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GENERAL INFORMATION

The genetic expression of water-soluble vitamins

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Abstract
In the year 400 BCE, Hippocrates said: "Whenever man can be cured with food, do not use medication". However, Nutrition as a science was only born at the end of the 17th century and the early 19th century when Lavoisier began studying metabolism. We now know that health depends on genetic structure and a great deal of the elements that integrate the environment. The interaction between these two factors (genes and nutrients) is currently under investigation by a new science called Nutritional Genomics. This science describes the functional interactions between food and its components and the genome at the molecular, cellular and systemic levels with the sole purpose of either preventing or treating diseases through diet. Nutritional genomics involves both nutrigenomics and nutrigenetics. The former studies the effects of nutrients and substances we eat in food on genetic expression. Nutrigenetics deals with the way different genetic variants (polymorphisms) favour different responses to specific nutrients, which eventually lead to both different health status and diseases among individuals. Nutritional Genomics is a young science. The role of water-soluble vitamins in health is no longer considered only enzyme cofactors; they are active regulators of gene expression. Nevertheless, more research is necessary to understand their role and to use that knowledge for both prevention and management of disease, particularly cancer and degenerative chronic diseases.

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La expresión génica de las vitaminas hidrosolubles

Resumen
En el año 400 a.C., Hipócrates pregonaba que: "mientras se pueda curar al hombre con alimentos, no se empleen las drogas". Sin embargo, la nutrición como ciencia surgió hacia finales del siglo XIII y principios del XIX, cuando Lavoisier inició el estudio del metabolismo. Actualmente se reconoce que el estado de salud depende de la constitución genética y de muchos elementos que conforman el ambiente. Las interacciones entre estos 2 factores (genes y nutrientes) es estudiada por una nueva ciencia denominada genómica nutricional. Esta se encarga de describir las interacciones funcionales de los alimentos y sus componentes con el genoma a niveles molecular, celular y sistémico, con el objetivo de prevenir o tratar enfermedades con la dieta. La genómica nutricional incluye la nutrigenómica y la nutrigenética. La primera estudia el efecto que tienen los nutrientes y sustancias que se ingieren y sobre la estructura y la expresión génica. La nutrigenética se encarga de dilucidar cómo las diversas variantes genéticas (polimorfismos) favorecen respuestas distintas a nutrientes específicos, lo que eventualmente lleva a diferencias en el estado de salud y enfermedad entre los individuos. La genómica nutricional es una ciencia joven. El rol de las vitaminas hidrosolubles en salud ya no es solo de cofactores enzimáticos; actualmente son reguladores activos de la expresión de genes. Sin embargo, se requiere más investigación para entender su función y poder utilizar ese conocimiento en la prevención y tratamiento de enfermedades, particularmente el cáncer y las patologías crónico-degenerativas.

Basic molecular mechanisms of gene expression

Gene expression involves the entire process by which the information contained in a gene is decoded in order to synthesise a protein or RNA in the case of noncoding genes. The regulation of gene expression includes all processes that determine which genes are expressed in a given moment, with what intensity and under which conditions in a specific cell, which together defines the type and amount of synthesised proteins (Fig. 1)[1-3]. Gene expression is regulated at different levels: pretranscriptional; transcriptional; at the level of processing, transportation and stabilisation of messenger RNA (mRNA) and at a translational level (Fig. 2). Pretranscriptional control refers to the regulation of the availability of DNA for its transcription. This point can be regulated by the physical or biochemical condition of the DNA. DNA has different levels of structural organisation. The degree of supercoiling determines the chromatin regions that are available or not for transcription. Chromatin with active transcription exists in an extended open conformation in the form of a "pearl necklace". These "pearls" correspond to nucleosomes, structures formed by a octameric histone core of proteins and double stranded DNA wound around this core[4].

