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Current views on the functions of IL-17-producing cells in atherosclerosis

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Summary

Multiple components of the immune response are involved in the initiation, progression and persistence of atherosclerosis. IL-17A is produced by a broad variety of leukocytes and plays an important role in host defense. IL-17A is also involved in the pathology of several autoimmune diseases mainly via the regulation of chemokine expression and leukocyte migration to the site of inflammation. There is an increasing body of evidence indicating an association between elevated levels of IL-17A and cardiovascular diseases. Interestingly, this IL-17A-dependent response occurs in parallel with the Th1-dominant immune response during atherogenesis. To date, the precise role of IL-17A⁺ cells in atherosclerosis is controversial. Several studies have suggested a pro-atherogenic role of IL-17A via the regulation of aortic macrophage numbers, Th1-related cytokines and aortic chemokine expression. However, two studies recently described anti-inflammatory effects of IL-17A on mouse plaque burden via possible regulation of aortic VCAM-1 expression and T cell content. Furthermore, an initial study using IL-17A-deficient mice demonstrated that IL-17A affects the immune composition and inflammatory phenotype of the aortic wall; however, no effects were observed on atherosclerosis. Further studies are necessary to fully address the role of IL-17A and other IL-17 family members in atherosclerosis.

Keywords

atherosclerosis; interleukin-17; immune response; T helper cells; cytokines

Introduction

Atherosclerosis continues to be the leading cause of cardiovascular disease. Atherosclerotic lesion progression depends on chronic inflammation in the artery wall and the innate and adaptive immune responses are involved in these processes (1, 2). There are several subsets of T cells such as naïve, T helper (Th) 1, Th2 and T regulatory cells (Tregs) that are present within non-inflamed and atherosclerosis-prone aortas. Recent studies have demonstrated the existence of IL-17A⁺ cells within atherosclerotic aortas, suggesting a potential role for IL-17A-producing cells in atherosclerosis (3–5). Over the last decade, CD4⁺IL-17⁺ cells (Th17), and lately other IL-17A-producing cells such as NK and NKT cells, $\gamma\delta$ T cells, and neutrophils have been shown to participate in host defense against extracellular pathogens as well as in the pathogenesis of multiple autoimmune diseases, suggesting a dual role for IL-17A⁺ cells during inflammation that depends on microenvironmental factors (6, 7). As

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Conflict of interest

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we will discuss in this review, several reports investigated the effects of IL-17A in atherogenesis; however, due to conflicting results, the role of Th17 and other IL-17A-producing cells remains unclear. Many intriguing questions concerning the mechanisms of the induction of IL-17⁺ cells, the functions of the remaining IL-17 family members in atherogenesis, and the effects of other T cell subsets on IL-17-producing cell functions have yet to be explored. In this review, we will focus on the role of IL-17A-producing cells in atherogenesis and discuss recent findings in this area of research.

T cells in atherosclerosis

Atherosclerosis, a chronic inflammatory disease of large and medium sized arteries, continues to be the leading cause of cardiovascular events and one of the most common causes of mortality worldwide (8). As a part of the adaptive immune response, T cells are present in human and murine atherosclerotic plaques (9, 10) as well as in the adventitia of atherosclerotic and normal arteries (11). The majority of aortic T cells are $\alpha\beta$ T cell receptor (TCR $\alpha\beta$) CD4⁺ effector memory T cells. CD8⁺, $\gamma\delta$ ⁺T cells, and NKT cells are also present to a lesser extent (reviewed in [1, 12]). In addition, while it is unclear whether local antigen presentation and T cell activation occurs during atherosclerosis, aortic and cardiac valve dendritic cells are nonetheless present within normal and atherosclerosis-prone regions (13–16). Intriguingly, all known subsets of T cells are generated during atherogenesis and numerous reports have implicated Th1, Th2, and Treg subsets in this disease (1, 2). The presence of heat shock protein (HSP)-60 specific T cells (17), other oligoclonal T cells (18), and LDL reactive T cells (8, 19) in the aorta suggests a T cell-mediated immune response occurs during atherogenesis (20). Furthermore, recent evidence suggests that the immune response towards native LDL may play a pro-inflammatory role in atherogenesis (21).

Th1 cells play a pro-atherogenic role via elevated production of Interferon- γ (IFN γ), Interleukin-6 (IL-6) and IgG2a, increased expression of major histocompatibility complex class II, and up-regulation of chemokines and adhesion molecules that are involved in leukocyte recruitment into aortas (1, 12). In contrast, IL-4⁺ Th2 cells are less frequent in atherosclerotic plaques and may play pro-inflammatory (22, 23) or protective (24) roles in atherogenesis. Tregs are able to recognize specific self-antigens and participate in maintaining self-tolerance by suppressing auto-reactive leukocytes (25). Tregs reduce atherogenesis and accompanied inflammation in an IL-10-dependent manner (reviewed in [26]). Recently, a new lineage of CD4⁺IL-17⁺ (Th17) cells has been described (reviewed in [27, 28]). Th17 cells play an important role in host defense, but also participate in several pathologies that are characterized by low grade chronic inflammation. While the precise mechanisms behind IL-17 cytokine signaling are still being examined, recent work on the biology of the IL-17 cytokine family as well as the role of IL-17-producing cells in atherogenesis will be explored in the following sections.

Family of IL-17 cytokines

The IL-17 family of cytokines consists of six members, including IL-17 (known as IL-17A), IL-17B, IL-17C, IL-17D, IL-17E (known as IL-25) and IL-17F. IL-17A, the most studied IL-17 family member, is produced by Th17 cells, lymphoid tissue inducer (LTi) cells, NK, NKT and $\gamma\delta$ T cells (6, 7). As IL-17RA and IL-17RC, the receptor subunits for IL-17A, are ubiquitously expressed, IL-17A can elicit responses from a variety of tissues (28–31). In general, all of the IL-17 family members may, to various degrees, activate the NF- κ B, ERK1/2, C/EBP β , C/EBP δ signaling pathways in target cells, resulting in the production of stromal chemokines (including CCL2, CXCL1, and others), and cytokines (IL-6, IL-1 β , etc.) (28–31). In many inflammatory conditions these cells release not only IL-17A, but also IL-17F (30). Interestingly, homodimeric IL-17A, IL-17F and IL-17A/IL-17F heterodimers

have been reported; however, the dominant form of these cytokines *in vivo* remains to be determined (32, 33). In contrast, relatively little is known about the biological functions of IL-17B, IL-17C, IL-17D, and IL-17E. IL-17E is expressed by mucosal epithelial cells as well as mast cells, basophils, Th2 cells, and alveolar macrophages and stimulates the production of Th2 cytokines (34). IL-17B and IL-17C stimulate release of tumor necrosis factor (TNF) α and IL-1 β from the monocytic cell line THP-1 (35). As adenovirally-delivered IL-17A, IL-17C, IL-17E and IL-17F induced bronchoalveolar lavage neutrophilia (34), and ectopic expression of IL-17B and IL-17C aggravated collagen-induced arthritis (36), IL-17A and other members of the Interleukin-17 family may function similarly *in vivo*. Future *in vivo* studies will further help to identify the precise functions of these cytokines in host defense and autoimmunity. However, based on the known functional activities of IL-17B, IL-17C and IL-17D, it can be speculated that not only IL-17A, but other IL-17 family members might be simultaneously involved in the pathogenesis of many autoimmune disorders.

The IL-17 cytokine receptor family

The IL-17 receptor family consists of five related single transmembrane domain proteins – IL-17RA, IL-17RB, IL-17RC, IL-17RD, and IL-17RE. The IL-17R family contains several conserved structural motifs, including an extracellular fibronectin III-like domain and a cytoplasmic SEF/IL-17R (SEFIR) domain. In addition to these domains, IL-17RA is unique amongst the IL-17R family members in that it possesses a Toll IL-1 receptor-like BB-loop (TILL) and C/EBP β activation domain (CBAD) motifs (reviewed in [29]). Interestingly, the IL-17RA TILL domain is necessary for the functionality of IL-17RA, as deletions and point mutations in these regions render IL-17RA inert (37, 38). In addition, IL-17RA may serve as a co-receptor for several IL-17 family members, including IL-17A/IL-17A homodimers and IL-17A/IL-17F heterodimers (39), and IL-17E (40). Further studies should determine whether IL-17RA serves as a co-receptor for other IL-17 family members. Interestingly, the IL-17 cytokine receptor family signals through a distinct pathway that involves the adaptor protein CIKS (connection to I κ B Kinase and Stress-activated protein kinases) also known as Act1, nuclear factor- κ B (NF- κ B), TNFR-associated factor-6 (TRAF-6) suggesting a close relationship of this pathway with the innate immune response (reviewed in [29]).

