

Atherosclerosis: cell biology and lipoproteins Alan Daugherty

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Abbreviation

SAA serum amyloid A

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The term inflammation commonly implies a localized response elicited by tissue injury that leads to the infiltration of leukocytes. The type of infiltrating leukocyte displays some degree of selectivity in different forms of inflammation. For example, the most abundant inflammatory cells in atherosclerotic lesions are macrophages and T lymphocytes. There are also smaller numbers of plasma cells, mast cells, and natural killer cells. Unlike many other inflammatory responses, neutrophils are not considered to participate in atherogenesis. While the presence of inflammatory cell types is a recurrent observation in atherosclerosis research, there are many facets of these cells that have not been unequivocally defined. These include the mechanisms by which inflammatory cells are recruited to evolving lesions, the specific function of these cells within lesions, and the local and systemic consequences of the vascular infiltration.

One of the consequences of the influx of inflammatory cells is an increase in the tissue content of myeloperoxidase. Although myeloperoxidase is most commonly thought of as a neutrophil protein, it is present in copious amounts in monocytes. In atherosclerotic lesions, it was found to co-localize with antigens for macrophages and neutrophils [1]. The function of myeloperoxidase in atherosclerosis is not clearly defined. In fact, it remains an enigma that mice deficient in myeloperoxidase had a small increase in the extent of atherosclerosis, rather than the hypothesized decrease [2]. However, studies in humans have demonstrated positive correlations of plasma myeloperoxidase concentrations and products with adverse outcomes of atherosclerotic disease [3]. It is generally appreciated that myeloperoxidase catalyzes several well characterized oxidant reactions that include several lipid and protein modifications. The protein modifications that have received the most attention include the ability to

facilitate nitration and halogenation of proteins. A recent study [4••] has demonstrated that apoAI is remarkably susceptible to modification by myeloperoxidase in a manner that could impact arterial cholesterol fluxes. Western blotting of plasma samples for nitration vividly demonstrated the predominance of immunoreactivity in a 29 kDa protein that was identified as apoAI by peptide sequencing. Interestingly, this product was apparent both in individuals that were healthy and those that had overt cardiovascular disease. Similar selectivity of modification was also noted in apoAI isolated from human atherosclerotic lesions. Surprisingly, it was found both in plasma and lesional apoAI that myeloperoxidase was directly associated. Mass spectrometric analysis demonstrated that myeloperoxidase associated via an interaction with a portion of helix 8 of apoAI. The functional significance of this modification was demonstrated by showing that it decreased ATP-binding cassette transporter A1 (ABCA1)-dependent cholesterol efflux from macrophages. The effect of myeloperoxidase modifications to impact ABCA1-mediated cholesterol fluxes has been a consistent finding in different laboratories [5,6].

Acute phase proteins are also receiving considerable attention as indicators of inflammation of the vessel wall. The most extensively studied marker of inflammation is C reactive protein [7]. Serum amyloid A (SAA) also displays similar characteristics in terms of rapidity and magnitude of acute phase responses and has been correlated to the severity of atherosclerotic disease [8]. A common question on these acute phase proteins is whether they are only markers or also actively involved in the disease process. Lewis and colleagues [9•] have recently studied the role of SAA in LDL receptor deficient mice. Several findings led them to conclude that SAA was an active participant in lesion development. A major point is that graded increases in cholesterol content of the diet lead to increases in extent of atherosclerosis that correlated with plasma concentrations of SAA, but not cholesterol. Furthermore, SAA influenced the HDL binding of proteoglycans. Finally, abundant SAA was present in atherosclerotic lesions. The associative steps are important steps in the process of defining a participatory role of SAA in atherosclerosis. These results provide further justification for development of genetically engineered mice in which specific forms of SAA are either overexpressed or deleted.

A common consequence of inflammatory reactions is the development of antibodies against determinants of the

damaged tissue. There has been interest in the role of antibodies against specific epitopes of oxidized forms of LDL [10]. One of the most intensely studied modifications has been maleylation. The early associative studies led to the hypothesis that antibodies against malondialdehyde-modified LDL were atherogenic. However, subsequent studies in which malondialdehyde-modified LDL autoantibody titers were increased provided the unanticipated result that lesion size was greatly decreased in a number of different animal models of the disease [10]. One of the further quandaries of these studies is that immunization with malondialdehyde-modified LDL led to increased titers of a natural antibody, termed T15. This antibody has a demonstrated specificity against oxidized forms of 1-palmitoyl-2-oxovaleroyl-sn-glycero-3-phosphorylcholine (POVPC) that is not present in the immunogen. Binder *et al.* [11^{••}] determined that the mechanism of this is a sequence in which malondialdehyde-modified LDL injection stimulates a Th2-orientated lymphocyte response with elaboration of IL-5. This secretion of IL-5 subsequently promotes the synthesis of T15 antibody that decreases the size of lesions. This fascinating scenario now provides further impetus to defining the specific mechanism for the protective effect of this humoral immunity.

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Recommended reading

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A demonstration that myeloperoxidase has a specific role in nitrating ApoA1 leading to a reduction in ABCA1 cholesterol efflux from macrophages.