Effects of Food Components on Intestinal Flora, Intestinal Immune System and their Mutualism

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INTRODUCTION

Foods are essential for maintaining life and health. Extensive and detailed studies have recently been carried out on the roles played by foods, yielding many findings. In the past, foods were considered as being necessary as a source of raw materials for the cells constituting our body and as a source of energy needed for physical activity.

During the past two decades, however, views on the roles of foods have undergone modification. Recently it has become increasingly clear that foods additionally regulate the physiological functions of the human body through their action on the immune, nervous, endocrine and other systems.

It has been shown that appropriate amounts of particular food components need to be replenished so that the immune, nervous and endocrine systems can function normally.

It is also known that the intestine (small bowel and large bowel) is equipped with an immune system, that the large bowel has intestinal flora, and that there is a cooperative relationship between the intestinal flora and the intestinal immune system (“mutualism”) (11).

This paper will deal with the effects of orally ingested functional components of food on the mutualism between intestinal flora and the intestinal immune system as well as their effects on the systemic immune system. Furthermore, the relationship between the collapse of the mutualism and onset of diseases is discussed.

Key words: functional food component; intestinal flora; intestinal immune system; probiotics; prebiotics

INTESTINAL FLORA

There are more than 500 kinds of bacteria, amounting to 100 trillion cells weigh 1 kg in the human intestine. These bacteria help or antagonize each other, forming the intestinal flora (11). Major bacteria constituting the intestinal flora are the anaerobes (Bifidobacterium, Lactobacillus, Streptococcus, Eubacterium, Ruminococcus, Megasphaera, Megamonas, Clostridium, Bacteroides, etc.) and the aerobes (Enterobacteriaceae, Staphylococcus, Pseudomonas aeruginosa, Yeasts, etc.) (65).
The counts of representative bacteria in the intestine are given in Table 1 (66).

The composition of the intestinal flora varies greatly depending on various factors such as individual characteristics, age, and the host’s health status, mental status (stress, etc.) and diet.

The intestinal flora have a pronounced effect on the host’s immune system. In experiments using germ-free mice, the presence of intestinal flora was shown to be closely involved in the formation and development of the mucosal immune system (25, 26, 62, 85). Furthermore, the intestinal flora permanently contributes to activation of the immune system so that homeostasis of the intestinal and systemic immune systems may be maintained.

Beneficial bacteria in the intestine such as Lactobacillus and Bifidobacterium utilize non-digestible fibers and polysaccharides (oligosaccharide, etc.) to produce short-chain fatty acids, stimulating intestinal peristalsis and additionally reducing intestinal pH to create environments unfavorable to harmful bacteria, thereby suppressing the colonization and proliferation of these bacteria in the intestine and preventing infection and intestinal tissue injury.

The bacteria constituting the intestinal flora produce diverse products through degradation which largely determine the host’s health status. For example, substances produced by harmful bacteria in the intestine directly injure the intestinal tissue. A bias in the intestinal flora balance can alter the immune system, occasionally elevating the risk of infection, allergy, autoimmune disease, obesity, cancer, etc.

Probiotics are a form of beneficial bacteria selected from the intestinal flora and incubated for oral administration, while components such as oligosaccharide, capable of increasing beneficial bacteria such as Bifidobacterium and Lactobacillus in the intestinal flora, are called prebiotics.

### INTESTINAL IMMUNE SYSTEM

The intestine has a length of 7 m and its surface area is equivalent to that of a tennis court. There are multiple organs of the immune system surrounding the intestine, and these organs are composed of immunocompetent cells such as dendritic cells, T cells, B cells and IgA-producing cells (a mature form of B cells) (Fig. 1). These cells and the antibodies produced by interactions among them account for more than 50% of the systemic immunocompetent cells and antibodies (51, 53). These factors constitute the host’s self-defense system against invading pathogenic bacteria which select the oral route most frequently as the route of invasion into organisms. For this reason, the intestinal immune system is greater in scale than any other immune system of the living body.