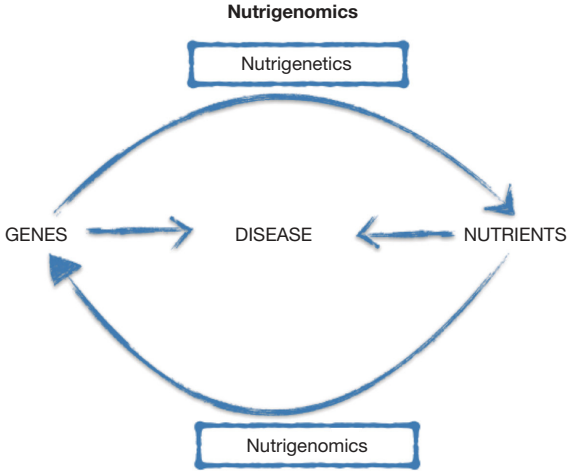

Figure 1 The interaction of genes and nutrients largely determines an individual's health status or disease. These interactions are studied by nutritional genomics that, in turn, includes nutrigenetics and nutrigenomics.

The biochemical availability of DNA may vary according to a number of reversible modifications of DNA or its associated proteins (epigenetic changes). DNA molecules can be methylated. DNA methylation is carried out on cytosine residues located between guanine residues (CpG islands), and this modification implies changes to the affinity of DNA binding proteins. In general, methylation is associated with gene silencing, i.e., a decrease in transcription[4]. Histone proteins are susceptible of being covalently modified by acetylation, biotinylation, methylation, phosphorylation, ubiquitination and poly(ADP) ribosylation. Acetylation is one of the most common mechanisms for controlling gene expression at an epigenetic level. Acetylation of lysine residues at the amino terminus of histones decreases the positive charge of these proteins and, consequently, reduces its affinity for DNA. This facilitates the release of DNA from the nucleosome and its greater availability for transcription. The histone deacetylation, however, is associated with a lower rate of transcription[5,6].

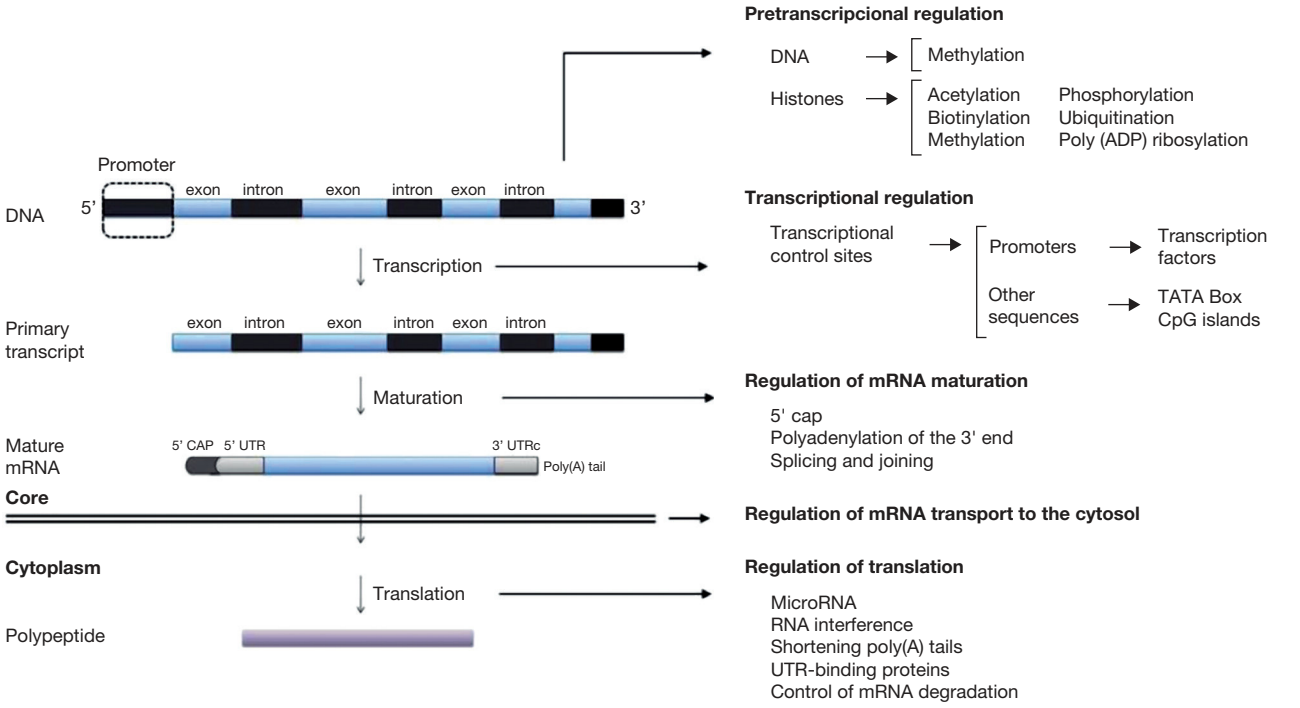

Figure 2 Basic molecular mechanisms of gene expression and its regulation in different control levels (see text).

