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Nampt: Linking NAD biology, metabolism, and cancer

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Abstract

Nicotinamide phosphoribosyltransferase (Nampt) converts nicotinamide to nicotinamide mononucleotide (NMN), a key NAD intermediate. Previously identified as a cytokine PBEF and controversially claimed as an insulin-mimetic hormone visfatin, Nampt has recently drawn much attention in different fields, including NAD biology, metabolism, and inflammation. As an NAD biosynthetic enzyme, Nampt regulates the activity of NAD-consuming enzymes such as sirtuins and influences a variety of metabolic and stress responses. Nampt also plays an important role in the regulation of insulin secretion in pancreatic β cells. Nampt appears to have another function as an immunomodulatory cytokine and plays a role in inflammation. This review summarizes these various functional aspects of Nampt and discusses its potential roles in diseases, including type 2 diabetes and cancer.

Introduction

Nicotinamide adenine dinucleotide (NAD) is a classic coenzyme with a well-established role in cellular redox reactions. Recently, several lines of evidence have implicated NAD biochemistry in a broad range of biological functions. For example, NAD is required in a number of important signaling pathways in mammalian cells, including poly(ADP-ribosyl)ation in DNA repair[1], mono-ADP-ribosylation in both the immune response and G protein-coupled signaling[2], and synthesis of cyclic ADP-ribose and nicotinate adenine dinucleotide phosphate (NAADP) in intracellular calcium signaling[3]. Furthermore, NAD and its derivatives also play important roles in transcriptional regulation[4]. In particular, the discovery that yeast and mammalian Sir2 (*s*ilent *i*nformation *r*egulator 2) proteins require NAD for their deacetylase activity[5] has drawn much attention to this novel regulatory role for NAD.

In mammals, tryptophan, nicotinic acid, and nicotinamide are three major precursors for NAD biosynthesis, and nicotinamide is predominantly used to synthesize NAD[6,7]. In the NAD biosynthetic pathway from nicotinamide, Nampt (EC 2.4.2.12) is the rate-limiting enzyme that catalyses the transfer of a phosphoribosyl group from 5-phosphoribosyl-1-pyrophosphate (PRPP) to nicotinamide, forming nicotinamide mononucleotide (NMN) and pyrophosphate (PP_i)[8] (Figure 1). NMN is then converted to NAD by nicotinamide mononucleotide adenylyltransferase (Nmnat, EC 2.7.7.1) (Figure 1). Whereas Nampt enzymatic activity was originally reported in 1957[9], the gene encoding Nampt was first identified in *Haemophilus ducreyi* in 2001[10]. Since then, several groups have characterized the enzymological features of mammalian Nampt[11,12,13]. The K_m value of Nampt for nicotinamide is ~1 μM, and it

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does not use nicotinic acid as a substrate[12,11]. The crystal structure of Nampt has also been determined, which clearly demonstrates that this protein belongs to the dimeric class of type II phosphoribosyltransferases[14,15,16].

Recently, Nampt has drawn significant interests not only in the field of NAD biochemistry but also in several other fields, including metabolism, immune response, and cancer. Whereas the biochemical and structural basis of Nampt as an NAD biosynthetic enzyme has been established, the physiological functions of this protein have been controversial. Human Nampt was originally characterized as a presumptive cytokine named pre-B-cell colony enhancing factor (PBEF)[17]. Nampt was also claimed to function as an insulin-mimetic adipocytokine named visfatin[18], although the original paper has recently been retracted because of a concern on the reproducibility of the results[19]. While all three names (Nampt, PBEF, and visfatin) have been used in publications, Nampt has been approved as the official nomenclature of the protein and the gene by both the HUGO Gene Nomenclature Committee (HGNC) and the Mouse Genomic Nomenclature Committee (MGNC). Therefore, Nampt will be used throughout this review, and we will discuss different functional aspects of Nampt and its potential roles in a variety of pathophysiological conditions in metabolism, inflammation, and cancer in this review article.

Nampt vs. visfatin: Does this protein exhibit insulin-mimetic activity?

In mammals, Nampt has two different forms: intracellular and extracellular Nampt (iNampt and eNampt, respectively). While the function of iNampt as an NAD biosynthetic enzyme has been firmly supported by the biochemical and structural analyses of this protein, the significance and the function of eNampt have been a matter of debate. For example, because Nampt possesses neither a signal sequence nor a caspase I cleavage site[11], several studies have suggested that eNampt might be released simply by cell lysis or cell death[20,21]. On the other hand, we have shown that eNampt release is not due to cell death or cell lysis but governed by a highly regulated positive secretory process in a cell type-dependent manner[22]. In particular, fully differentiated mouse and human adipocytes are capable of secreting eNampt through a non-classical secretory pathway, which is not blocked by inhibitors of the classical ER-Golgi secretory pathway, such as brefeldin A and monensin[22,23]. Other cell types, such as human primary hepatocytes[24], might also positively secrete eNampt. Indeed, eNampt shows a slightly higher molecular weight compared to iNampt and appears to be produced through a posttranslational modification[12;22]. The molecular mechanism of eNampt secretion is currently under investigation.

