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. 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. 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.

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. One class of adhesion molecules and chemoattractants such as chemokines and their receptors. Of particular interest are the selectins. P-selectin (PSGL-1) and E-selectin (E-selectin) all can bind P-selectin glycoprotein ligand-1 (PSGL-1). 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 phosphorylation, but other types of covalent modifications exist. Sulfation of tyrosine residues turns out to be critical for the function of many secreted and transmembrane proteins, which are involved in both homeostasis and immune responses.

Two broadly expressed enzymes catalyzing the transfer of the sulfotransferases to the hydroxyl group of peptidyl-tyrosine within these proteins have been described in humans and mice, the tyrosylprotein sulfotransferases-1 and -2 (TPST-1, TPST-2). Disruption of Tpst genes by gene targeting and homologous recombination in mice demonstrates important roles for these enzymes in crucial biological functions, such as metabolism, reproduction, and cardiovascular development. For instance, Tpst1<sup>-/-</sup> mice have a significant decrease of postnatal body weight attributable to impaired digestion. Male Tpst2<sup>-/-</sup> mice have reduced fertility attributable to impaired sulfation of proteins responsible for male reproductive function. Although at least some Tpst1<sup>-/-</sup>Tpst2<sup>-/-</sup> double knockout animals were born alive, most of them died because of cardiopulmonary deficiency in the early postnatal period.

Previous work has shown that sulfation of tyrosine residues in N-terminal regions of chemokine receptors plays an important role in interaction with their chemokine ligands. Intriguingly, O-sulfation was observed in a number of chemokine receptors. Some of these are implicated in atherosclerosis progression, including the chemokine receptors CCR2, CCR5, CX3CR1. Selective ablation of CCR2, CCR5, CX3CR1. Selective ablation of CCR2, CCR5, CX3CR1. Selective ablation of CCR2, CCR5, CX3CR1 significantly decreases lesion formation in atherosclerosis-prone mice, likely because of impaired recruitment of mononuclear cells.

To study a functional role of tyrosine sulfation in chemokine receptors, several groups introduced point mutations to substitute Phe for Tyr. For example, cells bearing point mutations in tyrosine residues in CXCR3 were unable to migrate effectively toward the CXCR3 ligands CXCL9, CXCL10, and CXCL11. Mutation in one of two N-terminal tyrosine residues of CX3CR1 caused a 100-fold decrease of affinity for its ligand CX3CL1, whereas mutation in another tyrosine residue (Tyr 22) decreased cell adhesion. The function of both CCR5 and CXCR4 was also modified by tyrosine sulfation as shown by reduced migration to their cognate ligands when tyrosines were mutated to phenylalanines.

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.

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 vivo remains...
vivo remained unclear. The global pathophysiological role of tyrosine sulfation in atherosclerosis has never been examined.

A study published in this issue uncovers an important role for tyrosine sulfation in the atherosclerotic development. The authors generated bone marrow chimeric mice using hematopoietic progenitors from tyrosylprotein sulfotransferase–deficient animals lacking both TPST-1 and -2 and studied the TPST-deficient (TPST-1/−TPST-2/−) genetic background. TSPT-deficient (TPST-1/−TPST-2/−>Ldlr−/−) and control (WT>Ldlr−/−) mice were fed a high-fat atherogenic diet and atherosclerosis development was analyzed. The authors found significantly reduced atherosclerotic plaques in mice with defective tyrosine sulfation in hematopoietic cells. Importantly, necrotic areas and macrophage numbers were significantly decreased in these mice compared with the control group. The authors also showed that murine PSGL-1 and CX3CR1 are tyrosine sulfated (Figure). Tyrosine sulfation is completely absent in TPST-1/−TPST-2/− mice, and therefore PSGL-1 and CX3CR1 are likely nonfunctional in the absence of sulfation in bone marrow chimeric mice (TPST-1/−TPST-2/−>Ldlr−/−). Thus, their studies clearly establish that tyrosine sulfation in bone marrow–derived cells play a critical role in atherosclerotic plaque formation and growth. However, it remains unclear what type of hematopoietic cells play a major role in connecting tyrosine sulfation and atherosclerosis. It is tempting to speculate that both macrophages and T cells may be affected by the lack of tyrosine sulfation, because these cell types are the most important immune subsets enriched in the plaque. Although tyrosine sulfation was described for CCR2, CCR5, and CX3CR1, chemokine receptors involved in recruitment of inflammatory 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 TPST-1/−TPST-2/− mice described by Westmuckett and Moore, leukocytes 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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