Vitamin E
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Role of Vitamin E in Immune System

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Summary Vitamin E is a potent antioxidant and has an ability to modulate host immune functions. This manuscript consists of six parts: (1) vitamin E deficiency and immunity, (2) vitamin E supplementation and immunity, (3) vitamin E and the decreased cellular immunity with aging, (4) vitamin E and T-cell differentiation in the thymus, (5) vitamin E and acquired immune deficiency syndrome (AIDS), and (6) vitamin E and the abnormal increase of host immune functions such as allergy and autoimmune diseases. In vitamin E deficiency most of the immune parameters show a downward trend, which is associated with increased infectious diseases and the incidence of tumors. In contrast, vitamin E supplementation has various beneficial effects on the host immune system. The decreased cellular immunity with aging or during the development of AIDS is markedly improved by the intake of a high vitamin E diet. In addition, vitamin E plays an important role in the differentiation of immature T cells in thymus. Vitamin E deficiency induces the decreased differentiation of immature T cells, which results in the early decrease of cellular immunity with aging in spontaneously hypertensive rats. Conversely, vitamin E supplementation induces a higher differentiation of immature T cells via increased positive selection by thymic epithelial cells, which results in the improvement of decreased cellular immunity in the aged. Furthermore, some reports have shown that vitamin E has an ability to modulate the development of allergy or autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus. Taken together, all of the evidence suggest that vitamin E is a potent vitamin for modulating not only decreased immunity shown in the aged but also abnormally increased host immune system in patients with allergy or autoimmune diseases.

Key Words: vitamin E, aging, T-cell differentiation, AIDS, allergy

Introduction

Vitamin E, α-tocopherol, acts as an antioxidant in cellular membranes and as a free radical scavenger by blocking the peroxidation of polyunsaturated fatty acids (PUFA). The damage of cellular membrane induced by free radicals results in changes of membrane-related cellular functions, inducing in some cases, the destruction of cells. In immune cells, α-tocopherol content is known to be higher than in other cells, because the cellular membrane plays an important role in the immune response. This suggests that vitamin E is an important nutrient in maintaining normal immune functions. Furthermore, it is estimated that one-forth of Japan’s popu-
lation will be older than 65 years of age at the beginning of the twenty-first century. Accompanying this increased percentage of elderly people will be an increased incidence of geriatric disorders and infectious diseases associated with the decrease of cellular immunity that occurs during aging. If this decrease of cellular immunity can be diminished, it may improve the health state of elderly people and prolong their life expectancy. Meydani et al. have found that a higher intake of vitamin E is needed to maintain immune functions in the aged people [1] and improves the decreased cellular immune functions that occur with aging [2]. This finding is related to the decreases in the serum vitamin E level during aging and the actions of vitamin E as an antioxidant and immunostimulator. This review focuses on the effect of both vitamin E deficiency and supplementation on the immune responses in animals and humans, and the immunomodulating effects of vitamin E in aging. In addition, as recent topics in the research on vitamin E and the immune response, the actions of vitamin E on both T cell differentiation in the thymus and abnormal increases of immune functions such as allergy and autoimmune disease are discussed.

