

Gene Section

Review

BIN1 (bridging integrator 1)

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Abstract

The BIN1 gene encodes a set of BAR adapter proteins generated by alternate RNA splicing which function in membrane and actin dynamics, cell polarity and stress signaling. In cancer cells, BIN1 functions as a tumor suppressor gene and it is commonly silenced or misspliced during malignant progression. Genetic investigations in fission yeast, flies, mice and human cells suggest that BIN1 adapter proteins exert a 'moonlighting' function in the nucleus, integrating cell polarity signals generated by actin and vesicle dynamics with central regulators of cell cycle control, apoptosis, and immune surveillance (adapted from Prendergast et al., 2009).

Keywords

Tumor suppression, apoptosis, actin-membrane dynamics, vesicle trafficking, immune surveillance

Identity

Other names: AMPH-II, AMPH2, AMPHL, ALP, DKFZp547F068, MGC10367, SH3P9

HGNC (Hugo): BIN1

Location: 2q14.3

DNA/RNA

Description

The human BIN1 gene is encoded by at least 16 exons spanning at least 59258 bps at chromosome 2q14-2q21 (nucleotides 127522078-127581334). The murine Bin1 gene is similarly sized but

localized to a syntenic locus on mouse chromosome 8 (Wechsler-Reya et al., 1997).

Transcription

The Bin1 promoter is rich in CpG methylation residues and transcription of the gene produces more than 10 alternative transcripts that are from 2075 to 2637 bp mRNA in size: isoform 1 (2637 bp), isoform 2 (2508 bp), isoform 3 (2376 bp), isoform 4 (2333 bp), isoform 5 (2412 bp), isoform 6 (2289 bp), isoform 7 (2283 bp), isoform 8 (2210 bp), isoform 9 (2165bp), and isoform 10 (2075 bp). Isoforms 9 and 10 are ubiquitous in expression. Isoform 8 is expressed specifically in skeletal muscle.

Isoforms 1-7 are expressed predominantly in the central nervous system. An aberrant isoform has been reported to be expressed specifically in tumor cells (Wechsler-Reya et al., 1997).

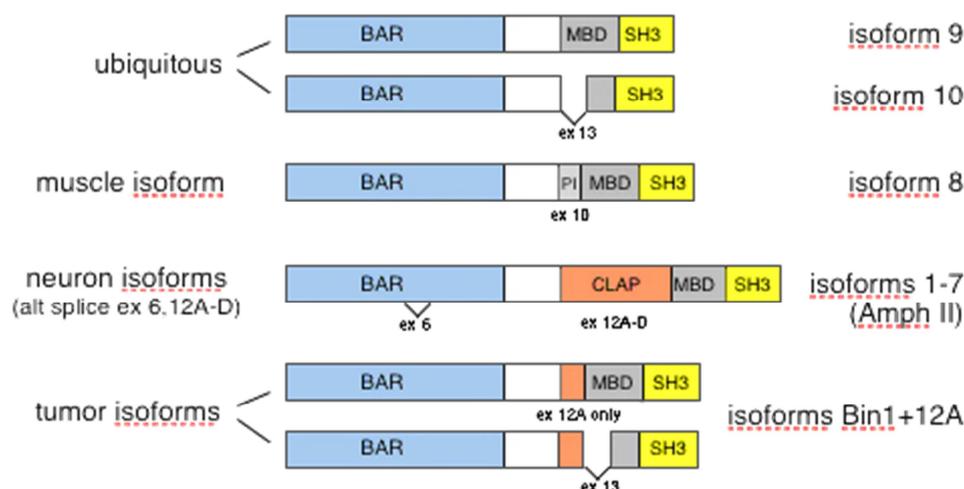
Pseudogene

None reported.

Protein

Description

Bin1 contains N-terminal BAR (Bin1/Amphihysin/Rvs) domain with predicted coiled-coil structure and a C-terminal SH3 domain (Sakamuro et al., 1996). Bin1 encodes proteins of 409 to 593 amino acids; isoform 1 (593 aa), isoform 2 (550 aa), isoform 3 (506 aa), isoform 4 (497 aa), isoform 5 (518 aa), isoform 6 (482 aa), isoform 7 (475 aa), isoform 8 (454 aa), isoform 9 (439 aa), and isoform 10 (409 aa).



