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Review
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The Impact of Gut Microbiota in Human Health and Diseases: Implication for Therapeutic Potential

Eun-Mi Ha[1,*]

[1]*Department of Pharmacology, College of Pharmacy, Catholic University of Daegu, Deagu 712-702, Republic of Korea*

Abstract

Humans have and hold 100 trillion intestinal bacteria that are essential for health. For millions of years human-microorganisms interaction has co-evolved, and maintained close symbiotic relationship. Gut bacteria contributes to human health and metabolism, and humans provides the optimum nutrition-rich environment for bacteria. What is the mechanism of the host distinguishing the intestinal bacteria as its cohabiting partner and what kind of benefits does the gut microbiota provide the human are the fundamental questions to be asked and solved in order to make human life a higher quality. This review explains the physiological relationship and mutualism between the host and gut microorganism, and highlights the potential therapeutic approach for treating diseases, maintaining and improving health based on these correlations.

Key Words: Gut microbiota, Host-microbes interaction, Probiotics, Homeostasis, Therapy

INTRODUCTION

Gut microbiota: basic characteristics and beneficial functions

Mammalian mucosal surface is the main habitat for microbe. There are over 100 trillion, thousands of bacteria phylotypes, and incredibly numerous consortia of microorganisms in our gastrointestinal (GI) tract (1×10^{13}-10^{14}, biomass >1.5 kg) (Hooper and Gordon 2001; Nicholson *et al*., 2005; Neish 2009). When humans are born, their intestines are aseptic, but commensal bacteria (normal flora; endogenous bacteria) are instantly colonized in gastrointestinal (GI) tract and develop into microorganism community (microbiota), which has correlations with its host until death. Depending on the colonization way of microbiota in its host, it is divided into prebiotics and probitoics. Prebiotics is defined as the non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and activity of one or limited number of the bacteria in the gut (Gibson and Roberfroid, 1995). And probiotics is referred as the live microorganism which confers a health benefit to the host when given orally in quantities adequate to allow colonization of the colon (Sanders, 2003). However, it is difficult to clearly differentiate these two types of microbiota, which affect the host by inhabiting there. For this, probiotics is the generally used term as normal gut flora.

These gut microbes are the major organism living in colon, and their genome is called microbiome. Mammals are referred as 'super-organisms', combining microbial cells, because the amount of microbes is 100 times that of human genome (Ley *et al*., 2006). GI microbiota provides immense functions for the host to maintain homeostasis. Human gut microbiota system is considered as another microbial organ because it closely contributes in various host processes. Therefore, the existence of these microbial organisms can be regarded as directly related to human health and diseases. These beneficial effects for host are: 1) improving intestinal barrier function, 2) inducing defensive function against pathogen, 3) strengthening the immune function, 4) enhancing protective activities on the inflammatory bowel diseases (IBD) (Strober *et al*., 2007), 5) regulating autoimmunity, 6) synthesizing several supplementation, 7) reducing obesity and influencing diabetes, and 8) even inhibiting cancer (Fig. 1). Composition of intestinal microorganism in humans varies according to genetic trait, diet, age, and gender of each individual. Furthermore, the intestinal diseases and medication can modulate gut flora composition and its activities. Despite the existence of intestinal microorganisms, the insight on their world is still left incomplete because many of the intestinal microorganisms are anaerobic and most of them cannot be cultured due to various technical limitations (Zoetendal *et al*., 2006). Several research techniques have been developed and adopted in the past decade. With this technology, the identity of gut microbiota from human

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***Corresponding Author**
E-mail: haem@cu.ac.kr
Tel: +82-53-850-3612, Fax: +82-53-850-3602

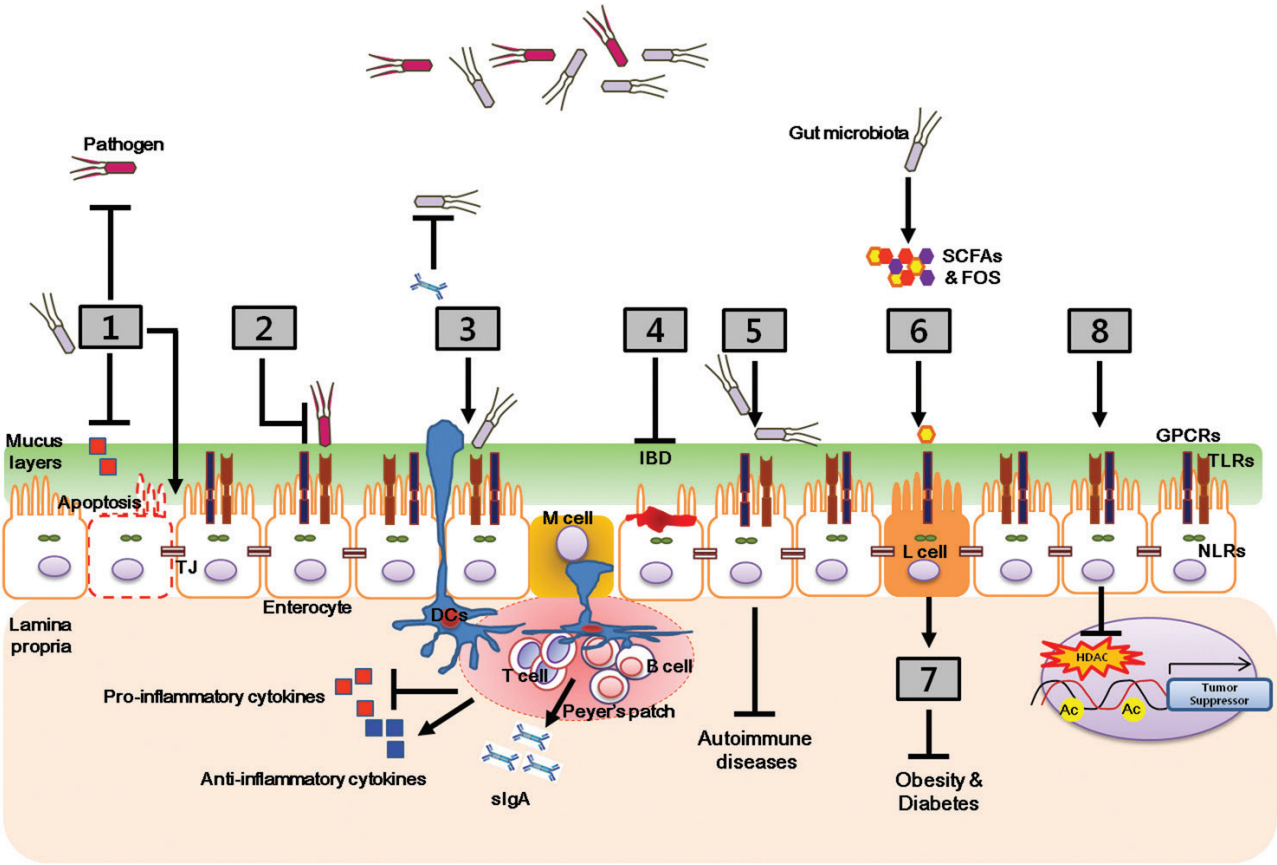

Fig. 1. Protective mechanisms of gut microbiota on host health and diseases. Gut flora induces several beneficial host responses. These include 1) strengthening the intestinal barrier function, increasing cell survival, inhibiting apoptosis as well as stabilizing tight junction and producing cell-protective proteins; 2) blocking pathogenic bacterial effects by producing antimicrobial factors and competing with pathogen; 3) controlling the balance between necessary and excessive defense immune responses (e.g., up-regulating anti-inflammatory cytokine production and down-regulating pro-inflammatory cytokine production) and limiting penetration of commensal organisms through secretion of sIgA; 4) protecting intestinal cell from inflammation by modulating IECs activity; 5) regulating the autoimmune diseases such as allergy, rheumatoid arthritis and type 1 diabetes; 6) supplying of several supplementation promoting mucosal function such as SCFAs and FOS; 7) influencing the pathophysiology of obesity, diabetes and its related disorders; 8) regulating cancer through inhibition of HDAC activity. ⊣: inhibition, →: activation, Ac: Acetylation, DCs: Dendritic cells, FOS: prebiotic-derived inulin-type fructooligosaccharides, GPCRs: G-protein coupled receptors, HDAC: histone deacetylases, IBD: inflammatory bowel diseases, IECs: intestinal epithelial cells, M cell: microfold cell, NLR: nod-like receptors, SCFAs: short chain fatty-acids, sIgA: secretory immunoglobulin A, TJ: tight junction, TLRs: Toll like receptors.

fecal sample was understood with phylogenetic microarrays that analyzes 16S ribosomal RNA (rRNA) sequence (Andersson *et al*., 2008; Claesson *et al*., 2009; Ventura *et al*., 2009). Afterwards, the microbial genome and the identity of their molecular markers were analyzed by the human intestinal tract (HIT) chip (Rajilic-Stojanovic *et al*., 2010). These analysis methods enabled the researchers to address variety and functions of host GI microbiota. Metagenome sequencing, metaproteome, and metabolome analysis are used as an approach providing their gene expression and functions of their products (Zoetendal *et al*., 2008). In the results of early studies revealed that each individual had unique and characteristic microbial community, and this community is related to the host genome (Palmer *et al*., 2007). Adult monozygotic twins have quite resemblant microbial composition although they have different life in different places. The results of metagenomics and HIT chip analysis showed that unlike human genome, the composition of intestinal microbiota can be changed (Turnbaugh *et al*., 2009). Such plasticity of gut microbiome suggests that manipulation of microbiota is possible and that it can improve the host health and/or diseases therapy (Jia *et al*., 2008).

