



*Review*

## The potential of lipid soluble thiamine in the treatment of cancer

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**Abstract:** The resurgence of interest in cancer metabolism has linked alterations in the regulation and exploitation of metabolic pathways with an anabolic phenotype that increases biomass production for the replication of new daughter cells. To support the increase in the metabolic rate of cancer cells, a coordinated increase in the supply of nutrients, such as glucose, as well as micronutrients functioning as enzyme cofactors is required. The majority of co-enzymes are derivatives of water-soluble vitamins such as niacin, folate, pantothenic acid, pyridoxine, biotin, riboflavin and thiamine (Vitamin B1). Continuous dietary intake of these micronutrients is essential for maintaining normal health. How cancer cells adaptively regulate cellular homeostasis of cofactors and how they can regulate expression and function of metabolic enzymes in cancer is under-appreciated. Exploitation of cofactor-dependent metabolic pathways with the advent of anti-folates highlights the potential vulnerabilities and importance of vitamins in cancer biology. Vitamin supplementation products are easily accessible and patients often perceive them as safe and beneficial without full knowledge of their effects. Thus, understanding the significance of enzyme cofactors in cancer cell metabolism will provide for important dietary strategies and new molecular targets to reduce disease progression. Recent studies have demonstrated the significance of thiamine-dependent enzymes in cancer cell metabolism. Therefore, this hypothesis discusses the current knowledge in the alterations in thiamine availability, homeostasis, and exploitation of thiamine-dependent pathways by cancer cells.

**Keywords:** thiamine; transketolase; vitamin; metabolism; cancer

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### 1. Introduction

Vitamin B1 (thiamine) is an essential, water-soluble vitamin integrally tied to mitochondrial energy metabolism. Altered mitochondrial metabolism has been implicated in oncogenesis and

tumorigenesis [1]. Studies have demonstrated the significance of thiamine-dependent enzymes in mitochondrial function and in cancer cell metabolism [2]. This paper discusses the current knowledge in the alterations in thiamine availability, homeostasis, and exploitation of thiamine-dependent pathways by cancer cells and proposes future avenues for research using the more physiologically potent, lipid-soluble, open ring thiamine derivatives, especially the disulfides, in the treatment of cancer.

## **2. Disturbed mitochondrial metabolism and cancer**

In the 1920s, Otto Heinrich Warburg and his group concluded that deprivation of glucose and oxygen in tumor cells leads to lack of energy resulting in cell death. Biochemist Herbert Grace Crabtree further extended Warburg's research by discovering environmental or genetic influences. Modern researchers came to the conclusion that the genetic influences were much more important and that the Warburg effect was secondary. Thus, for many years research has focused on the complex relationship of oncogenes with the etiology of cancer. Proto-oncogenes are cellular genes that are expressed during normal growth and developmental processes. They can be activated to cancer-causing oncogenes by point mutations or by gross DNA rearrangement. Activated versions have been observed in various human and rodent tumors [3]. These normal protocol-oncogenes are involved in the regulation of proliferation and differentiation. However, if mutated, they have the potential for inducing neoplastic transformation [4].

It is a longstanding debate whether cancer is one disease or a set of diverse disease processes. According to the medical literature there has been a recent tendency for research to move into the study of a metabolic cause. It has been suggested that the impairment of oxidative phosphorylation, leading as it does to a decrease of ATP concentration, gives rise to compensatory massive glucose uptake and anaerobic glycolysis. The authors suggest that most of the hallmarks of cancer could be the consequence of the Warburg effect and subsequent mitochondrial damage [5]. Recent mitochondrial research confirms this. Specifically, when highly metastatic cells are transplanted to media with healthy mitochondria, tumorigenesis is suppressed. Conversely, when healthy cells are paired with unhealthy mitochondria oncogenesis is induced. This suggests that disturbed oxidative metabolism is a key component of oncogenesis and that rectifying mitochondrial function may be a promising goal for cancer therapy [6].

