NAMPT (nicotinamide phosphoribosyltransferase)

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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 cytoplasm (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).
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 et 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 immunohistochemical 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% CI. 1.862-4.787, p<0.01) (Nakajima et al., 2010).

**Prognosis**

Serum Nampt 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.
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 a 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 H2O2 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**


This article should be referenced as such: