Human Heparanase: Activation and Inhibition

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Heparan sulfate (HS) and heparan sulfate proteoglycans, which are located in the extracellular matrix and on the external surface of cell membranes, play a major role in cell-cell and cell-extracellular interactions. Since HS chains tightly bind to a diverse repertoire of proteins under physiological conditions, the enzymatic cleavage of HS by heparanase is likely to be involved in several biological phenomena, including cancer metastasis and angiogenesis.

Human heparanase encodes endo-β-D-glucuronidase which is overexpressed in many human tumor types, such as those in the head and neck, pancreatic tumors, hepatocellular carcinoma, esophageal carcinoma, and cultured human tumor cell lines; such associations are thought to indicate the involvement of heparanase in tumor progression. In order to develop anti-metastatic drugs against tumors expressing heparanase, it will be necessary to fully understand the activation mechanisms of heparanase. We have demonstrated that i) overexpression of heparanase in tumor cells is due to the aberrant DNA methylation, ii) six *N*-glycosylation sites are necessary for the heparanase secretion, and iii) a disulfide bond is required for the heparanase activation. Thus, these present findings will provide a basis for the development of novel heparanase inhibitors.

Furthermore, we have screened for small-molecule heparanase inhibitors from 10,000 microbial broths of actinomyces, fungi, bacteria and synthetic compounds. We obtained 4-Bn-RK-682 as a heparanase-specific inhibitor. 4-Bn-RK-682 inhibited both tumor invasion and metastasis *in vitro* and *in vivo*.