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Modulation of Intestinal Functions by Dietary Substances: An Effective Approach to Health Promotion

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Abstract

Food contains a variety of substances than can modulate transport,barrier, detoxification, and immune functions of the intestines. Functional foods with those substances will be beneficial in promoting gut health, and eventually prevent lifestyle-related diseases.

Key words: Intestinal function, Gut barrier, Detoxification system, Immune system, Functional food

Digestion and Absorption Functions of the Gut and Functional Foods

In the gut, many enzymes and transporters are involved in digestion of food and transport of nutrients, respectively. Because the uptake of nutrients and beneficial food factors is highly dependent on these gut functions, digestive enzymes and transporters play crucial roles in regulating growth and promoting health in humans.

On the other hand, the effective nutrient uptake system of the gut may cause undesirable results; for example, in developed countries excess calorie and nutrient intake is recognized as a social and health issue. Many functional foods that may suppress nutrient absorption in the intestine and reduce the risk for metabolic syndrome have been accordingly developed. Food for Specified Health Uses (FoSHU) is an evidence-based functional food approved by the Consumer's Agency of Japan. Almost 1000 products have been approved as of March 2012 with about ten different health claims. Almost 40% of the current FoSHU products are foods that regulate digestion and absorption of nutrients in the intestines. These include foods to reduce blood glucose levels by suppressing gastrointestinal digestive enzymes, foods to suppress lipid absorption by regulating formation of mixed micelles, and foods to enhance mineral absorption. In addition, products to promote gut health with probiotics (e.g., *Lactobacillus*, and *Bifidobacterium*) and prebiotics (e.g., dietary fibers and oligosaccharides) have been developed, and they comprise more than 30% of the total FoSHU products. Therefore, modulation of intestinal conditions appears to be a promising target for FoSHU (Shimizu and Hachimura, 2011).

Barrier Functions of the Gut

The intestinal epithelium plays an important role as a barrier against exogenous harmful compounds, including pathogenic microorganisms and toxic chemicals. The intestinal barrier consists of physical, chemical, and biological components. The epithelial cell monolayer, the cells of which are connected with tight junctions, forms a physical barrier, preventing invasion by high molecular-weight components such as proteins

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and microbial substances. Intestinal epithelial cells have a detoxification system, which serves as a chemical barrier in the gut. Toxic xenobiotics are metabolized by detoxification enzymes, and the resultant less-harmful compounds are efficiently excreted from the cells to the intestinal lumen by efflux transporters. Thus, the detoxification system is in charge of eliminating harmful chemical compounds. The typical biological barrier may be represented by the intestinal immune system. The immune system recognizes the invasion of pathogens and builds up a defensive barrier against them by activating immune cells and producing such antibodies as IgA.

The gut possesses a variety of efficient systems for uptake of nutrients, elimination of toxins, and expulsion of pathogens. These systems are essential to keep us healthy. Recent studies have shown that the intestinal functions mentioned above are affected by food factors (Shimizu, 2010). Consumption of an appropriate diet to improve gut functions is expected to be beneficial in preventing lifestyle-related diseases and infectious diseases.

Detoxification System of the Gut

Intestinal epithelial cells have a detoxification and excretion system to prevent invasion by harmful xenobiotic chemicals. This system consists of drug-metabolizing enzymes and efflux transporters. The drug-metabolizing enzymes include the phase I enzymes, such as cytochrome P450 (CYPs), and Phase II enzymes, such as glutathione-S-transferase (GST) and UDP-glucuronosyltransferase (UGT). The efflux transporters include multidrug-resistant protein 1 (MDR1) or P-glycoprotein and multidrug resistance-associated proteins (MRPs). The activities of these enzymes and transporters are regulated at the transcriptional level, and such transcription factors as aryl hydrocarbon receptor (AhR) and pregnane X receptor (PXR) are known to be involved in this regulation (Jeong et al., 2005). Xenobiotics, including environmental chemicals, coming from outside the body will be recognized by the transcription factors in the intestinal cells, resulting in the up-regulation of expression of detoxification enzymes. Interestingly, regulation of the gut detoxification system by transcription factors is elicited not only by environmental chemicals but also by certain food substances. We have used reporter assay systems to search for food factors that could interact with AhR and PXR and found that some of the flavonoids could affect these transcription factors, thereby regulating the expression of detoxification enzymes and efflux transporters (Satsu et al., 2008; Hamada et al., 2006). Hence, eating vegetables and fruits rich in flavonoids will be beneficial to enhance intestinal barrier functions by building up the detoxification and excretion system. This may be a type of adaptive evolution of the gastrointestinal tract to phytochemical-rich plant food, and it may explain why we have a habit of eating vegetables and fruits.

Gut Immune System

The gut immune system plays important roles in preventing infectious diseases caused by pathogenic bacteria and viruses. It also has a unique regulatory function termed “oral immune tolerance”, by which allergic or inflammatory reactions to dietary substances are repressed. Recent studies have demonstrated that certain food substances may modulate the gut immune system.

Regarding the immune system that defends against infection, production and secretion of IgA in the intestinal mucosa are modulated by probiotics and prebiotics (Shimizu and Hachimura, 2011). Suppressive effects of food substances, such as amino acids, peptides, polyphenolic compounds, and carbohydrate, on the inflammatory and allergic reactions in the intestines have been reported (Romier et al., 2009.). Food substances that could enhance oral immune tolerance have also been reported (Mengheri, 2008).

Recent findings have demonstrated that AhR, the transcription factor responsible for the regulation of the gut detoxification system, is involved in the differentiation of regulatory T cells, which play a role in suppressing allergy and inflammation (Stevens et al., 2009). We have recently found that naringenin, a flavonoid abundant in citrus fruits and an AhR agonist, may induce differentiation of naïve T cells to regulatory T cells via the AhR-dependent pathway (Wang et al., 2012). PXR, another detoxification-regulating transcription factor, was shown to suppress the activation of NFκB, a master regulator of the inflammatory reactions in many cells (Xie and Tian, 2006). We have also observed that an intestinal metabolite of isoflavone, equol, activates PXR and suppresses intestinal inflammation in a dextran sulfate sodium (DSS)-induced colitis model (manuscript in preparation).

Thus, food contains a variety of substances that can

modulate many intestinal functions. This suggests that a sound gut can be maintained by dietary substances or foods. Studying the interaction between food and the gut may provide valuable information about how the gut has adapted to exogenous food substances during the process of evolution, which may be beneficial for designing new types of functional food in the future.

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