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IL-17D: A Less Studied Cytokine of IL-17 Family

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Abstract
The interleukin-17 (IL-17) family is a relatively new family of cytokines consisting of 6 related factors (IL-17A–IL-17F), while the receptor family consists of 5 members: IL-17RA–IL-17RE. IL-17A is the prototype member of this family, which is also the signature cytokine of T helper 17 (Th17) cells. Th17 cells are involved in the development of autoimmune disease, inflammation, and tumors. Although IL-17D is similar to IL-17A in its ability to induce inflammatory cytokine production, there are fewer studies on IL-17D. Recently, the role of IL-17D in tumors and infections has attracted our attention. Some knowledge of function of IL-17D has been gained by studies using nonmammalian species. In this review, we introduce the structural characteristics, expression patterns, and biological characteristics of IL-17D along with its potential function in the pathogenesis of disease.

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Introduction

Cytokines are small molecular proteins synthesized and secreted by immune cells and some nonimmune cells; cytokines serve as the main coordinators of the immune system. The interleukin-17 (IL-17) family is considered to be a unique family of cytokines that has significant immunological importance. IL-17A, the prototypic member of this family, was first identified in 1993 [1]. At present, 5 other members, IL-17B–IL-17F (shown in Fig. 1), have also been identified and cloned via human genome sequencing and proteomics [2–5]. Among them, IL-17F has the highest homology with IL-17A (40–55%), followed by IL-17B (29%), IL-17D (25%), IL-17C (23%), and IL-17E (17%) [6, 7]. IL-17A, also commonly called IL-17, is mainly produced by $CD4^+$ T cells, $CD8^+$ T cells, and some immune cells. T helper 17 (Th17) cells not only produce IL-17A but also secrete IL-17F, IL-21, and IL-22 [8]. Both IL-17A and IL-17F are involved in the development of inflammation and host defense infection by inducing the expression of proinflammatory cytokines, chemokines, antimicrobial peptides, and matrix metalloproteinases by fibroblasts, endothelial cells, and epithelial cells [9, 10]. IL-17A is involved in autoimmune, inflam-

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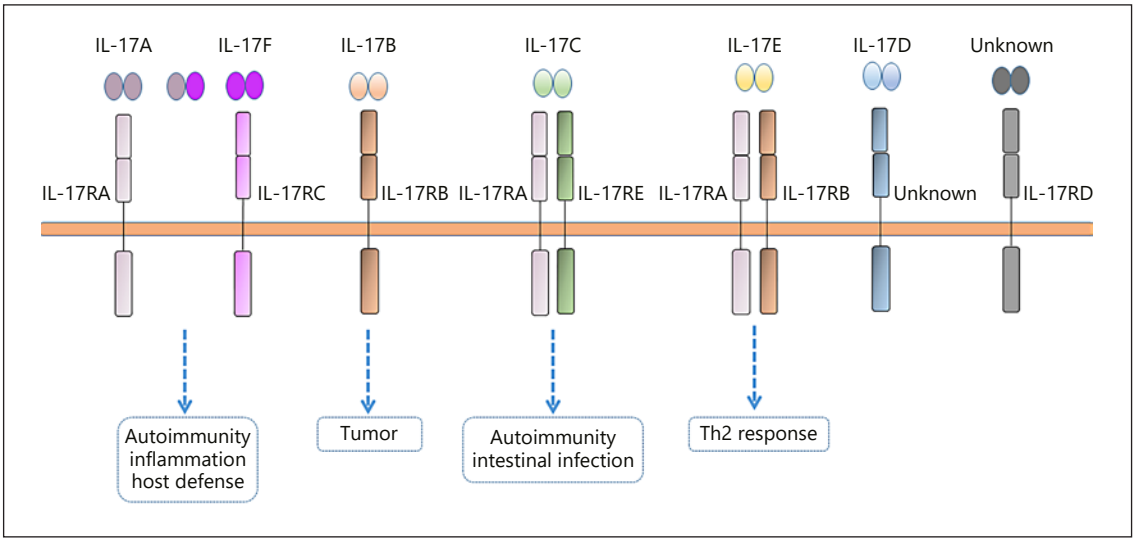

