Heparanase modulation of cell proliferation

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Heparan sulfate proteoglycans (HSPGs) are macromolecules associated with cells surface and extracellular matrix (ECM), composed of a core protein on which glycosaminoglycan (GAG) side chains are covalently attached. HSPGs are known to interact with variety of ligands in ECM, such as growth factors, morphogens, receptors, adhesion molecules, chemokines, etc. Basic-fibroblast growth factor (bFGF) was the first growth factor shown to depend on Heparan sulfate (HS) for interaction with its receptor. The interaction of HSPGs with different ligands may play important roles in control of normal and pathological processes, including morphogenesis, tissue repair, inflammation, vascularization and cancer metastasis.

Heparanase is an endo -B-D-glucuronidase that cleaves the HS chains, yielding fragments of variable size. The role of heparanse in the normal development is still not well understood, but it has been shown that heparanase is involved in embryonic development, wound healing, tissue remodeling, and immune surveillance. Moreover, there have been numerous studies showing upregulated expression of heparanase imply an important role in tumor metastasis.

In the current project we tried to investigate the roles of heparanase in cell proliferation. The project began with generation of mouse embryonic fibroblasts (MEFs) from transgenic mice overexpressing human heparanase (Hpa-tg) and control c57bl mice (Ctrl). In order to characterize MEF cells heparanase expression level was assessed by western blot on Hpa-tg and ctrl cells. Furthermore, interactions of HSPGs with growth factors such as fibroblast growth factor-2 (FGF-2) were assessed by FGF-2 induced cell signaling and nitrocellulose filter trapping assay. HS chain analysis was carried on with gel chromatography of ^{35}S-labled HS chains on a Superose-12 column. The results indicated that the Hpa-tg MEF cells overexpress heparanase, FGF-2 induces higher ERK-phosphorylation in Hpa-tg MEF cells, and Hpa-tg MEFs produce shorter free HS chains.

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