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The pleiotropic role of interleukin-17 in atherosclerosis

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ABSTRACT

Atherosclerosis is the main cause of cardiovascular diseases (CVDs), which considers the leading cause of mortality worldwide. Atherosclerosis is a chronic inflammatory condition of arterials' wall in which the development and the destabilization of plaque occur. Both innate and adaptive immunity play a significant role in modifying lipoproteins in arterials' wall. Recent investigations have demonstrated the opposing roles of $CD4^+$ T cells subtypes in atherosclerosis. T helper-1 (Th1) response and pro-inflammatory cytokines possess proatherogenic effects, whereas T regulatory (Treg) cells have an atheroprotective role. Th17 cells have emerged as a new $CD4^+$ T-cell subtype, which produce IL-17 that plays a crucial role in numerous inflammatory and autoimmune diseases. Recently, several studies have investigated the potential role of IL-17 in atherosclerosis. Some investigations have suggested a proatherogenic effect, however the others proposed an atheroprotective role. Hence, the exact role of IL-17 in the disease development and plaque stability is still debatable. In this review, we summarize the current knowledge on both atherogenesis and atheroprotective roles of IL-17. In addition, the synergistic and antagonistic effects of IL-17 with other cytokines in atherosclerosis will be discussed. On the basis of the current understanding of these roles, the possibility of developing novel therapeutic strategies against atherosclerosis may be evolved.

1. Introduction

Cardiovascular diseases (CVDs) represent the main factor of premature death all over the world [1]. CVDs resulted in more than 17.3 million death yearly, about 17.5 million people died in 2015 [2], and this number will be expected to reach about 23.6 million by 2030 [3]. Atherosclerosis is the foremost fundamental reason for different CVDs including coronary artery disorder (CAD), myocardial infarction [4] and it incorporates an intricate interchange between various cell sorts and cytokine systems [5]. Numerous cytokines have been proposed to play a vital role in atherogenesis such as IL-1β, IL-12, IL-18, IL-22, TNF-α and IFN-γ; whereas IL-10, IL-19, IL-33 and TGF-β are considered atheroprotective cytokines [6]. IL-17 was determined as a proinflammatory cytokine generated by a subset of $CD4^+$ T-helper (Th) cells termed Th17 [7]. Lately, several investigations have assessed the association between IL-17 A (henceforth referred as IL-17) and susceptibility to many CVDs [8]. Some reports have endorsed a proatherogenic effect of IL-17, whereas other investigations have reported an atheroprotective role of IL-17 [9]. Recently, several therapies directed towards Th17 related cytokines, including IL-17 and IL-23, have evolved, and some of them have been approved and the other being examined in ongoing clinical trials [10,11].

2. Interleukin-17

Th17 cell releases IL-17 (IL-17 A) which is the hallmark cytokine contains disulfide-linked homodimeric glycoprotein in its structure [12] and has critical functions in protecting the host from extracellular pathogens [13]. Nevertheless, IL-17 implicated in different inflammatory disorders such as autoimmune diseases, metabolic diseases, atherosclerosis, and cancer [14]. In addition to Th17 cells, various types of hematopoietic cells can produce IL-17 as well as some types of immune cells such as $CD8^+$ T cells, γδ T cells, invariant natural killer T cells (iNKT), natural killer (NK) cells, natural Th17 cells, lymphoid tissue inducer (LTi) cells, group 3 innate lymphoid (ILC3) cells, macrophages, neutrophils, and mast cells [15].

2.1. The proatherogenic effect of IL-17

The exact role of IL-17 in atherogenesis is still debatable. On one hand, the significance of IL-17 in atherosclerosis has been adduced by the observation of Th17 cells aggregation and IL-17 in murine and

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human atherosclerotic lesions [16]. In addition, Erbel et al. reported the accelerated expression of IL-17 mRNA in symptomatic carotid plaques as opposed to asymptomatic plaques and notified that IL-17 mRNA expression is correlated with complex, unstable, and lipid-rich lesions [17]. Moreover, investigators described the enhanced production of pro-inflammatory factors such as IL-6, CXCL8, and CXCL10 by vascular smooth muscle cells (VSMCs) in response to IL-17, without or with an assist from IFN-γ [18]. On the other hand, the anti-atherogenic impact of IL-17 may be referring to its inhibitory action on vascular cell adhesion molecule-1 (VCAM-1) expression and inflammatory adhesion molecules on fibroblasts and SMCs [19].

IL-17 has been observed to promote numerous downstream signaling pathways, inclusive of NF-κB, leading to the production of genes encoding pro-inflammatory cytokines [20]. IL-17 signaling induces the expression of growth mediators, tissue remodeling enzymes and other secondary factors in target cells [21]. IL-17 alone often stimulates a weak response, but it may synergize with different cytokines like TNF-α, IFN-γ, GM-CSF, IL-1β, and IL-22 to increased production of inflammatory mediators such as IL-6 and IL-8, leading to increased and prolonged pro-inflammatory response [15].

Animal models besides clinical research have observed direct evidence about the proatherogenic function of IL-17 [22]. Findings of the previous studies clearly show that IL-17 affects macrophages within atherosclerotic plaques [23]. Th17 cells plays an essential effect in atherosclerotic plaque development in mice, which can also have implications in patients with atherosclerosis [24]. Erbel et al. administered *in vivo* IL-17-blocking antibody in apolipoprotein E-deficient ($ApoE^{-/-}$) mice, and found that functional blockade of IL-17 reduced atherosclerotic lesion improvement and lowered plaque vulnerability, cellular infiltration, and tissue activation. They concluded that IL-17 plays a pivotal role in atherogenesis [25].

