FBLN5 (fibulin 5)

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Identity

Other names: ADCL2, ARCL1A, ARMD3, DANCE, EVEC, FIBL-5, UPS0
HGNC (Hugo): FBLN5
Location: 14q32.12

Note

Fibulin-5 is a matricellular glycoprotein, belonging to fibulin family which has 7 members (Yanagisawa et al., 2009). Compared with other fibulins, it has a unique arginine-glycine-aspartic acid (RGD) domain in the N-terminal region that mediates binding to integrins (Nakamura et al., 1999). Fibulin-5 is produced and secreted by endothelial cells, fibroblasts and vascular smooth muscle cells. The expression of Fibulin-5 is down-regulated in adult tissue but reactivated upon injury and various disease conditions (Yanagisawa et al., 2009). Fibulin-5 is essential for elastic fiber organization as shown by generation of Fibulin-5 knockout (Fbln5−/−) mice (Nakamura et al., 2002; Yanagisawa et al., 2002) and biochemical analysis (Hirai et al., 2007; Zheng et al., 2007). However, a mouse model with point mutation (D to E) (Fbln5RGE/RGE) in the RGD domain has exhibited intact elastic fibers (Budatha et al., 2011), indicating that Fibulin-5-Integrin interaction is not required for elastic fiber assembly. Fibulin-5 has also been implicated in various pathological conditions including cancer, cutis laxa and age-related macular degeneration.

**DNA/RNA**

**Description**

According to Ensembl Genome Browser, human Fbln5 gene locates on Chromosome 14q between region 92335756 and 92414331. This gene has 9 splicing variants transcriptionally. The only one with known protein function has 11 exons and 1347 nucleotides.

**Protein**

**Description**

Fibulin-5 is a secreted protein belonging to the fibulin family. It contains 448 amino acids with an approximate 66-Kda molecular weight.

It is mainly produced and secreted by endothelial cells, smooth muscle cells and fibroblasts (Yanagisawa et al., 2009).

It has six calcium-binding epidermal growth factor (cb EGF)-like domains, the first one of which contains a RGD motif responsible for cell surface integrin binding.

**Expression**

The expression of Fibulin-5 is most prominent in embryonic vasculature and neural crest cells and down-regulated in most adult organs (Nakamura et al., 1999). Fibulin-5 mRNA is detected mainly in heart, ovary and colon of adult human tissue (Nakamura et al., 1999).

However, Fibulin-5 expression can be reactivated upon tissue injury. It is reported that the expression of Fibulin-5 is elevated in human umbilical vein endothelial cells (HUVEC) by hypoxia in a HIF1α-dependent mechanism (Guadall et al., 2011).

Transforming growth factors β (TGF-β) can also increase the expression of Fibulin-5 in human lung fibroblasts (Kuang et al., 2006).

**Localisation**

Matricellular, secreted, extracellular matrix.

**Function**

Fibulin-5 is essential for the assembly of elastic fibers. Biochemical analysis shows that Fibulin-5 preferentially binds to monomeric tropoelastin through N- and C-terminal elastin-binding regions (Zheng et al., 2007). Fbn5−/− mice exhibit severe elastic fibre disorganization throughout the whole body (Nakamura et al., 2002; Yanagisawa et al., 2002).

Further studies have shown that Fibulin-5 regulates elastic fiber formation by increasing the efficacy of tropoelastin self-aggregation and cross-linking through direct binding to tropoelastin and lysyl oxidase like Loxl1, Loxl2 and Loxl4 (Yanagisawa et al., 2009).

In addition, Fibulin-5 binds cell surface α4β1 and α5β1 integrins, but does not support receptor activation (Lomas et al., 2007).

Additionally, Fibulin-5 competes with fibronectin for integrin binding. This competition serves to reduce fibronectin-mediated integrin-induced reactive oxygen species (ROS) generation (Schluterman et al., 2010).

**Mutations**

See table below.

**Implicated in**

**Bladder cancer**

**Note**

The expression of Fibulin-5 is downregulated in human bladder carcinoma samples (Hu et al., 2011). Increased proliferation and invasiveness were observed in a bladder cancer cell line with overexpression of Fibulin-5 (Hu et al., 2011).
Breast cancer

Note
The role of Fibulin-5 in breast cancer is still controversial. Oncomine database shows the reduction of Fibulin-5 mRNA in breast carcinomas, however, induction of Fibulin-5 expression is detected in breast cancer patient tissue by immunostaining (Lee et al., 2008). In addition, overexpression of Fibulin-5 can enhance tumor growth in an orthotopic mouse model of breast cancer (Lee et al., 2008). Meanwhile, overexpression of Fibulin-5 in breast cancer cells can reduce metastasis to liver and lung (Moller et al., 2011). The discrepancy between these studies could be due to cell line and mouse model differences. Fibulin-5 is also reported to participate in epithelial-mesenchymal-transition (EMT) in breast cancer cell lines in a MMP-dependent manner (Lee et al., 2008). However, the mechanism of Fibulin-5 regulation of MMP is unclear. For example, Fibulin-5 has been shown to inhibit and activate MMP9 activity, (Budatha et al., 2011; Lee et al., 2008; Moller et al., 2011).

