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Th1/Th2 Balance: A Natural Therapeutic Approach to Th2 Polarization in Allergy

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ABSTRACT: *T helper cells are the regulators of the immune system. In recent years, the role of T helper subsets—most specifically Th1 and Th2 cells—in immune function and immune pathologies has become an area of great focus. Th1 and Th2 responses drive cell-mediated and antibody-mediated immunity, respectively. The balance between Th1 and Th2 cells plays a key role in how well the body does against attacks. When genetic and/or environmental factors cause one or the other of these responses to become excessive or "dominant," an imbalance occurs that can lead to immune-related disorders. For instance, a Th2-dominated immune response is associated with allergy and atopic disease. Thus, natural therapies that help to re-establish Th1/Th2 balance, and address downstream processes in Th2-dominance, may provide relief for patients with allergic disorders.*

Science continues to make new and exciting discoveries relating to the role of T helper (Th) cells in immunity and immunopathology. As breakthroughs are made, new targets for addressing immune dysfunction are realized. In recent years there has been a significant focus on the role of Th subsets, most specifically Th1 and Th2, in the development of immune-related diseases ranging from rheumatoid arthritis to allergies.

Th1 and Th2 represent two polarized forms of Th-mediated immune responses. (The subsets T_R and Th3 are not discussed herein. For reviews of these cells and their role in immune function, readers are referred to other sources.[1,2]) Th1 cells defend against intracellular pathogens such as virus and certain bacteria by directing cell-mediated immunity. Th2 cells direct humoral immunity (antibody-mediated) fighting extracellular pathogens, and initiating allergic reactions.[3] Recent studies suggest that the immune response is in fact regulated by the balance between Th1 and Th2 cytokines. Cytokines are any of several regulatory proteins, such as the interleukins (ILs), that are produced by immune cells and act as intercellular messengers in the generation of an immune response. They intensify some facets of the immune system and suppress others.

TH CELL DIFFERENTIATION INTO TH1 OR TH2

When an antigen (e.g., pathogen, allergen) enters the body, it is processed and presented to a CD4+ Th cell by an antigen-presenting cell (APC), such as a macrophage or dendritic cell. Environmental and genetic factors acting at the time of antigen presentation to the Th cell may explain why a certain cytokine expression develops. Such factors include the type of antigen, the dose of antigen, the genetic background of the subject, co-stimulatory molecules from the APC, and the cytokine environment.[4,5] Two pivotal cytokines that control differentiation are IL-12 and IL-4. These cytokines, produced by the Th cell, induce the generation of their own T-helper subset.[6] That is, IL-12 supports Th1 responses and IL-4 supports Th2 responses. Differentiated Th1 and Th2 are further associated with the production of additional specific cytokine profiles that guide the immune response and are involved in subset cross-regulation (Table 1).[7,8]

Table 1. Th-Cell Subset Cytokine Profiles

Th Subset	Cytokine Profile
Th1	IFN-γ*, IL-2, TNF-β
Th2	IL-4*, IL-5, IL-6, IL-9, IL-10*, IL-13

*Cross-regulating cytokine.

A healthy immune system is both dynamic and balanced between Th1 and Th2 activity, switching back and forth between the two as needed. However, when genetic and/or environmental factors cause a Th1 or Th2-dominated response to occur, immunopathology can follow; and once a T cell response begins to develop along one pathway (Th1 or Th2), it tends to be progressively polarized in that direction.[3] Th1-dominated responses are implicated in organ-specific autoimmune disease and some delayed-type hypersensitivity reactions, while Th2-dominated responses can lead to allergic and atopic conditions, as well as systemic autoimmune disease.[8,9] Modulating the cytokine environment and influencing Th1/Th2 balance, therefore, are proving to be important approaches to addressing immunologic dysfunction.

TH2 POLARIZATION

There are many theories that may explain a tilt in Th1/Th2 balance toward Th2. These may include the decreasing incidence of infections in the industrialized world—a concept known as the hygiene hypothesis; the increasing success of immunizations and antibiotic therapies that deprive the body of signals that promote Th1 development; increased pollution; or exposure to environmental proteases that activate Th2 cells.[3,10] The shift in balance of Th subsets toward a polarized Th2 response is generally accepted to occur in atopic and allergic disorders and may account for the great increase seen in allergic diseases over the last 3 decades. (Atopy is a genetic tendency to develop classic allergic diseases such as rhinitis, asthma, or atopic dermatitis.)

