Sialyltransferase Activity and Atherosclerosis

Andrew P. Sage, Ziad Mallat

Leukocyte accumulation within the vascular wall is a major feature of atherosclerotic disease and plays crucial roles in the inception, progression, and complications of atherosclerosis. Several coordinated steps converge to promote subendothelial and perivascular accumulation of leukocytes. For example, hyperlipidemia triggers both medullary and extramedullary (spleen) hematopoiesis and induces leukocyte mobilization from these sites to the circulating blood. Concomitantly, hyperlipidemia induces an inflammatory response in the vascular wall (endothelial and smooth muscle cells) to promote recruitment of the mobilized circulating leukocytes. These events are controlled by the induction of selective chemoattractants and adhesion molecules, which interact with specific receptors and ligands expressed on leukocytes to tightly coordinate leukocyte mobilization and the sequential steps of leukocyte rolling, adhesion, and transmigration across the inflamed endothelium (reviewed in references 5 and 6). More particularly, extensive experimental work based on selective gene-targeting studies revealed specific roles for chemokine receptors (Ccr2, Ccr5, Cxcr2, and Cx3cr1), selectins (E- and P-selectins), and adhesion molecules (vascular cell adhesion molecule [Vcam-1]) in promoting intravascular leukocyte accumulation and atherosclerotic lesion development, whereas an antiatherogenic role has been assigned to specific chemokine receptors (Ccr1) and selectins (L-selectin).

Importantly, although some of these recruitment pathways may either be redundant or active in selective arterial sites, other pairs of chemokines and chemokine receptors have been shown to act in parallel and play additive roles to ensure optimal mobilization of leukocytes and recruitment into the developing arterial lesions. This is the case for Ccr2, Ccr5, and Cx3cr1 pathways whose simultaneous blockade in mice leads to 90% reduction in lesion size. Thus, in depth study of the cellular, biochemical, and molecular events leading to activation of these recruitment pathways is of major importance to our understanding of the mechanisms of atherosclerotic lesion development.

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The authors went on to test the role of St3Gal4 expression in mediating proatherogenic events in vivo and generated St3Gal4-deficient mice under an Apoe<sup>−/−</sup> background. Remarkably, St3Gal4 deficiency resulted in a substantial reduction of atherosclerosis associated with decreased accumulation of monocytes/macrophages and neutrophils within the developing lesions. These results were obtained despite no significant changes in circulating leukocyte numbers or plasma cholesterol levels between the 2 groups of mice and were attributed to reduced adhesion of monocytes and neutrophils to inflamed St3Gal4-deficient carotid arteries. A few questions remain unanswered however and merit further exploration. Because St3Gal4 deficiency is predicted to alter not only Ccl5-dependent but also E-selectin-mediated and Cxcr2-mediated leukocyte recruitment in vivo, one would like to address the distinct contribution of altered generation of functional Ccl5 binding sites on myeloid cells to the in vivo atheroprotective effects of St3Gal4 deficiency. The use of Ccl5 antagonists might have provided an answer. Another point relates to the relative contribution of Ccr1 and Ccr5 to the observed alterations in Ccl5-triggered leukocyte activation and adhesion, which was not explored fully by the authors. The use of Ccr1<sup>−/−</sup> or Ccr5<sup>−/−</sup> monocytes in functional assays would have been helpful in addressing this issue. Of note, the authors' data indicate a nonsignificant effect of sialidase treatment (compared with St3Gal4 deficiency), suggesting the involvement of other sialyltransferases in the generation of functional Ccl5 binding receptors on myeloid cells (although no information was provided about the selectivity of the sialidase used in the experiment). It should also be noted that the direct role of St3Gal4 in mediating the sialylation of Ccl5 receptors, Ccr1 or Ccr5, has not been addressed in the study.

In summary, Doring et al. presented solid evidence to implicate St3Gal4 in mediating Ccl5-dependent myeloid cell activation, adhesion, and recruitment into inflamed vessels and identified a substantial contribution of St3Gal4 activity, in general, to the development of atherosclerotic lesions in mice. The results will stimulate interesting research into the mechanisms of expression and activation of sialyltransferases and their relationship to lesion progression and complications. Increased plaque and plasma sialyltransferase activity has been reported in patients with atherosclerosis. Overall, the data suggest the intriguing possibility that sialyltransferase activity might be a biomarker of cardiovascular risk and a target for therapeutic modulation.

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**References**


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