Oncosuppressive functions of decorin

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The extracellular matrix is rapidly emerging as a prominent contributor to various fundamental processes of tumorigenesis. In particular, decorin, a member of the small leucine-rich proteoglycan gene family, is assuming a central role as a potent soluble tumor repressor. Decorin binds and antagonizes various receptor tyrosine kinases and inhibits downstream oncogenic signaling in several solid tumors. Among other functions, decorin evokes cell cycle arrest, apoptosis, and antimetastatic, and antiangiogenic programs. Recent work has revealed a paradigmatic shift in our understanding of the molecular mechanisms underlying its tumoricidal properties. Decorin adversely compromises the genetic signature of the tumor microenvironment and induces endothelial cell autophagy downstream of VEGFR2. Moreover, decorin selectively evokes destruction of tumor cell mitochondria downstream of Met through mitophagy. Acting as a partial agonist, decorin signals via proautophagic receptors and triggers procatabolic processes that parallel the classical tumoricidal properties of this multifaceted proteoglycan.

Introduction

Solid malignancies are complex entities that arise from intricate associations among a heterogeneous population of cells derived from several epigenetically and transcriptionally distinct lineages.[1,2] The impressive assortment of recruited mesenchymal and inflammatory cells within the elaborate network of the extracellular matrix (ECM) is emerging as a critical entity defining chemotherapeutic responsiveness and clinical outcomes.[3] The ECM acts as a bidirectional signaling hub, linking the local microenvironment with the tumor cells.[4] This communicative epicenter provides instructional cues in the form of solid-phase ligands[5] and/or soluble signals that are capable of modulating multiple aspects of tumorigenesis and angiogenesis.[6-9]

The diverse regulatory properties exerted by the multifunctional nature of ECM molecules are embodied and exemplified by the small leucine-rich proteoglycan (SLRP) gene family.[10,11] Decorin, the prototypical SLRP of this 18-member strong clan, is composed of a singular N-terminal glycosaminoglycan chain of dermatan or chondroitin sulfate, 12 leucine-rich tandem repeats, and a C-terminal Ear domain.[12] Decorin was named for its function as an avid collagen-binding partner for fibrillogenesis,[6,13] and regulates various biomechanical properties of collagen-containing tissue, including tendons and skin.[14-17] Subsequent paradigm-shifting work demonstrated a strong affinity of decorin for various receptor tyrosine kinases (RTKs) that resulted in potent and sustained oncostasis and angiostasis. Moreover, decorin binds and sequesters numerous growth factors,[18] multiple matrix constituents,[19] and indirectly suppresses downstream signaling.[19] Collectively, these studies revealed that

decorin functions as a soluble tumor repressor that counteracts tumorigenic and angiogenic growth, and the protein has aptly been designated "a guardian from the matrix."[19]

Decorin is currently emerging as a multifaceted and multifunctional signaling molecule with roles beyond the tumor stroma. Pertinent examples include inflammatory responses,[8,20,21] delayed hypersensitivity,[22] wound healing,[23,24] keratinocyte function,[25] hepatic healing,[26] asthma,[27] diabetic nephropathies,[28] myogenesis,[29] shaping hematopoietic stem cell niches,[30] convergent extension,[31] and renal diseases.[32,33] We are currently in the midst of a SLRP renaissance in which decorin is challenging established cancer biology precepts for tumorigenic and angiogenic suppression by matrix constituents.[34]

In this review, we will evaluate the consequences of autophagic and mitophagic processes that occur downstream of proautophagic RTKs and impinge upon the tumor microenvironment and the tumor proper. Importantly, autophagic and mitophagic processes evoked by decorin are above the operative threshold for ambient homeostatic function, thus controlled or limited autophagy may result in revitalization of cellular processes. The balance between excessive and insufficient autophagy is crucial as either may result in a pathological state. We will critically assess these novel avenues and their unique interfaces with the well-established tumoricidal properties of this versatile proteoglycan and discuss potential therapeutic interventions for decorin bioactivity.

Localization of Decorin Within the Tumor and the Tumor Stroma

Understanding the biological effects of decorin on the tumor first requires a discussion of its expression patterns and localization within the tumor compartments. The degree of decorin expression in various types and grades of tumors has recently been reported and reveals several apparent discrepancies. Clinically, loss of decorin within the tumor microenvironment serves as a poor prognosticator of invasive breast cancer.[12,35] Moreover, by querying the Human Protein Atlas, Bozoky et al.[36] demonstrated a marked reduction in decorin levels within the stroma of many solid tumors, including bladder, breast, cervical, colon, kidney, ovary, pancreas, prostate, rectal, skin, stomach, and testis. Additionally, decorin expression is significantly reduced in the stroma of low- and high-grade bladder carcinomas, but is high in the submucosa and deep tumor stroma.[37] Decorin expression is also decreased in multiple myeloma and monoclonal gammopathy of undetermined significance.[38,39]

