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Proteoglycans: Master Modulators of Paracrine Fibroblast - Carcinoma Cell Interactions

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Abstract

Reciprocal interactions between tumor and stromal cells govern carcinoma growth and progression. Signaling functions between these cell types in the tumor microenvironment are largely carried out by secreted growth factors and cytokines. This review discusses how proteoglycans, which are abundantly present in normal and neoplastic tissues, modulate paracrine growth factor signaling events. General principles of proteoglycan involvement in paracrine signaling include stromal induction, core protein processing by proteases and growth factor binding via proteoglycan glycosaminoglycan chains or core protein domains.

Keywords

cancer; proteoglycans; extracellular matrix; paracrine; tumor microenvironment; stroma

1. Introduction

Tumor formation and progression are governed by reciprocal paracrine interactions between cancer and stromal cells [1]. This review will explore evidence that proteoglycans (PGs) play key roles directly as paracrine signaling molecules and indirectly as modulators of signaling events. PGs are ubiquitous molecules composed of highly diverse core proteins and covalently attached glycosaminoglycan (GAG) polysaccharide chains [2]. Principally via heparan sulfate GAGs, PGs bind extracellular matrix (ECM) constituents and a variety of growth factors with crucial roles in cancer cell – stroma communication. Binding of growth factors to ECM PGs creates mitogen reservoirs and gradients. Importantly, PG heparan sulfate also participates in ternary growth factor ligand – receptor complexes, thus stabilizing these complexes and amplifying the signal [3].

Space restrictions prevent a discussion of “part-time” proteoglycans such as CD44 or “protein-free” GAGs such as hyaluronan and heparin in malignancy. Cell-autonomous co-receptor activities of PGs in growth factor receptor signaling or integrin-mediated adhesion have been reviewed [3,4] and will generally not be considered here. Critical functions of PGs in angiogenesis have been described [5] but their discussion would exceed the scope of this paper. Instead, this review will focus on paracrine signaling functions of the “classical” cell surface

PGs in the syndecan and glypican families and the secreted PGs perlecan, collagens XV and XVIII and decorin.

2. Cell Surface Proteoglycans

2.1 Syndecans

The syndecan family of PGs comprises four members (Sdc1–4), which are composed of transmembrane core proteins that are decorated with heparan sulfate (HS) and chondroitin sulfate (CS) GAG chains [4,6]. Sdc1 can be shed from the cell surface by proteolytic cleavage of the core protein [7]. Through its release from the cell surface, Sdc1 is converted from a cell surface receptor to a diffusible mediator, enabling this molecule to participate in paracrine signaling events. Sdc1 shedding occurs at a basal level in most cells but can be increased by a variety of stimuli, which include protein kinase C activators, epidermal growth factor family members, stromal cell derived factor-1 (SDF1, CXCL12), and thrombin [8,9]. A distinct proteolytic cleavage site is present between amino acids Ala-243 and Ser-244 in the juxtamembrane region of the Sdc1 ectodomain [10]. Proteolytic Sdc1 cleavage has been attributed to a variety of enzymes, which include matrix metalloprotease (MMP) 7, MMP9, and the membrane type MMPs MT1-MMP (MMP14) and MT3-MMP [8,10–13]. Interestingly, Sdc1 shedding is enhanced by the presence of the tumor promoting enzyme heparanase, which degrades heparan sulfate GAGs and clusters the Sdc1 protein cores [14,15].

In adult organisms, Sdc1 is found primarily on epithelial cells and plasma cells. In carcinomas, tumor cell Sdc1 can be either lost or upregulated [16–20]. Elevated tumor cell Sdc1 predicts poor clinical outcome in breast cancer [17,20,21]; an effect that might be related to cell autonomous growth factor receptor or integrin activation rather than paracrine signaling [22, 23].

