Chapter 5

Vitamin B12: Could It Be a Promising Immunotherapy?

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Additional information is available at the end of the chapter

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Abstract

Vitamin B12 is a water-soluble vitamin and an important micronutrient with critical role in DNA, protein, and lipid synthesis. It is responsible for one-carbon metabolism and cell division of nervous and hematopoietic cells. Among its various functions, the role as immunomodulator in cellular immunity, especially in elevating the number of CD8+ cells and NK cells, attracts scientific interest. Many alternative anticancer and anti-inflammatory treatments involve the use of B12 together with other vitamins and nutrients, but still the scientific information is too obscure and insufficient. Controversial data link tumorigenesis with either increased or decreased B12 blood levels in different types of cancer. Dietary intake and additional supplement with the vitamin do not protect against cancer risk, but the dominant opinion is to integrate B12 as part of rational and healthy nutrition to ensure proper function of the immune system. This chapter will review in brief the most important facts for vitamin B12 functions and properties. We will try also to present in concise way the human immune system and the exact role of B12 in immune activity with emphasis on the questionable participation of vitamin B12 in the process of carcinogenesis and its significance as anticancer immunotherapy.

Keywords: vitamin B12, immunonutrition, immunomodulation, immunotherapy, tumorigenesis, cancer, inflammation

1. Introduction

Cancer is the final outcome of uncontrolled overgrowth of normal cells. Cancer cells remain insensitive to antiproliferative signals and apoptosis. As a result, they replicate, proliferate, and invade infinitely and aggressively. Although the genetic events are thought to be the most important in the process of carcinogenesis, other factors can facilitate abnormal cell development. For many years, inflammation and anti-inflammatory response were widely associated with malignancy [1, 2] and recognized as major elements that trigger carcinogenesis.

Extended inflammation, especially in chronic infections, predisposes to cancer, but still the mechanism(s) involved is (are) not definitely known. Usually all inflammatory processes are followed rapidly by anti-inflammatory defense response—excessive production of pro-inflammatory signals (mediators) and reactive oxygen and nitrogen species. The pro-inflammatory mediators (cytokines, chemokines, and eicosanoids) may stimulate proliferation of both untransformed and tumor cells [2]. The reactive oxygen and nitrogen species lead to oxidative stress and damage of macromolecules, especially DNA to increase the risk of genetic mutations and tumorigenesis [3].

A continuously increasing number of microelements, vitamins, and mineral salts are reported to modulate the immune response and counter the inflammation and cancer, when taken as part of the healthy diet or as nutrient supplements. This concept is becoming more and more popular and nowadays is widely accepted and known as immunonutrition—an important part of each healthful dietary regime and immunotherapy approach. Immunonutrition means "modulation of the activities of the immune system, and the consequences on the patient of immune activation, by nutrients or specific food items fed in amounts above those normally encountered in the diet" [4]. Many formulations and routes of administration have been tested but with inconsistent results. Arginine, glutamine, omega-3 fatty acids, nucleotides, copper, selenium, zinc, vitamins of group B, C, and E are the most popular immunonutrients used alone or in different formulas. Among them, vitamin B12 attracts a great proportion of both scientific and wide public interest, because of its complex biological function. Unfortunately, as for the other promising immunonutrients, the real scientifically based information is too obscure or even missing. In the current work, we will try to summarize the available data and to elucidate the true implication of vitamin B12 in the proper function of the immune system and in the inflammatory response.

2. Vitamin B12: a miraculous molecule or a modern falsification

2.1. Chemical structure of vitamin B12 (cobalamin)

Vitamin B12 (cobalamin) is a water-soluble vitamin. It is the largest (molecular weight > 1000 g) and the most complex vitamin [5]. The chemical structure of B12 consists of a cobalt atom and four pyrroles in the center of corrin ring bound to a nucleotide part (ribose)—5,6-dimethylbenzimidazole (**Figure 1**) [6].

Cobalamin (Cbl) has the ability to bind to various functional groups. When the group is cyanide, it is called cyanocobalamin—represents the most stable active form of vitamin B12 and the most popular synthetic form. Other active forms in the human body are 5-deoxyadenosylcobalamin—with 5'-deoxyadenosine; methylcobalamin—with methyl group; and hydroxocobalamin—with hydroxyl group [6, 7].

