Immunomodulation by Food: Novel Collaborations between Food Components and Microbiota

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Summary
Recent studies have revealed that various food components affect the immune response. It has been shown that such components could act on the intestinal immune system. On the other hand, intestinal microbiota and their metabolites affect intestinal immunity. Such findings suggest the possibility that food components could act on the intestinal immune system directly, indirectly through intestinal microbiota, or through collaborative immunomodulation by both.

Key Words food, intestinal immunity, microbiota, lactic acid bacteria

The intestine is a large immune organ. In the gut lumen there are many antigens not only from pathogenic bacteria but also from food and commensal bacteria, and characteristic immune responses are induced by the intestinal immune system. These include IgA production and induction of regulatory T cells. IgA is the characteristic isotype induced in mucosal sites such as the intestine. IgA prevents pathogens and toxins from invading and also regulates intestinal microbiota. Regulatory T cells are induced preferentially in the intestinal immune system to mediate oral tolerance and homeostasis to ingested antigens, and to maintain homeostasis (1).

Recent studies have revealed that various food components including probiotics, prebiotics, polysaccharides, vitamins, minerals, fatty acids, peptides, and amino acids affect the intestinal immune response. These components act on various immune cells, and their effects are mediated through the intestinal immune system (1).

Food components may act directly on intestinal immune cells
We and others have shown that such food components could directly act on cells of the intestinal immune system. We have reported that lactic acid bacteria or compounds found could act on intestinal dendritic cells.

We showed that oral administration of a Lactobacillus plantarum strain to mice enhanced the production of IgA antibody in intestinal tissues. This bacterium acted on Peyer’s patch dendritic cells to enhance the production of IL-6, which promoted IgA production (2).

Another example we found was β-elemene, an herbal compound. Chronic inflammation leads to various diseases. For example, obesity can cause chronic inflammation and this may lead to lifestyle diseases such as diabetes. Feeding a high-fat diet to mice elicits inflammation in adipose tissue, and can be utilized as a model for chronic inflammation. We have been using this model to investigate the anti-inflammatory effects of food components via the intestinal immune system. We demonstrated in this model that feeding β-elemene alleviated inflammation in adipose tissue. Oral administration of β-elemene induced Foxp3+ T cells, considered to be regulatory T cells, and decreased inflammatory M1 macrophages in adipose tissue. Furthermore, β-elemene acted on intestinal dendritic cells to induce Foxp3+ T cells in the intestinal immune system. Our study demonstrated the effects of β-elemene in treating experimental obesity-induced chronic inflammation in fat tissue through the generation of regulatory T cells in the intestinal immune system by modulating dendritic cell function (3).

Concerning direct effects on dendritic cells by dietary polysaccharides, it was reported that mannan/β-1,6-glucan-containing polysaccharides (MGCP) facilitated the induction of regulatory T cells and suppressed Th1 cell differentiation (4).

Food components may act indirectly on immune cells via intestinal microbiota or metabolites
Abundant commensal bacteria inhabit the intestine. Approximately 1,000 species and 40 to one hundred trillion bacteria exist in the human intestine. It has been well accepted that such intestinal microbiota affect the intestinal immune response (1). Their effects on oral tolerance, IgA response, and Th17 response can be recognized by the impairment observed in germ-free mice.

Food components may exert their immunomodulatory effects through intestinal microbiota. Indeed, it has been considered that prebiotics act through the modulation of intestinal microbiota. In addition, it has been shown that metabolites such as short chain fatty acids (SCFAs) could regulate intestinal immunity. An extraordinary example is that butyrate induces regulatory T cells that inhibit inflammatory responses. In this case, a high fiber diet enhanced the production of SCFAs (5). Furthermore, it has been demonstrated that dietary ω3 fatty acids are converted to αKetoA by intestinal micro-

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biota to exert anti-inflammatory effects (6). Dietary tryptophan may be converted to aryl hydrocarbon receptor (AHR) agonists and modulate immune response (7). These observations suggest that food components may act on the intestinal immune system through microbiota and their metabolites.

**Food components may act both directly and indirectly on immune cells**

The above demonstrations suggest that food components could act on the intestinal immune system directly and indirectly through intestinal microbiota and their metabolites. Furthermore, this points to the possibility that food components may act through collaborative immunomodulation (Fig. 1); the same component may act directly on immune cells and simultaneously modulate microbiota indirectly influencing the immune system. Elucidation of such mechanisms is awaited.

**Disclosure of state of COI**

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**REFERENCES**


