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Gene Section
Review

TP53BP2 (tumor protein p53 binding protein, 2)

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Identity

Other names: 53BP2; ASPP2; BBP; P53BP2; PPP1R13A

HGNC (Hugo): TP53BP2

Location: 1q41

DNA/RNA

Description

The TP53BP2 gene spans about 66 kb on chromosome 1q42.1 on the minus strand (Yang et al., 1997). There are two transcripts as a result of alternative splicing (Takahashi et al., 2004). The transcript variant 1, which is shorter (4670 bp), does not contain exon 3 and gives rise to a longer form of the protein named TP53BPL (long) or ASPP2. The transcript variant 2, which is longer (4802 bp), contains exon 3 which harbors a stop codon. As a result, the transcription initiates at exon 6 giving rise to a shorter form of the protein named TP53BPS (short) or BBP.

Transcription

ASPP2 is a serum inducible protein and subject to transcriptional regulation by E2F and its family members (Chen et al., 2005; Fogal et al., 2005).

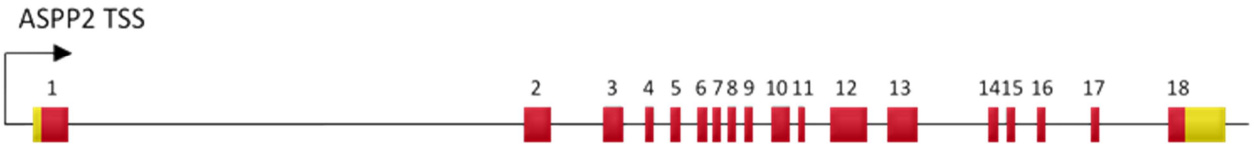
Pseudogene

Not known.

Protein

Description

ASPP2 is a pro-apoptotic protein with a predicted size of approximately 135 kDa. It is the founding member of a family of ASPP proteins that all share the common motifs of four Ankyrin-repeats, a Src-homology 3 (SH3) domain, and a Polyproline domain in their C-terminus (Iwabuchi et al., 1994). The N-terminus of ASPP2 is thought to be important for regulating its apoptotic function and contains a putative Ras-association domain as well as a ubiquitin-like fold (Tidow et al., 2007). ASPP2 has been most widely studied for its ability to interact with and stimulate the apoptotic function of the tumor suppressor p53 (and p63/p73) but several studies have also demonstrated p53-independent as well as apoptosis-independent functions for ASPP2 as well (Kampa et al., 2009a).
ASPP2 was originally pulled out of a yeast two-hybrid screen using the p53-binding domain as bait as a partial C-terminal clone named 53BP2 (Iwabuchi et al., 1994).



TSS=transcription start site.

ASPP2 protein domains. RA=Ras-association domain; PP=polyproline domain; AR=ankyrin repeats.

In 1996, Naumovski and Cleary determined that 53BP2 was a partial clone of a longer transcript they named Bcl-2 binding protein (Bbp or Bbp/53BP2) for its ability to bind the anti-apoptotic protein Bcl-2. It was later determined that Bbp is a splice isoform of the full length gene product from this locus, ASPP2 (Samuels-Lev et al., 2001).

Expression

Northern blot analysis, using a C-terminal probe, shows elevated levels of ASPP2 mRNA in several human tissues including heart, testis, and peripheral blood leukocytes (Yang et al., 1999). ASPP2 protein levels are controlled by proteasomal degradation (Zhu et al., 2005).

Localisation

ASPP2 contains a nuclear localization signal within its ankyrin repeat domain (amino acid residues 795-894) that when expressed alone or as a fusion with other proteins localizes in the nucleus of cells (Sachdev et al., 1998; Yang et al., 1999). Despite this signal however, full length ASPP2 is predominantly located in the cytoplasm and often seen near the cell periphery (Naumovski and Cleary, 1996; Iwabuchi et al., 1998; Yang et al., 1999).

