P-selectin as a therapeutic target in thrombosis, inflammation and cancer: the role of heparin analogues.

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The interface among different biological processes is beneficial but in many cases contributes to the pathogeneses of diseases. This is particularly relevant in the case of coagulation, inflammation and cancer. The inter-relationship among these processes is due to mechanisms that lead to the production of fundamental molecules common to the three diseases. P-selectin and PSGL-1 are vascular adhesion molecules that have important roles in the interactions between cells. In coagulation, P-selectin from activated platelets is responsible for the capture of leucocytes and pro-coagulant microparticles during thrombogenesis by a PSGL-1-involving mechanism. In inflammation, interaction of leukocyte PSGL-1 and endothelial P-selectin is essential for leukocyte rolling and transmigration. Similarly, platelet P-selectin and Sialy lewis-containing oligosaccharides from tumor cells mediate tumor cell-platelet interaction during hematogeneous metastasis. Therefore, inhibition of P-selectin and or PSGL-1 can attenuate thrombosis, inflammation and metastasis. Heparin is an antithrombotic agent commonly used in the treatment of thrombosis. Recently, it has been shown that in addition to its anticoagulant effect, heparin inhibits P-and L-selectin and as a consequence it attenuates inflammation and metastasis. However, the use of heparin as an anti-selectin agent is restricted by its potent hemorrhagic effect and the search of alternative anti-selectin compounds has increased recently. During the last years we have found unique sulfated glycans in marine invertebrates. We have isolated novel molecules with interesting characteristics that have not been previously described and showed unequivocally that these glycans can inhibit the binding of selectins to their natural ligands. In addition, recent results from our laboratory have shown that the invertebrate glycans inhibit thrombosis, inflammation and metastasis in experimental animals without significant bleeding effect.

Heparin analogues, thrombosis, inflammation, metastasis.