3-1-2022

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# Oncosuppressive roles of decorin through regulation of multiple receptors and diverse signaling pathways

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**Abstract**
Decorin is a stromal-derived prototype member of the small leucine-rich proteoglycan gene family. In addition to its functions as a regulator of collagen fibrillogenesis and TGFβ activity, soluble decorin acts as a pan-receptor tyrosine kinase (RTK) inhibitor. Decorin binds to various RTKs, including EGFR, HER2, HGFR/Met, VEGFR2, TLR and IGFR. Although the molecular mechanism for the action of decorin on these receptors is not entirely elucidated; overall, decorin evokes transient activation of these receptors with suppression of downstream signaling cascades culminating in growth inhibition, followed by their physical downregulation via caveosomal internalization and degradation. In the case of Met, decorin leads to decreased β-catenin signaling pathway and growth suppression. As most of these RTKs are responsible for providing a growth advantage to cancer cells, the result of decorin treatment is oncosuppression. Another decorin-driven mechanism to restrict cancer growth and dissemination is by impeding angiogenesis via VEGFR2 and the concurrent activation of protracted endothelial cell autophagy. In this review, we will dissect the multiple roles of decorin in cancer biology and its potential use as a next-generation protein-based adjuvant therapy to combat cancer.

**Keywords:** Small leucine-rich proteoglycans; receptor tyrosine kinase; angiogenesis; autophagy;

## INTRODUCTION

Decorin (DCN), is a well characterized small leucine-rich proteoglycan (SLRP) and serves as the archetype for this group of proteoglycans (1,2). SLRPs are an 18-member gene family, forming a distinct subgroup of proteoglycans that is a microcosm of the multifunctional nature of ECM proteins (2-5). SLRPs, aptly named after their identifiable leucine-rich structural motif repeats, contain three canonical classes, I-III, and two non-canonical classes, IV-V. These classifications are defined through parameters such as homologies at the genomic and protein levels. The distribution of SLRP-encoding genes is spread across seven chromosomes with some in gene clusters, indicating there is functional redundancy among the SLRPs. The evolutionary conservation of SLRP function underscores the critical function of these proteins in the ECM and overall organismal homeostasis (3,6). Decorin is one of these highly conserved SLRPs, and is present across species. In mammals, the proteoglycan consists of a central domain of ten leucine-rich repeats, a single glycosaminoglycan chain (GAG), and a 42 kDa conserved protein core. Originally categorized as a collagen-binding protein, decorin, a class I SLRP, was initially characterized as a critical structural factor in collagen fibrillogenesis and tissue integrity. The myriad of interactions decorin has with its ligands (7) primarily involves its protein core, but the single GAG chain, existing as either chondroitin or dermatan sulfate, also plays an essential role in tissue homeostasis (8).

## A BRIEF HISTORY OF DECORIN

In the latter half of the 1980s, a heavy emphasis was put on proteoglycan research, as understanding the associations and interactions between single gene products lied at the epicenter of advancing the field of biochemistry. Naturally, connective tissue became a locus of particular interest due to its layout as a complex multicellular system with different components working in tandem to sustain critical function in both maintaining shape and resisting physical stressors (9,10). The characterization of proteoglycans became a focal point in the study of connective tissue, with decorin identified as a chondroitin-dermatan sulfate proteoglycan. Decorin is indeed heavily involved in collagen fibrillogenesis and along with other dermatan sulfate-rich proteoglycans, was shown to associate with tendon collagen at the *d* band in the gap region (11). Thus the eponym of decorin was aptly proposed for its ability to “decorate” collagen fibrils (12). With further investigation, it was determined that decorin possesses a much broader range of function, with the discovery that the protein core inhibits, rather than aids, collagen fibrillogenesis by binding to type I collagen (13) and maintaining collagen fibril structure, fiber realignment, and mechanical properties of various tissues (14-21) that regulate homeostasis. Moreover, the realization that decorin harbored a single GAG chain at its N-terminus was “surprise" at that time as proteoglycans were believed to have a higher amount of carbohydrates related to the protein core. After its initial cloning in 1986 from human fibroblasts (22), the decorin gene was fully sequenced in both humans and mice (23,24), and its promoter region was also partially characterized (25,26). Notably, the transcriptional regulation of *DCN*

is quite complex and is induced by quiescence and repressed by tumor necrosis factor α (TNFα) (27), and is also transcriptionally repressed by FOXD1 (28) and MEIS1 (29). Moreover, decorin is involved in controlling cell proliferation, adhesion and migration (30,31). In order to fully understand the *in vivo* functions of decorin, we generated *Dcn*$^{-/-}$ mice and discovered that the lack of decorin caused lax and fragile skin, telltale of dermal thinning (32), consistent with its ascribed roles in collagen fibrillogenesis. As these mice are viable and fertile, they have been used in many studies and in various pathological processes, in both experimental and congenital settings.

Adding to its already versatile interactions, decorin potently binds TGFβ, effectively sequestering the cytokine, attenuating its function and blocking cell proliferation (33-36). It was this discovery that propelled decorin into the forefront of proteoglycan research, particularly in cancer as malignant progression requires constitutive cell proliferation, making decorin a promising target for oncogenic therapeutics. As study of the proteoglycan continued, it was revealed that the breadth and power of its biological function primarily lies in its functional interactions with multiple cell surface receptors tyrosine kinases, effectively ascribing ECM remodeling as a cardinal role of decorin (37-39). Because cancerous tissues require constant remodeling of the extracellular matrix, this groundbreaking discovery has wholly re-shaped our understanding of the physiological role of decorin and its significance in the tumor microenvironment, especially in terms of its potential as an oncosuppressive agent.

