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Nicotinamide N-methyltransferase as a potential marker for cancer

Minireview

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Cancer remains the main global cause of death despite noteworthy advances in cancer research over the past decades. Early detection is extremely important in improving successful therapy and further work is therefore urgently required to find novel tumor markers for treatment. Herein, we studied Nicotinamide N-methyltransferase (NNMT) which is a cytosolic enzyme that catalyzes the N-methylation of nicotinamide to form 1-methylnicotinamide (1-MNA). This plays an important role in controlling the intracellular concentration of nicotinamide, the precursor to NAD+ and an important cofactor which associates cellular redox states with energy metabolism. Growing evidence shows that NNMT protein levels are elevated in a variety of human cancers, and increased NNMT expression has been linked to tumor aggressiveness. This paper presents a review of the role of NNMT expression in a series of human cancers and the regulating mechanisms involved. We offer the potential value of NNMT in cancer detection and treatment.

Key words: Nicotinamide N-methyltransferase (NNMT), cancer, 1-methylnicotinamide (1-MNA)

Nicotinamide N-methyltransferase (NNMT) is a cytoplasmic enzyme in the N-methyltransferase family which catalyzes the N-methylation of pyridine, nicotinamide and structurally related compounds using S-adenosylmethionine (SAM) as the methyl donor [1–5]. NNMT is implicated in the regulation of multiple metabolic pathways in tissues, such as adipose and liver, through the consumption of methyl donors and the generation of active metabolites [6].

Nicotinamide is a form of vitamin B3 and a precursor for NAD+ which is crucial in modulating energy metabolism and influencing the cellular life span [8–12] Further, NNMT catalyzes nicotinamide into 1-methylnicotinamide (1-MNA) which has a vital role in controlling intracellular nicotinamide concentration [7].

Elevated NNMT activity can decrease cellular nicotinamide levels and effectively inhibit cell apoptosis [1, 13]. Many researchers have identified remarkably high NNMT expression in various cancer cells, and NNMT up-regulation is considered involved in cell proliferation in several malignancies [14–16]. While a growing number of studies demonstrate that NNMT may be a potential marker for cancer, the exact mechanism by which NNMT enhances tumorigenesis is poorly understood. This paper provides a short overview of the association between NNMT and various cancers and the possible regulating mechanisms involved.

NNMT expression

NNMT is a cytosolic enzyme with 29kDa molecular weight [3]. Although NNMT is mainly expressed in the liver in healthy tissues [17, 18] low NNMT expression has been detected in the brain, lung, heart, kidney, skeletal muscle and placenta [7]. In contrast, high expression is reported in the cerebellum and caudate nucleus of patients who have succumbed to Parkinson's disease (PD), and also in many other diseases including osteoarthritis, cirrhosis, chronic obstructive pulmonary disease, cardiovascular disease and cancer [19]. Most importantly, reports indicate that NNMT expression is significantly increased in tumors [20]. These include the following cancers: neuroblastoma [21], [8]; papillary thyroid cancer [18] and lung [22], breast [23], gastric [24], pancreatic [25] and colorectal cancers (CRC) [26]; and also in carcinomas including renal carcinoma [27] and

ovarian clear cell and squamous cell carcinomas (OSCC) [28]. Moreover, high NNMT expression in these cancers appears inversely associated with tumor size and progression, thus suggesting that NNMT has potential effect in the initial steps of malignant conversion.

Role of NNMT in cancer

Despite great improvements made in cancer studies and treatment, the disease spectrum remains a major public health problem in China and other countries worldwide [12]. NNMT is an important bio-transforming enzyme of many drugs and xenobiotic compounds. It is present in increased concentration in most cancer types and is considered a crucial marker in cancer development [12, 20].

The following reviews highlight NNMT expression in important cancers.

