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1 **Decorin as a multivalent therapeutic agent against cancer**

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10 **Running Head:** Decorin as a Therapeutic Agent

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34 **Abbreviations:** AMPK α , AMP-activated protein kinase, alpha; AP4, Activating enhancer binding
35 protein 4; ATG, Autophagy related gene; Bcl2, B-cell CLL/lymphoma 2; BRAF, proto-oncogene B-Raf;
36 ECM, extracellular matrix; EGFR, Epidermal growth factor receptor; ERK, extracellular regulated
37 kinase; GSK-3 β , glycogen synthase kinase 3 β ; HGF, hepatocyte growth factor; HIF-1 α , Hypoxia
38 inducible factor-1 α ; IGF-I, insulin-like growth factor 1; IGF-IR, insulin-like growth factor 1 receptor;
39 IgG, immunoglobulin G-like folds; IR-A, Insulin receptor isoform A; IRS, insulin receptor substrate 1;
40 LC3; Microtubule-associated protein 1A/1B-light chain 3; LRR, leucine-rich repeat; MAPK, Mitogen
41 activated protein kinase; MMP, Matrix metalloproteinase; mTOR, mechanistic target of rapamycin;
42 OXPHOS, oxidative phosphorylation; p70S6K, Ribosomal Protein S6 Kinase, 70kDa; PDGFR,
43 Platelet derived growth factor receptor; Peg3, Paternally expressed gene 3; PGC-1 α , Peroxisome
44 proliferator activated receptor γ co-activator-1 α ; PI3K, phosphoinositide 3 kinase; PINK1, PTEN-
45 induced putative kinase-1; PKB/Akt, Protein kinase B; Rheb, Ras homolog enriched in brain; RhoA,
46 Ras homolog gene family, member A; ROCK1, Rho-associated, coiled -coil-containing protein kinase
47 1; RRM, RNA recognition motif; RTK, receptor tyrosine kinase; SLRP, small leucine-rich proteoglycan;
48 TGF- β 1, Transforming growth factor beta 1; TIMP3, Tissue inhibitor of metalloproteinases 3; TSP1,
49 Thrombospondin 1; VDAC, Voltage-dependent anion channel; VEGFA, vascular endothelial growth
50 factor A; VEGFR2, vascular endothelial growth factor receptor 2; Vps34, Vacuolar Protein Sorting 34.

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69 **Abstract**

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

82

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

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140 **1. Introduction**

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

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

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

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

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

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

185

186 *1.1. General considerations: Decorin as an oncosuppressive entity*

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

190

191 *1.1.1. Localization and expression patterns of decorin within the tumor*

192 Despite a large literature describing decorin as an oncosuppressive proteoglycan [12,13,31,54], there
193 are still several incongruencies that need to be addressed. In particular, the absence of decorin in the
194 breast tumor stroma has been established as an important clinical prognosticator of invasive and
195 metastatic breast cancer [10,55-57] as well as in soft tumors [58]. A similar reduction of decorin
196 expression is seen in the microenvironments of low- and high-grade urothelial carcinoma [59] as well
197 as in the plasma of multiple myeloma and MGUS patients [60], cases of esophageal squamous cell
198 carcinoma [61] and instances of colon cancer [53]. An *in silico*-based query utilizing
199 immunohistochemical arrays spanning a variety of tissues has detected a marked reduction of decorin
200 expression in the stroma of many solid malignancies, including breast [62]. Other studies seemingly
201 report the opposite result inasmuch as certain tumor types, including colon and breast carcinomas
202 [54], have elevated amounts of stromally-deposited decorin. Functionally, the increased caches of
203 decorin within these tumors may still negatively regulate growth by physically constraining the tumor
204 (e.g. desmoplastic-type reaction) as well as acting in a paracrine manner to downregulate the
205 adjacent RTKs present on the tumor cell surface. As it pertains to the tumor proper, several studies
206 have clearly demonstrated a complete loss of decorin expression in several tumor types, such as
207 urothelial, prostate, myeloma, and hepatic carcinoma [63-68]. Utilizing an unbiased deep RNA
208 sequencing method of hepatocellular carcinomas, several prominent matrix constituents were
209 decreased, including decorin [69]. Moreover, poorly differentiated sarcomas completely lack decorin in

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

212

213 1.1.2. Genetic and cell biological evidence for decorin as a soluble tumor repressor