## A CURENT VIEW OF DECORIN

Today, decorin is understood as a far more complex unit of the ECM. Genetic ablation of this SLRP leads to a wide range of debilitating conditions that range from structurally compromised skin and tendon to impaired metabolism and obesity, abnormal angiogenesis, myocardial infarction and fibrosis, demonstrating its multifunctional nature via direct and indirect interactions with a multitude of diverse signaling molecules (18,32,40-43). *Dcn*$^{-/-}$ mice have been studied, and in addition to the skin fragility phenotype, they show a strong trend towards spontaneous tumor development (44-48) and metastatic spread (49). Early in its discovery, decorin was characterized as having an inhibitory role on cancer proliferation and metastasis in tumor cell lines (50,51) because *Dcn*$^{-/-}$ mice have a significantly increased potential to spontaneously develop solid tumors in a plethora of loci in the body, including the intestinal tract and liver, lymphoid tissue, and breast (52). Notably, decorin levels are markedly reduced in several solid malignancies including prostate, breast, colon, renal and esophageal carcinomas (53-61). Decorin's primary function can be attributed to cell cycle regulation via p21-induced G1 cell cycle arrest. Upon ectopic decorin expression, upregulation of p21 allows for nuclear translocation in cells with *de novo* decorin expression subsequently inhibiting cell cycle machinery. Recently, our studies have shown that decorin can induce autophagy in endothelial cells and mitophagy in breast cancer cells, independently of nutrient conditions (62-70).

## THE STRUCTURE AND FUNCTION OF DECORIN

Decorin is horseshoe-shaped, in which its 14 curved β-strands, located on the inner concave surface contains protein sequences for recognizing most of the known decorin-binding partners (7,71). In contrast, the outer convex surface of decorin contains multiple $\alpha$-helices (Fig. 1) (65). The LRR architecture of the decorin solenoid provides a plastic interface that encodes biological information necessary for coordinating a myriad of protein-protein interactions, the hallmark of decorin multiplicity of functions. To understand how decorin interacts, it is useful to think of the decorin structure as an amalgam of two parts. The central domain is composed of the characteristic twelve leucine-rich repeats forming short β-strands in a parallel conformation, and the N-terminal attachment of the GAG chain, of either dermatan or chondroitin sulfate (Fig. 1). The LRR protein core forms the interface for binding receptor tyrosine kinases, most notably vascular endothelial growth factor receptor 2 (VEGFR2). Specifically, $LRR_{V/VI}$ aid in the binding of decorin to VEGFR2 (72), whereas $LRR_{XII}$ is utilized for decorin binding to CCN2/CTGF and for suppressing its biological activity (73). Perhaps, the most established sequence (SYIRIADTNIT) is located in $LRR_{VII}$ and contains the area with high affinity for collagen type I (74), the most classic and well-known binding partner of decorin (75). The C-terminal includes a structure known as the “ear” repeat and participates in protein folding (Fig. 1). This structure has been investigated extensively and its functionality has been determined via truncation of the decorin C-terminal, which causes protein misfolding and endoplasmic reticulum stress. These issues subsequently cause disease manifestation, including congenital stromal corneal dystrophy (76-79). The GAG chain remains crucial for decorin-ligand interactions. The chondroitin/dermatan sulfate (CS/DS) chain attached to decorin performs many functions related to wound healing (80), keratinocyte function (81), and collagen assembly in adipose and skeletal muscle tissues (82). Additionally, the chain appears to increase the affinity of decorin to collagen, with its absence often phenotypically emerging as increased skin fragility (32). Because decorin appears in both a monomeric and dimeric form, it is likely that the dimeric complex would sterically hinder most of the core region, thus making binding to other substrates, especially cell surface receptors, quite difficult or impossible. Thus, although decorin forms a dimer in physiological solutions (83), its biologically active form is that of a monomer (84).

## ROLE OF DECORIN IN ANTI-TUMORIGENIC SIGNALING

Decorin has been considered a “*guardian from the matrix*” because of its anti-tumorigenic activity, which manifests itself by inhibiting several RTKs and their downstream signaling cascades that originate from the ECM (85). In general, by blocking these RTK-mediated pathways, decorin ultimately interferes with the continued growth and survival of the tumor by inhibiting key processes such as metastasis and angiogenesis. These two processes are integral in determining the fate of a tumor in terms of remaining

silent or becoming malignant. In angiogenesis, new blood vessels are formed from pre-existing blood vessels which enhances the survival of tumor cells, the so-called angiogenic switch (86). This is because a greater amount of nutrients and oxygen pertinent to cancer growth can reach tumorigenic tissue and feed metabolic processes (87). During metastatic dissemination tumors gain migratory abilities and spread to distal areas in relation to the primary site, which makes it a beneficiary of angiogenesis. After binding to RTKs, decorin mitigates both tumor metastasis and angiogenesis (88-93). The latter process is perfomed in a way similar to other proteoglycan-derived bioactive molecules such perlecan/endorepellin (94-96) or Collagen XVIII/endostatin (97-99)**.** Apart from RTKs, decorin can also bind other growth factor receptors like TGFβR and Toll-like receptors TLR2 and TLR4 to stimulate the anti-inflammatory response which similarly curbs cancer lethality (7,100). Below we provide a succinct summary of the functional involvement of several RTKs interacting with the decorin protein core.

