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Commentary

The potential of heparanase as a therapeutic target in cancer

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ABSTRACT

Heparanase has generated substantial interest as therapeutic target for antitumor therapy, because its activity is implicated in malignant behavior of cancer cells and in tumor progression. Increased heparanase expression was found in numerous tumor types and correlates with poor prognosis. Heparanase, an endoglucuronidase responsible for heparan sulfate cleavage, regulates the structure and function of heparan sulfate proteoglycans, leading to disassembly of the extracellular matrix. The action of heparanase is involved in multiple regulatory events related, among other effects, to augmented bioavailability of growth factors and cytokines. Inhibitors of heparanase suppress tumor growth, angiogenesis and metastasis by modulating growth factor-mediated signaling, ECM barrier function and cell interactions in the tumor microenvironment. Therefore, targeting heparanase has potential implications for anti-tumor, anti-angiogenic and anti-inflammatory therapies. Current approaches for heparanase inhibition include development of chemically modified heparins, small molecule inhibitors and neutralizing antibodies. The available evidence supports the emerging utility of heparanase inhibition as a promising antitumor strategy, specifically in rational combination with other agents. The recent studies with compounds designed to block heparanase (e.g., modified heparins) provide a rational basis for their therapeutic application and optimization.

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1. Introduction

Heparanase, an endoglucuronidase responsible for heparan sulfate (HS) cleavage, regulates the structure and function of heparan sulfate proteoglycans, thus resulting in structural alterations of the extracellular matrix (ECM) and release of bioactive saccharide fragments and HS-bound growth factors and cytokines (Fig. 1). Heparanase is a multifaceted protein endowed with enzymatic and non-enzymatic functions that appear to participate in major human pathological processes (1 and quoted references). Since the cloning of the human heparanase gene in 1999, heparanase was advanced from being an obscure enzyme with a poorly understood function to a promising drug target. While most attention was addressed to heparanase function in tumor biology, emerging evidence indicate that heparanase is also engaged in other disease conditions often associated with degradation of HS, release of bioactive molecules anchored within the ECM network, disregulated signaling cascades, gene transcription, and activation of innate immune cells. Among these diseases are chronic inflammation (i.e., inflammatory bowel disease, rheumatoid arthritis), autoimmunity (i.e., type 1 diabetes, psoriasis), diabetic nephropathy, bone osteolysis, thrombosis and atherosclerosis [2–9]. There is growing evidence that heparanase upregulates expression of genes that participate in cancer metastasis and angiogenesis, glucose metabolism, immune response, inflammation and atherosclerosis, suggesting that heparanase belongs to an emerging class of proteins that play a significant role in regulating transcription in addition to their well-recognized extra-nuclear functions [1,5,6,8,9].

Several up-to-date reviews summarize basic aspects related to the involvement of heparanase in cancer progression and inflammation [10–14]. The present commentary provides information on the biology of the heparanase protein in cancer and inflammation, with emphasis on translational aspects of heparanase-inhibiting strategies.

2. Heparanase and heparan sulfate proteoglycans

2.1. Heparan sulfate proteoglycans (HSPGs)

HSPGs exert their multiple functional repertoires via several distinct mechanisms that combine structural, biochemical and

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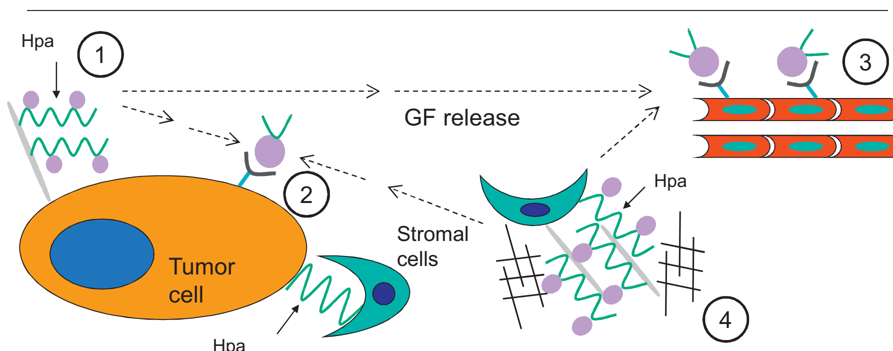

Fig. 1. Scheme showing the effects of heparanase (Hpa) involving tumor/microenvironment interactions: (1) cleavage of heparan sulfate (HS) by heparanase (as indicated by the solid arrows) and release of heparan sulfate-bound growth factors (GF) from proteoglycans; (2) growth factor-mediated signaling; (3) proangiogenic signaling; and (4) disassembly of extracellular matrix and release of HS-bound growth factors.

