ANP32A (acidic (leucine-rich) nuclear phosphoprotein 32 family, member A)

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Identity

Other names: C15orf1, HPPCn, I1PP2A, LANP, MAPM, PHAP1, PHAPI, PP32

HGNC (Hugo): ANP32A

Location: 15q23

Local order: The gene is 73682 bases long and oriented on the minus strand.

DNA/RNA

Description

One of 1265 total genes on chromosome 15 according to NCBI Mapviewer. According to Ensembl, a predicted 76 base pair non-coding RNA (ncRNA) for MIR4312-201 is present within the gene sequence on the reverse strand at chromosome 15: 69094189-69094264.

Pseudogene

There are multiple genomic regions that have a high degree of similarity with the ANP32A sequence (including anti-sense regions that are most likely abundantly expressed, our data not shown).

Protein

Note

N-terminal contains nuclear localization signals in amphipathic alpha helix with exceptionally acidic c-terminus with aspartic and glutamic acid residues making up about 70% of the domain (Chen et al., 1996). Important features contributing to protein function include the secondary structure of N-terminal leucine-rich repeat domains (Huyton and Wolberger, 2007). Protein is approximately 90% identical to family members pp32r1 and pp32r2, though function is dramatically different and ANP32A tumor suppressor function is dependent upon the region between amino acids 150-174 (Brody et al., 1999). Function is, in part, dependent on phosphorylation status. Casein kinase II has been identified as a mediator of ANP32A phosphorylation in vivo, specifically at serines 158 and 204 (Hong et al., 2004).
**Description**

ANP32A is a 249 amino acid protein (32 kDa) (Li et al., 1996) and represents the first member identified in a family of evolutionarily-conserved phosphoproteins that are involved in an array of gene regulatory and diverse network regulatory functions primarily through protein-protein interactions such as binding to phosphorylated retinoblastoma (Rb) gene product (Adegbola and Pasternack, 2005).

**Expression**

Ubiquitously expressed in human tissues.

**Localisation**

ANP32A is primarily nuclear (Matsuoka et al., 1994; Matilla et al., 1997; Kovacech et al., 2007; Khan et al., 2011) with variable cytoplasmic localization. It participates in nuclear-to-cytoplasmic shutting as a multi-protein complex with its binding partners (Williams et al., 2010; Santa-Coloma, 2003; Higashino et al., 2005; Mazroui et al., 2008; Pan et al., 2009; Fukumoto et al., 2011). This cytoplasmic translocation is dependent upon the nuclear export factor chromosomal region maintenance protein 1, or CRM1 (Brennan et al., 2000). Of particular importance is the capacity of ANP32A to translocate from the nucleus to the cytoplasm upon cellular stress to disrupt the pro-tumorigenic function of associated protein HuR (Hostetter et al., 2008; Williams et al., 2010). In some cases, ANP32A mediated disruption of HuR function can precipitate caspase-mediated cleavage of HuR (Mazroui et al., 2008). A trimeric form has been found to be located primarily in the cytosol in hamster models (Ulitzur et al., 1997; Itin et al., 1999).

**Function**

ANP32A has a diverse array of functions. The role of ANP32A in oncogenesis, tumor suppression, and cellular differentiation is well established. It has marked tumor suppressor activity and acts in part through the inhibition of ras/Kras-mediated transformation in both in vitro and in vivo studies (Bai et al., 2001). ANP32A participates in transcriptional gene regulation through histone modification as a member of the inhibitor of histone acetyl transferase (INHAT) protein complex (Brody et al., 2004; Santa-Coloma, 2003; Kular et al., 2009; Khan et al., 2011) and through interferon-dependent binding to gene promoters in conjunction with STAT1/STAT2 (Kadota and Nagata, 2011). Participation as a component of the INHAT protein complex is dependent upon its highly-acidic c-terminus interacting with template activating factor-Ibeta, or TAF-Ibeta (Seo et al., 2002; Lee et al., 2006). It participates in mRNA nuclear-to-cytoplasmic translocation and post-transcriptional gene regulation (Williams et al., 2010; Santa-Coloma, 2003; Fries et al., 2007; Mazroui et al., 2008; Pan et al., 2009) as a key binding partner of HuR and in an importin-alpha dependent manner (Fukumoto et al., 2011).