**EGFR signaling**

Decorin binds with several RTKs on the cell surface with high affinity. Epidermal growth factor receptor (EGFR) was the first RTK discovered as a binding partner of decorin (37-39). In A431 squamous carcinoma cells, decorin binding to EGFR induces dimerization, internalization and the subsequent degradation of EGFR via caveolar-mediated endocytosis (37,38,101). Moreover, soluble decorin elevates cytosolic $Ca^{2+}$ in squamous carcinoma cells overexpressing EGFR (102). After binding to the receptor, decorin evokes sustained down-regulation of EGFR and an overall attenuation of the EGFR signaling cascade (103), a mechanism for controlling tumor growth *in vivo*. Activation of this EGFR signaling through PI3 kinase (PI3K) and RAS is crucial for sustained tumor growth and proliferation (Fig. 2A). By suppressing oncogenic signaling, decorin is believed to restrict tumor growth, survival, and metastatic potential. On the other hand, through EGFR signaling, decorin can simultaneously activate an anti-oncogenic pathway that leads to cell cycle arrest. Decorin induces rapid trans-autophosphorylation of EGFR and concurrent activation of mitogen-activated protein (MAP) kinase for a protracted induction of endogenous p21 (104,105), a potent inhibitor of cyclin-dependent kinases, and induction of caspase-3, which ultimately results in cell cycle arrest (38) . In line with these findings, the anti-angiogenic effect of decorin is also reported to signal via EGFR in breast carcinoma cells (106). Decorin evokes the rapid secretion of thrombospondin-1 (TSP-1), a potent anti-angiogenic effector via inhibition of the RhoA/ROCK1 complex (Fig. 2A) (106). The importance of decorin in EGFR signaling is further emphasized when osteosarcoma cells that constitutively produce decorin were shown to be resistant to decorin-induced growth arrest through the sustained expression and activation of EGFR signaling (107). Decorin has recently been established as a suppressor of invasion and tumor growth in inflammatory breast cancer by inhibiting EGFR/Erk signaling. Additionally, its overexpression leads to decreased migration and invasion of the tumor both *in vitro* and in mouse xenograft models (108). Collectively,

through EGFR, decorin suppresses oncogenic signaling and activates oncosuppressive functions in tumor cells.

**MET signaling**

To investigate the possibility that the anti-oncogenic effects of decorin could integrate with RTKs other than EGFR and related ErbB receptors, we utilized an antibody array system to assess tyrosine phosphorylation of 42 RTKs (109). We discovered that the addition of soluble decorin affected phosphorylation of the hepatocyte growth factor (HGF) receptor Met in a serum-independent manner that resembled its effects on EGFR. Decorin can directly bind to the Met receptor, a proven mediator of malignant transformation, invasive growth, and metastasis (109-111). Decorin binds to the extracellular domain of Met that leads to receptor down-regulation through a combination of increased ectodomain shedding and internalization (112). Notably, decorin evokes a marked proteasome-dependent degradation of the transcription factor β-catenin and downregulates the protein expression of both β-catenin and Myc (Fig. 2B) (109,113). In tumor xenograft models, decorin downregulates Met with concurrent suppression of β-catenin, which is mechanistically implicated in mediating HGF- and Met-dependent cell invasion, and Myc, a key oncogenic factor for tumor progression (113). Not limited to this, decorin was also shown to suppress the expression of two pro-angiogenic genes, hypoxia inducible factor (HIF)-1$\alpha$ and vascular endothelial growth factor A (VEGFA) in breast carcinoma cells and inhibits VEGFA mediated angiogenesis (114). In line with this, decorin reduces the expression and activity of matrix metalloprotease (MMP)-9 and MMP-2, two pro-angiogenic proteases and evoke the expression of potent angiostatic agents like TIMP3 (106). Decorin antagonizes the angiogenic network by inhibiting pro-angiogenic factors and activating angiostatic agents via Met which reduces tumorigenicity. Additionally, in triple negative and luminal breast carcinoma cells, decorin triggered mitochondrial depolarization followed by augmented mitophagy downstream of Met. Mechanistically, decorin mobilizes PGC-1$\alpha$ for the cytosolic accumulation of mitostatin to evoke mitophagy (66). Thus, by increasing mitostatin levels and evoking the autophagic catabolism of mitochondria, decorin suppresses VEGFA ultimately leading to tumor angiostasis.

**VEGFR2 signaling**

In recent years, decorin has been established as a novel VEGFR2 antagonist in endothelial cells as well as in human trophoblasts (62,72,115). Presumably, these biological interactions affect *in vivo* neovascularization in several organs including the cornea (116) Decorin directly binds the ectodomain of VEGFR2 in a region that partially overlaps with its endogenous agonist, VEGFA and, as such, inhibits VEGFA-mediated angiogenesis. By interacting with VEGFR2, decorin induces AMPK to initiate a

signaling cascade that activates Vps34 (vacuolar protein sorting 34) and inhibits mTOR for excessive autophagy. Due to the protracted nature of decorin-evoked autophagy in endothelial cells, decorin transcriptionally activates Paternally Expressed Gene 3 (PEG3). Peg3 is critical for sustaining the decorin-evoked autophagy response as it necessary and sufficient for driving the expression and accumulation of Beclin-1 and LC3 (117), two key proteins required for successful autophagy (Fig. 2C) (62,117). Moreover, Peg3 has been conclusively implicated in mediating autophagic flux downstream of decorin/VEGFR2 interactions (62), in part by transcriptionally promoting *TFEB* expression (115). Loss of Peg3 or Beclin 1 significantly abrogates decorin-evoked autophagy. Decorin-VEGFR2 binding also inhibits the Akt phosphorylation axis that ultimately blocks oncogenic signaling via mTOR pathway (118). Recently, a connection that unifies the pro-autophagic properties of decorin with the well-established anti-angiogenic functions has been uncovered. Decorin clears intracellular VEGFA by mobilizing this potent pro-angiogenic growth factor into LC3-positive autophagosomes in a Peg3-dependent manner (119). Moreover, VEGFA is sensitive to autophagic flux *in vivo* as application of chloroquine prevented a starvation-induced reduction of VEGFA in cardiac and aortic tissues (119). Thus, decorin induced VEGFR2 signaling attenuates tumor progression by blocking angiogenesis or by inhibiting oncogenic signaling through autophagy.

