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Heparan sulfate signaling in cancer

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Heparan sulfate (HS) is a biopolymer consisting of variably sulfated repeating disaccharide units. The anticoagulant heparin is a highly sulfated intracellular variant of HS. HS has demonstrated roles in embryonic development, homeostasis, and human disease via non-covalent interactions with numerous cellular proteins, including growth factors and their receptors. HS can function as a co-receptor by enhancing receptor–complex formation. In other contexts, HS disrupts signaling complexes or serves as a ligand sink. The effects of HS on growth factor signaling are tightly regulated by the actions of sulfyltransferases, sulfatases, and heparanases. HS has important emerging roles in oncogenesis, and heparin derivatives represent potential therapeutic strategies for human cancers. Here we review recent insights into HS signaling in tumor proliferation, angiogenesis, metastasis, and differentiation. A cancer-specific understanding of HS signaling could uncover potential therapeutic targets in this highly actionable signaling network.

Heparan sulfate proteoglycans

The anticoagulant heparin represents one of the oldest and most successful natural therapeutic agents. Heparin was discovered in 1916 and derives its name from its abundance in hepatic tissue [1]. Heparan sulfate (HS, originally called heparatin sulfate) is a member of the glycosaminoglycan family of carbohydrates initially identified as an impurity of heparin isolations that was found to be widely distributed in human tissues [2]. Heparin and HS both consist of repeating unbranched negatively charged disaccharide units variably sulfated at the 3-O, 6-O, or N sites on glucosamine, and the 6-O site on glucuronic/iduronic acid (Box 1). Heparin represents a highly sulfated intracellular variant of HS, although its physiologic roles remain unclear.

A critical pentasaccharide within heparin and endothelial HS binds specific basic residues of the circulating extracellular serine protease inhibitor antithrombin III, causing a conformational change that allows the enzyme to inactivate the prothrombotic proteases thrombin, factor IXa, and factor Xa, thereby preventing clot formation [3] (Figure 1). Sulfation at each of the available sites shown in Figure 1 is necessary for heparin to recognize its binding site on antithrombin III.

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Although heparin is primarily synthesized by mast cells [4], HS is found across mammalian cell types as a post-translational modification, generating heparan sulfate proteoglycans (HSPGs) that serve numerous biological functions [5,6]. Variation in saccharide length and number of attached sulfate groups provide important variability with functional consequences. Unlike heparin, HSPGs are often incompletely sulfated, providing an additional layer of regulation. Similar to many surface proteins, HSPGs are constantly internalized for lysosomal degradation or membrane recycling. The typical HSPG half-life is 4–24 h, with complete turnover typically occurring by 48 h [7]. HSPGs are classified as 'full-time' if their function is restricted to HS effects on cell signaling, or 'part-time' if they have additional structural features and roles in multiple signaling pathways. Full-time HSPGs include the four transmembrane syndecans (SDCs), six glycosylphosphatidylinositol (GPI)-anchored glypicans (GPCs), and three basement membrane HSPGs (agrin, perlecan, and collagen XVIII). The type III transforming growth factor β (TGF-β) receptor (TβRIII or betaglycan), neuropilins 1 and 2, and CD44 are part-time HSPGs with major roles as co-receptors in additional signaling pathways independent of their HS modification [8,9]. As examples, TβRIII is required for TGF-β2 surface binding and downstream SMAD signaling in many cellular contexts including cancers, and the neuropilins function as co-receptors for class 3 semaphorins.

The majority of the hundreds of protein interactions ascribed to HS are mediated by specific ionic binding to lysine/arginine residues aligned in 'Cardin–Weintraub' sequences [10,11]. A number of cytokines and growth factors contain these sequences. HS can bind cytokines (Box 2) to control their localization, set up gradients in the extracellular matrix, and alter their activity [6]. HS can also bind growth factors (Box 2). Fibroblast growth factor (FGF) binding interactions are the best characterized: the HS modifications on HSPGs, including SDCs, GPCs, and TβRIII, bind both FGF ligands and receptors to form a ternary complex and enhance signaling (Figure 2), which can promote carcinogenesis [6,12,13]. By contrast, a high local concentration of cell surface HSPGs can function to disrupt growth factor signaling complexes or serve as a ligand sink. HSPGs can be found at the surface of cancer cells and can also be shed by cancer and stromal cells to enhance or suppress cell signaling and influence cancer cell biology (Figure 3).

