Seminars in Cell and Developmental Biology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

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

Targeting metabolic reprogramming in metastatic melanoma: The key role of nicotinamide phosphoribosyltransferase (NAMPT)

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ARTICLE INFO

Keywords:
Metabolic reprogramming
BRAF
NAD^+ metabolism
NAMPT
Melanoma
Combination therapy

ABSTRACT

Cancer cells rewire their metabolism to support proliferation, growth and survival. In metastatic melanoma the BRAF oncogenic pathway is a master regulator of this process, highlighting the importance of metabolic reprogramming in the pathogenesis of this tumor and offering potential therapeutic approaches.

Metabolic adaptation of melanoma cells generally requires increased amounts of NAD^+, an essential redox cofactor in cellular metabolism and a signaling molecule. Nicotinamide phosphoribosyltransferase (NAMPT) is the most important NAD^+ biosynthetic enzyme in mammalian cells and a direct target of the BRAF oncogenic signaling pathway. These findings suggest that NAMPT is an attractive new therapeutic target, particularly in combination strategies with BRAF or MEK inhibitors.

Here we review current knowledge on how oncogenic signaling reprograms metabolism in BRAF-mutated melanoma, and discuss how NAMPT/NAD^+ axis contributes to these processes. Lastly, we present evidence supporting a role of NAMPT as a novel therapeutic target in metastatic melanoma.

1. Introduction

The finding that 35–60% of melanoma patients harbor activating mutations in the v-Raf murine sarcoma viral oncogene homolog B (BRAF) paved the way to the use of BRAF inhibitors (BRAFi) as the treatment of choice for this patient subset [1]. The most typical mutation is a single base change at position 600 (V600E) [2], which results in the over-activation of BRAF-MEK-ERK axis and mitogen-activated protein kinase (MAPK) signaling. This finding resulted in the introduction of BRAFi in the treatment of these patients, with dramatic, even if short lived, clinical responses. In fact, the majority of patients rapidly develop acquired/secondary resistance, leading to disease progression. Acquired resistance arises via multiple mechanisms that converge on the reactivation of MAPK signaling, supporting the idea of combining multiple inhibitors of the pathway. For example, the combination of BRAFi with MEK inhibitors (MEKi) is associated with longer progression-free and overall survival, compared to BRAFi alone [3,4]. Relapse and resistance however, continue to occur in the majority of patients, prompting investigations into new combination of therapeutic strategies.

Melanoma has long been a major focus of immunotherapy clinical development efforts [5]. In 2011, the FDA approved the use of ipilimumab, a monoclonal antibody (mAb) that blocks cytotoxic T-lymphocyte antigen (CTLA)-4, for patients with metastatic melanoma [6,7]. The binding of CTLA-4, expressed by T cells, to CD80 or CD86 expressed by antigen-presenting cells, switches off T cell activation by transmitting an inhibitory signal [8]. CTLA-4 can be expressed also by regulatory T cells (Tregs), contributing to their immunosuppressive functions [9]. Nivolumab and pembrolizumab, two anti-programmed cell death-1 (PD-1) mAbs, were also recently approved for treatment of these patients, demonstrating promising clinical activity and efficacy [10,11]. PD-1, an inhibitory receptor expressed by T-cells infiltrating tumor lesions, is activated through binding of surface ligands, which may be expressed by tumor cells, including melanoma [12,13]. Although single agent anti-PD-1/PD-L1 therapy has demonstrated promising clinical activity in diverse tumor types including melanoma, renal cell carcinoma and lung cancer, there is still a significant proportion of patients displaying primary resistance [10,14]. More recent reports indicate that a proportion of melanoma patients, who were previously responsive to anti-PD-1, relapse demonstrating that similarly to what happens with targeted therapies, acquired resistance to immunotherapy can be developed. Even if only in a subset of patients, the combination of anti-CTLA-4 and anti-PD-1 antibodies proved more efficacious than either drug used alone, demonstrating the coexistence of

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https://doi.org/10.1016/j.semcdb.2019.05.001
Received 14 March 2019; Received in revised form 2 May 2019; Accepted 2 May 2019