Allergic respiratory diseases have increased in prevalence and severity over the past 30 years in all industrialized countries. In the United States alone, more than 50 million suffer from allergic diseases caused by everyday exposures to agents such as dust mites, pet dander, molds, and pollens; furthermore, allergies are the 6th leading cause of chronic disease.[10-12]

THE ALLERGIC PROCESS (Figure 1)

The term "allergy" is most commonly associated with IgE-mediated hypersensitivity, which will be described herein.[7] In susceptible individuals, the first exposure to an antigen (allergen) causes a mild immune response that sensitizes the immune system (so that it will recognize the substance when presented again). The second exposure and subsequent exposures to the same allergen usually result in symptoms.[13]

Initial Exposure: The Sensitization Stage

As before stated, the first time an allergen enters the body, it is processed and presented to the CD4+ Th via an APC (e.g., dendritic cell, macrophage). The Th cell responds by generating a cytokine message that stimulates its differentiation. A cytokine environment dominated by IL-4 favors Th2 development and IgE production in response to the allergen. Th2 development propagates the release of cytokines that induce eosinophil recruitment, mast cell growth, B cell proliferation and differentiation (into antibody-secreting plasma cells), and the synthesis and secretion of large amounts of specific IgE antibodies (Table 2).[7,8] These IgE antibodies attach themselves to the surfaces of mast cells (concentrated in the lungs, skin, tongue, and linings of the nose and intestinal tract) or basophils (in circulation) and remain bound to them for weeks or months.

Second and Subsequent Exposures: Allergic Symptoms

The next time a person comes in contact with the same allergen, it will be identified and bound by the IgE antibodies (which are present on the surfaces of mast cells and basophils after sensitization). The allergen-antibody complex then activates the mast cell or basophil, causing the cell to "degranulate" and release preformed (histamine, proteases, chemotaxins) and newly formed (leukotrienes, prostaglandins) mediators into the bloodstream.[5,7,13] These mediators induce localized inflammation and other responses that cause symptoms associated with allergy. Because mast cells and basophils can be located in diverse areas of the body, allergic symptoms can occur in a variety of locations and cause such varied symptoms as mucus production/nasal congestion; hives; coughing and wheezing; muscle spasm; itchy, watery eyes; swelling; and nausea.[13]

It is important to note that cytokines produced by Th2 can account directly or indirectly for a great majority of pathophysiologic manifestations of allergic patients (Table 2).

Table 2. Roles of Th2 Cytokines in Allergy

IL-6	B cell differentiation
IL-4, IL-13	IgE antibody production
IL-4, IL-10	Mast cell growth
IL-5	Eosinophil accumulation
IL-9, IL-13	Mucus hyperproduction

DIAGNOSIS

Personal history is important in diagnosing all allergies and may include time of the day or season, possible exposure to pets, geography, type of work, as well as other factors. In addition, a variety of laboratory assessments can aid in diagnosis. Common tests include:

- Skin testing that may include intradermal, scratch, patch, or other.
- Antibody/immunoglobulin levels or RAST (radio-allergosorbent test). Elevations, especially of IgE, are indicative of a "primed" immune response.
- A complete blood count (CBC). An elevated eosinophil count may indicate allergies.

Other important tools for assessment are "elimination" tests and "use" tests wherein suspected items are eliminated and/or introduced while the patient is observed for a response.[14]

TREATMENTS

There are essentially three common approaches to clinical management of allergies. These include avoidance, medication, or immunotherapy. Unfortunately, many allergens cannot be avoided. When this is the case, common medications include anti-histamines, decongestants, sodium cromoglycate, nedocromil sodium, and leukotriene antagonists. Although effective, some of these medications can cause drowsiness, sedation, hyperactivity, or other side effects, making them unappealing to many patients. Furthermore, relief is often temporary. More concerning, the long-term use of high-doses of corticosteroids, particularly when taken orally, can result in numerous side effects including facial swelling, muscle weakness, peptic ulcer, osteoporosis, cataracts, and a reduced growth rate in children.[14,15] Immunotherapies, although effective, are both time consuming and expensive. For these reasons, many turn to natural therapies.

TARGETS FOR NATURAL INTERVENTION

TH1/TH2 BALANCE

Inhibiting Th2-type cytokines may downregulate an overactive Th2 response. In addition, inducing the Th1 response, and therefore production of its cytokines, including cross-regulating IFN-γ, may shift the system and produce balance in some individuals. Many nutritional factors and herbs are thought to influence Th1 and Th2 responses. By addressing this initial step in the allergic process, the incidence and/or severity of an allergic reaction may be manipulated. Furthermore, combining Th1/Th2 balancing therapies with natural therapies that address certain downstream events may offer even greater protection and/or relief.[1,3-5] These additional targets are discussed below.