Fig. 1. IL-17 family cytokines and receptors. IL-17 family cytokines contain 6 members (IL-17A–F), and the receptor family consists of 5 members (IL-17RA–RE). IL-17A and IL-17F form homodimers or heterodimers to bind IL-17RA or IL-17RC, which leads to the upregulation of proinflammatory genes for host defense and the inflammatory pathogenesis of autoimmune diseases. Binding of IL-17B to IL-17RB promoted breast cancer cell invasion. IL-17C is essential for preventing intestinal infections and autoimmune diseases via IL-17RA and IL-17RE. IL-17E was believed to promote Th2 cell-type immune responses through the IL-17RA and IL-17RB heterodimer receptor complexes. The receptor for IL-17D and the ligand(s) for IL-17RD have not been identified. IL-17, interleukin-17.

mation, and tumor development, while also playing an important role in host defense against bacterial and fungal infections [11, 12]; IL-17F is mainly involved in mucosal host defense [10]. The study found that the dual neutralization of IL-17A and IL-17F in psoriatic arthritis resulted in more effectively suppressing inflammation than the blockade of IL-17A alone, which indicated that IL-17F was similar to IL-17A in inducing an inflammatory response including the expression of proinflammatory cytokines and neutrophil recruitment [13]. *IL-17B* mRNA has been detected in adult human pancreas, small intestine, and stomach [2], although high expression was detected in chondrocytes and neurons [3, 14]. IL-17C is expressed in $CD4^+$ T cells, dendritic cells, and macrophages at the site of inflammation, but not in most normal tissues [2, 15, 16]. Both IL-17B and IL-17C can induce the expression of TNF and IL-1β in monocyte cell lines and cause neutrophil infiltration [2, 3]. IL-17E (IL-25) is an amplifier of Th2 immune responses [9], which enhances type II immune responses by inducing cytokines (IL-4, IL-5, and IL-13) in auxiliary cells and induces IgE production and eosinophils, helping the host defend against nematodes and allergic diseases [17–19].

The IL-17 family of receptors consisting of IL-17RA, IL-17RB, IL-17RC, IL-17RD (SEF), and IL-17RE was also identified by the typical structural homology between members (shown in Fig. 1) [14, 20]. All receptor members include a fibronectin III-like domain in their extracellular domain and a SEF/IL-17R (SEFIR) domain in their intracellular region [21]. The SEFIR domain was previously identified as part of a cytosolic protein called Act1, which was identified as a key molecule for IL-17-mediated signaling [21, 22]. IL-17 family members act by binding to either homodimers or heterodimers of the IL-17 receptor family [23, 24]. IL-17A and IL-17F form homodimers or heterodimers to bind IL-17RA or IL-17RC, which leads to the upregulation of proinflammatory genes [25]. IL-17C is essential for preventing intestinal infections and autoimmune diseases via IL-17RE [26–28]. Binding of IL-17B to IL-17RB promoted breast cancer cell invasion [29], while IL-17RB overexpression was associated with poor prognosis in patients with gastric cancer [30]. IL-17E was believed to promote Th2 cell-type immune responses through the IL-17RA and IL-17RB heterodimer receptor complexes [31]. At present, the receptor of IL-17D is still unknown [32]; however, unlike other members of the IL-17 family, IL-17D possesses an extended C-terminal domain that can mediate unique receptor interactions [33]. Some studies have reported an interaction between IL-17D and IL-17RA, which indicates that

Table 1. Nucleotide/amino acid identity of human IL-17D with IL-17D in other species

Nucleotide/AA	1	2	3	4	5
Human IL-17D		59.9	61.8	62.1	58.7
Zebrafish IL-17D	64.9		65.7	67.9	84.4
Atlantic salmon IL-17D	50.5	65.4		62.6	65.1
Takifugu IL-17D	45.0	59.8	64.9		59.8
Grass carp IL-17D	52.5	85.3	66.7	55.8	

IL-17, interleukin-17.

IL-17RA may be a potential receptor for IL-17D [34]. IL-17D expression was detected in both teleosts as well as tetrapods [35–37]; thus, it is considered to be the most ancient member of the IL-17 family [38]. Homology analysis revealed that human IL-17D shared different similarities to other species IL-17D (Table 1), which shows that different species IL-17D have similar functions [35, 36, 39, 40]. However, there is little knowledge available regarding the biological functions of IL-17D at present. In this review, we describe recent advances in the function of IL-17D, clarify its role in disease, and discuss areas for future research.