#### Organs of the intestinal immune system

The intestinal immune system is composed of intestinal epithelial cells, lymphocytes located within intestinal epithelium, Peyer’s patches, lamina propria and isolated lymphoid follicles. A Peyer’s patch assumes a dome-like form. There are 6–12 Peyer’s patches in the small bowel of the mouse and 180–240 Peyer’s patches in the human small bowel. A Peyer’s patch is covered with a layer of columnar epithelium. Its entrance is made of M cells which take up pathogenic microorganisms. The lower layer of the Peyer’s patch includes cells necessary for immune reactions, i.e., antigen-presenting cells such as dendritic cells, T cells and B cells (Fig. 1). The center of the Peyer’s patch is composed of the germinatal center and the surrounding B cell-gathering area. Around the Peyer’s patch, there is a T cell-gathering area.

The intestinal surface is covered with epithelial cells. The lamina propria, which underlies the intestinal mucosa, contains more than 50% of the systemic antibody-producing cells (a mature form of B cells), most of which are IgA-producing cells. Usually, pathogenic bacteria enter M cells at the entrance to the Peyer’s patch. Within the Peyer’s patch, the interaction between the antigen-presenting cells, T cells and B cells causes conversion of B cells into IgA-producing cells, which move beneath the epithelial cell layer to produce IgA. These IgA-producing cells also move to the mucosa of the oral cavity, nose and airway where they release IgA.

### Table 1. Intestinal flora of a healthy adult

| Bacteria              | Log Number of Bacteria per g/feces |
|-----------------------|-------------------------------------|
| Total                 | 11.2 ± 0.2                          |
| Bacteroidaceae        | 10.9 ± 0.2                          |
| Escherichia           | 10.4 ± 0.4                          |
| Peptococcaceae        | 10.2 ± 0.3                          |
| Bifidobacterium       | 10.0 ± 0.8                          |
| Veillonella           | 7.4 ± 1.2                           |
| Megasperaera          | 9.0 ± 0.5                           |
| Curved rods           | 9.7 ± 0.5                           |
| Clostridium perfringens | 4.4 ± 1.2                        |
| Clostridium other     | 9.5 ± 0.5                           |
| Lactobacillus         | 5.8 ± 2.1                           |
| Enterobactericeae     | 7.8 ± 0.8                           |
| Streptococcus         | 7.9 ± 1.4                           |
| Micrococcaceae        | 3.1 ± 0.7                           |
| Corynebacterium       | 5.3 ± 2.2                           |
| Yeasts                | 3.9 ± 1.6                           |

(Mitsuoka et al. (66), 1976)
Intestinal immune function—IgA production and oral tolerance

The intestinal immune system prevents invasion of pathogenic microorganisms at the entrance to the living body, i.e., at the front line of the immune system. Many pathogenic microorganisms invade the living body via the oral route and reach the intestine. The intestine has small devices for the absorption of food components. Pathogenic bacteria can invade the living body via these devices. The intestinal immune system is equipped with a very sophisticated mechanism capable of distinguishing pathogenic bacteria and preventing invasion by these bacteria while allowing entry of necessary food components (Fig. 2). Furthermore, beneficial bacteria in the intestine are not purged by the intestinal immune system. Thus, the intestinal immune system is capable of distinguishing harmful bacteria from beneficial bacteria.

Oral immune tolerance is a mechanism that has evolved to enable the intestine to incorporate food components as nutrients instead of rejecting them as foreign matter. If oral immune tolerance does not function, the risk of allergy is elevated (51, 53).

INTERACTION BETWEEN INTESTINAL FLORA AND THE INTESTINAL IMMUNE SYSTEM

The intestinal flora has substantial effects on the formation of the intestinal immune system. The cecum of germ-free mice is about 10 times larger than that of ordinary mice (16). It has also been shown that germ-free mice have a small number of Peyer’s patches and reduced numbers of cells constituting the intestinal immune system (39, 79, 90), lymphocytes between the intestinal epithelium (30), IgA-producing cells in the lamina propria (71) and so on. These features are demonstrative of the beneficial effects of the intestinal flora on the intestinal immune system. In germ-free mice, immaturity of the spleen and lymph nodes is seen as a systemic and peripheral feature in the absence of direct stimulation by the intestinal flora. The immune responses in germ-free mice are biased to Th2 type immune responses (responses likely to lead to allergic reactions) (61). Furthermore, oral immune tolerance is unlikely to be induced in germ-free mice (59, 69, 70, 92). These findings indicate that the intestinal flora plays an important role in the structure, functional development and maturation of not only the
intestinal immune system but also the systemic immune system.

