Review

Pivotal role for decorin in angiogenesis

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Abstract

Angiogenesis, the formation of new blood vessels from preexisting vessels, is a highly complex process. It is regulated in a finely-tuned manner by numerous molecules including not only soluble growth factors such as vascular endothelial growth factor and several other growth factors, but also a diverse set of insoluble molecules, particularly collagenous and non-collagenous matrix constituents. In this review we have focused on the role and potential mechanisms of a multifunctional small leucine-rich proteoglycan decorin in angiogenesis. Depending on the cellular and molecular microenvironment where angiogenesis occurs, decorin can exhibit either a proangiogenic or an antiangiogenic activity. Nevertheless, in tumorigenesis-associated angiogenesis and in various inflammatory processes, particularly foreign body reactions and scarring, decorin exhibits an antiangiogenic activity, thus providing a potential basis for the development of decorin-based therapies in these pathological situations.

Introduction

Angiogenesis, the formation of new blood vessels from preexisting vessels through sprouting or intussusception, is a fundamental process in mammalian reproduction, development, and wound repair [1–3]. Angiogenesis also plays a critical role in a variety of pathological situations including malignant, inflammatory, and ischemic disorders [4]. Furthermore, there is an association between angiogenesis, scarring, and fibrosis [5].

For some time, we have understood that in addition to soluble molecules, particularly growth factors such as vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), and several other growth factors, insoluble extracellular matrix (ECM) macromolecules are of great importance in the angiogenic process [6–8]. Indeed, today we know that the structure of the ECM in itself has a great impact on angiogenesis via directly or indirectly regulating endothelial cell (EC) behavior [8–11]. Angiogenesis requires the generation of "activated migratory" ECs (tip cells) which guide the developing vascular sprout [12–15]. Remodeling of the ECM by ECs as angiogenesis proceeds enables initiation, formation, and finally, the stabilization of new blood vessels.

ECM and angiogenesis

A number of individual ECM macromolecules participate in angiogenesis, either promoting or restricting events involved in this process [6,8,9]. Different collagens such as types I, III, IV, and VI collagen [16–19], a variety of glycoproteins, particularly fibronectin [20,21], vitronectin [22], laminins [23] and matricellular proteins such as thrombospondin [24] and SPARC (Secreted Protein Acidic and Rich in Cysteine) [25] have been shown to contribute to angiogenesis. Furthermore, specific proteoglycans (PGs) and glycosaminoglycans (GAGs) including

the heparan sulfate PGs perlecan [26] and syndecans [27,28], the dermatan sulfate PGs decorin [29,30] and biglycan [14,31], the chondroitin sulfate PG versican [14,32,33], the keratan sulfate PGs fibromodulin [34] and lumican [35], and, finally, hyaluronan (HA) [7,36,37] are involved in angiogenesis as well. In addition, several proteolytically cleaved fragments of the matrix macromolecules, called matrikines and matricryptins, are active in modulating angiogenesis [8,14,33,38–41]. One of the most well-known examples of these cleavage products is the carboxyl terminal fragment of type XVIII collagen, called endostatin, which is a potent angiogenesis inhibitor [42]. Other similar cleavage products with antiangiogenic activity are canstatin and tumstatin, both derived from type IV collagen [43,44], endorepellin, the C-terminus of the heparan sulfate PG perlecan [45], and hyaluronan fragments [7,46]. Matrix macromolecules and/or their cleavage products can participate in angiogenesis at all different stages beginning with vascular sprouting and eventually ending in vessel stabilization [47].

Almost 30 years ago, we made the observation that ECs in confluent monolayer culture synthesized primarily biglycan, but not the highly homologous SLRP (small leucine-rich proteoglycan) family member decorin [48,49]. However, ECs switched to synthesis of decorin when they were stimulated to sprout and form tubes in vitro [29]. Subsequently, it was demonstrated that when ECs were co-cultured with fibroblasts in a collagen gel, they formed cord-like structures which was accompanied by a 100-fold increase in the synthesis of decorin [30].

