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Review

The Biological Role of Chondroitin Sulfate in Cancer and Chondroitin-based Anticancer Agents

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Abstract. *Chondroitin sulfate proteoglycans (CSPGs) such as versican accumulate in tumor stroma and play a key role in tumor growth and invasion. The high expression of CSPGs in fast growing tissues and cells is correlated with chondroitin sulfate (CS) chains and the sulfation pattern. The negatively charged CS chains interact with a large number of ligands and receptors and activate signalling pathways which stimulate tumor growth. However, the role of chondroitin sulfate in cancer promotion seems to be controversial, as recent studies support the use of modified CS as a potent anticancer agent. In this review, the biological roles of CSPGs in cancer and the anticancer effects of modified CS are presented and discussed.*

Proteoglycans (PGs) are highly anionic macromolecules located primarily at the cell surface and the extracellular matrix (ECM). PGs are important structural molecules for proper ECM assembly providing structural integrity to tissues and regulating several cellular processes, such as cell proliferation, differentiation and migration. In particular, chondroitin sulfate PGs (CSPGs) and hyaluronan are necessary for ECM organization as they are key bioactive molecules and are directly implicated in a large variety of human diseases (1).

PGs are composed of a core protein onto which a variable numbers of glycosaminoglycan (GAG) chains and types are covalently attached. GAGs are linear polysaccharides comprising four chemically distinct subsets: the chondroitin sulfate and dermatan sulfate (CS and DS, respectively), the heparin and heparan sulfate (HS), keratin sulfate (KS), and hyaluronic acid (HA).

CS is an anionic linear polysaccharide which consists of alternating disaccharide units of D-glucuronic acid and D-*N*-acetyl-galactosamine (→4GlcAβ1→3GalNAcβ1→) and can be variously modified by sulfate groups (Figure 1) (2, 3). Sulfate groups occur mainly at C-4 and/or C-6 of *N*-acetyl-galactosamine and/or C-2 of glucuronic acid (Figure 1). CS is attached to serine (Ser) residues of the protein cores *via* a tetrasaccharide linkage consisting of xylose, two galactose molecules and glucuronic acid (3). The biosynthesis of CS chains on core proteins results in the formation of certain CSPGs, such as aggrecan (the major PG of cartilage), versican (the common PG of noncartilaginous connective tissues), decorin and biglycan.

Despite the simplicity of the backbone structure, the CS molecule is complex enough to carry biological information and thus determine many biological functions. CS interacts with a wide variety of molecules, such as growth factors, cytokines, chemokines, adhesion molecules and lipoproteins. These interactions seem to be directed from specific saccharide domains within the CS chain.

The Biological Role of Chondroitin Sulfate Proteoglycans in Cancer

PGs seem to be implicated in cancer through direct involvement in cellular functions, or by their modulating the activity of other effective molecules, such as growth factors and cytokines. Furthermore, PGs are abnormally expressed in a wide variety of malignant tumors. Tumor stroma and tumor fibrotic tissue contain abnormally higher concentrations of PGs than the corresponding surrounding tissue. Marked production of versican has been observed in various tumor types such as vessels of brain tumors, stroma of prostate cancer and breast cancer, histiocytoma, malignant

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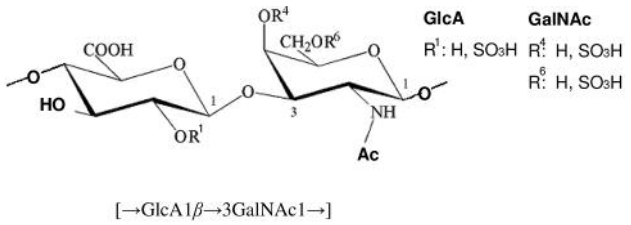

Figure 1. *Structure of repeating disaccharide unit of CS. Reprinted from reference (3).*

melanoma, testicular tumors and colon, pancreatic, laryngeal and gastric cancer (4-6).

