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Review article

Heparanase: Potential roles in multiple sclerosis

Benjarat Changyaleket[a], Zane Deliu[a], Andreia Z. Chignalia[a], Douglas L. Feinstein[a,b,*]

[a] Department of Anesthesiology, University of Illinois, Chicago, IL 60612, USA
[b] Jesse Brown Veteran Affairs Medical Center, Chicago, IL 60612, USA

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ABSTRACT

Heparanase is a heparan sulfate degrading enzyme that cleaves heparan sulfate (HS) chains present on HS proteoglycans (HSPGs), and has been well characterized for its roles in tumor metastasis and inflammation. However, heparanase is emerging as a contributing factor in the genesis and severity of a variety of neurodegenerative diseases and conditions. This is in part due to the wide variety of HSPGs on which the presence or absence of HS moieties dictates protein function. This includes growth factors, chemokines, cytokines, as well as components of the extracellular matrix (ECM) which in turn regulate leukocyte infiltration into the CNS. Roles for heparanase in stroke, Alzheimer's disease, and glioma growth have been described; roles for heparanase in other disease such as multiple sclerosis (MS) are less well established. However, given its known roles in inflammation and leukocyte infiltration, it is likely that heparanase also contributes to MS pathology. In this review, we will briefly summarize what is known about heparanase roles in the CNS, and speculate as to its potential role in regulating disease progression in MS and its animal model EAE (experimental autoimmune encephalitis), which may justify testing of heparanase inhibitors for MS treatment.

1. Introduction

The enzyme heparanase is a ubiquitously expressed protein endoglycosidase that has been well studied with regard to its role in tumorogenesis, fibrosis, angiogenesis, autophagy, inflammation, and coagulation. Heparanase cleaves heparin sulfate (HS) groups from proteoglycan proteins (HSPGs) located within the extracellular matrix. Removal of HS from the ECM reduces the integrity of the underlying endothelial cell barrier, and regulates the interaction of numerous signaling molecules (cytokines, chemokines, growth factors) with their cognate receptors. In recent years, roles for heparanase in certain neurological diseases and conditions has been described, particularly in the areas of stroke, sub-arachnoid hemorrhage (SAH), and more recently in Alzheimer's disease (AD). Those studies, in addition to characterization of changes in leukocyte trafficking into the CNS have also shown that heparanase regulates neuroinflammatory events including activation of astrocytes and microglial cells. Together with early observations that heparanase can regulate migration of Tcells across endothelial cells suggests that heparanase could play a role in the development or progression of multiple sclerosis (MS), an autoimmune demyelinating disease involving Tcell activation, migration across the blood brain barrier (BBB), and activation of the resident innate immune responses in astrocytes and microglial cells; eventually leading to damage to myelinating oligodendrocytes (OLs) and demyelination of axons. In this review, we will briefly summarize the structure and functions of HSPGs with a focus on actions in the CNS, go over examples of heparanase involvement in other diseases, and describe evidence for heparanase in regulating inflammation. We will then summarize the existing, albeit limited literature regarding possible roles for heparanase in MS and its animal model EAE (experimental autoimmune encephalomyelitis), which to this point remains equivocal as to whether it heparanase plays protective or detrimental roles.

1.1. Heparan sulfate proteoglycans (HSPGs)

Proteoglycans (PG) are large, complex molecules with a protein core and various side chains. Their function was originally thought be a “gap filler” in the extracellular matrix (ECM), providing structural support and membrane stability (Yanagishita, 1993). The protein core of PGs either spans the entire cell membrane or inserts into the membrane, to which glycosaminoglycan (GAG) side chains are attached. The three major classes of PG, characterized by their side chains, are the heparin

Abbreviations: AD, Alzheimer's disease; APC, antigen presenting cell; DC-HIL, HSPG dependent integrin ligand; EAE, experimental autoimmune encephalitis; EC, endothelial cell; ECM, extracellular matrix; GAG, glycosaminoglycan; GBM, glioblastoma; GPI, glycosyl-phosphatidylinositol; HS, heparan sulfate; HSPG, HS proteoglycan; IL1, interleukin-1; LPS, lipopolysaccharide; MS, multiple sclerosis; PG, proteoglycan; SAH, subarachnoid hemorrhage; TLR, toll like receptor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor

* Corresponding author at: Department of Anesthesiology, University of Illinois, Chicago, IL 60612, USA.
E-mail address: dlfeins@uic.edu (D.L. Feinstein).