Compared to the function of iNampt as an NAD biosynthetic enzyme, the physiological role of eNampt has been controversial because at least three different functions have been assigned to eNampt - a cytokine, an insulin-mimetic hormone, and a NAD biosynthetic enzyme[25,8, 26,27]. The most controversial function assigned to this protein was the insulin-mimetic activity as an adipocytokine named “visfatin” described by Fukuhara *et al.*[18]. This study found that eNampt acted like insulin by binding to the insulin receptor, activating the associated downstream signalling pathway, and exerting similar biological effects *in vitro* and *in vivo* on adipogenesis, cellular glucose uptake, and blood glucose levels[18]. Their results immediately drew attention to a possible connection between eNampt and metabolic complications, such as obesity and type 2 diabetes mellitus (T2DM). Nonetheless, there has been no evidence supporting the direct binding of eNampt/visfatin to the insulin receptor. Furthermore, this paper has recently been retracted[19]. Three subsequent studies have so far provided indirect evidence for the connection between eNampt and insulin signalling[28,29,30]. One group has reported an insulin-like action of eNampt on osteoblasts. After stimulation with eNampt, the phosphorylation of the insulin receptor and its downstream targets IRS-1 and IRS-2 was observed, and just like insulin, eNampt stimulated various responses, including glucose uptake,

proliferation, type I collagenase production, which were blocked by the pretreatment with the insulin receptor kinase inhibitor HNMPA-$(AM)_3$[28]. In another study, it has been reported that the same inhibitor blocked the effect of eNampt on matrix metalloproteinase-9 activity in THP-1 cells and the production of TNF-α and IL-8 in peripheral blood mononuclear cells [29]. The third group has found multiple actions of eNampt on cultured kidney mesangial cells. eNampt induced uptake of glucose, GLUT-1 protein expression, and synthesis of profibrotic molecules, including TGF-β1, plasminogen activator inhibitor-1, and type I collagen. Whereas a potent Nampt inhibitor FK866[31] blocks this eNampt-mediated glucose uptake, knockdown of the insulin receptor also inhibits this effect[30]. Unfortunately, none of these studies have examined whether eNampt directly binds to the insulin receptor in each biological context nor which activity, between the NAD biosynthetic and the insulin-mimetic activities, is mainly required for the observed biological effects.

Recently, we have demonstrated that eNampt does not exert insulin-mimetic effects *in vitro* or *in vivo* but rather exhibits robust NAD biosynthetic activity. As discussed in the next section, we have also demonstrated that Nampt-mediated NAD biosynthesis plays a critical role in the regulation of glucose-stimulated insulin secretion in pancreatic β cells *in vitro* and *in vivo* [22]. In our efforts to reproduce the claimed insulin-mimetic effects, two different sources of recombinant human eNampt (prokaryotically and eukaryotically expressed) were tested in several cell lines, including human SGBS and mouse 3T3-L1 preadipocytic cell lines and another mouse fibroblast cell line that overexpresses the human insulin receptor. However, eNampt did not induce morphologic signs of differentiation or expression of typical markers of differentiated adipocytes. Glucose uptake into eNampt-stimulated SGBS and 3T3-L1 adipocytes was also examined and again, no response was observed upon addition of eNampt. Furthermore, upon stimulation with increasing doses of recombinant eNampt or conditioned media from *Nampt*-transfected and eNampt-secreting COS cells, no phosphorylation of the insulin receptor or its downstream kinase Akt was detected. In mice, the injection of recombinant eNampt did not reduce blood glucose levels. Therefore, in contrast to the original report[18], we conclude that this protein possesses no insulin-mimetic activity[22].

One possible explanation for these contradictory results is that there might be some crosstalk between eNampt-mediated and insulin signaling pathways in a cell type-dependent manner. In this scenario, eNampt could possibly bind to and activate an unidentified receptor that might indirectly affect insulin signaling. Another possibility is that Nampt-mediated NAD biosynthesis might have an impact on the insulin signaling pathway. To address these possibilities in future studies, it is critical to examine 1) whether the existence of the insulin receptor is necessary for the observed insulin-mimetic effects in each biological context by using mutant cells that lack the insulin receptor, 2) whether nicotinamide, which is usually included at very high concentrations in major culture media, is necessary to observe those effects, and 3) whether mutant Nampt proteins that significantly lack NAD biosynthetic activity can still mediate the activity of interest in each condition. These careful and thorough analyses will resolve contradictory results around the claimed insulin-mimetic activity of Nampt.

Nampt and metabolic disorders

Since the original report of visfatin, numerous studies have been published, addressing possible associations between plasma eNampt/visfatin levels and anthropometric and metabolic parameters in obesity and T2DM (summarized in Table 1). So far, results have been conflicting, showing positive, negative or no association[8,20,25,32]. For example, one study reported a positive correlation of plasma eNampt concentrations with body mass index (BMI) and percent body fat[33], while another study found that plasma eNampt is reduced in human obesity and not related to insulin resistance[34]. Yet another study reported that higher plasma eNampt levels are independently and significantly associated with T2DM even after adjusting for

known biomarkers[35]. These contradictory findings appear to be due in part to significant differences in immunoassays and the treatment and type of samples. Freeze-thaw cycles and different sample additives have considerable influence on the measurement of eNampt concentrations[36]. Also, commercially available immunoassays differ considerably in the specificity and sensitivity of eNampt detection in human serum and plasma[37]. Recently, one group has found that circulating eNampt levels, measured by a new ELISA kit with increased sensitivity and specificity for eNampt, are independently associated with type 2 diabetes but not with anthropometric and metabolic parameters[38]. Our group has also used an ELISA kit from the same company and has found that there is no correlation between plasma eNampt levels and anthropometric and metabolic parameters in visceral obese patients[37,39]. Therefore, the association between plasma eNampt levels and metabolic disorders, such as obesity and T2DM, is still unclear, and careful assessments with highly accurate assays for the measurement of eNampt will be necessary to address this critical issue.

In the pathophysiology of obesity and T2DM, it has been revealed that chronic inflammation plays an important role in the development of insulin resistance and other associated complications, such as atherosclerosis[39,40,41,42]. In this regard, one might speculate that eNampt could show an association with the development of vascular inflammation induced by obesity and T2DM, instead of an association with anthropometric and metabolic parameters. Indeed, it has been shown that eNampt induces the adhesion of leukocytes to endothelial cells and aortic endothelium by activating intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1[43]. This phenomenon appears to be mediated through the pro-inflammatory transcription factor nuclear factor-κB (NF-κB) in a reactive oxygen species (ROS)-dependent manner. This same study has also shown that eNampt significantly increases the transcriptional activity of NF-κB in human vascular endothelial cells, resulting in the activation of the matrix-metalloproteinases (MMP)-2/9. These findings provide supportive evidence for a potential role of eNampt in the pathogenesis of vascular inflammation in obesity and T2DM[43]. Therefore, eNampt might play an important role in the progression and/or the associated complications, especially inflammatory complications, of obesity and T2DM. The connection between eNampt and inflammation will be discussed later in this review.

Nampt-mediated systemic NAD biosynthesis and β cell function

In the pathogenesis of T2DM, a delicate balance between insulin sensitivity and secretion is compromised by both environmental and genetic factors. While the physiological significance of Nampt (especially, eNampt) in obesity, T2DM, and other metabolic disorders is still unclear, a new study has recently revealed an interesting connection between Nampt and the regulation of insulin secretion. We have demonstrated that Nampt-mediated NAD biosynthesis regulates glucose-stimulated insulin secretion (GSIS) in pancreatic β cells[22]. As mentioned in the previous section, we have also demonstrated that Nampt functions as an intra- and extracellular NAD biosynthetic enzyme. To address the physiological significance of Nampt function *in vivo*, we generated *Nampt*-deficient mice. While *Nampt* homozygous ($Nampt^{-/-}$) mice are embryonic lethal likely due to failure of adequate NAD biosynthesis, *Nampt* heterozygous ($Nampt^{+/-}$) mice look overtly normal but show significant decreases in total NAD levels in tissues[22]. Both male and female $Nampt^{+/-}$ mice display normal body weight and mostly normal fed and fasted glucose levels. However, $Nampt^{+/-}$ female mice show moderately impaired glucose tolerance and a significant defect in GSIS. Whereas islet morphology and size in $Nampt^{+/-}$ mice do not differ from control mice, further analyses of isolated primary islets revealed that $Nampt^{+/-}$ islets have functional defects in NAD biosynthesis and GSIS. Remarkably, insulin secretion defects in $Nampt^{+/-}$ mice and islets can be corrected by administration of NMN, confirming that the defects observed in $Nampt^{+/-}$ mice and islets are due to a lack of the NAD biosynthetic activity of Nampt. Furthermore, FK866, a potent chemical inhibitor of Nampt, significantly inhibits NAD biosynthesis and GSIS in isolated

wild-type primary islets. Again, administration of NMN ameliorates defects in NAD biosynthesis and GSIS in FK866-treated wild-type islets. Thus, pancreatic β cells require Nampt-mediated NAD biosynthesis to maintain normal NAD biosynthesis and GSIS and are capable of incorporating NMN from the outside of cells.