Downstream Processes

IgE Antibody Production—Because of the very significant role played by IgE in the development and propagation of allergic inflammation, inhibiting IgE production creates an important target for intervening in the allergic cascade.[7,13,15]

Release of Histamine and Other Propagating Factors—During mast cell and basophil degranulation, chemical mediators such as histamine and cytokines (e.g., IL-4, IL-5, IL8, TNF-α, etc.) are released into the bloodstream. These mediators may act on various target tissues to produce allergic symptoms, perpetuate Th2 polarization and inflammation, and continue the allergic response.[7] Reduction of these mediators or inhibition of their activities may play an important role in providing relief to those suffering from allergic disease.[7]

Leukotriene and Prostaglandin Synthesis—Arachidonic acid (AA) is liberated from the mast cell or basophil phospholipid membrane during degranulation through the action of phospholipase A2. The lipoxygenase (LOX) and cyclooxygenase (COX) enzymes metabolize AA to produce the potent eicosanoids: leukotrienes and prostaglandins, respectively. Leukotrienes are extraordinarily potent activators of allergic responses and can cause fatal anaphylactic shock; they are also direct mediators of asthma symptoms.[13] Both leukotrienes and prostaglandins are involved in the allergic process and cause such symptoms as broncho- and vasoconstriction and inflammation. Limiting or inhibiting the formation of these eicosanoids is a critical and necessary component of any anti-allergy therapy.[7,13]

Oxidative Stress—Low tissue antioxidant levels are associated with allergies and asthma. In addition, inflammatory cells involved in the allergic process generate and release reactive oxygen species, which can promote damage of affected tissues.[16,17] Combating these harmful free radicals is another important aspect of therapy.

NATURAL SUBSTANCES THAT ADDRESS TH1/TH2 BALANCE AND THE ALLERGIC RESPONSE

Research suggests that a number of natural compounds have the ability to modulate the allergic response on a variety of the levels discussed above (Figure 1). Combined use of such compounds may

offer an excellent alternative to therapies that may carry side effects when used chronically.

Perilla

Commonly known as purple mint, perilla (*Perilla frutescens*) has long been used in Traditional Chinese Medicine (TCM) to relieve symptoms such as cough, labored breathing, and indigestion.[18] In Kampo (a Japanese variant of TCM), perilla is an active ingredient in Saiboku-to—a medicinal preparation prescribed for asthma.[19] The medicinal use of perilla also spread to India and Korea, where it has been used to treat respiratory conditions.[20,21]

Perilla extract seems to modulate the allergic response in a number of ways. Studies suggest that perilla extract may:

- Inhibit the production of cytokines including IL-4, -5, -6, and -10, suggesting it may prevent Th2 polarization.
- Reduce IgE levels.
- Inhibit histamine release from mast cells.
- Inhibit 5- and 12-LOX activity.
- Inhibit the production of TNF-α—a proinflammatory cytokine released by mast cells that can augment allergic inflammatory reactions.
- Scavenge free radicals via its rich flavonoid and phenolic acid content.

In a preliminary animal study conducted and published in Japan, perilla seed extract was observed to significantly reduce the production of the Th2-type cytokines IL-4, -5, -10 and decrease serum IgE levels.[22] Further study suggests IL-6 production in cell culture is inhibited by luteolin, an active flavonoid in perilla extract.[23] IL-6 is suspected of directing Th cell differentiation toward Th2, and blocking IL-6 appears to halt the activation of Th2 cells by antigen presenting cells.[24]

Research conducted on humans also suggests perilla extract may influence serum IgE levels. In a 2-week preliminary study conducted in Japan, 20 allergic patients given 150 mg/day of perilla seed extract were observed to have decreased symptoms of sneezing, stuffy nose, nasal discharge, and itchy eyes. Researchers correlated reduced serum IgE levels with symptom reduction.[25] An animal study, also published in Japan, supports these findings and the researchers suggest perilla seed extract may be useful in suppressing IgE in individuals with certain allergic disorders.[26]

In addition to these activities, flavonoids, phenolic acids, and other compounds found in perilla seed extract have shown marked influence on LOX activity in the allergic response. In a study of defatted perilla seed extract, researchers isolated certain compounds and investigated their LOX-inhibiting ability. Results showed that luteolin, chrysoeriol, and rosmarinic acid and its methyl ester significantly inhibited 5- and 12-LOX activity. The most effective compound was shown to be luteolin. These results provide further data that defatted perilla seed extract is a useful agent in the prevention of allergic hyper-reactivity and inflammatory responses.[27] These results were supported in a study designed to screen 39 flavonoids for LOX-inhibitory activity, wherein luteolin was among the most effective.[28]

Research also suggests that perilla extract may influence mast cell activity in the allergic response. In an animal study of the effects of perilla extract on mast cell-mediated, immediate-type allergic reactions, induced local and systemic allergic reactions were significantly inhibited.[29] Subsequently, the researchers also studied the effects of perilla extract on mast cells in vitro, wherein perilla extract significantly inhibited IgE-induced histamine release.[29] These results were again supported in an animal study, whereby oral administration of perilla extract significantly inhibited a serum-induced overproduction of TNF-α. Researchers suggested that while TNF-α inhibition occurred, other factors involving IgE and histamine were also inhibited, suggesting that perilla extract may be useful in regulating the host defense system.[30]

The accumulation of studies on perilla extract suggests it is capable of modulating multiple processes in the allergic response, possibly beginning with the suppression of Th2 cytokine production.[22-32] These findings support the traditional use of perilla in relieving allergy-related symptoms.

