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REVIEW

Effects of vitamin B6 metabolism on oncogenesis, tumor progression and therapeutic responses

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Pyridoxal-5′-phosphate (PLP), the bioactive form of vitamin B6, reportedly functions as a prosthetic group for >4% of classified enzymatic activities of the cell. It is therefore not surprising that alterations of vitamin B6 metabolism have been associated with multiple human diseases. As a striking example, mutations in the gene coding for antiquitin, an evolutionary old aldehyde dehydrogenase, result in pyridoxine-dependent seizures, owing to the accumulation of a metabolic intermediate that inactivates PLP. In addition, PLP is required for the catabolism of homocysteine by transsulfuration. Hence, reduced circulating levels of B6 vitamers (including PLP as well as its major precursor pyridoxine) are frequently paralleled by hyperhomocysteinemia, a condition that has been associated with an increased risk for multiple cardiovascular diseases. During the past 30 years, an intense wave of clinical investigation has attempted to dissect the putative links between vitamin B6 and cancer. Thus, high circulating levels of vitamin B6, as such or as they reflected reduced amounts of circulating homocysteine, have been associated with improved disease outcome in patients bearing a wide range of hematological and solid neoplasms. More recently, the proficiency of vitamin B6 metabolism has been shown to modulate the adaptive response of tumor cells to a plethora of physical and chemical stress conditions. Moreover, elevated levels of pyridoxal kinase (PDXK), the enzyme that converts pyridoxine and other vitamin B6 precursors into PLP, have been shown to constitute a good, therapy-independent prognostic marker in patients affected by non-small cell lung carcinoma (NSCLC). Here, we will discuss the clinical relevance of vitamin B6 metabolism as a prognostic factor in cancer patients.

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INTRODUCTION

Pyridoxal-5′-phosphate (PLP) constitutes the bioactive form of vitamin B6, a water-soluble vitamin originally identified in the 1930s for its capacity to resolve dermatitis acrodynia in rats.[1] Bioactive vitamin B6 is generated intracellularly by pyridoxal kinase (PDXK), which catalyzes the conversion of three non-phosphorylated vitamin B6 precursors, that is, pyridoxine (PN), pyridoxamine (PM) and pyridoxal (PL), into their phosphorylated counterparts, that is, pyridoxine-5′-phosphate (PNP), pyridoxamine-5′-phosphate (PMP) and PLP, respectively. The dephosphorylation of PNP, PMP and PLP is mediated by the PDXK-antagonistic enzyme pyridoxal phosphatase (PDXP). In addition, PN, PM and PL as well as their phosphorylated forms can be converted into each other thanks to the activity of PMP oxidase. In humans, PLP catabolism mainly proceeds via the aldehyde oxidase 1-mediated generation of 4-pyridoxic acid, which is excreted in urine (Figure 1).[2]

Vitamin B6 is abundant in food, both in its non-phosphorylated forms (which are absorbed in the jejunum and ileum via passive diffusion) and in its phosphorylated variants, whose absorption obligatorily ensues a dephosphorylation reaction catalyzed by a membrane-bound intestinal alkaline phosphatase.[3] The major sources of vitamin B6 include whole grain, nuts, vegetables and bananas, which are particularly rich in PN, as well as raw milk and distinct types of meat, which contain high amounts of PM and PL.[4]

According to the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (http://www.chem.qmul.ac.uk/iubmb/enzyme/),[5] >4% of all classified enzymatic activities rely on PLP as an obligate prosthetic group. Thus, PLP appears to be required not only for all transamination reactions but also for multiple instances of transsulfuration, phosphorylation, deamination and decarboxylation.[2] Prominent metabolic circuitries in which vitamin B6 exerts a critical co-enzymatic activity encompass, but are not limited to: (1) the synthesis and catabolism of standard and nonstandard amino acids, including homocysteine;[6,7] (2) the conversion of amino acids into bioactive amines, including histamine (synthesized from histidine by histidine decarboxylase), serotonin (synthesized from the tryptophan derivative 5-hydroxy-L-tryptophan by aromatic L-amino acid decarboxylase), γ-aminobutyric acid (synthesized from glutamate by glutamate decarboxylase) and dopamine (synthesized from the tyrosine derivative L-3,4-dihydroxyphenylalanine, DOPA, by aromatic L-amino acid decarboxylase);[2,8] (3) glycogenolysis, PLP being an obligate cofactor for the rate-limiting reaction catalyzed by glycogen

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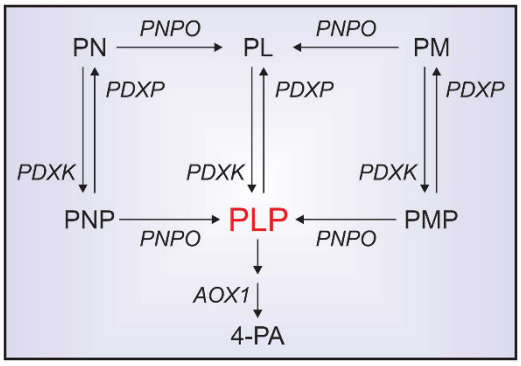