I. Effects of Vitamin E Deficiency and Supplementation on Immunity

Vitamin E Deficiency and Immunity

As summarized in Table 1, most studies have shown that vitamin E deficiency induces the impairment of both humoral and cellular immunity. These immunosuppressive effects of vitamin E deficiency are associated with increased production of free radicals, which results in increased lipid peroxidation in cell membranes. In fact, macrophages and neutrophils from vitamin E deficient rats had higher \( \text{O}_2^- \) consumption, \( \text{H}_2\text{O}_2 \) release, and peroxidized lipids in their membranes [3, 4]. Although vitamin E deficiency appears to induce the decreased cellular immunity as described above, the phagocytic function of alveolar macrophages (AM) from rats fed a vitamin E deficient diet for 4 months was 2 times higher than that of control rats (Fig. 1) [5]. In addition, those AM did not respond to the in vitro treatment with macrophage-activating factor (MAF) prepared from Con A-activated rat splenic lymphocytes. Since MAF production from splenocytes activated in vitro with Con A-Sepharose beads decreased in vitamin E deficient rats, the higher phagocytic activity of AM from rats fed the vitamin E deficient diet does not appear to be induced by MAF. Sharp and Colston demonstrated the presence of highly activated macrophages in nude mice and considered that hyperactivity seen in the macrophages of nude mice resulted from a lack of T cell-mediated suppression [6]. As described above, vitamin E deficiency causes immunodepression, including T and B cell responses, which may result in inducing the higher phagocytic activity of AM.

Table 1. Vitamin E deficiency and the immune response.

<table>
<thead>
<tr>
<th>Immune response</th>
<th>Result</th>
<th>Species</th>
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<tbody>
<tr>
<td>T-cell mitogenesis</td>
<td>Decreased</td>
<td>Humans, mice, rats, pigs, dogs</td>
</tr>
<tr>
<td>Interleukin-2 production</td>
<td>Decreased</td>
<td>Humans, rats</td>
</tr>
<tr>
<td>B-cell mitogenesis</td>
<td>Decreased</td>
<td>Mice, rats</td>
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<tr>
<td>Natural killer cell activity</td>
<td>Decreased</td>
<td>Mice, rats</td>
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<tr>
<td>Plaque-forming cell</td>
<td>Decreased</td>
<td>Mice</td>
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<tr>
<td>Antibody titer</td>
<td>Decreased</td>
<td>Mice, chickens</td>
</tr>
<tr>
<td>Macrophage phagocytosis</td>
<td>Decreased</td>
<td>Rats</td>
</tr>
<tr>
<td>Polymorphonuclear leucocyte phagocytosis</td>
<td>Increased</td>
<td>Rats</td>
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<tr>
<td>Polymorphonuclear leucocyte chemotaxis</td>
<td>Decreased</td>
<td>Humans, rats</td>
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Fig. 1. Phagocytosis of \(^{51}\text{Cr}\)-labeled opsonized SRBC by AM of rats fed a control diet or vitamin E-deficient diet. AM \((2\times10^5)\) were preincubated for 4 h in a medium consisting of RPMI 1640 with 5% fetal bovine serum (Med) or in a medium with macrophage-activating factor (MAF, 1/162 dilution). They were then incubated with \(^{51}\text{Cr}\)-labeled opsonized SRBC for 2 h. Each value is the mean± SD for triplicate cultures. * Significantly different from cultures with medium \((p<0.05)\); ** significantly different from cultures with medium in control rat \((p<0.01)\). (Moriguchi et al.: J. Nutr. Sci. Vitaminol., 35, 419–430, 1989)
Fig. 2. Phagocytic activity of fractionated AM (A) and the proportions of fractionated AM (B) in rats fed a control or vitamin E-deficient diet. After AM were collected by tracheopulmonary lavage with warm saline, separation of the AM fraction was performed by using discontinuous Percoll gradient centrifugation. Discontinuous Percoll solutions were prepared by diluting a stock of Percoll with sterile saline to specific gravities of 1.050, 1.060, 1.070, and 1.080 and subsequently layered into centrifuge tubes. AM suspensions were carefully layered on the top of the diluted Percoll solutions and centrifuged at 400 g for 30 min. The cells localized at each interface area were then carefully collected with a Pasteur pipette. The fractions were designated I to IV in order of increasing density. In this experiment, the phagocytic activity of AM was assessed by measuring the absorbance of SRBC phagocytosed within AM. * Significantly different from other fractions (p<0.05).