Omega-3 Fatty Acids

Dietary fatty acids may exert beneficial effects on the immune system at multiple levels including regulation of gene expression, signal transduction pathways, and production of eicosanoids and cytokines.[33]

The increased prevalence of atopic disease has recently been associated with an imbalanced consumption of omega-3 and omega-6 fatty acids.[34-37] A typical Western diet contains nearly 10 times more omega-6 than omega-3, potentially resulting in higher AA-derived eicosanoids (e.g., prostaglandin E2) that can alter the cytokine milieu affecting Th1/Th2 differentiation.[35,38] Indeed, high intakes of omega-6 combined *with low intakes of omega-3* have been associated with increased prostaglandin E2 (PGE2) production, and inhibition of Th1 proliferation and cytokine production.[39,40] However, in vitro and ex vivo studies on the effect of omega-3 on Th1 and Th2 responses are equivocal; and both positive and negative effects of omega-3 fatty acids have been reported in the treatment of patients with allergic conditions.[41-43] Response may be dose dependent, and research suggests that the upper limit for the dietary omega-3/omega-6 ratio to suppress antigen-induced, IgE-mediated allergic reaction is approximately 1:1.[44]

In a study of nonsmoking atopic asthmatic subjects, the benefits of supplementary fish oil on allergy-related leukotriene levels were investigated. Supplementation lasted 4 weeks and was individualized to achieve omega-3 to -6 intake ratios of 0.5:1 (high) and 0.1:1 (low). The results indicated that improving the intake ratio to 0.5:1 decreased allergy-related leukotriene biosynthesis, resulting in improved respiratory capacity; while subjects with the low omega-3 ingestion suffered increased respiratory distress.[45] Another study on bronchial hyper-reactivity in subjects with seasonal asthma due to airborne allergens showed that 3 g/day of fatty acids significantly improved measures of forced expiratory volume (FEV) and airway resistance.[46] Furthermore, the suppression of nasal blood flow and nasal eosinophils to ryegrass allergen challenge by 3 g/day of EPA suggests a supportive role for omega-3 as phospholipid mediators in allergic rhinitis, but clinical assessment did not provide evidence of symptomatic relief.[47] In contrast to these positive results, in a study of 48 patients with atopic dermatitis, 3 g/day of linoleic acid was found to be beneficial, whereas 3.3 g/day of EPA and DHA was found to worsen symptoms.[48]

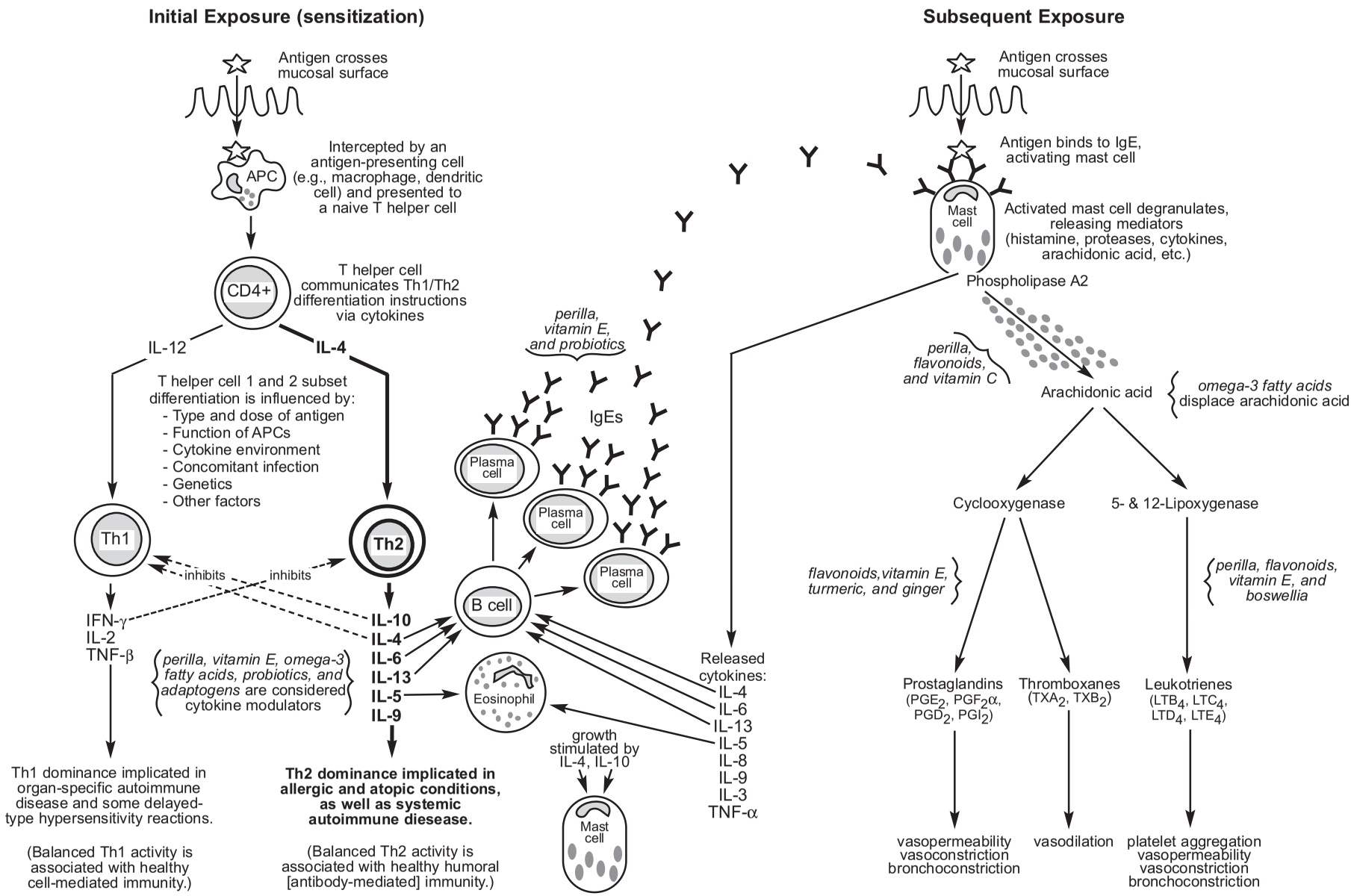
Taken together, these data suggest that omega-3 fatty acids strongly influence immune and inflammatory responses and may provide significant benefits to many subjects with allergic disorders. However, dosage as well as balance with omega-6 fatty acids should be considered when using fatty acids therapeutically.

