Cancer Letters 661 (2026) 218875



Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet



Review Articles

Coordinated nicotinamide metabolism by NAMPT and NNMT: Integrating metabolic, epigenetic and immune crosstalk

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ARTICLE INFO

Keywords:
NAD
NAMPT
NNMT
Metabolism
Epigenetics
Drug resistance
Immune crosstalk
Microenvironment

ABSTRACT

Cancer cells adapt to microenvironmental cues through the coordinated integration of metabolic reprogramming, epigenetic remodeling, and immune regulation. An emerging central regulator of this adaptive network is coordinated nicotinamide metabolism, which controls both nicotinamide adenine dinucleotide (NAD) biosynthesis and cellular methylation potential. Within this network, the nicotinamide-metabolizing enzymes nicotinamide phosphoribosyltransferase (NAMPT) and nicotinamide *N*-methyltransferase (NNMT) govern the metabolic fate of nicotinamide (NAM), thereby coupling energy metabolism to epigenetic regulation and adaptive cellular responses.

NAMPT, the rate-limiting enzyme of the NAD salvage pathway, sustains intracellular NAD pools required for redox homeostasis, mitochondrial function, DNA repair, and stress responses. Conversely, NNMT diverts NAM from NAD biosynthesis by catalyzing its methylation while consuming S-adenosylmethionine (SAM), thereby creating a methylation sink that remodels chromatin organization and promotes transcriptional plasticity. Beyond intracellular metabolism, coordinated nicotinamide metabolism extends to the tumor microenvironment through extracellular mediators, including extracellular NAMPT (eNAMPT), the emerging extracellular functions of NNMT (eNNMT) and its metabolite 1-methylnicotinamide (1-MNA), which regulate stromal remodeling, immune cell function, chronic inflammation, and immune evasion. Collectively, these complementary intracellular and extracellular activities establish a multilevel adaptive network that integrates metabolic homeostasis, epigenetic remodeling, and immunometabolic communication, thereby promoting tumor plasticity, therapeutic adaptation, and resistance.

Here, we propose a conceptual framework in which NAMPT and NNMT function as complementary regulators of coordinated nicotinamide metabolism operating across interconnected intracellular and extracellular levels. By integrating metabolic, epigenetic, and immune crosstalk into a unified model of tumor adaptation, this perspective provides new insights into tumor progression and therapy resistance while highlighting context-dependent opportunities for mechanism-based combination therapies in cancer.

1. Introduction

The ability of cancer cells to survive and adapt to microenvironmental signals relies on a finely tuned coordination between metabolic reprogramming and epigenetic plasticity [1–4]. An important component of this adaptive network is coordinated nicotinamide metabolism, which regulates the cellular fate of nicotinamide (NAM) while integrating NAD biosynthesis with methyl donor utilization [5–7]. NAD functions not only as a critical electron carrier in redox reactions, supporting ATP production and mitochondrial homeostasis, but also as a substrate for NAD-consuming enzymes, including sirtuins, ADP-ribosyltransferases (ARTs) and NADases, which regulate DNA repair, gene expression, signaling and stress responses [8–10]. However, these reactions are intrinsically coupled to NAD degradation, leading to the continuous generation of NAM as a metabolic

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https://doi.org/10.1016/j.canlet.2026.218875
Received 14 August 2026; Received in revised form 21 September 2026; Accepted 1 October 2026
Available online 7 October 2026
0304-3835/© 2026 Published by Elsevier B.V.

byproduct [5]. Thus, NAM occupies a dual role as both a precursor and a metabolic product, creating a dynamic metabolic partitioning that ultimately determines its cellular fate. This balance is primarily governed by two key enzymes: nicotinamide phosphoribosyltransferase (NAMPT) and nicotinamide *N*-methyltransferase (NNMT) [11] (Fig. 1).

NAMPT, the rate-limiting enzyme of the NAD salvage pathway sustains intracellular NAD pools and metabolic rewiring. It can also function extracellularly as a cytokine/adipokine-like mediator, shaping the tumor microenvironment [12–15]. In parallel, NNMT acts as a metabolic-epigenetic regulator by diverting NAM from NAD biosynthesis through its methylation and consuming S-adenosylmethionine (SAM), thereby influencing global methylation potential, chromatin organization, and cellular plasticity [16–18].

Interestingly, both NAMPT and NNMT have also been detected in the extracellular milieu as soluble proteins or associated with extracellular vesicles (EVs) [19,20], while increasing evidence supports an immunomodulatory and stromal remodeling role for the principal NNMT-derived metabolite, 1-methylnicotinamide (1-MNA), within the tumor microenvironment (TME) [16,21–23]. Together, these complementary intracellular and extracellular activities establish a multilevel regulatory network that integrates metabolic homeostasis, epigenetic remodeling, and immunometabolic communication (Fig. 1).

Rather than representing isolated metabolic pathways, coordinated regulation of NAMPT and NNMT enables the dynamic allocation of NAM toward NAD biosynthesis or methylation-dependent metabolism according to cellular demands. Here, the term "coordinated" refers to the functional convergence of these two pathways through shared substrate availability and interconnected metabolic outputs, without implying established direct reciprocal regulation or physical interaction between NAMPT and NNMT. Dysregulation of this network profoundly alters metabolic homeostasis, chromatin organization, and extracellular signaling, thereby promoting tumor progression, adaptive plasticity, immune evasion, and therapy resistance. Maintenance of NAD homeostasis is essential for cellular function, but this equilibrium is frequently disrupted in cancer by oncogenic pathways such as BRAF/MAPK or YAP/TAZ signaling, which contributes to metabolic adaptation and therapeutic resistance [24–28]. Understanding coordinated nicotinamide metabolism is therefore essential for identifying novel therapeutic vulnerabilities and developing strategies to overcome treatment-induced resistance.

In this review, we propose a conceptual framework in which NAMPT and NNMT are viewed as complementary regulators of coordinated

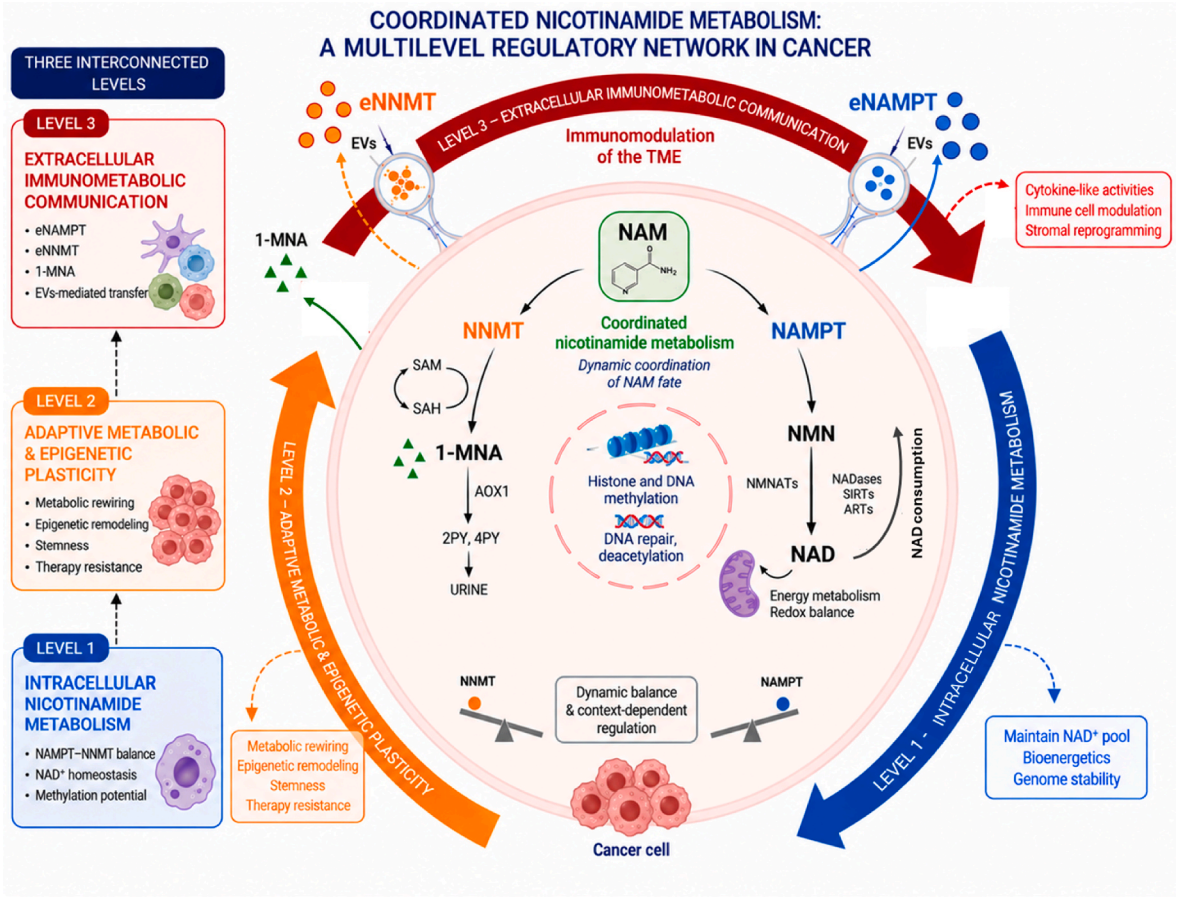


Fig. 1. Coordinated nicotinamide metabolism as a multilevel regulatory network in cancer. Nicotinamide (NAM) occupies a central position in coordinated nicotinamide metabolism, where its intracellular fate is determined by the complementary activities of nicotinamide phosphoribosyltransferase (NAMPT) and nicotinamide N-methyltransferase (NNMT). At the intracellular level (Level 1), NAMPT sustains NAD biosynthesis through the salvage pathway, whereas NNMT diverts NAM toward 1-methylnicotinamide (1-MNA) while consuming S-adenosylmethionine (SAM), thereby linking NAD metabolism with methylation potential. At the cellular level (Level 2), these complementary activities contribute to metabolic and epigenetic plasticity, including metabolic rewiring, chromatin remodeling, stemness, and therapy resistance. At the extracellular level (Level 3), soluble and extracellular vesicle-associated NAMPT (eNAMPT) and emerging NNMT (eNNMT), together with extracellular 1-MNA, contribute to immunometabolic communication, stromal remodeling, and tumor–host interactions. The dashed line adjacent to eNNMT indicates that evidence supporting its extracellular functions remains limited. Together, these interconnected processes define coordinated nicotinamide metabolism as a multilevel framework for tumor adaptation and progression. NMNATs: nicotinamide mononucleotide adenylyltransferases; NMN: nicotinamide mononucleotide; SIRTs: sirtuins; ARTs: ADP-ribosyltransferases; AOX1: aldehyde oxidase 1; 2PY: N1-methyl-2-pyridone-5-carboxamide; 4PY: N1-methyl-4-pyridone-3-carboxamide; SAH: S-adenosylhomocysteine; TME: tumor microenvironment; EVs: extracellular vesicles.

nicotinamide metabolism rather than independent metabolic enzymes. We discuss how this multilevel regulatory network integrates intracellular NAD homeostasis, metabolic and epigenetic plasticity, and extracellular immunometabolic communication to sustain tumor adaptation and therapy resistance (Fig. 1). Finally, we examine current and emerging therapeutic strategies targeting distinct components of this network and discuss future opportunities for exploiting coordinated nicotinamide metabolism as a therapeutic vulnerability in cancer.

2. Coordinated regulation of nicotinamide metabolism by NAMPT and NNMT: balancing NAD biosynthesis and methylation dynamics

2.1. Molecular organization of nicotinamide metabolism

NAM metabolism is orchestrated by two complementary and coordinated enzymatic reactions that determine whether NAM is recycled into NAD (NAMPT activity) or irreversibly diverted toward a methylated metabolite (NNMT activity) [5,12,13,16,29–31].