In a recent study, we separated AM into four fractions (I to IV) by discontinuous Percoll density-gradient centrifugation. The degree of AM maturation is high from Fraction IV to Fraction I. As shown in Fig. 2A, the phagocytic activity of AM is the highest in Fraction III. We have found that vitamin E deficiency decreased the number of AM and increased the percentage of AM in Fraction III having the higher phagocytic ability against opsonized sheep red blood cells (SRBC) (Fig. 2B) [7]. These results suggest that vitamin E deficiency appears to induce the destruction of highly matured AM (Fraction I), which results in a decreased number of AM and a higher phagocytic activity of AM.

### Vitamin E supplementation and immunity

Contrary to the effect of vitamin E deficiency on the immune response, most studies have shown that vitamin E supplementation enhances the immune response as summarized in Table 2. As its mechanism, Meydani et al. found that vitamin E supplementation suppresses Prostaglandin E2 (PGE2) synthesis in spleen homogenate from old mice [2] and Baehner et al. showed that the in vitro administration of vitamin E prevents antioxidative damage to the membrane of polymorphonuclear leukocytes by scavenging H2O2 [8]. Because both PGE2 and H2O2 are potent inhibitors of several lymphocyte functions, including mitogenesis, cytolysis and antibody production [9-11], vitamin E supplementation decreases the formation of PGE2 and H2O2, which may result in the enhancement of mitogenic response and natural killer cell activity in splenic lymphocytes.

Studies on the effect of vitamin E supplementation on macrophage function are exceedingly few compared with those on lymphocyte functions. In particular, studies concerning AM, which play an important role in the defense against bacteria and neoplasms in the lung, are very limited. As shown in

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<tr>
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<td>Humans</td>
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<td>phagocytosis</td>
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<td>Delayed type hypersensitivity</td>
<td>Increased</td>
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Fig. 3. Phagocytosis of $^{51}$Cr-labeled opsonized SRBC by AM of rats fed high vitamin E diets. AM ($2 \times 10^5$) were preincubated for 4 h in medium or in medium with macrophage-activating factor (MAF, 1/162 dilution). They were then incubated with $^{51}$Cr-labeled opsonized SRBC for 2 h. (A) Phagocytic activity of AM incubated with medium only. Each value represents the radioactivity of $^{51}$Cr-labeled opsonized SRBC within AM and is the mean±SD for 10 rats. (B) The enhancement of phagocytic activity following in vitro treatment with MAF. Each value represents the stimulation index and is the mean±SD for 10 rats. The stimulation index was calculated by assigning a value of 1 to the phagocytic activity of control AM incubated with medium only and by comparing this to the phagocytic activity of AM from each group treated with MAF. *Significantly different from the controls (50 mg of vitamin E/kg of diet) ($p<0.05$). (Moriguchi et al.: J. Nutr., 120, 1096-1102, 1990)

Fig. 3A, the ability of AM to phagocytose opsonized SRBC was significantly and dose-dependently enhanced by feeding high vitamin E diets [12]. In addition, those AM from rats fed high vitamin E diets exhibited decreasing responses to MAF, prepared from splenic lymphocytes in vitro activated with Con A for 48 h, with increasing contents of vitamin E (Fig. 3B). These results suggest that AM from rats fed high vitamin E diets had already been activated by MAF.

Macrophages are known to be major prostaglandin-producing cells and also play a critical role in the regulation of immune responses by releasing cytokines that affect lymphocyte functions [13, 14]. As described previously, it has been reported that a high vitamin E diet decreases the production of PGE$_2$ from macrophages and enhances cellular immune functions [12, 15]. However, the precise mechanism by which vitamin E stimulates lymphocyte proliferation remains unclear. Specifically, it is not known whether vitamin E first stimulates macrophage function or lymphocyte functions. Oonishi et al. investigated the in vitro effect of vitamin E on the proliferation of both whole splenocytes and macrophage-depleted splenocytes [16]. They found that the proliferation of whole splenocytes was significantly higher than that of macrophage-depleted splenocytes at all concentration of Con A (0.5-10 µg/ml). In addition, when whole and macrophage-depleted splenocytes were preincubated with vitamin E (2 µg/ml) for 24 h, the proliferation of whole splenocytes was significantly enhanced compared with that of whole splenocytes preincubated with medium alone. In contrast, macrophage-depleted splenocytes did not show any increase of splenic lymphocyte proliferation following in vitro pretreatment with vita-
Vitamin E and Immunity 101

