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Review

Biological functions of decorin in cancer

Xiu-Li Bi[1] and Wancai Yang[2,3]

Abstract

Decorin is a member of the extracellular matrix small leucine-rich proteoglycans family that exists and functions in stromal and epithelial cells. Accumulating evidence suggests that decorin affects the biology of various types of cancer by directly or indirectly targeting the signaling molecules involved in cell growth, survival, metastasis, and angiogenesis. More recent studies show that decorin plays important roles during tumor development and progression and is a potential cancer therapeutic agent. In this article, we summarize recent studies of decorin in cancer and discuss decorin's therapeutic and prognostic value.

Key words Decorin, cancer, proliferation, angiogenesis, metastasis, prognosis, therapy

Decorin is a member of the extracellular matrix (ECM) small leucine-rich proteoglycan (SLRP) family of proteins[1]. Initially thought to act exclusively as structural components, SLRPs are now recognized as key players in cell signaling, influencing cellular functions such as proliferation, differentiation, survival, adhesion, migration, and inflammatory response[2,3]. Among all SLRPs, decorin is the most studied one in cancer and has been found to play a role in tumor development and progression, angiogenesis, and metastasis. Nevertheless, a role for other SLRPs in these processes cannot be excluded. In this review, we focus on the latest findings on decorin.

Decorin in Tumor Development and Progression

Early genetic studies suggest that a lack of decorin is permissive for tumor development. More specifically, crossing decorin-null mice with the p53-null mice caused early lethality of the double mutant animals because of massive organ infiltration by T-cell lymphoma[4]. A more recent publication from our group demonstrates that decorin can indeed act as a tumor suppressor gene in the intestinal epithelium. We found that approximately 30% of decorin-null mice developed spontaneous intestinal tumors, and this process was accelerated and amplified by subjecting the decorin-null mice to a Western diet enriched in fat and low in calcium and vitamin D. Tumor development involved down-regulation of p21 and p27 and up-regulation of β-catenin signaling[5]. Notably, decorin binds directly to epidermal growth factor receptor (EGFR) and down-regulates its activity, as well as the activity of other members of the ErbB family[6,7]. These receptors are overexpressed and/or mutated in many cancers, driving tumor progression[7-10]. Decorin competes with EGF for receptor binding on the surface of tumor cells. After binding decorin, the receptor dimerizes and subsequently undergoes caveolin-mediated internalization and degradation in the lysosomes[9]. Decorin inhibits tumor cell proliferation by evoking a signaling cascade distinct from EGF, possibly by inducing a different EGFR confirmation and selectively activating phosphotyrosines in the receptor autophosphorylation domain. In addition, decorin suppresses the activity of the ErbB2 and ErbB4 receptors via degradation[7,10]. Decorin also interacts with Met, the hepatocyte growth factor receptor, and induces transient receptor activation, recruitment of the E3 ubiquitin ligase c-Cbl, and rapid intracellular degradation of the receptor. Furthermore, decorin suppresses intracellular levels of β-catenin, a key downstream effector of Met, and inhibits cell migration and growth. Thus, by antagonistically targeting multiple tyrosine kinase receptors, decorin reduces primary tumor development and progression[11].

Authors' Affiliations: [1]School of Life Science, Liaoning University, Shenyang, Liaoning 110036, P. R. China; [2]Department of Pathology, Xinxiang Medical University, Xinxiang, Henan 453003, P. R. China; [3]Department of Pathology, University of Illinois at Chicago, IL 60563, USA.

Corresponding Authors:

Wancai Yang, Department of Pathology, Xinxiang Medical University, 601 East Jinsui Dadao, Xinxiang, Henan 453003, P. R. China. Tel: +86-373-3029106; Email: wancaiyang@xxmu.edu.cn.

Xiu-Li Bi, School of Life Science, Liaoning University, 66 Chongshan Middle Road, Shenyang, Liaoning 110036, P. R. China. Tel: +86-24-62202232; Email: xiulibi@gmail.com.

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Decorin in Tumor Angiogenesis

Another important step in cancer progression is angiogenesis, the process whereby new vessels grow from preexisting blood vessels. Decorin affects this process by inducing endothelial cell sprouting and activating intracellular pathways. Notably, by binding transforming growth factor-β (TGF-β), decorin interacts with TGF-β, preventing TGF-β from binding to its receptor, and therefore plays a significant role in tumor progression and angiogenesis[12]. Decorin can also play a proangiogenic role by facilitating endothelial cell adhesion and migration on type I collagen[13]. Specifically, decorin mediates adhesion by binding to α2β1 integrin and promoting the integrin-collagen interaction[14]. Interestingly, decorin mediates endothelial cell migration by modulating insulin-like growth factor (IGF)/insulin receptor 1 (IR1) signaling, confirming that the decorin/IGF-1R interaction plays a role in angiogenesis. By contrast, decorin has antiangiogenic activities in other experimental conditions. Two potential mechanisms may underlie these antiangiogenic activities: interfering with thrombospondin-1[14,15] or suppressing the production of endogenous vascular endothelial growth factor (VEGF) in tumor cells, which in turn attenuates migration and capillary-like formation of endothelial cells[15]. A more recent study showed that decorin antagonizes the angiogenic network in breast cancer cells via inhibition of Met, hypoxia inducible factor-1α (HIF-1α), and VEGFA, as well as induction of the angiostatic proteins thrombospordin-1 and tissue inhibitor of metallo-proteinases-3 (TIMP3)[16]. Thus, one of decorin′s roles in the microenvironment is the modulation of angiogenesis, albeit in a cell-specific context, upon the physiological or pathological stimulation.

Decorin in Tumor Metastasis

The involvement of decorin in metastasis is still open to investigation and is far from being resolved. However, because of its functions in the microenvironment and extracellular matrix, we postulate that decorin plays a significant role in tumor metastasis. Loss of E-cadherin promotes metastasis by inducing cancer cell disaggregation, activating specific downstream signal transduction pathways, and causing epithelial-mesenchymal transition (EMT), which facilitates metastasis. Our recent studies in decorin-null mice and increasing decorin expression in human colon cancer cells *in vitro* have demonstrated an interaction between decorin and E-cadherin, which may underlie another mechanism of the antimigratory and antimetastatic actions of decorin in colorectal carcinoma[5,11,17,18]. Interestingly, decorin has also been implicated in down-regulating the E-cadherin binding partner β-catenin *in vitro*, *in vivo*, and in xenograft models[5,11,18]. However, the full significance of this finding still needs to be explored.

Accumulating evidence suggests that the stromal-epithelial interaction is important for tumor progression and metastasis. Tumor stroma represents the surrounding normal ECM or the microenvironment of the tumor cell through which stromal and tumor cells talk[19]. Reduced decorin levels in cancer tissues might alter several signal pathways due to the well known interactions between decorin and the tyrosine kinase receptors described above. Alternatively, one could postulate that abundant expression of decorin may lead to an "organized" ECM, potentially providing a physical barrier against tumor cell metastasis. Indeed, there is a regulation among decorin and stromal components including matrix metalloproteinases (MMPs). An earlier study also indicated decorin may affect signaling via chemokine receptor CXCR4, possibly affecting metastasis[20].

Decorin as a Potential Anticancer Agent

Decorin syngerizes with carboplatin to inhibit ovarian cancer cell growth[21] but antagonizes the effects of carboplatin and gemcitabine on pancreatic cancer cells[22]. Considering that decorin can be administered alone or concomitantly with a variety of compounds, we anticipate that decorin will attract more interest in the future as an anticancer therapeutic agent. Several studies have explored decorin′s antitumor effects *in vivo*. Administration of decorin core protein in an A431 squamous carcinoma model resulted in decorin localizing specifically within the tumor, antagonizing EGFR activity, and inducing apoptosis[23]. Systemic injection of decorin reduced breast tumor growth and metabolism and halted metastatic spread to the lungs[24]. Earlier studies also show that decorin delivered by adenovirus slowed the growth of lung, squamous, and colon carcinoma tumor xenografts in immune-compromised mice[25,26]. Adenovirus-delivered decorin also slowed the growth of mammary adenocarcinoma and prevented metastatic spreading to the lungs by down-regulating ErbB2 receptor levels[25]. Ectopic expression of decorin in a rat glioma model prolonged the animals′ survival. Notably, the size of the tumors in that model was directly proportional to how early and how much decorin was expressed[27].

The finding that decorin antagonizes primary tumor growth and metastasis *in vivo* raises hope for clinical application. Decorin might be utilized in the near future as an adjunct "protein therapeutic" for solid tumors in which receptor tyrosine kinases play a key role. However, additional *in vivo* studies in other tumor models

are desirable. SLRPs, including decorin, are characterized by a protein core containing leucine repeats with a glycosaminoglycan chain, consisting of either chondroitin sulfate or dermatan sulfate [1]. Cancer cells and normal cells display a different set of glycoaminoglycans [28,29]. In particular, highly metastatic cell lines show the prevalence of chondroitin sulfate, but not dermatan sulfate. Future studies should also be undertaken to elucidate the functional interaction between decorin and existing anticancer chemotherapeutics to evaluate potential limitations.

Decorin as a Biomarker for Prognosis

There are very few studies on the prognostic significance of decorin expression levels. Because decorin expression is altered in several types of cancer, it is considered a possible prognostic marker in cancer patients. Reduced decorin levels were associated with poor prognosis in node-negative, invasive breast cancer [30] and some soft-tissue tumors [31]. Specifically, low decorin levels correlated with large primary breast tumor burden, high risk of early recurrence, and overall poor prognosis. Breast cancer patients with tumors high in EGFR and low in decorin had an even worse outcome. This reinforces the notion that decorin is a key player in EGFR signal modulation *in vivo*. Low decorin levels in liposarcomas and malignant peripheral nerve sheath tumors were also associated with low disease-free survival and overall survival rates [31]. A recent study suggested that stromal decorin expression provides additional prognostic value in breast cancer when used with established primary markers [32]. We foresee that decorin will attract more interest in the future as a promising prognostic marker for cancer patients.

Concluding Remarks

Decorin's biological activity is rather complex; it regulates multiple processes in the extracellular matrix and in tumor cells (Figure 1). Studies in mouse models and cancer patients suggest that decorin plays an important role throughout the tumor growth and development process and may be a promising antitumor agent. *In vivo* studies with more tumor models are desirable.

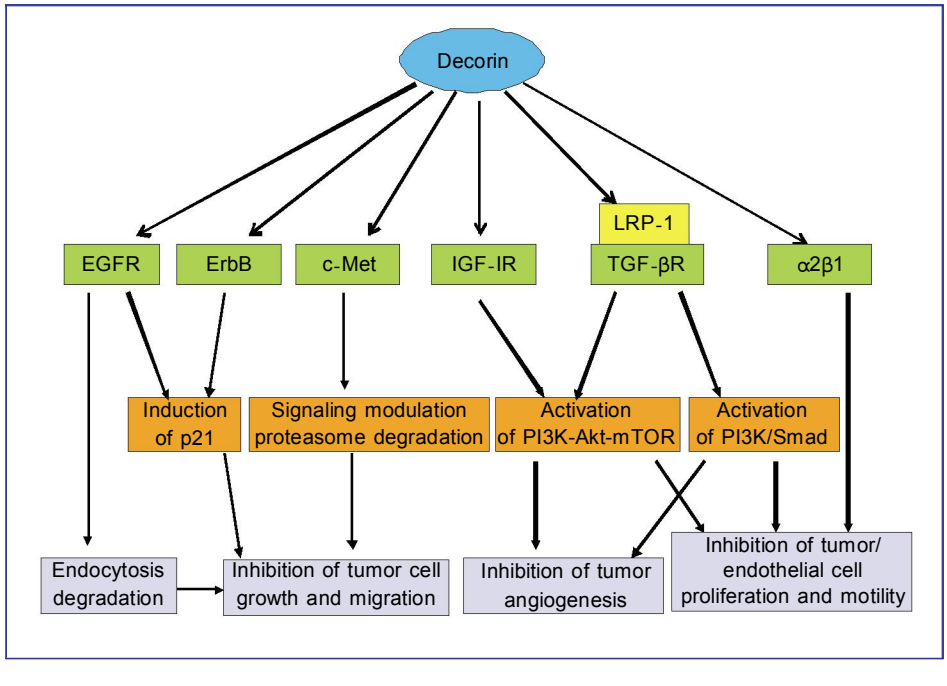

Figure 1. **Proposed biological functions and regulating targets of decorin in cancers.** Decorin interacts with EGFR, ErbB, c-Met, IGF-IR, TGFβR, and α2β1, respectively, leads to induction of p21WAF1, signaling modulation, proteasome deregulation, activation of PI3K/Akt/mTOR and PI3K/Smad signaling, finally causes degradation of endocytosis, inhibition of tumor cell growth, migration, angiogenesis, endothelial cell proliferation, and motility, exerting tumor suppressor. EGFR, epidermal growth factor receptor; IGF-IR, insulin-like growth factor-insulin receptor; TGF-β, transforming growth factor-β; α2β1, integrin alpha2-beta1; PI3K, phosphatidylinositol 3-kinase; mTOR, mammalian target of rapamycin.

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