Transcription in eukaryotic organisms consists of transferring the information stored in DNA into RNA[4]. The main point of regulating gene expression is the transcription stage. Each gene contains one or more promoter sequences that indicate the transcription start site, although they usually have a basal promoter. The basal promoter is identified by the RNA polymerase II (RNApol II) aided by general transcription factors. The RNApol II binds to the DNA and starts transcription on one of the strands with the addition of ribonucleotide triphosphate. The elongation of the nascent RNA chain continues towards 3'→5' to complete its synthesis. At this time, the complete RNA molecule (primary transcript) is released from the RNApol which, in turn, dissociates from the DNA.

Transcriptional control sites are sequences of DNA binding proteins. They include promoters and sequences that can be located near or at great distances from the promoter. Among the most studied is a conserved sequence called the "TATA box". This sequence is recognised by transcription factors, which in turn are associated with RNApol, indicating the precise transcription start site. The TATA box is associated with genes that have a high transcription rate, although it is only present in ~20% of genes in mammals. Other abundant sequence promoters are "CpG islands", regions rich in CG repeats (cytosine and guanine). CpG islands are characteristic of genes whose transcription rate is low.

Transcription factors are proteins that stimulate or repress gene expression. They interact with different transcription regulatory sequences. Typically, a gene has binding sequences for multiple transcription factors and only one factor can modify the rate of transcription of various genes[5,6]. Therefore, the regulation of gene expression at this level is a result of combinatorial events where the synthesis, activation and availability of various transcription factors according to the conditions of cell medium are important.

Once the transcription is complete, the RNA molecule formed should be modified to become a functional mRNA. These modifications consist of the synthesis of 5' cap and polyadenylation of the 3' end. The formation of the 5' cap consists of the addition of a 7-methylguanylate at the 5' end, which prevents enzymatic digestion of the mRNA and participates in its transportation to the cytoplasm and facilitates the initiation of the translation. A long chain of polyadenylate residues is added to the 3' end in the polyadenylation. This modification stabilises the mRNA molecule in the cytosol, thereby preventing its degradation by nucleases, prolonging its half-life and facilitating its binding to initiation of translation factors. Finally, the transcribed RNA undergoes modification through a process of "splicing" wherein the gene introns (non-coding sequences) are removed and exons (coding sequences) remain. This issue can vary even between transcripts of the same gene, giving rise to different variants of the same protein or isoforms. At both ends of the mRNA molecule, short noncoding sequences (UTR) remain that participate in translation control[4,6].

Translation consists of transferring the message encoded in mRNA as nucleotides towards a corresponding sequence of amino acids in order to synthesise a polypeptide. The translation process can be controlled at different levels. There are variants of RNA (microRNA and interference RNA) that repress the translation or destroy the mRNA molecules. The polyA tails of mRNAs gradually shorten once they are in the cytoplasm. This shortening favours, at a given moment, the degradation of mRNA mediated by exonuclease. In turn, there are translational control proteins of specific

sequence whose binding sites are located in the noncoding UTR regions. The effects of these adapter proteins on translation control are varied as they can stabilise or induce mRNA degradation and increase or decrease translation. This effect depends on the type of binding protein and association of other factors, which together influence the correct spatial and temporal expression of genes in a cell. Finally, error detection transcription in the mRNA molecule favours degradation to prevent the synthesis of dysfunctional proteins[4].

Regulation of gene expression by water-soluble vitamins

Vitamins are organic compounds the body cannot synthesise (with some exceptions), that are needed in small quantities and essential to maintain an adequate metabolism[7]. Based on its properties of solubility in water and fats, the most accepted classification is that it divides water-soluble and fat-soluble vitamins[6]. The group of water-soluble vitamins consists of vitamins called B complex and vitamin C.