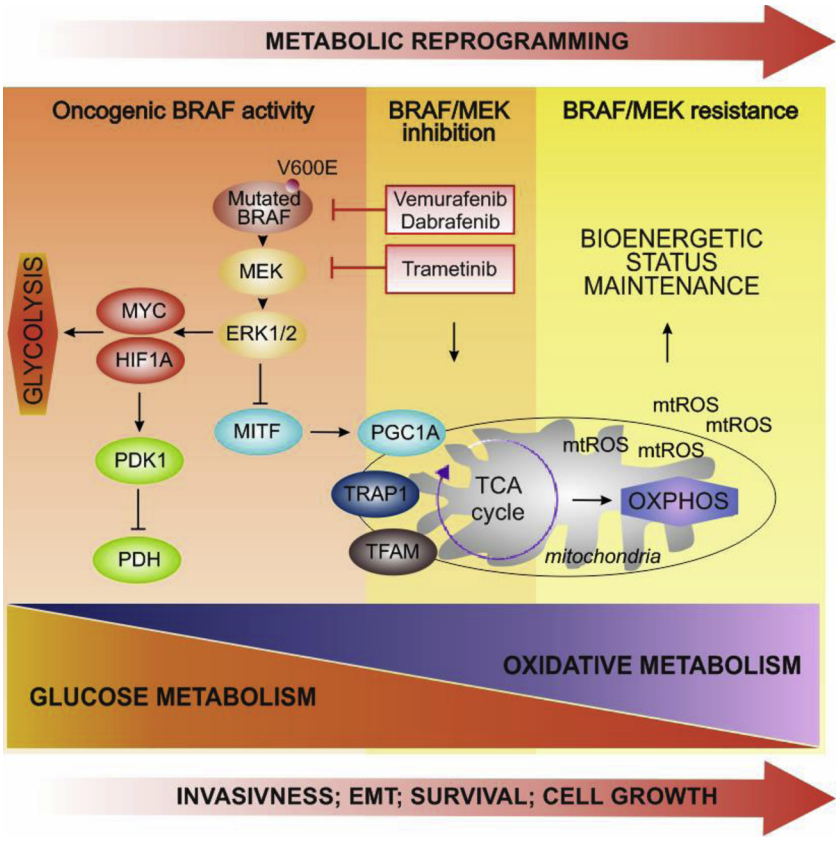

Fig. 1. Metabolic adaptation in BRAFV600E melanoma. The oncogenic BRAF-mutated molecular pathway, leading to the overactivation of MAPK, drives metabolic reprogramming in melanoma cells promoting glucose metabolism. Inhibition of BRAF/MEK decreases glycolysis, leading to a dependence on mitochondrial metabolism. The progressive metabolic reprogramming in melanoma is accompanied by a drastic increase in tumor aggressiveness.
PDK1: pyruvate dehydrogenase kinase, PDH: pyruvate dehydrogenase, HIF1A: hypoxia-inducible factor 1α, MITF: microphthalmia-associated transcription factor, PGC1A: peroxisome proliferator-activated receptor gamma coactivator 1-alpha, TFAM: mitochondrial transcription factor A, TRAP1: TNF receptor-associated protein 1, mtROS: mitochondrial reactive oxygen species, EMT: epithelial-mesenchymal transition.

multiple immunosuppressive pathways in the tumor microenvironment [15,16].

In order to support continued proliferation and growth and to adapt to unfavorable microenvironmental conditions, such as low nutrient concentrations and hypoxia, tumor cells must metabolically adjust to balance their bioenergetic and biosynthetic needs [17,18], a process known as metabolic rewiring [19,20]. Oncogenic signals, including those mediated through BRAF, are critical regulators of metabolic processes, by activating specific transcriptional programs [21–24]. Probably the best studied adaptive phenomenon, the “Warburg effect”, is based on increased capability of cancer cells to uptake glucose and metabolize it [17]. This implies that transformed cells switch from the highly efficient mitochondrial oxidative phosphorylation (OXPHOS) to the less efficient aerobic glycolysis. The acquisition of a Warburg phenotype is also associated to increased invasiveness and metastatization of cancer cells [25]. However, more recently, evidence showed that also mitochondrial metabolism plays a critical role in cancer progression [26]. Mitochondria are signaling hubs and bioenergetics organelles, which play an important role in cellular adaptation to environmental changes, directly responding to nutrient availability. The major player responsible for the enhanced mitochondrial metabolic plasticity of aggressive cancer is the transcriptional coactivator peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PPARGC1A, best known as PGC1α) [27]. Moreover, also reactive oxygen species (ROS), generated by mitochondria as a natural by-product of electron transport chain (ETC) activity, can activate tumorigenic signaling and metabolic reprogramming [26].

Metabolic adaptation is not a prerogative of cancer cells, but also occurs in T cells and macrophages present in the tumor microenvironment. For example, depletion of glucose and essential nutrients is detrimental for tumor-infiltrating $CD8^+$ T lymphocytes (TILs), which cannot exert their cytotoxic functions. In addition, hypoxia and metabolic acidosis favor the development of tolerogenic cells, including Tregs and tumor-associated macrophages (TAM) [28,29]. Thus, metabolic dysregulation in the tumor microenvironment is intrinsically responsible for failure of immunotherapy [30]. Targeting metabolic abnormalities of cancer cells and restoring a metabolic balance in the tumor microenvironment is a promising direction for anti-cancer therapy development, including melanoma [31–34].

Nicotinamide adenine dinucleotide (NAD^+) is an essential cofactor with critical roles in redox reactions. By modulating NAD^+-metabolizing enzymes, NAD^+ controls key processes, including energy metabolism and cell survival [35,36]. NAD^+ levels steadily decline with age, resulting in altered metabolism and increased disease susceptibility [37,38].

The enzyme nicotinamide phosphoribosyltransferase [NAMPT, also known as pre-B colony enhancing factor (PBEF) or visfatin] catalyzes the first reversible step in NAD^+ biosynthesis from nicotinamide (Nam) [37,39]. Besides its canonical intracellular activity, NAMPT can be secreted in the extracellular milieu (eNAMPT) where it exerts cytokine/adipokine-like actions. Intracellular (i) and eNAMPT levels are generally increased in metabolic-inflammatory diseases and in many tumors, suggesting that this enzyme may be a novel player in tumor-host interactions [40]. Considering the close relationship between cancer progression, metabolism and microenvironmental signals, it was hypothesized that drugs interfering with NAD^+ synthesis could block tumor growth, representing an efficient way to treat cancer [41].

In this review, we focus on NAD^+ metabolism and NAMPT expression in BRAF-mutated metastatic melanoma before and after metabolic reprogramming and discuss potential pharmacological applications.

2. Metabolic reprogramming in melanoma

When comparing normal melanocytes to melanoma cells, it is clear that tumor transformation has impacted on key metabolic processes [22,23,42]. Much of our knowledge on the molecular mechanisms underlying metabolic reprogramming of melanoma cells derives from

investigations of the BRAF oncogenic signaling [2]. By over-activating the MAPK axis, BRAF mutations in melanoma drive transcription of master regulators of metabolic responses, including hypoxia-inducible factor 1α (HIF-1α), MYC, microphthalmia-associated transcription factor (MITF), PGC1α, PI3K and STAT3 [21,43–45].

