Review

Pivotal role for decorin in angiogenesis

Hannu Järveläinen [1,2], Annele Sainio [1] and Thomas N. Wight [3]

*1 - **Department of Medical Biochemistry and Genetics,** University of Turku, Turku, Finland*
*2 - **Department of Medicine,** Division of Endocrinology, Turku University Hospital, Turku, Finland*
*3 - **Matrix Biology Program,** Benaroya Research Institute at Virginia Mason, Seattle, WA, USA*

***Correspondence to Hannu Järveläinen:** Turku University Hospital, Department of Medicine, Division of Endocrinology, Kiinamyllynkatu 4–8, FI-20520 Turku, Finland. Tel.: +358 2 333 7583; fax: +358 2 230 1280. hannu.jarvelainen@utu.fi*
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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-

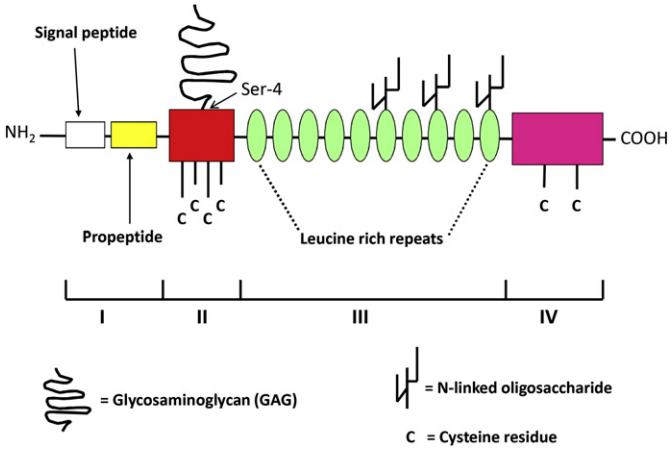

Fig. 1. Schematic drawing of the molecular structure of decorin. All four domains I–IV of decorin core protein are indicated (for details see the text). The GAG side chain attached to serine residue 4 of the second domain is also shown.