II. Vitamin E and Decreased Cellular Immunity with Aging

Animal Studies

Even though the life expectancy of experimental animals such as mice and rats is very short, it needs at least 1 to 2 years to investigate the effect of vitamin E on immune functions with aging. A good model for studying aging has been established in mice, which are called as the senescence-accelerated mouse (SAM) [18]. It is known that this mouse strain shows a marked decrease of splenic lymphocyte proliferation with mitogens from 6 months of age [19]. Muraga et al. have tried to investigate whether the decreased mitogen response of splenic lymphocytes in SAM is associated with the nutritional status of vitamin E and whether a high vitamin E diet can restore the decreased mitogen response of splenic lymphocytes in SAM. They found that there was no significant difference in serum vitamin E concentration between old SAM-P1 and SAM-R1 as control. Since a high vitamin E diet induced a similar increase of serum vitamin E concentration in both old SAM-P1 and SAM-R1, the vitamin E status in SAM-P1 appears not to be impaired and maintain a normal level [20]. In addition, a high vitamin E diet did not restore the decreased mitogen response of splenic lymphocytes in SAM-P1. Because Muraga et al. found that the percentage of adherent cells, mainly macrophages, in splenocytes was remarkably decreased in old SAM-P1 and their macrophages did not have the enhancing effect on proliferation of splenic lymphocytes from young SAM-R1, they came to conclusion that the decreased mitogen response of splenic lymphocytes in SAM-P1 is not associated with vitamin E status and is due to the decreases of both number and function of macrophages.

In rats, since spontaneously hypertensive rats (SHR) were derived from Wistar Kyoto rats (WKY) by Okamoto and Aoki [21], they are now widely used as an animal model for the study of human essential hypertension. Because SHR exhibit an accelerated decrease in, and abnormalities of, cellular immune functions with aging, Takeichi et al. proposed that SHR are a good model for the study of not only human essential hypertension but also the mechanism of aging [22]. It has been found that SHR show the remarkable decreases in mitogenesis and NK activity of splenic lymphocytes in the early stage of life (3 months old), and vitamin E levels in

Fig. 5. Scheme on the activation of macrophages or natural killer (NK) cells by vitamin E.
S. Moriguchi and M. Kaneyasu

Fig. 6. Proliferation of thymocytes with Con A in WKY and SHR fed a control or high vitamin E diet for 40 weeks. (○) WKY; (●) WKY + vitamin E; (■) SHR; (▲) SHR + vitamin E. *Significantly different from thymocyte proliferation with Con A in WKY or SHR fed a control diet at 4 weeks old (p<0.05). †Significantly different from WKY fed a control diet at the same age (p<0.05). ‡Significantly different from SHR fed a control diet at the same age (p<0.05). (Moriguchi et al.: Nutr. Res., 15, 401–414, 1995)

The decrease in T cell function in SHR is also associated with increased production of natural thymocytotoxic autoantibody (NTA) with aging [25]. We have also found that NTA titer in the serum of SHR steadily increased with aging and that vitamin E supplementation suppressed this increase [26]. The increase of NTA in SHR is relevant to the impairment of T cell differentiation in the thymus. In other words, the decrease of NTA titer in the serum of SHR may be a mechanism in which the high vitamin E diet restores cellular immune responses decreased with aging. This is related to normalize T cell differentiation in the thymus of SHR.

In fact, we have found that vitamin E supplementation improves the decreased expressions of CD4 and CD8 antigens on the membrane of thymic lymphocytes of SHR [26]. These data support that SHR is a good model for aging, especially for studying the effect of vitamin E supplementation and the possibility exists that high vitamin E diet has a potent effect on T cell differentiation in thymus. The effect of vitamin E on T cell differentiation in thymus will be described in the following head.

