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Gene Section
Mini Review

TNC (tenascin C (hexabrachion))

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Identity

Hugo: TNC
Other names: Cytotactin; GMEM; GP (150-225); Glioma associated extracellular matrix antigen; Hexabrachion; J1; Myotendinous antigen; Neuronectin; TN
Location: 9q33.1

DNA/RNA

Description

The tenascin-C gene consists of 27 exons spanning 97.63 kb of genomic DNA.

Transcription

7271 bp mRNA transcribed on the reverse strand; 6333 bp open reading frame.
The transcript starts with a non-coding exon 1 (179 bp) followed by exon 2, which contains the start codon (ATG) for translation initiation. Exon 1 is located 26827 bp upstream of exon 2.

Protein

Description

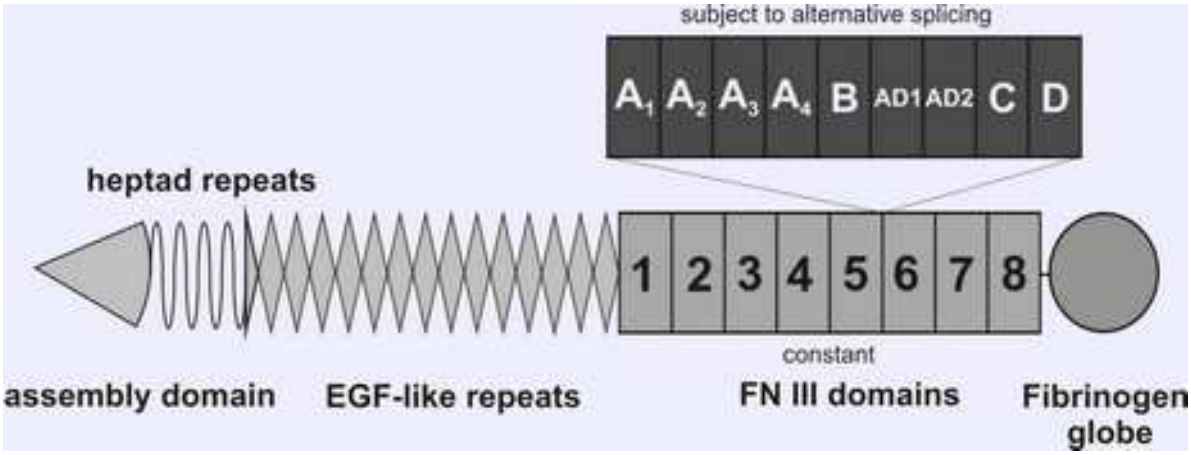
Tenascin-C consists of structural motifs arranged in a linear order. Mammalian tenascin-C proteins contain amino-terminal heptad repeats, 14.5 EGF-like repeats, 8 constant FN III domains, whereas 9 additional FN III domains can be included in a combinatorial manner by alternative splicing, and a carboxyl-terminal fibrinogen globe. A prominent feature of tenascin-C is the assembly into hexamers, so-called hexabrachions.

exon	1	2	3	4	5	6	7	8	9	10
exon length (bp)	179	593	1410	264	116	157	270	186	90	264
intron length (bp)	26827	3288	1391	1401	763	3559	1367	268	2165	8683

exon	11	12	13	14	15	16	17	18	19	20
exon length (bp)	273	273	273	273	273	273	123	144	120	144
intron length (bp)	578	606	2914	2304	10470	4068	1134	2560	2019	763

exon	21	22	23	24	25	26	27
exon length (bp)	131	133	152	97	162	164	734
intron length (bp)	3518	1147	797	2664	2397	2705	

Table shows the lengths of the exons and introns of human tenascin-C.



Schematic representation of a monomeric tenascin-C subunit.

The primary sequence encodes a protein of 2110 amino acids. Amino acids 1-22 represent the secretion signal, amino acids 189-621 constitute the EGF-like repeats, and amino acids 622-1882 account for the FNIII domains. SDS-Page analysis revealed a molecular weight of full-length tenascin-C of 250 kDa - 300 kDa per subunit under reducing conditions.
Alternative splicing within the stretch of FN III domains results in a great number and diversity in tenascin-C isoforms.

