Emerging Roles of Neural Guidance Molecules in Atherosclerosis
Sorting Out the Complexity

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Neural guidance cues are attracting attention in atherosclerosis. In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Wanschel et al1 add yet another neural guidance molecule, Semaphorin 3E, to the growing list of neural guidance cues that may contribute to atherosclerosis. Indeed, this team of scientists, led by Kathryn Moore at New York University, has in the last year implicated 3 other neural guidance cues in atherosclerosis, including netrin-1,2,3 semaphorin 3A,4 and ephrin B5 in the regulation of inflammatory atherosclerosis.

See accompanying article on page 886

In the first of a series of papers on these molecules, this group showed that netrin-1-deficient bone marrow transplanted into LDLR−/− mice led to markedly reduced atherosclerotic plaques.2 Using a method to track monocyte entry and persistence in a quantitative manner,4,5 the authors argued that netrin-1 was essential for retaining monocyte-derived foamy macrophages in plaques. In the absence of netrin-1, monocytes could enter lesions efficiently but did not stay.2 Although the key experiment was based on limited observation, a single trial with 3 to 4 mice per group, further evidence for the model includes data that netrin-1 inhibited chemotaxis of a macrophage cell line to CCL19. CCL19 is a ligand for the chemokine receptor CCR7 that seems to be required for regression of atherosclerosis in some models,6,7 but not others.5 In the present work, the authors extend the concept laid out in their earlier work on netrin-1 by showing that the role of semaphorin 3E in atherosclerotic plaque is not similar to that of netrin-1, as the authors assume.

Future studies are also needed to better understand the link between the guidance cues and CCR7. Both the work on netrin-1 and the new semaphorin 3E study proposed that CCR7 was a key receptor that was triggered to promote retention,1,2 through rac-1 activation,1,8 and both studies used in vitro experiments to demonstrate macrophage chemotaxis to CCL19. This is puzzling because macrophages do not express CCR7 mRNA,9,10 even those from the inflamed peritoneum as apparently used herein.10 An explanation might lie in the fact that the authors did not purify macrophages from the peritoneum, but seem to have used the entire lavage. Perhaps, the authors were inadvertently assessing chemotaxis of lymphocytes or other cell types present in the lavage. B and T lymphocytes both abundantly express CCR7.

Will blocking netrin-1 and semaphorin 3E be the next therapeutic for atherosclerosis? In particular, does lifting the blockade on egress that these molecules are proposed to provide promote plaque regression? It does not seem to be that simple. The original study by van Gils et al2 indicated that loss of netrin-1 in the hematopoietic compartment was atheroprotective, as proposed here for semaphorin 3E. However, very recently, this same group also found that loss of netrin-1 on endothelium lifted signals that repelled monocytes and thereby promoted monocyte transendothelial migration,3 an outcome that would promote atherosclerosis. Semaphorin 3A acted similarly. Given these complex and opposing roles of netrin-1 expressed by different cells (Figure), netrin-1 is unlikely a viable therapeutic target for atherosclerosis. On the contrary, the story might be different for semaphorin 3E. If it plays no role at promoting monocyte recruitment at the level of the endothelium, it remains possible that blocking semaphorin 3E may cause macrophages to scurry away from plaques. However, our own ongoing work has left us skeptical about the importance of migratory egress as a means to clear macrophages from atherosclerotic plaque5 or even sites of acute inflammation. Nonetheless,
biology is full of surprises. Hence, we will stay tuned to find out what role semaphorin 3E plays in plaque progression and regression.

Disclosures

None.

References


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