2.1. BRAF oncogenic signaling and aerobic glycolysis

The presence of the BRAFV600E mutation has been associated with highly glycolytic metabolism [22,46]. BRAFV600E-mutated melanomas are more reliant on glucose utilization than the counterparts, and this metabolic feature was demonstrated also in patients and exploited for detection of tumors by positron emission tomography [47]. The activation of MYC and HIF-1α induces transcription of several genes involved in glucose metabolism, including glucose transporter 1 (GLUT1) and lactate dehydrogenase (LDH), which positively affect glycolysis [21,43,46] (Fig. 1). At the same time, BRAFV600E actively represses OXPHOS, negatively modulating expression of MITF and its target PGC1α [24,45,48] (Fig. 1). Physiologically, the balance between HIF-1α and PGC1α is dynamically regulated by metabolic demands, and provides compensatory responses to bioenergetics challenges. Many melanomas display a pattern of HIF-1α activation and PGC1α suppression, thereby maintaining a state of aerobic glycolysis [45,49,50]. A second mechanism suppressing OXPHOS is linked to the expression and activity of pyruvate dehydrogenase kinase (PDK) and pyruvate dehydrogenase (PDH) [51]. PDK, a target gene of HIF-1α, controls and inhibits the PDH activity in the oxidation of glucose-derived pyruvate, lowering mitochondrial functions [44,49] (Fig. 1).

In keeping with the effects of MAPK oncogenic signaling, BRAFi/MEKi treatment suppresses glucose metabolism, reducing the activation of ERK and the downstream transcription factors HIF-1α and MYC [43,44].

2.2. Mitochondrial oxidative phenotype and resistance to BRAFi/MEKi

In BRAFi- and MEKi-treated patients, the metabolic drug-resistant phenotype reverts to mitochondrial respiration [22,23] (Fig. 1). The reliance of drug resistant cells on mitochondrial metabolism can explain how these cells survive to glycolysis inhibition induced by BRAFi or MEKi. This metabolic profile can be interpreted as an attempt to maintain ATP levels and escape cell death despite a block in glycolysis. In general, this is obtained through enhancement of mitochondrial activity and mitochondrial content [24,45,52]. One hypothesis to explain this phenomenon is that this metabolic oxidative profile pre-exists in some clones prior to treatment with BRAFi/MEKi and that treatment simply selects them. The alternative possibility is that resistance is acquired as a consequence of treatment, following drug exposure.

When melanoma cells are treated with BRAFi, a concomitant reactivation of MITF/PCG1α axis occurs, and this in turn activates mitochondrial biogenesis, as well as an OXPHOS gene program and thereby mitochondrial activity. This adaptive metabolic program limits the efficacy of BRAFi and is responsible for adaptive resistance [48,52].

Other important genes that play a role in the intrinsic resistance of melanoma cells to BRAFi are those encoding mitochondrial transcription factor A (TFAM), which controls mitochondrial genome replication and transcription, and TNF receptor-associated protein 1 (TRAP1), which regulates mitochondrial protein folding [53].

Another factor that enhances mitochondrial activity following exposure to BRAFi/MEKi is endoplasmic reticulum (ER) stress that triggers a calcium release from ER toward the mitochondrial matrix, an event known to upregulate mitochondrial oxidative capacity [52].

As a consequence of high mitochondrial activity, resistant cells show higher level of ROS, the by-product of mitochondrial activity [54]. BRAFi-induced increase in mitochondrial ROS can lead to a proliferative advantage, due to the involvement of ROS in amplifying proliferative signals, and to a higher sensitivity to pro-oxidants. Also, BRAFi-resistant cells show higher levels of ROS, becoming more prone to apoptosis induced by pro-oxidants. We know that when ROS exceed a certain threshold in the cells, they can directly trigger cell death [55]. Consistently, Elesclomol, a drug that induces oxidative stress, promotes cell apoptosis [56]. Likewise, Honokiol (HKL), a well-tolerated inhibitor of complexes I, II and V of the ETC, which also increases ROS production, disrupts mitochondrial function decreasing ATP levels. The consequence is mitochondria fusion and cell cycle arrest, with induction of apoptosis in drug-resistant tumor cells [57]. ROS release can also be induced by several mitochondrial ion channel inhibitors [58]. In a recent paper, Bauer and colleagues showed that the potassium channel inhibitor TRAM-34 is highly effective in combination with BRAFi and that the combination BRAFi/TRAM-34 is effective in resistant cells [59].

The combination of BRAFi/MEKi with agents targeting OXPHOS is a highly promising therapeutic strategy to enhance the impact of MAPK pathway inhibition, overcoming drug resistance [52,53,60] (Fig. 1). Several drugs increase the efficacy of MAPKi to induce cell death in melanoma by acting on mitochondrial bioenergetics of tumor cells. Examples are the HSP90 inhibitor Gamitrinib [53], the nonsteroidal anti-inflammatory drugs (NSAID) diclofenac and lumiracoxib [34] and the mitochondrial complex I inhibitor, phenformin [61].

Recently, also the glutamine pathway emerged as a possible metabolic reprogramming strategy in melanoma resistant to targeted therapies [62]. In fact, BRAFi-resistant melanoma cells increase uptake of glutamine and show overexpression of glutaminase (GLS). The mechanisms that drive this switch from glucose utilization to glutamine remain unclear, but treatment with GLS inhibitors re-sensitizes resistant cells to BRAFi [62] and also to the chemotherapeutic drug temozolomide (TMZ) [63]. Consistently, high-OXPHOS melanoma could be supported by glutamine and fatty acid oxidation, via PGC1α axis as demonstrated also in other cancer types [64].

3. NAD^+ metabolism: bioenergetics and signaling

NAD^+ is an essential redox co-factor in energy metabolism and a substrate of a number of NAD^+-metabolizing enzymes [36,65–68].

Metabolic alterations of cancer cells require increased amounts of NAD^+, mainly generated through NAMPT activity [37,39]. Due to the central role of NAD^+ in important cell signaling pathways, NAD^+-dependent processes have emerged as highly promising targets for cancer therapy [37,69–71].

