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Gene Section

Review

BNIP3L (BCL2/adenovirus E1B 19kDa interacting protein 3-like)

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Identity

Other names: BNIP3a, NIX

HGNC (Hugo): BNIP3L

Location: 8p21.2

Local order: Cdca2 -Ebf2 - Ppp2r2a - **Bnip3l** - Pnma2 - Dpysl2 - Adra1a

DNA/RNA

Description

The gene spans 30122 bp and has 6 exons. The cytogenetic location of the gene is 8p21.2. The genomic coordinates are 8: 26240522 - 26270643.

Transcription

The mRNA is 3505 bp, and has a 657 bp open reading frame.

Protein

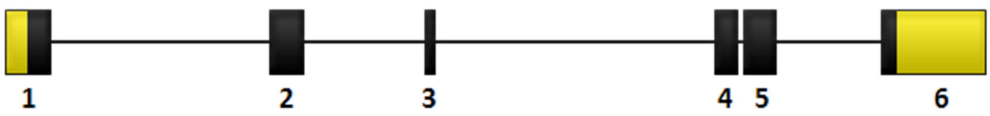
Description

The protein is 219 amino acids, with a predicted MW of 23,8 kDa. The carboxy-terminal transmembrane domain of BNIP3L has been characterized by nuclear magnetic resonance and shown to form a kinked α-helix (Bocharov et al., 2007). Structural bioinformatics analysis indicates that the rest of the protein is mostly disordered. The LIR and the MER are predicted to form secondary structure (β-strand and α-helix, respectively) (Zhang et al., 2012).

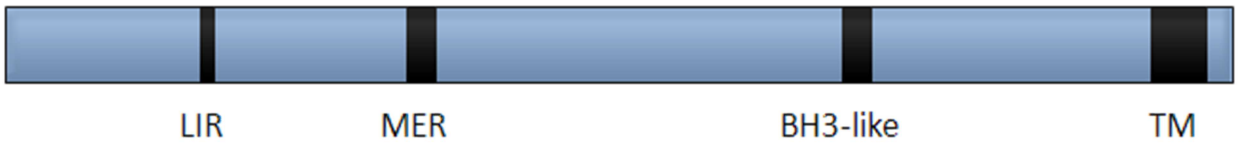
Expression

BNIP3L is ubiquitously expressed. Northern blot hybridization reveals two transcripts of 1,6 kb and 3,9 kb. These are expressed in heart, brain, placenta, lung, liver, skeletal muscle, kidney, and pancreas (Yasuda et al., 1999). In another study, transcripts were identified in heart, brain, placenta, lung (low), liver, skeletal muscle (low), kidney, pancreas, spleen, thymus, prostate, testis, ovary, small intestine, colon, and peripheral blood leukocyte (Farooq et al., 2001). In the same study, there was also expression in cancer cell lines, including promyelocytic HL-60 (low), Hela S3 (low), K562, lymphoblastic leukemia Molt-5, Burkitt's lymphoma-Raji, colorectal adenocarcinoma SW480, and lung carcinoma A549 cells. In another study, 1,4 and 4,0 kb BNIP3L transcripts were found in primary hematopoietic cells and in cell lines, including K562, Hela, and Jurkat cells (Aerbajinai et al., 2003). BNIP3L is upregulated during erythroid maturation.

BNIP3L protein can form an SDS-resistant dimer, which migrates at twice its predicted MW in SDS-PAGE gels. BNIP3L dimerization is mediated through its transmembrane domain (Imazu et al., 1999).



Organization of the human BNIP3L gene. The boxes represent exons, the line introns (not drawn to scale). Black areas represent coding sequence.



Functional domains of BNIP3L protein. LIR: LC3-interaction region (WVEL) (Schwarten et al., 2009; Novak et al., 2010); MER: minimal essential region (DMEKILLDAQHE) (Zhang et al., 2012); BH3-like: BCL2 homology 3-like domain (LKKSADWVSDW) (Yasuda et al., 1999); TM: transmembrane domain.

Localisation

BNIP3L primarily localizes to the mitochondrial outer membrane (Chen et al., 1999; Imazu et al., 1999; Yasuda et al., 1999; Vande Velde et al., 2000).
BNIP3L is oriented so that its amino terminus is in the cytoplasm, and its carboxy-terminal tail is in the mitochondrial intermembrane space.
It also localizes to nuclear envelope, sarcoplasmic reticulum, and endoplasmic reticulum (Ohi et al., 1999; Diwan et al., 2009).