Induction of IL-17-producing cells

Small numbers of Th17 cells reside in non-inflamed tissues, but their number rapidly increases in response to infection. Orphan nuclear receptor ROR γ t controls the development of IL-17A-producing cells, and additional transcriptional factors such as Stat3, Stat4, Runx3, Runx1, and aryl hydrocarbon receptor (AHR) may be required for the expression of IL-17 in Th cells, and ROR γ t upregulation upon polarization (reviewed in [41]). TGF β , IL-1 and IL-6 play key roles in the induction of Th17 cells from naive T cells (6). Notably, TGF β is mainly produced by Tregs and has been described to play an atheroprotective role (42). How does TGF β , a cytokine related to the suppressor arm of the immune response, induce the production of pro-inflammatory IL-17A cytokine? TGF β orchestrates Th17 cell differentiation in a concentration-dependent manner (43). At low concentrations, TGF β synergizes with IL-6 and IL-21 to promote Th17 cell differentiation; however, higher concentrations of TGF β induce Tregs. The plasma levels of IL-17A in coronary artery disease patients correlate closely with the IL-12/IFN γ /CXCL10 axis (44) and negatively with TGF β (45), suggesting that high levels of TGF β may antagonize Th17 induction during atherosclerosis. However, Th17 cells can be also induced via the combination of IL-6, IL-23 and IL-1 β with naive T cells, independently of TGF β (46). Whether or not Th17 cells are generated in a TGF β -independent manner during atherogenesis remains to be determined. HSP-10 and HSP-60 are potential antigens (Ag) in atherosclerosis that induce IL-12 and IL-23 expression by dendritic cells (DCs) (47), which have been demonstrated to be present

within atherosclerotic regions (13–16). IL-23 initiates IL-17⁺ cell expansion from the pool of memory T cells (48) that are present in aortas (49). Therefore, HSP-10 and HSP-60 may serve as one of the potential Ags for Th17 cell expansion. Further studies are necessary to investigate the mechanisms of Th17 cell induction during atherogenesis.

Recently it became clear that other immune cells including $\gamma\delta$ T cells, neutrophils, NK and NKT cells, LTI-like cells, may also produce IL-17A (7). Mechanisms of the induction of IL-17-producing cells are not well understood, but ROR γ t, STAT-3 and aryl hydrocarbon receptor (AHR) are potential transcriptional regulators of IL-17A innate immune cells (7). Interestingly, $\gamma\delta$ T cells express Toll-like receptor-2 (TLR-2), which is likely to be involved in IL-17A production by $\gamma\delta$ T cells (7). TLRs serve as receptors for oxLDL, oxidized lipids and HSP-60 (50), supporting the innate immune response during atherogenesis. It remains to be determined whether atherogenic conditions affect the induction of IL-17⁺ $\gamma\delta$ T cells during atherogenesis.

Functions of IL-17A-producing cells

Innate IL-17A⁺ cells are mainly detected in gut mucosal tissues (51), participate in maintaining of mucosal barrier integrity in normal/non-inflamed and pathological conditions (52) via enhancing synthesis of tight junction proteins (53). Innate IL-17A⁺ cells can also participate in autoimmune pathologies via modulation of the cytokine profile to favor the induction of chronic inflammation (7). IL-17⁺ $\gamma\delta$ T cells may induce Ag-dependent Th17 cell differentiation and further acceleration of chronic inflammation (54). In addition, IL-17A⁺ $\gamma\delta$ T cells may also affect the migration of Th1 cells via the induction of Th1-related chemokines at the site of infections (55).

Th17 cells display a broad spectrum of functions: from being one of the key cells in host defense to powerful participants in autoimmunity (6, 31). Th17 cells express IL-17A, IL-17F, IL-22, IL-26, CCL20, IL-23R, and ROR γ t (56, 57). Th17 cytokines induce the production of IL-6, TNF α , CXCL1, CXCL2, CXCL8, CCL2, and metalloproteinases MMP-3, MMP-6 and MMP-13 from various tissues and cell types (Fig. 1). Upon bacterial infection, IL-17A induces CXCL8-dependent neutrophil recruitment to the site of the infections (58, 59). As neutrophils are present in atherosclerotic lesions and play an inflammatory role (1), these results are particularly interesting. In addition, since CXCL1 triggers monocyte arrest on the early atherosclerotic endothelium (60), IL-17A may participate in regulating the CXCL1-dependent accumulation of monocytes in aortas. Monocytes also respond to IL-17A stimulation by the production of TNF α and IL-1 β (61). Thus, IL-17A may positively regulate monocyte recruitment and activation within aortic microenvironment. As IL-17A and IFN γ can synergistically induce several inflammatory factors, such as IL-1, IL-6, IL-8, TNF α and CXCL10, IL-17A is likely to have telling effects on inflammatory disorders. Indeed, increased levels of IL-17A are detected in patients with rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease and psoriasis, suggesting a role for this cytokine in their respective pathologies (reviewed in (6)). Additional levels of complexity recently came from multiple experimental autoimmune encephalitis (EAE) studies, which have suggested both pathological (62–64) and anti-inflammatory roles for IL-17A (65). Intriguingly, both protective and pathogenic roles for IL-17A⁺ cells have been also proposed in different experimental colitis models (66–69). Nevertheless, genetic studies have demonstrated that Th17-related genes play important roles in these pathologies.