NAMPT, a homodimeric class type II phosphoribosyltransferase (EC 2.4.2.12), catalyzes the conversion of NAM into nicotinamide mononucleotide (NMN) using 5-phosphoribosyl-1-pyrophosphate (PRPP). NMN is subsequently converted to NAD by nicotinamide nucleotide adenylyltransferases (NMNATs), using ATP as the donor of the adenylyl moiety [32]. As the rate-limiting enzyme of the NAD salvage pathway, NAMPT plays a central role in sustaining intracellular NAD pools required for metabolism, DNA repair, redox homeostasis, epigenetic gene expression regulation, senescence, lifespan, and cell signaling [10,12,13,33,34]. Conversely, NNMT, a methyltransferase (EC 2.1.1.1), irreversibly methylates NAM to generate 1-MNA, consuming SAM and producing S-adenosyl-L-homocysteine (SAH) [29,30,35]. By diverting NAM away from NAD biosynthesis while simultaneously influencing methyl donor availability, NNMT establishes a direct biochemical connection between nicotinamide metabolism and cellular methylation reactions.

Importantly, because NAMPT and NNMT utilize the same metabolic substrate, alterations in the activity of one pathway may influence the availability of NAM for the other, thereby establishing a metabolically interconnected system rather than two independent enzymatic reactions. Although direct reciprocal regulatory mechanisms between the two enzymes remain largely unexplored, their shared dependence on NAM provides the biochemical basis for functional convergence between the two pathways, influencing the balance between NAD biosynthesis and methylation metabolism according to cellular metabolic demands.

Interestingly, Bockwoldt et al. some years ago well highlighted that the coexistence of.

NAMPT and NNMT has been a prerequisite to allow the evolutionary development of versatile NAD-dependent signaling mechanisms present in vertebrates [36]. In fact, under physiological conditions, the metabolic equilibrium is intrinsically biased toward NAD biosynthesis. Indeed, NAMPT displays a substantially higher affinity for NAM (nanomolar range) [37], at least in mammals, than NNMT, thereby preferentially channeling NAM into the salvage pathway while preventing its intracellular accumulation, which itself can inhibit several NAD-dependent enzymes, including ARTs and sirtuins [36]. This kinetic organization ensures efficient maintenance of intracellular NAD pools under physiological conditions while preserving metabolic flexibility during environmental or energetic challenges.

Experimental evidence suggests that alterations in NAMPT activity can dynamically influence the metabolic partitioning of NAM. For example, genetic or pharmacological inhibition of NAMPT increases substrate availability for NNMT, supporting the concept that nicotinamide flux can be redistributed between NAD biosynthesis and methylation pathways according to cellular metabolic demands rather than through direct transcriptional cross-regulation [38].

The metabolic products generated by these enzymes further illustrate their complementary biological functions. NMN produced by NAMPT is rapidly converted into NAD, thereby fueling the activity of multiple NAD-dependent enzymes involved in mitochondrial metabolism, DNA repair, stress responses, and chromatin regulation (Fig. 1). In contrast, 1-MNA is subsequently metabolized by aldehyde oxidase (AOX) into N1-methyl-2-pyridone-5-carboxamide (2PY) and N1-methyl-4-pyridone-3-carboxamide (4PY), metabolites that are eventually excreted in urine [29] (Fig. 1). Beyond serving as a metabolic intermediate, 1-MNA exerts several biological activities (discussed extensively in 2.3 section), including anti-inflammatory, vasodilatory, and cytoprotective effects, whereas its downstream metabolites have been associated with pathological conditions such as chronic kidney disease [39–41].

Despite catalyzing opposite metabolic reactions, both enzymes possess highly specialized catalytic domains that ensure efficient substrate recognition and enzymatic specificity. NAMPT functions as an obligate homodimer, with each monomer contributing to the formation of the catalytic pocket required for enzymatic activity [42]. Crystallographic studies identified several highly conserved residues, including Tyr18, Phe193, Asp219, His247, Asp279, Arg311 and Asp313, that coordinate substrate recognition, stabilization, and catalysis [42,43]. Mutations affecting these residues markedly impair enzymatic activity, resulting in NAD depletion and cellular dysfunction associated with metabolic and age-related disorders [44,45]. The catalytic pocket of NNMT selectively accommodates both NAM and SAM, ensuring efficient methyl transfer and product formation [46,47]. Interestingly, 1-MNA acts as a feedback inhibitor of NNMT, suggesting the existence of an intrinsic autoregulatory mechanism controlling methylation flux [16,46]. Although structurally unrelated, both NAMPT and NNMT exhibit highly optimized catalytic architectures that enable cells to precisely regulate the partitioning of NAM between NAD biosynthesis and methylation pathways.

2.1.1. Subcellular localization of NAMPT and NNMT

The distinct intracellular localization of NAMPT and NNMT further reflects their complementary metabolic functions, adding a spatial dimension to the coordinated regulation of nicotinamide metabolism. NAMPT exhibits remarkable compartmental plasticity. Although predominantly localized in the cytoplasm, iNAMPT dynamically redistributes to the nucleus and mitochondria according to cellular metabolic demands [48]. Nuclear NAMPT is actively imported in a cell cycle-dependent manner, where it sustains local NAD synthesis required for the activity of nuclear and chromatin-associated NAD-consuming enzymes, mainly including PARP1 and SIRT1, thereby contributing to DNA repair, chromatin remodeling, and transcriptional regulation [49,50]. A distinct mitochondrial pool of NAMPT maintains compartment-specific NAD pools that sustain oxidative phosphorylation, SIRT3 activity, redox balance, and protection against oxidative stress [51]. This dynamic intracellular distribution allows NAMPT to regulate compartment-specific NAD availability, enabling independent modulation of nuclear and mitochondrial NAD-dependent signaling pathways according to cellular metabolic requirements [48,51].

By comparison, NNMT appears to remain predominantly confined to the cytosol, where it regulates the intracellular availability of both NAM and methyl donors. To date, no evidence supports the existence of nuclear or mitochondrial pools of NNMT, nor have nuclear or mitochondrial targeting sequences been identified [30,52]. Nevertheless, despite its apparently restricted localization, NNMT exerts biological effects that extend beyond the cytoplasm. By consuming SAM and generating SAH, cytosolic NNMT lowers the intracellular SAM/SAH ratio, thereby indirectly limiting the activity of nuclear histone methyltransferases and promoting the loss of repressive histone marks such as H3K9me3 and H3K27me3 [31]. Likewise, NNMT-dependent modulation of nicotinamide availability indirectly influences mitochondrial NAD metabolism and sirtuin-dependent regulation of respiratory chain activity without requiring physical translocation of the enzyme. However, we cannot

exclude a presence of NNMT within other compartments, to date not investigated.

Thus, although NAMPT and NNMT occupy distinct intracellular compartments, both regulate metabolic and epigenetic processes across multiple cellular organelles through complementary mechanisms.

Emerging evidence suggests that NAMPT and NNMT participate in partially overlapping regulatory networks. STRING protein-association analysis identified several shared putative interactors, including SIRT1, SIRT2, SIRT3, SIRT6 and BST1, together with enzyme-specific partners reflecting their distinct roles within nicotinamide metabolism [53]. While SIRT1 and SIRT3 are supported by experimental evidence, the remaining associations derive primarily from curated databases, co-expression and text-mining analyses and should therefore be regarded as hypothesis-generating. Collectively, these observations further support the concept that coordinated nicotinamide metabolism relies on complementary enzymatic functions integrated within partially shared NAD-dependent regulatory networks.

2.1.2. Regulation of NAMPT and NNMT expression

Beyond their distinct catalytic properties and subcellular localization, both NAMPT and NNMT are dynamically regulated at multiple levels in response to metabolic, inflammatory, and environmental cues. Although the molecular mechanisms controlling their expression differ, both enzymes behave as highly responsive metabolic sensors that enable cells to adapt NAM metabolism according to energetic demands, nutrient availability, and pathological stimuli.

NAMPT is encoded by a gene located on chromosome 7q22.3 (Gene ID: 10135). NAMPT protein is composed of 491 amino acids and has a molecular weight of 52 kDa. NAMPT is expressed in all mammalian tissues [54,55], and *NAMPT* gene deletion in mice is embryonically lethal [56], suggesting the importance of this pathway to regenerate NAD.

The regulation of NAMPT has been extensively characterized and involves coordinated transcriptional, post-transcriptional, and post-translational mechanisms. At the transcriptional level, oncogenic signaling pathways play a central role, with c-MYC directly inducing NAMPT expression to sustain NAD biosynthesis in rapidly proliferating cancer cells [57], and BRAF/MAPK signaling inducing NAMPT overexpression to support tumor metabolic needs and plasticity [24,25,58]. Within the TME, hypoxia further enhances NAMPT transcription through hypoxia-inducible factors (HIFs), particularly HIF-2α, which directly binds the NAMPT promoter [12,59,60]. Cellular energetic stress also contributes to NAMPT induction through AMP-activated protein kinase (AMPK), thereby coupling NAD biosynthesis to cellular energy sensing [61–63]. Inflammatory stimuli represent an additional major regulatory input. Pro-inflammatory cytokines, including Tumor Necrosis Factor-alpha (TNF-α), IL-1β, IL-6 and Interferon-gamma (IFN-γ), together with pathogen-associated signals such as lipopolysaccharide (LPS), activate transcription factors including NF-κB, STAT1, STAT3 and STAT5, resulting in increased NAMPT expression and secretion [64–69]. In metastatic melanoma, our group recently demonstrated that IFN-γ induces NAMPT transcription through a Bromodomain and Extra-Terminal motif (BRD4)/IRF1-dependent mechanism, highlighting the integration of inflammatory signaling with epigenetic regulation of nicotinamide metabolism [70]. Moreover, circadian regulators such as CLOCK and BMAL1 impose rhythmic oscillations of NAMPT expression, further linking NAD metabolism to physiological metabolic cycles [71].

NNMT is encoded by a gene located on chromosome 11q23 (Gene ID: 4837), spanning approximately 55.5 kb, and encodes a protein of approximately 29 kDa [29,30]. Although the regulatory mechanisms governing this enzyme are less comprehensively understood than those controlling NAMPT, increasing evidence indicates that NNMT, constitutively expressed in metabolically active tissues such as liver, adipose tissue and kidney, is highly dynamic and strongly influenced by tissue-specific metabolic demands, aging, chronic inflammation, and tumor-associated metabolic rewiring [30,72,73]. NNMT is significantly up-regulated in several human cancers. STAT3 and NF-κB are identified as NNMT expression regulators in tumors [74,75]. Transcriptional regulation of NNMT has also been directly linked to the integrated stress response and, in particular, to activating transcription factor 4 (ATF4) [76,77]. In hepatocytes, chronic alcohol consumption-induced endoplasmic reticulum (ER) stress upregulates NNMT through activation of the pERK–ATF4 pathway. Notably, alcohol consumption fails to induce NNMT expression in liver-specific ATF4 knockout mice, providing direct in vivo evidence that ATF4 regulates NNMT expression [76]. Functionally, genetic or pharmacological inhibition of NNMT increases intracellular NAD levels and activates AMPK, linking stress-induced NNMT expression to NAD homeostasis [76]. Related studies from the same group further showed that palmitate induces NNMT expression through an ATF4-dependent mechanism downstream of mTORC1 activation [77]. Accordingly, palmitate exposure reduces intracellular NAD^+ levels in hepatocytes, whereas genetic or pharmacological NNMT inhibition restores NAD^+ content and protects against palmitate-induced cell death [77,78]. These findings identify the mTORC1–ATF4–NNMT pathway as a stress-responsive regulatory circuit linking nutrient sensing, NNMT expression, and NAD homeostasis in hepatocytes. However, whether this regulatory circuit is similarly engaged in cancer cells remains to be established.