To elucidate the roles played by the intestinal flora, we investigated how \textit{Bacteroides} or \textit{Lactobacillus} are involved in the formation of the intestinal immune system. The investigation revealed, for example, that \textit{Bacteroides} plays a very important role in the formation of IgA (105). It was additionally shown that the formation of the germinal center (a central zone for immune reactions in the large bowel) involves \textit{Bacteroides} (unpublished data).

**MECHANISM OF MUTUALISM IN THE INTESTINE—WHY AREN’T SYMBIOTIC BACTERIA REJECTED?**

The intestinal immune system functions in a very sophisticated manner, rejecting pathogenic bacteria but accepting symbiotic bacteria (Fig. 3). Below we illustrate and evaluate a system capable of recognizing the difference between symbiotic and pathogenic bacteria. For example, the expression of Toll-like receptors (TLR) which recognize bacteria is very low in the intestinal epithelium. A protein called “Tollip” is capable of suppressing signals from Toll-like receptors, and immune reactions to symbiotic bacteria are suppressed by specific dendritic cells and regulatory T cells. In addition, the intestinal immune system is equipped with a system capable of powerfully rejecting pathogenic bacteria.

In spite of the presence of such a symbiotic system, loss of the normal intestinal flora, particularly a decrease in beneficial bacteria constituting the intestinal flora, is reported to elevate the risk for infection, allergy, cancer and, occasionally, obesity and other conditions as well. Research conducted in our laboratory on the requirements for such a symbiotic mechanism is presented below (94).

Intestinal epithelial cells serve not only as a physical partition between the intestinal lumen, containing massive numbers of intestinal flora, and the other parts of the living body, but also as a factor playing an important role in the induction of immune responses in the intestine. The expression of TLR and related molecules by intestinal epithelial cells is suppressed when appropriate, and this mechanism seems to contribute to maintaining intestinal homeostasis.

In an experiment using several lines of human intestinal epithelial cells, we found that the low responsiveness of intestinal epithelial cells to TLR4 ligand was maintained by suppression at the TLR4 gene transcription level. It was additionally demonstrated that in the intestinal epithelial cells, deacetylation of histone bound to the TLR4 gene and DNA methylation of the TLR4 gene are induced, and that TLR4 gene transcription is suppressed through such epigenetic regulation (94).

On the other hand, transcription of the Tollip gene, involved in negative regulation of signals from TLR, was enhanced in intestinal epithelial cells over that seen in monocytes as control cells. We then determined an important sequence in the Tollip gene involved in regulation of transcription. Elf-1, identified as a transcription factor bound to this sequence, suppressed Tollip gene transcription in monocytes alone and did not suppress it in intestinal epithelial cell lines (unpublished data).
The count of aerobic bacteria was higher compared to controls. These results reveal mechanisms by which the mutualism between the intestinal flora and the intestinal immune system may be maintained.

**INTESTINAL FLORA AND IMMUNITY OR ALLERGY**

It is interesting to know the influence of intestinal flora on the intestinal immune system and the immunological condition of the living body.

We evaluated the influence of intestinal flora on the immune system and allergic reactions by comparing the immune function in germ-free and normal mice, each treated orally with ovalbumin (unpublished data).

In this study, the immune responses such as cytokine production were markedly less intense in the normal mice compared to the germ-free mice. Furthermore, regulatory T cells were induced more intensely in the normal mice. These results indicate that the intestinal flora suppresses excessive immune responses, i.e., allergic reactions. In this manner, several published studies have suggested the involvement of particular intestinal bacteria in the suppression of allergy. Björkstén et al. analyzed the intestinal flora of 2-year-old children in Sweden and Estonia and reported that the count of Bifidobacterium and Lactobacillus was lower and the count of aerobic bacteria was higher compared to controls (17). Kalliomaki et al. reported that allergen-sensitized children in Finland had a lower count of Bifidobacterium and a higher count of Clostridium compared to allergy-free children (49). These results indicate that the intestinal flora has a marked influence on the onset of allergy. We found, in germ-free mice, that colonization of Bifidobacterium suppressed antibody production (101). Therefore, if the immunomodulatory characteristics of individual intestinal bacteria can be clarified, they may be useful in facilitating the prevention and treatment of allergic diseases.