## **3. Epigenetics, cancer, and thiamine**

Cancer is said to arise from a series of genetic and epigenetic changes which result in abnormal expression or mutational activation of oncogenes, as well as suppression/inactivation of tumor suppressor genes. Dispersed across the human genome, endogenous retroviruses provide an enormous reservoir of autonomous gene regulatory modules, some of which have been co-opted by the host during evolution to play an important role in normal regulation of genes and gene networks [7]. Vitamins involved in one-carbon metabolism are hypothesized to influence breast cancer risk. However, epidemiologic studies that examined associations between B vitamin intake and breast cancer risk have hitherto provided inconsistent results [8]. Most recent investigations into cancer etiology have identified a key role played by epigenetics. DNA methylation profiles have been linked to hormone receptor status and tumor progression. The role of nutritional intervention affecting

epigenetic changes particularly holds promise [9]. A chapter focuses on the tight relationship between epigenetics and micro RNAs and provides some insights on the translational implications of these findings. Micro RNAs are short non-coding RNAs with gene regulatory functions [10]. The epigenetic regulation of DNA-templated processes has been intensely studied over the last 15 years. DNA methylation, histone modification, nucleosome remodeling and RNA-mediated targeting regulate many biological processes that are fundamental to the genesis of cancer [11], and once again, may be linked to vitamin B status. Most notably, vitamins B6, B9, and B12 have been implicated, but the research is conflicting. Both increases and deficiencies have been observed, associated with oncogenesis [12]. This suggests another mechanism affecting methylation may be responsible. In light of Warburg's revelations and the subsequent research linking mitochondrial energetics to cancer, we believe thiamine holds the key to both processes. As the rate limiting nutrient in oxidative phosphorylation, a fundamental co-factor for amino acid and fatty acid metabolism, thiamine, in its biological active form, thiamine pyrophosphate is central to effective energy management, and as such, it can become indispensable to the energy consuming methylation cycle [13]. Inasmuch as thiamine insufficiency, irrespective of B6, B9, and B12 status, can limit methylation, and initiate the epigenetic cascades commonly noted in many cancers, it seems likely that thiamine would be a critical nutrient to assess.

Similarly, thiamine connects other common patterns observed in oncogenesis; namely, hypoxia, low glutathione, and elevated or dysregulated reactive oxygen species (ROS). Thiamine insufficiency causes what is called pseudo-hypoxia, an inability to utilize molecular oxygen, via its interaction with hypoxia inducible factors (HIF) [14]. This forces the shift towards the telltale anaerobic metabolism common in cancer. On the other hand, thiamine sufficiency is requisite for glutathione synthesis, reactive oxygen species and lactate management [15]; all are dysregulated in cancer. This suggests that thiamine insufficiency may be the underlying factor linking Warburg's insights and mitochondrial function to modern epigenetic and genetic theories of cancer.

#### **4. The thiamine conundrum in cancer**

The resurgence of interest in cancer metabolism has linked alterations in the regulation and exploitation of metabolic pathways with an anabolic phenotype that increases biomass production for the replication of new daughter cells. Recent studies have demonstrated the significance of thiamine-dependent enzymes in cancer cell metabolism [16]. Thiamine deficiency (TD) is increasingly recognized in medically ill patients. The prevalence among cancer patients is largely unknown. However, among 217 patients with various cancers, TD was found in 55.3%. Measurement of serum thiamine concentration preceded psychiatric consultation in only 10.6% of cases. This indicates that the symptoms arising from TD are often regarded as "psychological" and curiously enough, without concluding that even psychological manifestations must have a brain function mechanism. These authors concluded that TD is highly prevalent among inpatients with cancer, even among normal weight and overweight individuals, in the absence of other vitamin deficiencies and even while receiving multivitamin supplements [17].

Similarly, a retrospective study investigating TD in cancer patients who were referred for psychiatric consultation with delirium found of the 76 admitted into the study, 32 (43%) were thiamine deficient [18]. A 2016 review of the case literature identified 45 cases of Wernicke's encephalopathy (WE), in addition to the case they were reporting. Of note, most cases were not

identified until an MRI was performed [19]. Inasmuch as WE represents the later stages of TD and MRIs provide poor diagnostic sensitivity for WE (~53% in one study [20]), it is likely that TD in both its earlier manifestations, but also as it progresses in severity, is under-recognized in this population. Very few studies examine TD in advance of treatment and in those that do, the findings are equivocal. One study (n = 14) found TD in 35% of patients tested with untreated B-chronic lymphocytic leukemia [21]. While a larger study (n = 87) involving patients with myeloproliferative neoplasms found only one case of TD pre-treatment [22] and none across the treatment period.