In addition to epithelial expression, Sdc1 is also transiently produced by mesenchymal cells at sites of epithelial induction during development, *e.g.* in the developing tooth and kidney [24, 25]. This mesenchymal expression is recapitulated in cancer, when Sdc1 is induced in fibroblasts within the desmoplastic stroma in a variety of tumor types including breast cancer [26,27]. Sdc1 expression in stromal myofibroblasts is particularly well documented in breast cancer, where it is seen in the majority of breast carcinomas, independent of tumor subtype or prognostic markers (Fig. 1A) [26,27]. Initially, the biologic consequences of stromal Sdc1 expression were unclear but subsequent *in vitro* and *in vivo* work established stromal Sdc1 as a central mediator of paracrine growth stimulation [27–30]. Murine or human mammary fibroblasts stimulate breast carcinoma cell growth both in 2D and 3D co-culture, an activity that coincides with Sdc1 expression in the fibroblasts [27,29]. Importantly, the growth advantage attributable to the fibroblasts is abolished when Sdc1 induction is prevented either by genetic manipulation (using MEF from Sdc1 knock-out mice) [27] or by siRNA knock-down in human mammary fibroblasts [29]. *In vivo*, the growth of highly malignant MDA-MB-231 human breast carcinoma cells is accelerated when Sdc1-positive fibroblasts are admixed in the xenografts [28]. The paracrine growth promoting activity of Sdc1 depends on intact HS chains, since a core protein in which three serine GAG attachment domains are mutated to alanine fails to substitute for wild-type Sdc1 in the fibroblasts [29].

A further exploration of the underlying mechanism revealed that stromal Sdc1-mediated carcinoma cell growth stimulation requires Sdc1 shedding, because an “uncleavable” Sdc1 mutant was inactive [29]. In 3D co-cultures of immortalized human mammary fibroblasts and T47D breast carcinoma cells, Sdc1 release from the cell surface is mediated by fibroblast-derived membrane-type 1 matrix metalloprotease (MT1-MMP, aka MMP14), assigning another cancer-promoting function to this enzyme [30]. The soluble Sdc1 extracellular domain stimulates carcinoma cell growth in concert with fibroblast growth factor 2 (FGF2) and SDF1,

as blocking of either one abolishes the growth advantage imparted on the carcinoma cells by the presence of fibroblasts [29]. Possibly, Sdc1 ectodomain shuttles SDF1 and/or FGF2 from the fibroblasts to the carcinoma cells and facilitates the formation of an active signaling complex. The apparent privileged role for Sdc1 is surprising, considering that human mammary fibroblasts produce abundant Sdc2 (also known as fibroglycan) and Sdc4, both of which can also be shed [8,31]. The specificity may be conveyed by a potential Sdc1 substrate selectivity of the MT1-MMP enzyme [10]. Notably, the Sdc2 and Sdc4 core proteins share little homology with Sdc1. Together, these findings are consistent with a complex, reciprocal paracrine signaling loop that involves Sdc1, an MMP and growth factors (schematically shown in Fig. 2).

The role of the other syndecan family members in paracrine signaling events in cancer is less clear. The migration of fibroblasts into the fibrin-rich matrix of a wound site requires Sdc4 [32], which at least in part explains the wound healing defects seen in Sdc4 knockout mice [33]. It is therefore plausible that Sdc4 is also required for the recruitment of fibroblasts (from the local environment or the bone marrow) into the tumor stroma. In murine Lewis lung carcinomas, tumor cell Sdc2 expression and core protein phosphorylation lead to fibronectin binding followed by tumor stroma formation [34]. One can only speculate that the provisional ECM tethered to Sdc2 around the tumor cells facilitates the recruitment of stromal fibroblasts. A recently discovered unexpected activity of Sdc2 is the inhibition of MMP2, which results in the suppression of tumor invasion and metastasis [35]. Sdc2 and Sdc3 are found in human ovarian carcinoma stroma but their functions in this tumor type are unknown [18].