Communication between gut microbiota and intestines

The major function of host immunity is to defend against bacteria. However, mammals coexist with various types of bacteria, and maintain immunological tolerance (Hooper and Macpherson, 2010; Round and Mazmanian, 2009). Because pathogens and commensals (symbionts) share the same motif that induces the immunity of host (Lebeer *et al*., 2010), the questions of how the host defends against pathogens and protects commensals are left unanswered. First of all, many study results present that the commensal consortium of intestinal organisms are actively tolerated, not ignored by their host (Hooper and Macpherson, 2010). The mechanisms involved in this hypoimmunity remains largely unknown.

This study will analyze the close correlations between the host and microbes, suggest benefits of commensals regarding health and medical treatment for the host. Furthermore this

review is meant to provide insights about the clinical relevance and underlying molecular mechanisms of gut microbial activity in the context of human health and diseases (Table 1).

GUT MICROBIOTA POSITIVELY REGULATES THE INTESTINAL BARRIER FUNCTIONS

Intestinal epithelium takes an important role in maintaining normal GI functions including the defense systems that protect the host from pathogens and noxious substance in the intestinal lumen. Loss of integrity in the intestine monolayer is the key defect that appears in IBD (Strober *et al*., 2007; Xavier and Podolsky, 2007). According to many evidential matters, gut bacteria stimulate intestinal epithelial cells (IEC)s response including the reconstruction of damaged epithelial cell wall, production of antibiotic substances, protein molecules that has cell protection effects, and prevention of intestinal epithelial apoptosis induced by cytokine. These reactions result from gut microbiota stimulation of specific signal transduction pathways in the IECs.

Strengthening and stabilizing the tight junctions of epithelial cells

Intestine has the largest mucosal surface in the human body. IECs form single layer of cells between the intestinal lumens so that they demarcate themselves from the rest of the body. In this way, IECs become the frontline that defends and fights against the invasion of the microorganisms, as well as the first-line to communicate with gut bacteria. IECs have specialized goblet cells that have mucus epithelial layer, which secret mucin glycoproteins to limit microbe penetration (McCool *et al*., 1994). Furthermore, it is not surprising to find Toll like receptors (TLR)s, which can induce immune reaction through IECs recognize bacteria, and dispersed immune reaction effecters (Abreu *et al*., 2005). As stated above, the major function of intestinal barrier is the defense mechanism of intestinal epithelium, which requires effective tight junction structure between intestinal epithelial cells. Destruction or dysfunctions of tight junctions bring crisis in the intestinal integrity and permeability. Recent studies proved that intestinal microorganisms have wound healing effects in the IECs. For example, gut resident *E. coli Nissle 1917* improved protection effects of tight junction barriers in T84 human intestinal epithelial cell line for enteropathogenic *E. coli*-induced disruption (Zyrek *et al*., 2007). *Lactobacillus* GG (LGG) and LGG-derived soluble proteins (p40 and p75) accelerate Zonula ocludens (ZO)-2 synthesis, which has a protection mechanism for the tight junctions of IECs. They protect intestinal barrier function via the mechanism in which protein kinase C (PKC) β1 and PKCε improve membrane translocation in extracellular signal-regulated kinase (ERK) 1/2 and mitogen-activated protein kinase (MAPK)-dependent manner (Seth *et al*., 2008). Gut microbe such as *L. casei DN-114 001* (Otte and Podolsky, 2004; Parassol *et al*., 2005) and VSL#3, which is a mixture of 8 probiotic bacteria, also prevent fusion of tight junctions that is induced by *Salmonella Dublin*, and inhibit paracellular permeability that is induced by enteropathogenic *E. coli* in T84 cells. Furthermore, *L. acidophilus* and *B. thetaiotaomicron* also inhibit paracellular permeability that is induced by cytokine, thus these gut bacteria protect the intestinal epithelial cells. p38/MAPK and Akt signal transduction pathways in IECs have also been suggested to be the major mediator regarding these protection effects (Resta-Lenert and Barrett, 2006). Therefore gut microbiota attenuates cellular atrophy, increases tight junction strength, and thus takes significant pathological roles in human IECs.

Production of cytoprotective factors for intestinal stabilization

Intestinal epithelium controls intestinal microenvironment by producing cell-protective proteins. Heat shock protein (HSP) is constantly expressed in epithelial cells, and is induced by stress to maintain intestinal homeostasis. The soluble factors that exist in LGG-cultured supernatant induce HSP synthesis, which has cellular protection effect in intestinal epithelial cells through c-Jun-N-terminal kinase (JNK)/p38 MAPK dependent manner (Tao *et al*., 2006). β-Defensin is an inducible antibacterial peptide that is synthesized by intestinal epithelial cells to prevent invasion and adhesion of bacteria. This is upregulated by *E. coli Nissle 1917* via NF-κB and activator protein (AP)-1-dependent transcriptional pathway (Wehkamp *et al*., 2004). Through bacterial deletion mutant study, a research team found flagellin, the main stimulant that induces β-defensin expression, in the supernatant of cultured *E. coli Nissle 1917* bacteria (Schlee *et al*., 2007). VSL#3 increases β-defensin in Caco-2 cells via MAPK-dependent mechanism (Schlee *et al*., 2008). Moreover, gut microorganisms promote production of antibacterial substances other than β-defensin. For example, *B. thetaiotaomicron* stimulates peneth cells to secrete angiogenin 4 (Ang-4), which has bactericidal activity against various pathogens (Hooper *et al*., 2003). Therefore, the physiological controlling mechanism of the host via gut bacteria, which can protect cell membranes and improve antibacterial activity, takes an important role in the intestinal epithelium in stabilizing the intestinal environment.

The increment of IECs survival by inhibition cytokine-induced apoptosis

Another potential mechanism that is related to the clinical effects of gut flora is to increase intestinal epithelial cell survival by preventing epithelial damage induced by cytokine. Apoptosis is a major factor in the colonic inflammatory responses and the pathogenesis of IBD (Lichtenberger *et al*., 2004; Lugering *et al*., 2006). LGG prevented the apoptosis that was induced by cytokine in human and mouse intestinal epithelial cells (Yan *et al*., 2007). This reaction occurs by activating anti-apoptotic Akt in a phosphatidylinositol-3'-kinase (PI3K)-dependent manner, and inhibiting the activation of pro-apoptotic p38/MAPK (Yan and Polk 2002). These anti-apoptotic factors are p75 and p40, the two soluble novel proteins that are separated from LGG (Yan *et al*., 2007). It was proven in both *ex vivo* colon organ culture models and cultured cells, and these results suggest that it may be possible to discovery probiotic bacteria products for prevention or/and therapy for gastrointestinal diseases. Thus, further studies are needed to identify specific gut microbiota for advanced clinical trials.

GUT MICROBIOTA HAS ANTI-PATHOGENIC EFFECTS

Well established normal flora-host interactions are very important factors in host health. If the balance of intestinal microorganisms breaks and the homeostasis is not maintained, fatal

Table 1. Summary of beneficial effects by gut microbiota on host physiology *in vivo* and *in vitro*