With such a paucity of research, it is difficult to discern the role of thiamine in cancer. Important questions to ask are whether TD is part of the etiology of cancer and if so, how, or whether it is simply related to the treatment of cancer? It is clear that treatment protocols can and do initiate thiamine deficiency by a myriad of mechanisms. These include the increased consumption of thiamine by fast growing neoplastic cells, poor dietary intake, vomiting and gastrointestinal distress, and the interference of specific types of chemotherapy with thiamine transport and activation [23,24]. What remains unclear, however, is whether lifelong thiamine status impacts oncogenesis. In other words, could thiamine status underlie the multitude of mechanisms by which mitochondria respond to carcinogenic insults, including those that lead to manifestations of cancer itself?

The answer, of course, depends upon whether one holds to a more traditional somatic mutation framework, where nuclear mutations drive oncogenesis and tumorigenesis and subsequently alter mitochondrial respiration in a compensatory fashion, or to cancer as metabolic disease first, where impaired mitochondrial respiration initiates and maintains the disease process including genetic and epigenetic manifestations. If it is the former, the role of thiamine is unimportant to disease progression inasmuch as genetics drive the metabolic adaptations central to cancer. It is similarly unimportant as a treatment possibility, except in cases where other treatments induce thiamine deficiency. If, on the other hand, cancer is viewed as a metabolic disease first and foremost, and there is ample evidence to suggest that it is [25], thiamine becomes fundamental to both the origins of the disease process, and its treatment. As the rate-limiting co-factor in the enzymes responsible for oxidative metabolism, thiamine is essential for mitochondrial respiratory competence; that same competence capable of resisting oncogenesis in response to a carcinogenic insult and suppressing tumorigenesis in already compromised cells [6]. In other words, thiamine insufficiency may be at the crux of many, if not most, of the seemingly disparate metabolic, genetic and epigenetic functions dysregulated in cancer, and as such, points to a potential treatment approach.

In vitro studies, though inconsistent, suggest this may be true. These studies reveal a modulating role for thiamine in oncogenesis, tumor cell proliferation, and apoptosis; one that varies by administered dose. That is, moderately high doses of thiamine (up to ~ 75 times the RDI) seem to stimulate cell proliferation while supra-physiological doses (from ~ 250–2500 times RDI) stifle it. Since processed foods commonly consumed by Westerners are fortified with thiamine and thiamine supplements are readily available, the implication is that cancer develops in relationship to moderately high thiamine levels [26]. This, of course, ignores the contributions to carcinogenesis of the processed foods themselves e.g. the much higher sugar content, the hydrogenated oils, preservatives, and other chemicals that render metabolic instability by overwhelming, and thus, compromising mitochondrial energetics. It similarly ignores the growing body of data suggesting that despite nutrient fortification and enrichment programs, diets comprised of highly processed foods are linked not only to metabolic disruption, the precursors of which would lead to cancer [27], but also, leave the consumer highly nutrient deficient [28,29].

A more tenable explanation for the low dose/high dose conundrum would suggest that the type of cancer, the oxygen status of the tumor microenvironment, and methylation and histone acetylation pattern of key proteins involved in mitochondrial bioenergetics determines the thiamine treatment response i.e. the larger the disruption, the greater the need for thiamine. To that end, some have suggested that lower doses of thiamine are sufficient to support energy metabolism inside the tumor, and thus, enhance cell proliferation but are not high enough to correct the more global energy deficiency systemically and unwind the aberrant metabolic processes endemic of cancer [16]. This makes more sense, particularly if we consider the extended time course of most cancers. Time entrenches metabolic disruption and its associated adaptive cascades in a manner that no *in vitro* study can emulate.

Insofar as each of the variables associated with the metabolic phenotype of cancer are themselves sensitive to thiamine deficiency, it suggests that they may be equally amenable to thiamine administration. For example, the expression of solute carrier (SLC) transporter genes is often significantly different in cancer cells compared to non-cancerous cells [30]. Though much of the research has shown a downregulation of the SLC19A3 transporter relative to cancer [31], when hypoxia is a factor [32], the transporter is upregulated substantially, some 40 times, in fact. Tumor hypoxia, as measured by the stabilization of HIF1a, is associated with poor prognosis and treatment failure. In the aforementioned study, hypoxia was identified in 43 of the 77 breast cancer specimens tested. Molecular hypoxia and the activation by the HIF proteins are induced by thiamine deficiency [14]. It is conceivable that the disparity in SLC activity is not specific strictly to the type of cancer, but rather, to the time course and/or severity of the disease process [33]. That is, marginal decrements in thiamine would downregulate transporter (s) locally whereas more chronic or severe decrements would induce cell level hypoxia necessitating an upregulation of the transporters in order to maintain thiamine pyrophosphate homeostasis [34].