Structural Characteristics and Expression of IL-17D

All members of the IL-17 family share 4 highly conserved cysteine residues, which are involved in the formation of intrachain disulfide bonds. Human *IL-17D* was mapped to chromosome 13p11. As the largest member of the IL-17 family, IL-17D is a glycoprotein consisting of 202 amino acids, with a predicted monomer molecular weight of 26.3 kDa and a dimer molecular weight of 52.6 kDa. IL-17D also has 4 other cysteine residues, which may participate in interchain disulfide linkages, thereby forming homodimers [33]. Starnes et al. [33] examined the expression of *IL17D* through RT-PCR. They observed that *IL17D* was highly expressed in skeletal muscle, brain, adipose tissue, heart, lung, and pancreas, while it was expressed at low levels in bone marrow, fetal liver, kidney, leukocytes, liver, lymph nodes, placenta, spleen, thymus, and tonsils. In addition, *IL17D* is also expressed at low levels in resting $CD4^+$ T cells and resting $CD19^+$ B cells. *IL17D* was poorly expressed in activated $CD4^+$ T cells, resting and activated $CD8^+$ T cells, resting and activated $CD14^+$ monocytes, and activated $CD19^+$ B cells [33].

Biological Activities of IL-17D

IL-17D did not seem to induce immune cell proliferation, but similar to other IL-17 family members, IL-17D had the ability to stimulate the production of other cytokines such as IL-6, IL-8, and GM-CSF [41]. It has been suggested that IL-17D plays a role in local immune responses because it can induce myeloid growth factors and chemokines, stimulating local infiltration and proliferation of leukocytes [33]. IL-17D suppressed the proliferation of myeloid progenitor cells as IL-17D increased IL-8 in an NF-kB-dependent manner [33]. IL-17D stimulated human umbilical vein endothelial cells to produce IL-8 to levels that were in the physiological range to inhibit hemopoiesis [42], while the levels of GM-CSF produced in human umbilical vein endothelial cells were 10-fold lower than that required for stimulation of myeloid proliferation [43]. IL-17D plays a role in chronic anemia and sustained immune stimulation, while increased IL-17D resulted in decreased hemopoiesis; thus, IL-17D may play a direct or indirect role in regulating the hematopoietic response of inflammation by inducing the production of other cytokines [42, 44].

Potential Roles of IL-17D in Diseases

IL-17D in Autoimmune Diseases

The members of the IL-17 family have been implicated in autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, psoriasis, and allogeneic rejection [10]. Although IL-17D has not been found in synovial fluid or peripheral blood mononuclear cells from patients with rheumatoid arthritis, it was detected in rheumatoid nodules [15, 45], and the potential pathogenic roles remain to be elucidated. However, mRNA expression of *IL17D* was decreased in psoriatic skin [46]. These results indicate that IL-17D plays multiple roles in autoimmune disease, although future research studies to clarify its role are needed.

IL-17D in Tumors

Cytokine-based immunotherapy will become an important treatment for human cancer [47, 48]. IL-17D is a potential target for tumor immunotherapy as it was found that injection of recombinant IL-17D into B16-OVA melanoma cells transplanted into WT mice caused a significant growth delay as compared to control-treated tumors, demonstrating the antitumor effect of IL-17D [49]. Unlike the chemokines and cytokines expressed in immune

cells, such as GM-CSF and IL-15 [50, 51], IL-17D is a cytokine that can be expressed by tumor cells. IL-17D stimulates production of monocyte chemotactic protein-1 (MCP-1), which recruits natural killer (NK) cells to the tumor microenvironment [52], and promotes M1 macrophage development and an adaptive immune response [49]. NK cells have been shown to promote antitumor T cell [53] and macrophage responses [54]. IL-17D-recruited NK cells primarily express high levels of CD27; chemokine receptor 3 (CXCR3) is thought to mediate the recruitment of $CD27^{high}$ NK cells that secrete cytokines in lymph nodes [55, 56]. The expression of CXCR3 ligands such as ITAC, MIG, and IP-10 can be induced by interferons (IFN) during tumor development [57]; therefore, IL-17D may also directly or indirectly induce production of IFN-γ by NK cells to induce CXCR3 ligand expression on tumor cells. As a primary regulator of the response to oxidative stress [58], Nrf2 protects somatic and premalignant cells from carcinogenesis [59]. Analysis gene expression of fibrosarcoma cell lines treated with the chemical carcinogen, 3-methylcholanthrene (3-MCA), revealed that Nrf2 and IL-17D were coexpressed in murine tumor cell lines [60]. At the same time, Nrf2 activated by *tert*-butylhydroquinone (tBHQ), which was an antioxidant, resulted in an increase in *IL17D* transcripts in a murine melanoma cell line (B16), a human Burkitt's lymphoma cell line (Ramos), and an MCA-induced sarcoma cell line (F244) [60]. Nrf2 not only directly bound to the *IL17D* promoter region but also was required for efficient induction of IL-17D by oxidative stress [60].

