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Gene Section
Review

VCAN (versican)

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Identity

Other names: CSPG2, DKFZp686K06110, ERVR, GHAP, PG-M, WGN, WGN1

HGNC (Hugo): VCAN

Location: 5q14.3

DNA/RNA

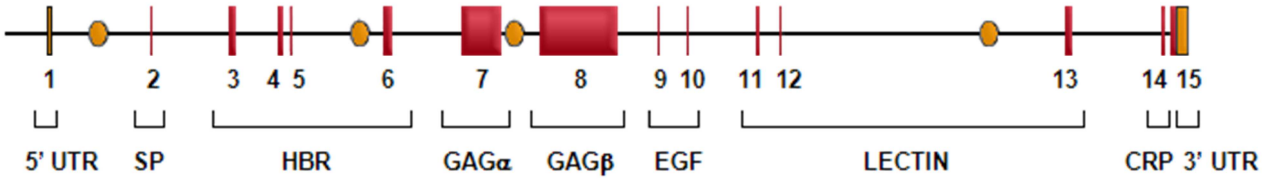
Description

Versican is encoded by a single gene and is located on chromosome 5q12-14 in the human genome. The human VCAN gene is divided into 15 exons over 90-100 kb. The structure of versican was originally deduced by the analysis of cDNA from a human placental library (Naso et al., 1994). The entire primary structures of versican have been generated from human, murine, bovine and chick cDNA clones. The chick form was originally named PG-M (Shinomura et al., 1993).