Both versican and HA secreted by prostate fibroblasts are overexpressed and act together promoting cancer metastasis. The role of versican through its HA-binding property and its highly negatively charged CS side chains enhances the assembly of a pericellular matrix and promotes prostate cancer cell motility and invasion *in vitro* (8). Versican, HA and CD44 form a macromolecular complex which promotes the motility of prostate cancer cells and leads to tumor invasion. Similar observations have been made for versican overexpression in breast cancer (7-10). Versican is the predominant CSPG present in the peritumoral stromal tissue of breast cancer and is responsible for cancer cell metastasis in node-negative, primary breast cancer (11). Studies suggest that elevated expression of versican in peritumoral stroma could be a reliable predictor of early relapse for both breast and prostate cancer (9, 12).

The effect of various growth factors on PG synthesis by human malignant mesothelioma cells has also been studied, showing that there is a close correlation between the presence of the appropriate growth factor, the process of cell differentiation and the synthesis of GAGs. It has been shown that mitogenic substances affect both synthesis and distribution of GAGs/PGs on human malignant mesothelioma cells, independently of their effect on cell proliferation. Especially for platelet-derived growth factor (PDGF)-BB in particular affects the PG synthesis *via* interaction with its specific receptor (13). According to these results, each growth factor exerts distinct effects on PG synthesis (13-15).

Structural alterations of CS chains seem to affect the biological properties of CSPGs. Structural alterations of versican and decorin have been observed in human colon carcinoma where the DS chains were substituted by CS chains containing mainly non- and 6-sulfated disaccharides. These structural alterations, regarding the chain length, sulfation pattern and the extent of epimerization of GAGs, have been recorded in rectal, pancreatic and gastric carcinomas, where the CS/CSPGs (versican, decorin) content significantly increases and CS chains contain increased amounts of 6-sulfated and non-sulfated disaccharides (4, 17).

CD44 is a cell adhesion molecule that exists in the standard form CD44H, or as higher molecular mass isoforms due to alternative splicing. It has been shown that the interaction of CD44 with aggrecan derived from rat chondrosarcoma and bovine articular cartilage *via* the CS chains mediates cell adhesion and CD44 clustering, which may play an important role at inflammatory sites *in vivo* (18-20). The binding of CD44 to aggrecan derived from rat chondrosarcoma was dependent on the CS chains of aggrecan, mainly that of CS-A chains. CD44 is also able to bind serglycin modified with either CS-A or CS-C, or a mixture of both (depending on the cell type). These data suggest that CD44 may be able to interact with other proteoglycans modified with these CS chains (18, 20, 21)

In 1992, Faassen *et al.* (22) proposed that a cell surface CSPG is responsible for the initial contact of the cell with the ECM. Melanoma cell surface CSPG contains a core protein which is immunologically related to CD44. This CD44-related CSPG mediates tumor cell migration and invasion, possibly through cell cell and cell ECM interactions. The CD44-related CSPG is capable of binding fibrinogen/fibrin- mediating endothelial cell migration and invasion into the fibrin provisional matrix during wound repair. After the inhibition of CSPG synthesis with β-D-xyloside in wound microvascular endothelial cells, a reduction (50% inhibition of endothelial adhesion to fibrinogen) in microvascular endothelial cell adhesion and migration on fibrinogen and invasion into a three-dimensional fibrin gel was observed (23). Similar results were observed after pretreatment with chondroitinase ABC (23). These data suggest that CS chains possibly play an important role in facilitating cell migration.

The GAG chains are also involved in cell surface interactions of various myeloma cell lines. Recent studies have demonstrated the role of serglycin, which carries GAG chains, in tumor spread and survival. Serglycin synthesized and secreted by multiple myeloma (MM) cells, carries exclusively CS side chains which are predominately 4-sulfated. These CS chains seem to mediate the serglycin cell surface interaction which is critical fro the tumor progression (24).

