Atlas of Genetics and Cytogenetics
in Oncology and Haematology

OPEN ACCESS JOURNAL

INIST-CNRS

Gene Section

Review

NAMPT (nicotinamide phosphoribosyltransferase)

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Published in Atlas Database: June 2012

Online updated version : http://AtlasGeneticsOncology.org/Genes/NAMPTID43890ch7q22.html
DOI: 10.4267/2042/48363

Identity

Other names: 1110035O14Rik, PBEF, PBEF1, VF, VISFATIN

HGNC (Hugo): NAMPT

Location: 7q22.3

DNA/RNA

Description

The human NAMPT gene spans a length of 36908 bp. The NAPMT structural gene is composed of 11 exons and 10 introns.

Transcription

Transcription produces 19 different mRNAs, 14 alternatively spliced variants and 5 unspliced forms. There are 5 probable alternative promoters, 6 non overlapping alternative last exons and 13 alternative polyadenylation sites. The mRNAs appear to differ by truncation of the 3' end, presence or absence of 2 cassette exons, overlapping exons with different boundaries, alternative splicing or retention of 4 introns (Zhang et al., 2011).

Pseudogene

This gene has a pseudogene on chromosome 10 (provided by RefSeq 2011).

Protein

Description

The reference human NAMPT protein sequence (NP_005737) consists of 491 amino acids.

Expression

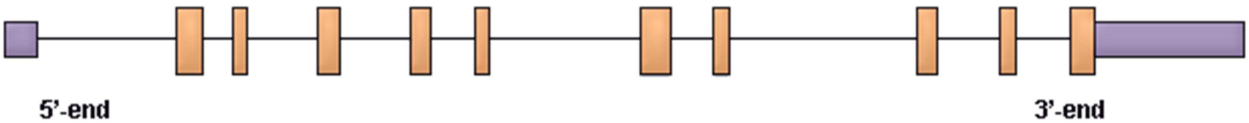
NAMPT is expressed in human heart, brain, placenta, lungs, liver, skeletal muscle, kidney and pancreas with the maximum amount in muscle tissue (Samal et al.,1994).

Localisation

NAMPT is localized both in the nucleus and the cytosplasm (Kitani et al., 2003).

Function

The three major functions of NAMPT: growth factor, cytokine and nicotinamide phosphoribosyltransferase.
Accumulating evidence suggests that NAMPT can function as a growth factor or a cytokine though the underlying molecular mechanisms remain to be established.
It is beyond any dispute that NAMPT can function as a nicotinamide phosphoribosyltransferase (Zhang et al., 2011).



Genomic structure of NAMPT. Orange boxes indicate exons and purple boxes indicate untranslated regions.

Enzymatic activity: because of its pivotal role in the recycling pathway allowing NAD generation from nicotinamide, NAMPT occupies a central position in controlling the activity of several NAD-dependent enzymes (Gallí et al., 2010). NAD, a universal energy- and signal-carrying molecule and its phosphorylated form, NADP, are required in several intracellular processes such as redox reactions, DNA repair, G-protein coupled receptor signaling, intra-cellular calcium-mobilizing molecules, transcriptional regulation, mono-adenosine diphosphate (ADP)-ribosylation in immune response, and activity of poly-ADP ribosyltransferases and deacetylases (sirtuins) with roles in regulating cell survival and cytokine responses (Garten et al., 2009). Under the influence of NAMPT, adequate levels of NAD control SIRT-6 (sirtuin) activity, which in turn positively regulates TNF-α mRNA translation favoring cell survival (Gallí et al., 2010). NAMPT activity enhances cellular proliferation, tips the balance toward cellular survival following a genotoxic insult and controls the circadian clock machinery of some key transcriptions factors (Garten et al., 2009; Moschen et al., 2010).

Homology

Significant sequence homology has been shared among prokaryotic organisms such as the bacterium Haemophilus ducreyi, primitive metazoan such as marine sponge, and humans (Martin et al., 2001). Amino acid sequence alignment revealed that the NAMPT gene is evolutionarily highly conserved, with the canine NAMPT protein sequence 96% identical to human NAMPT and 94% identical to both murine and rat PBEF counterparts (McGlothlin et al., 2005).

Mutations

Homozygous deletion confers embryonic lethality in mouse (Ye at al., 2005).
Up to June 2012 NCBI dbSNP reports 730 SNPs in the human NAMPT gene.
Functional consequences of most of these SNPs are currently unknown (Zhang et al., 2011).
Acquired resistance to inhibitors of NAMPT has been associated with mutations of NAMPT located in the vicinity of the active site or in the dimer interface of NAMPT (Olesen et al., 2010).