However, other studies report an increase in the amount of stromal decorin in cancer, primarily within colon[40-42] and breast[43,44] carcinomas. Given the breadth of the decorin interactome with multiple matrix constituents,[19] a role for decorin in orchestrating higher-order matrix assemblies and coordinating a desmoplastic reaction emerges. Formation of these collagen-rich structures (comprised of collagen II and IV microfibrils) and the propensity for sequestering potent antitumorigenic (e.g., decorin) and antiangiogenic factors (e.g., decorin and matrilin-1[45]) into large complexes favor tumor suppression.[7,19] We believe that

profuse amounts of decorin within the stromal compartments of these tumor types would negatively regulate the juxtapositioned RTKs expressed by the growing neoplasm in a paracrine fashion.

Moreover, and pertinent for tumor parenchyma, multiple studies demonstrate a complete loss of decorin expression by the tumor cells.[19,46] Deficiencies of decorin have been found in multiple tumors including prostate carcinomas,[47] urothelial malignancies,[48] and hepatic carcinomas.[49] Interestingly, an unbiased deep transcriptome sequencing approach revealed that decorin expression is markedly decreased in hepatocellular carcinomas.[50] In the case of urothelial carcinomas, decorin mRNA expression is highly reduced in superficial[51] and infiltrating tumors.[52] Certain neoplasms have an avid proclivity for hypermethylation of the decorin promoter, thereby effectively silencing expression for unchecked tumor progression.[19]

Further evidence for the oncostatic role of decorin as a tumor repressor stems from strong genetic models in which decorin was unconditionally ablated.[53] Under conditions of a high-fat (i.e., Western) diet, decorin (Dcn)-null mice develop spontaneous intestinal tumors.[54] Moreover, compound knockout mice for Dcn and Tp53 accede to aggressive lymphomas,[55] whereas reintroduction of decorin via adenoviral delivery or systemic administration significantly counters tumorigenic and angiogenic growth in a variety of solid tumors.[46,56–60] Collectively, these data provide firm support for a tumor repressive role of decorin in a physiologically relevant setting.

Decorin Promotes a Proautophagic Signaling Program in the Tumor Microenvironment

Intravital imaging of exogenously delivered near infrared-labeled decorin via tail vein injection demonstrated avid and exclusive targeting of orthotopic tumor xenografts.[61,62] Importantly, decorin is not targeted to or retained by any other organ system and is subsequently secreted via the urine.[61] Systemic delivery of decorin after establishment of triple-negative breast carcinoma orthotopic xenografts permitted high-resolution and simultaneous transcriptomic profiling of the host stromal compartment of mouse origin and the tumor parenchyma of human origin.[59] Unexpectedly, decorin evoked significant transcriptomic changes within the host-provided tumor microenvironment without significantly modulating the mRNA profile of the human breast carcinoma[63] Collectively, these changes reprogrammed the tumor stroma in a manner that disfavored tumorigenic growth and metastases.[19,59]

Of the multitude of genes that are differentially expressed upon chronic decorin treatment, a small subset of targets have emerged that include a poorly-studied imprinted tumor suppressor known as Peg3.[63-65] The induction of a tumor suppressor gene is clearly congruent with the antitumorigenic activity of decorin[19] Furthermore, PEG3 is epigenetically silenced (via promoter hypermethylation of the active allele) in multiple gynecologic and neural tumors.[66,67] Our interest in pursuing Peg3 stemmed from its previously described role in the suppression of Wnt/β-catenin signaling in a non-canonical manner,[68] which mirrored the bioactivity

of decorin in a cervical carcinoma model.[61] Our interest intensified when we found that Peg3 colocalized with subcellular structures highly reminiscent of autophagosomes upon decorin stimulation of macrovascular and microvascular endothelial cells used as a surrogate for the tumor stroma.[69] Further investigation using the specific autophagic markers Beclin 1 and LC, confirmed that these Peg3-positive structures were autophagosomes (**Fig. 1A, B**).[70] Intriguingly, Peg3 is required for the decorin-induced transcriptional activation and accumulation of Beclin 1 and LC3; moreover, Peg3 is required for maintenance of basal Beclin 1 levels in endothelial cells.[70,71]