Selectin-mediated binding of tumor cells to platelets, leukocytes and vascular endothelium may regulate their hematogenous spread in the microvasculature. It has been suggested that HS and CSPGs on endothelial cells are potential ligands for E-selectin (25). A recent study provided evidence that versican derived from a renal adenocarcinoma cell line interacts with L-selectin, P-selectin and CD44 through the CS chains. In the absence of any core protein, a specific subset of GAG chains, including CS-B, CS-E and HS, bind L- and P-selectin, whereas a relatively wide range of GAG chains, including CS-A, CS-B, CS-C, CS-D and CS-E and HA, bind CD44. These findings show that sulfation

plays an important role in the interactions of selectins with their ligands and may affect the signal transduction into cells (19). CS chains are also major P-selectin ligands on metastatic breast cancer cell lines. P-selectin binding to the 4T1 (metastatic breast cancer cell line) cells is sulfation dependent and heparinase/chondroitinase sensitive, suggesting that P-selectin ligands on the surface of 4T1 cells are mainly HS/CS PGs (26).

Human melanoma invasion and gelatinolysis is enhanced by the formation of molecular complexes consisting of melanoma chondroitin sulfate proteoglycan (MCSP), membrane-type 3 metalloproteinase (MT3-MMP) and metalloproteinase 2 (MMP-2) on the melanoma surface. The mechanisms by which pro-MMP-2 associates on the cell surface may be cell-type dependent on the expression of specific binding patterns. According to a mechanism suggested by Iida *et al*., CS expressed on the core protein of MCSP binds pro-MMP-2, while the core protein could associate with MT3-MMP (27). Furthermore, the sulfation pattern on the CS polymer is important in facilitating activation of pro-MMP-2 by MT3-MMP. In particular, C4S (CS A) seems to significantly contribute to enhanced MT3-MMP-mediated activation of pro-MMP-2 and therefore facilitates invasion through basement membranes and connective tissue (27).

The role of CS in various signaling pathways has also been studied. PDGF, a major polypeptide mitogen for mesenchymal cells, is suggested to deliver a survival signal *via* its receptors which possess tyrosine kinase properties, by inhibiting cell apoptosis and promoting cell proliferation. CS chains found in the ECM, physically interact with PDGF-Rβ and modulate its biological function. Experiments showed that free CS chains caused significant down regulation of the PDGF-BB-mediated and chemostatic responses in normal human fibroblasts (28, 29). Other studies concerning the effect of CS/DS on cell proliferation have been performed with normal osteoblasts and human osteosarcoma cells. According to the results obtained, CS-A and DS inhibited cell proliferation of all osteoblastic cell lines at high concentrations (100 μg/ml). The inhibitory effect seems to be closely related with the chemical structure of GAGs (30).

Modified Chondroitin Sulfate: A Potential Anticancer Agent

During recent years, CS has been widely used in supplements and drugs for the treatment of osteoarthritis, the prevention of subsequent coronary events, the treatment of psoriasis and of ophalmic diseases. Its biological role in various diseases has been reported in numerous studies and this has promoted the development of new, more efficient, drugs. Knowledge on the role of CS in cancer biology, tumor angiogenesis and invasion has favored the development of a new series of drugs which target the tumor cells and the interactions with other effective molecules of the ECM or the cell surface. In the newly developed pharmaceuticals, CS is used directly as an anticancer agent, or it can be used for efficient drug delivery.

Table I. *The common modifications of CS derived Δ-disaccharides*.

CS type	Predominant disaccharide unit
CS-A (A unit)	[GlcA-GalNAc(4S)]
CS-C (C unit)	[GlcA-GalNAc(6S)]
CS-B (DS)	[IdoA(2S)-GalNAc(4S and/or 6S)]
CS-D	[GlcA(2S)-GalNAc(6S)]
CS-E	[GlcA-GalNAc(4S, 6S)]
CS-H	[IdoA-GalNAc(4S, 6S)]

Reprinted from reference (3).

Novel molecules, called neoglycans, produced by exposing CS and heparin chains to carbodiimide (EDAC) seem to reduce cell viability by induction of apoptosis of myeloma and cancer cells *in vitro*. It has been reported, EDAC-modified CS reduced or abolished tumor growth, when injected directly into breast tumors growing in nude mice (31).

