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Revisión

Gut microbiota and the development of obesity

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Abstract

Introduction: **Advances in tools for molecular investigations have allowed deeper understanding of how microbes can influence host physiology. A very interesting field of research that has gained attention recently is the possible role of gut microbiota in the development of obesity and metabolic disorders.**

Objective: **The aim of this review is to discuss mechanisms that explain the influence of gut microbiota on host metabolism.**

Results and discussion: **The gut microbiota is important for normal physiology of the host. However, differences in their composition may have different impacts on host metabolism. It has been shown that obese and lean subjects present different microbiota composition profile. These differences in microbiota composition may contribute to weight imbalance and impaired metabolism. The evidences from animal models suggest that it is possible that the microbiota of obese subjects has higher capacity to harvest energy from the diet providing substrates that can activate lipogenic pathways. In addition, microorganisms can also influence the activity of lipoprotein lipase interfering in the accumulation of triglycerides in the adipose tissue. The interaction of gut microbiota with the endocannabinoid system provides a route through which intestinal permeability can be altered. Increased intestinal permeability allows the entrance of endotoxins to the circulation, which are related to the induction of inflammation and insulin resistance in mice. The impact of the proposed mechanisms for humans still needs further investigations. However, the fact that gut microbiota can be modulated through dietary components highlights the importance to study how fatty acids, carbohydrates, micronutrients, prebiotics, and probiotics can influence gut microbiota composition and the management of obesity. Gut microbiota seems to be an important and promising target in the prevention and treatment of obesity and its related metabolic disturbances in future studies and in clinical practice.**

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Key words: *Gut microbiota. Obesity. Intestinal permeability. Inflammation. Endocannabinoid system.*

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LA MICROBIOTA INTESTINAL Y EL DESARROLLO DE LA OBESIDAD

Resumen

Introducción: **Los avances en herramientas para la investigación molecular han permitido una mayor comprensión de cómo los microbios pueden influir en la fisiología del huésped. Un campo de investigación muy interesante que se ha llamado la atención recientemente es el posible papel de la microbiota intestinal en el desarrollo de la obesidad y de los trastornos metabólicos.**

Objetivos: **El objetivo de esta revisión es discutir los mecanismos que explican la influencia de la microbiota intestinal en el metabolismo del huésped.**

Resultados y discusión: **La microbiota intestinal es importante para la fisiología normal del huésped. Sin embargo, las diferencias en su composición pueden tener efectos diferentes sobre el metabolismo del huésped. Se ha demostrado que las personas obesas y delgadas tienen un perfil de composición diferente de la microbiota. Estas diferencias en la composición de la microbiota pueden contribuir a un desequilibrio de peso y alteración del metabolismo. Las evidencias de los modelos animales sugieren que es posible que la microbiota de los sujetos obesos tienen una mayor capacidad para captar energía de la dieta proporcionando sustratos que pueden activar las vías lipogénicas. Además, los microorganismos también pueden influir en la actividad de la lipoproteína lipasa lo que interfiere con la acumulación de triglicéridos en el tejido adiposo. La interacción de la microbiota intestinal con el sistema endocannabinoide proporciona una ruta a través del cual puede alterar la permeabilidad intestinal. Aumento de la permeabilidad intestinal permite la entrada de la circulación de endotoxinas, que están relacionados con la inducción de la inflamación y la resistencia a la insulina en los ratones. El impacto de los mecanismos propuestos para los seres humanos todavía necesita uma mayor investigación. Sin embargo, el hecho de que la microbiota intestinal puede ser modulada por componentes de la dieta refuerza la importancia de estudiar cómo los ácidos grasos, hidratos de carbono, micronutrientes, prebióticos y probióticos pueden influir en la composición de la microbiota intestinal y el desarrollo de la obesidad. La microbiota intestinal parece ser un objetivo importante y prometedor en la prevención y el tratamiento de la obesidad y trastornos metabólicos relacionados en la investigación futura y la práctica clínica.**

