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Heparan sulfate proteoglycan – A common receptor for diverse cytokines

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ABSTRACT

Heparan sulfate proteoglycans (HSPG) are macromolecular glyco-conjugates expressed ubiquitously on the cell surface and in the extracellular matrix where they interact with a wide range of ligands to regulate many aspects of cellular function. The capacity of the side glycosaminoglycan chain heparan sulfate (HS) being able to interact with diverse protein ligands relies on its complex structure that is generated by a controlled biosynthesis process, involving the actions of glycosyl-transferases, sulfotransferases and the glucuronyl C5-epimerase. It is believed that activities of the modification enzymes control the HS structures that are designed to serve the biological functions in a given cell or biological status. In this review, we briefly discuss recent understandings on the roles of HSPG in cytokine stimulated cellular signaling, focusing on FGF, TGF-β, Wnt, Hh, HGF and VEGF.

1. Introduction

Heparan sulfate proteoglycans (HSPGs) are macromolecules, typically composed of a core protein, to which several heparan sulfate (HS) glycosaminoglycan chains are covalently attached [1,2]. HSPGs expressed in mammals are categorized into two major families based on their location: cell surface bound HSPGs, including the glypican family (7 members) and the syndecan family (4 members); and the extracellular matrix (ECM) type, including perlecan and agrin [3]. The biological functions of HSPG are mostly ascribed to their negatively charged HS side chains that interact with a spectrum of protein ligands to exert their essential functions in animal development, cellular homeostasis and certain pathological conditions.

One of the most important biological functions of HSPG is to modulate the activities of cytokines and cellular signaling. In the ECM it functions as a storage for the cytokines by binding to them, thereby controlling the availability and mobility of these biological molecules; while on the cell-surface HSPGs function as co-receptors to mediate the interactions between cytokines and their receptors by binding to both the ligands and the receptors (Fig. 1). Up to date, a number of cytokines are demonstrated to be dependent on cell-surface HS for their receptor activation and signaling, including FGF, TGF-β family, HGF, VEGF, hedgehog (Hh) and Wnt. This review will briefly summarize the recent advances in the understanding of HSPG-regulated activity of selected cytokine, e.g. growth factors, in various developmental and pathophysiological contexts. A review on HS regulation of chemokines was recently published [4] and therefore will not be discussed here.

2. Biosynthesis of HS

The capacity of HS to interact with a wide diversity of cytokines is attributed to its complex structures that are formed by a controlled enzyme-catalyzed multi-step reaction [2,3,5]. The biosynthetic process is initiated by formation of the core-linkage region constituted of 4 sugar units that are covalently linked to a serine residue within the core protein. The sugar chains are elongated by several glycosyltransferases (HS polymerases) to build up a polysaccharide chain composed of alternating *D*-glucuronic acid (GlcA) and *N*-acetylglucosamine (GlcNAc) units. The sugar units are modified through a number of reactions, including *N*-deacetylation/*N*-sulfation of GlcNAc residues, C5-epimerization of GlcA to *L*-iduronic acid (IdoA) units and *O*-sulfation at various positions of the hexuronic acid and glucosamine residues [3,5], generating the eventual complicated and diverse HS molecular structures that display a spatial and temporal distinct form, with regard to chain length and sulfation pattern [3,6] (Fig. 2). Studies over the past decades have revealed each step of the modification reactions and characterized all the essential enzymes involved in the biosynthetic process; however, an intriguing question still remains: how such a diverse structure is generated in different cell types by the same set of biosynthetic enzymes? Current available information points to stochastic reactions of the modification enzymes that are strictly regulated by yet unknown mechanisms. Nevertheless, this diversity of HS structure enables the molecule to interact with different protein ligands. The interactions are often non-specific, but can be selective, and are essentially dependent on the charge density and pattern, which is defined

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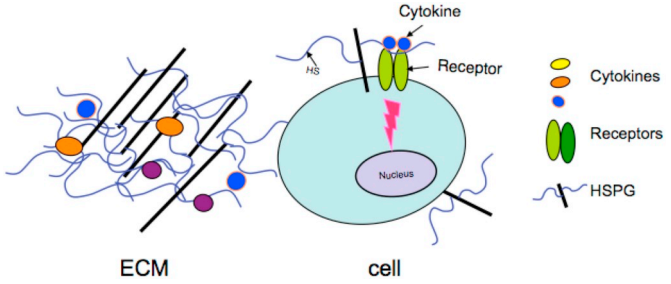

Fig. 1. Illustration of the HSPG functions in the ECM and on the cell surface. Cytokines are stored in the ECM through binding to HS; the cell surface HS functions as a canonical co-receptor for the cytokines and their receptors to mediate their signaling activities.

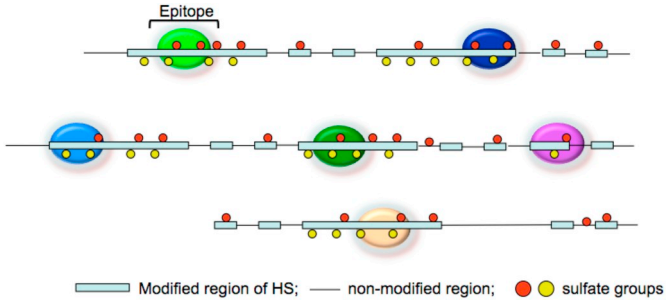

Fig. 2. Illustration of 6 different cytokines that selectively bind to special epitopes of HS formed by distinct sulfation patterns. Several such epitopes may present in one HS chain, allowing to interact with different cytokines.

as 'domain', 'motif' or 'epitope' formed by sulfate groups of varied number and distribution in a given HS chain. For convenience, the term 'epitope' is used in this review to describe a sequence within the HS molecule that selectively binds to a given ligand (Fig. 2). The macromolecular property of HS allows presence of more than one epitope in a single chain that has the potential to selectively interact with more than one protein ligand (Fig. 2).

To understand the characteristics of HS molecular structure and their interactions with protein ligands, biochemical, cellular and animal experiments have been applied. Binding of cytokines to HS is investigated by incubation of the molecules in free solution [7,8], by electrophoresis [9], or in chromatographic settings [10,11]. Numerous cellular models offer information on the biological relevance of HS structure and cytokine activity [12–18]. Recent studies by targeted interruption of the genes coding for the HS modification enzymes in animals have provided convinced information regarding the selectivity of cytokines in interaction with different epitopes in HS. For example, elimination of the gene, *Glce,* coding for glucuronyl C5-epimerase (Hsepi) in mice, resulted in abnormal HS structure, completely lacking IdoA residues with severely distorted sulfation pattern. The *Glce* mutants displayed differential developmental defects in different organs, e.g. complete lack of kidneys, but a seemingly normal liver. This is plausibly ascribed to a selectivity of different cytokines towards the molecular structures of HS [7,16,19,20].

Apart from the enzymes that are directly involved in HS biosynthesis, there are two additional post-synthesis modification enzymes that contribute to the action of HS in modulating cytokine activities. One is 6-O-endosulfatase (Sulf) that has two forms in mammalian, and selectively removes 6-O-sulfate group of glucosamine residue in a given HS polymer [21]. Through modification of HS molecular structure, the activity of Sulf has been associated with several cytokine-stimulated signaling pathways, e.g. GDNF [13], TGF-β [22], FGF [23] and Wnt [24]. The other modification enzyme is heparanase that is an endoglycosidase, specifically cleaving the bond between glucuronic acid and glucosamine residues in a given HS chain [25]. Similar to Sulf, heparanase has been implicated in regulating the activity of several cytokines through degradation of HS, including EGF [26], VEGF [27], FGF [10] and TGF-β [14].

