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Gut Microbiota in The Pathogenesis of Type 2 Diabetes Mellitus

Kaset Chimplee, M.D.[1], Kamonaree Chotinuntakul, Ph.D.[2]
[1]Department of Internal Medicine, School of Medicine, Mae Fah Luang University, Chiang Rai 57100, Thailand
[2]Department of Microbiology, School of Medicine, Mae Fah Luang University, Chiang Rai 57100, Thailand
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Abstract:

There are increased evidences of association between gut bacteria and the pathogenesis of type 2 diabetes mellitus. In humans, the gut bacteria comprise of six main phyla, including *Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, Fusobacteria* and *Verrucomicrobia*. Gut bacteria maintain in a certain composition between each phylum and subphylum. Disturbance in gut microbiota composition is called dysbiosis. The microbial dysbiosis could result in many diseases, for examples: Celiac disease, obesity and certainly diabetes mellitus. The proposed mechanisms of gut microbiota on the pathogenesis of type 2 diabetes mellitus are resulted from: effects of gut microbiota on energy metabolisms, effects on intestinal integrity, effects on metabolic endotoxemia and low-grade inflammation, effects on intestinal motility, effects on immune system. Clinical information from the treatments to alter the gut flora composition by probiotics, prebiotics and fecal transplantation potentiate the novel alternatives for the future treatment of type 2 diabetes mellitus.

Keywords: Gut Microbiota, Type 2 DM, Pathogenesis

Introduction

Type 2 Diabetes Mellitus is a leading global health problem, with resultant long term social and economic dilemmas. The International Diabetes Federation reported in IDF Atlas 2021 that 537 million people live with diabetes and 783 million people of the world will have developed diabetes by 2045, leading to one person dying of diabetes every 5 seconds.[1] In Thailand, the prevalence of diabetes mellitus in adults is 9.9 percent.[2] The pathogenesis of type 2 diabetes is an interplay between genetic predisposition and environmental factors. Characterized by pathophysiologic abnormality, there are at least 8 organs of the body involved and this reality can be described as follows.[3]

1. Muscle insulin resistance, characterized by reduced muscle glucose uptake and reduced glycogen synthesis.[4,5]

2. Hepatic insulin resistance, leading to excessive hepatic glucose output.

3. Adipocyte insulin resistance, characterized by accelerated lipolysis and abnormal adipocytokine production (for example:increased resistin, decreased adiponectin).[6,7]

4. Progressive beta cell failure and apoptosis.

Corresponding author: Kaset Chimplee, M.D.
School of Medicine, Mae Fah Luang University, Chiang Rai 57100, Thailand
E-mail: kaset.chi@mfu.ac.th
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5. Increased glucagon secretion by alpha cells and increased liver sensitivity to glucagon.

6. Reduced incretin effects, related to a reduction of Glucagon like peptide -1(GLP-1) levels and beta cell resistance to GLP-1 and Glucagon inhibitory peptide (GIP).[8,9]

7. Increased renal tubular glucose reabsorption, as a result of increased expression of SGLT-2 gene.[10]

8. Inappropriate function of the hypothalamus, via insulin receptor antisense oligodeoxynucleotides, leading to impaired appetite suppression.

The range of pathophysiology as mentioned above, is already known to be responsible for the development of type 2 diabetes mellitus This pathogenesis is evoked by interactions between genetic predisposition and environmental factors. However, there is an unexplored environmental factor that is related to the essential environment inside of the human body, that also contributes to the pathogenesis of type2 diabetes mellitus: the gut environment and the organisms living in this environment – the gut bacteria.