It is a central component of the SET complex at the core of the granzyme A-mediated apoptosis pathway and affects the activation of caspase-9, cytochrome c-induced caspase activation, Apaf-1, and caspase-3 (Hill et al., 2004; Hoffarth et al., 2008; Kim et al., 2008; Li et al., 2012). ANP32A has also been identified as an inhibitor of protein phosphatase 2A, leading to changes in the ERK, MEK, and WNT signaling pathways (Li et al., 1995; Li et al., 1996; Yu et al., 2004; Stelzl et al., 2005; Habruckowich et al., 2010).

Also protective of neuronal excitotoxicity and apoptosis through interaction with the retinoblastoma (Rb) gene product (Adegbola and Pasternack, 2005; Khan et al., 2011) and may play a role in the pathogenesis of spinocerebellar ataxia type 1 through an interaction with ataxin-1 in a manner that is enhanced with expanding CAG repeats of the gene (Matilla et al., 1997).

As a necessary component of the template activating factor-I/SET oncoprotein complex it is associated with andeno-associated virus replication (Pegoraro et al., 2006). Finally, its association with the alpha chain of HLA class II molecule DR2 is of unclear significance (Vaesen et al., 1994).

**Mutations**

**Note**

There are currently 607 known single nucleotide polymorphisms (SNP) registered with the NCBI SNP database. Of these, only one is suggested to have clinical relevance thus far.

A single nucleotide polymorphism of the minor allele (rs7164503) appears to be associated with the pathogenesis of osteoarthritis of the hip (Valdes et al., 2009).

**Implicated in**

**Prostate adenocarcinoma**

**Note**

In 1998, Kadkol et al. used in situ hybridization techniques to compare ANP32A expression in prostatic adenocarcinoma with expression in benign prostatic hyperplasia.

While finding only moderate expression in the basal cells, 98% of prostatic adenocarcinomas with high Gleason scores demonstrated elevated levels of ANP32A (Kadkol et al., 1998).
In an effort to clarify the paradoxical finding of elevated levels of a tumor suppressor in transformed pancreatic adenocarcinoma tissue, in 1999 Kadkol and colleagues compared the sequence and function of members of this phosphoprotein family in a series of three patient tumors (compared to adjacent normal pancreatic tissue). They found ANP32A to be expressed in normal tissue, while closely related gene products pp32r1 and pp32r2 were dominant in the tumor samples (Kadkol et al., 1999).

In 2001, Bai et al. continued the focus from this laboratory on ANP32A with experiments aimed to clarify its tumor suppressor function. They utilized the fibroblast cell line NIH3T3 and showed that anti-sense inhibition of ANP32A lead to reduced serum dependence and loss of contact inhibition. They further demonstrated that ANP32A expression abrogated ras-mediated transformation in both in-vitro and in-vivo models (Bai et al., 2001).

Continuing work from the same laboratory, Brody and colleagues reported in 2004 that reduction of ANP32A expression in a prostate carcinoma cell line induced transformation into a neuronal phenotype associated with growth arrest. This change was associated with reduced SET expression and changes to the acetylation status of histone H4. Further downstream changes in gene expression were noted with effects pathways including: cell cycle, MAP kinases, apoptosis, cytokines, metabolism, PP2A, p53 stabilization, and growth factor receptors (Brody et al., 2004).

Finally, in 2011 Schramedei et al. reported results from a proteomic analysis of changes following miR-21 expression in LNCaP prostate cancer cells. They found ANP32A to be the most strongly down-regulated protein upon miR-21 expression suggesting a regulatory role of miR-21 on ANP32A expression. They also found that enhanced cell viability conferred by miR-21 expression in this prostate cancer cell line was mimicked by direct ANP32A knock-down and mitigated by ANP32A overexpression (Schramedei et al., 2011).

**Prognosis**

Increased ANP32A is associated with higher Gleason score in prostate adenocarcinoma despite equivalent rates of capsular invasion, seminal vesical invasion, and positive surgical margins at the time of resection (Kadkol et al., 1998).

**Pancreatic cancer**

**Note**

In 2007, Brody et al. found dramatically decreased levels of ANP32A in poorly differentiated pancreatic tumors and intraductal papillary mucinous neoplasms with moderate dysplasia when compared to healthy pancreatic tissue or well-to-moderately differentiated tumors. Exogenous overexpression of ANP32A in a low-expression pancreatic cancer cell line lead to increased G1 arrest (Brody et al., 2007).