Function

BNIP3L and BNIP3 can cause cell death by several mechanisms, which are mediated by their BH3-like and transmembrane domains.
In cardiomyocytes, mitochondria-targeted BNIP3L causes BAX/BAK-dependent mitochondrial outer membrane permeabilization, whereas ER/SR-targeted BNIP3L causes cyclophilin D-dependent opening of the MPT pore and mitochondrial depolarization (Chen et al., 2010).
In tumor cells, BNIP3 expression is associated with opening of the MPT pore and autophagy (Vande Velde et al., 2000).
Another property of BNIP3L and BNIP3 is their ability to mediate mitochondrial clearance during erythroid development (Schweers et al., 2007; Sandoval et al., 2008) and in response to hypoxia (Zhang et al., 2008; Liu et al., 2012), respectively. BNIP3L mediates mitochondrial clearance in erythroid cells through its LIR (Schwarten et al., 2009; Novak et al., 2010) and MER (Zhang et al., 2012) domains.

Homology

BNIP3L is conserved from zebrafish to man.

Mutations

Note
Not yet described.

Implicated in

Various cancers

Oncogenesis
BNIP3L and the related protein BNIP3 (56% identical overall) are implicated in cancer progression.

BNIP3 deregulation is more often implicated in cancer than BNIP3L, but the two proteins have a similar mechanism of action, so both are potentially relevant. BNIP3 and BNIP3L are reported to function as both tumor suppressors and oncogenes. This dual nature presumably reflects the roles of BNIP3 and BNIP3L in cell death pathways and autophagy; autophagy can promote cell survival. The frequent finding of BNIP3 deregulation in cancer is likely related to its induction by hypoxia, and HIF1α signaling (Bruick, 2000).
BNIP3L is also induced during hypoxia, by p53 (Fei et al., 2004). There are several mechanisms of BNIP3 and BNIP3L-induced cell death, which have recently been reviewed (Zhang and Ney, 2011).
The role of BNIP3 and BNIP3L in cell death may explain their frequent deletion and silencing in tumors by promoter methylation (see below).
By contrast, some advanced cancers express abnormally high levels of BNIP3 and BNIP3L. In these cases, the prosurvival role of these proteins in the induction of autophagy appears to dominate.

Prostate cancer

Note
BNIP3 is expressed in 95% of prostate cancer samples and is either nuclear, cytoplasmic, or both. Cytoplasmic BNIP3 expression correlates with Gleason score, but not other clinicopathological parameters. By contrast, nuclear BNIP3 correlates with HIF1α and HIF2α expression (Shaida et al., 2008). BNIP3 promoter hypermethylation is present in 16% of prostate cancers, and BNIP3 expression is decreased in 21% of prostate cancers, but the two do not correlate (Murphy et al., 2011).
BNIP3L exhibits homozygous deletion in a prostate cancer cell line and primary prostate tumor (Liu et al., 2008). Another study showed LOH of BNIP3L in 5% of prostate cancers, and a correlation with increasing disease stage (Cheng et al., 2012).

Breast cancer

Note
BNIP3 expression in ductal carcinoma in situ is associated with higher grade, necrosis and invasive disease, whereas BNIP3L expression does not correlate with these parameters (Sowter et al., 2003). BNIP3L is not deregulated and infrequently mutated in ovarian and breast cancer (Lai et al., 2003). Loss of BNIP3

expression correlates with lymph node metastases and mitotic index, but not with the hypoxic response (Koop et al., 2009). Proteasome inhibition with Bortezomib blocks autophagy-mediated catabolism of long-lived proteins, and is associated with increased BNIP3 and cell death in breast cancer cell lines (Periyasamy-Thandavan et al., 2010). On the other hand, resistance to the cytotoxic effects of TNFα in a subclone of breast cancer MCF-7 cells is associated with increased BNIP3 and upregulation of the autophagy program (Moussay et al., 2011). Notably, hypoxic induction of BNIP3 and BNIP3L can cause breast cancer cell death and at the same time promote the survival of cancer-associated fibroblasts (Chiavarina et al., 2010). Thus, BNIP3 and BNIP3L may have compartment-specific effects on cell death and survival.

Colorectal and gastric cancers

Note

BNIP3 promoter hypermethylation is found in 66% of primary colorectal and 49% of gastric cancers, but not in adjacent normal tissue (Murai et al., 2005b). Promoter hypermethylation but not gene mutation correlates with decreased BNIP3 expression.