It has also been reported that IL-17D is expressed on neutrophils both in healthy subjects and patients with B-cell chronic lymphocytic leukemia. The expression of IL-17D in neutrophils of patients was higher than that of healthy subjects [61], likely because IL-17D can affect the recruitment of neutrophils by inducing the production of IL-6, IL-8, and GM-CSF [33, 62]. Although studies investigating the role of IL-17 family cytokines in tumor progression have focused mainly on IL-17A, a major effect of IL-17A in the antitumor response is the recruitment of neutrophils [63]. IL-17D has previously been shown to play a role in the recruitment of neutrophils and other immune cells, such as NK cells, in tumors [52]. Based on these observations, the effective use of IL-17D for antitumor immunotherapy will depend on the specific clinical situation.

IL-17D in Infection

Studies have shown that mice deficient in *IL17D* exhibit signs of more severe infection after infection vaccinia virus (VV) or murine cytomegalovirus (MCMV) as compared to WT mice [60]. At the same time, mouse cytomegalovirus infection induces the increase of *IL17D* transcription in both fibroblasts [60] and peritoneal cells (mainly macrophages and B cells) [64] in vitro. These studies conclude that IL-17D mediates the early local recruitment of innate immune cells, which made mice more resistant to MCMV infection. Lee et al. [65] found that IL-17D exerted a pathogenic effect by inhibiting the activation of dendritic cells to reduce $CD8^+$ T cells activity during *Listeria* infection. Therefore, the effect of IL-17D in infection may depend on both the specific pathogen and the nature of inflammation.

In chicken, following *Eimeria maxima* infection, *IL17D* transcript levels were increased in intestinal epithelial lymphocytes ($CD4^+$, $CD8^+$, and $TCR1^+$ cells), bursa, lung, and spleen but decreased in thymus. Treatment of chicken fibroblasts (CHCC-OU2) with chIL-17D recombinant protein induced the expression of IL-6 and IL-8. These results indicated that IL-17D plays an important role in intestinal innate immunity during avian experimental coccidiosis [66].

Knowledge of IL-17D in lower vertebrates is limited. Grass carp IL-17D was preferentially expressed in mucosal tissues including skin, intestine, and gills; in addition, expression of IL-17D in head kidney and head kidney leukocytes was increased during in vivo bacterial infection and in vitro LPS treatment. Recombinant gcIL-17D increased gene expression of some proinflammatory cytokines such as *IL-1β*, *TNF-α*, and *CXCL8* in grass carp primary head kidney cells. Recombinant gcIL-17D seems to activate the NF-kB signaling pathway by regulating the phosphorylation of IkBα, thereby upregulating the expression of *CXCL8* mRNA [40]. Moreover, IL-17D in *Larimichthys crocea* also increased the expression of the above chemokines and proinflammatory cytokines and mediated the migration of peripheral blood leukocytes [32], which further supported the immunoregulatory role of IL-17D in inflammation.

Conclusion

In this review, we summarize the structural characteristics, expression patterns, and biological activities of IL-17D and its role in disease. Recent reports have mainly focused on the role of IL-17D in tumors and infections. The Nrf2-IL-17D regulatory axis is activated during primary tumorigenesis and infection. It is likely that IL-17D can induce a more consistent antitumor re-

sponse by recruiting NK cells, but its role in infection varies according to the specific type of pathogen and degree of inflammation present. Although there has been no research on the function of IL-17D in other diseases, future research on the endogenous role of IL-17D in infection, autoimmunity, and cancer and its regulation is necessary.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Xuying Liu drafted the manuscript, Siyu Sun drafted and revised the article critically for important intellectual content, and Dongyan Liu gave the final approval of the submitted manuscript. All authors read and approved the manuscript and agree to be accountable for all aspects of the research in ensuring that the accuracy and integrity of any part of the work are appropriately investigated and resolved.

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