—Review—

Nutrition and Atopic Dermatitis

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Atopic dermatitis (AD) is a chronic eczematous disease characterized by T helper 2 (Th2)-shifted allergic immunity, skin barrier impairment, and pruritus. Oral intake of certain nutrients might help regulate AD. Serum 25-hydroxyvitamin D levels are often low in patients with AD, and oral vitamin D supplementation improves AD. Vitamin D increases regulatory T (Treg) cells, which promote tolerance to allergens and prevent allergic inflammation by inducing expression of filaggrin and cathelicidin in keratinocytes. Vitamin A strengthens Treg cells by inducing expression of forkhead box P3 and inhibits mediator release from mast cells and eosinophils. Serum levels of γ-linolenic acid and its metabolite, dihomo-γ-linolenic acid, are low in patients with AD, and oral γ-linolenic acid improves AD through anti-inflammatory prostaglandin D_1 and E_1 derived from dihomo-γ-linolenic acid. Eicosapentaenoic acid and docosahexaenoic acid ameliorate AD by suppressing production of leukotriene B_4, increasing ceramides in the stratum corneum, and through their metabolites, resolvin E1 and D1, which resolve inflammation. The probiotics *Lactobacillus* and *Bifidobacteria* improve the intestinal permeability barrier and induce Treg cells. Zinc levels in serum, hair, and erythrocytes are diminished in patients with AD. Zinc induces forkhead box P3 expression and increases Treg cells, and zinc-finger protein A20 suppresses nuclear factor-κB-dependent expression of inflammatory cytokines and cell-adhesion molecules. Oral supplementation of the above nutrients might have therapeutic or preventive roles in AD.
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Key words: atopic dermatitis, probiotic, regulatory T cell, vitamin D, zinc

Introduction

Atopic dermatitis (AD) is a chronic eczematous disease characterized by abnormal T helper 2 (Th2)-shifted allergic immunity, skin barrier impairment, and pruritus (**Fig. 1**)[1–4]. These elements are mutually related and are involved in the pathogenesis of AD. Patients with AD have diminished filaggrin[3,4], water content, and ceramides in the stratum corneum[3,4]. Tight junctions in the granular layer are dysfunctional, with a decrease in zonula occludens-1 and claudin-1[5]. These impaired barriers allow penetration of allergens such as house dust mites, food, and pathogens, thus inducing sensitization by these allergens[3,4]. In early AD, allergens or scratches on keratinocytes induce secretion of thymic stromal lymphopoietin (TSLP), interleukin (IL)-33, and IL-25, thereby inducing innate lymphoid cell (ILC) 2 and basophils to secrete IL-4, IL-5, and IL-13. These type 2 cytokines induce dendritic cells (DCs) to migrate to draining lymph nodes and produce the chemokine CCL17, which attracts Th2 cells. Keratinocyte-derived TSLP induces Langerhans cells and DCs to promote differentiation of naïve T cells into Th2 cells via OX40-OX40L interaction. AD lesions are infiltrated by Th2 cells producing IL-4, IL-13, and IL-31, and by IL-22-producing T cells, while chronic lesions are associated with Th1 cells producing interferon-γ (IFN-γ). Furthermore, Th17 cells are infiltrated in AD lesions[6]. Patients with AD frequently have elevated serum IgE levels and IgE antibodies against allergens[3,4]. These patients develop pruritus owing to pruritogens such as histamine, TSLP, IL-31, IL-4, IL-13, and neuropeptides, and sensory nerves extend into the epidermis because of the increase in nerve growth factor and artemin and the de-

