Mast Cells as Mediators and Modulators of Atherogenesis

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The central role of inflammation in atherogenesis has gained broad acceptance and has revolutionized our understanding of this common disease. This recognition has heightened interest in identifying the specific mediators and mechanisms that contribute to the interplay between risk factors (traditional and emerging), inflammation, and the altered biology of the arterial wall that regulates plaque development and complication. In particular, leukocytes have come to occupy center stage as the major cellular effectors of inflammation. When these inflammatory cells join endothelial and smooth-muscle cells in the artery wall, they spur much of the biology that drives atherogenesis and plaque complication.

The list of leukocyte subtypes involved in arterial inflammation has entered a flourishing phase of refinement. Our understanding of leukocyte involvement in atherogenesis has gone through several strata of discovery and probing. During the initial descriptive phase, the use of rigorous molecular markers buttressed venerable morphological observations and verified the presence of various leukocyte classes within lesions. Later, a phase of experimental validation established the causal relationship between leukocyte accumulation in lesions and the aspects of atherogenesis. Next, continuing mechanistic exploration has probed the precise molecular pathways by which a given leukocyte population can promote or otherwise modify disease. Ultimately, the human relevance of in vitro and animal experiments requires observations in human tissues and in patients.

First Monocyte/Macrophage.

The saga of the macrophage in atherosclerosis followed this pattern. Initial morphological observations supported an early role of monocyte recruitment in the formation of experimental atherosclerotic lesions in rabbits—observations that extend back to the middle of the last century. With the advent of rigorously characterized monoclonal antibodies, studies in the 1980s solidly documented the presence of mononuclear phagocytes in human and experimental atherosclerotic plaques. Subsequent studies in the closing decade of the last century highlighted specific molecular pathways that mediate the recruitment and activation of mononuclear phagocytes in the context of atherosclerosis. Notably, adhesion molecules such as vascular cell adhesion molecule-1, chemoattractants such as monocyte chemoattractant protein-1, and macrophage activators, including macrophage colony–stimulating factor and their cognate receptors, among others, underwent rigorous validation as participants in the pathogenesis of experimental atherosclerosis. Parallel observations in humans validated the relevance of these animal studies to the human disease.

The picture of the participation of monocytes in atherosclerosis continues to grow in complexity. Our initial concepts of monocyte recruitment to nascent atheroma did not take into account the considerable heterogeneity of this cell population. More recent refinements have called attention to the importance of monocyte subsets in hypercholesterolemic mice and selective recruitment of “inflammatory” populations of monocytes to the early lesion.

Then Lymphocytes

T lymphocytes joined the ranks of leukocytes involved in atherogenesis at a later phase, quite possibly because of their lower abundance compared with the mononuclear phagocytic cells in lesions. Although fewer in number, T lymphocytes seem to exert key regulatory influences during atherogenesis. Indeed, signals from the T lymphocyte may orchestrate the behavior of mononuclear phagocytes and intrinsic vascular wall cells during all phases of this disease. Although interest in monocyte/macrophage heterogeneity in atherogenesis has only recently come to the fore, the diverse functions of various subclasses of T lymphocytes have garnered considerable attention through the years. Whereas some T cell classes and products seem to promote lesion formation, others may mute aspects of atherogenesis. Ultimately, the adaptive immune response spearheaded by the T lymphocyte may act as a “double-edged sword” during disease evolution. Such a tug of war between opposing lymphocyte subsets may explain some of the chronicity and temporal heterogeneity in atheroma formation and complication.

And Now Mast Cells

Now the spotlight turns to mast cells, another potentially important minority constituency of lesional leukocytes. It is no small irony that Paris Constantinides, who championed the concept of plaque rupture long before it became popular, called attention to the potential roles of mast cells in atherosclerosis in a pioneering article published in Science in 1953. The modern era of mast cell biology included important discoveries from a number of laboratories that called attention to the presence and potential functions of mast cells in atherosclerotic plaques. Kovanen and colleagues not only have identified mast cells in plaques using contemporary techniques; they also postulate roles for these cells in lipid
Putative functions of mast cells during atherogenesis. Evidence has accumulated that mast cells, once relegated to the adventitia, also inhabit the atherosclerotic intima, as shown here. Mast cell precursors recruited by eotaxin interacting with chemokine receptor 3 (CCR3) enter the arterial intima and can degranulate, releasing their granular contents, including autacoids, cytokines, proteinases, and heparin, among many other products. These mediators, in turn, can activate arterial endothelial and smooth-muscle cells (SMC), promote foam-cell formation by macrophages, and sensitize macrophages and SMCs to apoptosis. The proteinases can contribute to extracellular matrix remodeling and can process proteins (eg, matrix metalloproteinases [MMPs]) and peptides (eg, angiotensin [Ang]) to active forms. Cytokines and autacoids such as histamine can promote the permeability of the endothelium, including that of the plaque’s microvasculature. Extravasation of erythrocytes can lead to heme-derived iron accumulation and can catalyze Fenton chemistry, giving rise to reactive oxygen species (ROS). TNF-α indicates tumor necrosis factor-α.

metabolism within the atheroma. Moreover, they propose important roles for mast cell–derived cytokines and proteases in aspects of atherogenesis.19,20 Excellent descriptions of mast cell distribution and evidence for their activation in human atherosclerotic plaques emerged from Manchester.21 In particular, mast cells seem to colocalize to areas of fissure and hemorrhage in human atherosclerotic plaques.

