disparate collection of microbial cues is unlikely to elicit a uniform response from the gut. For example, the microbial structural component polysaccharide A present on *Bacteroides fragilis* contributes to intestinal homeostasis by promoting differentiation of Foxp3$^+$ Treg cells (Round and Mazmanian, 2010), whereas *segmented filamentous bacterium* (SFB) favors the differentiation of CD4$^+$ T helper cells into Th17 cells, a more proinflammatory phenotype (Ivanov et al., 2009). Similarly, as reported here and in other studies, microbial-derived metabolites (SCFA) also trigger an immune response from the host. How are these numerous and disparate microbial cues (structural products, metabolites, etc.) integrated into a cohesive and coordinate response by the host? This dichotomy between the deleterious and protecting function of the microbiota and associated microbial products clearly illustrate challenges facing researchers working on this complex system. Regardless, manipulating host immune response by altering microbial composition and activities through dietary intervention and/or specific host receptors could represent a powerful mean to promote and/or maintain intestinal homeostasis. Understanding the various elements implicated in the complex dialog between bacteria and the host holds much promise for pathologies such as IBD and CRC.

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Th17 Cells at the Crossroads of Autoimmunity, Inflammation, and Atherosclerosis

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The connection between inflammation, autoimmunity, and atherosclerosis is long established. In this issue of *Immunity*, Lim et al. (2014) demonstrate that oxidized low-density lipoprotein is one of the key environmental factors driving the development of inflammatory T helper 17 cells in atherosclerosis.

Atherosclerosis is the major culprit in cardiovascular disease and results from a complex interaction between a hypercholesterolemic state and chronically inflamed blood vessels. The contribution of inflammation to the pathophysiology of atherosclerosis is well recognized and became widely accepted after the 1999 publication of the poignantly titled "Atherosclerosis—An Inflammatory Disease," an influential commentary in the *New England Journal of Medicine* by Ross Russel (Ross, 1999). Indeed, even the so-called fatty streaks detected in infants and children—the first evidence of vascular injury—are characteristically inflamed and composed of monocyte-derived macrophages and T lymphocytes. These early and asymptomatic lesions are mainly lipid-laden macrophages (foam cells) with some T cells, but if the inflammatory response continues unabated, a mature and complex plaque rich in activated immune cells will form and become prone to rupture and thrombosis (Hansson, 2005). People with autoimmune diseases, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), are significantly more likely to develop cardiovascular diseases (Kahlenberg and Kaplan, 2013). Interestingly, elevated CD4$^+$ T helper 17 (Th17) cells, which produce proinflammatory interleukin-17A (IL-17A), not only are associated with these autoimmune diseases but have also been identified in atherosclerotic lesions (Eid et al., 2009; Erbel et al., 2009; Hansson, 2005). Thus, Th17 cells and increased IL-17A

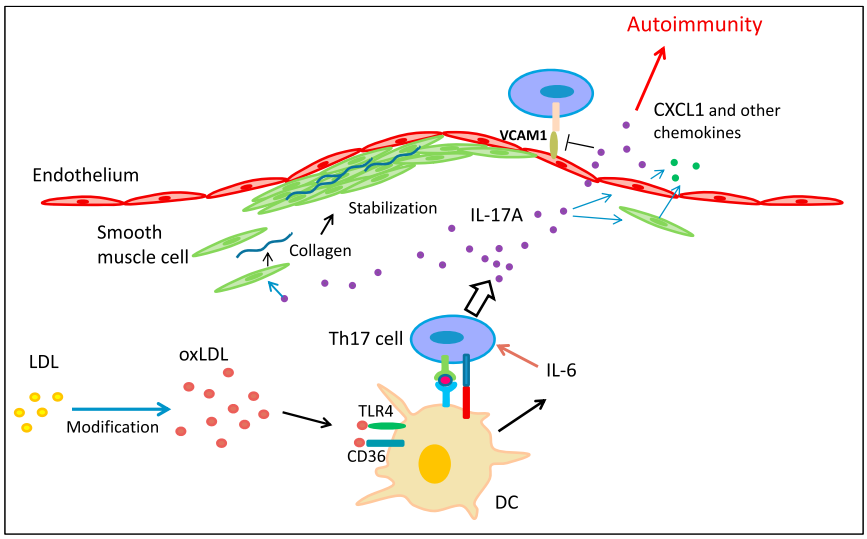

Figure 1. Development of Th17 Cells in the Atherosclerotic Plaque
In the atherosclerotic plaque, oxLDL can activate infiltrating DCs by binding to TLR4 and CD36, resulting in the production of IL-6. IL-6 enhances Th17 cells to produce IL-17A. IL-17A not only exerts an essential role in promoting autoimmunity but also modifies the atherosclerotic plaque. IL-17A can act on smooth muscle cells and endothelial cells to induce proinflammatory cytokines and chemokines, such as CXCL1, which might enhance the recruitment and activation of myeloid cells. IL-17 can also help stabilize the plaque through the induction of collagen production from smooth muscle cells. In addition, IL-17 can downregulate the expression of VCAM-1 on endothelial cells, thus blocking the infiltration of T cells.

production might provide additional inflammatory links between these diseases.

