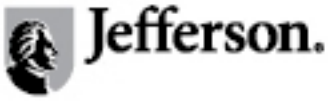

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Decorin as a multivalent therapeutic agent against cancer

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Abbreviations: AMPKα, AMP-activated protein kinase, alpha; AP4, Activating enhancer binding protein 4; ATG, Autophagy related gene; Bcl2, B-cell CLL/lymphoma 2; BRAF, proto-oncogene B-Raf; ECM, extracellular matrix; EGFR, Epidermal growth factor receptor; ERK, extracellular regulated kinase; GSK-3β, glycogen synthase kinase 3β; HGF, hepatocyte growth factor; HIF-1α, Hypoxia inducible factor-1α; IGF-I, insulin-like growth factor 1; IGF-IR, insulin-like growth factor 1 receptor; IgG, immunoglobulin G-like folds; IR-A, Insulin receptor isoform A; IRS, insulin receptor substrate 1; LC3; Microtubule-associated protein 1A/1B-light chain 3; LRR, leucine-rich repeat; MAPK, Mitogen activated protein kinase; MMP, Matrix metalloproteinase; mTOR, mechanistic target of rapamycin; OXPHOS, oxidative phosphorylation; p70S6K, Ribosomal Protein S6 Kinase, 70kDa; PDGFR, Platelet derived growth factor receptor; Peg3, Paternally expressed gene 3; PGC-1α, Peroxisome proliferator activated receptor γ co-activator-1α; PI3K, phosphoinositide 3 kinase; PINK1, PTEN-induced putative kinase-1; PKB/Akt, Protein kinase B; Rheb, Ras homolog enriched in brain; RhoA, Ras homolog gene family, member A; ROCK1, Rho-associated, coiled -coil-containing protein kinase 1; RRM, RNA recognition motif; RTK, receptor tyrosine kinase; SLRP, small leucine-rich proteoglycan; TGF-β1, Transforming growth factor beta 1; TIMP3, Tissue inhibitor of metalloproteinases 3; TSP1, Thrombospondin 1; VDAC, Voltage-dependent anion channel; VEGFA, vascular endothelial growth factor A; VEGFR2, vascular endothelial growth factor receptor 2; Vps34, Vacuolar Protein Sorting 34.

Abstract

Decorin is a prototypical small leucine-rich proteoglycan and epitomizes the multifunctional nature of this critical gene family. Soluble decorin engages multiple receptor tyrosine kinases within the target rich environment of the tumor stroma and tumor parenchyma. Upon receptor binding, decorin initiates signaling pathways within endothelial cells downstream of VEGFR2 that ultimately culminate in a Peg3/Beclin 1/LC3-dependent autophagic program. Concomitant with autophagic induction, decorin blunts capillary morphogenesis and endothelial cell migration, thereby significantly compromising tumor angiogenesis. In parallel within the tumor proper, decorin binds multiple RTKs with high affinity, including Met, for a multitude of oncosuppressive functions including growth inhibition, tumor cell mitophagy, and angiostasis. Decorin is also pro-inflammatory by modulating macrophage function and cytokine secretion. Decorin suppresses tumorigenic growth, angiogenesis, and prevents metastatic lesions in a variety of *in vitro* and *in vivo* tumor models. Therefore, decorin would be an ideal therapeutic candidate for combatting solid malignancies.

Keywords: small leucine-rich proteoglycan, autophagy, mitophagy, angiogenesis, endothelial cells, receptor tyrosine kinases

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1. Introduction

Fundamental for all facets of multicellular life and evolutionarily conserved, the extracellular matrix (ECM) is a diverse network of instructional cues linking the local tissue microenvironment with the juxtaposed tumor cells [1-3]. Emerging as a critical entity in chemotherapeutics, tumorigenic progression, and predicting clinical outcome [4-6], the ECM is a nexus of signal integration for a plethora of cell-derived factors while synchronously regulating cellular behaviors [7]. This symbiotic relationship facilitates bidirectional parsing of intrinsic biological information into functionally relevant processes responsible for orchestrating tumorigenesis and angiogenesis [8-10].

The small leucine-rich proteoglycans (SLRPs) are an emerging subset of matrix-derived, soluble regulators that are inextricably woven into the fabric of the ECM. They reflect the multifactorial propensity of the matrix, and subsume crucial roles over a spectrum of homeostatic and pathological conditions [11]. This 18-member strong gene family is proving critical for restraining the development, progression, and dissemination of various solid tumors [12-14]. Decorin, the archetypical SLRP, harbors a single, covalently-attached N-terminal glycosaminoglycan (GAG) chain consisting of either dermatan or chondroitin sulfate, twelve leucine-rich tandem repeats (LRR), and a class-specific C-terminal Ear domain [15]. Although the crystal structure of decorin has been solved a head-to-tail dimer [16], it is likely that soluble decorin is active as a monomer in solution [17,18].

Decorin was originally discovered as an avid collagen-binding protein necessary for appropriate fibrillogenesis [19-22], thereby originating the eponym of decorin [15]. Akin with a role in orchestrating and ensuring proper collagen fibril network assembly, decorin regulates tissue integrity by modulating key biomechanical parameters of tendons and skin [23-26]. However, seminal work heralded a major paradigm shift in understanding the function of SLRPs by demonstrating that soluble decorin is a high affinity, antagonistic ligand for several key receptor tyrosine kinases resulting in protracted oncostasis and angiostasis [27]. As a further mechanism for the oncosuppressive propensities of decorin, numerous growth factors-e.g. TGF-β [28,29] and CCN2/CTGF [30], to name a few-and matrix constituents are sequestered [31], and manifest as an indirect attenuation of downstream signaling apparati. More recently, decorin has emerged as a soluble pro-autophagic cue by initiating endothelial cell autophagy and evoking tumor cell mitophagy as the mechanistic basis for the documented oncostatic effects [32]. Cumulatively, decorin is a soluble tumor repressor and anti-angiogenic factor and has rightfully earned the designation of "*a guardian from the matrix*" [31].

Beyond the emerging literature regarding the role of decorin within the tumor stroma, decorin is genuinely a multifaceted signaling effector and exemplifies the growing role of SLRPs in organismal homeostasis and pathology. Germane examples include immunomodulation [33,34], cutaneous wound healing [35], proper keratinocyte function [36], diabetic nephropathies [37], fetal membrane homeostasis [38], obesity and type II diabetes [39], allergen-induced asthma [40], allergic

inflammation [41], delayed hypersensitivity reactions [42], hepatic fibrosis [43], myogenesis and muscular dystrophy [44,45], post myocardial infarction remodeling [46], and mediating proper vertebrate convergent extension [47]. Moreover, decorin has been identified as a potential biomarker for ischemic stroke [48], renal and pulmonary diseases [49-51] and for maintaining hematopoietic stem cell niches [52].

In this review, we will critically evaluate decorin as a tumoricidal agent by examining the classical mechanisms of decorin-mediated oncogenic suppression and the newly discovered signaling pathways that are exploited for autophagic induction. The biofunctionality of decorin and associated mechanisms discussed herein represent novel targets for future therapeutic intervention, as derived from this versatile proteoglycan, that will satisfy a growing and unmet medical need.

1.1. General considerations: Decorin as an oncosuppressive entity

An important construct for understanding the anti-tumorigenic effects of decorin concerns the localization and corresponding expression patterns of this prototypical SLRP within the various tumorigenic compartments [53].

1.1.1. Localization and expression patterns of decorin within the tumor

Despite a large literature describing decorin as an oncosuppressive proteoglycan [12,13,31,54], there are still several incongruencies that need to be addressed. In particular, the absence of decorin in the breast tumor stroma has been established as an important clinical prognosticator of invasive and metastatic breast cancer [10,55-57] as well as in soft tumors [58]. A similar reduction of decorin expression is seen in the microenvironments of low- and high-grade urothelial carcinoma [59] as well as in the plasma of multiple myeloma and MGUS patients [60], cases of esophageal squamous cell carcinoma [61] and instances of colon cancer [53]. An *in silico*-based query utilizing immunohistochemical arrays spanning a variety of tissues has detected a marked reduction of decorin expression in the stroma of many solid malignancies, including breast [62]. Other studies seemingly report the opposite result inasmuch as certain tumor types, including colon and breast carcinomas [54], have elevated amounts of stromally-deposited decorin. Functionally, the increased caches of decorin within these tumors may still negatively regulate growth by physically constraining the tumor (e.g. desmoplastic-type reaction) as well as acting in a paracrine manner to downregulate the adjacent RTKs present on the tumor cell surface. As it pertains to the tumor proper, several studies have clearly demonstrated a complete loss of decorin expression in several tumor types, such as urothelial, prostate, myeloma, and hepatic carcinoma [63-68]. Utilizing an unbiased deep RNA sequencing method of hepatocellular carcinomas, several prominent matrix constituents were decreased, including decorin [69]. Moreover, poorly differentiated sarcomas completely lack decorin in

contrast to hemangiomas which have considerable expression of decorin [66]. Therefore, the malignancy of a tumor may be linked to endogenous decorin expression.

1.1.2. Genetic and cell biological evidence for decorin as a soluble tumor repressor

As mentioned in the preceding section (1.1.1.), decorin is found to be profusely expressed within the stroma of colon cancer. This was the very first indication of a possible connection between decorin and an oncogenic setting [70-72]. Like p53, decorin was initially perceived as an oncogene. Since this discovery, strong genetic evidence has emerged confirming the oncostatic role of decorin following the unconditional ablation of decorin from the *M. musculus* genome [73]. Mice lacking the *Dcn* gene and given a Western diet (e.g. high-fat) develop intestinal tumors [74]. Mechanistically, loss of decorin disrupts appropriate intestinal cell maturation, leading to aberrant turnover (decreased differentiation and increased proliferation consistent with suppressed p21 and p27 with elevated β-catenin) of the intestinal epithelium [74]. Moreover, the inhibition of colon carcinoma by decorin involves modulating E-cadherin levels *in vitro* and *in vivo* [75]. Moreover, when both p53 and Dcn genes are concurrently ablated, there is a genetic cooperation demonstrated by the rapid onset of aggressive T-cell lymphomas and premature death of the double mutant mice [76]. These studies indicate that genetic loss of decorin is permissive for tumorigenic initiation.