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

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

239

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

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

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

254 255 *2.1. The LRR constitutes the basic unit of decorin structure and function*

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

265 This fundamental LRR architecture permits a plastic interface capable of coordinating a myriad of
266 protein-protein interactions. Indeed, this hallmark is crucial for the widespread functionality of decorin
267 [95], and related SLRPs, and is mediated by residues located on the internal surface of the protein
268 [15]. Moreover, each LRR confers various functional properties for the well-established bioactivities of
269 decorin. For example, LRR XII binds CCN2/CTGF [30], LRR V/VI aid in the binding of decorin to
270 VEGFR2 [96], and the collagen binding sequence (SYIRIADTNIT) of LRR VII, located on the interior
271 surface of the solenoid [97], mediates direct binding of decorin to type I collagen (Fig. 1A). A feature
272 of decorin, also shared by Class I-III SLRPs, is the presence of an elongated (~30 amino acids) LRR
273 known as the “ear” repeat (Fig. 1A). In decorin, this is found in the penultimate LRR, LRR XI.
274 Interestingly, truncation or mutations arising in the ear repeat of decorin cause congenital stromal
275 corneal dystrophy [20,98]. Mechanistically, mouse models of decorin lacking this ear repeat trigger
276 intracellular accumulation of decorin within the endoplasmic reticulum, thereby causing ER stress, and
277 compromising proper corneal collagen deposition and assembly [99].

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

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

292

293 *2.2. Decorin is a soluble pan-RTK inhibitor and binds multiple cell surface receptors*

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

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

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

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

324

325 *2.3. Decorin is pro-inflammatory by engaging TLR2/4 on the surface of macrophages*

326 It is becoming evident that soluble decorin can regulate the innate immune response [33] via toll-
327 like receptors 2 and 4 (Fig. 1B) and is considered a damage-associated molecular pattern member
328 [107]. This pro-inflammatory property is analogous to that of circulating biglycan [108,109]. Via high-
329 affinity interactions, decorin engages TLR2/4 and promotes a pro-inflammatory state by triggering the
330 synthesis and secretion of TNF- α and IL-12p70 [33]. Indirectly, via the formation of decorin/TGF- β
331 complexes, anti-inflammatory mediators (such as IL-10) are translationally suppressed by PDCCD4
332 [33]. Thus, circulating decorin is a pro-inflammatory proteoglycan for innate immune modulation [33].
333 It has emerged that biglycan is a viable biomarker of inflammatory renal diseases [110]. Likewise,
334 cancer patients have significantly increased levels of circulating decorin [33], positing decorin as a
335 desirable therapeutic target.

336

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

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

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

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

356

357 *3.1. Decorin binds EGFR for tumor cell cycle arrest and apoptosis*

358 The concept of decorin-mediated RTK-antagonism was pioneered following the discovery that EGFR
359 is a main target [118] and that decorin represents an endogenous ligand for receptor occupancy and
360 modulation [119]. In mouse models carrying A431 orthotopic tumor xenografts, it was established that
361 decorin, by targeting EGFR, significantly subverts tumorigenic growth *in vivo* [120]. Decorin indirectly
362 inhibits Her/ErbB2 activity [121], potentially via the titration of active ErbB1/ErbB2 dimers [54]. Decorin
363 also directly binds and represses ErbB4/STAT3 signaling [122] in the central nervous system.
364 Mechanistically, decorin triggers transient activation of downstream ERK1/2 signaling (following
365 stimulation of the innate EGFR kinase) [87] concurrent with a regulated burst of cytosolic Ca²⁺ [123].
366 Paradoxically, positive EGFR/MAPK signaling (despite total EGFR being reduced by >50%) evokes
367 induction of the cyclin-dependent kinase inhibitor, p21^{WAF1} with concomitant conversion of pro-
368 caspase-3 into active caspase 3 [87]. Collectively, this promotes cell cycle arrest and induces the
369 intrinsic apoptotic pathway, respectively (Fig. 2). Imperative for the protracted function of decorin,
370 decorin/EGFR complexes are shuttled into caveolin-1 coated pits [31]. Specific phospho-residues are
371 required for the association of caveolin-1 with EGFR [124] and internalized via endocytosis for
372 degradation. This system prevents recycling of EGFR for additional rounds of signaling, in contrast to
373 active ligands which sort EGFR into clathrin-coated pits. This leads to endosomal recycling and,
374 ultimately, to repopulation of the cell surface with activated EGFR for additional signal transduction
375 (Fig. 2).