3. HS and FGF signaling

The family of mammalian fibroblast growth factor (FGF) comprises 18 secreted signaling proteins and 4 tyrosine kinase receptors that together regulate a broad spectrum of developmental programs, ranging from organogenesis during embryonic and postnatal development to tissue repair and regeneration [28]. The interaction between FGF and HS was among one of the first findings that demonstrates the HS participation in modulation of cytokine activity [29]. The first genetic evidence that HS is involved in FGF signaling regulation was revealed in *Drosophila*. Different from mammals, *Drosophila* expresses only two FGF receptors, encoded by the *breathless* and *heartless* loci respectively. Disturbance of HS synthesis in the animal impaired the signaling of both receptors, demonstrating that the activity of both receptors in *Drosophila* is associated with HS [30,31]. Recently, it has been shown in zebrafish that loss of HS resulted in collective cell migration deficiency along the lateral line system due to elevated FGF ligand diffusion at the cell surface and loss of FGF signal transduction [32]. Several in vitro studies revealed the importance of FGF interaction with HS, so it probably represents the most studied model of interaction between HS and cytokines. Mechanistically, HS directly interact with both FGF and their receptors (FGFR) by forming FGF-FGFR-HS ternary complex on the cell surface [33–36]. Functionally, HS serves as a co-receptor to facilitate the FGF-induced FGF receptor dimerization and activation [37]. There are evidences showing that the subtypes of FGF are differentially dependent on HS. A recent structural study of HS interaction with FGF-1 and -2 and their receptor complex revealed distinct binding specificities for different HS epitopes between the two FGFs, suggesting the potential to generate specific HS epitopes to selectively activate certain FGF pathways [38]. Such binding specificity of the FGFs for HS has been shown to follow the phylogenetic tree of FGFs during evolution to accommodate the FGF family expansion upon natural selection pressures [39]. Our earlier in vitro study showed that the HS isolated from the *Hsepi* mutant mice had significantly lower affinity for FGF-2, but essentially no difference for FGF-10 in comparison to the HS isolated from the wildtype littermates [7], indicating that FGF-2 requires an epitope of HS with IdoA residues, while FGF-10 does not, because the HS expressed in the *Hsepi* mutant animals completely lack IdoA. In contrast, FGF-10 induced ectopic lacrimal gland budding in explant cultures was found to be dependent on another modification enzyme, NDST1 [40]. Mutation of NDST1 in mice led to multiple cardiac anomalies accompanied by downregulation of HS-dependent FGF-8 assembling with its receptor and FGF8-dependent downstream phosphorylation [41]. Since different subtypes of FGF have distinct biological functions, it can be assumed that each subtype may have a different dependence and structural requirement for HS.

4. HS and TGF-β signaling

The mammalian transforming growth factor (TGF-β) superfamily of about 30 cytokines regulates cell proliferation, differentiation and maintenance in various developmental and homeostatic contexts [42,43]. TGF-β induced activation of Smad controls transcription of target genes, thereby modulating cell differentiation and proliferation. Perturbation of TGF-β signaling is linked to several pathological conditions, including inflammation and cancer. TGF-β1 was the first member in the family identified as a HS-binding protein [44]. Several studies have demonstrated the involvement of HS in TGF-β induced signaling [22,45–48]. Unlike most of the cytokines, TGF-β is a bifunctional regulator [49] that has both stimulatory and inhibitory activity in the same cells [50]. This effect of TGF-β is believed to be dependent on the molecular context of the cells. Our recent results suggest

that the molecular structure of HS on the cell surface plays a role in the pluripotent activity of TGF-β1. Tumor cells overexpressing heparanase displayed a reduced level of TGF-β1-stimulated Smad phosphorylation and led to a slower proliferation of the cells [14]. Analysis of HS isolated from the tumor cells revealed an increase in the degree of sulfation, indicating that the structural alterations of HS affected the ability of TGF-β1 to signal via its receptors and elicit a growth response. HS biosynthesis and post-modification are spatially and temporally regulated in a given cell, which may offer an explanation for the apparently contradictory activity of TGF-β1 on the same cell type cultured under different conditions [50]. It is possible that there is a potential interplay between heparanase and Sulf in modulation of HS structure, as heparanase overexpression is often associated with elevated sulfation degree while Sulf expression reduces sulfation degree.

Bone morphogenetic proteins (BMPs) are important members of the TGF-β super family, playing complementary roles to TGF-β1 during animal development and in tumorigenesis. One of the most distinguished functions of BMPs, as reflected by the name, is stimulating osteogenesis and bone formation during development. Earlier studies reported a co-receptor role of HS in BMP-induced receptor dimerization [51]; however, further information regarding the molecular property of HS required for the BMP-receptor interaction is circumstantial. Important information became available using mouse and cell models with altered HS molecular structure. The cells lacking NDST1 produced HS with substantially reduced N-sulfation, which impaired BMP internalization in lung development [52]. While cells lacking Hsepi produced HS completely lacking IdoA displayed a higher level of phosphorylated Smad1/5/8 upon BMP-2 stimulation [15]. HS isolated from the *Hsepi* mutant MEF cells exhibited a higher binding capacity to BMP-2. The abnormal functions of BMP in the *Hsepi* mutant cells most likely contributed to the defect of bone development displayed in the knockout animals [19,53]. These examples clearly show a structural-functional correlation of BMP with HS, though further studies are needed to pinpoint the epitopes of HS binding to different BMPs. In vitro studies on the affinity of BMP binding to HS isolated from different mutant cells should provide more information regarding the correlation of HS molecular structure with different BMPs.

5. HS and Wnt signaling

The Wnt family plays vital roles as intracellular signaling molecules in many developmental processes [54]. Wnts can propagate their signal via either canonical or non-canonical pathway by binding to the Frizzled (Fz) family of G-protein coupled receptors (GPCRs). The canonical pathway is transduced via β-catenin [54] and the non-canonical pathway is relayed through either planar cell polarity (PCP) or Ca^{2+} [55]. Wnt signaling is identified as a critical regulator in the osteogenic differentiation of mesenchymal stem cells. Many human bone pathologies, such as osteoporosis pseudoglioma syndrome, sclerosteosis and van Buchem's disease have been shown to be closely associated with mutations in the Wnt signaling pathway [56]. Therefore, therapeutic strategies against osteoporosis are designed by targeting endogenous Wnt activities and the treatments demonstrated promising outcome in preclinical trials [57]. In addition, aberrant Wnt signaling has long been considered as one major theme in cancer biology. Tumor genome sequencing has revealed components of the Wnt signaling pathway as a central mechanism for tumor progression [58,59].

