BBA - Molecular Basis of Disease 1865 (2019) 165539

Contents lists available at ScienceDirect

BBA - Molecular Basis of Disease

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

Review

Heparan sulfate proteoglycans: The sweet side of development turns sour in mucopolysaccharidoses

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ARTICLE INFO

Keywords:
Heparan sulfate proteoglycans (HSPGs)
Glycosaminoglycans (GAGs)
Central nervous system (CNS) and skeletal system development
Lysosomal storage diseases (LSDs)
Mucopolysaccharidoses (MPSs)

ABSTRACT

Heparan sulfate proteoglycans (HSPGs) are complex carbohydrate-modified proteins ubiquitously expressed on cell surfaces, extracellular matrix and basement membrane of mammalian tissues. Beside to serve as structural constituents, they regulate multiple cellular activities. A critical involvement of HSPGs in development has been established, and perturbations of HSPG-dependent pathways are associated with many human diseases. Recent evidence suggest a role of HSPGs in the pathogenesis of mucopolysaccharidoses (MPSs) where the accumulation of undigested HS results in the loss of cellular functions, tissue damage and organ dysfunctions accounting for clinical manifestations which include central nervous system (CNS) involvement, degenerative joint disease and reduced bone growth. Current therapies are not curative but only ameliorate the disease symptoms. Here, we highlight the link between HSPG functions in the development of CNS and musculoskeletal structures and the etiology of some MPS phenotypes, suggesting that HSPGs may represent potential targets for the therapy of such incurable diseases.

1. Introduction

The heparan sulfate proteoglycans (HSPGs) are molecular complexes, consisting of a core protein carrying heparan sulfate (HS) chains, that are ubiquitously distributed on the cell surface and in the extracellular matrix (ECM) of all vertebrate and invertebrate species [1–4]. Depending on their core protein structure, HSGPs are commonly distinguished in three classes: the transmembrane type syndecans, the glycosylphosphatidylinositol-anchored (GPI) glypicans, and secreted ECM types including perlecan, agrin and collagen type XVIII. Both syndecans and glypicans are localized at cell surface, but they can be cleaved by a proteinase or heparanase, and their detached forms can be also distributed in the ECM. Conversely, the ECM types of HSPGs are directly secreted and localized in the ECM including the basement membrane [3]. Acting as intermediaries between the ECM and intracellular signaling pathways, HSPGs contribute to development and tissue homeostasis, influencing a variety of cellular processes including cell fate determination, cell proliferation, migration, adhesion, differentiation, and survival (Fig. 1) [5–8].

The HS chains of HSPGs are formed by a long linear backbone of repeating disaccharide units of D-glucosamine and uronic acid (D-glucuronic and L-iduronic acids) that can variably be N- and O-sulfated, and are assembled through an elaborate post-translational biosynthetic pathway in the Golgi apparatus upon the arrival of the core protein from the endoplasmic reticulum [4]. The process starts with the addition of a tetrasaccharide linker (xylose-galactose-galactose-glucuronic acid) to the core protein via O-glycosylation of a serine residue. Subsequently, HS backbone undergoes to extensive modifications by the action of different enzymes, including the N-deacetylation and N-sulfation of glucosamine, C-5 epimerization of glucuronic acid to iduronic acid, 2-O-sulfation and 3-O-sulfation of uronic acid and glucosamine, respectively, and 6-O-sulfation of *N*-acetylated or N-sulfated glucosamine residues. Additional modifications occurring at the cell surface or ECM through the action of 6-O-endo-sulfatases and/or the endoglycosidase heparanase enhance the heterogeneity and complexity of HSPGs accounting for the amplitude of their functions [2–4,7,8].

The presence of sulfate groups at specific positions in HS chains imparts an overall high negative charge, and their arrangement in short segments of the chain creates binding sites for protein ligands. Indeed, HSPGs bind and interact with a variety of ligands such as morphogens, growth factors, plasma proteins, immune-modulators, ECM components, enzymes, and other factors [2,3,7–10]. The binding to a ligand allows HSPGs to regulate the distribution, availability, and signaling activity of the ligand. The binding activity of HSPGs is largely dictated by the sulfated pattern and size of HS chains [11,12]. For example, heavily sulfated HS fragments strongly facilitate the formation of ternary complexes with fibroblast growth factor (FGF) and FGF receptor (FGFR) in genetically modified mouse models and cellular tools

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https://doi.org/10.1016/j.bbadis.2019.165539
Received 13 June 2019; Received in revised form 5 August 2019; Accepted 23 August 2019
Available online 26 August 2019

Fig. 1. Physiological and pathological processes regulated by heparan sulfate proteoglycans (HSPGs).

[13,14]. On the other hand, desulfation of HS has been proved to reduce the binding of Wingless (Wnt) proteins to HSPGs, allowing Wnt to interact with Frizzled receptor, thus enhancing its signaling [15,16]. Although most of the ligands interact with sulfated domains of HS chains, the protein core of HSPGs can also bind ligands. Indeed, a *Drosophila* glypican ortholog and mammalian glypican-3 core proteins directly interact with some morphogens in the absence of HS [17], while syndecan-1 core protein interacts with specific integrins to modulate cell adhesion and motility [18]. Moreover, the ECM secreted HSPGs perlecan, agrin and collagen XVIII contain functionally independent domains that bind other ECM components and growth factors [3,19].

