Critical Balance of Dendritic Cells is Destined for Plaque Rupture

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It is widely accepted that atherosclerotic lesions contain various immune-competent cells, including macrophages and T cells. In addition to metabolic disorders such as dyslipidemia and diabetes, the immuno-inflammatory pathway plays a crucial role in all stages of atherosclerosis. Recent studies indicate that these inflammatory reactions play a crucial role in acute coronary syndrome (ACS). In particular, the presence of T cells in atherosclerotic lesions suggests that they play an immunomodulatory role during atherogenesis and may make a final push to the onset of ACS.1 Because the local immune response of the activated T cells may be directed against local antigens in the plaque, the mechanisms by which such an immune response is generated is of great interest. Coincidently, a number of studies have demonstrated the presence of dendritic cells (DCs) in the vascular wall, which become activated during atherogenesis.2,3 DCs are antigen-presenting cells with a unique ability to induce primary immune responses. They capture and transfer information to the adaptive immune system.4 Therefore, DCs are not only critical for the induction of primary immune responses, but may also be important for the regulation of T-cell-mediated immune response. Two major subsets of DCs, myeloid DCs (mDCs) and plasmacytoid DCs (pDCs), have been identified in humans. mDCs comprise the “classical” antigen-presenting cell population of the immune system, whereas little information is available for pDCs, a recently identified new subset characterized by a high expression level of IL-33Rα (CD123).4 Although pDCs specialize in the recognition of bacterial and viral components, their potential contribution to inflammatory diseases is not fully understood. pDCs circulate in human peripheral blood as CD11c–MHC class II+ lineage precursors that express high levels of CD123 and L-selectin (CD62L). Vascular endothelium activated with hypoxia and tumor necrosis factor-α significantly supports the adhesion and transmigration of DCs in vitro.5 Evidence suggests that pDCs are recruited to non-lymphoid organs in inflammatory conditions, utilizing the CD62L, β2 and α4 integrins on the surface of pDCs.5 In atherosclerotic lesions, the majority of activated DCs are located within the neovascularization areas and co-localized with T cells.6 Therefore, the role of DCs in atherosclerosis has become a focus of current attention. Figure. Several observations support a view that DCs are involved in antigen capture and antigen processing in the vasculature, as are DCs in other peripheral tissues. The migratory routes of vascular-associated DCs are thus considered similar to those known for other peripheral tissues. After engulfing antigens in the arterial wall, vascular DCs likely migrate via the afferent lymph into regional lymph nodes where they activate T cells. In parallel, immunohistochemical analysis of human atherosclerotic lesions indicates that only some DCs migrate to the lymph nodes whereas others activate T cells directly within the intima. Considering that DCs are most frequently observed in atherosclerotic lesions enriched with T cells, direct communication between DCs and T cells in situ may also play a role with immunological consequences within atherosclerosis.

In this issue of the Journal, Fukunaga et al report that the ratio of circulating mDCs to pDCs may be a novel marker of vulnerable plaque in patients with coronary heart diseases.7 They enrolled 3 groups: patients with ACS, stable angina (SAP) and controls. The numbers of peripheral mDCs and pDCs were calculated by flow cytometry analysis. They found that the proportion of pDCs was significantly lower in the ACS and SAP groups compared with controls, and the proportion of mDCs exhibited a similar pattern of trend, although not statistically significant. Furthermore, the ratio of mDCs to pDCs was significantly different among the 3 groups: highest in ACS, second in SAP and third in controls. Because the total number of lymphocytes was unchanged among the 3 groups, the increase in the mDCs/pDCs ratio was primarily because of the relatively large drop in circulating pDCs. This study confirms the recent report by Yilmaz et al in which they found a similar decrease in DCs in coronary artery diseases,8 and extends our knowledge to emphasizing the superiority of the ratio of the 2 subsets. In other inflammatory diseases, such as rheumatoid arthritis, circulating mDC and pDC levels have been inversely correlated with disease activity, suggesting a similar reduction of peripheral DCs during active inflammation. Therefore, the recruitment of pDCs to the site of active immunological reaction might occur universally as a self-defense mechanism. Although the precise mechanisms of the reduction of pDCs in the systemic circulation remain unclear, the authors propose a potential contribution of pDC accumulation in the vulnerable plaque area and a reduction of pDC precu-
sors in the bone marrow. Recent large clinical trials repeatedly suggest the importance of inflammatory markers such as C-reactive protein and cytokines. This study clearly adds another potential marker for the prevention and treatment of ACS. In their receiver operating characteristic analysis, a mDCs/pDCs ratio > 4 is a strong indicator for ACS, with a sensitivity of 85.0% and a specificity of 83.4%.

There are scientific questions associated with this interesting finding. First, the molecular and cellular mechanisms by which circulating pDCs are recruited to the site of atherosclerotic plaque and the causative contribution to plaque rupture are not known. The elucidation of this pathway may provide a novel approach to controlling plaque stability via immune regulation. Second, it is not known what type of antigen (bacterial and/or viral component or modified lipoproteins) triggers pDCs to activate T cells. Moreover, it is not clearly understood whether pDCs activate T cells in the vascular lymph node, as is considered in other immunological disorders, or whether these reactions take place in the neointimal area of the atherosclerotic plaque. Third, because the cytokine repertoire produced from DCs changes during their maturation and activation, analysis of the serum cytokine profile may discover a novel combination reflecting the ratio of mDCs/pDCs, which could be a better marker for rapid identification of ACS. Further clinical as well as basic research regarding the pathophysiology of DCs in the vasculature will throw new light on the understanding and treatment of coronary heart disease.

References