IL-17A Family, Receptors, Proinflammatory Effects, and Production

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Abstract IL-17A is a proinflammatory cytokine with critical effects on many cell types. It is part of a larger family of cytokines with important roles in protection against pathogens. The IL-17A receptors are IL-17RA and IL-17RC. They are expressed on most cell types. IL-17A, in synergy with other cytokines such as TNF-α, induces the production of cytokines, chemokines, and mediators of tissue destruction in several cell types. The identification of IL-17A and, later on, of Th17 cells has modified the established Th1 and Th2 paradigm, led to the definition of a new CD3+ CD4+ effector T cell subset, and introduced a new paradigm to explain the origin of several autoimmune events. However, this paradigm shift tended also to identify the effects of IL-17A with those of Th17 cells and vice versa. This view might be insufficient to explain the role of IL-17A in infections and autoimmune models. IL-17A is in fact produced by several other cell types involved in host defense, autoimmunity, and inflammation, and they might also be involved in IL-17A induced pathology.

Keywords IL-17A • IL17F • IL-17RA • IL17RC • Th17 cell

1 IL-17A and Other IL17 Family Members

In 1993, Rouvier et al. [1] described the cloning of a rodent cDNA sequence, termed CTLA8, from an activated T cell hybridoma using a subtractive hybridization approach and reported the sequence of the corresponding protein. This sequence

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had homology to an open reading frame encoded within a T cell-tropic c-herpesvirus, Herpesvirus Saimiri, and they suggested that it might be a novel cytokine [1]. Later on, the protein described was found to be a rat protein [2]. The human homologue was reported in 1995 and was mainly produced by activated CD4+ T cells, induced the secretion of IL-6 and IL-8 in human foreskin fibroblasts, and enhanced the expression of ICAM-1 [2]. This molecule was named IL-17. The mouse homolog was reported a year later [3, 4] and, in one case, was cloned from mouse NKT cells [3].

Human IL-17A is a glycoprotein containing 155 amino acid residues and shares 63 % amino acid identity with murine IL-17A (147 amino acids). Both human and mouse IL-17A are secreted as disulfide-linked homodimers. Now, the IL-17 family includes seven members (IL-17 or IL-17A, IL-17B, IL-17C, IL-17D, IL-17E or IL-25, and IL-17F plus the viral homologue ORF13 or vIL-17). In the mouse system, IL-17F has 45 % amino acid homology to IL-17A, followed by IL-17C (24 %), IL-17B (21 %), IL-17D (16 %), and IL-17E (16 %) [5]. IL-17A and IL-17F are secreted by overlapping populations of T cells and form both homodimers and heterodimers [6, 7]. IL-17B, IL-17C, and IL-17E differ substantially from IL-17A and IL-17F in the N terminus, having longer extensions. Furthermore, IL-17B is secreted as a noncovalent dimer [8]. Common features of the IL-17 family are a highly conserved carboxyl terminus and five spatially conserved cysteine residues. Four of these cysteines form a cystine knot fold. Transforming growth factor (TGF)-β, bone morphogenic protein, and nerve growth factor superfamilies show structural similarities but have an additional disulfide bond [8].

The genes for IL-17A and IL-17F are located on human chromosome 6p12.2, while the genes of the other IL-17 family members are located on different chromosomes: IL-17B on Chr 5q32, IL-17C on Chr 16q24.3, IL-17D on Chr 13q12.111, and IL-25 on Chr 14q11.2. Polymorphisms in IL-17A (rs2275913) gene have been weakly associated with rheumatoid arthritis [9], while polymorphism in IL-17F (rs763780) gene has been associated with a protective role in asthma [10]. Polymorphism at the 197A (IL-17A) and 7488T (IL-17F) alleles may influence the susceptibility to and pathophysiological features of ulcerative colitis [11]. In the Chinese population, rs2275913 and rs763780 are associated with immune diseases and infectious diseases, including asthma, Vogt–Koyanagi–Harada syndrome, bacterial bronchiolitis, and neuromyelitis optica [12–14].

2 The Receptors

When the mouse and the human IL-17 receptors (IL-17RA) were cloned, IL-17RA was found to be ubiquitously expressed and unique. It consisted of a single transmembrane receptor with an unusually long cytoplasmic tail [15, 16]. Now, five different receptors have been described, IL-17RA, IL-17RB, IL-17RC, IL-17RD, and IL-17RE [17]. The IL-17R family contains conserved structural characteristics such as extracellular fibronectin III-like domains and cytoplasmic similar expression to fibroblast growth factor, IL-17R, and Toll-IL-1R family

(SEFIR) domains. IL-17A and IL-17F signal through a receptor complex composed of IL-17RA and IL-17RC [18]. In humans IL-17RA binds with higher affinity to IL-17A than to IL-17F, whereas IL-17RC associates with both IL-17A and IL-17F [18, 19]. Cristal structure of the IL-17F-IL-17RA interaction reveals the presence of a loop of IL-17RA which interacts with the deep groove at the interface of IL-17F homodimer [18]. IL-17RD has also been associated with the IL-17R complex and may contribute to IL-17A signaling [20]. IL-17RB is the receptor chain for IL-25 and IL-17B [21, 22]. The receptor for IL-17C appears to be a heterodimeric complex formed by IL-17RA (low-affinity interaction) and IL-17RE (high-affinity interaction) [23–25].