**IGF-IR signaling**

Activation of signaling cascades through insulin like growth factor receptor I (IGF-IR) is involved in the development of many carcinomas. In some experimental models, it has been established that activation of IGF-IR is directly linked to tumor progression and epithelial-mesenchymal transition (EMT) (120,121). Notably, previous studies have shown that in invasive bladder cancer IGF-IR expression is generally up-regulated whereas *Dcn* mRNA expression is down-regulated (122-124). In addition, it has been shown that decorin binds IGF-IR and inhibits IGF-I induced migration and invasion of bladder cancer through the inhibition of downstream signaling cascades (123). Decorin severely mitigates IGF-I-stimulated activation of Akt and ERK1/2, two key pathways for tumor development and progression (Fig. 2D). Therefore, decorin binding with IGF-IR inhibits the oncogenic signaling through Akt and ERK whereas loss of decorin indirectly induces IGF-IR activity and signaling, thereby promoting enhanced cellular motility, invasion, and tumor progression.

**TGFβ signaling**

Limited reports are available concerning the role of decorin in transforming growth factor β (TGFβ) signaling. In 2002, decorin was shown to disrupt the TGFβ/Smad signaling pathway in human mesangial cells where decorin induced the phosphorylation of different Smad proteins (125). This initial discovery was supported by subsequent reports whereby decorin has been genetically ablated. This was sufficient

to allow for rampant Erk and Smad signaling favoring the development of hepatic (126,127) and renal fibrosis (128,129). Another way in which decorin affects TGFβ is through interaction with LDL receptor-related protein 1 (LRP-1) (130), is a large endocytic receptor involved in in lipoprotein metabolism, catabolism of proteinases, coagulation (131) and cancer cell migration (132). Notably, the internal $LRR_{VI}$ is responsible for decorin binding to LRP-1 and subsequent TGFβ-evoked signaling (133). Very recently, decorin has also been reported as an antagonist of TGFβ in astrocytes of the optic nerve (134). In this report also, decorin deficiency has been shown to increase the expression and synthesis of TGFβs. Importantly, treatment with decorin reduced TGFβ expression in murine astrocytes. In addition, this report claims Smad-independent TGFβ signaling where decorin exerts its suppressive effect over TGFβ expression via pAKT/AKT signaling (Fig. 2E) (134).

### TLR signaling

Beyond the interactions with growth factors and cytokines to control cell growth and proliferation, decorin also mediates inflammatory responses by acting as an endogenous ligand for TLR2/4 (toll-like receptor) (135,136). Decorin binds to TLR2 and TLR4 on macrophages with high affinity and in turn causes rapid activation of p38, MAPK, and NFκB pathways, all of which are involved in pro-inflammatory responses (136,137). Decorin binding to the TLRs prevents transcriptional repression of PDCD4 (programmed cell death protein 4) by decreasing TGFβ1 activity; this leads to an increase of oncogenic miR-21, a post-transcriptional repressor of PDCD4 (Fig. 2F). (136,138). Subsequently, increased PDCD4 decreased the release of IL-10, an anti-inflammatory cytokine, thereby making the overall cytokine environment more pro-inflammatory. Additionally, through these toll-like receptors, decorin enhances the synthesis of the pro-inflammatory cytokines TNFα and IL-12 (Fig. 2F). Thus by stimulating pro-inflammatory molecules and reducing the abundance of anti-inflammatory ones, decorin shifts the immune response to a more pro-inflammatory state that is associated with reduced tumor growth. It is important to note that inflammation in cancer remains a highly debated topic, in which the current outlook diverges for the effects of acute versus chronic inflammation on tumorigenesis.

## CONSEQUENCES OF DECORIN INTERACTION WITH VARIOUS RECEPTORS

To curb the lethality of tumorigenesis and malignant transformation, the interaction of SLRPs with different cell surface receptors has become an emerging field of study in the fight against cancer. After binding with different receptors, decorin modulates key processes vital for tumor growth, invasion and progression such as autophagy, mitophagy, cell cycle arrest, inflammation and angiogenesis. By attenuating several oncogenic processes, promoting oncosuppressive functions and/or inducing inflammation and autophagy, decorin acts as a soluble master tumor repressor to determine whether a

tumor remains silent or becomes malignant (57,58,139-142). Because decorin is ubiquitously expressed in all tissue types, its presence and potential use as a therapeutic agent is relevant to all types of carcinomas (Fig. 3A). Interestingly, in cancer patients, the expression of decorin is downregulated in most tumorigenic tissues (Fig. 3B). It is believed this facilitates tumor metastases due to reduced decorin expression from the homeostatic level. Therefore, abundant expression of decorin or treatment with decorin may lead to an “organized” ECM presenting itself as a physical barrier against tumor cell metastasis.

## DECORIN IN CANCER STUDIES

Although clinical studies involving decorin date to the 1990s, knowledge of this proteoglycan was rather limited and was thought to strictly involve collage fibrillogenesis for tissue integrity. Therefore, in these initial studies, the focus was more on tissue and wound healing (143,144). In comparison, after experimental findings suggested that decorin evokes autophagy (145), there has been remarkable interest in evaluating decorin in clinical studies involving a wide spectrum of malignancies. Its effectiveness in animal models has inspired numerous groups to use decorin for prognosis and intervention. Since the 2000s, there have been numerable noteworthy studies concerning decorin and various forms of cancer. For instance, in 2003, Troup et al analyzed 140 invasive breast carcinomas without axillary node involvement that were treated with adjuvant endocrine therapy (146). In their study, an increase in tumor size was associated with a statistically significant ($p$=0.0496) reduction in decorin levels (146). Over the years, this proteoglycan has only snowballed in attention. Recently, Kawaguchi et al set out to examine the relationship between decorin levels, exercising, and hepatocellular carcinoma (HCC) (147). In their study, 65 patients with a history of HCC that were treated with embolization were enrolled. The study population was divided into two groups, high decorin and low decorin, after performing enzyme-linked immunosorbent assays. Increased serum decorin levels correlated with an increase in 6 minute walking distance with overall survival being significantly higher in the high decorin group ($p$=0.0353) (147). Glioblastoma multiforme (GBM) is a devastating cancer with a poor prognosis due to being very invasive and the current chemotherapy regimens generally failing fight it effectively. Therefore, the five-year survival rate from this cancer is as low as 5.1% in recent studies (148). A 2021 study by Jia et al focused on the effects of decorin on GBM. In their multifaceted study, they obtained tumors from 42 GBM patients and analyzed decorin expression via qRT-PCR. After dividing their patients to two groups, high and low expression, they have observed that the high *DCN* expression group had an overall higher survival rate ($p$=0.0159). Although this is an impressive finding by itself, the group took it a step further by utilizing patient derived xenograft models. As such, some of the tumors were implanted into nude mice and their metastatic behaviors were observed. Remarkably, the tumors with high decorin expression had markedly less invasive cells when compared to those possessing low decorin expression