The classical function attributed to cell surface-tethered HSPGs is to serve as signaling co-receptor for growth factor activity, allowing a proper presentation of them to their cognate receptors [1–5,7–10,20]. The ability of HSPGs to facilitate the formation and signaling of growth factor-receptor complexes usually occurs by promoting conformational changes of the ligand and/or receptor or by acting as a template to approximate ligand and receptor. One of the most studied examples of such a mechanism is related to the interaction of FGF family members with their tyrosine kinases receptors. These studies, while establishing the mandatory requirement of HSPGs for receptor activation by the FGF proteins, have also provided insights into the molecular mechanism of ligand-receptor complex formation and subsequent signaling [13,14,21–24]. Although HSPGs are generally thought to enhance the activity of receptors on the same cell, transactivation of receptors in adjacent cells by HSPGs may also occur by trapping the receptor at cell surface in an activated state, thus eliciting stronger signaling activation [1,2]. For example, vascular endothelial growth factor (VEGF) signaling in endothelial cells during angiogenesis is fully supported by HS expressed by adjacent perivascular smooth muscle cells [25]. Thereby, transactivation of tyrosine kinase receptors by HSPGs constitutes a mechanism for crosstalk between adjacent cells. Membrane-bound cell surface HSPGs may undergo to a process called shedding which implies the proteolytic cleavage of their ectodomain by metalloproteinases (MMPs), and an additional cleavage of HS chains by heparanase [13,26]. The enzymatic release of HSPGs from the cell membrane allows them to transport or move growth factors, with different functional consequences [18,26]. On the other hand, ECM-associated HSPGs may function as a reservoir or a barrier of growth factor depending on their cellular context [11]. Indeed, ECM-associated HSPGs are considered to trap the growth factors diffused in the ECM as a reservoir and supply them to target cells when needed. Otherwise, they may act as a barrier for growth factor, by preventing their passive diffusion over longer distances, instead confining them to the vicinity of producing cells [11,27]. In addition to function as co-receptor, HSPGs may also act as receptors themselves [1,8]. This is the case of the syndecan family members which modulate integrin-mediated adhesion of leukocytes to the endothelium [18,28], or activate ADP-ribosylation factor 6 (ARF6), a Ras superfamily GTPase involved in membrane trafficking, actin cytoskeletal remodeling and cell motility [29,30]. Noticeably, in addition to serving as co-receptors for FGF receptor activation, HSPGs also function directly as receptors for FGF2-induced ERK1/2 activation [31]. Furthermore, HSPGs have been shown to participate in endocytosis and vesicular trafficking, thus regulating the movement of molecules between intracellular and extracellular compartments (Fig. 2) [32–34]. Indeed, HSPGs act as endocytic receptors and undergo constitutive as well as ligand-induced endocytosis: exosomes, cell penetrating peptides, polycation–nucleic acid complexes, viruses, lipoproteins, growth factors and morphogens among other ligands enter cells through HSPG-

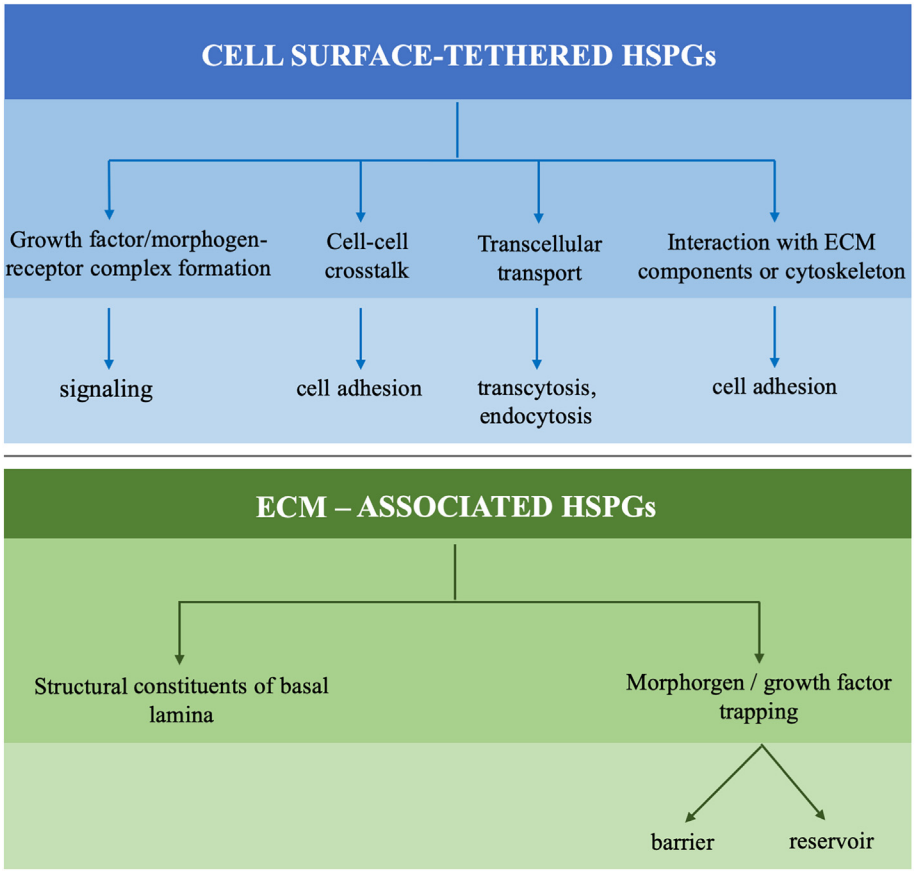

Fig. 2. Biological activities of cell surface-tethered and extracellular matrix (ECM)-associated heparan sulfate proteoglycans (HSPGs).

mediated endocytosis [2,33]. Internalized cargo can be sorted for lysosomal degradation, escape into the cytosol, e.g. nuclear translocation, or recycle back to the plasma membrane. Studies of morphogen gradient in *Drosophila* and mice have highlighted the importance of glypican endocytosis in the regulation of Hedgehog (Hh) and Wnt signaling [35–38], thus suggesting that HSPG endocytic activity is particularly important in generating and long-range maintaining gradients for morphogens during embryogenesis and regenerative processes.