Function

Apoptosis. Before ASPP2 was known to be the full length gene product from the TP53BP2 locus, Yang and colleagues showed that overexpression of Bbp/53BP2 in cells induces apoptosis (Yang et al., 1999). In 2000, Lopez et al. demonstrated that Bbp/53BP2 was UV-damage inducible and that loss of this endogenous protein promotes cell survival in response to damage, thus implicating a function in the damage response pathway. In 2001, Samuels-Lev et al. provided evidence that not only does full length ASPP2 promote apoptosis but that it does so, at least in part, through a p53-mediated mechanism that may involve preferential binding of p53 to its apoptotic target genes. ASPP2 has also been shown to modulate the apoptotic activity of the p53 family members, p63/p73 (Bergamaschi et al., 2004), and is known to bind other proteins involved in apoptosis such as Bcl-2 and NF-kappaB (Naumovski and Cleary, 1996; Yang et al., 1999). However, the functional ramifications of these interactions remain unclear. Additionally, there is evidence to indicate ASPP2 as a player in mitochondrial-mediated apoptosis (Kobayashi et al., 2005).

Tumor suppressor. Several clinical studies demonstrate low ASPP2 expression in a variety of human tumors (breast, lung, lymphoma) and this low expression often correlates with poor clinical outcome, suggesting that ASPP2 may function as a tumor suppressor (Mori et al., 2000; Samuels-Lev et al., 2001; Lossos et al., 2002; Cobleigh et al., 2005). In support of this concept, Iwabuchi et al. demonstrated in 1998 that transfection of 53BP2 inhibits Ras/E1A-mediated transformation in rat embryonic fibroblasts. Since then two separate mouse models targeting the ASPP2 locus via homologous recombination have demonstrated that loss of only one copy of ASPP2 increases spontaneous and irradiation-induced tumor formation in vivo (Vives et al., 2006; Kampa et al., 2009b). Taken together these data strongly suggest that ASPP2 is a haplo-insufficient tumor suppressor.

Cell cycle. Bbp, a splice isoform of ASPP2, can induce accumulation of cells in G_2/M and thus impede cell cycle progression (Naumovski and Cleary, 1996). Additionally, ASPP2 appears to play a role in the G_0/G_1 cell cycle checkpoint in response to gamma-irradiation as murine thymocytes that lack one copy of the ASPP2 locus did not arrest at G_0/G_1 as efficiently as wild type thymocytes (Kampa et al., 2009b).

Cell polarity. ASPP2 is often seen near the cell periphery and has been shown to co-localize with and bind to the tight junction protein PAR-3. Furthermore, loss of ASPP2 expression correlates with a loss of tight junction integrity and an impaired ability to maintain apical domains in polarized cells in culture (Cong et al., 2010). Interestingly these findings hold true in vivo as well. ASPP2 co-localizes with the PAR-3 complex and apical junctions in the brain and is necessary for tight junction integrity. Targeted deletion of ASPP2 in the mouse leads to defects associated with a loss of structural organization in the brain and retina (Sottocornola et al., 2010).

Senescence. Senescence, a type of irreversible cell cycle arrest, is considered an intrinsic protective response against malignant transformation. Wang et al. recently identified ASPP2 as a mediator of Ras-induced senescence by demonstrating that mouse embryonic fibroblasts with a targeted deletion of

Putative interactor	Putative function of pathway interactions	Reference(s)
	Modulates functions/pathways:	
p53 (p73/p63)	Enhances p53 transcriptional activity/Promotes p53-mediated apoptosis	Samuels-Lev 2001; Iwabuchi 1998; Bergamaschi 2004
Bcl-2 (Bcl-X_L)	Impedes cell cycle progression/Induces mitochondrial-mediated apoptosis	Naumovski 1996; Kobayashi 2005; Takahashi 2005
IRS-1	Modulates insulin signaling mediated by IRSs	Hakuno 2007
dCsk	*Drosophila* ASPP interacts with dCsk to regulate dSrc kinase	Langton 2007
APP-BP1	Inhibits neddylation pathway via interaction with APP-BP1	Chen 2003
PP1	Inhibits Protein Phosphatase 1 activity	Helps 1995; Liu 2010
PAR-3	Facilitates establishment and maintenance of cell polarity	Cong 2010; Sottocornola 2010
	Functions modulated by:	
NFκB/p65 subunit	Apoptosis inhibited by NFκB pathway	Yang 1999; Takahashi 2005
HCV core protein	Apoptosis inhibited by HCV core protein	Cao 2004
Ddx42p	Apoptosis/cell growth suppression inhibited by DEAD box protein Ddx42p	Uhlmann-Schiffler 2009
DDA3	Stimulation of p53-mediated BAX activation inhibited by DDA3	Sun 2008
	Undefined functional association:	
YAP	Phosphorylation by c-Yes inhibits interaction with YAP (a p73 co-activator)	Espanel 2001
APCL	Intracellular localization modulated by APCL	Nakagawa 2000
14-3-3s	Associates with 14-3-s during interphase	Meek 2004
Regulation of ASPP2 expression		
Epigenetic	Promoter methylation can silence transcription	Liu 2005; Sarraf 2004
Transcriptional	Induced by activating E2Fs	Chen 2004; Fogal 2005; Hershko 2005
Posttranscriptional	Splice isoform can truncate N-terminus	Takahashi 2004
Posttranslational	Controlled by proteasomal degradation	Zhu 2005

