IL-17 and Th17 Cells in Atherosclerosis
Subtle and Contextual Roles
Soraya Taleb, Alain Tedgui, Ziad Mallat

Abstract—Atherosclerosis is a chronic inflammatory arterial disease driven by both innate and adaptive immune responses to modified lipoproteins and components of the injured vascular wall. Specific T lymphocyte responses driven by T helper-1 or T regulatory cells play distinct and opposing roles in atherosclerosis. More recently, T helper-17 cells, which produce the prototype cytokine interleukin-17, have been characterized and shown to be critical in mucosal host defense against microbial and fungal pathogens. Sustained production of interleukin-17 in an inflammatory context has been linked to the pathology of several autoimmune and inflammatory diseases. However, regulatory and protective roles have also been reported in selective disease settings. Studies in atherosclerosis led to conflicting results on the roles of interleukin-17 and T helper-17 cells in disease development and plaque stability. The present review provides a summary of the available evidence and putative mechanisms linking this pathway to atherosclerosis, as well as a perspective on the risks and benefits of interleukin-17–targeted cytokine therapy in patients at high cardiovascular risk. (Arterioscler Thromb Vasc Biol. 2015;35:258-264. DOI: 10.1161/ATVBAHA.114.303567.)

Key Words: atherosclerosis ■ cardiovascular disease ■ cytokines ■ immunity ■ interleukins

T Helper-17 Differentiation and Function
In the past decade, increasing attention has been focused on a subset of CD4+ T cells, commonly known as T helper-17 (Th17) cells, which on differentiation specializes in the secretion of interleukin (IL)-17, and also others factors, such as IL-21, granulocyte–macrophage colony-stimulating factor, and IL-6. IL-17 cytokine family consists of 6 members; among them, the major isofrom is IL-17A (referred to here as IL-17). Apart from Th17 cells, IL-17 is also produced by selective cell subtypes, including γδ T cells, natural killer cells, and natural killer-T cells. Th17 may be generated in the thymus and are then called natural Th17 (nTh17) cells, but can also be induced in the periphery from naïve cells or result from the conversion of other cell types.

Microenvironmental Factors Involved in Th17 Differentiation
Th17 differentiation requires the coordinated activities of several microenvironmental cues. Transforming growth factor (TGF)-β and the inflammatory cytokines IL-6, IL-21, IL-1β, and IL-23 play central roles in the generation and maintenance of Th17 cells. In mice, both TGF-β and IL-6, which are extensively linked to atherosclerosis, seem to be instrumental for Th17 differentiation. TGF-β cannot induce Th17 differentiation directly, but rather inhibits Th1 and Th2 transcriptional factors, which in turn, allows Th17 differentiation in the presence of IL-6. IL-6 activates STAT3, which is required for RORγt expression and function (for review, see Ref. 11). TGF-β is produced by multiple lineages of leukocytes and stromal cells,

1,4 to induce IL-17 expression. The transcription factor basic leucine zipper transcription factor controls the differentiation of IL-17–producing Th17 cells by regulating the expression of RORγt. However, these transcription factors are not specific for Th17 because they are also involved in the differentiation of other cell types.6 Recently, it was shown that the bromo-domain and extraterminal domain (BET) family of chromatin adaptors was instrumental for human and murine Th17 differentiation, highlighting the role of chromatin dynamics in the control of Th17 immune lineage specification.8

Transcription Factors Involved in Th17 Differentiation
Th17 cell differentiation requires retinoid-related orphan receptor (ROR)-γt, which cooperates with other transcriptional factors, including ROR-α, signal transducer and activator of transcription 3 (STAT3), and runt-related transcription factor 1, to induce IL-17 expression. The transcription factor basic leucine zipper transcription factor controls the differentiation of IL-17–producing Th17 cells by regulating the expression of RORγt. However, these transcription factors are not specific for Th17 because they are also involved in the differentiation of other cell types. Recently, it was shown that the bromo-domain and extraterminal domain (BET) family of chromatin adaptors was instrumental for human and murine Th17 differentiation, highlighting the role of chromatin dynamics in the control of Th17 immune lineage specification.8

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but is also expressed at high levels in Th17 cells and may act in an autocrine manner to maintain Th17 cells in vivo. Still, the absolute requirement of TGF-β for in vivo Th17 differentiation in mice has been questioned. Indeed, Th17 cells are present in the gut of TGF-β−/− mice has been questioned. Indeed, Th17 cells are present in the gut of TGF-β−/− murine and human Th17 cells.20

