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Nicotinic acid: A case for a vitamin that moonlights for cancer?

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Nicotinic acid (Na) and its amide, nicotinamide, are the most common forms of vitamin B3, also known as niacin.[1] Severe niacin deficiency results in a clinical condition termed pellagra, which, in turn, is defined by the presence of dermatitis, diarrhea and dementia. Pellagra is now effectively prevented through dietary advice to vulnerable groups and/or by commonly available vitamin supplements. Pharmacologic doses of nicotinic acid (usually in the range of 1–3 g/d) are also used in clinical practice to treat dyslipidemia.

Na and nicotinamide are both precursors of nicotinamide adenine dinucleotide (NAD^+), which, in turn, acts as a coenzyme in hundreds of intracellular redox reactions, but also as a substrate of NAD^+-degrading enzymes, such as poly (ADP-ribose) polymerases (PARPs), CD38 and sirtuins.[1] NAD^+ degradation by PARP1/2 allows for PAR production and DNA repair, unless DNA damage is excessive, in which case PARP1/2 activity rather leads to cell demise by apoptosis.[2] In addition, other NAD^+-utilizing enzymes, such as sirtuins (e.g. SIRT6), also play roles in DNA repair and have tumor suppressive effects.[3] Consistent with these notions, studies show that in animal models, niacin deficiency leads to delayed DNA excision repair, accumulation of single and double strand breaks, impaired cell cycle arrest and apoptosis, and to an increased predisposition to cancer development.[2] Thus, overall, there is little doubt that niacin is important for genomic stability and, possibly, to reduce cancer risk.[2]

However, a recent study by our group showed another side of Na and suggested that defined types of cancer could actually use this vitamin to their advantage.[4] We found the gene encoding nicotinic acid phosphoribosyltransferase (NAPRT), the rate limiting enzyme for Na conversion to NAD^+, to be amplified and overexpressed in a subset of common types of cancer, including ovarian, pancreatic, prostate, and breast cancer (with *NAPRT* amplification being present in 33%, 32%, 27% and 20% of the cases, respectively).[5] These types of cancer are also those that most frequently exhibit defects in their homologous recombination DNA repair (HRR), a condition termed BRCAness.[6] Tumors with defective HRR are critically reliant on PARP activity to avoid catastrophic DNA damage.[6] Thus, we hypothesized that such neoplasms may well use NAPRT-mediated Na conversion to NAD^+ to fuel their DNA repair machinery, including PARP itself. Consistent with this hypothesis, in epithelial ovarian cancer, we found a correlation between high-NAPRT expression and a BRCAness gene expression profile. We were able to show reduced PAR levels in NAPRT silenced Capan-1 cells (a model of BRCA2-deficient cancer cells) and to demonstrate a role for NAPRT in the DNA repair process of this cell line. Thus, it seems plausible that at least in some cancer with defective HRR,[6] *NAPRT* amplification and its consequent overexpression could become positively selected to ensure that sufficient NAD^+ is produced to support PARP activity (Figure 1). Interestingly, we found that NAPRT-overexpressing cancer cells ultimately also become reliant on NAPRT for the maintenance of their mitochondrial NAD^+ pool and, consequently, for ATP synthesis, protein synthesis and for the regulation of their cell size.[4] In addition, a high NAPRT expression was also found to confer resistance to inhibitors of nicotinamide phosphoribosyltransferase (NAMPT), a second NAD^+-producing enzyme and an emerging target for treating cancer.

Our study opened the question whether temporarily restricting Na intake and possibly also preventing Na production by the gut microbial flora (e.g., by antibiotics), could be a viable strategy to increase the activity of NAMPT inhibitors, chemotherapeutics, and of PARP inhibitors. Chemical NAPRT inhibitors are also available,[7] and, in our hands, one of these, 2-hydroxynicotinic acid (2-HNa), effectively recreated the effects of NAPRT silencing, including sensitizing cancer cells to NAMPT inhibitors, both *in vitro* and *in vivo*.[4] Thus, NAPRT inhibitors could in principle be adopted as an alternative to Na-deficient

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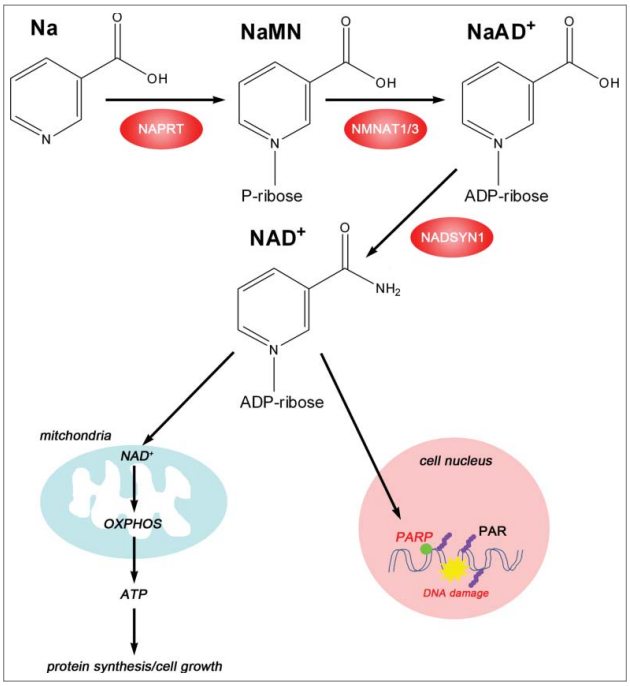

Figure 1. Biosynthetic pathway of NAD^+ production starting from Na. Nicotinic acid (Na) is converted to NAD^+ through the 3-step Preiss-Handler pathway. NAPRT catalyzes the formation of nicotinic acid mononucleotide (NaMN) by adding a 5-phosphoribose group (P-ribose) from 5-phosphoribosyl-1-pyrophosphate to Na. NaMN is converted to nicotinic acid adenine dinucleotide ($NaAD^+$) by nicotinamide mononucleotide adenylyltransferase 1/3 (NMNAT1–3). Finally, NAD^+ synthase 1 (NADSYN1) converts $NaAD^+$ to NAD^+. The *NAPRT* gene is amplified and overexpressed in a subset of tumors, including ovarian, breast, pancreatic and prostate cancer. NAPRT-derived NAD^+ supports the activity of DNA repair enzymes, such as PARP1/2, which, in turn, may be especially important in cancer cells with defective homologous recombination DNA repair to avoid catastrophic DNA damage. In addition, NAPRT-mediated NAD^+ production turns out to be especially important for replenishing the mitochondrial NAD^+ stores, for promoting OXPHOS, ATP synthesis, and protein synthesis and, ultimately, for regulating cell size. PAR: poly (ADP-ribose).

diets as a means to enhance the activity of NAMPT inhibitors and of other anticancer drugs. Clearly, potential advantages of combining NAPRT inhibitors or a Na-deficient diet with other therapies in terms of increased anticancer activity should ideally not be at the cost of an enhanced treatment toxicity and/or of an increased risk of secondary cancer.[2] Selecting the appropriate types of cancer for clinical studies (e.g., tumors in advanced disease stage with high NAPRT expression with or without BRCA1/2 mutations) is probably going to be key for a successful assessment of this type of approach.

Disclosure of potential conflicts of interest

The authors have no potential conflict of interest to disclose.

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