**EFFECTS OF FOOD COMPONENTS ON INTESTINAL IMMUNITY AND SYSTEMIC IMMUNITY**

Orally ingested foods pass through the oral cavity, esophagus and stomach, finally reaching the intestine, where they are digested and absorbed. All of these organs serve as the mucosal tissue separating the outer world from the inner world and function as the frontline barrier of host defenses. Because digestion and absorption of foods takes place in an intestine equipped with the most comprehensive immune system in the body, food components can have a profound influence on the intestinal immune function. Here, the effects of food components on the intestinal and systemic immune systems are described.

**Probiotics**

Close attention has recently been paid to probiotics which are defined as “viable microorganisms exerting beneficial effects on the host through improving the balance of intestinal flora” and are used to improve the balance in the intestinal flora (35). Probiotics are microorganisms primarily originating from humans or microorganisms used as starters for fermented dairy products. They include Lactobacillus, Bifidobacterium, Enterococcus, Streptococcus and so on. Recently, the effects of probiotics on the immune system have begun to receive close attention. For example, probiotics have been reported to activate the responses of NK cells, etc. (95, 96) and to suppress antibody (IgE) production and allergic reactions (87, 88, 89). Probiotics have additionally been reported to have biological activity in the suppression of cancers (46). Probiotics have also been reported to alleviate diarrhea (29).

i) Transfer of probiotics into the immune system

Findings from a recent study (45) on the distribution and fate of orally ingested probiotics are presented below. Probiotics ingested orally reach the small bowel. Subsequent transfer of probiotics to the immune system in vivo was analyzed using fluorescence-labeled viable Bifidobacterium. The bacterium was detected in the Peyer’s patches and lamina propria one hour after administration of a dose and in the mesenteric lymph nodes 24 hr after administration. However, the bacterium was not detected in the spleen or thymocytes (unpublished data). The viable Bifidobacterium taken up by M cells at the entrance of the Peyer’s patches were then incorporated into dendritic cells.

The surface of the small bowel has a dense villous structure, with the villi covered with intestinal epithelial cells and very narrow spaces called “tight junctions” present between these epithelial cells. Relatively large molecules can also enter the villi through these tight junctions (58). The dendritic cells inhabiting the lamina propria below the intestinal epithelium reach the intestinal lumen through the tight junctions and recognize antigens (84).

These findings suggest that orally administered viable Bifidobacterium are taken up into the body through the M cells and the tight junctions between intestinal epithelial
cells. These results also reveal that orally administered viable *Bifidobacterium* modify the immune system after direct uptake by the intestinal immune system or after arrival in the intestinal immune system through inter-tissue transfer.

It seems likely that the orally ingested viable *Bifidobacterium* move to each site of the intestinal immune system (Peyer’s patch, lamina propria, mesenteric lymph node, etc.) directly or after uptake by dendritic cells to stimulate immune responses. Such an immune-modifying effect is seen not only with *Bifidobacterium* but also with other probiotics such as *Lactobacillus* (37).

ii) Mechanism of activation of immunocompetent cells by probiotics

Clarification of TLR function has been rapidly unveiling the mechanism for activation of immunocompetent cells by probiotics. Viruses and other pathogenic microorganisms are recognized by the natural immunocompetent cells of the host as foreign matter to be rejected. Recently, TLR have been revealed to play a very important role in the activation of immunocompetent cells (6). Although the number of TLR types identified varies depending on the animal species under consideration, about ten types of TLR have been identified to date. Microorganisms have their unique molecules, such as peptidoglycan and teichoic acid which constitute the cell walls of Gram-positive bacteria as well as lipopolysaccharides, bacterial lipoprotein and DNA with bacteria-derived motifs found in Gram-negative bacteria (102). TLR can precisely recognize and distinguish these molecules (7).

Probiotics modify the immune system through the TLR or other receptors on immunocompetent cells.

iii) Anti-infective and anti-allergic activity of probiotics

The infection-preventive effect of probiotics is attributable to the above-mentioned effects of probiotics in regulating or modifying the immune system. In clinical studies involving human subjects, probiotics activated natural killer cells (38, 96), and reduced the incidence of respiratory infection (43).