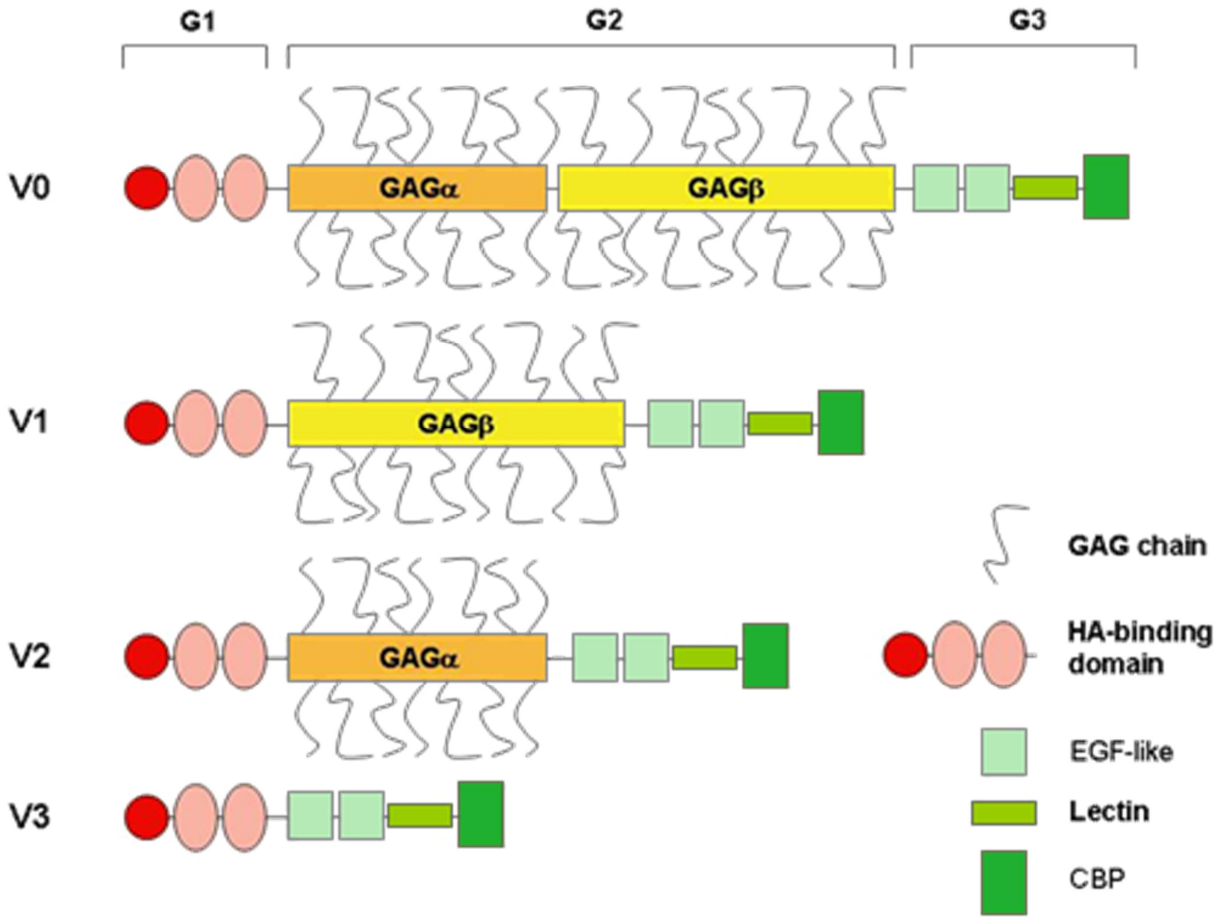
Transcription

RNA splicing occurs in the two large exons encoding the GAG attachment sites. The region encoded by exon 7 is called GAG alpha, the region encoded by exon 8, GAG beta. Four mRNA transcripts arise from alternative splicing, giving rise to V0, V1, V2 and V3. V0 possesses both exon 7 and exon 8, V1 possesses exon 8 but not exon 7, V2 possesses exon 7 but not exon 8; and V3 possesses neither exon 7 nor exon 8 (Wight, 2002).

The expression of the versican gene (CSPG2) is regulated by a promoter that harbors a typical TATA box and potential binding sites for several transcription factors, including AP1, AP2, CCAAT enhancer protein, TCF-4 and cAMP-responsive element (Naso et al., 1994; Rahmani et al., 2006; Domenzain-Reyna et al., 2009). Regulation of the versican gene through an androgen response element in the proximal promoter has been reported in prostate (Read et al., 2007).



Adapted from Naso et al., 2004.



Versican isoforms

Protein

Description

Versican belongs to the extracellular matrix chondroitin sulphate proteoglycan family.

The largest versican isoform (V0) consists of 3396 aa. The core protein can be divided into three domains: the globular N-terminal domain (G1), the central domain (G2) where glycosaminoglycan (GAG) chains attach, and the globular C-terminal domain (G3). The G1 domain is composed of an immunoglobulin-like motif, followed by two tandem repeats which bind hyaluronan (HA). The G3 domain contains two EGF-like repeats, a lectin-like subdomain and a complement binding protein (CBP)-like subdomain. The central domain G2 can be alternatively spliced to give rise to the four versican isoforms: V0 (containing both GAG alpha and GAG beta), V1 (containing GAG beta), V2 (containing GAG alpha) and V3, lacking any GAG subdomain (Wight, 2002).

A new alternatively spliced versican isoform, referred to as V4, has been identified and found to be upregulated in human breast cancer (Kischel et al., 2010).

Posttranslational modifications (PTM): the consensus sequence for chondroitin sulphate attachment sites reveals the number of potential GAG attachment sites: the number of GAG chains attached to the protein core depends on the isoforms since the GAG alpha subdomain bears 12-17 chondroitin sulphate (CS) chains, whereas the GAG beta subdomain bears 5-8 CS chains (Ricciardelli et al., 2009).

Expression

Versican was initially identified in the culture medium of human IMR-90 lung fibroblasts (Zimmermann and Ruoslahti, 1989).

Versican is highly expressed in tissue compartments undergoing active cell proliferation and migration. V0 and V1 isoforms are highly expressed during embryonic development, and their expression decreases after tissue maturation. In adult tissues, versican is present in the loose connective tissues of various organs and often associated with the elastic fibre network. It is localized in most smooth muscle tissues, in cartilage, in the basal layer of the epidermis, and in blood vessels (Bode-Lesniewska et al., 1996). Versican V2 is abundant in the central nervous system

(Schmalfeldt et al., 2000). The V3 isoform has been identified at the mRNA levels but very scarcely at the protein level (Cattaruzza et al., 2002).

Localisation

Versican is a component of the extracellular matrix.

Function

The name versican comes from versatile, with regard to the diversity of biological actions of this highly interactive molecule that can be attributed both to the amino- and carboxy-terminal domains and to the GAGs side chains attached to the middle portion of the core protein. Versican is involved in the control of cell adhesion, proliferation, migration, apoptosis and in ECM assembly (Wight, 2002; Theocharis, 2008; Ricciardelli et al., 2009). Its domain organization allows modulation of a large variety of cell behaviours through interaction with a wide range of binding partners, including ECM components (HA, type I collagen, tenascin and fibronectin among others), chemokines, and cell surface proteins (CD44, integrin beta1, epidermal growth factor receptor) (Wu et al., 2005).

Versican belongs to the hyalectan family, characterized by its ability to bind hyaluronan. The overall consensus is that versican together with

hyaluronan forms a pericellular matrix that modulates cell proliferation, adhesion and migration in conditions such as in development and wound healing cell. Some of these actions have been ascribed to specific domains in the molecule. Thus, overexpression of versican G1 domain can enhance cell proliferation and reduce cell adhesion (Ang et al., 1999; Zhang et al., 1999). G3 domain has also been involved in several processes like cell proliferation and invasion (Zhang et al., 1998; Yang et al., 2003; Zheng et al., 2004; Yee et al., 2007), and GAG chains have been considered partially responsible for the antiadhesive properties of versican (Yamagata and Kimata, 1994; Sakko et al., 2003).

