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Mini-Review: Decorin, a Guardian from the Matrix

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Decorin, a Guardian from the Matrix

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Abstract

Decorin, an archetypical member of the small leucine-rich proteoglycan gene family, has a broad binding repertory that encompasses matrix structural components such as collagens, and growth factors, particularly those belonging to the TGFβ ligand superfamily. Within the tumor microenvironment, stromal decorin has an inherent proclivity to directly bind and downregulate several receptor tyrosine kinases, which are often overexpressed in cancer cells. The decorin interactome commands a powerful anti-tumorigenic signal by potently repressing and attenuating tumor cell proliferation, survival, migration, and angiogenesis. It also regulates key downstream signaling processes indirectly by sequestering growth factors or directly via receptor tyrosine kinase antagonism. We propose that decorin can be considered a "guardian from the matrix" because of its innate ability to oppose pro-tumorigenic cues.

Introduction

Neoplastic growth has long been viewed in the paradigm of activating mutations in oncogenes and silencing of tumor suppressor genes that, collectively over time, confer selective advantages to fundamental cellular processes such as cell proliferation, survival, migration, and metastasis. However, over a relatively short period of time, the profound importance of the surrounding tumor stroma, encompassing that of abnormal synthesis and deposition of several proteoglycans, began to emerge as an active participant in coordinating many aspects of tumor growth and progression. Indeed, an early defining histopathological feature of certain carcinomas is the presence of a strong desmoplastic reaction surrounding the tumor proper which is inherently enriched in various proteoglycan species[1,2].

Decorin represents a prototypical member of the small leucine-rich proteoglycan (SLRP) gene family that houses 18 distinct members segregating into five discrete classes with sequence conservation across multiple species[3]. Decorin contains a single glycosaminoglycan (GAG) chain composed of either dermatan or chondroitin sulfate and 12 leucine-rich repeats comprising the protein core. Decorin is a stromal proteoglycan synthesized chiefly by fibroblasts, stressed vascular endothelial cells, and smooth muscle cells. Initially decorin was named for and characterized by its high affinity interaction with collagen fibers and for subsequent regulation of collagen fibrillogenesis[4-7]. It was subsequently discovered that decorin sequesters multiple growth factors, such as TGFβ1 and directly antagonizes several members of the receptor tyrosine kinase (RTK) family, including the epidermal growth factor receptor (EGFR), the insulin-like growth factor receptor I (IGF-IR) and the hepatocyte growth factor receptor (Met)[1] (Fig. 1). Consequently, these latter bioactivities have been attributed to evoke a potent tumor repressive property. The unique nature of this repressive activity is provided by fact that it functions wholly within the extracellular matrix to attenuate, in an integrated and protracted fashion, key pro-survival, migratory, proliferative, and angiogenic signaling pathways[2]. In a novel discovery, decorin has been implicated in modulating the inflammatory response as it pertains to cancer progression via engagement of Toll-like receptors[8]. Moreover, reduced decorin within the tumor stroma has been established as a poor prognosticator of invasive breast cancer and in mouse models of spontaneous breast cancer with mammary gland carcinogenesis[2]. Endogenously, certain neoplasms have a proclivity to hypermethylate the decorin promoter, effectively silencing expression to allow for tumor progression[2,9]. Thus, loss of decorin expression may also favor tumor growth.

In this review, we propose the concept of decorin as a guardian from the matrix, that is, a powerful endogenous tumor repressor acting in a paracrine fashion to limit tumor growth and angiogenesis.