Lung cancer

Note
Fibulin-5 expression is silenced in multiple lung cancer cell lines and human lung cancer samples by hypermethylation of the promoter region (Yue et al., 2009). Overexpression of Fibulin-5 reduces lung cancer invasion and metastasis through suppression of the MMP-7 expression and ERK phosphorylation (Yue et al., 2009).

Ovarian cancer

Note
The expression level of Fibulin-5 correlates inversely with the severity of disease (Wang et al., 2010). Expression of Fibulin-5 is also remarkably decreased in metastatic sites.

Pancreatic cancer

Note
Fibulin-5 is required for aggressive tumor growth and angiogenesis in a mouse model of pancreatic cancer (Schluterman et al., 2010). Tumor weight and blood vessel density in Fbln5<sup>−/−</sup> or Fbln5<sup>RGE/RGE</sup> mice are significantly reduced compared with wildtype mice in subcutaneous and orthotopic models. Increased level of ROS, DNA damage and apoptotic endothelial cells were detected in tumors grown in Fibulin-5 deficient mice. In vitro analysis identified that Fibulin-5 reduces ROS production in a fibronectin and integrin β1-dependent manner (Schluterman et al., 2010).

Age-related macular degeneration (AMD)

Note
DNA sequencing revealed 10 distinct heterozygous missense mutations in Fbln5 in 1-2% of AMD patients (Auer-Grumbach et al., 2011; Lotery et al., 2006; Stone et al., 2004). The underlying biochemical basis of two missense mutations, I169T and G267S was further studied by
nuclear magnetic resonance (NMR) and chromophoric calcium chelation experiments. The results show that G267S substitution leads to protein misfolding and inhibition of secretion, but not the I169T substitution (Schneider et al., 2010).

**Disease**

Age-related macular degeneration (AMD) is an eye disease affecting the macula and is the main reason for irreversible version loss in elderly people (Lotery et al., 2006).

**Charcot-Marie-Tooth disease (CMT)**

**Note**

Missense mutations of Fbln5 were detected in CMT neuropathy patients (Auer-Grumbach et al., 2011).

**Disease**

Charcot-Marie-Tooth disease (CMT) is an autosomal dominantly inherited disorder of peripheral nervous system (Auer-Grumbach et al., 2011). It is characterized by lifelong disabilities because of muscle weakness and loss of touch sensation (Auer-Grumbach et al., 2011).

**Cutis laxa**

**Note**

Mutations in Fbln5 have been identified in hereditary and acquired forms of cutis laxa. Three homozygous mutations (C217R, S227P and R284X) in Fbln5 have been reported in autosomal recessive cutis laxa patients (Claus et al., 2008; Elahi et al., 2006; Loey et al., 2002). In addition, a heterozygous in-frame tandem duplication of Fbln5 exon 5-8 has been discovered in a sporadic cutis laxa patient (Markova et al., 2003).

Mutational analysis also shows that a cutis laxa patient has a heterozygous missense mutation (G202R) in Fbln5 and compound heterozygous mutation in elastin alleles (A55V and G773D) (Hu et al., 2006b).

These findings further support that Fibulin-5 is essential for the formation and maturation of the tropoelastin self-aggregation process, which is required for elastic fiber assembly (Hu et al., 2006a).

**Disease**

Cutis laxa is a connective tissue disorder characterized by loose and redundant skin and multiple internal organ abnormalities due to fragmentation and paucity of elastic fibers.

**Pelvic organ prolapse (POP)**

**Note**

Lower level expression of Fibulin-5 was identified in patients with POP (Soderberg et al., 2009; Takacs et al., 2009). It is reported that Fibulin-5 can prevent the development of POP by regulating elastic fiber homeostasis and inactivating MMP-9 in the vaginal wall (Budatha et al., 2011).

**Disease**

Pelvic organ prolapse (POP) is a common disease for elder women characterized by loss of pelvic floor support leading to protrusion of pelvic organs like uterus, bladder and vagina.

**Thoracic aortic aneurysmal disease (TAD)**

**Note**

The expression of aortic Fibulin-5 is significantly decreased in patients with TAD. The low level of Fibulin-5 strongly correlates with disorganization of elastic fibers, which may contribute to aorta abnormality (Wang et al., 2005).

**Disease**

Thoracic aortic aneurysmal disease (TAD) is an aortic disorder characterized by loss of elastin in the wall of aorta (Wang et al., 2005).

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