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Enzymatic Remodeling of Heparan Sulfate Proteoglycans Within the Tumor Microenvironment: Growth Regulation and the Prospect of New Cancer Therapies

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Abstract Heparan sulfate proteoglycans (HSPGs), via their interactions with numerous effector molecules such as FGF-2, IL-8, and VEGF, regulate the biological activity of cells by acting as co-receptors that promote signaling. The extent and nature of their role as co-receptors is often misregulated in cancer as manifested by alterations in HSPG structure and expression level. This misregulation of HSPGs can aid in promoting the malignant phenotype. In addition to expression-related changes in HSPGs, recent discoveries indicate that HSPGs localized within the tumor microenvironment can be attacked by enzymes that alter proteoglycan structure resulting in dramatic effects on tumor growth and metastasis. This review focuses on remodeling of HSPGs by three distinct mechanisms that occur in vivo; (i) shedding of proteoglycan extracellular domains from cell surfaces, (ii) fragmentation of heparan sulfate chains by heparanase, and (iii) removal of sulfates from the 6-*O* position of heparan sulfate chains by extracellular sulfatases. Assessing or monitoring the remodeling of HSPGs has important implications for tumor diagnosis and patient prognosis while therapeutic manipulation of the remodeling process represents an exciting new possibility for treating cancer. J. Cell. Biochem. 96: 897–905, 2005.
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Heparan sulfate proteoglycans consist of a protein core with covalently attached heparan sulfate chains. These macromolecules can be present at the cell surface where they are anchored by transmembrane domains (syndecans) or by GPI linkage (glypicans), or they can be secreted into the extracellular matrix (perlecan). Because of their ability to bind numerous proteins, the heparan sulfate chains are responsible for the bulk of the known biological functions of proteoglycans including their role as co-receptors that potentiate growth factor signaling [Bernfield et al., 1999]. The binding versatility of heparan sulfate is due at least in part to extensive heterogeneity in its structure. Within the Golgi apparatus, heparan sulfate chains are assembled onto the core proteins by a series of enzymes including those that polymerize and then modify the chain. The general molecular organization of the chains includes repeating disaccharides composed of *N*-acetylglucosamine and a uronic acid. Further modifications of a single disaccharide can include sulfation in the N, 3-*O* or 6-*O* position of N-acetylglucosamine, or the 2-*O* position of the uronic acid. Thus, there can be extensive heterogeneity among individual disaccharide units depending largely on the extent of sulfation at these positions. To date, there have been 23 distinct disaccharides identified in heparin or heparan sulfate [Esko and Selleck, 2002]. Thus, even in a relatively short heparan sulfate chain composed of 40 disaccharides, there are millions of distinct structural possibilities. For this reason, heparan sulfate has been called the most information-dense biopolymer in nature [Venkataraman et al., 1999].

Heparan sulfate chains can be over 100 disaccharide units in length and are not randomly ordered. Rather, they have a distinct domain structure composed of regions of high sulfation

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known as S-domains, interspersed with regions of low sulfation [Merry et al., 1999]. Generally, the frequency and clustering of S-domains influence the affinity of heparan sulfate for many of its ligands. Some heparan sulfate interactions with proteins require specific domain structure within heparan sulfate chains. The most striking example is binding of antithrombin-III that requires a pentasaccharide of specific structure. However, this degree of specificity seems to be the exception and not the rule. Most proteins studied are somewhat promiscuous in their binding requirements. One of the best studied interactions is between FGF-2 and heparan sulfate. This interaction requires at least some degree of 2-*O* sulfation, and a chain length of at least an octasaccharide, but there is flexibility beyond these requirements. Interestingly, for heparan sulfate to promote FGF-2 signaling, there must also be 6-*O* sulfation present, but this appears to be important for interactions between heparan sulfate and the FGF receptor [Guimond et al., 1993]. Thus, to form the ternary signaling complex, there must be FGF-2, FGF receptor, and a heparan sulfate chain having appropriately spaced 2-*O* and 6-*O* sulfation.