**Human studies**

Recent reviews on the beneficial effect of vitamin E for the immune system in the elderly have been summarized by Landmark [27], and Meydani and Beharka [28]. The effects of vitamin E supplementation on immune responses have been epidemiologically investigated on free-living elderly people. Goodwin and Garry failed to find any correlation between vitamin E intake and immune responses such as mitogen response, delayed cutaneous hypersensitivity, and serum antibodies in a population of healthy adults (65–94 years old) [29]. As its reason, they proposed the possibility that some of the previously reported immunoenhancing properties of megadose vitamins may be due to a nonspecific adjuvant effect disappearing with time. On the other hand, Chavance et al. found that plasma vitamin E levels were positively correlated with delayed type hypersensitivity response to diphtheria toxoid, candida, and trichophyton in 100 healthy subjects (>60 years old) [30]. They have also found that blood vitamin E concentrations were negatively correlated with the incidence of infectious disease episodes. Payette et al. also found that a negative correlation between dietary vitamin E level and IL-2 production in free-living elderly people [31]. However, because this study was performed by using dietary vitamin E...
rather than plasma vitamin E level, further study was needed to clarify the relationship between vitamin E and IL-2 production in elderly people. Meydani et al. [1] and Nagel et al. [32] have already found that IL-2 production in healthy elderly people is lower than that of healthy young subjects. In addition, Nagel et al. found that decreased expressions of both IL-2 and IL-2R mRNA contribute to the low synthesis of IL-2 and membrane IL-2R, respectively, which is partially responsible for the diminished proliferative response observed in lymphocytes from the elderly. De Waart et al. studied the effect of a daily dose of 100 mg of dl-α-tocopheryl acetate on the cellular and humoral immune systems in a 3-month, double-blind, placebo-controlled intervention trial among elderly subjects over 65 years old [33]. Although plasma α-tocopherol concentration increased by 51% during intervention in the vitamin E group, no significant changes were observed in cellular immune response and, after the trial period, responses between the control and vitamin E groups were not significantly different. Similarly, no significant changes were found in levels of IgG and IgA raised against penicillium or IgG4 raised against egg, milk, or wheat proteins in the vitamin E group. From these results, they concluded that the relatively low dose of dl-α-tocopheryl acetate does not support the claims of a beneficial effect of vitamin E on the overall immune response of elderly subjects. On the other hand, De la Fuente et al. succeeded in finding a beneficial effect of vitamin E supplementation on cellular immune responses in the elderly [34]. They investigated the effects of supplementation of the diet with the antioxidant vitamins C and E on several functions of the immune response of aged women. Ten healthy women and 20 women (72±6 years old) suffering two diseases (10 with major depression disorders, and 10 with coronary heart disease) were administered 1 g of vitamin C and 200 mg of vitamin E daily for 16 weeks. As its result, they found that intake of vitamins resulted in a significant increase in the lymphoproliferative capacity and in the phagocytic functions of polymorphonuclear neutrophils as well as in a significant decrease of serum levels of lipid peroxides and cortisol, both in the healthy aged women and in the aged women with a disease. These findings suggest an important role of antioxidant supplementation in the improvement of immune functions in aged women as well as in the prevention and treatment of specific diseases associated with aging that are quite prevalent in the developed countries. Although we could not find any correlation between plasma α-tocopherol and cellular immune functions in the survey investigating in 68 men (aged 66 to 89) and 127 women (aged 65 to 88), we have found a significant positive correlation between α-tocopherol/very low density lipoprotein (VLDL)-cholesterol and proliferation of peripheral
blood lymphocytes with Con A (p<0.05) (Fig. 7B) [35]. This evidence suggests that the correction using plasma lipids needs to assess the effect of vitamin E on immune functions in the aged. In addition, although Meydani et al. found that PGE2 level in blood was significantly increased in the aged, which is associated with decreased cellular immunity in the aged [36], nitric oxide (NO) produced from macrophage and other cells has also an inhibitory effect on T cell proliferation with mitogen [37]. NO activates cyclooxygenase (Cox), leading to the production of PGE2. Age-related increase in the production of PGE2 may be due to increased NO production with aging, which appears to cause the decreased cellular immunity in the aged as shown in Fig. 7A. In other words, the decreased cellular immunity in the aged with the increased level of blood PGE2 is closely associated with the increased NO production and the action of vitamin E improving the decreased cellular immunity in the aged is due to inhibit NO production from macrophages and other cells (Fig. 8). In fact, a negative correlation between plasma NO concentration and α-tocopherol/VLDL-cholesterol was seen as shown in Fig. 7C. These data support that it is important for elderly to take an enough intake of vitamin E for preventing the decrease of cellular immunity.