Neuroblastoma. NNMT expression in the brain has been found only in neurons, but it has regional differences. For example, although the SH-SY5Y human neuroblastoma derived cell line has no endogenous NNMT expression, it is continually used to study NNMT roles. Studies have suggested that NNMT presence could significantly decrease apoptosis in SH-SY5Y cells [29] and NNMT effects have also been linked to the following; increased intracellular ATP content, ATP/ADP ratio and Complex I (CxI) activity and reduction in the degradation of the NADH dehydrogenase (ubiquinone) iron-sulfur protein 3 (NDUFS3) subunit of CxI [21].

In addition, 1-MNA has a key role in mediating the cellular actions of NNMT, and NNMT expression can increase neurite branching, synaptophysin expression and dopamine accumulation and release [30]. Furthermore, the sequential activation of ephrin B2 (EFNB2) and Akt cellular signaling pathways were confirmed to be involved in the mechanism [30]**,** together with the 1-MNA mediated effects of NNMT on neuron morphology. While further experimentation demonstrated that NNMT expression in SH-SY5Y cells notably induced the expression of all three sirtuins (SirTs), siRNA-mediated silencing of SirT3 expression decreased CxI activity and significantly reduced cellular ATP content. [19]

Colorectal cancer. Colorectal cancer (CRC) is one of the most common malignancies in the world and it continues to be a serious public health concern [31]. While raised NNMT levels can be observed in CRC patient serum samples, the molecular mechanisms involved are not clear [26]. Determining NNMT serum levels was therefore proposed for CRC patient early diagnosis and management [17, 26] and experiments confirmed that NNMT expression was enhanced in CRC tissues mediated by the Stat3-regulated pathway [32], and therefore involved in CRC tumorigenesis.

While studies reported that NNMT was more sensitive in CRC detection than the accepted CEA biomarker, thus suggesting that NNMT has potential in diagnosing CRC [26, 32, 43], further research is required to determine the precise relationship between NNMT levels and CRC.

Loss of apoptotic control contributes to the survival of tumor cells and this is one of the main causes of resistance to anti-cancer agents. Xie et al. [12] reported that NNMT could promote CRC cell proliferation through the p53-p21 and p27 pathways, and 1-MNA, as the metabolic product of NNMT, had potential effect in increasing intracellular ATP levels and reducing ROS. This resulted in decreased tumor cells apoptosis and CRC genesis and development. It is also previously recorded that NNMT could increase CxI activity and ATP level in cells via 1-MNA [21], and the most recent report [33] also showed that NNMT and 1-MNA inhibit activation of the ASK1-p38 MAPK pathway to stop apoptosis and induce 5-FU resistance in CRC cells (Figure 1). 5-FU is a recognized first-line chemotherapy for CRC, and NNMT may be a potential therapeutic target for enhancing the pro-apoptotic effect of 5-FU in CRC treatment.

Oral squamous cells carcinoma. Oral squamous cells carcinoma (OSCCs) is the most familiar malignancy in the oral cavity, and OSCC patient survival remains unimproved despite recent advances in cancer treatment.

Increased salivary NNMT was originally found in this tumor, and Sartini et al's investigation into the correlation between NNMT expression and OSCC recorded that NNMT was markedly increased in OSCC patients with a favorable prognosis compared to unfavorable cases, but no significant changes in NNMT expression were detected in most metastatic tumors [8]. Although the function of NNMT in tumor growth remains unknown, this report [8] identified the association of NNMT and tumor metastases, with possible prognostic significance. Their following experiments indicated that NNMT enzyme activity was obviously higher in OSCC than in non-tumor tissues; and it paralleled with increasing tumor development [34]. In addition, NNMT expression effected oral cancer cell differentiation, but its silencing suppressed human cell proliferation *in vitro* and tumor growth *in vivo* [35]. NNMT is therefore strongly suggested as a prognostic marker in OSCC. Further, Jiang et al's micro-array analysis revealed remarkable NNMT up-regulation in OSCC compared to normal tissue [36] and it is therefore reasonable to expect NNMT to be successful as a new molecular target in OSCC therapy.