Although biological functions of heparan sulfate proteoglycans have been ascribed predominantly to their heparan sulfate chains, evidence is accumulating that core proteins can also play important functional roles. For example, recent studies have shown that the core protein of syndecan-1 is a critical regulator of $\alpha V\beta 3$ integrin signaling events that control breast cancer cell spreading [Beauvais et al., 2004]. The core protein of betaglycan, the type II receptor for TGF beta, mediates binding of TGF beta independently of its heparan sulfate chains [Andres et al., 1989]. Proteoglycan function may also depend on cooperation between the heparan sulfate chains and the core protein to which those chains are attached. This has been shown for syndecan-1 in which both heparan sulfate and a specific region of the core protein are required for syndecan-1-mediated inhibition of myeloma cell invasion into collagen gels [Langford et al., 2005]. Also, the co-operation between heparan sulfate and the glypican-1 core protein appears to regulate Wnt signaling that when misregulated causes Simpson–Golabi–Behmel syndrome [De Cat et al., 2003], a syndrome characterized by misregulation of growth.

Together these data demonstrate that the function of HSPGs is dictated in large part by the specific structural composition of the core protein and its attached heparan sulfate chains as well as their pattern of expression. However, emerging data indicate that another layer of functional regulation of HSPGs occurs, not during heparan sulfate synthesis, but within the extracellular compartment where enzymes selectively cleave HSPG core protein or heparan sulfate. Expression of these enzymes is tightly regulated, suggesting that they play important regulatory functions. This review focuses on three types of modifications to HSPGs that can occur within the extracellular compartment (Fig. 1). These alterations can dramatically alter proteoglycan function and cell behavior within the tumor microenvironment and thus are critical regulators of tumor growth and progression and provide new targets for cancer therapy.

SHEDDING OF SYNDECAN-1 PROMOTES TUMOR GROWTH AND METASTASIS

All members of the syndecan family (syndecan -1, -2, -3, and -4) are constitutively shed

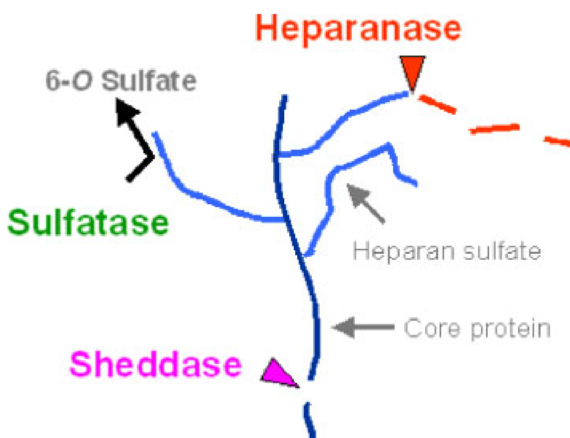

Fig. 1. The activity of sheddases, heparanase, and sulfatases represent three mechanisms of enzyme-mediated remodeling of heparan sulfate proteoglycans. Cell surface proteoglycans (e.g., syndecans) can be released from the cell surface by sheddases, such as MMP-7 and MT1-MMP. The solubilized proteoglycan remains biologically active and can become attached to the extracellular matrix or enter the circulation. Heparanase cleaves heparan sulfate chains into fragments 10–20 disaccharides in length. These fragments retain their biological activity and can bind to and potentiate the activity of growth factors. Endosulfatases remove 6-*O* sulfates from trisulfated disaccharides. This alters the affinity of the heparan sulfate chain for growth factors and growth factor receptors. Both heparanase and endosulfatases have been localized to the cell surface although they may have some intracellular activity as well.

from the surface of cells in culture [Kim et al., 1994]. In addition, a number of events can accelerate syndecan shedding, including cleavage by proteases and cell stress [Bernfield et al., 1999]. Accelerated shedding occurs in a highly regulated manner and can have a dramatic impact on cell behavior. For example, shedding immediately renders the cell surface proteoglycan incapable of mediating cell adhesion, and if soluble effector molecules (growth factors, cytokines) are bound to the heparan sulfate chains, they too are no longer sequestered at the cell surface. Thus, shedding can impact cell adhesion and growth factor gradients.

