Cytokine & Growth Factor Reviews 32 (2016) 3–15

Contents lists available at ScienceDirect

Cytokine & Growth Factor Reviews

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

Interleukin-4 receptor signaling and its binding mechanism: A therapeutic insight from inhibitors tool box

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ARTICLE INFO

Article history:
Received 5 January 2016
Received in revised form 23 March 2016
Accepted 15 April 2016
Available online 30 April 2016

Keywords:
Interleukin-4
Allergic asthma
Cancers
Antagonistic antibodies
Immunotoxins
IL-4 mutant analogs

ABSTRACT

Studies on Interlukin-4 (IL-4) disclosed great deal of information about its various physiological and pathological roles. All these roles depend upon its interaction and signaling through either type-I (IL-4Rα/common γ-chain) or type-II (IL-4Rα/IL-13Rα) receptors. Another cytokine, IL-13, shares some of the functions of IL-4, because both cytokines use a common receptor subunit, IL-4Rα. Here in this review, we discuss the structural details of IL-4 and IL-4Rα subunit and the structural similarities between IL-4 and IL-13. We also describe detailed chemistry of type-I and type-II receptor complexes and their signaling pathways. Furthermore, we elaborate the strength of type-II hetero dimer signals in response to IL-4 and IL-13. These cytokines are prime players in pathogenesis of allergic asthma, allergic hypersensitivity, different cancers, and HIV infection. Recent advances in the structural and binding chemistry of these cytokines various types of inhibitors were designed to block the interaction of IL-4 and IL-13 with their receptor, including several IL-4 mutant analogs and IL-4 antagonistic antibodies. Moreover, different targeted immunotoxins, which is a fusion of cytokine protein with a toxin or suicidal gene, are the new class of inhibitors to prevent cancer progression. In addition few small molecular inhibitors such as flavonoids have also been developed which are capable of binding with high affinity to IL-4Rα and, therefore, can be very effective in blocking IL-4-mediated responses.

Contents

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http://dx.doi.org/10.1016/j.cytogfr.2016.04.002
1359-6101/

1. Introduction

IL-4, a cytokine discovered in the 1980's, remains in the spotlight as a target for designing a potent small molecular inhibitor. This cytokine is primarily produced by basophils, mast cells, and eosinophils, beside Th2 lymphocytes [1]. Its molecular weight varies between 12 and 20 KDa because of irregular pattern of post-translational modification, particularly glycosylation. This cytokine shares most of cell surface receptors, sequence homology, intracellular signaling and limited functional effects with the IL-13 cytokine [2]. Practically, IL-4 is involved in determining cell proliferation, expression of various genes, and in preventing apoptosis in various cell types like lymphocytes, macrophages, epithelial cells, fibroblasts, as well as endothelial cells [1,2].

Naïve helper T lymphocytic cell differentiation and transformation to the T- helper-2 cells (TH2) is the function of IL-4 protein along with production of series of other cytokines including IL-13, IL-5 and IL-10 [3]. It vigorously ceases T helper-1 (Th-1) cell differentiation and down regulates their IFN production. The second dominating function of IL-4 is to regulate immunoglobulin class switching, especially the expression of IgE and IgG4 in human B-cells [4], and IgG1 and IgE in mouse B-cells [5]. IgE production is reduced to 100-fold or more in IL-4, IL-4 receptor (IL-4R) and STAT-6 (substrate of IL-4Rα) [6] knockout mice. While STAT-6 knockout mice infected with helminthic parasites are devoid of differentiating naïve T-cells to IL-4 producing Th-2 cells [6e]. These physiological functions made IL-4 an ultimate player in regulation of allergic conditions. It also acts as a primary source in providing protective immune response against extra-cellular parasites and helminthes. Moreover, in various clinical and experimental trials, it also appears to be responsible for tissue damaging auto immunity effects [7].

IL-4 has a diverse role in hematopoietic tissues by serving as a co-mitogen for B cell growth [8]. It increases the expression of IL-4 receptor [9], CD 23 [10], and class II MHC molecules [11] along with enhanced ThY-1 expression on B cells in combination with lipopolysaccharides [12]. It can prolong the life of B and T lymphocytes in culture without acting as growth factor by itself for resting lymphocytes [13], and can avert apoptosis on IL-4 expressing cells by factor dependent myeloid lineages [14].

IL-4 also has a significant role in tissue adhesion and inflammation. It causes vascular endothelial cells to express vascular cell adhesion molecule-1(VCAM-1) with tumor necrosis factor (TNF) [15], and reduces expression of the E-selectin protein molecules [16]. This alteration in correspondence to the expression of adhesion molecules by IL-4 is assumed to mediate T-cells and eosinophil recruitment to the site of inflammation rather than other granulocytes [17].