2.2. Food sources of vitamin B12

The main dietary sources of vitamin B12 are animal foods—meat, liver, fish, and dairy products. It is also found in cobalamin-synthesizing bacteria and oysters. Plant foods do not contain

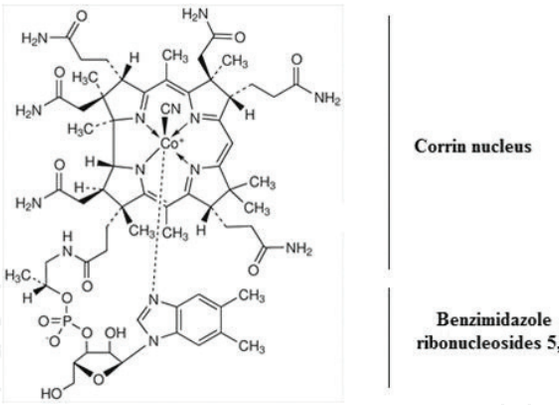

Figure 1. Chemical structure of cyanocobalamin.

vitamin B12 [8]. Some authors disagree with this fact [9, 10], but recent studies have shown that plant cell has the ability to produce only similar to B12 compounds (called pseudo-B12), which compete with B12 for the same cellular receptors, i.e., prevent normal physiological absorption of B12 [11].

2.3. Metabolism of vitamin B12

In the human body, cyanocobalamin is easily hydrolyzed to hydroxocobalamin. After the hydrolysis, it is converted to one of the two active forms—methylcobalamin or adenosylcobalamin (also known as coenzyme B12) [12]. Both forms act as enzyme cofactors.

Vitamin B12 is involved in two main enzymatic reactions. The first reaction, involving methylcobalamin, is remethylation of amino acid homocysteine to methionine and is catalyzed by methionine synthase (**Figure 2**) [9, 11, 13]. In this reaction, 5-methyltetrahydrofolic acid participates as a methyl group donor, while cobalamin is only an intermediate acceptor of the group.

In cobalamin deficiency, the synthesis of methionine is impaired and toxic amino acid homocysteine accumulates [11]. Vitamins B12, B6, and B9 are working together to control the levels of homocysteine in the blood (**Figure 2**). Homocysteine acts as a neurotoxin and as a toxin for the blood vessels increasing the risk of cardiovascular disease. In the laboratory diagnostics, high level of homocysteine is one of the signs of B12 deficiency [14].

The synthesis of methionine also produces tetrahydrofolic acid, which is essential for a number of folate-dependent reactions [11, 15], such as DNA synthesis [16]. The loss of this function is demonstrated in individuals with vitamin B12 deficiency, which explains why cobalamin deficiency often mimics folic acid deficiency.

The second enzymatic reaction requires adenosylcobalamin, which is located in the mitochondria and acts as coenzyme for methylmalonyl-CoA mutase [11, 17]. Methylmalonyl-CoA mutase catalyzes conversion of methylmalonyl-CoA to succinyl-CoA (**Figure 2**), an important metabolite in the Krebs cycle [16] and essential factor for the degradation of odd-chain fatty acids. In individuals with B12 deficiency, the activity of methylmalonyl-CoA mutase is dam-

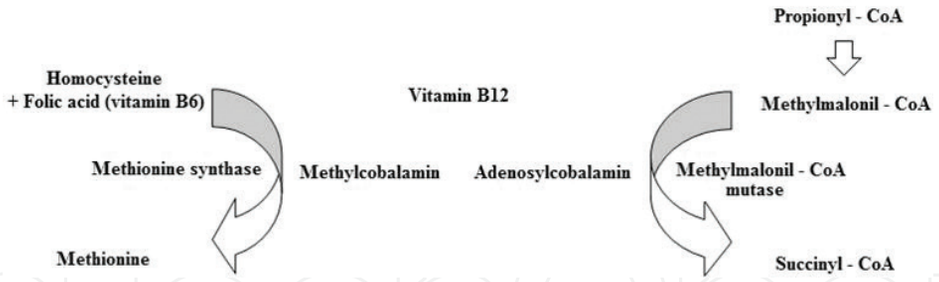

Figure 2. Metabolism of cobalamin (vitamin B12) in humans.

aged, and as a result, the levels of methylmalonic acid (MMA) in the body increase [11, 18]. The demonstration of elevated levels of MMA in urine or blood is a diagnostic sign of B12 deficiency too [14].

