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Gene Section
Review

FBLN2 (fibulin 2)

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Abstract

Fibulin-2 is an extracellular matrix glycoprotein with an important function in maintaining elastic properties in different tissues. Fibulin-2 belongs to a protein family with seven members characterized by sharing a globular domain at the carboxy-terminus, which is called "fibulin-like", "FC domain" or domain III. Together with fibulin-1, fibulin-2 forms the so called subgroup 1 in the fibulin family which contains three anaphylatoxin modules in their sequence. Fibulin-2 does not only form part of elastic fibers but is also present in basement membranes and other connective tissue structures. Besides its structural function, alterations in fibulin-2 expression have also been related to several pathological processes. Thus, fibulin-2 has been shown to be implicated in blood pressure regulation, vascular injury protection or with a protective role in some heart malfunctioning. Also, fibulin-2 participation has been described in cancer showing both oncogenic or tumor-suppressor properties.

Keywords
Extracellular matrix, elastic fibers.

Identity

HGNC (Hugo): FBLN2

Location : 3p25.1

DNA/RNA

According to NCBI (National Center for Biotechnology Information) fibulin-2 (NC_000003.12) is encoded in 19 exons in chromosome 3, spans approximately 89.3 Kb of genomic DNA in the telomere-to-centromere orientation.
The translation initiation codon is located to exon 3, and the stop codon to exon 19.

Transcription

Northern blot analysis of mRNA from various human tissues reveals an abundant 4.5-kb transcript in heart, placenta, and ovary tissue (Zhang et al., 1994).

Protein

The open reading frame encodes a 1231 amino acid protein, with an estimated molecular weight of 131,9 kDa.
Fibulin-2 shares a structural multidomain complex architecture with the rest of the members of the fibulin family, specially with fibulin-1.
This organization includes a signal peptide, a cystein rich domain, a cystein free domain, three anaphylotoxyn domains, an EGF-like (Epidermal Growth Factor) domain following the first out of a total of ten cbEGF (calcium-binding Epidermal Growht Factor) domains and finally, at the carboxy-terminus the fibulin-like domain, characteristic of the fibulin family (Figure 1) (Timpl et al., 2003; de Vega et al., 2009; Obaya et al., 2012).
An alternative splicing has been described for fibulin-2 mRNA by which exon 10 is removed resulting in a short fibulin-2 (FBLN2S) of 1184 amino which lacks the third EFG-like domain in comparison to the long fibulin-2 (FBLN2L) (Zhang et al., 1994; Grassel et al., 1999; Law et al., 2012).

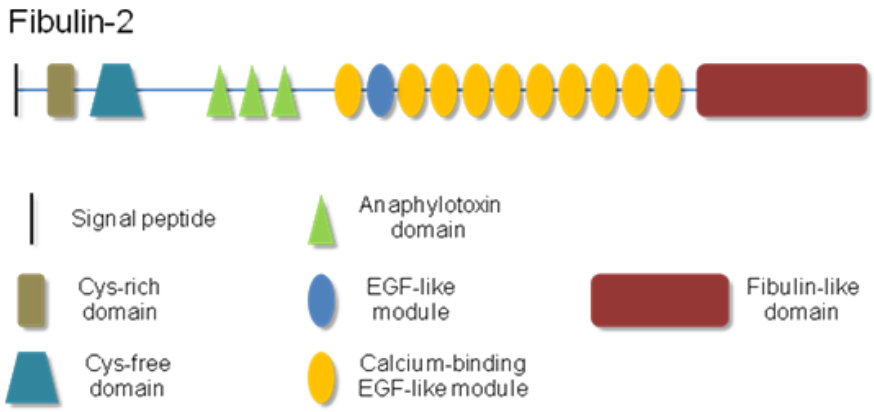

Figure 1. Fibulin-2 domain organization. EGF : Epidermal Growth Factor.

It has been described that fibulin-2 forms anti-paralel homodimers stabilized by a single disulfide bond throug a cysteine residue located in the second anaphylotoxin domain. As seen by electron microscopy, fibulin-2 homodimerization produces a set of star-like particles consisting in two-, three- or four-arm structures as well as some larger aggregates. Thus, the complexity of fibulin-2 structure allows different combinations and possibilities to interact with other extracellular matrix proteins (Pan et al., 1993; Sasaki et al., 1997).