Cell proliferation. Versican is associated with a proliferative cell phenotype and it is often found in tissues showing elevated proliferation such as in development and in a variety of tumours (Wight, 2002; Ricciardelli et al., 2009). Purified versican added to the culture media in a melanoma cell line induces proliferation (Touab et al., 2002). Silencing experiments with siRNA have lead to the same conclusion in vascular smooth muscle cells (Huang et al., 2006) and preadipocytes (Zizola et al., 2007).

Cell adhesion. Versican is an anti-adhesive substrate (Yamagata and Kimata, 1994). The anti-adhesive role of versican has been also shown in melanoma cells (Touab et al., 2002), prostate carcinoma cells (Sakko et al., 2003) or neural crest cells (Dutt et al., 2006). This inhibitory effect on cell adhesion may be mainly due to the presence of the GAG chains that might create a more hydrated extracellular matrix less suitable for cell adhesion.

Nevertheless, the G3 domain of versican has pro-adhesive properties raising the possibility that different breakdown products might differentially affect cell adhesion (Wu et al., 2002).

Cell migration and invasion. Versican can increase cell motility in embryonic as well as tumour cells. This activity may be mostly associated with its antiadhesive activities. Silencing of V0/V1 versican expression reduces cell migration in wound healing assays in smooth muscle cells (Huang et al., 2006), or in prostate cancer cells, where addition of purified versican to the cells caused an increase in the invasion ability (Ricciardelli et al., 2007). In glioma, treatment of the cells with TGF-beta2 caused an increase in cell migration associated to an increase in versican production (Arslan et al., 2007). In the nervous system and in axonal growth, the V2 splice variant inhibits axonal growth and migration (Schmalfeldt et al., 2000).

Apoptosis. The effect of versican on apoptosis is complex and anti- as well as pro-apoptotic functions have been reported. Overexpression of the V1 versican isoform in cultured fibroblasts increases apoptotic resistance, but cells were also sensitized to a wide range of cytotoxic agents (LaPierre et al., 2007).

Cell differentiation and epithelial-mesenchymal transition (EMT). Versican modulates cell differentiation and morphogenesis, since it is involved in EMT interactions and in mesenchymal cell condensation required for organogenesis. V1 (but not V2) has been shown to trigger MET in fibroblasts by inducing a switch from N-cadherin to E-cadherin and subsequent acquirement of epithelioid phenotype. Silencing of endogenous versican prevents condensation and MET in metanephric mesenchyme (Sheng et al., 2006). Versican is highly expressed in the mesenchymal cell condensation area during development of cartilage, heart, hair follicles and kidney, and in vitro evidences show that versican V0 and V1 isoforms are involved in the process of precartilage mesenchymal condensation and subsequent chondrogenesis (Kamiya et al., 2006). The requirement of versican in development is highlighted by the finding that deficiency of versican in a transgenic mouse model is embryonic lethal, due to defects on cardiac formation, limb mesenchymal aggregation and chondrogenesis (Williams et al., 2005).

Others. In neural cells, versican plays an important role in regulating axonal guidance (Perissinotto et al., 2000). It is also an important molecule in inflammatory processes since it is able to interact with immune cell receptors and chemokines (Hirose et al., 2001).

Homology

Versican belongs to the hyalectan gene family of proteoglycans that include aggrecan, neurocan and brevican.

Mutations

Note

No missense, regulatory, small and gross deletions and insertions, complex rearrangements, or repeat variations have been described.

In this context, disruption of the versican gene in mouse and chick leads to severe cardiac defects and alterations in chondrogenesis in the hdf (heart defect) mouse. This animal model has lead to the conclusion that normal expression of the VCAN (Cspg2) gene is required for the successful development of the heart and for cartilage differentiation, leading to correct limb chondrogenesis (Mjaatvedt et al., 1998).

Only mutations affecting the splicing of exons 7 and 8 have been described associated to Wagner syndrome, a rare disorder belonging to the group of hereditary vitreoretinal degenerations (Miyamoto et al., 2005; Kloeckener-Gruissem et al., 2006).

Implicated in

Various cancers

Note

Versican, specially the large V0 and V1 isoforms, is overproduced by many cancer types of all kind of origins: brain tumours, melanoma, osteosarcoma, breast, prostate, colon, lung, pancreatic, endometrial, oral and ovarian cancers. Versican is expressed by tumour stromal cells as fibroblasts, and also by tumour cells in melanoma, prostate, pancreatic, endometrial and ovarian carcinomas. Versican has a positive effect on cell proliferation, migration and invasion, and exerts a negative effect on cell adhesion. In cancer cells, it is also involved in the control of the epithelial-mesenchymal transition. The expression of particular domains enhances angiogenesis and metastasis in several tumour models (Ricciardelli et al., 2009). Versican has also been involved in metastasis by playing a role in the immune response. Versican acts on macrophages through the Toll-receptor 2 (TLR2) inducing TNF-alpha secretion and provoking lung metastatic growth (Kim et al., 2009).