In addition to influencing transporter activity, HIF stabilization can be tied to the activity levels of other key thiamine enzymes including transketolase (TKT), the transketolase-like enzymes (TKTL1, TKTL2) and the pyruvate dehydrogenase complex (PDC). In the cytosol, thiamine is a cofactor in the transketolase enzyme, which appears twice in the pentose phosphate pathway (PPP). The PPP is an alternative glucose oxidation pathway that provides nicotinamide adenine dinucleotide phosphate (NADPH) and ribose 5-phosphate (R5P) for glutathione, nucleic acid and fatty acid synthesis and steroid hydroxylation, respectively [35]. Thiamine deficiency downregulates transketolase activity in the early stages, but upregulates expression over time, and once again, induces hypoxia. Hypoxia related HIF1a activates TKTL1. TKTL1 expression is upregulated in many cancers. Upregulated TKTL1 provides acetate that can be converted to acetyl CoA for the pyruvate pathway, driving PPP flux and contributing to the Warburg effect [36].

Under normal state conditions, the mitochondrial PDC irreversibly decarboxylates pyruvate to acetyl coenzyme A, thereby linking glycolysis to the tricarboxylic acid cycle and defining a critical step in cellular bioenergetics. HIF1 $\alpha$  stabilization activates the gene encoding the pyruvate dehydrogenase kinase 1 enzyme. This subsequently inactivates the PDC [37]. Inhibition of PDC activity by pyruvate dehydrogenase kinase (PDK) mediated phosphorylation has been associated with the pathophysiology of many disorders, including cancer and this association has long been a thiamine precursors therapeutic target [38]. Cancer cells inactivate pyruvate dehydrogenase through phosphorylation by overexpression of PDK. Inhibition of PDK by dichloroacetate exhibits a gross suppressive effect in many cancers. Recently, it has been shown that thiamine pyrophosphate also

reduces PDK-mediated phosphorylation of pyruvate dehydrogenase [39]. Additionally, the treatment of breast cancer cells with thiamine significantly reduced their proliferation. This was associated with a reduction in glycolysis and activation of PDC [40]. Of note, when the PDC enzymes face severe stress, the enzymes are effectively transported from the mitochondria to the cell nucleus where they remain constitutively active, as no kinase activity has been observed. This allows for a nuclear pool of acetyl-CoA from pyruvate and increases the acetylation of core histones important for cell-cycle progression [41]. In sum, thiamine deficiency may be implicated in multiple mechanisms associated with the onset and progression of cancer.

## 5. Understanding thiamine derivatives

In 1965, a group of university-based scientists published an English translation of a book that covered the clinical and laboratory data concerning beriberi and thiamine [42]. It contained a chapter that described clinical and laboratory details of a large number of thiamine derivatives, starting with the discovery of allithiamine. Some researchers were examining the chemistry of garlic. They discovered that when a garlic bulb is cut or crushed, an enzyme converts thiamine to a disulfide derivative. Originally thinking that the biologic effect of thiamine was lost in this chemical reaction, animal studies proved that its biologic effect was more powerful than the thiamine from which it was derived. They called it allithiamine because garlic is a member of the allium species of plants and it can be found in other members of the species. This discovery led to much research, including the synthesis of many different synthetic derivatives. They can be divided into two major groups, the disulfides and the S-acyls.

### 5.1. The disulfides

The chemical structure of thiamine consists of two rings, a pyridinium and a thiazole, joined by a methylene bridge. A prosthetic group is used to create a disulfide by joining it to the sulfur atom of the thiazolium ring, thus forming an open ring. When this open ring form comes into contact with a cell membrane, the disulfide is reduced non-enzymatically and it passes through the cell membrane into the cytosol. The ring closes to give an intact molecule of thiamine. It is this ability to pass through the lipid barrier of the cell membrane that gives rise to the disulfide group of derivatives being termed fat-soluble.