Figure 1. Schematic metabolism of vitamin B6 in humans. Both the non-phosphorylated (that is, pyridoxal, PL; pyridoxine, PN; pyridoxamine, PM) and the phosphorylated (that is, pyridoxal-5′-phosphate, PLP; pyridoxine-5′-phosphate, PNP; pyridoxamine-5′-phosphate, PMP) variants of vitamin B6 are relatively abundant in food. While the former are readily absorbed in the jejunum and ileum via passive diffusion, the intestinal absorption of the latter involves a dephosphorylation reaction catalyzed by a membrane-bound alkaline phosphatase. In the cytoplasm, PLP is generated by the phosphorylation of PL by pyridoxal kinase (PDXK), which also catalyzes the conversion of and PN and PM into their phosphorylated counterparts. The reverse of this reaction, that is, the dephosphorylation of PLP, PNP and PMP, is catalyzed by pyridoxal phosphatase (PDXP). Moreover, both non-phosphorylated and phosphorylated B6 vitamers can be converted into each other by PMP oxidase (PNPO). In humans, the catabolism of PLP mainly proceeds via the aldehyde oxidase 1 (AOX1)-mediated production of 4-pyridoxic acid (4-PA), which is excreted in urine.

phosphorylase;[9] (4) the synthesis and function of hemoglobin, first, as PLP assists the enzymatic functions of δ-aminolevulinic acid synthase (an enzyme that participates in heme biosynthesis)[10] and, second, as PLP binds to two sites on hemoglobin, hence enhancing oxygen binding;[11] and (5) sphingolipid metabolism, as PLP is required for the activity of both serine C-palmitoyltransferase and sphingosine-1-phosphate lyase, which *de facto* constitute the entry and exit gates of this metabolic module.[12]

Altogether, these observations indicate that vitamin B6 plays a critical role in multiple facets of cellular and organismal metabolism. Accordingly, dietary issues as well as molecular defects influencing the vitamin B6 status have been associated with a number of clinically relevant diseases. Dietary vitamin B6 deficiency is rare and most often represents a pediatric condition manifesting with cheilitis (inflammation of the lips), conjunctivitis and neurological symptoms, including irritability and seizures.[13] Alternatively, a decreased availability of vitamin B6 can stem from (1) mutually inactivating interactions with isoniazid, a drug commonly used for the prevention and treatment of tuberculosis; (2) celiac disease, leading to the intestinal malabsorption of dietary vitamin B6; (3) renal dialysis, which reportedly results in an increased loss of B6 vitamers from the circulation,[13] and alcoholism, as alcohol stimulates vitamin B6 urinary excretion.[14] Finally, loss-of-function mutations in the gene coding for antiquitin (*ALDH7A1*, for aldehyde dehydrogenase 7 family, member A1), an evolutionary old aldehyde dehydrogenase, have been shown to account for pyridoxine-dependent seizures.[15] In this setting, the accumulation of one of the substrates of antiquitin, namely Δ^1-piperideine-6-carboxylate, results in the inactivation of PLP upon the nonenzymatic formation of a Knoevenagel condensation product.[15]

According to the Food and Nutrition Board of the Institute of Medicine of the National Academies (Washington, DC, USA), the recommended dietary allowances of vitamin B6 (comprising PN, PM, PL, PNP, PMP and PLP) for a healthy adult vary between 1.3 and 1.7 mg/day, depending on sex and age range. The same organization has set a maximum intake limit for healthy adults to 100 mg/day, while specifying that no adverse effects associated with dietary vitamin B6 have ever been described (http://www.iom.edu/~/media/Files/Activity%20Files/Nutrition/DRIs/DRI_Vitamins.ashx). This said, a few instances of vitamin B6 abuse have been reported, mainly manifesting with moderate dermatological problems and moderate/severe neurological disorders.[16–19] Among these, one notable case is represented by a 75-year-old male patient who self-administered 9.6 g PN/day for 3 years. At admission, this patient was bound to the wheel chair, exhibited a remarkably yellowish-brown skin, and manifested severe neurological symptoms including, but not limited to, symmetric tetraparesis, pronounced muscle weakness and reduced/absent deep-tendon reflexes. Electrophysiological studies demonstrated a sensorimotor mixed axonal-demyelinating polyneuropathy and circulating PN levels were found to be ~1850 μg/l (normal range: 40–120 μg/l). Upon PN discontinuation, the clinical and electrophysiological conditions of the patient improved very rapidly, the color of his skin progressively normalized and he was able to walk independently in ~1 year, demonstrating that symptoms indeed were caused by vitamin B6 abuse.[17] This report suggests that even the prolonged intake of very high doses of vitamin B6 may not cause any permanent and life-threatening adverse effects.

In the subsequent sections, we will discuss several aspects of the interrelationship between the metabolism of vitamin B6 and malignant cells, which often exhibit an extensive metabolic rewiring,[20–24] with particular emphasis on the prognostic value of parameters that reflect the status of the vitamin B6 system in cancer patients.

PRECLINICAL OBSERVATIONS

Starting from the 1950s, the possibility that alterations in the bioavailability of vitamin B6 might influence oncogenesis and tumor progression has been extensively investigated in preclinical tumor models. The vast majority of such early studies, most of which were performed in immunodeficient rodents, concluded that systemic vitamin B6 deficiency exerts consistent antineoplastic effects,[25–29] most likely as highly proliferating malignant cells are characterized by an intense metabolic activity that requires adequate levels of bioactive PLP.[30–35] These observations ignited an intense experimental effort aimed at the identification and characterization of vitamin B6 antagonists with potential antineoplastic applications.[36–41] Unfortunately, none of these agents has ever exhibited a preclinical activity profile compatible with clinical development. Moreover, a few groups reported that vitamin B6 deficiency may promote, rather than inhibit, tumor development, at least in some settings.[42] Nevertheless, until the early 1980s it was commonly believed that restricting the bioavailability of vitamin B6 would constitute a promising therapeutic approach against cancer.[43,44]

The idea that—at least in some settings—vitamin B6 may exert *bona fide* antineoplastic effects begun to be taken into consideration in the 1980s, following four lines of evidence. First, the exogenous administration of B6 vitamers, most often PN or PL, was shown to arrest the growth of (or kill) distinct cancer cell lines *in vitro*, including rat hepatoma[45] as well as human and murine melanoma cells.[46–48] Second, the injection or dietary supplementation of B6 vitamers to tumor-bearing mice was reported to suppress neoplastic growth, *in vivo*.[49–52] Third, tumor incidence and/or progression was found to be increased in multiple models of vitamin B6 deficiency *in vivo*,[50,53] leading to the hypothesis that vitamin B6 is required for optimal immune responses.[50,54–56] Fourth, an inverse correlation between the progression of experimental hepatomas and the intratumoral levels and

bioavailability of PLP was reported.[57,58] In addition, studies of the metabolic transformation of labeled PN by hepatoma cells growing in rats led to the identification of a novel vitamin B6 metabolite, adenosine-N6-diethylthioether N1-pyridoximine 5′-phosphate.[59]

Since then, additional reports based on *in vitro* and *in vivo* observations have been published to support the hypotheses that (1) vitamin B6 would *per se* promote antiproliferative or cytotoxic effects on cancer cells,[60–65] and (2) vitamin B6 would synergize with other micronutrients,[66,67] tumor necrosis factor stimulation[68] and hypertriglyceridemia[69] in exerting antineoplastic effects. In the late 1990s, Rosenthal[70] reported prominent antitumor effects for L-canaline, a structural analog of L-ornithine that covalently inactivates PLP-dependent enzymes. A couple of years later, however, the antitumor activity of L-canavanine, a precursor of L-canaline, was shown to be independent of its intracellular conversion into L-canaline, casting doubts on the true relevance of Rosenthal's findings.[71] Later on, the interest on the potential antineoplastic effects provided by vitamin B6 antagonists dropped and most of the preclinical studies on vitamin B6 aimed at testing its potential cytoprotective effects,[72–75] and hence whether it might be employed to limit the adverse effects of radio- and chemotherapy.[76,77]

In 2012, our group has demonstrated that PN synergizes with a large panel of chemotherapeutics (including the DNA-damaging agent cisplatin) as well as several chemotherapy-unrelated stress conditions (for example, hyperthermia, hypoxia, nutrient deprivation, irradiation, inhibition of the respiratory chain and endoplasmic reticulum stress) in the killing of a large panel of cancer cells *in vitro*.[78] In addition, we have shown that the intratumoral injection of PN exacerbates the antineoplastic effects of cisplatin *in vivo*, in both syngenic, immunocompetent and xenogenic, immunodeficient mouse models of non-small cell lung carcinoma (NSCLC).[78] Of note, the ability of PN to potentiate the cytotoxic response of human NSCLC cells to cisplatin appears to rely—at least in part—on a pharmacokinetic effect, as PN has been found to stimulate the intracellular accumulation of cisplatin.[79]

Taken together, these preclinical observations suggest that vitamin B6 metabolism plays a critical role not only during the initial phases of oncogenesis and tumor progression but also when malignant cells must face adverse conditions that are associated with the development of large tumor masses (for example, hypoxia, nutrient shortage) as well as chemotherapeutic challenges.

EARLY CLINICAL FINDINGS

Initially, the putative clinical relevance of vitamin B6 metabolism in cancer patients was investigated following three major hypotheses: (1) translating early preclinical findings (see above), that vitamin B6 deficiency would exert antineoplastic effects;[80,81] (2) along similar lines of reasoning, that tumor-bearing individuals would exhibit lower levels of bioavailable (circulating) B6 vitamers than healthy subjects;[82–85] and (3) that adenosine-N6-diethylthioether N1-pyridoximine 5′-phosphate might constitute a *bona fide* circulating marker for tumor progression in humans.[86,87]

As early as in late 1960s, driven by encouraging results obtained with a single patient affected by metastatic bronchial adenoma,[80] Gailani *et al*.[81] investigated in a small clinical trial the antineoplastic effects of vitamin B6 deficiency. To this aim, a total of 26 patients affected by advanced neoplasms were enrolled and either subjected to a vitamin B6-deficient diet for 10–80 days or administered the B6 antagonist 4-deoxypyridoxine for 6–46 days. In spite of ample biochemical evidence for vitamin B6 depletion, which was also accompanied by neurologic and dermatological side effects, the authors were unable to document any antineoplastic activity.[81] To the best of our knowledge, this was the last study on the anticancer effects of vitamin B6 depletion in humans to be published.