Several studies have been completed wherein decorin is potently anti-metastatic for breast carcinomas [56,57,77] while compromising otherwise rampant tumor angiogenesis [78,79]. In a murine model of osteosarcoma, decorin prevents lung metastases [80] and inhibits B16V melanoma cell migration [81]. Of clinical and therapeutic importance, re-introduction of decorin via adenoviral delivery, *de novo* ectopic expression, or systemic administration counteracts the tumorigenicity in several animal models of cancer that recapitulate solid neoplastic growth [82-88]. Notably, pre-clinical studies using infrared-labeled decorin have shown that it preferentially targets the tumor xenografts with prolonged retention of the active agent [89]. Recently, adenoviral mediated decorin expression has been shown to decrease the growth of bone metastases caused by intracardiac injections of prostate [90] and breast [91] carcinomas. Taken together, the aforementioned genetic and pre-clinical studies establish and authenticate decorin as a viable tumor repressor for combating several types of cancer.

2. Decorin structure: High-affinity interactions with several receptors

Harboring the largest known gene family of proteoglycans, decorin and related classes of SLRPs share a common core architecture [92]. They are ubiquitously expressed in all major organs during development [93], and are present within all matrix assemblies. The various members have been

organized into five distinct classes based on the criteria of evolutionarily conserved structural homology (including organization at the genomic and protein levels) as well as by shared functional properties [15]. The closest SLRP to decorin is biglycan, which shares more than 65% homology. These properties include the innate ability of collagen binding [20,94], growth factor binding and sequestration (predominantly those from the TGF-β superfamily) [12,31], and cell surface receptor modulation as a soluble mediator [54,95]. Moreover, a specific subclass of solubilized SLRP and matrix components can regulate autophagy [32]. Finally, these classes can be subdivided further into canonical SLRPs (classes I-III) and non-canonical SLRPs (classes IV, V) based on various structural considerations (see below). In this fashion, decorin embodies all of these principles while pioneering new functions and paradigms.

2.1. The LRR constitutes the basic unit of decorin structure and function

Leucine-rich repeats are about 24 amino acids in length and contain a conserved stretch of hydrophobic residues that form short β-sheets on the interior or internal (concave) surface of the solenoid. These short β-sheets are further arranged in a parallel conformation with the adjacent LRRs in the core (Fig. 1A). In total, there are 12 LRRs (designated with roman numerals I-XII) that constitute the protein core of decorin (Fig. 1A). Conversely, on the exterior or external (convex) surface of the solenoid, these β-sheets are flanked by and intertwined with equally short β-strands connected by several types of α-helices (Fig. 1A). Terminating each LRR at the N- and C-termini are disulfide bonds that function as a cap. The inherent structural determinants of these caps aid in further distinction among the various classes of SLRPs (e.g. classes I-III vs. classes IV, V), as discussed above [15].

This fundamental LRR architecture permits a plastic interface capable of coordinating a myriad of protein-protein interactions. Indeed, this hallmark is crucial for the widespread functionality of decorin [95], and related SLRPs, and is mediated by residues located on the internal surface of the protein [15]. Moreover, each LRR confers various functional properties for the well-established bioactivities of decorin. For example, LRR XII binds CCN2/CTGF [30], LRR V/VI aid in the binding of decorin to VEGFR2 [96], and the collagen binding sequence (SYIRIADTNIT) of LRR VII, located on the interior surface of the solenoid [97], mediates direct binding of decorin to type I collagen (Fig. 1A). A feature of decorin, also shared by Class I-III SLRPs, is the presence of an elongated (~30 amino acids) LRR known as the “ear” repeat (Fig. 1A). In decorin, this is found in the penultimate LRR, LRR XI. Interestingly, truncation or mutations arising in the ear repeat of decorin cause congenital stromal corneal dystrophy [20,98]. Mechanistically, mouse models of decorin lacking this ear repeat trigger intracellular accumulation of decorin within the endoplasmic reticulum, thereby causing ER stress, and compromising proper corneal collagen deposition and assembly [99].

Importantly, the covalently attached glycosaminoglycan chain plays a pivotal role in the regulation of collagen fibrillogenesis [15]. However, in the context of controlling intracellular signaling cascades via cell surface receptors, the glycosaminoglycan chain is dispensable.

The glycosaminoglycan chain has a pivotal role in various connective tissue disorders insofar as alterations in the chain are found in congenital stromal corneal dystrophy and Ehlers-Danlos syndrome [100] as well as in cancer [12]. Improperly modified or missing chains can disrupt structural functions as mediated by decorin by compromising the architecture of the surrounding matrix. This is exemplified in the skin fragility phenotype of patients with Ehlers-Danlos syndrome, where roughly half of the secreted decorin lacks the chain [101]. Mechanistically, early stages of collagen fibril formation are impaired following the loss of the glycosaminoglycan chain. Moreover, the type and composition of the attached glycosaminoglycan can also vary, particularly in cancer (colon, ovarian, pancreatic, gastric), where it is predominantly chondroitin sulfate [10,12,72,102]. In contrast, the chemically more complex dermatan sulfate is less abundant in these types of tumors [102]. The presence of CS is postulated to facilitate cell migration, thereby increasing the malignancy of the tumor [102].

2.2. Decorin is a soluble pan-RTK inhibitor and binds multiple cell surface receptors

As discussed above (section 2.1), the overall arrangement of decorin, in conjunction with the individual composition of the LRRs, endows a rather promiscuous nature of binding multiple targets expressed within the tumor microenvironment and by the tumor proper. Of critical importance for attenuating tumorigenic progression and preventing metastases, decorin avidly binds numerous cell surface receptors [95] (Fig. 1B). Decorin can be considered an endogenous, soluble pan-RTK inhibitor, especially targeting cells enriched in EGFR, Met, and VEGFR2. These three RTKs are the most established and instrumental for transducing signals necessary for oncogenic and angiogenic suppression [31,54] (Fig. 1B). As such, this trio of receptors will be discussed in more depth in the forthcoming sections (see below, sections 3 and 4).