The connection of Wnt activity with HSPG was initially established in *Drosophila* models [30,60–62]. Several recent studies have potentiated our understanding on how HSPGs modulate Wnt signaling in various vertebrate developmental scenarios. The canonical Wnt pathways are long known as one of the major regulator for bone formation process [63]. During mouse embryonic development, the cell-surface HSPG, syndecan-2 starts to express in the periosteum as soon as osteogenesis initiates and the expression gradually increases during the osteoblast differentiation process [64]. Recently, in a transgenic mouse model overexpressing syndecan-2 the canonical Wnt signaling during postnatal development was inhibited to improve osteogenesis through crosstalk between the osteoblasts and their microenvironment [65]. Similarly, heparanase degradation of cell surface and extracellular HS led to suppression of osteoblastogenesis and bone ossification via the canonical Wnt pathway in several myeloma bone disease models [66]. In addition, syndecan-4 has also been shown to promote bone fracture reconstruction in mouse models by modulating Wnt activity [67]. Expression of syndecan-1 on the cell surface is an indication of multiple myeloma (MM) [68,69]. HS appeared to be critical for mediating the interaction between MM cells and the surrounding bone marrow matrix. Recently, it was shown that prevention of HS-chain polymerization in MM cells resulted in a decrease in the canonical Wnt pathway activity that has stimulation effect on cell proliferation in normal MM cells [70]. These results indicate that the major function of HSPG is through interaction of HS with Wnt.

Level of glypican-3 was found to be significantly increased in hepatocellular carcinoma (HCC) [71] and was a recognized biomarker for HCC diagnosis and prognosis [72]. Increased glypican-3 expression is essential to promote hepatoma cell proliferation for the progression of HCC, mainly by activating the canonical Wnt pathway [73]. Ectopic expression of glypican-3 in HCC cells could increase the expression level of c-Myc, a classical downstream target of the canonical Wnt pathway [74]; while expression of a soluble version of the glypican-3 that can be removed from the cell membrane blocked the canonical Wnt pathway [75]. Mechanistically, glypican-3 directly interacts with the Fz GPCRs to facilitate the recruitment of Wnt into the signaling complex at the cell membrane and later translocate into the cytoplasm via endocytosis [76]. Glypican-5, another member of the glypican family, was identified as a tumor suppressor gene in lung adenocarcinoma (LAC) [77] and its mechanism of action was uncovered recently [78]. Overexpression of glypican-5 in a LAC cell line suppressed the epithelial-mesenchymal transition (EMT) process accompanied by a significant enrichment of the canonical Wnt pathway activity. Specifically, the overexpressed glypican-5 interacted with Wnt3a to prevent it from binding to the Fz GPCR, resulting in cytoplasm retention of β-catenin. Similar mechanism was also observed in prostate cancer cells where overexpression of glypican-5 led to hindered EMT and suppressed canonical Wnt pathway activation, which eventually inhibited cancer cell proliferation and invasion [79]. Presumably, these functions of glypican-5 might be exerted through interaction of HS with Wnt, which should be further explored. In the context of pancreatic tumor genesis, a mimetic form of HS prevented endogenous HS from cleavage at the cell surface and consequently inhibited the proliferation of pancreatic cancer cells. This activity is by directly interacting with Wnt3a and Wnt7 to suppress the canonical Wnt pathway [80]. A recent epitope mapping study revealed specific binding domains within the HS molecule for Wnt ligand [81]. These results support the assumption that the functions of glypican in modulation of the Wnt pathway are mainly through interaction of HS with Wnt. Nonetheless, it should be noted that up to date, the Wnt activity has been mostly associated with HSPGs, although detailed information on the functional properties of HS, e.g. Wnt binding epitopes and interaction with the receptors, is circumstantial. One aspect is the characteristic of Wnt receptor as GPCR, which may increase the difficulty for studying complex formation of cytokine-HS-receptor.

6. HS and Hh signaling

Hedgehog (Hh) was first identified in *Drosophila* [82] and the Hh signaling pathway is one of the key regulators for animal development. Three mammalian homologues of Hh have been identified, i.e. sonic hedgehog (SHH), Indian hedgehog (IHH) and desert hedgehog (DHH), each has its own evolutionarily conserved role during animal development despite of certain redundancy.

The first evidence of HSPG regulation on Hh activity was

demonstrated in the development of *Drosophila* wing disc where it was found that HSPG is required for Hh diffusion [83]. Hh proteins need to go through several post-translational modification steps before becoming fully activated, including an initial cleavage of the C-terminal domain [84] followed by covalent cholesterol modification and palmitoylation at the remaining N-terminal domain [85,86]. The cholesterol moiety anchors the Hh to the cell membrane by interacting with the cell-surface HSPGs, which is critical for Hh transport and signaling [87]. In *Drosophila*, the cell-surface glypican recruits lipophorin, a lipoprotein particle, to form a complex that colocalizes with Hh proteins and enhances Hh signaling efficiency [88]. Interestingly, SHH with a mutation within the HS-interaction motif only affected cell proliferation but not tissue patterning, suggesting a differential dependence on HS [89]. Glypican-3 has been shown to suppress Hh signaling by directly binding to the Hh ligands, preventing them from binding to their receptor, Patched [90]. A recent study showed that processing by convertase, an enzyme that cleaves glypican-3 into two loosely connected subunits, is essential for its inhibition of the Hh signaling [91]; however, the stimulation on Wnt signaling was not affected in the convertase-resistant mutants [73].

The importance of HS in Hh medicated signaling has been exemplified in a transgenic mouse model that is deficient in the HS polymerase, EXT1 [92]. An elevated level of IHH signaling in differentiating chondrocytes led to delayed hypertrophic differentiation and increased chondrocyte proliferation in the mutant mice. On the other hand, loss of the endosulfatase (Sulf) accelerated chondrocyte hypertrophy due to increased level of IHH activity [93]. Available evidences show that the IHH activity is dependent on the molecular structure of HS. For example, mice deficient in Hsepi exhibited multiple skeletal development defects, which was, at least partly, attributed to elevated IHH signaling activity as reflected by the expression level of Patched1 gene, both of which led to delayed hypertrophic differentiation during endochondral bone formation [16]. It has also been shown that HS deficiency caused growth retardation of postnatal long bone growth, accompanied by a severe disorganized chondrocyte column in long bone growth plates in mice [94]. Although the study did not show any direct evidence of altered IHH expression in the mutants, the growth plate phenotype observed in the HS mutant mice resembled that found in a IHH mutants [95].

Apart from the skeletal system, recent studies have extended our understanding on the biological roles of HSPG-Hh interaction in development of other organs. During lung morphogenesis, epithelial deletion of the HS polymerase EXT1 resulted in aberrant lung morphology due to reduced level of active SHH despite of normal gene expression and stability of the protein [17], suggesting a modulation role of HS on SHH activity. A novel role of glypican-1 in guiding commissural axons to exit the floorplate and form longitudinal projections during neural circuit formation has been reported [96]. Glypican-1 acts as a co-receptor for SHH to induce the expression of Hedgehog-interacting protein, which is critical for the axonal responsiveness switching process [96]. Furthermore, a study identified glypican-5 as co-receptors for SHH in cerebellar granule precursor cells to promote neural precursor proliferation [97]. Particularly, it was found that the 2-O-sulfated iduronic acid residue of HS was important for its interaction with SHH. In gastric cancer cells, expression of the endosulfatase-1 has been shown to significantly suppress cell proliferation by down-regulating many of the Hh target genes, including Gli1, Ptch1/2 and c-Myc [98]. These studies have enhanced our understanding for the properties of molecular structures (epitopes) in a given HS chain that interacts with Hh.