(149). Like other proteins and proteoglycans in the human body, decorin is differentially expressed across different tissues. The abundance of decorin also varies among different types of cancer. Using the recently developed Xena platform (150) and data from resources like TCGA (The Cancer Genome Atlas), we analyzed decorin expression profiles across different cancers and their normal counterparts (Fig. 3B). According to this database, decorin expression is suppressed in a variety of primary tumors indicative of the pertinent oncosuppressive role decorin plays (150). Additionally, in breast, uterine, liver, and lung carcinomas, survival is markedly lower in patients with lower decorin expression levels as measured by the Kaplan-Meier cancer survival estimator database (Fig. 4). Following these studies, the reasonable way forward would be to utilize decorin isolates directly in a clinical trial. Unfortunately, at the time of writing, there are no studies utilizing this proteoglycan in such a way.

## CONCLUSIONS

The extracellular matrix has emerged as a novel locus for cancer therapeutics, especially considering the interactions between proteoglycans and cell surface growth factor receptors. Tumor tissue differs greatly in terms of extracellular matrix composition and RTK density when compared with healthy tissue. Indeed, the emergence of the matrisome as a bioinformatic ensemble of extracellular matrix-associated proteins (151,152) needs to be considered as tumors can show unique features and variants of the matrisome (153,154). Decorin acts as a vital SLRP that helps reprogram constitutive metabolic activity tailored towards cell growth, proliferation, and migration. Decorin is an endogenous matrix-centric pan-RTK inhibitor that possesses hierarchical binding for various RTKs expressed by a “target-rich” environment such as tumor cells. This property might function to integrate the activity of decorin across multiple RTKs with differential binding kinetics for sustained and proficient cross-talk for optimal tumorigenic suppression. In this manner, decorin acts as a soluble cell cycle arrest agent against metastasis by inhibiting the activities of known oncogenic genes such as mTOR, ERK, β-catenin, and Myc while simultaneously upregulating genes such as p21 which serve oncosuppressive roles. Clinically, decorin was found to be ubiquitously expressed in most bodily tissues. Utilizing cancer databases that measure gene expression in normal and tumor tissues, decorin was found to be significantly downregulated in most solid tumors. Results of the clinical investigations and *in vivo* animal studies strongly suggest that decorin might be used in the near future as an adjuvant “protein therapeutic” for solid tumors where RTKs play a pivotal role. Decorin could be delivered as either fully glycanated proteoglycan or as a protein core, the size of which is similar to that of antibodies routinely used in the clinics. It could also be delivered as bioactive fragments harboring the internal leucine-rich repeats where all the bindings occur. Notably, it has been recently generated a fusion protein of decorin harboring a CAR peptide that targets inflammatory and angiogenic vasculature (155). This CAR-DCN is a multifunctional biotherapeutic that inhibits numerous growth factor signaling pathways involved in fibrosis

(156,157). It has been safely administered to mice to block fibrosis and the formation of abdominal aortic aneurysms (158) as well as to attenuate the pathology of murine muscular dystrophy (159). Thus, we believe that the strategy of “monitoring from the matrix” with SLRPs like decorin provides a new paradigm that could be exploited as an additional therapeutic tool in the fight against cancer.

**ACKNOWLEDGMENTS**

We wish to thank all past and present members of the laboratory and apologize for not referencing many valuable contributions to the fields because of space limitation.

**GRANTS**

The original research was supported, in part, by National Institutes of Health Grants RO1 CA39481and RO1 CA245311 (RVI).

**DISCLOSURE**

The authors declare no conflict of interest.

**AUTHOR CONTRIBUTION**

All the authors contributed to conceptualization, drafting and editing of the manuscript, as well as the design and generation of figures and graphics. RVI was responsible for the final editing and proofing of the manuscript.

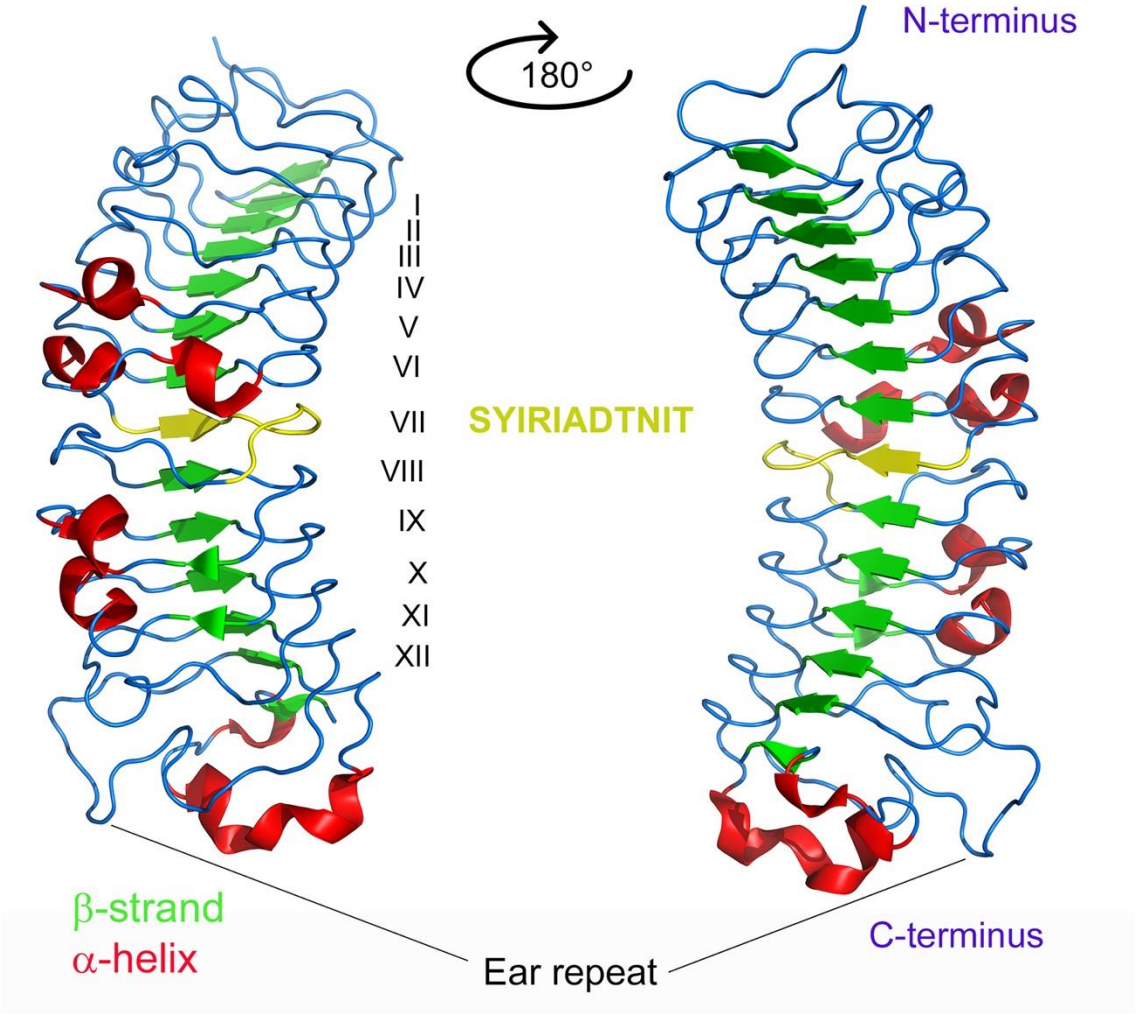


**Figure 1.** Three-dimensional (3D) structure of decorin visualized as a cartoon ribbon diagram rendered with Incentive PyMOL (PDB accession number:1XKU). Monomeric bovine decorin is depicted where secondary structures are color coded: vertical arrows designate β-strands and are shaded in green whereas coiled ribbons indicate α-helices and shaded red. The leucine rich repeats are numbered in Roman numerals I-XII. Decorin contains a central domain composed of fourteen β-strands, twelve of which are leucine rich repeats. This domain mainly participates in interaction with RTKs, collagen, and growth factors. The type I collagen binding sequence, SYIRIADTNIT, located in $LRR_{VII}$ is shaded in yellow. Other noteworthy areas include the C-terminal LRR Cys capping motif, known as the ear repeat, which is involved in protein folding, and the single GAG chain which is located between the N-terminus and the leucine-rich region. Please consult the text for additional information.

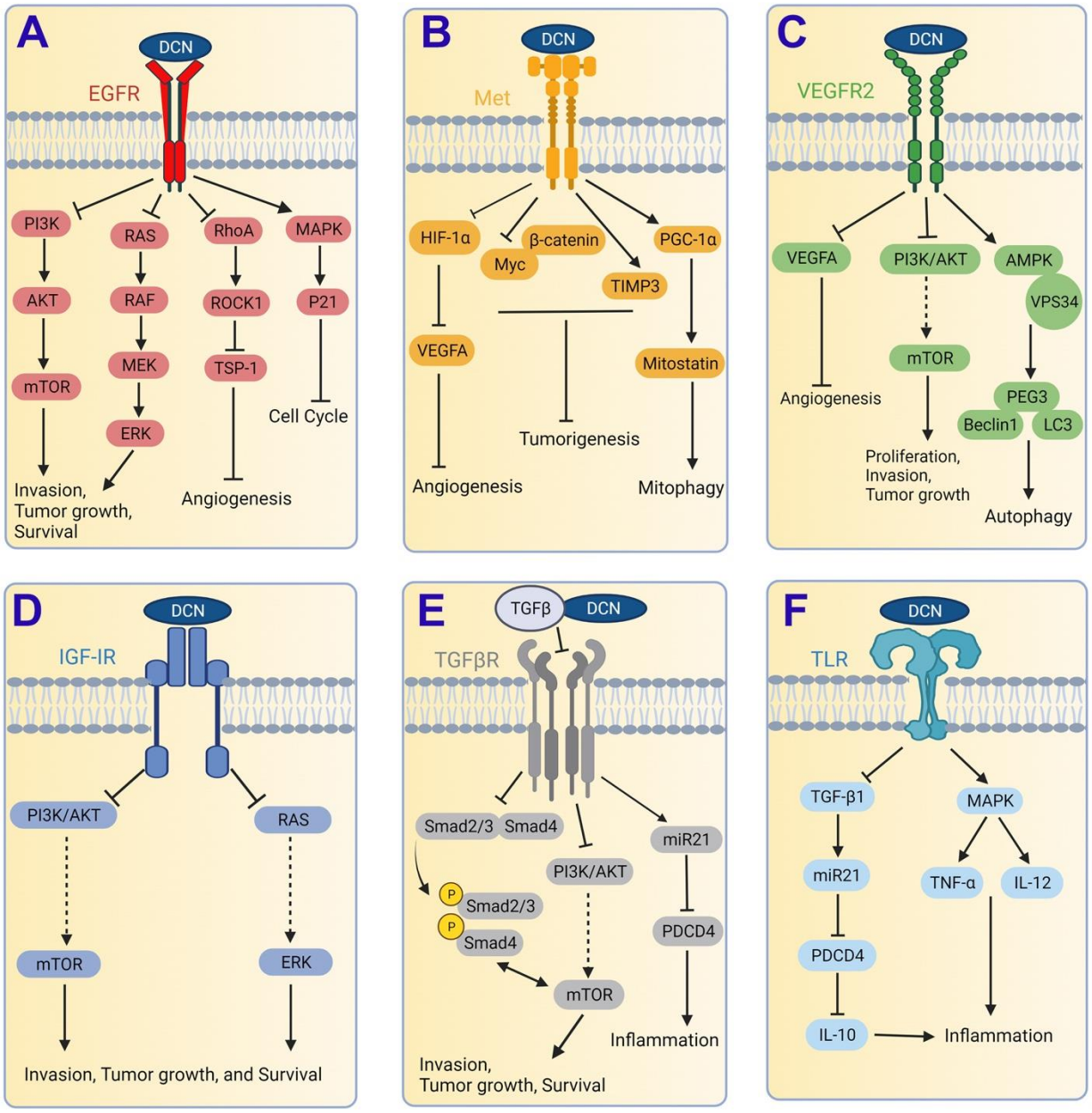


**Figure 2.** Interaction of decorin with different receptor tyrosine kinase (RTKs) and other receptors (***A-F***). As it pertains to the TGFβ receptor, decorin binds the ligand, TGFβ, and inhibits its downstream signaling. After binding with variety of receptors or ligand, decorin inhibits several oncogenic biochemical pathways and activates some oncosuppressive genes to restrict the growth and proliferation of the tumor. Abbreviations used: EGFR, epidermal growth factor receptor; PI3K, PI3 Kinase; mTOR, mammalian target of rapamycin; Rho, RAS homolog family member A; ROCK1, Rho-associated coiled-coil kinase 1; MAPK, mitogen activated protein kinase; TSP-1, thrombospondin-1; Met, mesenchymal-epithelial transition factor also known as hepatocyte growth factor receptor (HGFR); HIF-1α, hypoxia-inducible factor 1α; VEGFA, vascular endothelial growth factor A; Myc, Myelocytomatosis proto-oncogene transcription factor; TIMP3, tissue inhibitor metalloprotease 3; PGC-1α, Peroxisome proliferator-activated receptor-gamma coactivator 1α; VEGFR2, vascular endothelial growth factor receptor 2; AMPK, AMP activated protein kinase; VPS34, vacuolar protein sorting 34; Peg3, paternally expressed 3; IGF-IR, insulin like growth factor receptor 1; miR21, microRNA 21; PDCD4, programmed cell death protein 4; IL, interleukin; TGFβ1, transforming growth factor β isoform 1; TLR, Toll-like receptor; TNFα, tumor necrosis factor α.

