− Review −

Insights into the Roles of Prebiotics and Probiotics in the Large Intestine

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According to facts revealed up until the present, there are a total of 68 known phyla on earth, including 55 phyla of bacteria and 13 phyla of archaea. The human large intestine has 9 phyla of microorganisms, which is a relatively lower diversity compared to the general environments of soil or sea. The diversity of intestinal microorganisms is affected by the characteristics of the host (genetic background, sex, age, immune system, and gut motility), the diet (non-digestible carbohydrates, fat, prebiotics, probiotics), and the intake of antibiotics, which in turn have an effect on energy storage processes, gene expressions, and even metabolic diseases like obesity. Probiotics are referred to as living microorganisms that improve the intestinal microbiota and contribute to the health of the host; in addition, probiotics usually comprise lactic acid bacteria. Recently, bacteriotherapy using probiotics has been utilized to treat sicknesses like diarrhea and irritable bowel syndrome. Prebiotics are a food ingredient which can selectively adjust intestinal microorganisms and which comprise inulin, fructooligosaccharides, galactooligosaccharides, and lactulose. In recent days, attention has been paid to the use of dietary cellulose in the large intestine and the production of short chain fatty acids (short-chain fatty acids) in relation to obesity and anticancer. More research into microorganisms in the large intestine is necessary to identify specific microorganism species, which are adjusted by diverse non-digestible carbohydrates, prebiotics, and probiotics in the large intestine and to understand the connection between sicknesses and metabolites like short chain fatty acids produced by these microorganism species.

Key words : Probiotics, prebiotics, large intestine, gut microbium, SCFA

Introduction

100 years ago, Elie Metchnikoff (a Russian scientist, Nobel laureate, and professor at the Pasteur Institute in Paris) said that intestinal autointoxication and resultant aging adjust gut microbiota or decomposes proteins, substitute proteolytic microbes such as *Clostridium* (which produce toxicants like phenols, indoles, and ammonia with useful microbes), and inhibit toxicity. He developed milk that is fermented by a bacterium called *Bulgarian bacillus* [18, 48]. *Bifidobacterium* is called *Bacillus bifidus communis,* since it was first separated from a breast-fed infant by Henry Tissier (of the Pasteur Institute), and the administration of *bifidobacteria* to children was recommended because it can substitute proteolytic bacteria, which causes diarrhea [2, 38]

The term probiotics was defined in 1965 by Lilly and Stillwell as microbially derived factors that stimulate the growth of other microorganisms, and in 1989 Roy Fuller added significance to the definition, saying that probiotics have viability and should have a beneficial effect on the host [2, 32]. Probiotics may be defined as a living microbe that is beneficial to the health of the host, and a substance that is turned into various products such as food, drugs, and dietary supplements to help improve intestinal microbiota in humans or animals [43, 45]. In general, such microorganisms as *Lactobacillus* and *Bifidobacterium* species are used as probiotics; the yeast *Saccharomyces cerevisiae,* and some *E. coli* and *Bacillus* species are used as well. Lactic acid bacteria (LAB) including the *Lactobacillus* species have been used for dual functions of food fermentation and health benefits for thousands of years and are widely used for fermented milk products like yoghurt [24]. *L. casei* was first separated from Emmental cheese and is used as an acid-producing-starter to ferment milk and add flavor to it; being a microorganism