Additional key regulators that are involved in vascular remodeling and thus associated to cardiovascular disease have been recently identified as key regulators of Th17 differentiation. For example, nitric oxide mediates nitration of tyrosine residues in RORγt, leading to the suppression of RORγt-induced IL-17 promoter activation, which highlights a negative role for nitric oxide in Th17 differentiation.29 Salt (sodium chloride) concentrations found locally under physiological conditions in vivo markedly boost the induction of murine and human Th17 cells.20

**IL-17 Signaling**

IL-17 receptor (IL-17R) family consists of 5 subunits. IL-17 binds to the heterodimeric receptor, IL-17RA and IL-17RC, and stimulates its signaling pathway. IL-17RA is ubiquitously expressed throughout the body, resulting in pleiotropic actions of IL-17 on a wide range of cell types (for review, see Ref. 21). IL-17 binds to the receptor in homodimers (IL-17A/IL-17A or IL-17F/IL-17F) or heterodimers (IL-17A/IL-17F) configurations, with IL-17A and IL-17F sharing the highest degree of homology. IL-17 signaling activates various downstream pathways, which include nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinases to induce various mediators with relevance to atherosclerosis, for example, CXC chemokines, such as CXCL1 and CXCL2, involved in the attraction of neutrophils, and inflammatory factors, such as IL-6 and granulocyte–macrophage colony-stimulating factor (for review, see Ref. 22). However, IL-17 is considered a weak activator of NF-κB,23 which implies that other factors have to synergize with this cytokine to promote a substantial inflammatory response.

**IL-17 Function**

In the periphery, cells that produce IL-17 are prominent in the gut, where they influence its barrier function and help to protect against extracellular pathogens and fungi. More generally, Th17 cells play an important homeostatic role in the clearance of extracellular pathogens by recruiting neutrophils and by producing antimicrobial proteins and inflammatory factors (for review, see Ref. 24). This role of IL-17 and Th17 cells in clearing infections has been highlighted in patients with the hyper-IgE syndrome, in whom dominant negative mutations of STAT3 are responsible for a marked decrease of Th17 cells, resulting in increased susceptibility to Candida albicans and Staphylococcus aureus infections in the lungs and skin.25 However, in some settings, these cells are also considered important drivers of autoimmune and inflammatory diseases, such as rheumatoid arthritis, multiple sclerosis, psoriasis, and inflammatory bowel disease (for review, see Refs. 26,27).

The effectors that determine Th17 pathogenicity are still incompletely determined. A pathogenic role for Th17 cells might be related to IL-6 and granulocyte–macrophage colony-stimulating factor production28,29 rather than IL-17. However, in humans, granulocyte–macrophage colony-stimulating factor expression was shown to be inhibited by the IL-23/RORγt/Th17 axis.30 On the other hand, a pathogenic role of IL-17 might not be related to Th17 cells, given that IL-17 is also produced by other cell types, including γδ T cells, myeloid cells, and innate lymphoid cells. For example, the latter cell type has been suggested to be a source of pathogenic IL-17 in colitis models.31 Interestingly, recent data identified distinct roles for specific TGF-β isoforms in the generation of pathogenic and nonpathogenic Th17 cells. TGF-β3, which is specifically produced by developing Th17 cells in an IL-23-dependent manner, drives pathogenic Th17 phenotype. This induced the conversion of IL-17A single-positive Th17 cells into IL-17A/interferon (IFN)-γ double producers in vivo,32 which possess a high pathogenic potential in autoimmune models.14 Moreover, IL-1β was shown to induce pathogenic Th17 cells through repressing IL-10 production in vitro and in vivo.33 Pathogenic Th17 can also result from the conversion of other cell types, such as T regulatory cells, which lose the expression of the specific regulatory T-cell transcriptional factor, forkhead box P3 (Foxp3), during their differentiation toward the Th17 lineage.34 Recently, conversion of IL-6–induced Th17 cells from Foxp3− T cells was shown to play a key role in the pathogenesis of autoimmune arthritis, highlighting the importance of Foxp3 instability in the generation of pathogenic Th17 cells.35

Although Th17 cells were initially thought to be uniformly pathogenic,27,36 accumulating data revealed the existence of nonpathogenic IL-17–producing cells. For example, the combination of TGF-β1 and IL-6 promoted the formation of regulatory Th17, which also produced IL-10, a cytokine with potent anti-inflammatory and immune regulatory properties.37,38 In the same line, the induction of immune tolerance by CD3-specific antibody was associated with the presence of a Th17 cell
subset that acquired an immune-suppressive function through the production of IL-10. Also, the protective role of Th17 in selective disease settings may be related to the inhibition of pathogenic Th1 pathway, as was shown in a colitis model.

