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Mini-review

The extracellular matrix in cancer progression: Role of hyalectan proteoglycans and ADAMTS enzymes

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ABSTRACT

Remodelling of the extracellular matrix (ECM) has emerged as a key factor in cancer progression. Proteoglycans, including versican and other hyalectans, represent major structural elements of the ECM where they interact with other important molecules, including the glycosaminoglycan hyaluronan and the CD44 cell surface receptor. The hyalectan proteoglycans are regulated through cleavage by the proteolytic actions of A Disintegrin-like And Metalloproteinase domain with Thrombospondin-1 motif (ADAMTS) family members. Alteration in the balance between hyalectan proteoglycans and ADAMTS enzymes has been proposed to be a crucial factor in cancer progression either in a positive or negative manner depending on the context. Further complexity arises due to the formation of bioactive cleavage products, such as versikine, which may also play a role, and non-enzymatic functions for ADAMTS proteins. This research is providing fresh insights into cancer biology and opportunities for the development of new diagnostic and treatment strategies.

Introduction

The extracellular matrix (ECM) has important functions in tissue architecture, forming a penetrable barrier surrounding tissues that can be dynamically remodelled [1]. Recent studies have linked ECM remodelling as a key factor in several cancers, including melanoma, ovarian, cervical, breast, prostate and colon cancer [2–7]. For example, the ECM has been shown to play an integral role in maintaining the architecture of the stroma, loss of which can contribute to epithelial to mesenchymal transition, a key step in cancer progression [8]. This review investigates the significance of hyalectan proteoglycan (PG) components of the ECM and their regulation by A Disintegrin-like And Metalloproteinase domain with Thrombospondin-1 motif (ADAMTS) metalloproteinases in cancer.

Extracellular matrix

Overview

The ECM is composed of a basement membrane and interstitial matrix, both of which contain fibrous proteins and numerous PGs [1,9]. The latter contribute to various biological functions such as maintenance of tissue structure and regulation of cell proliferation, adhesion, migration and differentiation [10]. A defining feature of PGs is the presence of covalently linked glycosaminoglycan (GAG)

Abbreviations: ACAN, aggrecan; ADAMTS, A Disintegrin-like And Metalloproteinase domain with Thrombospondin-1 motif; BCAN, brevican; CS, chondroitin sulphate; DHT, 5α-dihydrotestosterone; ECM, extracellular matrix; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; EIF4E-BP1, eukaryotic initiation factor 4E binding protein 1; ERK, extracellular regulated kinase; GAG, glycosaminoglycan; HIF, hypoxia inducible factor; HS, heparan sulphate; HA, hyaluronan; KS, keratan sulphate; LMW, low molecular weight; MDCK, Madin–Darby canine kidney; MMP, matrix metalloproteinase; NCAN, neurocan; NG2, neural/glial 2; PCM, pericellular matrix; PG, proteoglycan; PI3K, phosphatidylinositol 3-kinase; RHAMM, receptor for hyaluronic acid-mediated motility; RPS6K, ribosomal protein S6 kinase; SNP, single nucleotide polymorphism; TGF-β, transforming growth factor beta; TIMP, tissue inhibitor of metalloproteinase; VCAN, versican; VEGF, vascular endothelial growth factor; vWF, von Willebrand factor.

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side chains. Four classes of GAGs have been implicated in cancer progression: heparan sulphate (HS), chondroitin sulphate (CS), keratan sulphate (KS) and hyaluronan (HA) [11]. A pericellular matrix (PCM) resides in close proximity to the cell membrane [12–15], which aids in communication between the cell and the ECM, and also regulates proliferation and migration [13,15–18]. The composition of the PCM is unique to different cell types, but the major component is typically HA [12–18]. HA elicits its effects largely through interactions with CD44 and Receptor for Hyaluronic Acid-Mediated Motility (RHAMM, CD168), both of which are expressed on the cell surface [19–22]. This interaction stimulates activation of extracellular regulated kinase (ERK)1/2 via the RAS/RAF/MEK pathway and of AKT via the phosphatidylinositol 3-kinase (PI3K) pathway, which in turn stimulate downstream effectors such as ribosomal protein S6 kinase (RPS6K), elongation initiation factor 4E binding protein (EIF4E-BP1) and hypoxia inducible factor (HIF)-1 [20,23]. However, HA exists in a variety of forms, including low molecular weight (LMW) fragments that can act via alternative mechanisms [24,25].

Versican and other hyalectans

Versican (VCAN) belongs to the hyalectan family of PGs, which represent crucial components of the ECM. VCAN allows the ECM to maintain a loose hydrated structure during key remodelling events, including those modulated in carcinogenesis, such as cell adhesion, migration, proliferation and angiogenesis [26,27]. Five VCAN isoforms are generated through alternative splicing, including full-length versican (V0) and the variants V1, V2, V3 and V4 [26–31]. All isoforms of VCAN consist of globular N-terminal and C-terminal domains, termed G1 and G3 respectively, with the differences between the isoforms located in the intervening GAG region (Fig. 1). The G1 domain consists of an immunoglobulin-like motif along with linking sequences that act to facilitate binding of HA with CD44 [30,32,33]. The G3 domain contains two epidermal growth factor (EGF)-like repeats along with a lectin-like motif and a complement binding region. The EGF-like motifs can directly regulate proliferation through binding of the epidermal growth factor receptor (EGFR) [30,32–34].