An increase in particular intestinal bacteria can cause an imbalance in the immune system, elevating the risk for allergy. It is also possible, however, to reduce the risk of allergy by increasing the numbers of other specific bacteria.

It has been shown that administration of probiotics in animal models of allergy resulted in transition from an allergy-prone state (Th2) to an allergy-unlikely state (Th1). This change was accompanied by reduction in the levels of immunoglobulinE which is directly involved in the onset of allergy (87, 88, 89). When probiotics were administered to pregnant women and newborns, the incidence of atopic dermatitis was halved, endorsing the efficacy of probiotics (50). However, some investigators reported that no such effect was noted when the type or level of bacteria constituting the probiotics was changed (83). More detailed studies are thus needed on this topic.

We recently demonstrated that the intestinal flora acts directly on mast cells to suppress their activity. It has been reported that TLR are expressed on the mast cells playing a central role in the induction of allergic inflammation in peripheral tissues, suggesting the possibility that bacterial components can directly regulate the allergic responses of mast cells via TLR (55). With this possibility in mind, we evaluated the direct effects of intestinal flora on the allergic responses of mast cells.

In that study, human feces-derived *Bifidobacterium pseudocatenulatum* suppressed degranulation of mast cells in the presence of IgE/antigen stimulus. Furthermore, elevation of vascular permeability induced by mast cells in vivo was suppressed by this bacterium. These results indicate that particular bacteria constituting the intestinal flora can directly regulate the allergic responses of mast cells (55).

**Prebiotics**

Close attention has also been paid to prebiotics which have been defined as “food components such as nondigestible oligosaccharide which selectively activate intestinal bacteria beneficial to the host” (52). Poorly digestible oligosaccharides are typical of prebiotics, and their use is aimed at maintaining and promoting the host’s health through optimizing the intestinal flora. These food components can selectively utilize and stimulate the proliferation of mainly *Bifidobacteria* and *Lactobacilli* which are beneficial bacteria in the intestine. These oligosaccharides are also contained in abundant quantities in human milk and have been considered to be important components in the adjustment of the intestinal flora of babies. In addition to the oligosaccharides contained in human milk, prebiotics are also found in foods and are considered to contribute to an increase in beneficial bacteria in the intestine and to activate the intestinal immune system. Examples of prebiotics used as food stuffs are fructooligosaccharide, galactooligosaccharide and raffinose.

Prebiotics pass through the stomach and small intestine without being digested and reach the large bowel. Here they increase the beneficial bacteria which stimulate the immune function, contributing to the prevention of infection and allergy. These beneficial bacteria are
additionally known to decompose non-digestible fibers to yield short-chain fatty acids which stimulate large bowel peristalsis. It was recently shown that the large bowel has receptors for short-chain fatty acids (98).

Next, we consider an experiment we conducted using fructooligosaccharide, which can be divided into multiple oligosaccharides, i.e., kestose (GF2), nistose (GF3) and GF4 (76). Following an oral dose of this family of oligosaccharides, changes in intestinal flora were analyzed. Changes were noted in Bacteroides, Clostridia and Lactobacilli. The count of Bacteroides was increased in a marked manner by GF3. This experiment indicates that oligosaccharides, etc., contained in foods, are helpful in normalizing the intestinal flora.

When raffinose was orally administered in a mouse model of food allergy, IgE tended to be decreased compared to the control group (75). This suggests that raffinose may affect intestinal flora and the intestinal immune system, resulting in suppression of allergy.

**Vitamins**

i) Vitamin A

Vitamin A and its metabolite retinoic acid play important roles in the regulation of immune responses (14) in the intestine. Vitamin A-deficient mice showed reduced numbers of CD4+ and CD8+ T cells in the lamina propria of the small bowel and of CD8+ T cells within the epithelium. Furthermore, a marked reduction of IgA+ cells in the lamina propria of the small bowel was noted in these mice.

Retinoic acid is actively produced in the intestinal epithelial cells. It stimulates differentiation of epithelial cells and IgA class switching of B cells in the same way as TGF-β, thus contributing to maintaining the barrier function of the intestine (72). Furthermore, dendritic cells in intestine-associated lymphatic tissue also express retinoic acid synthetase and produce retinoic acid from retinol to stimulate the expression of their B and T cell receptors (67, 68).