Initially, regulation of Th17 cell differentiation by IFN γ and IL-4 was shown in *in vitro* assays (6), implicating Th1 and Th2 cell signals as potent inhibitors of Th17 cell differentiation. However, an increasing body of evidence demonstrates the existence of

simultaneous Th1 and Th17 responses *in vivo* (44, 70–74). Furthermore, double positive IFN γ ⁺IL-17A⁺ CD4 T cells have been observed in multiple inflammatory diseases (reviewed in [75]), including atherosclerosis (44). Indeed, in coronary artery disease patients, elevated plasma levels of both IFN γ and IL-17A are detected in atherosclerotic conditions. Interestingly, IFN γ and IL-17A synergistically induced the activation of VSMCs demonstrating a potential functional importance of these two cytokines (44). These findings suggest that there is an unexplored relationship between the Th1 and Th17 cell differentiation programs, *in vivo*. Recent studies demonstrated the ability of Treg to differentiate into Th17 cells (43, 76). Foxp3⁺ROR γ t⁺ cells are found *in vivo* in both mice and humans (43, 77); however, the functions of these cells are unclear. To date, lineage relationships, interactions and the specific roles played by each of the different T helper subsets are still an evolving subject of investigation (75).

Th17 and IL-17A⁺ T cells are associated with inflammation in atherosclerosis

While the effects of IL-17A on atherosclerotic arteries are not well defined, several lines of evidence suggest that Th17 cells and other IL-17A⁺ cells participate in atherosclerosis-associated inflammation (Table 1). Although IL-17A⁺ cells are less abundant than Th1 cells, IL-17A⁺ T cells are present in both atherosclerotic human (5, 44, 45, 78–80) and mouse (3–5, 45, 81–83) arteries. Elevated plasma levels of IL-17A is detected in patients with coronary artery disease (CAD) in comparison with healthy controls (44) and in the carotid plaques of symptomatic patients undergoing endarterectomy (78). High ROR γ t, IL-17A and low Foxp3 PBMC mRNA expression in acute myocardial infarction (AMI) and unstable angina (UA), in comparison to stable angina (SA) and chest pain syndrome (CPS) patients, suggest that Th17 cells are elevated at the expense of Tregs during atherogenesis (45, 79). In the line with this hypothesis, mRNA expression of IFN γ , Tbet, Stat4, IL-17A, ROR γ t, and Stat3 was found to be elevated in UA and AMI patients in comparison to controls, supporting the notion that both Th1 and Th17 immune responses occur in CAD patients (79, 80). In addition, as Th17 and IL-17A cells positively correlate with peripheral blood neutrophilia, and elevated IL-8, CXCL10, IFN γ , IL-6 and IL-23 levels in CAD patients, these cells likely participate in CAD-associated inflammation (79). It is worthy of note, that the plasma IL-17A levels of healthy aged (50–69 years) individuals have shown no correlation with the carotid artery intimal medial thickness, suggesting that IL-17A may play a role in modulating plaque stability and the immune cell composition in advanced stages of atherogenesis rather than at initial stages in healthy carotid artery (84).

Recent studies demonstrated that IL-17A⁺ T cells are present within murine atherosclerotic plaques. Flow cytometric analysis of *Apoe*^{−/−} and *C57/BL6* aortas revealed the existence of Th17 and $\gamma\delta$ IL-17⁺ T cells within the aortic wall, aortic adventitia, and secondary lymphoid organs of aged *Apoe*^{−/−} and *C57/BL6* mice (4). IL-17A⁺ cells were also detected in the aortic sinus (5), and in the aortas of *Apoe*^{−/−} mice fed a western diet (WD) (4, 81). Interestingly, an inverse relationship between ROR γ t and Foxp3 expression was demonstrated in young and aged *Apoe*^{−/−} mice (83). Together, these results imply that IL-17A⁺ cells are present during atherogenesis within mice.

The controversial role of IL-17A in atherosclerosis

Despite the clear association between atherogenesis and elevated levels of IL-17A⁺ cells, early mechanistic studies in mice have yielded incompatible conclusions - due primarily to indirect methods of knocking down IL-17A or IL-17RA and different measurements of atherosclerosis (Table 2). To examine the role of IL-17A signaling on leukocytes during atherogenesis, *Il17ra*^{+/+} or *Il17ra*^{−/−} bone marrow were transplanted into lethally irradiated

Ldlr^{-/-} mice (82). Hematopoietic deficiency of IL-17RA within *Ldlr*^{-/-} mice fed WD for 12 weeks (*Il17ra*^{-/-}*Ldlr*^{-/-} chimeras) resulted in a 46% reduction in aortic root lesion size in comparison with *Il17ra*^{+/+}*Ldlr*^{-/-} mice with a concomitant slight increase in aortic root macrophage content and a decrease in neutrophil and mast cell content (Table 2). Interestingly, polyclonal stimulation of *Il17ra*^{-/-}*Ldlr*^{-/-} chimeric T cells resulted in decreased IL-6 and elevated IL-10 levels (82), suggesting that hematopoietic deficiency of IL-17RA constrained systemic inflammation.