There are several specific examples of the importance of shed syndecans. Li et al. [2002] demonstrated that shed syndecan-1 is required for shuttling the chemokine KC into the alveolar space following lung injury in mice. In the absence of shed syndecan-1, the KC-mediated infiltration of neutrophils does not occur within alveoli, thus leading to a greatly diminished inflammatory response. Importantly, this work also demonstrates that MMP-7 is one enzyme responsible for the physiological shedding of syndecan-1. Together the findings establish that a dynamic interaction between MMP-7, syndecan-1, and KC occurs to facilitate the acute inflammatory response. Interestingly, in the bleomycin-induced lung injury model that was explored in this study, attenuation of inflammation due to the lack of shed syndecan-1 results in enhanced animal survival. This suggests that clinical modulation of shed syndecan-1 may be a means to decrease the negative impact of acute inflammatory responses.

Shed syndecan-1 is also important in tumor growth and progression. Several years ago, we discovered that soluble syndecan-1 is present in high levels in the serum of some myeloma patients [Dhodapkar et al., 1997]. Subsequent studies have demonstrated that high levels of serum syndecan-1 are an indicator of poor prognosis in both myeloma and lung cancer [Seidel et al., 2000; Joensuu et al., 2002].

To determine if high levels of soluble syndecan-1 actually contribute to promotion of tumor growth, a form of syndecan-1 lacking its cytoplasmic and transmembrane domains was expressed in ARH-77 lymphoid cells. The transfectants produce and secrete high levels of the truncated syndecan-1 core protein with attached heparan sulfate chains. This form of syndecan-1 is a structural and functional mimic of the form of syndecan-1 shed by tumor cells in vivo. When injected into human bones that were implanted in SCID mice, these syndecan-1-secreting cells grow much faster than either control-transfected cells that lack syndecan-1 or cells transfected with full-length syndecan-1 that is retained predominantly on the cell surface [Yang et al., 2002]. This work provides the first experimental evidence that once shed, a cell surface HSPG can act as a strong promoter of tumor growth in vivo. Importantly, this effect of syndecan-1 appears to be regulating growth via critical interactions with the bone marrow microenvironment in vivo because the transfected ARH-77 cells, when growing in vitro, grow at the same rate as control cells not secreting high levels of syndecan-1. Thus, syndecan-1 in myeloma patients may be playing a key role in mediating cross-talk between tumor cells and the bone marrow stroma. These interactions most likely include binding of syndecan-1 heparan sulfate to growth factors, chemokines, and other effector molecules that initiate signaling pathways critical for controlling tumor growth.

Our in vivo studies using ARH-77 cells also revealed that, in addition to enhancing tumor growth, soluble syndecan-1 promotes metastasis from bone to bone [Yang et al., 2002]. This is a critical finding because a hallmark of myeloma tumors is that they eventually spread throughout the skeleton. Thus, the enhanced shedding of syndecan-1 seen in myeloma appears to play an active and important role in promoting both the growth and dissemination of the tumor. Because some tumors exhibit higher levels of syndecan-1 shedding than others, the mechanisms controlling shedding can be an important determinant of disease severity and progression [San Antonio et al., 1994; Dhodapkar et al., 1997; Seidel et al., 2000]. Thus, shed HSPGs remain highly biologically active and can regulate cell growth and metastasis. It will be interesting to learn if soluble proteoglycans are also in the serum and are of prognostic significance in cancers such as breast carcinoma and pancreatic cancer, where high levels of heparan sulfate proteoglycans are present within the tumor tissue [Kleeff et al., 1999; Conejo et al., 2000; Barbareschi et al., 2003; Leivonen et al., 2004]. If this occurs, then targeting enzymes that mediate HSPG shedding

may be a viable therapeutic strategy for numerous malignancies.

