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REVIEW

Interactions between gut microbes and host cells control gut barrier and metabolism

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Gut microbes are now considered as key partners involved in human physiology. Data have shown that microbes contribute to regulate energy, lipid, and glucose homeostasis through several mechanisms. Among them, the role of pathogen-associated molecular pattern and bacterial metabolites has been proposed (for example, metabolic endotoxemia and bioactive lipids). This short review, briefly discusses the role of the gut barrier as well as the impact of both the innate immune system and bioactive molecules (for example, endocannabinoids, cytochrome P450 derived arachidonic acids compounds) in the framework of gut microbes and cardiometabolic disorders.

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Nowadays, the gut bacteria are viewed from an ecological perspective. Ecological studies are dedicated to explain how interactions with the environment may influence species distribution over space and time. Thus, considerable efforts are now underway to identify and characterize the vast collection of microorganisms that inhabit our gut (that is, the gut microbiota), and more importantly how they interact with host cells and host metabolism. The human gut microbiota is the result of a continuous co-evolutionary history of interactions, this intimate association has affected both humans and microbes.[1] Consequently, the gut microbiota is considered as a significant companion helping balance important vital functions for the host such as, for example, host defense and immunity, food digestion and nutrient bioavailability that participates in the maintenance of health.[2,3]

THE GUT MICROBIOTA

The gut microbiota consist of as many as 100 trillion microorganisms; therefore, the total number of microbial cells outnumber human cells by one order of magnitude, thus as previously suggested, we are not 100% human, but rather 50% human and 50% microbes[4] (Figure 1). This observation supports the surprising concept that the bacteria living inside our gut contribute to important biological and metabolic functions in humans.

Gut bacteria are members of different dominant *phyla* such as the Bacteroidetes (encompassing Gram-negative genera, for example, *Bacteroides, Prevotella*) and the Firmicutes (encompassing Gram-positive genera, for example, *Anaerostipes, Butyrivibrio, Clostridium*, *Faecalibacterium, Lactobacillus, Ruminococcus* and *Roseburia*), followed by the Actinobacteria (encompassing Gram-positive genera, for example, *Bifidobacterium*), Proteobacteria (encompassing Gram-negative genera, for example, *Escherichia, Helicobacter*) and Verrucomicrobia (encompassing the Gram-negative species *Akkermansia muciniphila*).[5–8] As depicted in Figure 2, each phylum is then subdivided at the class, order, family, genus and species levels (Figure 2). Most gut microbiota data reported to date have focused on changes at the phylum level, but numerous recent studies have also identified the potential impact of one or several specific species that may have an important role in host metabolism.[9–11]

Changes in the composition of the gut microbiota, as well as specific gut microbial communities, have been associated with obesity and type 2 diabetes in both animal and human studies.[12] Several researchers have uncovered a fascinating potential link between gut microbes and metabolism in the context of obesity and cardiometabolic risk factors including insulin resistance, type 2 diabetes, non-alcoholic fatty liver diseases and metabolic inflammation.[13–16] This short review discusses recent evidence

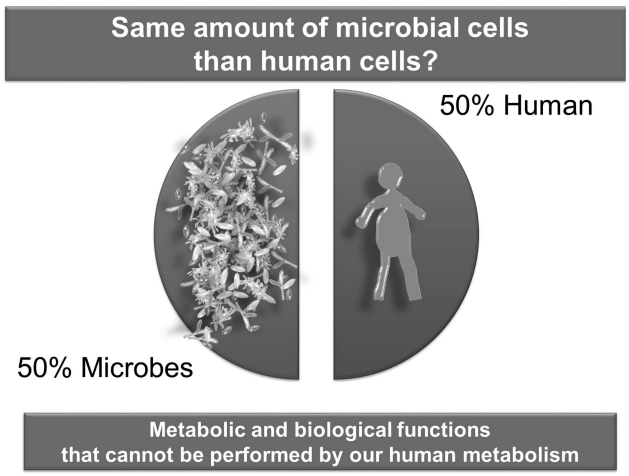

Figure 1. Microbes and host cells. Gut microbiota represents about 100 trillion cells. This microbial census outnumbers our eukaryotic cells by an order of magnitude, thereby supporting the concept that we, as human, are merely 50% microbes and 50% humans in term of cell number.

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Phylum	Class	Order	Family	Genus
Bacteroidetes	Bacteroidia	Bacteroidales	Bacteroidaceae	*Bacteroides*
Bacteroidetes	Bacteroidia	Bacteroidales	Porphyromonadaceae	*Barnesiella*
Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	*Blautia*
Firmicutes	Clostridia	Clostridiales	Ruminococcaceae	*Faecalibacterium*
Firmicutes	Bacilli	Lactobacillales	Lactobacillaceae	*Lactobacillus*
Actinobacteria	Actinobacteridae	Bifidobacteriales	Bifidobacteriaceae	*Bifidobacterium*
Proteobacteria	Gammaproteobacteria	Enterobacteriales	Enterobacteriaceae	*Escherichia*
Verrucomicrobia	Verrucomicrobiae	Verrucomicrobiales	Verrucomicrobiaceae	*Akkermansia*

Figure 2. Few words about bacterial taxonomy. Gut bacteria are members of different dominant phyla, class, order, family, genus and species. In the vertebrate gut, the most numerically dominant are Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria and Verrucomicrobia. Several examples are shown such as *Akkermansia mucniphila* from phyla to species, as well as a table with the major dominant phyla with each time one example of genera that belongs to the phylum.

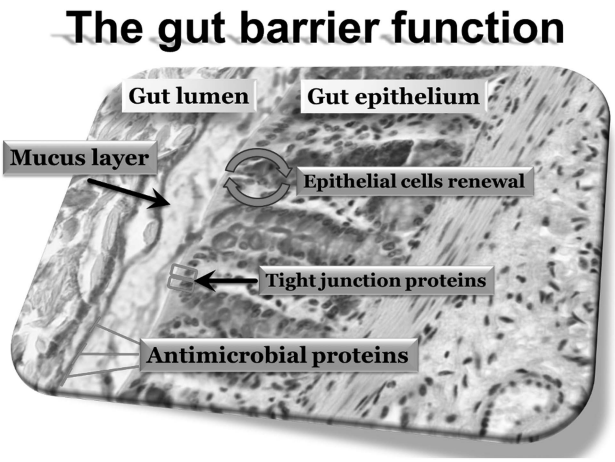

Figure 3. Major components of the gut barrier functions found to be altered during obesity and type 2 diabetes. The gut barrier is enhanced by the presence of a mucus layer and immune factors such as antimicrobial factors and IgA. Other factors such as epithelial tight junction proteins or the expression of protein involved in epithelial cell renewal such as intectin contributes to maintain an efficient gut barrier. All these factors are influenced by the composition and the activity of the gut microbiota.

linking the gut microbiota and obesity, exploring links between gut microbiota composition, gut barrier function and specific members of the innate immune system that may interfere with the onset of metabolic disorders.

THE INNATE IMMUNE SYSTEM AND METABOLISM

Gut bacteria directly interact with host cells through specific molecules called pattern recognition receptors. These pattern recognition receptors recognize molecular patterns of bacteria and other microorganisms (that is, the pathogens-associated molecular pattern). Among the different pattern recognition receptors the most studied are the toll-like receptors (TLRs). Some years ago, Cani and colleagues have described a link between gut microbes and the onset of insulin resistance, inflammation and type 2 diabetes. They discovered that constituent of Gram-negative bacteria triggers low-grade inflammation and alters glucose and lipid metabolism. More precisely, the investigators first discovered in rodents that both diet-induced obesity and genetic obesity was associated with the increase of plasma lipopolysaccharides, defined as metabolic endotoxemia.[13] Alongside this finding, similar observations have been demonstrated in humans.[17–19]

In obese and type 2 diabetic rodents, metabolic endotoxemia is also associated with an altered gut microbiota composition, as well as an increased intestinal permeability that clearly contributes to the development of metabolic endotoxemia.[13,20,21] Although this link is still a matter of debate in humans, several novel studies have described increased gut permeability in obese and type 2 diabetic subjects.[22–27]

Because the intestinal epithelium is adjacent to the gut bacteria, interactions between gut microbes and host tissues are permanent, however, the gut barrier function is a complex system controlled through multifaceted mechanisms. Over the last decade, the role of the gut barrier function has been highlighted and numerous studies have discovered that to maintain an adequate gut barrier requires finely tuned mechanisms that are dependent on the diet and the microbial composition.

As an example, the gut barrier is enhanced by the presence of a mucus layer and immune factors that are produced by the host (Figure 3). Together, the mucus layer with antimicrobial factors from the innate immune system (for example, α-defensins, lysozyme C, phospholipases and C-type lectin, primarily regenerating islet-derived 3-gamma, Reg3γ) constitute an efficient barrier that contribute to segregate microbes from the intestinal epithelial cells.[28–30] Other effectors, this time from the adaptive immune system, are also secreted into the intestinal lumen (that is, immunoglobulin A (IgA)) and are able to restrict bacterial penetration into the host mucus and mucosal tissue.[31] It has been demonstrated that these immune factors allow the host to control its interactions with the gut microbiota and shape its microbial communities during diet-induced obesity, diabetes and metabolic inflammation (for review).[12,21] At the level of the epithelial cells, tight junction proteins contribute to maintain an efficient gut barrier.[20,32] Everard and colleagues discovered that the expression of intectin (a small intestine-specific glycosylphosphatidylinositol-anchored protein)[33] was increased by prebiotic treatment under both control and high-fat diet feeding.[34] Importantly, intectin is involved in the turnover of intestinal mucosa.[33] Thus, they suggest that prebiotic feeding increases epithelial cell turnover thereby contributing to reinforce gut barrier function[34–36] (Figure 3).