Interestingly, while tissue iNampt levels are significantly reduced in *Nampt*$^{+/-}$ males and females, plasma eNampt and NMN levels are reduced only in *Nampt*$^{+/-}$ females, but not males [22]. This finding implies that plasma NMN levels are regulated by circulating eNampt, independent of iNampt-mediated NMN synthesis in tissues, although a possibility that circulating NMN is also originated from some other sources cannot be excluded. This disparity in plasma eNampt and NMN levels between genders also explains why only *Nampt*$^{+/-}$ females show the defects in glucose metabolism and why NMN administration ameliorates the defects in those females, although the reason for this disparity is currently unknown. Given that pancreatic islets have very low levels of iNampt, it has been proposed that systemic NAD biosynthesis mediated by iNampt and eNampt plays a critical role in the regulation of β cell function and that the maintenance of circulating NMN by eNampt is also critical for normal β cell function[22]. In humans, it has been reported that individuals who carry specific single nucleotide polymorphism variants in the *Nampt* gene promoter region have lower fasting plasma insulin levels[44], suggesting that Nampt-mediated NAD biosynthesis might also regulate insulin secretion in humans. Although further investigation will be required to address this model, the finding that Nampt-mediated systemic NAD biosynthesis regulates β cell function sheds new light on the physiological significance of Nampt and its potential role in the pathogenesis of β cell dysfunction in T2DM.

Nampt and mammalian sirtuins

Recently, a group of enzymes called sirtuins has attracted many researchers into the field of NAD biology[45,46,47]. Sirtuins deacetylate and/or ADP-ribosylate lysine residues of target proteins by consuming NAD [45]. In their NAD-dependent deacetylation reactions, sirtuins produce acetyl-ADP-ribose, nicotinamide, and deacetylated proteins. Silent information regulator 2 (Sir2), as the prototypical enzyme of this group, regulates the replicative life span of yeast mother cells[48]. Strikingly, Sir2 homologs also regulate life span in worms and flies [49,50] and, depending on the genetic background, mediate life span extension caused by caloric restriction, the only dietary regimen that can retard aging and extend life span in a wide variety of organisms[51]. In mammals, it is not yet known whether Sirt1, the mammalian Sir2 ortholog, regulates aging and longevity. However, it has been established that Sirt1 regulates metabolic responses to nutritional availability in different tissues and cellular responses to a variety of stresses and damages through the NAD-dependent deacetylation of many target regulatory factors[45,47].

Because Sirt1 absolutely requires NAD for its function, NAD biosynthesis plays a critical role in Sirt1 activity (as well as activities of other sirtuins). For example, it has been demonstrated that increased Nampt-mediated NAD biosynthesis enhances Sirt1 activity in mouse fibroblasts [12]. In human vascular smooth muscle cells (SMCs), iNampt expression levels are up-regulated during SMC maturation, and knockdown of endogenous iNampt reduces NAD biosynthesis and SMC survival and maturation. On the other hand, overexpression of iNampt promotes SMC maturation by increasing NAD biosynthesis and enhancing Sirt1 activity[13]. Additionally, iNampt-overexpressing SMCs are able to mature and form nascent endothelial channels at a higher efficiency *in vivo*[13]. Furthermore, it has been reported that iNampt promotes cellular life span of SMCs through increasing Sirt1-mediated p53 degradation[53]. In cardiac myocytes, overexpression of iNampt maintains cellular NAD levels and thereby stimulates Sirt1 activity, resulting in the protection of cardiac myocytes from PARP-induced cell death during heart failure[52]. Most recently, it has been reported that glucose restriction

suppresses differentiation of skeletal myoblasts by increased production of iNampt and consequential activation of Sirt1[54]. The activation of the AMP-activated protein kinase (AMPK) is required to promote glucose restriction-induced transcription of the *Nampt* gene [54]. Therefore, the AMPK-iNampt-Sirt1 pathway might be critical for skeletal muscle cells as well as other cell types in response to nutritional restriction. These studies suggest that Nampt is involved in various biological processes through the activation of Sirt1 in mammals.

iNampt also plays an important role in regulating cellular stress resistance through the mitochondrial sirtuins, Sirt3 and Sirt4[55]. iNampt expression levels increase under cellular stress and nutrient restriction. Under genotoxic stress, increased iNampt plays an important role in maintaining NAD levels in mitochondria and providing protection against cell death by suppressing translocation of apoptosis-inducing factor (AIF) from mitochondria to the nucleus [56]. These protective effects of iNampt require mitochondrial Sirt3 and Sirt4[55].