3.1. NAD^+ in cancer metabolism and signaling

As mentioned above, most cancer cells use aerobic glycolysis to fuel their growth. During glycolysis, NAD^+ is used by glyceraldehyde phosphate dehydrogenase (GAPDH) and LDH. In this process, GAPDH requires two molecules of NAD^+ per molecule of glucose to oxidize glyceraldehyde-3-phosphate to 1,3-biphosphoglycerate. LDH catalyzes the interconversion of pyruvate and lactate with concomitant interconversion of NADH and NAD^+. It converts pyruvate, the final product of glycolysis, to lactate in condition of low oxygen tension or in cancer aerobic glycolysis [25,72]. Consistently, LDH inhibition alters the cellular balance between NAD^+ and NADH, potentially blocking aerobic glycolysis [72].

For maximal energy, pyruvate is metabolized by the pyruvate dehydrogenase complex (PDC) to form acetylCoA accompanied by NAD^+ reduction to NADH. AcetylCoA can then enter the tricarboxylic acid (TCA) cycle, where NAD^+ equivalents are reduced to NADH moieties in several key steps by isocitrate dehydrogenase (IDH), oxoglutarate dehydrogenase (OGD) and malate dehydrogenase (MDH) [69].

IDH catalyzes the oxidative decarboxylation of isocitrate, producing α-ketoglutarate and CO_2, while converting NAD^+ to NADH. Interestingly, mutation of *IDH1* in cancers modifies IDH1 enzymatic activity, reprogramming metabolite flux and markedly elevating 2-

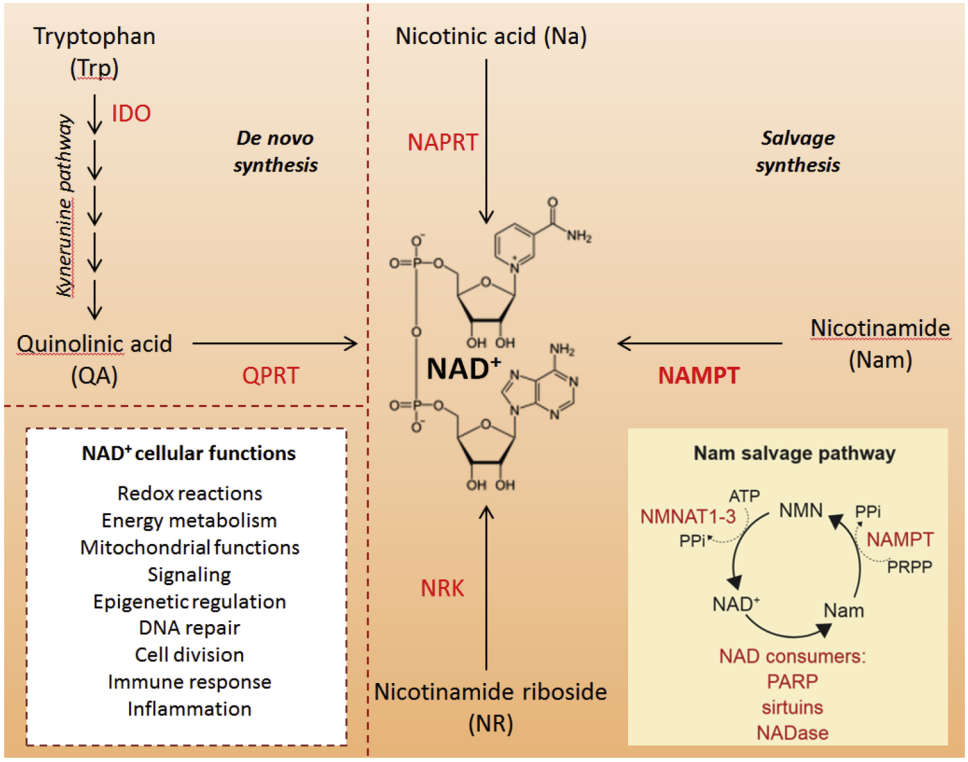

Fig. 2. NAD^+ metabolism: synthesis and functions. NAD^+ can be synthetized *de novo* or through three salvage routes. The rate-limiting enzymes of each biosynthetic pathway are indicated in red. Highlighted in the square on the right are the molecular reactions of NAD^+ synthesis from Nam via NAMPT, an ubiquitous enzyme due to its pivotal role in recycling Nam to NAD^+. In turn, NAD^+ can be used by NAD-consuming enzyme activities that release Nam, making it available for NAD^+ regeneration. In the white square, on the left, the main NAD^+-dependent biological processes.
NAMPT: nicotinamide phosphoribosyltransferase; NAPRT: nicotinate phosphoribosyltransferase; NRK: nicotinamide riboside kinase; IDO: indoleamine 2,3-dioxygenase; QPRT: quinolinate phosphoribosyltransferase; NMN: nicotinamide mononucleotide; NMNAT1-3: nicotinamide mononucleotide adenylltransferases; PRPP: phosphoribosyl pyrophosphate, PPi: pyrophosphate.

hydroxyglutarate (2-HG). Consistently, cancer cells carrying IDH1 mutations are profoundly sensitive to NAD^+ depletion through NAMPT inhibition [73,74].

In the last part of the oxidative metabolism, mitochondrial ATP production through the ETC requires NADH [69,70,75]. Because the TCA cycle and the ETC require NAD^+ and NADH, respectively, an optimal NAD^+/NADH ratio is needed for efficient mitochondrial metabolism. Therefore, the mechanisms and the subcellular localization of NAD^+ biosynthesis and consumption pathways is receiving increasing attention [65,76–79].