The hypothesis that tumor progression would coincide with significant imbalances in the systemic metabolism of vitamin B6 has been extensively tested starting from the 1970s. Thus, the circulating levels of PLP and/or the urinary excretion of 4-pyridoxic acid have been found to be altered in patients affected by multiple types of hematological and solid tumors, including—but not limited to—acute lymphoblastic and nonlymphoblastic leukemia,[85] breast carcinoma,[82] bladder cancer[88] and cervical carcinoma.[83] As in some studies circulating PLP levels did not correlate with tumor stage and/or burden but did so with reported dietary vitamin B6 intake,[85] one of the hypotheses put forward was that cancer patients would exhibit vitamin B6 deficiency mainly because of a suboptimal nutritional status.[85] Although this appears as a plausible explanation, it does not entirely account for cancer-associated vitamin B6 deficiency, as elegantly shown in 1997 by Inculet *et al*.[84] In this prospective study, the recommended daily dose (40 mg) of vitamin B6 given on parenteral nutrition to cancer patients failed to elevate circulating levels in 4–40% of cases, and only a few patients manifested some improvement in response to 80 mg vitamin B6 per day.[84]

Thus, factors other than the patient nutritional status must be implicated in the systemic imbalance of vitamin B6 metabolism provoked by cancer. In line with this notion, the vitamin B6 content of neoplastic lesions has been found to not only significantly differ from that of corresponding normal tissues but also to change along with tumor progression.[89] For instance, 24 colon adenocarcinoma samples obtained at surgery or autopsy contained 1.8–3.5-fold higher amounts of vitamin B6 than adjacent, nonneoplastic tissue specimens from the same subjects, whereas vitamin B6 was found to be significantly lower in hepatic metastasis of colorectal carcinoma than in the normal liver.[89] In addition, vitamin B6 metabolism may be considerably influenced by both chemo- and immunotherapy.[90,91] On one hand, vitamin B6 levels probably decrease through subsequent courses of chemotherapy along with a progressive decline in the global nutritional status of patients.[90] On the other hand, immunostimulatory interventions such as the administration of interleukin-2 may promote a drop in circulating vitamin B6 along with the expansion of cells from the immune system, most of which require vitamin B6 for optimal activity.[50,54–56] This notion has been substantiated in multiple clinical scenarios in which the immunological status of immunodeficient cancer patients was consistently ameliorated by the supplementation of PN.[92,93]

In the 1990s, Tryfiates *et al*.[59] investigated the clinical relevance of their preclinical observations, indicating that the conversion of vitamin B6 differs in malignant versus normal cells as well as in tumor-bearing versus healthy rodents. Thus, besides being found in the serum and neoplastic lesions of tumor-bearing rats, adenosine-N6-diethylthioether N1-pyridoximine 5′-phosphate could be detected in cultured human cancer cells as well as in the blood and tumor tissue of cancer patients.[86] The circulating levels of this metabolite were shown to be fourfold higher in cancer patients than in healthy individuals or in subjects affected by nonmalignant diseases.[94] Moreover, adenosine-N6-diethylthioether N1-pyridoximine 5′-phosphate was found to be elevated in patients bearing progressing tumors as compared with individuals whose disease responded to therapy.[87] In spite of these encouraging results and for reasons that we ignore, the possibility of using a derivative of vitamin B6 as a *bona fide* circulating tumor marker has been abandoned.

Nevertheless, these early clinical observations lend support to the notion that oncogenesis and tumor progression cause alterations in the systemic balance of vitamin B6 that reflect both tumor-intrinsic and tumor-extrinsic (including nutritional and immunological) phenomena.

VITAMIN B6 METABOLISM AS A RISK OR PROGNOSTIC BIOMARKER

Along with the first wave of observational clinical studies, a few groups attempted to employ vitamin B6 as a supplement to cancer therapy. For instance, as early as in 1977, Byar and Blackard[95] reported the results of a prospective clinical trial involving 121 superficial bladder cancer patients randomized to receive placebo, systemic PN or topical thiotepa (an alkylating agent). In this study, the percentage of overall tumor recurrence did not differ in a statistically fashion between patients who were allocated to different treatment modalities, unless patients relapsing during the first 10 months or followed up for <10 months were excluded. Only under these conditions, PN (as well as thiotepa) reduced the incidence of recurrence as compared with placebo.[95] Nearly 20 years later, two other groups tested whether PN, alone or as part of a high-dose multi-vitamin cocktail combined with Bacillus Calmette–Guérin (BCG)-based immunotherapy, would influence recurrence in transitional cell carcinoma patients, reporting contrasting outcomes.[96,97] Indeed, whereas in a cohort of 291 patients PN provided no advantages over placebo in terms of time to first recurrence and recurrence rate,[97] high-dose vitamins efficiently ameliorated disease outcome in 65 BCG-treated patients.[96] This said, the relative contribution of PN to the apparent clinical efficacy of high-dose vitamins in bladder cancer patients has never been determined in detail.

