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Review

Interleukin-22: A likely target for treatment of autoimmune diseases☆,☆☆

Xuyan Yang [a,*], Song Guo Zheng [b,*]

[a] Department of Rheumatology, Second Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou 310009, PR China
[b] Division of Rheumatology, Department of Medicine at Penn State University Hershey College of Medicine, Hershey 17033, USA

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ABSTRACT

Interleukin-22 (IL-22) is a member of IL-10 family cytokines that is produced by many different types of lymphocytes including both those of the innate and adaptive immune systems. This includes activated T cells, most notably Th17 and Th22 cells, and NK cells, γδ T cells, LTi cells and LTi-like cells. IL-22 mediates its effects *via* the IL-22–IL-22R complex and subsequent Janus kinase–signal transducer and activators of transcription (JAK–STAT) signaling pathway. Recently accumulated evidence has indicated that IL-22 also plays an important role in the pathogenesis of many autoimmune diseases. In this review, we discuss the recent findings and advancement of the role for IL-22 in several autoimmune diseases, such as psoriasis, rheumatoid arthritis (RA), hepatitis, graft *versus* host disease (GHVD) and allergic diseases, implicating that target IL-22 may have a therapeutic potential in those autoimmune diseases.

Contents

1. Introduction

IL-22 was firstly identified in murine IL-9-stimulated BW5147 T-lymphoma cells [1], and followed by the identification of human IL-22 in two studies [1,2]. IL-22 is a member of the IL-10 cytokine family. Its structure is similar to the well-known anti-inflammatory and immunosuppressive cytokine IL-10, for which IL-22 was initially

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* Corresponding authors.
E-mail addresses: yangxuyan@163.com (X. Yang), szheng1@hmc.psu.edu (S.G. Zheng).

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named as IL-10-related-T-cell-derived inducible factor (IL-TIF). Human and mouse IL-TIF both consist of 179 amino acid residues including four aminothiopropionic acids, which show an overall sequence identity with IL-10 of 22% in the mouse and 25% in the human [3].

The human IL-22-encoding gene is located on chromosome 12q15, approximately 52- and 99-kbp, at 90 kb from the IFN-γ gene, and 27 kb from the AK155 gene. The human IL-22 gene comprises five exons. The first 53 bp of exon 1 encodes the 5′-untranslated region. The other portions of exon 1 (186 bp), the exons 2–4 (66, 144, and 66 bp), and the first portion (79) of exon 5 contain the protein-coding part and the stop codon. The rest portions of exon 5 (554 bp) encode the 3′-untranslated region, which includes six single and two overlapping copies of the ATTTA motif known to be involved in the regulation of mRNA degradation. The open reading frame is comprised of 537 bp (without the stop codon), predicting a length of 179 AA for the encoded protein. In the mouse, IL-22-encoding gene is located on chromosome 10, also near the IFN-γ gene. There are two copies in different mouse strains, which show 98% nucleotide identity in the coding region, named IL-TIFα and IL-TIFβ [4]. With the knowledge of IL-22, numerous studies regarding the role of IL-22 in autoimmune diseases are emerging.

2. The cellular sources of IL-22

IL-22 was originally thought to be a Th1-associated cytokine. With the discovery of new T helper cells, it has been determined that specific populations of T cells have the capacity to express IL-22, several of which accumulate at barrier surfaces. Th17 and Th22 cells were demonstrated to be important producers [5–7]. In Th17 cells, IL-22 expression differs from IL-17 and other Th17-associated cytokines. The presence of transforming growth factor-β (TGF-β) and IL-6, which is mainly required for the generating IL-17A does not lead to optimal IL-22 expression; this is because TGF-β is inhibitory to IL-22 expression [8]. Moreover, IL-17A is highly dependent on the nuclear hormone receptor transcription factors retinoic acid-related orphan receptor γt (RORγt) and RORα, whereas IL-22 expression requires the ligand-dependent transcription factor aryl hydrocarbon receptor (AHR) [9,10]. In humans, a population of $CD4^+$ T cells that localizes to the skin and can express IL-22, TNF-a, and IL-13, but not IL-17A, has been reported. Given the predominant expression of IL-22, these cells have been termed Th22 cells [7]. If cultured in Th1-, Th2-, Th17- or Treg-polarizing conditions, Th22 clones continue to express IL-22 and not the other cytokines associated with these Th subsets [11]. Th22 cells appear to be important for skin homeostasis and in inflammation.

In addition to $CD4^+$ T cells, $CD8^+$ T cells also express IL-22 when differentiated into Tc17 cells. Increased population of $CD8^+$ T cells expressing IL-22 has also been observed in the skin of patients with atopic dermatitis and correlated with increased disease severity [12]. Additionally, similar to Th17 cells, the γδ T-cell has been showed to coexpress IL-22 and IL-17A, and has been implicated in pulmonary immune responses [13,14].