In this review, we have focused on highlighting the multifunctionality of decorin in angiogenesis, as has become apparent over the last several years. We describe its role in regulating ECM stiffness and rigidity, in modulating angiogenic growth factor activation/deactivation, in binding to several cell surface receptors involved in angiogenesis and exciting new studies that highlight its role in autophagy as possible mechanism(s) by which this PG contributes to angiogenesis.

Decorin

Decorin, in earlier literature also called PG-II, PG-40 and PG-S2 [50–52], is the prototype molecule of the SLRP gene family that encompasses 18 members [53,54]. The name decorin originates from its ability to decorate collagen type I fibrils. Decorin has been shown to bind to the d and e bands of type I collagen via its core protein, “decoron,” thereby controlling fibril formation [55–57] and regulating mechanical properties of these fibrils [58]. The effects of decorin on fibrillogenesis are also true in vivo [59]. In addition, decorin has been suggested to play a regulatory role in several other biological and physiological processes such as myogenesis [60] and fetal membrane development [61] as well as tissue repair [62]. Notably, the importance of decorin in various pathological conditions e.g. cancer, is also established [63,64]. Decorin is mainly expressed by various mesenchymal cells, such as fibroblasts, chondrocytes, and smooth muscle cells [49,65], but in specific situations also by ECs as will be described below.

Decorin is usually composed of a core glycoprotein with the relative molecular weight of about 40 kDa and one either chondroitin or dermatan sulfate GAG side chain which is attached to the serine residue 4 [66,67] (Fig. 1). In the core protein of decorin, four distinct domains can be identified [68]. The first domain consists of a 14-amino acid signal peptide and a 16-amino acid propeptide, both of which are cleaved before decorin is secreted. The second domain that is rich in cysteine is the GAG side chain-

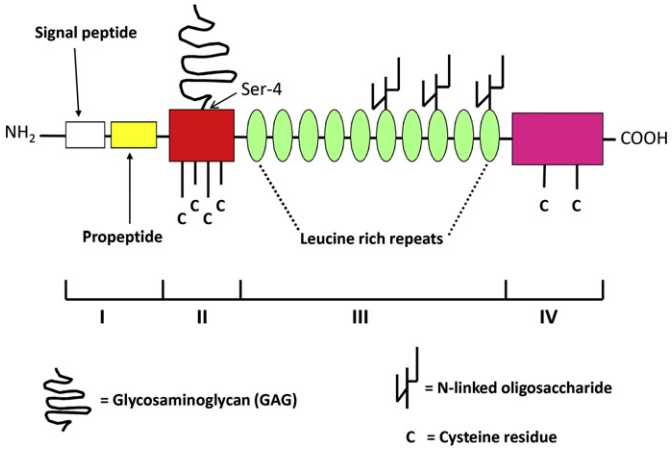

Fig. 1. Schematic drawing of the molecular structure of decorin. All four domains I–IV of decorin core protein are indicated (for details see the text). The GAG side chain attached to serine residue 4 of the second domain is also shown.

carrying domain. The third domain is the leucine-rich repeat region consisting of 10 repeats of 24 amino acids rich in leucine. This domain results in the three-dimensional structure of decorin resembling an arch [69], a typical architecture of all proteins with leucine-rich repeat motifs [70]. The fourth domain of the decorin core protein is the carboxyl terminal domain which contains two cysteine residues and a conserved disulfide loop. These structural features of decorin enable it to bind and interact with numerous other ECM macromolecules as well as with different growth factors and cytokines [63,68]. Furthermore, when in a soluble form, decorin can interact with certain cell surface receptors and thereby it can have a direct influence on intracellular signaling [54,71]. Both the core protein and the GAG chain are variously responsible for the different effects of decorin on cellular functions [72–74]. For example, the core protein of decorin can act as an inhibitor of tumor growth in different xenograft models such as breast and prostate cancers via downregulating the members of the ErbB receptor tyrosine kinase family [75,76]. The GAG chain, on the other hand, is able to influence migration of cells such as smooth muscle cells and melanoma cells via mechanisms including intracellular acidification [77,78]. In addition, the length of the decorin GAG chain affects matrix assembly by determining the distance between separate collagen fibrils [79], affecting angiogenesis [80]. Thus, as with most PGs, the bioactivity of decorin as a molecule must be considered as a sum of its parts [74].

