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Review

The role of proteoglycans in the reactive stroma on tumor growth and progression

Yvette May Coulson-Thomas[1], Tarsis Gesteira Ferreira[1,2], Andrew Lawrence Norton[3], Winston W-Y Kao[2], Helena Bonciani Nader[1] and Vivien Jane Coulson-Thomas[1,2,*]

[1]Department of Biochemistry, Universidade Federal de São Paulo, São Paulo, Brazil, [2]Department of Ophthalmology, University of Cincinnati, Cincinnati, OH, USA and [3]Durham University, Durham, UK

*Current address: John van Geest Centre for Brain Repair, Univesity of Cambridge, Forvie Site. Robinson Way, Cambridge, UK

Summary. The stroma surrounding tumors can either restrict or promote tumor growth and progression, and both the cellular and non-cellular components of the stroma play an active role. The cellular components in the surrounding stroma include tumor-associated fibroblasts, host tissue cells and immune cells. The non-cellular components, which form the extracellular matrix (ECM) scaffold, include proteoglycans, collagen, proteinases, growth factors and cytokines. For tumorigenesis to occur it is necessary for tumor cells to modify the surrounding stroma. Tumor cells have mechanisms for achieving this, such as co-opting fibroblasts and modifying the ECM they produce, degrading the surrounding ECM and/or synthesizing a favorable ECM to support invasion. Proteoglycans are an important component of the ECM and play an active role in tumor growth and progression. The expression and glycosylation patterns of proteoglycans are altered in the stroma surrounding tumors and these molecules may support or restrict tumor growth and progression depending on the type and stage of tumor. In the present review we discuss the difference between the tumor promoting and restricting stromal reactions surrounding tumors and the role proteoglycans play.

Offprint requests to: Vivien Jane Coulson-Thomas, John van Geest Centre for Brain Repair, University of Cambridge, Robinson Way, Cambridge CB2 0PY, UK. e-mail: vcoulsonthomas@gmail.com or vc315@cam.ac.uk; and Yvette May Coulson-Thomas, Department of Biochemistry, Universidade Federal de São Paulo, Rua Três de Maio 100, São Paulo, 04044-020, Brazil. e-mail: ycoulsonthomas@gmail.com.

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Introduction

During tumorigenesis tumor cells undergo active differentiation and more aggressive cells are selected which can invade the surrounding stroma, enter the blood stream or lymphatic system, and create a metastatic niche at a distant site (van Zijl et al., 2011). All these steps involve vital interactions between the cancer cells and the surrounding stroma. In order for the tumor cells to invade the surrounding stroma they must develop the ability to modulate this stroma and secrete factors which aid their invasion.

Studies have shown that during the initial stages of tumorigenesis both the immune surveillance system and the surrounding fibroblasts may play an inhibitory role in tumor growth (Blankenstein, 2004; Angeli et al., 2009; Coulson-Thomas et al., 2011). However, cancer cells develop different mechanisms to modify and "activate" the surrounding stroma enabling invasion. These include co-opting fibroblasts and modifying the ECM they produce, degrading the surrounding ECM and/or synthesizing a favorable ECM to support growth and invasion. During cancer progression the ECM can, for example, be modulated by proteolytic degradation by matrix metalloproteinases (MMPs) (Coussens et al., 2000; Egeblad and Werb, 2002), cysteine cathepsins (Almeida et al., 2001; Mohamed and Sloane, 2006; Gocheva and Joyce, 2007), serine proteinases (Tan et al., 2013), and endoglycosidases, such as heparinase (Peretti

et al., 2008; Fux et al., 2009) and hyaluronidases (Stern, 2008). One important component of the stroma surrounding tumors is proteoglycans, which are active constituents synthesized by both the tumor cells and the stroma cells. These molecules may support or restrict tumor growth and progression depending on the type and stage of tumor.

This review describes the role the stroma surrounding tumors plays in tumorigenesis and the outcome of the intricate cancer-stroma cross-talk, with a focus on proteoglycans.