2.2 Glypicans

The glypicans constitute a six-member family of cell surface proteoglycans (Gpc1–6) [36]. Because glypicans are anchored in the cell membrane by a glycosylphosphatidylinositol (GPI)-linked lipid tail, they can be released into the pericellular environment by phosphoinositide-specific phospholipase-C; however, the regulation and physiologic relevance of glypican shedding are poorly understood. All glypicans share a globular domain, which regulates heparan sulfate synthesis [37]. Elevated Gpc1 expression has been documented in pancreas carcinoma, breast cancer and in glioma, and this proteoglycan appears to play a privileged role in promoting growth factor activity [38–40]. The involvement of Gpc3 in cancer is complex and context-dependent. Gpc3 is overexpressed in the majority of hepatocellular carcinomas and has in fact utility as a serum and tissue marker in the diagnosis of this malignancy [41–43]. In the majority of breast carcinomas, Gpc3 expression is silenced. Re-expression of Gpc3 suppresses invasion and promotes apoptosis [44,45]. Many of the cellular activities of Gpc3 are reportedly mediated by a modulation of paracrine canonical wnt signaling. Interestingly, binding interactions between wnt and the Gpc3 core protein rather than heparan sulfate chains appear to mediate this effect [44]. While glypicans may act on the tumor cells in a cell-autonomous fashion, they are also expressed by stromal fibroblasts (Fig. 1B) and are released from the tumor cell surfaces into the stromal microenvironment [18,38]. Regardless of the cell type of origin, glypicans modulate paracrine, stroma-derived signals and act primarily as pro-tumorigenic agents.

3. Secreted Extracellular Matrix Proteoglycans

3.1 Perlecan

Perlecan is a secreted PG, which consists of a large (~450 kDa) core protein, composed of modules homologous to growth factors and domains implicated in lipid metabolism or cell adhesion [46]. Heparan sulfate GAG chains are covalently attached at the N-terminus. This abundant and ubiquitous PG is incorporated into basement membranes and the pericellular space upon secretion. Its deposition at a strategic extracellular location makes perlecan a natural

candidate for a paracrine mediator. Perlecan-derived HS was initially thought to carry a specific and privileged activity as a FGF2 co-factor [47,48] but later, other heparan sulfate PGs were implicated in FGF2 signaling as well [49,50]. Heparan sulfate sulfation pattern and growth factor binding affinities vary greatly between perlecan preparations isolated from different cell types [51]. This and other observations suggest that the cell source and context are more important determinants of heparan sulfate structure and function than the identity of the core protein.

The cumulative evidence indicates that perlecan is an important mediator of paracrine stroma-tumor cell interactions in a variety of cancers. Perlecan expression is greatly increased in metastatic human melanomas [52] and compared to normal pancreatic epithelial cells, perlecan is found in the secretome of pancreas carcinoma cells [53]. Tumor growth is retarded in mice genetically deficient in this PG [54]. In prostate cancer, perlecan production correlates with high Gleason grade and thus clinical outcome [55]. *In vitro*, silencing of perlecan expression diminishes carcinoma cell proliferation. Perlecan and the growth factor and morphogen Sonic hedgehog homolog (Shh) not only co-immunoprecipitate but mitogenesis is restored in perlecan siRNA-treated cells by simultaneous expression of the Shh downstream effector Gli1, indicating a critical role for perlecan in a growth promoting, paracrine Shh-mediated signaling pathway [55,56]. The importance of perlecan in prostate carcinoma may extend beyond Shh, as perlecan knock-down reduces the response to other growth factors [57].

The perlecan activities discussed so far are mediated by its heparan sulfate chains. Interestingly, binding interactions between the perlecan core protein and growth factors or other paracrine mediators have also been reported. The perlecan core protein not only binds FGF7 (also known as keratinocyte growth factor) [58] but is also required for the activation of FGFR2iiib, the cognate FGF7 receptor [59]. As a prototypic paracrine mediator, FGF7 is secreted by stromal fibroblasts and acts specifically on epithelia, including carcinoma cells [60]. Other perlecan core protein binding partners include FGF binding protein (FGF-BP), itself a modulator of FGF signaling [61], and progranulin [62], an autocrine, pro-tumorigenic growth factor [63, 64].

3.2 Multiplexins (Collagens XVIII and XV)

The basement membrane constituents collagen XVIII and XV share characteristics of collagens and PGs [65]. These molecules are composed of interrupted triple-helical modules and non-collagenous domains at the N- and C-termini. Three Ser-Gly consensus sites are glycanated with heparan sulfate chains. Collagen XVIII prevents the invasion of squamous cell carcinoma cells by blocking the activation of MMPs 2, 9 and 13 [66]. A cryptic domain within collagen XVIII (but not the intact parent molecule) displays frizzled-like activity upon its proteolytic release and blocks canonical wnt/beta-catenin signaling [67]. Consequently, cyclin D1 and c-myc are down-regulated and tumor growth is abated. The forced overexpression of collagen XV in highly malignant human cervical carcinoma cells results in the deposition of this PG in the pericellular environment and a suppression of tumor cell growth in 3D cultures and of tumor growth *in vivo* [68]. The molecular mechanism of collagen XV-mediated tumor growth suppression is unclear.