III. Vitamin E and T-Cell Differentiation in the Thymus

From the experimental results in SHR described previously, Moriguchi et al. speculated that vitamin is an important nutrient in T-cell differentiation in thymus. To test this hypothesis, 6-week-old Fisher rats were separated into three groups and fed diets containing various levels of α-tocopherol acetate: 0 (vitamin E free), 50 (regular), and 500 (high vitamin E)/kg of diet for 7 weeks. In this experiment rats fed the vitamin E free diet showed not only a decreased number of thymocytes but also a significant decrease of the percentage of CD4+CD8- (helper/inducer) T cells in thymocytes compared with rats fed the regular diet (Fig. 9) [38]. In rats fed a high vitamin E diet, the number of thymocytes was not altered, but the percentages of both CD4+CD8- and CD4+CD8+ T cells in their thymocytes increased significantly. Furthermore, IL-2 production by thymocytes was significantly greater than that in rats fed the regular diet. As Moriguchi et al. [12] have previously noted that AM can be greatly activated by high vitamin E diets, it is conceivable that an increase of macrophage function as antigen-presenting cells (APC) in the thymus may bring about the increased production of IL-2. In addition, the marked increases of CD4+CD8- and CD4+CD8+ T cells in thymocytes may be directly related to the increased production of
IL-2 by thymocytes in the thymic medulla of rats fed the high vitamin E diet. It is known that PGE2 has an inhibitory effect on IL-2 production by activated T cells [39]. A marked decrease of IL-2 production following consumption of a high vitamin E diet may be closely related to the degree of PGE2 synthesis. In fact, Moriguchi et al. have reported an increase in PGE2 production in vitamin E deficiency and a decrease after high vitamin E supplementation [38]. These changes in PGE2 production by thymocytes may affect production of IL-2 by T cells in thymocytes and result in a decreased percentage of CD4+CD8- T cells in thymocytes of the vitamin E free group and increased percentage in those of the high vitamin E group. In fact, since addition of indomethacin, an inhibitor of PGE2 synthesis, to the thymocyte cultures enhanced IL-2 production by thymocytes of rats fed a vitamin E free diet, the increased production of PGE2 in thymocytes appears to be closely related to the decreased production of IL-2 in the vitamin E free group.

Thymic epithelial cells (TEC) play an important role in the differentiation of T cells [40]. Moriguchi and Itoh have found that the ability of TEC isolated from thymocytes of rats fed a high vitamin E diet to bind to immature T cells was greater than that of TEC from rats fed a regular diet [41]. Anderson et al. showed that the contact of immature T cells to TEC is more important than soluble factors from TEC in positive selection of CD4+CD8- T cells [42]. Moriguchi and Itoh have also found that the supernatant of a TEC culture does not affect the differentiation of T cells in vitro. These results suggest that vitamin E enhances T cell differentiation through increased binding of immature T cells to TEC in the thymic cortex. Although it is not known how vitamin E increases the binding of immature T cells to TEC, vitamin E may enhance the expression of adhesion molecules. Moriguchi and Itoh have found that vitamin E supplementation or in vitro addition of vitamin E to the culture medium enhances the expression of intracellular adhesion molecule-1 (ICAM-1) in TEC. However, they have failed to find that in vitro incubation with macrophages isolated from rats fed a high vitamin E diet induces a significant change in T cell subsets in immature T cells. These results suggest that vitamin E enhances T-cell differentiation not through macrophage function (negative selection) but through an increased binding capacity of TEC to immature T cells via increased expression of ICAM-1 (positive selection).