Aging also affects Nampt-mediated systemic NAD biosynthesis, resulting in reduced Sirt1 activity in pancreatic β cells. Pancreatic β cell-specific Sirt1-overexpressing (BESTO) mice exhibit significantly enhanced GSIS and improved glucose tolerance[57]. However, these phenotypes are completely lost in both BESTO males and females when they reach 18-24 months of age[58]. Plasma NMN levels are significantly reduced in those aged BESTO mice, and Sirt1 activity is also reduced in pancreatic islets from aged BESTO mice. Consistent with this finding, NMN administration can restore enhanced GSIS and improved glucose tolerance in aged BESTO females[58], although the reason for the observed sex-dependent difference in response to NMN again remains unknown, similar to the case of *Nampt*$^{+/-}$ males. These findings suggest that an age-dependent decline in Nampt-mediated systemic NAD biosynthesis contributes to reduced Sirt1 activity in aged pancreatic islets and likely in other aged tissues. Because sirtuins have recently emerged as promising pharmaceutical targets to develop therapeutic interventions against age-associated diseases[59,60], the systemic enhancement of NAD biosynthesis might provide another pharmacological means to activate Sirt1 and to convey benefits against age-associated diseases[61].

In conclusion, Nampt-mediated NAD biosynthesis influences cellular differentiation, stress resistance, and metabolic responses in different cell types by raising intracellular NAD levels and thereby regulating the activity of NAD-consuming enzymes such as sirtuins and PARPs [12,52,13,53,55,54].

Nampt and inflammation

Human Nampt was originally identified by a screen of a human peripheral blood lymphocyte cDNA library and named PBEF. This 52 kD protein was reported to act as a presumptive cytokine that increased pre-B-cell colony forming activity together with interleukin (IL)-7 and stem cell factor (SCF)[62]. iNampt is also highly expressed in human fetal membranes, amnion, and placenta. Nampt mRNA expression increases in fetal membranes after labour and in severely infected amnion membranes. Interestingly, eNampt treatment up-regulates the expression of inflammatory cytokines, such as IL-6 and IL-8, in amnion-like epithelial cells. Thus, it has been speculated that eNampt might have a cytokine-like function involved in regulation of labour and in infection-induced preterm birth[63,64].

eNampt has also been shown to be involved in the regulation of apoptosis as a cytokine. In human neutrophils, eNampt inhibits their apoptosis in response to various inflammatory stimuli, although this particular effect of eNampt requires the presence of iNampt to some extent[65]. Furthermore, serum eNampt levels are found to be up-regulated in sepsis patients, and rates of neutrophil apoptosis are profoundly delayed in those patients[65]. In amniotic epithelial cells, eNampt treatment appears to confer protection from apoptosis as a stretch-responsive cytokine[66]. In patients with inflammatory bowel disease (Crohn's disease and

ulcerative colitis), Nampt mRNA levels are increased in their colon biopsy samples, and plasma eNampt levels are elevated[67]. Because eNampt stimulates the production of proinflammatory cytokines in human peripheral blood mononuclear cells (PBMCs) and up-regulates IL-6 mRNA and serum levels *in vivo* when given intraperitoneally to mice, it has been suggested that eNampt itself also functions as a proinflammatory cytokine[67]. Stimulation of the tumour necrosis factor family member TNF- and APOL-related leukocyte expressed ligand (TALL)-1, which is involved in lupus-like autoimmune diseases, increased Nampt mRNA[68]. Additionally, Nampt has been found to be up-regulated in a variety of other immunological disorders including acute lung injury, rheumatoid arthritis, and myocardial infarction and is considered a novel mediator of innate immunity[69].

These studies all suggest that eNampt might possess another function as an inflammatory cytokine. In those studies, however, it has not been fully addressed which activity of eNampt, NAD biosynthetic activity vs. cytokine-like activity, is responsible for the observed effects of eNampt. Recently, it has been reported that the inhibition of Nampt by FK866 suppresses proinflammatory cytokine secretion in inflammatory cells *in vitro* and in joints affected with rheumatoid arthritis *in vivo*[70]. Most recently, another group has definitively demonstrated that eNampt protects macrophages from ER stress-induced apoptosis through its cytokine-like activity that is totally separated from its NAD biosynthetic activity[71]. Therefore, although how eNampt exerts its cytokine-like activity still needs to be investigated, this protein has another function as an immunomodulatory cytokine.

Nampt as a potential target for cancer therapy

There appears to be an interesting connection between Nampt and cancer. For example, iNampt expression has been reported to increase in primary colorectal cancer[72,73]. iNampt is also involved in angiogenesis by activating the extracellular signal regulated kinase (ERK)1/2 pathway and inducing vascular endothelial growth factor (VEGF) and MMP2/9 production [74]. Additionally, iNampt induces the proliferation and capillary-like tube formation in human umbilical vein endothelial cells (HUVECs) in a dose- and time-dependent manner[75]. These findings suggest that iNampt might have pro-angiogenic activity and support the growth of some types of tumours.

