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Decorin Effect on Hemostasis: What Is New?

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ABSTRACT

There is growing evidence that many environmental factors control how fibrin clots. Fibrinogen's D regions are bound by decorin and regulates the action of transforming growth factor and collagen fibrillogenesis. The construction, structure, and clearance of fibrin fibres are modified by the interaction between decorin and fibrinogen. Compared to fibrinogen, decorin core protein-controlled clotting in substoichiometric levels, however, for a comparable impact, the active decorin peptide needed to be in excess. These concentration-dependent outcomes suggest that decorin binds to the D regions to sterically influence fibrin synthesis. Images of fibrin that has clot in the presence of increasing amounts of the decorin core protein taken using scanning electron microscopy indicated successively decreased fibre diameter. The budget cuts of Zn^{2+} ions from the fibrinogen-binding domain at the N-terminus prevented decorin from integrating into the fibrin network. The decorin-formed curving thin fibres underwent quicker plasminogen activator-dependent fibrinolysis of the tissue-type as opposed to the linear bulkier fibrin fibres. Together, our findings show that decorin can control fibrin organisation and provide new insight into how extracellular matrix elements might affect hemostasis, thrombosis, and wound healing.

INTRODUCTION

Hemostasis is the process of creating a blood clot to cover a broken vessel, followed by its removal once it is no longer necessary. The clot starts tissue healing while stopping further blood loss. Successful hemostasis can be separated into several phases, which include the formation of a platelet plug (primary hemostasis) and stabilization of the platelet plug with cross-linked fibrin (secondary hemostasis) followed by destruction of the clot by fibrinolysis **(1).**

DECORIN

The small leucine-rich proteoglycan (SLRP) family's prototype and best-characterized member is the decorin proteoglycan. The tight bond it has with collagen fibres is hinted at in its name, which manifests as fibril "decoration" **(2-4)**.

A 42-kDa decorin (DCN) contains a protein core that is conserved and participates in protein-protein interactions **(5,6)**.

In a zinc-dependent manner, A powerful muscle development inhibitor called myostatin is bound to by decorin and rendered inactive, and reduces its anti-myogenic effects. During muscle contraction, skeletal muscles secrete it **(7).**

Moreover, in 1986, the DCN gene was cloned, and it was found that macrophages, smooth muscle cells, and fibroblasts primarily produce and secrete DCN in their rough endoplasmic reticula and Golgi apparatuses (5,6).

Decorin was discovered to have an impact on several cellular processes, including as migration and proliferation, and spreading as well as inflammatory responses and fibrillogenesis (8,9).

DCN has drawn interest for its essential roles in managing as well as its possible involvement in the biological processes of inflammatory diseases, fibrotic disorders, and cancer. DCN has also been applied in a number of anticancer treatment procedures(10).

Inactivation of DCN:

Many proteases and growth factors, including matrix metalloproteinase, also known as membrane type 1-matrix metalloproteinase (MT1-MMP) -2 (MMP-2), MMP-3, and MMP-7, have been shown to break down DCN into smaller pieces and biologically inactivate it in experiments (10).

Additionally, proteases produced by inflammatory cells can also inactivate DCN **(39)**, through processes known as damage-associated molecular patterns (DAMPs), which can be discerned by pattern recognition receptors (PRRs), such as Toll-like receptors (TLR) 2/4, sparking an inflammatory response (12).

DCN'S MAIN BIOLOGICAL FUNCTIONS:

Anti-fibrosis growth factor interaction:

The harmful process of fibrosis can affect many different organs, including the skin, kidneys, lungs, heart, and chronic metabolic illnesses including diabetes and hypertension that is characterized by excessive deposition of Extracellular matrix (ECM) resulting from an imbalance between synthesis and degradation, which occurs in multiple organs, including the lungs, heart, kidneys and skin (13-16).

The most effective pro-fibrotic cytokine in the process of fibrogenesis is without a doubt transforming growth factor (TGF), which can stimulate fibroblasts, stop them from dying, and cause them to create excessive amounts of matrix substances such as collagen types I, III, and IV and fibronectin (17-19).

Together, DCN inhibits collagen I maturation, promotes collagenase, and controls the extracellular matrix components, such as thrombospondin-1 and fibronectin, which are produced (20).

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Pro-inflammation and innate immunity:

Many studies have shown that DCN is able to regulate cellular functions by fettering to extracellular matrix (ECM) molecules or through receptors in cell surface, such as transforming growth factor beta (TGF-β), epidermal growth factor receptor (EGFR), insulin-like growth factor-1 receptor (IGF-1R), vascular endothelial growth factor receptor 2 (VEGFR2) [(21)]. Thereby, DCN has multiple beneficial effects, such as anti-inflammation [(22)].

Decorin effectively blocks the activation of TGF-RI/II, which is Smad2, Smad3, and signalling is then carried out by the extracellular-signal regulated kinase (Erk) proteins. Through modifying the activity of mitogen-activated protein kinases (MAPKs) and nuclear factor kappa light chain enhancer of activated B cells (NF-B), decorin also lessens the signalling of inflammatory cytokines (MAPK) [(23)].

