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Gene Section
Review

FOSL1 (FOS-like antigen 1)

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Identity

Other names: FRA, FRA1, fra-1

HGNC (Hugo): FOSL1

Location: 11q13.1

DNA/RNA

Description

Fra-1 (Fosl-1) is a basic leucine zipper (bZIP) transcription factor and a member of Fos family of proteins (Cohen and Curran, 1988). The Fra-1 gene spans about 8.31 kb including four exons and is located on chromosome 11q13. It contains two regulatory elements, an upstream 5'-flanking region and an intragenic sequence, that are known to regulate its transcriptional induction (Verde et al., 2007). Two critical elements of the promoter, the upstream TPA response element (TRE) and the serum response element (SRE), are required for Fra-1 transcriptional induction in response to external stimuli, such as mitogens and cytokines (Adiseshaiah et al., 2003; Adiseshaiah et al., 2005). The intragenic regulatory element containing the TRE/TRE-like elements also contribute to Fra-1 induction (Bergers et al., 2005).

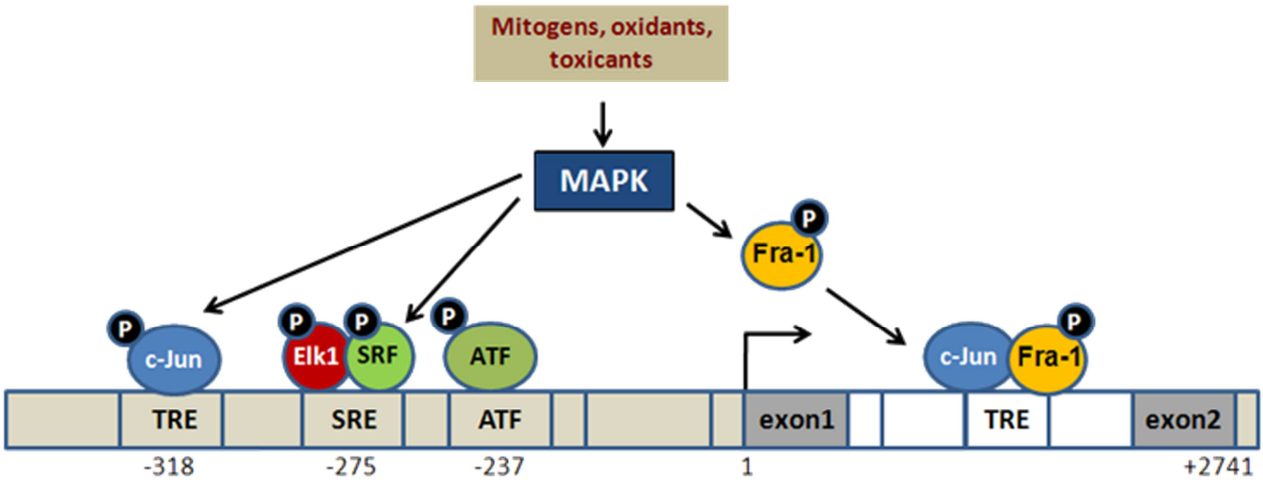
Transcription

Fra-1 transcription is strongly inducible by mitogens and inflammatory cytokines as well by a wide variety of environmental toxicants, carcinogens, and pathogens. In contrast to the early activation of c-Jun and c-Fos (which peaks at 15-30 min), the induction of Fra-1 by various mitogenic and stressful stimuli peaks at 90-180 min, and this delayed induction is postulated to play important role in modulating the transcriptional response initiated by the AP-1 complex composed of Jun/c-Fos dimers. The Fra-1 promoter region contains a c-Fos-like serum response element (SRE), which is constitutively occupied by the serum response factor (SRF) and the ternary complex factor, Elk1. Recruitment of c-Jun to the upstream TRE and the presence of downstream SRE as well as the activating transcription factor (ATF) site are essential for Fra-1 induction by mitogenic and cytokine stimuli (Adiseshaiah et al., 2007). Sp1 family members also regulate Fra-1 transcription (Adiseshaiah et al., 2005).