Expression

Northern blot analysis of mRNA from various human tissues reveals the presence of fibulin-2 transcript in heart, placenta and ovary tissue (Zhang et al., 1994). Fibulin-2 expression is restricted to certain tissues and partially overlaps with that of fibulin-1. Both proteins are localized in basement membranes, elastic fibers, and other connective tissue structures (Pan et al., 1993; Roark et al., 1995; Miosge et al., 1996; Reinhardt et al., 1996; Zhang et al., 1996). Both proteins can be detected in early stages of embryonic development although fibulin-2 synthesis is delayed with respect to fibulin-1. However, both are at relatively high levels at the onset of organogenesis in mouse and humans (Miosge, 1996; Zhang et al., 1996). Fibulin-2 is expressed during the epithelial to mesenchymal transformation in the endocardial cushion matrix, aortic arch vessels and coronary vessels during embryonic heart development (Zhang et al., 1995; Tsuda et al., 2001). Fibulin-1 and fibulin-2 are also expressed and deposited in several, although different neuronal structures. Specifically, fibulin-2 was detected primarily within the neuropithelium, spinal ganglia and peripheral nerves (Zhang et al., 1996). Furthermore, fibulin-2 has also been detected during skin wound healing, in the developing cartilage (perichondrium) or deposited in the organization of corneal structures (Zhang et al., 1995; Ducros et al., 2007; Kobayashi et al., 2007).

Localisation

Secreted, extracellular matrix.

Function

Fibulin-2 as well as other members of the fibulin family play essential role for the correct assembly of elastic fibers in connective tissues (Kielty et al., 2002).

In particular, fibulin-2 is localized in the interface between the two main components of elastic fibers, microfibrils and the elastin core (Reinhardt et al., 1996; Kobayashhi et al., 2007). In its structural function, fibulin-2 is able to interact with several other extracellular components to maintain specific connective tissues properties. Thus, fibulin-2 is able to interact with troposlatin-2 (Sasaki et al., 1999), aggrecan and versican (Olin et al., 2001), fibronectin and nidogen-1 (Sasaki et al., 1995). All those bindings partners overlap with those of fibulin-1 but, fibulin-2 is also able to specifically interact with fibrillin-1 and perlecan (Reinhardt et al., 1996; Hopf et al., 2001).

Fibulin-2 is also suggested to regulate steroid hormone action since it is able to interact with sex hormone globulin (SHBG) (Ng et al., 2006). Mutations in SHGB alter its binding capacities to fibulin-2 and sex hormones suggesting participation in human diseases (Wu and Hammond, 2014). In relation with steroid hormones, progesterone, dexamethasone, estradiol and glucocorticoids are able to regulate fibulin-2 expression levels in different tissues and contexts (Talts et al., 1995; Gu et al., 2001; Okada et al., 2003; Eyster et al., 2014 ; Olijnyk et al., 2014).

Homology

The FBLN2 gene is conserved in chimpanzee (Refseq: NC_006490.3), dog (Refseq: NC_006602.3), cow (Refseq: AC_000179.1),

mouse (Refseq: NC_000072.6), rat (Refseq: NC_005103.4), chicken (Refseq: NC_006099.3), and zebrafish (Refseq: NC_007122.5).

Implicated in

Various cancers

Fibulin-2 was early related to cancer in a study aimed to look for genes differently expressed between adenocarcinoma metastases of multiple tumor types and the unmatched primary adenocarcinomas (breast, prostate, lung, colon, uterus and ovary) (Ramaswamy et al., 2003).

Nasopharyngeal carcinoma

Genome-wide Human Mapping Array analysis showed that the chromosome 3p25 region, where FBLN2 maps, is often deleted in esophageal squamous cell carcinoma patients (Chattopadhyay et al., 2010). More recently, fibulin-2 RNA downregulation has been described in 100% of nasopharingeal carcinoma cell lines as well as 46.7% of biopsies tested. Deletion and promoter hypermethylation events contribute to the silencing of FBLN2 expression (Law et al., 2012). Functional analysis of fibulin-2 role as a tumor suppressor gene showed angio-inhibitory and tumor-suppressive properties that are linked to a short isoform of FBLN2, FBLN2S, in nasopharingeal carcinoma (Law et al., 2012). Interestingly, FBLN2-associated anti-angiogenic activity is concomitant with a downregulation of two pro-angiogenic factors such as VEGF and matrix-metalloprotease-2 (MMP-2).

Breast cancer

Fibulin-2 was suggested to be a putative biomarker of breast cancer attending to the proteomic analysis performed in a breast cancer mouse model (Whiteaker et al., 2007). A role of fibulin-2 as a tumor suppressor gene in breast cancer came after the observation of its down-regulation in several cancer cell lines (Yi et al., 2007). Exogenous expression of fibulin-2 in breast cancer cell lines was able to reduce cell motility as well as invasion capacities, some of the tumor properties of those cells (Yi et al., 2007). One of the mechanisms to reduce FBLN2 gene expression is throuh promoter hypermethylation as it has been described in breast cancer cell lines (60%), primary breast tumors (34%) and matched tumor/normal pairs (32%) biopsies (Hill et al., 2010). Fibulin-2 might exert its tumor suppressor function by interaction with other proteins of the extracellular matrix as is the case of ADAMTS-12 (Fontanil et al., 2014). ADAMTS-12 is a secreted metalloprotease (Cal et al., 2001; Cal and Obaya, 2014) and different studies have suggested a role for this metalloprotease in tissue remodeling and cell migration or adhesion (Noel et al., 2012). Fibulin-2/ADAMTS-12 interaction has been shown to inhibit the migration, invasion and tumorigenicity properties of cancer breast cell lines after exogenous expression of ADAMTS-12 (Fontanil et al., 2014).