Non-small-cell lung cancer. Non-small cell lung cancer (NSCLC) account for 85% of all lung cancer cases diagnosed at a late stage, and it is the leading cause of malignancy-related mortality in the world [31]. Therefore, a specific target is required for early diagnosis and effective treatment. One study clarified that NNMT appeared a potential therapeutic target because NNMT obviously improved NSCLC detection sensitivity [22], and Sartini et al. highlighted that NNMT activity was significantly increased in NSCLC compared to adjacent and surrounding tissue [37]. Both adjacent and surrounding tissues in unfavorable NSCLCs exhibited higher activity than in favorable cases, and experimental results demonstrated that decreased NNMT expression significantly inhibits tumorigenicity *in vitro*. This further shows that

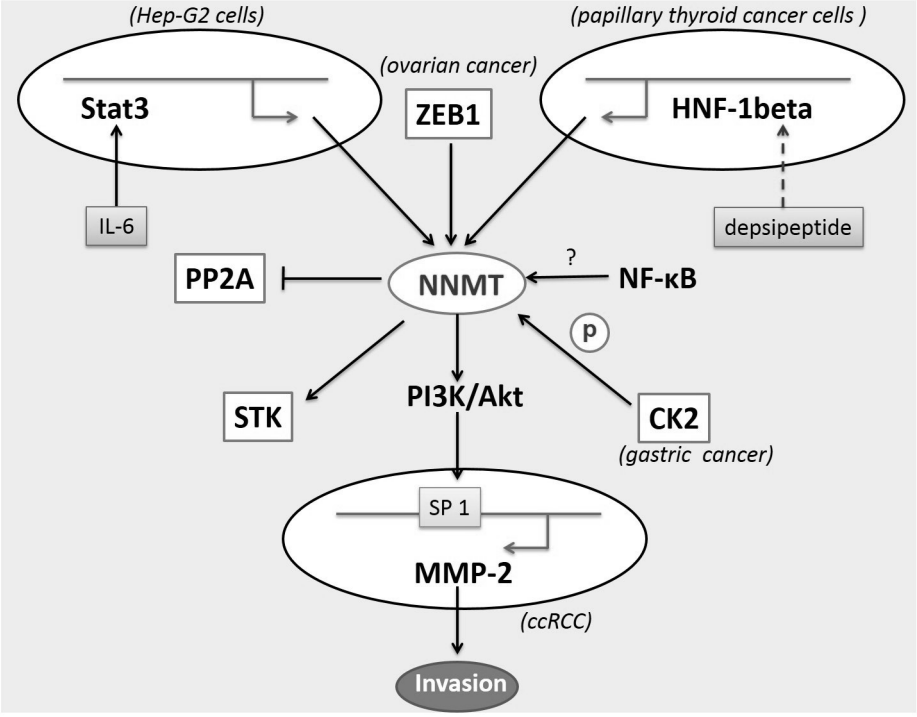

Figure 1. Model of the signaling pathways involved in the regulation of NNMT expression. (Arrows and tee-arrows indicate substrate-protein activation and inactivation, respectively. Dashed arrows show NNMT phosphorylated by CK2, and the question-mark indicates that the NF-κB pathway mechanism regulating NNMT expression remains unknown)

NNMT could be a novel and useful therapeutic target in lung cancer [38].

Papillary thyroid cancer. NNMT is highly expressed in many papillary thyroid cancer cells and cell lines. Immunohistochemical staining established abundant NNMT expression in papillary carcinoma but very little in normal thyroid tissue [18]. It was also recorded that HNF-1beta has a critical role in NNMT transcript activation in some thyroid papillary carcinoma cells [39] and that depsipeptide is useful as a selective inhibitor in decreasing NNMT gene expression through repressing the HNF-1beta transcriptional activator [40] (Figure 1).