Beneficial effects	Bacterial strains	Actions	Mechanisms	Experimental model systems	References
IECs barrier function/ ↑Tight junction	*E. coli Nissle 1917*	↑Protect against pathogens	Unknown	T84, HT-29	Zyrek *et al.*, 2007
	LGG, LGG p40 and p74	↑protective protein (ZO-2)	↑PKC and ERK1/2 MAPK	Caco-2	Seth *et al.*, 2008
	L. casei DN-114	↓permeability against pathogens	Unknown	T84	Parassol *et al.*, 2005
	VSL#3	↑Barrier integrity	↑ERK1/2 and p38 MAPK	T84	Otte and Podolsky, 2004
	L. acidophilus, B. thetaiotaomicron	↓induced leak by cytokines	↑p38, ERK1/2 MAPK and PI3K	HT-29, Caco-2	Resta-Lenert and Barrett, 2006
IECs barrier function/ ↑cytoprotective factors	LGG, LGG soluble protein	↑HSP	↑p38 and JNK MAPK	YAMC	Tao *et al.*, 2006
	E. coli Nissle 1917	↑β-defensin	↑NK-κB and AP-1	Caco-2	Wehkamp *et al.,* 2004
	VSL#3	↑β-defensin	↑NK-κB and AP-1 ↑p38, ERK1/2 and JNK MAPK	Caco-2	Schlee *et al.*, 2008
	B. thetaiotaomicron	↑Ang 4	Unknown	Peneth cell	
IECs barrier function/ ↑IECs survival	LGG, LGG p40 and p74	↓apoptosis ↓epithelial damage	↑Akt ↓p38	YAMC	Yan and Polk, 2002 Yan *et al.*, 2007
Anti-pathogenic effects/ ↑antibacterial factors	*L. lactis*	↑lantibiotics	Target of Lipid II from pathogens	*in vitro*	Cotter *et al.*, 2005 Lawton *et al.*, 2007 Morgan *et al.*, 2005
	Bifidobacteria spp.	↑bacteriocin	Formation of membrane holes	*in vitro*	Collado *et al.*, 2005
Anti-pathogenic effects/ ↓pathogen adherence	*Lactobacillus spp.* and *Bifidobacteria spp.*	↑mannose and Galβ-3GalNAc	Competitive inhibition against pathogen lectins	Caco-2	Mukai *et al.*, 2004 Sun *et al.*, 2007
Immune system/ ↑innate immune response	*B. animalis and LGG*	↑sIgA	Unknown	Fecal in infants	Bakker-Zierikzee *et al.*, 2006
	Clostridium	↑IL-17, IL-22, IL-23	↑serum amyloid ↑Th17 cell differentiation	Mice	Ivanov *et al.*, 2009
Immune system/ ↑anti-inflammatory cytokine	VSL#3, *B. infants, E. coli Nissle 1917 L. reuteri and L. casei*	↑IL-10 ↓IFN-γ, TNF and IL-12 ↓inflammation	↑Treg2 ↓TNF induced NK-κB	DCs, Tregs, T84	Drakes *et al.*, 2004 Hart *et al.*, 2004 Sturm *et al.*, 2005 Smits *et al.*, 2005
	Clostridium cluster IV and XIVa	↑TGF-β, ↑IL-10, CTLA4	↑Foxp3 Tregs		Atarashi *et al.*, 2011
Immune system/ ↓pro-inflammatory cytokine	LGG and *L. rhamnosus GR-1*	↓LPS induced TNF	↑G-CSF, ↓STAT3 and JNK	Macrophage, mice	Pena and Versalociv, 2003
	L. casei Shirota	↓LPS induced IL-6 and IFN-γ		Blood mononuclear cells from normal and chronic colitis mice	Matsumoto *et al.*, 2005
Immune system/ ↑defense against infection	*B.fagilis*	↑IL-10, IL-14, IL-12 and IFN-γ ↓colitis	↑retain bacterial PSA ↑toleragenic T cell	Mice DCs	Mazmanian *et al.*, 2005
	L. gasseri, L reuteri and *L. johnsonil*	↑IL-12, IL-18 and IFN-γ	↑Polarization of Th1 and Tc1	Mice DCs	Mohamadzaden *et al.*, 2005
	VSL#3 DNA	↓LPS activated IL-8, ↓TNF and IFN-γ	↓NK-κB and p38 MAPK	HT-29 mouse colon in vivo	Jijon *et al.*, 2004
	Probiotic unmethylated CpG DNA	↑Repair for colitis	↑TLR9 activation	DSS-treated mice	Rachilewitz *et al.*, 2004

Table 1. Continued

Beneficial effects	Bacterial strains	Actions	Mechanisms	Experimental model systems	References
Extra-intestinal disease/autoimmunity	*B. thetaiotaomicron*	↑c-type lectin and RegIIIγ ↑kill VRE	Unknown	Fecal sample in mice	Brandl *et al.*, 2008 Cash *et al.*, 2006
	Normal flora	↓allergy	↓allergen challenge	Allergic airway disease mice	Noverr and Huffnagle, 2005
	Bifidobacteria spp., Bacteroides spp., Porphyromonas spp., Prevotella spp. and *B. fragilis spp.*	↓RA	Unknown	RA patient	Vaahtovuo *et al.*, 2008
	Normal flora	↑T1D	↑TLRs and Myd88	NOD mice, Myd88 deficient mice	Wen *et al.*, 2008
Metabolic syndrome/ obesity and T2DM	Normal flora vs. germ free flora	↑body fat	↓Fiaf ↑LPL	Normal, germ free and Germ free Fiaf−/− mice	Backhed *et al.*, 2004
	Normal flora vs. germ free flora	↓Insulin sensitivity ↑Glycogen level	AMPK	Mice	Backhed *et al.*, 2007
	Normal flora vs. germ free flora	↑SCFAs ↑leptin ↑PYY ↑lipogenesis ↑energy harvest	↑Glycoside hydrolase ↑Gpr41 and 42	Normal, germ free and Germ free Gpr41 −/− mice	Brown *et al.*, 2003 Le Poul *et al.*, 2003 Flint *et al.*, 2008 Xiong *et al.*, 2004 Samuel *et al.*, 2008
	↑*Firmicutes spp.* ↓*Bacteridetes*	↑odesity		Mice	Ley *et al.*, 2005 Backhed *et al.*, 2004 Turnbaugh *et al.*, 2006
	FOS, *Bifidobacterium spp.* and *Latobacillus spp.*	↓LPS ↓pro-cytokine ↓hepatic steatosis, hunger, body weight and food ingestion	↓CD14/ TLR4 ↓NK-κB ↑Gpr43	CD14−/− mice	Cani and Delzenne, 2007 Pappo *et al.*, 1991 Bouhnik *et al.*, 2004 Macfarlane *et al.*, 2006 Kolida *et al.*, 2007 van Baarlen *et al.*, 2009 Parnell and Reimer, 2009
Other Diseases/ ↓Cancer	SCFAs-butyrate	↑cell differentiation ↑apoptosis ↓cancer	↓HDAC	HT-29, Caco-2 and HCT-116	Alcarraz-Vizan *et al.*, 2010 Perrine *et al.*, 2007 Wilson *et al.*, 2006 Waldecker *et al.*, 2008

↑: increased, ↓: decreased, AMPK: activated protein kinase, Ang: angiogenin, DCs: dendritic cells, DSS: dextran sodium sulfate, ERK: extracellular signal-regulated kinase, G-CSF: granulocyte-colony stimulating factor, GLP: glucagon-like peptide, Gpr: G-protein receptor, HDAC: histone deacetylase, HSP: heat shock protein, IECs: intestinal epithelial cells, IFN: interferon, IL: interleukin, JNK: c-Jun-N-terminal kinase, LGG: *Lactobacillus* GG, LPS: lipopolysaccharide, MAPK: mitogen-activated protein kinase, MS: multiple sclerosis, Myd: myeloid differentiation primary response gene, ZO-2: Zonula ocludens-2, PI3K: phosphatidylinositol-3'-kinase, PSA: polysaccharide A, RA: rheumatoid arthritis, SCFAs: short chain fatty-acids, sIgA: secretory immunoglobilin A, STAT: signal transducer and activator of transcription, T1D: type 1 diabetes, T2DM: type 2 diabetes mellitus, TLR: toll-like receptor, TNF: tumor necrosis factor, Treg: regulatory T cell, VRE: vancomycin resistant Enterococcus, TGF: transforming growth factor, CTLA4: cytotoxic T lymphocyte antigen 4, Foxp3: forkhead box P3.

pathological symptoms such as IBD or diabetes are induced. Actually, harmful intestinal microorganisms are predominant in the patients with IBD, and beneficial microorganisms such as *Lactobacillus* and *Bifidobacterium* showed to be decreasing (Ott *et al*., 2004; Mylonaki *et al*., 2005; Conte *et al*., 2006).

Therefore, controlling of intestinal microorganism communities may be useful when applied as IBD prevention and treatment.

Producing antibacterial factors from gut-microbiota

Gut microbiota has direct effects on pathogens because they inhibit pathogenic growth by producing antibacterial substance, bacteriocins, and acid (Servin, 2004; Cotter *et al*., 2005). Lantibiotics, which is one type of bacteriocins that a Gram-positive bacteria such as *Lactococcus lactis* produces is a small antimicrobial peptide (Cotter *et al*., 2005; Lawton *et al*., 2007). This peptide is activated in nanomolar concentration, targets lipid II which composes the cell walls of bacteria, and inhibits multidrug-resistant pathogens (Morgan *et al*., 2005). Another non-lanthionine containing bacteriocin is the small antimicrobial peptide that is produced by *Lactobacilli.* These peptides are mostly toxic to Gram-positive bacteria, including *Lactococcus*, *Streptococcus*, *Staphylococcus*, *Listeria*, and *Mycobacteria*. The basic mechanism of bacteriocin is making a hole in cell membrane of the targeted bacteria, and thus inhibiting the biochemical enzymic activity that is pathologically needed. In addition, *Bifidobacteria* types are known to produce bacteriocin-like component which is toxic to both Gram-positive and Gram-negative bacteria (Collado *et al*., 2005).

Probiotic bacteria, especially *Latobacilli*, secretes acetic, lactic, and propionic aids which acidize intestinal environment, and thus has vast antibacterial/antifungal effects (Levison, 1973). Some *Lactobacilli* strains specifically inhibit the growth of *salmonella enterica* by secreting lactic acid (Makras *et al*., 2006).

Competitive inhibition of pathogen binding to the intestinal epithelium

Gut microbiota in GI tract decreases pathogens and their toxin to adhere to the intestinal epithelium. Special types such as *Lactobacilli* and *bifidobacterium* can inhibit adherence or disconnect various pathogens including *Bacteroides vulgates*, *Clostridium hostoluticum*, *C. difficile*, *Enterobacter aerogenes*, *Listeria monocytogenes*, *Staphylococcus aureus* (Collado *et al*., 2007), *Salmonella enteric*, *Yersinia enterocolitica* (Candela *et al*., 2005; Collado *et al*., 2007), enterotoxigenic *E. coli* (Roselli *et al*., 2006; Collado *et al*., 2007) and enteropathogenic *E. coli* (Sherman *et al*., 2005).