At least 10 alternate protein isoforms of Bin1 are expressed in different tissues. Isoforms 9 and 10 are ubiquitous. Isoform 8 is muscle-specific. Isoforms 1-7 are expressed predominantly in the central nervous system. Two tumor-specific isoforms include an exon termed 12A that is normally spliced into Bin1 mRNA only with other exons expressed in the central nervous system. These tumor-specific isoforms occur commonly in cancer and they represent loss of function with regard to tumor suppression activity and nuclear localization capability. BAR, BAR domain; SH3, SH3 domain; MBD, Myc binding domain; CLAP, clathrin-associated protein binding region; PI, phosphoinositide binding region. Exons are numbered by reference to Wechsler-Reya et al. (1997).

Isoform 10 is the smallest and isoform 1 is the largest in size. Also, Bin1 has predicted molecular weight of 45432 to 64568 Da; isoform 1 (64568 Da), isoform 2 (59806 Da), isoform 3 (55044 Da), isoform 4 (54817 Da), isoform 5 (56368 Da), isoform 6 (52889 Da), isoform 7 (51606 Da), isoform 8 (50054 Da), isoform 9 (48127 Da), and isoform 10 (45432 Da). Isoforms 9 and 10 are ubiquitous in expression. Isoform 8 is expressed specifically in skeletal muscle. Isoforms 1-7 are expressed predominantly in the central nervous system. These 10 different splice isoforms differ widely in subcellular localization, tissue distribution, and ascribed functions, with isoforms 1-7 predominantly cytosolic but isoforms 8-10 found in both the nucleus and/or cytosol of certain cell types (Sakamuro et al., 1996; Muller et al., 2003). Recent studies demonstrated that the coiled-coil BIN1 BAR peptide encodes a novel BIN1 MID domain, through which BIN1 acts as a MYC-independent cancer suppressor (Lundgaard et al., 2011).

Expression

Bin1 is widely expressed (Wechsler-Reya et al., 1997; Chapuis et al., 2013). Patterns of isoform expression are noted above in the diagram legend.

Localisation

Bin1 is localized both in nuclear and cytosolic in the cerebral cortex and cerebellum of brain. Bin1 is localized mainly in nuclear in bone marrow cells whereas it is localized mainly in cytosolic in peripheral lymphoid cells. Bin1 is nuclear or nucleocytosolic in basal cells of skin, breast, or prostate, whereas it is cytosolic or plasma

membrane localized in gastrointestinal cells (DuHadaway et al., 2003). In cardiac muscles Bin1 generate T-tubules and also designates T-tubules as the appropriate site for delivery of L-type calcium channels (Hong et al., 2010).

Function

Bin1 encodes members of the BAR (Bin/Amphiphysin/Rvs) adapter family which have been implicated in membrane dynamics, such as vesicle fusion and trafficking, specialized membrane organization, actin organization, cell polarity, stress signaling, transcription, immunomodulation and tumor suppression. BAR adapter proteins are now recognized to be part of a larger superfamily of structurally related proteins that includes the so-called F-BAR and I-BAR adapter proteins (Ren et al., 2006; Prendergast et al., 2009).

Membrane binding and tubulation: The Bin1 BAR domain can mediate binding and tubulation of curved membranes (Lee et al., 2002; Wu et al., 2014). Crystal structures of the BAR domains from human BIN1 and its fruit fly homolog reveal a dimeric banana-shaped 6- α -helix bundle that can nestle against the charged head groups on a curved lipid bilayer. Structural studies implicate specific α -helices in tubulation activity. Biochemical analyses implicate Bin1 in vesicle fission and fusion processes, with the SH3 domain providing an essential contribution to these processes through the recruitment of dynamins (Ren et al., 2006).

Vesicle trafficking: Bin1 is implicated in endocytosis and intracellular endosome traffic through interactions with Rab5 guanine nucleotide

exchange factors (Rab GEFs) and the sorting nexin protein Snx4. Complexes of neuronal Amph-I with neuron-specific isoforms of Bin1 (Amph-II) have been implicated in synaptic vesicle recycling in the brain. Genetic studies of the Bin1 homolog in budding yeast indicate an essential role in endocytosis, however, this role appears to be non-essential for homologs in fission yeast, fruit flies, and mice (LePrince et al., 2003).