Gastric cancer. Gastric cancer is one of the most common malignant tumors in the world. Lim et al. showed that NNMT was highly expressed by post-translational regulation in gastric cancer tissues compared to normal tissues, thus suggesting NNMT's potential role in gastric cancer [24]. Recent evidence has also confirmed NNMT prognostic function, and that its expression significantly correlates with tumor size, clinical pathologic stage and lymph node status. In contrast, NNMT gene silencing inhibited cellular proliferation, invasion and migration ability [15]. This emphasizes NNMT's promise as a prognostic indicator in gastric cancer.

Hepatic cancer. Hepatic cancer has high global incidence; especially in developing countries but it also has increasing occurrence in the western world [41]. In 1998, it was asserted that NNMT activity in the liver was related to cancerous cachexia [42], and it was later verified that the NNMT gene is linked to tumor stage by increasing hepatoma cell invasion and adhesion ability. It was further suggested that higher NNMT mRNA levels could lead to shorter overall patient survival (OS) and also disease-free survival (DFS) [4, 43]. While a recent report indicates that NNMT influences liver nutrient metabolism through Sirt1 protein stabilization [44], further research is required to identify the role of Sirt1 proteins in NNMT's influence on hepatic cancer.

Pancreatic cancer. Pancreatic cancer is a devastating disease with high mortality rate. Early studies established elevated NNMT RNA and NNMT expression in pancreatic cancer secretions [25] and later experiments identified obvious increase in NNMT mRNA levels in the pancreatic cancer cells [45, 46]. Under metabolic stress, NNMT influences cell proliferation and metastases in pancreatic carcinoma [47] and therefore plays an important role in pancreatic carcinogenesis and development [45].

Xu et al most recently reported greater NNMT over-expression in pancreatic cancer than in chronic pancreatitis and para-cancerous tissues [14]. These authors concluded that NNMT over-expression was related to unfavorable clinic pathological features including tumor size, differentiation and TNM stage, and that it ultimately influences patient

survival [48] NNMT could therefore serve as an independent predictor of mortality risk in pancreatic cancer [14].

Renal cancer. Renal cell carcinoma (RCC), accounts for 90% of kidney cancer and kills more than 100,000 people worldwide annually. However, there is currently no independent diagnostic biomarker for RCC [49, 50]. NNMT, as a known inhibitor of cellular DNA repair, causes resistance to cellular damage by consumption of accessible nicotinamide [51]. Researchers have previously identified enhanced NNMT expression in clear cell papillary renal cell carcinoma (ccRCC) compared to other non-clear-cell tumor subtypes, and this enhancement inversely correlates with tumor size [49, 52–54]. Tang et al. further demonstrated that NNMT could influence ccRCC cellular invasion by activating the PI3K/Akt/SP1/MMP-2 pathway [49] (Figure 1). These studies support NNMT as an independent and powerful candidate biomarker for diagnosis in all types of RCC [55]. Furthermore, NNMT is considered a promising new serum marker for early detection and diagnosis of kidney malignant tumors, especially including the RCC sub-types [56].

Bladder cancer. Bladder cancer (BCa) is a most common occupational cancer, with an estimated 74,000 new cases diagnosed each year [57]. The NNMT enzyme was originally found to be highly expressed in bladder cancer; and increased NNMT appeared to be associated with cancer cell invasion, migration and tumor stages [58]. Subsequent study also indicated that NNMT transcript and protein levels were remarkably higher in patients with bladder tumor than in controls [59]. The latest clinical study analyzing NNMT expression in urine samples from 55 BCa patients and 107 controls suggests that there is increased urinary NNMT level in BCa patients and that the histological grade negatively correlates with NNMT expression [60].