Much of the experimental work was carried out using thiamine propyl disulfide (TPD) because this had the best biological performance in animal studies. However, it gave rise to an overwhelming garlic odor emanating from the animal or human subject to whom it was given. An alternative disulfide derivative was sought in a deliberate attempt to prevent the garlic smell, resulting in synthesis of thiamine tetrahydrofurfuryl disulfide (TTFD). It is soluble in water and can be administered intravenously.

Using TPD preventively had shown that mice could be partially protected from cyanide toxicity by stimulation of rhodanese. This enzyme converts cyanide to non-toxic thiocyanate, and the reaction involves thiamine. It could also prevent the effect of toxicity by carbon tetrachloride in liver. The biologic properties are much the same with all the disulfide derivatives and TTFD is the most modern member. The prosthetic group that separates from the thiazolium ring on the reduction of the disulfide has been well studied and is broken down to sulfones that are excreted in urine [43,44,45].

It is obvious that this is not simple vitamin replacement. These disulfide derivatives of thiamine are clearly being used as non-toxic drugs.

### 5.2. The S-acyl derivatives

Also known as open ring thiamine derivatives, the prosthetic group has to be removed from the thiazolium ring by an enzyme in the liver or kidney. Although well absorbed from the intestine, these derivatives do not have the same property of entering blood cells like the disulfides. The best known derivative is benfotiamine.

Lipid-soluble thiamine precursors have a much higher bio-availability than naturally occurring thiamine and therefore are more suitable for therapeutic purposes. Benfotiamine, an amphiphilic S-acyl derivative was given to mice in a single oral dose of 100 mg/kg. Though thiamine level rapidly increased in blood and liver, no significant increase was observed in the brain. This would explain why beneficial effects of this derivative have only been observed in peripheral tissues while sulbutiamine, a disulfide derivative, increases thiamine in the brain and acts as a central nervous system drug. Benfotiamine should therefore be differentiated from the disulfide group of derivatives. With a different mechanism of absorption and different pharmacological properties [46], clinical use should be selective.

The use of TTFD as a therapeutic agent is hardly known in the West [47]. Thiamine deficiency from dietary abuse, together with genetic mutations that appear to be relatively common, are producing widespread polysymptomatic disease, often misdiagnosed as psychological [48]. It has been hypothesized that these symptoms, readily reversible at this stage if recognized, give rise to the irreversible symptoms of neurodegeneration at a later date [15,24]. TTFD may also provide opportunity for cancer treatment.

## 6. Conclusions

Hans Selye published his detailed work on stress many years ago. He came to the conclusion that the General Adaptation Syndrome (GAS) was a programmed state of metabolic resistance to both physical and mental stress that depended on the mobilization of sufficient energy. The end stage of the GAS represented a failure to meet the demands of the imposed stress. The laboratory findings from the stressed animals were similar to the laboratory findings in severely ill humans. Selye stated that human diseases were "diseases of adaptation" [49]. One of his students was even able to produce the GAS by making the animal thiamine deficient [50]. Thiamine, in light of role in energy metabolism, is central to mitochondrial competence and thus, may be the missing link connecting Warburg's insights to the genetic and epigenetic aberrations observed in cancer.

In the early 1960s, Zbinden was able to find 696 published papers in which 242 different diseases had been treated with megadoses of thiamine with variable degrees of success [51]. In the intervening decades, the mechanisms by which thiamine deficiency emerges have changed significantly. Where once thiamine deficiency was considered primarily in relation to malnutrition associated with sparsity and alcoholism, it is now associated with variety of factors from medication induced nutrient deficiencies or mitochondrial damage from bariatric surgery, among just a few. Most notably, thiamine insufficiency is a common outgrowth of the modern Western diet. That is, the same diet recognized for the host of metabolic disturbances currently plaguing western populations,

also leads to thiamine insufficiency and outright deficiency. High calorie malnutrition is widespread in America. Similarly, a variety of mutations affecting thiamine metabolism and implicated in cancer appear to be surprisingly common. Since TTFD has been successfully used in the treatment of many different conditions, is non-toxic at extremely large doses, and does not require a thiamine transporter [15] we argue that it should be investigated further for use in cancer treatment.

### Conflict of interest

Clinical studies of TTFD have been performed by Dr. Lonsdale since 1973 under independent investigator license IND 11019. Dr. Marrs declares no conflicts of interest.

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