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Program Member Type
Affiliated
Research Interest

We currently are pursuing two main areas of research: 1) molecular mechanisms of leukocyte-endothelial adhesion; and 2) the role of heparan sulfate-degrading sulfatases in cancer. The first project focuses on the role of L-selectin, a lectin-type receptor on leukocytes that mediates leukocyte adhesion to activated endothelium. This receptor recognizes endothelial ligands which contain key sulfated carbohydrate determinants. We are interested in the sulfotransferases that synthesize these ligands and how these enzymes are regulated within activated endothelium at inflammatory sites. Toward this end, we are studying mice that are null for two sulfotransferases that are expressed in high endothelial venules of lymphoid organs. These mice exhibit marked deficiency in lymphocyte homing to lymph nodes. We are studying the role of the L-selectin/endothelial ligand adhesion system in the recruitment of lymphocytes and other leukocytes to sites of chronic inflammation, in particular joints in rheumatoid arthritis and inflamed airways in asthma. We are further interested in the signaling responses that are induced in leukocytes when L-selectin is ligated through interaction with specific ligands.

The second main direction of the laboratory concerns two novel sulfatases, called Sulf-1 and Sulf-2 which we cloned a few years ago. These enzymes are targeted to the cell surface and act extracellularly. They remove specific internal sulfate residues (i.e., glucosamine-6-sulfate) from heparan sulfate proteoglycans (HSPGs) on the cell surface and in the extracellular matrix. This desulfation step regulates the ability of heparan sulfate chains to bind specific protein ligands and therefore exerts control on the bioavailability of the ligands. Marked upregulation of Sulf expression is seen in several cancers, notably breast, pancreatic, and lung cancers. We are investigating the possible causal role of the Sulfs in regulating cell proliferation and angiogenesis during tumor growth through their ability to modulate the interaction of growth factors and angiogenic factors with HSPGs. The Wnt signaling pathway is promoted by the action of the Sulfs. In a number of cancers, this developmental signaling pathway is reactivated where it promotes cell proliferation and antagonizes apoptosis. We are therefore investigating the role of the Sulfs in several examples of Wnt-signaling dependent

cancers: pancreatic, breast, and lung.

Complete Publications [3]

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