The main activity of the water-soluble vitamins is to act as enzyme cofactors. This role has been widely identified for all of them. However, in recent years they have been attributed specific functions in the regulation of gene expression, a function that was previously considered more typical of macronutrients and fat-soluble vitamins. A brief analysis of the main actions exerted by the water-soluble vitamins on the regulation in the genome expression is made below.

Thiamine (vitamin B_1)

Its active form is thiamine diphosphate. It is a coenzyme that participates in reactions of oxidative decarboxylation. It operates in the metabolism of carbohydrates (pyruvate dehydrogenase), the citric acid cycle (α-ketoglutarate dehydrogenase), in the pentose phosphate pathway (transketolase) and in the metabolism of isoleucine, leucine and valine (α-ketoacid dehydrogenase)[6-8]. Its absorption is carried out through the cell membrane via two transporters: thiamine transporter of type 1 (THTR-1) and type 2 (THTR-2). There is evidence that extracellular concentrations of thiamine in the pancreatic islet β-cells in human and mice regulate the absorption of this vitamin. High concentrations of thiamine diphosphate adversely affect the amount of mRNA and protein of its transporters. The decreased activity of the promoter is the major regulatory mechanism in this case[9]. Also, variations in the activity of thiamine and THTR-1 and THTR-2 are associated with different forms of cancer[10]. Liu et al.[11] (2003) demonstrated that THTR-2 expression is low in a breast cancer cell line resistant to methotrexate (MTX^R ZR-75). In this same cell line, it was shown that the values of exogenous thiamine and variations in gene THTR-2 expression regulate, in turn, gene expression associated with the tumorigenic process[12].

Thiamine is also able to regulate gene expression of some of the enzymes that use thiamine diphosphate as a coenzyme. Pekovich et al.[13] (1998) demonstrated in cultures of lymphocytes, fibroblasts and human neuroblastoma cells in normal conditions and deficiency of thiamine diphosphate, the lack of this coenzyme decreases transketolase mRNA levels and pyruvate dehydrogenase subunit E1-β[13]. The clinical application of these findings is still not very clear, but they could contribute to the study of breast cancer therapy or diseases due to thiamine deficiency.

Riboflavin (vitamin B_2)

Active riboflavin is found as part of two coenzymes: FMN (flavin mononucleotide) and FAD (flavin adenine dinucleotide). These coenzymes are transporters of electrons in oxidation-reduction reactions of the intermediary metabolism. They participate in the metabolic pathways of fatty acid and amino acid oxidations and in some of the citric acid cycle reactions, among others[6,14]. Due to the wide range of flavin-dependent reactions that exist, the information about the influence of riboflavin in gene expression is diverse and complex. Some studies highlight their role as photosensitizers in ultraviolet radiation-damaged models where its presence promotes damage due to oxidation of the DNA and mutagenesis[15,16]. Another study, however, highlights its antioxidant activity upon catalysing the glutathione reductase activity and thus preventing oxidative damage to the DNA and expression of proapoptotic genes in human hepatocarcinoma cells[17]. Manthey et al.[18] (2005) showed how flavoproteins participated in secreted protein folding in the endoplasmic reticulum. When faced with a deficiency of riboflavin, the accumulation of these misfolded proteins leads to the activation of anti-stress genes of the endoplasmic reticulum mediated by transcription factors such as ATF (activating transcription factor)-4, ATF-6, XBP-1 (X-box binding protein 1) and CHOP (C/EBP homologous protein)[18]. This condition affects the production of IL-2 in Jurkat cells[19] and apo B-100 in a human hepatocarcinoma cell line[18].

Finally, there is evidence that riboflavin is necessary to maintain DNA repair mechanisms of damage caused by cytosine methylation or single-stranded break. This is reflected in an increase of concentration of mRNA for the enzyme poly (ADP-ribose) polymerase[20-22]. This enzyme participates in DNA repair processes for damage by single-strand and excision of bases associated with inflammatory processes, cell death and cancer[4].