Decorin, non-canonically, engages IGF-IR (Fig. 1B), but does not trigger internalization nor compromise the stability of the receptor complex at the cell surface [59,103], unlike EGFR and Met (see below) [54]. Instead, decorin decreases the stability of critical downstream signaling effectors such as IRS-1 [59], thereby attenuating sufficient activation of the Akt/MAPK/Paxillin pathway for IGF-I induced mobility [104]. Moreover, the role of decorin as an IGF-IR ligand is strictly context-dependent as decorin is an IGF-IR agonist in normal tissues, but functions as an obligate IGF-IR antagonist in cancer [103]. Adding an additional layer of complexity in modulating the IGF-IR signaling axis, decorin exerts control over discrete IR-A ligands by differentially binding and sequestering (analogous with requisitioning TGF-β members) the various IR-A ligand isoforms [105]. The role of decorin and related

proteoglycans, particularly SLRP members, in mediating receptor cross-talk between EGFR and IGF-IR is emerging as a central mechanism in estrogen-responsive breast carcinomas [106].

A prime example can be made from PDGFR-α/β that will reinforce the central dogma of decorin. Screening the RTKome of two different chemically induced models of hepatocellular carcinoma (HCC), it was found that, in a Dcn null background, many RTKs are constitutively activated [68]. Indeed, the global loss of decorin permits inappropriate, basal activation of several RTKs as measured by an increase in the phospho-Tyr signal. From this screen, PDGFR-α/β emerged (Fig. 1B) as a viable candidate to which decorin engages with high affinity and suppresses the formation of HCC [68]. Importantly, these results are congruent with the finding that decorin is suppressed, at the transcriptomic level, in HCC [69]. These strong genetic data clearly demonstrate the importance of decorin in preventing aberrant and constitutive RTK activation while maintaining proper tissue homeostasis.

2.3. Decorin is pro-inflammatory by engaging TLR2/4 on the surface of macrophages

It is becoming evident that soluble decorin can regulate the innate immune response [33] via toll-like receptors 2 and 4 (Fig. 1B) and is considered a damage-associated molecular pattern member [107]. This pro-inflammatory property is analogous to that of circulating biglycan [108,109]. Via high-affinity interactions, decorin engages TLR2/4 and promotes a pro-inflammatory state by triggering the synthesis and secretion of TNF-α and IL-12p70 [33]. Indirectly, via the formation of decorin/TGF-β complexes, anti-inflammatory mediators (such as IL-10) are translationally suppressed by PDCD4 [33]. Thus, circulating decorin is a pro-inflammatory proteoglycan for innate immune modulation [33]. It has emerged that biglycan is a viable biomarker of inflammatory renal diseases [110]. Likewise, cancer patients have significantly increased levels of circulating decorin [33], positing decorin as a desirable therapeutic target.

3. Suppression of growth and tumor angiogenesis via EGFR and Met

Innate and distinct biological information pertinent for abrogating tumorigenic growth and suppressing tumor angiogenesis is stored within the solenoid structure of decorin [31]. This information is interpreted and transduced via engagements to a specific subset of RTKs (Fig. 2) that are amplified and enriched within the tumor parenchyma [10,12]. In the context of Met and EGFR, monomeric decorin [17] binds a narrow region that partially overlaps with that of the agonist binding cleft [111]. This binding subsequently promotes receptor dimerization, analogous to the natural ligand EGF [112], followed by a rapid and transient phosphorylation of the unstructured intracellular tails. This is followed by recruitment and activation of downstream effectors, caveosome-mediated internalization of the decorin/receptor complex, and eventual lysosomal degradation [9,14,113,114]. The latter

causes a protracted cessation of intracellular receptor signaling. Overall, this mechanism of action is a hallmark of decorin activity in the contextual framework of tumorigenic RTK signaling.

Seemingly, receptors harboring specific structural motifs, specifically members of the IgG superfamily, may provide essential docking platforms for decorin engagement [111,115]. Indeed, the ectodomains of EGFR, Met and VEGFR2 all contain multiple IgG folds [116,117]. Mechanistically, decorin binding may promote a combinatorially different phosphorylation signature than the pattern obtained with natural agonist (e.g. TGFα, EGF, HGF/SF, VEGFA). Collectively, the decorin-bound receptors initiate a signaling program than can lead to cell cycle arrest, apoptosis, and angiosuppression (Fig. 2).