Further regulatory complexity arises from post-translational modifications. NAMPT activity, intracellular trafficking, and secretion are modulated by phosphorylation, acetylation and ubiquitination [79–81]. Interestingly, deacetylation by SIRT1 promotes extracellular NAMPT release, establishing a direct feedback loop between intracellular NAD availability and extracellular NAMPT signaling [82]. Conversely, SIRT6-mediated deacetylation enhances NAMPT enzymatic activity, further reinforcing NAD homeostasis [79]. At the post-transcriptional level, microRNAs, including miR-146a and miR-34a, together with long non-coding RNAs such as NAMPT-AS, provide an additional regulatory layer that fine-tunes NAMPT expression in both physiological and pathological settings [83–86]. Although comparable post-translational mechanisms have not yet been comprehensively defined for NNMT, accumulating evidence indicates that multiple levels of regulation contribute to dynamically modulating its expression and activity in response to metabolic remodeling [75].

2.2. Balancing NAD biosynthesis and methylation potential

The coordinated regulation of nicotinamide metabolism by NAMPT and NNMT establishes a dynamic equilibrium between NAD biosynthesis and methylation potential, thereby linking nicotinamide metabolism to cellular adaptation (Fig. 1).

The enzymatic activity of NAMPT sustains intracellular NAD pools that are essential for energy metabolism, mitochondrial function, DNA repair, and transcriptional regulation (Fig. 2) [11,55]. Cellular NAD homeostasis is maintained through a dynamic balance between continuous biosynthesis and consumption, which is tightly regulated by substrate availability, feedback mechanisms, and cellular stress signals [11,12,34,55,61,87]. NAD consumption is primarily mediated by three classes of NAD-dependent enzymes, namely ARTs, sirtuins, and the NAD glycohydrolases CD38/CD157, all of which continuously recycle nicotinamide and therefore depend on NAMPT activity to sustain intracellular NAD levels [88].

Among these enzymes, ARTs play a central role in maintaining genome integrity by catalyzing poly-ADP-ribosylation reactions that recruit and coordinate DNA repair complexes following genotoxic stress [89,90]. However, sustained ARTs activation dramatically accelerates NAD consumption and, when excessive, can deplete intracellular NAD pools, ultimately leading to ATP depletion, metabolic collapse, and cell death [90]. Conversely, sirtuins utilize NAD as a co-substrate to regulate mitochondrial function, oxidative metabolism, chromatin remodeling, and cellular stress responses. During their deacetylase activity, sirtuins generate NAM as a reaction product, thereby reinforcing the dependence on NAMPT-mediated NAD recycling [89,91].

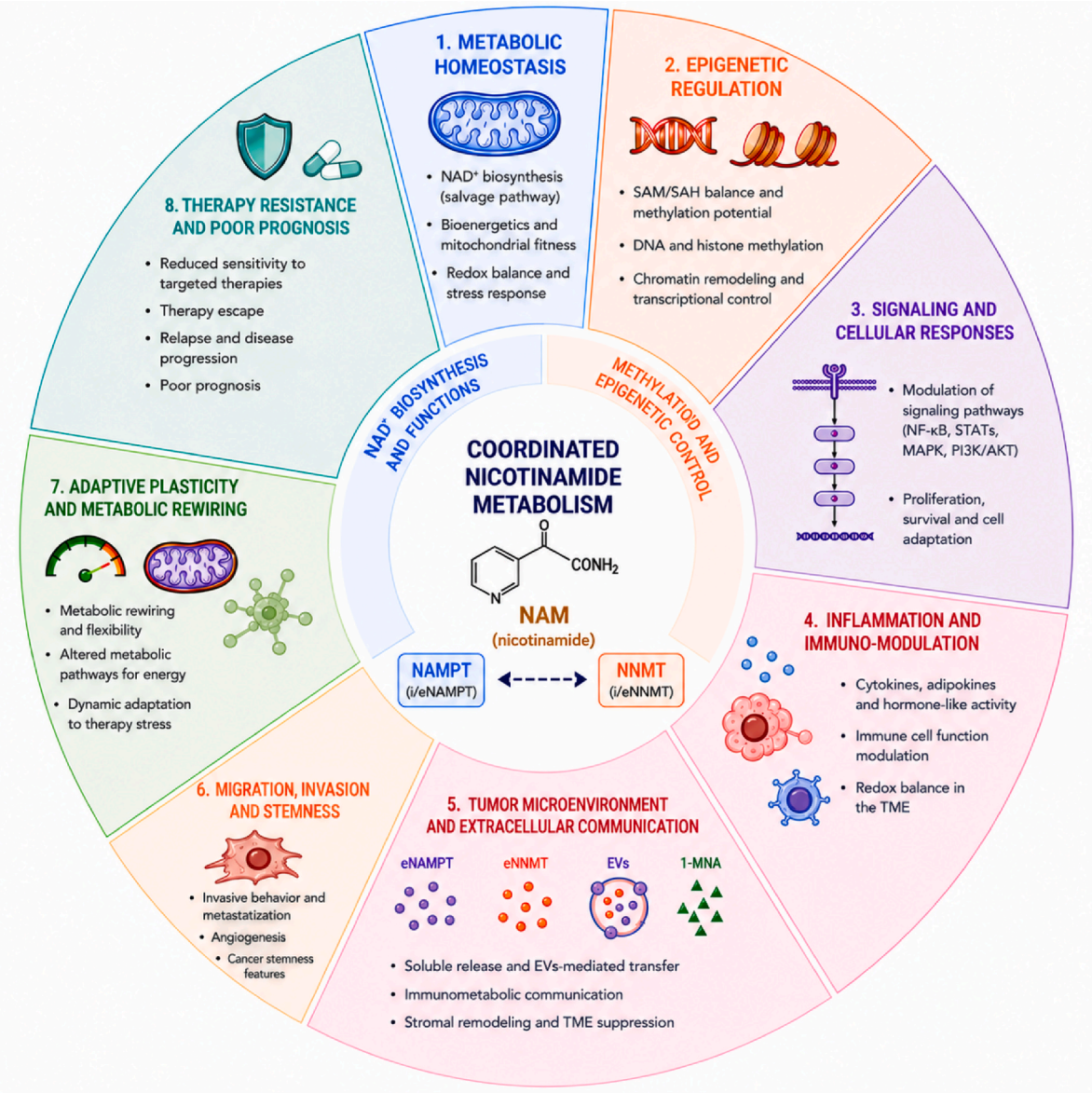


Fig. 2. Functional integration of NAMPT and NNMT within coordinated nicotinamide metabolism in cancer. The figure summarizes the major biological processes influenced by NAMPT- and NNMT-dependent nicotinamide metabolism, including metabolic homeostasis, epigenetic regulation, signaling, inflammation and immunomodulation, tumor–microenvironment communication, migration and invasion, adaptive plasticity, and therapy resistance. These processes reflect complementary and context-dependent contributions of NAMPT and NNMT across intracellular and extracellular compartments. The extracellular functions attributed to eNNMT remain insufficiently characterized and require further investigation.

Beyond regenerating NAM, sirtuins also participate in regulatory feedback loops linking NAD availability to epigenetic homeostasis. For instance, SIRT1 has been shown to modulate the activity of DNA methylation regulators, thereby providing an additional molecular connection between NAD metabolism and chromatin remodeling [92].

Age-associated NAD decline compromises sirtuin activity, contributing to mitochondrial dysfunction, chronic inflammation, and metabolic disorders including type 2 diabetes, cardiovascular diseases, and neurodegeneration [44,45]. In parallel, CD38 and CD157 regulate NAD turnover by hydrolyzing NAD into ADP-ribose and cyclic ADP-ribose (cADPR), key mediators of intracellular calcium signaling [10,93]. Through their enzymatic activity, particularly that of CD38, these ectoenzymes substantially influence both intra- and extracellular NAD availability, representing major determinants of systemic NAD homeostasis, also in pathological conditions [94,95].

Collectively, these NAD-consuming enzymes establish a continuous demand for NAD regeneration, making NAMPT indispensable for preserving cellular bioenergetics, DNA repair capacity, mitochondrial fitness, and stress adaptation. Therefore, fluctuations in NAMPT expression or activity rapidly translate into profound metabolic and functional consequences by altering the intracellular balance between NAD synthesis and consumption.

In parallel with the regulation of NAD homeostasis, cells must preserve adequate methyl donor availability to sustain DNA, RNA, and histone methylation. In this context, NNMT functions as a major regulator of cellular methylation potential through its ability to methylate nicotinamide while consuming SAM (Fig. 2) [16,30]. As one of the major cellular consumers of SAM, NNMT acts as a metabolic “methylation sink”, reducing the availability of methyl donors required for epigenetic modifications [31,52,72]. Simultaneously, the production of SAH, a potent inhibitor of methyltransferases, further suppresses methylation reactions, leading to a marked reduction in the SAM/SAH ratio and promoting widespread epigenetic remodeling [31,96].

In addition to regulating methylation reactions, fluctuations in

intracellular SAM levels are sensed by SAMTOR, a nutrient sensor that negatively regulates mTORC1 under conditions of methyl donor depletion [97]. Consequently, excessive NNMT activity may influence not only epigenetic regulation but also nutrient-sensing pathways controlling cellular growth and metabolism.

The impact of NNMT on methylation potential is partially buffered by the methionine cycle, which regenerates SAM from SAH and functionally connects one-carbon metabolism with nicotinamide metabolism, thereby contributing to the maintenance of cellular methylation capacity under fluctuating metabolic conditions [98]. However, sustained NNMT overexpression may overwhelm this compensatory mechanism, leading to persistent depletion of methyl donors and impaired methylation reactions.

The depletion of SAM together with SAH-mediated inhibition of methyltransferases compromises the deposition of repressive histone methylation marks, particularly H3K9me3 and H3K27me3, which are essential for chromatin compaction and transcriptional silencing [31,99]. Consequently, NNMT-driven methylation stress promotes chromatin relaxation, increases accessibility of regulatory genomic regions, and facilitates the activation of transcriptional programs involved in proliferation, survival, metabolic rewiring, and cellular adaptation [16,72,99]. Beyond enhancing transcriptional flexibility, these epigenetic alterations contribute to the acquisition and maintenance of stem-like phenotypes, promoting tumor heterogeneity, invasiveness, and therapeutic resistance [26].

Collectively, these observations indicate that NAD homeostasis and methylation potential represent two interconnected metabolic currencies that contribute to cellular adaptation rather than independent metabolic processes. While NAMPT preserves intracellular NAD availability required for bioenergetics, DNA repair, redox homeostasis, and stress signaling, NNMT controls methyl donor utilization and chromatin accessibility by modulating the SAM/SAH balance. Through these complementary activities, the two enzymes integrate metabolic status with epigenetic regulation, enabling cells to dynamically respond to energetic, genotoxic, and environmental challenges. Thus, coordinated nicotinamide metabolism emerges as a fundamental adaptive mechanism linking cellular energetics to transcriptional plasticity under both physiological and pathological conditions, providing the basis for the metabolic and epigenetic rewiring discussed in the following section.

2.3. Metabolic and epigenetic plasticity in pathological adaptation driven by coordinated nicotinamide metabolism

Increasing evidence demonstrated that the coordinated regulation of NAD homeostasis and methylation potential by NAMPT and NNMT provides cells with the capacity to dynamically adapt to fluctuations in nutrient availability, environmental stress and therapeutic pressure. This adaptive flexibility is essential for maintaining tissue homeostasis under physiological conditions but is frequently diverted during tumorigenesis and other chronic diseases to sustain disease progression.