Furthermore, it has been reported that vitamin A suppressed the production of TNF-α and IL-1, which are inflammatory cytokines found in serum, and elevated the level of IL-10 which is a suppressor cytokine (10).

ii) Vitamin C

Ingestion of vitamin C stimulates antibacterial activity and NK cell activity and alleviates immunological diseases such as delayed hypersensitivity (20, 44, 60). These effects of vitamin C are attributable to the reinforcement of anti-infective activity through elevation of intracellular cyclic nucleotide levels (9). Furthermore, stimulation of NK cells has been suggested to be achieved by activation of protein kinase C (44).

In a study involving humans, ingestion of 1 g vitamin C/day for 16 weeks resulted in significant elevation of the lymphocyte proliferating potential and the phagocytic activity of peripheral neutrophils, accompanied by a reduction in blood levels of lipid peroxide and cortisol. It has also been reported that vitamin C is effective against symptoms of upper airway infection, particularly in the symptoms of cold. Therefore, ingestion of vitamin C is useful during recovery from infection, probably because this vitamin directly or indirectly stimulates regeneration of vitamin E and facilitates recovery from lymphocyte damage caused by intermediate oxygen radicals (18).

iii) Vitamin D

Vitamin D suppresses autoimmune diseases through the direct or indirect regulation of the differentiation and activation of CD4+ T cells (4, 22). Its active metabolite 1,25-dihydrocholecalciferol suppresses the differentation of dendritic cells important for the induction and maintenance of T cell-dependent immune responses and reduces the count of antigen-presenting cells (15, 32, 78, 104). Vitamin D additionally suppressed the expression of the dendritic cell MHC II molecule and costimulatory molecules (15, 21, 78, 104).

In animal experiments, vitamin D suppressed IL-12 production by dendritic cells and suppressed Th1 responses. The above-mentioned metabolite of vitamin D regulates inflammatory reactions by initiating a shift from the Th17-predominant state (production of IL-17 is involved in the induction of autoimmune diseases) to Th2 or Treg profiles, and it induces regulatory T cells through induction of the tolerance-inducing type of dendritic cell (5, 12, 39). Deficiency of this vitamin D metabolite is known to be associated with a reduction in the count and function of regulatory T cells and with the onset of autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis (3, 93).

Vitamin D ingestion correlates with a reduced incidence of type I diabetes mellitus, multiple sclerosis, rheumatoid arthritis and ulcerative colitis, indicating that the serum vitamin D level is an important indicator of the onset of autoimmune diseases (93).

Patients with inflammatory bowel disease (IBD) have low blood vitamin levels and often develop other autoimmune diseases as well. Also, in IL-10-deficient mice with ulcerative colitis, vitamin D deficiency induced diarrhea, malabsorption, malnutrition and an increase in death rate; these phenomena were suppressed by ingestion of 1,25-dihydrocholecalciferol (34). It has also been shown that in patients with colitis, treatment with a ligand to the vitamin D receptor suppressed the
proliferation of intestinal epithelial cells and T cells (93). This finding suggests that vitamin D is useful as a means of treating these bowel diseases.

iv) Vitamin E

Vitamin E is involved in the maintenance and activation of the immune system through its antioxidative activity (77). Vitamin E deficiency is known to reduce splenic lymphocyte proliferation, NK cell activity, specific antibody production following vaccination and the phagocytic activity of neutrophils (63). Ingestion of vitamin E, on the other hand, enhances lymphocyte production after stimulation with lipopolysaccharide or ConA, IL-2 production, NK cell activity and the phagocytic activity of macrophages (64). Furthermore, vitamin E ingestion is also known to stimulate responses mediated by Th1-type cytokines and to suppress Th2-type responses (2, 42). Administration of vitamin E to elderly people is reported to activate the immune function, particularly cellular immunity.