Apart from expression of IL-22 by T cells, innate immune cells also have the capacity to express IL-22. IL-22 was reported to be expressed by blood-derived NK cells [9]. There is also described mucosa-associated lymphoid tissue-residing NK cell population in humans, which expresses IL-22 in response to IL-23 (the so-called NK-22). Despite the absence of the classical NK cell effector functions, they rather provide the protection and regulate the mucosal homeostasis. They express NKp44, CCR6, and the transcription factors RORγt, RORα, AHR and IRF4, and produce IL-22, IL-26 and LIF [15,16].

Furthermore, IL-22 expression has been described in several populations of innate lymphoid cells (ILCs) with the capacity to produce IL-22 and coexpress NK cell and myeloid cell markers [17]. IL-22-expressing ILCs constitute a heterogeneous population composed of $CD4^+$ lymphoid tissue inducer (LTi) cells characterized by the repression of IL-17, lymphotoxin α1β2 and RORγt, LTi-like cells expressing RORγt, AHR and IL-17, and $NKp46^+$ ILCs expressing RORγt mouse [18–20]. Sharing a number of similar phenotypic and transcriptional profiles, these ILC populations are present at barrier surfaces, and can express IL-22 following stimulation with IL-23 alone. Recent studies have showed that these populations have been implicated in promoting innate immunity and intestinal inflammation, and may represent a more primitive form of IL-22-producing adaptive immune cells [21].

3. IL-22 acts by the IL-22–IL-22R pathway

3.1. IL-22R expressed only by non-hematopoietic cell lineages

IL-10 and IL-22 receptors are composed of heterodimeric chains. IL-10 is made up of IL-10R1 and IL-10R2. IL-22 receptor complex consists of IL-22R1 and IL-10R2. The unique signaling and the functional outcome of these two cytokines are maintained by the exclusive use of independent receptor subunits. the IL-22R1 subunit is restricted to cell lineages of a non-hematopoietic origin. In particular, non-hematopoietic cells that have been found to constitutively express a functional IL-22R1 are resident in the pancreas, kidney, and liver, as well as at barrier surfaces such as the skin, intestine, and lung [22,23]. In contrast, the bone marrow, peripheral blood mononuclear (PBMC), spleen or thymus, all of which contain a high proportion of immune cells, do not express IL-22R1 [23]. Furthermore, immune cells in general lack IL-22R1 expression and therefore are not targets of IL-22, which is different from its conventional designation as an interleukin [23]. The restricted distribution of the IL-22R governs the functions of IL-22 as it restricts the biological effects of IL-22 to non-hematopoietic tissue-resident cells. Interestingly, IL-22R expression is up-regulated following stimulation of human skin cells with INF-γ and TNF-α, or following Con-A or LPS challenge of hepatocytes [23,24], suggesting that the IL-22 action may be affected by the dynamic expression of IL-22R1.

In addition to the surface-bound receptor, a soluble secreted receptor for IL-22 exists, termed IL-22BP or IL-22RA2. IL-22BP is expressed in various tissues, including the breast, lungs, and colon [25]. However, the cellular sources of IL-22BP in these tissues remain unclear. IL-22BP binds IL-22 with a sufficient affinity to block IL-22R binding, therefore acting as a natural cytokine antagonist. IL-22BP expression in tissues can be regulated. During acute inflammation, while IL-22 was up-regulated in murine models of infection and colitis, IL-22BP was down-regulated, suggesting that IL-22BP may be important in regulating the *in vivo* biological consequences of IL-22 expression [26,27]. However, further investigations are required to advance our understanding of the regulation and functions of IL-22BP in the context of infection and inflammation, as it may be an important pathway to consider when targeting IL-22.

3.2. Signal transduction pathways activated downstream of IL-22R ligation

IL-22 binding to IL-22R complex leads to a cascade of downstream signaling pathways. Initial studies utilizing a murine kidney cell line revealed that IL-22R ligation induced phosphorylation of STAT3, and to a lesser extent, STAT5, while other studies observed phosphorylation of STAT1, STAT3, and STAT5 in a human kidney cell line [1]. Further analysis also demonstrated that IL-22 signaling utilizes JAK1 and TYK2 to propagate downstream phosphorylation signals, including several MAPK pathways (ERK1/2, MEK1/2, JNK, and p38 kinase), and STAT1, STAT3, and STAT5 [28]. IL-22 as well as other members of the IL-10 cytokine family utilizes the common pathway of STAT3-mediated signaling. However, IL-22 signaling exhibits a number of unique properties. For example, in comparison to IL-10 stimulation that induces phosphorylation of tyrosine residues on STAT3, IL-22 stimulation induces STAT3 phosphorylation on both tyrosine and serine residues, and also strongly activates the ERK1/2 pathway [28]. The observed differences in signal transduction pathways can likely be attributed to differences between