Additionally, a chemical screen to identify compounds that might affect mechanisms of cellular growth, survival, or death has yielded a potent small molecule inhibitor termed FK-866 ((E)-N-[4-(1-benzoylpiperidin-4-yl) butyl]-3-(pyridin-3-yl) acrylamide)[31]. FK866 induces apoptosis in HepG2 cells without having primary effects on cellular energy metabolism. Instead of causing immediate cytotoxicity, it inhibits Nampt and depletes the cells of NAD, suggesting that FK866 could be a promising agent against cancer cells that rely on nicotinamide to synthesize NAD[31]. The crystal structure of the Nampt-FK866 complex reveals that the compound binds at the nicotinamide-binding site of Nampt to inhibit its activity[15]. FK866 has been tested in a murine renal cell carcinoma model and shown to display anti-tumor, anti-metastatic, and anti-angiogenic activities[76]. In a mouse mammary carcinoma model, FK866 also induces a delay in tumour growth and an enhancement in tumour radiosensitivity accompanied with dose-dependent decreases in NAD levels, pH, and energy status. A chemosensitizing effect of FK866 has also been observed on anti-neoplastic 1-methyl-3-nitro-1-nitrosoguanidinium (MNNG)-induced cell death in THP-1 and K562 leukemia cell lines[78]. Recently, another potential anti-cancer agent termed CHS-828 has been identified as an Nampt inhibitor[79]. It has been shown that this new compound potently inhibits cell growth in a broad range of tumour cell lines, although the detailed mechanism for this inhibitory effect of CHS-828 remains undetermined[80]. Both FK866 and CHS-828 are currently in clinical trials for cancer treatments.

Conclusion

Nampt functions as an intra- and extracellular NAD biosynthetic enzyme that is important for the regulation of metabolism and stress resistance through sirtuins and other NAD-consuming regulators. On the other hand, there are new lines of evidence supporting that eNampt acts as a cytokine, independent of its enzymatic activity, and plays a major role in the regulation of immune responses. The distinction between the cytokine-like and the enzymatic functions of Nampt in physiological contexts still needs to be investigated extensively. In this regard, it will be of great importance to identify the receptor of eNampt and to elucidate its signaling mechanism (Figure 2). Furthermore, the mechanism and regulation of eNampt secretion, especially the molecular difference between secreted eNampt proteins as the enzyme vs. the cytokine, is poorly understood. Careful, thorough assessments for these two distinct functions of eNampt will enrich our knowledge of this multifunctional protein in various physiological contexts.

To better understand the effects of iNampt on cellular metabolism, it will also be important to understand the subcellular compartmentalization of Nampt and other enzymes involved in the biosynthesis and the breakdown of NAD and the regulation of their localization (Figure 2). Additionally, very little is known about the flux of NAD substrates, intermediates, and metabolites. Therefore, it will be critical to study not only the regulation of NAD biosynthesis and breakdown in each cellular compartment, but also the special and temporal dynamics of NAD metabolism at a systemic level using a metabolomics approach. For example, it will be of great interest to clarify how NMN as a product from the eNampt enzymatic reaction is distributed to other target tissues as well as pancreatic β cells and how it mediates its physiological and pharmacological effects in each tissue.

To date, a substantial part of the studies on the biological functions of Nampt has been conducted in cell culture and mouse models, and the studies on possible correlations between human plasma eNampt levels and metabolic parameters have been contradictory. Therefore, more work needs to be done to elucidate the physiological relevance of the eNampt function in normal individuals and patients with metabolic and other diseases in humans.

The most pertinent questions concerning Nampt are summarized in Box 1 (see Outstanding Questions). Nampt itself or any component in Nampt-mediated systemic NAD biosynthesis could be an effective therapeutic target/reagent for the prevention and the treatment of metabolic disorders including obesity and T2DM, inflammation, and cancer. Because downstream regulators, such as sirtuins and PARPs, have pleiotropic functions, more rigorous investigations will be necessary to clarify possible benefits from the manipulation of Nampt-mediated NAD biosynthesis.

Box 1: Ten Outstanding Questions

1. What is the mechanism by which eNampt secretion is regulated?
2. What is the molecular difference between secreted eNampt proteins as an NAD biosynthetic enzyme vs. a cytokine?
3. How does eNampt exert its actions as a cytokine and what receptor does it bind to?
4. Is Nampt-mediated NAD biosynthesis also important for β cell function in humans?
5. Could plasma eNampt levels be a diagnostic or prognostic biomarker for metabolic disorders, such as obesity and T2DM, and/or inflammatory complications?

6. Is Nampt-mediated NAD biosynthesis important for the Sirt1-mediated regulation of aging and longevity in mammals?
7. What is the mechanism by which Nampt-mediated NAD biosynthesis influences carcinogenesis?
8. Is Nampt inhibition an effective anti-cancer therapy in humans and if so, what type of cancer can be treated?
9. What are the regulatory mechanisms for the compartmentalization of NAD biosynthesis and the distribution of NAD precursors, intermediates, and metabolites?
10. Could Nampt itself and NAD intermediates/metabolites be effective therapeutic targets/reagents for metabolic disorders and other diseases?

