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On the Role of Cell Surface Chondroitin Sulfates and Their Core Proteins in Breast Cancer Metastasis

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1. Introduction

Breast cancer is the most common cancer diagnosis among women worldwide (Jemal et al., 2011). Significant numbers of women present with advanced metastatic breast cancer despite major improvements in population screening and health awareness (Breast Cancer Facts & Figures 2009-2010, 2009; Autier et al., 2011). Metastatic spread leads to the poor prognosis and incurring low survival rates of patients presenting with advanced stage breast cancer or tumor recurrence. Therefore, effective therapies targeting metastatic spread should be designed to prevent the devastating consequences of breast cancer progression. In this regard, novel pro-metastatic molecules must be identified and their functional roles in the progression of the disease need to be addressed.

Cell–cell and cell–matrix adhesions have a profound role in the hematogenous phase of cancer metastasis. Tumor-associated glycans participate in these cell–cell and cell–matrix adhesions and their expression is associated with the metastatic potential of tumor cells and the prognosis of cancer patients (Hakomori, 1996; Couldrey and Green, 2000; Gorelik et al., 2001; Kawaguchi, 2005; Korourian et al., 2008).

We have been studying the role carbohydrates play in breast cancer metastasis (Monzavi-Karbassi et al., 2005; Carcel-Trullols et al., 2006; Monzavi-Karbassi et al., 2007). A large body of evidence indicates that P-selectin expressed on endothelial cells and platelets plays a crucial role during hematogenous metastasis (Borsig et al., 2001; Kohler et al., 2010). In a murine model of breast cancer we observed that the expression of carbohydrates that react with the P-selectin receptor plays a major role in metastasis (Monzavi-Karbassi et al., 2005). This evidence indicates that P-selectin-mediated interaction of breast cancer cells with platelets is a relevant cellular adhesion mechanism that participates in establishing distant metastases. A novel finding in our work is the observation that chondroitin sulfate glycosaminoglycans (CS-GAGs) can serve as P-selectin ligands on breast cancer cells. This observation links CS-GAGs to P-selectin binding in defining the metastatic phenotype dependent on the interaction of cancer cells with platelets (Monzavi-Karbassi et al., 2007). Therefore, CS-GAGs can be targeted for development of novel anti-metastatic therapies.

Large variation exists in CS-GAG sequences and in proteoglycans (PGs) presenting them. The prevalence of a presenting core protein may predict the functional outcomes of P-selectin-mediated adhesion of tumor cells. To use these molecules as targets for diagnostic or therapeutic purposes, a thorough understanding of their presentation and expression is necessary. This chapter reviews the biological roles of chondroitin sulfates (CS) in tumor development and metastasis and the role of different types of CS and the core protein carrying these polysaccharides.