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which is mostly used as a microorganism for manufacturing liquid yoghurt, it has an anticancer effect and it also increases IgA, an immunity ingredient on the mucous membrane of the small intestine, to strengthen immunity [35]. *L. acidophilus* was first separated in 1900 by Moro from excrement samples of a newborn baby, and then once again separated by Metchnikoff from Bulgarian yoghurts. This microorganism settles down well in the small intestine and has functions to reduce the blood cholesterol, intensify immunity, and improve constipation. It shows good resistance to bile acid and acidity and produces antimicrobial substances; therefore, it is mostly used as an industrial probiotic for milk products [35, 52]. *L. reuteri* settles down well in the stomach, small intestine, large intestine, and vagina, and has better acid resistance than *L. acidophilus;* it also composes antimicrobial substances (reuterin) and strongly inhibits almost all harmful bacteria. It is useful as a probiotic for infants as well, since it has an excellent effect in improving diarrhea and intensifying immunity [35]. *Bifidobacterium longum* was separated from the excrement samples of men, and many researchers have found that it is a microorganism subservient to the health of men [35]. It is also widely used as a probiotic along with *L. acidophilus* since it has such merits as reducing blood cholesterol concentration, anticancer effects, and increasing immunity [24, 26]. Table 1 presents the most common probiotics such as dairy products and probiotic-fortified foods, which may be used in the form of tablets, capsules, or sachets (containing the bacteria in freeze-dried form). Patrizia et al. [8] conducted an experiment on 10 patients contracted with functional diarrhea or irritable bowel syndrome by using probiotics mixed with *B. longum, L. casei, L. delbrueckiisup, bulgaricus,* and *L. plantarum.* An observation was made of changes in excrement samples before the treatment, during the 20-day treatment, and 10 days after the treatment; it was found that the conditions of the patients gradually improved as the number of *Bifidobacterium* and *Lactobacillus* microorganisms increased in the intestine during the treatment when probiotics were administered. However, 10 days after the treatment, their conditions returned to those before the treatment. This demonstrates that probiotics can be used to treat specific diseases in the intestine of humans, which is a basic theory of the newly emerging 'bacteriotherapy' [34, 49]. Another example of the therapy is that, when *Streptococcus aureus* is taken orally, this microorganism significantly reduces the formation of other harmful microorganisms [47]. A research into men found

that probiotic strains endure in the intestine only for a short time [53]. Yet, it was also found that, once microbes inputted from the outside have successfully settled down, they would change the previous structure of microorganism colonies [27]. Such a change in the structure may have an effect on the digestion or physiology on the brush border of men. Research on mice had a very encouraging result. It was found that, when *Lactobacillus paracasei* was administered to mice infected with *Trichinella Spiralis,* they could successfully settle down and normalize their energy, fat, amino acid, and metabolism [33].

Prebiotics

Probiotics are used to directly administer living microorganisms so as to help improve intestinal microbiota, while prebiotics are a product used by useful microorganisms in the large intestine and which have a function of promoting the growth or activity of intestinal microorganisms. Prebiotics are a dietary substance which is composed of non-starch polysaccharides and oligosaccharides, most of which are not digested well by the enzymes of humans, and which can selectively promote the growth of intestinal microorganisms that are not harmful to the body but beneficial [20]. Unlike probiotics, prebiotics (which are a food ingredient) should not be digested or absorbed in the small intestine, and they selectively activate useful microorganisms such as *lactobacillus* and *Bifidobacterium* from among microorganisms in the large intestine, and inhibit germs and other harmful microbes [20]. Commonly known prebiotics include inulin, fructooligosaccharides, galactooligosaccharides, lactulose, and breast milk oligosaccharides. Lactulose is a synthetic disaccharide used as a drug to treat constipation and hepatic encephalopathy; fructooligosaccharides are naturally contained in such foods as wheat, onions, bananas, honey, garlic, and leeks, and may be separated from chicory root or composed through enzymes from sucrose. When the fructooligosaccharides are fermented in the colon, they increase the *bifidobacteria* number, calcium absorption, and fecal weight and shorten the gastrointestinal transit time, lowering the blood lipid levels [19, 21, 36]. Hermie et al. [23] report that, when inulin is taken, *Bifidobacterium* (an intestinal useful microbe) will increase and secrete IgA and mucin, which have an effect on the maintenance of intestinal functions [37]. Also, *bifidobacteria* ferment inulin and generate acetic acid, propionic acid, and butyric acid; acetic acid and propionic acid are used to gen-

Table 1. Examples of probiotic strains in products [20]