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sulfate PGs (HSPGs), chondroitin sulfate PGs, and keratan sulfate PGs. A major part of the cell surface and extracellular matrix is comprised of HSPGs. The various HPSGs can be classified into four different families based on where they are located, their attachments to membranes, and their core protein structures. Syndecans are transmembrane spanning proteins; glypicans are membrane-associated glycosyl-phosphatidylinositol (GPI)-anchored proteins; secreted forms (perlecan, agrin, collagen XVIII) are associated with the extracellular matrix; and serglycin granules are present in intracellular storage granules (Lindahl and Li, 2009). HSPGs interact with numerous proteins through the HS side chains, including heparin-binding growth factors, chemokines, morphogens, proteases, and other ECM proteins (Sarrazin et al., 2011). These interactions are dependent on the structure and modifications of the HSPGs and regulate processes during development as well as in the adult (Maeda et al., 2011). Each type of HSPG can undergo multiple modifications, furthering their functional versatility, including modification of membrane-associated forms allowing their secretion as soluble proteins.

HSPGs play crucial roles throughout the body including in cell signaling, endocytosis, ECM binding, and cell migration (Sarrazin et al., 2011). HSPGs play a role in cell signaling by mediating interactions between basic fibroblast growth factor and its high affinity receptor (Yayon et al., 1991), and facilitating endocytosis of macromolecules and other ligands (Christianson and Belting, 2014). In the ECM, HSPGs play a role in cellular locomotion by stimulating the binding of platelet derived growth factors to fibronectin while the removal of HSPGs has been shown to impair cellular motility (Smith et al., 2009). In intestinal cells, HSPGs seem to regulate structural stability of the ECM by providing a barrier against protein degradation (Bode et al., 2006). As HSPG structural variety renders its ability to interact with a host of different proteins, and that HSPGs are ubiquitously found at the cell surface and extracellular matrix, it is not surprising that HSPGs affect organs throughout the body including the central nervous system.

1.2. HSPGs in the CNS

Proteoglycans have multiple and important roles in CNS physiology (Fitch and Silver, 2008; Galtrey et al., 2008; Hartmann and Maurer, 2001; Smith et al., 2015) participating in the accurate wiring of the nervous system (Margolis and Margolis, 1993) as well as in repair and reorganization following CNS injury (Beller and Snow, 2014). HSPGs play an integral part in macrophage and microglial-mediated CNS inflammation (O'Callaghan et al., 2015; Zhang et al., 2012) and a variety of events involving neural growth and proliferation (Siddiqui et al., 2013; Wang et al., 2012). Syndecans, glypicans, perlecan, agrin and collegen XVIII have been shown through studies with knockout mice to mediate synaptogenesis, blood-brain-barrier integrity, post-brain injury repair and neuronal viability (Farhy Tselnicker et al., 2014). Furthermore, brain endothelial HSPGs can modulate leukocyte migration across the blood brain barrier and contribute to the formation of neuroinflammatory lesions (Floris et al., 2003). Fifteen HSPGs, both cell-membrane associated and secretory forms, have been identified in the brain which and participate in neuronal development through to adulthood (Farhy Tselnicker et al., 2014, Maeda et al., 2011). HSPG expression is regulated temporally and spatially during different points in development and in different cell types, particularly in astrocytes and neurons (Farhy Tselnicker et al., 2014). Additionally, enzymes involved in HSPG synthesis have been identified that are critical to proper brain development (Lin et al., 2000; Maeda, 2015). Lack of exostosin-1 (Ext-1), a glycosyltransferase essential for HSPG synthesis, led to failure of gastrulation and lack of organized mesoderm and extraembryonic tissues. Ext-1 knock out mice displayed microcephaly and impaired neurogenesis (Costell et al., 1999; Giros et al., 2007; Inatani et al., 2003) indicating a role for HSPGs in neurogenesis. Brain specific HSPG conditional knockouts also resulted in mice with abnormalities in brain areas such as the midbrain/cerebellum, cerebral cortex, and olfactory bulb (Maeda et al., 2011). These abnormalities may be due to disruption of axon guidance, suggested by studies showing that the proteins Slit-1 and Slit-2, molecules involved in the formation of the forebrain commissure, interact with HSPGs, thus the lack of HSPGs likely disrupts their activity (Bagri et al., 2002; Hu, 2001). In addition to deletion, modifications to HSPGs are also critical to normal brain development, as indicated by studies showing that genetic depletion of Sulf1 and Sulf2, sulfatases which remove sulfate groups from HSPGs, leads to deficits in neuritogenesis and brain development (Kalus et al., 2015).

