**Immune mechanisms of atherosclerosis**

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**Adaptive immune responses in atherosclerosis**

Atherosclerosis is a chronic inflammatory disease of the arterial wall initiated in response to various stimuli, mostly modified lipids\(^1\). Innate immune responses involving both vascular and immune cells, mostly monocytes/macrophages are rapidly activated in response to vascular injury, play important roles in vascular remodeling and orchestrate the development of a more specific adaptive immunity\(^2\). Most lymphocytes of murine and human atherosclerotic plaques are CD4+ T cells of the Th1 cell type, producing interleukin (IL)-2 and interferon (IFN)-γ and play critical pathogenic roles in atherosclerosis\(^3\). Recent studies indicate that CD4+ T lymphocytes recognize epitopes on native ApoB100 in a MHC-II-dependent manner, leading to pro-atherogenic T cell responses\(^4\). Dendritic cells are specialized antigen-presenting cells and localize to normal and atherosclerotic vascular lesions\(^5\). Different dendritic cell subsets appear to play differential roles in atherosclerosis, promoting or restraining disease development\(^6-12\). We will discuss the roles of these different dendritic cells and present original data on the role of a specific subset in the presentation of LDL-derived antigen in the context of atherosclerosis.

**Roles of Th1/Tregs and Th17 subsets**

Once CD4+ T cells have been activated, they develop into several types of T helper cells, Th1, Th2 or Th17. Th1 cell type has been attributed pro-atherogenic properties\(^13,14\), which are counter-regulated by the anti-inflammatory and homeostatic properties of regulatory T cells (Tregs)\(^15\), mainly through IL-10\(^14,16\) and TGF-b-dependent\(^17\) pathways. The roles of the other Th2 and Th17 subsets remain debated\(^13,18\). We will present intriguing data on the potential roles of STAT3/IL-17 signaling in vascular diseases. We have recently shown that loss of suppressor of cytokine signaling (SOCS) 3 in T cells increases both IL-17 and IL-10 production, and leads to unexpected IL-17-dependent reduction in lesion development and vascular inflammation in mice\(^19\). We also showed that in vivo inhibition of STAT3 signaling or blockade of IL-17A resulted in a marked increase in aneurysm severity and fatal rupture in mouse models\(^19\). STAT3 deficiency is responsible for autosomal dominant hyper-IgE syndrome characterized by recurrent bacterial and fungal infections, connective tissue abnormalities, hyper-IgE and Th17 lymphopenia. We prospectively screened 21 adult STAT3-deficient patients (median age: 26 years; range 17-44) for vascular abnormalities. They were explored with whole-body magnetic resonance imaging angiography, coronary multislice computed tomography and echo-tracking-based imaging of the carotid arteries. Brain abnormalities (white matter hyperintensities, lacunar lesions suggestive of ischemic infarcts, atrophy) were found in 95% of patients. Peripheral and brain artery abnormalities were reported in 84% of patients, whereas coronary artery abnormalities were detected in 50%. The most frequent vascular abnormalities were ectasia and aneurysm. The carotid intima-media thickness was markedly decreased, with a substantial increase in circumferential wall stress indicating the occurrence of hypotrophic arterial remodeling in this STAT3-deficient population\(^20\). We also show that in human atherosclerotic lesions, increased levels of STAT3 phosphorylation and IL-17 are associated with a stable plaque phenotype\(^19\). In conclusion, STAT3 signaling plays an important vasculo-protective role both in mice and humans.

**Roles of B lymphocyte subsets**

The development of atherosclerosis is also associated with signs of B lymphocyte activation, particularly manifested by enhanced production of natural IgM type and adaptive IgG type anti-oxidized low-density lipoprotein autoantibodies\(^20\). Recent studies have re-defined the roles of the different B cell subsets in atherosclerosis. Innate B1 cell subset protects against lesion development in an IgM-dependent manner\(^22\), whereas B2 cells promote atherosclerosis, at least in part through activation of adaptive T cell responses. Indeed, we and others reported that depletion of mature B cells using CD20 monoclonal antibody induced a significant reduction of atherosclerosis in various mouse models of atherosclerosis\(^23,24\). B cell depletion diminished T cell-derived IFN-gamma secretion and enhanced production of IL-17; neutralization of the latter abrogated CD20 antibody-mediated atheroprotection. The pro-atherogenic effect of B2 cells is confirmed by the reduction of atherosclerosis in BAFF-R-deficient mice\(^25,26\).

**Conclusion**

Atherosclerosis is a chronic inflammatory disease of the arterial wall responsible for most ischaemic cardiovascular diseases\(^27\). Circulating levels of several cytokines are associated with disease burden, and CRP levels predict the risk of future cardiovascular events. Furthermore, the incidence of cardiovascular disease is increased in patients with chronic systemic inflammatory diseases such as rheumatoid arthritis and systemic lupus erythematosus\(^28,29\). Our results suggest that impairment of Treg cell function and activation of B cell responses may be important pathophysiological links between immune-mediated inflammatory diseases and atherosclerosis progression. This increasing knowledge of the immune mechanisms of atherosclerosis
will have a tremendous impact on our understanding of the disease and is paving the way to the development of novel therapeutic strategies based on immune modulation.

References