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Gene Section
Review

FUBP1 (far upstream element (FUSE) binding protein 1)

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Identity

Other names: FBP, FUBP

HGNC (Hugo): FUBP1

Location: 1p31.1

DNA/RNA

Description

The human FUBP1 gene is located on the reverse strand of chromosome 1 (bases 78413591 to 78444777; according to NCBI Refseq Gene Database (gene ID: 8880, RefSeq ID: NM_003902.3), genome assembly GRCh37 from February 2009) of the human genome and is comprised of 31187 bp.

FUBP1 is composed of 20 protein-coding exons ranging between approx. 40 bp and 170 bp in length and 19 introns which vary greatly in size (approx. 100 bp - 8800 bp). It has a short (approx. 90 bp) 5' untranslated region (UTR) and a long 3' UTR (approx. 860 bp).

According to the Ensembl genome browser database 14 transcript variants of human FUBP1 have been reported (ENSG00000162613). One of them is composed of 21 exons (ENST00000436586).

Transcription

According to NCBI the human FUBP1 gene encodes a 2884 bp mRNA transcript, the coding sequence (CDS) located from base pairs 90 to 2024 (NM_003902.3). The CDS from the Ensembl genome browser database (ENST00000370768, transcript length 2378 bp) and NCBI (NM_003902.3) are identical. Transcripts NM_003902.3 and ENST00000370768 are also included in the human CCDS set (CCDS683) and encode a 644 aa long protein.

Pseudogene

None known.

Protein

Description

Human FUBP1 is composed of 644 amino acids, has a calculated molecular mass of 67,5 kDa and consists of three different protein domains. The N-terminal domain (amino acids 1 to 106) is able to repress transcriptional activation mediated by the C-terminal transactivation domain. The central domain (amino acids 107 to 447) contains four conserved KH motifs (K homology motif, first identified in the human heterogeneous nuclear ribonucleoprotein K protein (hnRNP K) (Siomi et al., 1993)) which facilitate the binding of FUBP1 to a single stranded DNA element (FUSE element, Braddock et al., 2002). A flexible glycine/proline-rich linker (amino acids 448 - 511) connects the central domain with the C-terminal transactivation domain (amino acids 448 - 644). This region contains three tyrosine-rich motifs which are required to activate transcription (Duncan et al., 1996; Duncan et al., 1994). Nuclear trafficking of FUBP1 is mediated by three nuclear localization signals (NLS): a classical NLS in the N-terminal domain and two non-canonical signals in the third KH motif and the third tyrosine-rich motifs (He et al., 2000b).

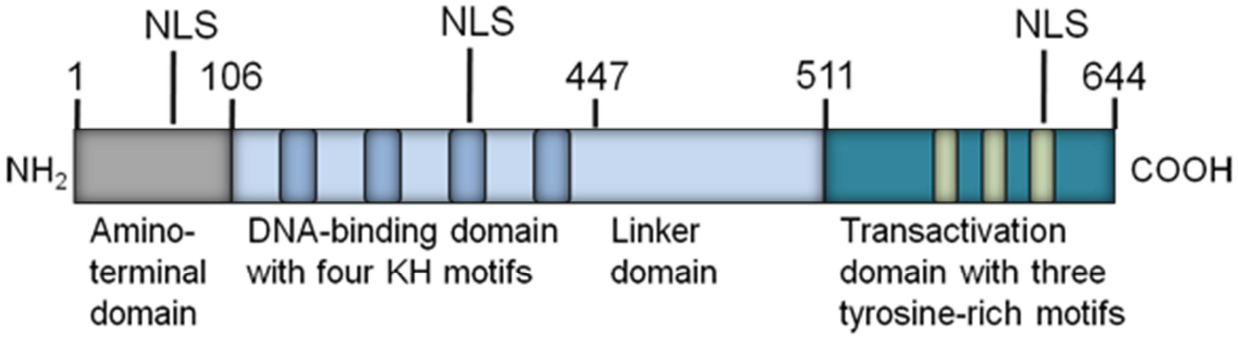

Figure 1. FUBP1 is composed of an N-terminal domain, a central DNA-binding domain containing four KH (K homology) motifs and a C-terminal domain (with three tyrosine-rich motifs). A flexible linker domain connects the central and the C-terminal domain. The numbers above the diagram indicate the amino acid positions of the domains. Sites of the nuclear localization signals (NLS) are indicated. Adapted from Duncan et al., 1996.