Potential functions and putative interacting partners of ASPP2. Modified from Kampa et al., 2009a.

exon 3 of the ASPP2 gene (TP53BP2) are less prone to senescence in the presence of activated Ras as compared to wild type fibroblasts (as measured by beta-galactosidase staining). Data also suggests that Ras-induced senescence may be mediated by ASPP2 through its ability to inhibit Ras from inducing accumulation of cyclin D1 in the nucleus (Wang et al., 2011).

Homology

ASPP2 is a member of the ASPP family of proteins that share a significant amount of homology in their C-terminal domains. ASPP1, ASPP2, and the splice isoform of ASPP2, BBP, share homology in both their N-terminal and C-terminal domains while the family member iASPP only retains C-terminal homology (Samuels-Lev et al., 2001; Bergamaschi et al., 2003).

Mutations

Note

No mutations at the ASPP2 locus, TP53BP2, have been reported. However, single nucleotide polymorphisms in TP53BP2 have been found associated with gastric cancer susceptibility (Ju et al., 2005) and epigenetic silencing of the promoter by methylation is frequently observed (Sarraf and Stancheva, 2004; Liu et al., 2005; Zhao et al., 2010).

Implicated in

Breast cancer

Note

ASPP2 mRNA expression is frequently downregulated in human breast cancer samples as compared to adjacent normal tissue (Sgroi et al., 1999; Samuels-Lev et al., 2001; Cobleigh et al., 2005). Reduced levels of ASPP2 expression are seen in both invasive and metastatic breast tumor tissue (Sgroi et al., 1999) and ASPP2 downregulation may be favored in tumor cells expressing wild type but not mutant p53 (Samuels-Lev et al., 2001).

Prognosis

Elevated levels of ASPP2 mRNA were correlated with a lower risk of distant recurrence of disease among a

panel of 78 patients with extensive lymph node involvement (Cobleigh et al., 2005).

Non-Hodgkin's lymphoma specifically diffuse large B-cell lymphoma, follicular center lymphoma, and Burkitt's lymphoma

Note

Overall, ASPP2 expression (as measured by Real-time RT-PCR) was found to be significantly higher in diffuse large B-cell lymphoma as compared to follicular center lymphoma. However, the variability of ASPP2 expression in diffuse large B-cell lymphoma was much greater than that seen in follicular center lymphoma. ASPP2 expression appeared inversely proportional to serum lactate dehydrogenase levels. Additionally, levels of ASPP2 expression are extremely low or undetectable in cell lines derived from Burkitt's lymphoma (Lossos et al., 2002).

Prognosis

In general, patients with high ASPP2 expression tended to have a longer median survival than those with low ASPP2 expression (Lossos et al., 2002).

Gastric cancer

Note

Four single nucleotide polymorphisms within the ASPP2 gene locus, TP53BP2, show significant correlation with gastric cancer susceptibility (Ju et al., 2005).

Hepatitis B virus-positive hepatocellular carcinoma

Note

Downregulation of ASPP2 (and ASPP1) as a result of promoter hypermethylation (as measured by methylation-specific PCR) is frequently observed in human patient samples of HBV-positive hepatocellular carcinoma as compared to surrounding non-tumor tissue (Zhao et al., 2010).

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