Niacin (vitamin B_3)

Niacin provides the nicotinamide ring to NAD and NADP, coenzymes with a fundamental participation in the cellular energy metabolism. NAD is also the substrate of multiple ADP-ribosylation reactions[6]. These latter, rather than the redox reactions, are sensitive to the values of niacin in the diet. The transfer of ADP-ribose units to proteins is associated with, among other phenomena, processes that modify the chromatin structure[20]. Poly (ADP-ribose) polymerase 1 (PARP1) can modify histone proteins by covalent (H1, H2A, H2B, H3, H4 and H5) or noncovalent (H1, H2A, H2B, H3 and H4) binding in the presence of NAD^+. These mechanisms temporarily alter that structure of nucleosomes and release DNA. During this period, processes can take place such as DNA repair and regulation of transcriptional phenomena. PARP also operate in the elongation of chromosomal regions

known as telomeres. Incomplete replication of telomeres is associated with the ageing process. The tankyrase 1 (a type of PARP enzyme) covalently ribosylating to telomeric repeat binding factors (TRF1 and 2) protect telomere instability during elongation. With the poly(ADP-ribosylation), the telomeric region relaxes and allows replication. The sirtuins (acetyl-ADP-ribose NAD^+-dependent) deacetylate proteins such as histones. The histone deacetylation removes negative charges from lysine tails increasing their affinity for DNA. This leads to the compaction of chromatin and transcriptional inhibition[4,5].

Pyridoxine (vitamin B_6)

The active form of pyridoxine —and of most biological interest— is the coenzyme pyridoxal 5' phosphate (PLP). It participates in >100 enzymatic reactions, most of which are transamination reactions and decarboxylation of amino acids[6]. Numerous examples have been described on the control of pyridoxine in gene expression. The most studied is the modulation of nuclear response to steroids by PLP. Steroid hormone receptors, once bound to their ligand, have affinity for specific DNA sequences located in the promoter and are called "hormone response elements". The binding of the hormone-receptor complex on this region and other transcription factors (such as nuclear transcription factor-1 [NF1]) modulates the transcription rate[23]. Studies into cell cultures by Allgood et al.[24] (1993) evidenced that PLP decreases the rate of transcription in steroid target tissues, whereas vitamin deficiency has the opposite effectthrough inhibiting the binding of the NF1 transcription factor to the promoter region[24]. Vitamin B_6 deficiency would therefore cause greater sensitivity of target cells to low concentrations of steroid hormones.

Other actions of pyridoxine are transcriptional modulation aspartate aminotransferase[25], glycogen phosphorylase[26], and albumin[27] in rat liver as well as human platelet GPIIb receptor,[28] all by a mechanism similar to inhibition of their respective transcription factors. However, Oka et al.[29] (1993) showed that in rat liver pyridoxine not only alters the functionality of transcription factors, but negatively modulates the ability of RNApol II to bind to the TATA box of the promoter region of various genes such as β-actin, apo α-1, phenylalanine hydroxylase and glyceraldehyde 3-phosphate dehydrogenase[29]. In adipose tissue, PLP covalently modifies RIP140, a transcription factor associated with lipid metabolism, promoting fat accumulation in adipocytes[30]. Moreover, in a murine model of colon cancer, dietary supplementation with vitamin B_6 reduced the rate of neoplastic transformation[31]. However, in some epidemiological studies, a decreased cancer risk has not been as evident as it has at an experimental level[32].

Biotin (vitamin B_8)

Carboxibiotin is the active form of biotin. It participates in intermediary metabolism as a coenzyme of four carboxylases: propionyl CoA (PCC), β-methylcrotonyl CoA (MCC), pyruvate carboxylase (PC) and acetyl-CoA carboxylase (ACC1 and ACC2)[7,33]. Biotin binding with these enzymes (and other proteins) is secondary to the action of biotin ligase: holocarboxylase synthetase (HCS)[33]. More than 2,000 human genes whose expression is regulated by biotin have been identified[34]. Such action is exercised mainly by epigenetic and transcriptional control. Epigenetic regulation is through biotinylation of histones. It consists of the covalent binding of biotin to the lysine residues at the amino end of histones H2A, H3 and H4, reaction catalysed by HCS[35,36]. Biotinylation of histone H4 is primarily detected in the pericentromeric heterochromatin. It is associated with gene silencing, mitotic chromatin condensation and DNA cellular response to damage[37]. Modification of other histones possibly associated with the ability to regulate the transcriptional activity of many of the genes depends on the biotin. Among these genes is the HCS itself, whose abundance in the cytoplasm (mRNA) and nuclear translocation rate depend on exogenous intake of biotin[38]. Other genes regulated by biotin are related to glucose metabolism, particularly in liver and pancreas[39-41].