Pancreatic cancer

Note

BNIP3 is silenced by promoter hypermethylation in 80% of pancreatic adenocarcinoma samples (Okami et al., 2004). BNIP3 expression is diminished in chronic pancreatitis and pancreatic ductal adenocarcinoma, and loss of BNIP3 expression correlates with decreased survival and chemotherapy resistance (Erkan et al., 2005). Similarly, BNIP3L is reduced in liver metastases and the tumor invasion front compared with the primary pancreatic tumor, in an orthotopic SCID mouse model (Niedergethmann et al., 2007).

Liver cancer

Note

Epigenetic silencing of BNIP3 and BNIP3L is associated with poor prognosis in hepatocellular carcinoma (Calvisi et al., 2007). In addition, a cSNP that causes premature termination of BNIP3L was reported in 40% of hepatocellular carcinoma cases (Wang et al., 2005). BNIP3 is a HIF1α target in HepG2 tumor spheroids, and its expression is associated with increased autophagy and attenuation of apoptosis (Menrad et al., 2010).

Lung cancer

Note

There is strong cytoplasmic expression of BNIP3 in 38% of non-small cell lung cancer, which was associated with an aggressive phenotype and decreased survival (Giatromanolaki et al., 2004).

Malignant glioblastoma

Note

BNIP3 is expressed in hypoxic regions of glioblastoma multiforme (GBM), but is sequestered in the nucleus in ~80% of tumors (Burton et al., 2006). In another study, BNIP3L appeared to act as a tumor suppressor in low-grade astrocytomas, and as an oncogene in high grade GBM. In the latter case, BNIP3L expression correlated with NFκB activation through an unknown mechanism (Lu et al., 2012).

Hematopoietic malignancy

Note

BNIP3 promoter hypermethylation is found in 15% of acute lymphocytic leukemia, 17% of acute myelogenous leukemia, and 21% of multiple myeloma. Promoter hypermethylation correlates with decreased BNIP3 expression (Murai et al., 2005a). BNIP3 promoter hypermethylation correlates with decreased survival in multiple myeloma (Heller et al., 2008). Another study found BNIP3 promoter hypermethylation in 13% of newly diagnosed multiple myeloma but no association with prognosis (Braggio et al., 2010).

Ischemic and hypertrophic heart disease

Note

Most of the evidence that BNIP3 and BNIP3L have a role in heart disease comes from animal models. BNIP3 is regulated by hypoxia in cardiomyocytes through HIF1α binding sites in its promoter (Bruick, 2000). By contrast, BNIP3L is regulated by Gαq signaling in the setting of cardiac hypertrophy (Gálvez et al., 2006). Enforced expression of BNIP3L causes lethal cardiomyopathy in mice, whereas BNIP3L deficiency protects mice from Gαq-mediated and pressure overload cardiomyopathy (Yussman et al., 2002; Diwan et al., 2008). Further, BNIP3 deficiency protects against post-infarction ventricular remodeling (Diwan et al., 2007). Mice with combined deficiency of BNIP3 and BNIP3L in the heart develop normally, but by 30 weeks exhibit cardiac enlargement and decreased left ventricular ejection fraction (Dorn, 2010). Mitochondria in the hearts of these mice are increased in number and show variation in size and internal structure. Furthermore, young BNIP3/BNIP3L-deficient mice subjected to aortic banding rapidly develop heart failure.

Cerebral ischemia

Note

Animal models and in vitro studies also provide evidence that BNIP3 and to a lesser extent BNIP3L are a cause of neuronal cell death after hypoxia or denervation. BNIP3 is expressed in striatal and cortical neurons following transient focal ischemia in rats; prolonged BNIP3 expression in this setting is associated with delayed neuronal cell death (Althaus et al., 2006). BNIP3 knockdown inhibits nuclear translocation of EndoG and protects against hypoxia-induced, caspase-independent, delayed neuronal cell

death (Zhang et al., 2007). Hypoxic mimetics cause BAX/BAK- and caspase-dependent neuronal precursor cell death in vitro, but also cause HIF1α and BNIP3 upregulation. BNIP3 knockdown failed to prevent caspase activation, but inhibits nuclear translocation of apoptosis-inducing factor and cell death (Walls et al., 2009). Thus, BNIP3 mediates hypoxia-induced, caspase-independent neuronal cell death. Also, following neonatal nerve axotomy, BNIP3 and to a lesser extent BNIP3L, are induced in facial motoneurons and associated with cell death (Cho et al., 2012).

Breakpoints

Note
Not yet described.

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