Strain (alternative designations)	Brand name	Producer
Bifidobacterium animalis DN 173 010	Activia	Danon-e/Dannon-
Bifidobacterium animalis subsp. *lactis* Bb-12	Chr. Hansen	
Bifidobacterium breve Yakult	Bifiene	Yakult
Bifidobacterium infantis 35624	Align	Procter & Gamble
Bifidobacterium lactis HN019 (DR10)	Howaru Bifido	Danisco
Bifidobacterium longum BB536		Morinaga Milk Industry
Enterococcus LAB SF 68	Bioflorin	Cerbios-Pharma
Escherichia coli Nissle 1917	Mutaflor	Ardeypharm
Lactobacillus acidophilus LA-5		Chr. Hansen
Lactobacillus acidophilus NCFM		Danisco
Lactobacillus casei DN-114 001	Actimel, DanActive	Danon-e/Dannon-
Lactobacillus casei CRL431		Chr. Hansen
Lactobacillus casei F19	Cultura	Arla Foods
Lactobacillus casei Shirota	Yakult	Yakult
Lactobacillus johnsonii La1 (Lj1)	LC1	Nestlé
Lactococcus lactis L1A	Norrmejerier	
Lactobacillus plantarum 299V	GoodBelly, ProViva	NextFoods Probi
Lactobacillus reuteri DSM 17938	L. reuteri Protectis	BioGaia
Lactobacillus rhamnosus ATCC 53013 (LGG)	Vifit and others	Valio
Lactobacillus rhamnosus LB21	Verum	Norrmejerier
Lactobacillus salivarius UCC118		
Saccharomyces cerevisiae (boulardii) lyo	DiarSafe, Ultralevure, etc.	Wren Laboratories, Biocodex, etc.
Tested as mixture: *Lactobacillus acidophilus* CL1285 & *L.casei* Lbc80r	Bio K+	Bio K+ International
Tested as mixture: *Lactobacillus rhamnosus* GR-1 & *L. reuteri* RC-14	FemDophilus	Chr. Hansen
Tested as mixture: VSL#3 (mixture of one strain of *Streptococcus thermophilus*, four *Lactobacillus* spp., & three *Bifidobacterium* spp. strains	VSL#3	Sigma-Tau Pharmaceuticals, Inc.
Tested as mixture: *Lactobacillus acidophilus* CUL60 & *Bifidobacterium bifidum* CUL 20		
Tested as mixture: *Lactobacillus helveticus* R0052 & *L. rhamnosus* R0011	A'Biotica and others	Institut Rosell
Tested as mixture: *Bacillus clausii* strains O/C, NR, SIN, and T	Enterogermina	Sanofi-Aventis

erate energy in the liver and butyric acid also has an effect to prevent colorectal cancer in the large intestine [37, 42]

Gut microbiota

Among the digestive organs of humans, microorganisms exist mostly in the large intestine, comprise hundreds of species, and have about 600,000 genes [2, 13, 41]. In recent days, a biopsy was conducted of the feces and the large intestine of humans and determined that there are 9 phyla of microorganisms (*Firmicutes, Bacteroidetes, Actinobacteria, Fusobacteria, Proteobacteria, Verrucomicrobia, Cyanobacteria, Spirochaetes,* and *VadinBE97*) [5]. However, as for the dominance ratio of these microorganisms, *Firmicutes* account for 65%, *Bacteroidetes* for 25%, and the remaining 10% is ascribed to *Proteobacteria,*

Actinobacteria, and *Fusobacteria* in that order [3, 9, 15, 50]. Of the microorganisms, *Firmicutes* is the greatest player in the mouth, the gullet, the small intestine, and the large intestine. In contrast, in the stomach, *Actinobacteria* is the greatest player, followed by *Firmicutes* and *Proteobacteria.* In the gullet, the small intestine, and the large intestine, the dominance ratio of *Firmicutes* is the highest followed by *Bacteroidetes.* In the mouth, the dominance ratio of *Firmicutes* is still high, but unlike in the case of the gullet, small intestine, and large intestine, the dominance ratio of *Firmicutes* is followed by that of *Proteobacteria.* Such facts show a very simple aspect, considering the fact that that there are 55 phyla of bacteria in total and 13 phyla of archaea presently known on earth, and considering the microbial diversity of microbial communities in general soil or sea environments. A wide range of heterogeneous soil environments contributes to the expansion of the diversity of microorganisms [54, 56]. In comparison, in environments where the ingredients and the structure of foods are not much different in each region of the intestines, since foods are evenly mixed and digested due to a peristaltic movement of the intestines, a relatively lower diversity of microorganisms is expected [15, 30].