7. HS and VEGF signaling

Vascular endothelial growth factor (VEGF) was originally identified as a vascular permeability factor that was present in tumor ascites fluid [99] and now known as a potent angiogenesis stimulator, playing critical roles in neovascularization under both physiological and pathological conditions. Earlier studies reported that the signaling activity of VEGF is through binding to both the receptors and cell surface HSPG [100]. Notably, the splice isoforms are different in the affinity towards the receptors and HSPG. Analysis of HS binding sites on the most common form of VEGF revealed that the interaction is not dependent on single sulfated domains (epitopes) in a given HS chain, but rather a cooperation of two sulfated domains within the VEGF dimer [101]. Like most of other cytokines, sulfation degree and pattern of HS play important roles in their binding towards VEGF. One example is that Sulf1 action affected VEGF-mediated arterial-venous identity in zebrafish [102]. Suppression of HS sulfation by microRNA not only resulted in reduced binding affinity to VEGF, but also led to decreased VEGF protein expression in endothelial cells [103]. Sulfation at C3 of glucosamine is usually rare in HS; however, it was found that expression of glucosamine 3-O-sulfotransferase 3B1 subtype promoted angiogenesis and proliferation by inducing VEGF expression and shedding in acute myeloid leukemia cells [104]. Deletion of the N-sulfotransferase, NDST1, resulted in significantly reduced N-sulfation of glucosamine, and accordingly, attenuated VEGF signaling in tumor angiogenesis [105]; but it did not affect the VEGF signaling activity in development of congenital diaphragmatic hernia [106]. Our ongoing study shows that the lungs from the *Hsepi* KO mice displayed significantly lower levels of VEGFR and p-VEGFR (unpublished data). Collectively, the information indicates that VEGF may require different HS structures in different cells or conditions. Though majority of studies found that heparin or HS promoted VEGF activity, accordingly angiogenesis, while recent report also found that heparin impaired angiogenic signaling through reducing VEGFR2 activation [107].

HS is abundantly expressed in developing and mature blood vessels where they are generally believed to play a pro-angiogenic role in both normal and pathological angiogenesis by interacting with VEGFs. One important role of HS was to spatially restrict VEGF to create a concentration gradient that is essential for blood vessel branching [108]. A number of recent studies have advanced our understanding on the roles of HS-VEGF interaction in multiple cellular contexts of pathophysiological conditions. Delivery of a purified HS significantly improved the recovery from limb ischemia in the skeletal tissues of a mouse model by stabilizing VEGF against thermal and enzyme degradation [109]. In the context of cancer development, heparanase-induced shedding of HS from hepatocarcinoma cell surface induced release of VEGF into the medium, which promoted the surrounding lymphatic endothelial cell growth [110]. Aging was identified as a factor affecting the structure of HS, that is associated with a decline in the migratory response of human outgrowth endothelial cell towards VEGF signaling [111].

8. HS and HGF signaling

Hepatocyte growth factor (HGF) was identified based on its ability to promote mitogenesis of rat hepatocytes [112] by binding to and activation of the Met receptor tyrosine kinase [113]. Signaling mediated via this complex is essential for a wide range of cellular activities, including embryogenesis and tissue regeneration. Disruption of this signaling complex is a typical feature of many malignant tumors. HGF is known to interact with HS via the N-terminal domain of the ligand [114,115], but direct evidences showing the biological activities of HGF-HS-Met interaction in cell models are still lacking. Nevertheless, one role of HS is to concentrate the HGFs at the cell surface via direct interaction to promote their interactions with Met in an energetically favourable manner. Several studies have reported the direct involvement of HS in HGF stimulated cell signaling [116,117]. Levels of CD44, HS, c-Met and HGF are used to assess the metastatic process of colorectal cancer due to their simultaneous overexpression in colon carcinoma cells [118]. Similar co-activation mechanism was also observed in multiple myeloma where syndecan-1 acts as a functional co-receptor for HGF to facilitate HGF/c-Met signaling [68]. The HS-stimulated HGF

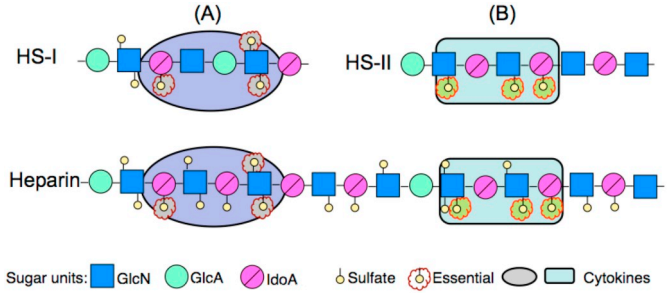

Fig. 3. Heparin and HS are synthesized by formation of polysaccharide chain of glucosamine (GlcN) and glucuronic acid (GlcA) that are modified by several sulfotransferases to add sulfate groups at various positions, and by C5-epimerase to convert GlcA to iduronic acid (IdoA). Cytokine (A) requires three sulfate groups two of which are at the position of $GlcNOS_3$ and $GlcN6OS_3$, respectively; while cytokine (B) also requires three sulfate groups, but two of which are located at $GlcNSO_3$. HS-I will not be able to bind to cytokine (B), vice versa for HS-II. Heparin harbours both epitopes and can bind to both cytokines.

signaling was shown to be mediated via interaction with c-Met at the cell surface, but not with HGF, to recruit specific intracellular effectors that transmit distinct HGF responses for mitogenesis and cell motility [119].

A number of recent studies have further improved our understanding on the roles of HGF-HS complex in multiple cellular contexts. In a variety of human cancer cell lines, it has been shown that targeted disruption of HS – HGF interaction by substitution of the specific amino acids within the HS binding site of HGF can transform it into selective competitive antagonists of their original form, consequently, blocking oncogenic signaling and cancer progression [120]. Addition of HS increased the mitogenic potency of HGF in cell culture [121]. HS is also suggested to induce a conformational change in HGF to enable and stabilize their dimerization that is required for stable binding to Met [122]. In many myeloma cell types, syndecan-1 is proteolytically shed from the cell surface into the bone marrow where it enhances tumor growth, angiogenesis and metastasis [123,124]. Recently, it has been shown that the shed syndecan-1in the medium of tumor cells together with the bound HGF was taken up by bone-marrow-derived stromal cells and transported to the nucleus where they prevent histone acetylation through binding to the histone acetyltransferase enzyme p300 [125]. Removal of the HGF cargo from the shed syndecan-1 abolished the translocation process. In the context of skeletal muscle development and tissue regeneration the presence of glypican-1 in the lipid raft membrane domains of myoblasts is essential for a maximum cellular response to HGF [126]. It stabilized Met and HGF by forming a signaling harbor for activa phospho-Met receptors to be concentrated.