In this issue of *Immunity*, Lim et al. noticed increased expression of IL-17A in both the aortic sinus and the circulation in atherosclerotic-prone *Ldlr*$^{-/-}$*Apobec1*$^{-/-}$ (LDb) mice, which have a "human-like" lipid profile and develop mature and complex plaque on a chow diet (Lim et al., 2014; Powell-Braxton et al., 1998). Although there was a moderate but significant increase in the frequencies of IL-17A-producing γδ T cells, significant increases in Th17 cells were detected in LDb mice (Lim et al., 2014). These results are consistent with previous reports that augmented circulating IL-17A and peripheral Th17 cell frequency are associated with atherosclerosis in patients or in preclinical models (Eid et al., 2009; Erbel et al., 2009; Gisterå et al., 2013; Taleb et al., 2009). Lim et al. hypothesized that in vivo atherogenic factors might promote Th17 cell development. They transferred myelin oligodendrocyte glycoprotein (MOG)-specific splenocytes derived from 2D2 transgenic mice into sublethally irradiated wild-type (WT) and LDb mice (Lim et al., 2014). The frequencies of both Th17 and Th1 cells were significantly higher in the spleens from the LDb recipient mice than in those from the WT mice. By using this elegant system, they demonstrated that environmental factors other than dysregulated immune cells in LDb mice enhanced Th17 cell responses. Elevated plasma low-density lipoprotein (LDL) is the major risk factor for cardiovascular disease and is also evident in LDb mice (Powell-Braxton et al., 1998). Native LDL diffuses from the blood into the innermost layer of the artery, where it is modified to form oxidized LDL (oxLDL). Lim et al. showed that the level of oxLDL was increased in LDb mice. Importantly, oxLDL, but not native LDL, was able to enhance Th17 cell differentiation in vitro when T cells were cocultured with dendritic cells (DCs) and stimulated with anti-CD3, LPS, and TGF-β, whereas Th1 cell differentiation remained unchanged (Lim et al., 2014) (Figure 1). Anti-oxLDL administration in the 2D2 splenocyte transfer model was able to significantly reduce the number of Th17 cells while only mildly affecting the number of Th1 cells. Mechanistically, Lim et al. revealed that oxLDL can directly act on DCs through oxLDL receptors, including TLR4 and CD36, to promote the production of IL-6, which is critical for Th17 cell differentiation (Figure 1). Either TLR4- or CD36-deficient DCs induced significantly less IL-17A production from T cells in the previously mentioned coculture system in vitro. The precise mechanism and cellular interactions between oxLDL and leukocytes within the mature atherosclerotic plaque are complex and remain unclear partly because of the lack of precise biochemical and cellular tools to recapitulate the modified LDL found in human atheroma. Nevertheless, the current paper by Lim et al. adds some clarity around these processes. They suggest that oxLDL can promote DC-mediated Th17 cell polarization by triggering IL-6 production.

Elevated inflammatory cytokines such as tumor necrosis factor α (TNF-α), IL-17, and IL-6 in RA and SLE are proposed to promote premature atherosclerosis (Kahlenberg and Kaplan, 2013). In this study, however, Lim and colleagues proposed that atherosclerosis conditions, especially with the increased level oxLDL, could also drive the progression of autoimmunity through the induction of Th17 cell development (Lim et al., 2014). Indeed, upon in vivo challenge of $MOG_{35–55}$ peptide in the 2D2 splenocyte transfer model, the 2D2 transgenic T cells triggered severe experimental autoimmune encephalomyelitis (EAE), a model of human multiple sclerosis, in LDb recipients compared to in WT recipient mice, and anti-IL-17A treatment alleviated the disease severity (Lim et al., 2014). Although this hypothesis needs to be further evaluated in other relevant models of autoimmunity and in human diseases, the results of Lim et al. shed new light on the connection between autoimmune diseases and cardiovascular diseases.

In addition, this study provides a chance to reevaluate the antigenic and atherogenic role of oxLDL in atherosclerosis. Although neutralizing antibodies to oxLDL have shown to be efficacious in rodent models of atherosclerosis and are known to improve insulin resistance in diet-induced obese primates (Li et al., 2013), similar approaches in clinical trials have been disappointing (www.clinicaltrials.gov ID NCT01258907). The roles of IL-17A in the development of atherosclerosis are still controversial. Although blocking the IL-17A pathway attenuates the progression of atherosclerosis in some models, a protective role of the IL-17 pathway, especially in the stabilization of atherosclerotic plaques, has also been revealed (Erbel et al.,

2009; Gisterå et al., 2013; Taleb et al., 2009) (Figure 1). Future studies to further define the functions of IL-17A in human atherosclerotic diseases and to confirm the link between oxLDL and the IL-17 pathway will provide novel insight into targeting these pathways for the treatment of cardiovascular disease.

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