One of the major consequences of this coordinated regulation is the establishment of adaptive metabolic rewiring, a dynamic process through which cells continuously remodel bioenergetic pathways. Through sustained NAD biosynthesis, NAMPT supports mitochondrial respiration, redox homeostasis, ATP production, and biosynthetic pathways required for cell survival under metabolic stress. Consistently, heterozygous NAMPT-deficient models exhibit defective NAD biosynthesis and increased sensitivity to metabolic stress, highlighting the essential role of NAMPT in maintaining cellular energetic homeostasis [100]. Conversely, NNMT remodels cellular metabolism by redirecting nicotinamide utilization while simultaneously altering methyl donor availability, thereby influencing the transcription of genes involved in glucose and lipid metabolism [96,99,101,102]. In hepatocytes, NNMT knockdown increases intracellular SAM levels, reduces 1-MNA production, and suppresses lipogenic gene expression, whereas restoration of 1-MNA promotes lipid accumulation and lipogenesis [96,99]. Similarly, in adipose tissue, elevated NNMT expression correlates with obesity and insulin resistance, while genetic or pharmacological inhibition enhances insulin sensitivity and increases energy expenditure [96,103]. Through these mechanisms, NNMT contributes to the regulation of gluconeogenesis, glycolysis, and lipid metabolism, reinforcing the intimate connection between nicotinamide metabolism and systemic metabolic homeostasis [101,102].

Metabolic rewiring is tightly coupled with epigenetic remodeling. As discussed above, NNMT-mediated consumption of SAM and accumulation of SAH reduce cellular methylation potential, leading to widespread chromatin remodeling and increased transcriptional accessibility. However, these epigenetic alterations do not occur independently of cellular metabolism. Rather, fluctuations in NAD availability influence the activity of NAD-dependent enzymes such as sirtuins and ARTs, while changes in methyl donor availability regulate histone and DNA methylation. Interestingly, epigenetic remodeling may also feedback to regulate NAD metabolism itself. For example, the activity of a c-MYC/MAX-responsive distal enhancer controlling NAMPT transcription has been shown to depend on histone methylation, suggesting that alterations in methylation potential may directly influence NAMPT expression and reinforce adaptive metabolic programs [104].

Even if NAMPT directly controls NAD salvage, increasing evidence indicates that NNMT also contributes to the dynamic regulation of intracellular NAD metabolism. Genetic silencing of NNMT in adipocytes, fibroblasts, and colon cancer cells increases intracellular NAD levels, whereas NNMT overexpression exerts the opposite effect by diverting nicotinamide toward methylation-dependent metabolism [41,96,99,105,106]. Similar metabolic effects have also been reported following pharmacological inhibition of NNMT in obese mouse models [107], supporting the notion that both enzymes contribute to the adaptive control of intracellular nicotinamide availability.

The integration of metabolic and epigenetic remodeling ultimately promotes phenotypic cellular plasticity, a hallmark of cancer initiation and progression. Increased chromatin accessibility facilitates the activation of gene networks controlling proliferation, survival, metabolic flexibility, epithelial-to-mesenchymal transition (EMT), and stress responses [58,72]. Moreover, these adaptive programs support the acquisition and maintenance of stem-like phenotypes by promoting the expression of stemness-associated transcriptional networks and increasing intratumoral heterogeneity [106,108]. Consequently, metabolic and epigenetic plasticity provides cancer cells with a remarkable capacity to survive hostile microenvironmental conditions and rapidly adapt to therapeutic pressure (discussed in Section 4).

Accordingly, dysregulation of NAMPT and NNMT has been documented across numerous pathological conditions, where persistent metabolic/epigenetic adaptation becomes maladaptive. In several cancers, dysregulation of NAMPT and NNMT contributes, through complementary mechanisms, to tumor growth, metabolic reprogramming, invasion, angiogenesis, metastatic dissemination, stemness, and therapeutic resistance [13–16,24,30,109–112], as summarized in Table 1. In melanoma, NAMPT is overexpressed compared benign nevi and supports resistance to BRAF inhibitors by maintaining intracellular NAD pools under MAPK inhibition [24,112], whereas increased NNMT expression has been associated with metastatic progression, enhanced migration, and reduced sensitivity to chemotherapeutic agents [19,113–115]. Similarly, elevated NAMPT expression sustains DNA repair and cancer stem cell maintenance in glioblastoma [108], while NNMT promotes aggressive phenotypes and chemoresistance in colorectal, gastric, ovarian, pancreatic, renal, and other solid tumors through metabolic and epigenetic remodeling [116–120]. In contrast, in hepatocellular carcinoma NNMT is downregulated and leads to a loss of detoxification capacity, relieves the inhibition of fatty acid and cholesterol biosynthesis and preserves intracellular SAM levels, making it available for other essential methylation reactions. This metabolic reprogramming contributes to tumor progression by enhancing lipid synthesis and altering the cell's epigenetic and redox balance [121].

Table 1
Comparative summary of NAMPT and NNMT expression, functional convergence, and therapeutic implications across cancer types.

Tumor type	Disease setting	NAMPT	NNMT	Evidence of functional convergence	Metabolic/epigenetic effects	Immune/TME effects	Therapeutic implications
Melanoma [19,24]	BRAFi resistance	↑ iNAMPT; ↑ eNAMPT release	↑ iNNMT; ↑ eNNMT release	Concurrent upregulation following MAPK inhibition	Maintains NAD homeostasis and adaptive metabolic rewiring	Increased release of immunomodulatory eNAMPT/eNNMT	Potential rationale for investigating dual NAMPT/NNMT targeting in combination with BRAF-targeted therapy
Prostate cancer [26]	YAP-dependent stem-like subtype	iNAMPT-dependent NAD salvage	↑ iNNMT	NNMT expression modulates cellular response to NAMPT inhibition	FK866 sensitivity depends on NNMT-mediated NAM utilization	Not characterized	NNMT expression as a potential biomarker of NAMPT inhibitor response
NSCLC [28]	EGFR-TKI resistance	Compensatory NAMPT upregulation	↑ iNNMT	Functional convergence through NAM utilization and NAD homeostasis under TKI stress	NNMT diverts NAM toward 1-MNA while NAMPT restores NAD pool	Not characterized	Potential rationale for combined NAMPT/NNMT targeting; circulating 1-MNA as a potential biomarker
Gastric cancer [122]	Stromal remodeling (CAFs/macrophages)	Macrophage-derived EV-associated NAMPT	↓ CAF NNMT	EV-NAMPT suppresses CAF NNMT through the SIRT1/NICD axis	Shifts NAM utilization toward NAD synthesis; ↑ NAM/1-MNA ratio	Reduced 1-MNA-mediated impairment of $CD8^+$ T-cell function	Plasma NAM/1-MNA ratio as a potential biomarker of anti-PD-1 response
Glioblastoma [123,124]	Mesenchymal stem-like state	↑ iNAMPT in stem-like cells	↑ iNNMT in stem-like cells	Convergent remodeling during stemness and senescence	NNMT-dependent methylation sink promotes DNA hypomethylation and stemness	Not characterized	NNMT inhibition as a strategy to disrupt epigenetic plasticity

Collectively, these observations highlight that the biological functions of NNMT are highly context-dependent rather than universally oncogenic. While NNMT overexpression promotes methylation-sink-dependent metabolic and epigenetic plasticity associated with stemness and therapy resistance in most epithelial malignancies, hepatocellular carcinoma represents a notable exception. The liver represents the major site of methionine turnover, one-carbon metabolism, lipid biosynthesis and nicotinamide detoxification. Consequently, alterations in NNMT activity may have fundamentally different metabolic consequences in hepatocytes than in other tissues, shifting the balance from methylation-sink-dependent plasticity toward broader changes in hepatic metabolic homeostasis. Although this hypothesis requires further experimental validation, it provides a plausible framework to explain why reduced NNMT expression may promote tumor progression in hepatocellular carcinoma, whereas NNMT overexpression favors adaptive metabolic and epigenetic remodeling in many other solid tumors. Elucidating the tissue-specific determinants that govern NNMT function will be essential for understanding its context-dependent role in cancer and for the rational development of NNMT-targeted therapeutic strategies.

Beyond cancer, alterations in nicotinamide metabolism have also been implicated in obesity, insulin resistance, type 2 diabetes, cardiovascular diseases, and neurodegenerative disorders. In these settings, dysregulated NAD homeostasis, mitochondrial dysfunction, impaired methylation dynamics, and defective metabolic adaptation collectively contribute to disease progression [30,44,45,96,103,125–127]. Increased iNAMPT and eNAMPT levels have been observed in a variety of autoimmune diseases, such as psoriasis [128], rheumatoid arthritis (RA) [129], systemic lupus erythematosus [130], inflammatory bowel disease (IBD) [131]; highlighting a potential association between NAMPT dysregulation and disease progression and raising interest in its utility as a biomarker [14]. NNMT has also been implicated in the pathogenesis of different neurodegenerative diseases, including Parkinson's disease (PD) and Alzheimer's disease (AD). Research using *Caenorhabditis elegans* has demonstrated that the *NNMT* ortholog, *ANMT-1*, competes with the methyltransferase LCMT-1 for SAM, suggesting that NNMT may influence neuronal function by modulating methylation processes [125]. In AD, elevated NNMT expression has been observed in the medial temporal lobe of affected individuals, with levels significantly higher compared to healthy controls. This increase in NNMT expression may contribute to the characteristic AD neuropathological changes [126]. Furthermore, specific single nucleotide polymorphisms (SNPs) within the NNMT gene, such as rs694539, have been associated with neurodegenerative disorders, including bipolar disorder, schizophrenia and epilepsy. These mutations may influence NNMT activity and consequently affect susceptibility to neurodegeneration [127].

Collectively, by coupling metabolic, energetic, and epigenetic signals, NAMPT and NNMT enable cells to dynamically respond to environmental challenges while providing molecular flexibility that, under pathological conditions, supports chronic inflammation, tumor progression, and therapeutic resistance (Fig. 2). Although the relative contribution of each enzyme varies among tumor types, accumulating evidence indicates that their complementary activities converge in promoting tumor cell plasticity and adaptive fitness (Table 1).

Importantly, this adaptive network is not confined to intracellular metabolism but extends to the tissue level through extracellular signaling mechanisms and immunometabolic communication, as discussed in the following section.