Taken together, the pathogenic potential of IL-17–producing cells may be greatly determined by the specific tissue, cellular, and inflammatory context in which they operate (Figure).

Role of IL-17 in Atherosclerosis

Atherosclerosis involves a complicated interplay between many different cell types and cytokine networks, which link several cardiovascular risk factors to immuno-inflammatory activation of the vascular wall. The initial vascular activation induces the recruitment, activation, and differentiation of monocytes into macrophages and dendritic cells, which is rapidly followed by an adaptive immune response on recruitment of T cells. The acquired immune response is directed against a range of antigens, including modified low-density lipoprotein (LDL) and heat shock proteins. Th1 lineage, which produces mainly IFN-γ, is considered a major pathogenic effector involved in a variety of autoimmune diseases and inflammatory conditions, including atherosclerosis. Th2 cells have been involved in diseases, such as atopy and asthma, but their pathogenic role in atherosclerosis is still debated, with cytokines, such as IL-5 and IL-13, showing protective effects, whereas other Th2 mediators like IL-4 may promote vascular inflammation (reviewed in Refs. 43, 44). Both Th1 and Th2 pathways are inhibited by T regulatory cells, which play important roles in the protection against atherosclerosis.45–47

After the discovery of Th17 cells, several groups addressed their potential contribution to atherogenesis. IL-17–positive cells were detected in the aortic sinus of mice deficient for low-density lipoprotein receptor (Ldlr−/−) and aortas of apolipoprotein E deficient (Apoε−/−) mice fed a western diet. Also, an increase of Th17 and IL-17+ T cells within the aortic wall, aortic adventitia, and secondary lymphoid organs of aged Apoe−/− and C57BL/6 mice was described.

Immune responses to potential auto-antigens, such as oxidized LDL and collagen V, have also been shown to promote a Th17 pathway. In particular, Lim et al noticed that Ldb mice lacking the genes encoding both LDL receptor and apolipoprotein B mRNA editing enzyme (Ldlr−/−Apobec1−/− [LDb] mice) developed hyperlipidemia and atherosclerosis with concomitant increase in IL-17. Mechanistically, the authors showed that oxidized LDL promoted IL-6 production, which then induced Th17 cell differentiation. Furthermore, high production of reactive oxygen species associated with atherosclerosis was shown to induce cAMP response element–binding protein–dependent IL-17, suggesting a contribution of IL-17 pathway to vascular inflammation. Conversely, the use of immunosuppressive and atheroprotective agents, such as mycophenolate mofetil, was associated with a decrease of IL-17 production in mice.

These findings suggested a proatherogenic role for IL-17 and led to several mechanistic studies aimed to address the distinct contribution of IL-17 and IL-17–producing cells to the development of atherosclerosis. Intriguingly, the results were (apparently) controversial.

IL-17 Neutralizing Strategies

Several experimental studies in which IL-17A signaling was inhibited proposed a proatherogenic role for IL-17. However, the evidence for effective and sustained blockade of IL-17 signaling was relatively weak in some of the previous work.

In the study by Smith et al, the use of an adenovirus encoding soluble IL-17R to interfere with IL-17 signaling led to a reduction of lesion size in Apoe−/− mice. However, IL-17R fusion protein levels dramatically dropped between the day of adenovirus injection and the end of the study, which might have substantially altered the efficiency and sustainability of IL-17 blockade during the study period. Indeed, according to the same group, a transient blockade of IL-17 signaling might lead to a feedback increase of IL-17 and Th17 cells, which might complicate the interpretation of the atherosclerosis results after short-term inhibition of IL-17 signaling.

Administration of a monoclonal anti–IL-17 antibody raised in rats led to reduced atherosclerosis in Apoe−/− mice. The effect was associated with a reduction of IFN-γ and an increase of IL-4 after administration of the rat antibody, which was not observed with a mouse antimouse IL-17 antibody. Our interpretation is that an IL-17A–independent Th polarization toward a Th2 response was responsible, at least in part, for the atheroprotective effect seen with the rat-derived IL-17A antibody. Indeed, when we used a rat antimouse IL-17A treatment, we similarly observed a reduction in atherosclerosis but, intriguingly, the atheroprotective effect was not associated with convincing evidence of reduced IL-17A signaling, as assessed by the expression of an IL-17-target gene, IL-6. In contrast, treatment with a monoclonal antimouse IL-17 antibody produced in mice efficiently blocked IL-17A signaling as assessed by a decrease of IL-6, but did not alter atherosclerosis development. Similarly, we had previously reported that neutralization of IL-17 with a mouse monoclonal anti–IL-17 antibody had no effect on lesion development in young Ldlr−/− mice.