The interactions of CS/DS chains of CSPGs, such as versican, with L- and P-selectin and chemokines are sulfation dependent. Over sulfated CS/DS chains containing [GlcAβ1→3GalNAc (4,6-*O*-disulfate)] or [IdoAβ1→3GalNAc (4,6-*O*-disulfate)] binds those molecules with high affinity. It has also been suggested that PGs sufficiently modified with CS-B and/or CS-E should bind L-selectin and P-selectin (19). In a recent study, the effect of various CS types (CS-A, CS-B, CS-C and CS-E) (Table I) on P-selectin mediated interactions was tested. P-selectin ligands on the surface of a metastatic breast cancer cell line (4T1) are sulfated PGs, most likely the containing HS or CS. Treatment with chondroitinase ABC reduced P-selectin binding, while heparinase did not exhibit the same effect (26). These data suggest that CSPGs are the major P-selectin ligands on the murine and human breast cancer cell lines. Interestingly, CS-A and CS-C did not exhibit inhibitory effects, whereas CS-B and, in particular CS-E blocked the P-selectin from binding to its receptors. These findings consolidate the fact that over sulfation and generated negative charges of CS may play a key role in the inhibition of interactions that enhance tumor metastasis (19, 26, 32). Another study was performed with a naturally modified CS type that was isolated from sea cucumber (33). A fucosylated chondroitin sulfate (FucCS) was isolated from sea cucumber and tested *in vivo* against selectin-mediated interactions. FucCS is a polysaccharide composed of CS backbone mostly 6-sulfated and substituted at the 3-position of the β-D-

glucuronic acid residues with 2,4-disulfated α-L-fucopyranosyl branches. The results of this study showed that FucCS is a potent inhibitor of selectin-mediated events in tumor metastasis and inflammation *in vivo* (33). These findings support the use of oversulfated CS for preventing the cascade of events which favors the survival of tumor cells, their extravasation into the bloodstream and, furthermore, tumor metastasis.

Cancer metastasis depends on various biological events that occur under inappropriate conditions. A crucial factor for tumor progression is abnormal monocyte migration resulting in angiogenesis. A recent study showed that exogenous CS-A is capable of decreasing monocyte migration *in vitro* and therefore of preventing tumor angiogenesis (34). Other agents reported for their antitumor activity are a series of platinum complexes with high bioavailability. These complexes consist of trans(+/–)-1,2-cyclohexanediammineplatinum(II) which is conjugated to acid polysulfated CS, CS-A and CS-C (35). Furthermore, synthetic carbohydrates are suggested for use as potential pharmaceuticals as the carbohydrates present on cell surfaces participate in various functions including, cancer metastasis. For this purpose, oligosaccharides such as the human milk type oligosaccharide LNDFH I and LNnT were conjugated by reductive amination to amine-modified chondroitin oligomer and gamma-cyclodextrin (36). The use of liposomes for effective drug delivery has also been reported. Generally, liposomes serve as drug-carrier systems because of their favourable characteristics as a biodegradable drug reservoir to prolong retention times (37). In one study, various types of CS (CS-B, CS-D and CS-E) were bound to liposomes and used to prevent local tumor growth and metastasis (38). Polyethylene glycol (PEG)-coated liposomes that contained a new cationic lipid 3,5-dipentadecyclo-xybenzamidine hydrochloride (TRX-20) were bound to the CSs. When tested *in vitro*, the TRX-20 liposomes loaded with cisplatin sufficiently killed the CS-expressing tumor cells. Encouraging results were also observed *in vivo*, as the TRX-20 liposomes loaded with cisplatin reduced the local tumor cells in mice and suppressed the metastatic spreading of tumor cells to the liver (38). In another recent study, it was reported that biodegradable polymers such as CS could be used successfully in oral colon-specific drug-delivery systems (39).

Conclusively, CS plays an important role in cancer biology as it is involved in various interactions with tumor cells and other effective molecules, such as growth factors, and affects several signalling pathways. Numerous studies report the role of CS in promoting tumor growth and mediating events that enhance tumor invasion and metastasis, effects that can be abolished by chemically modified CS, or the use of CS with altered sulfation patterns. Encouraging studies have proved the potential use of modified CS as a potent anticancer agent.

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