Desmoplastic reaction

Desmoplasia is the unorganized production of fibrous or connective tissue, composed mainly of collagen fibers and myofibroblasts. To date studies have shown that desmoplasia may play either a restricting or supportive role in cancer progression, and this may depend on the type and stage of tumor (Abbas and Mahalingam, 2011). The initial phase of the desmoplastic reaction could represent an effort of the healthy tissue to entrap the tumor by up-regulating ECM production thereby forming a dense physical barrier to cancer invasion. However, given the adaptive capabilities of the cancer cells, these cells develop alternative pathways to modify the desmoplastic ECM into an environment which is favorable for cancer cell invasion. The primary producers of ECM during desmoplasia are stromal fibroblasts surrounding the tumor which have been activated to cancer-associated fibroblasts (CAFs) and present myofibroblastic characteristics, similar to wound healing associated myofibroblasts (Kunz-Schughart and Knuechel, 2002). Tumor-derived cytokines, such as transforming growth factor-β (TGF-β), activate the surrounding fibroblasts into myofibroblasts, which are characterized by the expression of α-smooth muscle actin (αSMA) (Todaro et al., 1980).

Desmoplasia has been shown to play a restricting role in colorectal cancer invasion, as a result of the direct cell-cell contact between fibroblasts and colorectal cancer cells, which evokes an increase in ECM density, composed of unorganized collagens (I, III, IV and V) and proteoglycans (biglycan, fibromodulin, perlecan and versican), which inhibits the migration and invasion of the colorectal tumor cells (Coulson-Thomas et al., 2011). Karagiannis and collaborators suggest that during carcinogenesis the cancer cells may induce the CAFs to secrete collagen XII in an attempt to reorganize the collagen present in the initial cancer-associated desmoplastic reaction in order to create an environment that supports invasion (Karagiannis et al., 2012).

Studies have also indicated that during the desmoplastic reaction CAFs may secrete organized ECM, composed of collagen fibrils perpendicular to the migrating front, which serve as a vital substrate for breast cancer cell invasion (Conklin et al., 2011). Moreover, carcinomas have been shown to secrete collagen α1 homotrimers, a form of collagen I which is resistant to MMP digestion, unconventionally present in healthy tissues, which were shown to be a prime substrate for cancer cell invasion (Makareeva et al., 2010).

Tumor promoting environment at metastatic sites

Metastatic cancer cells are extremely specialized and are capable of altering the phenotype of host stromal cells and creating a metastatic niche. Metastatic prostate cancer cells, for example, induce down-regulation of TGF-β, up-regulation of vimentin, α5β1 integrin and MT1-MMP, and actin depolymerization in stromal cells through crosstalk (Coulson-Thomas et al., 2010). In addition, metastatic prostate cancer cells reduce the expression of ECM components, such as collagens I, II, III and IV and the SLRPs decorin, biglycan, lumican and fibromodulin, by stromal cells (Coulson-Thomas et al., 2010). Upon establishing a metastatic niche in the bone, tumor cells target the mineralized type I collagen matrix by co-opting the osteoclasts and/or osteoblasts (Clines and Guise, 2008). Moreover, disruption of the TGF-β signaling axis during bone metastasis leads to a down-regulation of Endo180 which in turn leads to the formation of bone deposits with multiple layers of poorly organized collagen fibrils, which further emphasizes the role of TGF-β signaling in modulating ECM production during the establishment of a metastatic niche (Caley et al., 2012).

Proteoglycans play a vital role in the reactive stroma

Proteoglycans are ubiquitous molecules of the ECM and cell surface and can be up- or down-regulated and structurally altered in the tumoral reactive stroma, playing a role in tumor progression (Wegrowski and Maquart, 2004). Proteoglycans are macromolecules comprised of one or more glycosaminoglycan chains covalently bound to a protein core (Kjellen and Lindahl, 1991). Glycosaminoglycans are linear polysaccharides composed of repeating disaccharide units which consist of a hexosamine and either hexuronic acid or galactose units, and may be sulfated in various positions. Glycosaminoglycans are classified into six groups: chondroitin 4- and 6-sulfate (C4S, C6S), keratan sulfate (KS), hyaluronic acid (HA), dermatan sulfate (DS), heparin and heparan sulfate (HS).