Minerals

i) Zinc

Zinc is a coenzyme for many enzymes and is important for the regulation of many biochemical processes in the living body. For this reason, zinc also plays an important role in regulation of the immune system. Zinc is also an indispensable cofactor for thymulin which regulates cytokine production and cell proliferation and affects both natural and acquired immunity (60). Ingestion of zinc reinforces Th1 responses and maintains the skin and mucosa. In clinical studies, ingestion of zinc by infants, small children and elderly people reduced the incidence of infection (33, 80). Zinc deficiency can inhibit the proliferation and function of T and B cells and reduce NK cell activity, etc., resulting in attenuation of immune responses (81).

Zinc is a component of superoxide dismutase, an oxygen radical scavenging enzyme that suppresses oxidative stress (81). Zinc is also involved in the production of inflammatory cytokines such as TNF-α and IL-1β (82). It has been reported that zinc has anti-cancer activity by suppressing the activation of transcription factor NF-κB in cancer cells or by stimulating the expression of NF-κB activation suppressor and its binding to DNA (103).

ii) Selenium

Ingestion of selenium stimulates the proliferation and differentiation of lymphocytes, leading to an increase in IL-2 receptor expression and assists tumor destruction by cytotoxic T cells. In the presence of HIV-1 infection, selenium has been shown to be useful for reducing oxidative stress, regulating cytokine synthesis and suppressing cytokine-induced HIV-1 replication (13).

Fatty acids

Factors possibly underlying the recent increase in the prevalence of inflammatory immunological diseases such as atopic dermatitis include an increase in the ingestion of saturated fatty acids and n-6 unsaturated fatty acids and inadequate ingestion of n-3 unsaturated fatty acids. For example, n-6 unsaturated fatty acids, particularly arachidonic acid, are known to serve as precursors of inflammatory mediators, causing aggravation of inflammation and elevating the incidence of inflammatory disease (19, 86, 91). On the other hand, n-3 unsaturated fatty acids act directly on T cells and regulate intracellular signals, resulting in not only regulation of T cell activation but also indirect suppression of T cell activation through the action of n-3 unsaturated fatty acids on macrophages, leading to the suppression of delayed allergic responses (27, 47).

Ingestion of n-3 fatty acids such as eicosapentaenoic acid suppresses the formation of TNF-α in splenic CD4+ T cells. Furthermore, n-3 unsaturated fatty acids suppressed the formation of IFN-γ and PGE_2 after stimulation of mononucleated cells by LPS or Con A in patients with Crohn’s disease. It has also been reported that ingestion of n-3 fatty acids alleviated inflammation and suppressed TNF-α in IL-10 knockout mice (a model of IBD). It has thus been shown that n-3 unsaturated fatty acids can prevent colitis (8, 27, 100).

Amino acids

i) Glutamine

Glutamine is an important source of energy for lymphocytes, macrophages and neutrophils and is an amino acid essential for differentiation and maturation. Glutamine ingestion is known to increase the percentage of helper T cells and regulatory T cells (24) and to activate the intestinal flora (23). It has many other effects such as suppression of the production of inflammatory and suppressor cytokines, improvement of the intestinal barrier and potentiation of the function of immunocompetent cells (56, 99, 106). Furthermore, glutamine increases peripheral blood lymphocyte numbers and reduces the incidence and mortality of infection and the incidence of complications following infection (36, 40, 107). It has been shown that glutamine ingestion by bone marrow recipients reduces the production of inflammatory cytokines in the intestinal mucosa, leading to the reduction of infection and complications thereby shortening the hospital stay period.
specific IgA within intestinal epithelia and the formation of OVA-intestinal epithelia, resulting in an increase in 
indispensable for differentiation of lymphocytes within 
Nucleotide ingestion also induced the formation of IL-7, 
production of TGF-beta in intestinal epithelial cells 
specific TCR transgenic mice resulted in increased 
activity than those fed nucleotide-free milk. 
children fed milk with nucleotides showed higher NK cell 
cells 
type cytokines and antibodies, and proliferation of spleen 
nucleotide ingestion stimulates the production of Th1- 
elevating the risk of infection. On the other hand, 
production of antibodies and cytokine formation, thus 
immunity, the activity of NK cells and macrophages, 
nucleotide-free diet reduces cellular or humoral 
and induction of Th1-type immune responses. A 
immunopotentiation, protection from bacterial infection 
pathogenic microorganisms and the death rate from 
Ingestion of nucleotides exerts diverse effects such as 
immunopotentiation, protection from bacterial infection and induction of Th1-type immune responses. A 
nucleotide-free diet reduces cellular or humoral immunity, the activity of NK cells and macrophages, production of antibodies and cytokine formation, thus elevating the risk of infection. On the other hand, nucleotide ingestion stimulates the production of Th1-type cytokines and antibodies, and proliferation of spleen cells (1, 48). It has been reported that infants and small children fed milk with nucleotides showed higher NK cell activity than those fed nucleotide-free milk.

Furthermore, administration of nucleotides to OVA-specific TCR transgenic mice resulted in increased production of TGF-beta in intestinal epithelial cells (73). Nucleotide ingestion also induced the formation of IL-7, indispensable for differentiation of lymphocytes within intestinal epithelia, resulting in an increase in γδT cells within intestinal epithelia and the formation of OVA-specific IgA (74).

The effects of individual food components on immune responses have been described above. Some of these food components exert synergistic effects when combined with other components. For example, the combination of vitamin C and zinc elevates the resistance to pathogens and the combination of vitamin E and selenium effectively suppresses damage to the membrane lipids arising from oxygen radicals during infection. These findings indicate that a well-balanced diet is important in potentiating immune activity.

FOOD COMPONENTS AND ORGANS OF THE IMMUNE SYSTEM AND THEIR INTERACTIONS WITH INTESTINAL FLORA

Interactions with intestinal immunocompetent cells

Intestinal epithelial cells are the most important cells that come in direct contact with the food components reaching the intestine. They express several transporters which specifically recognize and transport nutrients. For example, transporters for glucose, peptides, amino acids, vitamins and minerals are known to be present on intestinal epithelial cells. Macromolecules such as protein are often taken up into the body by means of transcytosis without undergoing decomposition. The intestinal epithelium has Peyer’s patches and there are M cells at the entrance to the Peyer’s patches. M cells can take up macromolecules and there are antigen-presenting cells immediately below the M cells, resulting in induction of a series of immune responses. Probiotics etc., enter the living body via this route.

Small pores in the tight junctions between epithelial cells provide a route for transport via passive diffusion. The opening and closing of these small pores are reported to be adjusted by the activity of cytokines, etc., and food components are also involved in this regulation.

Various receptors such as TLR are expressed by intestinal epithelial cells. These receptors transmit the signals from the luminal to the basal side of the membrane. There are diverse immunocompetent cells on the side of the basal membrane, and these cells can receive signals from food components absorbed or transmitted via the intestinal epithelial cells. For example, antigen-presenting cells such as dendritic cells immediately below the intestinal epithelium, and cytokines produced by dendritic cells determine the direction of T cell differentiation, resulting in varying immune reactions depending on that direction. Therefore, these cells serve as an important target for regulation by food components. Food components keep the complex immune network normal and contribute to the development and preservation of the intestinal immune system. In premature infants and small children, and in elderly people whose immune function is deteriorating,
intake of food components is important as a means of reinforcing the immune system. Also, in adults, utilization of food components is advisable as a means of maintaining health especially when their immune function has been weakened through stress or other factors.

Metabolism of food components by the intestinal flora

Of the food components which have undergone degradation or not during passage through the small bowel, many components are degraded by the intestinal flora after reaching the large bowel.

Non-digestible fibers, oligosaccharides, isoflavone and other chemicals constituting foods are degraded by the intestinal flora, occasionally yielding beneficial or harmful metabolites. However, since the intestinal flora is composed of many types of bacteria and its composition differs from individual to individual, no systemic study elucidating the mechanism for degradation of food components by the intestinal flora has yet been performed. However, detailed analysis of this function of intestinal flora will yield important information concerning the preservation of normal intestinal flora. Advances in research in this field are desirable.

CONCLUSION

One of the most important means for human beings to survive is to produce adequate amounts of food of sufficient quality to meet our dietary needs and to maintain health.

To meet such demands, new fields of science are now being developed through fusion of food science with life science fields of investigation. One of these new fields pertains to research on the importance of intestinal flora, intestinal immunity and symbiotic bacteria in the intestine and to research on functional food components to facilitate their satisfactory functioning. Advances in these new fields will greatly contribute to the promotion of human health.

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