More recently, great attention has been attracted by the possibility that dietary vitamin B6 intake, mostly as a determinant of one-carbon metabolism, may influence the overall risk of developing cancer (Table 1). This hypothesis has been investigated in a plethora of distinct, retrospective and prospective, clinical settings. Most of these studies involved the assessment not only of circulating B6 vitamers but also of (1) other parameters linked to one-carbon metabolism, including the plasma levels of folate, methionine and vitamin B12, as well as polymorphisms in genes coding for thymidylate synthase (TS) and methylenetetrahydrofolate reductase (MTHFR),[98] or (2) homocysteine, a nonstandard amino acid that has been associated with an increased risk for cardiovascular diseases.[6]

With two notable exceptions, reporting a positive association between a high dietary intake of vitamin B6 (and folate) and rectal cancer risk among women,[99,100] not less than 60 distinct articles published between 1997 and 2012 demonstrate either no independent association between vitamin B6 intake and the risk of developing various malignancies or a reduction in risk associated with high vitamin B6 consumption, as monitored by food-related questionnaires or—more directly—by the quantification of circulating vitamers. Often, but not always, high folate and vitamin B12 intake also correlated with reduced cancer risk, whereas elevated circulating levels of methionine and homocysteine frequently constituted *bona fide* risk factors (Table 1).

The clinical series that have been investigated in this respect include—but are not limited to—cohorts of patients with non-Hodgkin's lymphoma (4 studies),[101–104] multiple myeloma (1 study),[102] head and neck cancer (5 studies),[105,106] breast carcinoma (9 studies),[107–115] lung adenocarcinoma (2 studies),[116,117] esophageal and gastric cancer (7 studies),[118–124] pancreatic cancer (2 studies),[125,126] colorectal carcinoma (27 studies),[99,100,127–151] renal cell carcinoma (1 study),[152] bladder cancer (1 study),[153] urothelial cell carcinoma (1 study),[154] prostate cancer (3 studies)[155–157] and ovarian carcinoma (2 studies).[158,159] Interestingly, in a consistent number of studies, the vitamin B6 status stands out as a nonindependent risk factor, interacting with other nutritional indicators (such as the levels of folate, vitamin B12, methionine and homocysteine) or with *TS* and *MTHFR* polymorphisms. Thus, at least in some settings, vitamin B6 appears to affect cancer risk as it impinges on one-carbon metabolism, and hence on DNA repair and genome stability.[72,160,161]

In 2012, we have demonstrated that an elevated expression of PDXK by tumor cells constitutes an indicator of good prognosis in two distinct cohorts of ($n=114$ and $n=218$) NSCLC patients (Table 1).[78] Of note, the prognostic value of high PDXK expression levels as assessed by immunohistochemistry on paraffinized tumor sections (1) was not influenced by therapy (in line with the role that we unveiled for PDXK in adaptive responses); (2) was lost when PDXK levels were quantified on normal lung tissues from the same patients as well as (3) when PDXK expression was monitored in (heterogeneous) tumor lesions at the mRNA, rather than the protein, level.[78] Interestingly, both the disease-free and the overall survival of these patients were not influenced by the expression levels of PDXP.[78] The reasons that may underlie such an observation remain obscure. Nevertheless, these findings demonstrate not only that PDXK is subjected to a consistent degree of post-translational regulation but also that human tumors exhibit cell-intrinsic, enzymatic alterations of the vitamin B6 metabolism. At least in part, such alterations might contribute to the systemic imbalance of vitamin B6 metabolism that often characterize cancer patients.[82–85]

Altogether, these clinical findings suggest that—in a majority of settings—the metabolism of vitamin B6 exerts *bona fide* oncosuppressive functions. Of note, other vitamins (for example, L-ascorbate, tocopherols)[162–164] and vitamin-like substances (for example, lycopene)[165] have been shown to mediate conspicuous anticancer effects. However, at odds with vitamin B6, these compounds most often (if not always) appear to exert oncosuppressive activity as they mediate robust antioxidant functions.[166–168]

CONCLUDING REMARKS

As discussed above, (1) cancer patients often manifest decreased levels of circulating B6 vitamers as compared with age-matched healthy individuals; (2) elevated circulating amounts of B6 vitamers (as documented by direct biochemical tests) as well as an intense consumption of vitamin B6-containing food (as documented by food-related questionnaires) correlate with a reduced incidence of several distinct neoplasms; and (3) high intratumoral expression levels of PDXK, the enzyme that generates PLP from dietary precursors, improve disease outcome among NSCLC patients, irrespective of therapy. Hence, bioactive vitamin B6 stands out as a central brake to oncogenesis and tumor progression.