Mechanistically, decorin induces Peg3-dependent autophagy downstream of VEGFR2,[71] the primary RTK for endothelial cell homeostasis. In contrast to the aforementioned function of decorin as a pan-RTK inhibitor, decorin acts as a partial VEGFR2 agonist for autophagic initiation (**Fig. 1A**).[71] Decorin binds the VEGFR2 ectodomain (IgG domains 3–5) that partially overlaps with the binding site of VEGFA (IgG domains 1–3). By doing so, it activates the proautophagic AMPKα/Vps34 signaling arm[72,73] and concurrently represses the antiautophagic PI3K/Akt/mTOR/p70S6K pathway (**Fig. 1A**).[74,75] Collectively, the net cellular output of these concerted signaling events promotes the formation of a Peg3–Beclin 1–LC3 ternary complex,

induction of proautophagic gene targets, and concomitant disruption of the inhibitory Bcl-2–Beclin 1 complex.[75,76] Decorin rapidly promotes activation of the catalytic core of the central energy sensor, AMPKα, at Thr172 in a VEGFR2-dependent manner within a nutrient-rich setting.[75]

In theory, it is possible that decorin mediates activation of AMPKα by recruiting ULK1 (also known as ATG1) and promoting the formation of AMPKα–ULK1 heterodimers for the initiation of autophagy,[77,78] with further and protracted antagonism of mTORC1 components (such as Raptor, Rheb, and GβL).[77] Notably, recent studies have elaborated an inhibitory function for EGFR and Akt signaling through phosphorylation and consequent inactivation of Beclin 1 (BSCN1) that is conducive to autophagic suppression and chemoresistance.[73,79] As many RTKs share the core signaling machinery, it is possible that decorin abrogates phosphorylated Beclin 1 downstream of VEGFR2, thereby permitting autophagic activation and downstream supramolecular complex assembly.[75]

Successful autophagy relies on positive flux, lysosomal fusion, and the successful formation of autophagolysosomes.[80,81] Decorin may positively regulate transcription factor EB (TFEB), a crucial sensory node between autophagy and lysosomal formation.[82] Intriguingly, TFEB is held inactive and sequestered
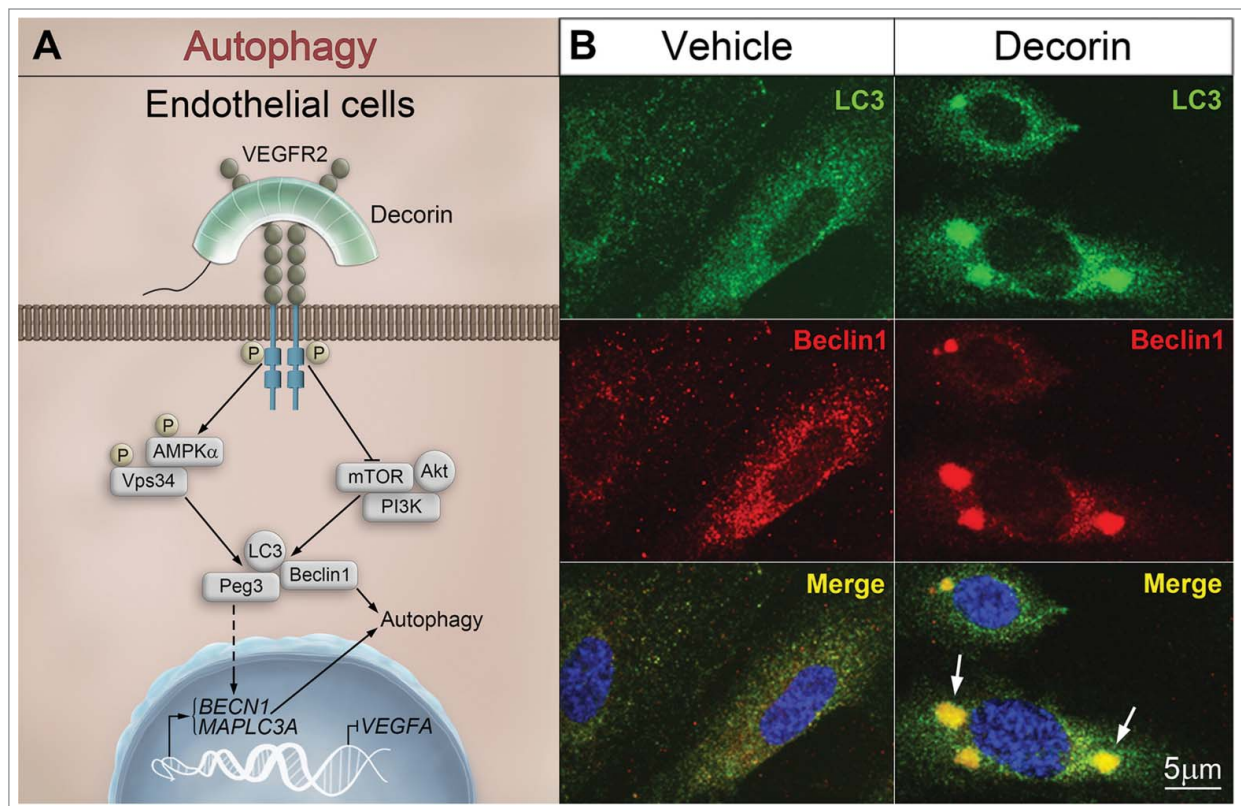
Figure 1. (**A**) Schematic representation of the downstream signaling events following binding of decorin to VEGFR2 and Peg-3–dependent endothelial cell autophagy. Please refer to the text for details. (**B**) Confocal laser microscopy of human umbilical vein endothelial cells (HUVECs) after treatment for 6 hours with vehicle or 200 nm human recombinant decorin. Please note the formation of autophagosomes, as identified by immunostaining for LC3 (green) or beclin 1 (red). The bottom row of panels demonstrates colocalization of autophagic markers (yellow), thereby confirming the identify of these subcellular structures. Nuclei are stained blue with DAPI. All images were taken with the same exposure, gain, and intensity. Scale bar = 5 μm.