2. Chondroitin sulfate biosynthesis and presentation

A relative variation in the composition of CS/DS has been reported in neoplastic tissues (Chiarugi and Dietrich, 1979; Bumol et al., 1982; Reisfeld and Cheresh, 1987; Olsen et al., 1988; Alini and Losa, 1991; Vijayagopal et al., 1998; Vynios et al., 2008).
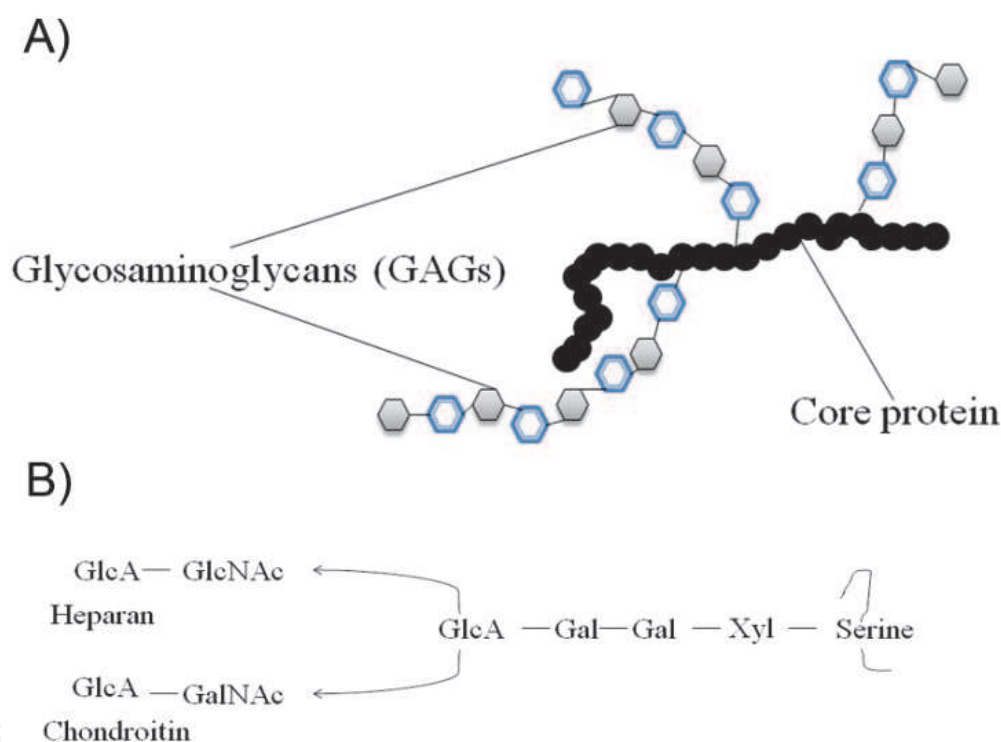

Fig. 1. **A)** Proteoglycans consist of a core protein and covalently attached GAG chains. **B)** Biosynthesis of chondroitin and heparan sulfate building blocks initiates by the formation of a linkage tetrasaccharide attached to serine residue on the core protein. GlcA: Glucuronic acid; GlcNAc: N-acetyl-D-glucosamine; GalNAc: N-acetyl-D-galactosamine; Gal: Galactose; Xyl: xylose.

Chondroitin sulfate (CS)/ dermatan sulfate (DS) polysaccharides are widely distributed in extracellular matrices and at cell surfaces as PGs, in which glycosaminoglycan (GAG) chains are covalently attached to a variety of core proteins (**Figure 1A**) (Esko et al., 1999). Chondroitin or heparan backbone is synthesized on the common GAG-protein linkage region tetrasaccharide (GlcUA-Galactose-Galactose-Xlylose) (**Figure 1B**), which is attached to specific serine residues in the respective core protein (Silbert and Sugumaran, 2002; Sugahara et al., 2003).

The Chondroitin chain backbone consists of repetitive disaccharide units containing D-glucuronic acid (GlcUA) and *N*-acetyl-D-galactosamine (GalNAc) residues. They further differentiate into variable chains with distinct structures and functions after various modifications. Sulfation and epimerization will further generate CS/DS isomers (**Table 1**). DS or CS-B is a stereoisomeric variant of CS with varying proportions of L-iduronic acid (IdoUA) in place of GlcUA, which forms by epimerization of GlcUA to IdoUA (**Table 1**).

Chondroitin type	Disaccharide repeat	Modifying enzymes	
		Sulfotransferase	Epimerase
A	[GlcUAβ1-3GalNAc(4S)]	Carbohydrate (chondroitin-4) sulfotransferase 11, 12 and 13 (CHST11, CHST12 and CHST13)	-
B	[IdoUA(2s)α1-3GalNAc(4S)]	Uronyl-2-O-sulfotransferase (UST) and CHST11, CHST12 and Carbohydrate (N-acetylgalactosamine 4-O) Sulfotransferase 14 (CHST14)	Dermatan-sulfate 5-epimerase
C	[GlcUAβ1-3GalNAc(6S)]	Carbohydrate (chondroitin 6) sulfotransferase 3 (CHST3) and Carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 7 (CHST7)	-
D	[GlcUA(2S)β1-3GalNAc(6S)]	UST, CHST3 and CHST7	-
E	[GlcUAβ1-3GalNAc(4S,6S)]	CHST11, CHST12, CHST13 and CHST15 (N-acetylgalactosamine 4-sulfate 6-O-sulfotransferase)	-
iE	[IdoUAα1-3GalNAc(4S,6S)]	CHST11, CHST12, CHST14 and CHST15	Dermatan-sulfate 5-epimerase