Cell polarity: Genetic analyses of the Bin1 homologs in yeast and fruit flies suggest a integrative function in cell polarity, possibly mediated by effects on actin organization and vesicle trafficking. In budding yeast, the Bin1 homolog RVS167 lies at a central nodal point for integrating cell polarity signaling (Balguerie et al., 1999). Genetic ablation of the Bin1 homolog in fruit flies causes mislocalization of the cell polarity complex Dlg/Scr/Lgl, normally localized to the tight junction, that is implicated in epithelial polarity and suppression of tumor-like growths in flies (Humbert et al., 2003).

Transcription: Ubiquitous and muscle-specific isoforms of Bin1 that can localize to the nucleus can bind to c-Myc and suppress its transcriptional transactivation activity (Elliott et al., 1999). Tethering the BAR domain of Bin1 to DNA is sufficient to repress transcription. Genetic studies in fission yeast demonstrate that the functional homolog *hob1+* is essential to silence transcription of heterochromatin at telomeric and centromeric chromosomal loci by supporting a Rad6-Set1 pathway of transcriptional repression (Ramalingam and Prendergast, 2007).

Muscle function: Mutations of the human BIN1 gene are associated with centronuclear myopathy, a disorder marked by severe muscle weakness (Nicot et al., 2007; Wu et al., 2014). In skeletal muscle, Bin1 localizes to T tubules where it appears to support ion flux (Lee et al., 2002; Butler et al., 1997). In vitro studies of terminal muscle differentiation implicate Bin1 in myoblast cell cycle arrest and fusion during tubule formation (Wechsler-Reya et al., 1998).

Cardiac function: Mouse genetic studies indicate that Bin1 is required for cardiac development (Hong et al., 2010). Bin1 levels decreases in failing hearts and low level of plasma Bin1 correlates with heart failure and predicts arrhythmia in patients with arrhythmogenic right ventricular cardiomyopathy (Hong et al., 2012).

Cognition and Memory: Bin1 is one of the candidate genes involved in Alzheimer's disease. Bin1 is the most important risk locus for late onset Alzheimer's disease. Bin1 affects AD risk primarily by modulating tau pathology (Tan et al., 2013; Kingwell, 2013; Chapius et al., 2013).

Immunomodulation and Barrier Function: Bin1 is a genetic modifier of experimental colitis that

controls the paracellular pathway of transcellular ion transport regulated by cellular tight junctions (Chang et al., 2012).

Apoptosis and Senescence: Bin1 is crucial for the function of default pathways of classical apoptosis or senescence triggered by the Myc or Raf oncogenes in primary cells (Prendergast et al., 2009). In human tumor cells, enforced expression of Bin1 triggers a non-classical program of cell death that is caspase independent and associated with activation of serine proteases (Elliott et al., 2000).

Tumor suppression: Attenuation of Bin1 function by silencing or missplicing is a frequent event in multiple human cancers including breast, prostate, skin, lung, and colon cancers (Sakamuro et al., 1996; Ge et al., 2000b). In breast cancer, attenuated expression of Bin1 is associated with increased metastasis and poor clinical outcome (Chang et al., 2007b). In human tumor cells, ectopic expression of ubiquitous or muscle Bin1 isoforms causes growth arrest or caspase-independent cell death (Prendergast et al., 2009). A Bin1 missplicing event that occurs frequently in human cancers is sufficient to extinguish these activities. In primary rodent cells, Bin1 inhibits oncogenic co-transformation by Myc, adenovirus E1A, or mutant p53 but not SV40 T antigen (Elliott et al., 1999; Elliott et al., 2000). Mouse genetic studies establish that loss of Bin1 causes lung and liver cancers during aging (Chang et al., 2007a). In mice where breast or colon tumors are initiated by carcinogen treatment, Bin1 deletion causes progression to more aggressive malignant states (Chang et al., 2007b). Oncogenically transformed cells lacking Bin1 exhibit reduced susceptibility to apoptosis and increased proliferation, invasion, immune escape, and tumor formation (Muller et al., 2004; Muller et al., 2005). Activation of metalloproteinase MMP9 and immunosuppressive enzyme indoleamine 2,3-dioxygenase (IDO) have been implicated respectively in invasion and immune escape caused by Bin1 loss (Chang et al., 2007b). Cisplatin is the most important and efficacious chemotherapeutic agent for the treatment of advanced gastric cancer. The oncoprotein c-Myc suppresses bridging integrator 1 (BIN1), thereby releasing poly(ADP-ribose)polymerase 1, which results in increased DNA repair activity and allows cancer cells to acquire cisplatin resistance (Tanida et al., 2012).