9. Implications of heparin in cell signaling activity

Heparin shares a high structural similarity with HS, and is synthesized by the same set of enzymes as for HS biosynthesis. However, unlike the ubiquitous expression pattern of HS, heparin is exclusively expressed in the connective tissue mast cells in the proteoglycan form of serglycin that is the only proteoglycan found intracellularly present in the secretary granules of mast cell [127]. Although the physiological functions are still not fully understood, heparin has been used as a powerful anticoagulant in clinic since 1950's. The anticoagulant activity of heparin is through its highly specific interaction with antithrombin (AT), and coagulation factors [128]. This high AT binding affinity depends on a unique penta-saccharide sequence present in heparin [129], but rarely in HS [130]. Nevertheless, apart from the penta-saccharide sequence, the molecular structure of heparin can be described as highly sulfated epitopes in HS (Fig. 3). Thus, heparin is often used as a replacement of HS for in vitro studies of cytokine-HS interaction, since heparin essentially contains all the epitopes present in HS (Fig. 3). Since only a small portion of the heparin chains contains the AT-binding penta-saccharide sequence, rest part of the heparin chains are potentially able to interact with the cytokines that bind to HS (Fig. 3). This feature of heparin was not recognized in the clinic when applying heparin as an anticoagulant, and the potential 'side effect' of heparin has been largely overlooked until recently. In connection with the treatment of thrombotic symptoms, several non-anticoagulant, yet beneficial, activities of heparin have been discovered. Clinical observation has revealed that cancer patients received treatment with low molecular weight heparin (LMWH) exhibited a better outcome in comparison to the patients of similar status who had not been treated with LMWH [131]. Though the mechanisms for such a favourable effect has not been clarified, one possible mechanism is that the heparin may compete with cell surface HS for binding to mitogenic cytokines, e.g. FGF, therefore neutralizing their activity in promoting tumor growth. One more example is that pregnant women on prophylactic treatment with LMWH (due to thromboembolic complications) had a 30% decreased parturition time compared to matched controls [132]. The finding pointed to a functional role of heparin in uterine contractility during childbirth. These effects of heparin are most likely through interfering with the biological roles of HS, which are not yet elucidated. The interaction of heparin with cytokines can be either promotable or inhibitory to the biological activities of HS with the respective cytokines or their receptors. Due to the overall higher degree of sulfation, heparin molecules are more homogenous and lack the distinct domain/epitope structure that is typical for HS. Thus, different epitopes expressed in different HS chains can be present in any individual heparin polysaccharide, making heparin more potent in binding to HS-binding proteins. Thus, it should be kept in mind that application of heparin for anticoagulation purpose may also affect diverse signaling pathways.

10. Conclusion

In the past several years, significant progress has been made in unveiling the roles of HSPG in cytokine-stimulated cellular signaling in various developmental and functional contexts. Though substantial information has been collected as briefly discussed in this review, it can be assumed that these macromolecules may have more unknown functions to be discovered. In many cases, HS is modulating more than one of the above-mentioned pathways by acting as a master switch at the cell surface that integrates multiple extracellular signals into different intracellular responses. In consideration of the fact that majority of cytokine-receptor interaction is based on or results in dimerization or oligomerization of receptors, it is rational to assume that the core protein of HSPG tethers their polysaccharide chains on the surface to facilitate ligand-receptor interaction, for which the detailed mechanisms may have not been elucidated yet. Thus, future study should focus on defining the epitopes of HS that selectively interact with individual cytokines, enabling tailored design of HS-mimetics that can be used for therapeutic purposes, through interfering the HSPG-cytokine interaction. In addition, it is also important to find out the mechanisms of HS as a signal integrator and how it rallies these different signals into various cellular responses by applying cell models that express structurally altered HS.

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References

[1] J.D. Esko, S.B. Selleck, Order out of chaos: assembly of ligand binding sites in heparan sulfate, Annu. Rev. Biochem. 71 (2002) 435–471.
[2] U. Lindahl, J.P. Li, Interactions between heparan sulfate and proteins-design and functional implications, Int. Rev. Cell Mol. Biol. 276 (2009) 105–159.

