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EDITORIAL

VITAMINS AND MAST CELLS

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The immune system is a highly complex, intricately regulated group of cells whose integrated function is essential to health. The mast cell inflammatory response is characterized by an early phase with massive discharge of mediators stored in cytoplasmic secretory granules. Through multigranular/ compound exocytosis and a late phase that involves generation of arachidonic acid metabolites and *de novo* synthesis of cytokines/chemokines and growth factors. Vitamins have been shown to have a protective effect on the body's immune cells. Vitamin C and E are necessary in allergic disease treatment where mast cells are involved. In addition, ascorbic acid and pyridoxine are useful compounds for the treatment of inflammatory disorder of the respiratory airways. Here we revisited the inter-relationship between vitamins and mast cells.

Mast cells are the derivatives of hematopoietic progenitor cells that migrate into virtually all vascularized tissues, where they complete tissue-specific maturation (1-10). They are a normal component of connective and mucosal tissues and play an important role in immediate (Type I) hypersensitivity and late phase reactions but also in innate immunity (11-17) and inflammation (18-21) by secreting a large variety of chemical mediators either from storage sites in their granules, or producing immuno-regulatory proteins upon stimulation (23-27). Regulation of their secretion is therefore critical for our understanding of a key biological process and for the development of effective anti-allergic/anti-inflammatory molecules (28-29). Mast cells have a relevant role in the immune system by interacting

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with B and T cells and by releasing several mediators involved in activating other cells. Mast cell mediators include cytokines and chemokines, arachidonic acid products, biogenic amines, chemoattractants, growth factors, neuropeptides, proteoglycans and proteolytic enzymes (30-31). Since mast cells reside in close physical proximity to blood vessels and facilitate T-cell infiltration in allergy inflamed tissues, it is pertinent that the production of several cytokines and chemokines could contribute to mast cell proliferation/activation (32). On the other hand, activated mast cells can lead to T-cell activation and cytokine and chemokine production.

VITAMINS

Historically, the majority of our medicines originate from natural products and their synthetic derivatives, many of which have taught us valuable lessons about biology. Vitamins are abundant in fruits and vegetables and also can be obtained in supplement form. Dietary supplements include a large group of products, such as vitamins, minerals, plant, or animal extracts, as well as herbal preparations.

It has been reported that many subjects do not meet their basic nutrient needs, particularly vitamin D, folic acid and vitamin A; vice versa, a daily vitamin intake contributes to nutritional status of the subject and can be a great way to support the nutritional needs by filling the nutrient gaps that may exist (33-34). Dietary vegetables and fruits can be a great way to support the nutritional needs by filling the nutrient gap that may exist.

The immune system mission is simple: to recognize foreign invaders and eliminate them. When the immune system is healthy, the body is doing a good job of fighting off the invaders and keeping the body health strong. Vitamins have been shown to have a protective effect on the body's immune cells (35-36). Many studies have reported that vitamins have been found to protect the integrity of cells and stimulate the production and function of the immune cells and play an important role in the maintenance of a healthy immune system. Even a slight vitamin deficiency can compromise the body's ability to fight infections. Most of the vitamins also protect against infections and several are powerful antioxidants and help to fight against free radicals in the body. Antioxidant nutrients, especially vitamins C and E, selenium, and zinc appear to be necessary in asthma treatment (37). Vitamins B6 and B12 also may be helpful. Free radicals are compounds that can harm the healthy cells, including the immune cells. Environmental pollution, the sun's ultraviolet rays, cigarette smoke and certain health conditions are all capable of triggering free-radical damage in the body. Vitamins are involved in many aspects of the health such as growth, development, nervous system function, antioxidant activity and reproduction.

INTER-RELATIONSHIP BETWEEN VITAMINS AND MAST CELLS

Vitamin B6 in the body is involved in many biochemical processes. Two vitamins, ascorbic acid and pyridoxine have been suggested by others as useful drugs for the treatment of inflammatory disorder of the respiratory airways. Pyridoxine (200 mg daily), one of the B vitamins, is useful in the treatment of childhood bronchial asthma (1) and at concentrations of 10^{-3} M, or greater, significantly inhibits rat mast cell degranulation and histamine release induced by phospholipase A, compound 48/80. In addition, it has been shown that nicotinamide like pyridoxine, another B vitamin, has an inhibitory activity in rat mast cell degranulation and histamine release (23). However, there is no experimental basis for considering ascorbic acid as a prophylactic anti-asthmatic drug as is disodium cromoglycate. Therefore, pyridoxine merits additional research and more studies are required to clarify its effects.