Moreover, decorin binds to the tumour stroma's TLR2/4 endogenous ligands to reduce swelling and tumour development [(23)]. DCN eventually changes a pro-inflammatory state of the immune system and causes a slowing of tumour growth. Moreover, DCN keeps the inflammatory state active by luring mononuclear cells to the site of injury and by stimulating the synthesis of C-C motif chemokine ligands2 (CCL2) [(24)]. It guards against the tissue's activation of apoptosis in macrophages [(25)].

DCN as tumor growth inhibition:

Clinically, it has been determined that the absence of DCN expression is a potent biomarker for the prognosis of soft tumours and invasive and metastatic breast cancer [(26,27)].

Several solid malignancy tissues, such as breast and colon cancers, hepatocellular carcinomas, hemangiomas, oesophageal squamous cell carcinomas, and low-high grade urothelial tumours, and prostate cancer, have notable reductions in matrix constituents, including DCN [(28,29)].

DCN and angiogenesis:

DCN exhibition of complex angiogenesis is regulated in two directions, depending on the molecular environment, either pro- or anti-angiogenic [(30)].

DCN directly promotes angiogenesis in a healthy, non-tumorigenic milieu, such as the cornea, by increasing attachment of endothelial cells to 12 integrin and collagen I [(31)].

All of these processes can create a stiffer fibril network, be resistant to proteolytic enzymes, and at the same time make the ECM more elastic and resilient by altering its biological properties. DCN provides endothelial cells with templates of the collagen structure to promote endothelial cell aggregation and assist in the development of blood vessel walls throughout this process [(2)].

DCN also suppresses the endogenous angiostatin proteins thrombospordin-1 and tissue inhibitor of metallo-proteinases-3 (TIMP3), as well as hypoxia inducible factor-1 (HIF-1), vascular endothelial growth factors A and vascular endothelial growth factor A (VEGFA) to further increase anti-angiogenesis and reduce tumour growth and metastasis [(32)].

Decorin effect on hemostasis:

A particular cell membrane receptor called the connection between decorin and platelets is mediated by integrin 21. When decorin binds to this receptor, multiple intracellular proteins undergo an increase in tyrosine phosphorylation, which is related to platelet activation [(33)].

In addition, the decorin-fibrinogen interactionin alters the assembly, structure, and clearance of fibrin fibers. Decorin bound to the D regions of fibrinogen sterically modulates fibrin assembly. Accelerated tissue-type plasminogen activator-dependent fibrinolysis **[(34)]**.

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REFERENCES

1. **Carvalho C (1998)**: Hemostasis and thrombosis, In: Schiffman FJ. ed. Hematologic Pathophysiology. Philadelphia: Lippincott-Raven, 2: 161–244.
2. **Reese S, Underwood C, Weiss J (2013):** Effects of decorin proteoglycan on fibrillogenesis, ultrastructure, and mechanics of type I collagen gels. Matrix Biol., 2(5): 32:414–423.
3. **Chen S, Young F, Chakravarti S *et al.* (2014):** Interclass small leucine-rich repeat proteoglycan interactions regulate collagen fibrillogenesis and corneal stromal assembly. Matrix Biol., 35:103–111.
4. **Iozzo V, Schaefer L (2015):** Proteoglycan form and function: A comprehensive nomenclature of proteoglycans. Matrix Biol., 42:11–55.
5. **Krusius T, Ruoslahti E (1986):** Primary structure of an extracellular matrix proteoglycan core protein deduced from cloned cDNA. Proc Natl Acad Sci U S A., 83:7683–7687.
6. **Mann M, Yamaguchi Y, Bourdon A *et al.* (1990):** Analysis of glycosaminoglycan substitution in decorin by site-directed mutagenesis. J Biol Chem., 265:5317–5323.
7. **El Shafey N, Guesnon M, Simon F *et al.* (2016):** Inhibition of the myostatin/Smad signaling pathway by short decorin-derived peptides. *Exp. Cell Res.*, 341: 187–195. doi: 10.1016/j..01.019
8. **Border A, Noble N, Yamamoto T *et al.* (1992):** Natural inhibitor of transforming growth factor-beta protects against scarring in experimental kidney disease. Nature, 360(6402): 361–364
9. **Jarvinen A, Prince S (2015):** Decorin: a growth factor antagonist for tumor growth inhibition. Biomed Res Int., 9(3): 277-293.