Human gut microbiome and their functions

The human gut contains a microbial community, termed microbiome. The number of gut microbiotas in individuals is diverse, up to 1,500 species having been reported.[11] There are six main phyla of gut bacteria in humans, comprising *Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, Fusobacteria* and *Verrucomicrobia*. Generally, a normal balance of gut microbiota in the eubiosis contains a predominance of beneficial microbiota species, mainly comprised of phyla *Bacteroidetes* and *Firmicutes*.[12] However, variation in infants depends on the mode of delivery. Metagenome analysis has demonstrated that the maternal gut is the major source for microbiota in the gastrointestinal tract of healthy infants.[13] Breast-feeding and the mode of delivery affect the early gut composition and plays a role in the development of the immune system.[14,15] The colonization rate of *Bacteroide*s is higher in vaginal delivery-born infants compared to those in the cesarean delivery group. while cesarean delivery infants have a greater abundance of *Clostridium, Lactobacillus, Enterobacter, Streptococcus,* and *Enterococcus*.[14] The colonization of the gut microbiome during neonatal life is thought to affect gut maturation, metabolism, immunity, and brain development.[15] Infants exposed to antibiotics at birth showed an effect on mother-to-infant colonization and an increased the risk of horizontal transfer from the environment.[16] For example, antimicrobial resistance strains from the hospital may be the cause of infection in the perinatal period. The use of intrapartum antimicrobial prophylaxis increased the incidence of some β-lactamase coding genes and related aberrant profiles, with lower relative proportions of *Actinobacteria* and *Bacteroidetes* and increased proportions of *Proteobacteria* and *Firmicutes*.[17] This intestinal microbiota modulation, during the first month of life, can alter the development of individual microbiota-induced host homeostasis.[18,19]

A recent paper reported bacterial dispersal strategies, describing strong correlations among bacterial persistence, family association, and the phylogeography of the human gut flora.[20] The first group are termed *tenacious bacteria*. These bacteria live permanently during childhood through to adult life. They are well-adapted in the human hosts, with different nutritional needs, but tend to be lost permanently by antibiotic intervention. The second group, *herediper-sistant bacteria*, notably *Firmicutes*, have strong family associations and persistence. However, they lack notable phylogeographic signals. The third group, *spatiopersistent bacteria*. show a strong cluster to their own

geographic regions but family associations are not observed, due to a reduced strain persistence in infants.[20] Clearly, the variation of the individual microbiome is related to exposure to environmental factors.

Host and microbes live in association by depending on each other, described as symbiosis.[21] The host serves nutrients and provides an environment for microbes to survive, whilst the gut microbiome confers several advantages to its host, such as fermentation of some undigested food into absorbable compounds, to modify xenobiotics for human health benefit, reduction of toxicity of harmful industrial compounds and pollutants, synthesis of essential nutrients, competing with pathogens, and modulation of mucosal homeostasis by interaction with host immunity.[22-26] The intestinal microbiome can activate the immune system through presentation of microbe-associated molecular patterns (MAMPs), can maintain the intestinal barrier integrity and control mucosal inflammation, particularly during early life, and can therefore educate the immune system to protect the body from harmful microbes later in life.[22,27] Perturbation of optimal host-commensal interactions during this time may result in potentially persistent immune abnormalities.[27]