within the cytosol (at the lysosomal membrane) by inhibitory mTOR/LYNUS signaling.[83,84] As decorin inactivates mTOR downstream of VEGFR2, in the presence of decorin TFEB may become dephosphorylated (either passively or actively) and translocate into the nucleoplasm for the activation of proautophagic targets (e.g., BECN1 and CLEAR network genes such as PPARGC1A),[82] potentially in a Peg3-dependent manner.

One of the key tenets of decorin bioactivity is the suppression of rampant neovascularization.[85] Notably, biglycan, the closest member of the SLRP gene family, has opposite effects to decorin in both inflammation[86-88] and angiogenesis,[89,90] demonstrating specific bioactivities for individual SLRPs. As endothelial cells play a critical role in vascularization of an oxygen- and nutrient-starved solid tumor, we propose that increased autophagy may represent a novel mechanism by which decorin triggers a halt in migration, proliferation, and capillary morphogenesis,[69] and, ultimately, in angiogenesis—all key properties orchestrated by positive VEGFA signaling. This may be achieved by the concerted activation of VEGFR2/ULK1/AMPKα/Peg3/TFEB signaling for the repression of endothelial cell-derived VEGFA and/or by rendering endothelial cells refractory to the aberrant angiogenic stimuli derived from the growing tumor cells.

In conclusion, endothelial cell autophagy heralds a paradigmatic shift in the role of decorin in tumorigenic and angiogenic suppression via RTKs. Indeed, autophagic induction in a tissue-specific manner may be a conserved mechanism of action for matrix-derived signals.[34,91] Furthermore, these findings alter the established model of nutrient-dependent autophagic induction in favor of soluble signaling cues, present within the stroma, for the activation of the autophagic machinery.

Growth Suppression Via Pan-Rtk Inhibition in the Tumor

In the classic model, decorin exerts its ascribed tumoricidal properties by directly engaging a multitude of RTKs within the target-rich environment that constitutes the tumor parenchyma.[19,92–95] Mechanistically, monomeric decorin[96] binds RTKs with high affinity and evokes receptor dimerization, transient autophosphorylation, caveolin-1–mediated internalization,[97] and eventual lysosomal degradation.[19,97] Solid tumors that are dependent upon RTK signaling are severely suppressed following the introduction of decorin.[35,46,56] In contrast to the response to naturally occurring receptor agonists, upon decorin exposure the unstructured intracellular tail of EGFR and Met acquires a unique phosphorylation signature,[19] perhaps as a result of altered conformational states of the receptor ectodomain and transmembrane region[98] upon decorin binding. In contrast with active signaling agents, this phosphorylation pattern instructs cell cycle arrest, apoptosis, angiostasis, and protracted oncogene suppression (**Fig. 2**, left panel).[19]

A prime example is EGFR, in which decorin initiates a rapid phosphorylation that activates the MAPK signaling system.[58] This counterintuitively results in apoptosis and cell cycle arrest concomitant with the cleavage and subsequent activation of caspase-3 and induction of p21^{WAF1}(p21), (**Fig. 2**, left panel), despite the fact that total cell surface EGFR levels are diminished by 50%.[58] A second example is the recently discovered Met receptor, which undergoes a strong Tyr phosphorylation signal on a phosphotyrosine array following decorin treatment;[99] this transient activation results in recruitment of c-Cbl and receptor downregulation. The transient nature of decorin-evoked receptor phosphorylation and the downstream transduction mechanisms represents a key tenet in cell signaling in which the duration, frequency, and strength of the signal combinatorially dictate cellular behaviors.[100] The oscillatory nature of the downstream signaling molecules (receptors, MAKP, PI3K/Akt/mTOR) framed within this conceptual scaffold may prove crucial for decorin-transduced signals and biological outcomes.