Table 1. Chondroitin sulfate types

The monosulfated disaccharide A-unit [GlcUA-GalNAc(4S)] and C-unit [GlcUA-GalNAc(6S)] are common and major components of mammalian CS chains. Disulfated disaccharide D-unit [GlcUA(2S)-GalNAc(6S)] and E-unit [GlcUA-GalNAc(4S,6S)] also exist that are based on further sulfation of monosulfated C and A units, respectively.

CS/DS chains that often found as CS/DS hybrid structures have the potential to display an enormous structural diversity by embedding multiple overlapping sequences constructed with distinct disaccharide blocks modified by different patterns of sulfation (Kusche-Gullberg and Kjellen, 2003; Sugahara et al., 2003). Given the complexity of these structures, the expression of modifying enzymes may correlate better with an aggressive tumor phenotype. Therefore, linking the expression of these enzymes with a functional role of cell surface CS glycans is highly significant

2.1 Biological functions of CS/DS chains
CS/DS chains specifically interact with heparin binding proteins. The interaction of DS chains with fibroblast growth factor (FGF) activates FGF-2 to signal cell proliferation (Penc et al., 1998). DS also acts as a cofactor for FGF-7 (Trowbridge et al., 2002). In addition, DS has been shown to bind and activate hepatocyte growth factor/scatter factor (HGF/SF), a

paracrine growth factor whose receptor, c-met (previously characterized as a proto-oncogene), is also a transmembrane tyrosine kinase.

The CS/DS chains of the PG versican, which is expressed in many tissues including kidney, skin, aorta, and brain, bind the adhesion molecules L- and P-selectin (Kawashima et al., 2002), molecules that have been implicated in leukocyte trafficking, inflammatory disease, and tumor dissemination. Interestingly, these interactions are specifically inhibited by CS or DS containing the 'E' disaccharide unit GlcUA-GalNAc (4S, 6S) or the 'iE' unit IdoUA-GalNAc (4S, 6S), respectively.

In previous studies we found that CS/DS-GAGs are expressed on the cell surface of murine and human breast cancer cell lines with high metastatic capacity. This suggests that CS/DS-GAGs can mediate P-selectin binding and P-selectin-mediated adhesion of cancer cells to platelets and endothelial cells (Monzavi-Karbassi et al., 2007). In inhibition assays performed in vitro, we showed that among the CS types only CS-B (DS), and CS-E can efficiently block P-selectin binding to tumor cells (Monzavi-Karbassi et al., 2007). Other studies have also suggested important interactions mediated by CS-A and CS-E in tumor progression and metastasis (Iida et al., 2007; Li et al., 2008; Basappa et al., 2009). Therefore, enzymes involved in sulfation (sulfotransferases) or epimerization (DS epimerase) of CS chains may play a fundamental role in defining the malignant phenotype of breast tumors.

The expression of several sulfotransferases including CHST11 and CHST15 appears to be greater in human breast carcinoma compared to normal breast tissue (Potapenko et al., 2010). An increase in CHST11 expression is observed in malignant plasma cells from myeloma patients compared to normal bone-marrow plasma cells (Bret et al., 2009). In searches for genes involved in the transition of DCIS to IDC, Schuetz et al. (Schuetz et al., 2006) found a significant increase in DS epimerase (Maccarana et al., 2006).

