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Review

Interleukin-17 and innate immunity in infections and chronic inflammation

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ABSTRACT

Interleukin 17 (IL-17) includes several cytokines among which IL-17A is considered as one of the major pro-inflammatory cytokine being central to the innate and adaptive immune responses. IL-17 is produced by unconventional T cells, members of innate lymphoid cells (ILCs), mast cells, as well as typical innate immune cells, such as neutrophils and macrophages located in the epithelial barriers and characterised by a rapid response to infectious agents by recruiting neutrophils as first line of defence and inducing the production of antimicrobial peptides. Th17 responses appear pivotal in chronic and acute infections by bacteria, parasites, and fungi, as well as in autoimmune and chronic inflammatory diseases, including rheumatoid arthritis, psoriasis, and psoriatic arthritis. The data discussed in this review cumulatively indicate that innate-derived IL-17 constitutes a major element in the altered immune response against self antigens or the perpetuation of inflammation, particularly at mucosal sites. New drugs targeting the IL17 pathway include brodalumab, ixekizumab, and secukinumab and their use in psoriatic disease is expected to dramatically impact our approach to this systemic condition.

1. Introduction

Innate immunity represents the first and phylogenetically oldest line of defense against infections for all multicellular organism including plants and insects. In general terms, innate immunity provides the initial acute inflammatory response to microorganisms to prevent, control and eliminate infections while it has the ability to modulate and stimulate adaptive immune responses usually secreting different kind of cytokines to activate and attract cells that are considered effector cells of adaptive immunity [1]. The acute inflammatory response is generally self-limiting and results in tissue repair and return of tissue homeostasis while the persistence of inflammatory stimuli or the dysregulation of resolution mechanisms result in chronic inflammation, recognized to be a key underlying factor in the progression of complex diseases, including metabolic and cardiovascular ones [2].

CD4+ T cells are the central players in the adaptive immune response [3] and naïve CD4+ T cells upon stimulation and activation differentiate into distinct subsets according to the corresponding cytokine profile. Two separate Th subsets were originally defined by the secretion of interferon γ (IFNγ, for Th1) or interleukin 4 (IL-4, for Th2) [4]. Th1 are helper cells involved in the elimination of intracellular pathogens and characterize organ-specific autoimmune diseases. The key Th1 effector-cytokines include IFNγ, lymphotoxin α (Lfα), and IL-2 [5,6]. Th2 helper cells play major role in immune responses against extracellular parasites, in the pathogenesis of asthma and other related allergic conditions. Th2 cells are significant producers of IL-4, IL-5, IL-9, IL-13, IL-10, IL-25, and amphiregulin [7]. Over the past years, additional effector populations of CD4+ T cell were identified and consequently referred to as Th9 [8], Th17, and Th22 [9,10] with a considerable degree of plasticity [11] and Th17 characterized by the production of IL-17 as the signature cytokine [12]. The IL-17 cytokine family includes six members, i.e. IL-17A, IL-17B, IL-17C, IL-17D, IL-17E - referred also as IL-25 and IL-17F (Table 1). IL-17A

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Table 1
Members and functional features of the IL-17 cytokine family.

Name	Murine synonym	Human synonym	Cell source	Effector function
IL-17A/IL-17F	CTLA-8/ML-1	CTLA8	Th17, γδ T cells, RORγt + ILC, mast cells, macrophages, neutrophils, keratinocyte, iNKT	Production of IL-1β,IL-6, IL-8, IL-11, Gro-α, G-CSF and GM-CSF, antimicrobial peptide, activation of NF-κB, MAPK pathways, neutrophils
IL-17B	NIRF[a], CX1	IL-20, NIRF		
IL-17C	CX2	CX2	Epithelial cells	Production of antimicrobial peptides
IL-17D	/	IL-27		
IL-17E	IL-25	IL-25	Th17, Eosinophils, basophils	Production of IL-4, IL-5, IL-13, IgE, and eotaxin, eosinophilia, basophilia

[a] NIRF-Neuronal interleukin-17-related factor.

