FST (follistatin)

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Identity
Other names: FS
HGNC (Hugo): FST
Location: 5q11.2
Local order
RPS19P4 (ribosomal protein S19 pseudogene 4) - FST - NDUFS4 (NADH dehydrogenase (ubiquinone) Fe-S protein 4).

DNA/RNA
Description
The human FST gene is comprised of six exons spanning 5329 bp on chromosome 5q11.2 and gives rise to two main transcripts of 1122 bp (transcript variant FST344) and 1386 bp (transcript variant FST317). The first exon encodes the signal peptide, the second exon the N-terminal domain and exons 3-5 each code for a follistatin module. Alternative splicing leads to usage of either exon 6A, which codes for an acidic region in FST344 or exon 6B, which contains two bases of the stop codon of FST317 (Shimasaki et al., 1988).

Transcription
Transcription of FST mRNA was shown to be stimulated by TGF beta and activin A via Smad proteins (Bartholin et al., 2002), which seems to be part of a negative feedback loop as FST can antagonize activin A (see below).
Other factors and pathways that have been demonstrated to stimulate follistatin gene transcription are gonadotropin-releasing hormone (GnRH) acting via cAMP and CREB (Winters et al., 2007), GLI2, a transcription factor activated by hedgehog signaling (Eichberger et al., 2008), dexamethasone (Hayashi et al., 2009), androgens and activators of Wnt signaling (Willert et al., 2002; Yao et al., 2004; Singh et al., 2009). Repression of the follistatin promoter in response to peroxisome proliferator-activated receptor gamma was mediated via SP1 (Necela et al., 2008).

**Protein**

**Description**

Mature secreted follistatin protein exists in three main forms consisting of 288, 303, and 315 amino acids (Sugino et al., 1993). The FST344 transcript gives rise to a protein precursor of 344 amino acids, which results in the mature 315 amino acid form after removal of the signal peptide. A fraction of follistatin 315 is further converted to the 303 amino acid form by proteolytic cleavage at the C-terminus. Signal peptide removal of FST317 leads to the mature 288 amino acid form of follistatin. All forms of follistatin contain three follistatin domains (FSD) characterized by a conserved arrangement of 10 cysteine residues. The N-terminal subdomains of the FSD have similarity with EGF-like modules, whereas the C-terminal regions resemble the Kazal domains found in multiple serine protease inhibitors. The follistatin protein contains two potential N-glycosilation sites on asparagines 124 and 288.

**Localisation**

Follistatin is expressed in a wide variety of tissues and organs with the highest expression in the ovaries and testes (Phillips and de Kretser, 1998; Tortoriello et al., 2001). The signal peptide directs the nascent protein to the secretory pathway and follistatin has been detected in human serum and in cell culture supernatants of multiple cell lines (Phillips and de Kretser, 1998). Among the follistatin isoforms FST315 was secreted faster than FST288 (Schneyer et al., 2003) and due to the lack of binding to cell-surface heparin-sulfated proteoglycans, a larger fraction of FST315 enters the circulation (Schneyer et al., 1996).

**Function**

Follistatin binds to several members of the TGF beta family and blocks the interaction of these cytokines with their cognate receptors. Follistatin was first identified as a factor that could inhibit the release of follicle-stimulating hormone from pituitary cells (Ueno et al., 1987). It binds activins A, B and AB with high affinity and was also reported to bind activin E but not activin C (Nakamura et al., 1990; Schneyer et al., 1994; Hashimoto et al., 2002; Wada et al., 2004). Follistatin-bound activin is unable to initiate signal transduction and consequently follistatin is a potent antagonist of physiological activin signals. Of the three follistatin domains present in all follistatin isoforms, (Shimasaki et al., 1988) the first two, but not the third, are necessary for activin A binding (Keutmann et al., 2004; Harrington et al., 2006). Aside from activins, follistatin also binds several bone morphogenetic proteins (BMP) including BMP2, BMP4, BMP6 and BMP7 (Iemura et al., 1998; Glistter et al., 2004). In 2004 it was shown that follistatin binds myostatin (also known as growth and differentiation factor 8, GDF8) with high affinity and thereby is able to antagonize the inhibitory effect of myostatin on muscle growth (Amthor et al., 2004). The functional significance of the interaction between follistatin and angiogenin, a pro-angiogenic factor unrelated to the TGF beta family, remains to be determined (Gao et al., 2007). The interaction of follistatin with heparin and heparan sulfates is isoform specific. Follistatin 288 binds to heparan sulfates, whereas this binding is blocked by the acidic tail of follistatin 315 (Sugino et al., 1993).