376

377 *3.2. Decorin evokes oncoprotein degradation and suppresses angiogenesis via Met*

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

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

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

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

417 is likely that this indirect activity of decorin in malignant cells could have a protective role against
418 cancer growth and metabolism. Taken together, decorin differentially regulates potent angiokines
419 [139] that favor silencing rampant tumor neovascularization, thereby contributing further to the
420 ascribed anti-tumorigenic and anti-metastatic properties.

421

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

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

435

436 *4.1. Decorin evokes endothelial cell autophagy in a Peg3-dependent manner*

437 Using the decorin-treated breast carcinoma xenografts described above, several novel tumor-derived
438 genes were discovered [88]. Among these genes, the genomically-imprinted zinc-finger transcription
439 factor, *PEG3* [140-143] was selected [88]. Previously, Peg3 has been implicated in regulating stem
440 cell progenitors [144,145], mediating p53-dependent apoptosis of myogenic and neural lineages [146-
441 150], and maternal/paternal behavioral patterns [151,152]. Peg3 has been implicated in the
442 pathogenesis of cervical and ovarian carcinoma as its expression is frequently lost via promoter
443 hypermethylation and/or loss of heterozygosity [153-156]. Thus, Peg3 is considered a *bona fide* tumor
444 suppressor [157]. Importantly, Peg3 represents another tumor suppressor induced by decorin in
445 addition to mitostatin and Beclin 1 (see below). Moreover, in analogy to decorin bioactivity in cancer
446 cells, Peg3 non-canonically suppresses the Wnt/ β -catenin pathway [158].

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

452 structures reminiscent of autophagosomes [159] in primary endothelial cells (HUVEC). Co-
453 immunocolocalization and co-immunoprecipitation studies of canonical autophagic markers, e.g.,
454 Beclin 1 and LC3 [160,161], and Peg3 have clearly demonstrated that decorin evokes a novel gene
455 involved in autophagy initiation [159] (Fig. 3, *left*). Intriguingly, Peg3 is required for decorin-mediated
456 *BECN1* and *MAP1LC3A* expression and is responsible for maintaining basal levels of Beclin 1
457 [159,162]. Mechanistically, decorin promotes a competent pro-autophagic signaling composed of
458 Peg3, Beclin 1 and LC3 while combinatorially precluding Bcl-2, a known autophagic inhibitor [163]. At
459 the endothelial cell surface, decorin engages VEGFR2, the central receptor for endothelial cells, for
460 autophagic induction [159] (Fig. 3, *left*). Pharmacological inhibition with the small molecule inhibitor
461 (SU5416) abrogates the autophagic response, suggesting that decorin requires the VEGFR2 kinase
462 for successful autophagy [159,162]. Downstream of stimulated VEGFR2, decorin differentially
463 regulates decisive signaling complexes by activating pro-autophagic modules (e.g. AMPK α and
464 Vps34) while concurrently attenuating, in a protracted fashion, anti-autophagic nodes (e.g.
465 PI3K/Akt/mTOR) [164] (Fig. 3, *left*). Concomitant with autophagic initiation, decorin also impairs
466 capillary morphogenesis [78,79,159]. Therefore, it is plausible that decorin evokes autophagy as the
467 molecular underpinning for suppressing tumor angiogenesis from the perspective of endothelial cell-
468 driven angiogenesis (Fig. 3, *left*).

469

470 *4.2. Decorin induces tumor cell mitophagy in a mitostatin-dependent manner*

471 As a novel constituent of the multi-pronged approach for curtailing tumorigenesis and halting
472 angiogenesis (differential modulation of pro- and anti-angiogenic factors and induction of endothelial
473 cell autophagy) decorin directly influences catabolic programs and organelle turnover within the tumor
474 proper (Fig.3, *right*). Induction of tumor cell mitochondrial autophagy (mitophagy) [165] may
475 functionally reconcile the canonical tumoricidal effects of decorin with the emerging biology of matrix-
476 mediated autophagic induction for retarding tumorigenic and angiogenic progression. In a mechanism
477 analogous to that of VEGFR2, decorin requires the kinase activity of Met for proper mitophagic
478 induction in breast carcinoma cells [165] (Fig. 3, *right*). Both forms of autophagic induction require the
479 presence of a cell surface receptor (VEGFR2 or Met) and the intrinsic kinase activity of referenced
480 receptor. At the nexus of decorin-evoked mitophagy is a poorly characterized tumor suppressor gene
481 known as mitostatin or trichoplein (mitostatin has the HuGO gene symbol, *TCHP*, and is located on
482 chromosome 12q24.1). Mitostatin was originally identified as a decorin-inducible gene using
483 subtractive hybridization and probes from decorin-transfected (and thereby, growth suppressed) cells
484 [166]. Notably, mitostatin is downregulated in bladder and breast carcinomas [166,167], suggesting
485 that it might represent a potential tumor suppressor gene. Mitostatin primarily resides at the outer
486 mitochondrial membrane [167] and at specialized membrane:membrane contact sites at the