In embryonic development, HSPGs play crucial roles as regulators of the distribution and signaling of the extracellular ligands involved in the specification of cell fate and the formation of tissue architectures [6,11,27,32,36,39]. The involvement of HSPGs in developmental events such as neurogenesis, axon guidance, synaptogenesis, and angiogenesis has been definitely assessed [40–48]. Furthermore, HSPGs, which are the major proteoglycans present in the basal lamina and cell surface of skeletal muscle, have been shown to regulate FGF, Hh, Wnt, and bone morphogenetic protein (BMP) pathways that cooperate in the morphogenetic, proliferative and differentiation processes underlying the development and growth of skeletal structures [49–60]. Thereby, HSPGs greatly contribute to the development of both the central nervous system (CNS) and the musculoskeletal system. Mutations affecting the biosynthesis or degradation of HSPGs are responsible for many human diseases affecting either the CNS such as the Alzheimer's disease, neuroinflammation, malignant glioma and other brain cancers [61–65], or skeletal system such as osteoarthritis, osteochondroma syndrome, and muscular dystrophies [50,52,53,66–70]. Interestingly, an involvement of HSPGs in the pathogenesis of Mucopolysaccharidoses (MPSs), a group of inherited metabolic diseases belonging to the group of lysosomal storage diseases (LSDs) has been recently ascertained [71–90]. This review aims to work toward an exploration of the link between the functions of HSPGs in the development of CNS and musculoskeletal structures and the pathogenesis of MPS phenotypes, and to point a way forward toward the application of HSPG-targeting as a novel therapeutic strategy for MPS subtypes that are refractory to current therapies.

2. Role of heparan sulfate proteoglycans in the development of central nervous system and musculoskeletal structures

Molecular genetic tools including *Drosophila melanogaster*, *Caenorhabditis elegans*, *Xenopus tropicalis*, *Danio rerio*, *Gallus gallus domesticus*, and *Mus musculus* models have allowed to address the functions of HSPGs in the regulation of significant developmental events, such as the formation of morphogen gradients, nervous system, and the stem cell niche [6,11,17,24,36,39–46,48,91–94]. HSPGs regulate not only the formation of a morphogen gradient but also morphogen movement, signaling, and intracellular trafficking (Fig. 3A) [24,35,43,91,93–95]. In particular, the binding of morphogens to HSPGs restricts their diffusion along the surface of receiving cells, preventing them from aberrant signaling to other layers of cells [35]. Moreover, due to their ability to bind cell surface co-receptors and secreted proteins, HSPGs provide a signaling platform for morphogens to interact with other important components such as lipoproteins that may be required for morphogen movement and distribution [94]. During development, secreted morphogens such as Hh, Wnt/Wg, FGF and BMP proteins spread from the producing cells in a morphogenetic field and specify different cell fates in a concentration-dependent fashion [11,17,39,46,60,91,94,96]. Down-regulation of HSPGs with consequent impairment of FGF and BMP signaling in mouse embryonic stem cells (ESC) causes the loss of ESC differentiation competence, in particular lineage specification into mesoderm [97]. HSPGs regulate the distribution of Wnt proteins along the morphogenetic gradient and allow a proper activity of them by concentrating the molecules at the cell