Nevertheless, the molecular and cellular circuitries underlying these observations remain largely obscure, although a few key facts on the mutual relationship between vitamin B6 and cancer have been unveiled (Figure 2). First, a proficient metabolism of vitamin B6 is required to sustain the anabolic needs of highly proliferating cells, including tumor cells as well as cells from the immune system.[30,31] On one hand, this explains (at least in part) why cancer patients frequently suffer from vitamin B6 deficiency, even in the absence of apparent nutritional causes.[84] On the other hand, this suggests (1) that cancer-associated immunosuppression may derive, at least partially, from vitamin B6 deficits,[169,170] and (2) that vitamin B6 may exert antineoplastic effects by promoting antitumor immune responses.[55,92] Second, vitamin B6 directly impinges on one-carbon metabolism,[98] and hence may have an oncosuppressive activity by promoting DNA repair and genomic stability.[72,160,161,171] Third, vitamin B6 metabolism is implicated in the adaptive response to a wide array of adverse conditions, including multiple settings that malignant cells normally experience during tumor progression (for example, nutrient deprivation, hypoxia).[78] As vitamin B6-deficient cancer cells appear to be much more resistant to stress-induced death than their vitamin B6-proficient counterparts,[78] tumor progression may be facilitated in settings in which the production of PLP is limited, for instance owing to the downregulation of PDXK or the

Table 1. Clinical studies addressing the value of vitamin B6 metabolism as a risk/prognostic indicator in cancer

Setting	N	*Type*	*Nutritional parameters*[a]	*HR, RR or OR (CI), P-value*[b]	*Genetic interactions*	*Notes*	*Reference no.*
Bladder cancer	912	R	Multiple	0.6 (0.4–1.0), $P=0.0006$	*GSTM1* and *NAT2*	High intake associated with reduced risk	153
Breast cancer	379	R	B12 and F	ND	ND	No association between intake and risk	110
Breast cancer	388	R	B2, B12 and F	$P=0.764$	*MTHFR* and *MTR*	No association between intake and risk	112
Breast cancer	391	R	B12 and F	ND	ND	High intake associated with reduced risk of developing ER^- lesions	113
Breast cancer	438	R	B12 and M	0.46 (0.30–0.69), $P<0.001$	ND	High intake associated with reduced risk	114
Breast cancer	458	R	B12 and F	ND	*MTHFR* and *MTR*	No association between B6 intake and risk, significant interaction between intake and *MTHFR* status ($P=0.043$)	111
Breast cancer	475	R	B12 and F	$P=0.41$	ND	No association between intake and risk	108
Breast cancer	706	P	None	0.70 (0.50–0.98), $P=0.02$	ND	High plasma levels associated with reduced risk of developing ER^+ lesions	115
Breast cancer	712	R	B12, F and H	0.70 (0.48–1.02), $P=0.09$	ND	No association between intake and risk	107
Breast cancer	848	P	B12 and F	0.91 (0.63–1.30), $P=0.48$ 0.64 (0.42–0.99), $P=0.04$	ND	No association between plasma levels and risk Elevated intake associated with reduced risk for postmenopausal, ER^+ or PR^+ tumors	109
Colon cancer	152	R	B2, B12, F and H	0.30 (0.11–0.82), $P=0.01$	ND	High plasma levels associated with reduced risk	143
Colon cancer	527	P	B12, F and M	ND	Multiple	No association between intake and risk of developing CIMP-high and CIMP-low/0 tumors	149
Colon cancer	598	R	A, B12, F and M	0.95 (0.67–1.36), $P=0.88$	ND	No association between intake and risk	100
Colon cancer	669	P	A, B12, F and M	ND	*KRAS* and MSI	High intake associated with reduced risk regardless of MSI or *KRAS* status	139
Colon cancer	3283	R	A, B12, F and M	ND	*MTHFR*	High intake and TT genotype associated with reduced risk	127
CRA	177	R	B2, B12 and F	ND	*MTHFR*	No association between intake and risk	129
CRA	241	R	B12 and F	0.44 (0.26–0.74), $P=0.002$	*MTHFR*	High plasma levels associated with reduced risk	148
CRA	410	P	Multiple	ND	ND	No association between intake and risk	133
CRA	471	P	B2, B12 and F	0.78 (0.61–1.00), $P=0.08$	*CBS*, *MTHFR* and *MTR*	High plasma levels associated with reduced risk No association between intake and risk No association between plasma levels and genotype	138
CRA	673	R	Multiple	$P=0.006$	Multiple	Interaction between intake and *TS*, but not *MTHFR*, genotype	136
CRA	1809	R	Multiple	0.69 (0.51–0.95), $P=0.004$	Multiple	High plasma levels associated with reduced risk	147
CRC	70	R	Multiple	0.43 (0.37–0.47), $P=0.02$	ND	High intake associated with reduced risk	132
CRC	107	R	B2, B12 and F	$P=0.77$ 0.59 (0.23–1.5), $P=0.021$	*ALDH2*, *MTHFR* and *MTRR*	No association between intake and risk Interaction between intake and *MTRR* genotype	131
CRC	194	P	Multiple	0.51 (0.27–0.97), $P=0.007$	ND	High intake associated with reduced risk	133
CRC	197	P	Multiple	$P=0.01$	ND	High intake associated with reduced risk	145
CRC	220	R	Multiple	0.69 (0.41–1.15), $P=0.047$ 0.84 (0.56–1.27), $P=0.18$ 1.14 (0.77–1.69), $P=0.07$	ND	High dietary intake (excluding supplement users) associated with reduced risk No association between dietary and total intake and risk	135
CRC	224	P	Multiple	0.49 (0.29–0.83), $P=0.009$	*MTHFR*	High plasma levels associated with reduced risk	144
CRC	245	R	Multiple	0.26 (0.30–0.67), $P=0.05$	ND	High intake associated with reduced risk	150
CRC	264	R	Multiple	0.71 (0.41–1.24), $P=0.016$ 1.82 (0.99–3.33), $P=0.033$	*MTHFR*	Interaction between intake and *MTHFR* genotype No association between intake and risk	141
CRC	399	P	A and F	0.57 (0.35–0.94) 1.19 (0.78–1.83)	*TP53*	High intake associated with reduced risk in TP53-overexpressing, but not WT, lesions	140
CRC	526	P	A, B12, F and M	0.69 (0.48–0.98), $P=0.03$	ND	High intake associated with reduced risk in men (mainly in case of high alcohol intake)	137
CRC	715	R	Multiple	0.52 (0.34–0.80)	ND	High intake associated with reduced risk	134
CRC	727	R	F	0.8 (0.6–1.1) and 0.7 (0.5–1.1), $P=0.04$	Multiple	Interaction between intake and *MTHFR* genotype	128
CRC	805	R	A	0.66 (0.50–0.86), $P=0.002$	ND	High intake associated with reduced risk	130
CRC	1365	P	B2 and B12	0.68 (0.53–0.87), $P<0.001$	Multiple	High plasma levels associated with reduced risk	146
CRC	1614	P	None	ND	ND	No association between intake and risk	151
CRC	2028	R	F	0.70 (0.60–0.83), $P<0.0005$ 0.71 (0.57–0.89), $P=0.002$ 0.77 (0.61–0.98), $P=0.03$	*MTHFR*, *MTR* and *MTRR*	High intake associated with reduced risk	142
CRC	2349	R	B2, F and M	3.57 (1.56–8.17), $P=0.01$ 1.35 (0.76–2.41), $P=0.31$	ND	High intake associated with reduced risk in women No association between intake and risk in men	99
Esophageal adenocarcinoma	282	R	Multiple	0.53 (0.38–0.73)	ND	High intake associated with reduced risk	121
Gastric cancer	90	R	Multiple	0.6 (0.3–0.9), $P=0.0188$	ND	High intake associated with reduced risk	119