Implicated in

Various diseases

The dysregulation of NAMPT gene as well as abnormalities in circulating NAMPT levels have been implicated in the susceptibility and pathogenesis of a number of human diseases and pathologic conditions given NAMPT's pleiotropic physiological functions.
NAMPT has been implicated in cancer as described below, diabetes, obesity, aging, atherosclerosis, sepsis, acute lung injury, rheumatoid arthritis, etc (Zhang et al., 2011).

Colorectal cancer (CC)

NAMPT expression was increased in primary colorectal cancer comparing to normal control mucosa using the suppression subtractive hybridization technique to identify new candidate genes in cancer (Hufton et al., 1999).
This observation was later confirmed at tissue and protein level by Western blotting and immune-histochemical analyses (Van Beijnum et al., 2002). Serum Nampt levels were significantly higher in 115 CC patients than in 115 age-, gender- and body mass index (BMI)-matched controls both in univariate ($p<0.01$) and multivariable analyses (OR: 2.95, 95% C.I. 1.862-4.787, $p<0.01$) (Nakajima et al., 2010).

Prognosis

Serum Nampt levels may represent a promising biomarker of CC malignant potential and stage progression. Circulating Nampt gradually increased with tumor stage progression ($p<0.01$) (Nakajima et al., 2010).

Breast cancer (BC)

NAMPT is expressed in BC tissues, in MCF-7 BC cells and in doxorubicin-responsive BC (Folgueira et al., 2005; Gallí et al., 2010; Zhang et al., 2011; Moschen et al., 2010; Garten et al., 2009). Additionally, Nampt is present in bovine mammary epithelium, lactating mammary glands, and milk (Yonezawa et al., 2006). NAMPT stimulated the proliferation and DNA synthesis rate of MCF-7 human BC cells (Kim et al., 2010).
More specifically, NAMPT upregulated mRNA levels of cyclin D1 and cdk2, well-known regulators for the G1-S progression (Kim et al.,

2010). Circulating levels of Nampt were significantly elevated in women suffering from postmenopausal BC than in controls independently from known risk factors of BC, anthropometric and metabolic parameters as well as serum concentrations of leptin and adiponectin (Dalamaga et al., 2011). Stratification by BMI depicted that the association of serum Nampt with PBC risk was more pronounced among overweight/obese postmenopausal women after adjustment for the aforementioned parameters (Dalamaga et al., 2011; Dalamaga et al., 2012b).

Prognosis

High NAMPT expression in BC tissues was reported to be associated with more malignant cancer behavior as well as adverse prognosis (Lee et al., 2011). In the high NAMPT expression group, the majority of patients were estrogen and progesterone negative (Lee et al., 2011). Serum Nampt could be used as potential diagnostic and prognostic biomarker in the armamentarium of BC monitoring and management. In

postmenopausal women, circulating Nampt could provide additional information in conjunction with tumor markers CA 15-3 and carcinoembryonic antigen, particularly in discriminating early stage cases and estrogen/progesterone negative breast tumors (Dalamaga et al., 2012b). In multivariable regression analysis, the most significant predictors/determinants of serum Nampt levels were the hormone receptor status, the late stage of PBC and the lymph node involvement (Dalamaga et al., 2012b).

Gastric cancer (GC)

Using real-time PCR and Western blotting, NAMPT was overexpressed at the mRNA and protein levels in gastric cancer cells and human gastric cancer tissues (Bi et al., 2011). The specific NAMPT inhibitor FK866 repressed gastric cancer cell proliferation in vitro (Bi et al., 2011). Serum Nampt levels were significantly higher in 156 GC patients than in 156 age- and gender-matched controls using multivariable analysis (p= 0.0013) (Nakajima et al., 2009).

Prognosis

Nampt may be good biomarker of GC as its circulating levels gradually increased with stage progression (P<0.0001) (Nakajima et al., 2009).

Prostate cancer (PC)

Oncogenesis

In prostate carcinogenesis, NAMPT increased PC3 cell proliferation activating the mitogen-activated protein kinases (MAPKs) ERK-1/ERK-2 and p38 signaling pathways (Patel et al., 2010). NAMPT promoted the activity and expression of MMP-2/MMP-9 which represent important proteases involved in the breakdown of the extracellular matrix, indicating a possible role for NAMPT in PC metastasis (Patel et al., 2010). Upregulation of NAMPT expression occurs early in prostate neoplasia (Wang et al., 2011). Inhibition of NAMPT significantly suppresses cell growth in culture, soft agar colony formation, cell invasion and growth of xenografted prostate cancer cells in mice. NAMPT knockdown sensitizes prostate cancer cells to oxidative stress caused by H_2O_2 or chemotherapeutic treatment. Overexpression of NAMPT increases prostate cancer cell resistance to oxidative stress, which is partially blocked by SIRT1 knockdown (Wang et al., 2011).

