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.1 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 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.13,14

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.15 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.16 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 can 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,17 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 colleagues18 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 proteases 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.
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 cromalyn to modify mouse atherosclerosis, shown by Bot et al 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 pathogenic 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, fleshing 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.

References
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