2.4. Digestion and absorption of vitamin B12

Simultaneously, with the digestion of animal products, vitamin B12 reaches the stomach. Under the action of the low pH (HCl) and pepsin, cobalamin is separated from the proteins to which it is connected in the food [19]. Then, it is associated with R-binders (or haptocorrins, transcobalamin I, R-factors)—glycoproteins secreted from the stomach cells and salivary glands. Their role is to protect vitamin B12 from chemical denaturation in the stomach (**Figure 3**) [19].

The intrinsic factors (IFs) have the main role in the vitamin B12 transport. IFs represent stomach-specific glycoproteins secreted by the stomach parietal cells and are essential for the absorption of B12 from the intestinal lumen into the bloodstream [17, 21]. Some genetic

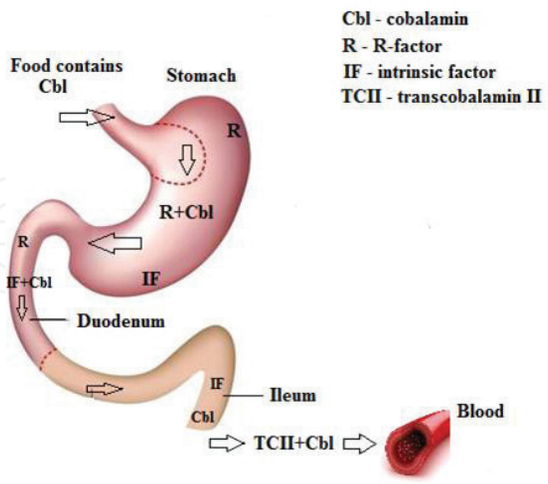

Figure 3. Absorption mechanism of vitamin B12 (based on Ref. [20]). Cobalamin (Cbl) is released from the food in the stomach, where it competes with the intrinsic factor (IF) to bind the R-factors. In duodenum R-factors are proteolytically degradated by pancreatic enzymes and released Cbl from the complex. IF and Cbl form a complex (IF-Cbl) which moves to the ileum and binds ileum receptors. The cells of the ileum absorb Cbl. Finally, Cbl binds to transcobalamin II (TC II), which delivers the complex to cells outside the intestinal tract.

defects or pathological changes in gastric and intestinal mucosa may lead to a deficiency of IF, in which case the transport of vitamin B12 is impeded and deficiency is present [17].

In circulation, B12 binds to other protein—transcobalamin II (TC II) [22], which ensures the transport to the liver, where the vitamin is stored for short time and finally is released and transported by the transcobalamin I to other tissues in the body. The excess vitamin B12 is stored for several hours in the liver without forming deposits (in contrast to fat-soluble vitamins) and is excreted in the urine.

2.5. Functions of vitamin B12 in the human body

The important reactions involved in the metabolism of vitamin B12 define its crucial role in a series of body processes. The main functions of vitamin B12 are summarized as follows [23]:

1. It carries and delivers methyl group to other molecules (including DNA and neurotransmitters). In this way, it has a significant role in cell division.
2. Vitamin B12 has activity as a coenzyme in many enzymatic reactions.
3. It participates in the synthesis of porphyrins, which are an important component of hemoglobin.
4. Together with folic acid, it is involved in the synthesis of red and white blood cells.
5. Without vitamin B12 folic acid cannot be absorbed and remains "trapped" in the intestinal wall (this is the reason why vitamin B12 deficiency causes the same symptoms as folate deficiency).
6. It supports the iron activity in the body and is involved in the synthesis of choline.
7. Vitamin B12 is necessary for reproduction and stability of DNA and RNA.
8. It helps the metabolism of vitamin A and more particularly absorption of carotene.
9. Vitamin B12, together with vitamin B6, facilitates the conversion of amino acids into hormones and neurotransmitters.
10. It supports the myelin sheath around nerve structures, working together with folic acid.

