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Mini review

Implications of heparan sulfate and heparanase in neuroinflammation

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ABSTRACT

Heparan sulfate proteoglycans (HSPGs), expressed on the cell surface and in the extracellular matrix of most animal tissues, have essential functions in development and homeostasis, and have been implicated in several pathological conditions. The functions of HSPGs are mainly mediated through interactions of the heparan sulfate (HS) polysaccharide side chains with different protein ligands. The molecular structure of HS is highly diverse, expressed in a cell-type specific manner. The flexible yet controlled structure of HS is primarily generated through a strictly regulated biosynthesis process and is further modified post-synthetically, such as desulfation by endosulfatases and fragmentation by heparanase. Heparanase is an endo-glucuronidase expressed in all tissues. The enzyme has been found up-regulated in a number of pathological conditions, implying a role in diseases mainly through degradation of HS. Emerging evidence demonstrates important roles of HS and heparanase in inflammatory reactions, particularly in the regulation of leukocyte activation and extravasation. Neuroinflammation is a common feature of various central nervous system disorders, thus it is a great interest to understand the implications of HS and heparanase in neuroinflammation.

Contents

1. Introduction

Heparan sulfate (HS) is a sulfated polysaccharide expressed on the cell surface and in the extracellular matrix (ECM) of all tissues in the form of different types of proteoglycans. Heparan sulfate proteoglycans (HSPGs) are major components of the ECM, playing key roles in maintaining ECM architecture, regulating differentiation/proliferation of vascular cells as well as cell–cell signaling. These functions are medicated mostly by interactions of the HS side chains with protein ligands. For example, the cell surface HS functions as a co-receptor for a number of

Abbreviations: HS, heparan sulfate; HSPG, heparan sulfate proteoglycan; SDC, syndecan; GPC, glypican; -OST, -O-sulfotransferase; NDST, N-deacetylase–N-sulfotransferase; FGF, fibroblast growth factor; CNS, central nervous system; BBB, Blood Brain Barrier; ECM, extracellular matrix; AD, Alzheimer's disease; PD, Parkinson's disease; NSAID, nonsteroidal anti-inflammatory drug; Aβ, β-amyloid peptides; AβPP, Amyloid-β Precursor Protein; Hpa-tg, Transgenic mouse model overexpressing heparanase; CHO, Chinese hamster ovary.

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growth factors; the most representative one is fibroblast growth factor (FGF). Binding of FGF to its receptor requires HS to form ternary complex for initiating signaling activity. Thus, HS is critical for fundamental physiological and pathological processes ranging from pregnancy, embryonic development, tissue morphogenesis and feeding behavior to inflammation, cancer metastasis and amyloidosis (Bishop et al., 2007; Lindahl and Li, 2009). The diverse functions of HS are ascribed to the structural variability of the polysaccharide chain that is generated through a strictly controlled biosynthesis process involving formation of the sugar chain and a series of enzyme-catalyzed modification reactions (Lindahl and Li, 2009). The HS polysaccharide chains are also subjected to various postsynthetic modifications e.g., selectively de-sulfation at glucosamine C6 catalyzed by 6-O-endosulfatase (Ai et al., 2003). Heparanase is an endo-glucuronidase so far only found in mammalians. The enzyme degrades specifically HS (as well as heparin, an analog of HS) long chains in a selective manner (Gong et al., 2003). As a metabolic enzyme heparanase was believed to be solely involved in HS catabolism; however, previous studies proposed that heparanase possesses more functional activities e.g., postsynthetic modification of HS molecular structures including fragmentation and modulation of sulfation (Escobar Galvis et al., 2007), and even non-enzymatic activities e.g., directly activation by latent heparanase of protein kinase PI3K-AKT pathway associated with activation of endothelial cells (Gingis-Velitski et al., 2004) and proliferation of different cell lines (Riaz et al., 2013).

1.1. Heparan sulfate proteoglycans in the brain

Available evidences show that cell surface HSPGs are implicated in a multitude of physiological events in the brain (e.g., development and tissue morphogenesis) through interactions with various proteins including growth factors, morphogens and ECM molecules. Syndecans (SDCs) are transmembrane HSPGs composed of four isoforms: SDC-1,-2,-3,-4. SDC-3, a major HSPG species expressed in the brain, has been found to mediate neurite outgrowth-promoting signal from pleiotrophin to the cytoskeleton of growing neurites (Raulo et al., 1994), and SDC-1 is implicated in regulation of proliferation and maintenance of neural progenitor cells through modulating the cells' response to Wnt ligands (Wang et al., 2012). Glypicans (GPCs) are membrane associated HSPGs, attached to cell membrane via a glycosylphosphatidylinositol (GPI) anchor. Both GPCs and SDCs are found to interact with postsynaptic adhesion molecule LRRTM4 to promote synapse development in mouse (Siddiqui et al., 2013). HSPGs have also been found to be involved in regulation of physiological activities such as food intake and memory. In mouse hypothalamus, cell surface SDC-3 controls energy balance and its HS chain functions as a co-receptor in the binding of agouti-related peptide to melanocortin receptor-3/4. The expression level of SDC-3 varies in response to food deprivation and its ectodomain is shed in response to feeding (Reizes et al., 2003). Targeted interruption of SDC-3 led the mice to become resistant to diet-induced obesity (Strader et al., 2004). SDC-3 expressed in the hippocampus has been found to act as an important modulator of synaptic plasticity implicated in hippocampus-dependent memory (Kaksonen et al., 2002).