Perlecan and collagens XVIII and XV, the three basement membrane PGs discussed here, are subject to proteolytic cleavage, which produces the diffusible peptide fragments endorepellin, endostatin, and restin, respectively. These fragments possess potent anti-angiogenic activities only after their release from the parent molecules. These intriguing activities have been reviewed elsewhere [65,69].

3.3 Decorin

Decorin belongs to a diverse family of extracellular small leucine-rich proteoglycans (SLRP) [reviewed in [70]]. Decorin participates in paracrine signaling events in normal and neoplastic tissues at multiple levels [71]. Decorin is produced primarily by fibroblasts (and carcinoma-associated myofibroblasts) and is essential for the proper assembly of collagen fibrils [72]. Genetically decorin-deficient mice develop spontaneous colon adenocarcinomas whereas *de novo* expression of decorin in human colon carcinoma cells suppresses the malignant phenotype [73,74]. These findings suggest a tumor suppressor role for this PG. Loss of decorin in the mouse model is accompanied by a decrease in E-cadherin, accompanied by elevated beta-catenin signaling and a reduction of the cyclin-dependent kinase inhibitor p21 [73].

The most extensively documented roles for decorin in stroma-carcinoma communication are mediated through its binding affinities for the epidermal growth factor receptor (EGFR) and transforming growth factor beta 1 (TGFβ1). Decorin binds to the EGFR, which results in transient phosphorylation followed by dephosphorylation, internalization and degradation of this receptor [75]. Findings by Goldoni and co-workers indicate that decorin also downregulates other Erb family members including ErbB2 [76]. *In vivo*, decorin effectively blocks the metastatic spread of ErbB2 overexpressing mammary carcinoma cells, whereas an ErbB2 receptor tyrosine kinase inhibitor lacks this activity [76]. More recently, the same group showed that decorin also binds to the Met receptor and acts as natural antagonist to its ligand, the pro-invasive and tumor promoting cytokine scatter factor/hepatocyte growth factor (SF/HGF) [77].

In the extracellular compartment, decorin binds and sequesters TGFβ1 and thus dampens the activity of this cytokine. TGFβ1 has complex roles in reciprocal paracrine signaling between carcinoma cells and stromal fibroblasts [reviewed in [78]]. Carcinoma cell-derived TGFβ1 contributes to the induction of a reactive, desmoplastic tumor stroma [79–81]. Conversely, fibroblast/myofibroblast-derived TGFβ1 either decelerates carcinoma cell proliferation or promotes tumorigenesis, dependent on the cellular context [82]. Based on its modulating activity on TGFβ1 signaling and direct effects on collagen fibril assembly, the absence of decorin in carcinomas leads to higher collagen density (schematically shown in Fig. 2) [83]. This finding is of great interest in the context of the well-established correlation between increased breast density and breast carcinoma risk [84] and the fact that *in vitro*, increased collagen density promotes tumorigenesis, invasion and metastasis [85–87].

4. Conclusions

Abundant evidence implicates PGs as crucial players in paracrine signaling between stromal fibroblasts/myofibroblasts and carcinoma cells. In general, this involves overexpression (example: Sdc1 induction in fibroblasts) or reduced secretion (example: decorin) in the stromal compartment (Fig. 2). Altered rates of PG processing by elevated activities of MMPs and heparanase enzymes likely contribute to generating abnormal levels of diffusible stromal PGs in tumors. The major mechanisms of action of the stromal PGs consist of the modulation of paracrine signals by shuttling cytokines from the stromal compartment to the carcinoma cell surface and forming an active complex with signaling receptors (example: Sdc1 ectodomain/FGF2/FGFR1), sequestering paracrine mediators (example: decorin/TGFβ1) or directly regulating carcinoma cell receptor tyrosine kinases (example: decorin/ErbB).