To examine the effects of IL-17A during atherosclerosis, several groups have utilized neutralizing strategies to knockdown circulating IL-17A in *Apoe*^{-/-} and *Ldlr*^{-/-} mice (3–5, 79, 81) (Table 2). Administration of a rat-anti-mouse IL-17A antibody into *Apoe*^{-/-} mice fed a 12 week chow diet (CD) resulted in a 50% reduction in aortic root lesions (3). Relative collagen content was elevated in the aortic roots, while the relative CD3⁺ T cells, macrophage (Mac-2⁺), *Vcam1* and apoptotic cell content were decreased within anti-IL-17A-treated recipients (3). In *in vitro* assays, IL-17A and TNF α potently induced IL-8 and VCAM-1 expression in HUVEC and apoptosis in vSMCs, suggesting that IL-17A may exert pro-inflammatory effects on vascular cells in concert with other cytokines (3).

A similar study examined the effect of rat-anti-mouse IL-17A neutralizing or isotype control Abs on rapid carotid stenosis and atherosclerosis in *Apoe*^{-/-} mice fed an eight week WD (81). Anti-IL-17A-treated mice displayed a marked reduction in aortic root plaque size, and carotid artery stenosis, which corresponded with a reduction in immunohistochemical MoMA2 and α -smooth muscle actin staining within carotid arteries. The administration of exogenous rIL-17A for five weeks of an eight week WD increased aortic root plaque size (~175%) in *Apoe*^{-/-} mice (81). To block IL-17A in *Apoe*^{-/-} mice, a fusion protein comprised of the IL-17 receptor A extracellular domain (IL-17RA/Fc) was expressed *in vivo* from an adenovirus construct (AdIL-17RA/Fc (58)) in *Apoe*^{-/-} mice fed a WD for 15 wks (4). Ad-IL17RA/Fc-treated *Apoe*^{-/-} mice developed 54% smaller lesions and aortic root plaque burden compared to *Apoe*^{-/-} mice (4). The reduction in atherosclerosis correlated with decreases in circulating IL-6 and G-CSF levels and aortic root Mac-2⁺ macrophage content in Ad-IL-17RA-Fc recipients. Additionally, IL-17A strongly promoted *Cxcl1* expression and monocyte adherence to explanted atherosclerotic aortas, suggesting that IL-17A may play a role in monocyte recruitment to atherosclerotic aortas. Thus, taken together, the results of these studies suggest that IL-17A plays a pro-inflammatory role in atherosclerosis through the induction of aortic chemokines, cytokines, and accumulation of macrophages within atherosclerotic plaques.

In sharp contrast to these studies, Taleb et al. (5) recently proposed an atheroprotective role for IL-17A. Based on prior studies demonstrating that *Socs3* negatively regulates Stat3-dependent expression of both IL-17A and IL-10 in T cells, Lck-Cre *Socs3*^{+/+} and Lck-Cre *Socs3*^{flox/flox} bone marrow was transplanted into lethally irradiated *Ldlr*^{-/-} mice. *Socs3*^{-/-}*Ldlr*^{-/-} chimeric mice fed a six-week WD had 50% smaller lesions within the aortic roots compared to *Socs3*^{+/+}*Ldlr*^{-/-} controls. Mouse anti-IL-17A-treated *Socs3*^{-/-}*Ldlr*^{-/-} chimeric mice displayed elevated aortic root lesions compared to *Socs3*^{+/+}*Ldlr*^{-/-} mice. The administration of rIL-17A into *Ldlr*^{-/-} decreased aortic root lesions, CD3⁺ cells, and VCAM-1 expression in *Ldlr*^{-/-} mice (5). In the line with this notion, no difference in aortic root plaques was observed between *Il17a*^{-/-}*Ldlr*^{-/-} and *Ldlr*^{-/-} mice fed a six-week WD or between mouse-anti-mouse IL-17A recipient and isotype recipient *Ldlr*^{-/-} mice fed a 12 week CD (85). Together these results indicate that the neutralizing Abs used in these studies may have had different effects on atherosclerosis in the aortic roots.