The mechanism of pathogens adhering to the epithelial cells is based on the interaction between the lectin of pathogen and the surface of host intestinal epithelium or the glycoconjugate receptor molecule on top of mucus (Mukai *et al*., 2004; Sun *et al*., 2007; Tallon *et al*., 2007). Studies proved that *Lactobacilli* and *Bifidobacteria* form mannose and Galβ1-3GalNAc, and that this compound competitively hinders lectin bonding of the pathogen, showing the pathogen inhibition effect (Mukai *et al*., 2004; Sun *et al*., 2007). These mechanisms present major effects of gut bacteria regarding the intestinal microorganism environment, and this is considered to be the main part of therapeutic application for specific cure and prevention of corresponding diseases.

GUT MICROBIOTA REGULATES INTESTINAL IMMUNE SYSTEM

Relationship between host immune responses and gut bacteria: Germ free animal experiment

Innate/adaptive immune reaction that is not well controlled takes an important role in pathogenesis of IBD. Therefore, maintaining well balanced control of immune reactions can be a major factor in IBD therapy. The animals that lack colonization of microorganisms are called germ-free animals, have allowed for understanding of whether and how microbiota affects development of the host. The range of developmental defects in germ-free animals is very wide, and germ-free mice especially have multiple serious intestinal defects in GI (Noverr and Huffnagle, 2004). Many research studies have been suggest that the commensal organisms affect intestinal cell development, and interestingly, microbes can shape systemic immunity (Smith *et al*., 2007; Round and Mazmanian, 2009). Mucosal dendritic cells (DC)s are an immune cell that is one of the luminal contents that directly combines with commensal microbiota. DCs connect innate and adaptive immunity, and take a part in serially presenting bacteria to the T cell by expressing TLRs and nod-like receptors (NLR)s (Kraehenbuhl and Corbett, 2004; Macpherson and Uhr, 2004). Especially in intestine, DCs greatly induce tolerogenic T and B cell reaction, mediating hypoimmunity of gut microbiota. Moreover, the DCs that express tumor necrosis factor (TNF)-α and inducible nitric oxide synthase (iNOS) induce T cell independent immunoglobulin (Ig) A secretion from B cells and limit penetration of commensal organisms, making commensal bacteria stay in the intestines (Macpherson and Uhr, 2004). Therefore, The DCs that can protect the commensals are locally distributed in intestinal mucosal lymphoid tissues, and latently can avoid systemic immune responses (Macpherson and Uhr, 2004). The mice that do not have microbial colonization lack or have small germinal center in the spleen, and have small gamma-globulin-containing cells. One of the studies reported that the spleens of germ-free mice have defective immunoglobulin G (IgG) and IgM antibody reaction towards infection (Bauer *et al*., 1963; Ohwaki *et al*., 1977). The effects of microbiota not only extend to systemic immunity and development but germ-free mice are also more sensitive to infectious pathogens such as *Shigella flexneri*, *Bacillus anthracis*, and *Leishmania* (Smith *et al*., 2007).

Strengthening host innate immunity

Innate immunity is the primary biological reaction that obstructs the invasion of pathogens. Probiotics potentially stimulate the innate immunity that fights against the microorganisms or dietary antigens that enter the host every day. Use of gut flora can re-strengthen the functions of innate immunity. According to the recent report, *B. animalis*-enriched formula increases fecal secretory IgA (sIgA) in infants (Bakker-Zierikzee *et al*., 2006). Interestingly, in addition to fecal sIgA appeared to increase significantly by nonviable LGG, the spleen of the nonviable LGG- fed mice show enhanced secretion of interleukin (IL)-6 (He *et al*., 2005).

Stimulated immune response without inflammatory reaction is the mechanisms to protect the host from serious injury. LGG stimulates only moderate expression of co-stimulating molecules, produces small amount of tumor necrosis factor (TNF) and CCL20, and does not produce IL-2, IL-12, IL-23, and IL-

27. This differs from vigorous Th1 reaction that fights against pathogenic *Streptococcus pyogenes* in DCs (Veckman *et al*., 2004). The differential control of DCs has been reported between *Klebsiella pneumonia* and *L. rhamnosus* (Braat *et al*., 2004); it suggests discriminative responses of DCs towards pathogenic and nonpathogenic gut bacteria. According to recent interesting study, Ivanov *et al*. (2009), reported that colonization of the small intestine of mice with a specific commensal microbes, segmented filamentous bacterium (SFB), with the candidate name *Arthromitus*, is sufficient to trigger the Th17 cell differentiation and production of inflammatory cytokines such as IL-17and IL-22, as well as IL-23 (Ivanov *et al*., 2009). SFB, spore-forming gram-positive bacteria most closely related to the genus *Clostridium*, have been reported to colonize the intestines of numerous species, including humans (Davis and Savage, 1974; Klaasen *et al*., 1993). Colonization with SFB induced Th17 cell effector cytokine, which is required for Th17 cell function and inhibited growth of an intestinal pathogen *Citrobacter rodentium* and *Salmonella*. SFB colonization induced production of serum amyloid (SAA) in the gut, and SAA acted on lamina propria DCs to promote the differentiation of Th17. Therefore, SFB-dependent antimicrobial defense may hence protect the host from lethal outgrowth of the pathogenic bacteria. Thus, manipulation of beneficial commensal regulated pathway may provide new opportunities for enhancing mucosal immunity and treating immune disease.

Balanced control of infection-induced inflammatory responses

The innate defense system of the host has to properly control the level of threat from the infectious pathogens. If the immune reaction is too weak, it cannot defense the infection, and the host will be in fatal condition. However, when the immune reaction is too strong, it can cause excessive tissue damage. The main mechanism of the probiotics protection from injuries and inflammation by pathogens is controlling the balance production of pro- and anti-inflammatory cytokine.

Increase of anti-inflammatory cytokine production: Maturation of DCs increases the molecular expression that is required for secretion of cytokines and activity of T/ B cells. Most of the studies showed that gut bacteria stimulate DCs in order to produce anti-inflammatory cytokines such as IL-10, in which suppress Th1 response. For example, probiotic mixture VSL#3 induces IL-10 production in humans and murine DCs (Drakes *et al*., 2004; Hart *et al*., 2004). *Latobacillus reuteri* and *L. casei* prepares monocyte-derived DCs that drive regulatory T cells (Tregs) development in order to produce high levels of IL-10 (Smits *et al*., 2005). Tregs are a lineage of helper T cells that directly inhibit immune responses, and downregulate the T cell activity. Certain commensal bacteria affected the genesis of Tregs. *Bifidobacteria infants* can increase the number of Tregs in the spleen. The spore-forming component of indigenous intestinal microbiota, particularly clusters IV and XIVa of the genus *Clostridium* (also known as *Clostridium leptum* and *coccoides*), promoted Tregs accumulation (Atarashi *et al*., 2011). Tregs expressing transcription factor forkhead box P3 (Foxp3) were most abundant in the gut lamina propria (Hill *et al*., 2008). Colonization of mice by *Clostridium* induced transforming growth factor (TGF)-β and affected Foxp3 Tregs number producing IL-10 and expressed high levels of cytotoxic T lymphocyte antigen 4 (CTLA4) in colon. Furthermore, conventionally reared mice ingested with *Clostridium* resulted in resistance to colitis. These finding suggested identifying mechanisms underlying the *Clostridium*-host crosstalk will provide invaluable information toward searching a new therapeutic approach to IBD and allergy. Enteric flora seems to express the specialized molecules that adjust lenient host responses. More detailed studies are needed since the molecular movement and the receptors that recognize these molecules are not yet identified.

Suppression of pro-inflammatory cytokine production: Gut microbes also inhibit the production of pro-inflammtory cytokine. LGG inhibits *Helicobacter pylori*-drived lipopolysaccharide (LPS) and stimulated TNF production by murine macrophage (Pena and Versalovic, 2003). More studies showed that LGG, *L. rhamnosus* GR-1, and their cell-cultured supernatant induced high quantity of granulocyte-colony stimulating factor (G-CSF) which was produced by macrophage. This is compared with the stimulation reaction by the pathogenic *E. coli* GR-12. The increased production of this G-CSF is required in inhibiting *E. coli* or LPS-induced TNF production in macrophage and mice. The inhibitory effects of TNF caused by G-CSF are mediated by signal transducer and activator of transcription (STAT) 3 pathways, and JNKs inhibition process occurs (Kim *et al*., 2006). *L. casei Shirota* (LcS) downregulates the production of LPS-induced IL-6 and IFN-γ by the peripheral blood mononuclear cells that are separated from normal and chronic colitis mice (Matsumoto *et al*., 2005). Moreover, *E.coli Nissle 1917* inhibits peripheral blood T-cell cycle progression and expansion, increases IL-10, and decreases TNF, IFN-γ and IL-12 secretion by these immune cells. *B. infants*-induced Tregs suppress pro-inflammatory NF-κB activity (Sturm *et al*., 2005).