The same group of researchers discovered that inactivating, specifically in intestinal epithelial cells or in the hepatocyte, a protein of the innate immune system, which is involved in the signaling of most of the TLRs (that is, MyD88 (myeloid differentiation primary response gene 88)), modifies energy, glucose and lipid metabolism.[37,38] Interestingly, the role of MyD88 and its implication in the onset of diseases associated with obesity is clearly organ and cell specific. More precisely, they found that modifying the response of the immune system by deactivating this protein, MyD88, in the intestinal epithelial cells delays the development of type 2 diabetes induced by a high-fat diet, reduces the development of fat mass, reduces the deleterious inflammation observed during obesity and reinforces the gut barrier thereby preventing the leakage of unsuitable bacterial compounds from the intestine to the organism. More strikingly, when deleting MyD88 in the hepatocytes, mice do not display any changes in fat mass and body weight gain when consuming a high-fat diet, however, they develop insulin resistance, hepatic steatosis, inflammation and diabetes. Interestingly, Duparc *et al.*

found a profound reduction in the expression of several cytochromes P450. Among them, numerous Cyp450 have been shown to contribute to the synthesis of bioactive lipids such as the epoxyeicosatrienoic acids (EETs), hydroxyepoxyeicosatrienoic (HETEs) and dihydroxyepoxyeicosatrienoic (DHETs) acids family.[37] It is important to note that several of these lipids have been shown to act as insulin sensitizers, and to reduce hepatic steatosis and inflammation. Therefore, thanks to these animal models, they discovered that the innate immune system deeply contribute to the regulation of metabolism by mechanisms involving specific bioactive lipids (for example, endocannabinoids and related compounds, DHETs, HETEs, EETs) and change in the gut microbiota composition.[37,38]

THE ENDOCANNABINOID SYSTEM, GUT MICROBIOTA AND GUT BARRIER

Among the metabolic system involved in the regulation of this barrier, Cani *et al.* found that the endocannabinoid (eCB) system has a major role (for review, Cani *et al.)*.[21] This system is composed of different bioactive lipids that belong to specific *N*-acylethanolamines and acylglycerol families. The best characterized are AEA (anandamide or *N*-arachidonoylethanolamine) and 2-AG (2-arachidonoylglycerol). Both eCBs activate G-coupled cannabinoid receptors (CBR), namely CB1R and CB2R. Muccioli *et al.* discovered that during obesity and diabetes, the intestinal eCB system is altered with an increased abundance of AEA that triggers gut permeability via CB1R-dependent mechanisms.[39] Interestingly, they have associated this modification of the eCB system tone with gut microbiota.[39] More recently, it has been shown that other bioactive lipids related to the eCB system were positively associated with an improved gut barrier function and reduced metabolic endotoxemia (for review).[21] More explicitly, *Akkermansia muciniphila* treatment increased the intestinal levels of 2-oleoylglycerol (2-OG), 2-arachidonoylglycerol (2-AG) and 2-palmitoylglycerol (2-PG).[10] It has also been observed that in the absence of intestinal epithelial cells MyD88, AEA was decreased whereas both 2-OG and 2-AG were increased during high-fat diet feeding.[38] Thus, these two studies clearly show that specific gut microbes and the innate immune system are involved in the regulation of intestinal eCB system tone. Remarkably, these bioactive lipids (that is, 2-AG, 2-PG and 2-OG) have been described as putative anti-inflammatory molecules (that is, reduced metabolic endotoxemia and inflammation[40,41]) or ligands for receptors involved in the secretion of gut peptides such as glucagon-like peptide-1 (GLP-1) and glucagon-like peptide-2 (GLP-2) released from intestinal L-cells,[20,42] two peptides implicated in the control of glucose homeostasis and gut barrier function, respectively. The link between eCB and gut barrier is not limited to the intestinal tissue since Geurts *et al.* recently discovered that in the absence of a functional synthesis of *N*-acylethanolamines in the adipose tissue mice develop spontaneous obesity, adipose tissue inflammation, insulin resistance, glucose intolerance and altered lipid metabolism. Again, this phenotype was partly mediated by a profound alteration of gut microbiota composition and by an alteration in the adipose tissue browning and beiging programme.[43] However, the mechanisms linking bioactive lipids produced by the adipose tissue and gut barrier function remain elusive. Taken together, all these data highlight a strong connection between gut microbes, bioactive lipids, inflammation and metabolic disturbances.

CONCLUSION

In conclusion, the influence of gut microbiota on energy metabolism is multifactorial, different targets involving immunity, bioactive lipids production or bacterial metabolites have been highlighted in recent studies and clearly show the role of the gut barrier in the development of metabolic inflammation during obesity and type 2 diabetes. Finally, these numerous pre-clinical studies provide a rationale for investigating such specific questions in clinical interventions.

CONFLICT OF INTEREST

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