At present, the use of neutralizing antibodies is an acceptable method for neutralizing proteins of interest; however, off-target effects can occur *in vivo*. As IL-17A is fairly homologous to the other members of the IL-17 family and IL-17A may heterodimerize with IL-17F, it is unclear if other members of the IL-17 family have cross-reactivity with anti-IL-17A Abs and therefore, can be similarly neutralized. Indeed, aside from Taleb et al. (5), none of the neutralizing studies (3, 81, 85) demonstrated the specificity of their strategies. However, while Taleb et al. (5) validated their mouse-anti-IL-17A antibodies *in vitro*, this study did not assess if heterodimeric IL-17A/IL-17F or other plasma proteins are similarly recognized *in vivo*. In an attempt to resolve these discrepancies, Cheng et al. (85) tested the effects of both rat-anti-IL-17A and mouse-anti-IL-17A antibodies in *Apoe*^{-/-} mice. In this study, the rat-anti-IL-17A antibody reduced aortic root lesions, but the mouse-anti-IL-17A antibody did not. While all of the aforementioned studies examined aortic root lesions, only one study directly examined whole aortic lesions by *en face* analysis (4). Therefore, despite the differences in aortic root lesions, the effects of IL-17A neutralizing Abs on aortic or innominate artery plaques are unknown.

Since indirect knockdown methods have yielded incompatible conclusions, examination of atherosclerosis in IL-17A or IL-17RA deficient *Apoe*^{-/-} or *Ldlr*^{-/-} mice should clarify the role of IL-17A in atherosclerosis. Recently *Il17a*^{-/-}*Apoe*^{-/-} mice were generated to directly examine the effects of IL-17A on atherosclerosis (84). As IL-17A and IL-17F form three different cytokines including IL-17A/IL-17A, IL-17F/IL-17F, and IL-17F/IL-17A, IL-17A-deficient mice have only IL-17F/IL-17F functional cytokine. The deficiency of IL-17A had no effect on plaque burden within the aortic roots and thoracoabdominal aorta of *Il17a*^{-/-}*Apoe*^{-/-} and *Apoe*^{-/-} mice fed WD for 12 weeks. Intriguingly, decreased numbers of T cells, macrophages, DCs, and total leukocytes were detected in *Il17a*^{-/-}*Apoe*^{-/-} compared with *Apoe*^{-/-} aortas, indicating that IL-17A plays a role in controlling the overall cellularity of aortic leukocytes during atherogenesis. The authors also observed a marked increase in IL-17F levels within *Il17a*^{-/-}*Apoe*^{-/-} mice (84). In agreement with these results, our group recently detected mRNA expression of several IL-17 family members, including IL-17C, IL-17D, and IL-17F within the aortas of aged *Apoe*^{-/-} mice (4), suggesting that these cytokines may similarly participate in atherosclerosis-associated inflammation. To examine the effects of IL-17F neutralization in a rapid partial carotid ligation model of atherosclerosis, Madhur, et al., treated *Il17a*^{-/-}*Apoe*^{-/-} mice with a polyclonal goat-anti-mouse IL-17F neutralizing or an isotype control Abs (84). Although the percentage of stenosis of ligated carotid arteries were unaffected, there was a significant decrease in vessel diameter, suggesting that IL-17A affects outward remodeling (84). Nevertheless, the role and significance of IL-17F up-regulation as well as the roles of other IL-17 family members on atherogenesis in other anatomical sites merit further investigation. Since IL-17RA serves as the co-receptor for several cytokines of the IL-17 family, additional studies with IL-17RA-deficient mice might help to identify a complementary role for other members of IL-17 cytokine family and shed light on the inconsistency in the results between published studies with IL-17A and IL-17RA-deficient mice.

Conclusion

Over the last decade, several studies have highlighted different roles for Th17 cells and other IL-17A-producing cells including NK and NKT cells, $\gamma\delta$ T cells, and neutrophils in host defense as well as the pathogenesis of multiple autoimmune diseases. Several recent studies have similarly demonstrated that IL-17A cells are present in atherosclerotic plaques, however, the specific role of these cells are currently debated. The controversy surrounding the role of IL-17A in atherosclerosis stems primarily from contradictory results obtained from IL-17A neutralizing studies. Therefore, the effects of IL-17A in knockout mice should help to clarify the role of this cytokine in atherosclerosis. Future work investigating the role

of other Th17 related cytokines and IL-17 family members will further delineate the exact role Th17 cells play in atherosclerosis.