Studies of 16S rRNA gene amplicon sequencing and metagenomics explores the structure of gut microbiota on human physiology, and also explores links affecting the association between the microbiome and the host's diet, chemistry and health.[28] However, pinpointing specific functions of specific microbiota, requires more sensitive functional omics studies from metatranscriptomic, metaproteomic, and metabolomic analyses.[29-31] Metabolites, mainly short chain fatty acids (SCFAs), are produced by the gut microbiome via the fermentation of dietary fiber, particularly by anaerobic bacteria. Acetic acid (acetate), propionic acid (propionate), and butyric acid (butyrate) are the main bacterial metabolites with immunomodulatory and homeostasis roles.[32] After SCFAs are synthesized in the gut lumen, these metabolites are transported into the intestinal epithelial cells, where butyrate becomes the major energy fuel for metabolism of the intestinal epithelial cells. On the other hand, acetate and propionate are transferred to other organs via the blood circulation.[33,34] Moreover, acetate and propionate are primarily produced by the gut bacteria phylum Bacteroidetes, whilst butyrate is synthesized mostly by the phylum Firmicutes.[35] Interaction between SCFAs and the host cells activates cellular responses, resulting in the proliferation and differentiation of the cells, including inhibition of the zinc-dependent histone deacetylases (HDACs), that act as epigenomic erasers on the chromatin architecture.[33] The inhibition of HDACs provokes the hyperacetylation of histones, leading to anti-inflammatory gene activation.[36] In addition, a recent study has shown that SCFAs can induce neutrophil extracellular traps (NETs) formation, which is mediated, in part, by the free fatty acid 2 receptor expressed in neutrophils.[37] NETs play a role in protection against infection, for example the sequential step of stimulation is mediated by intracellular mediator production, such as reactive oxygen species (ROS), neutrophil elastase (NE) and protein-arginine deiminase type 4 (PAD4).[37] Studies on lymphoid (Epstein-Barr virus-positive) and cancerous epithelial cells, demonstrate that butyrate can stimulate interleukin-6 (IL-6) and interleukin-8 (IL-8) expression, including enhanced NF-kB activity. The consequence of this stimulation results in the removal of the EBV-infected cells and cancerous cells.[38] Microbiota-derived butyrate exhibits increasing antimicrobial activity.[39] Butyrate enhances macrophage differentiation though the inhibition of histone deacetylase 3 (HDAC3), to drive metabolic changes and microbicidal function without inflammation,

and inhibits mTOR kinase activity.[39] SCFAs could also play a role in the activation of adaptive immune response. The promotion of T cell differentiation into effector T cells and regulatory T cells (Treg) is mediated by the inhibition of HDAC and the regulation of mTOR pathway.[40] The mTOR pathway is also found to be involved in the promotion of some regulatory cytokine expressions, such as IL-10, IFN-γ, and IL-17, via STAT3 activation.[41,42]

Gut microflora and dysbiosis

The intestinal microbiome maintains homeostasis of immune reactions, host-pathogen interactions, and pathogen clearance.[42,43] Loss of balance between the gut microbiome composition in the host results in impaired intestinal cell function and increased gut permeability, including altered host immune responses, potentially increasing host susceptibility to infectious pathogens.[44] Some diseases have been found to be linked to dysbiosis of the gut microbiota. However, so far there is no clear evidence whether this is the cause of these diseases or is simply related to the progression towards the dysbiosis.

The microbial dysbiosis and related lower level of butyrate are believed to contribute to inflammatory bowel disease (IBD) immunopathogenesis.[45] Patients and animal models with IBD and colorectal cancer showed lowered levels of butyrate-forming bacterial species, including *Faecalibacterium prausnitzii*, the major bacterium of the *Clostridium leptum* group.[46,47] In addition, it has been found that butyrate production from *F. prausnitzii* could regulate T helper-17 cell/ Treg balance, and exert anti-inflammatory effects in colorectal colitis in murine models.[48] Furthermore, a reduction of butyrate may impair the function of bactericidal activities of macrophages, as described earlier.

Disturbance in microbiota components could also result in susceptibility to *Clostridium difficile*-induced colitis infection. Fachi et al. demonstrated that butyrate could protect intestinal epithelial cells damage by *C. difficile* toxin in infected mice via HIF-1 stabilization, while acetate administration could lessen the disease sequelae via promotion of innate immunity.[49] Several studies reported a decrease in phyla Bacteroidetes and Firmicutes in the human gut in *C. difficile* infection.[50-52] These groups of bacteria play a role in carbohydrate metabolism and SCFAs synthesis. However, a recent study has shown that the composition of these phyla were increased in *C. difficile* infections with community acquired onset. This contradiction may be due to the physical and nutritional components available from the community, which help preserve stable gut community and immune homeostasis, leading to a slower progression of *C. difficile* infection states.[53]

