editorial

Thematic Review Series: The Immune System and Atherogenesis

Bridging the innate and adaptive immune systems

Godfrey S. Getz[1]

Department of Pathology and Department of Biochemistry and Molecular Biology, University of Chicago, Chicago, IL 60637

So far in this series of thematic reviews, we have dealt with aspects of the innate immune system in relation to atherosclerosis. Forthcoming reviews will focus more on aspects of the adaptive immune system or in some cases on the way the two systems, innate and adaptive immunity, may "talk" to one another.

In innate immunity, signaling is through germ-line receptors of limited repertoires that respond by pattern recognition of exogenous agents and antigens. The promptness of the response is a consequence of the availability of innate or natural immune cells that express their responding receptors before exposure to the stimulants. These receptors include the scavenger receptors discussed in this series by Greaves and Gordon (1) and the Toll-like receptors (TLRs) reviewed by Tobias and Curtiss (2). These receptors are primarily present on monocytes/macrophages and dendritic cells, which may be activated as antigen-presenting cells. They may also be present on natural killer (NK) cells, endothelial cells, and cells of the adaptive immune system. On the other hand, the adaptive immune system is composed of cells bearing rearranged cell surface receptors, generating an almost unlimited diversity of recognition response elements.

Bridging these two branches of the immune response are a number of cell types that have functional characteristics of both systems. Among these cells are the B1 cells, the γδ T-cells, and perhaps natural killer T (NKT) cells. These cells express immunoglobulins or T-cell receptors that have much more limited diversity than traditional B- and T-cells of the adaptive immune system. The majority of B1 cells produce natural IgM antibodies that recognize altered self molecules such as oxidized LDL. These cells are present at birth, having been selected during ontogeny, perhaps in response to apoptotic cells. This characteristic allows them to respond promptly like an innate immune cell, for example to a mimic molecule such as the phosphatidylcholine of *Streptococcus pneumoniae* (3). B1 cells and the natural antibodies that they secrete will be discussed in detail in a forthcoming review by Binder and colleagues. γδ T-cells and NKT cells also recognize antigens of limited diversity. The former does so in some cases without the necessary involvement of major histocompatibility complex (MHC) molecules, whereas the invariant T cell receptor on NKT cells recognizes lipid antigens in the context of CD1, a MHC class I-related protein. Recent work has implicated these cells in atherosclerosis, which will be discussed in more detail in a forthcoming review by VanderLaan and Reardon.

The immune system as a whole represents a very complex interacting network that includes within it proinflammatory and anti-inflammatory mediators. The communication between the innate and adaptive immune systems involves cell-cell interactions in relation to antigen presentation or soluble molecules such as cytokines or chemokines. These are not necessarily mutually exclusive interactions. The response to presented antigens is often a major basis for the stimulation of adaptive immune cells to produce cytokines. These interactions can result in either target cell activation or suppression. Such networks of communication are likely at play between innate and adaptive immune systems or between components within each of these systems themselves. For example, NK cells can lyse immature dendritic cells as well as positively regulate dendritic cell maturation (4, 5).

Furthermore, cross-talk between the innate and adaptive systems may be bidirectional. The major cytokines implicated in atherosclerosis are produced by cells of both the adaptive and innate immune systems, acting upon one another in both a paracrine and an autocrine manner. For instance, IFNγ produced by the effector T-helper 1 (Th1) cell activates phagocytes such as macrophages, and interleukin-4 (IL-4) and IL-5 produced by Th2 cells may stimulate some macrophage and dendritic cell subsets, as discussed below. IL-5 in particular mediates a link between adaptive and natural immunity (6), and this will be discussed in detail in a forthcoming review by Binder et al.

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[1] To whom correspondence should be addressed.
e-mail: getz@bsd.uchicago.edu

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On the other hand, IL-12, IL-18, and type I interferons promote the differentiation of Th1 cells (7), and IL-12 can stimulate the production of IFNγ by NK cells (8). IL-10, which can be produced by T-cells, dendritic cells, and macrophages, inhibits IL-12 production and Th1-mediated inflammation. The effects of cytokines on various target cells will be addressed in more detail in two forthcoming reviews in this series. Elaine Raines will discuss the smooth muscle and endothelial cell targets, and Alan Daugherty will focus on monocytes and other leukocytes.