Lung adenocarcinoma

Based on the previous study of Ramaswamy et al. comparing primary a metastatic tumors in the search of a gene metastatic signature (Ramaswamy et al., 2003), a proteomic screen of highly and poorly metastatic tumor cell lines derived from mice that develop lung adenocarcinoma revealed that fibulin-2 was preferentially expressed in highly metastatic cells (Schliekelman et al., 2011). A more profound and functional study revealed that fibulin-2 shows an oncogenic potential in lung adenocarcinoma (Baird et al., 2013). Fibulin-2 is found expressed in metastatic-derived cell lines and tumor growth depends on the endogenously expressed fibulin-2 since they are able to grow equally in Fbln2-null and wild-type mice. Furthermore, fibulin-2 requires the presence of collagen in the extracellular matrix in order to promote tumorigenic properties of these cells lines (Baird et al., 2013).

Pancreatic cancer

Expression of MUC4, a transmembrane type I glycoprotein, is elevated in pancreatic cancer. It is also known that MUC4 is able to interact through its nidogen-like domain with fibulin-2 and authors suggest that this association contributes to the MUC4-mediated metastasis of pancreatic tumor cells (Senapati et al., 2012).

Kaposí's sarcoma

Infection of dermal microvascular endothelial cells (DMVEC) with Kaposi's sarcoma-associated herpesvirus (KSHV) reduced fibulin-2 protein and RNA. Furthermore, a decrease in the expression of fibronectin and tropoelastin, binding partners of fibulin-2, was also detected in infected cells (Alcendor et al., 2011). Since downregulataion of other fibulins is observed, authors suggest that dysregulation of fibulin family members such as fibulin-2, fibulin-3, fibulin-5, fibulin 1C, and fibulin 1D likely contribute to KSHV-induced pathogenesis in Kaposi's sarcoma (Alcendor et al., 2011).

Various diseases

Fibulin-2 participation in disease has been somehow elusive due to functional redundacy with other members of the fibulin family. Thus, fibulin-1 staining is highly detected in the absence of fibulin-2 in the viable, fertile and free of anatomic abnormalities fibulin-2 knock-out mice (Sicot et al., 2008; Olijnyk et al.,2014). However, several studies support fibulin-2 functions in disease and cancer. In

the case of cancer, fibulin-2 shows a dual function, showing either suppresor gene or oncogenic activities (Obaya et al., 2012).

Skin damage

In normal skin, regulation of skin elastogenesis depends on the association between fibulin-2 and fibulin-5 with fibrillin-1 matrix (Lemaire et al., 2004). Fibulin-2 is not only known to participate in the elastic structure of the skin but also participates in skin wound healing where it shows an increased expression with mRNA levels returning to normal after skin repair (Fässler el al., 1996). Fibulin-2 deposition is also high in a mice model of chronic contact dermatitis as well as in models of solar elastosis which suggests a protective role of fibulin-2 in skin formation and maintenance (Kusubata et al., 1999; Hunzelmann et al., 2001). Furthermore, fibulin-2 reduction in fbln2 null mice or due to the lack of integrin α3β1-laminin interaction contributes to loss of the integrity of basement membrane and skin blistering (Sicot et al., 2008; Longmate el al., 2014). In fact, the latest occurs since fibulin-2 is one of the genes regulated by integrin α3β1 in inmortalized keratinocytes and seems to be one of the mediators in the invasive capacities exerted by integrin α3β1 (Missan et al., 2014).

Cardiaovascular pathologies

Fibulin-2 has been detected in the endocardial cushion tissue, endocardium and the basement membrane zones and adventitia of blood vessels of developing human and mouse embryo (Zhang et al., 1995; Miosge et al., 1996). Fibulin-2 is also up-regulated in transformed cells that migrate into the extracellular matrix of cardiac valves and aortic arch vessels and authors suggest that fibulin-2 is also required for the correct formation of coronary arteries and veins in postnatal life (Tsuda et al., 2001). However, although mice lacking fibulin-2 do not show any obvious phenotypic anomalies (Sicot et al., 2008), loss of fibulin-2 significantly improved the survival rate after experimental myocardial infarction through attenuating progressive ventricular dysfunction accompanied by reduced activation of the TGFβ-dependent pathway (Tsuda et al., 2012). The modulation of this signalling pathway by fibulin-2 in heart homeostasis has also been described in an angiotensin II-induced heart hypertrophy model (Zhang et al., 2014). In both cases, fibulin-2 deficiency results in a better outcome of the pathologies.

Fibulin-2 is required, in cooperation with fibulin-5, in the maintenance of vessel integrity as well as in vessel recovery after injury (Chapman et al., 2010). In this regard, participation of fibulin-2 in artery integrity and stiffnes is also important in order to control blood pressure and it has been described the existence of some polymorphisms of FBLN2 associated with reduced levels of systolic blood pressure and decreased risk of hypertension (Vallvé et al., 2012).

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