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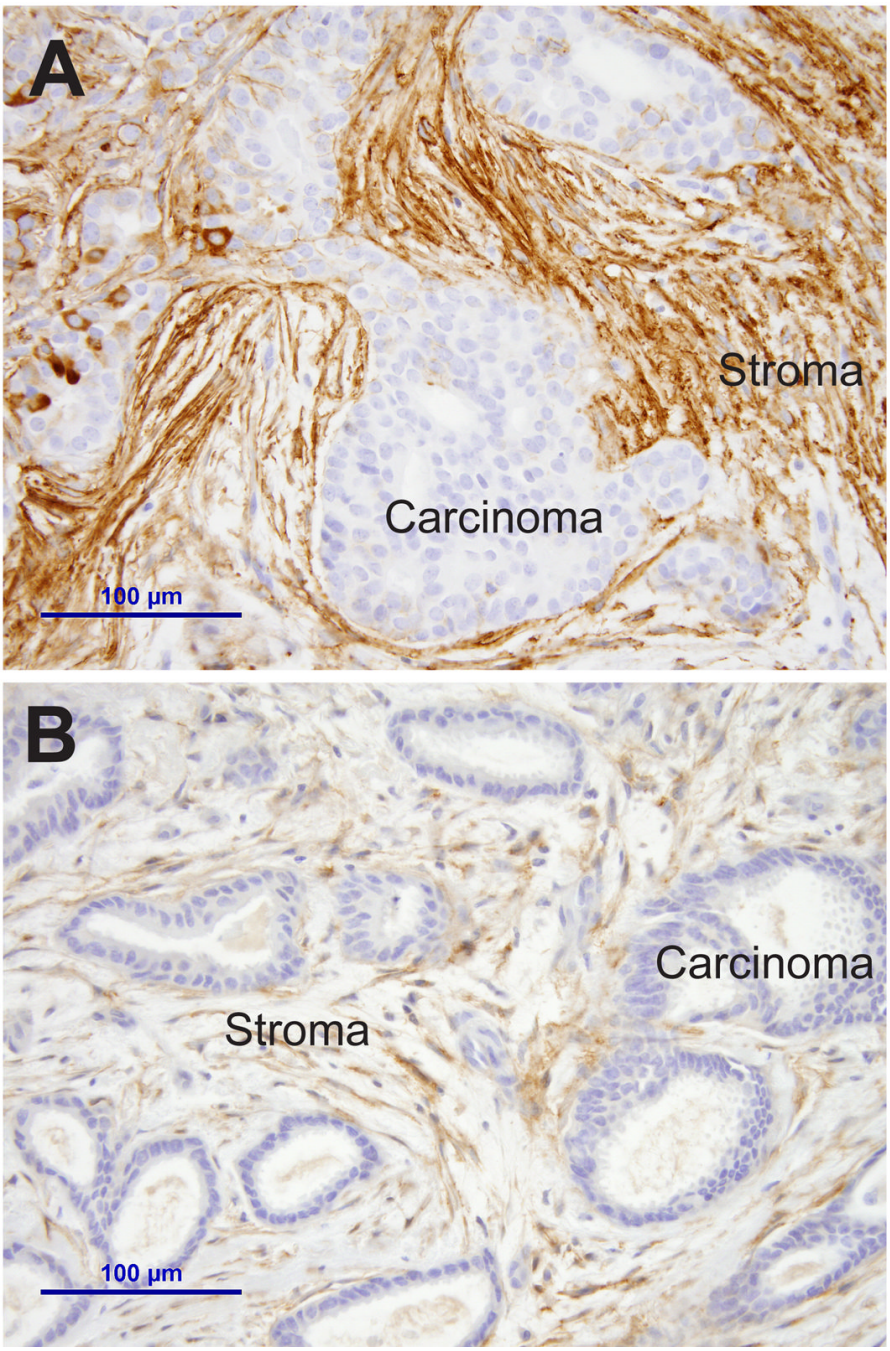

Figure 1.
Aberrant stromal expression of cell surface proteoglycans: A) Strong and diffuse syndecan-1 expression in stromal fibroblasts of a breast carcinoma. B) Glypican-1 expression in stromal fibroblasts of a breast carcinoma.

