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Review

Effects of Interleukin 17 on the cardiovascular system

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ABSTRACT

Cardiovascular diseases remain the leading cause of death worldwide and account for most of the premature mortality observed in chronic inflammatory diseases. Common mechanisms underlie these two types of disorders, where the contribution of Interleukin (IL)-17A, the founding member of the IL-17 family, is highly suspected. While the local effects of IL-17A in inflammatory disorders have been well described, those on the cardiovascular system remain less studied. This review focuses on the effects of IL-17 on the cardiovascular system both on isolated cells and *in vivo*. IL-17A acts on vessel and cardiac cells, leading to inflammation, coagulation and thrombosis. *In vivo* and clinical studies have shown its involvement in the pathogenesis of cardiovascular diseases including atherosclerosis and myocardial infarction that occur prematurely in chronic inflammatory disorders. As new therapeutic approaches are targeting the IL-17 pathway, this review should help to better understand their positive and negative outcomes on the cardio-vascular system.

Contents

Abbreviations: CV, cardiovascular; RA, rheumatoid arthritis; TNFα, tumor necrosis factor-α; IL, interleukin; Th, T helper; TGF-β, transforming growth factor-β; ROR, retinoic acid receptor-related orphan receptor; IFNγ, interferon-γ; Treg, regulatory T cell; FoxP3, Forkhead Box Protein 3; IL-17R, IL-17 receptor; EC, endothelial cells; VSMC, vascular smooth muscle cells; GM-CSF, granulocyte-macrophage colony-stimulating factor; ICAM, intercellular adhesion molecule; CCL, chemokine CC motif ligand; ROS, reactive oxygen species; VCAM1, vascular cell adhesion molecule 1; MMP, matrix metalloproteinases; NOS, nitric oxide synthase; LDLr, low density lipoprotein receptor; KO, knockout; ApoE, apolipoprotein E; SOCS3, suppressor of cytokine signaling 3; AAA, abdominal aortic aneurysm; I/R, ischemia/reperfusion; MI, myocardial infarction; ACS, acute coronary syndrome.

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1. Introduction

Cardiovascular (CV) diseases remain a major cause of death worldwide [1]. Traditional CV risk factors have been identified and interact with demographic changes and aging of the population [2]. More recently, the contribution of inflammation has been recognized as a CV risk [3,4]. All chronic inflammatory diseases are associated with a massive increase of CV mortality despite no or modest changes in the traditional risk factors [5]. This is well known in systemic lupus erythematosus where the disease itself has been recognized as a risk factor for developing accelerated atherosclerosis [6,7]. Similar observations apply to rheumatoid arthritis (RA) and other chronic inflammatory disorders [8,9]. These diseases are characterized by an increased production of pro-inflammatory cytokines triggering local and systemic inflammation. This has led to major progress in treatments with the targeting of tumor necrosis factor-α (TNFα) and interleukin (IL)-6, regimens mainly used in RA [10].

More recently, the new cytokine IL-17A, the founding member of the IL-17 family, has been identified for its key role in chronic inflammation [11,12]. As there are common mechanisms underlying CV dysfunction and immune diseases [5,13], cytokines such as IL-17A could be involved in both processes. The effects of IL-17A on atherosclerosis are in line with those found in chronic inflammatory disorders [3,14]. Similar results refer to thrombotic events [15]. Since IL-17A is now targeted in a growing number of chronic inflammatory diseases [16], it is important to anticipate their positive or negative effects on the CV system and related outcomes.

The aim of this review is to discuss the effects of the IL-17 family members on the CV system. First, the IL-17 family and its signaling pathway are defined. Then, their effects on the vascular and cardiac systems are described and these aspects applied to CV diseases. Finally, IL-17 targeting and its CV effects in chronic inflammatory diseases are addressed.

2. The IL-17 family

2.1. The IL-17 protein

IL-17 was first described in 1993 as cytotoxic T lymphocyte associated-antigen 8 (CTLA-8), a product of T cells in rodents and in humans [17]. IL-17 now refers to IL-17A, the founding member of the IL-17 family which is composed of six isoforms: IL-17A to IL-17F [12]. The six members were identified by sequence analysis showing a common carboxy-terminal domain with cysteine residues [18]. IL-17A and IL-17F share a 50% amino acids identity and can be secreted as homodimer or heterodimer (Fig. 1) [19].

2.2. IL-17 producing cells

IL-17 production was first associated with a subtype of CD4 + T cells with a particular cytokine phenotype [20]. Then, the T helper (Th)-17 subset was identified in 2005 in the mouse as the cellular source of IL-17, being distinct from the classical Th1 and Th2 cells [21]. The differentiation of Th17 cells is a multi-step process [22]. Briefly, in mice, IL-6 and transforming growth factor-β (TGF-β) initiate the differentiation from naive Th0 into Th17 precursors by activating the lineage specific transcription factor, retinoic acid receptor-related orphan receptor-γt (RORγt, known as RORc in humans). IL-21 induces the proliferation and IL-23 the final stabilization of Th17 population. Rather similar cytokine requirements are described in humans, TGF-β being necessary for activating RORc [23].