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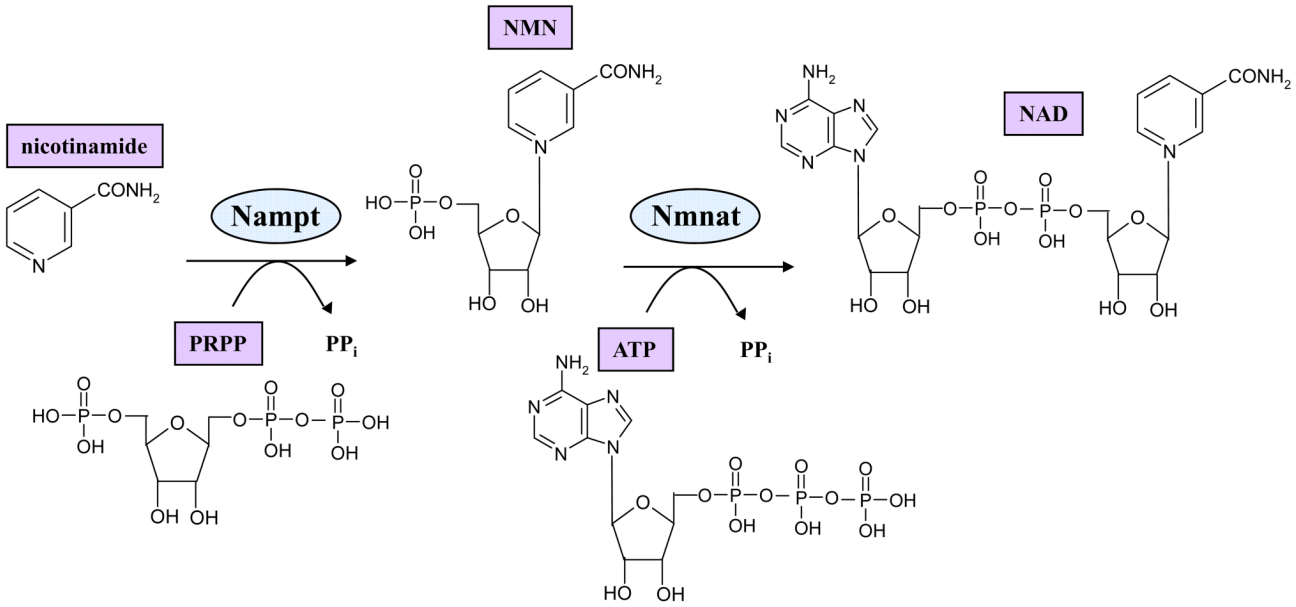

Fig 1. NAD biosynthetis from nicotinamide

The rate-limiting step in mammalian NAD biosynthesis from nicotinamide is the transfer of a phosphoribosyl residue from 5-phosphoribosyl-1-pyrophosphate (PRPP) to nicotinamide catalysed by nicotinamide phosphoribosyltransferase (Nampt) to produce nicotinamide mononucleotide (NMN), which is then converted to NAD by nicotinamide mononucleotide adenylyltransferase (Nmnat).