Dysbiosis in the gut microbiome was reported in Celiac disease, which is an autoimmune disorder, affected by genetic predisposition and triggered by gluten ingestion.[54] The impaired immunity and deficiencies in modulation of intestinal permeability result in mucosal inflammation and contribute to the pathogenesis of Celiac disease.[55] A decrease in *Bifidobacteria* and *Lactobacilli*, which play a role in the protective effect against inflammation, was reported in patients with Celiac disease.[56] On the other hand, rod-shaped bacteria, *Bacteroides, Clostridium*, and Prevotella, were more frequently reported in the small bowel of children with Celiac disease.[57-59] Nonetheless, there has been no specific bacterial strain identified as causing the disease or acting as a specific marker for the diagnosis of Celiac disease. Research in intestinal cell culture conditions has demonstrated that *Bifidobacteria* and *Lactabacilli* inhibit the breakdown of gluten and its peptide derivatives that are the cause of this toxicity.[60] So far, the proven therapy for Celiac disease is a gluten-free diet, with supplementation of probiotics, to regulate intestinal integrity and decrease inflammatory responses.[61]

The composition of the gut microbiome in obesity has been studied in both animal and human subjects. It has been proposed that relationships of gut microbiome may act as the pathogenesis of obesity. Studies in obese mice showed an increased ratio of *Firmicutes* and *Bacteroidetes* as compared to the control.[62,63] Findings on overweight pig models also demonstrated a lower abundance of *Bacteroidetes* in the colon compared to lean animals.[64] The transplantation of fecal microbiota from lean twin mice showed modulation of metabolism and prevention of increased adiposity phenotypes, including reconstitution of the number of *Bacteroidetes* in the gut of obese twins.[65] In addition, several studies have reported the major composition of the gut bacteria in obese humans. *Bacteroidetes* are frequently found in a lower abundance in the gut microbiota of obesity versus lean controls.[66-68] Species-specific variations of *Lactobacillus* in obesity were also reported.[66] On the other hand, Patil et al. compared the proportion of dominant bacteria between lean, normal, obese and surgically treated obese individuals of Indian origin and found that there was no correlation in the trends between *Firmicutes* and *Bacteroidetes* among these groups.[69] Observation in obese women showed an increase in levels of inflammatory markers. Calorie restriction improved the inflammatory markers transiently and reduced gut permeability.[70] However, the overall bacterial phylogenetic make up was not changed statistically after the calorie restriction. More specifically, a recent study demonstrated that obese subjects, who lost at least 5 percent of their body weight, had significantly different baseline microbiomes when compared to those that did not lose weight. *Escherichia, Shigella, Klebsiella, Megasphaera,* and *Actinomyces* were substantially enriched in the subjects who did not lose their weight. These bacteria, therefore, have been suggested as the gut microbiota associated with weight response to a calorie-restricted diet.[71]

Proposed mechanisms of gut microbiota on pathogenesis of type 2 Diabetes Mellitus

Effects of gut microbiota on energy metabolism

Dietary polysaccharides and oligosaccharides are digested by gut microbiota into monosaccharides and short chain fatty acids (SCFAs). The main SCFAs are composed of acetate, propionate and butyrate, which contribute to 5-10 percent of energy resource.[72] These SCFAs are the direct energy resource of intestinal epithelial cells (IEC).[73] In adipose tissue, SCFAs and free fatty acids (FFA) interact with the G-protein coupled recepter-41 (GPR-41) and G-protein coupled recepter-43 (GPR-43), located on the adipocyte membrane, to create energy accumulation.[74] At the L-cells of the small intestine SCFAs interact with GPR-41 and GPR-43 to promote GLP-1 production.[75,76] Consequently, SCFAs act as metabolomics, exerting effects on insulin secretion, glucose homeostasis and energy metabolism. Comparison of the individual major SCFAs reveals that acetate diminishes food intake while butyrate and propionate suppress weight gain, as shown in studies on healthy mice.[77,78] In addition, a study of normal laboratory mice, compared with germ free mice (GF), revealed that the level of triglycerides in the normal mice adipose tissue and liver was higher than that of germ-free mice.[79] Hence this study suggested the role of gut microbiota in lipid metabolism and energy storage. In the liver when lipogenesis take places, gut microbiota increases synthesis of hepatic triglycerides via activation of both ChREBP and SREBP-1C.[77,80]