3.1. Decorin binds EGFR for tumor cell cycle arrest and apoptosis

The concept of decorin-mediated RTK-antagonism was pioneered following the discovery that EGFR is a main target [118] and that decorin represents an endogenous ligand for receptor occupancy and modulation [119]. In mouse models carrying A431 orthotopic tumor xenografts, it was established that decorin, by targeting EGFR, significantly subverts tumorigenic growth *in vivo* [120]. Decorin indirectly inhibits Her/ErbB2 activity [121], potentially via the titration of active ErbB1/ErbB2 dimers [54]. Decorin also directly binds and represses ErbB4/STAT3 signaling [122] in the central nervous system. Mechanistically, decorin triggers transient activation of downstream ERK1/2 signaling (following stimulation of the innate EGFR kinase) [87] concurrent with a regulated burst of cytosolic Ca^{2+} [123]. Paradoxically, positive EGFR/MAPK signaling (despite total EGFR being reduced by >50%) evokes induction of the cyclin-dependent kinase inhibitor, $p21^{WAF1}$ with concomitant conversion of pro-caspase-3 into active caspase 3 [87]. Collectively, this promotes cell cycle arrest and induces the intrinsic apoptotic pathway, respectively (Fig. 2). Imperative for the protracted function of decorin, decorin/EGFR complexes are shuttled into caveolin-1 coated pits [31]. Specific phopho-residues are required for the association of caveolin-1 with EGFR [124] and internalized via endocytosis for degradation. This system prevents recycling of EGFR for additional rounds of signaling, in contrast to active ligands which sort EGFR into clathrin-coated pits. This leads to endosomal recycling and, ultimately, to repopulation of the cell surface with activated EGFR for additional signal transduction (Fig. 2).

3.2. Decorin evokes oncoprotein degradation and suppresses angiogenesis via Met

A major tenet of decorin-mediated suppression of oncogenesis involves transient activation of the receptor complex [31]. Using a discovery tool, such as a phosphotyrosine RTK array, it was found that a second RTK, Met or HGF receptor, is specifically activated by soluble decorin proteoglycan or decorin protein core [115] (Fig. 2). Met is the key receptor for decorin and is responsible for relaying

signals applicable for anti-tumorigenesis, angiostasis and pro-mitophagic functionalities (see below, section 4.2) [54,115]. Moreover, decorin exhibits a tighter binding affinity for Met when compared with EGFR, (Kd~2 vs 87 nM, respectively). [115]. Heterodimeric decorin/Met complexes are shuttled from the cell surface into caveolin-1 positive endosomes following recruitment of the c-Cbl E3-ubiqtuin ligase to Met via Tyr1003 (Fig. 2), a residue phosphorylated and favored by decorin treatment [115]. Association of decorin/Met with caveolin-1 ensures termination of oncogenic signaling, which in parallel with decorin/EGFR is in stark contrast with HGF/Met (and EGF/EGFR) complexes localizing within clathrin-coated endocytic vescicles for proficient receptor recycling [89].

As a major consequence of inhibiting Met, two potent oncogenes, β-catenin and Myc, are targeted for unremitting degradation via the 26S proteasome [89] (Fig. 2). Decorin-evoked transcriptional suppression coupled with phosphorylation-dependent protein degradation of Myc (at Thr58, the effector kinase(s) remains unknown) permits de-repression of the *CDKN1A* locus via loss of the AP4 repressor [89]. Moreover, decorin suppresses β-catenin signaling in a non-canonical fashion insofar as being independent from Axin/DSH/GSK-3β activity [89]. In this scenario, β-catenin is phosphorylated, not for increased protein stability, and is instead targeted for degradation [125] in a manner consistent with direct phosphorylation of β-catenin by an RTK, such as Met [126-129] (Fig. 2). The observation that Myc and β-catenin signaling is governed by decorin may account for the intestinal tumor formation seen upon decorin ablation, as β-catenin is a major oncogenic driver for intestinal epithelium turnover and maturation [130]. Constitutive activation of Met is found in many cases of colon carcinoma and directly influences β-catenin signaling [131]. Therefore, as global loss of decorin relieves the basal inhibition of several RTKs [68], this could certainly contribute to Met/β-catenin driven transformation of the intestinal epithelium and/or other solid malignancies directed by this axis.

Concomitant with the concerted suppression of two potent oncogenes, Met also serves as the primary node for angiogenic suppression in cervical and breast carcinomas [79] (Fig. 2). Positive signaling via Met non-canonically suppresses the transcription of *HIF1A* regardless of oxygen concentration [79]. Correspondingly, *VEGFA* mRNA and proteins are compromised in several *in vitro* studies utilizing primary endothelial cells, MDA-MB-231 triple-negative breast carcinoma cells, and *in vivo* as demonstrated with HeLa tumor xenografts [79]. Moreover, MMP2/9 (Gelatinase A and B, respectively) which liberate matrix bound VEGFA, are also significantly suppressed [79]. In parallel with a protracted suppression of pro-angiogenic effectors, decorin also evokes the expression and secretion of anti-angiogenic factors such as TIMP3 and TSP-1 [79] (Fig. 2). Further studies have indicated that decorin triggers the rapid secretion of TSP-1 from MDA-MB-231 cells in an EGFR-dependent manner by attenuating the RhoA/ROCK1 pathway [132]. Given the powerful anti-angiogenic activity of TSP-1 and the involvement in several pathophysiological processes [133-138], it

is likely that this indirect activity of decorin in malignant cells could have a protective role against cancer growth and metabolism. Taken together, decorin differentially regulates potent angiokines [139] that favor silencing rampant tumor neovascularization, thereby contributing further to the ascribed anti-tumorigenic and anti-metastatic properties.

4. Decorin ameliorates tumorigenesis by evoking stromal autophagy and tumor mitophagy

A major breakthrough in deciphering the *in vivo* bioactivity of decorin came from a pre-clinical screen that sought novel decorin-regulated genes [88]. With this goal, triple-negative breast carcinoma orthotopic xenografts were established and treated systemically with decorin, for downstream utilization on a high-resolution transcriptomic platform [88]. Unlike traditional microarrays, this chip was designed for the simultaneous analysis and detection of species-specific genes modulated within the host stroma (*Mus musculus*) and those originating from the tumor xenograft (*Homo sapiens*) [88]. Following validated bioinformatics approaches, it was found that decorin regulates a small subset of genes; however, this signature showed differential regulation exclusively within the tumor microenvironment derived from the murine host [88], with minimal transcriptomic changes in the tumor cells of human origin [88]. The transcriptomic profile obtained implies that exogenous decorin treatment reprograms the tumor stroma in a fashion that disfavors tumorigenic growth, consistent with the function of decorin acting as a soluble tumor repressor from the outside.

4.1. Decorin evokes endothelial cell autophagy in a Peg3-dependent manner

Using the decorin-treated breast carcinoma xenografts described above, several novel tumor-derived genes were discovered [88]. Among these genes, the genomically-imprinted zinc-finger transcription factor, *PEG3* [140-143] was selected [88]. Previously, Peg3 has been implicated in regulating stem cell progenitors [144,145], mediating p53-dependent apoptosis of myogenic and neural lineages [146-150], and maternal/paternal behavioral patterns [151,152]. Peg3 has been implicated in the pathogenesis of cervical and ovarian carcinoma as its expression is frequently lost via promoter hypermethylation and/or loss of heterozygosity [153-156]. Thus, Peg3 is considered a *bona fide* tumor suppressor [157]. Importantly, Peg3 represents another tumor suppressor induced by decorin in addition to mitostatin and Beclin 1 (see below). Moreover, in analogy to decorin bioactivity in cancer cells, Peg3 non-canonically suppresses the Wnt/β-catenin pathway [158].

As a proxy for the tumor stroma, we investigated the function of Peg3 within endothelial cells, as this particular cell type conveys major angiogenic advantages for a growing tumor and constitutes the primary cell type involved in capillary morphogenesis and patent vessel formation. Moreover, these cells are significantly responsive to soluble decorin, which suppresses the expression of VEGFA, a major survival factor [79]. Serendipitously, we found that Peg3 mobilizes into large intracellular

structures reminiscent of autophagosomes [159] in primary endothelial cells (HUVEC). Co-immunocolocalization and co-immunoprecipitation studies of canonical autophagic markers, e.g., Beclin 1 and LC3 [160,161], and Peg3 have clearly demonstrated that decorin evokes a novel gene involved in autophagy initiation [159] (Fig. 3, *left*). Intriguingly, Peg3 is required for decorin-mediated *BECN1* and *MAP1LC3A* expression and is responsible for maintaining basal levels of Beclin 1 [159,162]. Mechanistically, decorin promotes a competent pro-autophagic signaling composed of Peg3, Beclin 1 and LC3 while combinatorially precluding Bcl-2, a known autophagic inhibitor [163]. At the endothelial cell surface, decorin engages VEGFR2, the central receptor for endothelial cells, for autophagic induction [159] (Fig. 3, *left*). Pharmacological inhibition with the small molecule inhibitor (SU5416) abrogates the autophagic response, suggesting that decorin requires the VEGFR2 kinase for successful autophagy [159,162]. Downstream of stimulated VEGFR2, decorin differentially regulates decisive signaling complexes by activating pro-autophagic modules (e.g. AMPKα and Vps34) while concurrently attenuating, in a protracted fashion, anti-autophagic nodes (e.g. PI3K/Akt/mTOR) [164] (Fig. 3, *left*). Concomitant with autophagic initiation, decorin also impairs capillary morphogenesis [78,79,159]. Therefore, it is plausible that decorin evokes autophagy as the molecular underpinning for suppressing tumor angiogenesis from the perspective of endothelial cell-driven angiogenesis (Fig. 3, *left*).

4.2. Decorin induces tumor cell mitophagy in a mitostatin-dependent manner

As a novel constituent of the multi-pronged approach for curtailing tumorigenesis and halting angiogenesis (differential modulation of pro- and anti-angiogenic factors and induction of endothelial cell autophagy) decorin directly influences catabolic programs and organelle turnover within the tumor proper (Fig.3, *right*). Induction of tumor cell mitochondrial autophagy (mitophagy) [165] may functionally reconcile the canonical tumoricidal effects of decorin with the emerging biology of matrix-mediated autophagic induction for retarding tumorigenic and angiogenic progression. In a mechanism analogous to that of VEGFR2, decorin requires the kinase activity of Met for proper mitophagic induction in breast carcinoma cells [165] (Fig. 3, *right*). Both forms of autophagic induction require the presence of a cell surface receptor (VEGFR2 or Met) and the intrinsic kinase activity of referenced receptor. At the nexus of decorin-evoked mitophagy is a poorly characterized tumor suppressor gene known as mitostatin or trichoplein (mitostatin has the HuGO gene symbol, *TCHP*, and is located on chromosome 12q24.1). Mitostatin was originally identified as a decorin-inducible gene using subtractive hybridization and probes from decorin-transfected (and thereby, growth suppressed) cells [166]. Notably, mitostatin is downregulated in bladder and breast carcinomas [166,167], suggesting that it might represent a potential tumor suppressor gene. Mitostatin primarily resides at the outer mitochondrial membrane [167] and at specialized membrane:membrane contact sites at the

juxtaposition of the endoplasmic reticulum and mitochondria where it interacts with mitofusion-2 [168]. Hence the given eponym for mitostatin, mitochondrial protein with oncostatic activity.

During the early stages of mitophagy, downstream of Met, a master regulator of mitochondrial homeostasis and biogenesis, PGC-1α [169] is mobilized into the nucleus and binds *TCHP* mRNA directly for rapid stabilization coincident with mitostatin protein accumulation [165] (Fig. 3, *right*). Mediating the interaction of PGC-1α with *TCHP* mRNA via the C-terminal RNA recognition motif [165] is critical for stabilization. Truncating this domain or silencing PRMT1, for appropriate arginine methylation, compromises mitostatin mRNA stabilization [165]. The delineation of this pathway has revealed a unique cooperation between a novel mitophagic effector and a known oncogenic driver. PGC-1α mediates B-Raf mediated oxidative metabolism [170] while defining a subset of aggressive melanoma characterized by an augmented mitochondrial capacity for increased resistance to oxidative stress [171].

The process of decorin-evoked mitophagy depends on the presence and yet-to-be-elucidated-function of mitostatin [165] (Fig. 3, *right*). RNAi-mediated silencing of mitostatin prevents turnover of respiratory chain components (OXPHOS), decreased mtDNA content, VDAC clearance, and collapse of the mitochondrial network [165], all established markers of mitophagy [172]. Moreover, failure of mitophagic induction precludes the ability of decorin in suppressing VEGFA expression and protein [165] (Fig. 3, *right*), suggesting that mitophagy is key for understanding a fundamental hallmark of decorin biology. Subsequent to the collapse and aggregation of the tubular mitochondrial network, decorin triggers mitochondrial depolarization [165], with an activity comparable to that of an established depolarization agent (FCCP). This loss of membrane potential across the outer and inner mitochondrial membrane is a harbinger for mitochondrial dysfunction and eventual turnover [173,174]. Depolarized mitochondria may be the end product of increased Ca^{+2} levels as occur downstream from decorin/EGFR interactions [123]. As mitostatin is positioned at mitochondrial-associated membrane and interacts with Mfn-2, it may permit an efflux of Ca^{+2} from the ER directly into the mitochondria as the initial event for decorin-evoked mitophagy.

In either scenario, depolarization of the mitochondria triggers recruitment of the PINK1/Parkin complex for eventual clearance of the damaged organelle. The E3-ubiquitin ligase, Parkin is strictly required for proper mitochondrial homeostasis, as recessive mutations in Parkin are found in the neurodegenerative disease, Parkinson's [173,175,176]. It remains plausible that mitostatin may interact with or facilitate the conscription of PINK1/Parkin for mitochondrial turnover (Fig. 3, *right*). Alternatively, mitostatin may directly stimulate the inherent PINK1 kinase activity for proper recruitment, ubiquitin activation [177,178], and/or Parkin-mediated ubiquitination of target mitochondrial proteins [179-181]. Indeed, this axis is key for recycling respiratory chain complexes [182,183].

Collectively, the above findings imply that decorin transduces biological information via the Met kinase for mitophagic stimulation, in a mitostatin-dependent manner, within the tumor parenchyma of breast and prostate carcinomas [90]. This conserved catabolic process, coupled with the induction of endothelial cell autophagy, may form the molecular basis for the various outputs of decorin-mediated RTK regulation. Indeed, this newly-found activity may lie at the crossroads of controlling tumorigenic growth and unchecked tumor vascularization.

5. Gene and protein therapy in various preclinical tumor studies

Delivery of decorin via adenovirus (Ad) vectors together with the systemic administration of decorin proteoglycan or protein core, has been tested in a variety of preclinical studies. In Table 1 we summarize past and current studies utilizing these two approaches focused exclusively on cancer treatment and delivery. Although the therapeutic efficacy varies among these studies, it is clear that decorin has a deleterious effect on growth, apoptosis, metabolism and angiogenesis.

This concept was established by initial studies demonstrating that ectopically expressing decorin for the rapid neutralization and inhibition of tumorigenic growth from various histogenetically distinct origins held potential clinical relevance [84]. These studies provided further evidence that administering decorin, either decorin proteoglycan or protein core, in a systemic fashion prevented growth and metastases of orthotopic tumor xenografts [87]. Several studies (Table 1), have subsequently evaluated the feasibility of delivering decorin via adenovirus in several tumor types including breast and prostate carcinoma. Collectively, these studies have reaffirmed the *in vivo* applicability of utilizing decorin as a therapeutic modality for the prevention of metastatic lesions as well as suppressing the oncogenic and angiogenic properties of tumors.

6. Conclusions

The extracellular matrix is rapidly emerging as a crucial component for better understanding fundamental cellular processes and behaviors as well as providing novel therapeutic targets for combating complex pathological conditions [6] after these pathways have gone awry. Our pursuit of comprehending the varied intricacies and subtleties of reciprocal cell:matrix signaling for homeostatic and tumorigenic processes has been facilitated by an exhaustive proteomics approach, organized into an invaluable resource accessible for query [184]. As this database will undoubtably aid research concerning the contributions of matrix in various pathologies, the plenary discoveries of decorin mediated RTK-antagonism have revealed heretofore unknown signaling roles encoded within members of the soluble matrix. Since this pioneering breakthrough, similar mechanisms have been proposed as the underlying molecular explanation for a variety of biological phenomena [15] across diverse tissues and microenvironments. Indeed, the ever-expanding decorin interactome [31] encompasses a plethora of critical matrix-bound and cell-localized binding partners that substantially

attenuate pro-tumorigenic and pro-angiogenic signaling cues [54] while simultaneously inducing conserved, intracellular catabolic processes [32,95]. In summation, this manifests as patent and long-lasting oncosuppression [88,89] that is efficacious and clinically-relevant in a variety of solid tumors.

