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Interleukin-17 contributes to cardiovascular diseases

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Abstract Interleukin (IL)-17 (also known as IL-17A), as the signature cytokine of the newly described T helper 17 (Th17) cell population, is the founding member of a new subclass of cytokines that have highly proinflammatory properties. Recently there is accumulating evidence that stipulates the involvement of IL-17 in the pathogenesis of cardiovascular diseases via amplifying the inflammation induced by other cytokines in synergistic interactions. The present review provides a summary of the potential roles of IL-17 in the context derived from both animal models and clinical settings in cardiovascular diseases, and perspectives for IL-17-targeted cytokine therapy.

Keywords Interleukin-17 · T helper 17 cells · Inflammatary response · Cardiovascular diseases

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Introduction

$CD4^+$ T cells which can be induced to differentiate into various T helper (Th) subsets after activation are pivotal in regulating the immune and inflammation response in that they coordinate the functions of other immune cell types [1]. Traditionally, Th cells are thought to develop into Th1 and Th2 cell subsets with distinct cytokine profiles and functions. Th1 cells are involved in autoimmune diseases and the eradication of intracellular pathogens (by producing *interferon-γ*, *IFN-γ*) while the Th2 cell lineage is important for participating the elimination of extracellular organisms (by producing interleukin (IL)-4, IL-5, and IL-13) [2–4]. Recent findings have demonstrated that a new subset of preferential IL-17-producing cells (named Th17 cells) which is distinct from the Th1 or Th2 cells plays a critical role in inducing inflammatory tissue injury [5–12]. IL-17 is implicated in numerous immune and inflammatory responses primarily as a pro-inflammatory regulator by inducing the expression of various inflammatory mediators, such as cytokines, chemokines, adhesion molecules, and growth factors [6, 13–16]. There is emerging evidence that an increase in IL-17 level is closely associated with a range of inflammatory diseases including inflammatory bowel diseases, systemic lupus erythematosus, osteoporosis [17–19]. Consistently, recent studies have demonstrated that IL-17 has a pivotal role in cardiovascular diseases and has been considered as a crucial regulator in cardiovascular diseases. In this review, we highlight our current knowledge on IL-17 and its role in cardiovascular diseases and hope that this information may aid the development of novel therapeutic strategies for cardiovascular diseases.

IL-17: structure, sources and function

This cytokine was first described as a rodent complementary DNA transcript in 1993 and was originally termed cytotoxic T-lymphocyte-associated antigen 8 (CTLA-8), and later renamed IL-17(also called IL-17A) [20–22]. Subsequent genomic sequencing resulted in the discovery of other five additional family members called IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F and they all exerted proinflammatory activities [23, 24]. Among the IL-17 family members, IL-17 as a disulfide-linked homodimeric glycoprotein, is the most intensively investigated cytokine and has 155 amino acids with a molecular weight of 35 kDa [21, 25]. IL-17 gene is located on chromosome 6p12 and the cellular source of IL-17 is produced predominantly by a specific subset of Th cells, namely Th17 cells, but has more recently been expanded to include $\gamma\delta$ T cells, $CD8^+$ memory T cells, natural killer T cells, neutrophils eosinophils, macrophages and monocytes [18, 25–28]. After binding to its receptors, the key biological function of IL-17 is it involvement in inducing and mediating immune and proinflammatory responses via other cytokines in synergistic interactions. Many studies demonstrated that IL-17 as a proinflammatory cytokine is involved in inflammatory bowel diseases, systemic lupus erythematosus, osteoporosis [17–19].