HEPARANASE ENHANCES TUMOR GROWTH AND METASTASIS

Human heparanase is an endoglycosidase that is rare in normal tissues but is often expressed in tumors where it promotes invasion, angiogenesis, and metastasis [Hulett et al., 1999; Miao et al., 1999; Parish et al., 1999; Vlodavsky et al., 1999; Elkin et al., 2001; Uno et al., 2001; Marchetti et al., 2003; Roy et al., 2005]. The heparanase enzyme cleaves heparan sulfate in a manner that releases fragments that are 10–20 sugar residues long, and there is evidence that these fragments are biologically more active than the native heparan sulfate chain from which they are derived [Kato et al., 1998; Elkin et al., 2001; Vlodavsky and Friedmann, 2001; Bitan et al., 2002]. Although the consequences of heparanase activity are still under investigation, it clearly influences the activity and availability of numerous heparan sulfate-binding growth factors that regulate cell behavior of both the tumor cells and host cells within the tumor microenvironment. For example, heparanase directly promotes angiogenesis by releasing heparin-binding angiogenic growth factors such as FGF-2 and VEGF that are trapped within the extracellular matrix [Whitelock et al., 1996; Iozzo and San Antonio, 2001]. These reservoirs of trapped growth factors may be particularly important for tumor relapse following conventional cancer treatments, such as chemotherapy. A chemo-resistant tumor cell lodged within the tumor microenvironment may simply need to initiate expression of heparanase to access a store of heparan sulfate-bound factors that subsequently stimulate growth and expansion of the residual tumor.

Multiple myeloma is an example where heparanase appears to play a major role in regulating the tumor microenvironment. These tumor cells express high levels of syndecan-1 that is shed in abundance from the cell surface and can accumulate within the bone microenvironment and in the serum [Dhodapkar et al., 1997; Bayer-Garner et al., 2001]. We have demonstrated that heparanase expression and activity are elevated in the marrow of some myeloma patients [Kelly et al., 2003]. Analysis of microvessel density within the marrow revealed a strikingly higher density of blood vessels in patients with high heparanase activity (79 vessels/mm^2) as compared to patients negative for heparanase activity (25 vessels/mm^2; $P < 0.0001$). Moreover, a myeloma cell line transfected with the cDNA for heparanase when grown in vivo, exhibited enhanced growth and a significantly higher microvessel density than control cells [Kelly et al., 2003]. The relationship between high heparanase activity and enhanced microvessel density is particularly significant in myeloma because high microvessel density correlates with poor prognosis in this cancer [Sezer et al., 2000; Munshi and Wilson, 2001; Pruneri et al., 2002].

In subsequent studies, we have demonstrated that as compared to controls, the elevation of heparanase expression accelerates the initial growth of the primary myeloma tumor, increases whole-body tumor burden, and enhances both the number and size of microvessels [Yang et al., 2005]. Moreover, we made the important discovery that heparanase dramatically enhanced spontaneous metastasis of myeloma tumor cells to bone [Yang et al., 2005]. This spontaneous metastasis occurs following establishment of a primary tumor either subcutaneously or directly within the bone. Also in these studies we were able to demonstrate that the syndecan-1 expressed by the primary tumors formed by heparanase-transfected cells was greatly diminished in molecular size as compared to controls. This provides direct evidence that expression of heparanase promotes the degradation of heparan sulfate proteoglycans within the tumor. This dramatic change in heparan sulfate likely alters proteoglycan function on the cell surface and also generates high levels of biologically active heparan sulfate fragments that permeate throughout the tumor microenvironment.