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Figure 1. Possible role for IL-17A during atherosclerosis

Upon encountering foreign antigen, naïve T cells differentiate under specific cytokine conditions into several T cell subsets such as Th1, inducible Tregs and Th17 cells (Fig. 1) and Th2, Th9, and Tfh cells (not shown). IL-17A is produced by Th17 cells, but other leukocytes ($\gamma\delta$ T cells, NK and NKT cells, neutrophils and LTi cells) can also produce IL-17A. As the expression of IL-17RA is ubiquitous, IL-17A⁺ derived from multiple subsets of leukocytes may directly induce synthesis of chemokines, cytokines, reactive oxygen species, and MMPs by smooth muscle and endothelial cells, monocytes/macrophages and neutrophils. IL-17A might also affect the recruitment of neutrophils, Th1 cells and monocytes.

Table 1

Elevated levels of IL-17A are detected in human plasma and aortic tissues in the patients with cardiovascular diseases (CVD).

Study	Patient Classes	Measurements	Results
Eid, R.E., et al. (44)	Male caucasian healthy subjects, referent patients, and CAD patients	<ul style="list-style-type: none"> Plasma IL-17A, IFNγ, IL-12, CXCL10, IL-6, IL-23 levels Cytokine levels following polyclonal T cell stimulation Th17 and Th1 content in coronary arteries and blood 	<ul style="list-style-type: none"> Elevated IL-17A in CAD patients vs healthy subjects Plasma IL-17A levels correlated with IFNγ, IL-12, and CXCL10 levels
Cheng, X., et al. (45)	Acute myocardial infarction (AMI), unstable angina (UA), stable angina (SA), and chest pain syndrome (CPS) patients	<ul style="list-style-type: none"> Peripheral blood Th17 and natural Treg content Plasma IL-17A, IL-6, IL-23, IL-10, TGFβ1, and CRP levels 	<ul style="list-style-type: none"> Elevated Th17 and reduced Tregs in the peripheral blood of AMI and UA patients Positive correlation between plasma IL-23 and IL-17A, and TGFβ1 and Tregs
Wang, Z., et al. (79)	Male and female stable angina (SA), and acute coronary syndrome (ACS) patients	<ul style="list-style-type: none"> Peripheral blood neutrophil and Th17 cell content Plasma IL-8, IL-17A levels Peripheral blood IL-8 and IL-17A mRNA expression 	<ul style="list-style-type: none"> Elevated peripheral blood Th17 cells and neutrophils in SA and ACS patients Peripheral blood IL-8 levels correlated with IL-17A and neutrophil content
Zhao, Z., et al. (80)	Male and female stable angina (SA), unstable angina (UA), and acute myocardial infarction (AMI) patients	<ul style="list-style-type: none"> Peripheral blood Th1, Th17, Th2 and Treg content Peripheral blood <i>Ifng</i>, <i>Tbet</i>, <i>Stat4</i>, <i>Il17a</i>, <i>Rorgt</i>, <i>Stat3</i>, <i>Foxp3</i>, <i>Il4</i>, and <i>Gata3</i> mRNA expression 	<ul style="list-style-type: none"> Elevated Th1/Th17 and Th1 cells in UA and AMI patients Elevated levels of Th1-related IFNγ, Tbet, Stat4, and Th17-related IL-17A, RORγt, Stat3 in UA and AMI patients
Patel, S., et al. (86)	Symptomatic and asymptomatic Caucasian carotid artery disease patients.	<ul style="list-style-type: none"> Histologic examination of carotid artery plaque for CCL2, Myeloperoxidase (MPO), Foxp3, IL-17A, and IL-10 content. 	<ul style="list-style-type: none"> Elevated CCL2, MPO, Foxp3, IL-17A, and IL-10 staining in symptomatic carotid plaques
Erbel, C., et al. (78)	Symptomatic and asymptomatic Caucasian carotid artery disease patients	<ul style="list-style-type: none"> Histologic examination of carotid artery plaque IL-17A content Carotid artery IL-21, IL-17, IL-10 mRNA expression 	<ul style="list-style-type: none"> IL-17A⁺ T cells and MΦ are present in carotid artery plaques. Increased carotid artery IL-17, IL-21, and IL-23 levels in symptomatic individuals

Table 2

Implication of IL-17A producing cells in murine models of atherosclerosis.