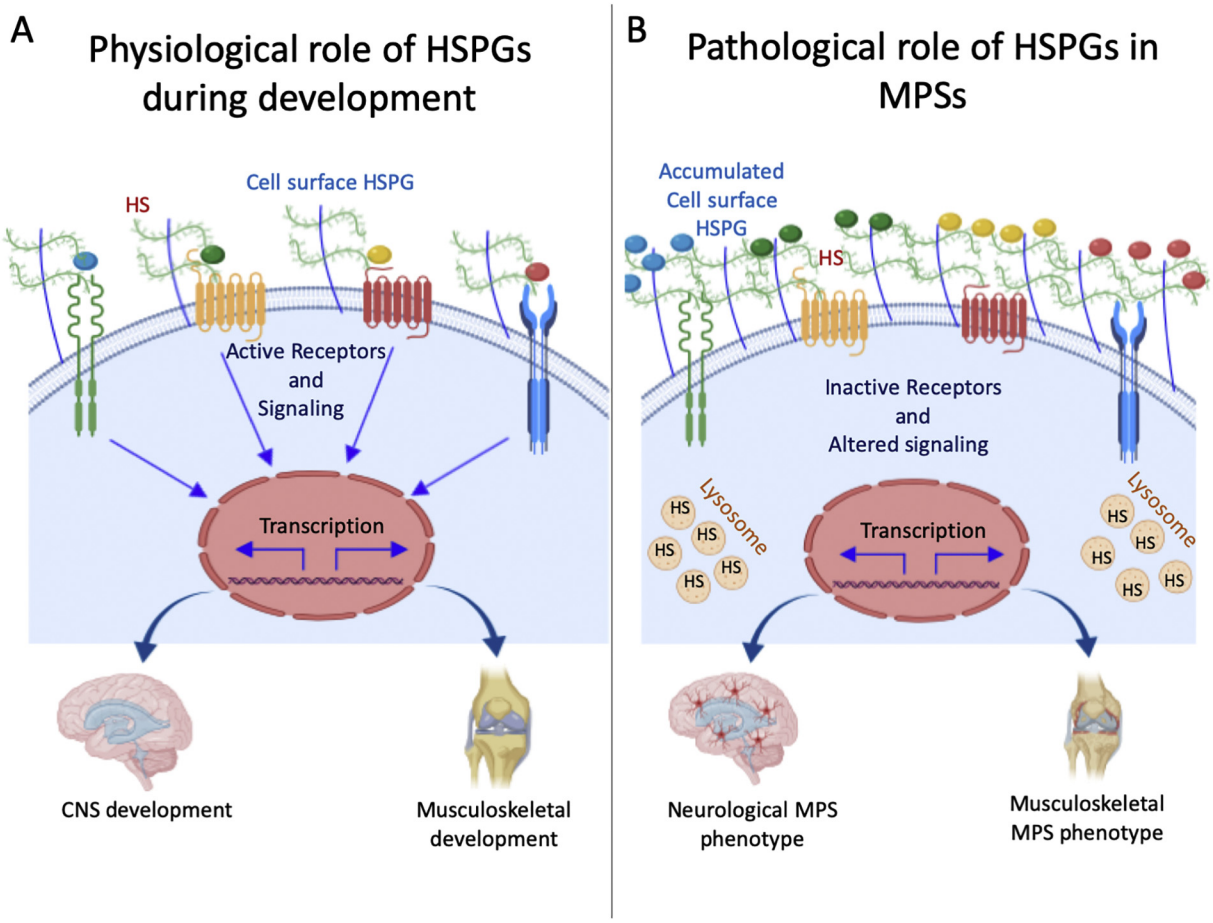

Fig. 3. Schematic representation of the mechanism of action of membrane bound cell surface HSPGs during central nervous system (CNS) and skeletal development (A) and in MPS diseases (B). Physiological levels of cell surface HSPGs account for proper interaction of morphogen/growth factor-receptor interaction and signaling activation leading to the development of both the CNS and musculoskeletal system (A). In some MPS subtypes, concomitantly with HS accumulation in lysosomal compartment, abnormal levels of membrane-bound cell surface HSPGs are found with a consequent deregulation of morphogen/growth factor-receptor interactions and signaling, finally resulting in severe neurological and skeletal phenotypes. Brain and joint images were adapted from Smart Servier Medical Art under Creative Commons Attribution 3.0 Unported License.

surface and preventing their aggregation in the ECM environment, finally resulting in the signaling activation [38,98,99]. In the syndecan-1 knockdown murine model, canonical Wnt signaling is disrupted, resulting in reduced neural progenitor cell proliferation and premature differentiation during cortical neurogenesis [98]. It has been well established that Hh gradient formation requires HSPG expression, and that HSPGs act as both positive and negative regulators of Hh function [35–37,96]. Targeted inactivation of HS biosynthetic or modifying enzymes in mouse models results in Hh-related developmental defects of the forebrain and related structures, axon guidance errors as well as bone developmental abnormalities [58,96].

Great attention has been paid to the pivotal role of HSPGs in the development of tissues from the ectodermal lineage. The ectodermal layer differentiates to form the nervous system (including the spine, peripheral nerves and brain), eye, epidermis, skin appendages and tooth enamel [100]. During mammalian nervous system development, a functional impact of HSPGs has been demonstrated on the proliferation and differentiation of neural progenitors, the migration of neurons to established locations [40,46,48,97,98,101], the extension of axons and dendrites [44,102,103], and the development, maturation and plasticity of synapses [45,104]. From the earliest stage of brain patterning, HSPGs play a critical role on the regionalization of neural tube into the three major CNS domains and into the differentiation of the three main cell lineages (neurons, astrocytes and oligodendrocytes) from neural stem cells [46,63,105]. Early evidence showed that HSPG regulation of FGF and Wnt signaling controls both proliferation and self-renewal of neural precursor cells and differentiation of neuronal and glial cell subtypes [5]. A reduction of brain size, impairment of FGF signaling and premature differentiation of postmitotic neurons is observed in glypican-1 null mice [106]. Syndecan-3 knockout mice exhibit a disorganized cortical laminar structure due to impaired radial migration along the glial fibers [40]. Mutant mice bearing a targeted disruption of the HS modifying enzyme *N*-deacetylase/N-sulfotransferase 1 (Ndst1) exhibit severe developmental defects of the forebrain and forebrain-derived structures, including cerebral hypoplasia, lack of olfactory bulbs, eye defects, and axon guidance errors [103]. The HSPG perlecan, expressed in the basal lamina of neuroepithelium, also plays important roles during neural development by interacting with FGF-2 and other growth factors [107]. Perlecan null mice display impaired forebrain development through disrupted Hh signaling [41]. Furthermore, perlecan is an essential regulator of gliogenesis, promoting terminal differentiation of mature oligodendrocytes [46]. The functional involvement of HSPGs in the CNS development correlates with the timing of their expression and their regional or cell type localization (Table 1) [104,108]. For example, syndecan-3 is more highly expressed in developing brain and concentrated in axons, whereas syndecan-2 is more strongly expressed in mature brain and localizes to synapses [63]. Syndecan-2 plays a major role in synapse formation process, interacting with a number of adaptor proteins such as CASK, synbindin and synectin required for spine formation,

Table 1
Cell-type localization of heparan sulfate proteoglycans (HSPGs) in developing central nervous system (CNS) and musculoskeletal system.

Cell surface HSPGs		
HSPG	CNS	Musculoskeletal system
Syndecan-1	Radial glia, oligodendrocyte precursor cells	Osteoblast precursors and osteoclasts
Syndecan-2	Immature and mature neurons, oligodendrocytes	Precursors of connective tissue cells
Syndecan-3	Immature and mature neurons, oligodendrocyte precursor cells	Chondrocytes
Syndecan-4	Astrocytes, oligodendrocytes	Chondrocytes, myogenic satellite cells, osteoblasts
Glypican-1	Neural progenitor cells, immature and mature neurons, radial glia, astrocytes, progenitor and differentiated oligodendrocytes	Satellite cells, osteoblasts, skeletal muscle precursor cells
Glypican-2	Neurons	Not reported
Glypican-3	Neurons of the spinal cord and dorsal root ganglia	Osteoblasts
Glypican-4	Neural progenitor cells, mature neurons, radial glia, astrocytes	Muscle precursor cells
Glypican-5	Precursor and mature oligodendrocytes	Chondrocytes
Glypican-6	Astrocytes	Chondrocytes

Matrix-associated HSPGs		
HSPG	CNS	Musculoskeletal system
Perlecan	Astrocytes and oligodendrocytes	Growth plate chondrocytes
Agrin	Axons, dendrites, neuromuscular synapses	Skeletal muscle cells
Collagen XVIII	Neuroblasts in the central and peripheral nervous system	Skeletal muscle cells

neurofibromin which triggers filopodia generation, and the EphB2 tyrosine kinase receptor required for induction of dendritic spines [43,92]. The expression of glypican members of HSPGs is also strictly regulated during neurogenesis, as glypican-4 is expressed in neural stem cells, glypican-1 in post-mitotic neurons, glypican-2 and glypican-5 are only expressed in committed neurons [46,63,109]. Astrocytes secrete glypican-4 and glypican-6 that promote synapse formation in retinal ganglion cells [42,46,105]. A deregulation of expression and/or localization and/or activity of HSPGs has been associated with many genetic CNS disorders, neurodegenerative diseases, and brain-specific malignancies [1,2,12,27,61–63,69,110,111].