Collectively, the evidence implicates CS/DS GAGs in a wide array of molecular and cellular interactions resulting in tumorigenesis and metastasis.

3. Potential cell membrane CS/DS-carrying PGs of breast carcinoma

Malignant neoplasms exhibit changes in production of PGs (Bumol and Reisfeld, 1982; Iozzo, 1985; Iozzo, 1988; Stylianou et al., 2008). The variation, abundance and function of CS/DS-GAGs are also affected by the expression of the PG core protein presenting them. Therefore, it is imperative to study these polysaccharides in the context of their carrying PG. PG are involved in signaling and tumorigenicity and their attached GAG contributes to their functions. There is a growing list of PGs that have been implicated as possessing CS/DS side chains (Esko et al., 1999; Taylor and Gallo, 2006). PGs that may be modified by CS/DS chains include aggrecan, neurocan, brevican, bamacan, a CD44 isoform, chondroitin sulfate proteoglycan 4 (CSPG4), syndecans, betaglycan, serglycin, versican, decorin, biglycan, and endocan, most of which are extracellular matrix PGs. Our focus is on the cell membrane PGs that are able to bind to P-selectin (Monzavi-Karbassi et al., 2007). CD44 variants (CD44v), CSPG4, syndecan-1 (SDC-1) and syndecan-4 (SDC-4) are among the cell surface candidates (Faassen et al., 1992; Jackson et al., 1995; Barbareschi et al., 2003; Burbach et al., 2003; Baba et al., 2006; Gotte et al., 2007; Wang et al., 2010). Recently, It has been demonstrated that substantial fraction of neuropilin-1 (NRP-1), a membrane glycoprotein, is a PG modified with either HS or CS-GAG chains (Shintani et al., 2006).

Many articles are now devoted to CD44 in cancer stem cells and its role in cancer progression and metastasis (Lesley et al., 1997; Naor et al., 1997; Lesley and Hyman, 1998; Kalish et al., 1999; Toole, 2009). Here we focus on SDC-1, SDC-4, CSPG4 and NRP-1 as potential CS-carrying PGs on the surface of breast tumor cells.

3.1 Role of CS-carrying PGs in tumor progression and metastasis

Alteration in the production and structure of GAG chains and the functional consequences of such alterations is dependent on the PG carrying the GAG chain. PGs isolated from carcinomas contained 32.2% more CS, 18% less DS, and 30% less HS than PGs of normal breast tissue (Vijayagopal et al., 1998). Chondroitin sulfate proteoglycans (CSPGs) were expressed significantly more often in metastases than in primary tumors of uveal melanoma (Kiewe et al., 2006). We have recently found that CSPGs on breast cancer cells also bind to P-selectin receptors, and interruption of this interaction leads to significant reduction in hematogenous metastasis (Monzavi-Karbassi et al., 2007).

Selectin-mediated binding of tumor cells to platelets, leukocytes, and vascular endothelium may regulate their hematogenous spread in the microvasculature (Krause and Turner, 1999). Among selectin molecules, evidence strongly supports P-selectin involvement in tumor metastasis (Kim et al., 1998; Stevenson et al., 2005). Our data suggest that inhibition of P-selectin interaction with CS-GAGs significantly attenuates hematogenous lung metastasis (Monzavi-Karbassi et al., 2007). We have demonstrated that P-selectin binding to the surface of the aggressive breast cancer cell line MDA-MB-231 and MDA-MET is also CS-dependent, suggesting a role for CSPGs in metastatic behavior of human cancer cells. Because of the role of some of these PGs in signaling and tumor phenotype, we speculate that P-selectin interaction with a particular PG may lead to an exclusive tumor cell activation, and consequently survival in circulation. Here, we review the role of the surface PGs able to present CS-GAGs in malignancy.