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Palabras clave: *Microbiota intestinal. Obesidad. Permeabilidad intestinal. Inflamación. Sistema endocanabinoide.*

Abbreviations

2-AG: Glycerol 2-arachidonoyl.
AEA: N-arachidonyl ethanolamine.
CM: Chylomicron.
DAG: Sn-1-diacylglycerol lipase selective.
eCB: Endocannabinoid system.
ERK: Extracellular signal-related kinase.
FAAH: Fatty acid amide hydrolase.
FIAF: Fasting-induced adipose factor.
GPR: G protein-coupled receptor.
IFN: Interferon.
IκB: inhibitor of kappa B.
IKK: IkB kinase.
IL: Interleukin.
iNOS: Inducible nitric oxide synthase.
IRAK: Interleukin-1 receptor-associated kinase.
JNK: c-Jun NH_2-terminal kinase.
LBP: Lipopolysaccharide-binding protein.
LPL: Lipoprotein lipase.
LPS: Lipopolysaccharides.
PYY: Peptide YY.
MAPK: Mitogen-activated protein kinase.
MCP1: Monocyte chemotactic protein-1.
MD-2: Myeloid differentiation protein-2.
MGL: Monoacylglycerol lipase.
MyD88: Myeloid differentiation primary response gene (88).
NAPE-PLD: N-acilfosfatidiletanolamida selective phospholipase.
NF-κB: Nuclear factor kappa B.
NIK: NF-κB-inducing kinase.
SCFA: Short chain fatty acids.
TLR: Toll-like receptor.
TNF: Tumor necrosis factor.
TRAF6: TNF receptor-associated factor 6.

Introduction

Obesity is one of the most relevant public health concerns due to its high prevalence worldwide and to its contribution for high morbidity and mortality rates. Metabolic diseases such as type 2 diabetes mellitus, fatty liver and cardiovascular diseases are associated with obesity[1,2] impacting on public health costs.

Traditionally, the interaction between genetic and environmental factors, mainly the diet (high energy intake) and physical activity level (low energy expenditure), are considered the main contributors for the development of obesity. However, gut microbiota has emerged as a possible important endogenous factor that influences obesity epidemic.[3]

The elucidation of the participation of gut microbiota on host metabolism has been possible due to advances in the use of culture-independent molecular methods based on 16S ribosomal-RNA encoding gene analysis. The limited knowledge on microbial composition within the gastrointestinal tract is expanding not only in terms of which microorganisms are present, but also their functionality (microbiome).[4] This will contribute to deepen the understanding of the physiopathological role of gut microbiota in obesity development. Thus, the aim of this review is to discuss mechanisms that have been proposed to explain how gut microbiota contributes to weight gain.

Methods

Medline/PubMed, Scielo and Lilacs were searched using the following terms: obesity, chronic diseases, intestinal or gut microbiota, lipopolysaccharide, endotoxins, metabolic endotoxemia, inflammation, intestinal or gut permeability, endocannabinoid system, and inflammatory mediators. For data searches, the terms in English, Spanish and Portuguese were used either alone or in association. Review and original articles were selected according to their titles and abstracts. Each selected manuscript was then read critically.

The gastrointestinal microbiota

The gastrointestinal tract starts to be colonized during the delivery of the baby. During the first two years of life de microbiota is unstable and less diverse than in the adulthood, when the complexity and diversity is higher.[5] Many external factors influence the composition of the microbiota, especially the diet, the hygiene conditions and the use of antibiotics.[6]

The distribution of microorganisms throughout the gastrointestinal tract is not homogenous. The stressful environment (gastric juice, bile, pancreatic juice, peristalsis) in the stomach and small intestine limits bacterial growth and the number of microorganisms. The ileum is a site of transition between the scarce bacterial population of jejunum and the dense and diverse population of colon. The colon provides optimal conditions for the growth of microorganisms due to absence of digestive secretions, slow peristalsis and abundant nutritional supply.[7,8]

The gut microbiota plays different roles that are important for the host. They exert a trophic effect in the intestinal epithelium, favoring the development of the microvilli, which in turn favors the absorption of nutrients.[9] The influence of microbiota in innate and adaptive immune system maturation contributes to systemic and local immune homeostasis and immune tolerance for a variety of antigens. The modulation of the immune system activity can influence the intestinal barrier function. The capacity to break down non-digested dietary molecules into metabolites such as short chain fatty acids (SCFS) and to synthesize vitamins demonstrates their importance to human nutrition.[8]

The roles played by the microbiota are related to the microbiome within the gut, which contains 150 times more genes than the human genome.[10,11] The micro-

biome of obese animals and subjects was showed to be enriched with sequences of enzymes related to carbohydrate metabolism.[12,13] It is possible that this enrichment can affect host metabolism, favoring the occurence of lipogenesis. In fact, a distinct composition of gut microbiota in obesity has been detected in animals and humans, suggesting that these differences may influence adiposity.[14-16]

The variability of methods and of the profile of subjects between studies that aim to analyze the microbiota explains why there is still no consensus in the literature about which bacterial groups are increased or reduced in the gut of obese in comparison to lean individuals. For example, according to Ley et al.[17] obese subjects present lower proportion of *Bacteroidetes* in comparison to lean subjects. In contrary, Schwiertz et al.[18] reported higher proportion of *Bacteroidetes* in overweight and obese subjects. A review by Lyra et al.[14] provides a clear description of controversial results of studies on this topic.

It is important to highlight that the majority of studies on gut microbiota so far are based on fecal samples analyses, which does not reflect the microbiota composition from small intestine and even from the colon.[19] This is an indication that we are just beginning to understand the top of the iceberg.

Influence of gut microbiota on obesity development

Gordon and co-workers were the pioneers in investigating the role of gut microbiota as an environmental factor that influences body composition. They verified that mice conventionally raised had 42% more body fat than germ-free mice even though their food intake was lower. Then, they verified that the colonization of germ-free mice with microbiota from conventionally raised animals produced a 60% increase in body fat, which was associated with insulin resistance.[16] These initial findings have stimulated the conductance of new researches in this area.

The exact mechanism through which gut microbiota contributes to obesity is still unclear. However, it has been suggested that the main routes under influence of gut microbiota that could contribute to obesity development are provision of extra calories, increased lipoprotein lipase (LPL) activity, lipogenesis, increased intestinal permeability, endotoxemia and endocannabinoid (eCB) system.[20]

Gut microbiota can convert undigested carbohydrate into SCFA. The most important SCFA produced are acetate, propionate and butyrate. In animal models, it has been suggested that the higher production of SCFA reflects the increased capacity for dietary energy harvest by the ob/ob microbiome. These SCFA can provide additional calories when they are oxidized by the host, favoring the higher weight and fat gain observed in these animals.[13,21] In addition, the binding of SCFA to G protein-coupled receptor (GPR) in the intestine induces the secretion of the hormone peptide YY (PYY).[22] This hormone reduces intestinal transit time, increasing the time for nutrient absorption from the intestinal lumen.[21] In fact, obese and overweight subjects presented higher concentration of SCFA in their feces in comparison to lean individuals.[18]

However, it may be possible that the additional calories provided to the host by the fermentation of undigested dietary molecules by the microbiota are not sufficient to induce significant changes in weight.[4,23] One of the arguments to support this hypothesis is that the consumption of a diet rich in fiber could increase SCFA production, which usually help to reduce weigh and adipose tissue.[24-26]

The LPL activity influences the accumulation of triglycerides in the adipose tissue. The microbiota can affect the activity of this enzyme by the influence on the expression of the protein fasting-induced adipose factor (FIAF). In the absence of microbiota (germ-free mice) it is observed higher expression of FIAF.[16] On the other hand, the conventionalization of the germ-free animal causes inhibition of the expression of the FIAF and also stimulates body fat gain. It is suggested that FIAF is a circulating inhibitor of LPL activity. Thus, the inhibition of FIAF expression by the presence of microbiota allows higher activity of LPL and accumulation of triglycerides in adipocytes.[16]

However, it cannot be generalized that germ-free animals are protected against obesity. Fleissner et al.[27] showed that germ-free animals are not protected from weight gain induced by a high-fat diet, because the components of the diet rather than the macronutrient composition determine the extent of protection. Although different high-fat diets resulted in increased intestinal mRNA expression of FIAF in germ-free animals, no major changes were observed for the circulating levels compared with conventional mice. Based on the results of this study, the intestinal production of FIAF might not play a causal role in gut microbiota-mediated effects on fat storage.

The hypertrophy of adipocytes due to increased triglycerides uptake to these cells has been considered one of the main causes of the induction of chronic inflammatory state by the recruitment of macrophages within the adipose tissue. This impairs further deposition of triglycerides in the adipose tissue, starting an ectopic accumulation of fat in other organs that will lead to the development of insulin resistance.[28] It is known that obesity and insulin resistance share a low-grade chronic inflammatory state.[29]

Lipopolysaccharides (LPS) are external components of the cell membrane of gram-negative bacteria and they have the property of inducing inflammation. The intestinal lumen is a reservoir of LPS. LPS are also called endotoxins since they can activate immune cells and induce chronic inflammation in low doses. The access of this molecule from the intestinal lumen to the circulation may occur through two routes: direct diffusion through increased intestinal permeability (due to

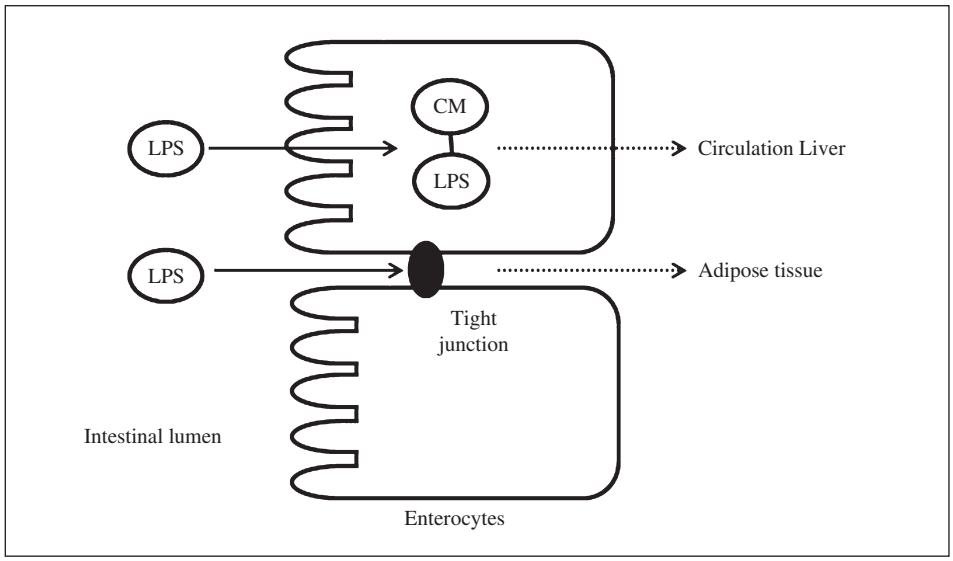

Fig. 1.—Transport of LPS through the intestinal epithelium. 1) Direct diffusion due to increased intestinal permeability (loosening of paracellular space); 2) Absorption through the incorporation of LPS into the chylomicron structure. Inside enterocyte, LPS is transported to the golgi apparatus where chylomicrons are freshly synthesized. CM: chylomicron; LPS: lipopolysaccharide.[30,31]

the loosening of the intestinal paracellular space between intestinal cells) or through the absorption and incorporation of LPS into chylomicron structure.[30] The increase in the circulatory levels of LPS is denominated endotoxemia. The target tissues for LPS are the adipose tissue, liver and endothelium (fig. 1) where they can interact with specific receptors (toll like receptors, especially TLR-4) and induce the secretion of inflammatory cytokines (fig. 2). As germ-free animals are not exposed to elevated levels of LPS, their resistance to develop obesity may be partially related to a reduced stimulation of inflammatory pathways. It is important to remind that gut microbiota is also a source of many other inflammatory molecules such as peptideoglycan, lipoproteins, flagelin, which can also bind to TLR receptors or other pattern recognition receptors.[30]

The diet can contribute to the occurrence of endotoxemia and consequently induce low-intensity chronic inflammation.[36-38] High-fat intake can increase intestinal permeability through inhibition of the expression of proteins from the tight junctions (zonulin and occludin). The changes in intestinal permeability induced by the diet are also accompanied by changes in gut microbiota composition,[39] suggesting that microorganisms might be directly related to modulation of intestinal permeability. This role is supported by the results of studies where the administration of *Bifidobaterium infantis* reduced colonic permeability in mice. Even in mice deficient in the anti-inflammatory cytokine IL-10, the supplementation with probiotic attenuated inflammation. The addition of *B infantis* to a cell culture of human epithelial cells (T84) increased the transepithelial resistance of the membrane and stimulated higher expression of the proteins zonulin-1 and occludin. In addition, this probiotic prevented the reduction of transepithelial resistance when the inflammatory molecules tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) were added to the medium.[40]

The interaction of gut microbiota with the eCB system provides an endogenous signaling route that controls the intestinal permeability. Muccioli et al.[41] hypothesize that adipogenesis is regulated by gut microbiota through LPS and eCB system.

The eCB system is very important in the context of obesity since it modulates food intake by the regulation of the expression of anorexigenic and orexigenic mediators in different areas of the hypothalamus.[41,42] This system is composed by endogenous lipids (endocannabinoids) and cannabinoids receptors (CB_1 and CB_2). Both receptors CB_1 and CB_2 are coupled with G protein. When activated, they inhibit adenylate cyclase and the production of cAMP, attenuating the protein kinase A pathway. CB_1 and CB_2 receptors activation stimulates second messenger signalling pathways involving MAPK, ERK and NF-κB. Through these latter actions on second messenger signalling, CB_1 and CB_2 activation modulates gene expression.[41]

The endogenous lipids capable of activating CB_1 and CB_2 are N-arachidonyl ethanolamine (anadamide, AEA) and glycerol 2-arachidonoyl (2-AG). AEA and 2-AG are largely present in tissues and their concentrations are regulated by an equilibrium between synthesis and inactivation processes. The majority of endocannabinoids are derived from polyunsaturated fatty acids, more specifically arachidonic acid. AEA and 2-AG are respectively synthesized by the enzymes N-acilfosfatidiletanolamida selective phospholipase D (NAPE-PLD) and sn-1-diacylglycerol lipase selective (DAG lipase), through pathways dependent on phospholipids. The endocannabinoids AEA and 2-AG are rapidly metabolized and hydrolyzed into inactive compounds by fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MGL), respectively.[41] Obese mice present elevated concentrations of AEA, higher expression of NAPE-PLD and CB_1, and lower expression of FAAH in the adipose tissue.[41,42] This suggests

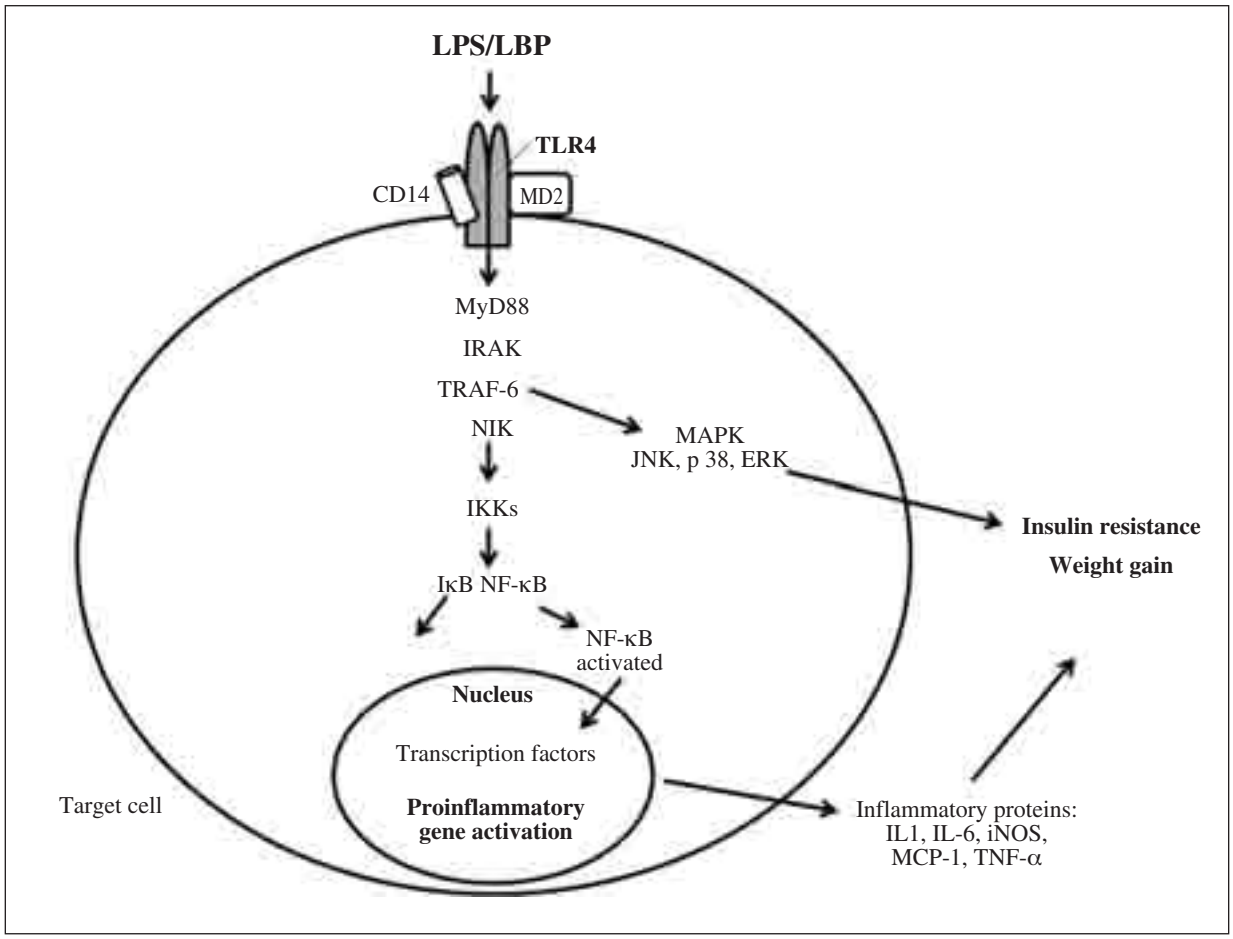

Fig. 2.—Signalling of LPS via NF- B and MAPK. The lipid A portion of LPS is responsible for the endotoxic activity. It binds to the TLR-4 present in the plasma membranes of immune cells (monocytes, macrophages, Kupffer cells and preadipocytes) and non-immune cells (adipocytes, hepatocytes and endothelial cells). LBP, CD14 and MD-2 are adaptor molecules to assist the recognition of LPS by TLR-4. After interaction with LPS, TLR-4 dimerizes and undergoes conformational changes that allow the recruitment of the adaptors molecules to the intracellular domain: MyD88 protein, IRAK, TRAF6, NIK. This culminates in the phosphorylation of the complex IKK, which promotes the degradation of NF-κB inhibitors. This allows the translocation of NF-κB to the nucleus and the posterior expression of inflammatory proteins. The activation of TLR-4, through LPS, can trigger various signaling pathways, and the main ones are: NF-κB and MAPK. MAPK signaling pathway includes the extracellular signal-regulated kinases such as JNK, p38 MAPK and ERK. JNK, p38 and ERK can induce insulin resistance through different mechanisms. ERK: extracellular signal-related kinase; IL: interleukin; IκB: inhibitor of kappa B; IKK: IkB kinase; iNOS: inducible nitric oxide synthase; IRAK: Interleukin-1 receptor-associated kinase; JNK: c-Jun NH2-terminal kinase; LBP: Lipopolysaccharide binding protein; LPS: lipopolysaccharide; MAPK: mitogen-activated protein kinase; MCP-1: monocyte chemotactic protein-1; MD-2: myeloid differentiation protein-2; MyD88: Myeloid differentiation primary response gene (88); NF-κB: nuclear factor kappa B; NIK: NF-κB-inducing kinase; TLR: toll-like receptor; TNF: tumor necrosis factor; TRAF6: TNF receptor-associated factor 6.[31-35]