Folic acid (vitamin B_9)

Folic acid operates in amino acid metabolism and nucleotide synthesis as a simple transporter of carbon units. The coenzymatic active form of folic acid is tetrahydrofolate (THF). It is generated from two consecutive reductions of folic acid by dihydrofolate reductase[6]. THF can be methylated. In this condition it is capable of being reduced by the THF reductase (THFR), for thymidylate oxidation synthesis to synthesise purine bases, or reduced to participate in the methylation of homocysteine and methionine synthesis. This methionine, in turn, becomes S-adenosylmethionine, which is the methyl group's main donor in the body. These methyl groups are essential for methylation of nucleic acids[6,42,43]. When folic acid is limited, this affects the production of both purine bases and pyrimidine and the metabolic pathways necessary to maintain the patterns of DNA methylation are altered. Both conditions increase the risk of cancer, particularly colorectal[44,45].

Folic acid deficiency is also associated with neurodegenerative diseases. The mechanisms that have been proposed are the changes in genomic methylation patterns and abnormal uracil incorporation into DNA, which together lead to neurodegeneration. Homocysteine is also increased in conditions of lack of folic acid, as with vitamin B_{12}, because both are directly involved in their metabolism. This amino acid can act as a neurotoxin by increasing oxidative stress and contributing to the excitotoxicity and mitochondrial dysfunction[44,45].

Cyanocobalamin (vitamin B_{12})

B12 or cyanocobalamin is a corrinoid compound. Its absorption requires binding to the intrinsic factor produced in the stomach. It acts as coenzyme of the mitochondrial methylmalonyl CoA mutase and cytoplasmic methionine synthetase[6,7]. The study of the influence of vitamin B_{12} on gene expression focuses on two areas: the regulation of serum concentrations of homocysteine and induction of neuropathy associated with vitamin B_{12} deficiency.

Methionine synthetase transforms homocysteine to methionine by transferring methyl groups. Therefore, the proper function of this enzyme will largely determine the homocysteine serum concentrations. High values of this

amino acid in the blood are associated with a low methylation potential, arteriosclerosis and high cardiovascular risk[7]. In the 1960s they described the ability of vitamin B_{12} to increase the enzymatic activity of methionine synthase in culture, but the mechanisms by which this effect was exerted were not studied. It was not until 1999 that an increase in the enzymatic activity of methionine synthase was reported due to an increase in the amount of protein available[6]. However, this effect was not accompanied by changes in the concentration of mRNA, so that the control exercised by vitamin B_{12} on this gene must necessarily be posttranscriptional. Finally, it was reported that the mRNA molecule from the methionine synthase contains an element of response to vitamin B_{12} in the 5' UTR region, which makes the translation more efficient by binding to the vitamin[4]. Therefore, the amount of protein rises even though the amount of mRNA is not modified.

Subacute degeneration of the spinal cord by deficiency of vitamin B_{12} has been extensively studied by several research groups according to Shils et al.[7]. This group developed an experimental model of B_{12} deficiency in gastrectomised rats in which manifestations of neuropathy were reproduced in a similar manner asit occurs in humans[7]. With studies conducted with these rats, the group demonstrated that cobalamin deficiency induces a decrease in the concentration of epidermal growth factor (EGF) in cerebrospinal fluid (CSF) and a decrease in its mRNA in neurons and glial cells of specific brain regions. EGF is a neurotrophic factor in the central nervous system of mammals essential for proper development and operation. In the same study the authors reported that there was an increase in the concentration of a potent proinflammatory cytokine: tumour necrosis factor alpha (TNF-α), which could be collaborating in the induction of damage. Supplementation of the diet with vitamin B_{12} restored EGF and TNF-α values to almost normal levels[7,32]. These same findings were found in humans with vitamin B_{12} deficiency. Subsequently they showed that the concentrations of IL-6 in CSF are also positively regulated by cobalamin. Recently, it was reported that a decrease of EGF in cerebrospinal fluid and in the liver in gastrectomised rats was accompanied by a decrease, both at protein and mRNA levels, of the EGF receptor (EGFR)[2]. Therefore, it has been suggested that regulation by cobalamin of EGF values could be at transcriptional level, both for the EGF itself and its receptor. Together, these findings indicate the important role of B_{12} in maintaining a normal metabolism of the nervous system and how its deficit decreases the synthesis of trophic factors and increases the production of inflammatory mediators that induce damage.