Small leucine rich proteoglycans in the reactive stroma

Small leucine-rich proteoglycans (SLRPs), such as lumican, decorin, biglycan and fibromodulin, are an important family of proteoglycans. SLRPs are biologically active components of the ECM, which can be altered in the tumor stroma and may support or restrict tumor growth and progression depending on the

type of tumor. Lumican expression, for example, is up-regulated around primary prostate tumors and has been shown to inhibit prostate cancer cell migration and invasion (Coulson-Thomas et al., 2013). In addition, lumican has been shown to inhibit the development of B16F1 primary tumors in mice and B16F1 melanoma cell lung metastasis in mice (Vuillermoz et al., 2004; Brezillon et al., 2009a). On the other hand, whilst lumican expression is also up-regulated in the stroma surrounding breast tumors, this SLRP has been associated with higher tumor grade, lower tumor estrogen receptor levels, and younger age of the patients, which are associated with increased tumor aggressiveness (Leygue et al., 1998). Lumican expression has been shown to correlate with poor prognosis in invasive breast carcinoma (Troup et al., 2003) and advanced colorectal cancer (Seya et al., 2006). In pancreatic cancer, prognosis has been shown to depend on whether the cancer cells or stromal cells express lumican; lumican expression in pancreatic cancer cells tends to correlate with longer survival, whilst lumican expression in stromal cells tends to correlate with shorter survival (Ishiwata et al., 2007).

In contrast to lumican, decorin expression has been shown to be down-regulated in the stroma surrounding breast tumors (Leygue et al., 2000). On the other hand, decorin expression is up-regulated in the tumor stroma of colon cancer (Adany et al., 1990). The effect of decorin on tumor cells has been described for colon, gastrointestinal, genital, skeletal, cutaneous and bone marrow tumor cells, where it has been shown to retard the growth of these cells (Santra et al., 1995, 1997). Ectopic expression of decorin has also been shown to suppress the growth and colony-forming ability of thymic lymphoma cells isolated from double knockout animals lacking decorin and p53 (Iozzo et al., 1999). In addition, decorin has been shown to inhibit primary tumor growth and lung metastasis in mice (Goldoni and Iozzo, 2008). Overexpression of lumican, decorin, and versican is observed in pancreatic cancer tissues compared to normal controls (Koninger et al., 2004). Decorin expression in the tumor stroma of colon cancer has been shown to be increased by hypomethylation of the decorin gene (Adany et al., 1990).

Biglycan expression is up-regulated in the ECM of pancreatic tumors and biglycan has been shown to inhibit the growth of pancreatic cancer cells (Weber et al., 2001). Ectopic expression of biglycan has also been shown to suppress the growth of bladder cancer cells and high biglycan expression is associated with favorable prognosis (Niedworok et al., 2013). On the other hand, high biglycan expression is associated with cancer progression in colorectal cancer (Caley et al., 2012) and poor prognosis in patients with esophageal squamous cell carcinoma (Zhu et al., 2013). Biglycan expression in pancreatic carcinoma cells has been shown to be stimulated by TGF-β1, and this process is dependent on Smad signaling and critically dependent on functional Smad4 (Chen et al., 2002).

Other proteoglycans in the reactive stroma

Syndecan-1 expression is up-regulated in endometrial carcinoma (Choi et al., 2007), breast carcinoma (Matsuda et al., 2001; Barbareschi et al., 2003) and pancreatic cancer (Conejo et al., 2000). High levels of soluble syndecan-1 have been shown to play a role in the growth and dissemination of malignant cells in myeloma, and are associated with poor prognosis (Yang et al., 2002). All types of syndecans (syndecan-1, -2, -3, and -4) have been shown to be expressed by malignant glioma cells (Watanabe et al., 2006) and malignant ovarian tumors (Davies et al., 2004).

Glypican-1 is highly expressed in gliomas (Su et al., 2006), pancreatic cancer (Kleeff et al., 1998) and breast cancer (Matsuda et al., 2001). This proteoglycan has been shown to be crucial for the growth, metastasis, and angiogenesis of cancer cells (Aikawa et al., 2008). Glypican-5 expression is down-regulated in lung cancer tissues, probably due to the fact that this proteoglycan is capable of suppressing cancer cell migration, proliferation and invasion (Yang et al., 2013). Glypican-3 expression is increased in hepatocellular carcinomas (Zhu et al., 2001) and is a tumor marker for this type of tumor (Capurro et al., 2003; Nakatsura et al., 2003; Zhou et al., 2006). On the other hand, there is a decrease of glypican-3 in malignant mesothelioma cell lines and primary tumors (Murthy et al., 2000). This HS proteoglycan has been shown to inhibit mesothelioma and breast cancer cell proliferation, and induce apoptosis of these cells but not of colorectal tumor cells (Gonzalez et al., 1998). It is suggested that the expression of glypican-3 in tumors is dependent on whether the normal tissue of origin expressed this proteoglycan (Filmus, 2001). Glypican-3 is also an emerging therapeutic target for anti-cancer therapies (Feng and Ho, 2014).

