Cytokine & Growth Factor Reviews 26 (2015) 471–474

Contents lists available at ScienceDirect

Cytokine & Growth Factor Reviews

journal homepage: www.elsevier.com/locate/cytogfr

Guest editorial

"Family reunion" – A structured view on the composition of the receptor complexes of interleukin-6-type and interleukin-12-type cytokines

Keywords:
Interleukin-6
Interleukin-12
Receptor
Cytokine
Composite cytokines
gp130
IL-12R
Inflammation

1. Introduction

The Cytokine and Growth Factor Reviews Special Issue on interleukin-6/interleukin-12-type cytokines aims to create a structured view on the composition of the receptor complexes of IL-6-type and IL-12 type cytokines and to summarize our current knowledge on the signal transduction and (patho-) physiology of these cytokines. The following articles in this special issue are dedicated to the structure and biology of interleukin-6/interleukin-12 type cytokines.

2. The family dynasty of IL-6/IL-12 type cytokines

Interleukin-6 type cytokines as well as interleukin-12 type cytokines activate receptor complexes containing two signal transducing receptor subunits. Basically, the receptor complexes for interleukin-6-type cytokines contain at least one signal transducing subunit glycoprotein 130. Some of these cytokines require additional α-receptors for functional receptor complex formation. However, the receptor complexes bound by interleukin-12 type cytokines contain at least one subunit of glycoprotein 130, interleukin-12 receptor β1, or the interleukin-12 receptor β2. All interleukin-12 type cytokines are composite cytokines of two subunits: a soluble accessory receptor protein comparable to the α-receptors of interleukin-6 type cytokines and a ligand subunit. Thus, several aspects link receptor complex organization of interleukin-6- and interleukin-12 type cytokines. These facts argue for presenting IL-6- and IL-12-type cytokines as one superfamily of interleukin-6/interleukin-12 type cytokines. Here, we present a simplified structured view on the composition of these receptor complexes and refer to complementary reviews on the specific cytokines published in this special issue of Cytokine and Growth Factor Reviews on IL-6/IL-12-type cytokines.

3. The branch of IL-6-type cytokines

Interleukin (IL)-6, the name giving cytokine for the IL-6-type cytokine family signals through a receptor complex composed of the IL-6Rα [1] and glycoprotein 130 (gp130) [2–4] (Fig. 1). First, IL-6 binds the IL-6 receptor α (IL-6Rα) to form an IL-6/IL-6Rα complex, which can now interact with the signal transducing subunit gp130 to form a high-affinity receptor complex [5]. Of note, agonistic soluble IL-6R (sIL-6R) can substitute the membrane bound IL-6Rα [2,6]. Furthermore, soluble gp130 binds IL-6/sIL6R complexes and thus inhibits cytokine signaling [7–10]. Details on IL-6 signal transduction and its blockade by soluble receptors are summarized by the review of Schaper and Rose-John [in this issue]. Aberrant signaling through mutated gp130 and other components of IL-6-type cytokine signaling has been identified in numerous solid and hematological tumors. These mutations, especially those associated with inflammatory hepatocellular adenomas are discussed in the review article contributed by Pilati and Zucman-Rossi [in this issue]. Very similar to IL-6, IL-11 acts through an IL-11Rα/gp130 receptor complex [11–13]. A review article on this topic is contributed by Johnstone, Chand, Putoczki, and Ernst [in this issue]. Recently, IL-30/IL-27p28 has been found to bind IL-6Rα to trigger gp130-dependent signaling [14,15]. Our current knowledge on the signal transduction and biological function of IL-30 is summarized in the context of IL-27 by Aparicio-Siegmund and Garbers [in this issue]. As signal transduction by IL-6 type cytokines (especially IL-6) has extensively been studied using systems biology approaches, a review article by Dittrich, Hessenkemper, and Schaper summarizes these studies and lists parameters required for a quantitative view and reliable modeling approaches on IL-6-type cytokine signaling [in this issue].

Ciliary neurotrophic factor (CNTF) [16], cardiotrophin-like cytokine (CLC, also known as novel neurotopin-1 (NNT-1) or B