Vitamin E

Research suggests that vitamin E may protect against allergic disorders not only by reducing the associated free radical damage, but also by influencing Th2-type cytokine expression, serum IgE levels, and inflammatory prostaglandin synthesis.

After examining its effects on human blood T cells, researchers discovered that vitamin E (α-tocopherol) downregulates IL-4 expression at the mRNA (transcription) level. In the absence of IL-4,

Figure 1: The effects of Th1/Th2 imbalance manifesting as Th2 polarization in allergy



Key: APC: antigen-presenting cell; CD4+: T helper cell; IFN-γ: interferon-gamma; IgE: immunoglobulin E; IL: interleukin; Th1: T helper cell subset 1; Th2: T helper cell subset 2; TNF-α: tumor necrosis factor-alpha; TNF-β: tumor necrosis factor-beta.

Th cells develop mainly into Th1. This suggests that Th2 differentiation is not supported in the presence of vitamin E. These findings may help elucidate the suppressive effect of vitamin E on IgE and allergic reactions.[49] Other studies support these finding by demonstrating that vitamin E supplementation increases the Th1 response.[50,51]

To study the effects of vitamin E (dl-alpha-tocopherol acetate) supplementation on nasal allergies, mice were randomly divided into 2 groups. For 4 weeks, the vitamin E group received 585 mg/kg of vitamin E while the control group received 50 mg/kg of vitamin E. Upon completion of the study, the high-dose vitamin E group showed less nasal irritation than the control group. In addition, IgE, IL-4, and IL-5 levels were lower in the vitamin E group than in the control group. These results indicate that higher doses of vitamin E supplementation may suppress nasal allergic responses.[52]

In a recent study, 2,663 patients (aged 18 to 70 years) were tested for various allergies and asked questions regarding daily vitamin E intake, as well as the frequency and severity of their symptoms. Researchers found that vitamin E intake decreased allergen sensitization and serum IgE levels by more than 5% in a dose-dependent manner.[53] In another human trial, the effects of placebo versus vitamin E in 96 subjects with atopic dermatitis were studied in a single-blind method. Fifty of the subjects received 400 IU of natural vitamin E for 8 months; 23 of these showed "great improvement" in eczematous lesions, compared to only one in the placebo group. In fact, there was almost complete remission in 7 of the 23 subjects who showed great improvement. Furthermore, subjects with great improvement also demonstrated a 62% decrease in serum IgE levels based on initial conditions.[54]

By scavenging hydroperoxide, which promotes COX activation, vitamin E may decrease COX activity, and therefore, the production of inflammatory prostaglandins and thromboxanes.[55,56] Altogether, these data suggest that vitamin E may hold true value in the treatment of allergic disorders.