Null phenotype in mouse: Bin1 knockout mice are perinatal lethal owing to myocardial hypertrophy where myofibrils of ventricular cardiomyocytes are severely disorganized (Muller et al., 2003). Genetic mosaic mice display increased susceptibility to inflammation, premalignant lesions in prostate and pancreas, and formation of liver and lung carcinoma. Female mosaic mice exhibit increased fecundity during aging. Tissue-specific gene

ablation in skin or breast facilitates carcinogenesis (Chang et al., 2007a).

Homology

The longest Bin1 alternate splice variant in human brain exhibits 71% amino acid sequences similarity and 55% amino acid sequence identity with amphiphysin-I (amph-I) (Ren et al., 2006). Bin1 is also closely related to the mammalian amphiphysin-like genes Bin2 and Bin3 (Routhier et al., 2003). Genetic homologs of Bin1 that exist in budding and fission yeast (RVS167 and hob1+) and in fruit flies (amphiphysin) are well-characterized (Ren et al., 2006; Prendergast et al., 2009).

Mutations

Note

Epigenetics: Attenuated expression or missplicing occurs in many cases of breast, prostate, lung, skin, brain and colon cancers. Expression analyses have identified Bin1 missplicing as among the most common missplicing events occurring in cancer (Chang et al., 2007).

Germinal

Germ-line mutations leading to nonsynonymous alterations in Bin1 have been associated with the familial muscle weakness disorder centronuclear myopathy, a disorder characterized by abnormal centralization of nuclei in muscle fibers. Two missense alterations the BAR domain that have been identified as loss of function mutations for membrane binding are K35N and D151N (Nicot et al., 2007). Another mutation that has been identified, K575X, generates a prematurely terminated Bin1 protein implicated in loss of function (Nicot et al., 2007).

Somatic

Loss of heterozygosity of Bin1 in cases of metastatic prostate cancer has been reported in the absence of mutation of the remaining allele. Infrequent instances of gene deletions have been reported in breast tumor cell lines (Chang et al., 2007b; Kuznetsova et al., 2007).

Implicated in

Breast cancer

Oncogenesis

Breast cancer is the second leading cause of cancer death in women following lung cancer. Bin1 expression is attenuated significantly in >50% of cases of malignant breast cancer by immunohistochemical or RT-PCR analysis (Ge et al., 2000a). Reduced levels of Bin1 are correlated to increased nodal metastasis and reduced survival in low or middle grade carcinomas.

Mouse genetic studies indicate that Bin1 is non-essential for mammary gland development but that it is needed for the rapid kinetics of ductal remodeling during pregnancy and weaning.

In mammary gland tumors initiated by the ras-activating carcinogen 7,12-dimethylbenzanthracene (DMBA), Bin1 loss strongly accentuates the formation of poorly differentiated tumors characterized by low tubule formation, high mitotic indices, and high degree of nuclear pleomorphism. Bin1 loss facilitates tumor progression at several intrinsic levels, including increased proliferation, survival, and motility of mouse mammary epithelial cells (MMECs) established from DMBA-induced tumors (Chang et al., 2007b).

Lung cancer

Oncogenesis

Lung cancer is a leading cause of death from cancer.

Bin1 expression has been reported to be attenuated significantly in cases of lung adenocarcinoma by immunohistochemical analysis.

Mouse genetic studies demonstrate that Bin1 loss is associated with formation of lung adenocarcinoma during aging, indicating that Bin1 attenuation drives disease incidence (Chang et al., 2007a).

Colon cancer

Oncogenesis

Colorectal cancer is the third most common cancer in the developed world.

Bin1 expression has been reported to be attenuated significantly in ~50% of cases of colon cancer by Immunohistochemical analysis.