Structure always determines function; this axiom is epitomized within the leucine rich repeats composing the protein core of decorin. This regularly patterned structure inherently provides for a high affinity and multivalent interface capable of binding and interacting with a large number of effector proteins to potentiate probable cellular outcomes. As such, decorin requires and depends on this proclivity for binding multiple partners for competently executing downstream events under a variety of conditions. This concept is exemplified in the context of RTK binding. Canonically, decorin is characterized as an unwavering and unbridled antagonistic ligand for the EGFR and Met receptor, resulting in the inhibition of potent oncoproteins and pro-angiogenic factors. The mechanistic perspective for decorin (at the receptor level) has shifted after identifying a decorin-specific transcriptomic signature exclusively within the tumor stroma, and the subsequent discovery of endothelial cell autophagy in which VEGFR2 kinase activity is required. Therefore, decorin acts as a partial receptor agonist. A similar requirement is operational in Met kinase activity during the process of mitophagic initiation in breast carcinoma cells [165]. These findings support the hypothesis that decorin could engage a receptor for autophagic induction as a basis for oncostasis. Indeed, the oncogenic EGFR/Akt signaling suppresses Beclin 1 for increased chemo-resistance and tumorigenicity [185,186]. Moreover, a novel mechanism detailing the transcriptional induction and enhanced secretion of decorin from cardiac tissue and isolated mouse embryonic fibroblasts following a 25-hour fast has been recently identified [187]. Notably, the global ablation of decorin attenuates autophagic responses and blunts autophagic flux, further underscoring the critical importance of decorin as a soluble, *in vivo* pro-autophagic regulator [187]. This study may wield clinical relevance as a starting point for drug development towards molecules targeting *Dcn* induction and secretion for organismal-wide autophagic regulation and tumor suppression [188].

Furthermore, the clinical efficacy of decorin as a novel therapeutic is exemplified by the diverse array of studies employing decorin as a potent soluble tumor repressor.

In conclusion, the work on decorin provides a new paradigm in the more general scheme of matrix-dependent regulation of cancer growth: soluble ECM constituents can act as pro-autophagic factors by interacting with various cell surface receptors for the proficient modulation of the intracellular catabolic network. This new function integrates well with the traditional oncosuppressive properties of decorin exerted on RTKs. Thus, decorin and related SLRPs, including soluble ECM fragments derived from larger parental molecules [95,189], hold great therapeutic potential and clinical benefit for combating cancer.

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Figure Legends

Fig. 1. The solved crystal structure of decorin permits association with a multitude of cell surface receptors. (A) Cartoon ribbon diagram of monomeric bovine decorin rendered with PyMol v1.8. (PDB accession #: 1XKU). Vertical arrows designate β-strands whereas coiled ribbons indicate α-helices. Roman numerals situated above the diagram define each LRR from left to right, by convention. The type I collagen binding sequence has been included and is shaded yellow. (B). Schematic depiction of the various RTKs and innate immune receptors that decorin engages. Please, consult the text for additional information.

Fig. 2. EGFR and Met coordinate growth inhibition, apoptosis, and angiostasis. Schematic representation of the signaling pathways modulated in response to decorin binding. Please, consult the text for additional information.

Fig. 3. VEGFR2 and Met evoke endothelial cell autophagy and tumor cell mitophagy. Schematic representation delineating the signaling pathways active in response to decorin acting as a partial agonist of VEGFR2 or Met for endothelial cell autophagy or tumor cell mitophagy induction, respectively. Please, consult the manuscript for additional information concerning these pathways.

Table 1

Pre-clinical studies exploiting several delivery mechanisms for decorin as a therapeutic modality against cancer and across multiple species.

Tumor type	Origin	Delivery system	Reference(s)
Orthotopic squamous cell carcinoma	Human	Ectopic expression	Santra *et al* [84]
Orthotopic squamous cell carcinoma	Human	Recombinant decorin proteoglycan or protein core	Seidler *et al* [87]
Orthoptopic breast carcinoma	Human	Ad-Decorin	Reed *et al* [85]
Lung adenocarcinoma	Human	Ad-Decorin	Tralhão *et al* [86]
Breast metastases	Human	Ad-Decorin	Reed *et al* [57]
Breast metastases	Human, Rat	Ad-Decorin	Goldoni *et al* [56]
Multiple myeloma	Human	Rercombinant decorin proteoglycan	Li *et al* [63]
Orthotopic glioma	Rat	Ectopic expression	Stander *et al* [190]
Orthotopic glioma	Rat	Ectopic expression	Biglari *et al* [191]
Orthotopic breast carcinoma	Human	Recombinant decorin proteoglycan or protein core	Buraschi *et al* [88]
Bone metastases of prostate carcinoma	Human	Ad-Decorin	Xu *et al* [90]
Bone metastases of breast carcinoma	Human	Ad-Decorin	Yang *et al* [91]