Heparanase Role in Cancer and Physiology

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Heparan sulfate proteoglycans (HSPGs) are widely distributed among animal cells. These protein and glycosaminoglycan conjugates are one of the major constituents of basement membranes as well as plasma membranes. HSPGs present on the cell surface or in extracellular matrices (ECMs) specifically interact with variety of biologically active molecules including heparin-binding growth factors, cytokines, proteins involved in cell-cell interactions or cell-ECM interactions, and pathogens, such as viruses, prion or plasmodium, thereby regulating biological activities of these molecules. The cell surface location of HSPGs makes them to be used in intercepting and regulating biological signals coming into cells. ECM-bound HSPGs anchor fibronectin and collagen in the ECM and work also as high-affinity storage depots of growth factors and chemokines. Thus, mechanisms involved in expressing HSPGs with proper carbohydrate modification, in maintaining them on the cell surface and in shedding them into ECM would all play important roles regulating biological functions of HSPGs.

Heparanase, an endo-β-glucuronidase specifically cleaving HS, has drawn much attention for many years for its potential importance in HS degradation. Heparanase activity is attributed to an 8 kDa and a 50 kDa heterodimer arisen from a 65 kDa precursor due to specific proteolytic cleavages. Heparanase activities have been detected in various tissues and cells, including placenta, platelets and liver. High levels of heparanase activities also have been attributed to some cancer cells, such as melanoma, hepatoma and other carcinomas. Heparanases related to cancer cells appear to contribute to the

disintegration of ECM and basement membrane by degrading HSPGs present, and therefore facilitating metastasis. In addition, they are proposed to release growth factors bound to HSPG either at the cell surface or in the ECM, and enhance cancer growth. Heparanase inhibitors such as synthetic sulfated oligosaccharides and phosphorothioate oligodeoxynucleotides have been shown to inhibit tumor growth and angiogenesis in rats and reduce tumor growth in mice. However, recent studies with human glioma cell lines, pointed dual effects of heparanase in tumor growth. Depending on its expression level, heparanase may activate signal transduction pathways leading either to activation or suppression of tumor growth.

As most of the studies emphasize role of heparanase in pathophysiology, only limited information about physiological role of heparanase is available. Heparanase during the normal cellular processes seems to contribute to physiological degradation of HSPGs. It has been reported that cell surface HSPGs undergo unique intracellular degradation pathways after they are endocytosed from the cell surface. Such intracellular degradation processes of HS involving heparanase have been found in a variety of cells, suggesting the enzyme plays a pivotal role in regulating biological functions of HS. Heparanase is also suggested to play an important role in intracellular processing of heparin proteoglycan (serglycin), found in mouse mast cells. Finally, heparanase present in the interface between embryonic and maternal tissues is likely to be utilized for ECM remodeling during implantation and placentogenesis.

Many questions regarding heparanase biology, its mechanism of action and exact roles in ECM remodeling and HSPG degradation, still remained. Detailed characterization of the enzyme will allow us better understanding of processes regulated by heparanase substrate – HSPG.