3.1.1 CSPG4

CSPG4 is a human homolog of Rat neuroglycan 2 (NG2), which is also known as High Molecular Weight Melanoma Associated Antigen and Melanoma Chondroitin Sulfate Proteoglycan (Stallcup, 1981; Bumol and Reisfeld, 1982; Pluschke et al., 1996) and exclusively carries CS chains (Bumol and Reisfeld, 1982; Nishiyama et al., 1991). This tumor-associated cell surface PG potentiates cell motility, promotes invasiveness and the metastatic potential of tumor cells in melanoma (Burg et al., 1998; Campoli et al., 2004; Iida et al., 2007; Wang et al., 2010), and modulates responses to growth factors (Grako and Stallcup, 1995; Yang et al., 2009), processes that are critical for the proliferation and migration of tumor cells. It is suggested that CSPG4 facilitates the invasion of aggressive primary tumors within the dermis by enhancing the local concentration and/or activation of specific matrix metalloproteinases (MMPs) at sites of contact between melanoma cells and the underlying ECM (Iida et al., 2001). The authors demonstrated that CSPG4 on WM1341D cells, interacts with membrane-type matrix metalloproteinase (MT3-MMP), facilitating invasion, and that the interaction is CS-dependent. Inhibiting CS presentation by treating cells with p-nitrophenyl beta-D-xylopyranoside (beta-D-xyloside or βDX), a compound that uncouples the CS chain from the PG, led to a decrease in melanoma cell invasion into type I collagen (Faassen et al., 1992). CSPG4 is highly expressed on aggressive breast cancer cell lines **(Figure 2)** and is considered as a major CS-carrying PG.
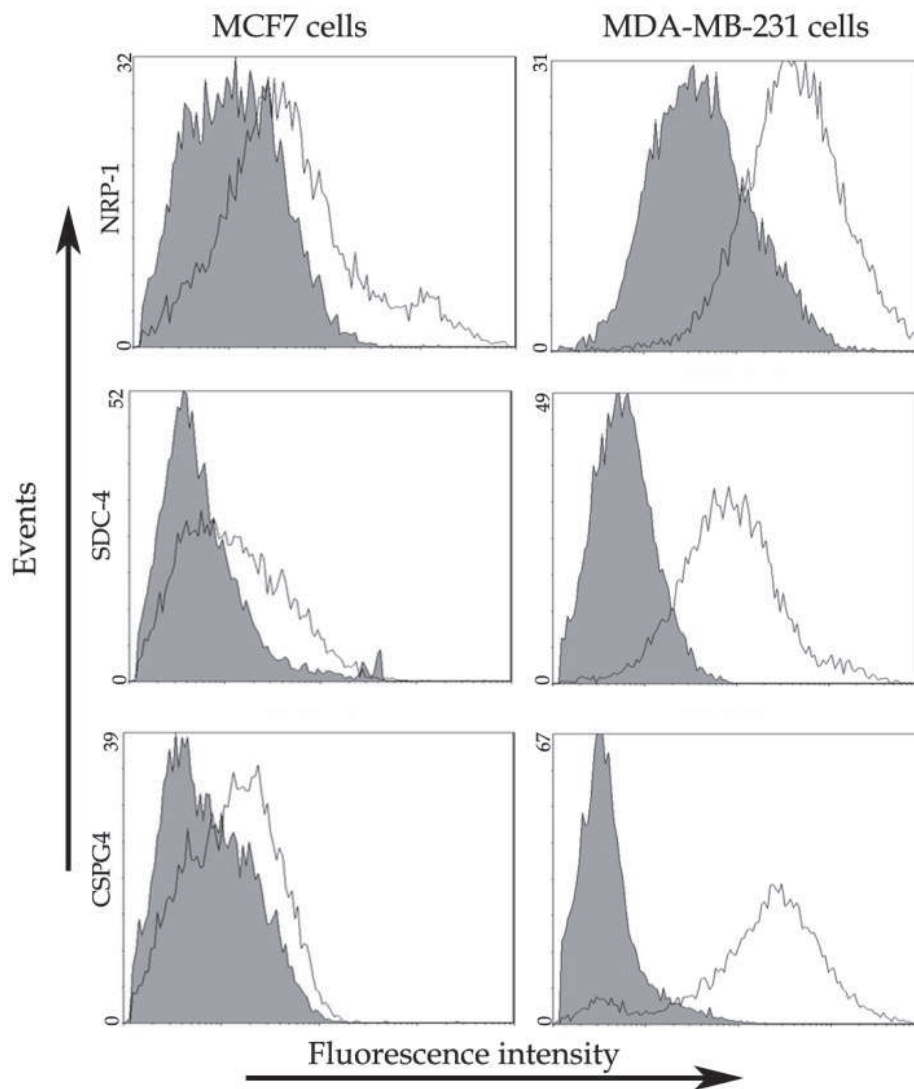
Fig. 2. Expression of NRP-1, SDC-4 and CSPG4 in breast cancer cells. Cells were grown in standard medium, harvested and then stained with monoclonal antibodies against the indicated targets. Stained cells were then analyzed by flow cytometry.