Knock-out mice for follistatin die within hours after birth and show multiple abnormalities of muscles, skin and skeleton (Matzuk et al., 1995). Evidence from many organs and tissues shows that counterbalancing of signals from TGF beta family members by follistatin is crucial for normal tissue development, architecture and function (de Kretser et al., 2004; McDowell et al., 2008; Kreidl et al., 2009; antisiferova et al., 2009). Due to the capability for efficient antagonization of signals from activin and myostatin, the therapeutic application of follistatin has been discussed in several clinical conditions involving elevated activin/myostatin activity. Potential areas of application include blocking increased activin expression in inflammation (Phillips et al., 2009) and fibrotic disorders (Aoki and Kojima, 2007) and inhibition of myostatin in muscle diseases (Rodino-Klapac et al., 2009).

**Homology**

The follistatin module with its characteristic spacing of cysteines represents a conserved protein domain. Follistatin modules are found in varying numbers in a wider set of secreted proteins including FSTL1, SPARC/osteonectin, or agrin (Ullman and Perkins, 1997). Among these, follistatin-like 3 (FSTL3, FLRG) shares a similar overall domain architecture with follistatin, but harbors only two instead of three follistatin modules (Tortoriello et al., 2001). With respect to activin binding ability, functional homology among follistatin domain-containing proteins is only found between follistatin and FSTL3, whereas all other follistatin family proteins have not been demonstrated to bind proteins of the TGF beta family (Tsuchida et al., 2000). Follistatin is also highly conserved between species with around 97% amino acid identity in human, mouse and rat.
Implicated in

**Malignancy**

*Note*

Overexpression of follistatin has been found in rat and mouse models of hepatocellular carcinoma (HCC) (Rossmanith et al., 2002; Fujiwara et al., 2008) as well as in tumor tissue and serum of HCC patients (Yuen et al., 2002; Grusch et al., 2006; Beale et al., 2008). However, follistatin had no benefit as surveillance biomarker for HCC development in patients with alcoholic and non-alcoholic liver disease (ALD and NAFLD) due to the already elevated levels in the underlying liver pathologies (Beale et al., 2008). Follistatin overexpression was also demonstrated in human melanoma cell lines (Stove et al., 2004) and has been suggested as candidate biomarker for lung cancer (Plaqué et al., 2009).

**Endometriosis**

*Note*

Follistatin was increased in serum of women with ovarian endometriosis and suggested as biomarker for endometrioma (Florio et al., 2009).

**Polycystic ovary syndrome**

*Note*

A genetic linkage analysis found evidence for linkage of follistatin with polycystic ovary syndrome (PCOS) (Urbanek et al., 1999). Another study reported that the follistatin gene is not a susceptibility locus for PCOS but a single nucleotide polymorphism of the gene may be involved in the hyperandrogenaeemia of the disease (Jones et al., 2007).

**Liver failure**

*Note*

Serum levels of follistatin and activin A were increased in patients with acute liver failure and it was suggested that a decreased follistatin/activin A ratio in the blood may be an indicator for the severity of liver injury in hepatitis-related acute liver disease (Hughes and Evans, 2003; Lin et al., 2006).

**References**


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