Regulation a balance between pro- and anti-inflammatory responses: Gut microbiota stimulates the immune reaction of the host including Th-1 reaction via DCs-directed T cell activation. It was recently proven that colitis was able to be protected by inducing toleragenic T cells which are produced by IL-10. More importantly, this activity is associated with a single capsular polysaccharide A (PSA) made by prominent human commensal *B. fragilis*. While the mice are colonized with *B. fragilis*, DCs takes hold of, and maintains bacterial PSA. This PSA accelerates maturation of DCs, production of Th1 type cytokines (including IL-4, 1L-12 and IFN-γ), and subsequently induces CD4+ T cell expansion (Mazmanian *et al*., 2005). *L. gasseri*, *L. reuteri*, and *L. johnsonil* upregulate the production of IL-12 and IL-18 by DCs, and *Lactobacilli*-exposed DCs skew CD4+ and CD8+ T cells to increase the production of IFN-γ and induce the Th1 and Tc1 polarization (Mohamadzadeh *et al*., 2005).

Therefore, commensal flora is considered to be controlling the balance of pro- and anti-inflammatory mucosal responses in order to keep intestinal homeostasis.

Regulation of immune responses by gut microbial DNA: Gut microbes and immune cells have direct interactions. Gut microbial DNA controls the immune functions of human and mouse. The DNA separated from Probiotic VSL#3 mixture decreases the production of LPS-activated IL-8 and secretion of TNF and IFN-γ *in vivo* and *in vitro*. VSL#3 DNA also inhibits p38 MAPK, and decreases NF-κB activation (Jijon *et al*., 2004). They are unmethylated dinucleotides, CpGs, that is often found in bacteria genomes activates the innate immunity through TLR9 (Krieg, 2003). Importantly, the administration of unmethylated probiotic DNA protects the injuries from colitis, which is TLR-dependent dextran sulfate sodium (DSS) model

(Rachmilewitz *et al*., 2004). Mammals or methylated bacterial DNA did not have the functions to protect the host, and the TLR9-deficient mouse did not have the therapeutic benefits of CpGs, thus these reactions have been confirmed to be very unique.

Specific regulation of host for gut flora in immune cells: Gut microbiota has the molecular recognition patterns, which are recognized by the TLRs (Cario and Podolsky, 2006), similar to the ones that pathogenic microorganisms have, but these organisms do not initiate normal inflammatory reaction (Lebeer *et al*., 2010). Human T84 cells that are cultured with probiotic organism *E. coli Nissle 1917* all increased in both TLR2 and TLR4 expression. Moreover, unlike normal mice, the cytokine production control by *E. coli Nissle 1917* and improvement in colitis were failed in TLR2 and TLR4 knockout mice. On the other hand, the processing of probiotic VSL#3 mixture decreased the severity of DSS-induced colitis in TLR2 and TLR4-deficient mice, but not in TLR9-deficient mice. This bacterial mixture shows that it mediates the host immune response depending on TLR9 signal (Rachmilewitz *et al*., 2004). Because each different probiotics stimulate specific TLRs of the host, these contents are suggested to be one of the necessary considerations in designing therapeutic trials. Through the evidential results to date, we know that both the pathogens and commensal bacteria are recognized by TLRs. It is important to understand how probiotics can share such limited TLRs and avoid inflammatory reaction, and have biologically and clinically beneficial relationships with the host. Commensals will show differentiated effects and immune reactions by activation of special TLRs due to many factors that are distinct from pathogens. These factors can be summarized like the following. 1) The TLRs that combine with gut microbes have differentiated recognition by having different locations on the polarized intestinal epidermis. TLR9 in the intestinal epithelial cells inhibit NF-κB through apical stimulation not through basolateral stimulation (Lee *et al*., 2006). 2) Probiotics are different from pathogens, and might have the innate components that can induce differentiated TLRs activation. These is why the LPS of the pathogens and nonpathogens do not have clear structural difference, but have different reactions in recognizing probiotics and TLR4, which induces inflammation by recognizing pathogens (Hajjar *et al*., 2002).

Further studies are needed to find out the difference of stimulating factors in gut microbes and pathogens, and the difference between recognition receptor and cellular reaction signals.

There is a mechanism related to reactive oxygen species (ROS) as the recognition of intestinal microorganism and immune reaction (Ha *et al*., 2009). ROS secretion is one of the fastest innate immune response to the inflow of intestinal microorganism (Ha *et al*., 2005). When a pathogen enters intestines, a specific receptor recognizes it and secretes bactericidal ROS; this is produced by ROS generator enzyme, Dual oxidase (DUOX), which is located in IECs. As IECs recognize an infection of microorganism, Phospholipase C-β (PLC-β) - endoplasmic reticulum (ER)-dependent-calcium influx is induced, and the bactericidal ROS secretion is stimulated by qualitatively activating DUOX. Also, transcription of activating transcription factor (ATF)-2 is increased through p38/MAPK signal pathway in myeloid differentiation primary response gene (Myd) 88-dependent manner, and the expression of DUOX is additionally induced, showing the synergic effect of ROS production, which strengthens defense reaction towards pathogens as a result (Bae *et al*., 2010; Ha *et al*., 2009). Interestingly, when live or the cultured supernatant of *Latobacilli*, and *Acetobactor* species are treated to colonic Caco-2 cell, PLC-β- calcium-DUOX- and p38/MAPK signal pathway-dependent ROS production events do not take place. This result implies different cellular reactions in the host can be induced by specific factors from different germs and indicates that malfunction of these mechanisms can result in serious diseases such as IBD

GUT MICROBIOTA ARE CLOSELY RELATED TO HUMAN HEALTH AND DISEASES

Gut microbiota has been studied for various intestinal inflammatory disorders and extra-intestinal diseases as therapeutic potential. However, further studies on molecular mechanism and effects of probiotics are needed because the clinical studies and application of probiotics are yet limited.

Clinical application of gut microbiota for intestinal inflammatory disorder: the relationship between IBD treatment and gut microbes

IBD is a chronic inflammatory disease in the GI tract that persists life long, and it includes two main diseases: Crohn's diseases (CD) and ulcerative colitis (UC). The etiological cause of this disease, the genetic sensitivity, and immunopathogenesis have been well identified, but there are not enough prevention or treatment methods for the diseases, and thus studies are desperately needed. According to recent interesting study (the one on intestinal immune response mechanism part; stated in this review), intestinal microflora takes an important role in the pathogenesis of IBD, and manipulates consortia of intestinal microorganisms, thus the clinical studies to find out its therapeutic effects are getting attention (Xavier and Podolsky, 2007; Chichlowski and Hale, 2008; Knight *et al*., 2008). Recently, clinical effects of microflora are reported to be effective in adults, children, and infants, also for IBD, diarrhea, irritable bowel syndrome, gluten intolerance, gastroenteritis, *Helicobater pylori* infection, severe metabolic malfunction symptoms and colon cancer (Yan and Polk, 2004; Yan and Polkm, 2006). IBD is actually one of the very well studied diseases, and gut flora as its treatment medication that is provisionally effective and clinically tested (Kruis *et al*., 1997; Malchow, 1997; Michetti *et al*., 1999; Rembacken *et al*., 1999; Venturi *et al*., 1999; Canducci *et al*., 2000; Gionchetti *et al*., 2000; Armuzzi *et al*., 2001a; 2001b; Felley *et al*., 2001; Szajewska and Mrukowicz, 2001; Cremonini *et al*., 2002a; 2002b; D'Souza *et al*., 2002; Huang *et al*., 2002; Prantera *et al*., 2002; Van Niel *et al*., 2002; Cats *et al*., 2003; Cruchet *et al*., 2003; Gionchetti *et al*., 2003; Guslandi *et al*., 2003; Ishikawa *et al*., 2003; Lodinova-Zadnikova *et al*., 2003; Allen *et al*., 2004; Gosselink *et al*., 2004; Kato *et al*., 2004; Kruis *et al*., 2004; Mimura *et al*., 2004; Schultz *et al*., 2004; Tursi *et al*., 2004; Bibiloni *et al*., 2005; Bousvaros *et al*., 2005; Furrie *et al*., 2005; Hawrelak *et al*., 2005; Laake *et al*., 2005; Myllyluoma *et al*., 2005; Sykora *et al*., 2005; Szajewska and Mrukowicz, 2005; Johnston *et al*., 2006; Lionetti *et al*., 2006; Marteau *et al*., 2006; McFarland, 2006; Sazawal *et al*., 2006; Sheu *et al*., 2006; Szajewska *et al*., 2006; Zocco *et al*., 2006; Cindoruk *et al*., 2007; de Bortoli, *et al*., 2007; Fujimonri *et al*., 2007;