3.1.2 NRP-1

NRP-1 is a 120-130 kDa transmembrane glycoprotein, initially characterized as a neuronal receptor for specific secreted members of the semaphorin family involved in exon repulsation (Kolodkin et al., 1997). A substantial fraction of NRP-1 is a PG with a GAG chain attached (Shintani et al., 2006). In addition to being a receptor for a number of class 3 semaphorins, NRP-1 also serves as a receptor for some members of vascular endothelial growth factor (VEGF), and placental growth factor (PlGF) (Migdal et al., 1998; Soker et al., 1998; Makinen et al., 1999; Wise et al., 1999; Klagsbrun et al., 2002).

Considerable data support a functional role for NRP-1 in regulating VEGF activities in endothelium. It has been shown that semaphorin-3A competes with $VEGF_{165}$ binding to NRP-1 and inhibits angiogenesis *in vitro* (Miao et al., 1999). NRP-1 knock-out mice, in addition to neural defects, exhibit transposition of large vessels, disorganized and insufficient capillary

formation, and defects in heart development (Kawasaki et al., 1999). In contrast, over-expression of NRP-1 leads to over-stimulation of blood vessel formation (Kitsukawa et al., 1995). Studies have shown that NRP-1interacts with a subset of heparin binding proteins like FGF-1, FGF-2, FGF-4, FGF-7, FGF receptor-1, and HGF/SF (West et al., 2005). Investigation of the role of NRP-1 in human glioma progression, Hu et al. (Hu et al., 2007) have shown that NRP-1 expression correlates with tumor progression in clinical setting, and that NRP-1 expression promotes tumor growth and survival through an autocrine HGF/SF/c-met signaling pathway. We observed an overexpression of NRP-1 in aggressive human breast cancer cell line MDA-MB-231 compare to MCF-7 cells (**Figure 2**). This PG is also considered as a potential CS-carrying PG that can present CS-GAGs to P-selectin.

3.1.3 SDC-1 and SDC-4
SDC-1 is mainly expressed by epithelia and plasma cells. Although there are inconsistent reports (Barbareschi et al., 2003; Tsanou et al., 2004), the expression of SDC-1 is generally down-regulated in malignant tumors, and lower levels of expression have been associated with high metastatic/aggressive potential in many tumors (Nackaerts et al., 1997; Kumar-Singh et al., 1998; Mikami et al., 2001; Numa et al., 2002). SDC-1 has also been shown to act as a tumor suppressor molecule by inhibiting cell growth and inducing apoptosis (Mali et al., 1994; Dhodapkar et al., 1998). Therefore, during tumor development the decrease of SDC-1 expression may be an important step from tumorigenesis to a metastatic phenotype. However, there are conflicting data on the role of SDC-1; both its loss and over-expression in carcinoma cells have been associated with malignant progression (Baba et al., 2006).