Expression

Widely expressed (Su et al., 2004).

Localisation

Nucleus (He et al., 2000b).

Function

FUBP1 is a transcriptional regulator and fulfills an important function in the precise control of c-myc transcription (mechanism described below). The c-Myc protein is a transcription factor which regulates the transcription of many different target genes that play a role in proliferation, cell cycle progression, differentiation, apoptosis and cell metabolism. Consequently, FUBP1 is also involved in the regulation of proliferation and differentiation, as confirmed by different experimental approaches. Knockdown of FUBP1 or expression of a dominant-negative FUBP1 (DNA-binding domain lacking effector activity) led to proliferation arrest in U2OS and Saos-2 osteosarcoma cells due to reduced c-myc expression (He et al., 2000a). Upon induction of differentiation in leukemia cells (HL-60 and U937), binding activity of FUBP1 to the c-myc promoter is lost. This indicates an important role of FUBP1 in maintaining c-myc transcription to prevent its downregulation and differentiation (Avigan et al., 1990).

As the KH motifs were first found to be involved in RNA-binding, it is not surprising that FUBP1 also interacts with specific RNAs. It was shown that FUBP1 interacts with the 3' UTR of GAP-43 mRNA (encoding a membrane phosphoprotein that is important for the development and plasticity of neuronal cells), hepatitis C virus RNA, nucleophosmin mRNA (a nucleolar oncoprotein involved in several cellular processes) and the 5' UTR of the p27 mRNA (a cyclin dependent kinase inhibitor), regulating their stabilities and translation (Irwin et al., 1997; Olanich et al., 2011; Zhang et al., 2008; Zheng and Miskimins, 2011). Although the regulatory mechanisms behind these interactions are still not fully characterized, these results implicate additional functions of FUBP1 in the regulation of neuronal differentiation, viral replication, cell growth and cell cycle progression.

Transcriptional regulation of the c-myc promoter by the FUBP family

Because of the unconventional binding properties of FUBP1 (single stranded DNA (ssDNA) instead of double stranded DNA (dsDNA) as for most other regular transcription factors), its mechanism in the regulation of c-myc transcription has been extensively studied. In the absence of serum, the c-myc locus is transcriptionally inactive.

In this state, the FUSE element upstream of the promoter is in a double stranded conformation and masked by a nucleosome.

Upon addition of serum, chromatin remodelling occurs, which results in the exposure of the FUSE element (Brooks and Hurley, 2009). Basal transcription of c-myc is initiated and leads to torsional stress and negative supercoiling of the DNA.

Under sufficient supercoiling, the DNA of the AT-rich FUSE element melts and enables binding of FUBP3, which later is replaced by FUBP1 (Chung et al., 2006; Kouzine et al., 2008; Kouzine et al., 2004; Michelotti et al., 1996). Upon recruitment, FUBP1 interacts with the general transcription factor TFIIH and enhances its helicase activity, thereby facilitating promoter escape of the polymerase complex which enhances transcription of c-myc (Bazar et al., 1995; Liu et al., 2001). Therefore, c-myc transcription reaches a maximum approx. two hours after serum addition.

Shortly after reaching the maximal transcription rate, FBP interacting repressor (FIR) binds to the FUSE element and FUBP1, forming a stable tripartite FUSE-FUBP1-FIR complex. This complex reverts the activated transcription back to a basal level, due to FIR-mediated inhibition of the 3' to 5' helicase activity of TFIIH (Brooks and Hurley, 2009; Hsiao et al., 2010; Liu et al., 2000). Shorty after formation of the tripartite complex, FUBP1 is ejected while FIR remains bound to the FUSE element.

