"Heparin analogs from marine invertebrates: structure and biological properties in inflammation and cancer"

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Heparin has been largely used in the clinical practice for anticoagulation and prevention/treatment of vascular thromboembolism. However, recent studies have shown that in addition to its well-established antithrombin-mediated thrombin and Factor-Xa inhibitory activity, heparin inhibits leukocyte recruitment and tumor cell-platelet aggregation by a mechanism involving P- and L-selectin inhibition. Although heparin is currently approved only as an anticoagulant and/or antithrombotic, its potent anti-selectin activity suggests that heparin could be used as an adjuvant therapeutic drug in the treatment of selectin-mediated diseases, such as inflammation and metastasis. In fact, a recent human clinical trial has been conducted to evaluate the effects of low-molecular-weight heparin on survival and disease progression in patients with hormone-refractory prostate cancer, locally advanced pancreatic cancer or non-small-cell lung carcinoma (ClinicalTrials.gov identifier: NCT00312013).

Invasion and metastasis has recently become my main interest. This started in 2002 after a discussion with Jeff Esko (University of California, San Diego) and Lubor Borsig (University of Zurich) during the Gordon Research Conferences on Proteoglycans, which resulted in a nice work published in 2007 in JBC. In this work we showed that unique heparin analogs from marine organisms are potent inhibitors of P- and L-selectin, resulting in a drastic attenuation of metastasis in animals as a consequence of the inhibition of tumor cell-platelet in circulation (hematogeneous metastasis). My interest in this topic was revigorated after I attended the Nature/Miami Winter Symposium entitled “Targeting cancer invasion and metastasis”, early this year, and the A.C. Camargo Global Meeting of Translational Science in São Paulo in late April, especially because of the essential role of glycoconjugates in growth factor signalling and in P- and L-selectin function. In both events two subjects called my attention: 1-) Endothelial to Mesenchimal Transition; 2-) Formation of tumor cell complexes in blood vessels.

Heparan sulfate proteoglycans play critical roles in major signaling pathways including the fibroblast growth factor (FGF), hepatocyte growth factor (HGF), transforming growth factor-β (TGF-β) and Wnt pathways. The HSPGs act as co-receptors and facilitate the interaction between specific signaling molecules and their signal-transducing receptors. Interaction of HSPGs with these extracellular ligands thus represents an important step in the initiation and regulation of growth and development. There is also biochemical evidence
suggesting that several of these signaling molecules are modulated by heparin, indicating a possible therapeutic use of this glycosaminoglycan. P- and L-selectin are vacular receptors involved in the recruitment of leukocytes from the blood and in the interaction of tumor cell-platelet during hemotogeneous metastasis. Heparin inhibits the binding of P and L-selectin to their natural ligants attenuating the recruitment of leukocytes and tumor metastasis.

Metastatic disease is the main cause of death in patients with carcinoma. It is a complex process, which involves Epithelium to Mesenchimal Transition, tumor cell-platelet aggregation in the vascular system, recruitment of bone marrow derived cells to the primary tumor and to pre-metastatic sites, and angiogenesis. Taking into account the critical role of heparan sulfate-dependent growth factors and selectins, as well as the modulatory effect of heparin, there is an urgent need to evaluate the effect of non-anticoagulant heparin analogs in the different steps of the metastatic disease.

Several heparin analogs obtained from different marine invertebrate sources have been discovered. Some of these compounds have been extensively studied in terms of structure, biological activity and mechanism of action, and evaluated in pre-clinical experiments in rodent animals with promising results. For example, heparin-like polymers with significant antithrombotic activity and devoid of bleeding effects occur in ascidians and molluscs. A unique fucosylated chondroitin sulfate possessing anticoagulant activity after oral administration and high anti-metastatic and anti-inflammatory activities is present in sea cucumbers. Moreover, dermatan sulfates with significant antimetastatic effect occur in high quantities in ascidians.

A critical question related to therapeutics from natural sources is the technical and economic possibility to obtain very large quantities of the compounds in a constant and ecologically correct manner. Overall, the invertebrate glycans are isolated at reasonable yields (about 0.5% of the dry weight, comparing to 0.022 % from pig intestinal mucosa, by procedures similar to those already employed in the preparation of pharmaceutical heparin. Several species of mollusks and sea cucumbers, including those containing high quantities of heparin analogs, have been successfully cultivated in different parts of the world. The cultivate employs developed aquaculture technologies capable to produce ton-quantities of starting material. For example, in 2001, the world’s production of sea cucumber reached about 21,000 tons, and that of scallops, in 1999, about 73,000 tons. Therefore, the critical conditions required to use marine invertebrates as source of natural therapeutic compounds have already been established. What is necessary now is a cooperative effort from scientists of related areas to specifically adapt current methodologies.