2.4. Beyond intracellular metabolism: extracellular mediators and immunometabolic communication

NAM metabolism operates not only as an intracellular metabolic network controlling NAD homeostasis and methylation dynamics, but also as an intercellular signaling system that orchestrates immune responses, stromal remodeling, and tissue adaptation. Among the extracellular mediators identified to date, eNAMPT, the emerging extracellular form of NNMT (eNNMT), and the bioactive metabolite 1-MNA have been identified as key regulators of intercellular immunometabolic communication (Figs. 2 and 3). Although the available evidence differs considerably among these mediators, with eNAMPT representing the best-characterized extracellular effector [12–14,19,88,132,133], suggest that all three contribute, through distinct mechanisms, to coordinating responses of tissues and microenvironmental levels, beyond their intracellular metabolic functions.

eNAMPT/Pre-B cell colony-enhancing factor (PBEF) was first

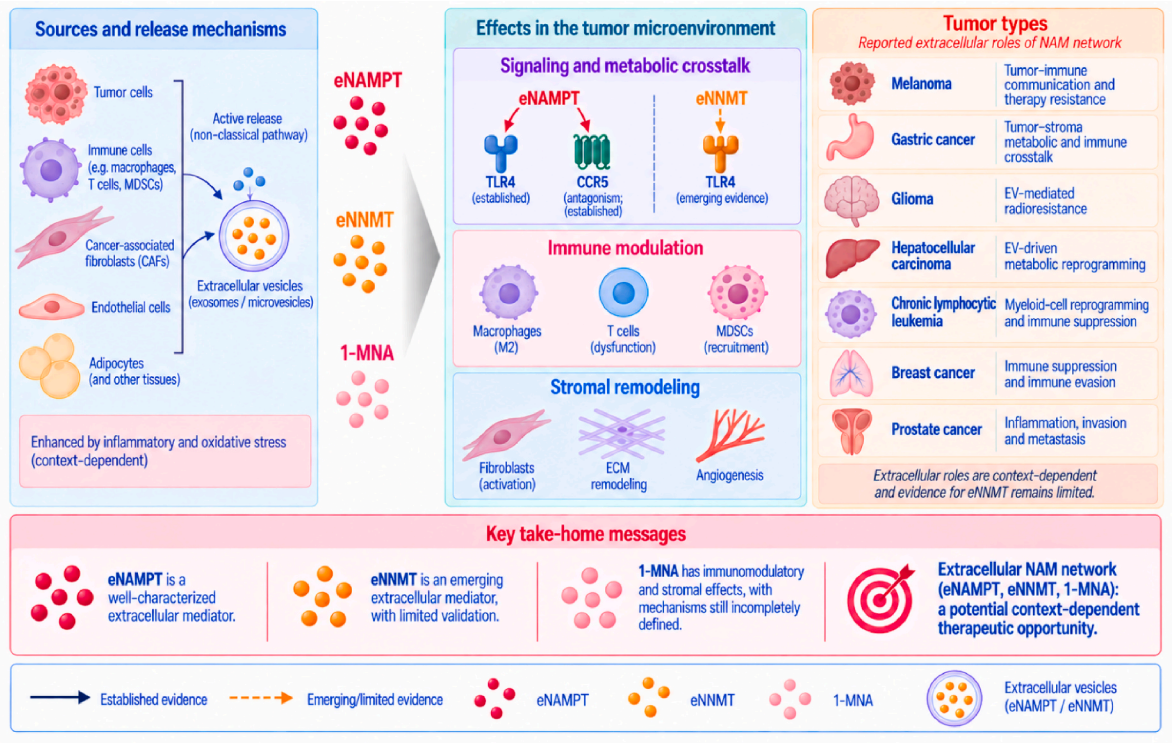


Fig. 3. Extracellular NAM network in tumor–microenvironment communication. Extracellular NAMPT (eNAMPT), the emerging eNNMT, and the NNMT-derived metabolite 1-MNA may contribute to tumor–microenvironment communication through complementary effects on signaling, immune modulation, and stromal remodeling. NAMPT and NNMT can be released as soluble proteins or associated with extracellular vesicles (EVs), while 1-MNA may act as a bioactive metabolite in the extracellular milieu. The tumor-type panel summarizes cancer contexts in which extracellular roles of these components have been reported, highlighting the context-dependent nature of their biological effects. Solid arrows indicate established evidence, whereas dashed arrows indicate emerging or limited evidence. Overall, the figure highlights the extracellular NAM network as a potential context-dependent therapeutic opportunity, while emphasizing that evidence for eNNMT remains limited.

identified as an immunomodulatory cytokine able to synergize with interleukin 7 (IL-7) and stem cell factor (SCF) to promote pre-B cell colony formation [134]. eNAMPT is actively released by multiple cell types, including immune cells, adipocytes, endothelial cells, hepatocytes, cardiomyocytes and cancer cells, despite lacking a canonical signal peptide [12,14,19,132]. Its secretion occurs through non-classical pathways, including extracellular vesicles (EVs), and is markedly enhanced under inflammatory and oxidative stress conditions [19,20,69]. Beyond its enzymatic activity, eNAMPT functions as a cytokine-like immunometabolic mediator capable of regulating inflammation, immune cell activation and tumor progression, thereby extending the biological impact of nicotinamide metabolism beyond intracellular NAD biosynthesis [12,14] (Fig. 3).

eNAMPT acts independently of its enzymatic activity by engaging cell-surface receptors and activating inflammatory signaling pathways. Among the receptors proposed to mediate its biological activity, Toll-like receptor 4 (TLR4) has been the most extensively characterized [64,135]. Structural studies have identified multiple interaction regions within the N- and C-terminal domains of eNAMPT that bind the leucine-rich repeat domain of TLR4 [136], leading to activation of NF-κB, MAPK, and STAT3 signaling cascades and the subsequent production of pro-inflammatory cytokines and chemokines [64,69,136,137]. In addition, eNAMPT has been proposed to function as a C-C chemokine receptor type 5 (CCR5) antagonist because of structural similarities with the chemokine CCL7, further supporting its role as a regulator of immune cell trafficking and inflammatory responses [14,138,139]. These findings have established eNAMPT as both a damage-associated molecular pattern (DAMP) and a cytokine-like mediator capable of translating metabolic alterations into inflammatory signals (Fig. 3).

Within the TME, eNAMPT orchestrates extensive immunometabolic remodeling by regulating the recruitment, differentiation, and functional polarization of both innate and adaptive immune cells. Several studies have demonstrated that eNAMPT promotes macrophage polarization toward an immunosuppressive M2-like phenotype while favoring the expansion and recruitment of myeloid-derived suppressor cells (MDSCs) through NAD/SIRT1/HIF-1α-dependent mechanisms [140–144]. These myeloid populations produce immunosuppressive mediators, including IL-10, IL-6, IL-8, CCL18, and indoleamine 2,3-dioxygenase (IDO), thereby establishing a microenvironment that suppresses effective antitumor immunity while simultaneously supporting tumor growth and progression [64,140,141,145]. Moreover, activation of NF-κB and STAT3 signaling further amplifies inflammatory circuits that reinforce immune suppression and chronic inflammation [69,144].

Beyond its effects on innate immunity, increasing evidence indicates that eNAMPT indirectly regulates adaptive immune responses by reshaping the tumor immune landscape. NAMPT has been shown to sustain PD-L1 expression through NAD-dependent epigenetic mechanisms while simultaneously promoting signaling pathways that impair T-cell activation and favor immune evasion [141–143]. Through the establishment of an immunosuppressive myeloid compartment and sustained expression of immune checkpoint molecules, eNAMPT contributes to T-cell dysfunction and exhaustion, ultimately limiting productive antitumor immune responses. Although direct effects of eNAMPT on T lymphocytes remain incompletely understood, current evidence consistently supports its role as a central regulator of tumor–immune crosstalk (Figs. 2 and 3).

Interestingly, the immunological functions of NAMPT are not restricted to its extracellular form. Recent genome-wide CRISPR and metabolic inhibitor screens have demonstrated that intracellular

NAMPT also represents a critical metabolic checkpoint within tumor-infiltrating lymphocytes (TILs) [146]. Reduced NAMPT expression in activated T cells results in intracellular NAD depletion, impaired glycolysis and mitochondrial respiration, and defective ATP production, ultimately compromising T-cell effector functions. Conversely, restoration of intracellular NAD levels by nicotinamide supplementation rescues T-cell metabolic fitness, enhances tumor cell killing, and markedly improves the efficacy of adoptive CAR-T cell therapy and immune checkpoint blockade in preclinical models [146]. In addition, we recently demonstrated that, using functional co-culture experiments, the manipulation of NAMPT activity in melanoma cells alters T-cell migration and cytotoxicity, demonstrating that tumor NAD metabolism actively shapes antitumor immunity [70]. Of note, NAMPT expression also correlates with IFN-γ-responsive signatures and PD-L1 in melanoma patient cohorts. The net therapeutic consequence is context dependent: NAMPT can reinforce adaptive immune resistance, yet high IFN-γ/NAMPT states may also identify inflamed tumors with higher susceptibility to checkpoint blockade. These findings caution against assuming that metabolic perturbation will have identical effects across tumor and immune compartments.

Emerging, but still limited evidence indicates that NNMT can also be released extracellularly, like NAMPT, as a soluble free protein under pathological conditions [16,19,147]. Its extracellular function is not fully elucidated, but it seems to emerge as a mediator of intercellular communication activating pro-inflammatory signaling pathways potentially via TLR4 binding [19]. Our group proposed for the first time a tetrameric NNMT:TLR4 binding model offering a plausible structural and mechanistic basis for their association. Our functional results indicated that exogenous NNMT treatment is able to trigger NF-κB pathway, main pathway triggered by TLR4 engagement [19] (Fig. 3).

Beyond soluble secretion, both NAMPT and NNMT have also been identified within extracellular vesicles (EVs), supporting the concept that enzymes involved in nicotinamide metabolism may themselves function as extracellular messengers [19,143,148]. The importance of extracellular NAMPT-containing EVs (eNAMPT-EVs) has been demonstrated in different models. Tumor-derived EV-associated NAMPT contributes to tumor–host communication by promoting metabolism, drug resistance, cell survival and tumor progression [19,149–151]. Recently, Imai's group reported that eNAMPT-EVs derived from human plasma boosted hypothalamic NAD levels in mice. The authors proposed that enhancing circulating eNAMPT-EVs can be an effective strategy for NAD boosting and potentially an effective anti-aging intervention in humans [152]. Proteomic analyses have identified NNMT among the proteins enriched in EVs released by aggressive melanoma and gastric tumors [19,153].

These observations challenge the traditional view of metabolic enzymes as exclusively intracellular catalysts, supporting the emerging concept that enzymes involved in nicotinamide metabolism, particularly NAMPT and, potentially, NNMT, may acquire cytokine-like or signaling functions once released into the extracellular milieu (Figs. 2 and 3).

Emerging evidence further indicates that the biological impact of NNMT extends through its enzymatic product, 1-MNA, which is increasingly recognized as a bioactive metabolite rather than merely the end-product of nicotinamide catabolism. Extracellular 1-MNA has been shown to exert anti-inflammatory and vasoprotective effects by regulating endothelial function, nitric oxide bioavailability, oxidative stress, and inflammatory cytokine production [39,40]. In addition, recent studies suggest that 1-MNA may influence the behavior of stromal and immune cells within pathological tissues, thereby participating in paracrine communication between tumor cells and their microenvironment [19,153]. Although the molecular mechanisms responsible for these effects remain incompletely understood, these observations support the emerging concept that the NNMT/1-MNA pathway contributes to immunometabolic communication linking cellular metabolism with tissue homeostasis and inflammatory responses.

Collectively, these findings suggest that extracellular signaling mediated by NAM metabolism is not restricted to proteins but also involves bioactive metabolites capable of shaping tissue homeostasis, establishing an additional layer of regulation that coordinates immune cell function, stromal remodeling, inflammatory signaling, and tumor–host interactions (Figs. 2 and 3). This emerging extracellular dimension transforms NAM metabolism from a predominantly cell-autonomous metabolic network into a complex system of intercellular communication that integrates metabolic adaptation with immune regulation across physiological and pathological conditions.

Collectively, the evidence presented throughout this section supports a model in which NAMPT and NNMT function as complementary regulators of nicotinamide metabolism across multiple biological scales. By coordinating intracellular NAD homeostasis, methylation dynamics, metabolic and epigenetic adaptation, and extracellular immunometabolic communication, these enzymes establish an integrated regulatory network that enables cells and tissues to dynamically respond to physiological and pathological challenges. Recognizing this multilayered organization shifts the perspective from targeting individual enzymes toward therapeutically exploiting coordinated nicotinamide metabolism in a context-dependent manner.

3. Therapeutic targeting of coordinated nicotinamide metabolism

3.1. *Targeting intracellular nicotinamide metabolism*

The recognition of coordinated nicotinamide metabolism as a central regulator of cellular bioenergetics, epigenetic homeostasis, and adaptive plasticity has stimulated the development of therapeutic strategies aimed at disrupting intracellular NAD metabolism. Among the different components of this network, NAMPT and NNMT have emerged as the principal pharmacological targets because of their complementary roles in controlling NAD biosynthesis, methyl donor utilization, and metabolic adaptation. Although these enzymes regulate distinct biochemical processes, their complementary contributions to tumor adaptation provide a rationale for investigating coordinated therapeutic targeting of intracellular nicotinamide metabolism. Importantly, the relative dependence on NAMPT-versus NNMT-mediated pathways is expected to be context-dependent, and the potential benefit of combined targeting will likely depend on the metabolic and phenotypic state of individual tumors. Among the intracellular components of the pathway, NAMPT represents the most extensively investigated therapeutic target (Fig. 4). Pharmacological inhibition of NAMPT depletes intracellular NAD pools, resulting in impaired ATP production, mitochondrial dysfunction, inhibition of NAD-dependent enzymes, cell cycle arrest and ultimately apoptotic cell death [6,13,154,155]. These effects are particularly pronounced in highly proliferative tumors that rely on the NAD salvage pathway to sustain their elevated metabolic demand.

Over the past decade, several generations of NAMPT inhibitors have been developed, with encouraging preclinical activity and varying degrees of clinical advancement (www.clinicaltrials.gov) [6,13,155,156]. The first highly specific inhibitor, FK866 (APO866), binds the catalytic tunnel of NAMPT, suppressing NAD biosynthesis and progressively impairing mitochondrial respiration and cellular energy metabolism at nanomolar doses [155]. This pioneering compound established proof-of-concept for pharmacological NAD depletion as an anticancer strategy and stimulated the development of additional inhibitors with improved pharmacological properties. Among these, CHS828, a structural analogue of FK866, demonstrated antitumor activity in lung and breast cancer models [154,157], while GEN617 and LSN3154567 exhibited potent nanomolar activity both in vitro and in vivo, although their clinical development was limited by retinal toxicity [158]. More recently, KPT-9274, a dual inhibitor of NAMPT and PAK4, has entered phase I clinical trials for advanced solid tumors and Hodgkin lymphoma, either as monotherapy or in combination with niacin and nivolumab (clinicaltrials.gov; NCT02702492, NCT04281420, NCT04914845) [6,

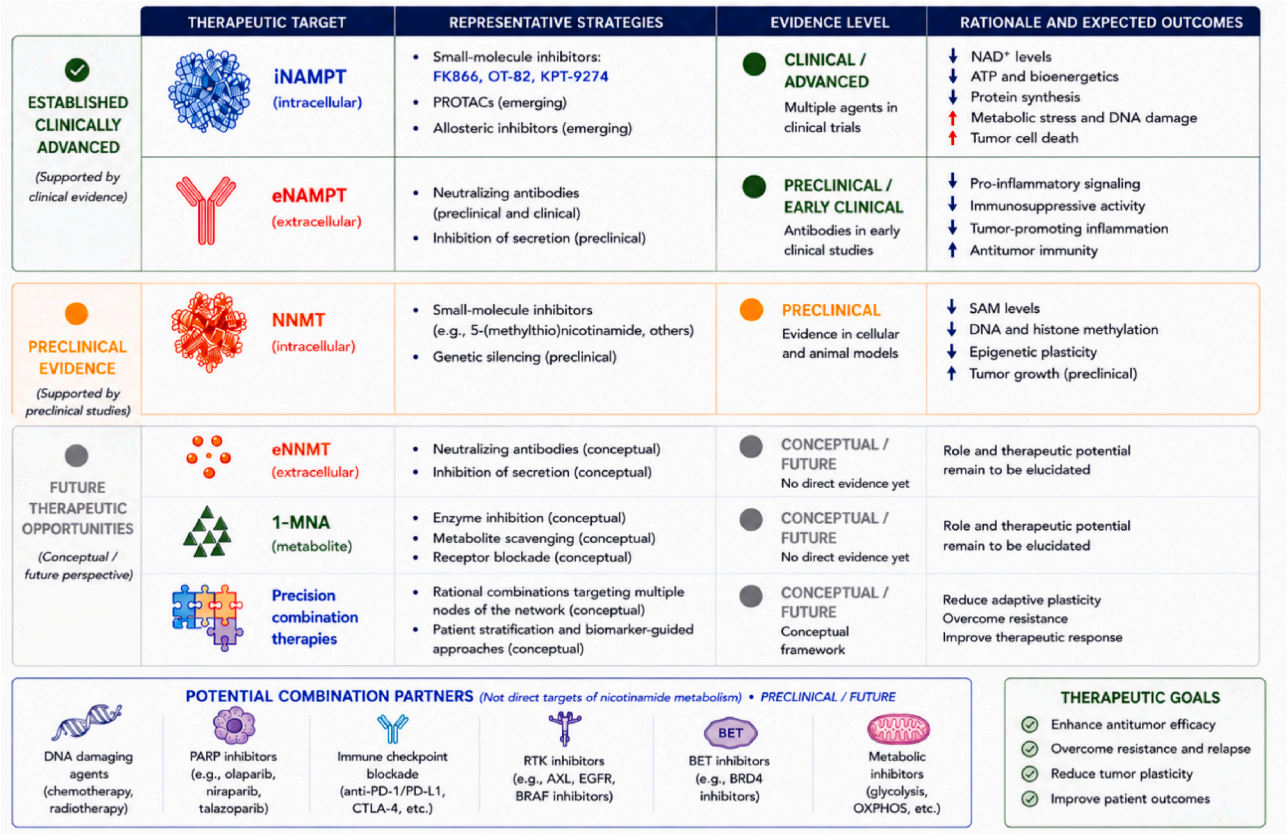


Fig. 4. Therapeutic intervention points within coordinated nicotinamide metabolism. Coordinated nicotinamide metabolism offers therapeutic opportunities at distinct biological and translational levels. This figure summarizes the main therapeutic targets and classifies them according to the available evidence. Clinically advanced strategies include intracellular NAMPT inhibition and eNAMPT targeting, whereas preclinical strategies include NNMT inhibition, eNAMPT vaccination, and extracellular vesicle (EV)-targeting approaches. Future opportunities include eNNMT, the NNMT-derived metabolite 1-MNA, and biomarker-guided combination therapies, whose therapeutic potential remains to be established.Several established anticancer treatments, including DNA-damaging agents, PARP inhibitors, immune checkpoint inhibitors, RTK inhibitors, BET inhibitors, and metabolic or epigenetic drugs, may represent potential combination partners, depending on tumor context and biological rationale. Collectively, these approaches highlight the potential of multi-level therapeutic targeting to limit tumor plasticity and overcome therapy resistance.

13,159]. Another promising compound, OT-82, has shown potent antitumor activity in hematological malignancies by efficiently reducing intracellular NAD and ATP levels while displaying a more favorable toxicity profile than earlier inhibitors [160,161]. Lastly, using proteolysis-targeting chimera (PROTAC) technology, Wu et al. identified PROTAC A7 as a potent and selective degrader of NAMPT, which degrades iNAMPT via the ubiquitin-proteasome system, and in turn decreases the secretion of eNAMPT, blocking its pro-tumoral activities [162]. Galli et al. recently developed PROTACs targeting for NAMPT in breast cancer [163].

In parallel with strategies targeting intracellular NAMPT enzymatic activity, increasing attention has been devoted to NNMT as a therapeutic target. Unlike NAMPT inhibition, which directly compromises NAD biosynthesis, NNMT inhibition aims to restore methyl donor availability, reverse aberrant epigenetic remodeling, and attenuate the metabolic plasticity that supports tumor progression (Fig. 4). Although no NNMT-targeting agents have yet reached clinical evaluation, significant advances in medicinal chemistry have generated several highly selective inhibitors with promising preclinical activity.

Among the most advanced compounds is JBSNF-000088, a substrate-mimetic small molecule that competes with nicotinamide for the catalytic pocket of NNMT [164]. Additional approaches have focused on the development of bisubstrate inhibitors, including LL320 and NS1, which simultaneously occupy both the nicotinamide- and SAM-binding sites, thereby achieving remarkable potency and selectivity [165]. More recently, the second-generation inhibitor II399, generated through optimization of the LL320 scaffold with an unconventional SAM mimic, has substantially improved cellular activity while maintaining nanomolar affinity for NNMT ($K_i = 5.9$ nM) and enhanced intracellular efficacy ($IC_{50} = 1.9\,\mu M$) [166]. In melanoma, our group used HY-131042 NNMTi, a potent NNMT inhibitor ($IC_{50} = 1.2\,\mu M$) that significantly block melanoma proliferation [19]. Collectively, these compounds provide important proof-of-concept that pharmacological targeting of NNMT is feasible and may reverse the metabolic and epigenetic alterations associated with tumor progression.

Taken together, these studies demonstrate that intracellular nicotinamide metabolism is therapeutically tractable at multiple levels. While NAMPT inhibitors primarily induce metabolic collapse through NAD depletion, NNMT inhibitors aim to restore methylation homeostasis and limit adaptive cellular plasticity. Rather than representing alternative strategies, these complementary approaches may ultimately provide the basis for rational combinatorial interventions targeting distinct but interconnected nodes of coordinated nicotinamide metabolism. To date, no data are available on the simultaneous targeting of NAMPT and NNMT to determine potential synergistic, additive, or competitive effects.

3.2. *Targeting extracellular immunometabolic communication*

Compared with intracellular enzyme inhibition, therapeutic targeting of extracellular signaling offers the opportunity to interfere with the non-canonical cytokine-like functions of nicotinamide metabolism

without directly perturbing cellular bioenergetics. To date, therapeutic strategies targeting extracellular nicotinamide metabolism have focused exclusively on counteracting the cytokine-like functions of eNAMPT. Unlike intracellular NAMPT inhibitors, which disrupt NAD biosynthesis in both normal and malignant cells, strategies targeting eNAMPT aim to selectively neutralize its pro-inflammatory and immunomodulatory activities while preserving intracellular NAD homeostasis (Fig. 4). This distinction is particularly relevant given the central role of eNAMPT in orchestrating chronic inflammation, immune cell recruitment, stromal activation, and tumor-host communication. Neutralization of eNAMPT using monoclonal antibodies has demonstrated significant anti-inflammatory efficacy in multiple preclinical models of inflammatory and fibrotic diseases [13,14]. Among these, ALT-100 is currently the most advanced therapeutic candidate and has entered phase II clinical evaluation for acute respiratory distress syndrome (ARDS; NCT05938036), where blockade of eNAMPT has shown protective effects against inflammatory tissue injury and fibrosis [167]. These findings support the concept that selectively targeting eNAMPT may provide therapeutic benefit while avoiding the systemic metabolic toxicities associated with iNAMPT inhibition. Functional studies using eNAMPT-neutralizing antibodies have provided direct causal evidence of its immunosuppressive activity within the tumor microenvironment. In chronic lymphocytic leukemia, eNAMPT drives the differentiation of monocytes into CD163highCD206high nurse-like cells that express indoleamine 2,3-dioxygenase (IDO) and secrete IL-10, CCL18, IL-6, and IL-8, thereby sustaining leukemic cell survival while dampening T-cell responses independently of its enzymatic activity through non-catalytic activation of ERK1/2, STAT3, and NF-κB signaling. Neutralizing antibody reduced the differentiation of these pro-tumoral myeloid cell [140]. Consistently, neutralization of eNAMPT with the murine monoclonal antibody C269 in murine model of triple-negative breast cancer restored CD8+IFN-γ+GRZB + effector T-cell activity, reduced the immunosuppressive phenotype of tumor-infiltrating regulatory T cells, and decreased tumor growth and lung metastases by interrupting eNAMPT-driven PD-L1/PD-1 signaling [132]. Comparable results were obtained with the humanized eNAMPT-neutralizing antibody ALT-100 in orthotopic prostate cancer xenografts, where antibody-mediated blockade of the eNAMPT/TLR4/NF-κB axis reduced tumor proliferation, local invasion, and metastatic spread while improving overall survival [168]. A decreased inflammation was also observed in murine colitis, upon eNAMPT blocking [131]. Collectively, these findings, obtained across distinct tumor types and neutralizing strategies, converge on a model in which eNAMPT functions as an immunomodulatory DAMP that actively restrains antitumor immunity, reinforcing its candidacy as a therapeutic target to combine with immune checkpoint blockade.