regulatory aspects. By interacting with other macromolecules such as laminin, fibronectin, and collagens I and IV, HSPGs contribute to the structural integrity, self-assembly and insolubility of the extracellular matrix (ECM) and basement membrane (BM), thus intimately modulating cell–ECM interactions [15,16]. HSPGs also directly transfer information from the extracellular space to intracellular kinases and cytoskeletal elements, thus affecting cell signaling, adhesion and motility [16,17]. The sulfated saccharide domains of HS provide numerous docking sites for a multitude of protein ligands, ensuring that a wide variety of bioactive molecules (i.e., cytokines, chemokines, growth factors, enzymes, protease inhibitors, ECM proteins) bind to the cell surface and ECM [15,18] and thereby function in the control of normal and pathological processes, among which are morphogenesis, tissue repair, vascularization, cancer metastasis, inflammation, atherosclerosis, thrombosis and diabetes [18,19]. Heparanase-mediated cleavage of HSPGs would ultimately release these proteins and convert them into bioactive mediators, ensuring rapid tissue response to local or systemic cues. As a result, HS provides cells with a rapidly accessible reservoir, precluding the need for de novo synthesis when the requirement for a particular protein is increased (Fig. 1) [6,7].

The biosynthesis of HS takes place in the Golgi system and has been studied in great detail. Briefly, the polysaccharide chains are modified at various positions by sulfation, epimerization and N-acetylation, yielding clusters of sulfated disaccharides separated by low or non-sulfated regions [18,19]. Unlike the well resolved biosynthetic pathway, the mode of HS breakdown is less characterized. While synthesis and modification of HS chains require the activity of an array of enzymes, degradation of mammalian HS is primarily carried out by one enzyme, heparanase (HPSE), which cleaves the HS side chains of HSPGs into fragments of 10–20 sugar units. Cleavage of HS by heparanase has multiple downstream effects due to the broad regulatory activity of HS. For example, HS promote growth factor signaling, mediate cell adhesion and sequester growth factors within the ECM, thereby facilitating storage of growth factors and the establishment of growth factor/chemokine gradients [19]. Additionally, heparanase upregulates expression of the HSPG syndecan-1 and also enhances its shedding from the cell surface. This is important because shed syndecan-1 is known to regulate tumor growth, metastasis and angiogenesis, largely by promoting growth factor signaling within the tumor microenvironment [6].

2.2. Mammalian heparanase

Heparanase cleaves HS side chains presumably at sites of low sulfation, releasing saccharide products with appreciable size (4–7 kDa) that can still associate with protein ligands and facilitate their biological potency. Elucidating the substrate specificity of heparanase has been complicated by the heterogeneity of heparan sulfate chains and the lack of highly pure homogeneous substrates. The enzyme cleaves the linkage between a GlcA unit and an N-sulfo glucosamine residue carrying either a 3-*O*-sulfo or a 6-*O*-sulfo group. In addition, heparanase cleaves such linkages with a 2-*O*-sulfated GlcA residue, but not a 2-*O*-sulfated IdoA residue, in proximity. This suggests that heparanase recognizes certain sulfation patterns rather than specific monosaccharide sequences and that cleavage occurs in the mixed domains between the sulfated and non-sulfated spacer domains. Use of structurally defined oligosaccharides indicates that heparanase displays different cleavage modes by recognizing structural features at the non-reducing ends of HS, thus suggesting a regulatory role in the release or preservation of specific HS structures [20].

Mammalian cells express a single dominant functional heparanase enzyme (heparanase-1) [21]. The heparanase mRNA encodes a 65 kDa pro-enzyme that is post-translationally cleaved into 8 and 50 kDa subunits that non-covalently associate to form the active heparanase. The heparanase structure delineates a TIM-barrel fold harboring the enzyme' active site and substrate binding domains, and a C-terminus domain (C-domain) that is critical for heparanase secretion and signaling function [1]. Similar to other glycosyl hydrolases, heparanase has a common catalytic mechanism that involves two conserved acidic residues, a putative proton donor at Glu_{225} and a nucleophile at Glu_{343} [22]. Cellular processing of the secreted latent enzyme involves uptake and delivery into late endosomes and lysosomes followed by removal of a 6 kDa linker segment brought about by cathepsin L [23]. Importantly, heparanase functions beyond its enzymatic activity. Although enzymatic activity requires both the TIM-barrel and C-terminus domains, the C-domain can function independently of the TIM-barrel fold, promoting AKT signaling and leading to enhanced tumor growth in animal models [1]. Of increasing significance are observations that heparanase through both enzymatic and non-enzymatic activities promotes gene expression (i.e., VEGF, tissue factor, MMP-9, HGF, RANKL, TNFα) and signaling pathways (i.e., phosphorylation of Akt, Src, Erk, EGF-receptor, insulin receptor) of which some are mediated by its C-domain, devoid of heparanase enzymatic activity [1,5–7,21].

2.3. Heparanase in cancer progression

The clinical significance of heparanase in tumor progression emerged from a systematic evaluation of heparanase expression in primary human tumors. Immunohistochemistry, in situ hybridization, RT-PCR and real time-PCR analyses revealed that heparanase is up-regulated in essentially all major types of human cancer, namely carcinomas, sarcomas and hematological

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