Table 1. (Continued)

Setting	N	*Type*	*Nutritional parameters*[a]	*HR, RR or OR (CI), P-value*[b]	*Genetic interactions*	*Notes*	*Reference no.*
Gastric cancer	91	R	Multiple	ND	ND	High intake associated with reduced risk	118
Gastric cancer	230	R	Multiple	$P=0.81$	ND	No association between intake and risk	123
Gastric cancer	235	P	B2 and B6	0.78 (0.65–0.93), $P=0.006$	Multiple	High plasma levels associated with reduced risk	124
Gastric cancer	301	R	Multiple	$P<0.001$	ND	High intake associated with reduced risk	120
Gastric cancer	255	R	Multiple	0.65 (0.47–0.88)	ND	High intake associated with reduced risk	121
Gastric cancer	352	R	Multiple	0.59 (0.45–0.79)	ND	High intake associated with reduced risk	121
HNC	410	R	Multiple	0.59 (0.46–0.74), $P<0.0001$	ND	High intake associated with reduced risk	105
HNC	527	R	Multiple	0.6 (0.4–0.9)	ND	High intake associated with reduced risk	106
Lung cancer	899	P	B2, B12, F, H and M	0.44 (0.33–0.60), $P<0.00001$	ND	High plasma levels associated with reduced risk	117
Lung cancer	1051	R	Multiple	0.29 (0.15–0.56), $P=0.006$	*MTHFR*	Interaction between intake and *MTHFR* genotype in women	116
MM	32	R	A, B2, B12, F and M	ND	ND	No association between intake and risk	102
NHL	190	R	B2, F and M	0.8 (0.5–1.2)	ND	No association between intake and risk	104
NHL	195	R	A, B2, B12, F and M	$P=0.42$	ND	No association between intake and risk	102
NHL	386	R	F and M	0.22 (0.10–0.52), $P=0.002$ 0.55 (0.35–0.86), $P=0.05$ 0.54 (0.36–0.81), $P=0.06$	Multiple	Interaction between intake and *FPGS–MTR* genotype No association between intake and *MTHFS* genotypes	103
NHL	425	R	A, B2, B12, F and M	0.57 (0.34–0.95), $P=0.01$	ND	High intake associated with reduced risk	101
NSCLC	332	R	None	ND	ND	High *PDXK* associated with improved DFS and OS	78
OSCC	344	R	Multiple	0.59 (0.46–0.74), $P<0.0001$	ND	High intake associated with reduced risk	105
OSCC	206	R	Multiple	0.45 (0.30–0.69)	ND	High intake associated with reduced risk	121
OSCC	351	R	F and M	0.88 (0.60–1.31), $P=0.55$	ND	High intake associated with reduced risk	122
Ovarian cancer	152	R	F and M	ND	ND	No association between intake and risk	158
Ovarian cancer	1910	R	A, B2, B12, F and M	0.76 (0.64–0.92), $P=0.002$ 0.49 (0.32–0.77), $P=0.001$ 0.74 (0.58–0.94), $P=0.012$	ND	High intake associated with reduced risk	159
Pancreatic cancer	208	P	B12, F and H	0.80 (0.51–1.25), $P=0.25$	ND	No association between intake and risk	125
Pancreatic cancer	532	R	B12, F and M	$P=0.12$ $P=0.68$	ND	No association between intake and risk	126
Prostate cancer	144	R	B12, F and M	0.92 (0.55–1.54), $P=0.76$	*MTHFR*	No association between intake and risk	157
Prostate cancer	224	R	B12, F and H	1.11 (0.71–1.75), $P=0.64$	ND	No association between intake and risk	156
Prostate cancer	328	R	Multiple	0.70 (0.48–1.03), $P=0.029$	ND	High intake associated with reduced risk	155
RCC	767	R	Multiple	0.85 (0.64–1.13)	ND	No association between intake and risk	152
Rectal cancer	123	R	A, B12, F and M	1.97 (1.08–3.62), $P=0.03$	ND	High intake associated with reduced risk	100
Rectal cancer	126	R	B2, B12, F, and H	0.91 (0.35–2.42), $P=0.93$	ND	No association between plasma levels and risk	143
Urothelial cell carcinoma	330	R	Multiple	0.88 (0.62–1.24), $P=0.761$	ND	No association between intake and risk	154