The ability of HS to bind growth factors leads to numerous biological and pathological roles for HSPGs, including demonstrated effects on tumor angiogenesis, proliferation,

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Box 1. Synthesis and modification of HSPGs

A specific amino acid motif directs protein glycanation in the Golgi apparatus to form a HSPG [79] (Figure I). HS polymers stretch from 5 to 70 kDa [5], and HSPGs contain from one to >100 HS chains [7]. Following saccharide extension by the enzymes *ext1* and *ext2* [6], HS is further modified by sulfation at the 3-O, 6-O, and N sites on glucosamine, as well as the 2-O site on glucuronic acid [6]. These modifications impart functional specificity to HS and proceed in a highly regulated and orderly sequence.

The role of sulfotransferases in carcinogenesis has recently been explored. Expression of HS3ST2 is epigenetically silenced in lung cancers, where it functions to suppress tumor growth and invasion [80]. By contrast, HS2ST1, HS3ST3B1, HS3ST4, HS6ST1, and HS6ST2 promote cell proliferation, invasiveness, and tumor angiogenesis [77,81–83], presumably via increased HS sulfation and enhanced growth factor signaling.

HS modifications continue after synthesis and sulfation due to the actions of heparanase and sulfatase enzymes [17,84,85]. Heparanase at the cell surface or in the extracellular matrix recognizes a HS sulfation motif and hydrolyzes the glycosidic bond between glucuronic acid and glucosamine (Figure I), enabling rapid alterations with demonstrated roles in tumor metastasis and angiogenesis in neuroblastoma, breast, prostate, colon, lung, liver, ovarian, and pancreatic cancers [84,86]. Heparanase-targeting strategies, including PI-88, SST0001, M402, and PG545, have shown promise in suppressing tumor growth and metastasis in preclinical models and early clinical trials [87–92].

The two known human sulfatases, Sulf1 and Sulf2, are released as soluble enzymes that can cleave the 6-O sulfate on glucosamine (Figure I) [85]. Despite mechanistic similarities, the sulfatases have opposing roles in carcinogenesis, which is best demonstrated in HCC [93]; Sulf1 suppresses FGF2-mediated tumor cell proliferation and invasion, whereas Sulf2 enhances these processes to promote disease progression [94]. Sulf1 is downregulated in breast, pancreatic, ovarian, and head and neck cancers, where it functions to suppress tumor cell proliferation and invasion by inhibiting the co-receptor function of HSPGs [85]. Consistent with its role in promoting tumor progression, Sulf2 has additional roles in the pathogenesis of NSCLC, pancreatic cancer, and glioblastoma despite unaltered expression levels [95,96]. The heparanase-inhibiting compound PI-88 also suppresses Sulf2 activity, representing a therapeutic strategy for tumors in which Sulf2 drives carcinogenesis [67]. These studies demonstrate the critical importance of HS modifying enzymes in the growth factor signaling effects of HS in cancer cells.