In addition, several studies demonstrate that HSPGs play key roles in modulating signaling events during vertebrate skeletal development (Fig. 3A) [49,60,69,112,113]. Most elements of the vertebrate skeleton including long bones are formed from cartilage tissue through endochondral ossification [114]. This process is initiated with mesenchymal cells that condense and differentiate into chondrocytes which undergo several steps of differentiation from proliferating into hypertrophic chondrocytes subsequently replaced by bone. Chondrocyte proliferation and differentiation are tightly controlled by a complex network of signaling molecules such as hormones, morphogens, soluble growth factors, and cytokines, whose distribution and activity are tightly regulated by HSPGs [58–60]. On the other hand, multiple studies have demonstrated that the expression and localization of HSPGs is strictly regulated during skeletogenesis to fulfill distinct functional roles (Table 1) [54,56,113,115]. Analyses of gene knockout models and the human conditions of Simpson-Golabi-Behmel syndrome and omodysplasia which arise from mutations in glypican-3 and glypican-6, respectively, highlighted both subtle and striking effects of glypicans on bone growth [49,53,58]. Mice carrying mutant alleles of glypican-3 created by either targeted gene disruption or gene trapping display skeletal abnormalities and impaired BMP-4 signaling [49]. Glypican-6 null embryos exhibit most of the abnormalities found in omodysplasia affected patients, and Hh signaling is significantly reduced in the long bones of the embryos [58]. The same models also allowed demonstrating the essential role of perlecan in cartilage formation [69,112,116]. Mutations in perlecan result in several distinct phenotypes observed across a spectrum of different organisms [69,112,116]. In zebrafish, targeted perlecan depletion resulted in a severe myopathy characterized by abnormal fiber orientation, reduced amounts of actin filaments, and disorganized sarcomeres, suggesting a potential role for perlecan in human myopathies [112]. In a murine model of Schwartz-Jampel syndrome, in which perlecan is knocked down, a significant decrease of the stiffness of both the chondrocytes and the interstitial matrix during cartilage development was observed [116]. The transmembrane syndecan isoforms, differentially expressed during skeletal muscle development, are instrumental in orchestrating cell adhesion and migration, satellite cell maintenance and muscle regeneration as well as accelerating myogenesis [50,115]. A mouse model over-expressing syndecan-2 demonstrated the association of this HSPG with osteoblastic differentiation: syndecan-2 appears to control bone remodeling by regulating Wnt signaling and the crosstalk between bone surface and marrow cells [59]. Syndecan-4 is induced specifically in hypertrophic chondrocytes and its expression is elevated in the cartilage of patients affected by osteoarthritis [68,70]. In addition, syndecan-4 null mice were shown to develop less severe osteoarthritis -like cartilage destruction [68]. Furthermore, knockdown of syndecan-4 reduced basal activation of B-Raf/ERK1/2 signaling and impaired its activation by Wnt-3a in human primary chondrocytes [117]. Syndecan-4 and glypican-1, which link the satellite cell niche to the intracellular environment, are differentially expressed with age in turkey satellite cells and their over-expression impacts FGF-2 signal transduction and satellite cell proliferation and differentiation [113]. Other studies have established that the matrix-associated HSPG agrin strongly promotes chondrocyte differentiation and cartilage formation in vivo [57]. Mutant zebrafish lines that have diminished HS levels show defects in chondrocyte stacking and aberrant craniofacial morphogenesis [54]. Defective skeleton development due to a reduced binding of Hh and FGF-2 to HSPGs has been reported in mutant mice bearing a targeted disruption of the HS modifying enzyme Ndst1 [118]. In humans, mutations in HS synthetizing exostosin (EXT) enzymes EXT1 and EXT2, leading to HS deficiency, cause hereditary multiple exostoses, a complex musculoskeletal pediatric disorder characterized by osteochondromas that form next to the growth plates of many skeletal elements, including long bones, ribs, and vertebrate [55,119].

Noticeable, both CNS disorders and skeletal abnormalities are clinical manifestations of MPS diseases where HS is accumulated [71–90], thus suggesting an important role of HSPGs in the pathogenesis of such diseases.

3. Involvement of heparan sulfate proteoglycans in the pathogenesis of mucopolysaccharidoses

The inherited metabolic diseases MPSs are caused by the absence or

Table 2
Mucopolysaccharidoses (MPSs).