In conclusion, IL-17RA is shared among the members of the IL-17 family, while the specificity of the interaction mainly resides in the second subunit of the heterodimeric receptor complex. IL-17RC is common to IL-17A and IL-17F homo- and heterodimers; IL-17RB is specific for IL-25 and IL-17B, IL-17RE for IL-17C, and IL-17RD may be part of the IL-17A receptor complex [23–25]. Since IL-17RA is ubiquitously expressed, also the tissue specificity of the responses resides in the second receptor chain which is differently expressed in various tissues.

3 IL-17A as a Proinflammatory Cytokine

Several reports suggest that IL-17A has a critical role in the protection of the organism against bacteria and fungi due to the ability of IL-17A to recruit neutrophils to the infected organs/tissues [26, 27]. IL-17A and IL-17F can induce the production of proinflammatory cytokines (IL-1, IL-6, TNF-α, G-CSF, and GM-CSF), chemokines (CXCL1, CXCL5, IL-8, CCL2, and CCL7), antimicrobial peptides (defensins, lipocalin2, and S100 proteins), and matrix metalloproteinases (MMP1, MMP3, and MMP13) from different cell types. IL-17A also controls the expression of intercellular cell adhesion molecule 1 (ICAM-1) in keratinocytes as well as iNOS and cyclooxygenase-2 in chondrocytes. IL-17F is a weaker inducer of proinflammatory cytokine but seems to be produced by a wider range of cell types, including innate immune cells and epithelial cells. Not unexpectedly, IL-17A and IL-17F act in concert with other cytokines such as TNF-α, with which they strongly synergize in in vitro cellular assays and in vivo. It is expected that this characteristic is shared by the other IL-17 family members. Moreover, IL-17A contributes to germinal center formation and class switch recombination by its action on B cells [28, 29].

In summary, IL-17A, acting in synergy with other cytokines, contributes to modulate and control the inflammatory response. Some events, e.g., neutrophil recruitment, are indirectly mediated through the activity of IL-17A on cells which secrete chemotactic factors for neutrophils. Therefore, the mediators, secreted by activated cells, modulate the final outcome of the response to IL-17A.

4 IL-17A-Producing Cells

In 2000, Infante-Duarte et al. [30] recognized that IL-17A cannot be categorized as either a Th1 or a Th2 cytokine, but a major advance in IL-17 research came with the recognition of a novel T cell lineage producing IL-17A and/or IL-17F [31, 32]. This finding modified the established Th1-Th2 paradigm, led to the definition of the CD3+ CD4+ Th17 cell subset, and introduced a new paradigm to explain the origin of several autoimmune events.

In the mouse, IL-17A and/or IL-17F are however produced by several other cell types involved in host defense, autoimmunity, and inflammation, including subpopulations of CD8+ T cells (Tc17), γδ T cells [33], invariant natural killer (iNKT) cells [34], lymphoid tissue inducers [35], neutrophils [36], and macrophages [37]. In addition, IL-17A is produced by intestinal Paneth cells in an IL-23 independent fashion being one of the causes of a systemic inflammatory response syndrome [38], and IL-17F mRNA is expressed in colonic epithelial cells [39]. In particular, Jensen et al. [33] found that γδ T cells are uniquely suited for the initial IL-17A response, which often is elicited without a clear antigen exposure. They also found evidence for two distinct functional subsets of γδ T cells (Tγδ-17s and Tγδ-IFN-γs).

Yoshiga et al. [40] demonstrated that also iNKT cells synthesize and release IL-17A, accelerate IL-17 production by Th17 cells, and play a role in the development of collagen-induced arthritis (CIA). Moreover, they found that iNKT cells can be induced to secrete IL-17A through two pathways, one involving the direct activation of the TCR by glycolipid antigen and the other the IL-23-IL-23R signaling pathway [40]. It appears therefore that IL-17A is produced by different subsets of T cells, which are involved in both innate and adaptive immunity, and it is well suited to participate to both early and late phases of the immune response.

In addition, in IL-10- or IL-10R-deficient mice, even macrophages stimulated with lipopolysaccharide appear to produce high levels of IL-17A and IL-22 [41]. Addition of exogenous IL-10 abolishes IL-17A production both in Th17 cells and in macrophages [41], again suggesting that IL-17A production is highly regulated.

In humans, IL-17A has been detected in several T cell subsets, such as naive, central memory, and effector memory CD4+ IL-17+ T cells [42], NKT-like cells [43], macrophages [44], astrocytes [45], oligodendroglia [45], mast cells [46], neutrophils [47], and also a human myeloma cell line [48].

The large number of cell types able to secrete IL-17A and IL-17F, the migratory potential of the cells secreting these cytokines, the ubiquitous distribution of the receptor, and the synergism with other proinflammatory cytokines allow IL-17A and IL-17F to exert effects in multiple pathological conditions [26, 49]. In addition, Th17 cells act in close contact with their target cell, and IL-17A might have a short range of action and act in synergy with other cytokines secreted by Th-17 cells [50]. The role of other family members might be more restricted due to a more limited expression and tissue distribution of their receptors.

A pathological role for IL-17A in several autoimmune models of disease, such as experimental autoimmune encephalomyelitis (EAE) and arthritis, has been documented [5], and increased production of IL-17A has been reported in various

human autoimmune and allergic diseases, such as rheumatoid arthritis [51], multiple sclerosis [45], psoriasis [52], and asthma [53]. All these findings suggest a pathogenic role in several human diseases which has been confirmed by the clinical efficacy of IL-17A neutralization in different disease [54].

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