Other cancers. In addition to all the preceding reviews, NNMT is considered over-expressed in some breast cancer cell lines, and elevated NNMT can suppress apoptosis via the mitochondrial-mediated pathway [20, 23]. NNMT also contributes to prostate cancer (PCa) progression and is considered a favorable PCa biomarker for patient survival [61]. In addition, published data records that significant up-regulation of NNMT expression is evident in nasopharyngeal carcinoma [62] and that NNMT variants are linked to increased acute lymphoblastic leukemia susceptibility [63]. Enhanced NNMT expression has also been detected in metastatic and recurrent ovarian tumors, but not in normal ovarian and fallopian tube tissue [64]. All of these studies raise the possibility of using NNMT as a novel biomarker for cancer diagnosis and treatment.

Regulation of NNMT expression

NNMT is significantly up-regulated in several of human cancers [65], and researchers around the world have long been committed to establishing the mechanism involved.

Xu et al. [39] suggested that the activation of hepatocyte nuclear factor-1beta (HNF-1beta) contributed to NNMT up-regulation in papillary thyroid cancer cells and that the depsipeptide histone deacetylase inhibitor reduced NNMT and its catalytic activity [40]. Depsipeptide inhibition of NNMT is executed at the transcription level by down-regulating the HNF-1beta transcription activator [40] (Figure 1), and it is suggested that the methylation mediated by NNMT can not only modify histone-dependent gene expression but it can also extend beyond histones to include tumor suppressor proteins such as PP2A [66]. NNMT could inhibit PP2A both at the epigenome and proteome levels and concomitantly activate pro-survival STKs. However, NNMT effects can also be accomplished by FDA-approved perphenazine (PPZ) which is currently used to treat mood dysfunction in bipolar disorder and schizophrenia [66] (Figure 1).

Recent research has proposed a novel ZEB1/NNMT signaling axis where NNMT is able to increase ZEB1-induced cell migration in ovarian cancer. This knowledge could prove very useful in understanding the causes of cancer cell plasticity, tumor heterogeneity and recurrence [64] (Figure 1).

Further, NNMT was found significantly present in cellular invasion and in activation of the matrix metallopeptidase (MMP)-2 in cancer cells. Research has also indicated that the transcription factor SP-1-binding region of the MMP-2 promoter plays an essential role in NNMT-induced MMP-2 expression, and that the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathway could be involved in NNMT-dependent cellular invasion and MMP-2 activation [49] (Figure 1).

In addition, it has been shown that signal transducers and activators of transcription 3 (Stat3) [32], and nuclear factor (NF)-κB [67] signaling pathways are important in NNMT over-expression in tumors; where the rising levels of NNMT appear associated with epithelial-to-mesenchymal conversion. A further suggestion is that NNMT has post-translational modification in a cancer-specific manner; where recombinant NNMT is phosphorylated by casein kinase 2 (CK2) *in vitro* [24] (Figure 1). These studies provide impetus for further research into the underlying mechanism of NNMT action.

Conclusion

NNMT is a small molecule methyltransferase in the human body responsible for the N-methylation of nicotinamide and it so over-expressed in a variety of tumor cells that it is considered involved in the progression of these cancers [66]. A number of studies have revealed that elevated NNMT activity is linked to tumor metastasis and resistance to radiotherapy and anti-tumor agents [15, 18, 68–70]. NNMT expression was also proven inversely related to tumor size, and combined results indicate that NNMT has a crucial role in malignant conversion [8]. Studies have suggested that

NNMT over-expression *in vivo* can also be caused by cellular stress response to the underlying pathogenic processes in cancer; and this has increased the possibility of using NNMT inhibitors in cancer therapy [21, 71].

Most importantly, NNMT appears a promising prognostic predictor for several malignancies and its down-regulation could be an attractive drug target in cancer treatment. Furthermore, the functional relationship between methylation and expression changes in the specific protein mediated by NNMT and its pro-tumorigenic effect in cancer cells requires investigation, and finally NNMT expression in the liver has bimodal frequency distribution and this may cause differences in individual metabolism and response to cancer therapy [20]. Therefore, our combined results confirm that further study is required to elucidate NNMT's prognostic and therapeutic value in cancer.

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