2.6. Causes of B12 deficiency in humans

Vitamin B12 deficiency is a common diagnosis, especially in older people [24]. Often the deficiency is due to mutations in the genes encoding important proteins in cobalamin metabolism, diet (vegetarian, vegan diet), and reduced production of stomach acids that are needed for the absorption of vitamin B12 [11, 23]. Other common causes are pernicious anemia (malabsorption of vitamin B12); atrophic gastritis; gastrectomy; Zollinger-Ellison syndrome; intestinal diseases, especially of the ileum (celiac disease, Crohn's disease, ileitis); pancreatic insufficiency; parasitism; bacterial overgrowth; medicament use (antiepileptic agents, proton pump inhibitors, histamine receptor antagonists, metformin, antibiotics); diabetes mellitus; renal insufficiency; smoking; and alcohol abuse.

Traditionally, the vitamin B12 deficiency is considered to be accompanied by low levels of B12 in the serum (or plasma) of the patient. This fact is disputed by some authors who believe that a significant proportion of people with normal or high levels of vitamin B12 actually have a deficiency [14, 19, 25].

The lower levels of vitamin B12 in serum are often used to assess the state of the vitamin, but this approach generates a high rate of false-negative results. A number of studies have shown that holotranscobalamin (the complex between transcobalamin II and vitamin B12) may be more reliable indicator of the status of vitamin B12 [14]. The holotranscobalamin binds only 20–30% of vitamin B12 circulating in the blood but is responsible for delivery to the cells and is considered to be the functionally important fraction. Therefore, testing for it can identify low vitamin B12 status before the total serum vitamin B12 levels drop.

The increase in homocysteine and methylmalonic acid (MMA) in the plasma is also sensitive indicators of the status of vitamin B12. The levels of plasma homocysteine may also elevate in folic acid or vitamin B6 deficiency, but the increase in MMA always indicates a poor status of vitamin B12 (the only other reason that explains the increased levels of MMA is renal insufficiency). MMA is considered the most representative marker for vitamin B12 deficiency, but the low accessibility of the assay in laboratory practice reduces its clinical utility [14].

2.7. Vitamin B12 excess

Whereas vitamin B12 deficiency has been studied intensively, the reverse situation—abnormal high levels—is rarely discussed in the literature. High plasma levels (when not associated with exterior supply) refer in all cases to some alteration in the metabolism of vitamin B12—either increased synthesis or decreased clearance of B12-binding proteins. In a routine blood tests, elevated levels of B12 are found in approximately 8–15% of patients referred for the measurement [26, 27]. The significance of this fact still needs to be clarified and linked to clinically important outcomes.

3. The immune system: how it works?

The immune system is a complex of cells, tissues, and organs that are specialized in defending against foreign agents. It is a remarkable defense mechanism and makes rapid, specific, and protective response against the innumerable potentially pathogenic microorganisms. The immune system also has a role in rejection of tumors.

3.1. Immune cells and organs

Cells of immune system are formed from pluripotent hematopoietic stem cells, capable of self-renewal and differentiation into lymphoid and myeloid progenitor cells. Lymphoid progenitors differentiate into T cells, B cells, and natural killer (NK) cells. Myeloid progenitors differentiate into monocytes and macrophage, granulocytes (eosinophils, basophils, and neutrophils), and other cell types.

In the primary lymphoid tissues (thymus and bone morrow), lymphocytes develop and mature to a stage at which they are able to respond to a pathogen. T and B lymphocytes both originate from lymphoid precursors in the bone morrow, but whereas B cells complete their maturation in the bone marrow, before entering the circulation, T cells leave the bone marrow at an immature stage and migrate to the thymus where they mature [28].

In the secondary lymphoid tissue (lymph glands, lymphatic vessels, spleen, and mucosa-associated lymphoid tissue), mature lymphocytes become stimulated to respond to invading pathogens [28]. The main function of lymph nodes is to trap antigens that flow into them via afferent lymphatic and to provide place for clonal expansion of lymphocytes. The spleen is the lymphoid organ that serves as filter for the blood to remove damaged or senescent red cells and protect against blood-borne pathogens. Splenic macrophages and dendritic cells grab the microorganisms and microbial products in the blood and then stimulate the T and B cells that arrive in the spleen from the blood. The thymus is an organ that lies behind the breast bone and where the T lymphocytes mature.

3.2. Innate and adaptive immunity

In regard to its function, the immune system is divided into two major components: innate immunity and adaptive immunity.