and IL-17F share a high degree of similarity and bind the IL-17 receptor (IL-17R, a heterodimer of IL-17RA and IL-17RC subunits) [13]. IL-17A (in the literature often referred to as IL-17) was first described in 1993 [14] in human peripheral blood, as an important proinflammatory cytokine with a critical role against extracellular microorganisms and in the pathogenesis of different autoimmune diseases. Sodium chloride via the salt sensing kinase SGK1 promotes Th17 cell differentiation and autoimmunity [15,16]. Within the IL-17 family, IL-17A and IL-17F are central players in the adaptive immune response, particularly against bacteria and fungi [17,18] while the function of IL-17B, IL-17C and IL-17D is less understood [18]. Specialized Th17 cell subsets of the adaptive immune response are characterized as main sources of IL-17A *in vivo* and express the lineage-specific transcription factor retinoic acid receptor-related orphan receptor-γt (ROR γt), different from the Th1 and Th2 subsets. Th17 cells differentiate from naïve CD4+ T cells in the presence of IL-6 and TGFβ and are subject of studies predominantly in the correlation with autoimmunity [19]. IL-1 also influences the polarization of Th17 cells [20] and innate immunity components are more likely to contribute to the first line of defense creating a bridge between innate and adaptive inflammatory components [21]. The main function of IL-17 is to induce the production of chemokines and other cytokines (such as TNFα) which recruit neutrophils and monocytes at the site of T cell activation. IL-17 also contributes to granulopoiesis by increasing the production and secretion of GM-CSF as well the expression of GM-CSF receptors. Further, IL-17 stimulates the production of antimicrobial proteins (AMP) such as LL-37 [22] and matrix remodelling proteases by neutrophils and other cells [7]. Indeed, specific innate immunity sources readily produce Th17 cytokines in different physiological and disease conditions. It has been recently demonstrated that common characteristics (such as RORγ expression) can induce other lymphocytes to produce IL-17, including CD8+ αβ T cells, γδ T cells [23], LTi-like innate lymphoid cells (ILCs) [24], natural killer cells (NK) [25], and CD3+ invariant natural killer (iNKT) cells in mice and/or humans [26]. In addition, it is increasingly accepted that diverse innate myeloid immune cells are able to produce IL-17 and are strategically positioned in the barrier tissues, such as lungs, intestines, skin and peripheral lymph nodes to rapidly react to pathogens and allow an immediate response but also activate and amplify the adaptive immunity responses, as well illustrated by intestinal monocytes and macrophages in Crohn disease and ulcerative colitis [27,28], neutrophils in systemic vasculitis [29], mast cells in psoriatic skin lesions [22,30,31], and synovium mast cells in rheumatoid arthritis [32].

2. Innate immune IL-17-producing cells

The Th1/Th2 dichotomy has been increasingly overtaken by the report that IL17-expressing T cells are a third lineage of helper T cells, coined Th17 [4,33]. Studies dedicated to IL23 and its role in autoimmunity contributed to the discovery of the Th17 cell subset promoting chronic inflammation and tissue damage [34]. Since these earliest reports, Th17 cells received major attention and were defined as vigorously responsive to IL-1 receptor 1 (IL1R1) and IL-23 signalling, expressing the RORγt transcriptional regulator activated by IL-6-STAT3 cascade that leads to the production of IL-17A, IL-17F, IL-21, and IL22 [35]. However, IL-17 production driven by Th17 cells happens within hours after injury and cannot explain the prompt IL-17-mediated immune response and its role in rapid host defense and stress damaging responses especially in epithelial tissues [36]. Epithelia communicating with the environment, particularly the lungs, intestinal mucosa, urogenital system and skin contain most of the innate IL-17-producing cells [37]. Cells of the innate immune system producing IL-17 are illustrated in Fig. 1 and include γδ T cells, invariant natural killer cells (iNKT), IL-17 innate lymphoid cells (ILC17), LTi cells (also members of ILCs), natural killer (NK) cells, mast cells, macrophages, and neutrophils. All of these cell populations manifest common and peculiar characteristics and their function is vital in maintaining tissue integrity and regulating the late immune responses [38]. For instance, ILC play a role in directing the adaptive immune response acting like sentinel cells that secrete proinflammatory cytokines TNFα, IFNγ, IL-1, IL-6, IL-12, and IL-23 when challenged by the adequate stimulus. More specifically, IL-1 and IL-23 have been proven to be important in the production of IL-17 by innate immune cells such as γδ T cells and iNKT cells in mouse models [39]. Macrophages and dendritic cells also secrete IL-23 in response to microbial products and inflammatory cytokines [40]. IL-23 was the first cytokine proposed to act as a mediator of the differentiation of Th17 cells as the IL-23-deficient mice had reduced number of IL-17 producing CD4+ T cells compared to wild type mice [41]. Naïve murine T cells do not express IL-23R *in vitro* and the differentiation of Th17 cells is driven by IL-1, IL-6 and TGF-β but the expansion of Th17 cells from memory CD4+ T cells is IL-23-mediated [42]. However, several innate immune cells express the IL23 receptor, including IL-17-producing γδ T cells which are activated by IL-1 and IL-23 to produce IL-17A, IL-17F, IL-21 and IL-22 in the absence of TCR engagement or IL-6. Further, DCs and CD4+ cells both express IL-17R and secrete IL-23, as observed in the mouse model of multiple sclerosis [43].

2.1. γδ T cells

The first T cells found in the fetal thymus that provide immunity to newborns are γδ T cells [44] and their proportion decreases as the development of αβ T cells continues. Adult mice contain 1–4% γδ T cell pool and humans 0.5–16% approximately within the total T cell population and this percentage is higher at mucosal sites [45–48]. The γδ T cells are characterized by the existence of γδ TCR instead of αβ TCR. The generation of this receptor complex is provided by random rearrangement of genes encoded for γ and δ chains and sequence insertions during rearrangements but