In recent studies we have found that expression of heparanase has a significant growth-promoting effect in vivo on a cell line derived from MDA-MB-231 human breast cancer cells [Kelly et al., 2005]. The enhanced tumor growth within the mammary fat pad is accompanied by a high microvessel density as compared to controls, but, unlike what occurs in myeloma, heparanase expression does not promote metastasis of these tumor cells to bone. However, surprisingly, these tumors having high levels of heparanase when growing within the fat pad can stimulate bone resorption in the absence

of detectable tumor within the bone. Thus, heparanase expression within a tumor can have systemic effects. This effect may be either a direct effect of soluble enzyme on bone or an indirect effect occurring via heparanase-mediated release of soluble factors in the tumor, which travel to bone and upset the normal balance of bone turnover. This distal effect of heparanase on bone could be a precursor event leading to an altered bone microenvironment that is permissive of metastatic tumor cell growth. These data suggest that targeting heparanase in cancer may have multiple positive effects on both the tumor itself and the host.

ENDOSULFATASES ALTER HEPARAN SULFATE STRUCTURE, MODULATE GROWTH FACTOR SIGNALING, AND REGULATE TUMOR GROWTH

A recently discovered family of endosulfatases removes 6-*O* sulfate from heparan sulfate chains, thereby modulating growth factor activity. These enzymes are secreted via the Golgi and bind to the cell surface or are released into the extracellular matrix and thus, are distinct from the lysosomal exosulfatases that remove 6-*O* sulfates during heparan sulfate degradation. The first member of this endosulfatase family to be described was sulfatase-1 from quail (QSulf1), where it was shown to be required for Wnt-mediated signaling in developing muscle [Dhoot et al., 2001]. Subsequent studies revealed that in the absence of Qsulf1, wnt binds heparan sulfate with high affinity, thereby blocking Wnt-mediated activation of the Frizzled receptor [Ai et al., 2003]. Conversely, when Qsulf1 is present and removes 6-*O* sulfate, binding of Wnt to heparan sulfate is weakened and Frizzled is activated. The authors conclude that QSulf1 activity generates low affinity interactions between heparan sulfate and Wnt, thereby allowing Wnt interactions with Frizzled [Ai et al., 2003]. The role of sulfatase, therefore, may be particularly important in tumors that are promoted by Wnt. For example, studies have shown that Wnt-induced mammary tumorigenesis is dependent on expression of syndecan-1 [Alexander et al., 2000]. Sulfatase enzymes may play a key role in this process by removing 6-*O* sulfates. Qsulf1 can also restore bone morphogenetic protein signaling in cells by releasing its functional inhibitor, Noggin, from cell surfaces [Viviano et al., 2004]. In contrast to promoting growth factor activity, Qsulf1 can also inhibit growth factor signaling. FGF signaling is dramatically diminished by removing 6-*O* sulfate which is necessary for the formation of the FGF-HS-FGFR1 ternary complex [Wang et al., 2004].

Sulf1 has also been cloned from rat, mouse, and human and a second family member, Sulf2, has been cloned from both mice and humans [Morimoto-Tomita et al., 2002; Ohto et al., 2002]. Sulf2 is very similar in structural organization to Sulf1 but is somewhat divergent in sequence identity (64%) in humans. Both Sulf1 and Sulf2 show high specificity for 6-*O* sulfates of the trisulfated disaccharides of heparin at neutral pH [Morimoto-Tomita et al., 2002].

Studies are now emerging on the role of sulfatase in cancer. Human Sulf1 (HSulf1) is present in a variety of normal tissues but is down-regulated in tumor cell lines originating from ovarian, breast, pancreatic, renal, and hepatocellular carcinoma tumors [Lai et al., 2003], and in tissue isolated from a subset of human ovarian and hepatocellular carcinomas [Lai et al., 2003; Lai et al., 2004b]. In contrast to the reduced expression of HSulf1, subsets of some human tumors exhibit enhanced expression of the enzyme. For example, 70% of both hepatocellular and pancreatic cancers express elevated HSulf1 as compared to normal tissue [Lai et al., 2004b; Li et al., 2005]. Re-expression of HSulf1 in an ovarian cell line diminishes FGF-2 and HB-EGF signaling and cell proliferation, and enhances drug-induced apoptosis [Lai et al., 2003]. Further evidence of the role of HSulf1 as a negative regulator of tumor cell growth was subsequently found in cell lines derived from squamous cell carcinoma of the head and neck. In these cells, expression of HSulf1 inhibits HGF signaling, thereby blocking the motility, invasion, and growth normally stimulated by this growth factor [Lai et al., 2004a]. Interestingly, diminished HSulf1 expression may result from hypermethylation of its regulatory sequences because treatment of hepatocellular cancer cell lines with the DNA methylase inhibitor 5-aza-2′-deoxycytidine restores HSulf1 expression [Lai et al., 2004b]. Taken together, these data suggest that HSulf1 and HSulf2 may be critical regulators of tumor growth. Further studies using in vivo models of tumor growth are warranted to further define the effects of endosulfatases on malignant cell behavior.