SDC-4 is more ubiquitously expressed by most cell types, and little is known about its role in malignancy. Among the four members of the syndecan family, SDC-4 is the only one involved in the formation of fibronectin-induced focal adhesions, in cooperation with β1-integrin receptors (Woods and Couchman, 1994; Woods et al., 2000). SDC-4 has been implicated in cytoskeletal organization and regulation of cell adhesiveness. The migratory capacity of lymphocytes and dendritic cells has been reported to be mediated by SDC-4 (Kaneider et al., 2002; Greene et al., 2003; Feistritzer et al., 2004; Averbeck et al., 2007). Our data suggest a role for relative expression of SDC-1 and SDC-4, low SDC-1 and high SDC-4 expression, in metastatic breast cancer cells (**Figure 3**).
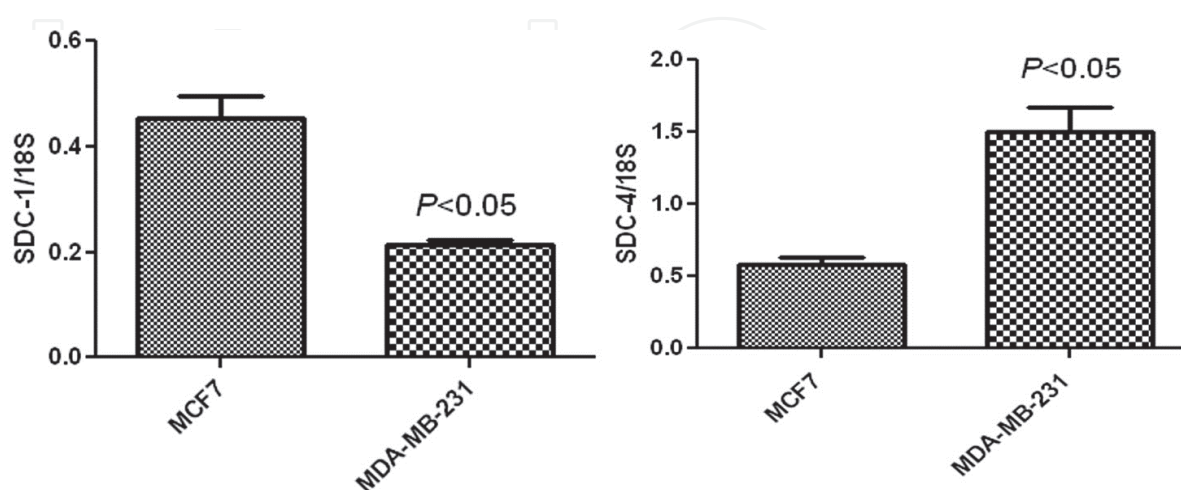

Fig. 3. Relative expression of SDC-1 and SDC-4 in human breast cancer cells using quantitative real-time PCR. Means of three independent experiments (±SD) are shown.

Therefore, relative expression of certain PGs or modification in their GAG chains may affect tumor aggressive phenotype through promoting survival, growth, and the metastatic capability of tumor cells. P-selectin can bind to CS-GAGs of these PGs and binding to each PG can have different functional consequences. These molecules has been linked to motility, invasion, angiogenesis, and cancer stem cell properties. Therefore, depending on the setting and expression of other molecules, P-selectin interaction may lead to various tumor promoting outcomes.

In studying the role of P-selectin in tumor growth and metastasis in a P-selectin-deficient Rag2-/- background, it was demonstrated that growth of subcutaneously challenged tumor cells were reduced significantly in the absence of P-selectin (Kim et al., 1998). This significantly slower growth rate in P-selectin deficient mice was unexpected because P-selectin is assumed to play a role in leukocytic infiltrates within tumors, which are generally inversely associated with tumor growth (Kreider et al., 1984). These findings, consistent with our hypothesis, demonstrate that the presence of P-selectin ligands on tumor cells and P-selectin-mediated interactions with stroma leads to tumorigenesis and tumor growth promotion.