Table 2. Clinical trials of gut microbiota for intestinal inflammatory diseases

Diseases	Strains of probiotics	Types of trial	Outcome	References
Crohn's disease	LGG	R, DB, PC, adults	No benefit or maintenance of remission	Schultz *et al.*, 2004 Bousvaros *et al.*, 2005
	L. johnsonii LA1	R, DB, PC, adults	Slight decrease in endoscopic recurrence at 6 months	Marteau *et al.*, 2006
	LGG	R, DB, PC, adults	No change in endoscopic recurrence or severity of lesions at 12 months	Prantera *et al.*, 2002
	Bifidobacteria, Lactobacilli, Pyllium	Open-label trail	Significant reduction of CD severity	Fujimonri *et al.*, 2007
	S. boulardii	R, adults	Slightly decrease in severity	Guslandi *et al.*, 2003
	E. coli Nissle 1917	PC, adults	Maintenance of remission	Malchow *et al.*, 1997
Ulcerative colitis	*E. coli Nissle 1917*	R, DB, adults	No difference in rate of and time to remission	Rembacken *et al.*, 1999
	L. acidophilus-fermented milk B. breve, B. bifidum	R, PC, adults	Improvement in clinical and endoscopic activity at 12 week of therapy Induction of remission	Kato *et al.*, 2004
	VSL#3	Open-label trial	Induction of remission in 53%. Response in 24% over 6 week of therapy	Bibiloni *et al.*, 2005 Soo *et al.*, 2008
	E. coli Nissle 1917	R, DB, adults	No difference in rate over 12 month	Kruis *et al.*, 2004
	B. longum	R, PC, adults	Induction of remission	Furrie *et al.*, 2005
	Bifidobacteria	R, PC, adults	Maintenance of remission	
	S. boulardii	R, adults	Induction of remission	Guslandi *et al.*, 2003
	Bifidobacteria	R, PC, adults	Maintenance of remission	Ishikawa *et al.*, 2003
	VSL#3	R, adults	Maintenance of remission	Venture *et al.*, 1999
Pouchitis	VSL#3	PC, adults	Effective prevention	Pronio *et al.*, 2008
	Lactobacillus and *bifidobacteria*-fermented milk	R, adults	Reduction of inflammation and disease symptoms	Laake *et al.*, 2005
	VSL#3	R, PC, adults	Maintenance of remission	Mimura *et al.*, 2004
	LGG	R, adults	Delay of pouchitis onset	Gosselink *et al.*, 2004
	VSL#3	R, PC, adults	Effective prevention	Gionchetti *et al.*, 2003
	VSL#3	R, PC, adults	Maintenance of remission	Gionchetti *et al.*, 2000
Diarrhea	*L. GG; L. reuteri, L. acidophilus LB, Streptococcus thermophilus lactis, L. acidophilus, L. bulgaricus, S. boulardii.*	R, PC, children	Reduction duration	Szajewska *et al.*, 2001
	L. rhamnosus GG, L. reuteri, L.acidophilus LB, Strep. Thermophilus lactis, L. acidophilus, L. bulgaricus, Enterococcus SF68, L. acidophilus, L. bifidus, L. casei, L. rhamnosus, L. reuteri, S. boulardii.	R, PC, children and adults	Reduction duration	Allen *et al.*, 2004
	L. rhamnosus GG, L. reuteri, L. acidophilus, L. bulgaricus.	R, PC, children	Reduction duration	Van Niel *et al.*, 2002
	L. rhamnosus GG, L. acidophilus, L. bulgaricus, S. thermophilus, L. rhamnosus, Yalacta, L. delbruckii, L. reuteri, Enterococcus SF68, S. boulardii, S. subtilis, B. bifidum, B. infantis.	R, PC, DB, open-label trial, children	Reduction duration	Huang *et al.*, 2002

Table 2. Continued

Diseases	Strains of probiotics	Types of trial	Outcome	References
Diarrhea	*L. acidophilus, L. bulgaricus , B. infantis, B. lactis Bb12, Str. Thermophilus, LGG, S. boulardii, L. sporogens, fructooligosaccharides*	R, PC, children	Prevention of diarrhea	Johnston *et al.*, 2006 Johnston *et al.*, 2007 Szajewska *et al.*, 2006
	S. boulardii, L. acidophilus, L. bulgaricus, B. longum, L. rhamnosus GG, E. feacium SF68, L. casei DN-114001, S. thermophilus	R, PC, children and adults	Prevention of diarrhea	D'Souza *et al.*, 2002 Cremonini *et al.*, 2002a; 2002b Szajewska *et al.*, 2006 Hawrelak *et al.*, 2005 Sazawal *et al.*, 2006 McFarland, 2006 Wenus *et al.*, 2008 Hickson *et al.*, 2007 Ruszczynski *et al.*, 2008 Szymanski *et al.*, 2008
	E. coli	R, infants	Reduction incidence	Lodinova-Zadnikova, 2003
	LGG, L. casei DG, S. boulardii, L, acidophilus La5, B. lactis Bb12, Propionibacterium freidenreichi spp., B. breve, L. reuteri ATCC 55730,	PC, DB, adults	Decrease of adverse effects	Armuzzi *et al.*, 2001a; 2001b Cremonini *et al.*, 2002a; 2002b Tursi *et al.*, 2004 Myllylumona *et al.*, 2005 Lionetti *et al.*, 2006 Cindoruk *et al.*, 2007
	L. La5, B. lactis, L. acidophilus (jonhsonii) La1, L. casei Shirota	PC, DB, R, open-label trial, adults	Decrease of urease activity	Sheu *et al.*, 2006 Michetti *et al.*, 1999 Felley *et al.*, 2001 Cruchet *et al.*, 2003 Cats *et al.*, 2003

DB: double blind, PC: placebo-controlled, R: randomized.

Hickson *et al*., 2007; Johnston *et al*., 2007; Pronio *et al*., 2008; Ruszczynski *et al*., 2008; Soo *et al*., 2008; Szymanski *et al*., 2008; Wenus *et al*., 2008) (Table 2).

Gut bacterial efficacy in extra-intestinal diseases: autoimmunity

The hygiene hypothesis was first suggested 20 years ago to explain predominant pathogenesis of atopic diseases and their spread (Strachan, 1989). This hypothesis accepts abnormal immune response such as allergy that is caused by small family structure and clean environment, which minimizes the exposure to microbial stimulus. This hypothesis was re-suggested as the expanded concept, the 'microflora hypothesis' (Noverr and Huffnagle, 2005). This hypothesis suggests "changes in GI microbiota due to changed food and use of antibiotics in the developed society cause the destruction of immunological tolerance mechanism" (Noverr and Huffnagle, 2005). Numerous epidemiologic and clinical data that support microflora hypothesis are being reported. This hypothesis has two main points: 1) environmental change can give shock to microbiota and 2) confusion of microflora composition can cause disease. Several studies are being reported that antibiotics can destruct the composition of microbiota. A study group collected fecal sample from three individuals pre- and post-ciprofloxacin treatment, and analyzed the results by using the 16S rRNA pyrosequencing technology (Dethlefsen *et al*., 2008). Antibiotic processing gave severe shock to more than 1/3 of the gut microorganisms, and its variety sharply dropped. After 4 weeks, parts of microbiota showed to be getting close to the normal condition of pre-antibiotic state, but most of the variety did not recover until after 6 months. This data proved that such phenomenon can be permanent, and that antibiotics can completely destroy the composition of microbial community. In the extensive perspective, the results of antibiotic treatment can cause antimicrobial resistant pathogens such as vancomycin resistant enterococcus (VRE) to multiply. The cause of how the removing commensals with antibiotics permit VRE colonization is unclear. One of the recent studies on antibiotic-treated mice showed that the expression of C-type lectin and RegIIIγ was decreased (Brandl *et al*., 2008). RegIIIγ is known to be induced by gram-negative symbionts such as *B. thetaiotaomicron*, and to kill Gram-positive bacteria such as

VRE (Cash *et al*., 2006).

Therefore, antibiotic administration can induce killing of host bacteria, and provide pathogens a chance to colonize. According to the microflora hypothesis, the change in microbial community composition can cause disease. Many reviews have studied and considered the expanded proof of microbiota's roles, regarding intestinal inflammatory autoimmunity (Round and Mazmanian, 2009). This review discusses the role of commensal bacteria in systemic autoimmune aberration including allergy, rheumatoid arthritis (RA), and type 1 diabetes (T1D).

Allergy: The hygiene hypothesis was originally set for the phenomenon in which there was an abrupt increase of allergies. With the start of this theory, at least 14 research papers have been published the correlation between allergy and an altered microbiota based on the clinical research study results of over 2,000 subjects (Noverr and Huffnagle, 2004). Most of these studies had decreased *Bifidobacteria* in the groups that had progressive allergy, and there were numerous *Costridial* species (such as *Clostridium difficile*). Therefore, the fact that there is a close correlation between the community of microbiota and allergy is getting attention. It is necessary to clearly establish whether the change in microbial composition is truly the etiological cause of allergy. In order to do so, well established animal model is needed to proceed the study on allergy, but there is no animal model that can explain what roles microbiota takes in pathogenesis of allergy. Recently, a research team realized the animal model for allergic airway diseases due to destructed microbiota caused by antibiotic administration (Noverr and Huffnagle, 2005). *Candida albicans* were orally administered to a mouse with normal immune functions in the gavage method, and ceforperazone was simultaneously injected for 5 days. This stabilized the increase of fungal microbiota, and the community of intestinal commensal bacteria was changed. When the allergen from *Aspergillus fumigates* was challenged to the nasal cavities of these mice, interestingly, the environment of natural intestinal microorganism was completely destructed, and airway autoimmunity by T cell was induced. The structure of this model and its study results directly proved that allergy can break out when the normal microbiota communities in the intestine are destructed, and allergy inducible specific pathogens flow in. Further studies need to find out the types of specific intestinal microorganisms that can prevent allergy, and their mechanisms.