Mast cells have numerous functions that might mediate or modulate atherogenesis (Figure).22 These cells can elaborate autacoids, such as histamine, that may augment vascular permeability and alter vascular tone. Mast cells can also produce cytokines—notably, tumor necrosis factor-α. Their particular proteinases, including the serine-dependent enzymes chymase and tryptase, can activate matrix metalloproteinases implicated in plaque remodeling and rupture. Indeed, mast cell proteinases seem to activate matrix metalloproteinases in situ in human atherosclerotic plaques.23 Mast cells can also elaborate numerous lipid mediators, including prostanoids and leukotrienes. These cells also produce antimicrobial peptides implicated in host defenses.24 Our laboratory postulated a role for the chemokine eotaxin and its receptor, chemokine receptor 3, in recruitment of mast cells to human atherosclerotic plaques some years ago.25 In addition to metalloproteinases, mast cell chymase can activate angiotensin I and thus function as an angiotensin-converting enzyme important in regulating vascular tone, oxidative stress, and inflammatory responses of vascular wall cells.26 When they degranulate, mast cells can release heparin that can bind growth-regulatory proteins, activate antithrombin III, and influence lipolysis through well-explored pathways. Thus, mast cells exhibit a panoply of functions that might modulate atherogenesis in vivo.

Mast cell biology in atherosclerosis has now gone beyond the descriptive, observational phase. For example, in this issue of Circulation, Bot and colleagues27 have performed pharmacological experiments that implicate mast cells in intraplaque hemorrhage, macrophage apoptosis, vascular permeability, and recruitment of further leukocytes to mouse atheromata. These investigators used a particular preparation that provides an adventitial stimulus to plaque complication and adventitial delivery of pharmacological agents used to probe the local biology of mast cells in vivo. Although intriguing, the use of this targeted periadventitial injury and delivery of experimental reagents may not reflect the role of vascular mast cells in unmanipulated atherosclerotic plaques.

Mast cells have undergone rigorous localization in human atherosclerotic plaques, possess a palette of functions of potential relevance to atherosclerosis, and have been experimentally implicated by pharmacological manipulation in disease progres-
sion and modulation; now, we must strive to gain more precise information on the molecular mechanisms of mast cell participation in atherosclerosis. Which of the myriad of mediators released by these pluripotent cells actually account for the apparent role of these cells in lesion formation and evolution? Harnessing the power of genetic modulation of mice can help elucidate the effects of specific mediators derived from mast cells in atherogenesis. For example, adoptive transfer of mast cell preparations from mice deficient in various cytokines, to reconstitute animals genetically lacking in mast cells, can furnish insight into the roles of particular cytokines in specific aspects of atherogenesis. Issues related to the redundancy of inflammatory pathways require further investigation. If mast cells are numerically a minority of the leukocytic infiltrate in atherosclerotic plaques, then why would they influence atherogenesis decisively? Many cells in the plaque can produce tumor necrosis factor-α. Why should that, derived from the mast cell, be particularly important?

Finally, the experimental usefulness and tractability of the mouse should not lead us to glib extrapolation to human disease. In particular, in regard to mast cells, rodents seem to have a more complex panel of mast cell functions and subtypes—notably, in regard to proteases. Whereas human mast cells express only 1 form of tryptase and chymase, mouse mast cells have at least 2 different tryptases (mMCP-6 and -7) and 6 chymases (mMCP-1, -2, -4, -5, -8, and -9). The more complex nature of the effectors in mouse mast cells may reflect a particular role for these cells in host defenses in rodents. Yet, the increasing knowledge of the inflammatory pathways that operate during atherosclerosis not only improves our fundamental understanding of pathogenesis; it also provides new potential therapeutic targets. The ability of the mast cell stabilizer cromolyn to modify mouse atherosclerosis, shown by Bot et al27 in this issue of Circulation, provides an enticing example. A wholesale inhibition of inflammatory responses, especially of long duration, might wreak havoc with host defenses. As we dissect the pathological pathways of atherogenesis in their full complexity, we may identify opportunities for more targeted intervention that could permit mitigation of atherogenesis without impairment of overall host defenses. In this way, frosting out the palette of the cellular participants and molecular mediators of inflammation during atherogenesis may prove to be of practical benefit in the future.

Disclosures

None.

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