MPS type (Syndrome)	Defective enzyme	Stored GAG	Neurological manifestations	Musculoskeletal manifestations
MPS I (*Hurler/Scheie*)	α-L-Iduronidase	DS, HS	Severe in Hurler, mild to absent in Scheie and Hurler-Scheie	Short stature, degenerative joint disease and skeletal dysplasia (multiplex dysostosis)
MPS II (*Hunter*)	Iduronate-2-sulphatase	DS, HS	Severe in rapidly progressing phenotypes, mild or absent in slowly progressing phenotypes	Short stature, multiplex dysostosis, joint stiffness, genu valgum, coxa valga
MPS IIIA (*Sanfilippo A*)	Heparan N-sulphatase (sulphamidase)	HS	Severe	Mild short stature and joint contractures
MPS IIIB (*Sanfilippo B*)	α-N-Acetyl-α-glucosaminidase	HS	Severe	Mild short stature and joint contractures
MPS IIIC (*Sanfilippo C*)	Acetyl-CoA: α-glucosamide *N*-acetyltransferase	HS	Severe	Mild short stature and joint contractures
MPS IIID (*Sanfilippo D*)	N-Acetylglucosamine-6-sulphatase	HS	Severe	Mild short stature and joint contractures
MPS IV A (*Morquio-A*)	N-Acetylgalactosamine-6-sulphatase	KS, CS	Absent	Severe skeletal dysplasia, short neck, genu valgum, flat feet, kyphoscoliosis, epiphyses, pectus carinatum
MPS IV B (*Morquio-B*)	β-Galactosidase	KS	Absent	Severe skeletal dysplasia, short neck, genu valgum, flat feet, kyphoscoliosis, epiphyses, pectus carinatum
MPS VI (*Maroteaux-Lamy*)	N-Acetylgalactosamine-4-sulphatase	DS	Absent	Multiplex dysostosis, short stature, pectus carinatum, joint contractures, genu valgum, coxa valga
MPS VII (*Sly*)	β-D-Glucuronidase	HS, DS, CS	Severe in rapidly progressing phenotypes, mild or absent in slowly progressing phenotypes	Multiplex dysostosis, short stature, pectus carinatum, joint contractures.
MPS IX (*Natowicz*)	Hyaluronidase	HA	Absent	Short stature, periarticular soft tissue masses, nodular synovial masses, joint effusions, acetabular erosions

GAG: glycosaminoglycan; DS: dermatan sulfate; HS: heparan sulfate; KS: keratan sulfate; CS: chondroitin sulfate; HA: hyaluronic acid.

defective lysosomal enzymes required to metabolize glycosaminoglycans (GAGs), including HS [120]. The accumulation of undigested GAGs results in the impairment of cellular functions, tissue damage, organ dysfunctions and reduced life expectancy. The GAGs that accumulate in MPSs include four main subgroups: hyaluronic acid or hyaluronan (HA), keratan sulfate (KS), chondroitin/dermatan sulfate (CS/DS), and HS/heparin. With the exception of HA, all GAGs form proteoglycans through their covalent binding to a core protein. Deficits of GAG degrading enzymes are responsible for seven different MPS diseases (MPS I, II, III, IV, VI, VII and IX) where the accumulation of the undegraded GAGs is responsible for multiple organ dysfunctions, with distinct clinical manifestations depending on the type of the lacking enzyme and the accumulated substrate (Table 2). Typical clinical symptoms of the disease include neurological disorders, cardiovascular dysfunction, skeletal, joint, airway, hearing, and vision defects, and death in the second or third decade of life [79,83,85,120–123].

Among the known seven MPS subtypes, HS-degrading enzyme mutations are associated with MPS I (Hurler's Syndrome), MPS II (Hunter's Syndrome), MPS III (Sanfilippo Syndrome), and MPS VII (Sly Syndrome). Affected patients exhibit severe CNS involvement, organomegaly, soft tissue disease, and affection of cartilage causes degenerative joint disease and reduced bone growth. The CNS involvement can manifest as impaired cognition, behavioral disorders, epileptic seizure, and other neuropathologies [124,125]. While the genetic defect for each MPS subtype has been well established, the precise mechanisms by which GAG accumulation results in the complex clinical signs of the disease are not yet fully explained. The lysosomal engulfment by undigested GAGs is considered the “primum movens” of the subsequent functional cell impairment, however, many evidence demonstrate that the accumulation of storage material interferes with various cellular processes such as receptor activation by ligands, receptor responses, intracellular trafficking, autophagy, and others [126–128]. Interestingly, many of these processes are associated with the accumulation of storage material in non-lysosomal compartments. For example, in MPS I, II, III, and VII subtypes, the excess of HS due to the enzymatic deficiency does not accumulate only in the lysosome compartment but it is also redistributed to different cellular (i.e., within the Golgi apparatus) and extracellular localizations [72,77,78,81,82,84–86,125,126,129]. Post-mortem and neuroimaging studies have revealed secondary accumulation of HS and variable composition of HSPGs at non lysosomal sites in the CNS of MPS I, II, III, and VII patients with consequences on CNS functioning [125]. In the murine model of MPS IIIA, neurological symptoms and extensive neurodegeneration correlated with augmented extracellular HS and glypican 4 levels in primary cultures of cortical neural cells, especially astrocytes [86]. In the mouse model of MPS I, increased levels of cell surface and ECM localized HS together with a substantial increase in overall HS sulfation were observed with respect to wild type mice [77]. In the brain of MPS IIIB mouse model, an up-regulation of either intracellular or membrane- bound and extracellular HS moieties was demonstrated [78].

The findings that abnormal levels of extracellular and cell surface-tethered HSPGs in MPSs might lead to an altered morphogen/growth factor receptor binding capacity and downstream signaling have allowed to identify a disease-induced developmental phenotype for some MPS subtypes [51,72,76–78,80–82,84–87,89,90,122–126,128–135]. In particular, the detrimental role of abnormal HSPGs in FGF signaling associated with CNS and skeletal defects has been established in cellular and animal models of MPS I, II, and III. Early studies demonstrated that abnormally sulfated HS levels perturb critical FGF-2-FGFR1-HS interactions, resulting in defective FGF-2-induced proliferation and survival in MPS I multipotent progenitor cells. Both the mitogenic and survival-promoting activities of FGF-2 were restored when HS located on the surface of MPS I progenitor cells was enzymatically removed and replaced by HS isolated from normal cells [72]. The impairment of the functional binding of FGF-2 to HS and downstream signaling, triggering increased rates of apoptosis in MPS I patients may contribute to neurodegeneration occurring in this disease [126]. Interestingly, the FGF-2 induced proliferation of neural progenitor cells appears to be reduced in the MPS IIIB mouse brain and in a dog model of MPS VII [71,73]. In the brain of MPS IIIB mouse model, a differential cell-specific and domain-specific HS distribution was supported by the demonstration of increased expression of multiple genes encoding enzymes essential for HS biosynthesis as well as FGFs [78]. On the other hand, high efficiency of