In further interventional studies in mice, introduction of gut bacteria, from normal mice to germ free mice, had the effect of increasing fat mass and insulin resistance.[81] This study proves that gut bacteria have the capacity to enhance energy harvest from food.[82]

Effects of gut microbiota on fatty acid oxidation and synthesis

Different kinds of gut microorganism have different effects on fatty acid oxidation and fatty acid synthesis. *Akkermansia muciniphila* enhances fatty acid oxidation in adipose tissue, via increased levels of 2-oleoyl glycerol, 2-palmito glycerol and 2-acylglycerol. This process leads to increased adipocyte differentiation.[83] *Bacteroides acidificiens* enhances fatty acid oxidation in adipose tissue, via the PPAR-γ pathway.[84] *Lactobacillus gasseri* increases fatty acid oxidation by enhancing fatty acid oxidation genes and reducing fatty acid synthesis related genes, to reduce obesity.[85]

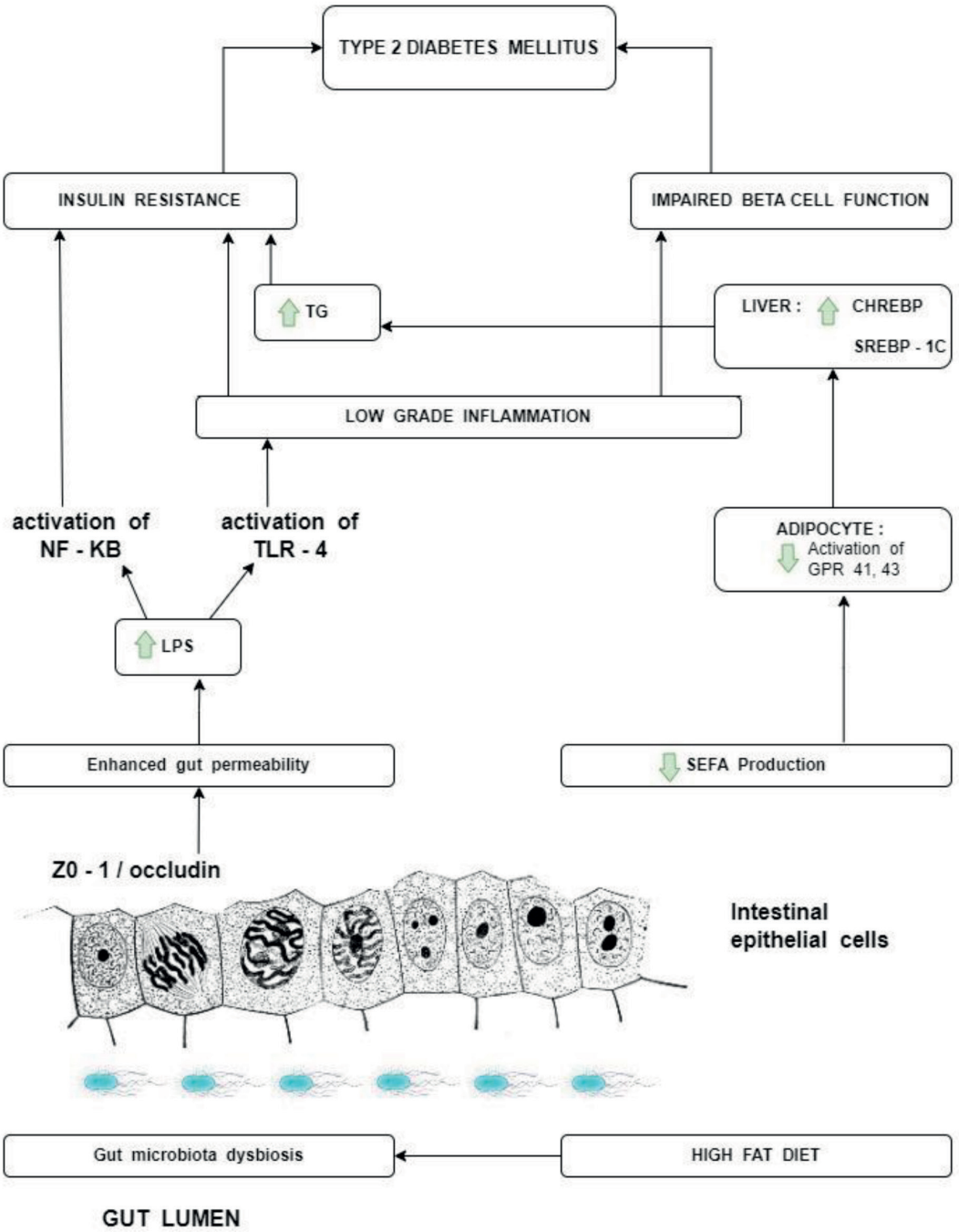

Figure 1 The proposed mechanisms of gut microbiota on contribution to pathogenesis of type 2 diabetes mellitus (modified from He C, Shan Y, Song W. Nutr Res. 2015; 35(5): 361-7.)

Effects of gut microbiota on glucose metabolism

The major organs involved in the development of type 2 diabetes, and creating insulin resistance, are the liver, muscles and adipose tissue. These functions of these organs are affected by gut microbiota and are related to glucose metabolism and homeostasis. There are published studies of certain gut bacteria that have demonstrated these associations. *Bifidobacterium lactis* has good effects on glucose homeostasis, by increasing glycogen synthesis in the liver and decreasing expression of hepatic gluconeogenesis related genes. This bacterium increased translocation of glucose transporter-4 (GLUT-4), in insulin sensitive tissue, to stimulate glucose uptake.[86] Similarly, a bacterium that can increase GLUT-4 expression in muscle is *Lactobacillus gasseri*.[85] Another of the same genus, *Lactobacillus casei*, has a beneficial effect on insulin resistance, by enhancing the mRNA level of phosphatidylinositol 3-kinase (PI3K), AMPK, which increases glycogen synthesis in the liver.[87,88] The Lactobacillus species *L. rhamnosus* increases insulin sensitivity in epididymal fat by increasing adiponectin levels.[89] *Akkermensia muciniphila* potentiates α-glucosidase inhibitor activity, to prevent the breakdown of complex carbohydrate, resulting in reduction of postprandial hyperglycemia.[90]