Decorin in angiogenesis

Immunostaining for decorin is present in microvessels in human atherosclerotic plaques [81], in ECs in human granulomatous tissue [30], and in newly formed microvessels within the thickened intima of human arterial wall in giant cell arteritis [82], whereas decorin immunostaining is absent from the endothelium of resting capillaries [83]. Furthermore, decorin positive microvessels have been detected at the base of pseudoaneurysms in the temporal artery of human patients [84]. Decorin has also been found to be expressed in significant amounts around neovessels after varicose vein surgery in patients [85]. Alternatively, although decorin null mice do not exhibit any abnormalities in their vasculature [59], decorin deficiency causes impaired angiogenesis in the injured cornea of these animals [86]. Similarly, reduced decorin expression in oral squamous cell carcinomas and in human microvascular ECs leads to decreased angiogenesis [87,88].

While the studies described above suggest that decorin has a stimulatory role in the angiogenic response, there are several studies supporting the opposite view. Decorin inhibits endothelial tube formation in vitro, which is potentiated with the addition of thrombospondin [89]. Decorin suppresses angiogenesis in tumors [90] and is differentially expressed in human benign versus malignant vascular tumors [91]. Specifically, in Kaposi's sarcoma and angiosarcoma, both of which represent malignant vascular neoplasms, decorin expression is completely lacking, whereas in benign vascular tumors, namely in hemangiomas, where capillary growth has ceased, decorin is expressed in readily detectable amounts. In addition, there is an increase in vascular invasion in polyvinyl alcohol sponges implanted in decorin-deficient mice compared to vascular invasion in sponges implanted in wild-type control mice [92]. Studies have also demonstrated that even fragments of decorin can exhibit antiangiogenic activity, partially through the ability of these fragments to depress VEGF-induced focal adhesion kinase phosphorylation and assembly of focal adhesions [93]. In addition, overexpression of decorin retards corneal neovascularization via downregulation of proangiogenic molecules including VEGF [94]. Thus, growing evidence since the 1990s indicates a critical role for decorin in the angiogenic response, particularly angiogenesis associated with inflammatory processes and tumor growth. However, whether decorin's activity will be pro- or antiangiogenic appears to depend on the physiological or pathological condition of the tissue.

Potential mechanism(s) for decorin in angiogenesis

There are a number of ways by which decorin can influence angiogenesis in either positive or negative ways. It may interact with various ECM macromolecules promoting assembly of a complex ECM and preventing turnover, enabling the formation of an ECM conducive for angiogenesis [59,95–99]. For example, decorin is known to control collagen fibril formation of, e.g., type I collagen [57] and type I collagen fibrils, in turn, provide a template for vascular tube formation when in contact with the apical side of the endothelium, thus promoting angiogenesis. The interaction of decorin with collagen fibrils also makes decorin resistant to proteolytic attack, resulting in a more stabilized fibrillar network [100]. Binding of decorin to the matrix proteins not only leads to the stabilization of the fibrillar network, but concomitantly causes alterations in the biomechanical properties of the ECM, particularly in the tensile strength and rigidity of the matrix [58,97,101]. Stiffness and rigidity are two central properties of the ECM that are known to influence angiogenesis [12,102].

While decorin can promote the formation and maintenance of the highly-ordered structures of fibrillar proteins, it may also have a role in either preserving

or destroying these fiber systems. Indeed, the core protein of decorin is capable of stimulating the expression of matrix metalloproteinase-1 (MMP-1) [103,104], a collagenase that is highly active during angiogenesis. This protease promotes the expression of vascular endothelial growth factor receptor-2 (VEGFR2) through stimulation of protease activated receptor-1 (PAR-1) and activation of nuclear factor-κB (NF-κB) [105]. Decorin also stimulates the synthesis of another collagenase, namely MMP-2 [106], that degrades type IV collagen, the major structural component of basement membranes. Similarly to MMP-1, MMP-2 has been reported to enhance vascular proliferation. On the other hand, decorin is able to stimulate synthesis of tissue inhibitors of matrix metalloproteinases (TIMPs), particularly TIMP-2 [106] and TIMP-3 [107], which both decrease angiogenesis [108–110].

Decorin can also influence cell-ECM interactions by affecting the integrin adhesion receptors. For example, decorin modulates the activity of α2β1 integrin [99]. More specifically, decorin can allosterically modulate α2β1 integrin's collagen binding activity by interacting with the α2 subunit of this integrin via its GAG moiety and/or core protein [111]. Furthermore, decorin can influence the expression of integrins. $DCN^{-/-}$ fibroblasts treated with decorin have reduced expression of α2β1 integrin [112]. In addition, in human airway smooth muscle cells, decorin increases the synthesis of integrin α_v subunit [113] that together with β3 subunit is abundantly expressed on angiogenic ECs, but not on normal, quiescent ECs [114]. However, although α_vß3 integrin has been suggested to play a key role in angiogenesis [115], there is currently no published data to demonstrate that decorin influences the expression or function of this integrin in ECs. Nevertheless, study of decorin's role in the regulation of integrin activity and function provides an intriguing field of angiogenic research.

Decorin may also impact angiogenesis by binding directly to other cell surface receptors or signaling molecules involved in angiogenesis. Currently decorin is known to be a ligand for several tyrosine kinases including the epidermal growth factor receptor (EGFR) [116,117], Met, which is the receptor for the hepatocyte growth factor (HGF) [118], insulin-like growth factor receptor-I (IGF-IR) [119–121] and VEGFR2 [122]. Furthermore, decorin has been suggested to bind to platelet derived growth factor receptor (PDGFR), but further studies are still required to confirm this [123]. Engagement of decorin with cell surface receptors can either activate or inhibit the function of the receptor [99,120], depending on the physiological state of the tissue. In disease, decorin is more likely to have an antagonizing effect on the aforementioned receptors [107,121,124].

Decorin also influences the expression and bioavailability of several angiogenic growth factors and cytokines. For example, decorin binds to VEGF and may impact the availability and activity of this angiogenic factor. Evidence is available that decorin-expressing sarcoma cells produce reduced amounts of VEGF, leading to suppressed tumor-cell mediated angiogenesis [90]. Similarly, virus-mediated decorin gene delivery decreases angiogenesis in the cornea of rabbits via downregulating VEGF expression, in addition to downregulating the expression of two other proangiogenic molecules, namely monocyte chemoattractant protein-1 (MCP-1) and angiopoietin [94]. However, others have found decorin to have the opposite effect on VEGF expression. In dysplastic and malignant oral epithelial cells aberrantly expressing nuclear localized decorin, knockdown of decorin expression attenuates angiogenesis via simultaneously silencing angiogenic mediators including VEGF [125]. Consistent with this finding, in fetal growth restriction, where decorin expression is decreased, VEGF-A expression as well as angiogenesis are decreased [88]. Additionally, mouse cerebral ECs treated with decorin stimulate VEGF expression via activation of specific transcription factors resulting in increased angiogenesis [126]. It still remains to be verified whether these observed effects of decorin on angiogenesis are truly VEGF-dependent. Thus, more in-depth studies are needed to decipher the molecular mechanism(s) involved in decorin's role in either stimulating or inhibiting angiogenesis through VEGF pathways.

Another growth factor vital not only in fibrosis [127] but also in angiogenesis is TGF-β [128–133]. Decorin can bind TGF-β and neutralize its activity [134–137]. Hence, the bioavailability of TGF-β is markedly under the control of decorin. Indeed, degradation of decorin by different proteases (e.g., MMP-2, −3 and −7 and granzyme B) releases sequestered TGF-β and restores its bioavailability [138,139]. Furthermore, overexpression of decorin inhibits TGF-β expression [140,141]. However, it still has to be clarified whether there is a causal relationship between decorin and TGF-β in the regulation of angiogenesis.