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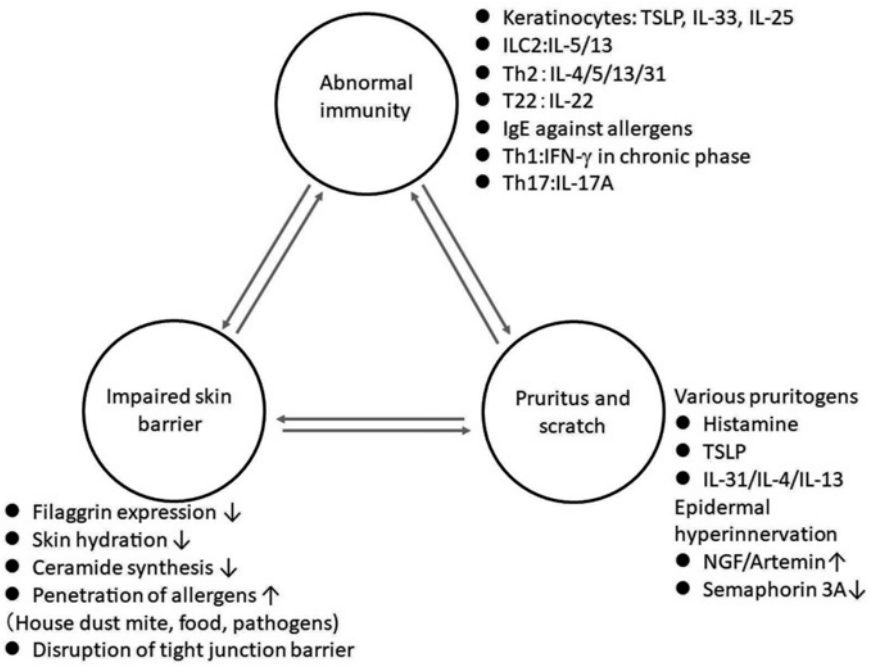

Fig. 1 The three elements involved in the pathogenesis of atopic dermatitis. Th2, T helper 2; IFN-γ, interferon-γ; IL-4, interleukin-4; ILC, innate lymphoid cells; NGF, nerve growth factor; TSLP, thymic stromal lymphopoietin.

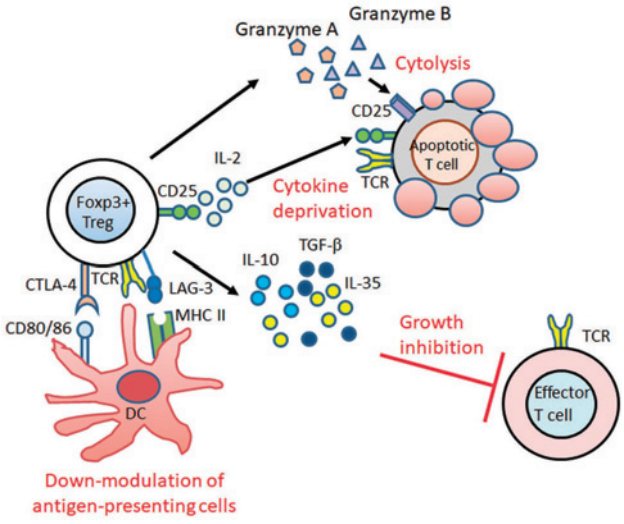

Fig. 2 Mechanisms underlying regulatory T (Treg) cell-mediated suppression. Treg cells mediate tolerance to allergens through diverse mechanisms, namely, T-cell lysis by granzymes; interleukin (IL)-2 deprivation by CD25; growth inhibition of effector T cells by inhibitory cytokines like IL-10, transforming growth factor-β (TGF-β), and IL-35; and downregulation of antigen-presenting cells through lymphocyte-activation gene 3 (LAG-3)-MHC class II and cytotoxic T-lymphocyte antigen 4 (CTLA-4)-CD80/86.
DC, dendritic cell; TCR, T cell receptor

crease in semaphorin 3A[1,3].