Tumor cells modify the surrounding stroma by enzyme secretion

Tumor cells are capable of modifying the ECM by synthesizing matrix constituents, degrading the surrounding ECM and modulating the synthesis of matrix components by host cells and tumor-associated fibroblasts. Haptotactic gradients are formed driving cells towards different stimuli, promoting metastasis by protecting the localization of proteinases and by blocking interactions between tumor cells and other adhesion molecules (Perrimon and Bernfield, 2000).

Many membrane-bound proteoglycans are co-receptors at the cell surface, but can also function as soluble autocrine or paracrine effectors when their extracellular domains, including the glycosaminoglycan chains, are enzymatically cleaved and released from the cell surface by ectodomain shedding (Nam and Park, 2012). The shedding mechanism provides a rapid change of the cell surface characteristics, as it reduces the population of glycosaminoglycans available for binding, resulting in altered cell functions. The shed ectodomains

can remain sequestered in the ECM or diffuse into the circulation, where they can be used as cancer markers (Iozzo and Sanderson, 2011).

Syndecans and CD44 are shed by metalloproteinases, whereas glypicans are released from the cell surface by cleavage of their GPI anchor by phospholipases. Several metalloproteinases can shed syndecan-1 ectodomains (Yang et al., 2002; Manon-Jensen et al., 2010). The majority of syndecan regulators enhance metalloproteinase-mediated syndecan-1 shedding at the cell surface in a protein tyrosine kinase-dependent manner. Glypican-1 and syndecans, both HS proteoglycans, are up-regulated by pancreatic (Conejo et al., 2000) and breast cancer cells (Matsuda et al., 2001; Su et al., 2007), and their removal by MMP-7 (matrilysin) renders such cells insensitive to many growth factors (Ding et al., 2005). In patients with colorectal cancer, there is a significant correlation between circulating VEGF and tumor tissue-derived Matrix Metalloproteinase-9 (MMP-9, gelatinase B) (Hawinkels et al., 2008), where VEGF is released from the ECM after HS proteoglycan shedding. Another important example of proteoglycan shedding occurs after intracellular activation by furin and proprotein convertases (PCs) (Remacle et al., 2006), where MMP-14 is expressed at the cell surface degrading breast cancer HSPGs (Chabottaux and Noel, 2007) and is important for the activation of other MMPs (Chakraborti et al., 2003). Membrane type-1 matrix metalloproteinase (MT1-MMP) may function in cancer cells as an oncogene and also as a mediator of proteolytic/shedding events on the cell surface/matrix. This activity requires proteolytic removal of the MT1-MMP prodomain sequence by furin (Remacle et al., 2006).

High levels of soluble syndecan-1 ectodomains are observed in the serum of patients with different types of cancers, such as lung cancer (Joensuu et al., 2002), myeloma (Yang et al., 2002), breast cancer (Nikolova et al., 2009) and lymphocytic leukemia (Jilani et al., 2009), and are related to greater tumor aggressiveness and poor prognosis. Evidence relating syndecan-1 ectodomains to increased tumor cell activity as measured by cell migration, adhesion and higher gelatinase activity has recently been reported; after stimulating tumorigenic cells (SCC-9) with phorbol-ester (PMA) these cells showed an increase in soluble syndecan-1ß which was associated with a decrease in membrane-bound syndecan-1 and promotes cell migration (Aragao et al., 2012).

Another important regulator of the shedding mechanism is heparanase. This enzyme is anendo-β-D-glucuronidase that cleaves HS chains into fragments of 5–7 kDa in size. The fragments and cytokines released upon digestion may enhance tumor progression by stimulating cell signaling and up-regulating the expression of genes that promote an aggressive tumor phenotype (Reiland et al., 2004; Fux et al., 2009; Arvatz et al., 2011). Heparanase is up-regulated in myeloma patients and high levels of heparanase expression correlate with enhanced angiogenesis and poor prognosis (Kelly et al., 2003; Mahtouk et al., 2007).

Perhaps one of the most studied regulation effects of tumor expressed heparanase is in breast cancer. Its expression regulates angiogenesis, metastasis, and tumor growth (Cohen et al., 2006), and contributes to an aggressive behavior of breast tumor cells and to poor prognosis in these patients (Maxhimer et al., 2005).