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

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

499 The process of decorin-evoked mitophagy depends on the presence and yet-to-be-elucidated-
500 function of mitostatin [165] (Fig. 3, *right*). RNAi-mediated silencing of mitostatin prevents turnover of
501 respiratory chain components (OXPHOS), decreased mtDNA content, VDAC clearance, and collapse
502 of the mitochondrial network [165], all established markers of mitophagy [172]. Moreover, failure of
503 mitophagic induction precludes the ability of decorin in suppressing VEGFA expression and protein
504 [165] (Fig. 3, *right*), suggesting that mitophagy is key for understanding a fundamental hallmark of
505 decorin biology. Subsequent to the collapse and aggregation of the tubular mitochondrial network,
506 decorin triggers mitochondrial depolarization [165], with an activity comparable to that of an
507 established depolarization agent (FCCP). This loss of membrane potential across the outer and inner
508 mitochondrial membrane is a harbinger for mitochondrial dysfunction and eventual turnover [173,174].
509 Depolarized mitochondria may be the end product of increased Ca⁺² levels as occur downstream from
510 decorin/EGFR interactions [123]. As mitostatin is positioned at mitochondrial-associated membrane
511 and interacts with Mfn-2, it may permit an efflux of Ca⁺² from the ER directly into the mitochondria as
512 the initial event for decorin-evoked mitophagy.

513 In either scenario, depolarization of the mitochondria triggers recruitment of the PINK1/Parkin
514 complex for eventual clearance of the damaged organelle. The E3-ubiquitin ligase, Parkin is strictly
515 required for proper mitochondrial homeostasis, as recessive mutations in Parkin are found in the
516 neurodegenerative disease, Parkinson's [173,175,176]. It remains plausible that mitostatin may
517 interact with or facilitate the conscription of PINK1/Parkin for mitochondrial turnover (Fig. 3, *right*).
518 Alternatively, mitostatin may directly stimulate the inherent PINK1 kinase activity for proper
519 recruitment, ubiquitin activation [177,178], and/or Parkin-mediated ubiquitination of target
520 mitochondrial proteins [179-181]. Indeed, this axis is key for recycling respiratory chain complexes
521 [182,183].

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

528

529 **5. Gene and protein therapy in various preclinical tumor studies**

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

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

544

545 **6. Conclusions**

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

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

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

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

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

592

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1178 **Figure Legends**

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1180 **Fig. 1.** The solved crystal structure of decorin permits association with a multitude of cell surface
1181 receptors. (A) Cartoon ribbon diagram of monomeric bovine decorin rendered with PyMol v1.8. (PDB
1182 accession #: 1XKU). Vertical arrows designate β -strands whereas coiled ribbons indicate α -helices.
1183 Roman numerals situated above the diagram define each LRR from left to right, by convention. The
1184 type I collagen binding sequence has been included and is shaded yellow. (B). Schematic depiction of
1185 the various RTKs and innate immune receptors that decorin engages. Please, consult the text for
1186 additional information.

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1188 **Fig. 2.** EGFR and Met coordinate growth inhibition, apoptosis, and angiostasis. Schematic
1189 representation of the signaling pathways modulated in response to decorin binding. Please, consult
1190 the text for additional information.

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1192 **Fig. 3.** VEGFR2 and Met evoke endothelial cell autophagy and tumor cell mitophagy. Schematic
1193 representation delineating the signaling pathways active in response to decorin acting as a partial
1194 agonist of VEGFR2 or Met for endothelial cell autophagy or tumor cell mitophagy induction,
1195 respectively. Please, consult the manuscript for additional information concerning these pathways.

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1213 **Table 1**

1214 Pre-clinical studies exploiting several delivery mechanisms for decorin as a therapeutic modality
1215 against cancer and across multiple species.

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

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