$CD4^+CD25^+$ forkhead box protein 3 $(FOXP3)^+$ regulatory T (Treg) cells sustain immune tolerance to allergens and prevent allergic inflammation. The induction of Treg cells is necessary for control of AD[7]. Treg cells are classified as natural Treg (nTreg) and induced Treg (iTreg) cells. nTreg cells arise in the thymus and stably express FOXP3 with T cell receptor (TCR) repertoires toward self-antigens. iTreg cells arise extrathymically from conventional T cells in the presence of transforming growth factor-β (TGF-β), retinoic acid (RA), and TCR-mediated antigen presentation, from either $CD103^+$ DCs in the intestines or $F4/80^+$ $CD11c^+$ macrophages in airways. In iTreg cells, FOXP3 expression is less stable with TCR repertoires toward allergens[7]. Treg cell suppressive functions are mediated by multiple mechanisms (**Fig. 2**), including T-cell cytolysis through granzymes; internalization and degradation of IL-2 after binding to CD25 on the target T cell (IL-2 deprivation); release of IL-10, TGF-β, and IL-35, which suppress proliferation of effector T cells; and downregulation of antigen-presenting cells through interaction of lymphocyte-activation gene 3-MHC class II and cytotoxic T-lymphocyte antigen 4-CD80/86. Treg cells suppress ILC2 expansion, mediator release from mast cells, conversion of conventional T cells into Th2 cells, and IgE production by B cells[7].

The pathogenesis of AD involves genetic and environ-

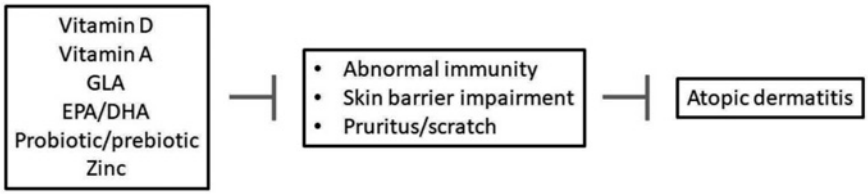

Fig. 3 Dietary nutrients may improve atopic dermatitis by suppressing abnormal immunity, skin barrier impairment, and pruritus.
GLA, γ-linolenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid

mental factors, including diet[8]. AD might be regulated by oral intake of certain nutrients, including vitamin D, vitamin A, γ-linolenic acid (GLA), eicosapentaenoic acid (EPA), probiotics, and zinc, via suppression of abnormal immunity, skin barrier impairment, and pruritus (**Fig. 3**)[8–10]. This article reviews recent studies of the regulatory effects of individual nutrients on AD and the possible therapeutic and preventive roles of oral supplementation of these nutrients in AD.

Vitamin D

Vitamin D binds vitamin D receptor (VDR), and ligand-bound VDR interacts with the retinoid X receptor (RXR). The complex vitamin D/VDR-RXR binds vitamin D response elements on various genes, thereby activating or repressing their expression[11]. There are two ways to obtain vitamin D: dietary intake and ultraviolet-induced synthesis in the skin[12]. Cod liver oil, salmon, tuna, beef liver, and eggs are rich in vitamin D.

During pregnancy, a vitamin D-deficient diet induced hypermethylation of the *IFN-γ* gene, reduced IFN-γ expression, and enhanced IL-4 expression in offspring rats[13]. 1,25-Hydroxyvitamin D3 inhibits DC maturation and induces tolerogenic DCs with lower antigen presentation but higher IL-10 production. 1,25-Hydroxyvitamin D3 enhances *FOXP3* gene expression by binding to the nuclear VDR that recognizes the target response element DNA sequence recently identified in the intronic region of the human *FOXP3* gene[14]. Additionally, 1,25-hydroxyvitamin D3 inhibits expressions of IFN-γ, tumor necrosis factor-α (TNF-α), IL-9, IL-17A, and IL-22 in T cells and inhibits Th2 differentiation[15]. In BALB/c mice, dietary vitamin D3 suppressed dinitrofluorobenzene-induced ear swelling, thereby increasing the number and suppressive activity of Treg cells in draining lymph nodes[16].

1,25-Hydroxyvitamin D3 promotes apoptosis of B cells and inhibits ILC2 activation[15]. 1,25-Hydroxyvitamin D3 inhibits peroxidase release from eosinophils[17] and promotes eosinophil surface expression of CXCR4, leading to eosinophil recruitment to non-inflammatory sites where CXCL12, the ligand of CXCR4, is constitutively expressed[18].