Mouse model	Intervention scheme	Effect on lesions	Site(s) examined	Effects on T cell subsets	Effects on myeloid cells
<i>Ldlr</i> ^{-/-} (82)	<i>Il17ra</i> ^{-/-} or <i>Il17ra</i> ^{+/+} bone marrow transfer 12 week WD	↓	Aortic root: 46% decrease	<ul style="list-style-type: none"> Decreased IL-6 and increased IL-10 in polyclonal stimulated T cells 	<ul style="list-style-type: none"> Increased aortic root MΦ content Decreased neutrophil and mast cell content
<i>Apoe</i> ^{-/-} (3)	Administration of rat-anti-mouse IL-17A Abs Chow diet	↓	Aortic root: 50% decrease	<ul style="list-style-type: none"> Decreased Th1 and Tregs content Decreased aortic root T cell content 	<ul style="list-style-type: none"> Decreased MΦ content
<i>Apoe</i> ^{-/-} (4)	Decoy IL-17A receptor (<i>adIL-17RA:Fc</i>) 15 week WD	↓	<ul style="list-style-type: none"> Aorta: 50% decrease Aortic root plaque reduction 	Circulating IFNγ and IL-17F were unaltered, while IL-6 and G-CSF were decreased	<ul style="list-style-type: none"> Reduced aortic root MΦ and <i>Cxcl1</i> content
<i>Apoe</i> ^{-/-} (81)	<ul style="list-style-type: none"> Rat-anti-mouse IL-17A Abs rIL-17A or albumin 12 week WD 	↓	<ul style="list-style-type: none"> Carotid arteries: 80% reduction Aortic root: 70% reduction 	not determined	<ul style="list-style-type: none"> Anti-IL17A- treated mice: reduced aortic root MΦ, SMCs rIL-17A mice: decreased aortic root SMC content
<i>Apoe</i> ^{-/-} and <i>Il17a</i> ^{-/-} <i>Apoe</i> ^{-/-} (84)	12 week WD	=	Aortic root, thoracoabdominal aorta	<ul style="list-style-type: none"> Reduced aortic CD3⁺ cells (~30% reduction) Reduced IFNγ in stimulated T cells 	<ul style="list-style-type: none"> Reduced aortic MΦ and DCs Reduced O₂⁻ in splenic cultures and elevated NO levels in <i>Il17a</i>^{-/-} <i>Apoe</i>^{-/-} aortas
<i>Apoe</i> ^{-/-} and <i>Il17a</i> ^{-/-} <i>Apoe</i> ^{-/-} (84)	<ul style="list-style-type: none"> anti-IL-17F neutralizing Abs (3 wks) 	= ↓	Ligation- induced carotid artery stenosis: no effects; internal elastic lamina area: 50% reduction		

Mouse model	Intervention scheme	Effect on lesions	Site(s) examined	Effects on T cell subsets	Effects on myeloid cells
<i>Ldlr</i> ^{-/-} (5)	<ul style="list-style-type: none"> <i>Socs3</i>^{-/-} and <i>Socs3</i>^{+/+} bone marrow transfers 6 week WD 	↓ in <i>Socs3</i> ^{-/-} chimeras	<ul style="list-style-type: none"> Decrease aortic root lesions, in <i>Socs3</i>^{-/-} <i>Ldlr</i>^{-/-} mice 	<ul style="list-style-type: none"> Increased IL-10, IL-17A, decreased IFNγ in <i>Socs3</i>^{-/-} <i>Ldlr</i>^{-/-} splenocytes, functions of Tregs were unaltered 	Increased aortic root VCAM-1 expression in anti- IL-17A-treated <i>Socs3</i> ^{-/-} <i>Ldlr</i> ^{-/-} mice
	<ul style="list-style-type: none"> Mouse anti- mouse IL-17A Abs, 6 wks 	↑ in anti- IL-17A treated <i>Socs3</i> ^{-/-} <i>Ldlr</i> ^{-/-} chimeras	<ul style="list-style-type: none"> Increased aortic root lesions in anti- IL17A treated <i>Socs3</i>^{-/-} <i>Ldlr</i>^{-/-} chimeras 		
	<ul style="list-style-type: none"> administration of rIL-17A for 5 wks to 12-17wk old <i>Socs3</i>^{-/-} and <i>Socs3</i>^{+/+} chimeric <i>Ldlr</i>^{-/-} mice 	↓ aortic root lesion area			
<i>Apoe</i> ^{-/-} and <i>Ldlr</i> ^{-/-} (85)	<ul style="list-style-type: none"> <i>Il17a</i>^{-/-} or <i>Il17a</i>^{+/+} bone marrow transfer to 16 wk-old <i>Ldlr</i>^{-/-} mice 6 week WD 	=	<ul style="list-style-type: none"> Aortic root 	not determined	not determined
	<ul style="list-style-type: none"> rat-anti-mouse IL-17A Abs, 8 wk- old <i>Apoe</i>^{-/-} mice on a 12 wk chow diet 	↓	<ul style="list-style-type: none"> Aortic root (50% reduction) 		
	<ul style="list-style-type: none"> mouse-anti- mouse IL-17A Abs, <i>Apoe</i>^{-/-} mice 12 wk chow diet 	=	<ul style="list-style-type: none"> Aortic root 		