Abstract

Heparanase is an endoglycosidase involved in cleavage of heparan sulfate and hence in degradation and remodeling of the basement membrane and extracellular matrix (ECM). Heparanase activity facilitates cell invasion associated with cancer metastasis, angiogenesis, autoimmunity and inflammation. The enzyme is preferentially expressed in human tumors and its over-expression in tumor cells confers an invasive phenotype. Heparanase also releases angiogenic factors from the ECM and thereby induces an angiogenic response in vivo. Heparanase upregulation correlates with increased tumor vascularity and poor postoperative survival of cancer patients. Moreover, heparanase levels in the urine and plasma of cancer patients often correlate with the severity of the disease and response to anti-cancer treatments. These observations, the anti-cancerous effect of heparanase gene silencing and of heparanase-inhibiting molecules, as well as the unexpected identification of a single functional heparanase, suggest that the enzyme is a valid target for anti-cancer drug development and a promising tumor marker. Heparanase also exhibits non-enzymatic activities, stimulating, among other effects, cell adhesion, Akt signaling and PI3K-dependent endothelial cell migration and invasion. It also promotes VEGF expression via the Src pathway and hence may activate endothelial cells and elicit angiogenic and survival responses. Studies with heparanase over-expressing transgenic mice revealed that the enzyme functions in normal processes (i.e., wound healing) involving cell mobilization, HS turnover, tissue vascularization and remodeling. Inhibitors directed against domains critical for heparanase secretion and signaling, combined with inhibitors of heparanase enzymatic activity (i.e., non-anticoagulant glycol-split heparin) are being developed to halt tumor growth, angiogenesis and metastasis. In this review, we summarize the current status of heparanase research, emphasizing molecular and cellular aspects of the enzyme, including its mode of processing and activation, control of heparanase gene expression, cytoplasmic vs. nuclear localization, enzymatic and non-enzymatic functions, causal involvement in cancer metastasis and angiogenesis, and strategies for the development of heparanase inhibitors.
14.1 Introduction

In a given organ, the cells normally occupy only a certain portion of the volume. A substantial part is filled with a network of macromolecules defined as extracellular matrix (ECM). The ECM is composed of a variety of proteins and polysaccharides secreted by the cells. Protein components are adhesive molecules such as laminin, fibronectin and vitronectin, and structural molecules such as collagen and elastin. Heparan sulfate proteoglycans (HSPGs) are members of the glycosaminoglycan (GAG) family, a class of molecules that consists of unbranched, repeated disaccharide units attached to a core protein. Heparan sulfate glycosaminoglycans (HS) are abundant components of the ECM. By binding several major ECM constituents (i.e., laminin, fibronectin, collagen type IV), HS are thought to contribute significantly to ECM self-assembly and integrity. HS also tether a multitude of growth factors, chemokines, cytokines and enzymes to the ECM and cell surface, providing a low-affinity storage depot (Bernfield et al. 1999; Folkman et al. 1988; Vlodavsky et al. 1987). Cleavage of HS side chains is expected not only to alter the integrity of the ECM, but also to release HS-bound biological mediators. In addition, HS fragments are also capable of modulating the activity of growth factors such as bFGF and enzymes such as thrombin. The ECM provides an essential physical barrier between cells and tissues, as well as a scaffold for cell growth, migration, differentiation and survival, and undergoes continuous remodeling during development and in certain pathological conditions such as wound healing and cancer (Fata et al. 2004). ECM-remodeling enzymes are thus expected to profoundly affect cell and tissue function. While intensive research focused on enzymes capable of degrading and remodeling protein components in the ECM (Vu and Werb 2000; Werb 1997), less attention was paid to enzymes cleaving GAG side chains. Heparanase is an endo-β-D-glucuronidase capable of cleaving HS side chains at a limited number of sites, yielding HS fragments of still appreciable size (~5–7 kDa) (Freeman and Parish 1998; Pikas et al. 1998; Vlodavsky and Goldshmidt 2001). Heparanase activity has long been detected in a number of cell types and tissues. Importantly, heparanase activity correlated with the metastatic potential of tumor-derived cells; this was attributed to enhanced cell dissemination as a consequence of HS cleavage and remodeling of the ECM barrier (Parish et al. 2001; Vlodavsky and Friedmann 2001). Similarly, heparanase activity was implicated in neovascularization, inflammation and autoimmunity, involving migration of vascular endothelial cells and activated cells of the immune system (Dempsey et al. 2000; Parish et al. 2001; Vlodavsky and Friedmann 2001). In spite of the attractive clinical relevance of the pro-metastatic, pro-inflammatory and pro-angiogenic activities of heparanase, progress in the field was slow, largely due to the lack of a simple bioassay to quantitative heparanase activity and the low abundance of the enzyme. Heparanase activity was attributed to proteins with molecular weights ranging from 8 to 130 kDa, raising the possible existence of several