AD lesions are associated with a decrease in cathelicidin levels, leading to microbial superinfections such as *Staphylococcus aureus* and allergic sensitization. 1,25-Hydroxyvitamin D3 induces cathelicidin expression in keratinocytes[19]. In mice, the intraperitoneal VDR agonist ZK203278 improved ovalbumin-triggered AD-like eczema and increased expressions of filaggrin, loricrin, involucrin, transglutaminase 1, and β-defensin-2 and -3 in lesional skin[20].

In patients with AD, serum 25-hydroxyvitamin D levels were lower than in controls (standardized mean difference = −2.03 ng/mL). Scoring of AD (SCORAD) and the eczema area and severity index decreased (standardized mean difference = −5.85) after daily vitamin D supplementation with 1,000 to 2,000 IU cholecalciferol for 1 to 2 months[21–25]. Future large-scale clinical trials should assess the effects of supplementation on AD outcomes over a longer period.

Vitamin A

Liver, fish, eggs, and butter are rich in vitamin A (retinol)[26]. Most vitamin A activity depends on its active metabolites, RAs, which are formed by retinal dehydrogenases in epithelial and immune cells[26,27]. RAs act via retinoic acid receptors and RXRs.

RA is produced by DCs and induces naïve T cells to differentiate into Treg cells[15] by promoting histone acetylation of *FOXP3* promoter in cooperation with TGF-β[28]. RA induces tolerogenic DCs expressing IL-10, TGF-β, and IL-27 and promotes production of IgA-producing B cells. Furthermore, RA suppresses IgE production by anti-CD 40 plus IL-4-stimulated human peripheral blood mononuclear cells[29], and it antagonizes ILC2 function and mediator release from mast cells and eosinophils[29].

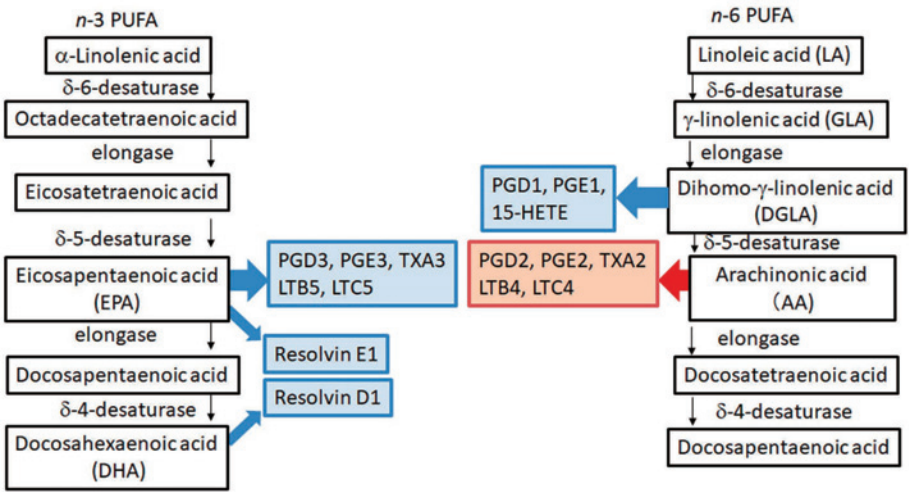

Fig. 4 Biosynthetic pathways of *n*-3 and *n*-6 polyunsaturated fatty acids (PUFAs) and their metabolized eicosanoids and resolvins. Eicosanoids and resolvins in the red box are pro-inflammatory; those in the blue box are anti-inflammatory. LT, leukotriene; PG, prostaglandin; TX, thromboxane; 15-HETE, 15-hydroxy-5,8,11,13-eicosatetraenoic acid.

As compared with mice fed a vitamin A-sufficient diet, mice fed a vitamin A-deficient diet had more severe eczema induced by ovalbumin and greater mast cell accumulation, higher IL-4 and IL-13 mRNAs, higher serum IgG1 and IgE levels, and lower IgG2a serum levels and lower IFN-γ mRNA expression in skin, which reflect lower Th1 immune response[30].