Interaction of gut microbiota and host genetics in obesity development

Current knowledge on the pathogenesis of obesity is concentrating on the role of gut flora, linking genetic predisposition and development of obesity. The host genome impacts on the individual gut microbiota composition and functions, those influence the breakdown of indigestible dietary polysaccharides, for body energy harvest from food.[73] Experimental studies in mice, by the transfer of gut microbiota from obese mice or humans into germ free mice, caused more weight gain when compared to transfer of gut microbiota from lean mice.[91] Early studies on the gut microbiota composition, comparing results obtained from obese mice and lean mice, gave similar results to those obtained from obese humans. The results showed an increase in Firmicutes and a decrease in Bacteroidetes or an increase in the Firmicutes/Bacteroidetes ratio.[92-95] Furthermore, various studies revealed an association of certain bacterial populations with weight gain, including *Akkermansia muciniphila, Faecalibacterium prausnitzii, Lactobacillus reuteri, Roseburia intestinalis*.[96] Not only were these specific bacterial groups linked to weight gain in human and animal studies, but a decrease in gut flora diversity was associated with obesity and certain metabolic diseases. Reduction of dietary diversity in most countries leads to loss of gut microbial diversity.[97]

Effects of gut microbiota on intestinal integrity (gut permeability)

Increased gut permeability or gut leakage has a deleterious effect on glucose homeostasis. The paracellular permeability of the gut is manipulated by multiple proteins, for example claudin, occludin and the zona occludens.[98] Experimental high fat feeding of mice revealed the expression of the tight junction proteins and zona occluden-1.[99] Hence, gut barrier disruption is responsible for microbes and molecules, derived from bacterial compound production, such as lipopolysaccharides (LPS), pepitidoglycans and flagellin, entering from the gut lumen into the circulation. This process is called metabolic endotoxemia.[82] Consequently, it can be surmised that gut barrier disruption leads to metabolic endotoxemia. Studies on obese mice showed disruption of intestinal barriers, enhanced intestinal mucosal permeability and leakage of LPS. LPS is a molecule that is derived from components of the cell wall of gram-negative bacteria.