3. Cytokines that induce Th17 cell development in atherosclerosis

3.1. Interleukin-23

The most important driver of pathogenic human Th17 cell responses is IL-23 [26,27]. The IL-23/IL-17 pivot is emerging as a crucial regulatory system that embankment the natural and acquired arms of the immune system within the complex mechanisms related to the improvement of atherosclerosis [28]. IL-23 settles the inflammatory phenotype of Th17 cells [29]. However, the differentiation of Th17 cells from immature $CD4^+$ T cell precursors cannot drive by IL-23 alone [30], demonstrating that extra factors are required for their lineage destiny determination. Both IL-21 and IL-23 are required for Th17 proliferation and maintenance [26].

3.2. Transforming growth factor β

TGF-β is a cytokine with double roles which has a mighty regulatory and inflammatory activities [31]. TGF-β adjusts the differentiation of both Treg and Th17 cells in an awareness-based way [32]. As represented in Fig. 1, in the presence of IL-6, TGF-β promotes the differentiation [33] and improvement of Th17 by inducing the expression of the transcription factors retinoic acid orphan receptor-γ thymus (ROR-γt) [34]. However, in the absence of IL-6, TGF-β induces differentiation of Treg cells [35]. On the other side, in atherosclerosis, TGF-β possess anti-inflammatory and anti-atherogenic role, as neutralization or genetic ablation of TGF-β promotes the development of atherosclerosis in $ApoE^{-/-}$ mice and facilitates the recruitment of pro-inflammatory macrophages and T cells into the site of inflammation [36].

3.3. Interleukin-6

IL-6 is a pleiotropic cytokine that performs a critical position in the development and progression of inflammation during atherogenesis

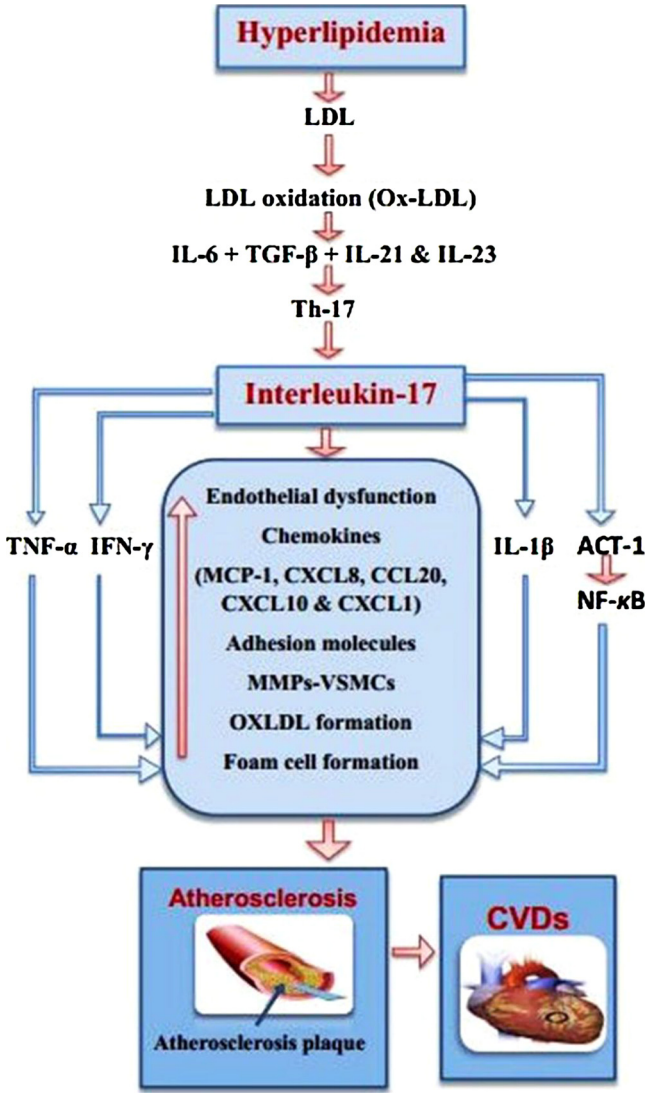

Fig. 1. The inflammatory pathway of IL-17 in the progression of atherosclerosis. Atherosclerosis started by many factors for example hyperlipidemia refers to high plasma levels of cholesterol i.e. growing of low-density lipoprotein (LDL) which considered as the fundamental transporter of cholesterol besides it is the most considerable atherogenic lipoprotein. Oxidized form of LDL (Ox-LDL) within the arterial wall cause initiation and progression of endothelial dysfunction and release inflammatory responses including IL-6 and TGF-β which can differentiate Th17 that produce IL-21 that, in turn, further amplifies Th17 generation. IL-21 and IL-23 stimulate ROR-γt, which in synergy with STAT3 induced IL-17 expression. IL-17 modulates the expression of several proinflammatory molecules involve TNF-α, IL-1β, and IFN-γ; in addition to inducing the activator of NF-κB (adaptor protein Act1). Pro-inflammatory mediators that induced by IL-17 reach a common downstream signaling pathway leading to atherosclerosis and CVDs.

[37]. IL-6 induces the improvement of Th17 cells rather than promoting Treg cells [38]. IL-6 regulates a cascade of 'downstream' cytokine-established signaling pathways that, in concert with TGF-β, amplify RORγt-based differentiation of Th17 cells [39]. Blocking of IL-6R lead to a marked reduction in Th17 cells and an increase in Treg cells [40]. In addition, IL-6 considers as a biomarker for progression of atherosclerotic diseases in the population [41].