EGFR and Met are not the only RTKs responsible for decorin bioactivities. Several members of the EGFR family, such as the ErbB2/ErbB4 heterodimers, are also targeted by decorin[6], although recent evidence now suggests direct ErbB4 antagonism.[101] Many other RTKs have been identified, including IGF-IR, IR-A, and their ligands,[62,102,103] PDGFRα[49] and associated PDGFA ligand,[104] and VEGFR2.[69,105,106] Notably, IGF-IR represents the only known exception where the receptor is not internalized and tagged for destruction by decorin binding;[62] instead, decorin suppresses the IRS-1/Akt/ERK/p70S6K pathway, blocks migration, and prevents IGF-I–dependent localization of IGF-IR into caveosomes.[37]

Suppression of Proliferative, Survival, and Migratory Signaling Pathways

Downstream of the robust binding events and receptor internalization and degradation, soluble decorin evokes potent and prolonged attenuation of several signaling pathways responsible for tumor cell proliferation, survival, and angiogenesis. Attenuation of Met results in the non-canonical and selective degradation of β-catenin and Myc[61,85] with concurrent induction of p21.[61] In the case of hepatocyte growth factor (HGF)/Met, this particular signaling system results in the direct stabilization and nuclear accumulation of β-catenin and transcriptional activation of β-catenin targets. Seemingly, this pathway functions independently of Wnt signaling via direct phosphorylation and inhibition of GSK-3β.[107] In contrast, binding of decorin to Met disrupts this signaling cascade[61] in what appears to be a GSK-3β−independent manner, resulting in prompt 26S-proteasomal degradation and suppression of β-catenin (CTNNB1) expression (**Fig. 2**, left panel). Furthermore, Myc is also destabilized by increased phosphorylation on Thr58, a known phospho-acceptor site that designates Myc for degradation via the proteasome with concurrent suppression of *MYC* mRNA[61] (**Fig. 2**, left panel). The increase in phosphorylated Myc at this position may be a result of derepressed GSK-3β downstream of attenuated Met signaling.[61] However, the nuclear-localized priming kinase DYRK1 that is adept for phospho-transfer at Ser62 of Myc might work in concert with the GSK-3β-mediated phosphorylation of Myc at Thr58[108] that occurs downstream of decorin/Met binding.
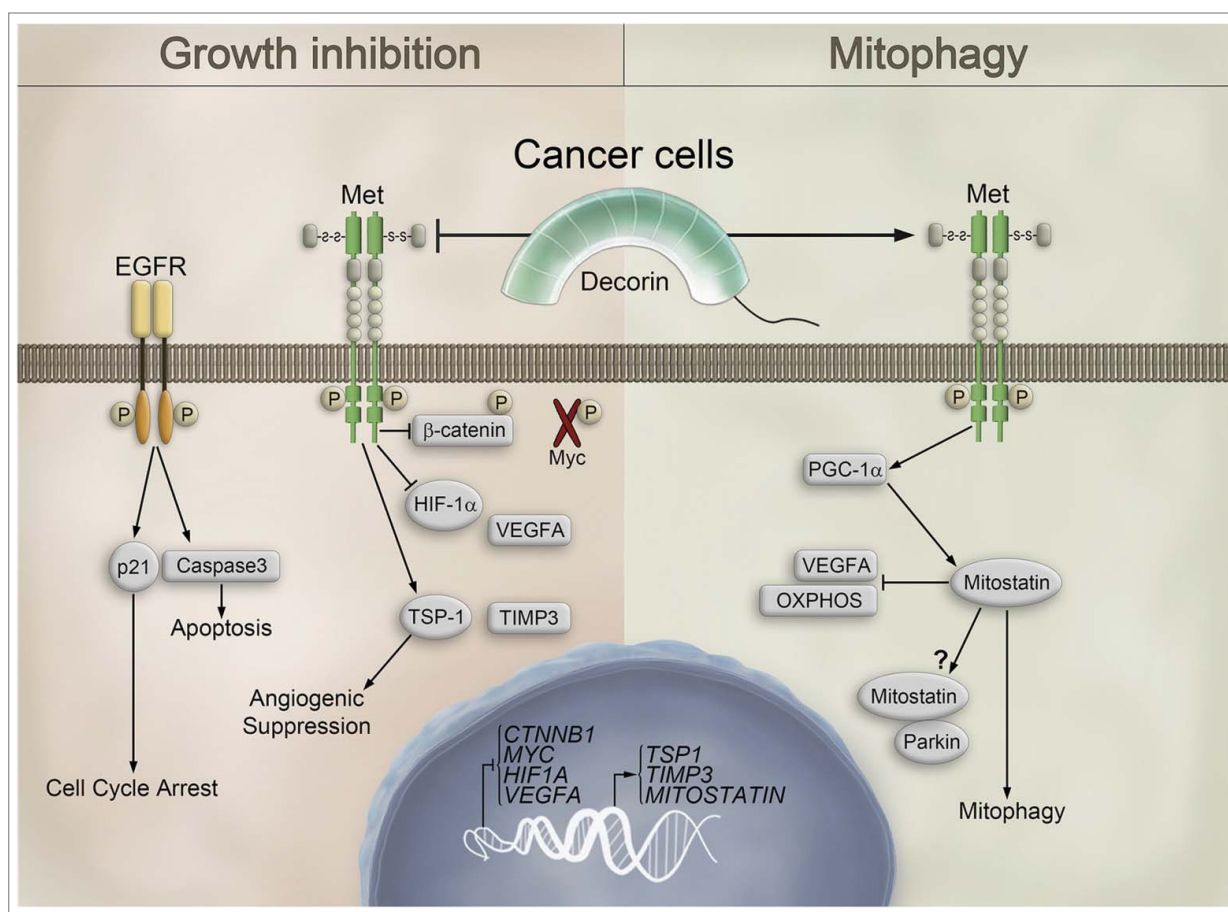
Figure 2. Schematic representations delineating the classic growth inhibitory functions (left panel) and novel promitophagic activities (right panel) of decorin in a tumor cell. Please refer to the text for a full mechanistic description.