[3] J.P. Li, M. Kusche-Gullberg, Heparan sulfate: biosynthesis, structure, and function, Int. Rev. Cell Mol. Biol. 325 (2016) 215–273.
[4] L.E. Collins, L. Troeberg, Heparan sulfate as a regulator of inflammation and immunity, J. Leukoc. Biol. (2018), https://doi.org/10.1002/JLB.3RU0618-246R.
[5] K. Sugahara, H. Kitagawa, Heparin and heparan sulfate biosynthesis, IUBMB Life 54 (4) (2002) 163–175.
[6] L. Kjellen, U. Lindahl, Specificity of glycosaminoglycan-protein interactions, Curr. Opin. Struct. Biol. 50 (2018) 101–108.
[7] J. Jia, et al., Lack of L-iduronic acid in heparan sulfate affects interaction with growth factors and cell signaling, J. Biol. Chem. 284 (23) (2009) 15942–15950.
[8] U. Lindahl, What else can 'Heparin' do? Haemostasis 29 (Suppl S1) (1999) 38–47.
[9] J.A. Deakin, et al., The binding properties of minimal oligosaccharides reveal a common heparan sulfate/dermatan sulfate-binding site in hepatocyte growth factor/scatter factor that can accommodate a wide variety of sulfation patterns, J. Biol. Chem. 284 (10) (2009) 6311–6321.
[10] M.L. Escobar Galvis, et al., Transgenic or tumor-induced expression of heparanase upregulates sulfation of heparan sulfate, Nat. Chem. Biol. 3 (12) (2007) 773–778.
[11] M. Lyon, et al., Interaction of hepatocyte growth factor with heparan sulfate. Elucidation of the major heparan sulfate structural determinants, J. Biol. Chem. 269 (15) (1994) 11216–11223.
[12] X. Ai, et al., QSulf1 remodels the 6-O sulfation states of cell surface heparan sulfate proteoglycans to promote Wnt signaling, J. Cell Biol. 162 (2) (2003) 341–351.
[13] X. Ai, et al., SULF1 and SULF2 regulate heparan sulfate-mediated GDNF signaling for esophageal innervation, Development 134 (18) (2007) 3327–3338.
[14] T. Batool, et al., Overexpression of heparanase attenuated TGF-beta-stimulated signaling in tumor cells, FEBS Open Biol. 7 (3) (2017) 405–413.
[15] T. Batool, H. Zhao, C. Gallant, A. Moustakas, J.-P. Li, Glucuronyl C5-epimerase regulates the BMP-Smad signaling pathway Glucuronyl C5-epimerase regulates the BMP-Smad signaling pathway, Cell. Signal. (2018, Nov 17) pii: S0898-6568(18)30280-8.
[16] T. Dierker, et al., Altered heparan sulfate structure in Glce(−/−) mice leads to increased Hedgehog signaling in endochondral bones, Matrix Biol. 49 (2016) 82–92.
[17] H. He, et al., Epithelial heparan sulfate regulates Sonic Hedgehog signaling in lung development, PLoS Genet. 13 (8) (2017) e1006992.
[18] K. Iwao, et al., Heparan sulfate deficiency leads to Peters anomaly in mice by disturbing neural crest TGF-beta2 signaling, J. Clin. Invest. 119 (7) (2009) 1997–2008.
[19] J.P. Li, et al., Targeted disruption of a murine glucuronyl C5-epimerase gene results in heparan sulfate lacking L-iduronic acid and in neonatal lethality, J. Biol. Chem. 278 (31) (2003) 28363–28366.
[20] R.M. Reijmers, et al., Impaired lymphoid organ development in mice lacking the heparan sulfate modifying enzyme glucuronyl C5-epimerase, J. Immunol. 184 (7) (2010) 3656–3664.
[21] S. Nagamine, et al., Organ-specific sulfation patterns of heparan sulfate generated by extracellular sulfatases Sulf1 and Sulf2 in mice, J. Biol. Chem. 287 (12) (2012) 9579–9590.
[22] R. Dhanasekaran, et al., Activation of the transforming growth factor-beta/SMAD transcriptional pathway underlies a novel tumor-promoting role of sulfatase 1 in hepatocellular carcinoma, Hepatology 61 (4) (2015) 1269–1283.
[23] J.R. Higginson, et al., Differential sulfation remodelling of heparan sulfate by extracellular 6-O-sulfatases regulates fibroblast growth factor-induced boundary formation by glial cells: implications for glial cell transplantation, J. Neurosci. 32 (45) (2012) 15902–15912.
[24] T.H. Tran, et al., Heparan sulfate 6-O-endosulfatases (Sulfs) coordinate the Wnt signaling pathways to regulate myoblast fusion during skeletal muscle regeneration, J. Biol. Chem. 287 (39) (2012) 32651–32664.
[25] D.S. Pikas, et al., Substrate specificity of heparanases from human hepatoma and platelets, J. Biol. Chem. 273 (30) (1998) 18770–18777.
[26] V. Cohen-Kaplan, et al., Heparanase augments epidermal growth factor receptor phosphorylation: correlation with head and neck tumor progression, Cancer Res. 68 (24) (2008) 10077–10085.
[27] D. Zhang, et al., Hyperglycemia-induced secretion of endothelial heparanase stimulates a vascular endothelial growth factor autocrine network in cardiomyocytes that promotes recruitment of lipoprotein lipase, Arterioscler. Thromb. Vasc. Biol. 33 (12) (2013) 2830–2838.
[28] D.M. Ornitz, N. Itoh, The fibroblast growth factor signaling pathway, Wiley Interdiscip. Rev. Dev. Biol. 4 (3) (2015) 215–266.
[29] P. Bashkin, et al., Basic fibroblast growth factor binds to subendothelial extracellular matrix and is released by heparitinase and heparin-like molecules, Biochemistry 28 (4) (1989) 1737–1743.
[30] X. Lin, N. Perrimon, Dally cooperates with Drosophila Frizzled 2 to transduce Wingless signalling, Nature 400 (6741) (1999) 281–284.
[31] K. Nybakken, N. Perrimon, Heparan sulfate proteoglycan modulation of developmental signaling in Drosophila, Biochim. Biophys. Acta 1573 (3) (2002) 280–291.
[32] M. Venero Galanternik, K.L. Kramer, T. Piotrowski, Heparan sulfate proteoglycans regulate Fgf signaling and cell polarity during collective cell migration, Cell Rep. (2015), https://doi.org/10.1016/j.celrep.2014.12.043 S2211-1247(14)01096-1.
[33] D.M. Ornitz, FGFs, heparan sulfate and FGFRs: complex interactions essential for development, BioEssays 22 (2) (2000) 108–112.
[34] L. Pellegrini, Role of heparan sulfate in fibroblast growth factor signalling: a structural view, Curr. Opin. Struct. Biol. 11 (5) (2001) 629–634.
[35] L. Pellegrini, et al., Crystal structure of fibroblast growth factor receptor ectodomain bound to ligand and heparin, Nature 407 (6807) (2000) 1029–1034.
