EDITORIAL COMMENT

Interleukin 5 Contributes to Human Atherosclerosis Development But not to Thrombotic Complications*

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Atherosclerosis is a complex disease that develops in medium and large arteries in response to lipoprotein retention and oxidation in the subendothelial space. Because of compensatory enlargement as lesion area increases, a process first described by Seymour Glagov in human coronary arteries more than 30 years ago, functional impairment of blood flow is delayed until an advanced stage when lumen stenosis becomes significant. Acute ischemia observed during stroke and myocardial infarction is mainly due to thrombotic complications of atherosclerosis that suddenly narrow the artery lumen and compromise blood flow and peripheral oxygen delivery. The use of genetically engineered atheroprone mice has been instrumental in understanding the major role for both innate and adaptive immunity in atherosclerotic plaque formation and growth; however, unfortunately, animal experiments were less helpful in deciphering the mechanisms of plaque rupture and subsequent occlusive thrombosis. Murine atherosclerotic plaques share common features with human lesions but do not display fibrous cap rupture even at advanced stages.

Interleukin 5 (IL-5) is a cytokine produced by eosinophils, mast cells, macrophages, CD4$^+$ T, and type 2-innate lymphoid cells (ILC2). Its expression is regulated by several transcription factors including GATA3. In atherosclerotic animal models, seminal studies from Witztum's laboratory [1] have shown that IL-5 production by CD4$^+$ T cells drives B1 cell activation and production of protective natural immunoglobulin M (IgM) antibodies against oxidation-specific epitopes, including oxidized low-density lipoprotein (oxLDL). Anti-oxLDL IgM are able to bind to oxidized phospholipid-rich apoptotic cells and block their pro-inflammatory properties. In addition, anti-oxLDL IgM promote the clearance of apoptotic cells that accumulate within advanced atherosclerotic lesions and participate to the growth of the necrotic core [1]. Hematopoietic Il-5 inactivation was found to decrease plasma levels of IgM levels and to accelerate atherosclerosis [1]. In addition, IL-5 might also be involved in the atheroprotective function of ILC2, independently of humoral B1 responses [2]. Yet, the clinical relevance of these experimental findings remained unclear.

In this issue of *JACC: Basic to Translational Science*, Knutsson et al. [3] investigated the role of IL-5 in atherothrombotic cardiac events in a prospective cohort of adults from the Malmö Diet and Cancer study (N = 696) with a 15-year follow-up, by analyzing the relationship between IL-5 plasma levels and either the presence of atherosclerotic plaque in the carotid artery or the occurrence of major adverse cardiac events (e.g., fatal and nonfatal myocardial infarction, coronary artery bypass grafting, and percutaneous coronary interventions). In univariate analysis, they found significantly lower plasma levels of IL-5 in patients with carotid atherosclerotic

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plaques measured by ultrasound, as compared with subjects without arterial lesions. Such an association remained significant after adjustment on sex, age, and cardiovascular risk factors. In a large European prospective cohort study of high-risk individuals (N = 3,534) free of clinically overt cardiovascular disease at enrollment, IL-5 plasma concentrations was previously shown to be significantly inversely correlated with changes in carotid intima-media thickness over a period of 30 months (4). Moreover, in diabetic patients, variants coding for *Il-5* receptor were found to be independently associated with ischemic stroke. A Finnish prospective observational study had shown previously that plasma IL-5 levels were significantly associated with antibody titers to copper oxLDL and IgM to malondialdehyde-modified LDL (5), and high levels of IgM autoantibodies to oxLDL have been reported to be predictive of better cardiovascular outcomes. However, in this study, Knutsson et al. (3) did not find any association between IL-5 plasma levels and IgM against oxidation-specific epitopes. They only found a weak significant association between IL-5 released from activated leukocytes and IgM against a malondialdehyde modified sequence of apo B-100. Therefore, although experimental and human evidence strongly suggest an atheroprotective role of IL-5, the mechanisms of vascular protection remain unclear, and might not be related to its effects on the modulation of natural IgM humoral responses.

Recently, Newland et al. (2) reported that ILC2 is a major source of IL-5. ILC2 deficiency leads to a 50% decrease of IL-5 plasma levels in an *Ldlr$^{-/-}$* chimeric mouse model and reduces atherosclerosis development. ILC2 deficiency had a significant but modest effect on B1 population in the spleen and the mesenteric lymph nodes but did not alter anti-oxLDL antibody titers suggesting that IL-5-related vascular protection was unlikely to be driven by humoral B1 cell activation (2). IL-5 modulated macrophage function within atherosclerotic lesions. In mice lacking ILC2, macrophage phenotype was switched toward pro-inflammatory M1, associated with higher content

of iNOS$^+$F4/80$^+$ macrophages and less Arg1$^+$F4/80$^+$ macrophages.

Knutsson et al. (3) speculated that the effects of IL-5 on atherosclerosis development vary according to hemodynamic parameters because they observed a significant relationship between IL-5 plasma levels and the presence of atherosclerotic plaque in the carotid bulb, a low shear stress region, but no association with atherosclerosis in the common carotid artery, where blood flow is laminar and shear stress high. To mimic such conditions, the authors applied a cast to the right carotid artery to generate a laminar low flow proximal to the cast and an oscillatory flow distal to the cast. After 14 weeks of fat diet, atherosclerosis was significantly increased in the distal oscillatory flow region in *Apoe$^{-/-}$Il-5$^{-/-}$* mice, as compared to control *Apoe$^{-/-}$Il-5$^{+/+}$* mice, but no difference was observed in the proximal laminar low shear stress area, in agreement with ultrasonographic observations in humans. This result suggests that IL-5 might directly target endothelial cells that are very sensitive to blood flow and shear stress variations. A recent in vitro study reported that IL-5 per se is able to modulate endothelial cell phenotype and activity. Further investigations are required to understand the mechanisms accounting for the direct effects of IL-5 on endothelial biology.

The translational study by Knutsson et al. (3) supports the protective role of IL-5 on atherosclerosis plaque growth. As monoclonal antibody targeting IL-5 are currently being developed to treat patients with severe asthma, cardiovascular side effects should be carefully recorded, especially in adult patients with cardiovascular risk factors. Such prospective epidemiologic monitoring should provide unique opportunity to decipher the role of IL-5 in human atherosclerotic plaque stability (6).

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