10. **Mimura T, Han Y, Onguchi T *et al.* (2009):** MT1-MMP-mediated cleavage of decorin in corneal angiogenesis. J Vasc Res., 46:541–550.
11. **Parkinson G, Toro A, Zhao H *et al.* (2015):** Granzyme B mediates both direct and indirect cleavage of extracellular matrix in skin after chronic low-dose ultraviolet light irradiation. Aging Cell, 14:67–77.
12. **Schaefer L (2014):** Complexity of danger: the diverse nature of damage-associated molecular patterns. J Biol Chem., 289:35237–35245.
13. **Rosenbloom J, Castro V, Jimenez A (2010):** Narrative review: fibrotic diseases: cellular and molecular mechanisms and novel therapies. Ann Intern Med., 52:159–166.
14. **Hellstrom M, Hellstrom S, Engstrom-Laurent A *et al.* (2014):** The structure of the basement membrane zone differs between keloids, hypertrophic scars and normal skin: a possible background to an impaired function. J Plast Reconstr Aesthet Surg., 67:1564–1572.
15. **Mack M, Yanagita M (2015):** Origin of myofibroblasts and cellular events triggering fibrosis. Kidney Int., 87:297–307.
16. **Kanisicak O, Khalil H, Ivey J *et al.* (2016):** Genetic lineage tracing defines myofibroblast origin and function in the injured heart. Nat Commun., 7:122-129.
17. **Kanzler S, Lohse W, Keil A *et al.* (1999):** TGF-beta1 in liver fibrosis: an inducible transgenic mouse model to study liver fibrogenesis. Am J Physiol., 276: 1059–1068.
18. **Merline R, Moreth K, Beckmann J *et al.* (2011):** Signaling by the matrix proteoglycan decorin controls inflammation and cancer through PDCD4 and MicroRNA-21. Sci Signal., 4: 75-82.
19. **Henke A, Grace C, Ashley R *et al.* (2012):** Stromal expression of decorin, Semaphorin6D, SPARC, Sprouty1 and Tsukushi in developing prostate and decreased levels of decorin in prostate cancer. PLoS One, 7: 15-25.
20. **Jarvinen A, Ruoslahti E (2010):** Target-seeking antifibrotic compound enhances wound healing and suppresses scar formation in mice. Proc Natl Acad., 107:21671–21676.
21. **Vu T, Marquez J, Le T *et al.* (2018):** The role of decorin in cardiovascular diseases: more than just a decoration. *Free Radic Res.*, 52(11):1210–9. doi: 10.1080/10715762.2018.1516285
22. **Jarvinen A, Ruoslahti E (2019)**: Generation of a multi-functional, target organ-specific, anti-fibrotic molecule by molecular engineering of the extracellular matrix protein, decorin. *Br J Pharmacol.*, 176(1):16–25.
23. **Zhang B, Wang J, Shen S *et al.* (2018):** Association of androgen excess with glucose intolerance in women with polycystic ovary syndrome. BioMed Research International, 3(1): 215-223.
24. **Koninger J, Giese A, Bartel M (2006):** The ECM proteoglycan decorin links desmoplasia and inflammation in chronic pancreatitis. J Clin Pathol., 59:21–27.
25. **Hinderer K, Sudrow M, Schneider M *et al.* (2018):** functionalization of electrospun scaffolds using recombinant human decorin attracts circulating endothelial progenitor cells Sci Rep., 8 (2): 110-119.
26. **Goldoni S, Iozzo V (2008):** Tumor microenvironment: modulation by decorin and related molecules harboring leucine-rich tandem motifs. Int J Cancer, 123:2473–2479.
27. **Matsumine A, Shintani K, Kusuzaki K *et al.* (2007):** Expression of decorin, a small leucine-rich proteoglycan, as a prognostic factor in soft tissue tumors. J Surg Oncol., 96:411–418.
28. **Iozzo V, Buraschi S, Genua M *et al.* (2011):** Decorin antagonizes IGF receptor I (IGF-IR) function by interfering with IGF-IR activity and attenuating downstream signaling. J Biol Chem., 286:34712–34721.
29. **Duncan B (2013):** Extracellular matrix transcriptome dynamics in hepatocellular carcinoma. Matrix Biol., 32:393–398.
30. **Jiang G, Sun C, Li H *et al.* (2015):** Enhanced antitumor efficacy of a novel oncolytic adenovirus combined with temozolomide in the treatment of melanoma in vivo. J Cancer Res Clin Oncol., 141:75–85.
31. **Stapor P, Wang X, Goveia J *et al.* (2014):** Angiogenesis revisited - role and therapeutic potential of targeting endothelial metabolism. J Cell Sci., 127:4331–4341.
32. **Mohan R, Tovey C, Sharma A (2011):** Targeted decorin gene therapy delivered with adeno-associated virus effectively retards corneal neovascularization in vivo. PLoS One, 6:13-22.
33. **Buraschi S, Pal N, Tyler-Rubinstein N *et al.* (2010):** Decorin antagonizes Met receptor activity and down-regulates {beta}-catenin and Myc levels. J Biol Chem., 285:42075–42085.
34. **Jung M, Moroi M (2000)**: Signal-transducing mechanisms involved in activation of the platelet collagen receptor integrin 21. J Biol Chem., 275:8016-8026.