Brain tumors

Increased NAMPT expression was found in glioblastoma samples using cDNA microarray based expression profiling, real-time RT-qPCR and immunohistochemical staining on an independent set of brain tumor samples (Reddy et al., 2008). APO866, a NAMPT inhibitor, is a potent growth inhibitor against glioblastoma through targeting NAMPT. APO866 depleted intracellular NAD, caused marked inhibition of ERK activation and induced G2/M cell-cycle arrest in C6 glioblastoma cells (Zhang et al., 2012).

Prognosis

Serum Nampt levels may be a potential serum biomarker for malignant astrocytoma and prognostic indicator in glioblastoma (Reddy et al., 2008).

Ovarian cancer

NAMPT protein expression is significantly increased in ovarian serous adenocarcinoma comparing to benign ovarian tissue using tissue microarray and the avidin-biotin complex immuno-histochemical technique (Shackelford et al., 2010).

Esophageal cancer

Prognosis

Using quantitative one-step real time RT-PCR, circulating Nampt mRNAs in postoperative esophagectomy patients were upregulated adjusting for other factors (p<0.01) and were independent predictors of mortality in the first year of follow-up (Takahashi et al., 2010).

Lymphoma

NAMPT expression was investigated in 53 samples of malignant lymphomas (diffuse large B-cell lymphoma, follicular B-cell lymphoma, Hodgkin's lymphoma and peripheral T-cell lymphoma).

The expression of NAMPT was generally elevated in the more aggressive malignant lymphomas, with >80% strong expression, whereas the expression in the more indolent follicular lymphoma (FL) was significantly lower (>75% moderate or low expression, p= 0.0002) (Olesen et al., 2011). In Hodgkin's lymphoma, NAMPT was very highly expressed in Hodgkin Reed-Sternberg cells (Olesen et al., 2011).

References

Samal B, Sun Y, Stearns G, Xie C, Suggs S, McNiece I. Cloning and characterization of the cDNA encoding a novel human pre-B-cell colony-enhancing factor. Mol Cell Biol. 1994 Feb;14(2):1431-7

Hufton SE, Moerkerk PT, Brandwijk R, de Bruïne AP, Arends JW, Hoogenboom HR. A profile of differentially expressed genes in primary colorectal cancer using suppression subtractive hybridization. FEBS Lett. 1999 Dec 10;463(1-2):77-82

Martin PR, Shea RJ, Mulks MH. Identification of a plasmid-encoded gene from Haemophilus ducreyi which confers NAD independence. J Bacteriol. 2001 Feb;183(4):1168-74

Van Beijnum JR, Moerkerk PT, Gerbers AJ, De Bruïne AP, Arends JW, Hoogenboom HR, Hufton SE. Target validation for genomics using peptide-specific phage antibodies: a study of five gene products overexpressed in colorectal cancer. Int J Cancer. 2002 Sep 10;101(2):118-27

Kitani T, Okuno S, Fujisawa H. Growth phase-dependent changes in the subcellular localization of pre-B-cell colony-enhancing factor. FEBS Lett. 2003 Jun 5;544(1-3):74-8

Folgueira MA, Carraro DM, Brentani H, et al.. Gene expression profile associated with response to doxorubicin-based therapy in breast cancer. Clin Cancer Res. 2005 Oct 15;11(20):7434-43

McGlothlin JR, Gao L, Lavoie T, Simon BA, Easley RB, Ma SF, Rumala BB, Garcia JG, Ye SQ. Molecular cloning and characterization of canine pre-B-cell colony-enhancing factor. Biochem Genet. 2005 Apr;43(3-4):127-41

Ye SQ, Zhang LQ, Adyshev D, Usatyuk PV, Garcia AN, Lavoie TL, Verin AD, Natarajan V, Garcia JG. Pre-B-cell-colony-enhancing factor is critically involved in thrombin-induced lung endothelial cell barrier dysregulation. Microvasc Res. 2005 Nov;70(3):142-51

Yonezawa T, Haga S, Kobayashi Y, Takahashi T, Obara Y. Visfatin is present in bovine mammary epithelial cells, lactating mammary gland and milk, and its expression is regulated by cAMP pathway. FEBS Lett. 2006 Dec 11;580(28-29):6635-43

Reddy PS, Umesh S, Thota B, Tandon A, et al. PBEF1/NAmPRTase/Visfatin: a potential malignant astrocytoma/glioblastoma serum marker with prognostic value. Cancer Biol Ther. 2008 May;7(5):663-8

Garten A, Petzold S, Körner A, Imai S, Kiess W. Nampt: linking NAD biology, metabolism and cancer. Trends Endocrinol Metab. 2009 Apr;20(3):130-8

