Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section

Mini Review

BNIP3 (Bcl-2/adenovirus E1B 19kD-interacting protein 3)

Sang-Gi Paik, Hayyoung Lee

Department of Biology, School of Biosciences and Biotechnology, Chungnam National University, Daejeon 305-764, Korea

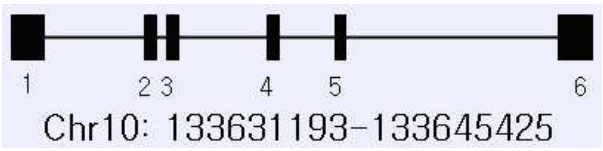
Published in Atlas Database: October 2007

Online updated version: http://AtlasGeneticsOncology.org/Genes/BNIP3ID822ch10q26.html
DOI: 10.4267/2042/38517

Identity

Hugo: BNIP3
Other names: NIP3
Location: 10q26.3

DNA/RNA



Description

14.23 kb on reverse strand; 6 exons

Transcription

mRNA in MCF-7 cells are 1.7kb (major) and 1.5 kb (minor) and 1.3 kb (minor).

Protein

Domain map of BNIP3 protein; BH3 domain (Bcl-2 holomogy 3 domain); TM domain (transmembrane domain)

Description

194 amino acids; 1 BH3 domain and 1 TM domain; BH3 only Bcl2 family member. The TM domain and C-terminal tail are essential for mitochondrial membrane localization and proapoptotic function. The predicted molecular weight is 21.5 kDa. BNIP3 migrates as 30 kDa monomeric form and 60 kDa dimeric form on SDS-PAGE.

Expression

BNIP3 is detected in mouse oviduct, uterus, spleen, lung, stomach, brain, seminal, lacrimal, submaxillary, heart, kidney, liver. It can be detected in cell lines such as HeLa, 293T, RAW264.7 and K562 cells. Its expression can be induced in both normal and cancer tissues that experience hypoxia or hypoxia-like conditions. Other stimuli, such as nitric oxide or arsenic trioxide, are also reported to induce BNIP3 expression.

Localisation

Outer mitochondrial membrane.

Function

Proapoptotic protein;
BNIP3 leads to opening of the mitochondrial permeability transition pore (PTP) thereby abolishing the proton electrochemical gradient and this is followed by chromatin condensation and DNA fragmentation. BNIP3 leads necrosis-like apoptosis. Unusually to the other Bcl-2 family proteins, the BNIP3-induced cell death depends not on BH3 domain but on C-terminal TM domain. BNIP3-induced cell death is known to be independent the nuclear translocation of AIF. However, whether caspase activation and cytochrome c release are involved in the cell death remains controversial. BNIP3 can induce autophagy. However whether the consequence of the autophagy is the cell death or survival remains to be established.
Since BNIP3 is induced by hypoxia through transcription factor HIF-1, it was postulated to play a role in hypoxia-induced cell death. Hypoxia-induced acidosis augments the proapoptotic function of BNIP3.

Homology

The close homologue: BNIP3L/BNIP3a/Nix/B5 (8q21).

The BH3-only Bcl2 family members: BBC3/PUMA (19q13), BCL2L11/BIM/BOD (2q13), BID (22q11), BIK/NBK/BBC1 (22q13), BLK (8q23), BMF (15q14), HRK/DP5/BID3 (12q24), PMAIP1/NOXA (18q21).

Implicated in

Pancreatic cancer

Prognosis

Pancreatic adenocarcinoma is highly resistant to chemical and radiation therapy, and has an extremely poor prognosis. Reduced expression of BNIP3 increased resistance to gemcitabine and 5-fluoro-uracil (5-FU) and showed a good correlation with reduced patient survival.

Oncogenesis

In most cases of pancreatic adenocarcinoma, BNIP3 expression was not detected even in response to hypoxia. The promoter of BNIP3 is located within a CpG island and is methylated in most pancreatic cancer cell lines. Restoration of BNIP3 expression by the methyltransferase inhibitor, 5-aza-deoxycytidine, induced death of pancreatic cancer cells in response to hypoxia.

Colorectal cancer

Oncogenesis

Methylation of BNIP3 in 66% of primary colorectal cancer.

References

Boyd JM, Malstrom S, Subramanian T, Venkatesh LK, Schaeper U, Elangovan B, D'Sa-Eipper C, Chinnadurai G. Adenovirus E1B 19 kDa and Bcl-2 proteins interact with a common set of cellular proteins. Cell 1994;79:341-351.

Chen G, Ray R, Dubik D, Shi L, Cizeau J, Bleackley RC, Saxena S, Gietz RD, Greenberg AH. The E1B 19K/Bcl-2-binding protein Nip3 is a dimeric mitochondrial protein that activates apoptosis. J Exp Med 1997;186:1975-1983.

