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Gene Section
Review

ETS1 (v-ets erythroblastosis virus E26 oncogene homolog 1 (avian))

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Identity

Other names: ETS-1; EWSR2; FLJ10768; p54

HGNC (Hugo): ETS1

Location: 11q24.3

DNA/RNA

Note

Ets-1 is a 63 kb large gene with 8 exons located on chromosome 11q24.3.

Several splice variants are known:

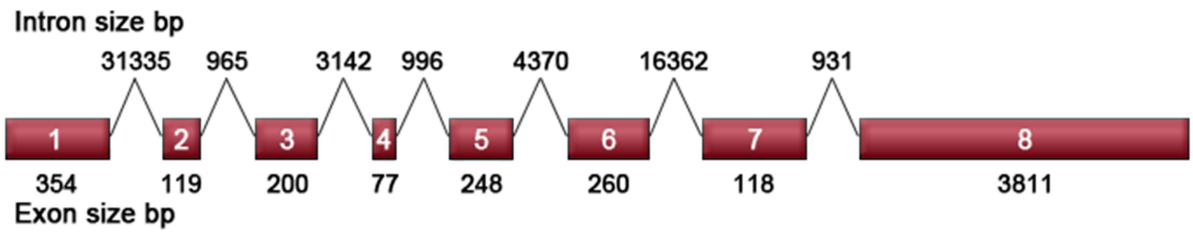
- full length including exons 1-8 (p51) (Macleod et al., 1992),
- without exon 7 (p42) (Koizumi et al., 1990; Jorcyk et al., 1991),
- without exon 4 (Jorcyk et al., 1991),
- without exon 4 and 7 (Jorcyk et al., 1991),
- without exon 6 (Rothhammer et al., 2004),
- without exon 3 to 6 (p27) (Laitem et al., 2009).

The full length protein p51 and the splice variants p42 and p27 have been investigated in functional terms (Laitem et al., 2009). The other splice variants have only been shown to exist without describing their functions. The full length (p51) is important for angiogenesis, vasculogenesis as well as T- and B-cell formation. In the presence of calcium the p42-form cannot be phosphorylated. Under these conditions its self-inhibitory function is disturbed (Lionneton, 2003). The p42-form can bind stronger to the target DNA than the full length protein (Fisher et al., 1994). The p27-form has a double inactivating function.

On the one hand it can bind to the Ets-binding site of the DNA without activating the transcription of the target gene.

On the other hand it can actively delocalize the p51 form out of the nucleus through a mechanism not yet known (Laitem et al., 2009).

The promoter region of Ets-1 lacks the TATA-box and CAAT-box, but has six GC rich consensus sequences, which are recognized by SP1, two consensus sequences detected by AP1 and one consensus sequence, which can be recognized by AP2 (Jorcyk et al., 1991).



Intron/exon arrangement of Ets-1. It is noteworthy, that the first intron is over 30 kb long, half of the length of the whole Ets-1 gene.

Protein

Description

The human Ets-1 protein consists of 441 amino acids.
Several functional domains have been characterized:
- The pointed domain comprises the amino acids 54 to 135. This domain consists of five alpha-helices, forming a globular structure (Slubsky et al., 1998).
- The second domain between amino acids 130 and 242 is the transactivating domain, necessary for activation of transcription (Gegonne et al., 1992).
- The third domain, called the exon VII domain, spans the amino acids 243 to 331. It contains two regulatory domains. The C-terminal of this domain includes a self-inhibitory domain, which inhibits the interaction between Ets-1 and its partner proteins (Petersen et al., 1995). In the presence of DNA the inhibitory domain is cleaved (Petersen et al., 1995). The N-terminal part of the exon VII domain is driven by a calcium-dependent phosphorylation. After phosphorylation the binding of Ets-1 to the specific DNA-region is disturbed (Rabault and Ghysdael, 1994).
- The fourth domain connected to the Exon VII domain is the ETS-domain. It includes amino acids 331 to 415. This domain contains three alpha-helices and four beta-strands and builds a helix-turn-helix motive (Werner et al., 1995; Werner et al., 1997).

All members of the Ets-transcription factor-family contain the ETS-domain which consists of approximately 80 amino acids with four tryptophan repeats (Walsylyk et al., 1993). The ETS-domain binds to double-stranded DNA of target genes containing a GGAA/T core motive and different flanking regions (Sharrocks, 2001; Dittmer, 2003; Karim et al., 1990; Oikawa and Yamada, 2003). The sequences flanking the GGAA/T core as well as binding of further proteins to Ets-1 determine the DNA-binding specificity (Walsylyk et al., 1993). Among these proteins are different transcription factors including members of the Ets-family (Lelièvre et al., 2000). The expression of Ets-family members is controlled by different proteins like angiogenic factors (e.g. VEGF, TNF-alpha, TGF-beta and fibroblast growth factor 2). The activity of the Ets-family members can be induced or repressed by several kinases (e.g. MAP kinases and tyrosine kinases) (Lelièvre et al., 2000).