Genetic Inactivation of IL-17 Signaling Pathway

Disruption of IL-17R signaling in bone marrow–derived cells of Ldlr−/− mice was associated with reduced atherosclerotic lesion size and decreased serum concentrations of anti-oxidized LDL IgG antibodies. However, a nonsignificant tendency toward increased production of IL-17 levels in that experiment, as previously seen in IL-17R−/− mice, might have led to enhanced IL-17R signaling in vascular cells of the chimeric model.

Ge et al showed that disruption of IL-17 expression in bone marrow–derived cells did not alter the development of atherosclerosis in Ldlr−/− mice, in line with what we had previously reported. Interestingly, however, reconstitution of Ldlr−/− mice with IL-17A−/− bone marrow abolished the effect of renal impairment on aortic leukocyte accumulation and proliferation and led to a reduction of lesion size, suggesting a pathogenic role of IL-17A in atherosclerosis in selective disease settings.

In the above-mentioned studies, the defect of IL-17 signaling was not complete because IL-17 or IL-17R were still expressed in vascular cells. This emphasizes the importance of studies using mice with complete abrogation of IL-17 signaling.
With regard to total deletion of IL-17, conflicting results have been reported. In the study by Madhur et al, IL-17A may have contributed to vascular and systemic inflammation but did not affect plaque burden in Apoe−/− mice fed a high-fat diet during 12 weeks. Usui et al observed that IL-17A deficiency protected against atherosclerosis in Apoe−/− mice fed a western diet for 12 weeks, which was attributed to reduced macrophage infiltration and inflammatory cytokine secretion in the lesions. Furthermore, Apoe−/− IL-17−/− and Apoe−/− IL-17R−/− mice fed a western diet during 15 weeks had smaller atherosclerotic plaques in the aortic arch and aortic roots, but showed little difference in plaque burden in the thoracoabdominal aorta in comparison with Apoe−/−, suggesting a proatherogenic role of IL-17 in selective arterial sites. In sharp contrast with those studies, Danzaki et al reported accelerated atherosclerosis and formation of vulnerable plaques after feeding Apoe−/− IL-17−/− mice a high-fat diet for 8 weeks, which was associated with enhanced IFN-γ and decreased IL-5 production.

The conflicting results may be caused by differential effect of the various strategies (eg, method used to block IL-17 signaling pathway, influence of diet composition, and feeding duration) on the immune response and, in particular, on Th1 pathway. Indeed, changes in plaque size in response to interference with IL-17 signaling seemed to mirror the effect of IL-17 modulation on the production of IFN-γ, enhanced Th1 pathway being associated with increased lesion size, and reduced IFN-γ going in parallel with a reduction in lesion size. Intriguingly, a neutral effect of IL-17 blockade on atherosclerosis was associated with a neutral effect on IFN-γ.

Increase of IL-17 Signaling Pathway

The inability of endogenous IL-17 signaling to reliably modulate the development of atherosclerosis may be because of the important proatherogenic Th1 bias that develops on a Bl6 background. To study the role of exogenous IL-17 in atherosclerosis, we supplemented Ldlr−/− mice with recombinant IL-17A (2 μg/mouse, once per week). This led to a moderate but significant increase of circulating IL-17, as well as IL-6 levels, and to inhibition of lesion development. This result was confirmed by Danzaki et al who showed that IL-17 supplementation in Apoe−/− and Apoe−/− IL-17−/− decreased lesion size. Conversely, in another study, treatment of Apoe−/− with recombinant IL-17 (2 μg/mouse, once per week) exacerbated plaque formation. Unfortunately, however, no data were provided concerning the efficiency of the IL-17 supplementation at enhancing IL-17 signaling in vivo.

