Secretory phospholipase A2 type IIA: a regulator of immune function in atherosclerosis?

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This editorial refers to ‘Secreted phospholipase A2 type IIA as a mediator connecting innate and adaptive immunity: new role in atherosclerosis’, by E. Ibeas et al., pp. 54–63, this issue.

Soluble phospholipase A2 type IIA (sPLA2-IIA) is an acute-phase reactant that is markedly increased in inflammatory disorders including cardiovascular disease. Inflammatory cytokines such as interleukins IL-6 and IL-1β, interferon (IFN)-γ, and tumour necrosis factor (TNF)-α increase its expression in vascular smooth muscle cells and hepatocytes, two cell types largely responsible for its elevations in plasma. sPLA2-IIA is also highly expressed in atherosclerotic lesions and associated with smooth muscle cells, macrophages, and glycoaminoglycans, where it exerts proatherogenic effects in part by modifying low- and high-density lipoproteins (LDL and HDL). It hydrolyses the sn-2 ester bond in the glycerylacyl phospholipids present in both LDL and HDL and cell membranes, releasing fatty acids and lysophospholipids. sPLA2-IIA can also exert effects that are independent of its hydrolytic functions. It elevates IL-6 production by macrophages and contributes to elevations in cyclooxygenase-2 expression by mast cells; two cell types with significant roles in atherosclerosis. Thus, sPLA2-IIA is thought to promote atherosclerosis by hydrolysing lipoproteins and regulating macrophage and mast cell responses via non-hydrolytic mechanisms.

In this issue of Cardiovascular Research, Ibeas et al. provide additional new and somewhat unexpected insights as to how sPLA2-IIA might promote atherosclerosis by stimulating the differentiation of monocytes to dendritic cells. Dendritic cells accumulate in lesions and are professional antigen-presenting cells required for the initiation of adaptive immune responses. The factors responsible for their accumulation within atherosclerotic lesions are largely unknown, although oxidized LDL has been implicated. The study of Ibeas et al. is important as it provides a novel mechanism that may explain how dendritic cells accumulate within developing atherosclerotic lesions. They demonstrate using cultured THP-1 monocytes and normal human blood-derived monocytes that sPLA2-IIA stimulates their differentiation into mature dendritic cells. Exposure of THP-1 monocytes to sPLA2-IIA resulted in a time- and concentration-dependent downregulation in CD14, a surface marker for monocytes. This downregulation was accompanied by morphological changes in THP-1 cells, and the cells exhibit numerous projections and laterally positioned nuclei, well-known morphological characteristics of monocyte-derived dendritic cells. Also, DC-SIGN and cell surface markers CD54, CD62L, and CD61 as well as the co-stimulatory molecules CD40 and CD83 were upregulated. DC-SIGN is highly characteristic of dendritic cells and implicated in the capture and uptake of viral particles, bacteria, and possibly also antigens within atherosclerotic lesions. These cells also exhibited some endocytotic activity, migrated more rapidly, and bound more avidly to plastic surfaces, consistent with dendritic cell maturation.

A number of dendritic cell subtypes have been identified in humans. Findings of Ibeas et al. of low expression of CD11b and CD11c in the sPLA2-IIA-exposed THP-1 cells and the absence of CD1a are suggestive that sPLA2-IIA may be stimulating monocytes towards a plasmacytoid dendritic subtype. Both CD11+ myeloid and CD11- plasmacytoid dendritic cells have been identified in human atherosclerotic lesions. Plasmacytoid dendritic cells are relatively poor T-cell stimulators, less efficient at endocytosing antigens, and secrete IFN-α. They are capable of activating diverse cell types including natural killer cells, macrophages, and CD11c+ dendritic cells. Although it is not known whether plasmacytoid dendritic cells respond to antigens such as oxidized LDL, they can respond to nucleotide fragments such as those released by necrotic cells within developing atherosclerosis. Plaque plasmacytoid dendritic cells respond to synthetic CpG-containing oligodeoxynucleotides, which bind to toll-like receptor 9, enhancing IFN-α transcription and secretion. Secretion of IFN-α correlates with plaque instability. IFN-α can function as an inflammatory amplifier, sensitizing antigen-presenting cells towards pathogen-derived TLR4 ligands and augmenting the production of TNF-α, IL-12, and matrix metalloproteinase-12, factors that reduce lesion stability. IFN-α released by
plasmacytoid dendritic cells in the vicinity of CD4+ T-cells within atheromas can also increase the surface expression of the apoptosis mediator TRAIL as well as increasing its transcription and abundance in vesicle stores of the lymphocytes. CD4 T-cells isolated from subjects with acute coronary syndromes effectively kill coronary smooth muscle cells in a TRAIL-dependent manner. Extension of the studies of Ibeas et al. to define the phenotype of the dendritic cells would provide a greater understanding of the role of sPLA2-IIA in regulating the innate and adaptive immune systems in atherosclerosis and its implications for plaque instability.

Considering potential mechanisms by which sPLA2-IIA stimulates dendritic cell maturation could also provide additional insights as to its importance compared with other factors such as oxidized LDL in stimulating dendritic cell maturation within atherosclerotic lesions. This effect of sPLA2-IIA is not unique to this phospholipase. Bee venom-derived phospholipase A2 has also been shown to stimulate monocytes into functionally mature dendritic cells. The ability of this phospholipase to stimulate dendritic cell maturation appears to be dependent on its hydrolytic activity and related to the generation of membrane-derived lysophosphatidicholine, which can also promote maturation of dendritic cells. In the future, it will be of interest to determine whether the ability of sPLA2-IIA to stimulate dendritic cell maturation is also dependent on its hydrolytic activity and how the presence of other sPLA2-IIA substrates, such as lipoproteins in atherosclerotic lesions, affects its ability to stimulate the differentiation of monocytes to dendritic cells.

There is now a growing body of evidence which indicates that sPLA2-IIA is important in most phases of atherosclerosis development. The study of Ibeas et al. demonstrating that sPLA2-IIA stimulates the differentiation of monocytes to dendritic cells may be particularly important as it provides a link between the innate and adaptive immune systems in atherosclerosis and should stimulate new investigations as to how the immune stimulatory effects of sPLA2-IIA might promote the progression of stable atheromas towards unstable rupture-prone lesions.

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References