Tyrosine Sulfation of Leukocyte Adhesion Molecules and Chemokine Receptors Promotes Atherosclerosis

Ekaterina Koltsova, Klaus Ley

In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Westmuckett and Moore describe a prominent role of tyrosine sulfation in hematopoietic cells during atherosclerosis development.1 Atherosclerosis represents a major health problem in developed and developing countries and is the most common underlying process precipitating myocardial infarctions, limb ischemia, and stroke. In the United States alone, more than 60 million people have some form of atherosclerotic vascular disease.2 Atherosclerosis is a complex disease associated with lipid accumulation and formation of atherosclerotic plaque in the major arteries of the body, which can rupture or erode to cause acute thrombosis, arterial occlusion, and necrosis of the dependent tissue.

See accompanying article on page 1730

In a last two decades, it has become clear that immune processes play an important role in atherosclerosis development, plaque formation, and progression of the disease. Although all major types of immune cells are involved in atherosclerosis (reviewed in3), the exact molecular and cellular mechanisms of disease development and progression are not completely understood. Two commonly used mouse models of atherosclerosis are apolipoprotein E–deficient Apoe−/− or low-density lipoprotein (LDL) receptor–deficient Ldlr−/− mice. In both models, LDL cholesterol is elevated, which promotes atherosclerotic lesion formation in locations similar to those in the human disease. Ldlr−/− mice can be reconstituted with bone marrow from donor mice to produce chimeric mice lacking targeted molecules of interest in hematopoietic cells only.

Leukocyte recruitment is critical for chronic inflammation and progression of atherosclerosis. This process is regulated by adhesion molecules and chemoattractants such as chemokines and their receptors.4 One class of adhesion molecules required for recruitment of inflammatory cells to sites of atherosclerotic lesion formation are selectins. P- E- and L-selectin all can bind P-selectin glycoprotein ligand-1 (PSGL-1).5

The expression and function of adhesion molecules and chemokine receptors is controlled at the transcriptional and translational levels as well as by posttranslational modifications. Many intracellular proteins are regulated by phosphor-

Tyrosine sulfation is also critical for PSGL-1 function, because mutation in N-terminal tyrosine residues dramatically reduced the affinity of PSGL-1 for P-selectin.18,19 Many of these studies addressing the role of tyrosine sulfation for the interaction of ligand-receptor pairs were performed in vitro, and the exact relevance of this process in
cells into atherosclerosis plaque, it remains to be investigated whether tyrosine sulfation of these (or possibly other) chemokine receptors plays a predominant role in atherosclerosis development. The role of PSGL-1 tyrosine sulfation also remains to be investigated in detail. From the Tpst1−/− Tpst2−/− mice described by Westmuckett and Moore, leucocytes could be isolated and tested in flow chambers for their ability to tether and roll on P-selectin, which is likely the PSGL-1 function most relevant for atherosclerosis.

Tyrosylprotein sulfotransferases might also be a target for pharmacological intervention to prevent or treat atherosclerosis or other inflammatory diseases. Potential side effects must be expected because of the broad expression of these enzymes. Tyrosylprotein sulfotransferases may be inhibitable by small molecules targeting their catalytic center. Development of specific antibodies, which could distinguish between sulfated and nonsulfated proteins in vivo, may be another potential direction for creating an antiatherosclerosis therapy based on limiting immune cell recruitment into the area of inflammation. To be successful, the key receptors that require tyrosine sulfation and are indispensable for atherosclerosis development must be determined. The study by Westmuckett and Moore suggests that such targets exist and can be found.

Disclosures

None.

References


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