Similarly, specific deletion of SOCS3 (suppressor of cytokine signaling) in T cells increased STAT3 signaling along with an increase of IL-17 (as well as IL-10) expression, which led to a decrease of lesion size in Ldlr−/− mice. Neutralization of IL-17A in this mouse model promoted Th1-producing IFN-γ pathway, which was associated with an acceleration of atherogenesis. Again, it is worth noticing that when IL-17 was shown to be atheroprotective, this was often associated with the inhibition of the proatherogenic cytokine, IFN-γ, and increased production of antiatherogenic mediators, that is, IL-5, IL-10. The observation is consistent with the described IL-17/IFN-γ reciprocal negative cross-regulation and with the regulatory properties of Th17 cells that produce IL-10 when differentiated in the presence of IL-6 and TGF-β.

Another possible explanation for the antiatherogenic role of IL-17 in this model may be related to its inhibitory effect on endothelial vascular cell adhesion molecule (VCAM)-1 expression, which led to reduced T-cell accumulation within the lesions. These results are consistent with other data showing inhibitory effect of IL-17 on VCAM-1 expression in fibroblasts and smooth muscle cells (SMC). In the same line, Gistera et al showed a stimulatory effect of IL-17 on fibrillar collagen synthesis by SMC, suggesting a profibrotic role of IL-17. In vivo, T cell–specific deletion of Sma7 in chimeric Ldlr−/− mice, inhibited TGF-β signaling and increased IL-17 production, which led to enrichment of atherosclerotic lesions with collagen, consistent with a more stable phenotype. Treatment of Sma7-deficient chimeras with neutralizing IL-17A antibody prevented fibrous cap expansion, supporting the notion that IL-17A may promote plaque stability through its contribution to fibrous cap formation.

Collectively, the results indicate that IL-17 may exert both anti- and proatherogenic effects, depending on the inflammatory context. In particular, IL-17 may have a protective effect if its signaling is sufficient enough to reduce IFN-γ production and promote IL-10 expression. At the opposite, a concomitant increase of IL-17 and IFN-γ may exert proatherogenic effects.

Role of IL-17 in Postischemic Injury

The role of IL-17 in the response to ischemic injury also needs further investigation. In stroke, the use of strategies aiming to block IL-17 differentiation and maintenance, such as IL-21 and IL-23, as well as IL-17 itself, led to protective effects. This pathogenic effect of IL-17 could be achieved through interaction of IL-17 with IL-17Rs on astrocytes, microglia, and neurons that activates many transcriptional factors, such as NF-κB, which then induces the expression of proinflammatory cytokines (eg, IL-6, TNFα, and IL-1β), chemokines (eg, CXCL1, CCL2, CXCL2, CCL7, CCL11, and CCL20), and metalloproteinases that facilitate trafficking of leukocytes across the vascular endothelial barrier and their entry into the parenchyma (for review, see Ref. 72).

After myocardial infarction (MI), mice showed a significant upregulation of IL-17 in both the infarcted and the non-infarcted areas, whereas mice deficient for IL-23 failed to do so. IL-23 deficiency led to increased myocardial inflammation and decreased cardiac fibroblast activation, associated with impaired remodeling after MI, suggesting protective roles for IL-23 and IL-17 in MI. It is interesting to note that in that study, IL-23 deficiency, through reduced IL-17 production, was able to suppress the deleterious Th1/IFN-γ response in the early stages after MI, thus reducing excessive myocardial inflammation. However, in another study, Yan et al reported a protective effect of IL-23 deficiency after MI, associated with no change of IFN-γ production and decreased myocardial inflammation. These discrepancies need to be addressed in future studies and may result from differences in mouse background and the study of different time courses after MI. Additional work showed that direct blockade of IL-17 by use of anti-IL-17A neutralizing antibody or IL-17–deficient mice
protected against ischemia/reperfusion injury, as demonstrated by reduced infarct size and improved cardiac function. The effects were attributed to IL-17–mediated cardiomyocyte apoptosis and neutrophil infiltration, supporting pathogenic effects of IL-17 in MI. However, the major source of IL-17 in this model was γδ T lymphocytes, not CD4+ T cells.