Although equivalent therapeutic approaches for eNNMT have not yet been developed, the emerging evidence supporting eNNMT release and the immunomodulatory activity of its metabolite 1-MNA suggests that extracellular nicotinamide metabolism may represent a broader therapeutic landscape than previously appreciated. These observations further reinforce the concept that coordinated nicotinamide metabolism can be therapeutically targeted at multiple biological levels, encompassing both intracellular metabolic functions and extracellular immunometabolic communication.

3.3. Challenges and emerging therapeutic strategies

Despite the encouraging preclinical activity of both NAMPT and NNMT inhibitors, their clinical translation has proven considerably more challenging than initially anticipated. Rather than reflecting inadequate target engagement, these limitations largely arise from the remarkable metabolic plasticity of cancer cells, which enables dynamic adaptation to therapeutic pressure through extensive rewiring of nicotinamide metabolism and interconnected signaling networks.

One of the major limitations of NAMPT inhibition is the ability of tumor cells to compensate for NAD depletion by activating alternative biosynthetic pathways. Increased utilization of the NAPRT-dependent Preiss–Handler pathway or the de novo tryptophan pathway enables resistant tumors to partially restore intracellular NAD levels, thereby reducing the efficacy of pharmacological NAMPT inhibition [6,13,169]. These adaptive responses are frequently accompanied by broader metabolic reprogramming, including enhanced glycolytic flux and mitochondrial remodeling, ultimately preserving cellular viability despite inhibition of the salvage pathway. Consequently, selective blockade of a single NAD biosynthetic route is often insufficient to achieve durable therapeutic responses [104,170,171]. Similarly, targeting NNMT alone may be limited by the remarkable adaptability of epigenetic regulatory networks. Of note, recently was reported that NAMPT inhibition using FK866 reduced NAM and NAD levels to a greater extent in prostate cancer cells expressing high levels of NNMT ($NNMT^{high}$) than in $NNMT^{low}$ cells, resulting in cellular toxicity that could be reversed by NNMT inhibition with SAH [26].

The coordinated biological functions of NAMPT and NNMT therefore suggest that future therapeutic strategies should move beyond single-enzyme inhibition toward simultaneous targeting of complementary components of nicotinamide metabolism. Dual interference with NAD biosynthesis and methyl donor metabolism may reduce the capacity of tumor cells to compensate through metabolic rewiring while simultaneously limiting epigenetic adaptation and phenotypic plasticity. Although direct dual NAMPT/NNMT inhibitors are not yet available, this concept provides a strong rationale for the development of rational combination therapies.

Additionally, growing evidence further indicates that nicotinamide metabolism should not be considered an isolated metabolic pathway but rather an integrated regulatory network interacting with multiple oncogenic signaling cascades and the tumor immune microenvironment. Accordingly, several combination strategies are currently being explored, at least in pre-clinical models (Fig. 4). These include the association of NAMPT inhibitors with targeted therapies, such as BRAF inhibitors, PARP inhibitors, and inhibitors of signaling pathways such as PAK4 and mTOR, aiming to simultaneously disrupt metabolic adaptation and oncogenic signaling [15,172–175]. Likewise, pharmacological inhibition of NNMT has shown the potential to enhance sensitivity to chemotherapy and immunotherapy by reversing epigenetic remodeling and reprogramming the tumor microenvironment [122,123,175,176].

Ultimately, the future of therapeutic intervention is likely to rely on patient stratification based on nicotinamide metabolic dependencies rather than on the expression of individual enzymes alone. Integrating biomarkers reflecting intracellular NAD metabolism, methylation status, extracellular eNAMPT activity, and tumor metabolic plasticity may enable the identification of patients most likely to benefit from therapies targeting coordinated nicotinamide metabolism. Rather than representing independent therapeutic opportunities, intracellular metabolism, extracellular signaling, and adaptive metabolic rewiring should therefore be considered complementary vulnerabilities within a single interconnected regulatory network.

4. Coordinated nicotinamide metabolism in therapy resistance

4.1. Adaptive metabolic rewiring under therapeutic stress

Anticancer therapies impose profound metabolic stress on tumor cells by disrupting signaling pathways that sustain proliferation, survival, and energy metabolism [176,177]. To survive this selective pressure, cancer cells undergo extensive metabolic rewiring [178], also dynamically reorganizing nicotinamide metabolism to preserve NAD homeostasis and maintain bioenergetic fitness. Accumulating evidence indicates that coordinated regulation of NAMPT and NNMT represents a central adaptive mechanism underlying this metabolic plasticity.

Therapeutic pressure further amplifies this coordinated metabolic response. Therapeutic pressure can induce remodeling of nicotinamide

metabolism as part of a broader adaptive rewiring program. In selected models of targeted therapy resistance, this involves increased NAMPT and/or NNMT activity or expression, depending on tumor type and cellular context. In BRAF-mutant melanoma, MAPK inhibition initially suppresses tumor growth but subsequently induces NAMPT upregulation, enabling resistant cells to restore NAD production, reprogram their metabolism and acquire a more aggressive and plastic phenotype [15,19,24,69,105]. Moreover, NAMPT activity is also supported by alteration of mTORC2/RICTOR. Ponzone et al. demonstrated that melanomas with reduced RICTOR expression are intrinsically tolerant to BRAF/MEKi and anticipate the onset of resistance to BRAFi upon prolonged drug exposure. This occurs by promoting adaptive rewiring toward an oxidative phosphorylation- and NAMPT-dependent state. In this context, NAMPT inhibition restores sensitivity to BRAFi [179]. Notably, recent evidence also demonstrates increased NNMT expression during the development of BRAF inhibitor resistance, supporting a model of convergent metabolic–epigenetic adaptation rather than implying direct reciprocal regulation of the two enzymes [19].

A similar adaptive mechanism has been described in EGFR-mutant non-small cell lung cancer (NSCLC), where increased NAMPT expression maintains NAD homeostasis during tyrosine kinase inhibitor (TKI) treatment [172,180]. More recently, Pulido et al. demonstrated that NNMT-dependent metabolic remodeling generates a therapeutically exploitable dependence on NAMPT in resistant EGFR-mutant tumors [28], further supporting the existence of functional convergence between the two enzymes under therapeutic stress. Acute myeloid leukemia (AML) often develops resistance to the BCL2 inhibitor venetoclax through metabolic reprogramming. Targeting these metabolic changes with metformin (a mitochondrial complex I inhibitor) or KPT-9274 (a NAMPT inhibitor) re-sensitized resistant cells to venetoclax [181]. In pancreatic neuroendocrine tumors, NAMPT inhibitors have also been shown to synergize with mTOR regulator PAK inhibitors (such as everolimus) in resistant pancreatic cancer cellular models, further supporting NAMPT as a node to overcome therapy resistance [182].

Several studies suggest that eNAMPT could mediate resistance to cancer therapies. A recent study revealed that eNAMPT, by boosting thymidylate synthase expression in cancer cells, reduced the sensitivity of colorectal cancer (CRC) to capecitabine [183]. Likewise, eNAMPT was shown to induce the phosphorylation of estrogen receptor α, contributing to breast cancer resistance to tamoxifen [184,185]. Finally, the fact that eNAMPT enhances the antioxidant capacity of tumor cells may also contribute to their resilience and drug resistance [186].

In Triple-Negative-Breast Cancer (TNBC), eNAMPT has been found to sustain stemness of cancer cells through post-translational modification of STAT3, up-regulating the STAT3 pathway [187].

Collectively, these findings indicate that coordinated nicotinamide metabolism functions as a dynamic metabolic buffering system that enables tumor cells to preserve bioenergetic homeostasis and survive therapy-induced metabolic stress.

4.2. Epigenetic plasticity and cancer stemness

Rather than simply maintaining cellular metabolism, coordinated nicotinamide metabolism also promotes the epigenetic plasticity required for long-term therapeutic adaptation. By simultaneously regulating NAD availability, methyl donor consumption, and chromatin organization, NAMPT and NNMT enable tumor cells to reversibly transition between differentiated and therapy-resistant cellular states.

Evidence supporting this concept has emerged from glioblastoma models, where nicotinamide-induced senescence is associated with the simultaneous downregulation of both NAMPT and NNMT, leading to chromatin remodeling, impaired DNA repair, and irreversible loss of cellular plasticity [124]. Interestingly, inhibition of either enzyme alone is insufficient to fully reproduce this phenotype, suggesting that the combined remodeling of nicotinamide metabolism may contribute to the maintenance of adaptive epigenetic states.

The importance of NNMT-mediated epigenetic remodeling is further illustrated in mesenchymal glioblastoma, where NNMT depletion more profoundly impairs tumor sphere formation and cancer stem-like properties than NAMPT inhibition alone [123]. These observations support the concept that although NAMPT primarily sustains metabolic fitness, NNMT reinforces the epigenetic programs required for stemness maintenance and phenotypic flexibility.

Together, these findings indicate that coordinated regulation of metabolism and chromatin remodeling enables tumor cells to dynamically adapt to therapeutic stress, promoting dedifferentiation, stemness, and long-term disease persistence.

4.3. Remodeling of the tumor microenvironment and immune resistance

Therapy resistance is increasingly recognized as a property emerging not only from tumor-intrinsic adaptations but also from dynamic interactions with the tumor microenvironment. Coordinated nicotinamide metabolism contributes to this process by reshaping stromal and immune cell functions through both intracellular metabolic reprogramming and extracellular signaling.

Recent evidence in gastric cancer demonstrated that the balance between extracellular NAMPT and NNMT-derived metabolites determines responsiveness to immune checkpoint blockade. In patients responding to anti-PD-1 therapy, cancer-associated fibroblasts preferentially channel nicotinamide toward NAD biosynthesis rather than NNMT-dependent methylation, resulting in an increased NAM/1-MNA ratio and preservation of T-cell cytotoxicity [122].

Conversely, NNMT-expressing cancer-associated fibroblasts undergo extensive epigenetic remodeling characterized by H3K27 hypomethylation, complement activation, and recruitment of myeloid-derived suppressor cells through activation of the C3–C5a–C5aR signaling axis [188]. Pharmacological inhibition of NNMT effectively reprogrammed CAFs, restored $CD8^+$ T-cell function, and markedly enhanced the efficacy of PD-1 and CD47 immune checkpoint blockade in otherwise resistant tumors [188].

Beyond stromal remodeling, extracellular components of nicotinamide metabolism may further contribute to immune escape by modulating inflammatory signaling and cytotoxic lymphocyte function [19,23,176].

These observations indicate that resistance emerges not only through intracellular metabolic adaptation but also through coordinated remodeling of the tumor ecosystem. By integrating metabolic rewiring, epigenetic plasticity, and extracellular immunometabolic communication, coordinated nicotinamide metabolism may contribute to support adaptive mechanisms that enable tumors to evade both targeted therapies and antitumor immunity (Fig. 5).