Vitamin D is relevant for healthy brain function and development (38-40). It has been reported that low vitamin D levels have a negative effect on the cognition and, in fact, decrease performance on cognitive tests. Topical vitamin D3 analogues are very effective in the treatment of mild to moderate plaque psoriasis. Vitamin D3 analogues have their effect on psoriasis via binding nuclear vitamin D3 receptors on genes involved in cellular proliferation, differentiation and inflammation. Synthetic vitamin D3 analogues include calcipotriol, maxacalcitol, tacalcitol and calcitriol, these compounds are only minimally systemically absorbed and therefore have few systemic side effects. Skin irritation is the most

frequently noted side effect and can be managed by combining vitamin D3 analogues with other topical or systemic therapies, such as narrow-band UVB phototherapy or topical corticosteroids. The use of a vitamin D agent helps improve the efficacy of topical corticosteroids for psoriasis and helps minimize the potential for adverse events associated with topical corticosteroid therapy (33). Recently, it was reported that vitamin D3 is involved in the production of IL-10 in cutaneous mast cells and can contribute to the mast cell's ability to suppress inflammation and skin pathology at sites of chronic UVB irradiation (18).

CRH may influence mast cell activation, direct modulation of immune cells, angiogenesis and induction of some receptors including receptors for steroids, retinoids and vitamin D; ligands of these receptors are effective in treating psoriasis.

It has been shown that mast cell granules contain vitamin D, which is not synthesized inside the granules. As mast cells may appear within the epidermis or in close proximity to it, it is reported that they do take-up vitamin D contained inside the epidermis' intercellular compartment. Therefore, vitamin D synthesized by the keratinocytes enter the intercellular compartment, where its synthesis is accomplished, and migrates towards the basement membrane. At the basal epidermis layer, or after passing through the basement membrane, vitamin D is taken up by mast cells, where it is stored inside its granules. (38).

Certain plants and spices containing flavonoids have been used for thousands of years in traditional Eastern medicine. Flavonoids are nearly ubiquitous in plants and are recognized as the pigments responsible for the colors of leaves, especially in autumn. Seeds, citrus fruits, olive oil, tea, and red wine are rich in flavonoids. They are low molecular weight compounds composed of a three-ring structure with various substitutions. This basic structure is shared by tocopherols (vitamin E). The particular hydroxylation pattern of the B ring of the flavonoles increases their activities, especially in inhibition of mast cell secretion. The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease, and cancer (35, 41).

Many studies show that vitamin E plays a relevant role in the maintenance of a healthy immune system. Even a slight vitamin E deficiency can compromise the body's ability to fight infection. Natural vitamin E covers a group of eight analogues - the alpha, beta-, gamma-, and delta-tocopherols and the alpha-, beta-, gamma-, and delta-tocotrienols, but only alpha-tocopherol is efficiently retained by the liver and distributed to peripheral tissues. Mast cells preferentially locate in the proximity of tissues that interface with the external environment (the epithelial surface of the skin, the gastrointestinal mucosa, and the respiratory system), which may render them accessible to treatment with inefficiently retained natural vitamin E analogues and synthetic derivatives. In addition to scavenging free radicals, the natural vitamin E analogues differently modulate signal transduction and gene expression in several cell lines; in mast cells, protein kinase C, protein phosphatase 2A, and protein kinase B are affected by vitamin E, leading to the modulation of proliferation, apoptosis, secretion, and migration (42).

In addition, vitamin E has preventive effects in cardiovascular disease which can be explained by the molecular and cellular effects of vitamin E observed in *in vitro* cell cultures. Coronary artery disease, cardiac events, inflammation and atherosclerosis are associated with elevated blood histamine levels, suggesting the involvement of this compound released by mast cells and other cells in these diseases. Increased numbers of mast cells were found in atherosclerotic lesions when compared with normal intima, and these mast cells are often associated with macrophages and extracellular lipids (42), in particular in fatty streaks and the shoulder regions of atheromas (43). In human blood vessels, mast cells have been observed in the intima of carotic arteries at sites of hemodynamic stress, together with monocytes, T-lymphocytes, and dendritic cells (44-45). It is still unclear, to what degree a higher density of mast cells in plaques is the result of increased recruitment or the consequence of higher proliferation. Mast cells are activated by oxidized lipoproteins (oxLDL) resulting in increased expression of inflammatory cytokines such as interleukin 8 (IL-8) (46), suggesting that the reduction of oxidation of LDL by vitamin E may also reduce mast cell activation. Moreover, activated mast cells can contribute to foam cells and fatty streak formation by stimulating LDL modification and uptake by macrophages (47), by secreting a variety of inflammatory mediators.

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