Substantial experimental evidence has revealed that the diverse functions of HSPGs are largely associated with its HS-side chains that interact with the molecules responsible for the respective physiological functions. Interrupted expression of the HS polymerase exostosin glycosyltransferase-1 in the brain resulted in multiple defects in neuronal development of the mice (Inatani et al., 2003), indicating the indispensable role of HS in brain development. Further, the molecular features of HS are likewise critical for its functions, which is evidenced by the finding that mouse embryonic stem cells expressing undersulfated HS impedes their differentiation potential and blocks maturation along the neural lineage (Forsberg et al., 2012). Modification of HS chains by targeted interruption of heparanase (see 1.2 "Heparanase in the brain") in mice resulted in maturity-onset obesity on a high-fat diet, whereas mice overexpressing heparanase displayed essentially the opposite phenotypes, with a reduced fat mass (Karlsson-Lindahl et al., 2012). These results proposed that changes in HS chain structure affect the binding of agouti-related peptide to melanocortin receptor-3/4; the results further support the findings by Reizes et al. (2001) and Strader et al. (2004).

Considering the unique anatomy and functions of central nervous system (CNS), particularly the brain, it is highly possible that HS has diverse spatiotemporal expression patterns and structures in the organ. However, due to the limitation of available techniques for de novo HS structure analysis, the fine structure of HS in different brain regions has not been elucidated. The structure diversity of HS polysaccharide chain mainly refers to its length and pattern of sulfation which is biosynthetically determined or dynamically remodeled required by changes of cell function. Specific sulfated saccharide sequences are essential for selective interaction with different proteins. Revealing the spatiotemporal expression patterns of HS biosynthesis enzymes, especially different sulfotransferases, in the brain may help to understand the structural diversity of HS with respect to its functions during development and in different brain regions. It has been reported that mRNAs of different isoforms of sulfotransferases (e.g., 2-OST (2-O-sulfotransferase), 6-OST (6-O-sulfotransferase) and NDST (N-deacetylase/N-sulfotransferase)) are stage-specifically expressed in developing neuroepithelium of embryonic mouse. (Turnbull et al., 2003). Furthermore, expressions of 3-OST (3-O-sulfotransferase) and 6-OST isoforms at postnatal stages of mouse brain have been found to be spatiotemporally regulated as illustrated by in situ hybridization and RT–PCR methods (Yabe et al., 2005). Obviously, elucidation of the spatiotemporal expression pattern of HS structure in the brain is of critical importance for understanding its dynamic functions. Thus, there is a great need to develop powerful techniques to pave the progress on molecular characterization of HS structures and its functions.

1.2. Heparanase in the brain

Heparanase is an endo-glucuronidase that specifically cleaves HS side chains, releasing oligosaccharide products of 4–7 kDa (Pikas et al., 1998). These small fragments are still able to interact with protein ligands, facilitating their biological potency (Escobar Galvis et al., 2007). Up to date, information regarding heparanase expression in the brain is circumstantial, though it is clear that the protein is expressed from early developmental stage of animals. In Xenopus, heparanase is expressed widely during development; the levels and places of expression are finely regulated at different developmental stages with strong expression in the developing nervous system (Bertolesi et al., 2011). In rat brain, the postnatal transcript and protein levels of heparanase are gradually increased, reaching the highest levels at early postnatal period, which may coincide with axonal and dendritic path finding (Navarro et al., 2008). The enzyme is normally expressed at a low level in the adult mouse brain, nearly undetectable by immunohistostaining (Fig. 1). Regardless its early and universal expression, surprisingly, this unique HS-specific endo-glycosidase is not essential for animal development and homeostasis, as targeted interruption of the single heparanase gene, *Hpse*, did not cause any apparent phenotypes in mice (Zcharia et al., 2009). The heparanase null mice are fertile and have a normal life span. The HS chains are averagely longer than the HS from corresponding wildtype mice, however, there is no accumulation of the polysaccharide in organs. These data support the suggestion for a more challenged function of heparanase as a postsynthetic modification enzyme for HS structure. Thus, heparanase is not an indispensable enzyme for HS catabolism. Changes in the expression of heparanase, mainly up-regulation, have been reported in a number of pathological conditions, particularly in cancers (Vlodavsky et al., 2012). Animal experiments provided clear evidence that heparanase overexpression promoted tumor progression and associated angiogenesis. Increased expression of heparanase is detected in brain tumor glioma tissues from human and

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