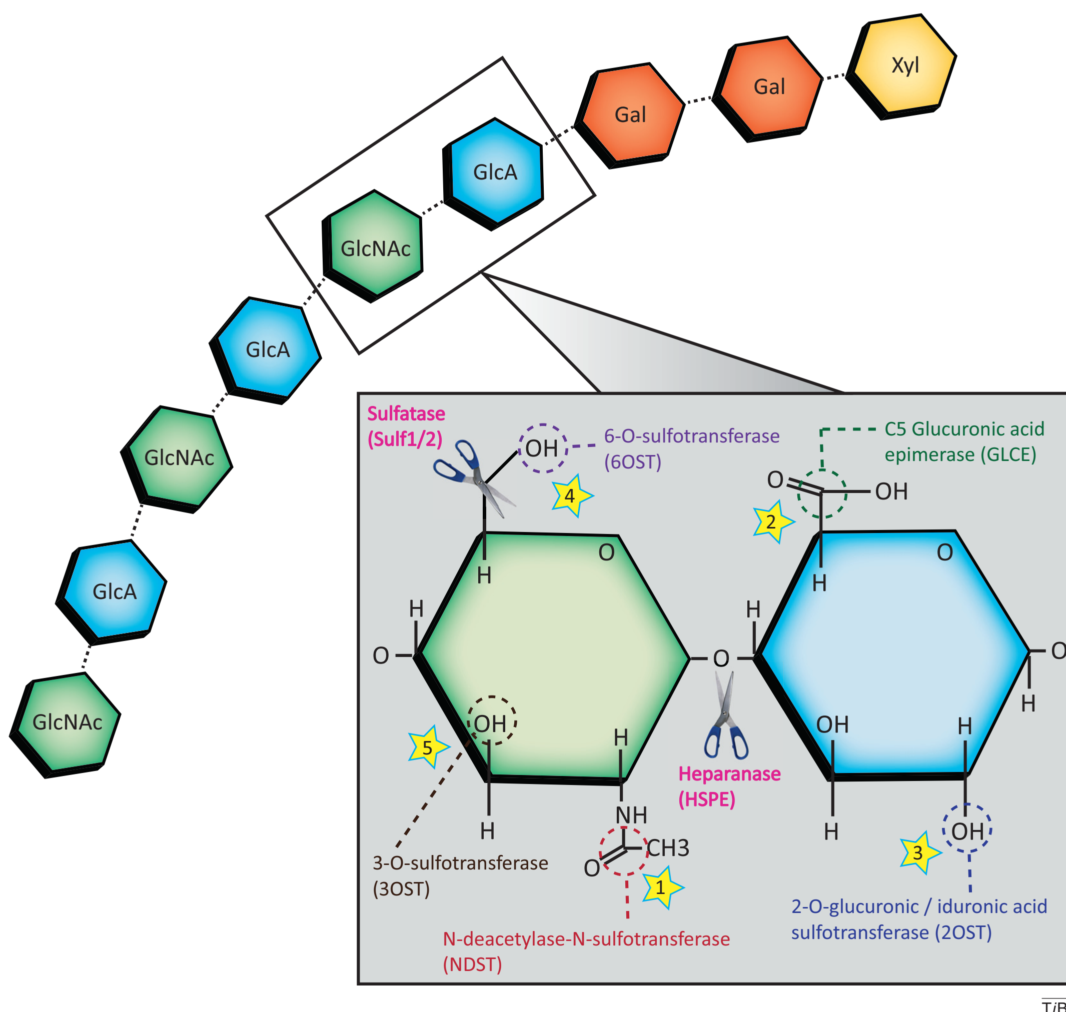

Figure I. Heparan sulfate (HS) structure and modification. Heparin and HS consist of a xylose(Xyl)-galactose(Gal)-galactose-glucuronic acid (GlcA) linkage tetrasaccharide followed by repeating disaccharide units (inset) variably sulfated at the 3-O, 6-O, or N sites on glucosamine (GlcNAc), and the 2-O site on glucuronic acid. Dashed circles indicate sulfation reactions. Starred numbers indicate the highly regulated order of reactions. Heparanases and sulfatases further modify HS structure (scissors).

and differentiation (Figure 4 and Box 2). Individual HSPGs have roles in specific cancers (Table 1). Some HSPGs, such as GPC1 and SDC2, are consistently upregulated and serve similar roles in promoting growth across cancer types [8]. Others, such as TβRIII, are downregulated in most cancers and function to suppress tumor growth [14,15]. A third group of HSPGs has conflicting roles in promoting or suppressing carcinogenesis, depending on tumor cell of

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