HSPGs also play important roles in the adult, ranging from maintenance of the blood brain barrier, regulation of synaptic plasticity, and regulation of inflammatory events. In Ext-1 neuronal conditional knockout mice, while the adult mice did not develop any significant changes in morphology or gross anatomy, the mice developed a range of symptoms resembling those seen in autistic patients, attributed to deficiencies in glutamatergic signaling (Irie et al., 2012). In adult mice, experimental removal of HS sides chains enzymatically from within the hippocampus led to reductions in neuronal excitability, indicating a role in maintaining synaptic plasticity in learning (Minge et al., 2017). HSPGs have also been shown to bind to and regulate the activity of voltage-dependent calcium channels, causing reductions in neuronal firing rates (Garau et al., 2015). Taken together, these observations suggest that modifications of HSPGs, which can lead to loss of activity, or more subtle changes in enzymatic activity or ligand bindings, have the potential to influence a variety of processes in the CNS relevant to the development of MS disease. This includes disruption of the BBB integrity which could facilitate leukocyte infiltration, exacerbation of ongoing inflammatory responses, reductions in neuronal excitability which could exacerbate clinical symptoms in the context of already diminished neuronal signaling, and reduced neuritogenesis which could limit the ability of a damaged CNS to undergo proper repair.

1.3. Heparanase

Heparanase is a HS degrading enzyme synthesized and secreted as a latent 65 kDa precursor and is retained at pericellular sites via binding to cell surface HS components (Gingis-Velitski et al., 2004; Goldshmidt et al., 2001). Proteolytic excision yields an active heterodimer of 8 and 50 kDa subunits. Acidic environments as observed in tumors and inflammatory conditions are optimal for the enzymatic activity (Gilat et al., 1995; Toyoshima and Nakajima, 1999; Vlodavsky and Goldshmidt, 2001). In contrast, heparanase expressed on the surface of cells does not enzymatically degrade HS in tissues under normal physiologic conditions (Goldshmidt et al., 2003). Heparanase is involved in a large variety of physiological processes including leukocyte migration, tumorogenesis (Heyman and Yang, 2016), fibrosis (Lv et al., 2016), angiogenesis, autophagy, inflammation (Sanderson et al., 2017) and coagulation (Nadir and Brenner, 2016). The expression of diverse HSPGs throughout the body parallels the functionality of heparanase in multiple biological processes. Given its known roles in leukocyte migration and inflammation, it is likely that heparanase plays similar roles in regulating Tcell invasiveness and glial cell activation in MS.

2. Heparanase in disease

To better understand how heparanase can influence the development and progression of MS, it is informative to first review its roles in other diseases, its proposed mechanisms of action, and the therapies developed to modify its expression or activities.

2.1. Tumor metastasis

Heparanase has been extensively studied with regard to its role in the development of cancers, and several recent excellent reviews have covered that area in great depth (Heyman and Yang, 2016, Sanderson et al., 2017). Heparanase has roles in a wide assortment of cancer types