NEW PROSPECTS FOR CANCER THERAPY

The fact that HSPGs play critical roles in cancer growth and metastasis makes them ripe targets for new therapies. Of course, strategies to block heparan sulfate expression or function in vivo clearly need to be investigated (reviewed in [Sanderson et al., 2004]), but what we are learning about enzymes that modify HSPGs, broadens the array of therapeutic targets available. Figure 2 shows a model of how enzymatic remodeling of heparan sulfate proteoglycans can regulate events within the tumor microenvironment. Several therapeutic strategies are evident from this model. For example, inhibitors that block the enzyme(s) responsible for shedding of HSPGs from the cell surface could significantly impact the tumor microenvironment by reducing the amount of heparan sulfate in the peritumor space and the adjacent extracellular matrix. This would effectively lower growth factor concentrations by reducing growth factors bound to HSPGs within the extracellular matrix. Because soluble syndecan-1 can promote angiogenesis, blocking and shedding may also dampen the angiogenic response to tumor growth. However, complicating this therapeutic approach is the fact that HSPGs shedding is mediated by multiple enzymes. For example, syndecan-1 can be shed by either MMP-7 or MT-MMP-1 and possibly by other MMPs as well [Li et al., 2002; Endo et al., 2003]. Thus, broad spectrum MMP inhibitors may be required to block shedding, although to date these inhibitors have had mixed success in human trials [Coussens et al., 2002]. Failure of MMP inhibitors may have been due at least in part to testing their effectiveness on tumors that are not reliant on HSPG shedding. An alternative approach to using broad spectrum MMP inhibitors would be to block expression of specific MMPs by anti-sense or interference RNA technology. Alternatively, it may be useful to target other classes of proteases (e.g., furin, cathepsin).

Regarding heparanase, there are currently several inhibitors of this enzyme under evaluation for their effects on tumor growth and metastasis. PI-88 has been shown in preclinical studies to have both anti-metastatic and anti-angiogenic activity and is currently in Phase II clinical trials for melanoma, liver, and lung carcinoma [Parish et al., 1999; Wall et al., 2001; Iversen et al., 2002]. PI-88 is a phosphomannopentaose that is highly sulfated and has multiple biological effects including inhibition