Rheumatoid arthritis: Rheumatoid arthritis (RA) is an autoimmune disease that shows musculoskeletal dysfunctions, and its etiological cause is not well known. The cause of this disease is considered to be genetic or environmental. However, the possibility of this disease to be inherited is estimated about 50-60%. This result implies that there is a higher chance for environmental factors to be the cause of RA (Edwards and Cooper, 2006). Various observations have lead to the idea that intestinal microorganisms might be the factors that are causing the disease. The degradation products of nucleic acid and the cell walls of bacteria were found in the patients with inflammatory arthritis. Injection of bacteria cell wall substances seems to be causing arthritis (Toivanen, 2003). It also indicated that the patients who have RA noticeably have less *Bifidobacteria* species and *Bacteroides-Porphyromonas-Prevotella* group and *B. fragilis* subgroup (Vaahtovuo *et al*., 2008). These results support the idea that intestinal microorganisms change with the disease, and the changed flora communities can cause the disease. Interestingly, more severe disease is found in the germ-free animal than in the animals that have normal complex composed microbiota. Specific microbiota was proved to have the effects to inhibit pathogenesis of RA (Breban *et al*., 1993). It shows that the microbial organism living in our intestines not only take the beneficial role in immune response of the host but also effectively and provisionally inhibits pathogenesis of arthritis. Therefore, these results imply that it is necessary to find the consortium and the component of intestinal microorganism in the patients with early stages of RA in order to develop and improve the treatment for joint inflammation

Type 1 diabetes (T1D): T1D is an autoimmune disease that the insulin-producing β cell is destroyed by T cell. Pathogenesis of T1D has been steadily increasing in the developed countries for the past several decades, and the cause has been considered to be the environmental factor (Karvonen *et al*., 1993). In the experiments using animal model systems, the occurrence of T1D changes according to the conditions of microorganisms in the residential environment (Patterson *et al*., 2001). Moreover, the diabetes development in the non-obese diabetic (NOD) mouse model increased even more in germ-free environment. TLR is the most well known receptor that recognizes microbial specifically. In relation to this, one of the recent studies explained how microbial sensing affects the T1D progression. Pathogenesis of T1D in NOD mice was monitored when it was crossed with Myd88 deficient animals (Wen *et al*., 2008). Wild-type NOD mice had diabetes in 10 weeks, but Myd88-deficient animals were completely devoid of autoimmunity. This result implies that microbial sensing signals cause this disease. However, when these animals are restored in germ-free environment, the pathogenesis dramatically increases, showing that the existence of microbiota is protective even without TLRs signals. Therefore, bacterial sensing by TLRs increases the occurrence of T1D, but it induces protective response on the other hand when the mechanism does not require TLRs. There was no correlation between commensal microbiota and the autoimmune condition multiple sclerosis (MS) or lupus, but some parts of TLRs routes showed to decrease the severity of the disease in specific mouse models. For example, the effect of TLR9 decreases illness in lupus, and incapacitates the T cell-mediated tissue damage in MS. This is a TLRs-dependent mechanism, which induces anti-inflammatory cytokines such as IL-10. Because TLRs recognize the motif found in commensal bacteria, it is reasonable that TLRs is related to commensal microbes in lupus and MS. It is very important to understand the mechanism of how the microbiota influences the immune health of the host and the pathogenesis of these various autoimmune diseases, and to have good animal model system that can properly adjust the composition of microbiota. The communication evidence between the host and microbes is the task that must be attended for the host health, and it implies the possibility of microbiota affecting other various human diseases.

The role of gut-microbiota in human metabolic syndrome

Obesity is a worldwide problem (Flegal *et al*., 2010). The health risks associated with obesity are serious. Obesity increases metabolic diseases, type 2 diabetes mellitus (T2DM) and cancer (Caballero, 2007; Cowie *et al*., 2009). Therefore the disorders that are related to obesity come as a social bur-

den in terms of cost and quality of life. Genetic factors, the environment, and life style or habits are included as the cause, but they cannot explain all of the obesity prevalence. Gut microbiota was suggested to be contributing to the difference in individual body weight, insulin sensitivity, glucose metabolism, and other cardio metabolic risk factors (Cani and Delzenne, 2007). These discoveries were reinforced into various studies which reported that the gut components act as the main effectors in the pathological symptoms of obesity and their related disorders (Murphy *et al*., 2006; Baggio and Drucker, 2007; Vetter *et al*., 2009). Starting from the preclinical research, the early data indicated that the composition of intestinal flora may affect the energy consumption of the ingested food, absorption of nutrition, and metabolism of fat and sugar, and may take an important role in occurrence of obesity and its related diseases (Backhed *et al*., 2004; Ley *et al*., 2005; Turnbaugh *et al*., 2006; Cani and Delzenne, 2007; Creely *et al*., 2007).

International Human Microbiome Project (HMP) that recently started out does not limit the function and structure of the microbial communities that live in the gut only to intestines, but includes niches of other parts of human body (Turnbaugh *et al*., 2007). Its goal is to understand their roles in human health and diseases better. The insights gained from HMP ultimately improve the condition of disease and prevent illness, helping to develop evidence-based prebiotic and/or probiotic interventions that can control intestinal microorganisms.

This review provides an overview on how the quantitative and quality difference in the gut bacteria acts on the occurrence of metabolic symptoms (host's obesity, insulin resistance, T2DM, fat storage, gut physiology), starting from small sized clinical research and animal studies. Lastly, this study reviews the studies on manipulation of gut microbiota by targeted interventions that improved illness of metabolic diseases.

The implication of gut microbiota in the development of obesity and energy balance: Gut microbiota affects metabolic process of the host with various mechanisms (Cani and Delzenne, 2007; Tilg *et al*., 2009). They seem to be providing host benefits by many different ways. For example, gut flora uses special enzymes that are not in human genome for digesting polysaccharids, which are hard to digest, and makes them to extract energy (Flint *et al*., 2008). The quantitative and quality difference of the gut microbiota communities have been implicated in the obesity and insulin resistance development (Backhed *et al*., 2004; Ley *et al*., 2005; Turnbaugh *et al*., 2006; Cani and Delzenne, 2007; Creely *et al*., 2007). Many process mechanisms have been suggested, but none of them can fully explain the correlation between diet, gut flora, and host metabolic phenotype. The relationship between obesity and gut microbiota are as shown below.

First, the conventionally raised normal mice had more than 40% body fat compared to germ-free mice (Backhed *et al*., 2004). Total body fat was noticeably increased when germ-free mice was conventionalized with GI-derived microbial community. The suggested mechanism to explain this body fat increase was the suppressed intestinal expression of fasting-induced adipose factor (Fiaf, or angiopoietin-like protein 4) acting as lipoprotein lipase (LPL) inhibitor in which specific gut microbiota groups. Increased activity of LPL leads accumulation of triglyceride in fat cells. Studies on Germ-free Fiaf $^{-/-}$ mice have confirmed that microbial regulation is the important mediator in fat storage (Backhed *et al*., 2004).

Second, adenosine monophosphate activated protein kinase (AMPK) is the fuel system that can monitor the level of cellular energy, and its activity increases insulin sensitivity and oxidation of fatty acid in liver and muscle, and decrease glycogen level. The existence of gut microbiota caused obesity by inactive metabolic process of AMPK (Backhed *et al*., 2007).

Third, gut microbiota synthesizes a large set of glycoside hydrolase, and digests complex dietary polysaccharides to monosaccharides and short chain fatty-acids (SCFAs, such as acetic acid, propionic acid, butyric acid) (Flint *et al*., 2008). Among SCFAs, acetic acid and propionic acid are mainly produced in −mM unit, and butylic acid is produced in ~nM unit, which is relatively a very small quantity. These SCFAs are essential factors for human body, and are ligands for the G-protein coupled receptors (GPCRs): Gpr 41 and Gpr 43 (Brown *et al*., 2003; Le Poul *et al*., 2003). These GPCRs are expressed in gut epithelial cells and adipocytes (Xiong *et al*., 2004). The SCFAs that stimulated Gpr41 increased the expression of leptin in the mouse-cultured adipocytes (Xiong *et al*., 2004). Gpr41$^{-/-}$ mice gained less body weight than the wild type although they had the same normal diet. Gpr41 deficiency was related to decreased expression of PYY (cell-derived enteroendocrine hormone that normally inhibits gut motility), increased intestinal transit rate, decreased energy extraction from the diet, and decreased hepatic lipogenesis (Samuel *et al*., 2008). For this reason, the manipulation of SCFAs activation through Gpr41 in the gut could provide as the therapeutic target that can control the effects of energy extraction from carbohydrate-rich diet.