The VCAN isoforms possess alternate GAG rich motifs, GAG-α and GAG-β, which differ in the number of CS side chains: 12–17 for GAG-α and 5–8 for GAG-β [29,30,35]. Full-length VCAN (V0) contains both GAG-α and GAG-β sub-domains [29,30]. In contrast, V1 contains only the GAG-β subdomain, V2 only the GAG-α subdomain and V4 just part of GAG-β, with the V3 isoform possessing neither GAG subdomain, and so is strictly a glycoprotein rather than a PG [29,30,36]. These differences in the GAG region are thought to lead to VCAN isoforms having different properties. The V0 and V1 isoforms have been shown to be widely expressed throughout the body, whereas the V2 and V3 isoforms were primarily expressed in the central nervous system [29,37–39]. V4 expression remains poorly characterized [36].

Other related hyalectans include aggrecan (ACAN), neurocan (NCAN) and brevican (BCAN). ACAN has been shown to be an important component of cartilage with decreased ACAN leading to impaired joint function [40–45]. NCAN is a major constituent of the brain with roles identified in adhesion, migration and growth of neurites [46–54]. BCAN is a brain-enriched HA-binding protein that potentially functions in the terminal differentiation of neurons [55–61].

The ADAMTS family

The metzincin super-family represents a large group of zinc-dependent metalloproteinases characterized by a conserved catalytic motif, which encompasses three histidine residues that bind a zinc ion and a conserved glutamate residue required for acid-base catalysis [62,63]. Amongst the metzincins, the ADAMTS family comprises 19 members (Fig. 2). These secreted enzymes participate in key ECM remodelling events associated with proliferation, cell–cell fusion and morphogenesis [64–66]. ADAMTS family members each consist of an N-terminal protease region containing a pro-domain, metalloproteinase domain and a disintegrin-like domain. Individual ADAMTS members are defined by differences in the C-terminal ancillary region, with variation in the presence and number of thrombospondin type-1 motifs, presence of a Gon-1 module, protease and lacunin domains, complement domains, mucin/PG domains and pro-collagen N-propeptidase sequences

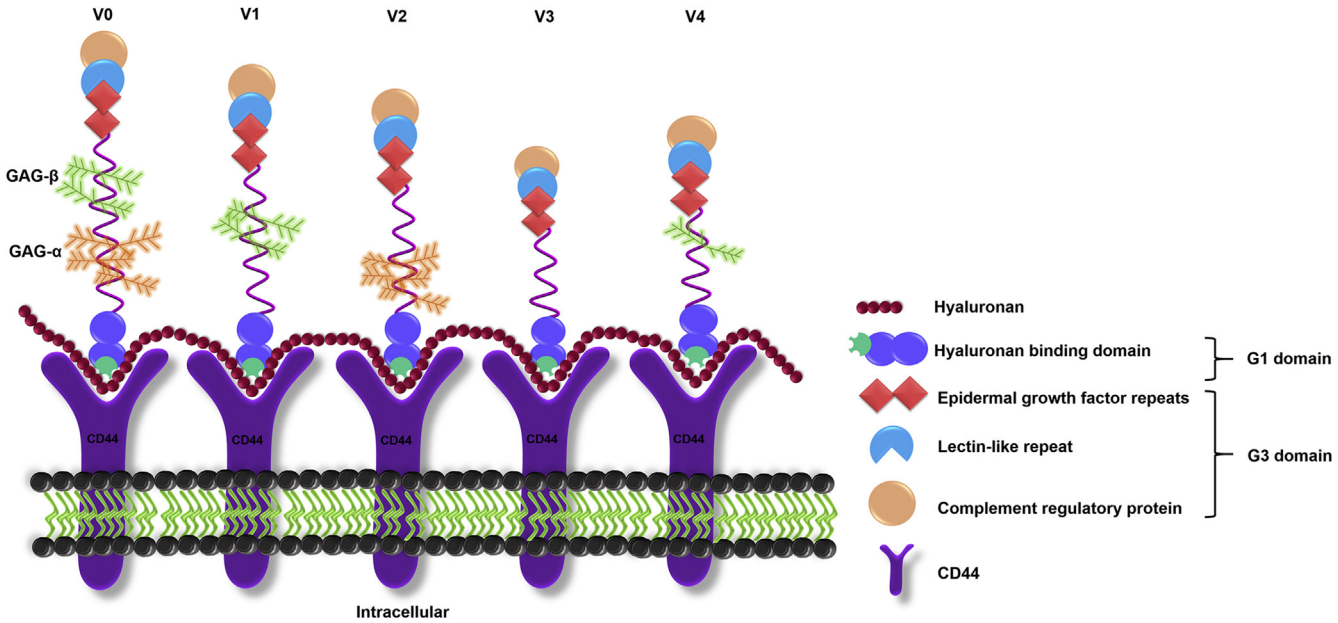

Fig. 1. Structure of versican isoforms. Schematic representation of the versican isoforms V0–V4 generated by alternate splicing, showing their constituent domains, which includes the G1, G3 and intervening GAG domains, and their interaction with hyaluronan and CD44.