Prognosis

Elevated levels of versican are usually associated with relapse and poor patient outcome in many cancer types, including breast and prostate.

Brain tumours

Disease

V2 is the major versican isoform of brain ECM and it is usually decreased in glioma ECM, whereas it is increased in tumour vessels. Since versican is antiadhesive, this may be related to marked local invasivity and rarity of extracranial metastasis of gliomas (Paulus et al., 1996). It has been described that versican in brain tumours originates from fibroblasts and monocytes of tumour stroma (Delpech et al., 1997).

Melanoma

Disease

Versican is absent in benign melanocytic nevi, weakly to strongly positive in dysplastic nevi, being proportional to the degree of nuclear atypia, and intensely positive in primary malignant melanomas and metastatic melanomas. Versican is involved in the progression of melanomas and may be a reliable marker for clinical diagnosis (Touab et al., 2002; Touab et al., 2003; Gambichler et al., 2008).

Oncogenesis

In melanoma, AP-1 and TCF-4 binding sites are the main regulatory regions directing versican production in undifferentiated cell lines (Domenzain-Reyna et al., 2009).

Breast tumour

Disease

Versican is overexpressed in breast carcinoma, and it is specially localized in the proliferating interstitial tissues, and in vascular and perivascular elastic tissues involved in carcinoma invasion (Nara et al., 1997). Relapse in women with node-negative breast cancer is related to the level of versican deposited in peritumoral stroma by mammary fibroblasts (Ricciardelli et al., 2002).

Prostate tumours

Disease

Versican is localized to the periacinar and peritumoral fibromuscular stroma in sections of nonmalignant and malignant human prostate tissues. Versican is increased in early-stage prostate cancer. Patients with low versican concentration had significantly better progression-free survival than patients with high levels of versican (Ricciardelli et al., 1998). Versican is also overexpressed in benign prostate hyperplasia (BPH) (True et al., 2009).

Colon tumours

Disease

DNA isolated from human colon carcinoma tissue exhibits a selective hypomethylation of versican gene, three times lower than that found in either normal colon or ulcerative colitis tissues (Adany and Iozzo, 1990). Colon adenocarcinoma is characterized by a remarkable increase in the concentration of versican, which is significantly modified at the post-translational level, i.e. the type, length and the sulphation pattern of the GAG chains (Theocharis, 2002).

Oncogenesis

Hypomethylation of the VCAN gene occurs in benign and malignant colon cancer compared to normal colon. These changes in methylation may occur prior to

malignant transformation and may be associated to increased versican levels in colon cancer.

Lung carcinoma

Disease

Increased stromal versican is associated with tumour recurrence, higher tumour stage, and lymph node metastases (Pirinen et al., 2005).

Pancreatic tumours

Disease

Versican presents a great increase (27-fold) in comparison to normal pancreas, which may be closely associated with the growth and aggressiveness of this carcinoma.

Significant specific post-translational modifications were also observed regarding the type, hydrodynamic size, sulphation pattern and extent of uronate epimerization of the GAG chains (Skandalis et al., 2006).

Endometrial tumours

Disease

Stromal versican expression was significantly higher in the advanced-stage and high-grade cancers, lymph node metastasis and ovarian metastasis. Epithelial versican expression was significantly higher in patients with lymph node metastasis and lymph-vascular space involvement. The disease-free survival and overall survival rates of patients exhibiting high stromal versican expression were significantly lower than those of patients exhibiting low stromal versican expression (Kodama et al., 2007).

Ovarian tumours

Disease

Elevated levels of versican have been associated with a poor prognosis of ovarian cancers (Ricciardelli and Rodgers, 2006). Ovarian clear cell carcinoma (OCCC) microarray signature contains versican, which is in part in part epigenetically regulated, as it was hypomethylated in OCCC cell lines (Yamaguchi et al., 2010). VCAN overexpression is associated with increased microvessel density (MVD) and invasion potential, which may lead to poorer overall and progression-free survival and platinum resistance (Ghosh et al., 2010).

Oral carcinoma

Disease

High stromal versican expression predicts unfavourable outcome in oral squamous cell carcinoma (Pukkila et al., 2007).

Lymphoma

Disease

Tumoral environment induces aberrant expression of versican in EL4 lymphoma cells (Rottiers et al., 1998).

Atherosclerosis

Disease

Versican accumulates in atherosclerotic lesions and restenosis. Versican is also prominent at the borders of lipid-filled necrotic cores and at the plaque-thrombus interface of the atherosclerotic lesion, suggesting roles in lipid accumulation, inflammation, and thrombosis (Wight and Merrilees, 2004).

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