Expression

More than two decades ago, tenascin-C was discovered as an extracellular matrix protein (ECM) enriched in the stroma of gliomas and as a myotendinous antigen. Tenascin-C expression is highly regulated both during development and in the adult. Tenascin-C levels are high during embryogenesis, but almost absent during normal postnatal life with some basal expression detectable in tendons and ligaments only. In adult life, tenascin-C is also expressed within the sub-ventricular zone in the central nervous system, a region that constitutes the neural stem cell niche. A prominent feature of tenascin-C is its re-appearance in response to pathological situations such as infection, inflammation and tissue remodeling. Another striking example of a pathological situation leading to the re-expression of tenascin-C is the onset of tumorigenesis, where tenascin-C is specifically expressed in the activated tumor stroma. Tenascin-C can be induced by various stimuli, such as the pro- and anti-inflammatory cytokines, interleukins, TNFa or IFNg and growth factors such as TGFb, EGF or PDGF. Furthermore, tenascin-C inducing stimuli include mechanical stress, hypoxia, and reactive oxygen species, factors or conditions which also might play a prominent role in tumors.

Localisation

Extracellular matrix.

Function

Adhesion: Tenascin-C acts as an anti-adhesive substratum for a large variety of cells. Active inhibition of cell spreading was further confirmed by mixing tenascin-C together with fibronectin, which is a classical adhesion protein. Whereas cells on fibronectin nicely spread, form focal contacts and actin stress fibers, the same cells plated on a mixed fibronectin-tenascin-C substratum are not able to spread and do not form focal contacts and actin cables.
Migration: Tenascin-C enhances migration and invasiveness of different cancer cells.
Proliferation: Tenascin-C stimulates cancer cell proliferation.
Angiogenesis: Tenascin-C is expressed around angiogenic vessels in many tumors and there is evidence that it promotes and regulates angiogenesis in vitro and in vivo. Moreover, in glioma patients, clinical studies revealed an inhibition of tumor angiogenesis by applying antibodies directed against tenascin-C.

Homology

Tenascin-C belongs to the tenascin family, which is a highly conserved family of large oligomeric extracellular matrix proteins. Vertebrate genomes harbor four tenascin genes, which have been termed tenascin-C, tenascin-XB (TNXB), tenascin-R, and tenascin-W.

Mutations

Germinal

A SNP was identified resulting in an amino acid substitution (Leu1677Ile in the tenascin-C FN III domain D) which strongly associates with adult bronchial asthma. Therefore, this SNP might be an asthma marker and may be important in its pathogenesis.

Implicated in

Cancer (general)

Oncogenesis

Tenascin-C is strongly expressed in the stroma of various cancers and has been reported to be associated with the invasive front of tumors. For cancers in the lung, colon, and brain, high tenascin-C expression correlates with poor prognosis, whereas in other cancers no clear correlation between tenascin-C and survival or malignancy exists. In search for new diagnostic or prognostic tumor markers, tenascin-C levels have often been analyzed in sera of cancer patients and its potential value as a biomarker has been evaluated. Although elevated tenascin-C serum levels have been found in certain cancers, it still remains a questionable tumor marker. Tenascin-C levels are scattered over a wide range with many cancer patients having normal tenascin-C concentrations and its expression strongly correlates with inflammation or infection.

Breast cancer

Oncogenesis

By means of in vivo selection and microarray analysis a gene expression signature was identified that mediates breast cancer metastasis to lung. Tenascin-C is one of those genes that have been found to belong to the lung metastasis signature genes.

A recent study identified tenascin-C as a direct target gene for the microRNA miR-335. This microRNA is specifically lost as human breast cancer cells develop metastatic potential. Knockdown of tenascin-C in the highly metastatic LM2 cells (a metastatic derivative of the human breast cancer cell line MDA-MB-231) reduced migration in a trans-well assay and significantly inhibited lung colonization by LM2 cells.

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