In children with AD, serum vitamin A levels are low and negatively correlated with SCORAD[31]. Oral alitretinoin (9-cis RA) reduced SCORAD in adult patients with AD[32,33]. Large randomized controlled trials are required in order to confirm the effects of oral vitamin A.

n-6 Polyunsaturated Fatty Acids (PUFAs)

The simplest members of the *n*-6 and *n*-3 PUFAs, linoleic acid (LA) and α-linolenic acid, respectively, make up greater than 95% of dietary PUFAs and cannot be synthesized by mammals (**Fig. 4**)[34]. Vegetable oils and margarine are rich in LA.

LA is converted to GLA by δ-6 desaturase, to dihomo-γ-linolenic acid (DGLA) by elongase, and to arachidonic acid (AA) by δ-5-desaturase[34]. AA is incorporated into the membranes of immune cells such as mast cells and macrophages. When tissues are exposed to injury or cytokines, AA is released from membranes and converted into four-series leukotrienes (LTs) like LTB_4, thus promoting IgE production by B cells or two-series prostaglandins (PGs) like PGD_2, activating IL-4, IL-5, and IL-13 production by Th2 cells, and exacerbating Th2 responses in AD[34].

Patients with AD have low serum GLA and DGLA levels, possibly because of impaired δ-6 desaturase activity. These levels are negatively correlated with transepidermal water loss and SCORAD[35]. Oral intake of GLA[36], GLA-rich borage oil[37], and evening primrose oil[38,39] improved AD. Moreover, oral intake of black currant seed oil containing GLA plus α-linolenic acid reduced AD prevalence in 12-month-old infants[40]. Dietary GLA is converted into DGLA by elongase but does not increase AA in the epidermis, since δ-5-desaturase, which converts DGLA into AA, is absent in the epidermis[35].

Dietary GLA may improve AD, at least partly, by conversion to DGLA. The DGLA-derived eicosanoids PGE_1 and 15-hydroxy-eicosatrienoic acid are anti-inflammatory, and PGE_1 inhibits histamine release from mast cells[35]. 15-Hydroxy-eicosatrienoic acid inhibits LTB_4 generation from basophils[35]. DGLA induces mast cells to release PGD_1, which suppresses mast cell degranulation and TSLP production in keratinocytes[41].

n-3 PUFAs

Fish are rich in *n*-3 PUFAs, EPA, and docosahexaenoic acid (DHA). EPA and DHA compete with AA for incorporation into membranes of inflammatory cells[34]. EPA acts as a substrate for cyclooxygenases and lipoxygenases, which convert AA into eicosanoids, thus reducing AA-derived inflammatory eicosanoids. Topical EPA/DHA ameliorated *Dermatophagoides farinae* extract-induced AD-like dermatitis by blocking LTB_4 production[42]. In mice, oral EPA ethyl ester ameliorated AD-like

eczema and increased ceramides in the stratum corneum[43]. EPA-derived eicosanoids, five-series LTs, and three-series PGs are anti-inflammatory. LTB_5 counteracts LTB_4-induced proliferation of keratinocytes and neutrophil chemokinesis[44]. Moreover, EPA and DHA are metabolized into resolvin E_1 and D_1, respectively, which resolve inflammation. In NC/Nga mice, intraperitoneal resolvin E_1 ameliorated 2,4-dinitrofluorobenzene-induced AD-like eczema by suppressing infiltration of eosinophils, mast cells, and CD4+ and CD8+ T cells in skin lesions and reducing serum IgE levels[45].

In pregnant women, intake of oral EPA plus DHA from the 25th gestational week through 3.5 months of breastfeeding reduced the prevalence of IgE-associated eczema in infants[46]. In adults with AD, oral intake of fish oil containing EPA plus DHA for 12 weeks improved AD[46]. Larger and longer randomized controlled trials should be conducted to assess the effects of oral EPA/DHA.