Abbreviations: A, alcohol; *ALDH2*, *aldehyde dehydrogenase 2 family*; B2, vitamin B2; B6, vitamin B6, B12, vitamin B12, *CBS*, *cystathionine-β-synthase*; CI, 95% confidence interval; CIMP, CpG island methylator phenotype; CRA, colorectal adenoma; CRC, colorectal carcinoma; DFS, disease-free survival; ER, estrogen receptor; F, folate; FPG, folylpolyglutamate synthase; *GSTM1*, *glutathione S-transferase μ1*; H, homocysteine; HNC, head and neck cancer; HR, hazard ratio; *MTHFR*, *methylenetetrahydrofolate reductase*; *MTHFS*, *5,10-methenyltetrahydrofolate synthetase*; *MTR*, *5-methyltetrahydrofolate-homocysteine methyltransferase*; *MTRR*, *5-methyltetrahydrofolate-homocysteine methyltransferase reductase*; *N*, number of patients; *NAT2*, *N-acetyltransferase 2*; ND, not determined; NHL, non-Hodgkin's lymphoma; NSCLC, non-small cell lung carcinoma; OD, odds ratio; OS, overall survival; OSCC, oral squamous cell carcinoma; P, prospective; PDXK, pyridoxal kinase; PR, progesterone receptor; R, retrospective; RCC, renal cell carcinoma; RR, relative risk; SMSI, sporadic microsatellite instability; TS, thymidylate synthase; WT, wild type. [a]Other than vitamin B6. [b]For high vitamin B6 dietary intake, supplementation or plasma levels.

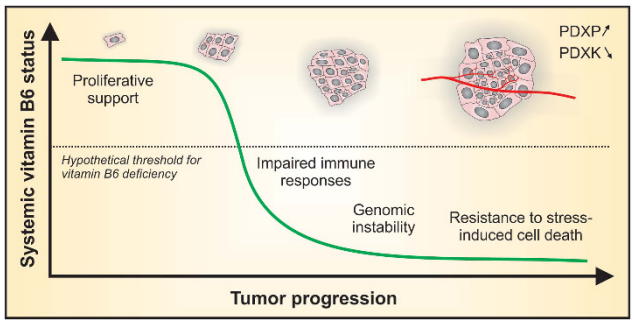

Figure 2. Relationships between vitamin B6 metabolism and cancer. As highly proliferating cells require a proficient metabolism of vitamin B6, forming tumors may favor the establishment of a systemic state of vitamin B6 deficiency. In turn, this may promote tumor progression as (1) vitamin B6 is necessary for optimal immune responses (and hence for tumor immunosurveillance); (2) vitamin B6 is profoundly involved in one-carbon metabolism, *de facto* contributing to the maintenance of genomic stability; and (3) defects in vitamin B6 metabolism, such as those ensuing the downregulation of PDXK or the upregulation of PDXP, compromise the ability of cancer cells to die in response to several distinct stress conditions including nutrient deprivation and hypoxia. In addition, when the systemic levels of vitamin B6 decrease below a certain threshold, neurological and dermatological symptoms may appear.

upregulation of PDXP. Hence, it is tempting to speculate that newly formed tumors may take advantage of high intracellular PLP levels to sustain their metabolic needs, whereas neoplastic lesions growing beyond a certain mass may benefit from a reduced bioavailability of vitamin B6, to avoid metabolic stress-induced cell death. Future studies are required to provide formal evidence in support of this hypothesis. In addition, it will be interesting to see to which extent genome stability-related and immune mechanisms contribute to the antineoplastic effects of vitamin B6.

ABBREVIATIONS

BCG, Bacillus Calmette–Guérin; MTHFR, methylenetetrahydrofolate reductase; NSCLC, non-small cell lung carcinoma; PDXK, pyridoxal kinase; PDXP, pyridoxal phosphatase; PL, pyridoxal; PLP, pyridoxal-5′-phosphate; PM, pyridoxamine; PMP, pyridoxamine-5′-phosphate; PN, pyridoxine; PNP, pyridoxine-5′-phosphate; TS, thymidylate synthase.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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