http://dx.doi.org/10.1016/j.cytogfr.2015.07.011

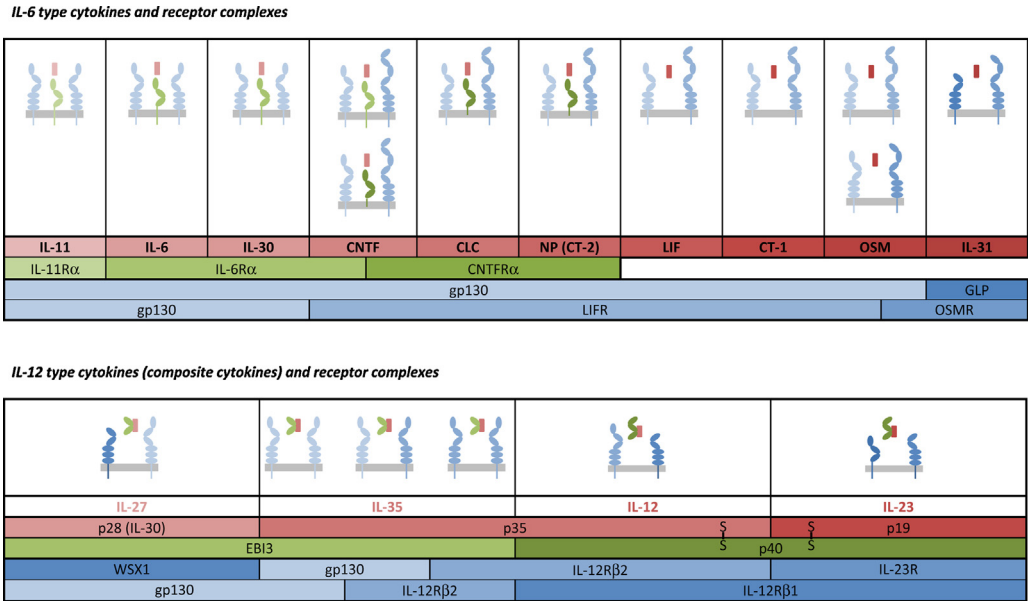

Fig. 1. Ligands are colored in maroon, α-receptors or receptor-like accessory proteins of composite cytokines are colored in green, signaling receptor subunits are colored in blue. Immuno-globulin like domains are indicated as vertical ellipses, fibronectin type III domains are indicated as horizontal ellipses, cytokine receptor homology domains are depicted as a pair of two angled ellipses. Transmembrane and cytoplasmic regions are drafted as lines. Lines not spanning the plasma membrane indicate GPI-anchored receptors. Reading the figure in vertical direction gives information on the specific composition of the cytokine (in case of composite cytokines) and the subunits of the respective receptor complex. Alternative receptor compositions are considered. S–S indicated the disulfide bridge between the specific subunits.

cell stimulating factor 3 (BSF3)) [17] and neuropoietin (NP)/cardiotrophin-2 (CT-2)) [18] utilize CNTFRα. Note that in humans but not in chimpanzees and mice, NP is a pseudogene, which has been inactivated by mutations [18]. The ligand/CNTFRα complexes signal through gp130/LIFR hetero dimers [16,19]. Additionally, CNTF operates through binding IL-6Rα and a gp130/LIFR hetero dimer [20]. Our current knowledge on CNTF and CLC and NP1 is summarized in the reviews by Pasquin, Sharma, and Gauchat [in this issue] and Sims [in this issue], respectively.

Leukemia inhibitory factor (LIF), cardiotrophin 1 (CT-1) and oncostatin (OSM) do not require specific α-receptors for receptor complex formation. Also these cytokines signal through gp130/LIFR heterodimeric complexes [21–23]. OSM additionally activates gp130/OSMR complexes [24]. However, OSM signaling through the gp130/LIFR complex has so far been exclusively found in human cells [25,26]. The OSMR is also utilized by IL-31, which signals through gp130-like protein (GLP)/OSMR heterodimers [27,28]. We dedicate three review articles to these cytokines: Nicola and Babon contribute with a comprehensive article on the structure-function relationship of LIF [in this issue] whereas López-Yoldi, Moreno-Aliaga and Bustos summarize our current knowledge on the biological function of CT-1 [in this issue]. OSM is reviewed together with IL-31 by Hermanns [in this issue] because of the joint usage of the OSMR by both cytokines and the still limited number of publications on IL-31.

4. The branch of IL-12-type cytokines

Signaling of IL-12 type cytokines does not depend on the binding to α-receptors. Instead, these cytokines are composed of two subunits, a typical ligand subunit and a soluble accessory receptor protein, which resembles the soluble form of the α-receptors of IL-6-type cytokines. Thus, in respect to full receptor complex formation IL-6 signaling through sIL-6R is somewhat comparable to signaling of 12-type composite cytokines.

Epstein-Barr virus-induced gene 3 (EBI3) and p40 act as accessory proteins and interact with IL-30/IL-27p28, IL-12p35 or IL-23p19. Whereas IL-27p28 interacts with EBI3 to build IL-27 [29], IL-23p19 interacts with p40 to build IL-23 [30]. IL-12p35 is part of both, IL-35 [31] and IL-12 [32,33] by binding to EBI3 and p40, respectively. Remarkably, the interaction of p40 with p35 [34] or p19 is stabilized by disulfide bonds [30]. P40 is an inhibitor of IL-12 and IL-23 signaling via binding to IL-12β1 [35].

Similar to IL-6-type cytokines, IL-27 and IL-35 signal through receptor complexes, which contain gp130 [36,37]. This explains why both cytokines could also be classified as IL-6-type cytokines. The 2nd signaling receptor component for IL-27 is WSX1, which is a type I cytokine receptor containing a WSXWS sequence motif [36]. IL-35 has been reported to activate three differentially composed receptor complexes, namely gp130/gp130, gp130/IL12Rβ2 but also IL-12Rβ2/IL-12Rβ2 [37]. Another study suggested that IL-12Rβ2 and WSX1 (IL-27Rα) are the IL-35 receptors [38]. Together with IL-12Rβ1, IL12Rβ2 is also part of the IL-12R-complex [39], whereas, IL-23R substitutes for IL-12β2 in the IL-23-activated receptor complex [40]. Although the specific receptor components are redundantly utilized by IL-12, IL-23, IL-27 and IL-35, these four cytokines are presented by four specific review articles. This approach helps dissecting and highlighting the specific biological functions and underlying molecular mechanisms. IL-12 and IL-23, both utilizing p40 are presented by Zundler and Neurath [in this issue] and by Floss, Schröder, Franke, and Scheller [in this issue], respectively. Our current knowledge on the EBI3 utilizing composite cytokines IL-35 is summarized in the article by Egwuagu, Yu, Sun, and Wang [in this issue]. IL-27 is addressed by the already mentioned review article contributed by Aparicio-Siegmund and Garbers [in this issue].

This summary supports the view, that a clear-cut classification of IL-6 type and IL-12-type cytokines into two independent families is almost impossible. Nevertheless, clustering the ligand and receptor components in the presented way (Fig. 1) may help to realize the complexity and connection of both types of cytokines.

Conflict of interest

The authors declare that they have no conflict of interest.