Mouse genetic studies indicate that, in colon tumors initiated by treatment with the carcinogen dimethylhydrazine (DMH), Bin1 loss facilitates progression to more aggressive tumors with a higher multiplicity (Chang et al., 2007a).

Skin cancer

Oncogenesis

Skin cancer is the most common form of cancer. Basal cell cancer and squamous cell cancer are most common and treatable whereas melanoma is less common and deadlier. Studies of human melanoma revealed that Bin1 is inappropriately expressed as tumor cell-specific isoforms that include exon 12A, which is alternately spliced into isoforms found in the central nervous system but not normally on its own in melanocytes or other non-neuronal cells. This aberrant splicing event abolishes the tumor suppressor functions of Bin1 based on the loss of its anti-oncogenic and programmed cell death inducing activities in oncogenically transformed cells and melanoma cells. Mouse genetic studies indicate that Bin1 loss facilitates skin carcinogenesis (Ge et al., 1999).

Prostate cancer

Oncogenesis

Prostate cancer is the leading cause of death in men older than 55 years of age. Loss of heterozygosity of the human BIN1 gene has been reported in ~40% of cases of metastatic prostate cancer. Bin1 is expressed in most primary tumors, even at slightly elevated levels relative to benign tissues, but it is frequently grossly attenuated in expression or inactivated by aberrant splicing in metastatic tumors and androgen-independent tumor cell lines. Ectopic expression suppresses the growth of prostate cancer cell lines in vitro. Mouse genetic studies indicate that Bin1 loss is associated with an increased incidence of prostate inflammation, atrophy, hypertrophy, and intraepithelial neoplasia during aging (Ge et al., 2000b).

Neuroblastoma

Oncogenesis

Neuroblastoma (NB) is the most common solid tumor of childhood and is responsible for 15% of childhood cancer-related deaths. Bin1 expression is grossly reduced in MYCN amplified and metastatic NB compared with MYCN single-copy and localized NB as evaluated by real-time RT-PCR. Enforced expression of Bin1 in MYCN amplified human NB cell lines markedly inhibits colony formation (Hogarty et al., 2000).

Cardiomyopathy

Note

Dilated cardiomyopathy (DCM) is a leading cause of heart failure with as much as >25% of cases of familial etiology. A whole genome screen performed in a three-generation family with 12 affected individuals with autosomal dominant familial DCM defined linkage to chromosome 2q14-q22 where the human BIN1 gene is located (Jung et al., 1999). While BIN1 was not specifically identified as the germline locus, mouse studies indicate that genetic ablation causes cardiomyopathy during development. Moreover, in mice where Bin1 is ablated after birth in a tissue-specific manner in cardiomyocytes, a progressive cardiomyopathy develops consistent with the possibility that Bin1 loss of function may be a cause of DCM (Muller et al., 2003).

Centronuclear myopathy

Note

Germ-line mutations of Bin1 are associated with formation of this rare familial disorder characterized by abnormal centralization of nuclei in muscle fibers and severe muscle weakness (Nicot et al., 2007; Smith et al., 2014). In five affected individuals studied from three non-sanguineous families, two mutations extinguishing the membrane binding activity of the BAR domain

were identified along one mutation causing a prematurely terminated Bin1 polypeptide (Nicot et al., 2007).

Chronic inflammation

Note

Mouse genetic studies indicate that Bin1 loss increases the general incidence of chronic inflammation in the heart, pancreas, liver, and prostate.

Female fecundity

Note

Mouse genetic studies indicate that mosaic loss of Bin1 increases reproductive physiology during aging. Specifically, female mosaic mice exhibit extended fecundity during aging, retaining reproductive capability ~6 months longer than control mice (Chang et al., 2007a).

Alzheimer's disease

Note

BIN1 transcript levels are increased in AD brains (Tan et al., 2013). Genome-wide association studies (GWAS) have identified the BIN1 gene as the most important genetic susceptibility locus in Alzheimer's disease (AD) after APOE. Decreased expression of the Drosophila BIN1 suppresses Tau-mediated neurotoxicity. Tau and BIN1 has been demonstrated to colocalize and interact in human neuroblastoma cells and in mouse brain (Chapuis et al., 2013; Kingwell, 2013).

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