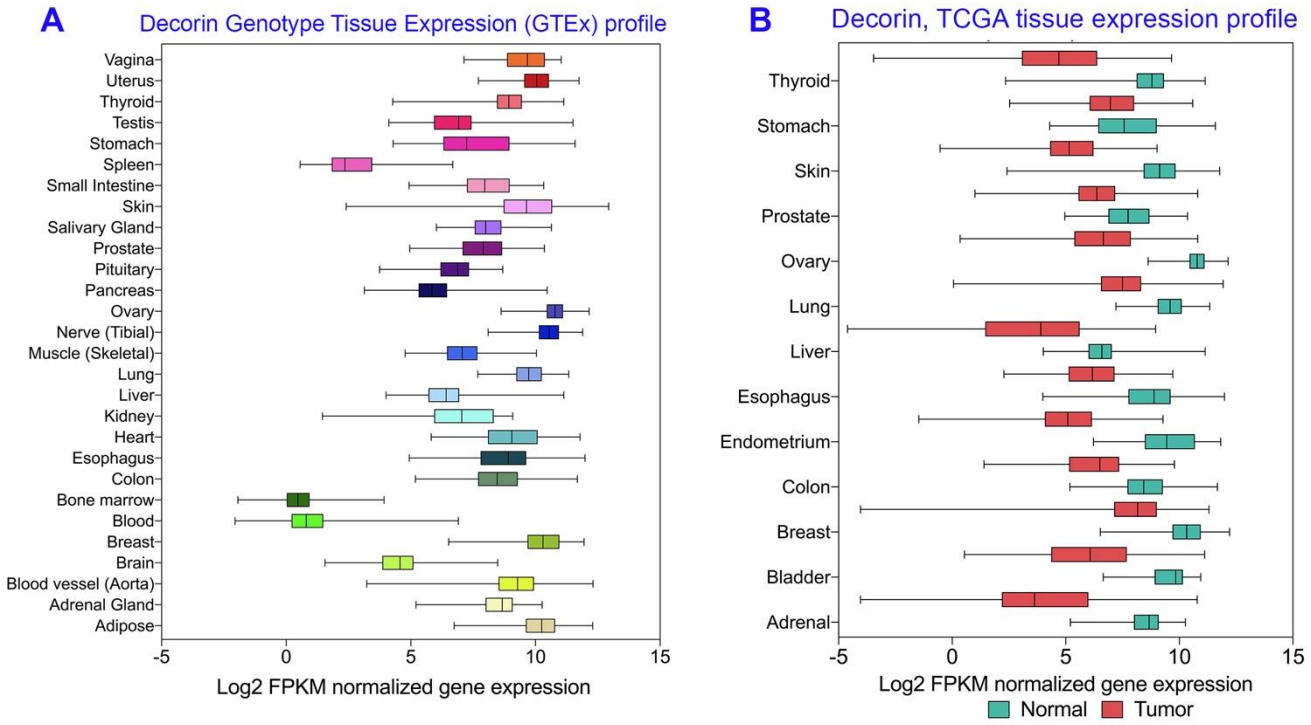


**Figure 3.** Ubiquitous expression of decorin and downregulation in various malignant tissues. ***A:*** from data generated in GTEX tissue expression via the Xena database provided by the University of California in San Diego, decorin is expressed at measurable levels ubiquitously in different tissue types, further expounding its pertinent function in maintaining wild type, and healthy tissue function. Expression is measured via Fragments Per Kilobase of transcript per Million mapped reads (FPKM). ***B:*** from a cohort of 19,131 cancer patients aggregate in the TCGA Target GTEx database published by UCSD, normal and tumor tissue RNASeq signaling was measured in a variety of tissue types ranging from esophageal to ovarian. These data illustrate a significant downregulation (*p* values ranging from $1.74 \times 10^{-8}$ to $2.63 \times 10^{-206}$) of decorin in tumorigenic tissue. These findings strongly indicate that higher decorin concentrations are beneficial in preventing primary tumor growth and proliferation. Along with its ubiquitous expression in mammalian tissue, decorin is a non-discriminant anti-tumorigenic agent.

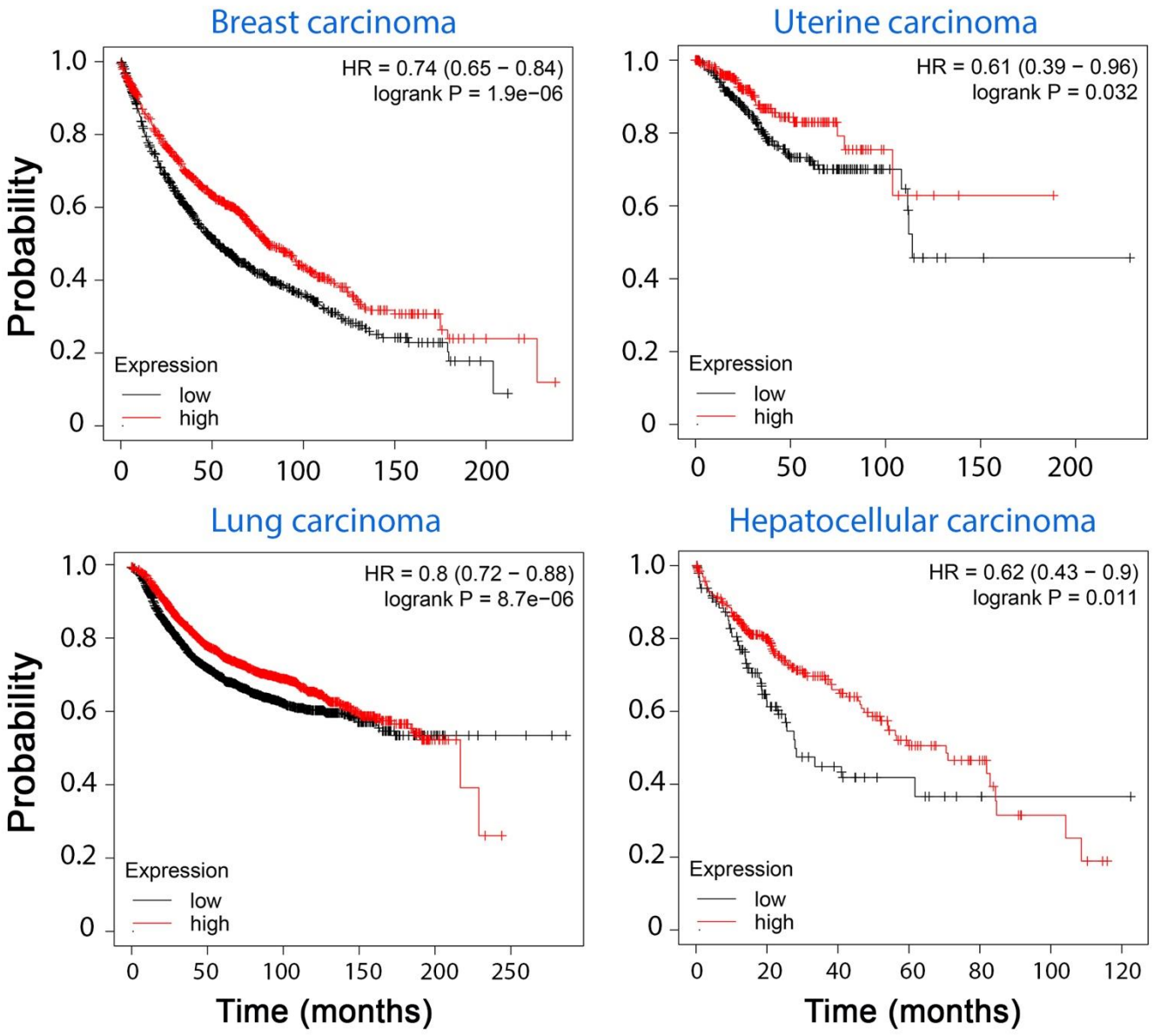


**Figure 4.** Kaplan-Meier database for cancer prognosis shows the survival probability of cancer patients in retrospective studies with high and low decorin levels. We used KMplotter (160,161) from GEO and EGA repositories. There is a clear correlation between low decorin expression and lower survival rates for patients suffering from breast, uterine, lung and hepatocellular carcinomas, which are some of the most common metastatic malignancies.

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