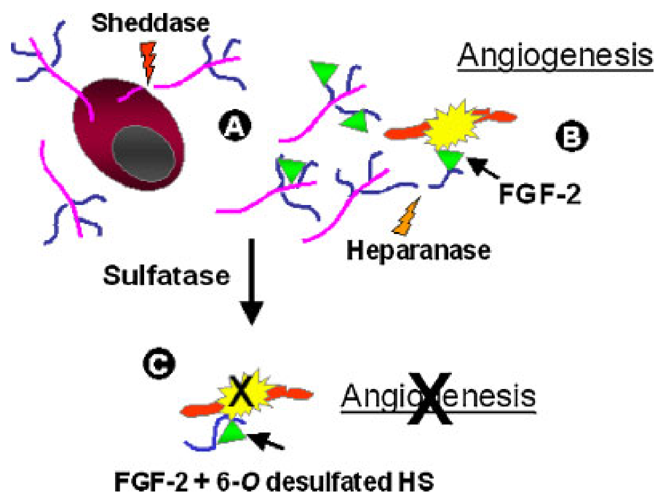

Fig. 2. Model of biological consequences of heparan sulfate proteoglycan remodeling within the tumor microenvironment. **A**: The action of a sheddase, such as MMP-7 releases the syndecan-1 extracellular domain from the surface of a myeloma tumor cell within the bone marrow. The shed syndecan-1 lodges and concentrates within the extracellular matrix via interactions between heparan sulfate and matrix components including collagen and fibronectin. Heparin-binding proteins, such as FGF-2 bind to the immobilized syndecan-1, thereby forming a reservoir of growth factors. **B**: Heparanase produced by the tumor cell or by stromal cells cleaves the intact heparan sulfate chain, releasing growth factors (in this case FGF-2) bound to the heparan sulfate fragment. The heparan sulfate and FGF-2 then form a ternary complex with the FGF receptor on an endothelial cell surface generating a proliferative signal to stimulate angiogenesis. **C**: When extracellular sulfatases (HSulf1 or HSulf2) are present, the 6-*O* sulfate groups are removed from the trisulfated disaccharides of heparan sulfate (HS). FGF-2 can bind to these heparan sulfates lacking 6-*O* sulfation but the heparan sulfate cannot interact with the FGF receptor on the endothelial cell surface. Thus, the ternary complex is not formed resulting in diminished FGF signaling and a poor angiogenic response.

of heparanase activity. Other sulfated polymers, such as laminarin sulfate, a polysaccharide primarily composed of beta-1, 3 glucan, has been shown to inhibit heparanase activity and tumor metastasis in preclinical animal models [Miao et al., 1999]. Yet another class of compounds that holds promise are the N-acetylated glycol-split heparins. These consist of chemically modified heparin chains that do not potentiate the activity of growth factors but do effectively inhibit heparanase activity [Naggi et al., 2005].

While human heparanase promotes cancer growth, another heparan sulfate degrading enzyme, bacterial heparinase III, has been shown to have anti-growth effects in murine models of melanoma and lung carcinoma [Liu et al., 2002]. In these studies, the presence of the enzyme or fragments of heparan sulfate generated by the enzyme attenuated growth factor signaling and inhibited tumor growth and metastasis. Once the structural characteristics of the fragments with the highest growth inhibitory activity are identified, this purified subset of fragments could be effective therapeutically. These fragments would likely escape immune recognition by the patient, thereby allowing effective administration over long periods of time.

Lastly, because sulfatase promotes Wnt signaling, blocking the activity of sulfatases might benefit those with tumors dependent on the Wnt/Frizzled pathway. In other tumors where HSulf activity has a growth inhibitory effect, strategies to enhance sulfatase expression should be explored. This will require further understanding of the effects of methylation on sulfatase gene silencing and also on transcriptional regulation of the gene. In addition, 6-*O* desulfated heparan sulfate might prove to be an effective competitive inhibitor of growth factor interactions, such as those that occur with FGF-2 where both 2-*O* and 6-*O* sulfation are required. Here, the heparan sulfate lacking 6-*O* sulfation would bind to FGF-2 but not the FGF receptor, thus acting as a soluble inhibitor of FGF signaling [Wang et al., 2004]. The finding that some tumor cell lines expressing HSulf1 exhibit enhanced drug-induced apoptosis [Lai et al., 2003] suggests that combination therapies that include agents to up-regulate sulfatase in tandem with chemotherapy may be a viable therapeutic strategy.

SUMMARY

HSPGs are key regulators of signaling events within the tumor microenvironment. Regulation of HSPG function can occur via the action of (i) sheddases that cleave the proteoglycans from the cell surface, thereby releasing functionally intact ectodomains, (ii) heparanase, which degrades heparan sulfate into fragments that retain biological activity, and (iii) endosulfatases that selectively remove 6-*O* sulfates from trisulfated disaccharides of heparan sulfate chains. The fine tuning of growth factor signaling and modulation of cell adhesion by the action of these enzymes that remodel HSPGs, represent an important aspect of cancer growth control. Refining our understanding of how HSPGs are structurally and functionally altered within the tumor microenvironment will likely lead to exciting new therapeutic opportunities.

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