Entry of LPS into the circulation was seen to promote inflammatory cytokines activation.[100]

The endocannabinoid system (eCB) is one of the body systems that has an important role in energy homeostasis. In the obese state the endocannabinoid system exerts its effects through gut epithelium permeability, by alteration of the tight junction protein, via activation of cannabinoid receptor1 (CB1) and 2 (CB2). CB1 and CB2 are expressed through the GI tract at various levels and gut microbiota can manipulate these CB1 receptors. The CB1 antagonist could decrease gut permeability and reduce metabolic endotoxemia.[101]

Intestinal alkali phosphatase (IAP) is the enzyme involved in the breaking down of dietary lipid. IAP acts on LPS detoxification and reduction of LPS level by dephosphorylation of the lipid portion of the LPS.[102] Gut microbiota regulated expression of IAP and a study in obesity showed a decrease in IAP activity.[103,104] Nevertheless, an increase in IAP activity also leads to reduction of metabolic endotoxemia.[105]

Glucagon like peptide-2 (GLP-2) is another system involved in gut permeability. Increased endogenous production of GLP-2 is associated with strengthening of the tight junctions of the intestinal epithelium cells.[106] A study in ob/ob mice, incorporating GLP-2 related pharmacological treatment, resulted in improvement of tight junctions and reduction of LPS levels in the plasma.[107] Certain gut bacteria have beneficial effects on tight junctions. *Bacteroidetes valgaris* and *Bacteriodetes dorei* upregulated the expression of the tight junction gene in the colon of mice, inducing reduction of gut permeability and metabolic endotoxemia. *Akkermansia muciniphila* augmented intestinal tight junctions via AMPK activation in intestinal epithelium cells to reduce gut permeability.[108] *Faecalibacterium* and *Roseburia* produce butylate that acts on serotonin transporters and PPAR-γ pathways, to reduce gut permeability and improve intestinal barrier functions.[109]

In human with type 2 diabetes, intestinal permeability substantially increased in comparison to controls.[110] In mice studies, a high fat diet reduced the epithelial integrity of the gut lining, via reduction in tight junction proteins: zonula occluding-1 (ZO-1) and occludin. Dietary fatty acid also activated toll-like receptor 2 (TLR-2) and toll-like receptor 4 (TLR-4). TLR-4 is the component of the complex proteins that mediate metabolic endotoxemia, by intervention of LPS translocation into the intestinal capillaries.[111]

Effects of gut microbiota on metabolic endotoxemia and low-grade inflammation

Low grade inflammation promotes the development of insulin resistance and diabetes.[112] As mentioned earlier, lipopolysaccharides (LPS): a glycol-lipid molecule derived from cell wall of gram-negative bacteria in the gut wall, can induce an innate immune response. LPS stimulates a cascade of responses that leads to release of proinflammatory molecules that contribute to insulin resistance and glucose homeostasis.[113] An increased level of LPS was found in high fat intake mice.[114] A similar study in obese and diabetic humans, with high fat intake, showed increased level of LPS in their blood.[115] LPS mediates inflammatory responses via TLR-2 and TLR-4 pathways.[116] TLR-2 incites inflammatory signaling by activation of nuclear factor kappa-B (NF-kB) and cellular pro-inflammatory cytokines.[117] Similarly, TLR-4 activates the release of pro-inflammatory cytokines which interfere with glucose and insulin metabolism.[118] A study in mice, lacking TLR-2, demonstrated improved insulin sensitivity with faster glucose clearance, according to reduced expression of inflammatory cytokines.[119]