HS synthesis has been shown in MPS IIIB, IIIA and II patients with severe neurological phenotype [75]. The excess of HS has been shown to activate integrin-based focal adhesions which result to be constitutively activated in MPS IIIB astrocytes and neural cells [81]. Furthermore, abnormal organization of the rostral migratory stream has been observed in the brain of MPS IIIB adult mice suggesting that defects in HGPS-mediated cell polarization and migration contribute to the neuropathology associated with the disease [81]. Our research group recently demonstrated that, in MPS I and MPS IIIB-cultured fibroblasts, the excess of extracellular HSPGs sequesters FGF-2 and inactivates its action. However, masking the excess of accumulated HSPGs by a HS high affinity ligand, the FGF-2 signaling activity was restored [134]. In the mouse and zebrafish models of MPS II, HSPG deregulation of FGF signaling pathway anticipated a slow but progressive defect in bone differentiation [89]. In both models, impaired HSPG assembly also caused Hh and Wnt/b-catenin signaling defects [85,135]. Fibroblasts from MPS II patient exhibited perturbed FGF signaling-related marker expression [89].

The contribution of extracellular and cell surface HSPGs to the progressive neurological and skeletal abnormalities in MPSs is further supported by the impairment of BMP-4 signaling due to the excess of GAGs observed in human multipotent stem cells from MPS I patients [51]. Indeed, HSPGs are critical determinants of the biological activity of BMPs which are members of the transforming growth factor-β superfamily of extracellular signaling molecules that regulate cell growth, differentiation, and apoptosis in the brain, bone, bone marrow and other tissues [49,52,136]. Proteomic and genomic analyses of microdissected growth plate tissue in the mouse model of MPS I demonstrated deregulation of key structural and signaling ECM components, suggesting that the alteration of ECM represents a very early event in the pathogenesis of MPSs, and that biomechanical failure of chondro-osseous tissue may underlie progressive bone and joint symptoms of the disease [82]. A subsequent study demonstrated altered HS distribution in MPS I chondrocytes, and altered distribution of GAGs and defective FGF-2 interaction in growth plates from MPS I mice [84].

An inflammatory component of both brain and joint disease in MPSs has been established [74,121,122,125–128,130–132,137–139]. On the other hand, HSPGs contain binding sites for many soluble mediators of the immune system and may either promote or inhibit their activity, thus playing a crucial role in regulating the immune responses [140]. For example, HSPGs bind and regulate the activity of a number of cytokines which sustain the microglial activation involved in the neurodegeneration observed in MPSs [121,126,128,131,137–141]. Molecular evidence for the involvement of microglia in brain pathology of MPS I, MPS IIIB and MPS IIIC mouse models have been reported [137,142]. Infant-pediatric-stage MPS IIIA canine brain exhibits substantial and progressive primary and secondary substrate accumulation, coupled with early and robust microgliosis [143]. In MPS I, IIIA and IIIB mouse brains, altered levels of total HS and abnormally N-, 6-O and 2-O sulphated HS correlated with astrocytosis, microgliosis and synaptic disorganization [132]. In the MPS I mouse model, the excess of extracellular HS binds and sequesters CXCL12 chemokine, limiting hematopoietic cell migration [80]. Among other chemokines, CXCL12 has recently attracted much attention in the brain as it can be produced not only by glial cells but also by neurons, and its G protein-coupled receptors are abundantly expressed in diverse brain areas [144]. This chemokine system plays important roles in brain plasticity processes occurring during development and both in normal and pathological conditions of the brain. Importantly, HSPGs which are implicated as inflammatory mediators in a variety of settings, including chemokine activation, have been shown to act as CXCL12 receptor, selectively involved in some transduction pathways [65,145]. More recently, CNS and joint inflammation in MPS III subtypes has been associated with HSPG ability to modulate cellular innate immune signaling impacting the Toll-like receptor 4 pathway [138,139].

Overall, these findings indicate that membrane-bound cell surface and extracellular HSPGs play major roles in the pathophysiology of MPS diseases (Fig. 3B), and in particular a deregulation of HSPG expression/composition/activity is involved in the CNS and skeletal phenotypes of MPSs subtypes where HS is the storage product.

4. Heparan sulfate proteoglycans as potential targets for the treatment of mucopolysaccharidoses

Current treatment options for MPSs include enzyme replacement therapy (ERT), substrate reduction therapy, pharmacological chaperone therapy, gene therapy, and hematopoietic stem cells transplantation (HSCT) [128,146]. Most of these therapies, showing variable and limited efficacy, are not curative but only ameliorate the symptoms of the disease [147–151]. Indeed, ERT, which is based on the administration of a recombinant enzyme replacing the deficient lysosomal one, results to be unable to correct the neurological disorders due to the inability of the recombinant enzymes to cross the blood-brain barrier [148]. Furthermore, ERT has very limited impact on avascular lesions in bone and cartilage in affected patients [151]. Host immune responses as well as the failure to prevent neurological deterioration limit the utility of HSCT therapy for MPSs [147,149,151]. In addition, this cell-based therapy may not be applicable to all patients because of the limited availability of matched donors and the mortality risk of the procedure such as graft-versus-host disease, infection disease, and additional complications. Despite improvements, the use of viral vectors in gene therapy is still under development for some MPS subtypes, and clinical trials are ongoing in several countries [150,151]. Due to the limits of these therapeutic strategies, research in progress is still focused to a better understanding of MPS physiopathology and the development of alternative strategies to approach the unmeet needs (i.e., bone disease and CNS involvement).