Localisation

Ets-1 protein is normally located in the nucleus. ETS1 mRNA and protein can also be detected in the cytoplasm of endothelial cells during angiogenesis (including tumor vascularization), in different tumor cells as well as in fibroblasts of the tumor stroma (Valter et al., 1999; Mylona et al., 2006; Takai et al., 2000; Takai et al., 2002; Wernert et al., 1994; Behrens et al., 2003). The de-localization of Ets-1 out of the nucleus into the cytoplasm could be mediated by the p27-form of the Ets-1 protein (Laitem et al., 2009).

Function

Ets-1 can transactivate or transrepress many target genes depending upon interaction partners of Ets-1 such as CREB binding protein (Hamzaoui et al., 2007). About 200 target genes of Ets-family members are known. They can be grouped according to their functions into genes involved in viruses, transcription, transformation, protein degradation, cell cycle regulation, apoptosis, cell signaling, growth and other processes (Sementchenko et al., 2000).
Among target genes of Ets-1 are those encoding several matrix metalloproteases (MMP-2, MMP-3, MMP-4 and MMP-9), TIMPs and uPA. Ets-1 is among the first genes up-regulated during chicken embryogenesis (Vandenbunder et al., 1989). It is particularly expressed in mesoderm, the neural crest as well as during haematopoiesis and blood vessel formation (Vandenbunder et al., 1989; Lincoln II and Bove, 2005). Ets-1 is also upregulated in lungs and kidneys, which undergo a branching remodeling (Raffetseder et al., 2004; Kola et al., 1993; Maroulakou and Bowe, 2000).
In adults Ets-1 is important for the maturation of B and T cells (Bories et al., 1995) and is highly expressed during wound healing and tumor angiogenesis (Wernert et al., 1992; Maroulakou and Bowe, 2000).
Ets-1 is also implicated in angiogenesis under normal and other pathological conditions, such as the menstrual cycle (Fujimoto et al., 2003), granulation tissue formation and inflammatory angiogenesis during rheumatoid arthritis (Wernert et al., 1992; Wernert et al., 2004). Ets-1 is not implicated in the formation of lymphoid vessels (Wernert et al., 2003).
Another function of Ets-1 is the regulation of apoptosis (Teruyama et al., 2001) by regulating genes encoding Bax, Bcl-2, Caspase-1 and Fas ligand (Nagarajan et al., 2009).

Homology

Ets-1 is very similar to Ets-2 and found in several different animals (Laudet et al., 1999). Animals without Ets-1 have a higher Ets-2 expression level. The sequence of DNA and protein differs by only 15% (DNA) and 5% (protein) between human and chicken (Watson et al., 1988).
Two different transcription initiation sites exist in birds and reptiles leading to the expression of p68 and p54 (Mcleod et al., 1992).

Implicated in

Tumors

Note

In tumors Ets-1 has also been shown to be implicated in proliferation, migration and invasion of neoplastic cells such as melanoma and Hela cells (Rothhammer et al., 2003; Turner et al., 2007; Hahne et al., 2005).

In-vivo high Ets-1 expression can already be found in early phases of tumor development (Behrens et al., 2001; Behrens et al., 2003). Fibroblasts of the tumour stroma express Ets-1 during tumor invasion (Wernert et al., 1994).

Prostate cancer

Note

Ets-1 is strongly upregulated in prostate cancer cells (Alipov et al., 2005). A positive correlation between ETS-1 expression and Gleason score of prostate cancers has been demonstrated (Alipov et al., 2004).

Breast cancer

Note

In breast cancer Ets-1 is a marker of poor prognosis (Lincoln II and Bove, 2005).

Lung cancer

Note

Ets-1 expression in lung cancer is more often found in males and in squamous cell carcinomas than in women and in adenocarcinomas. In adenocarcinomas Ets-1 expression correlates with tumour size and poor prognosis (Yamaguchi et al., 2007).

Colon cancer

Note

In colon cancer Ets-1 expression is directly related to malignancy with no expression in normal tissues and highest expression levels in adenocarcinomas with lymph node metastasis. Thus Ets-1 could be used as a prognosis-marker in colon cancer (Ito et al., 2002).

Pancreatic cancer

Note

In normal pancreatic tissue, Ets-1 expression is found to be weak in contrast to well differentiated carcinoma, in which Ets-1 is strongly expressed. The level of Ets-1 is downregulated again in poorly differentiated adenocarcinoma (Ito et al., 1998). Ets-1 has no effect upon tumor size, prognosis or TNM stage of pancreatic cancer (Ito et al., 1998).

Rheumatoid arthritis

Note

In rheumatoid arthritis Ets-1 is upregulated in synovial fibroblasts by TNF-alpha and IL-1, both mayor cytokines in inflammation. Ets-1 may affect the regulation of destructive metalloproteases (Redlich et al., 2001). Ets-1 is also considered responsible for the development of new blood vessels in rheumatoid tissues (Redlich et al., 2001; Wernert et al., 2002).

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