[36] J. Schlessinger, et al., Crystal structure of a ternary FGF-FGFR-heparin complex reveals a dual role for heparin in FGFR binding and dimerization, Mol. Cell 6 (3) (2000) 743–750.
[37] A.A. Belov, M. Mohammadi, Molecular mechanisms of fibroblast growth factor signaling in physiology and pathology, Cold Spring Harb. Perspect. Biol. (2013) 5(6).
[38] V. Schultz, et al., Heparan sulfate domains required for fibroblast growth factor 1 and 2 signaling through fibroblast growth factor receptor 1c, J. Biol. Chem. 292 (6) (2017) 2495–2509.
[39] Y. Li, et al., Heparin binding preference and structures in the fibroblast growth factor family parallel their evolutionary diversification, Open Biol. (2016) 6(3).
[40] Y. Pan, et al., Bud specific N-sulfation of heparan sulfate regulates Shp2-dependent FGF signaling during lacrimal gland induction, Development 135 (2) (2008) 301–310.
[41] Y. Pan, et al., Heparan sulfate expression in the neural crest is essential for mouse cardiogenesis, Matrix Biol. 35 (2014) 253–265.
[42] K. Fujio, et al., Revisiting the regulatory roles of the TGF-beta family of cytokines, Autoimmun. Rev. 15 (9) (2016) 917–922.
[43] C.C. Rider, B. Mulloy, Bone morphogenetic protein and growth differentiation factor cytokine families and their protein antagonists, Biochem. J. 429 (1) (2010) 1–12.
[44] T.A. McCaffrey, D.J. Falcone, B. Du, Transforming growth factor-beta 1 is a heparin-binding protein: identification of putative heparin-binding regions and isolation of heparins with varying affinity for TGF-beta 1, J. Cell. Physiol. 152 (2) (1992) 430–440.
[45] C.L. Chen, S.S. Huang, J.S. Huang, Cellular heparan sulfate negatively modulates transforming growth factor-beta1 (TGF-beta1) responsiveness in epithelial cells, J. Biol. Chem. 281 (17) (2006) 11506–11514.
[46] J. Chen, et al., Exogenous heparan sulfate enhances the TGF-beta3-induced chondrogenesis in human mesenchymal stem cells by activating TGF-beta/smad signaling, Stem Cells Int. 2016 (2016) 1520136.
[47] Y. Takashima, et al., Heparan sulfate 6-O-endosulfatases, Sulf1 and Sulf2, regulate glomerular integrity by modulating growth factor signaling, Am. J. Physiol. Ren. Physiol. 310 (5) (2016) F395–F408.
[48] X. Yue, et al., Overexpression of Sulf2 in idiopathic pulmonary fibrosis, Glycobiology 23 (6) (2013) 709–719.
[49] M. Morikawa, R. Derynck, K. Miyazono, TGF-beta and the TGF-beta Family: context-dependent roles in cell and tissue physiology, Cold Spring Harb. Perspect. Biol. 8 (5) (2016).
[50] A.B. Roberts, M.B. Sporn, Transforming growth factors, Cancer Surv. 4 (4) (1985) 683–705.
[51] W.J. Kuo, M.A. Digman, A.D. Lander, Heparan sulfate acts as a bone morphogenetic protein coreceptor by facilitating ligand-induced receptor hetero-oligomerization, Mol. Biol. Cell 21 (22) (2010) 4028–4041.
[52] Z. Hu, et al., NDST1-dependent heparan sulfate regulates BMP signaling and internalization in lung development, J. Cell Sci. 122 (Pt 8) (2009) 1145–1154.
[53] M. Ringvall, et al., Defective heparan sulfate biosynthesis and neonatal lethality in mice lacking N-deacetylase/N-sulfotransferase-1, J. Biol. Chem. 275 (34) (2000) 25926–25930.
[54] A. Wodarz, R. Nusse, Mechanisms of Wnt signaling in development, Annu. Rev. Cell Dev. Biol. 14 (1998) 59–88.
[55] M.T. Veeman, J.D. Axelrod, R.T. Moon, A second canon. Functions and mechanisms of beta-catenin-independent Wnt signaling, Dev. Cell 5 (3) (2003) 367–377.
[56] D.G. Monroe, et al., Update on Wnt signaling in bone cell biology and bone disease, Gene 492 (1) (2012) 1–18.
[57] T.D. Rachner, S. Khosla, L.C. Hofbauer, Osteoporosis: now and the future, Lancet 377 (9773) (2011) 1276–1287.
[58] A.J. Bass, et al., Genomic sequencing of colorectal adenocarcinomas identifies a recurrent VTI1A-TCF7L2 fusion, Nat. Genet. 43 (10) (2011) 964–968.
[59] T. Sjoblom, et al., The consensus coding sequences of human breast and colorectal cancers, Science 314 (5797) (2006) 268–274.
[60] R.C. Binari, et al., Genetic evidence that heparin-like glycosaminoglycans are involved in wingless signaling, Development 124 (13) (1997) 2623–2632.
[61] U. Hacker, X. Lin, N. Perrimon, The Drosophila sugarless gene modulates Wingless signaling and encodes an enzyme involved in polysaccharide biosynthesis, Development 124 (18) (1997) 3565–3573.
[62] T.E. Haerry, et al., Defects in glucuronate biosynthesis disrupt Wingless signaling in Drosophila, Development 124 (16) (1997) 3055–3064.
[63] E. Boudin, et al., The role of extracellular modulators of canonical Wnt signaling in bone metabolism and diseases, Semin. Arthritis Rheum. 43 (2) (2013) 220–240.
[64] G. David, et al., Spatial and temporal changes in the expression of fibroglycan (syndecan-2) during mouse embryonic development, Development 119 (3) (1993) 841–854.
[65] R. Mansouri, et al., Osteoblastic heparan sulfate glycosaminoglycans control bone remodeling by regulating Wnt signaling and the crosstalk between bone surface and marrow cells, Cell Death Dis. 8 (6) (2017) e2902.
[66] J. Ruan, et al., Heparanase inhibits osteoblastogenesis and shifts bone marrow progenitor cell fate in myeloma bone disease, Bone 57 (1) (2013) 10–17.
[67] J. Bertrand, et al., Syndecan 4 supports bone fracture repair, but not fetal skeletal development, in mice, Arthritis Rheum. 65 (3) (2013) 743–752.
[68] P.W. Derksen, et al., Cell surface proteoglycan syndecan-1 mediates hepatocyte growth factor binding and promotes Met signaling in multiple myeloma, Blood 99 (4) (2002) 1405–1410.
[69] R.M. Reijmers, et al., Targeting EXT1 reveals a crucial role for heparan sulfate in the growth of multiple myeloma, Blood 115 (3) (2010) 601–604.
[70] Z. Ren, et al., Syndecan-1 promotes Wnt/beta-catenin signaling in multiple myeloma by presenting Wnts and R-spondins, Blood 131 (9) (2018) 982–994.