Yasuda M, Theodorakis P, Subramanian T, Chinnadurai G. Adenovirus E1B-19K/BCL-2 interacting protein BNIP3 contains a BH3 domain and a mitochondrial targeting sequence. J Biol Chem 1998;273:12415-12421.

Bruick RK. Expression of the gene encoding the proapoptotic Nip3 protein is induced by hypoxia. Proc Natl Acad Sci USA 2000;97:9082-9087.

Ray R, Chen G, Vande Velde C, Cizeau J, Park JH, Reed JC, Gietz RD, Greenberg AH. BNIP3 heterodimerizes with Bcl-2/Bcl-X(L) and induces cell death independent of a Bcl-2 homology 3 (BH3) domain at both mitochondrial and nonmitochondrial sites. J Biol Chem 2000;275:1439-1448.

Vande Velde C, Cizeau J, Dubik D, Alimonti J, Brown T, Israels S, Hakem R, Greenberg AH. BNIP3 and genetic control of necrosis-like cell death through the mitochondrial permeability transition pore. Mol Cell Biol 2000;20:5454-5468.

Kim JY, Cho JJ, Ha J, Park JH. The carboxy terminal C-tail of BNip3 is crucial in induction of mitochondrial permeability transition in isolated mitochondria. Arch Biochem Biophys 2002;398:147-152.

Kubasiak LA, Hernandez OM, Bishopric NH, Webster KA. Hypoxia and acidosis activate cardiac myocyte death through the Bcl-2 family protein BNIP3. Proc Natl Acad Sci USA 2002;99:12825-12830.

Okami J, Simeone DM, Logsdon CD. Silencing of the hypoxia-inducible cell death protein BNIP3 in pancreatic cancer. Cancer Res 2004;64:5338-5346.

Yook YH, Kang KH, Maeng O, Kim TR, Lee JO, Kang KI, Kim YS, Paik SG, Lee H. Nitric oxide induces BNIP3 expression that causes cell death in macrophages. Biochem Biophys Res Commun 2004;321:298-305.

Abe T, Toyota M, Suzuki H, Murai M, Akino K, Ueno, M, Nojima M, Yawata A, Miyakawa H, Suga T, Ito H, Endo T, Tokino T, Hinoda Y, Imai K. Upregulation of BNIP3 by 5-aza-2'-deoxycytidine sensitizes pancreatic cancer cells to hypoxia-mediated cell death. J Gastroenterol 2005;40:504-510.

Akada M, Crnogorac-Jurcevic T, Lattimore S, Mahon P, Lopes R, Sunamura M, Matsuno S, Lemoine NR. Intrinsic chemoresistance to gemcitabine is associated with decreased expression of BNIP3 in pancreatic cancer. Clin Cancer Res 2005;11:3094-3101.

Erkan M, Kleeff J, Esposito I, Giese T, Ketterer K, Buchler MW, Giese NA, Friess H. Loss of BNIP3 expression is a late event in pancreatic cancer contributing to chemoresistance and worsened prognosis. Oncogene 2005;24:4421-4432.

Murai M, Toyota M, Satoh A, Suzuki H, Akino K, Mita H, Sasaki Y, Ishida T, Shen L, Garcia-Manero G, Issa JP, Hinoda Y, Tokino T, Imai K. Aberrant DNA methylation associated with silencing BNIP3 gene expression in haematopoietic tumours. Br J Cancer 2005;92:1165-1172.

Murai M, Toyota M, Suzuki H, Satoh A, Sasaki Y, Akino K, Ueno M, Takahashi F, Kusano M, Mita H, Yanagihara K, Endo T, Hinoda Y, Tokino T, Imai K. Aberrant methylation and silencing of the BNIP3 gene in colorectal and gastric cancer. Clin Cancer Res 2005;11:1021-1027.

Webster KA, Graham RM, Bishopric NH. BNip3 and signal-specific programmed death in the heart. J Mol Cell Cardiol 2005;38:35-45.

An HJ, Maeng O, Kang KH, Lee JO, Kim YS, Paik SG, Lee H. Activation of Ras upregulates pro-apoptotic BNIP3 in nitric oxide-induced cell death. J Biol Chem 2006;281:33939-33948.

Lee H, Paik SG. Regulation of BNIP3 in normal and cancer cells. Mol Cells 2006;21:1-6. (Review).

Bacon AL, Fox S, Turley H, Harris AL. Selective silencing of the hypoxia-inducible factor 1 target gene BNIP3 by histone deacetylation and methylation in colorectal cancer. Oncogene 2007;26:132-141.

This article should be referenced as such:

Paik SG, Lee H. BNIP3 (Bcl-2/adenovirus E1B 19kD-interacting protein 3). Atlas Genet Cytogenet Oncol Haematol.2008;12(3):195-196.