Decorin Modulates Tumor Inflammatory Properties of the Stroma

A rapidly emerging hallmark of cancer involves the inflammatory process as an active and critical participant in tumorigenesis[10]. Several articles have been published to indicate an immunomodulatory role of decorin to recruit monocytes to injury sites through inducing MCP-1[11], inhibiting apoptotic death of macrophages[12], and modulating allergen-induced asthma[13]. A recently identified mechanism has been elucidated that links decorin, inflammation, and tumor growth[8]. This entails direct binding of soluble decorin to Toll-like receptors (TLR) 2 and 4 on macrophages. This leads to enhanced production of the pro-inflammatory protein programmed cell death 4 (PDCD4) and of the oncomir miR-21 causing stabilization and increased translation of PDCD4. The increased abundance of PDCD4 concurrently causes a decrease of anti-inflammatory cytokines such as interleukin-10 (IL-10) (Fig. 2). As an endogenous inhibitor of TGFβ1 by sequestration (Fig. 1) decorin also attenuates the TGFβ1 signaling pathways thereby further curbing tumor growth and inflammation[8]. Thus, by antagonizing TGFβ1, decorin circumvents PDCD4 translational repression to generate a more pro-inflammatory tumor microenvironment. It also induces the synthesis of pro-inflammatory modulators (TNFα, IL-12b) for the suppression of tumorigenic growth. It is important to note that TNFα is a binding partner for decorin[14] (Fig 1) and shows a moderate affinity for this ligand, thus highlighting an important regulatory function to further fine tune TNFα activities.

Recent experiments utilizing an animal model of delayed-type hypersensitivity in decorin-null mice are also supportive of a role of decorin for stimulating a more pro-inflammatory environment[15]. In this setting, lack of decorin is associated with reduced TNFα levels and increased expression of leukocyte adhesion molecules coincident with an increased adherence of leukocytes to the endothelium[15]. Finally, the closest relative of decorin, biglycan, has been previously shown to modulate immune responses[16,17] by acting as an endogenous ligand for TLR-2/4 to increase pro-inflammatory signals. Thus, these studies offer a new functional paradigm for SLRPs and inflammation.

Decorin Curbs the Lethality of the Tumor Niche by Directly Sequestering a Multitude of Growth Factors and Structural Components

Decorin has exquisite binding affinities for members of the TGFβ superfamily (Fig.1) including TGFβ1, TGFβ2, and myostatin[1,2], and through this interaction, can effectively trap ligands within the matrix and indirectly attenuate downstream signaling pathways mediated by the TGFβ receptor complex, as recently shown, for instance, in a mouse model of hepatic fibrosis[18]. However, bone-derived decorin seems to enhance TGFβ activity[19]. This has broad implications on tumorigenicity since it can advocate tumor immunosuppression and growth retardation[20]. However, it is not known if decorin influences assembly of the large latent TGFβ1 complex on collagen fibers. In the case of myostatin, decorin sequestration quenches myostatin growth inhibitory effects and thus promotes myoblastic

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growth *in vitro*[21]. In an analogous antagonistic activity, direct sequestration of platelet derived growth factor (PDGF) results in a potent decrease of PDGF-dependent phosphorylation of PDGF receptor and attenuation of PDGF-evoked cellular migration[22].

Decorin binds to low density lipoprotein receptor related protein 1 (LRP-1) and causes endocytosis of the complex leading to PI3K activation and indirect crosstalk and modulation of TGFβ signaling via Smad 2/3/7[23]. Although the interaction with LRP-1 has not yet been evaluated in cancer models, but it could have implications for tumor cell bioenergetics.

Another binding partner of decorin is Wnt-1 induced secreted protein 1 (WISP-1), a protein mainly confined to the stroma of colon tumors[24]. Decorin binding to WISP-1 results in an inhibition of WISP-1 interactions with other partners, thus suggesting a regulatory function of decorin in Wnt signaling[24]. It is not known if WISP-1 activity is further modulated or antagonized, in either a Wnt-1 dependent or independent manner, by decorin in colon tumors. Notably, decorin downregulates β-catenin in a non-canonical way following binding to Met[25], and decorin-null mice have increased β-catenin levels in the intestinal epithelium[26].

In addition to the aforementioned interactions and attenuation of growth factors by direct binding, decorin also binds a multitude of structural components within the extracellular matrix, particularly numerous collagen molecules, tenascin X[27] and elastin[28] (Fig. 1). Aside from binding fibrillar collagens I, II and III, decorin also binds saturably to collagen XIV. Thus, decorin may mediate binding to fibril-forming collagens while simultaneously affecting collagen XIV biology. Analyses of the supramolecular composition of collagen VI complexes have determined that decorin and matrilin directly bind to link collagen VI to either aggrecan or collagen type II fibrils[29]. Taken together, it seems plausible that decorin can certainly participate in regulating the desmoplastic reaction and higher-order matrix structure formation in the tumor stroma. The abundant presence of decorin in the tumor stroma of solid tumors has been proposed to represent a negative feedback loop on the activity of adjacent RTKs expressed by the growing malignant cells[1].