Ascorbic acid (vitamin C)

The active forms of vitamin C are ascorbic acid and dehydroascorbic acid. It operates in hydroxylase reactions that contain copper or iron related to α-ketoglutarate. It works as a powerful reducing agent and increases intestinal iron absorption[6,7]. The influence of vitamin C on the gene expression has been recently studied in different areas such as coagulation, metabolism, inflammatory response and cancer[32]. Ascorbic acid plays a fundamental role in platelet aggregation reactions. These cells maintain constant reserves of ascorbic acid, so they express their SVCT1 and SVCT2 transporters. Changes in ascorbic acid intraplatelet concentration modulate SVCT2 expression at a translational level, thereby regulating its own concentration[2].

The effect of vitamin C on the expression of the apo A1 gene[3] was studied in lipid metabolism. The apo A1 gene is the major component of HDL (high-density lipoproteins). In ODS rats that are unable to synthesise ascorbic acid and have diets that lack vitamin C, it was found that vitamin C deficiency decreases apo A1 serum concentrations and the concentration of its mRNA in the liver, whereas its addition to the diet restored both values to normal levels within 3 days[6]. According to these results, supplementation of vitamin C in medication concentrations could be a therapeutic option for people with cardiovascular risk.

Vitamin C may also modulate the inflammatory response in various tissues. In ODS rats' livers, vitamin C deficiency induces an effect similar to the response to an acute phase with elevation of serum haptoglobin and a decreased apo A1 and albumin. Corresponding mRNA levels behave in the same way in liver tissue[2]. Under the same conditions of deficiency of vitamin C, an increase in the hepatic expression of chemokines was shown[4]. In endothelial cell cultures and human umbilical cord, ascorbic acid affects the activity of the NF-κB transcription factor. This heterodimeric factor is found in the cytoplasm of cells bound to an inhibitory protein (IκB). Upon translocation to the nucleus, NF-κB induces the expression of proinflammatory genes and genes associated with cell death and proliferation. The addition of ascorbic acid in medical concentrations decreased nuclear translocation and expression of their transcriptional targets. A similar effect was seen in a study in human macrophages[9].

In the study of cancer and vitamin C there have been promising findings that can provide tools in cancer therapy, primarily focused on its antioxidant capacity. According to Johnson[42], Lutsenko et al. (2002) demonstrated that vitamin C, in medication concentrations, decreased the rate of DNA mutations induced by H_2O_2 in human kidney cells in a dose-dependen manner[42]. Meanwhile, Knowles (2003) and Cuiper (2010) and collaborators demonstrated in human tumour cells that ascorbic acid deficiency raised the activity of the hypoxia inducible factor (HIF-1) transcription. This factor coordinates the response to hypoxia and its activity is elevated in different types of cancers. Ascorbic acid negatively regulates its concentration by hydroxylation of specific residues in its subunit-α. The concentration of ascorbic acid was negatively related to the concentration of HIF-1 and the expression of its transcriptional targets in both studies[5]. In non-tumorigenic human cells HaCaT, ascorbic acid increases the transcriptional activity of MLH1 and p73 genes. MLH1 is a protein that is part of the DNA repair machinery and p73 is p53 homologue, the main tumour suppressor gene. This rise in the rate of transcription facilitates the availability of both factors in situations of DNA damage, which enhances the reparative capacity[42]. This evidence indicates that vitamin C has significant effects on both cancer prevention and its development.

Conflict of interest

The authors declare no conflict of interest.

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