Interestingly, decorin evokes strong nuclear translocation and subsequent degradation of Myc, concomitant with p21 accumulation.[61] Additionally, transcriptional induction of p21 (also known as CDKN1A) may be linked to inactivation and destruction of the Met/β-catenin/Myc signaling axis as AP4, a gene target of Myc,[109] actively represses *CDKN1A* expression (**Fig 2**, left panel).

Broad clinical implications of decorin-mediated suppression of the Met/β-catenin axis have recently emerged from high-throughput transcriptomic screening.[110] Basal mammary carcinomas driven by Wnt/β-catenin and HGF/Met signaling have a unique genetic fingerprint known as the "Wnt-Met" signature, in which aberrant β-catenin activity drives self-renewal programs and Met suppresses differentiation commitments.[110] It is plausible that clinical cases expressing the Wnt-Met signature would greatly benefit from receiving decorin, or related SLRPs, as an adjuvant protein-based therapy. The expected results of such treatment would include a reduction in the capacity for tumor self-renewal and the induction of a more differentiated tumor phenotype with decreased metastatic capacity. Personalized genomics combined with an understanding of matrix-derived tumor repressors may represent an important therapeutic option in the future. Indeed, molecular therapies targeting this system greatly alleviate tumor burden and increase overall survival. Moreover, a similar genetic signature was found for synergistic cooperativity between Myc and Her2/Neu (ErbB2) for stem-like breast cancer cell phenotypes without the requisite epithelial-to-mesenchymal transition discussed elsewhere.[3,111,112] Therefore, decorin may suppress stem-like progenitors that would otherwise permit enhanced malignant states.

Intriguingly, as part of the newly described "Wnt-Met" signature, Wnt/β-catenin signaling actively drives expression of CXCL12, a critical chemokine for tumor migration and metastasis.[110] Moreover, HGF acting via the Akt/Rac1/PKCζ arm evokes CXCR4 expression in breast carcinoma.[113] Based on these findings, perturbation of the HGF/Met and Wnt/β-catenin axis by decorin may significantly nullify the CXCR4/CXCL12 chemotactic system and thereby provide a molecular basis for the observed antimetastatic role of this multifunctional proteoglycan. Alternatively, the antimetastatic properties of decorin may be linked to the tumor suppressive function of MMP8 via antagonism of miR-21 and induction of MMP8.[114]

Suppression of Angiogenic Signaling Pathways

The cellular and molecular mechanisms responsible for governing and orchestrating tumor neovascularization are becoming more clearly defined. Moreover, several endogenous cues, chiefly soluble and matrix-derived in nature,[115-118] that potently impede rampant tumor angiogenesis are being discovered. The literature surrounding the role of decorin in mediating angiogenic responses reflects the inherent intricacies of this vital developmental process. Perhaps the most striking example of complexity in decorin-mediated angiogenesis stems from studies on the normally developing cornea, in where dichotomous roles have been found;[119,120] however, literature on the role of decorin in mediating tumor angiogenesis favors an antiangiogenic role.[12,19,106,121] Furthermore, the observation that angiosarcomas exhibit a total lack of stromal decorin whereas hemangiomas have abundant decorin expression[122] implies an inverse relationship between vascularized tumor malignancy and decorin expression.