Decorin is an Endogenous Pan-Receptor Tyrosine Kinase Inhibitor

The initial finding that decorin bound with avid affinity to RTKs (Fig. 1) heralded a paradigm shift in the study of SLRPs and their contributions to cancer biology. EGFR was the first RTK discovered to bind decorin[30] and was considered the primary target of decorin in various types of cancer cells[2] for it triggered dimerization, internalization via caveosomes and ultimately degradation of the receptor complex within lysosomes[31] which presumably terminates EGFR signaling. This is in contrast to EGF-EGFR complexes competent to signal from endosomes following internalization where EGF is still capable of maximally stimulating tyrosine phosphorylation. Further, this stimulation engaged several signaling pathways, such as PLC-γ1, which is required for cell motility[32]. However, it is currently

unknown if decorin is proficient to stimulate signaling post-internalization in an analogous fashion to that of EGF.

Systemic delivery of decorin or viral vectors expressing decorin affects the growth of several types of solid cancers where RTKs play key roles[33-36]. Paramount to this feature is the ability of decorin to compete off EGF and exert a potent physiological downregulation of the receptor at the cell surface of tumor cells[2]. However in 2009, a new target of decorin was discovered via the utilization of an RTK phosphor-tyrosine array, which clearly demonstrated a rapid burst of phosphorylation of Met[37]. It was further shown that Met is the main target of decorin in HeLa cells since inhibition of the kinase domain of EGFR with the small molecule inhibitor AG1478 or with the monoclonal blocking antibody, mAb425, did not block the downregulation of met evoked by decorin. Moreover, Met exhibits a higher binding affinity for decorin when compared to that of EGFR[37].

It is a curious biologic feature of decorin to evoke differential phosphorylation signatures in EGFR and Met upon binding. This might reflect altered structural conformations of the receptors post-binding relative to the active conformation the receptor adopts after binding natural ligands. EGFR, for example, undergoes rapid phosphorylation to stimulate the MAPK signaling cascade, which paradoxically aids in cell cycle arrest and caspase-3 activation[38], despite total EGFR levels decreasing by up to 50%[2]. Further proof-of-concept for this phenomenon involves Met. A rapid burst of phosphorylation along the tyrosine residues of the intracellular tails of Met ensues and lasts for up to 30 minutes whereupon increased phospho-Y1003 recruits the E3 ubiquitin ligase c-Cbl for receptor internalization and degradation[37]. It is possible these signatures, particularly that of Met, has biological significance to convey the properties of decorin bioactivity. However, at this time, experimental evidence to evaluate these differential phosphorylation patterns is lacking but would be essential to gain a more mechanistic understanding into the biology of decorin. This is of essential importance considering the lack of endogenous ligands for Met, which, at present, only include hepatocyte growth factor (HGF), internalin B, and decorin[37,39].

Along these same lines, engagement of HGF with Met induces association of the receptor complex with clathrin coated pits[40] in HeLa cells for endosomal sorting and eventual recycling to the plasma membrane. However, this is not the case for decorin since this drives caveolin-1 to associate with Met[40] and concomitant lysosomal degradation in the same fashion as EGFR. Clearly, the differential phosphorylation patterns are encoding messages pertinent for decorin activity to selectively dictate finite biological outcomes.

Additional members of the Erb family of RTKs are also affected by decorin via degradation and signal suppression including ErbB2 and ErbB4, presumably via titration of EGFR away from functional signaling complexes composed of ErbB2 or ErbB4 heterodimers. However, new findings indicate a direct antagonism of the ErbB4 signaling by decorin[41]. During scar tissue repair in the central nervous

system, employment of small molecule inhibitors and siRNA specific for ErbB4 also blocks the decorin-mediated downregulation of semaphorin 3A, a target of ErbB4 activity[41].

Opposing roles of decorin in the signaling cascades of endothelial cells have also been documented. Since decorin binds collagen with nanomolar affinity, it has been reported that an interaction among $\alpha2\beta1$ integrin, collagen type I, and decorin increases endothelial cell migration by enhancing integrin-collagen interactions[42]. However, VEGF-R2 has been reported to be antagonized by decorin and more specifically via an engineered fragment encoding LRR5 via downstream attenuation of ERK1/2 signaling in human extravillous trophoblastic (EVT) cells[43].

A recurring theme concerning this form of receptor antagonism is the concept of receptor internalization and degradation evoked by decorin for most of the RTKs studied so far. However, this is not the case for IGF-IR where decorin binds to and attenuates downstream signaling of IRS-1 and blunts IGF-I activation of Akt and ERK, and p70S6K culminating in a migratory block[44]. In this case, decorin does not promote association of IGF-IR with caveolin-1 but is capable of preventing IGF-I from localizing IGF-IR to caveosomes. Subsequently, this receptor complex is not internalized or degraded in cellular models of urinary bladder carcinoma[44]. In contrast, in other cellular systems using non transformed cells decorin seems to be an agonist of IGF-IR[45,46].

Collectively, decorin can be considered as an endogenous matrix-centric pan RTK inhibitor that exhibits hierarchical binding affinities for various RTKs expressed at a given time by a tumor cell. This might aid in cross-talk signal integration as decorin would be able to bind multiple receptors with varying kinetics as a mechanism to subdue growth signals for tumor growth arrest. Further, a common thread uniting these receptors, with the exception of $\alpha2\beta1$ integrin, is the inclusion of Ig-like modules in their ectodomain. It is possible that decorin has an inherent ability to bind all receptors harboring this particular domain. However, these binding events and potential biological outputs have not yet been experimentally evaluated.

Decorin Antagonizes Tumorigenesis by Attenuating Multiple Signaling Pathways

Robust and high-affinity binding concurrent with rapid receptor internalization and degradation underlay the initial events for decorin-mediated tumor growth repression vis-á-vis broad RTK antagonism (Fig. 2). Subsequent to this binding, a potent attenuation of multiple pathways coordinating proliferation, survival, and angiogenesis ensues. Decorin mediated antagonism of Met specifically leads to a non-canonical repression of β-catenin and Myc[40]. HGF, signaling via Met, enhances β-catenin stability by two distinct modes including direct phosphorylation of β-catenin[47] and concomitant repression of glycogen synthase kinase 3β (GSK3β) via phosphorylation. This is an example of RTK-mediated stabilization of β-catenin independent of traditional Wnt signaling. Collectively, this cascade promotes nuclear translocation of β-catenin which drives transcription of

prosurvival and protumorigenic genes[10]. Myc, a target of β-catenin and downstream of HGF/Met[1], coordinates large networks conducive to growth and proliferation. Interestingly, among the repertoire of Myc targets is AP4, a transcriptional repressor of p21^{WAF1}[48], a cyclin-dependent kinase inhibitor that is specifically induced by decorin treatment of various cancer cells[1]. Conversely, addition of exogenous decorin induces a profound and maintained suppression of β-catenin and Myc leading to inhibition of several key Met-mediated pathways including migration, proliferation, survival, and scattering. This is in part mediated by relieving RTK inhibition of GSK3β, which in turn phosphorylates Myc at specific sites[40]. Phosphorylation of Thr58 on Myc by GSK3β is known to evoke Myc degradation via the proteasome. Notably, phosphorylation at this site is markedly induced by soluble decorin protein core coincident with nuclear translocation, and 26S proteasomal degradation[40]. It is tempting to speculate that protein phosphatase 2A, the serine-threonine phosphatase directly opposing GSK3β, might also be attenuated thereby allowing for enhanced β-catenin and Myc degradation. This would lead to de-repression and subsequent induction of the p21 locus while providing a mechanism for growth arrest (Fig. 2). Additionally, β-catenin drives cyclin D1 expression and this pathway is also antagonized by decorin[40].

Recently, a physical interaction between the armadillo repeats 10-11 of β-catenin with the forkhead domain of FoxM1 was identified as crucial for Wnt3a-directed β-catenin nuclear translocation and assembly of the ternary complex on promoters of target genes[49]. Hyperactivation of FoxM1 occurs primarily in various gastrointestinal tumors[50] where it is now believed to facilitate aberrant β-catenin activation. This is intriguing insofar as decorin-null mice exhibit abnormal intestinal tumor formation when exposed to a western diet, and show increased levels of β-catenin[26]. It is thus plausible that decorin in the intestine represents a safeguard against improper activity of the FoxM1/β-catenin signaling axis.