**IL-17 in Human Cardiovascular Disease**

Although de Boer et al failed to detect signatures of Th17 cells in human atherosclerotic lesions, we and others reported the presence of T cells expressing IL-17. Also, expression of IL-17–positive regulators, such as IL-21 and IL-23, has been described in human carotid plaques. In the study by Eid et al, IL-17/IFN-γ dual-producing T cells were detected within atherosclerotic coronary plaques, with in vitro results suggesting a synergistic proinflammatory effect of IL-17 and IFN-γ on vascular SMCs. However, other studies suggested a stabilizing role for IL-17 expression in human lesions. We found that IL-17 expression in carotid plaques was associated with a lower macrophage but a higher SMC content and a fibrous plaque phenotype, suggesting a role for IL-17 in promoting plaque stability. Consistent with these data, Gistera et al recently showed that RORγt and IL-17A expressions were positively associated with the SMC marker ACTA2 (encoding α-SM-actin) and with collagen I mRNA in human carotid plaques, supporting our previous results and the IL-17 profibrotic effect described in their mouse model. As indicated earlier, additional IL-17–protective effects may be related to its role in the downregulation of endothelial VCAM-1 expression. Consistent with this hypothesis, IL-17 was shown to inhibit human monocellular cell adherence to preactivated human umbilical vein endothelial cells in culture. Further studies are required to fully delineate the mechanisms by which IL-17 may modulate vascular inflammation and arterial remodeling.

A few studies also addressed the relationship between circulating IL-17 levels and cardiovascular risk. Despite initial small reports suggesting increased levels of IL-17 and Th17 subset in patients with acute coronary syndromes, the bulk of evidence indicate that circulating IL-17 levels are similar in patients with or without coronary artery disease. Nevertheless, the modulation of VCAM-1 expression by IL-17 prompted us to look at the interaction between IL-17 and VCAM-1 in vivo with relation to cardiovascular outcomes. We found that lower levels of circulating IL-17 in patients (n=981) admitted for acute MI were associated with a higher risk of major cardiovascular events, including all-cause death and recurrent MI, after 2 years of follow-up. Moreover, the highest risk of death and recurrent MI was observed in patients with low levels of IL-17 and high levels of VCAM-1, suggesting an important modulatory role for IL-17 on vascular inflammation. In this regard, it is noteworthy that major adverse cardiovascular events have been reported in psoriatic patients assigned to ustekinumab or brikumab, 2 anti-p40 antibodies that block IL-23 (and IL-12), which was not the case for patients assigned to placebo or treated with etanercept, an inhibitor of TNF-α. However, studies that evaluated the use of antibodies targeting IL-17 or its receptor did not report serious adverse cardiovascular events after 12 weeks of treatment. Nevertheless, a 12-week follow-up period is too short to assess cardiovascular safety. Outcomes of future trials involving larger numbers of patients treated and followed for a much longer period of time will be awaited. Until these data are available, we think that patients with identifiable high cardiovascular risk treated with inhibitors of the IL-17 pathway should be monitored closely for the development or progression of cardiovascular complications.

**Figure.** Summary of the putative protective and pathogenic effects of interleukin (IL)-17 in atherosclerosis. IL-6 and transforming growth factor (TGF)-β may induce a subtype of T helper (Th)17 cells that produce both IL-17 and IL-10. Conversely, IL-23 and IL-6 may be involved in the differentiation of pathogenic Th17 cells that produce IL-17 and interferon (IFN)-γ. In addition to Th17 cells, IL-17 can also be produced by other cell types, such as natural killer (NK)T, NK, and γδ T cells. Proatherogenic effects of IL-17 may result from the induction of proinflammatory cytokines (IL-6, granulocyte–macrophage colony-stimulating factor [GM-CSF]) or chemokines (such as CCL2, CXCL1, CXCL8, and CXCL10) by endothelial cells, smooth muscle cells (SMC), or macrophages, partly through increased attraction and recruitment of neutrophils and monocytes within the plaques. The atheroprotective effects of IL-17 may be caused by decreased production of the proatherogenic factor IFN-γ and to its inhibitory effect on the expression of vascular cell adhesion molecule (VCAM)-1, an adhesion molecule that plays a prominent role in mediating the accumulation of monocytes and T cells within the lesions. Moreover, IL-17 may activate the production of collagen type I by SMCs, which can promote plaque stability. oxLDL indicates oxidized low-density lipoprotein.

**Conclusions**

The overall data indicate that the role of IL-17 in cardiovascular disease is context-dependent and may vary according to the cell type producing IL-17 and the cytokine profile of the local microenvironment where IL-17 operates. Enhanced IL-17 production associated with increased IL-10 (regulatory Th17) and reduced IFN-γ will most probably limit lesion development and promote plaque stability. In contrast, dual production of IL-17 and IFN-γ will most likely promote lesion progression and instability.

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**Disclosures**

None.
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17–targeted cytokine therapy in patients at high cardiovascular risk. we provide a summary of the available evidence and putative mechanisms linking interleukin-17 to atherosclerosis and plaque stability


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