Mechanistically, decorin directly suppresses the HGF/Met signaling axis that ultimately inhibits VEGFA-mediated angiogenesis.[85,123] Under normoxic conditions, decorin transcriptionally silences a potent combination of proangiogenic transcription factors, including hypoxia inducible factor-1α (HIF-1α), β-catenin, and Myc, downstream of engaging Met (**Fig. 2**, left panel).[85] Moreover, decorin noncanonically promotes the degradation of HIF-1α protein in a manner dependent on Von-Hipple Lindau tumor suppressor protein (pVHL).[85] Within the extracellular milieu, decorin attenuates the liberation of matrix-bound VEGFA by inhibiting the expression and activity of MMP-2 and MMP-9, which depend on competent β-catenin for sufficient transactivation (**Fig. 2**, left panel). Decorin also promotes the induction and secretion of well-known antiangiogenic effectors such as TSP-1 and TIMP3.[85] Intriguingly, decorin promotes rapid secretion of TSP-1 by inhibiting the RhoA/ROCK1 signaling cascade[124] for early tempering of the initial angiogenicity of the tumor environment. Importantly, decorin significantly abrogates the HGF/Met signaling axis *in vivo* in the well-established matrigel plug assay, providing firm mechanistic evidence for decorin-mediated angiostasis. In essence, decorin subverts HGF signaling through Met and thus reduces vascularization and vessel density of the malignancy.[19,85]

The implications of attenuating HIF-1α and triggering the rapid release of TSP-1 under normoxic conditions open various possibilities of reprogramming the tumor parenchyma and tumor stroma that favor continued tumorigenic growth. It is plausible that decorin disrupts early vascularization events by quelling the angioplasticity of the stroma and repressing potent proangiogenic factors within the tumor proper. Collectively, inhibition of several key EGFR- and Met-mediated pathways including migration, proliferation, survival, and angiogenesis underlies many of the antioncogenic properties of soluble decorin.

New Antioncogenic Properties: Tumor Cell Mitophagy

Fulfilling its role as "a guardian from the matrix," decorin antagonizes tumorigenic progression indirectly by evoking endothelial autophagy and directly by circumventing the angiogenicity of the tumor proper via growth inhibition, suppression of proangiogenic promoters, and secretion of antiangiogenic factors. A novel mechanism that underlies and potentially unifies the classic tumoricidal effects evoked by decorin has been recently delineated.[125] Functionally akin with VEGFR2 (see above), decorin is a partial agonist of Met for the induction of tumor cell mitochondrial autophagy (mitophagy) (**Fig. 2**, right panel). At the core of this novel regulatory paradigm is a poorly understood decorin-inducible tumor suppressor gene known as mitostatin.[126,127] Mitostatin (a mitochondrial protein with oncostatic activity, also known as tricoplein),[128] embodies all known characteristics of a conventional tumor suppressor while residing at the mitochondria,[127] possibly at specialized interfaces between the mitochondria and endoplasmic reticulum.[128]

Downstream of Met signaling, decorin elicits rapid post-transcriptional regulation of mitostatin mRNA through PGC-1α[125], a master regulator of mitochondrial biogenesis.[129] The prompt stabilization of mitostatin mRNA is coordinated by its direct binding to the C-terminal RNA-recognition motif (RRM) of PGC-1α, which is dependent on arginine methylation of PGC-1α by PRMT1.[125] Methylation of RNA binding proteins is commonly required for interactions between this polybasic domain and mRNA target binding.[130] Interruption of the RRM of PGC-1α ablates the induction and accumulation of mitostatin protein.[125] Therefore, we have delineated an operative and mechanistic role for PGC-1α, a crucial factor for BRAF-mediated oncogenesis,[131,132] in stabilizing and permitting induction of a decorin-evoked tumor suppressor gene for mitophagic induction (**Fig. 2**, right panel).

Silencing of mitostatin abrogates the ability of breast carcinoma cells to undergo canonical or decorin-evoked mitophagy, as measured by oxidative phosphorylation (OXPHOS) complex turnover, voltage-dependent anion channel (VDAC) activity, and mtDNA depletion[125] (**Fig. 2**, right panel). An antitumorigenic consequence of mitophagic induction is demonstrated by the inability of decorin to suppress tumor-derived VEGFA in the absence of mitostatin[125] (**Fig. 2**, right panel). Therefore, mitophagy and decorin-evoked angiostasis may be functionally linked through mitostatin.