A connection might exist between decorin and a genomically-imprinted tumor suppressor known as paternally-expressed gene 3 (Peg3). First, morpholino-induced depletion of decorin in a zebrafish model results in stunted head-to-tail growth strongly suggesting a role for decorin in regulating convergent extension[51], a fundamental developmental process mediated primarily by β-catenin signaling via the planar cell polarity pathway. Interestingly, Peg3 decreases β-catenin expression thereby inhibiting zebrafish tail development in a Wnt-dependent manner[52], therefore indicating a possible relationship between decorin and Peg3. This connection is further reinforced by the observation that the molecular interaction between the Peg3 N-terminal domain and β-catenin is the basis for the GSK3β-independent antagonism of β-catenin signaling[52]. This is very analogous to the GSK3β, Wnt independent antagonism of β-catenin protein orchestrated by decorin via Met in various tumor cell lines. In the context of tumor progression, this potential link between decorin and non-

canonical β-catenin attenuation might prove crucial since there is a strong inverse association between decreased Peg3 mRNA expression and glioblastoma progression and grade[52].

A new study has evaluated the role of Wnt signaling in promoting a supportive hematopoietic niche for stem cell and progenitor development[53]. Importantly, Wnt3a was found to potently and consistently induce decorin expression in co-culture models. Further, it was demonstrated that mesenchymal stem cells, derived from the bone marrow, acts as decorin producing cells[53]. Surprisingly, decorin seems to phenocopy almost all the same biological effects of Wnt3a including stimulation of c-Kit expression, block of B-cell lymphopoiesis, and maintenance of undifferentiated hematopoietic stem/progenitor cells[53]. These data indicate an intricate role of decorin in modulating the hematopoietic microenvironment by mimicking, instead of opposing, in a non-canonical fashion, downstream effects promoted by canonical Wnt signaling.

Decorin Affects the Angiogenic Network

A key step in malignant tumor progression is neo-vascularization beginning with activation of the angiogenic switch. The molecular components and mechanisms involved are starting to come into clear focus. However, the role of decorin in tumor angiogenesis is quite controversial, with studies indicating a pro-angiogenic role such as enhanced endothelial cell migration via increased α2β1 integrin interaction with collagen type I[42]. However, a recent study has clearly shown an inhibitory and high-affinity binding of decorin to the vascular endothelial receptor 2 VEGFR2[43]. The intricacies of decorin in regulating angiogenesis are even more complex in the cornea, where pro-[54] and anti-angiogenic roles[55] exist. Again, we stress the fact that these studies reporting pro-angiogenic activity of decorin are typically seen in normal, non-tumorigenic settings. In contrast, as it pertains to tumor angiogenesis, decorin, applied as an exogenous or endogenous agent, exerts powerful angiostatic activities to curtail vascularization in a variety of tumor cell lines[56] and inversely correlates with the extent of vascularization[57].

Stromal decorin is able to directly abrogate the HGF/Met signaling axis to inhibit VEGF mediated angiogenesis[58] by transcriptionally repressing hypoxia inducible factor-1α (HIF-1α), β-catenin, Myc, and SP1 under normoxia, and non-canonically suppressing HIF-1α protein [58]. This net repression of critical transcription factors impairs HGF/Met-driven VEGFA. Further, Sp1 requires p42/44 mitogen-activated protein kinase (MAPK)-dependent phosphorylation for competent localization and activation of VEGF transcription, which is presumably attenuated via RTK antagonism[40,58]. Further repression of VEGF occurs through the attenuation of matrix metalloproteinase (MMP) 2 and 9 transcription which also depends on β-catenin. This disallows matrix-bound VEGFA from engaging VEGFR2 on endothelial cell surfaces[58].