Probiotics and Prebiotics

Probiotics are living microorganisms that are beneficial to the host, e.g., lactic acid-producing *Lactobacillus* and *Bifidobacteria*[47]. Prebiotics are non-digestible fructooligosaccharides, inulins, and galactooligosaccharides that stimulate growth of beneficial bacteria.

In patients with AD, intestinal permeability is increased, inducing transfer of exogenous antigens[48,49]. Probiotics modulate the intestinal microbiome, improve the intestinal barrier, and modulate the intestine-skin immune axis[48,49]. The number of Treg cells in CD4+ T cells is lower in patients with AD. Probiotics increase Treg cells and their secretion of IL-10 and TGF-β in mesenteric lymph nodes[49–51]. Treg cells migrate to inflammatory skin lesions and suppress IL-4, IL-5, IL-13, and IL-17A-mediated allergic responses and reduce TSLP expression in the epidermis[51]. Prebiotics enhance production of butyrate, which expands and stabilizes iTreg cells through histone acetylation of FOXP3 protein by inhibiting histone deacetylase[49,52]. Moreover, prebiotics increase intestinal IgA secretion[49].

Studies of probiotic supplementation reported positive and negative effects on the prevention and improvement of AD. A meta-analysis of random controlled trials (RCTs) showed that probiotics had a protective role in the development of AD when administered during the pre- and post-natal period (odds ratio [OR] 0.61, $p < 0.001$) but not when administered during the post-natal period only (OR 0.95, $p = 0.82$)[53]. However, an updated meta-analysis reported that probiotics did not produce siguificant preventive effects when administered solely to infants (OR 0.88, $p = 0.56$) while produced preventive effects when administered both to pregnant mothers and their infants (OR 0.71, $p = 0.0006$) and solely to pregnant mothers (OR 0.54, $p = 0.001$)[54]. The clinical outcomes of probiotics might be influenced by timing of administration, duration, strains, or dosage. More robust RCTs using standardized measurements, and studies of the mechanisms underlying the effects of probiotic supplementation on AD during pregnancy and the postpartum period, are necessary in order to evaluate the long-term effects of probiotics.

Zinc

Oysters, pork liver, and beef shoulder are rich in zinc, an essential trace element affecting the activity of more than 300 enzymes. Zinc induces the zinc-finger protein A20, which suppresses expression of nuclear factor-κB-dependent genes, such as adhesion molecules (intercellular adhesion molecule-1) and inflammatory cytokines (IL-1β, TNF-α)[55]. Zinc aspartate suppresses proliferation, and IFN-γ, IL-5, and IL-17A production in anti-CD3/CD28-activated human T cells[56]. In an allogeneic mixed lymphocyte culture, zinc sulfate increased and stabilized alloantigen-specific iTreg cells by increasing FOXP3 and Kruppel-like factor 10 mRNAs, while decreasing IFN regulatory factor 1 mRNA[57].

In patients with AD, zinc levels are low in serum, hair, and erythrocytes[58], and erythrocyte zinc levels are negatively correlated with SCORAD[9,59]. In children with AD, oral zinc oxide decreased trans-epidermal water loss, the eczema area and severity index, and pruritus[60]. Zinc should be supplemented with copper at a ratio of about 10:1, because zinc may interfere with intestinal copper absorption[9].

Conclusion

We reviewed studies of the effects of nutrients on AD and possible therapeutic and preventive roles of their oral supplementation in AD. Vitamin D, vitamin A, GLA, EPA/DHA, probiotics/prebiotics, and zinc might help regulate AD by inducing Treg cells or restoring the impaired skin barrier. Oral supplementation with these nutrients might improve or prevent AD. Future studies should explore the precise mechanisms underlying the improvement or prevention of AD by nutritional supplementation and should examine longitudinal effects, to obtain sufficient evidence regarding the effectiveness of these nutrients.

Conflict of Interest: The authors declare no conflicts of interest.

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