IV. Vitamin E and Immune Diseases

Vitamin E and acquired immune deficiency syndrome (AIDS)

Acquired immune deficiency syndrome (AIDS) is a clinical disorder caused by the human immunodeficiency virus (HIV). It represents the end point in a progressive sequence of immunosuppressive changes that render the body highly susceptible to tumors and opportunistic infections. Currently, AIDS is one of the most serious public health problems in the world. Although many studies have been done from the viewpoints of prevention and treatment for AIDS, there are still few studies on the effect of nutrition against the development of AIDS.

Since reactive oxygen species promote HIV replication [43], previous studies have found that antioxidants such as vitamin C and N-acetyl-L-cysteine (NAC), the precursor of glutathione (GSH), are effective in inhibiting HIV replication [44]. Odeleye and Watson have reviewed the potential role of vitamin E in the treatment of immunologic abnormalities during AIDS [45]. They described that vitamin E is nontoxic over a wide range of intakes and a moderately high dose may be used to target and stimulate some specific immune cells destroyed by HIV infection. Moseson et al. have also reviewed the potential role of nutritional factors in the induction of immunologic abnormalities in HIV-positive homosexual men [46]. Since malnutrition and intestinal nutrient malabsorption have been found in AIDS patients, they have described that dietary manipulations might diminish the immune defects in HIV infection and enhance resistance to opportunistic infections.

Murine AIDS has often been used as an AIDS model instead of human AIDS. Although the etiology between human and murine AIDS, induced by LP-BM5 retrovirus infection, is different in some points, including the changes of the T cell subsets, both are closely similar in the functional changes following development of AIDS. Murine AIDS is characterized by lymphadenopathy, splenomegaly, hypergammaglobulinemia, deficient B-cell response to mitogen, functional deficiency of T cells, and cytokine dysregulation as shown in human AIDS [47]. In addition, it is also known that azidodideoxythymi-
dine (AZT), a drug for treatment of human AIDS, is effective for treatment of murine AIDS [48]. These reports support that murine AIDS is a useful model for studying the treatment and prevention of human AIDS.

It is known that NK-κB enhances HIV replication through activation of the HIV long-terminal repeat (LTR) [49]. In addition, reactive oxygen species promote the dissociation of NF-κB from I-κB and subsequently increase the production of NF-κB [43, 44]. As shown in Fig. 10, Hamada et al. have found that vitamin E supplementation suppresses the expression of NF-κB in splenic lymphocytes from mice infected with LP-BM5 retrovirus [50]. Especially, the suppressive effect of vitamin E is strongly shown in the nucleus rather than in the cytoplasm. This fact suggests that the suppressive action of vitamin E against NF-κB expression is not only the dissociation of NF-κB from I-κB but also the translocation of NF-κB to the nucleus. Figure 11 shows that there are two systems of vitamin E actions improving immune dysfunction in murine AIDS. First, vitamin E increases the production of IFN-γ, an antiviral cytokine produced from activated T cells. Vitamin E may inhibit the development of murine AIDS through the enhancement of host antiviral activity. Second, since vitamin E is a potent antioxidant and decreases the production of TNF-α, which enhances the production of reactive oxygen species and subsequently increases the expression of NF-κB, vitamin E may directly and indirectly inhibit the production of reactive oxygen species and NF-κB expression.