Signaling pathways activated by proteoglycans in tumors

SLRPs can affect tumor growth and progression by modulating growth factor activity and matrix assembly. SLRPs bind to collagen and this interaction enhances collagen fibril stability (Keene et al., 2000; Neame et al., 2000) and protects collagen fibrils from proteolytic cleavage by various collagenases (Geng et al., 2006). This would affect matrix rigidity, which has been shown to influence cancer cell growth and malignancy (Paszek et al., 2005). In addition, collagen is a chemoattractant for cultured cancer cells (Mundy et al., 1981).

Ectopic expression of decorin, an archetypal SLRP, results in the regression of rat C6 gliomas by sequestering TGF-β released by the tumor cells, thus inhibiting TGF-β-induced immunosuppression in the host, and by modulating TGF-β synthesis (Stander et al., 1999). Decorin has also been shown to indirectly affect the TGF-β receptor pathway by modulating the insulin-like growth factor receptor and low-density lipoprotein receptor-related protein 1 (Goldoni and Iozzo, 2008). By decreasing the activity of TGF-β and decreasing the abundance of oncogenic microRNA-21, a translational inhibitor of PDCD4 (programmed cell death 4), decorin prevents translational repression of PDCD4 (Merline et al., 2011). An increase in PDCD4 leads to a decrease in the release of the anti-inflammatory cytokine interleukin-10, creating a more pro-inflammatory environment (Merline et al., 2011). Another means by which decorin controls inflammation is by acting as an endogenous ligand of Toll-like receptors 2 and 4 and stimulating the production of proinflammatory molecules such as PDCD4 (Merline et al., 2011). In addition to modulating the ECM, decorin is capable of inhibiting stromal genes necessary for immunomodulatory responses and inducing the expression of genes related to cellular adhesion and with tumor suppressive properties in breast carcinoma (Buraschi et al., 2012). Decorin has also been shown to reduce membrane ruffling of breast cancer cells and increase cell-cell adhesiveness (Pucci-Minafra et al., 2008).

Decorin is a well-known endogenous tumor repressor that suppresses tumor growth and angiogenesis (Buraschi et al., 2012). Decorin growth suppression of a variety of tumor cells is dependent on p21 (a potent inhibitor of cyclin-dependent kinases) as a downstream effector, which induces G1 arrest (Santra et al., 1997). This process involves decorin-induced phosphorylation

of the epidermal growth factor (EGF) receptor and concurrent activation of the mitogen-activated protein (MAP) kinase signaling pathway, which leads to sustained induction of endogenous p21 (Moscatello et al., 1998). In addition, decorin has been shown to inhibit tumor cell growth by down-regulating members of the ErbB receptor tyrosine kinase family and attenuating their signaling (Goldoni et al., 2008). Decorin-induced down-regulation of the ErbB2 tyrosine kinase cascade is implicated in reduced primary tumor growth and metastasis (Reed et al., 2005). Another receptor tyrosine kinase down-regulated by decorin is Met. Decorin binds to Met inducing transient receptor activation, recruitment of the E3 ubiquitin ligase c-Cbl, and rapid intracellular Met degradation, which results in suppression of Met-mediated cell migration and growth (Goldoni et al., 2009). Decorin also induces degradation of the transcription factor beta-catenin, which is a downstream Met effector (Goldoni et al., 2009). Decorin has also been shown to be a pro-apoptotic agent (Goldoni et al., 2008). Decorin induces apoptosis in squamous carcinoma xenografts by activating caspase-3 and specifically targets EGFR-overexpressing tumor cells (Seidler et al., 2006). Caspase-3 cleaves the intracellular domain of the EGFR starting the apoptotic process. Decorin-induced apoptosis of cholangiocarcinoma cells has been associated with E-cadherin (Yu et al., 2014).