[71] H.C. Hsu, W. Cheng, P.L. Lai, Cloning and expression of a developmentally regulated transcript MXR7 in hepatocellular carcinoma: biological significance and temporospatial distribution, Cancer Res. 57 (22) (1997) 5179–5184.
[72] M. Capurro, et al., Glypican-3: a novel serum and histochemical marker for hepatocellular carcinoma, Gastroenterology 125 (1) (2003) 89–97.
[73] M.I. Capurro, et al., Glypican-3 promotes the growth of hepatocellular carcinoma by stimulating canonical Wnt signaling, Cancer Res. 65 (14) (2005) 6245–6254.
[74] L. Li, et al., Oncogenic activation of glypican-3 by c-Myc in human hepatocellular carcinoma, Hepatology 56 (4) (2012) 1380–1390.
[75] S.I. Zittermann, et al., Soluble glypican 3 inhibits the growth of hepatocellular carcinoma in vitro and in vivo, Int. J. Cancer 126 (6) (2010) 1291–1301.
[76] M. Capurro, et al., Glypican-3 binds to Frizzled and plays a direct role in the stimulation of canonical Wnt signaling, J. Cell Sci. 127 (Pt 7) (2014) 1565–1575.
[77] Y. Li, P. Yang, GPC5 gene and its related pathways in lung cancer, J. Thorac. Oncol. 6 (1) (2011) 2–5.
[78] S. Wang, et al., Glypican-5 suppresses epithelial-mesenchymal transition of the lung adenocarcinoma by competitively binding to Wnt3a, Oncotarget 7 (48) (2016) 79736–79746.
[79] Y. Sun, et al., Overexpression of glypican 5 (GPC5) inhibits prostate cancer cell proliferation and invasion via suppressing Sp1-mediated EMT and activation of Wnt/beta-catenin signaling, Oncol. Res. 26 (4) (2017, 7) 565–572.
[80] D.B. Jung, et al., The heparan sulfate mimetic PG545 interferes with Wnt/beta-catenin signaling and significantly suppresses pancreatic tumorigenesis alone and in combination with gemcitabine, Oncotarget 6 (7) (2015) 4992–5004.
[81] W. Gao, et al., Epitope mapping by a Wnt-blocking antibody: evidence of the Wnt binding domain in heparan sulfate, Sci. Rep. 6 (2016) 26245.
[82] C. Nusslein-Volhard, E. Wieschaus, Mutations affecting segment number and polarity in Drosophila, Nature 287 (5785) (1980) 795–801.
[83] Y. Bellaiche, I. The, N. Perrimon, Tout-velu is a Drosophila homologue of the putative tumour suppressor EXT-1 and is needed for Hh diffusion, Nature 394 (6688) (1998) 85–88.
[84] J.A. Porter, et al., The product of hedgehog autoproteolytic cleavage active in local and long-range signalling, Nature 374 (6520) (1995) 363–366.
[85] R.B. Pepinsky, et al., Identification of a palmitic acid-modified form of human Sonic hedgehog, J. Biol. Chem. 273 (22) (1998) 14037–14045.
[86] J.A. Porter, et al., Hedgehog patterning activity: role of a lipophilic modification mediated by the carboxy-terminal autoprocessing domain, Cell 86 (1) (1996) 21–34.
[87] N. Vyas, et al., Nanoscale organization of hedgehog is essential for long-range signaling, Cell 133 (7) (2008) 1214–1227.
[88] C. Eugster, et al., Lipoprotein-heparan sulfate interactions in the Hh pathway, Dev. Cell 13 (1) (2007) 57–71.
[89] J.A. Chan, et al., Proteoglycan interactions with Sonic Hedgehog specify mitogenic responses, Nat. Neurosci. 12 (4) (2009) 409–417.
[90] M.I. Capurro, et al., Glypican-3 inhibits Hedgehog signaling during development by competing with patched for Hedgehog binding, Dev. Cell 14 (5) (2008) 700–711.
[91] M. Capurro, et al., Processing by convertases is required for glypican-3-induced inhibition of Hedgehog signaling, J. Biol. Chem. 290 (12) (2015) 7576–7585.
[92] L. Koziel, et al., Ext1-dependent heparan sulfate regulates the range of Ihh signaling during endochondral ossification, Dev. Cell 6 (6) (2004) 801–813.
[93] A. Ratzka, S. Mundlos, A. Vortkamp, Expression patterns of sulfatase genes in the developing mouse embryo, Dev. Dyn. 239 (6) (2010) 1779–1788.
[94] F. Sgariglia, et al., Epiphyseal abnormalities, trabecular bone loss and articular chondrocyte hypertrophy develop in the long bones of postnatal Ext1-deficient mice, Bone 57 (1) (2013) 220–231.
[95] M.S. Razzaque, et al., Conditional deletion of Indian hedgehog from collagen type 2alpha1-expressing cells results in abnormal endochondral bone formation, J. Pathol. 207 (4) (2005) 453–461.
[96] N.H. Wilson, E.T. Stoeckli, Sonic hedgehog regulates its own receptor on post-crossing commissural axons in a glypican1-dependent manner, Neuron 79 (3) (2013) 478–491.
[97] R.M. Witt, et al., Heparan sulfate proteoglycans containing a glypican 5 core and 2-O-sulfo-iduronic acid function as Sonic Hedgehog co-receptors to promote proliferation, J. Biol. Chem. 288 (36) (2013) 26275–26288.
[98] H.Y. Ma, et al., HSulf-1 suppresses cell growth and down-regulates Hedgehog signaling in human gastric cancer cells, Oncol. Lett. 2 (6) (2011) 1291–1295.
[99] D.R. Senger, et al., Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid, Science 219 (4587) (1983) 983–985.
[100] G. Neufeld, et al., Vascular endothelial growth factor (VEGF) and its receptors, FASEB J. 13 (1) (1999) 9–22.
[101] J.E. Turnbull, et al., Identification of the basic fibroblast growth factor binding sequence in fibroblast heparan sulfate, J. Biol. Chem. 267 (15) (1992) 10337–10341.
[102] B. Gorsi, et al., The heparan sulfate editing enzyme Sulf1 plays a novel role in zebrafish VegfA mediated arterial venous identity, Angiogenesis 17 (1) (2014) 77–91.
[103] Z. Kasza, et al., MicroRNA-24 suppression of N-deacetylase/N-sulfotransferase-1 (NDST1) reduces endothelial cell responsiveness to vascular endothelial growth factor A (VEGFA), J. Biol. Chem. 288 (36) (2013) 25956–25963.
[104] L. Zhang, et al., Heparan sulfate D-glucosaminyl 3-O-sulfotransferase-3B1 (HS3ST3B1) promotes angiogenesis and proliferation by induction of VEGF in acute myeloid leukemia cells, J. Cell. Biochem. 116 (6) (2015) 1101–1112.
[105] M.M. Fuster, et al., Genetic alteration of endothelial heparan sulfate selectively inhibits tumor angiogenesis, J. Cell Biol. 177 (3) (2007) 539–549.
[106] B. Zhang, et al., Heparan sulfate deficiency disrupts developmental angiogenesis and causes congenital diaphragmatic hernia, J. Clin. Invest. 124 (1) (2014) 209–221.
[107] D.T. Dao, et al., Heparin impairs angiogenic signaling and compensatory lung growth after left pneumonectomy, Angiogenesis 21 (4) (2018) 837–848.
[108] C. Ruhrberg, et al., Spatially restricted patterning cues provided by heparin-binding VEGF-A control blood vessel branching morphogenesis, Genes Dev. 16 (20) (2002) 2684–2698.
[109] S. Poon, et al., Improved recovery from limb ischaemia by delivery of an affinity-isolated heparan sulphate, Angiogenesis 21 (4) (2018) 777–791.
[110] S. Yu, et al., Heparanase-1-induced shedding of heparan sulfate from syndecan-1 in hepatocarcinoma cell facilitates lymphatic endothelial cell proliferation via VEGF-C/ERK pathway, Biochem. Biophys. Res. Commun. 485 (2) (2017) 432–439.
[111] K.A. Williamson, et al., Age-related impairment of endothelial progenitor cell migration correlates with structural alterations of heparan sulfate proteoglycans, Aging Cell 12 (1) (2013) 139–147.
[112] T. Nakamura, et al., Purification and subunit structure of hepatocyte growth factor from rat platelets, FEBS Lett. 224 (2) (1987) 311–316.
[113] D.P. Bottaro, et al., Identification of the hepatocyte growth factor receptor as the c-met proto-oncogene product, Science 251 (4995) (1991) 802–804.
[114] D. Lietha, et al., Crystal structures of NK1-heparin complexes reveal the basis for NK1 activity and enable engineering of potent agonists of the MET receptor, EMBO J. 20 (20) (2001) 5543–5555.
[115] M. Lyon, J.A. Deakin, J.T. Gallagher, The mode of action of heparan and dermatan sulfates in the regulation of hepatocyte growth factor/scatter factor, J. Biol. Chem. 277 (2) (2002) 1040–1046.
[116] H. Sakata, et al., Heparin binding and oligomerization of hepatocyte growth factor/scatter factor isoforms. Heparan sulfate glycosaminoglycan requirement for met binding and signaling, J. Biol. Chem. 272 (14) (1997) 9457–9463.
[117] J. Schlessinger, I. Lax, M. Lemmon, Regulation of growth factor activation by proteoglycans: what is the role of the low affinity receptors? Cell 83 (3) (1995) 357–360.
[118] V.J. Wielenga, et al., Expression of c-Met and heparan-sulfate proteoglycan forms of CD44 in colorectal cancer, Am. J. Pathol. 157 (5) (2000) 1563–1573.
[119] J.S. Rubin, et al., Dissociation of heparan sulfate and receptor binding domains of hepatocyte growth factor reveals that heparan sulfate-c-met interaction facilitates signaling, J. Biol. Chem. 276 (35) (2001) 32977–32983.
[120] F. Cecchi, et al., Targeted disruption of heparan sulfate interaction with hepatocyte and vascular endothelial growth factors blocks normal and oncogenic signaling, Cancer Cell 22 (2) (2012) 250–262.
[121] T.F. Zioncheck, et al., Sulfated oligosaccharides promote hepatocyte growth factor association and govern its mitogenic activity, J. Biol. Chem. 270 (28) (1995) 16871–16878.
[122] L.E. Kemp, B. Mulloy, E. Gherardi, Signalling by HGF/SF and Met: the role of heparan sulphate co-receptors, Biochem. Soc. Trans. 34 (Pt 3) (2006) 414–417.
[123] A. Purushothaman, et al., Heparanase-enhanced shedding of syndecan-1 by myeloma cells promotes endothelial invasion and angiogenesis, Blood 115 (12) (2010) 2449–2457.
[124] Y. Yang, et al., Soluble syndecan-1 promotes growth of myeloma tumors in vivo, Blood 100 (2) (2002) 610–617.
[125] M.D. Stewart, V.C. Ramani, R.D. Sanderson, Shed syndecan-1 translocates to the nucleus of cells delivering growth factors and inhibiting histone acetylation: a novel mechanism of tumor-host cross-talk, J. Biol. Chem. 290 (2) (2015) 941–949.
[126] J. Gutierrez, D. Cabrera, E. Brandan, Glypican-1 regulates myoblast response to HGF via Met in a lipid raft-dependent mechanism: effect on migration of skeletal muscle precursor cells, Skelet. Muscle 4 (1) (2014) 5.
[127] U. Lindahl, Biosynthesis of heparin, Biochem. Soc. Trans. 18 (5) (1990) 803–805.
[128] U. Lindahl, et al., Evidence for a 3-O-sulfated D-glucosamine residue in the antithrombin-binding sequence of heparin, Proc. Natl. Acad. Sci. U. S. A. 77 (11) (1980) 6551–6555.
[129] L.G. Oscarsson, G. Pejler, U. Lindahl, Location of the antithrombin-binding sequence in the heparin chain, J. Biol. Chem. 264 (1) (1989) 296–304.
[130] A.I. De Agostini, R.D. Rosenberg, New approaches for defining the molecular basis of anticoagulantly active heparan sulfate production, Ann. N. Y. Acad. Sci. 614 (1991) 279–288.
[131] A.K. Kakkar, et al., Low molecular weight heparin, therapy with dalteparin, and survival in advanced cancer: the fragmin advanced malignancy outcome study (FAMOUS), J. Clin. Oncol. 22 (10) (2004) 1944–1948.
[132] G. Ekman-Ordeberg, et al., Low molecular weight heparin stimulates myometrial contractility and cervical remodeling in vitro, Acta Obstet. Gynecol. Scand. 88 (9) (2009) 984–989.