Probiotics

At birth, Th responses are largely Th2-mediated; Th1 responses develop over time with exposure to pathogens such as bacteria. The suppressive effects of lactic acid bacteria on the development of allergy have been attributed to their Th1-inducing properties.[57,58] In a recent study, treatment with probiotics was shown to alleviate the allergic inflammation associated with Th2-dominant immunity in infants. In order to determine the mechanism of action, researchers studied the effects of maternal supplementation with bifidobacteria on 21 infants suffering from early onset atopic eczema and/or gastrointestinal symptoms and heightened risk of chronic allergic disease. Data suggested that supplementation appeared to modulate IgE levels in infants during weaning.[59] This effect was supported by a study on animals, wherein an induced elevation of serum IgE was positively affected by supplementation with *Lactobacillus acidophilus*.[60] These data suggest that adequate microflora colonization may prevent Th2-shifted immunity and thus prevent chronic allergic disease in infants. These researchers speculate that since probiotics are often effective for maintaining a healthy ecosystem during antibiotic treatment, they may also reverse an antibiotic-induced Th2-dominant immune response.[60]

While previous studies have primarily focused on the effects of probiotics on Th2-type immunity in newborn infants, recent research also suggests they may have a beneficial effect in allergic adults. The influence of 4 lactobacilli strains on Th2 cytokine production was studied in cells derived from patients suffering from dust mite allergy and healthy donors.[61] White blood cells (i.e., monocytes) stimulated for 48 hours with a related allergen were preincubated with live lactobacilli. The results showed that IFN-γ production was markedly increased and IL-4 and IL-5 were significantly decreased compared to healthy controls. Thus, lactobacilli appeared to induce Th1 activity and suppress Th2-type immunity. These data suggest that inoculation with probiotics may be beneficial in allergy prophylaxis.

Adaptogens

The impact of acute or chronic stress on immune function has been the subject of many scientific studies. Research indicates stress may cause increased susceptibility or progression of infection, autoimmunity, allergy/atopy, and tumors—conditions associated with suppressed cell-mediated immunity (Th1-mediated) and increased humoral immunity (Th2-mediated).[62,63] This alteration in immune function may result from the effect of stress hormones (e.g., glucocorticoids and catecholamines) on Th1/Th2 balance. It is thought that these hormones promote the dysregulation of cytokine production that is associated with Th2-dominant immunity.[64,65]

A study performed on mice showed that a 24-hour period of acute stress induced by physical restraint caused an elevation of corticosterone levels and a 90% inhibition of IFN-γ production compared to the control group. This correlation strongly suggests the skewing of Th1/Th2 toward Th2 polarization by endogenous glucocorticoids produced in the stress response.[64] Further study on the effects of stress on Th cells showed that glucocorticoids, as well as other stress hormones (i.e., the catecholamines, norepinephrine and epinephrine), may suppress IL-12 production. This study and others provide further evidence that certain stress hormones may alter Th1/Th2 balance by reducing Th1 responses and favoring Th2-type immunity.[63]

Adaptogens—herbs that have a balancing effect on the stress response—may prove to be helpful in individuals with allergies exacerbated by stress. Herbs such as cordyceps (*Cordyceps sinensis*), ashwagandha (*Withania somnifera*), and Asian ginseng (*Panax ginseng*) have been shown to increase resistance to certain biological stressors and decrease stress hormone levels. (For more information about the beneficial effects of adaptogens on the stress response, please refer to the Applied Nutritional Science Report entitled, *Nutritional Management of Stress-Induced Dysfunction* by Richard L. Shames, M.D.)

Vitamin C and Flavonoids

A variety of in vitro and in vivo experiments have shown that select flavonoids possess anti-allergic, anti-inflammatory, antiviral, and antioxidant activities. In addition to these activities, flavonoids have been shown to inhibit human basophil histamine release stimulated by various antigens.[66-69] In animal studies, flavonoids have also been shown to inhibit contraction of smooth muscle cells induced by histamine, acetylcholine, and pro-inflammatory PGE2.[70,71]

Data from animal and human studies have shown that vitamin C deficiencies result in significantly increased histamine levels and airway hyper-responsiveness.[72-74] One to 2 grams of vitamin C have shown beneficial effects in patients with allergic rhinitis and asthma.

In a double-blind, crossover study, 16 patients with allergic rhinitis (hay fever) were given either 2 grams of vitamin C or a placebo for 2 consecutive days. One hour after inducing bronchial responsiveness with histamine, researchers found that respiratory capacity was significantly increased in patients treated with vitamin C, but not in patients receiving the placebo.[75] In another study, asthmatic children given 1 gram of vitamin C per day for 14 weeks experienced less severe and less frequent asthma attacks than those who received the placebo. Upon cessation of vitamin C therapy, researchers reported a marked increase in the rate of asthma attacks in children previously taking vitamin C.[76]

These findings support the importance of vitamin C nutrition in patients with allergies. It is important to note that high doses of ascorbic acid can sometimes cause gastrointestinal disturbances. A

blend of mineral ascorbates including magnesium ascorbate, calcium ascorbate, and potassium ascorbate may be better tolerated and thus promote patient compliance.

Turmeric, Ginger, and Boswellia

Ginger (*Zingiber officinale*) and turmeric (*Curcuma longa*) are two popular herbs used within Ayurveda—an East Indian system of medicine. These herbs have long been used for a variety of both acute and chronic inflammatory conditions, and animal and in vitro studies support this traditional use by demonstrating their significant anti-inflammatory and antioxidant activities.[77-79] Studies suggest that components of ginger and turmeric modulate COX and LOX induction and/or activity, thereby inhibiting inflammatory prostaglandin and leukotriene synthesis.