Fig. 10. Effect of vitamin E supplementation on the expression of NF-κB in cytoplasm and nucleus of splenic lymphocytes of rats infected with LP-BM5 retrovirus. Twenty microgram of each protein was analyzed by Western blotting. (a) Control diet; (b) high vitamin E diet before LP-BM5 retrovirus infection; (c) high vitamin E diet after LP-BM5 retrovirus infection. (Hamada et al.: Nutr. Res., 20, 1163–1171, 2000)

Fig. 11. Mechanism of the improvement of immune dysfunction in murine AIDS following vitamin E supplementation.

Fig. 12. Effect of vitamin E supplementation on serum IgE production from TDI-sensitized mice. Mice were sensitized by dropping 2 µl of 5% toluene diisocyanate (TDI) dissolved in ethyl acetate from an autopipette into the nostrils under slight ether anesthesia for consecutive days. This was repeated after a week of rest. No sensitization groups were similarly treated with the vehicle, ethyl acetate. The mice were again allowed 1 week of rest, after which all groups were provoked with 5 µl of 2.5% TDI without anesthesia to induce nasal allergy-like symptoms. One week after provocation, the mice were anesthetized with sodium pentobarbital and were exsanguinated by cardiac puncture. Each value is the mean±SE. * Significantly different from no sensitization mice fed a control or vitamin E-supplemented diet (p<0.01). # Significantly different from TDI sensitized mice fed a control diet (p<0.01). (Zheng et al.: Am. J. Med. Sci., 318, 49–54, 1999)
and result in inhibiting the development of murine AIDS.

**Vitamin E and abnormal increase of immune system**

In this part, we describe effects of vitamin E supplementation on two types of diseases with immunological abnormality such as allergy and autoimmune disease. Zheng *et al.* have found that high doses of vitamin E supplementation suppress nasal allergy [51]. As shown in Fig. 12, groups B [control + toluene diisocyanate (TDI) sensitization] and D (vitamin E + TDI sensitization) had higher (p<0.01) serum IgE concentrations compared with groups A (control) and C (vitamin E). However, serum IgE concentrations in group D were significantly lower than those in group B (p<0.05). As its mechanism it has been shown that vitamin E has a direct inhibitory effect on serum IgE formation in mice [52]. In addition, vitamin E acts as an antioxidant in cellular membranes and scavenges free radicals by blocking the peroxidation of PUFA, modifying prostaglandin formation, and enhancing production of PGI2 [53]. It is known that PGI2 has an inhibitory effect on the formation of histamine [54], which is a major chemical mediator in the events of TDI-induced allergy, and causes itching, sneezing, and rhinorrhea. From these reports it appears that vitamin E may have reduced nasal allergic symptoms by inhibition of the production of histamine. Fogarty *et al.* have also investigated the relation between dietary vitamin E intake and serum IgE concentrations and atopy, measured as allergen skin sensitization, in a random sample of 2,633 adults [55]. As its result they found that higher concentrations of vitamin E intake were associated with lower serum IgE concentrations and a lower frequency of allergen sensitization.

By using MRL/MP-lpr/lpr (MRL/lpr) mice Weimann and Hermann have found that vitamin E beneficially affects the development of the SLE-like (systemic lupus erythematosus) autoimmune disease [56]. In addition, Kuenmerie *et al.* investigated the effects of fish oil, with and without α-tocopherol, on the course of IgA nephropathy [57] and found that vitamin E, more so than fish oil, mitigates the injury and promotes repair in experimental IgA nephropathy. Bae *et al.* investigated on plasma antioxidant/oxidant status and the dietary nutrient intake of 97 consecutive patients with SLE and 97 age- and sex-matched healthy controls [58]. They have found that plasma antioxidant status is impaired and dietary antioxidant intake is decreased in patients with SLE.

In particular, they found the plasma α-tocopherol concentration was lower in those patients. As described above, vitamin E supplementation may be effective for treatment of those patients having vitamin E deficient status. Further studies are necessary to define the exact mechanism of vitamin E modulating the immunoinflammatory response in allergy and autoimmune diseases.

**References**