IL-17: signaling pathway

Similar to the IL-17 cytokine family, IL-17 receptors form a unique family contained five members refer as to IL-17RA, IL-17RB, IL-17RC, IL-17RD, and IL-17RE [24]. The IL-17 receptors are expressed ubiquitously particularly in non-immune origin, particularly epithelial and mesenchymal cells within diseased or inflamed tissues [29, 30]. Among these IL-17 receptors, IL-17 binding to both the IL-17RA and IL-17RC subunits mediates signalling pathway [31]. The biological activity of IL-17 is dependent on a formation of receptor complex composed of IL-17RA and IL-17RC [32]. IL-17 signaling through its receptors is distinct compared to typical adaptive Th cell cytokines. Rather than activating JAK-STAT pathways, IL-17 stimulates proinflammatory pathways more typical of innate, proinflammatory cytokines such as IL-1 or TLR agonists [24]. It was demonstrated that IL-17 signaling can induce various downstream pathways which include nuclear factor-κB (NF-κB), mitogen-activated protein kinase (MAPK) pathways and the C/EBP transcription factors which can induce many production of various proinflammatory cytokines [33–35]. Recent studies have shown that Act-1(the adaptor protein NF-κB activator 1) plays an important role in IL-17-dependent signaling [36–38]. Additionally, the research by Schwander et al. showed that tumor necrosis factor receptor-associated factor 6 was essential for IL-17-induced NF-κB activation and the expression of IL-6 or intercellular adhesion molecule (ICAM)-1 [39]. Hence, the IL-17 signaling cascade is far from being completely understood.

IL-17 and cardiovascular diseases

Although significant advances in treatments, cardiovascular diseases remain the leading cause of morbidity and mortality around the world. There is accumulating evidence that inflammatory cytokines (such as IL-6, TLR4, NF-κB) play a key role in the occurrence and development of cardiovascular diseases including atherosclerosis, cardiac ischemia/reperfusion injury, heart failure, and myocarditis [40–43]. As its wide and intense proinflammation activity, the contribution of IL-17 in cardiovascular diseases has become investigative focus (**Tabel** 1).

IL-17 and Atherosclerosis

Atherosclerosis, defined as lipid-driven and chronic inflammation of the artery wall, involves a complicated interplay between many different cell types and cytokine networks. Both innate and adaptive immune responses have been demonstrated to regulate local and systemic inflammation during all stages of atherogenesis [44, 45]. Macrophages, T lymphocytes and, to a lesser extent, mast cells contribute to the smoldering inflammatory response in

Tabel 1 List role of IL-17 in cardiovascular diseases

Cardiovascular disease	Function	Experimental approaches	Reference
Atherosclerosis	Proatherogenesis	Clinic study; Animal model	[48–55]
	Atheroprotection	Clinic study; Animal model	[56]
Myocardial I/R	Promoting inflammation	Animal model	[63]
Heart failure	Inducing cardiac fibrosis	Animal model	[65, 66]
Myocarditis			
Viral myocarditis	Causing inflammatory response	Clinic study; Animal model	[67–70]
Dilated cardio-myopathy	Promoting inflammation	Animal model	[71]

the vessel wall [46, 47]. Recent research by Erbel and colleagues showed evidence for the proatherogenic role of IL-17 via proinflammatory changes at multiple levels such as cell adhesion, extravasation, cell activation, T cell (co) stimulation/proliferation, and antigen presentation [48]. In line with this result, several studies by various investigators have also demonstrated that IL-17 level is increased and IL-17 plays an essential proatherogenesis role in animal models and patients with coronary artery syndrome [49–55]. Interestingly, in contrast to these studies, Taleb et al. revealed that loss of suppressor of cytokine signaling-3 (SOCS-3) in mouse T cells increased IL-17A production and induced an anti-inflammatory macrophage phenotype which can lead to a reduction in lesion development and vascular inflammation [56]. They concluded that IL-17 may have a protective role in atherogenesis despite it was unclear as to whether IL-10 or IL-17 was leading to the suppressor phenotype, as IL-10 can function as a very potent regulatory cytokine which is atheroprotective [56]. Additionally, these investigators also found that in vivo administration of IL-17 to LDLR –/– mice resulted in reduced endothelial VCAM-1 expression, reduced vascular T cell infiltration and atherosclerotic lesion development and then they concluded that endogenous expression of SOCS3 in T cells can interrupt a major regulatory pathway in atherosclerosis through inhibition of IL-17 production and that IL-17 may function as an atheroprotective cytokine. Taken together, these findings indicate that IL-17 plays dual role in the development of atherosclerosis and these potential mechanisms await more direct studies to address.