This mechanism results in a sharp peak of c-myc expression upon serum addition (or other c-myc-inducing signals) and ensures the precise control of c-myc expression, which is important in normal cell homeostasis (Kelly and Siebenlist, 1986).

Homology

Two FUBP1 homologs, termed FUBP2/KHSRP and FUBP3, were also identified in the human genome. The three FUBP family members share the same protein architecture (three distinct domains). The central DNA-binding domain containing four KH motifs is the most conserved domain with 81,5% (FUBP2) and 80,9% (FUBP3) amino acids sequence homology to FUBP1 (Davis-Smyth et al., 1996). Although these proteins are highly conserved in their DNA-binding domains, divergences in their N- and C-termini lead to important functional differences.

The C-terminal transactivation domain of FUBP3 is by far the strongest of the FBP family members. Furthermore, variations in its N-terminal domain seem to prevent an interaction with the FBP interacting repressor (FIR) (Chung et al., 2006). As described in the previous paragraph these characteristics are important for the transcriptional regulation of the c-myc gene.

The transactivation domain of FUBP1 shows an intermediate strength whereas the one of FUBP2 displays the weakest activation capability. In contrast to FUBP3, FUBP1 and FUBP2 are able to interact with FIR (Chung et al., 2006). The weak transactivation domain already implicates that FUBP2 might not function as an important activator of transcription. In fact, FUBP2 (also named K homology splicing regulatory protein (KHSRP)) was shown to function as an mRNA binding protein, playing a role in mRNA splicing, trafficking, stabilization and degradation (Gherzi et al., 2004; Min et al., 1997).

Mutations

Somatic

Numerous reports about somatic mutations leading to the inactivation of FUBP1 in human oligodendrogliomas, oligoastrocytomas and astrocytomas (Bettegowda et al., 2011; Sahm et al., 2012; Jiao et al., 2012; Idbaih et al., 2012).

Implicated in

Various cancers

Note

FUBP1 is a potential oncogene that is overexpressed in different cancer entities.

Its expression is strongly increased in NSCLC cells compared to non-tumorous lung tissues. Furthermore it was shown that FUBP1 coordinates the expression of the microtubule-destabilizing proteins stathmin and SCLIP eventually leading to increased motility of NSCLC (Singer et al., 2009).

Elevated expression of FUBP1 was also reported for renal cell and prostate carcinomas (Weber et al., 2008).

The oncogenic role of FUBP1 in hepatocellular carcinoma is discussed in the following note.

In contrast to the above described oncogenic role of FUBP1 in the majority of cancer entities it seems to function as a tumor suppressor in oligodendrogliomas, astrocytomas and oligoastrocytomas. In these cancer entities the FUBP1 locus is frequently mutated leading to inactivation of the protein (Bettegowda et al., 2011; Sahm et al., 2012; Jiao et al., 2012; Idbaih et al., 2012).

Hepatocellular carcinoma

Note

FUBP1 is highly overexpressed in hepatocellular carcinoma. In HCC cells, knockdown of FUBP1 using stable shRNA (short hairpin RNA) expression resulted in increased apoptosis levels and decreased proliferation. In mouse xenograft experiments using these FUBP1-deficient HCC cells, tumor formation was impaired. Analysis of mRNA expression levels using quantitative real-time PCR revealed that c-myc expression was not influenced by knockdown of FUBP1, whereas several other so far unidentified target genes showed an altered expression pattern. The pro-apoptotic genes Bik, Noxa, TRAIL and TNF-α showed a reduced expression in the absence of FUBP1, whereas gene-expression of the cell cycle inhibitors p21 and p15 was increased. Cyclin D2 expression was also reduced in FUBP1 knockdown cells. Furthermore, p21 was identified as a direct FUBP1-target gene (Rabenhorst et al., 2009).

