Matrix Biology xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Matrix Biology

journal homepage: www.elsevier.com/locate/matbio

Mini review

Involvement of heparanase in atherosclerosis and other vessel wall pathologies

Israel Vlodavsky [a,b,*], Miry Blich [a], Jin-Ping Li [c], Ralph D. Sanderson [d], Neta Ilan [a]

[a] Cancer and Vascular Biology Research Center, The Rappaport Faculty of Medicine and Research Institute, Technion, Haifa, Israel
[b] Department of Cardiology, Rambam Health Care Campus, Haifa, Israel
[c] Department of Medical Biochemistry and Microbiology, Uppsala University, Uppsala, Sweden
[d] Department of Pathology and the Comprehensive Cancer Center, University of Alabama at Birmingham, Birmingham, AL, USA

ARTICLE INFO

Article history:
Received 30 December 2012
Received in revised form 24 January 2013
Accepted 4 March 2013
Available online xxxx

Keywords:
Extracellular matrix
Heparan sulfate
Heparanase
Atherosclerosis
Vulnerable plaque
Thrombosis
Stenosis
Inflammation
Macrophages
Colitis
Diabetic nephropathy

ABSTRACT

Heparanase, the sole mammalian endoglycosidase degrading heparan sulfate, is causally involved in cancer metastasis, angiogenesis, inflammation and kidney dysfunction. Despite the wide occurrence and impact of heparan sulfate proteoglycans in vascular biology, the significance of heparanase in vessel wall disorders is underestimated. Blood vessels are highly active structures whose morphology rapidly adapts to maintain vascular function under altered systemic and local conditions. In some pathologies (restenosis, thrombosis, atherosclerosis) this normally beneficial adaptation may be detrimental to overall function. Enzymatic dependent and independent effects of heparanase on arterial structure mechanics and repair closely regulate arterial compliance and neointimal proliferation following endovascular stenting. Additionally, heparanase promotes thrombosis after vascular injury and contributes to a pro-coagulant state in human carotid atherosclerosis. Importantly, heparanase is closely associated with development and progression of atherosclerotic plaques, including stable to unstable plaque transition. Consequently, heparanase levels are markedly increased in the plasma of patients with acute myocardial infarction. Noteworthy, heparanase activates macrophages, resulting in marked induction of cytokine expression associated with plaque progression towards vulnerability. Together, heparanase emerges as a regulator of vulnerable lesion development and potential target for therapeutic intervention in atherosclerosis and related vessel wall complications.

Contents

Abbreviations: ECM, extracellular matrix; HS, heparan sulfate; HSPGs, heparan sulfate proteoglycans; GAG, glycosaminoglycan; HAT, histone acetyltransferase; MMP, matrix metalloproteinase; VEGF, vascular endothelial growth factor; SMC, smooth muscle cells; TF, tissue factor, TNFα, tumor necrosis factor α; VP, vulnerable plaque; TLR, toll like receptor.

* Corresponding author at: Cancer and Vascular Biology Research Center Rappaport Faculty of Medicine, P. O. Box 9649, Haifa 31096, Israel. Tel.: +972 4 8295410; fax: +972 4 8510445.
E-mail address: vlodavsk@cc.huji.ac.il (I. Vlodavsky).

0945-053X/$ – see front matter © 2013 Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.matbio.2013.03.002

1. Introduction

1.1. Heparan sulfate proteoglycans (HSPGs)

HSPGs exert their multiple functional repertoires via several distinct mechanisms that combine structural, biochemical and 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, thus intimately modulating cell–ECM interactions (Timpl and Brown, 1996; Bernfield et al., 1999; Udo Hacker, 2005). HSPGs also directly transfer information from the extracellular space to intracellular kinases and cytoskeletal elements and thus affect cell signaling, adhesion and motility (Aalkjaer and Boedtkjer, 2009; Couchman, 2010). The sulfated saccharide domains of heparan sulfate (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 (Bernfield et al., 1999; Lindahl and Li, 2009) and thereby function in the control of normal and pathological processes, among which are morphogenesis, tissue repair, cancer metastasis, inflammation, vascularization, atherosclerosis, thrombosis and diabetes (Lindahl and Li, 2009; Iozzo and Sanderson, 2011). Cleavage of HSPGs would ultimately release these proteins and convert them into bioactive mediators, ensuring rapid tissue response to local or systemic cues. This function of HS provides the cell with a rapidly accessible reservoir, precluding the need for de novo synthesis when the requirement for a particular protein is increased (Vlodavsky et al., 1991, 2012).

