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Editorial commentary: Atherosclerosis and immunity: A perspective

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In vitro, experimental and clinical studies have convincingly demonstrated that atherosclerosis is an inflammatory disease in which both innate and adaptative immunity play a key role [1]. Recent clinical trials have further supported this view by directly confirming that pharmacologically controlling immunity may improve relevant atherosclerosis-related clinical endpoints [2].

Several cardiovascular risk factors have been found to trigger the immune system and inflammation, thus starting the cascade of events leading to atherosclerosis appearance, progression and complications [1,3,4]. In particular, exposure to one or more cardiovascular risk factors is now clear to alter endothelial homeostasis by promoting endothelial injury and impairing its repair and turnover [5,6]. Intriguingly, functional and anatomical endothelial injury is crucial for initiating arterial inflammation and early atherosclerosis development and, at the same time, it may result from an abnormal activation of the immune system. Accordingly, endothelial injury is considered the pass to recruit inflammatory cells within the arterial wall [1]. On the other hand, overactivation of the immune system and systemic inflammation cause endothelial dysfunction, initiate endothelial fragmentation and impair endothelial repair by adjacent healthy endothelial cells and by endothelial progenitor cells as well [7,8].

As detailed by Abdolmaleki et al. in this issue of Trends in Cardiovascular Medicine [9], as a result of the accumulation of lipids within the arterial wall, several types of immune cells, including mainly macrophages and T cells, but also B lymphocytes and other immune cells are directly involved in the etiopathogenesis of atherosclerosis. In particular, the Authors have described how macrophages become initially activated, the mechanisms by which the inflammatory adaptive immune response develops involving primarily Th1, Th2, Th17 and B cells, and how a progressive decrease in regulatory T cells occurs in the progression of atherosclerosis [9]. Also natural killer cells have been recalled by the Authors as potentially implicated in the progression of atherosclerosis [9].

In addition to the above mentioned events, different cytokines and immunological mediators may direct the prevalence of specific macrophage subtypes (e.g., M1, M2, Mox, etc.) in the atherosclerotic lesions, thus possibly explaining the transition from a stable into an unstable atherosclerotic plaque phenotype. Importantly, the Authors highlight that the atherosclerotic microenvironment is responsible for a sort of chronological plasticity of macrophages, whose pro-inflammatory and anti-inflammatory phenotype may change over time, thus possibly driving the destiny of the atherosclerotic plaque. Of particular relevance is the observation that macrophage polarization in extra-vascular tissues also may have an impact on the progression of atherosclerosis [9].

In order to further deepen the role of immunity and immune cells in atherosclerosis as reviewed by Abdolmaleki et al. [9], the involvement of additional immune cells should be acknowledged. Accordingly, also dendritic cells, neutrophils, mast cells, and eosinophils, have been found in human atherosclerotic lesions and have been shown to promote atherosclerosis [10].

Although a clear definition of dendritic cells and the exact distinction between dendritic cells and macrophages is often ambiguous, dendritic cells are believed to initiate antigen-specific adaptive immune responses and to maintain tolerance to self-antigens. Despite these limitations, the presence of different subsets of dendritic cells in the arterial wall, their accumulation in atherosclerotic plaques and the correlation between their abundance and plaque vulnerability in humans, suggest a pro-atherogenic role of these cells [11]. The role of neutrophils in atherosclerosis is still uncertain; however, it should be highlighted that many secretion products from activated neutrophils, including myeloperoxidase and reactive oxygen species, may be responsible for plaque destabilization and rupture. In addition, neutrophils have been found to stimulate other immune cells to enter atherosclerotic lesions and release proinflammatory mediators [12], thus supporting a role for these cells in promoting plaque instability. Accumulating evidence points towards

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a role for mast cells and eosinophils in the pathophysiology of atherosclerosis. Thus, secretion products from activated mast cells, including proteases chymase and tryptase, histamine, cytokines, chemokines and growth factors may promote plaque progression, matrix degradation and destabilization [13]. In addition, the association between eosinophil cationic protein (i.e., a sensitive marker of eosinophil activation) and eotaxin (i.e., a potent eosinophil chemoattractant/activator) with atherosclerosis seems to suggest a pro-atherogenic role of eosinophils. However, the degree and direction of the prospective association between eosinophil count and cardiovascular disease events are still unclear [14].

Along with the effector cells of the immune system, accumulating evidence suggests that regulatory T cells can act as a paramount factor in the inflammation of the atherosclerotic plaques, as also reported by Abdolmaleki et al. [9]. Regulatory T cells are recognized to exert their atheroprotective properties by suppressing T cell proliferation and promoting secretion of anti-inflammatory cytokines (e.g., interleukin-10 and transforming growth factor-β). The expression of the enzyme indoleamine 2,3-dioxygenase-1 (IDO1), which catalyzes the degradation of tryptophan, has been implicated in the induction and expansion of regulatory T cell populations. Conversely, regulatory T cells promote IDO1 expression in dendritic cells during antigen presentation. Intriguingly, IDO1 is expressed in human atherosclerosis, where it colocalizes with macrophages [15]. Given the positive relationship between IDO1 and regulatory T cells, an anti-atherogenic role of IDO1 can be expected. However, it has been found that IDO1 promoted an immunostimulatory effect through inhibition of interleukin-10, which translated into atherosclerotic disease exacerbation [16]. Conversely, in a recent study, promoting the expansion of antigen-specific FoxP3+ regulatory T cells in the artery wall has led to increased IDO1 expression and atheroprotection [17]. Moreover, vascular inflammation increased and plaque formation was accelerated in hypercholesterolemic mice by the inhibition of tryptophan metabolism with the IDO inhibitor 1-methyl tryptophan or the genetic ablation of IDO1 [18].

In summary, a comprehensive understanding of the role of immune cells and related secretory molecules in the pathophysiology of atherosclerosis has led to the unequivocal belief that atherosclerosis is an immune-inflammatory disease. Oxidized low-density lipoproteins and related compounds [1], dead cells and altered efferocytosis [19], heat shock proteins and infections [20] and other stimuli have been reported as potential triggers and amplifiers of the atherosclerotic process, by initiating and maintaining arterial wall inflammation. In addition, pro-inflammatory macrophages and effector T cells are clearly associated with disease exacerbation, whereas their inhibition is paralleled by a consistent attenuation of vascular wall inflammation and atherosclerotic degeneration. Although a pro-atherogenic role of additional immune cells, including mast cells, eosinophils and natural killer cells has been proposed, their exact involvement in the pathophysiology of atherosclerosis and the effects of their therapeutic modulation needs further study. Finally, despite accumulating evidence supporting the anti-atherogenic role of regulatory T cells, the modulation of their activity as well as the fine-tuning of their interaction with other immune and non-immune cells and with specific tolerogenic pathways remains an area of intense research aimed at minimizing the unpredictability of this intervention.

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