In addition to being critical for energy transduction in metabolic processes, NAD^+ is also a key component in the control of signaling pathways and gene transcription, modulating proliferation, epigenetic gene expression regulation, DNA repair, apoptosis, senescence and lifespan mainly through the activity of poly(ADP-ribose) polymerases (PARPs) and sirtuins (Fig. 2) [66,67]. The activity of sirtuins in particular is intrinsically linked to cellular metabolism [80,81]. For example, SIRT1, the best-known member of the family, can directly deacetylate PGC1α leading to the activation and possibly stabilization of the protein inducing mitochondrial biogenesis genes [65,82]. Both PARPs and sirtuins consume NAD^+ releasing Nam, the substrate of NAMPT, determining a dynamic balance in the synthesis/degradation of this essential molecule [65,69,71].

3.2. NAD^+ biosynthesis: NAMPT is the rate-limiting enzyme in Nam salvage pathway

Under physiologic conditions, total NAD^+ levels in mammalian cells are maintained at 200–500 μM [69]. NAD^+ levels in specific tissue districts may increase, especially during inflammation and cancer [37,83], while they generally decline with age [38,84]. A *de novo* biosynthetic pathway is active in mammals, especially in liver and kidney [85] but also in brain and endocrine tissue, that allows NAD formation via tryptophan catabolism (Trp, Fig. 2). The first reactions of this route, which comprise the so-called kynurenine pathway, lead to the formation of quinolinic acid (QA), which is metabolized by quinolinate phosphoribosyltransferase (QPRT), the rate limiting enzyme of the last steps of *de novo* NAD generation. In other cells and tissues salvage pathways from NAD^+ precursors are dominant. They include Nam, metabolized by NAMPT, nicotinic acid (Na), by nicotinic acid phosphoribosyltransferase (NAPRT), and nicotinamide riboside (NR), by nicotinamide riboside kinases (NRKs) (Fig. 2) [35,36,69].

The central challenge in NAD^+ homeostasis is the successful recycling of Nam, released from NAD^+-consuming processes, back to NAD^+ via NAMPT [65,86]. NAMPT, a homodimeric class type II phosphoribosyltrasferase (EC 2.4.2.12), catalyzes the reaction between Nam and 5-phosphoribosyl-1-pyrophosphate (PRPP) to form nicotinamide mononucleotide (NMN) [87]. NMN is then converted to NAD^+ by nicotinamide nucleotide adenyltransferase (NMNAT1-3), using ATP as the donor of adenylyl moiety [35], as shown in Fig. 2. NAMPT is expressed in all mammalian tissues [88], and *NAMPT* gene deletion in mice is embryonically lethal [89], suggesting the importance of this pathway to regenerate NAD^+.

4. The role of NAMPT in cancer

4.1. NAMPT in cancer: expression and function as metabolic enzyme

Cancer cells are more dependent on NAMPT salvage pathways to quickly restore NAD^+ levels for their survival and proliferation [37,40]. The following is evidence in favor of a role for NAMPT in tumor biology (reviewed in [40,41,90–92] and summarized in Fig. 3):

1) NAMPT is often overexpressed in tumor tissues [including in breast, gastric, pancreatic, colorectal, ovarian, prostate, thyroid and endometrial carcinomas as well as in brain tumors, sarcoma, melanoma and hematological malignancies (recently listed in [40]). In general, there is a direct correlation between NAMPT expression and tumor stage, prognosis and survival;
2) NAMPT is often associated with enhanced acquired resistance to chemotherapeutic agents;
3) NAMPT increases stemness properties of cancer cells [93–95];
4) NAMPT confers invasive features on cancer cells, by regulating epithelial to mesenchymal transition [96,97].

