligand binding and receptor complex formation lead to mutual activation of the associated Jaks and subsequent phosphorylation of intracellular tyrosine residues of gp130 and WSX-1 [21]. STAT proteins are then recruited to the phosphorylated receptor and likewise activated by the Janus Kinases through phosphorylation to induce their target genes.

In contrast to the other IL-6-type cytokines IL-27 induces a stronger phosphorylation of STAT1 but also the activation of other STATs like STAT3 and STAT6 [22,23]. The STAT binding site in the cytoplasmic region around Tyr^{613} of hWSX-1 is specific for the binding of STAT1. The conserved binding motif GYEKHF is closely

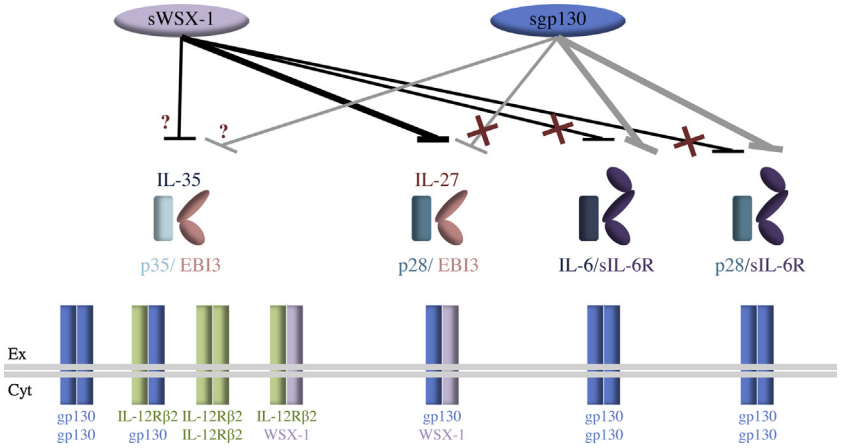

Fig. 2. *Plasticity among IL-6, IL-27 and IL-35.* IL-35 (p35/EBI3) has been described to signal via the four different β-receptor complexes gp130/gp130, IL-12Rβ2/gp130, IL-12Rβ2/IL-12Rβ2 and IL-12Rβ2/WSX-1. IL-27 (p28/EBI3) signals via gp130/WSX-1, whereas p28/sIL-6R and IL-6/sIL-6R induce formation of a gp130/gp130 homodimer. Soluble gp130 (sgp130) blocks signaling of IL-6/sIL-6R and p28/sIL-6R, but not IL-27. Soluble WSX-1 (sWSX-1) inhibits IL-27 signaling, but not IL-6/sIL-6R and p28/sIL-6R. Whether sgp130 or sWSX-1 interfere with IL-35 signaling is not known. Ex: extracellular space, Cyt: cytosol.

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