The anti-tumorigenic properties of decorin also relate to the fact that it is capable of suppressing tumor cell-mediated angiogenesis by suppressing tumor cell production of VEGF and inhibiting endothelial cell migration, attachment, and differentiation (Grant et al., 2002). Decorin has been shown to suppress angiogenesis by inhibiting both VEGF and basic fibroblast growth factor-induced angiogenesis (Sulochana et al., 2005). In addition, decorin suppresses the expression and enzymatic activity of MMP-9 and MMP-2, which are pro-angiogenic proteinases (Neill et al., 2012). The effect of decorin on endothelial cell migration has been analyzed by testing decorin-derived peptides, which were found to inhibit endothelial cell migration by interfering with VEGF-stimulated endothelial nitric oxide synthase (eNOS) activation and nitric oxide release through signaling pathways that involve PI3 kinase and Akt (Fan et al., 2008). In addition, decorin regulates endothelial cell migration and adhesion on collagen I by stimulating cytoskeletal and focal adhesion reorganization through activation of the insulin-like growth factor-I receptor (IGF-1R) and the small GTPase Rac and modulating alpha2beta1 integrin activity (Fiedler et al., 2008).

Lumican has been shown to decrease tumor formation in mice by inducing or increasing apoptosis in squamous carcinoma xenografts (Vuillermoz et al., 2004). Furthermore, lumican has been shown to decrease the development of lung metastasis in mice by inducing tumor cell apoptosis, decreasing VEGF expression and decreasing neovascularization (Brezillon et al., 2009a). The effect of lumican on neovascularization could be related to the fact that it suppresses endothelial cell migration and pseudotube formation in Matrigel® (Brezillon et al., 2009a). Lumican has been shown to inhibit the activation of p38 MAPK in endothelial cells, inhibiting the invasion, angiogenic sprouting and vessel formation of these cells (Albig et al., 2007). Lumican has also been shown to inhibit melanoma cell migration, which is correlated with altered cell morphology and rearranged actin filament organization (Radwanska et al., 2008). This inhibition involves binding between lumican and $\alpha 2\beta 1$ integrin cytoskeleton remodeling and a decrease in focal adhesion kinase phosphorylated at tyrosine-397 (pFAK) (D'Onofrio et al., 2008; Brezillon et al., 2009b; Zeltz et al., 2010). Furthermore, lumican has been shown to inhibit prostate cancer cell migration and invasion by inhibiting the formation of prostate cancer cell invadopodia (Coulson-Thomas et al., 2013). On the other hand, lumican increases the migration of human colon adenocarcinoma cells through actin cytoskeleton remodeling (Radwanska et al., 2012). Moreover, extensive studies have reported that lumican enhances epithelial cell migration promoting wound healing, and recently this was shown to be mediated through binding to TGFβRI (ALK5) (Yamanaka et al., 2013). In osteosarcoma cells lumican decreases cell adhesion by inhibiting TGFβ2 activity, which results in the modulation of pSmad2, integrin β1 and pFAK (Nikitovic et al., 2011).

Biglycan suppresses the growth of pancreatic cancer cells by inducing G1-arrest, which is accompanied by an increase in p27 and decrease in cyclin A and proliferating cell nuclear antigen (Weber et al., 2001). Decorin and biglycan interact with WISP-1, which is a growth factor linked to tumorigenesis (Desnoyers et al., 2001).

Glypican-5 has been shown to suppress the proliferation of non-small cell lung cancer cells by inducing G1/S phase arrest (Yang et al., 2013). Glypican-1, on the other hand, inactivates the G1/S checkpoint and stimulates DNA replication (Qiao et al., 2013). Glypican-1 also induces down-regulation of tumor suppressors and up-regulation of pro-oncogenic proteins (Qiao et al., 2013). Glypicans and syndecans are coreceptors for heparin-binding mitogenic growth factors, such as heparin-binding epidermal growth factor-like growth factor and fibroblast growth factor 2, which are up-regulated in tumors (Kleeff et al., 1998; Filmus, 2001; Matsuda et al., 2001).

Conclusion

Tumor cells must modify the surrounding stroma to create an environment that is favorable for tumor growth and metastasis. This is achieved by regulating the ECM produced by fibroblasts, degrading the surrounding ECM and/or synthesizing a favorable ECM to support invasion. One component of the ECM that is modified by tumors is proteoglycans, which play a vital role in the

reactive stroma. Some proteoglycans, such as syndecan-1 and glypican-1, support tumor growth and metastasis, whilst others, such as glypican-5, suppress cancer cell migration, proliferation and invasion. Other types of proteoglycans such as the SLRPs may support or restrict tumor growth and progression depending on the type of tumor. Glycosaminoglycan chains released from membrane-bound proteoglycans by shedding can also have an effect on tumor progression. Proteoglycans have also been shown to be useful as tumor markers and targets for anti-cancer therapies.

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