In addition to VEGF and TGF-β, decorin interacts with several other angiogenic growth factors, including platelet derived growth factor (PDGF) [123,142,143], fibroblast growth factor (FGF) [93,144], insulin-like growth factor (IGF) [120,121,145], connective tissue growth factor (CTGF) [146–148], and HGF [118,149]. Furthermore, decorin influences the availability of the proangiogenic factor angiopoietin, as well [94]. A summary of studies addressing the involvement of decorin in regulating the activity and availability of angiogenic growth factors is presented as Table 1 and diagrammatically as Fig. 2.

Apart from different angiogenic growth factors, decorin has also been shown to markedly contribute to the regulation of angiogenic cytokine expression [150]. Cytokines form a group of small proteins

Table 1. Angiogenic growth factors regulated by decorin.

Molecule	Abbreviation	Relationship with decorin	Reference
Angiopoietin	ANG	Inhibition by decorin	[90]
Connective tissue growth factor	CTGF	Induces decorin synthesis/decorin regulates CTGF activity in fibrotic conditions	[142–144]
Fibroblast growth factor	FGF	Decorin promotes activity after injury/inhibition by decorin	[140,89]
Hepatocyte growth factor	HGF	Inhibition by decorin	[114,145]
Insulin-like growth factor	IGF-I	In normal cells, DCN activates IGF-I/in transformed cells, decorin inhibits IGF-I activation	[116,117,141]
Platelet derived growth factor	PDGF	Inhibition by decorin	[119,138,139]
Transforming growth factor beta	TGF-β	Inhibition by decorin	[131,133,136]
Vascular endothelial growth factor	VEGF	Inhibition by decorin	[86,89,90]

(5–20 kDa) including chemokines, interferons, and interleukins that are vitally important for the immune system and the inflammatory process, and as such, they also play a crucial role in a variety of pathologies and associated phenomena, such as angiogenesis [151,152]. The finding that decorin is capable of downregulating the expression of chemokines, particularly MCP-1 [94], suggests that decorin potentially attenuates inflammation-associated angiogenesis [153]. In line with this, decorin could also decrease inflammation-associated angiogenesis by potentiating the activity of interferons, particularly interferon-γ, a well-known antiangiogenic molecule [154,155]. However, being an endogenous ligand of toll-like

