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Mini Review

The multiple functions of collagen XVIII in development and disease

Lotta Seppinen, Taina Pihlajaniemi *

Oulu Center for Cell-Matrix Research, Biocenter and Department of Medical Biochemistry and Molecular Biology, Institute of Biomedicine, University of Oulu, Finland

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ABSTRACT

Collagen XVIII is a heparan sulphate proteoglycan which is expressed ubiquitously in different basement membranes throughout the body. Its C-terminal fragment, endostatin, has been found to inhibit angiogenesis and tumor growth by restricting endothelial proliferation and migration and inducing apoptosis of endothelial cells. Collagen XVIII has three variants, of which the shortest one is found in most vascular and epithelial BM structures, whereas the longer variants are found especially in the liver. The longest or frizzled variant has a cysteine-rich domain in its N-terminus that has been shown to inhibit Wnt signaling *in vitro*. The presence of collagen XVIII homologues in organisms such as *C. elegans*, *Xenopus laevis*, zebrafish and chick suggests a fundamental role for this BM collagen. Mutations in the collagen XVIII gene lead to the Knobloch syndrome, which is characterized by high myopia, vitreoretinal degeneration with retinal detachment, macular abnormalities and occipital encephalocele. Mice lacking collagen XVIII also show several ocular abnormalities. This suggests that in physiological conditions collagen XVIII is mostly needed for the proper development of the eye. Moreover, it appears to be needed for the structural stability of basement membranes in several other organs, and increasing evidence shows its importance for other organs in non-physiological situations such as atherosclerosis, glomerulonephritis or other type of tissue damage. This review focuses on clarifying the roles of collagen XVIII and its variants and domains in various physiological and pathological conditions.

Contents

1. Introduction

Collagen XVIII is a basement membrane protein with structural similarities to another basement membrane collagen, namely collagen XV (Muragaki et al., 1994; Rehn and Pihlajaniemi, 1994). Both of these molecules contain an antiangiogenic C-terminal noncollagenous domain (O'Reilly et al., 1997) (Ramchandran et al., 1999; Sasaki

* Corresponding author. Department of Medical Biochemistry and Molecular Biology, University of Oulu, Aapistie 7, 90220 Oulu, Finland. Tel.: +358 8 537 5800; fax: +358 8 537 5810.
E-mail address: taina.pihlajaniemi@oulu.fi (T. Pihlajaniemi).

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et al., 2000). That of collagen XVIII, known as endostatin, is an inhibitor of angiogenesis and tumor growth (O'Reilly et al., 1997), and because of these properties it has been very widely studied. Collagen XVIII also has other biologically relevant domains, however, which seem to differ in function depending on whether they are cleaved from the parent molecule or embedded in the full-length collagen molecule. Moreover, collagen XVIII is expressed in three variants, which seem to have different biological roles. Some aspects of the biological activities of collagen XVIII have been recently reviewed by Iozzo et al. (2009) and Nicolae and Olsen (2010). This present review will focus on clarifying the biological roles of its variants and domains in various physiological and pathological situations.

1.1. Structure of collagen XVIII

The gene coding for collagen XVIII has been mapped to chromosome 21q22.3 in humans and chromosome 10 in the mouse (Oh et al., 1994b). The murine gene for the α1 chain of collagen XVIII (*Col18a1*) is over 102 kb long and contains 43 exons (Rehn et al., 1996). Collagen XVIII contains ten triple-helical collagenous domains separated by 11 non-collagenous regions (NC1-11; Oh et al., 1994a; Rehn et al., 1994). The 315-residue C-terminal NC1 endostatin domain shows high homology to the C-terminal domain of collagen XV (Rehn and Pihlajaniemi, 1994). The N-terminus of the NC1 domain contains a trimerization domain (Boudko et al., 2009). The sizes of the three variants of collagen XVIII, which are coded by two promoters, are 1315, 1527 and 1774 amino acid residues in the mouse. The short variant, coded by promoter 1, has its own signal peptide and two amino acids which are not found in the other two variants. Promoter 2 directs transcription of the two longer variants, which share the same signal peptide and a 215-amino acid residue domain of unknown function in the N-terminus (DUF959) followed by a 299-residue thrombospondin 1-like domain (TSP-1), which is also found in the N-terminus of the short variant. The longest form has an additional 247-residue frizzled domain in the middle of its N-terminal NC11 domain. This includes ten cysteine residues and shows high homology to the extracellular part of the Wnt-binding frizzled receptors. (Rehn and Pihlajaniemi, 1994, 1995; Rehn et al., 1996). Nine short NC domains (NC2–NC10) are found within a 654-residue collagenous domain (Rehn et al., 1994). (Fig. 1). Exons 1 and 2 code the sequence found in the short variant only, and exon 3 directs the synthesis of the two longer variants. The middle variant is generated by alternative splicing of exon 3, which leads to removal of the frizzled domain from the transcript. Exons 4-9 encode the N-terminal NC portion, which is common to all three variants, and exons 10–43 encode the common collagenous and C-terminal NC sequences. The human COL18A1 gene is highly similar in structure to the mouse gene (Rehn et al., 1996; Saarela et al., 1998b; Elamaa et al., 2003).