Fourth, two of the dominant bacteria phyla, *Baceteroidetes* and *Firmicutes* were found in the insulin resistant obese mice, and *Firmicutes* showed a higher existence than Baceteroidetes (Ley *et al*., 2005). The change in the relative existence of this '*Firmicultes*; obese gut microbiota' was associated with an increased capacity for energy harvest (Backhed *et al*., 2004). More SCFAs and *Firmicutes* contents were found in the appendix of the obese mice than in the lean mice. Transplantation of obese microbiota into germ-free mice increased total body fat gain even more (Turnbaugh *et al*., 2006). Furthermore, Clinical studies were tried out in order to explain and compare the gut microbiota composition and host metabolism in the lean and obese people (Ley *et al*., 2006; Creely *et al*., 2007; Collado *et al*., 2008; Duncan *et al*., 2008; Kalliomaki *et al*., 2008; Nadal *et al*., 2009). As the results from the studies, the ratio of gut microbiota composition in the obese people changed; *Firmicutes* had higher ratio than *Bacteroidetes.* In this study, the *Bacteroidetes*, 'lean microbiota' clearly decreased body weight although the total calorie acquisition was the same, on the other hand, the obese gut microbiota such as *Firmicutes* increased energy extraction ability of human (Ley *et al*., 2006).

Fifth, High-fat diet to the development of obesity and T2DM development is related to low level pro-inflammatory condition enhancement (Wellen and Hotamisligil, 2005; Hotamisligil 2006; Cani and Delzenne, 2007). Endotoxin LPS comes from Gram negative intestinal bacteria. It combines to CD14/TLR4 complex which is on the surface of IECs and immune cells, and stimulates pro-inflammatory cytokine (Wright *et al*., 1990; Neal *et al*., 2006; Wolowczuk *et al*., 2008). High fat diet increases Gram-negative/Gram positive bacteria ratio in mice. This leaded an increase in plasma LPS level, body weight, fat volume, liver steatosis, diabetes, and pro-inflammatory state

(Cani and Delzenne, 2007). On the other hand, CD14 knockout mice were resistant to these factors and phenomenon, thus these results support the role of LPS in the relationship between diet, gut microbiota, and host metabolism phenotype (Cani and Delzenne, 2007). Unlike WT mice, the increased LPS was found in the obese and diabetes mice (Pappo *et al*., 1991).

Finally, the antibiotic therapy lowered plasmic LPS and hepatic steatosis in rat and mice. Predictable gut microbiota composition in obesity was proved in children (Kalliomaki *et al*., 2008), obese adolescents (Nadal *et al*., 2009), and pregnant women (Collado *et al*., 2008). Therefore, individual metabolism is determined by the core bacterial group that is related to obesity and energy harvest (Larsen *et al*., 2010).

Dietary interventions to modify the gut microbiota and host metabolism: Manipulation of gut microbiota, biochemical capabilities that are related to digesting specific food and pharmacological treatments may affect host metabolism in a positive way. However, studies on human were uncertain, and therefore these effects need to be studied based on the relationship with the host phenotype to find out whether it is the diet-induced effect based on existing gut microbiota, which are orally consumed with food. In order to prove this, the tool to modulate gut microbiota is most important.

Supplements using gut flora-derived Inulin-type fructooligosaccharides (FOS) stimulated the growth of *Bifidobacterium* species and *Lactobacillus* species in human (Bouhnik *et al*., 2004; Macfarlane *et al*., 2006; Kolida *et al*., 2007). These groups of bacteria are probiotics, contributing in intestinal endotoxin level decrease and mucosal barrier function expansion (Griffiths *et al*., 2004; Wang *et al*., 2006; Cani *et al*., 2007). The *Bifidobacteria* count seems strongly associated with pre-existent gut microbiota composition and dietary intervention (Bouhnik *et al*., 2004). A recent human trial with a human *Latobacillius* isolate has confirmed that mucosal tolerance mediated by nuclear factor (NF)-κB has an effect (van Baarlen *et al*., 2009). Satiety increased, and hunger and food ingestion decreased in the study that supplemented FOS to the healthy group for 2 weeks (Cani *et al*., 2006a). Supplementary FOS provided to obese people for 12 weeks decreased body weight, and inhibited orexigenic hormone, ghrelin (Parnell and Reimer, 2009). Simultaneously, provided FOS and *Bifidobacteria* increased bioactive isomers of conjugated linoleic acid, increased omega-3 fatty acid levels in fat tissues, and decreased pro-inflammatory cytokines in mice and pig livers (Wall *et al*., 2009).

The role of gut-derived SCFAs, the cellulose formed by fermentation due to gut flora activity, is still controversial. As mentioned above, SCFAs increase energy extraction from food, and body weight increases as a consequence (Turnbaugh *et al*., 2006). On the other hand, supplementation of specific SCFAs (butyric acid) has great beneficial effects, including increased satiety, loss of body weight and fat, improved insulin sensitivity and glucose tolerance with several mechanisms (Kok *et al*., 1998; Cani *et al*., 2005; Cani *et al*., 2006b; Cani *et al*., 2007). In one interesting study, mice on a high fat diet were supplemented with butyrate, showed that increased energy consumption, induced mitochondria functions, and prevented diet-induced obesity and insulin resistance (Gao *et al*., 2009). Non-fermentable FOS or butyrate combined to Gpr43 in L-cell, and controls body weight, fat accumulation, and energy metabolism (Karaki *et al*., 2006). They also increase the number of enteroendocrine L-cell in colon, and portal glucagon-like peptide (GLP)-1/2 (Cani *et al*., 2006b).

Gut-microbiota-adipose tissue physiology: Bidirectional brain-gut interactions take an important role in mediating GI functions such as motility, secretion, blood flow, intestinal permeability, mucosal immune activity and visceral sensations (Rhee *et al*., 2009). Central nervous system (CNS) signaling can get indirectly involved in the interaction with the host enteric bacteria, and affect the GI functions mentioned above. Thus, stress-induced alterations (nervous balance and tone) that stimulate autonomic and enteric nervous system are related with complex and various GI disorders (Rhee *et al*., 2009). Gut microbiota can directly or indirectly change gut motility, secretion of intestinal hormone such as GLP-1/2 and PYY, and permeability via afferent neurocanal or signaling proteins, respectively.

These changes will ultimately affect the metabolism and immunity of the host. Total body weight mass, dysfunction of adipose tissue, lipid storage capacity confusion, and increased inflammatory response in the adipose tissue take crucial role in insulin resistance and T2DM (Goossens, 2008). Adipose tissue generally serves as a metabolic buffer that isolates fatty acid in postprandial state, and secretes them in starvation. In case of abdominal obesity, this buffering action causes excessive flux of fat, and gets exposed to the general non-adipose tissue, which leads to increased ectopic adipose storage and serial insulin resistance and T2DM occurrence, damaging health (Corpeleijn *et al*., 2009). The controlling system mechanism for obesity and insulin resistance, and the adipose tissue in T2DM is not fully understood. Various mechanisms that are related to the manipulation by prebiotic FOS or gut microbiota are suggested in adipose tissue (dys)function, hepatic steatosis and inflammation (Backhed *et al*., 2004; Cani *et al*., 2006b). However, these are not yet studied in human. The correlation between dietary intake and physiology has long been considered. Many researchers determine the tendency of disease as an important factor for reflecting individual traits such as environmental factors or eating behaviors, especially. Prebiotics and probiotics contribute to metabolic physiology of the host by modifying nutrition or enhancing health . Therefore, the correlation between nutritional modification and the host must be established by microbiota mechanism.

Cancer therapy and gut microbiota: A popular hypothesis of carcinogenesis refers to the clonogenic expansion of the cancer cell that has the nature of 'undifferentiated' cell. The biochemical process that induces cell differentiation is currently considered as a viable cancer treatment modality. Cell differentiation is the process that starts out with modification of genetic expression. This process is regulated by acetylation of histones. Removal of acetyl group by specific enzymes (histone deacetylases, HDAC) usually downregulates the genetic expression that can induce cell differentiation (de Ruijter *et al*., 2003) and control cancer progression (Goldsmith *et al*., 2007; Mariadason, 2008). The pharmacological inhibitors that hinder activation of HDAC enzymes have been shown to induce differentiation in multiple colon cancer cell lines (Villar-Garea and Esteller, 2004; Marks and Xu, 2009). Therefore these are often tried out in clinical treatment. Especially, gut flora-derived butyrate plays a role as a HDAC inhibitor in colon cancer (HT-29. Caco-2, HCT-116) (Alcarraz-Vizan, *et al*., 2010; Wilson *et al*., 2006; Perrine *et al*., 2007; Waldecker *et al*., 2008), and was proven to mainly control the host's cellu-

lar metabolic process as an anticancer effecter controlling cell differentiation and apoptosis (Heerdt *et al*., 1994; Litvak *et al*., 1998; Mariadason, 2008; Marks and Xu, 2009).

CONCLUSION

Gut microbiota support intestinal homeostasis by regulating their communities, innate/ adaptive immunity, intestinal barrier function, energy balance, and metabolic process. The diversity of gut flora or their bacterial products have been indentified various functions and beneficial effects in the contexts of IBD, autoimmune diseases, and diabetes through clinical studies. The discovery of specific bacterial strain that gives specific effects to the patients and the significant gut microbial factors would be the potential approach to develop effective treatment ways to cure the diseases and enhance human health.

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