Boswellia gum resin, derived from the *Boswellia serrata* tree, is another traditional Ayurvedic remedy used for inflammation.[79] The main constituents of the gum resin, boswellic acids, have been found to specifically inhibit 5-LOX.[80,81] In a double-blind, placebo-controlled study of patients with bronchial asthma, boswellia gum resin, at a dose of 300 mg three times daily for 6 weeks, improved symptoms in 70% of participants. Improvements were observed in symptoms such as labored breathing, airway noise, number of attacks, air-flow volume, and eosinophilic count.[82] Boswellic acids have also been shown in vitro to inhibit the complement system, enzymes that can contribute to allergic symptoms.[83]

***Xin Qin Ke Li*: A Complementary Therapy**

In TCM, *Wei ch'i*—the body's "protective shield"—is believed to reside within the skin and mucosal surfaces where it functions to keep foreign substances out. Furthermore, the Chinese believe that harmonization of physiological processes including immunity, mucus secretion, capillary function, circulation, and digestive function is believed to decrease a person's susceptibility to allergens, pollutants, and irritants.[84]

Xin Qin Ke Li is a traditional blend of Chinese herbs that supports *Wei ch'i* and bodily processes that increase a person's resistance to exogenous factors. The formula includes astragalus (*Astragalus membranaceus)*, Chinese skullcap (*Scutellaria baicalensis)*, schizonepeta (*Schizonepeta tenuifolia*), fragrant angelica (*Angelica dahurica*), atractylodes (*Atractylodes macrocephala*), siler (*Ledebouriella divaricata*), cinnamon (*Cinnamomum cassia*), and xanthium (*Xanthium sibiricum*), and it is primarily used in China to treat colds, allergic rhinitis, acute and chronic rhinitis, nasosinusitis, and other sinus and nose ailments.[84]

Although biochemical mechanisms remain uncertain, the efficacy of *Xin Qin Ke Li* has been clinically demonstrated to reduce symptoms of allergic rhinitis and chronic sinusitis. In a study of 690 patients suffering from chronic sinusitis, *Xin Qin Ke Li* was matched against a sinus inflammation medication. *Xin Qin Ke Li* was given to 360 patients (Group I), ages 8 to 71, at a dose of 1,800 mg 3 times daily for 10 days (patients under 12 years were given 900 mg 3 times daily), while Group II received the medication. Cessation of symptoms and improvements in symptoms of congestion, nasal drainage, headache, pus drainage, and swelling were higher in Group I. For instance, a 54% cessation in congestion was observed in Group I compared to 30% in Group II; a 46% cessation in headache was seen in Group I compared to 28% in Group II; and a 55% cessation in pus drainage was seen in Group I compared to 28% in Group II.[85]

In another study, the effects of *Xin Qin Ke Li* were compared to those of a sinus medication in 109 children with allergic rhinitis. For 15-30 days, subjects under 3 years were given 1,250 mg 3 times daily, and those over 3 years were given 2,500 mg 3 times daily. Again, greater improvements in symptoms (congestion, itching, sneezing, nasal discharge, headache, and dizziness), as well as a greater drop in eosinophils were observed in the group receiving *Xin Qin Ke Li*.[86]

These data suggest that *Xin Qin Ke Li* is very effective in reducing nasal and sinus symptoms and it appears to be safe—even in small children.

Conclusion

While the incidence and suffering associated with allergic disease continues to grow, so does the knowledge regarding its prevention and treatment. As further in-roads are made into the functioning of the immune system and the etiology of immune dysfunction, therapeutic targets become clearer. Scientific advances in immunology and innovative therapies give healthcare professionals new hope of tackling difficult conditions such as allergic disorders. By addressing Th1/Th2 imbalance and downstream processes including IgE antibody production, histamine levels, leukotriene and prostaglandin synthesis, and oxidative damage it may be possible to bring lasting relief to patients.

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TH1/TH2 BALANCE: A NATURAL THERAPEUTIC APPROACH TO TH2 POLARIZATION IN ALLERGY A SUMMARY

By Tom Sult, M.D.

Allergic respiratory diseases have increased in prevalence and severity over the past 30 years in all industrialized countries. The occurrence of allergic rhinitis (hay fever) alone has increased substantially over the past 15 years, accounting for approximately 16.7 million office visits to healthcare providers each year. Allergies are also a significant trigger of asthma. According to the Centers for Disease Control and Prevention, more Americans than ever before (over 15 million) suffer from asthma, transforming what was a relatively inconspicuous ailment into an epidemic illness of significant public health concern.[10-12] Recently, the role of T helper (Th) cells in the development of allergic disease has been described.