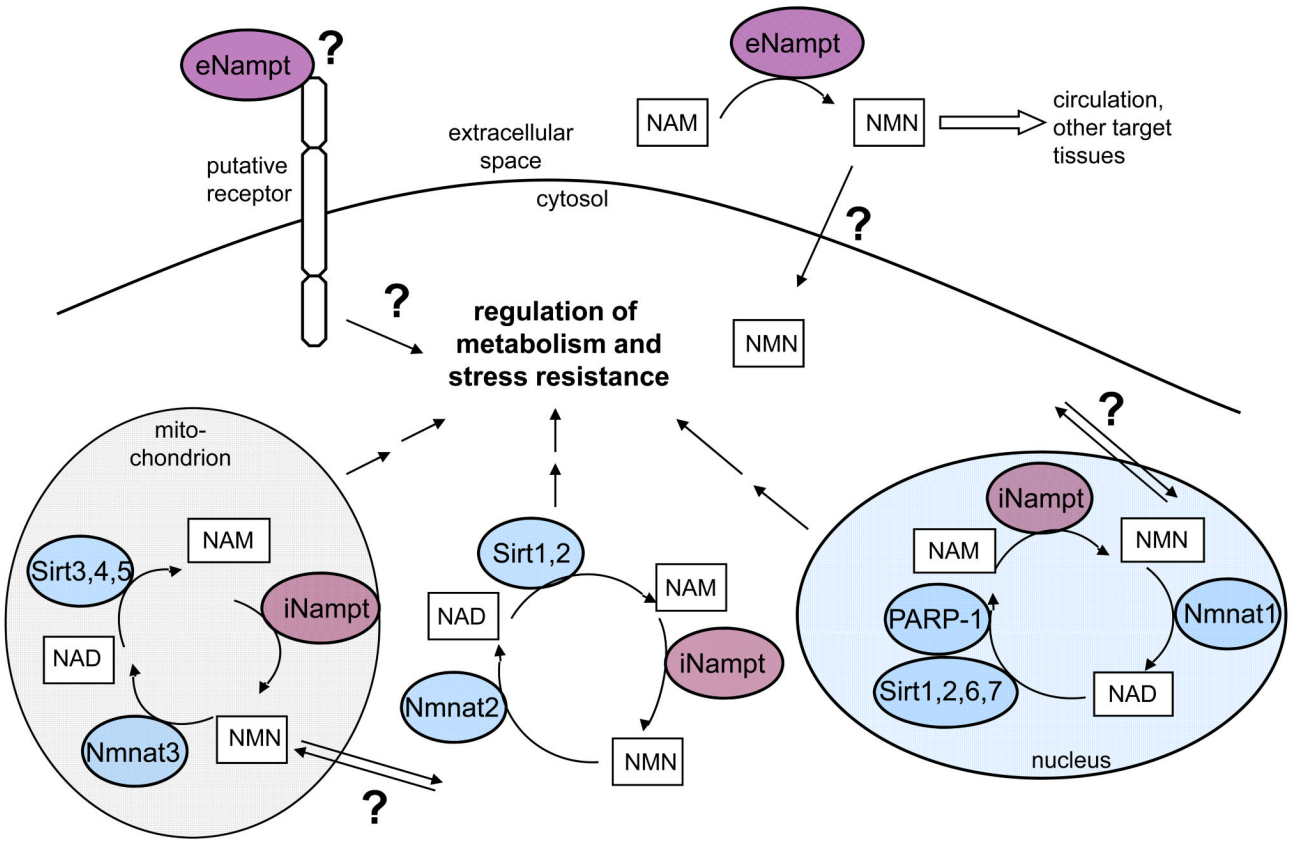

Fig 2. Model of putative modes of action for nicotinamide phosphoribosyltransferase (Nampt) to affect cell metabolism

Nampt functions as an intra- and extracellular NAD biosynthetic enzyme. Nampt catalyses the formation of nicotinamide mononucleotide (NMN) from nicotinamide (NAM). NMN is subsequently converted to NAD by three organelle-specific isoforms of nicotinamide mononucleotide adenylyltransferase (Nmnat1-3). Intracellularly, Nampt has been shown to be located in different cellular compartments. It affects the function of NAD degrading enzymes by raising cellular NAD levels and consequently influences the regulation of metabolism and stress resistance through sirtuins (Sirt1-7) and other NAD consuming enzymes, e.g. poly(ADP-ribose)polymerase-1 (PARP-1). The NAD metabolism of mitochondria and nucleus is possibly influenced by transport of NAD metabolites from and to the cytoplasm. Extracellularly, Nampt produces nicotinamide mononucleotide (NMN), which might act in an autocrine/paracrine fashion and/or be transported to other target tissues, where it acts on glucose stimulated insulin secretion in pancreatic β cells and might also elicit other biological responses. Possibly, Nampt also functions as a cytokine by binding to and activating an unidentified receptor.

Table 1

Most recent studies concerning correlation of plasma eNampt concentrations with antropometric and metabolic parameters.

Plasma eNampt concentrations	Correlation	Study
↑ in obese children	+ with visceral adipose tissue area	[81]
↑ in obese adolescents	± with anthropometric or lipid parameters in non-obese − with age + with high density lipoprotein (HDL)-cholesterol in obese	[82]
↑ in type 2 diabetes mellitus (T2DM) without macroangiopathy	± with body mass index (BMI), insulin, glucose or HOMA-insulin resistance index (HOMA-IR) − with high sensitive C reactive protein (hsCRP) and IL-6 plasma concentration	[83]
± in patiens with coronary heart disease	± with any variables of the metabolic syndrome	[84]
↑ in T2DM	+ with proteinuria	[85]
	+ with HDL-cholesterol − with triglycerides	[86]
↑ in obese women	+ with epicardial fat thickness	[87]
↑ in preeclampsia	+ with CRP − with HOMA-IR	[88]
	+ with HDL in women − with LDL in women and BMI in males ± with height, weight, body mass index, waist and hip circumferences, waist-to-hip ratio, blood pressure, fasting serum insulin and fasting plasma glucose, lipid profiles and uric acid levels	[89]
↑ in coronary artery disease (CAD) patients		[90]
	± with fat mass and bone mineral density in men	[91]
↑ in obese women ↓ after exercise	+ with BMI	[92]
	+ with IL-6 plasma concentration and diastolic blood pressure	[93]
↑ in obese patients with impaired fasting glucose and diabetes	+ with leptin plasma concentration	[94]

↑ increase, ↓ decrease, + positive correlation, − negative correlation, ± no correlation