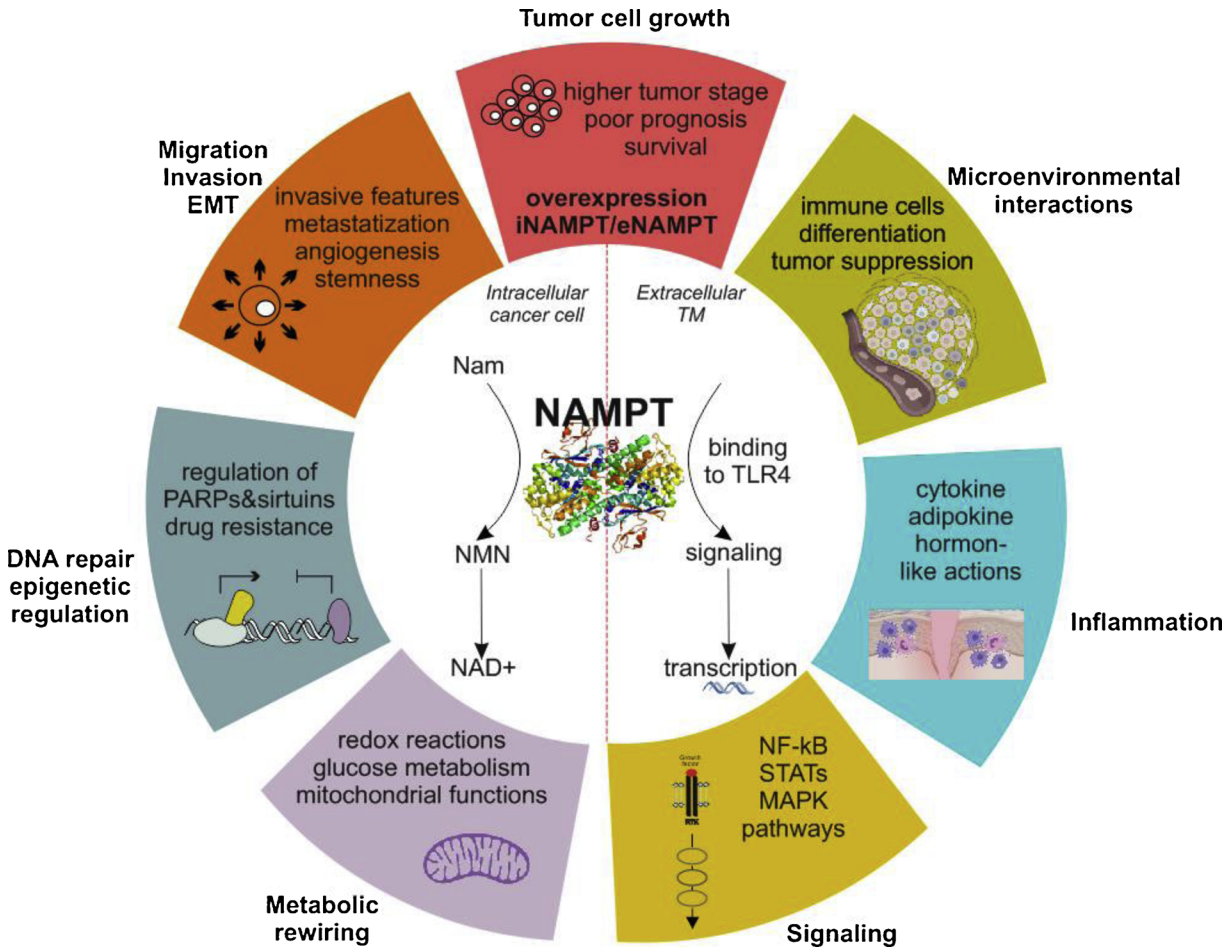

Fig. 3. Hallmarks and functions of iNAMPT and eNAMPT in cancer. NAMPT is a pleiotropic molecule regulating intracellular NAD^+ generation and a cytokine-like protein binding TLR4 in the extracellular space. The up-regulation of NAMPT in cancer affects cell growth and survival, immune responses and inflammation, signaling, redox reactions and metabolic pathways, DNA repair and epigenetic regulation of gene expression, and invasiveness properties of tumor.
In the middle of the Figure the crystal structure of human NAMPT is shown.
TM: tumor microenvironment, EMT: epithelial-mesenchymal transition, Nam: nicotinamide, NMN: nicotinamide mononucleotide, TLR4: toll-like receptor 4.

5) functional data underline a role of NAMPT in the regulation of cancer metabolic reprogramming and – consequently – in the activities of PARPs and sirtuins, affecting DNA repair process and epigenetic regulation.

These roles of NAMPT in tumors emerged mainly from experiments where NAMPT was blocked either via gene knockdown or pharmacological inhibition [98].

4.2. NAMPT in cancer: effects of NAD^+ depletion on cellular metabolism

At the metabolic level, inhibition of NAMPT decreases global cellular NAD^+ levels, altering glycolytic flux, lactate generation, mitochondrial function and ATP levels [70,99] (Fig. 3). In particular, NAMPT inhibition decreases activity of GAPDH and LDH, leading to accumulation of glycolytic intermediates before the step catalyzed by GAPDH and reduces conversion of pyruvate to lactate [99–101]. Furthermore, depletion of NAD^+ decreases glucose uptake and ATP levels both in vitro (lymphoma, pancreatic, ovarian, colon, glioblastoma cancer cells and adipocytes) and in vivo (human ovarian and mammary carcinoma), as reviewed [70]).

Furthermore, NAMPT inhibition causes mitochondrial dysfunction with a drop in mitochondrial potential and oxygen consumption (reviewed in [70]). For example, we recently demonstrated in melanoma model, that treatment with FK866, a NAMPT inhibitor, leads to i) decreased mitochondrial membrane potential and oxygen consumption, forcing mitochondrial swelling; ii) increased mitochondrial ROS; and iii) dramatic decrease of NAD^+ and ATP levels, ultimately inducing cell death [102]. Additionally, FK866 treatment causes a reduction in several TCA cycle intermediates including citrate, malate, fumarate and α-ketoglutarate in colon, breast, glioma, pancreatic cell lines [99]. In tumors carrying IDH mutations, which are highly sensitive to NAD^+ depletion [73], the combination of NAMPT and proteasome inhibitors induces a synergistic effects in metabolic disruption [103].

4.3. NAMPT in cancer: an extracellular cytokine

NAMPT is also present in the extracellular environment, where it can be considered as an immunomodulatory agent and an inflammatory mediator binding Toll-like receptor 4 (TLR4) [104,105]. The original description of eNAMPT is that of a soluble factor secreted by pre-B-cells, promoting colony formation synergizing with stem-cell factor and IL-7 [106]. As a result of these studies, eNAMPT was recognized as a cytokine and, later on, as an adipokine, called visfatin, because it was thought to be preferentially secreted by visceral adipose tissue [107]. It is now clear that eNAMPT can be released by several cell types, and its secretion increased in a variety of acute and chronic inflammatory states, including sepsis, acute lung injury, rheumatoid arthritis, inflammatory bowel disease, inflammatory bone disease, myocardial infarction/atherosclerosis and cancer [40,105,108]. Serum eNampt was

reported as a cancer biomarker, useful in the monitoring of certain malignancies [39,40,108]. Evidence, summarized in Fig. 3, supporting a role of eNAMPT in tumor progression is:

1) pro-inflammatory cytokine, activating signaling pathways such as nuclear factor NF-KB, MAPK and STAT3 and potentiating secretion of other cytokines, including IL-1α, IL-1β, IL-8, IL-6 and tumor necrosis factor- α (TNF-α), linking chronic inflammation with carcinogenesis [109,110];
2) pro-angiogenetic factor promoting expression of vascular endothelial growth factor (VEGF) through MAPK, phosphoinositide 3 kinases (PI3Ks)/Akt and STAT3 pathways [111,112];
3) pro-invasive and metastatic promoter stimulating matrix metalloproteinases (MMPs) activity and modulating epithelial-mesenchymal transition (EMT) via transforming growth factor-β (TGF-β) [96,111];
4) metabolic mediator in tumor microenvironment, by modulating glucose/insulin homeostasis acting on β pancreatic cell activity [89];
5) hormonal mediator in certain types of cancer [40,108,113];
6) immunosuppressive factor acting mainly on myeloid cell populations [114] by promoting their differentiation and polarization in tumor-supportive cells including TAMs [115] and myeloid-derived suppressor cells (MDSCs) [116].