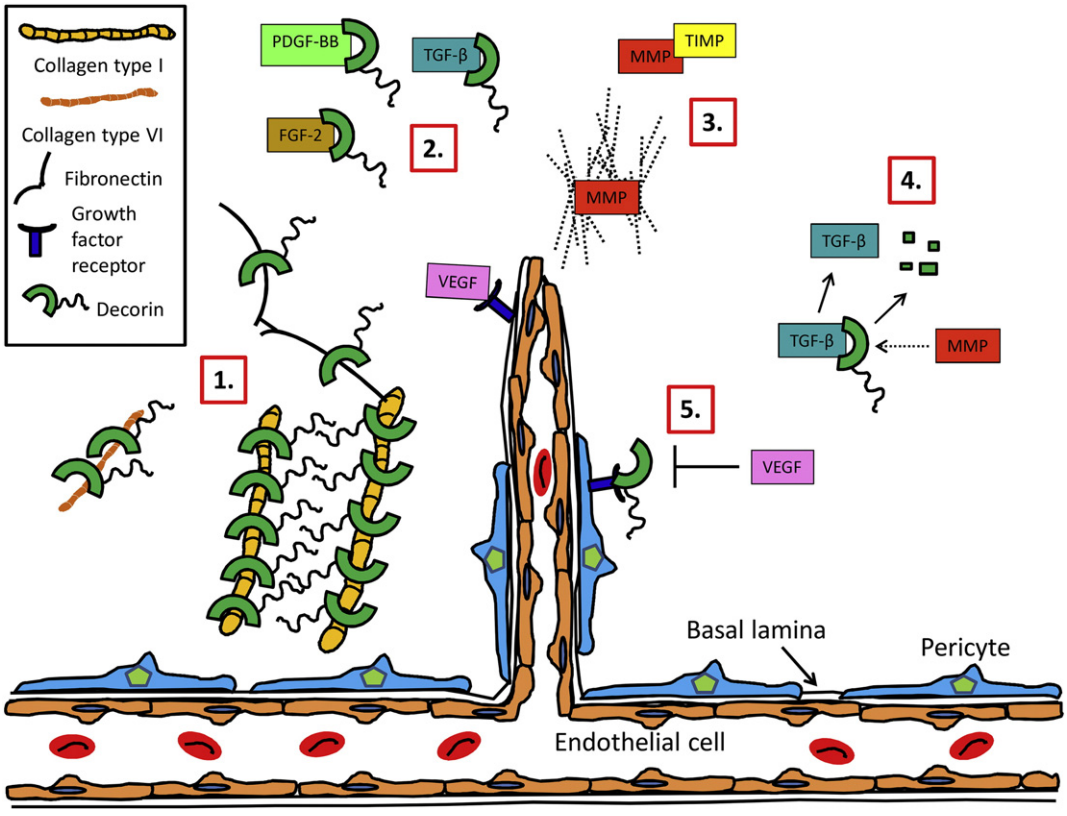

Fig. 2. Interaction of decorin with various ECM macromolecules and growth factors in the modulation of angiogenesis. (1.) Decorin is able to bind to other ECM macromolecules, especially types I and VI collagen, and fibronectin, and to modulate rigidity and stiffness of the ECM. (2.) By sequestering growth factors to the ECM, decorin can inhibit their angiogenic activity. (3.) Decorin can regulate the expression of specific MMPs and TIMPSs thereby influencing the structure and mechanochemical properties of the ECM. MMPs degrade the ECM structure and provide room for vascular sprouting while TIMPs inhibit the activity of MMPs. (4.) MMPs can free decorin-bound growth factors thus restoring their angiogenic activity. (5.) Decorin is also able to bind to growth factor receptors thus blocking their interaction with their natural ligands and their subsequent activation.

receptors 2 and 4 in macrophages, decorin stimulates the expression of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), and simultaneously reduces the expression of anti-inflammatory interleukin-10 (IL-10) [150]. This suggests that decorin plays a dual role in inflammation and consequently also a double role in inflammation-associated angiogenesis [82,92].

A completely new mechanism whereby decorin may be linked with the regulation of angiogenesis is its role in autophagy [156]. Autophagy is the major intracellular catabolic mechanism whereby unnecessary or dysfunctional cytosolic components, proteins, and organelles are degraded by lysosomes leading to cellular renovation and homeostasis [157]. Interestingly, angiogenesis inhibitors are known to activate autophagy in ECs [158]. Regarding decorin, its soluble form has been shown to cause autophagy in both microvascular and macrovascular ECs leading to decreased angiogenesis [159]. Mechanistically, this effect of decorin on EC autophagy has been shown to be mediated via direct interaction with VEGFR2 which causes activation of adenosine monophosphate (AMP) kinase signaling and inactivation of mTOR (mammalian target of rapamycin) [156,160]. AMP kinase phosphorylation leads to modulation of paternally-expressed gene 3 (Peg3), a key player in autophagy that then goes on to control the expression of beclin 1 and microtubule-associated protein 1A/1B-light chain 3 (LC3) [159–161].

Decorin may also modulate angiogenesis via influencing apoptosis of ECs. Originally, decorin has been suggested to have an antiapoptotic effect on ECs during angiogenesis [30]. However, it was later shown that the peptides derived from the decorin leucine-rich repeat cause induction of EC apoptosis concomitantly with the inhibition of EC tube formation [93]. The apoptosis-promoting activity of decorin has also been described for other cells, particularly for malignant cells such as breast cancer, cholangiocarcinoma, and hepatocellular carcinoma cells [162–164]. Thus, the action of decorin on EC apoptosis may be context-dependent [165].