5. Conclusions

Rather than acting as independent metabolic enzymes, NAMPT and NNMT emerge as complementary regulators of coordinated nicotinamide metabolism, integrating intracellular bioenergetics, methyl donor utilization, epigenetic remodeling, and extracellular immunometabolic communication. In cancer, dysregulation of this network extends beyond alterations in NAD^+ biosynthesis or methylation capacity alone, contributing to metabolic flexibility, epigenetic plasticity, stemness, immune evasion, and therapy resistance. Importantly, however, the extent to which these functions reflect direct functional crosstalk between NAMPT and NNMT, rather than convergent or context-dependent metabolic adaptations, remains incompletely defined.

This framework has important therapeutic implications. Although NAMPT and NNMT have largely been targeted independently, their complementary roles provide a rationale for investigating whether co-targeting both enzymes could limit compensatory metabolic and epigenetic rewiring more effectively than targeting either pathway alone. However, direct evidence supporting synergistic NAMPT/NNMT

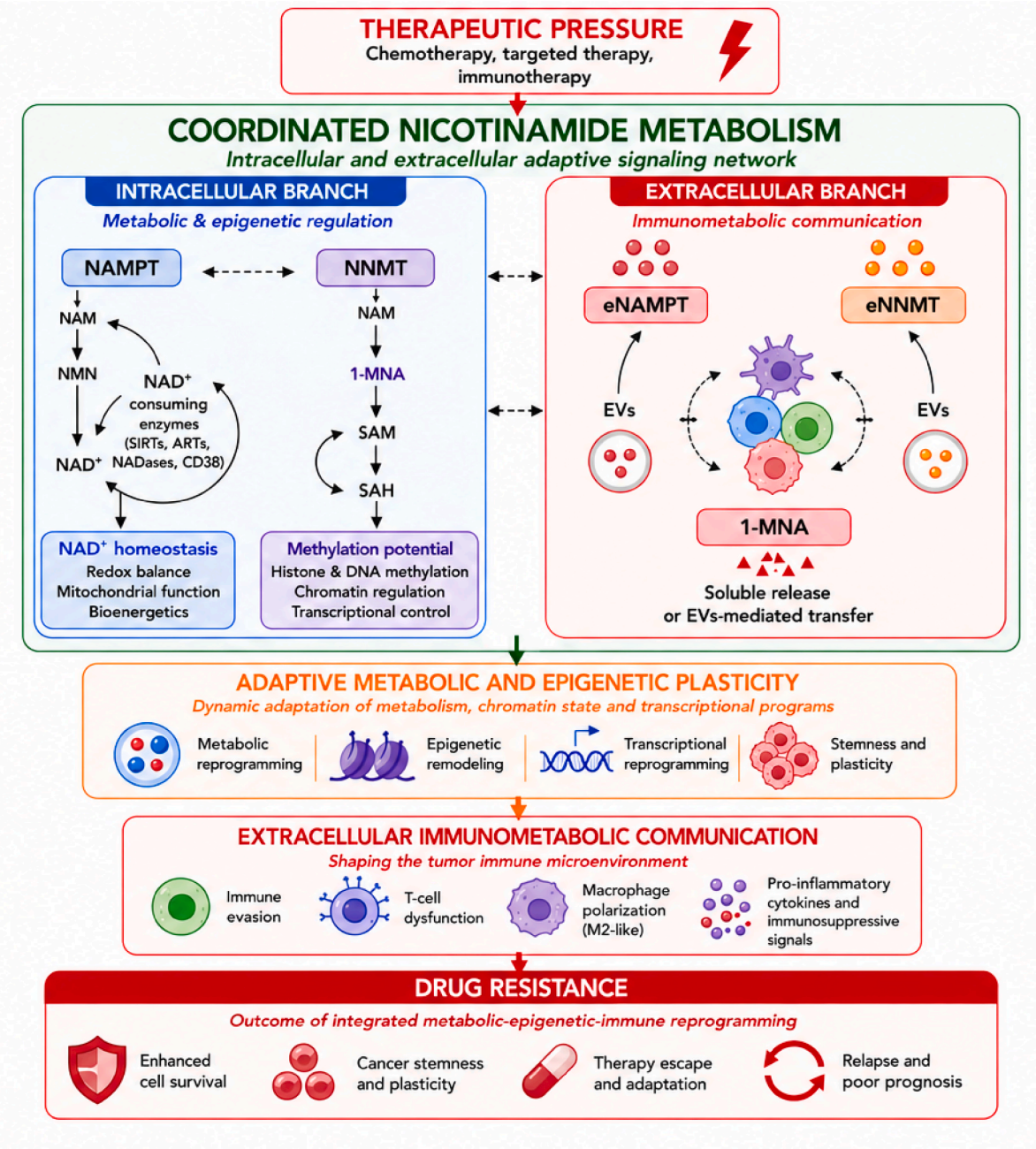


Fig. 5. Coordinated nicotinamide metabolism drives adaptive metabolic, epigenetic, and immunometabolic plasticity under therapeutic pressure. Therapeutic stress induces remodeling of intracellular NAMPT- and NNMT-dependent pathways, affecting NAD homeostasis, methylation potential, metabolic adaptation, and chromatin plasticity. In parallel, extracellular NAMPT, emerging eNNMT, and 1-MNA contribute to tumor–microenvironment communication and immune adaptation. While the extracellular functions of eNNMT remain insufficiently characterized, these interconnected intracellular and extracellular pathways may represent context-dependent therapeutic vulnerabilities that warrant investigation. Together, their coordinated remodeling may support tumor survival, immune evasion, and therapy resistance.

co-targeting remains limited, and dedicated studies will be required to determine whether such combinations provide a therapeutic advantage in specific tumor contexts. Similarly, the emerging extracellular dimension of NNMT biology warrants further investigation. Defining the mechanisms governing eNNMT release, its extracellular interactions, and its effects on immune and stromal cells will be important to establish whether eNNMT represents a therapeutically actionable component of coordinated nicotinamide metabolism.

Several important questions nevertheless remain unresolved. The relative contribution of intracellular versus extracellular NAMPT and NNMT, the mechanisms governing their context-dependent regulation across different tumor types, and the identification of predictive biomarkers for patient stratification all represent major priorities for future investigation. Particular attention should also be devoted to understanding how these regulatory layers interact during disease progression and in response to therapeutic pressure. Defining how nicotinamide metabolism is dynamically remodeled during tumor evolution and treatment will be essential for translating these biological insights into clinically effective therapeutic strategies.

Collectively, the evidence discussed throughout this review supports a model in which coordinated nicotinamide metabolism is organized across multiple interconnected biological levels. At the intracellular

level, NAMPT and NNMT influence NAD^+ homeostasis and methylation potential; at the cellular level, these metabolic outputs contribute to adaptive metabolic and epigenetic plasticity; and at the tissue level, extracellular mediators, including eNAMPT, emerging eNNMT, and 1-MNA, contribute to immunometabolic communication within the tumor microenvironment. Rather than representing independent biological processes, these interconnected layers provide a framework for understanding how nicotinamide metabolism contributes to tumor adaptation across different biological scales. We therefore propose that shifting the focus from individual enzymes toward coordinated nicotinamide metabolism provides a useful framework for integrating the metabolic, epigenetic, and immunological functions of NAMPT and NNMT, while identifying context-dependent opportunities for mechanism-based combination therapies aimed at limiting tumor plasticity and overcoming therapeutic resistance.

CRediT authorship contribution statement

Irene Fiorilla: Writing – review & editing, Writing – original draft. **Beatrice Ghezzi:** Writing – review & editing, Writing – original draft. **Agata Carreira:** Writing – review & editing, Writing – original draft. **Andrea Mantovan:** Writing – original draft. **Alessia Ponzano:** Writing – original draft. **Filippo Casone:** Visualization. **Giulia Rizza:** Visualization. **Valentina Audrito:** Writing – review & editing, Supervision, Resources, Conceptualization.

Consent for publication

All authors have read and consent to this publication.

Authors' contributions

Conceptualization, V.A.; writing-original draft preparation, I.F, B.G., A.C., A.M. and A.P; picture conceptualization and design B.G., F.C, G.R. and V.A.; writing-review and editing V.A. All authors have read and agreed to the published version of the manuscript.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work, we used ChatGPT (OpenAI) for images generation, reviewing and editing the output. ChatGPT was used to assist with language editing and textual refinement during manuscript preparation. All AI-assisted textual and visual content was critically reviewed and approved by the authors, who take full responsibility for the final manuscript and figures.

Funding

This work was supported by Associazione Italiana Ricerca sul Cancro (AIRC): My First AIRC Grant–MFAG2021 #26004 (to V.A.). V.A. is also supported by Fondo di Beneficenza Intesa SanPaolo grant Id: B/2024/0194 NAMPT. A.C. has received funding from the European Union's Horizon 2020 research and innovation program, under the grant agreement no. 101279563-eN-TIME-HORIZON-MSCA-2025-PF.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

List of abbreviations

1-MNA	1-methylnicotinamide.
2PY	N1-methyl-2-pyridone-5-carboxamide.
4PY	N1-methyl-4-pyridone-3-carboxamide.
5-methyl-THF	5,10-methyl-tetrahydrofolate
10-formyl-THF	10-formyl-tetrahydrofolate
AD	Alzheimer's Disease
ADP	Adenosine diphosphate
ADP-ribose	Adenosine diphosphate ribose
AHCY	Adenosylhomocysteine hydrolase
AMPK	AMP-activated protein kinase
AOX	Aldehyde oxidase
ARDS	Acute Respiratory Distress Syndrome
ARTs	ADP-ribosyltransferases
ATF4	activating transcription factor 4
ATP	Adenosine triphosphate
BMAL1	Brain and Muscle ARNT-Like 1
BRAF	B-Raf proto-oncogene
BRAFi	BRAF inhibitors
cADPR	Cyclic ADP-ribose
CAFs	Cancer-associated fibroblasts
CD38/CD157	Ectoenzymes (NAD + -glycohydrolases)
CF	Cystic Fibrosis
CKD	Chronic Kidney Disease
CLOCK	Circadian Locomotor Output Cycles Kaput
CXCR4	C-X-C motif chemokine receptor 4
DAMP	Damage-associated molecular pattern
EGFR	Epidermal growth factor receptor
eNAMPT	Extracellular nicotinamide phosphoribosyltransferase
eNNMT	Extracellular nicotinamide N-methyltransferase
EMT	Epithelial-mesenchymal transition
EVs	Extracellular vesicles
GBM	Glioblastoma
HIF-2α	Hypoxia-inducible factor-2 alpha
iNAMPT	Intracellular nicotinamide phosphoribosyltransferase
IBD	Inflammatory bowel disease
IFN	interferon
IRF1	Interferon regulatory factor 1
MAPK	Mitogen-activated protein kinase
MAT	Methionine adenosyltransferases
MDSCs	Myeloid-derived suppressor cells
MS	Methionine synthase
NAD	Nicotinamide adenine dinucleotide.
NAM	Nicotinamide.
NAMPT	Nicotinamide phosphoribosyltransferase
NAPRT	Nicotinic acid phosphoribosyltransferase
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NMN	Nicotinamide mononucleotide.
NNMT	Nicotinamide N-methyltransferase
NSCLC	Non-Small Cell Lung Cancer
PARP1	Poly (ADP-ribose) polymerase 1
PD	Parkinson's Disease
PD-L1	Programmed death-ligand 1
PRPP	Phosphoribosyl pyrophosphate
PTMs	Post-translational modifications
SAH	S-adenosyl-L-homocysteine.
SAM	S-adenosylmethionine.
SIRTs	Sirtuins
SNPs	Single nucleotide polymorphisms
STAT3	Signal transducer and activator of transcription 3
TKIs	Tyrosine kinase inhibitors
TLR4	Toll-like receptor 4
TME	Tumor microenvironment
TNF-alpha	Tumor Necrosis Factor alpha

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