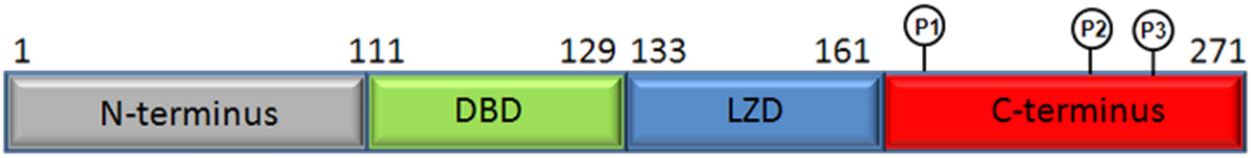
Other studies have shown that cis-elements, such as TRE and E boxes, located in the intragenic region also contribute to Fra-1 transcription (Bergers et al., 1995, Casalino et al., 2003,).

Histone modifications, such as the phosphorylation of Histone 3 by PIM1 on the nucleasome at the MYC binding sites, regulate the transcriptional activation of Fra-1 (Zippo et al., 2007).

In addition to transcriptional induction, ERK-dependent phosphorylation has been shown to play a key role in the protein stability and DNA binding activity of Fra-1 (Basbous et al., 2007, Young et al., 2002).



Transcriptional regulation of Fra-1 (Fosl-1): MAPK signaling activates transcriptional factors binding at the human Fra-1 promoter. Binding of Fra-1 and c-Jun to TRE sites of first intron regulates Fra-1 transcription. TRE - TPA response element, SRE - Serum response element, SRF - serum response factor, ATF - activating transcription factor binding site.



A schematic diagram showing the modular structure of Fra-1 (1-271 AA). DBD -DNA binding domain, LZD - leucine-zipper domain, N - amino terminus, C - carboxyl terminus. P1 - Thr 231, P2 - Ser252, P3 - Ser265. In this, ERK mediated phosphorylation of serine residues 252 and 265 requires for the stabilization of Fra-1 in certain tumor cell lines (Basbous et al., 2007).

Pseudogene

One pseudo gene is identified, the FOS-like antigen pseudogene, FOSL1P1 (NCBI, HGNC ID: 44055).

Protein

Description

Fra-1 (Fosl-1) protein encodes for 271 amino acids with an expected molecular weight of 29.4 kDa. However, in immunoblot analysis of cellular extracts isolated from cells stimulated with growth factors or from cancer cells, Fra-1 exhibits multiple forms ranging from 30-40 kDa. The appearance of these multiple forms is mainly attributed to post-translational modification (e.g., phosphorylation) of this protein. Human and mouse Fra-1 exhibits 6 and 1 splice variants, respectively, and both exhibit one unspliced form. These different transcripts encode proteins with different functional domains. The functional significance of these alternatively spliced variants of Fra-1 for both in physiology and pathological processes remains unclear.

Expression

The expression of Fra-1 is high in smooth muscle cells, bronchial epithelial cells (trachea), and the pancreas, but its expression is low in other tissues, such as the brain and prostate.

Localisation

Fra-1 (Fosl-1) contains a nuclear localization signal and is predominantly found in the nucleus. However, Fra-1 antigen is observed in the cytoplasm under certain conditions, such as elevated levels of oxidative stress (Burch et al., 2004) and in cancerous tissues (Song et al., 2006). Furthermore, a distinct cytoplasmic location of Fra-1 has been noted in non-small-cell lung cancer (Ma et al., 2009). Nuclear and cytoplasmic expression of Fra-1 is markedly elevated in human adenomas, adenocarcinomas and neuroendocrine carcinomas (Zhang et al., 2005).

Function

After dimerization, mainly with the Jun or ATF family of proteins, Fra-1 binds to the TPA response element (TRE, or AP-1 site) and regulates gene expression in a context-dependent manner (Cohen et al., 1989). Fra-1 plays important roles in various biological processes, including inflammation, transformation, proliferation, and metastasis. Increased expression levels of Fra-1 is detectable in breast, lung, brain, colon and prostate cancers and its knockdown affects cancer cell progression (see below).