While certain kinds of gut microbes and microbial products aggravate metabolic endotoxemia and low-grade inflammation, some gut microbiota exert beneficial effects by stimulation of anti-inflammatory cytokines. For instances, *Roseburia intestinalis, Bacteroides fragilis, Akkermansia muciniphila, Lactobacillus plantarum* and *Lactobacillus casei* increase IL-10 and IL-22 production. These anti-inflammatory cytokines are known to improve insulin sensitivity and reduce blood glucose excursion in diabetic patients.[120-125] Similarly, exerting beneficial effects on glucose homeostasis, *Lactobacillus, Bacteroides* and *Akkermansia* inhibit pro-inflammatory cytokines: TNF-α.[126-127] Certain species of *Lactobacillus (L. plantarum, L. paracasei, L. casei)* can reduce pro-inflammatory cytokines: IL-1β, IL-8, CD-30, C-reactive protein.[128-129] Some gut microbiota inhibits pro-inflammatory activity, via induction of short chain fatty acids, for example, *Roseburia* and *Faecalibacterium* produce butyrate to repress NF-kB.[130-131]

Effects of gut microbiota on intestinal motility

Microbiota can interact with gut motility through several mechanisms. By stimulation of pro-inflammatory cytokine production, and modulation of immune cell functions in the intestine, the increased inflammation affects Peptidergic Enteric Neurons, resulting in neurodegeneration. This process causes decreased gut motility.[132] In addition, gut microbiota can affect intestinal motility, by interaction with the gut-brain axis, through modification of afferent sensory nerve impulses, enhancing neuronal activity and modulation of pain perception.[133] Moreover, gut microbiota can modify enteric nervous system activity, via production of local gut neurotransmitters, for example GABA, serotonin, melatonin, histamine and acetylcholine, leading to effects on gut motility.[134]

Effects of gut microbiota on immune system

Malfunction of the innate intestinal immune system plays an important role in glucotoxicity and lipotoxicity, resulting in the development of obesity and metabolic syndrome.[135] The chronic inflammatory state, presenting in obesity, stimulates innate and adaptive immunity. The immune response process functions via a Toll like receptor (TLR) to promote production of inflammatory cytokines, such as IL-1β, resulting in beta cells destruction.[136]

TLR-5: one of the components of innate immune system, is expressed in intestinal mucosa.[137] A study on TLR-5 deficient mice showed features of hyperphagia, obesity, hyperlipidemia, high blood pressure and insulin resistance. A further study on transplantation of gut microbiota, from TLR-5 deficient mice to the wild type germ free mice, resulted in increased levels of inflammatory cytokines, development of features of insulin resistance as well as obesity in the recipients.[138] *Akkermansia muciniphila* stimulated FOXP3 regulatory T cells in visceral adipose tissue to enhance glucose tolerance.[139]

Conclusion and perspectives

With the advance of genomic medicine and the advent of novel techniques on genome sequencing, there is a great opportunity to understand the involvement of human gut bacteria on the pathogenesis of many diseases. New generation approaches such as metagenomics, metabolomics and transcriptomics have had tremendous effects on explanations of the molecular basis of interaction between gut microbes and the pathogenesis of type 2 diabetes mellitus and even the association between gut microbiota and diabetic related complications in humans. Then intervention, by alteration of composition of gut microbiota, is a novel therapeutic challenge for treatment of type 2 diabetes.

The use of probiotics, prebiotics and even fecal microbiota transplantation, constitute an explosion of new information, revealed in recent clinical studies in diabetic patients. In the near future, with more studies in human subjects, a better understanding of the molecular interaction of gut microbiota and type 2 diabetes will lead to the application of these measures on type 2 diabetic prevention, alongside treatment with conventional antidiabetic medications.

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Author contribution

Kaset Chimplee contributed on section 1,4,5 and Kamonaree Chotinuntakul contributed on section 2,3.

Conflict of interest

The authors declared no conflict of interest.

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