Collagen XVIII is a heparan sulphate proteoglycan, which in Western blotting occurs as a smear with a molecular weight of approximately 300 kDa, when isolated from human kidney or placenta or from chick vitreous body. Heparinase treatment reduces the molecule size to a protein core of 180 kDa (Halfter et al., 1998; Saarela et al., 1998a). Collagen XVIII has several potential glycosaminoglycan (GAG) attachment sites, three of which, located in the NC11, NC9 and NC8 domains, are conserved between mouse, human, *Xenopus* and chick samples and have also been found to be glycosylated in recombinant chick collagen XVIII produced in chick meningeal cells (Dong et al., 2003).

Collagens XVIII and XV are similar in their structures particularly regarding their N-terminal and C-terminal noncollagenous domains, and both contain a triple-helical collagenous domain separated by several noncollagenous domains (Muragaki et al., 1994; Kivirikko et al., 1994; Rehn and Pihlajaniemi, 1994; Rehn et al., 1994; Hägg

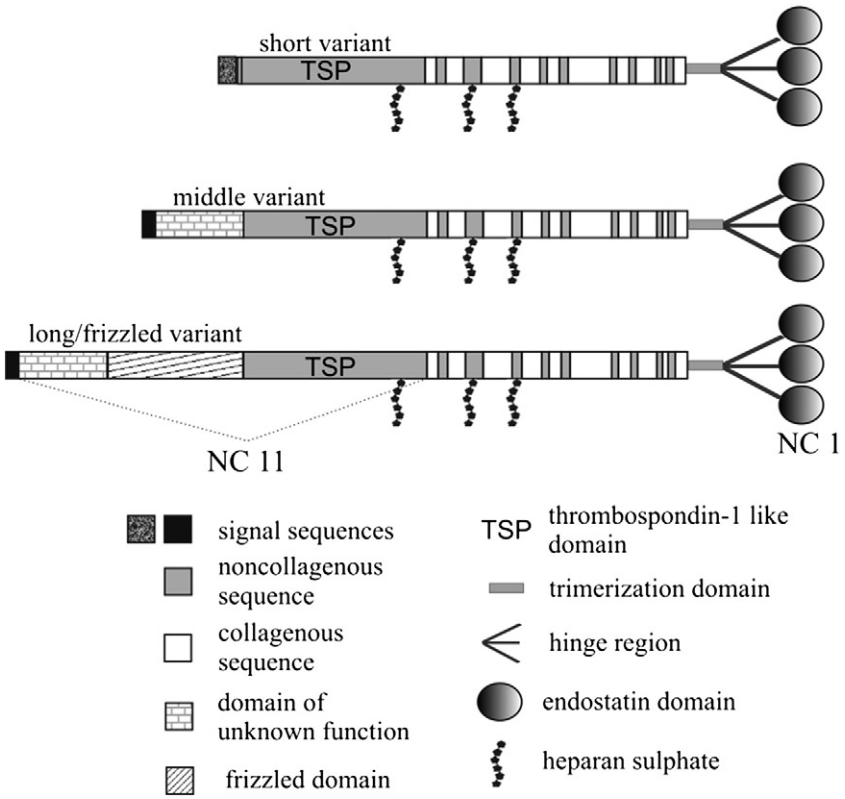

Fig. 1. Schematic picture of collagen XVIII. Collagen XVIII is expressed in three variants, which differ in their N-terminus. The short variant, coded by promoter 1, has its own signal sequence, while the middle and long variants, coded by promoter 2, have the same signal sequence. All the variants have a thrombospondin -like domain in their N-terminal non-collagenous part, and the longest variant contains a cysteine-rich frizzled domain in its N-terminus. All three variants contain globular C-terminal endostatin domains and heparin sulphate side chains.