Abrogation of HGF/Met *in vivo* provides mechanistic evidence for the action of decorin. In stark contrast to HGF, which promotes angiogenesis through positive VEGF and negative thrombospondin regulation[59], decorin retards angiogenesis by negative VEGFA and positive thrombospondin regulation. Indeed, in vivo studies, decorin can subvert HGF signaling through Met to achieve reduced tumor vascularization and vessel density[58].

Through degradation of β-catenin and HIF-1α, several intertwined feedback loops are interrupted. Potent loss of HIF-1α results in reduced expression of Met[58,60] thus compromising the ability of tumor cells to respond to HGF signaling. This is further enhanced by the well documented notion that HGF/Met potentiates β-catenin signaling and Myc expression[1]. Thus, decorin silences this important feedback loop for sustained cellular growth while mitigating the overall migratory, proliferative, and angiogenic capacity of malignant cells. Collectively, these findings indicate a tripartite attack on the Met including ectodomain shedding[37] despite TIMP3 induction, caveolin-mediated endocytosis and degradation[40], and disruption of positive feedback loops[58]. This is of paramount importance since decorin is only one of two known mammalian ligands for Met, the third being internalin B, a bacterial protein[39].

Decorin can simultaneously induce endogenous angiogenic inhibitors such as TIMP3 and thrombospondin-1, which act to enhance the blockade of VEGF signaling via HGF/Met (Fig. 2), consistent with suppressing Met activation to alleviate thrombospondin-1[59]. The ramifications and implications of normoxic attenuation of HIF-1α open multiple possibilities of modulating pertinent pathways that are active in the early stages of tumor development by circumventing the angiogenic switch from being engaged. An intriguing possibility relates to HIF-1α in orchestrating a metabolic adaptation that drives tumor vascularization, thus linking decorin to possibly modulate tumor metabolism prior to the onset of angiogenesis at early normoxic stages.

Relatives of Decorin in Tumorigenesis: Lumican and Bigylcan

Related members of the SLRP family include lumican (class II) and biglycan (class I) and share 26% and 57% homology with decorin, respectively. Lumican is a keratan sulfate proteoglycan normally found within the cornea. It was recently discovered that lumican is highly expressed within the stroma of high-grade breast cancers, while exhibiting an altered expression pattern in various other tumor types[1]. Interestingly, the biological and prognostic correlates of lumican, classified as either a pro- or anti-oncogenic agent, within the varied tumors is certainly diversified as specific tumors (colorectal, pancreatic, and pulmonary) exhibit a poor prognostic outcome as lumican expression increases within the stroma, which is typically indicative of advanced tumors. However, in the case of osteosarcoma and melanoma, decreased lumican expression correlates with increased tumor progression[1], suggesting lumican is anti-oncogenic. This apparent discrepancy for lumican function among different

tumor types is reminiscent of the context-dependent function of decorin in angiogenesis, thus, highlighting the complex intricacies of SLRPs in tumorigenesis.

Lumican induces cell cycle arrest by inducing the cyclin-dependent kinase inhibitor p21, decreasing the activity and abundance of multiple cyclins, including cyclin-D1, and activates pro-apoptotic pathways[61] akin to decorin. Further, lumican evokes anti-metastatic properties via high-affinity binding to the α2 I domain of the α2β1 integrin, thus suggesting a mechanism of action. In parallel, decorin binds to and antagonizes Met resulting in decreased migratory capacity, impaired cellular proliferation and survival. Finally, lumican and decorin are both capable of inhibiting metastasis[35,36,62].

Biglycan, the most closely related SLRP family member to decorin, has a very limited involvement in cancer progression. Primarily pro-inflammatory via TLR2/4 signaling, a study has implicated biglycan overexpression within human pancreatic cancer tissue is accompanied by a concomitant induction of p27 and decrease in cyclin A and PCNA[63], thereby resulting in an inhibition of tumor growth. Despite the relatively high degree of homology, it is interesting that decorin and biglycan do not have more extensive overlapping functions in tumorigenesis.