Homology

The Fra-1 gene is conserved in chimpanzee, dog, cow, mouse, rat, and Zebra fish.

Mutations

Note

No genetic mutations leading to activation or inactivation of this transcription factor in human disease development and in malignancies have been yet documented. Recently, the presence of SNPs was demonstrated in human Fra-1 (FOSL-1) gene, and these SNPs were shown to be associated with a decreased rate of lung function (Sandford et al., 2012).

Implicated in

Thyroid cancer

Note

Analysis of samples from thyroid cancer patients has shown an increase in Fra-1 protein expression in thyroid nodules (Chiappetta et al., 2000). Induction of Fra-1 expression has also been observed in human thyroid cancer cell lines (Battista et al., 1998).

Inhibition of Fra-1 prevents the retrovirally induced neoplastic transformation of rat thyroid cells (Vallone et al., 1997). In thyroid cancer cells, Fra-1 binds to the cyclin A promoter and regulates its expression during cell-cycle progression (Casalino et al., 2007).

Non-small-cell lung cancer (NSCLC)

Note

Expression of AP-1 family proteins, and particularly Fra-1 has been detected in NSCLC cell lines (Risse-Hackl et al., 1998). Decreased levels of Fra-1 protein expression have been noted in the tumor tissue of non small cell lung cancer patients (Ma et al., 2009), and these decreased levels have been positively correlated with progression of tumor stage and worsening prognosis. Ectopic expression of Fra-1 in lung adenocarcinoma cells induces cancer. Interestingly, it has been reported that a DNA vaccine specific to Fra-1 prevents pulmonary cancer metastasis in syngeneic mice (Luo et al., 2005).

Breast cancer

Note

Increased expression of Fra-1 was observed in human breast cancer cells (Philips et al., 1998). Several studies have shown its involvement in cancer cell proliferation, motility and invasiveness (Bamberger et al., 1999; Belguise et al., 2005; Logullo et al., 2011). An increase in nuclear or cytoplasmic localization of Fra-1 has been considered as a marker of progression of breast cancer (Song et al., 2006, Chiappetta et al., 2007). Knockdown of Fra-1 in tumor associated macrophages with small interfering RNA has been found to significantly suppress the invasion, angiogenesis and metastasis of breast cancer tumor cells (Luo et al., 2010). Likewise, knockdown of Fra-1 in estrogen- resistant MCF-7 cells significantly affected their growth and enhanced their susceptibility to cell death in response to estrogen treatment (Pennanen et al., 2011). An increased accumulation of Fra-1 protein in estrogen-negative breast cancer cells is mediated through PKCθ pathway (Belguise et al., 2012).

A mouse Fra-1 targeted DNA vaccine has been found to be effective in protection against breast cancer in mice (Luo et al., 2003). Low level of miRNA-34 has been correlated with an elevated level of Fra-1 expression in breast cancer tissues and cell lines, but ectopic miRNA-34 expression causes a down-regulation of Fra-1 levels and inhibits breast cancer cell progression (Yang et al., 2012). In a different study, Fra-1 overexpression was shown to increase the chemosensitive of breast cancer stem cells, suggesting Fra-1 can be considered as a prognostic responsive marker in breast cancer therapy (Lu et al., 2012).

Bladder cancer

Note

An increased level of Fra-1 expression is found in bladder tumor and cancer cell lines. Fra-1, via the transcriptional induction of the receptor tyrosine kinase AXL, promotes bladder cancer cell motility (Sayan et al., 2012).

Colon cancer

Note

Fra-1 and its dimeric partner, c-Jun, are up-regulated in human colorectal tumors (Zhang et al., 2005; Wang et al., 2002). In colon carcinoma cells, the basal induction and stabilization of Fra-1 has been shown to be regulated by ERK activity, and knockdown of Fra-1 suppresses colon cancer cell polarization and progression (Vial and Marshall, 2003). A potential role for Fra-1 in the regulation of vimentin during Ha-RAS-induced epithelial-to- mesenchymal transition and migration has been documented (Andreolas et al., 2008). By upregulating miR-34a, p53 indirectly down regulates Fra-1 mRNA and protein expression in colon cancer cells and inhibits cell migration and invasion (Wu et al., 2012).