IL-17 and myocardial ischemia/reperfusion injury

Myocardial ischemia reperfusion injury (IRI) refers to the tissue damage which occurs when blood supply returns to tissue after a period of ischemia and is predominantly associated with myocardial infarction but can also be seen in trauma, stroke, solid organ transplantation and coronary artery bypass graft (CABG) surgery [57, 58]. The shorter the ischemic period, the better the clinical outcome. Both T and B cells constituting the primary arms of the adaptive immune response, conventionally thought of as innocent bystanders, play a variety of roles during all phases of IRI [59, 60]. In brain, lung, liver, heart, intestine, and kidney models of IRI, T cells particularly $CD4^+$ T cells mediate tissue injury and possibly repair as well [59–62]. The expression of IL-17 was detected as early as 1 h after reperfusion, lasted for 24 h, and showed no peak in this period [63]. The study also found that $CD4^+$ T lymphocyte was a major source of IL-17 in myocardial tissue after reperfusion and administration of anti-IL-17 leaded to a dramatical decrease in serum troponin T and myocardial infarct size, suggesting that IL-17 might be involved in the pathogenesis of myocardial IRI [63].

IL-17 and heart failure

Chronic heart failure,mainly caused by cardiac fibrosis and ventricle remodeling, is a progressive syndrome and the outcome of a variety of cardiovascular diseases. The pathologic changes in heart failure occur in two steps: one is cardiomyocyte hypertrophy, necrosis, and apoptosis and the other is cardiac fibroblasts hyperplasia and cardiac fibrosis defined as a progressive accumulation of fibrillar extracellular matrix (ECM). IL-17 can upregulate and/or function synergically with local inflammatory mediators such as IL-6, IL-1β, and TNF-α, and enhance ECM injury by activating the production of matrix metalloproteinases(MMPs) and inhibiting the synthesis of matrix repair components, such as proteoglycans and collagens [64]. Previous research found that the regulation of Th1/Th2/Th17 balance may be one of the underlying mechanisms of inflammation-mediated cardiac remodeling [65]. Recent study by Feng et al. directly demonstrated that IL-17 can contribute to myocardial fibrosis in isoproterenol-induced heart failure and the receptor activator of NF-κB ligand/osteoprotegerin (RANKL/OPG) system may serve as a link between IL-17 and MMP-1 in cardiac fibroblasts [66].

IL-17 and Myocarditis

IL-17 is closely correlated with myocarditis. For instance, IL-17 mRNA and/or protein obviously elevated in the model of viral myocarditis (VMC) mice [67–69]**.** In addition, IL-17 inhibition ameliorated the myocardium inflammation in IL-17 monoclonal antibody (IL-17mAb)-treated VMC mice, indicating IL-17 is crucially involved in the pathogenesis of murine VMC [70]. Recently, Baldeviano GC et al. demonstrated a critical role for IL-17A in postmyocarditis cardiac remodeling and the progression to dilated cardiomyopathy (DCM) [71]. Hence, Targeting IL-17 may be an attractive therapy for patients with myocarditis via ameliorating the myocardium inflammation.

Conclusions and perspectives

The effect of the revision of the Th1/Th2 paradigm to add Th17 cells cannot be overstated as it becomes a watershed in our understanding of the T cell-mediated pathogenesis of cardiovascular diseases. As the predominant product of Th17 cells, IL-17 owns an imperative proinflammatory role

and clinical value in the occurence and development of cardiovascular diseases. Current cardiovascular researches suggest that the use of some drugs affecting the receptors and signal transduction pathway of IL-17 will become a hot area of clinical research and that the application of neutralizing antibodies or receptor antagonists of IL-17 to block its biological activity expression may provide a new therapeutic approach in cardiovascular disease research. With the mechanisms of IL-17 and its relevant cytokines to be further explored, IL-17 will have widespread application prospects in the prevention and clinical treatment of cardiovascular diseases.

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