Conclusions and Perspectives

Decorin, an archetypical small leucine-rich proteoglycan, possesses intrinsic and potent anti-tumorigenic capabilities. Initially having been characterized as an avid binding partner of collagen and inherent regulator of fibrillogenesis, soluble decorin is now emerging as a pan-RTK inhibitor coincident with powerful downstream signaling attenuation. Due to its highly-promiscuous and broad binding repertoire with extracellular matrix constituents, growth factors and cell surface receptors, decorin can be considered a "*guardian from the matrix*". Decorin functions as a guardian in the context of constraining the activity of a multitude of growth factors, receptor tyrosine kinases, and extracellular matrix components. The source of decorin bioactivity lies within this unique attenuation of potent growth signals and cues that would otherwise facilitate malignant transformation. Further, in most cases, these direct protein interactions act to ameliorate and counteract the overall tumorigenicity of the surrounding tumor microenvironment that would otherwise foster and promote malignant transformation and tumor progression. Thus, decorin, and perhaps other structurally related SLRPs, act at the crossroad between inflammation and cancer and could be determinant players in combatting many forms of solid tumors where RTKs are deregulated[64].

Additionally, we would like to draw a comparison between decorin action from outside the cells with that of transcription factors acting inside the cells. Several transcription factors such as p53 and Myc coordinately regulate the expression of large subsets of genes crucial for the viability of cellular processes, whereas decorin regulates growth factor bioavailability and receptor modulation within the

extracellular milieu. Notably, a genetic cooperation between decorin and the tumor suppressor p53, which has been widely regarded as the "*guardian of the genome*", has been already established insofar as germline null mutations in decorin and p53 genes cause enhanced lymphoma tumorigenesis[65]. Thus, it is plausible to connect stromal decorin to the intracellular regulation of the expression of a large genetic network.

One of the challenges of future research is finding and isolating the leucine-rich repeats of decorin that harbor distinct bioactivities. This could be of great clinical interest as adjuvant peptide therapy. Further engineering of these smaller domains to specifically target cognate receptors could underlie advanced therapeutic drug designs and serve as a potent addition to the growing armamentarium of matrix-derived cancer modalities.

Acknowledgments

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Figure Legends

Figure 1: Decorin interactome encompassing growth factors, receptors, and putative extracellular matrix components to which decorin physically, through high affinity interactions, binds and regulates either negatively or positively. Please refer to the text for additional details.