Bacteria in the small intestine has a major effect on immune function since there are many organized lymphoid structures in small-intestinal mucosa (Peyer's patches) and because the epithelium of the small intestine is specialized into cells which involve the uptake and sampling of antigens, and have lymphoid germinal centers where adaptive immune responses are induced. The intestine is the body's most important immune function‐related organ, and intestinal mucosa account for about 60% of a body's immune cells; such an immune system adjusts immune responses to dietary proteins, prevention of food allergies, pathogenic microorganisms, viruses (*rotavirus, poliovirus*), bacteria (*Salmonella, Listeria, Clostridium,* etc.), and parasites (*Toxoplasma*). Probiotics activate local macrophages and increases the antigen presentation of B lymphocytes, inducing immunoglobulin A (IgA) production [29, 40]

Gut microbiota and obesity

It is known that microorganisms have a slightly different composition in each human body and will change over time, and each person has a different response to microorganisms. Currently it is reported that changes in these microorganism communities are related to diverse sicknesses like autism

[17], ankylosing spodylitis [51], inflammatory bowel disease [39], obesity [6], and others. Of such sicknesses, obesity has been researched in more detail; a comparison between the ratios of *Firmicutes* and *Bacteroidetes,* which account for most intestinal microorganism communities, revealed that an increase in *Bacteroidetes* is connected to the reduction of body weight. Other research has found that genetically obese mice have a better ability to collect energy from foods than lean mice do. These results suggest that, as for obesity caused by intestinal microorganisms, the causal microbes may be used as a biomarker or a treatment goal for obesity [30]. Obesity is a result of surplus calories that have not been used are accumulated as body fat, when there is an imbalance between the calories absorbed into the body from nutrients and the calories consumed for bio-functions or physical exercise [6]. *Firmicutes* and *Bacteroidetes* phyla are predominant intestinal microbiota which account for more than 85% of intestinal microorganisms and that include some pathogenic microorganisms. *Firmicutes* is a class which takes the largest portion of intestinal microbiota, comprising about 250 genera such as *Lactobacillus, Mycoplasma, Bacillus, Clostridium,* and *Strpetococcus;* the microbe species have diverse physiological characteristics or a different effect in contributing to their host, and comprise many microbes like a well-known useful microbe or lactobacillus and a pathogenic microbe causing strep throat. Of the *Bacteroidetes* phyla, which include about 20 genera, *Bacteroides* genus as a single microbe takes the largest portion [7, 9]. According to a report released by professor Gordon and his team, the ratio of *Firmicutes* is higher among intestinal microbes, and that of *Bacteroidetes* is lower in an obese body compared to lean men; when an obese body shows body weight reduction for more than a year, the ratio of *Firmicutes* and *Bacteroidetes* becomes gradually similar to that of a lean body [30]. Insoluble polysaccharides (Xylans, manans, pectins, inuline) induce the generation of short-chain fatty acids (SCFA; acetate, propionate, butyrate), which are all decomposed by intestinal microorganisms and finally absorbed in the large intestine via intermediate products such as lactate and succinate (Fig. 2). As for *Firmicutes,* which inhabits the distal gut, such *clostridium* communities as *Roseburia, E. rectal, Eubacterim halli,* and *Anaerostips caccae* are important microorganisms generating butyrate [28], and acetate generation processes by intestinal microorganisms are another biochemical pathway to explain the relationship between the *clostridium* communities and obesity [30]. Polysaccharides,

which have a less complex composition (like soluble starch or fructooligosaccharides) are used by intestinal micro-organisms such as *Bacteroides* and *Bifidobacterium*, and which generate SCFA via intermediate products (Fig. 1) [47]. SCFA combine with specific Gprotein-coupled receptors (GPR41 and GPR43, also called the free fatty acid receptors FFAR3 and FFAR2, respectively) and promote the nutrient absorption and adipose tissue mass development. When SCFA are combined with GPR41 and activated, gut hormone PYY is discharged. This peptide increases the intestinal transit time and facilitates the absorption of nutriments like glucose [46]. Moreover, some SCFA are combined with GPR43 within fat tissues and inhibit lipolysis and increase PPARɣ (peroxisome proliferator-activated receptor ɣ)-related differentiation, the effect of which increases the adiposity. Intestinal microorganisms reduce the intestinal expression of angiopoietin-related protein 4 (ANGPTL4) and increase LPL (lipoprotein lipase)-controlled fatty acid storage in adipose tissues. A rise in the level of blood LPS (lipopolysaccharide) improves the intestinal permeability and increases the gut's permeability by means of the intestinal activation of an intestinal endocannabinoid system. Also, LPS produces serum amyloid A3 protein SAA3) pep-

tide in gut and adipose tissues. In obese animals, prebiotics increase the production of glucagon-like peptide (GLP)-1 and GLP-2, lower the intestinal wall's permeability, and inhibit the endocannabinoid system in gut and adipose tissues. In addition, prebiotics blunt the overexpression of GPR43 in adipose tissues and increase lipolysis, reducing the adiposity (Fig. 2) [12].

Microorganisms that generate butyrate are related to obesity-inducing processes, but butyrate itself may be regarded as a metabolite subservient to health [22]. Butyrate supplies more than 70% of the energy required by enterocyte and contributes to the growth regulation and differentiation of epithelial cells (Fig. 1) [7]. Also, butyrate has an impact on the generation of glucagon-like-peptide 1 (GLP-1), which is connected to anti-inflammatory effects and satiety; unlike butyrate, acetate and propionate generated in lumen move to the liver through a hematocele [11, 22]. Acetate activates cytosolic acetyl S CoA synthetase 2 in liver lipid and promotes the composition of lipid and cholesterol, while an animal experiment found that propionate hinders the action of acetate [55]. In fact, animal experiments show that propionate generated by the fermentation of starch or fructans lowers the cholesterol concentration in liver and blood, and that
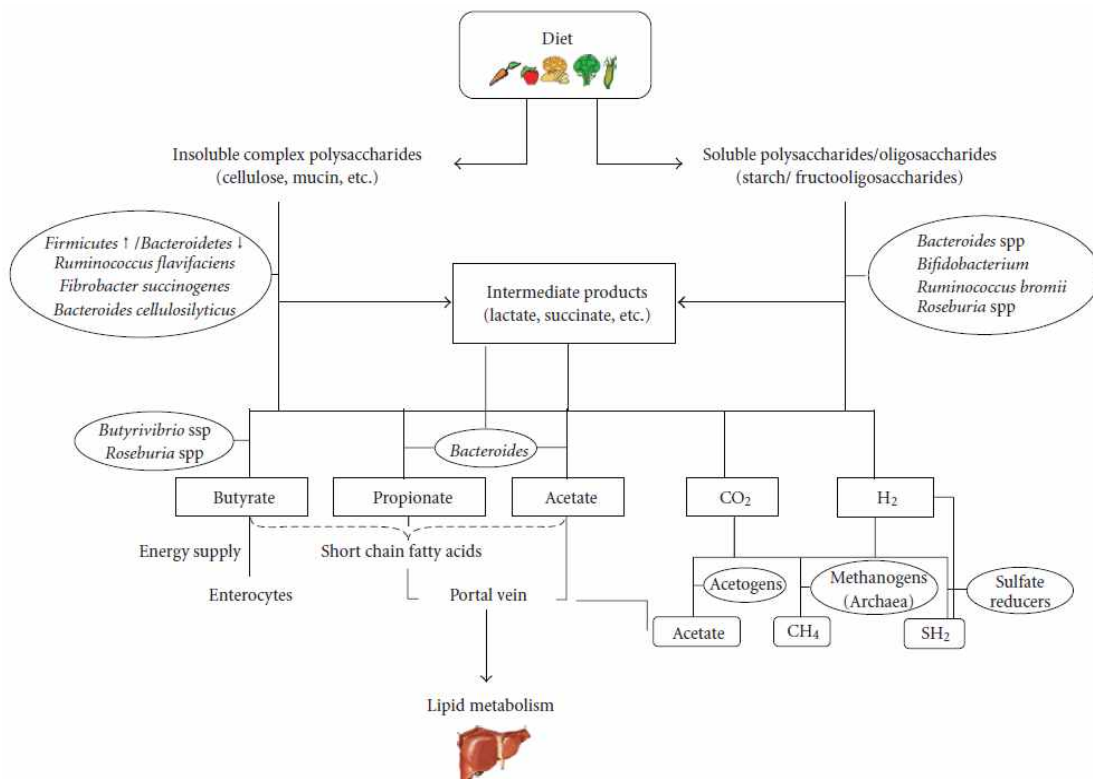

Fig. 1. Schematic diagram of the main metabolic pathways of dietary poly- and oligosaccharides in the gut ecosystem [11].
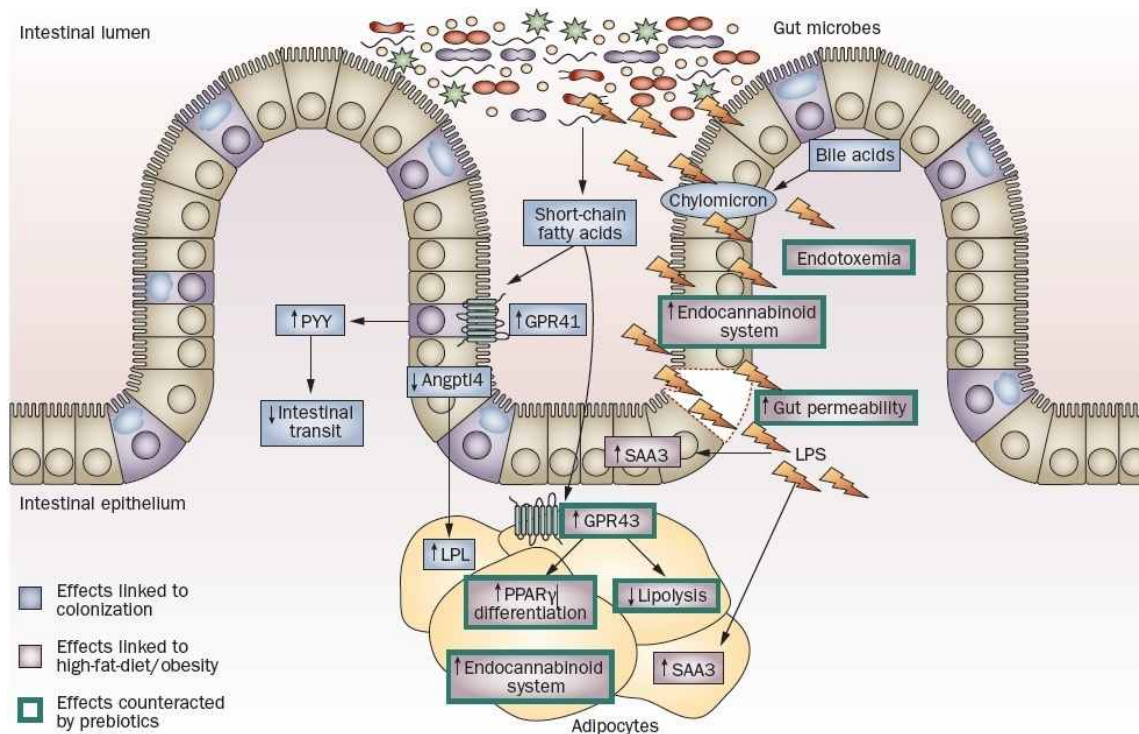
Fig. 2. The host's metabolic responses to changes affecting its gut microbiota, including colonization of the gut in germ-free mice, obesity and high-fat diet, and administration of prebiotics. Abbreviations: ANGPTL4, angiopoietin-related protein 4; GLP, glucagon-like peptide; GPR, G-protein coupled receptor; LPL, lipoprotein lipase; LPS, lipopolysaccharide; PPARɣ, peroxisome proliferator-activated receptor ɣ; PPY, peptide YY; SAA3, serum amyloid A3 protein [12].