The innate immune response occurs rapidly and can generate effective mechanisms that start rapidly after the infection. The innate immune system consists of physical barriers such as the skin, chemical and microbiological barriers in the mucous membranes, phagocytic cells, and soluble factors [29]. The cells of the innate immunity are phagocytic cells (neutrophils, monocytes, macrophage), cells that release inflammatory mediators (mast cells, basophils, and eosinophils) and NK cells [30].

Neutrophils are the first line of defense in the body. They are recruited at the site of infection immediately after the invasion of a foreign antigen.

Monocytes are leucocytes that circulate in the blood and travel to tissues where they mature into macrophages able to engulf dead cells or invading pathogens [28]. After exposition to inflammatory stimuli, macrophages secrete cytokines such as tumor necrosis factor (TNF), interleukins (IL), leukotrienes, and prostaglandins. All these molecules increase vascular permeability and recruit inflammatory cells [31].

Eosinophils can kill large pathogens which cannot be phagocytized, while basophils and mast cells are implicated in the regulation of the immune response to parasites [28]. These cells play substantial roles in the induction of allergic inflammatory responses too. Mast cells and basophils can produce cytokines such as ILs, granulocyte-macrophage colony-stimulating factor, and TNF which are important for late consequences in allergic inflammatory responses [32].

Natural killer (NK) cells have the morphology of lymphocytes, but they do not bear specific antigen receptors [29]. NK cells are important in the defense against viral infection by killing infected cells and secreting of cytokines that hamper viral replication [28].

Soluble factors include the complement, acute-phase proteins, and cytokines [30]. Complement represents a key component of the innate immunity. It is composed of more than 40 proteins and produced mainly by the liver. It is a cascade of soluble proteins and membrane-expressed receptors and regulators, which operates in plasma, on cell membranes, and within cells [33]. The main roles of the complement activation are (1) opsonization of microbes and promoting phagocytosis, (2) triggering of inflammation process after diffusion of complement components away from the site of activation, (3) elimination of large immune complexes from the blood, and (4) membrane rupture of foreign cells.

Acute-phase proteins are a class of plasma proteins that include C-reactive protein, serum amyloid A protein, proteinase inhibitors, and coagulation proteins. They enhance the resistance to infection and support the repair of damaged tissue [30].

Cytokines are chemical messengers secreted by one cell to modify its own behavior or the activity of other cells. Cytokines that are produced by leucocytes and affect other white cells are named interleukins. Chemokines have chemoattractant activity and colony-stimulating factors cause differentiation and proliferation of stem cells. Interferons are a major class of cytokines which have antiviral activity [29].

The soluble factors are important in engaging monocytes, macrophages, and neutrophils in the phagocytosis [34], during which the foreign agents are destroyed by lysosomal enzymes, acidic pH, and radical attacks.

The second line of defense against a pathogen is the adaptive immunity, which takes several days to fully develop. Adaptive immune responses involve the proliferation of T and B lymphocytes after expressing on their surface of antigen-specific receptors.

B cells secrete immunoglobulins—the antigen-specific antibodies responsible for eliminating extracellular bacteria.

T cells help B cells to make antibody and can eradicate intracellular pathogens by activating macrophages and killing infected cells. Mature T cells display different surface markers and have different roles in adaptive immunity: cytotoxic T lymphocytes (also named CD8+ T cells) directly attack and kill infected or tumor cells; helper T lymphocytes (also named CD4+ T cells) send signals (cytokines) to other types of immune cells (CD8+ T cells); and regulatory T cells, called suppressor T cells, suppress the immune response [28].

Innate immunity and adaptive immunity interact and work together to eliminate pathogens and to protect the body from infection and disease.

4. Vitamin B12 as immunomodulator

4.1. Specific role of vitamin B12 in immune system functioning

Vitamin B12 plays a crucial role in the proper functioning of immune system. Methionine synthase, which uses methylcobalamin as a cofactor, is essential for the synthesis of purines

and pyrimidines in all cells, including fast-dividing immune cells. Several studies (both in man and on animal models) have reported the exact function of vitamin B12 in the immune response.