Aberrant expression of IL-4 in number of pathological conditions, underscore its role not only in normal physiology but also in pathogenesis of number of diseases. Therefore, this review will focus on the therapeutic aspects of IL-4 and its receptor, where we will discuss its importance in various disorders such as allergic asthma, different cancers and HIV infections. We will also elaborate various type of inhibitors designed against IL4 and its receptor for treatment of the above mentioned diseases.

2. Biological aspects of IL-4

a) **IL-4 Synthesis**

In normal hematopoietic cells, IL-4 is synthesized by two different types of cells. First one are the matured lymphoid cells that synthesize IL-4 through specific antigen stimulation, and in turn the soluble IL-4 enhances the synthesis of IL-4 by Th2 cells [3a]. While second type of cells are the mast cells from myeloid cell lineage that developed and differentiated by different cytokines within the bone marrow and fully matured in their resident tissues. These mast cells do not require prior antigen exposure, but rather secrete pre-formed IL-4 hoarded in granules after binding of high affinity IgE with their cell surface receptors, and can also trigger new gene transcription for IL-4 synthesis [18].

b) **IL-4 Gene transcription**

IL-4 gene promoter region, which consists of 300 base pairs, harbors Nuclear Factor of Activated T-cells (NF-AT) transcription factor binding region [19]. Likewise, there are minimum five distinct members within the NF-AT family. These transcription factors work in a sequential order similar to NFkB, and remain as dormant cytoplasmic factor that go through calcineurin-dependent dephosphorylation after cell activation. This activation leads to its translocation to the nucleus where it is integrated with AP-1 transcription factor and ultimately results in initiation of IL-4 gene transcription [20].

IL-4 synthesis is focused around three transcription factors: STAT-6, GATA-3 and C-maf. First of all, Th2 cells must receive activation signals to provoke more IL-4 synthesis. The STAT-6 is a fundamental transcription factor for IL-4 receptor signaling and is involved in enhancing IL-4 synthesis. Therefore, the STAT-6 knockout mice were found deficient of yielding Th2 cells [6d]. GATA-3, just like STAT-6, is crucial for Th2 development and can interact with the distal region of IL-4 promoter gene [21]. Lastly, C-maf, a remote relative of AP-1 family, is particularly expressed by Th2 cells rather than Th1 cells [22]. Cells with C-maf deficiency have extremely reduced IL-4 expression, retaining normal expression of other Th2 cytokine. C-maf interacts with the proximal part of IL-4 promoter gene, and any manipulations in this region annihilate IL-4 synthesis completely [18].

3. IL-4 receptor complex scheme

Type I receptor complex was discovered first as a complex between IL-4Rα and γ chain [23]. Most of the hematopoietic, epithelial, endothelial, fibroblast, muscle, hepatocytes and brain tissues cells express IL-4 receptors at the rate of 100–5000 per cell which include [24a,24b]. Majority of cells display type I or type II receptors while a few cells express both types of the receptors.

In the type-I receptor complex, IL-4 first binds with the 140 KDa IL-4Rα chain with high affinity (Kd = 20–300 pM). Physiologically, the signaling cascade starts after hetero-dimerization of IL-4/IL-4Rα complex with the third γ chain (Fig. 1 (left)), while artificial homo-dimerization of IL-4Rα chain produces biochemical signaling within cells [25]. The second chain of IL-4 receptor i.e. common γ chain, which was initially discovered as an integral part of IL-2

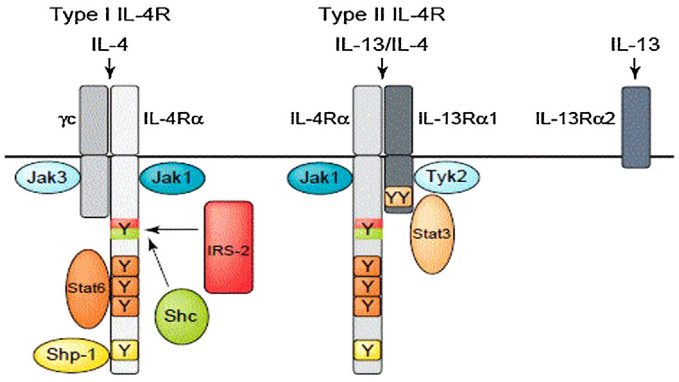

Fig. 1. Represents two type of IL-4 receptors. Left panel explaining type-I receptor with γ-chain while right panel representing type-II receptor with IL-13Rα shared with IL-4 and IL-13 cytokines. (Chatila, T.A., Interleukin-4 receptor signaling pathways in asthma pathogenesis. *Trends in molecular medicine* **2004**, *10* (10), 493–499).