Much of the communication between the innate immune system and its adaptive immune partner relies on the presentation of an antigen. Yet, the adaptive immune system is not required for the development of pronounced atherosclerosis (9). This places heavy emphasis on the role of the innate system in atherosclerosis.

The innate immune system is generally thought to yield prompt, blunt responses to stimuli. However, the innate immune response may not be as blunt as once supposed, and within each major class of innate cells there is considerable specificity and heterogeneity. Heterogeneity among innate immune cells is worthy of further consideration.

Because monocyte recruitment is central to the pathogenesis of this disease, the innate immune system is at the core of atherogenesis. Not widely recognized is the difference between the resident macrophage, of which the Kupffer cell is an example, and the inflammatory macrophage, which is presumably the macrophage subtype involved in atherosclerosis (10). Gordon (10) has defined five sets of activation/deactivation signals that influence macrophage phenotype. Activation of macrophages in response to microbial stimuli, mediated by unique microbial plasma membrane molecules through TLRs or scavenger receptors, results in the production of type I interferons and the upregulation of costimulatory molecules. Although microbial infection may modulate atherogenesis, it is most likely that endogenous altered self ligands such as oxidized LDL play a more significant role in atherosclerosis. As outlined by Tobias and Curtiss (2) in their review in this series, at least two TLRs have been implicated in atherosclerosis, TLR4 and TLR2. Engagement of the TLR facilitates the antigen-presenting capability of the innately activated macrophages. Of interest is the recent observation that TLR2 is regulated by hemodynamic forces (11). A second class of activating molecules influencing the macrophage response are complement and antibodies (via Fc receptors), which also result in the secretion of a variety of cytokine mediators of inflammation. IFNγ is a major activator of the third class of macrophages that is especially relevant to atherosclerosis. This activation results in MHC class II upregulation and the secretion of IL-6, tumor necrosis factor-α (TNF-α), and IL-1, which mediate the acute phase response. MHC class II upregulation may also occur when IL-4 or IL-13 activates macrophages. In this case, this is accompanied by an increased capacity for tissue repair, including collagen production. Finally, macrophages that express large numbers of scavenger receptors and become cholesteryl ester-loaded foam cells, and hence are highly involved in atherosclerosis, may no longer function as effective antigen-presenting cells. However, these cells exhibit increased secretion of anti-inflammatory cytokines, such as transforming growth factor-β (TGF-β) and IL-10, which in turn will enhance this macrophage phenotype by autocrine stimulation.

Each of these macrophage subsets can also be distinguished on the basis of its chemokine secretory profile (12). Whether these are separate macrophage lineages or represent a continuum of plastic cell lines is not clear. This differential activation and polarization of the macrophage would be of interest not only with respect to early lesion development but also with respect to the evolution of the macrophage phenotype as the lesion progresses. For example, it has been suggested that the Th2 cytokines IL-4 and IL-13 and chemokines are more abundant in late atherosclerotic lesions (13). Such a cytokine profile may induce a macrophage that improves the stability of the plaque, although this interaction remains to be clearly demonstrated experimentally. Similarly, the highly loaded macrophage foam cell may also play a role in immunosuppression in the lesion by its secretion of the anti-inflammatory cytokines IL-10 and TGF-β. Given the important role of the macrophage in lesion formation, the possibility that its phenotype may evolve during lesion progression and thus have different roles at different stages of the lesion is an important area of future atherosclerosis research.