Furthermore, Th17 cells are sensitive to plasticity depending on the environment. Some cells are double-producers of IL-17 and interferon-γ (IFNγ) especially during chronic inflammation and autoimmunity. These cells, characterized by the dual expression of RORγt (Th17 differentiation) and T-bet (Th1 differentiation), are synthesized under the influence of IL-1ß [24]. Stimulation of activated Th17 cells with TGF-β and IL-6 limits Th-17 cell-mediated pathology and enhances the production of IL-17 and IL-10. IL-17 and IL-10 producing cells are less pathogenic with a more regulatory function [25].

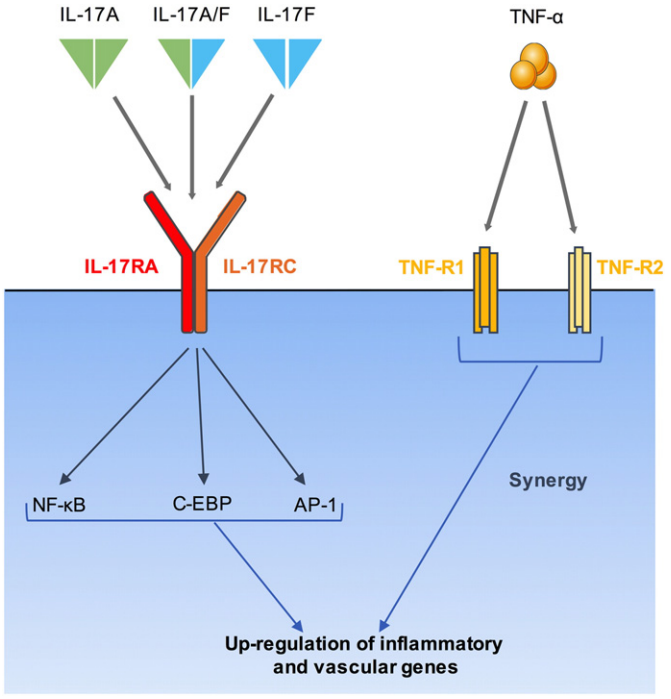

Fig. 1. IL-17 signaling pathway. Interleukin (IL)-17A and IL-17F homodimers or IL-17A/F heterodimer bind to the IL-17 receptor (IL-17R) composed of IL-17RA and IL-17RC. It induces the activation of either nuclear factor-κ B (NF-κB), activator-protein 1 (AP-1) or CCAAT/enhancer binding protein (C/EBP) pathways that up-regulates many inflammatory and vascular genes. Often there is a synergistic interaction with Tumor Necrosis Factor-α (TNFα), a homotrimer that acts on TNF Receptor I (TNF-RI) and TNF-RII.

Other subsets of cells are the source of IL-17 including both innate and adaptive immune cells: γδ T cells, natural killer (NK) cells, invariant natural killer T cells (iNKT), innate lymphoid cells (ILC), and CD8 + T cells [16].

Recent studies have highlighted the importance of the Th17/regulatory T cell (Treg) balance in auto-immune and inflammatory diseases [23]. While Treg cells prevent the development of autoimmunity, Th17 cells promote it. Their developmental pathways are interconnected as TGF-β can induce either Th17 or Treg cells depending on the cytokine environment [22,26]. In the absence of inflammation, TGF-β induces Forkhead Box Protein 3 (FoxP3), the transcription factor of Treg cells [27], and inhibits RORc. This favors Treg differentiation and maintains immune tolerance. Conversely, in the presence of inflammatory cytokines (mainly IL-6 and IL-1), it promotes Th17 differentiation, inhibiting FoxP3 and activating RORc [23]. The regulation of the Th17/Treg balance has important biological implications regarding its role in the control of immune responses.

2.3. The IL-17 receptor: discovery, structure and signaling

The first IL-17 receptor (IL-17R) was discovered in 1995 [28] and the family includes five subunits: IL-17RA to IL-17RE. Both IL-17RA and IL-17RC are required for cell signaling in response to IL-17A and IL-17F homodimers and IL-17A/F heterodimer [29].

The binding of IL-17A/IL-17F/IL-17A + F to its receptor complex activates either nuclear factor-κ B (NF-κB), activator-protein 1 (AP-1) or CCAAT/enhancer binding protein (C/EBP) pathways [30]. Such activation by IL-17A/F/A + F up-regulates the transcription of genes encoding inflammatory cytokines and chemokines. These genes could also be activated by the binding of TNFα to TNF receptor I and II [12]. This