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 (Lindahl and Li, 2009; Iozzo and Sanderson, 2011). 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 (Vlodavsky et al., 1999). Enzymatic activity capable of cleaving glucuronidic linkages and converting macromolecular heparin to physiologically active fragments was first identified by Ogren and Lindahl (1975). Subsequent studies revealed that the same enzyme (heparanase) is critically involved in various pathologies such as cancer (Parish et al., 2001; Vlodavsky and Friedmann, 2001; Ilan et al., 2006; Arvatz et al., 2011; Vlodavsky et al., 2012), chronic inflammation (Li and Vlodavsky, 2009; Lerner et al., 2011), thrombosis (Nadir et al., 2010; Baker et al., 2012), atherosclerosis (Planer et al., 2011; Blich et al., 2013; Osterholm et al., 2013) and kidney dysfunction (van den Hoven et al., 2006; Gil et al., 2012). As a direct result of these studies heparanase was advanced from being an obscure enzyme with a poorly understood function to a highly promising drug target, offering new treatment strategies for various cancers and other diseases. Several up-to-date reviews nicely summarize basic and translational aspects related to the involvement of heparanase in cancer progression and inflammation (McKenzie, 2007; Vreys and David, 2007; Li and Vlodavsky, 2009; Hermano et al., 2012). The present review focuses on the emerging role of heparanase in vessel wall pathologies such as atherosclerosis (Baker et al., 2010; Planer et al., 2011; Blich et al., 2013; Osterholm et al., 2013), restenosis (Baker et al., 2009) and thrombosis (Nadir et al., 2010; Baker et al., 2012).

1.2. Mammalian heparanase

Heparanase is an endo-β-glucuronidase that cleaves HS side chains presumably at sites of low sulfation (Pikas et al., 1998; Okada et al., 2002; Peterson and Liu, 2010; Peterson and Liu, 2012; Peterson and Liu, this series), releasing saccharide products with appreciable size (4–7 kDa) that can still associate with protein ligands and facilitate their biological potency. Mammalian cells express a single dominant functional heparanase enzyme (heparanase-1) (Ilan et al., 2006; Barash et al., 2010). A second heparanase (heparanase-2) has been cloned but has not been shown to have HS degrading activity (McKenzie et al., 2000; Levy-Adam et al., 2010). For simplification, we refer to heparanase-1 as heparanase. 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 (Levy-Adam et al., 2003; McKenzie et al., 2003). The heparanase structure delineates a TIM-barrel fold harboring the enzyme' active site and substrate binding domains, and a C-terminus domain that is critical for heparanase secretion and signaling function (Fux et al., 2009b). 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} (Hulett et al., 2000). 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 (Abboud-Jarrous et al., 2008; Arvatz et al., 2011).

1.3. Heparanase in cancer progression

Heparanase is up-regulated in essentially all human tumors examined (Vlodavsky et al., 2012). A direct role of heparanase in tumor metastasis was demonstrated by the increased lung, liver and bone colonization of cancer cells following over-expression of the heparanase gene, and by a marked decrease in the metastatic potential of cells subjected to heparanase gene silencing (Ilan et al., 2006; Vlodavsky et al., 2012). A significant role of heparanase in tumor angiogenesis and lymphangiogenesis was demonstrated applying a similar experimental approach (Ilan et al., 2006; Cohen-Kaplan et al., 2008). Notably, heparanase expression levels correlate with tumor vascularity in cancer patients, further indicating a significant role in tumor angiogenesis (Vlodavsky et al., 2012). Cancer patients exhibiting high levels of heparanase had a significantly shorter postoperative survival time than patients whose tumors contained low levels of heparanase (Vlodavsky et al., 2012). Collectively, these results indicate that heparanase is causally involved in cancer progression and hence is a valid target for anti-cancer drug development and a promising tumor marker. This statement was reinforced by in vivo studies indicating a marked inhibition of tumor progression in mice treated with heparanase-inhibiting compounds (Yang et al., 2007a,b; Casu et al., 2008; Dredge et al., 2011; Ritchie et al., 2011; Shafat et al., 2011a; Zhou et al., 2011). Of increasing significance are observations that heparanase promotes gene expression (i.e., VEGF, tissue factor, HGF, RANKL, TNFα) (Parish et al., this series; Sanderson et al., 2004; Nadir et al., 2006; Zetser et al., 2006; Yang et al., 2010; He et al., 2011; Ramani et al., 2011) and signaling pathways (i.e., phosphorylation of

Please cite this article as: Vlodavsky, I., et al., Involvement of heparanase in atherosclerosis and other vessel wall pathologies, Matrix Biology (2013), http://dx.doi.org/10.1016/j.matbio.2013.03.002