B12 deficiency leads to a low number of lymphocytes and impairs the activity of NK cells (the most important for destroying cancer cells) [35]. More specifically, CD8+ cells are decreased in patients with B12 deficiency anemia when compared to control population. Although the total number of CD4+ lymphocytes remains the same, the proportion of CD4+ is significantly elevated in such patients, and hence an abnormally high CD4/CD8 ratio is detected. A considerably suppressed NK cell activity was also noted in humans with B12 deficiency [35], as well as a decrease in the spleen NK activity was observed in rats on B12-deficient diet, although this effect was not statistically significant in the thymus or axillary nodes [36].

Intramuscular injections with B12 (under the form of methylcobalamin) in newly diagnosed B12-deficient patients completely restore the production of CD8+ T lymphocytes, the abnormally increased CD4/CD8 ratio, the CD3−CD16+ and CD16+CD57+ count (which possess strong NK cell activity), and hence the NK cells activity [35]. In contrast, serum levels of immunoglobulins are not affected by vitamin B12 deficiency or supplementation [35]. Intramuscular administration of cyanocobalamin in patients with pernicious anemia and low serum levels of vitamin B12 (three to ten times lower than reference level) increases the number of CD8+ and decreases CD4/CD8 ratio back to normal [37].

In addition, a significantly lower lymphoblastic response to *Mycobacterium paratuberculosis* and higher susceptibility toward gastrointestinal nematodes were reported in lambs put on B12-deficient diet, but no differences were found in white blood cell counts and antibody production against bovine herpesvirus type 1 and *M. paratuberculosis* [38].

An enhancing effect of methylcobalamin on the proliferative response to concanavalin A (a selective T cell mitogen) and autologous B cells was also observed in human T lymphocyte cultures in vitro [39].

Vitamin B12 could minimize the effects of protein malnutrition in the hematological or immune system—30-day addition of vitamin B12 to a low-protein diet restores white blood cell number in rats fed to protein-deficient diet [40]. All lymphocyte subpopulations are completely restored back to control levels except neutrophils and eosinophils. Rats fed a protein-deficient diet supplemented with vitamin B12 present also a normal CD4/CD8 ratio [40]. This finding is extremely important as protein malnutrition often happens in cancer patients in result of the higher demands of the tumor.

4.2. Vitamin B12 in cancer development

Most of the evidence does not absolutely clarify the role of vitamin B12 in the process of carcinogenesis and anticancer defense. This is due mainly on the dual modulatory effects that are constantly reported for vitamin B12. Another important question is the nature of

administrated vitamin B12—in some studies [41], a difference in the effect was noted between the food-administrated cobalamin and multivitamin-supplemented cobalamin.

One-carbon metabolism requires B vitamins, and hence the efficient dietary supply may protect against cancer by reducing DNA instability and by affecting DNA methylation [42], but vitamin B12, methylcobalamin, and coenzyme B12 were found to enhance DNA methylation in the presence of S-adenosylmethionine for concentrations up to 1 μM, but at higher concentrations, these compounds were found to inhibit DNA methylation [43].

The main immunological anticancer defenses in the organism include lymphocytes CD8+ and NK cells, which are strongly affected by B12 deficiency, as stated above. It is, therefore, intuitively logical that cobalamin will have positive effect on anticancer defense and will enhance anticancer treatment. One can also expect that vitamin B12 deficiency (mainly diagnosed as decreased plasma levels) will strongly correlate with the cancer risk. Interestingly, a considerable number of patients with different types of cancer or other chronic inflammatory diseases—acute and chronic liver diseases, malignant hemopathies (myelodysplasia, myeloproliferative diseases, and multiple myeloma) [44]; myeloproliferative disorders, such as chronic myeloid leukemia, polycythemia vera, and hypereosinophilic syndrome [26]; hepatocellular carcinoma [45]; and prostate cancer [46, 47]—have elevated levels of B12 in their blood. However, we should keep in mind that vitamin B12 deficiency can be present with either low or high serum levels of the vitamin, as the later ones can arise from impaired tissue uptake and activity at cellular level and it is irrelevant to establish direct causation.

In a population-based cohort study in Northern Denmark, which includes individuals without prevalent cancer and with plasma vitamin B12 levels ≥200 pmol/L (normal), the overall cancer risk was found to increase with high B12 levels [48]. This observation is especially significant in smoking-related, alcohol-related, and hematological cancers, thus provoking the authors to conclude that elevated B12 blood level can be successfully used as cancer markers. Furthermore, as patients on B12 therapy were excluded from the study and intestinal absorption capacity for B12 is limited, they hypothesized that elevated levels are directly related to malignization.