Figure 2: Broad receptor antagonism and attenuation of downstream signaling cascades mediated by decorin in tumor cells. Anti-proliferative, immunomodulatory, and anti-angiogenic properties are regulated following engagement of decorin to cell surface receptors. Please refer to the text for a detailed discussion of pathway modulation.
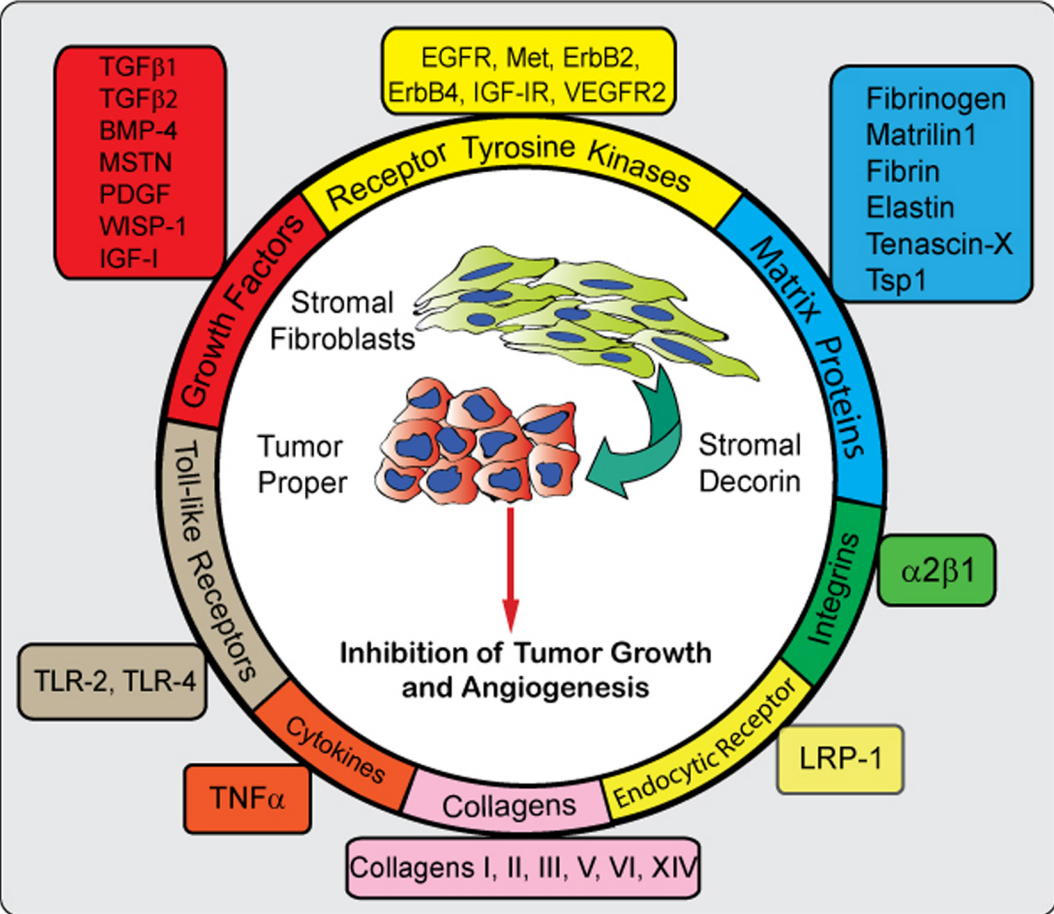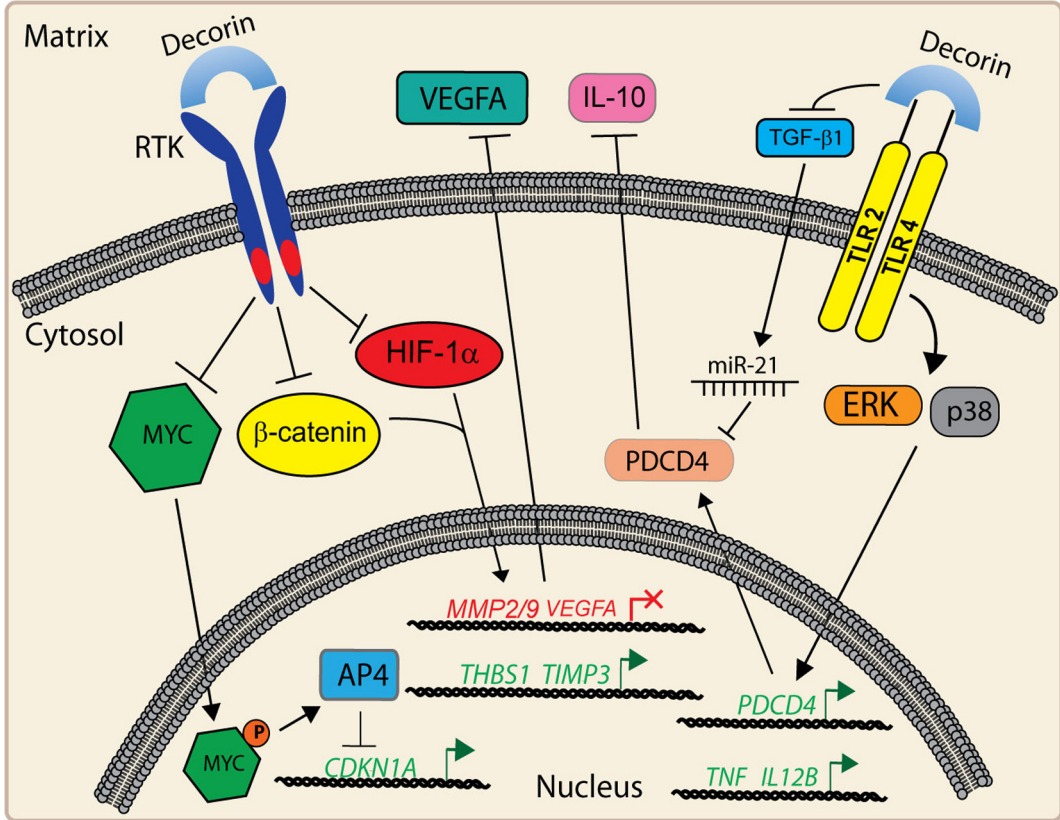
Figure 1

Figure 2