4. Diagnostic and therapeutic values

Overexpression of particular CS chains can be used to develop diagnostic tests predicting tumor behavior or for prognostic purposes. In this regard, further attempts should be made to link the expression of a combination of genes that define GAG remodeling to the initiation and outcome of the disease in clinical setting.

Expression of CS can also be used for drug delivery purposes. Polyethylene glycol coated liposomes, containing a cationic lipid with CS specificity were used to deliver cisplatin to metastatic tumor cells (Lee et al., 2002). The cisplatin loaded CS-reactive liposomes suppressed metastatic spread of the murine osteosarcoma cells to the liver.

We have shown CS interactions with P-selectin and the significance of P-selectin binding in metastasis of a murine mammary cell line (Monzavi-Karbassi et al., 2007). Our findings support the concept that CS chains promote survival in the circulation, and tumor cell extravasation via P-selectin-mediated binding to platelets and endothelial cells. Using heparin to block P-selectin binding to tumor cells as anti-metastatic therapy has been the subject of many studies (Borsig et al., 2001; Stevenson et al., 2005). However, blocking P-selectin action through the inhibition of binding to its many ligands may affect cellular immunity that could be a tumor friendly side effect of a potential treatment. To avoid unfavorable impact of such a treatment on lymphocyte trafficking and infiltration, targeting relevant tumor-specific P-selectin ligands should be prioritized as an alternative long-term therapeutic strategy for aggressive breast cancer.

To develop therapeutics targeting CS entity we envision three major strategies. 1) Targeting particular CS types through blocking the expression of particular CS structures or the usage of small molecules, is supposed to attenuate metastasis efficiency. In this category, blocking the expression of a key sulfotransferase with siRNA may be considered a potential therapeutic approach at this point. Development of small molecules with fine specificity can also be proposed for blocking particular isomers of CS with reactive molecules. 2) Specific targeting of a prominent CS-carrying PG with definite impact on tumor progression and metastasis. CSPG4 is considered a prominent CSPG with a tumor promoting role. MAb targeting CSPG4 have been developed in melanoma and testing them for treatment of

patients with aggressive breast cancer falls in line with our data (Wang et al., 2010a; Wang et al., 2010b). However, targeting a core protein may bring in specificity issues as these PGs are also expressed in stroma. Additionally, tumor cells can escape treatment by immune editing and replacing a PG with another one. 3) Targeting a combination of sugar and PG that can be accomplished by simultaneous targeting of the core protein and the polysaccharide, or by developing reagents like mAb specific for the whole entity (polysaccharide and the core protein).

5. Conclusion

Breast cancer cell surface CS-GAGs and their interaction with P-selectin should be considered as viable targets for the development of novel diagnostic or therapeutic strategies. Our studies suggest that CS-GAGs, their biosynthetic pathway, or the core protein carrying them, can be potential targets in dealing with aggressive breast tumors. However, in order to efficiently block tumor cell dissemination by interrupting P-selectin/CS interaction, targeting any single PG does not seem to be enough, as other PGs can probably compensate and support metastatic processes. In this regard, global targeting of specific CS isomers, or combined targeting of the glycan and the PG, may be effective approaches.

6. Acknowledgement

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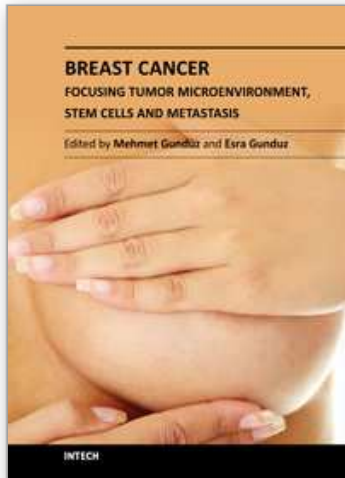
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