Together with vitamin B12, the haptocorrin levels (B12-binding protein) are also higher in cancer patients and may serve as additional cancer-provoking or cancer-resulting factor [48].

Additionally, patients with autoimmune lymphoproliferative syndrome also show high B12 levels [49], again without clear explanation of the nature of this finding—is it due to low absorption in gastrointestinal tract or inability to enter the cells and to serve its physiological role.

In contrast, circulating levels of vitamin B12 are not associated with pancreatic cancer risk, but this observation is limited to individuals using regular multivitamin supplements. Among individuals who do not use multivitamin supplements, the inverse relation (although modest) between circulating B12 and pancreatic cancer risk [41] was proven.

Inverse association of cobalamin to gastric cancer occurrence also exists, while MMA (which is elevated under vitamin B12 deficiency) is positively associated with gastric cancer [50]. This result could be due to worsen vitamin B12 status in atrophic gastritis that often precedes gastric cancer.

Similarly, plasma vitamin B12 levels are inversely associated with breast cancer risk, but again with one strong limitation—the finding is significant among premenopausal women but not

among postmenopausal women [51]. A more recent nested case-control study, in contrast, did not find any association between breast cancer risk and levels of vitamin B12 in the blood of tested patients [52].

In other case-control studies among multiethnic female population in Hawaii, vitamin B12 supplements showed inverse, dose-responsive associations with high-grade squamous intraepithelial lesions of the cervix [53], suggesting a protective role in cervical carcinogenesis.

Finally, vitamin B12 deficiency accelerates the development of AIDS in HIV-infected patients, whereas normalization of levels retards the development of immune dysfunction [54]. Decreased serum vitamin B12 levels occur in up to 20% of patients with AIDS and may adversely contribute to the hematologic and neurologic dysfunction [55].

4.3. Vitamin B12 as part of cancer immunotherapy

All these findings raise the question if there is a well-founded need to supplement our food with vitamin B12 in order to prevent future cancer development. Again no unanimous response exists. In a case-control study in Australia, vitamin B12 intake was not found to associate with childhood brain tumor risk [56]. Similarly, increased intake of it does not correlate with decreased risk of colorectal cancer [57], and also there is no significant effect when combine with folic acid and vitamin B6 on colorectal adenoma [58] and on total invasive cancer or breast cancer risk [59] among women at high risk for cardiovascular disease. Dietary and multivitamin supplement intake of cobalamin does not correlate with ovarian cancer diagnosis [60], nor with breast cancer [61]. In contrast, patients with high dietary intake of vitamin B12 have decreased tumor suppressor methylation of genes related to head and neck cancers [62]. Offspring of rats fed on vitamin B12-rich (together with methionine, choline, and folate) diet during pregnancy has significantly decreased breast cancer incidence, tumor multiplicity, and tumor volume [63].

The second question to answer is where it is relevant to include vitamin B12 in the nutrition scheme of cancer patients. To date, vitamin B12 is officially included as supplement to pemetrexed treatment (a chemotherapeutic used in pleural mesothelioma and non-small cell lung cancer because of its folate similarity and inhibition of purine and pyrimidine synthesis). In such patients, cobalamin efficiently reduces the toxicity of the main treatment [64].

Besides its direct effect in reducing the toxicity of anticancer drugs, as vitamin B12 is essential for red blood cell synthesis and neural functions, it should be included as part of the nutrition of cancer patients to avoid additional adverse effects (anemia, immune weakness, and cognitive problems). An eligible example is the use of cobalamin supplementation to decrease the severity of chemotherapy-induced peripheral neuropathy, which concerns approximately one third of all patients undergoing chemotherapy [65].

5. Conclusion

The current knowledge is insufficient to fully describe the link between tumorigenesis and vitamin B12 metabolism. Intuitively most of the specialists accept possible implication of B12 deficiency in the impairment of the immune system and hence a putative causation to cancer

development. Unfortunately, most of the studies do not support that elevated dietary intake and additional supplement with the vitamin could protect against cancer risk. However, the dominant opinion is to integrate B12 as part of rational and healthy nutrition to ensure proper function of the immune system.

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