the ratio of acetate/propionate in the portal vein is suggested as a marker to show the effects of dietary ingredients on the metabolism of lipids [10, 31]. Intestinal microorganisms also influence the expression of genes that are related to metabolic functions. When intestinal microorganism microbiota are transplanted into adult germ-free animals in which the generation of new peripheral blood vessels is stopped, the generation of new blood vessels can be observed after microorganism microbiota have settled down, and *B. thetaiotaomicron* raises the absorption rate for monosaccharides or short chain fatty acids and induces the composition of lipid in the liver [25, 55]. As fat composition processes in the liver are activated and shown as an increase in the concentration of insulin and glucose, so intestinal microorganism microbiota settling down in germ-free animals increase acetyl-CoA carboxylase and fatty acid synthase, which involves fatty acid biosynthesis pathways in the liver [4]. Germ-free animals that do not have intestinal microorganisms do not easily become fat, even when they are administered with a type of diet which increases FIAF (fasting induced adipose factor) inhibiting fat accumulation in adipocyte and promoting fat oxidation in muscle, which enhances

phosphorylated AMP-activated protein kinase and fatty acid β-oxidation in skeletal muscle and liver, and which raises the body weight so that fat or glucide content may be high [1, 44].

Conclusions

We are living along with numerous microorganisms. In particular, the number of microorganisms in the large intestine (colon) is about 10 times as many as the total number of cells in the human body, and the genes of the microorganisms number 100 times as many as those in the human body. These microorganisms make up for what we need not evolve by ourselves or what we cannot. Along with them, we are growing to be a complete individual. The effects of such microorganisms as surround us within and without on our health are startlingly great beyond our imagination, of which we are obtaining a greater awareness of as modern science develops. In a word, intestinal microorganisms act like another intestine inside of us. As our knowledge of them is accumulated, there is a good chance we will have to change our methods of keeping healthy in the future. We

will possibly see a day when we have the ability to prevent or cure various diseases such as obesity or immune system disorders through well-controlled microorganisms; continually observing their structures and functions, checking the conditions of our health, and restoring or transforming them into a desirable form.

Acknowledgement

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초록 : 대장에서 prebiotics와 probiotics 역할에 대한 조명

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현재까지 밝혀진 사실에 의하면 지구상에는 55개 phylum의 bacteria와 13개 phylum의 archaea가 존재하여 총 68개 phylum 있으며, 대장에는 9개 phylum의 미생물이 존재하여 일반 토양환경이나 해양환경에 비하여 상대적으로 낮은 미생물 다양성을 가지고 있다. 장내 미생물의 다양성은 Host의 고유특성(genetic background, sex, age, immune system, gut motility)과 식이(nondigestible carbohydrates fat, prebiotics or probiotics), 항생제 섭취 등으로 인하여 영향 받으며, 이러한 영향이 에너지 저장 과정과 유전자 발현을 영향을 주고 나아가 비만과 같은 대사질환에 영향을 미친다. Probiotics는 숙주의 장내 균총을 개선하여 건강에 유익함을 줄 수 있는 살아있는 미생물을 말하며, 주로 lactic acid bacteria들이 이용되어 왔다. 최근 probiotics를 이용한 설사나 과민성대장증후군 등과 같은 질병 치료를 위하여 bacteriotherapy가 활용되고 있다. Prebiotics는 장내 미생물을 선택적으로 조절할 수 있는 식품 성분으로 inulin, fructo-oligosaccharides, galacto-oligosaccharides, lactulose 등이 이용되고 있으며, 최근에는 비만, 항암과 관련하여 대장 내 식이섬유소의 이용과 단쇄지방산(short-chain fatty acids) 생산에 대한 관심이 집중되고 있다. 다양한 nondigestible carbohydrates와 prebiotics, probiotics에 의해서 조절되는 대장 내 특정 미생물 종을 규명하고, 이들 미생물 종이 생산하는 단쇄지방산과 같은 대사산물들과 질병과의 연관성 규명하는 대장 미생물 연구가 더욱 필요하다.