The open question is whether the cytokine-like actions of eNAMPT are related to (or independent from) its enzymatic activity. The enzymatic function of eNAMPT is still under debate. Evidence showed that two NAMPT mutants generated to lack enzymatic activity (H247E and H247A) were able to activate signaling pathways and stimulate cytokine production including IL-8, IL-6, as effectively as wild-type NAMPT [115,117,118]. However, other studies demonstrated the role of NAMPT enzymatic activity in inflammation [119], mainly through modulation of SIRT1 [120]. In addition, SIRT1 activity can directly regulate NAMPT secretion [121].

5. NAMPT functions in melanoma

In 2011 Wachsman et al. proposed 17-gene classifier useful to distinguish both in situ and invasive melanoma from nevi, which included NAMPT [122]. The authors proposed these identified genes as potential biomarkers for accurate diagnosis of pigmented lesions. However, in that paper, the analysis was based only on GeneChip microarray, using RNA samples, without protein expression confirmation. In 2012, Maldi et al. demonstrated over-expression of NAMPT in melanoma, compared to benign lesions and to melanocytes [123]. Zhao et al. also observed increased NAMPT activity in human melanoma cells compared to melanocytes [124]. Grolla et al. later showed that melanoma cell lines, or melanoma xenografts, actively secrete eNAMPT, with autocrine effects including activation of MAPK, AKT, NF-kB pathways and increase in colony-formation in anchorage-independent conditions [125]. eNAMPT also induces M1 polarization in human monocytes derived from healthy donors [125].

Our group recently confirmed the overexpression of NAMPT and a marked increase in NAD^+ levels in melanoma, secondary to BRAF oncogenic signaling, with the strongest up-regulation in BRAF-mutated melanoma cell lines and patients resistant to BRAFi, linking this enzyme to the onset of BRAFi resistance [102]. The NAD^+ boost derived from NAMPT over-expression drives metabolic adaptation, observed after chronic exposure to BRAFi. Furthermore, we found that treatment of melanoma cells with NAMPTi depleted NAD^+, inducing mitochondrial stress, cell cycle arrest and ultimately apoptosis [102]. Consistently, NAMPTi were highly effective in the treatment of melanoma xenografts, highlighting NAMPT as an actionable target for melanoma patients with BRAF mutations. Furthermore, eNAMPT could be dosed in patient plasma where it correlated with disease burden, response to therapy and overall survival [126].

Ohanna et al. showed that NAMPT expression induces transcriptomic and epigenetic reshuffling that steer melanoma cells toward an invasive phenotype associated with resistance to targeted therapies and immunotherapies [127]. A very recent paper highlights a function of NAMPT as a critical molecule in priming pro-tumor functions of tumor-associated neutrophils (TANs) in melanoma [128], including tumorigenic conversion of TANs and their pro-angiogenic switch [128].

Overall, these data confirm that NAMPT plays a central role in phenotypic plasticity of melanoma, becoming a rational therapeutic target for patients with this disease.

6. Combination therapy in melanoma: NAMPT as a new therapeutic target

Metabolic rewiring in metastatic melanoma is a therapeutic opportunity that should be considered, particularly for patients at risk of developing resistance to MAPK/ERK pathway inhibitors [33,44,60,98].

Given the existence of diverse resistance mechanisms to MAPK/ERK pathway inhibition (as described), the identification of NAD^+, as a common essential cofactor needed to support metabolic reprogramming [102], may represent a valid new therapeutic target alone or in combination with MAPK inhibitors, immunotherapy and/or other metabolic inhibitors [70]. Targeting NAMPT dramatically reduces NAD^+ levels, affecting both glycolytic and mitochondrial capacity. NAMPT inhibitors not only kill melanoma cells *per se,* but also sensitize melanoma cells exposed to BRAFi and MEKi, preventing resistance [102,127]. Because of the interest in NAMPT as a potential anti-cancer target, several inhibitors are already on the market, including FK866/APO866, CHS-828 (GMX1778) and the pro-drug GMX1777, GNE-618, the dual PAK4/NAMPT inhibitor (KPT-9274), among others [129–134]. These inhibitors have been studied in cancer cell lines and animal models showing cytotoxicity and tumor regression [40,41]. Despite these important results in vitro and in vivo, phase I clinical trials in advanced solid tumors and leukemia showed no objective tumor remission and toxicity [135,136]. These negative results could be due to 1) the wrong selection of tumors, incompletely dependent from NAMPT activity: it is known the activation of compensatory mechanisms to overcome NAMPT inhibition, for example the expression of NAPRT [137–141], QPRT [142] and NRK [71]; 2) pharmacokinetics and pharmacodynamics of the inhibitors; 3) acquisition of resistance [143–145]. These mechanisms should be addressed to design better therapeutic strategies that deplete NAD^+ in cancer cells achieving better efficacy for these therapeutic options in clinical settings. In any case, all these findings show that NAMPT inhibition makes cancer cells susceptible to drugs that further decrease energy. Therefore, combination of NAMPT inhibition with treatments targeting energy production and oncogenic pathways would likely result in increased cytotoxicity of cancer cells.

7. Current challenges and perspectives

By combining indications on the role of metabolic rewiring in supporting melanoma survival in response to BRAFi and MEKi and indications on the effects of NAD^+ depletion through NAMPT inhibition, it would seem logical to design therapeutic strategies associating these two different inhibitors. Our preclinical findings support this hypothesis [102]. An alternative approach could be to combine NAMPT inhibitors with OXPHOS antagonists (Fig. 4). Future clinical trials will tell the potential of these approaches.