A decrease in tumor cell viability and proliferation was observed after siRNA mediated knockdown of FUBP1 in HCC cells. mRNA expression analysis revealed that FUBP1 induces the expression of the pro-tumorigenic microtubule-destabilizing protein stathmin (Malz et al., 2009). Elevated stathmin expression has been linked to vascular invasion, increased tumor size and intrahepatic metastasis in HCC (Yuan et al., 2006). Knockdown of FUBP2 resulted in elevated FUBP1 expression, indicating that FUBP family members are coodinately regulated. Based on these findings Malz et al. (2009) proposed that FUBP1 and FUBP2 support the migration and proliferation of human liver cancer cells.

Because of its regulatory effects on apoptosis, cell cycle progression and migration, FUBP1 fulfills an oncogenic potential, which seems to be of importance in hepatocellular carcinoma. A model of the oncogenic function of FUBP1 in HCC proposed by Rabenhorst et al. (2009) is shown in figure 2.

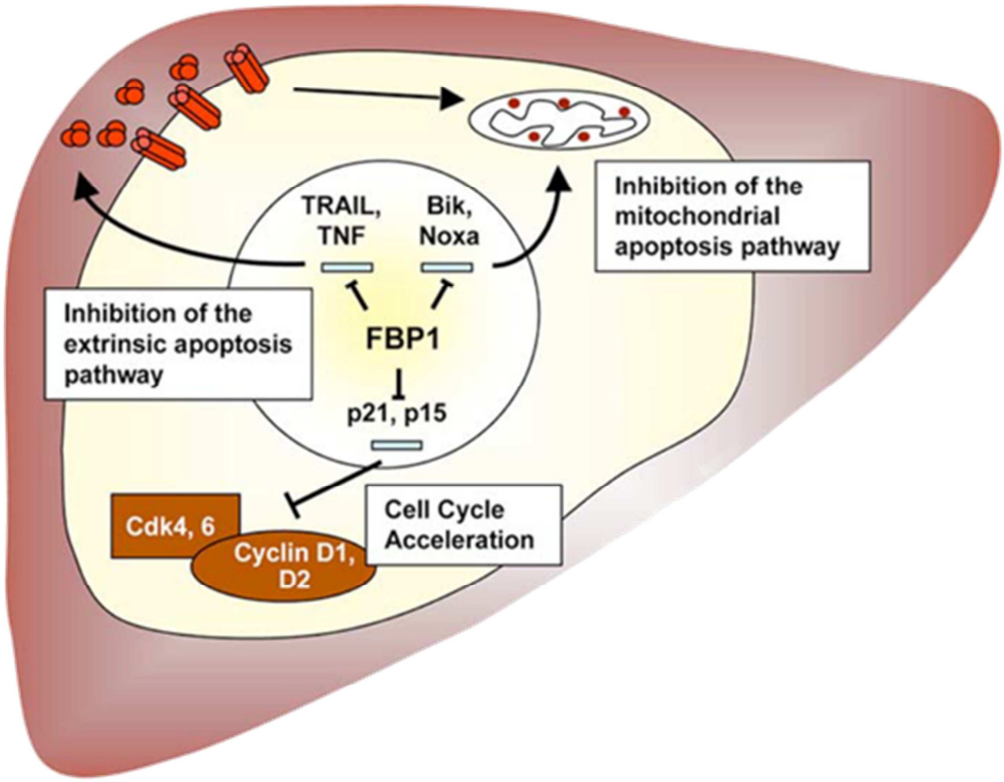

Figure 2. Model of the oncogenic FUBP1 function in hepatocellular carcinoma. Increased levels of FUBP1 in HCC lead to decreased expression of the pro-apoptotic genes of Bik, Noxa, TRAIL and TNF-α. As a consequence, both, the intrinsic and extrinsic apoptosis pathway are inhibited. Moreover, FUBP1 decreases the gene expression of the cell cycle inhibitors p21 and p15, which leads to cell cycle acceleration. Taken from Rabenhorst et al., 2009.

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