Nakajima TE, Yamada Y, Hamano T, Furuta K, Gotoda T, Katai H, Kato K, Hamaguchi T, Shimada Y. Adipocytokine levels in gastric cancer patients: resistin and visfatin as biomarkers of gastric cancer. J Gastroenterol. 2009;44(7):685-90

Gallí M, Van Gool F, Rongvaux A, Andris F, Leo O. The nicotinamide phosphoribosyltransferase: a molecular link between metabolism, inflammation, and cancer. Cancer Res. 2010 Jan 1;70(1):8-11

Kim JG, Kim EO, Jeong BR, Min YJ, Park JW, Kim ES, Namgoong IS, Kim YI, Lee BJ. Visfatin stimulates proliferation of MCF-7 human breast cancer cells. Mol Cells. 2010 Oct;30(4):341-5

Moschen AR, Gerner RR, Tilg H. Pre-B cell colony enhancing factor/NAMPT/visfatin in inflammation and obesity-related disorders. Curr Pharm Des. 2010 Jun;16(17):1913-20

Nakajima TE, Yamada Y, Hamano T, Furuta K, Matsuda T, Fujita S, Kato K, Hamaguchi T, Shimada Y. Adipocytokines as new promising markers of colorectal tumors: adiponectin for colorectal adenoma, and resistin and visfatin for colorectal cancer. Cancer Sci. 2010 May;101(5):1286-91

Olesen UH, Petersen JG, Garten A, Kiess W, et al.. Target enzyme mutations are the molecular basis for resistance towards pharmacological inhibition of nicotinamide phosphoribosyltransferase. BMC Cancer. 2010 Dec 12;10:677

Patel ST, Mistry T, Brown JE, Digby JE, Adya R, Desai KM, Randeva HS. A novel role for the adipokine visfatin/pre-B cell colony-enhancing factor 1 in prostate carcinogenesis. Peptides. 2010 Jan;31(1):51-7

Shackelford RE, Bui MM, Coppola D, Hakam A. Over-expression of nicotinamide phosphoribosyltransferase in ovarian cancers. Int J Clin Exp Pathol. 2010 Jun 12;3(5):522-7

Takahashi S, Miura N, Harada T, Wang Z, Wang X, Tsubokura H, Oshima Y, Hasegawa J, Inagaki Y, Shiota G. Prognostic impact of clinical course-specific mRNA expression profiles in the serum of perioperative patients with esophageal cancer in the ICU: a case control study. J Transl Med. 2010 Oct 22;8:103

Bi TQ, Che XM, Liao XH, Zhang DJ, Long HL, Li HJ, Zhao W. Overexpression of Nampt in gastric cancer and chemopotentiating effects of the Nampt inhibitor FK866 in combination with fluorouracil. Oncol Rep. 2011 Nov;26(5):1251-7

Dalamaga M, Karmaniolas K, Papadavid E, Pelekanos N, Sotiropoulos G, Lekka A. Elevated serum visfatin/nicotinamide phosphoribosyl-transferase levels are associated with risk of postmenopausal breast cancer independently from adiponectin, leptin, and anthropometric and metabolic parameters. Menopause. 2011 Nov;18(11):1198-204

Lee YC, Yang YH, Su JH, Chang HL, Hou MF, Yuan SS. High visfatin expression in breast cancer tissue is associated with poor survival. Cancer Epidemiol Biomarkers Prev. 2011 Sep;20(9):1892-901

Olesen UH, Hastrup N, Sehested M. Expression patterns of nicotinamide phosphoribosyltransferase and nicotinic acid phosphoribosyltransferase in human malignant lymphomas. APMIS. 2011 Apr;119(4-5):296-303

Zhang LQ, Heruth DP, Ye SQ. Nicotinamide Phosphoribosyltransferase in Human Diseases. J Bioanal Biomed. 2011 Jan 7;3:13-25

Dalamaga M, Archondakis S, Sotiropoulos G, Karmaniolas K, Pelekanos N, Papadavid E, Lekka A. Could serum visfatin be a potential biomarker for postmenopausal breast cancer? Maturitas. 2012a Mar;71(3):301-8

Dalamaga M, Diakopoulos KN, Mantzoros CS. The role of adiponectin in cancer: a review of current evidence. Endocr Rev. 2012b Aug;33(4):547-94

Zhang LY, Liu LY, Qie LL, Ling KN, Xu LH, Wang F, Fang SH, Lu YB, Hu H, Wei EQ, Zhang WP. Anti-proliferation effect of APO866 on C6 glioblastoma cells by inhibiting nicotinamide phosphoribosyltransferase. Eur J Pharmacol. 2012 Jan 15;674(2-3):163-70

This article should be referenced as such:

Koumaki V, Dalamaga M. NAMPT (nicotinamide phosphoribosyltransferase). Atlas Genet Cytogenet Oncol Haematol. 2012; 16(12):909-912.