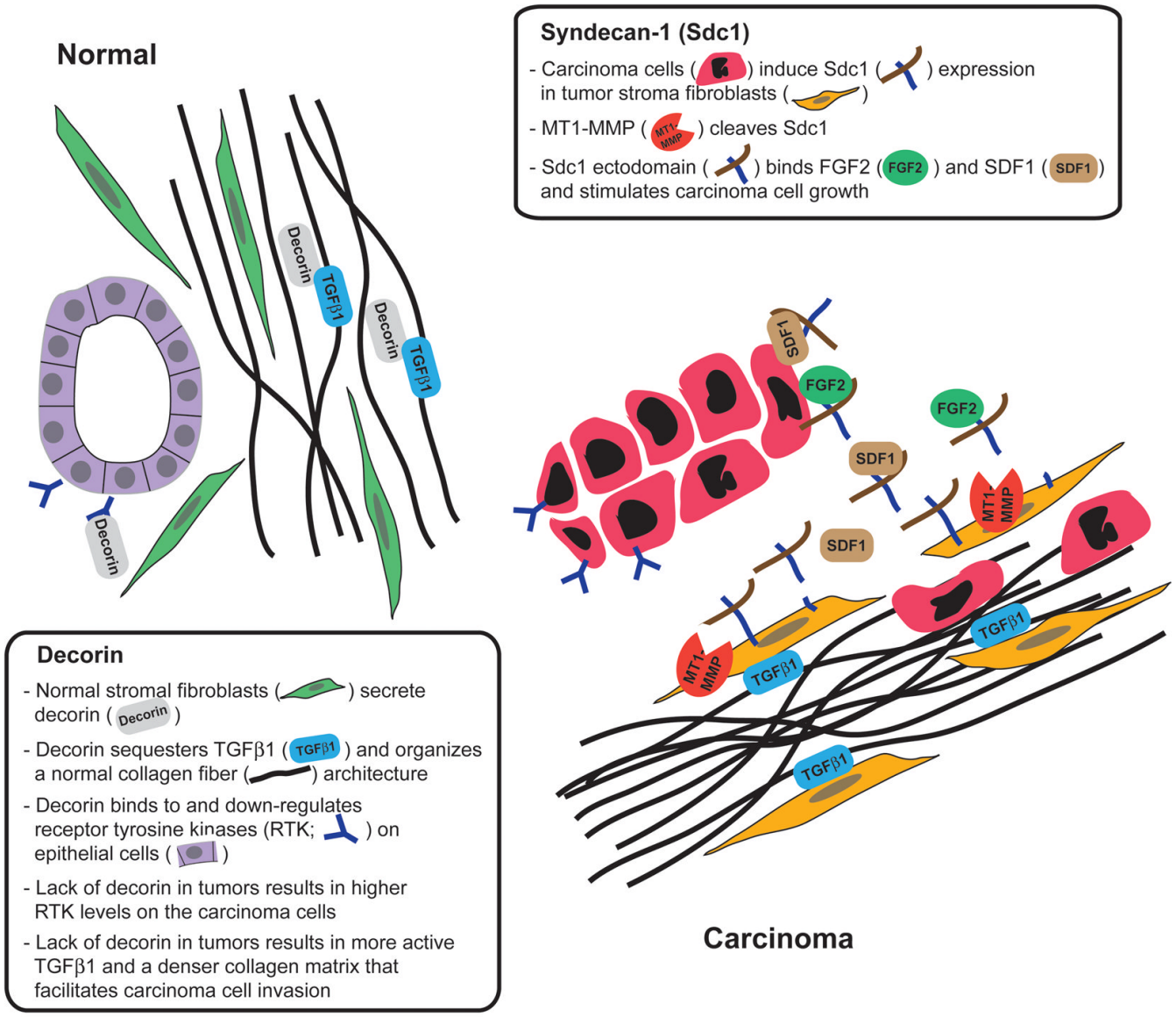

Figure 2.
Schematic representation of the role of stromal syndecan-1 and decorin in normal mammary gland and breast cancer.