Prostate cancer

Note

Akt signaling contributes to Fra-1 induction in the prostate cancer cells, mainly at the transcription level (Tiwari et al., 2003). An abnormal activation of Fra-1 has been linked to elevated expression levels of IL-6, which promote prostate cancer cell progression and resistance to chemotherapeutic agents (Zerbini et al., 2003).

Esophageal squamous cell carcinoma (ESCC)

Note

Immunoreactive analysis of two different ESCC cell lines (HKESC-1 and HKESC-2) derived from ESCC patients has demonstrated Fra-1 expression in these cell line (Hu et al., 2001). An elevated level of Fra-1 expression is associated with poor prognosis of ESCC.

Furthermore, Fra-1 knockdown in ESCC cell lines decreases tumor cell progression and invasion (Usui et al., 2012).

Nasopharyngeal carcinoma (NPC)

Note

Expression profiling of nasopharyngeal carcinoma and normal cells has revealed elevated expression levels of Fra-1 in NPC cancer cells (Fung et al., 2000). Fra-1 has been shown to play an important role in controlling latent membrane protein 2A (LMP2A)-induced NPC epithelial cell motility and invasiveness (Lan et al., 2012). Either inhibition of Fra-1 induction or suppression of ERK1 and ERK2 activation will block the LMP2A-induced MMP-9 expression required for cancer cell progression.

Glioma

Note

Ectopic Fra-1 expression in malignant glioma cells leads to phenotypic changes associated with invasiveness and tumorigenicity (Debinski and Gibo, 2005). In contrast, knock down of Fra-1 in high-grade glioma (HGG) cells alters the morphology, reduces both anchorage-independence and tumorigenic potential (Debinski and Gibo, 2011). In rat C6 glioma cells, Fra-1 overexpression suppresses their proliferation rate and tumorogenic potential and promotes cellular apoptosis (Shirsat and Shaikh, 2003).

Head and neck squamous cell carcinoma (HNSCC)

Note

Analysis of the tumor samples from patients with head and neck squamous cell carcinomas (HNSCC) has shown an increase in Fra-1 mRNA expression when compared to matched adjacent mucosa samples.

Furthermore, tumor tissue staining for Fra-1 in tumor tissues is intensely more reactive immunoreactive than that of adjacent normal tissue (Mangone et al., 2005).

Fibrosis

Note

Fra-1 transgenic mice have been shown to be prone to developing biliary hepatic fibrosis, and Fra-1 has been associated with ductular proliferation and infiltration of inflammatory cells (Kireva et al., 2011). On the other hand, it negatively regulates pulmonary fibrosis (Rajasekaran et al., 2012). Genetic disruption of Fra-1 causes increased levels of inflammation, collagen accumulation, and profibrotic and fibrotic gene expression following bleomycin treatment when compared to wild-type Fra-1.

Osteopetrosis

Note

Genetic disruption of Fos leads to osteopetrosis in mice (Matsuo et al., 2000). However, over expression of Fra-1 rescues this phenotype in c-Fos mutant mice. Rankl, an osteoclast differentiation factor, has been reported to induce Fra-1 expression in a c-Fos-dependent manner, suggesting the involvement of c-Fos-RANKL-Fra-1 signaling in osteoclast differentiation.

It has also been reported that overexpression of Fra-1 in mice increases bone mass up to 5-fold compared to wild-type mice (Roschger et al., 2004).

Acute lung injury and Sepsis

Note

Increased expression of Fra-1 has been reported in lung epithelial cell of acute respiratory syndrome patients (Fudala et al., 2011).

Mice lacking Fra-1 show decreased levels of acute lung injury and inflammation as well as increased survival following endotoxin (LPS) treatment when compared to their wild-type counterparts (Vaz et al., 2012); this improvement was associated with diminished and increased levels of NF-kB and c-Jun/AP-1 binding, respectively.

In agreement with this result, mice overexpressing Fra-1 were shown in another study to have enhanced susceptibility to endotoxin-induced death (Takada et al., 2011).

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