A second aspect to be considered concerns the role of eNAMPT, which appears linked to immunosuppression. Novel mAbs against eNAMPT are being produced: their use in immunocompetent mouse models will be essential to determine the role of eNAMPT [146].

It may also be worth exploring possible synergism between eNAMPT blockade or eNAMPT receptor interference and immunotherapy with checkpoint inhibitors (Fig. 4).

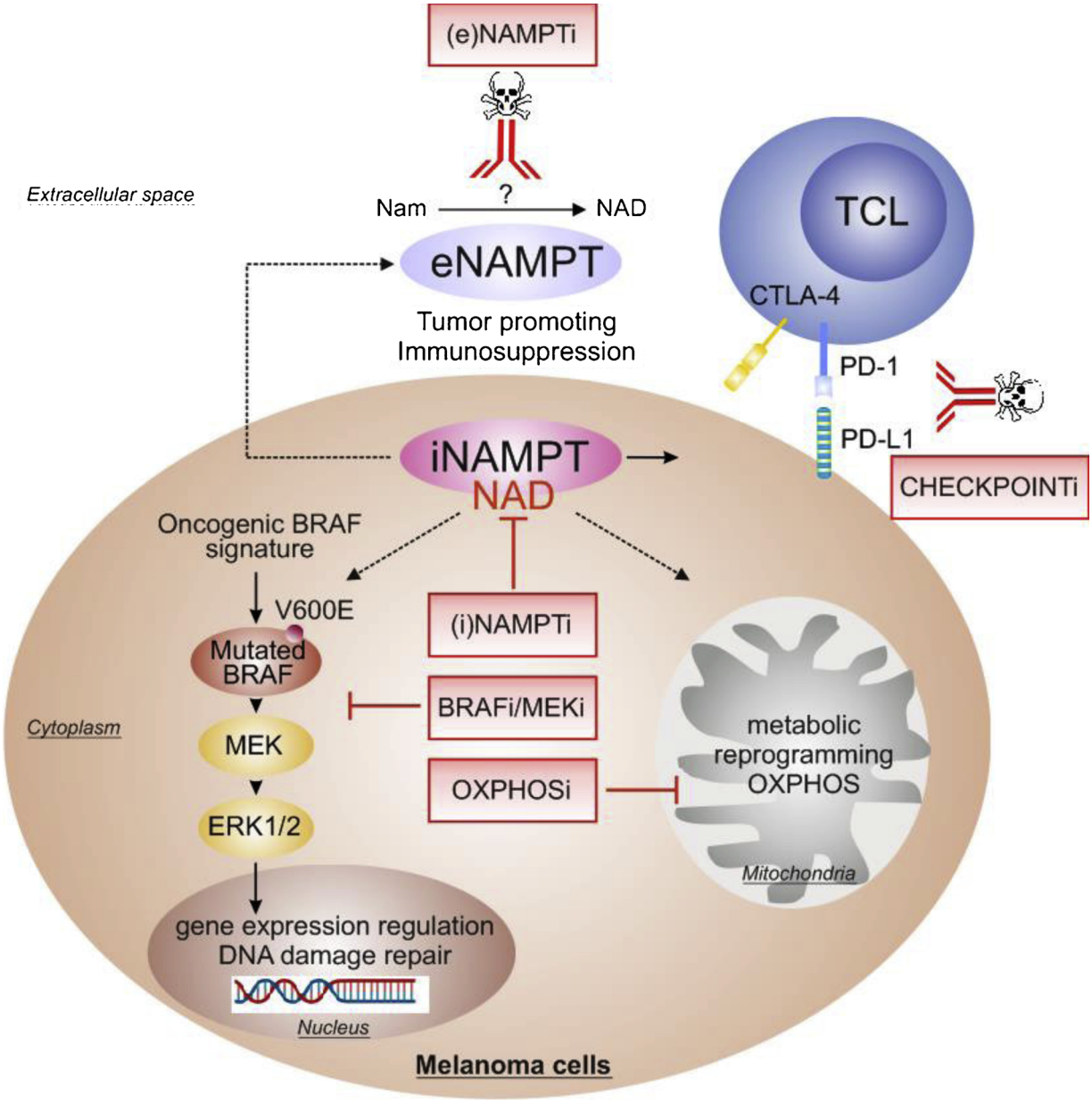

Fig. 4. Therapeutic strategies in melanoma: NAMPT as a new target. Overview of possible new combination therapeutic strategies in melanoma, including i) an intracellular targeting at multiple levels: NAMPT inhibitors (i) to deplete cellular NAD^+, BRAFi/MEKi to block oncogenic signaling, OXPHOSi to contrast metabolic reprogramming; ii) an extracellular targeting including well known immune CHECKPOINTi to block interaction between melanoma and T cell and antibodies anti-eNAMPT to reduce the extracellular function of eNAMPT in the tumor microenvironment.
CTLA-4: T-lymphocyte antigen-4, PD-1: programmed cell death-1, PD-L1: programmed cell death ligand-1

Lastly, it will be essential to correctly identify tumors that may be responsive to NAMPT blockade, both at the intracellular and extracellular level.

The next few years will tell whether this cytokine turned enzyme will finally fulfill its promises of marker and target for melanoma patients.

Conflict of interests

The authors have declared that no conflict of interest exists

Acknowledgements

This work was supported by the Italian Institute for Genomic Medicine Institutional funds, by Gilead Fellowship program 2018, by the Ministry of Education University and Research-MIUR, PRIN Project 2017CBNCYT and Progetto strategico di Eccellenza Dipartimentale#D15D18000410001 (the latter awarded to the Dept. of Medical Sciences, University of Turin) and ITN INTEGRATA program (grant agreeement 813284).

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