The analysis of current knowledge and findings clearly demonstrates that, beside primary storage of GAGs in the lysosomes, the deficit of GAG metabolizing enzymes in MPS diseases triggers the accumulation of GAGs on cell surface and ECM as well. In particular, in those MPS subtypes characterized by a deficiency of HS degradative enzymes, an up-regulation of HS moieties, involving membrane-bound cell surface HS domains, intracellular and ECM-localized HS epitopes, has been detected together with augmented HS biosynthesis [75,77,78,125]. It has been suggested that the enhancement of HS biosynthesis may represent a compensatory response to the disruption of normal HS recycling in the MPS cells. In physiological conditions, lysosomal digestion of HS moieties removes individual units of monosaccharides that are transported from the lysosomal compartment into the cytoplasm and reused in biosynthetic glycosylation pathways. By contrast, in MPS cells, the lysosomal storage of HS results in a shortage of HS to be reused for glycosylation which leads to enhanced HS biosynthesis to compensate for such effects [78]. In MPS diseases, the missing or malfunctioning of one of the lysosomal enzymes involved in GAG degradation not only causes an expansion of the volume of lysosomes due to the GAG storage, but also alters the functioning of lysosomes as end-point of the endocytic and autophagic transport pathways of the cells [79]. An impairment of lysosomal membrane integrity may have several consequences including the leakage of lysosomal proteases into the cytosol which contribute to secondary cellular events such as an impairment of apoptosis, mitochondrial and autophagy dysfunctions, and abnormal vesicular trafficking associated to altered endocytosis, and thereby ECM remodeling [121,126–131,138,142]. Such remodeling is also affected by the excess of proteoglycans on cell surface [79,82,129].

In addition, the advances in the knowledge of the fundamental role of HSPGs in the development of CNS and musculoskeletal structures have provided pathophysiologic explanations for neurological disorders and skeletal defects which are typical clinical manifestations of MPS subtypes where HS accumulates. A perturbation of the crucial interactions between HSPGs and ligands may represent a general mechanism

by which accumulated HS contributes to the onset and progression of severe MPS phenotypes. In this context, the development of HSPG-targeting therapies to be used for the cure of intractable MPS subtypes appears to be a promising avenue of research exploration.

Due to the ability of HSPGs to regulate multiple cellular functions including cell proliferation, differentiation, adhesion, migration, survival and signaling, these complex molecules have emerged as potential therapeutic drugs for the treatment of several diseases, including cancer, inflammation, infection, wound healing, lung diseases, Alzheimer's disease, and others diseases [152–154]. Targeting cell surface and extracellular HSPGs may involve different approaches such as the use of high affinity antibodies that recognize functional epitopes of HSPGs thus interfering with the binding and signaling of their ligands, HS mimetic compounds which competitively block HS-protein interactions, novel binding peptides, and GAG biosynthesis competing xylosides [10,153]. Enzymatic methods employing bacterial heparinases and mammalian endosulfatates to remove or modify HS have been also exploited as potential agents for the treatment of disorders involving HS-protein interactions such as HS-binding pathogen infections, tumor growth and metastasis, and amyloid-related diseases [10].

In MPS diseases, the potential use of GAG biosynthesis inhibitors has been tested [128]. This approach commonly referred to as “substrate reduction therapy” (SRT) employs small molecules that are able to cross the blood-brain barrier, thus having the potential to treat the CNS phenotype of the disease. The first molecule identified as a potential drug for SRT in MPS patients with neurological manifestation is genistein, a soy-derived isoflavon with structural similarity to 17β-estradiol, which inhibits GAG synthesis by affecting epidermal growth factor (EGF)-dependent pathway [155]. Genistein clinical trials in MPS III patients are ongoing. However, while clinical efficacy of genistein for the treatment of neurological manifestations in MPSs requires further evaluation, administration of genistein in MPS II patients has been shown to improve connective tissue elasticity and the range of joint motion [156]. The identification of novel molecules that interfere with GAG synthesis may provide a useful tool for improving the neurological outcome in MPS affected patients. On the other hand, the manipulation of GAG synthesis in several diseases has been performed by using synthetic xylosides that reduce proteoglycan-bound GAGs, mostly HS, thereby modulating HSPG biological functions [157].

Recently, our research group demonstrated that, in MPS I and MPS IIIB cell cultures, a defective FGF signaling, due to the accumulation of cell surface and extracellular HS, can be restored by the use of a recombinant protein with high affinity binding activity for HS [134]. In vivo experiments using the mouse model of MPS IIIB are in progress to evaluate the efficacy of the recombinant protein to attenuate the phenotype of the disease. Synthetic peptides, containing non-natural amino acids which prevent their proteolytic cleavage, with high affinity binding activity for HS chains of extracellular and cell-surface HSPGs are also being investigated for a potential therapeutic efficacy in MPS treatment. Thus, although extensive investigation are needed before any treatment could be set up, HSPG-targeting represents a novel approach worthy of being explored for the treatment of MPSs, and other LSDs as well.

5. Conclusions

In MPS diseases, the impairment of cellular processes and consequent tissue and organ dysfunctions are not caused by storage material in the lysosomes, but rather by its accumulation at other sites such as intracellular, cell surface and extracellular locations. Thus, in MPS I, II, III and VII subtypes, where HS-degrading enzymes are missing or malfunctioning, the accumulation of undigested or partially degraded HS in different cellular compartments leads to a variety of secondary changes in the homeostasis of the organs of affected patients resulting in severe phenotypes. Abnormalities in HSPG-dependent signaling pathways have been demonstrated in cellular and animal models of MPSs, and, interestingly, the altered pathways are those involved in the organ development. Thus, the occurrence of developmental defects in affected patients should be taken into account for a better understanding of the pathophysiological mechanisms underlying the onset and progression of the disease, and for exploring novel therapeutic strategies. In particular, HSPG targeting-based approach opens new challenges for the treatment of such incurable diseases, allowing the overcoming of limits associated with the therapeutic approaches developed to date. Nevertheless, the development of novel therapeutics that target HSPGs requires further investigations aimed to a deeper comprehension of the HSPG-dependent interacting networks underlying MPS pathophysiology.

Transparency document

The Transparency document associated with this article can be found, in online version.

Declaration of Competing Interest

LMP has granted a patent for the use of compounds that target HSPGs for the treatment of mucopolysaccharidoses. The authors declare no additional competing financial interests.

Acknowledgments

We apologize to all the authors whose work could not be cited due to space limitations.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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