THE SIGNIFICANCE OF T-HELPER CELLS

Th cells are the regulators of the immune system. After stimulation by any antigen (e.g., allergen, pathogen) that has entered the body, Th cells can develop into either Th1 or Th2 cells that trigger different immune processes, which protect the body in different ways. Whether Th cells develop into Th1 or Th2 cells is dependent on a variety of factors including the type of antigen, genetics, certain regulatory proteins (cytokines), and other factors.[8-10]

Researchers have found that imbalanced Th1/Th2 immune responses are linked to certain immune-related disorders. For instance, a Th1-dominated immune response has been implicated in organ-specific autoimmune disease (e.g., type 1 diabetes, thyroiditis) while a Th2-dominated immune response can lead to allergic disorders and systemic autoimmune disease (e.g., lupus). Such imbalanced immune activity can be caused by a number of things including genetics and environmental factors.[8,9]

TARGETS FOR TREATMENT: TH1/TH2 BALANCE AND DOWNSTREAM PROCESSES

Because those with an overactive Th2 response are often afflicted with allergic disease, the goal of allergy treatment should address downregulating the Th2 response and/or upregulating the Th1 response to produce a balance. In addition to balancing Th1 and Th2, treatment strategies should also address downstream processes including IgE production, histamine release, inflammation, and oxidative stress.

IgE Production—IgE is a type of antibody that, despite offering protection against certain pathogens, is responsible for driving hypersensitivity reactions such as hay fever, asthma, hives, and anaphylaxis.

Histamine Release—Histamine is released during an allergic reaction and it perpetuates allergic inflammation and the Th2 response.

Inflammatory Compound Production—Leukotrienes and prostaglandins are inflammatory mediators involved in the allergic process. They can cause symptoms such as constriction of the lung passageways and blood vessels and tissue swelling.

Oxidative Stress—Low antioxidant levels are associated with allergies and asthma. In addition, inflammatory cells involved in the allergic process release harmful free radicals.

NATURAL SUBSTANCES FOR THE TREATMENT OF ALLERGIC DISORDERS

Research suggests that the following natural compounds have the ability to modulate the allergic response, thereby offering an excellent alternative to conventional therapies whose chronic use is often accompanied by several side effects.

Perilla Seed Extract—Perilla seed extract (*Perilla frutescens*) has long been used in Traditional Chinese Medicine (TCM) and in Kampo—a Japanese variant of TCM. It is capable of modulating multiple processes in the allergic response, including histamine release, leukotriene synthesis, and oxidative stress. In addition, preliminary research performed in Japan suggests that perilla seed extract may suppress Th2 responses.

Omega-3 Fatty Acids—The increased prevalence of atopic disease has recently been associated with the over consumption of omega-6 fatty acids in relation to omega-3 fatty acids—an unhealthy imbalance common in the Western diet. Research suggests that a balanced intake of these fatty acids may have a powerful, positive effect in certain patients with allergic disorders.

Vitamin E—Research suggests that vitamin E may protect against allergies and allergic disease not only by reducing the associated free radical damage, but also by influencing Th2-type cytokine expression, IgE levels, and inflammatory compound production.

Probiotics—"Friendly" bacteria such as *Lactobacillus acidophilus* and bifidobacteria may help alleviate allergic inflammation and shift Th2-dominated immune responses, thereby reducing allergic symptoms.

Adaptogens—Adaptogenic herbs such as cordyceps (*Cordyceps sinensis*), ashwagandha (*Withania somnifera*), and Asian ginseng (*Panax ginseng*) may reduce the negative effects of acute or chronic stress. Research suggests that stress may promote an increased Th2 response, thus escalating susceptibility to allergic disorders.

V**itamin C and Flavonoids**—Flavonoids possess anti-allergic, anti-inflammatory, antiviral, and antioxidant activity. In addition, flavonoids have been shown to inhibit the release of histamine. Similar to flavonoids, data from animal and human studies have shown that vitamin C supplementation results in reduced histamine release and improved lung function.

Turmeric, Ginger, and Boswellia—Turmeric (*Curcuma longa*), ginger (*Zingiber officinale*), and boswellia (*Boswellia serrata*) are popular herbs used within Ayurveda—an East Indian system of medicine. These herbs have been shown to inhibit the production of inflammatory compounds involved in an allergic response.

Xin Qin Ke Li—This traditional blend of Chinese herbs including astragalus (*Astragalus membranaceus*), Chinese skullcap (*Scutellaria baicalensis*), schizonepeta (*Schizonepeta tenuifolia*), fragrant angelica (*Angelica dahurica*), atractylodes (*Atractylodes macrocephala*), and other herbs supports *Wei ch'i*—said to be the body's "protective shield." This formula is primarily used in China to treat colds, allergic rhinitis, acute and chronic rhinitis, nasosinusitis, and other sinus and nose ailments.

Conclusion

As the incidence and suffering associated with allergic disorders continue to grow, so does the knowledge regarding its prevention and treatment. By addressing Th1/Th2 imbalance and associated processes, natural therapies may bring lasting relief to patients.