In 2010, Williams and colleagues extended earlier work from the same group by associating low nuclear ANP32A levels with both high grade pancreatic tumors and the presence of lymph node metastasis. Overexpression of ANP32A conferred resistance to therapy with nucleoside analogs gemcitabine and cytarabine while increasing sensitivity to 5-fluorouracil therapy. In accordance with this result, silencing of ANP32A enhanced sensitivity to gemcitabine. A novel interaction with the RNA-binding protein ELAVL1 was described, whereby ANP32A disrupted binding between ELAVL1 and mRNA transcripts such as doxycyclidine kinase (dCK) and VEGF. Notably, dCK is the enzyme responsible for metabolism of gemcitabine from its prodrug to active metabolites (Williams et al., 2010).

**Breast cancer**

**Note**

In 2001, Kadkol and colleagues investigated the interplay between members of this phosphoprotein family (ANP32A, pp32r1, and pp32r2) in human breast cancer specimens as compared to benign tissue. After showing abundant protein belonging to this family in 100 of 102 specimens examined, they compared relative expression of each family member in five infiltrating breast carcinomas (compared to matching normal pancreatic tissue, early dysplasia, and even well differentiated adenocarcinomas (Brody et al., 2007; Williams et al., 2010).

**Non-small cell lung cancer**

**Note**

In 2008, Hoffarth and colleagues evaluated the effects of exogenous ANP32A expression on drug resistant non-small cell lung cancer cell (NSCLC) lines. They were able to correlate drug resistance with impaired caspase 9 and caspase 3 activation despite formation of the cytochrome-c induced apoptosome. Expression of ANP32A restored apoptosome activation both in vitro and murine in vivo models. Finally, they correlated...
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improved outcomes following chemotherapy in human NSCLC patients with expression of ANP32A on immunohistochemical staining of tumor samples (Hoffarth et al., 2008).

**Hepatocellular carcinoma**

**Note**
In 2012, Li and colleagues surveyed abnormal protein expression in hepatocellular carcinoma utilizing two-dimensional liquid chromatography-tandem mass spectrometry. Elevated expression of ANP32A was validated by western blot analysis and immunohistochemical staining of a tissue microarray comprised of 59 cases (Li et al., 2012).

**Colorectal cancer**

**Note**
In 2011, Shi et al. profiled the proteome changes found in laser capture microdissection samples of colorectal cancer. Amongst several novel protein changes found, ANP32A was overexpressed in tumor when compared to normal tissue (Shi et al., 2011).

**Neurotoxicity/neurodegenerative disease**

**Note**
An association with Rb-mediated gene repression plays a key role in neuronal protection against excitotoxicity (Khan et al., 2011). May contribute to altered tau protein phosphorylation contributing to the pathophysiology of Alzheimer’s disease (Tsujio et al., 2005; Kovacech et al., 2007). In the cerebellum it is primarily located in the nucleus of Purkinje cells where it interacts with ataxin-1, the gene product in spinocerebellar ataxia type 1 (Matilla et al., 1997).

**Disease**
Proposed: Alzheimer’s disease, spinocerebellar ataxia type 1.

**Cellular response to immunomodulatory and inflammatory factors**

**Note**
Interacts with STAT1/STAT2 and modulates transcriptional complex binding to interferon-stimulated gene promoters (Kadota and Nagata, 2011). Regulates cell signaling in response to inflammatory gene expression through target inhibition of protein phosphatase 2A (Khan et al., 2011). Association with HLA class II molecule DR2 alpha chain has yet to be fully elucidated (Vaesen et al., 1994).

**Embryogenesis**

**Note**
In a survey of this family of leucine-rich repeat genes, ANP32A was necessary for murine embryogenesis in a background of ANP32B absence (Reilly et al., 2011).

**Virology**

**Note**
ANP32A is required for adeno-associated virus replication in human cell line studies as a member of the template activating factor-I/SET oncoprotein complex (Pegoraro et al., 2006). As part of this process, nuclear-to-cytoplasmic shuttling with HuR takes place in a manner dependent on E4orf6 protein function (Higashino et al., 2005).

**References**


This article should be referenced as such: