Functional Food in Japan: Current Status and Future of Gut-Modulating Food

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ABSTRACT

Food for Specified Health Uses (FOSHU) is an official functional food approved by the Consumer Affairs Agency of Japan. The number of FOSHU items reached almost 970 as of October, 2011. It should be emphasized, however, that more than 70% of the current FOSHU products function in the gastrointestinal tract. They improve intestinal microflora or regulate nutrient absorption, thereby reducing the risks of metabolic syndrome. In addition to the gut-modulating FOSHU products already approved, many attempts have been made to develop new functional foods that regulate other intestinal functions. Modulation of the detoxification system is beneficial to reinforce the gut barrier, and also to suppress inflammatory reactions. Regulation of the T cell differentiation can also be a target for new gut-modulating foods to suppress allergy. Regulation of intestinal IgA production will be beneficial to lower the risks of infection. Recent studies have demonstrated that a variety of food factors, such as lactic acid bacteria, oligosaccharides, amino acids, and polyphenols, can be promising ingredients for the future development of gut-modulating functional foods.

Key words: functional food, FOSHU, gut microflora, gut immune-system, detoxification

FOSHU: THE FUNCTIONAL FOOD APPROVED BY JAPANESE GOVERNMENT

Studies on physiological effects of food were carried out in Japan from 1984 to 1995 under the support of large-scale grant-aided national research projects. Based on the scientific data accumulated by the projects, Japan established a unique regulation system for functional foods in 1991[(1)]. In this system, a functional food with sufficient evidence to support a health claim can be approved by the government as "food for specified health uses (FoSHU)", which can then be commercialized with a specific health claim[(1,2)]. Although regulation systems for functional foods are not yet internationally unified, the FoSHU system is recognized as the first one to review and approve label statements regarding effects of foods on the human body[(3,4)].

Since the first product was approved in 1993, the number of FOSHU items has progressively increased, reaching almost 970 as of October, 2011. Currently available FOSHU products can be roughly classified into eight categories according to their specific health claims[(5)]; those include (1)food to promote gut health, (2) food to promote tooth and gum health, (3) food to facilitate mineral absorption, (4) food to promote bone strength, (5) food for those who are concerned about hypertension, (6) food for those who are concerned about blood sugar level, (7) food for those who are concerned about blood cholesterol level, and (8) food for those who are concerned about body fat accumulation. However, more than 70% of the current FOSHU products function in the gastrointestinal tract. Considering that the intestinal epithelium is always exposed to foods, their digestion products, and intestinal bacteria, it is reasonable to think that food plays a role as one of the important modulators of gut functions.

FOSHU TO REGULATE GUT MICROFLORA

The first group of the gut-modulating FoSHU is food to improve intestinal microflora.. Probiotic bacteria (certain strains of *Bifidobacterium* and *Lactobacillus* that can survive in the intestinal tract) and prebiotics (indigestible oligosaccharides, dietary fiber including indigestible dextrin, and other dietary substances to enhance growth of beneficial bacteria in the intestinal tract), are used as functional ingredients of this category of FOSHU. Taking these FOSHU products may increase intestinal bifidobacteria, thus aiding in the maintenance of good gastrointestinal condition[(6)]. Changes in the number and ratio of intestinal bifidobacteria, and frequency and volume of evacuation after intake of the product, are used to validate the efficacy of this type of FoSHU products. Concentrations of short-chain fatty acids, such as propionic and butyric acid, produced by intestinal microbiota are also important indicators, because they may contribute to the acidification of the intestinal environment and also activate intestinal epithelial cell functions. Intestinal nervous system and smooth muscle cells may also be stimulated by the short-chain fatty acids, resulting in the activation of bowel movement and thus prevent or alleviate constipation.

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FOSHU TO REGULATE NUTRIENT ABSORPTION

The second group of gut-modulating FoSHU is food which regulates intestinal absorption of nutrients[5]. Facilitating mineral absorption can be one of the missions for this type of FoSHU, because the calcium intake of Japanese tends to be below the adequate intake level. Some of the foods which can enhance intestinal mineral absorption have been approved as FOSHU. Casein phosphopeptides (CPP) derived from milk caseins can bind with calcium, thereby maintaining calcium solubility in the lower small intestinal tract and increasing the efficiency of calcium absorption. CPP is therefore used for FOSHU products as a calcium absorption-enhancing ingredient, which may be helpful to promote bone health. Polyglutamic acid produced by certain fermentation bacteria is also used as an ingredient of FoSHU having a similar function. Certain oligosaccharide is also used as a functional ingredient, because oligosaccharides lower intestinal pH by enhancing growth and acid production of intestinal bacteria, thereby increasing calcium solubility in the gut.

Suppressing the increase in blood glucose, cholesterol, and triglyceride levels following a meal is one of health authorities in advanced countries, as these factors may increase the risks of lifestyle-related diseases, including diabetes, atherosclerosis, and obesity. To regulate the blood glucose level, inhibition of intestinal digestive enzymes may be an effective approach. Substances such as indigestible dextrin, wheat albumin, and tea catechin were found to inhibit α-amylase, and are therefore used as functional ingredients for FoSHU products for those who are concerned about the blood glucose level. A similar strategy has been used to develop FoSHU products with a cholesterol-lowering effect. Soybean proteins and peptides have capacity of binding with cholesterol and bile acids in the intestines. They are therefore expected to capture cholesterol/bile acids and inhibit their absorption at the intestinal epithelium. Plant sterols were found to be effective in inhibiting cholesterol incorporation into mixed micelles, which is an essential step of cholesterol absorption at the intestinal epithelium. Polymerized tea catechins contained in oolong tea and peptides derived from globin digests were found to suppress lipase action in the intestinal tract. The products using these functional ingredients have been approved as FOSHU items.

MODULATION OF INTESTINAL TRANSPORTER FUNCTIONS BY FOOD

Food substances that inhibit digestive enzymes are used as functional ingredients of FOSHU to suppress nutrient absorption as described earlier. In addition to the digestive enzymes, nutrient transporters may be the target for functional food.

We reported that green tea catechins, particularly epicatechin gallate, inhibited the sodium-dependent glucose transporter 1 (SGLT1), the major glucose transporter in the small intestine[7]. This may contribute, at least partly, to the blood glucose lowering effect of green tea. Inhibition of the monocarboxylic acid transporter (MCT) by tea catechins was also observed[8].

Regulation of transporters by probiotic bacteria or their metabolite has recently been given increased attention. Sodium-dependent monocarboxyric acid transporter (SMCT), which is responsible for the transport of butyric acid, was reported to be regulated by *L. plantarum in vitro* and also *in vivo* studies[9]. Regulation of several transporters, including those for glucose, peptide, and cholesterol, by microbes has also been suggested. Although the information concerning the mechanisms is limited, intestinal microbes and their metabolites may play a role as a regulator of intestinal transport functions.

MODULATION OF GUT DETOXIFICATION SYSTEM BY FOOD

Barrier functions of intestinal epithelial cell monolayers play important roles in protecting the body from external risk factors. The detoxification system is one of the major constituents of the chemical barrier.

The gut detoxification system catalyzes the oxidation and conjugation reactions to increase the hydrophilicity of harmful hydrophobic chemicals, thereby reducing their toxicity. Interestingly, the target molecule for the detoxification system is not only harmful substances such as environmental chemicals, but also certain food components. Flavonoids, which have recently been given increased attention because of their health-promoting functions, are often recognized as xenobiotics by the intestinal detoxification system[10]. Those flavonoids would be oxidized by Phase I enzymes, and then conjugated by Phase II enzymes. The resultant conjugates, such as glucuronate and sulfate conjugates, would be excreted from the cells *via* Phase III transporters.

Since the detoxification enzymes and transporters are regulated not only by xenobiotics but also by food factors, food can be a useful modulator of the gut detoxification system. Intracellular receptors such as AhR (arylhydrocarbon receptor) and PXR (pregnane X receptor) are known to be involved in the regulation of detoxification enzymes and transporters. Up-regulated detoxification enzymes would help oxidation/conjugation of xenobiotics, and eventually excrete the harmful compounds from the cells.

We are interested in how food substances are involved in the PXR- and AhR-mediated regulation of detoxification enzymes in intestinal epithelial cells. The effect of dietary phytochemicals on the PXR-dependent transcriptional activity was therefore examined by using a reporter assay system constructed with human intestinal LS180 cells[10]. Among many phytochemicals tested, some flavonoids and terpenoids activated the PXR-dependent transcriptional activity. Increased expression of phase-II detoxification enzymes and phase-III transporter MDR1 by these phytochemicals was also confirmed in *in vitro* and *in*

vivo experiments. This may suggest that daily intake of foods containing certain phytochemicals activates the intestinal detoxification system and promotes the barrier function of intestines against toxic chemicals. Some of the flavonoids are also known to suppress the TCDD-induced transcriptional activity of the CYP1A1 promoter in liver cells[11], suggesting that direct binding of flavonoids with AhR occurs.

Recent studies have demonstrated that AhR is involved in immune regulation[12]. Activation of AhR by its ligand induces the regulatory T cells (Tregs), thereby suppressing allergy and autoimmune diseases. We have found that certain flavonoid showing the AhR agonistic activity can induce Tregs.

MODULATION OF GUT IMMUNE SYSTEM BY FOOD

Modulation of the intestinal immune system can also be a target for functional foods. Inflammation, allergy, and infectious diseases may be suppressed by regulating the intestinal immune system, and food can play a part, although no immune-modulating foods or ingredients have yet been approved with this FoSHU category.

I. *Anti-Inflammatory Food*

Oxidative stress in intestinal epithelial cells has been shown to promote the production of several cytokines, including IL-8, IL-6, IL-1β, and TNF-α, each of which can induce neutrophil recruitment, thereby augmenting tissue damage. The secretion of these inflammatory cytokines may be an integral part of the immune response. Disturbed regulation of the balance of these cytokines plays a key role in the pathogenesis of inflammatory bowel diseases (IBDs). We have demonstrated that a variety of food substances inhibited the enhanced proinflammatory IL-8 secretion that was induced by a hydrogen peroxide treatment of Caco-2 cells[13]. Amino acids, such as histidine and taurine, showed an inhibitory effect on the chemokine production in *in vitro* and *in vivo* experiments. Anti-inflammatory effects of a dipeptide, carnosine, and such polyphenolic compounds as chlorogenic acid have also been observed.

II. *Anti-Allergic Food*

Certain food components can inhibit allergic reactions. Modulation of T cell responses may be important in this process, since allergy has been shown to be related with excess Th2 response. Previous studies have shown that certain lactic acid bacteria contained in fermented milk products are capable of inhibiting development of Th2 response through enhancement of IL-12 secretion by antigen presenting cell populations. Other proposed mechanisms may include induction of regulatory T cells[24], and apoptosis of activated cells.

Indigestible oligosaccharides have been shown to be effective in allergy models. Nagura *et al.*[14] have shown that raffinose could inhibit IgE responses in a mouse model of food allergy. Modulation of Peyer's patch cell functions by raffinose is thought to be the mechanism. This anti-allergic effect may be through modulation of intestinal flora since such oligosaccharides have been shown to alter intestinal microbiota. Anti-allergic effects of other food components such as polyphenols have also been reported. Tachibana *et al.*[15] have reported that epigallocatechin gallate can inhibit histamine release and expression of the high-affinity IgE receptor through binding to the 67kD laminin receptor.

III. *Food to Prevent Infection*

On the surface of the intestinal epithelial cells, there are specific receptors called Toll-like receptors (TLRs). About 10 types of TLRs are expressed in the intestinal epithelial cells, and they specifically recognize respective ligands derived from bacteria. For example, peptide glycan is recognized by TLR2, lipopolysaccharide by TLR4, flaggellin by TLR5, and so on. When pathogenic bacteria approach the surface of intestinal epithelium, they are recognized by TLRs, and chemokines are secreted accordingly. Secreted chemokines attract macrophages and neutrophils, which form a immunological barrier against pathogens. Recent studies have showed that some food factors may modulate TLR functions, thereby affecting the immunological barrier formation at the epithelium.

Regulation of intestinal IgA production by food factors will be beneficial to lower the risks of infection. The intestinal immune system responds to pathogens and commensal bacteria by producing IgA antibodies. It has been demonstrated that lactic acid bacteria and dietary oligosaccharides augment IgA responses. Such probiotic bacteria or prebiotic food components lower the risk of infection, and the elevation of IgA response may play a role in augmentation of host defense. Recently the importance of dendritic cells have been shown in the intestinal IgA response[16]. The cellular target of lactic acid bacteria and oligosaccharides in enhancement of IgA response may well be dendritic cells other than T and B cells. Concerning non-T non-B cells, intestinal epithelial cells also mediate IgA response. Feeding nucleotides was found to enhance intestinal IgA response. Production of TGF-β, a cytokine responsible for IgA induction, by intestinal epithelial cells is enhanced in nucleotide-fed mice[17].

CONCLUSIONS

FoSHU, an official functional food approved by the Consumer Affairs Agency of Japan, include many gut-modulating foods (Figure 1). Current gut-modulating FoSHU products consist of food to improve gut micrioflora and food to regulate nutrient absorption. Recent studies have revealed that other intestinal functions, including transport, detoxification, and immune functions, can be modulated by a variety of food factors. Those gut-modulating food factors

may provide novel strategy for the development of new foods with health-promoting functions.

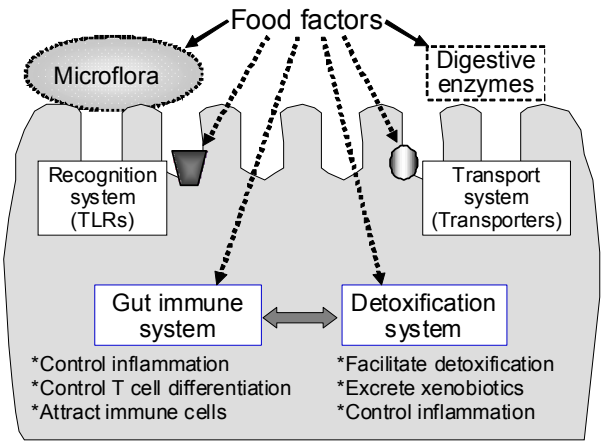

Figure 1. Possible targets for food factors to modulate gut functions.

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