Mitophagy is initially evoked following the depolarization of mitochondria.[133] Loss of mitochondrial membrane potential is recognized by Parkin, an E3-ubiquitin ligase that is implicated in recessive forms of neurodegenerative disease, such as Parkinson's disease.[133] This signal permits discrimination of healthy from failing mitochondria.[134] As a very early harbinger of mitophagic induction, decorin triggers depolarization of the mitochondrial membrane analogous to that induced by the protonophore FCCP.[125] Interestingly, cytosolic calcium fluxes are

reported for mitophagy, concomitant with depolarization.[134] As soluble decorin promotes oscillations of cytosolic calcium in an EGFR-dependent manner,[135,136] this release may precede and play a role in depolarizing the mitochondria. Furthermore, mitostatin may play a role in coordinating calcium release and subsequent mitochondrial depolarization, as it clusters with mitochondrial-associated membranes and interacts with mitofusion-2.[128]

Mitostatin may interact with, or even function as, an intracellular mitochondrial receptor for Parkin recruitment (**Fig. 2**, right panel). This scenario appears plausible as Parkin promotes mitophagy[133,137] and respiratory chain turnover *in vivo*,[138] mimicking the effects of decorin/mitostatin signaling. Parkin interacts with PINK1, a master mitophagic kinase that senses mitochondrial distress (e.g., loss of membrane potential) and permits activation of Parkin and downstream ubiquitination of target proteins for mitophagic progression.[139,140] As both Parkin[141] and mitostatin[128] interact with mitofusion-2, a quaternary complex may exist among PINK1, Parkin, mitostatin, and mitofusion-2 for mitophagic initiation in response to traditional stimuli (e.g., FCCP, CCCP, nutrient deprivation) or decorin.

Currently, no crystal structure of mitostatin exists[126]; however, an *in silico* analysis of the primary structure revealed an internal domain that shares homology with the DnaJ family of molecular chaperones. Intriguingly, selective destruction of mitochondrial proteins, primarily those associated with the outer mitochondrial membrane, promotes selective respiratory chain component turnover and mitophagy in a PINK1/Parkin-dependent manner.[134] It appears that mitophagy depends on an association between p62 (also known as sequestosome) and VDAC.[137] Decorin promotes loss of VDAC in a mitostatin-dependent manner.[125] Further, long-lived pools of p62/sequestosome promote mammary tumorigenesis via abnormal ErbB2, Akt, and β-catenin activation,[142] whereas mitochondrial turnover promotes degradation of p62/sequestosome.[143] As such, mitostatin may elicit mitophagy in a PINK1/Parkin-dependent fashion, resulting in the turnover of downstream targets involved in this process (e.g., via p62/sequestosome). Tantalizingly, given that mitostatin may function as a molecular chaperone, additional decorin targets including Myc, β-catenin, and HIF-1α may be targeted for degradation via mitostatin during the course of mitophagic signaling and progression.

Therefore, the induction of mitophagy within the tumor by soluble decorin via mitostatin may account for the molecular outcomes and biological manifestations of decorin, such as inhibition of tumorigenic growth and rampant tumor angiogenesis.

Conclusions and Perspectives

Our increased understanding of the biofunctionality of decorin parallels our evolving and expanding comprehension of the fundamental mechanisms underlying molecular and cellular oncology. Originally characterized as a collagen binding factor and key regulator of fibrillogenesis, decorin has recently emerged as the frontrunner for a novel class of soluble and matrix-derived tumor repressors that potently antagonizes RTK signaling.[7] The decorin interactome encompasses a broad and diverse repertoire of binding partners that effectively quell the tumor microenvironment and antagonize tumor angiogenesis and metastasis by multiple mechanisms.[19] Original studies investigating decorin as a potent tumoricidal molecule focused on the multitude of interactions between decorin and RTK-enriched tumor cells and downstream antioncogenic and antiangiogenic effects. However, a paradigmatic shift has recently emerged with the demonstration that decorin affects the transcriptomic profile of the tumor microenvironment without significantly perturbing the genetic signature of the tumor itself.[59] This discovery heralded a new interest in decorin biology to understand the mechanisms operative within the stroma and how these signals interface with the known effects of decorin on the biology of the tumor proper. As such, a new regulatory mechanism has emerged that posits decorin as a procatabolic agent that activates the conserved autophagic machinery.[34] Acting as a partial agonist, decorin engages a new class of proautophagic signaling receptors—VEGFR2 for endothelial cell autophagy and Met for tumor cell mitophagy—that are activated following decorin binding. Importantly, induction of autophagy and mitophagy may be required for the underlying antitumorigenic effects of decorin on a variety of tumors, including cell cycle arrest, apoptosis, angiogenesis, and metastasis. Such a model connects the secreted extracellular matrix component[20,144] with complex intracellular metabolic and bioenergetic systems.

Therefore decorin, related SLRPs, and matrix components may be of great clinical interest as advanced chemotherapeutic modalities that could be genetically matched with the patient's individual cancer. Matrix-derived therapies may prove to be valuable armaments in the continued war against cancer.

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