Therapeutic potential of decorin as an angiogenic modulator

As we have discussed above, decorin can impact angiogenesis in multiple ways. Although decorin has variously been shown to either promote or inhibit angiogenesis, its effect on tumorigenesis-associated angiogenesis has been shown to be an inhibitory one [90,91,166]. Because tumor growth and metastasis are crucially dependent on angiogenesis [167], the development of new decorin-based adjuvant therapies in malignancies is rational despite the fact that antiangiogenic drugs and therapies have not yet produced widespread or enduring clinical benefits [168]. In addition to inhibiting angiogenesis in tumors, decorin has been shown to inhibit angiogenesis associated with foreign body reactions [92]. This provides a mechanistic basis for why decorin would be a very promising biological agent to prevent scarring [5,169]. The multifunctional nature of decorin also enables it to be a potential therapeutic agent for a variety of other pathologies, even for those which are not angiogenesis-dependent. These pathologies include glomerulonephritis [140] and peritoneal fibrosis [170], both of which are highly dependent on TGF-β. On the other hand, therapeutic use of decorin as an angiogenesis-promoting molecule has also been indicated. For example, after partial hepatectomy in fibrotic mice, decorin has been found to accelerate liver generation [171].

Conclusion

Angiogenesis is the result of a dynamic interplay between numerous molecules in the ECM and cellular milieu. In this review, we have focused on the role and potential mechanisms of the multifunctional SLRP decorin in angiogenesis. We have aimed to convince the reader that decorin is not only associated with angiogenesis, but more importantly, it plays a causal role in this process. Furthermore, depending on the molecular microenvironment where angiogenesis is induced, decorin can either promote or inhibit angiogenesis. This regulation occurs via mechanisms involving decorin's ability to interact with and modulate the actions of other ECM macromolecules, a variety of growth factors and cytokines as well as certain cell surface receptors. Thus, it is clear that decorin impacts the life and death of endothelial cells and may have therapeutic potential to regulate the angiogenic response.

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This article is dedicated to the late Elke Schönherr, MD, PhD, who, together with Dr. Järveläinen, did her postdoctoral work in 1988–1991 in the laboratory of Thomas N. Wight at the University of Washington in Seattle. Elke passed away far too early in her career

(August 7, 2005), but her work has stimulated all of us to think about proteoglycans, such as decorin, as effectors of cell behavior and to recognize that single components of the ECM can regulate specific events in homeostasis and in disease. Her contributions have laid the foundation for much of the outstanding work on this molecule that has followed.

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Abbreviations used:
VEGF, vascular endothelial growth factor;
TGF-β, transforming growth factor-β;
ECM, extracellular matrix;
EC, endothelial cell;
SPARC, secreted protein acidic and rich in cysteine;
PG, proteoglycan;
GAG, glycosaminoglycan;
SLRP, small leucine-rich proteoglycan;
MMP-1, matrix metalloproteinase-1;
VEGFR2, vascular endothelial growth factor receptor-2;
PAR-1, protease activated receptor-1;
NF-κB, nuclear factor-κB;
TIMPs, tissue inhibitors of matrix metalloproteinases;
EGFR, epidermal growth factor receptor;
HGF, hepatocyte growth factor;
IGF-IR, insulin-like growth factor receptor-I;
PDGFR, platelet derived growth factor receptor;
MCP-1, monocyte chemoattractant protein-1;
PDGF, platelet-derived growth factor;
FGF, fibroblast growth factor;
IGF, insulin-like growth factor;
CTGF, connective tissue growth factor;
TNF-α, tumor necrosis factor-α;
IL, interleukin;
AMP, adenosine monophosphate;
mTOR, mammalian target of rapamycin;
Peg3, paternally-expressed gene 3;
and LC3, light chain 3.

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