that the obese subjects have a higher tonus of eCB activation, and that interventions capable of reducing this up-regulated activation may be beneficial.

The expression of eCB system is modified by feeding status. Under high-fat diet and in overweight animal models, it appears that this signaling pathway is involved in the development and/or maintenance of obesity.[43] The use of prebiotic has been shown to modulate negative effects of high-fat diets.[44] The modulation of gut microbiota after prebiotic ingestion decreased plasma LPS levels, decreased CB_1 expression in adipose tissue and fat mass, increased the expression of FAAH and MGL,[41] showing the importance of this pathway in controlling adipogenesis.

It is hypothesized that the gut microbiota stimulates the eCB system in the intestine, increasing intestinal permeability and the movement of microbiota-derived LPS out of the lumen into the circulatory system. This endotoxemia further compromises the tight junction integrity, creating a vicious-cycle where more LPS enters into the circulation. Adipogenesis is then stimulated by LPS-induced activation of the eCB system.[41]

Modulation of gut microbiota

The importance of gut microbiota in the maintenance of health has been receiving more attention worldwide.[45-49] The homeostasis of gut microbiota

depends on the characteristics of the host (age, gender, genetic factors) and the environment (stress, drugs, toxic agents, infections, diseases). However, the influence of diet is also evident.[1] The conductance of future studies aiming to understand how changes in diet modulate gut microbiota composition is of great interest to help menu plannings that simulate the achievement of a favorable microbiota.

Weight loss promotes changes in gut microbiota composition.[27,44,50,51] The intake of specific dietary components (fatty acids, carbohydrates, micronutrients, prebiotics, probiotics) can result in changes in the composition of gut microbiota and modulate the expression of genes in the host, especially in organs as intestine, muscle, liver and adipose tissue.[1,52]

The relevance of the use of prebiotics and probiotcs in human's obesity treatment is supported by few results obtained in interventional studies. However, animal models show potential beneficial effects. For example, genetically obese mice (ob/ob) and mice fed with high-fat diet were given the prebiotic oligofructose. After the intervention it was observed a reduction in the circulatory levels of IL-18 and IL-1β.[53] These cytokines are considered as gut microbial related immunologic factors that drive the obesity development.[54]

Amongst probiotics, *Lactobacillus plantaraum* shows a potential to modulate negative effects of high-fat diets. High dietary fat intake increased body weight gain, white adipose tissue weight, mean adipocyte size and serum total cholesterol and leptin concentrations, and decreased serum adiponectin concentration in mice. The administration of *L. plantaraum* to mice significantly reduced the mean adipocyte size and tended to reduce the white adipose tissue weight and serum total cholesterol and leptin concentrations as compared with the vehicle-administered mice.[55] Thus, it is suggested that gut microbiota is an important and promising target for the treatment of obesity and its related metabolic disturbances.

Conclusions

It is increasingly evident that the intestinal microbiota is involved in the pathogenesis of obesity. Various mechanisms have been proposed to explain this role of microbiota, especially in animal models. The magnitude of this influence in humans is still unclear and many questions remain without answers. More studies are needed to establish the real impact of microbiota in the development of obesity.

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