In recent years, a new understanding has developed of the relationship between lipid metabolism in the artery wall, especially in macrophages, and inflammation. Oxidized LDL is regarded as a major neoantigen in atherogenesis and is probably the major source of the lipids that are stored in the macrophage foam cells. Although the bulk of the lipid stored in foam cells is cholesteryl ester, it is likely that increased concentrations of lipid signaling molecules, such as unsaturated fatty acid and oxysterol, are also present. These serve as ligands for the peroxisome proliferator-activated receptor (PPAR) and liver X receptor (LXR) families of nuclear hormone receptors, respectively (14, 15). In addition to their role in lipid metabolism, PPARα and PPARγ are also anti-inflammatory and antiatherogenic (16). The anti-inflammatory action of PPARβ does not appear to be sufficient for the inhibition of atherogenesis (16). The fatty acid binding protein aP2, found in lesion macrophages, appears to influence atherogenesis by competing for the fatty acid ligand of PPARγ, thus influencing such inflammatory gene activity as cyclooxygenase 2 (COX2) and inducible nitric oxide synthase (iNOS) (17). Cross-talk between the PPAR family and the LXR family may also be important. PPAR increases LXR activity, although this is not obligatory for all of the antiatherogenic influences of PPARγ (16). Several studies have suggested the reciprocal regulation of the lipid efflux pathway in macrophages and the inflammatory phenotype of these cells. LXR agonists increase the expression of apolipoprotein E (apoE), apoC-II, and ABCA1 in macrophages, whereas they reduce the expression of iNOS, COX2, IL-6, and IL-1 (18) that have been induced by lipopolysaccharide or bacterial infection. On the other hand, the stimulation of TLR4 or TLR3 results in the downregulation of

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the LXR target genes apoE and ABCA1 (19). Furthermore, LXR-dependent genes have been implicated in macrophage cell survival (20). This cross-talk does not require the participation of the adaptive immune system.

Similar to macrophages, there are several subclasses of dendritic cells that are differentiated by their TLR profiles. The major subsets are the myeloid or classical dendritic cells and the plasmacytoid dendritic cells. CD8+ dendritic cells and CD11b+ dendritic cells are additional subtypes. In responding to various microorganisms, dendritic cells produce different cytokine profiles: IL-12, TNF-α, and IL-6 for the myeloid cell; type I interferons for the plasmacytoid cell; IL-12 from the CD8+ dendritic cell; and IL-10 by the CD11b+ dendritic cell (21). Classical dendritic cells are highly efficient antigen-presenting cells. The plasmacytoid dendritic cells are much less efficient at presenting antigens (22), and the type I interferon they produce induces NK cells to produce IFNγ and promote B-cell differentiation to plasma cells, resulting in the production of immunoglobulins of the IgG class. The origin of these dendritic cell subsets is not clear (23), although each may have the capacity to program Th1 or Th2 development depending upon its TLR profile and the antigen dose to which it is exposed (24). Like the subsets of macrophages, the dendritic cell subsets produce different profiles of chemokines. The dendritic cell has received relatively little attention in atherosclerosis research, although this is bound to change soon (25, 26; see VanderLaan and Reardon in this series). Recent studies also are notable for the interaction between lipid mediators and the behavior of dendritic cells in the atherosclerotic plaque (25, 26).

The third major cell of the innate immune system that should be discussed is the NK cell. It effect on atherosclerosis is modest (see VanderLaan and Reardon in this series). The NK cells express some diversity in receptors, and their biological activity is probably the result of the repertoire of stimulatory and inhibitory cell surface receptors (4). Among human NK cells, two distinct phenotypes can be distinguished on the basis of their cytotoxicity and cytokine production. The cells that express high levels of CD56 (bright) and low levels of CD16 (dim) tend to produce high concentrations of cytokines, especially IFNγ, but are poorly cytotoxic. Those NK cells that are CD56 dim and CD16 bright are mainly cytotoxic. The first subset represents 10% of NK cells, and the latter represents 90% of the NK cell population (27). The reported modest influence of NK cells on atherosclerosis may be related to the fact that the cytokine producers have the major effect on atherosclerosis but are only a small proportion of the total NK cell population (28).

In conclusion, this review has drawn attention to a limited aspect of the complexity of the immune network. There is much more heterogeneity among cells of both the innate and adaptive immune systems than was previously supposed. There is also a complexity of communications between the elements of this network. This indicates that many opportunities remain for research to improve our understanding of these systems as they operate in the context of atherosclerosis. A more system-based approach may prove rewarding. The improved understanding will present many possibilities for therapeutic intervention in the process of atherosclerosis.

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