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Obesity: More Than an Inflammatory, an Infectious Disease?

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Much is discussed if obesity or diet components modify the "healthy" microbiota or if microbiota modifications trigger events that culminate in obesity. This association is probably reciprocal, and inflammation has crucial participation on it. We will discuss recent studies showing gut microbiome as an obesogenic factor and the mechanisms linked to the associated of diet, microbiota, and low-grade inflammation.

CAN THE GUT MICROBIOTA REGULATE BODY WEIGHT?

Obesity is a growing epidemy, despite the efforts to contain it. The inflammation generated by the adipocyte hypertrophy and hyperplasia initiates crosstalk between adipocyte and resident macrophage (M2) in white adipose tissue (WAT). Once activated, both adipocyte and activated macrophage (M1) release several adipokines that trigger the infiltration of other immune cells such as neutrophils, CD8+ and CD4+ T cells (1). Tissue-resident innate lymphocytes also play an important role in the homeostasis of WAT and, consequently, in obesity. Although this resident lymphocyte plays regulatory and anti-inflammatory properties in non-obese individuals, obesity promotes changes in the profile of these cells (2). Invariant Natural Killer cells (iNKT) and mucosal-associated invariant T cells (MAIT) are important examples. The frequency of iNKT is reduced in WAT in obesity and is inversely related to the degree of obesity, insulin resistance and fasting blood glucose, suggesting that these cells play a role against metabolic disorders associated with obesity (1, 2). MAIT cells also present reduced frequency and change of phenotype in WAT in obesity, reducing IL-10 synthesis and gamma interferon (IFNγ) and increasing IL-17 production (1, 2) and can play an important role in the progression of inflammation (3).

Adipocytes also produce macrophage colony-stimulating factor (M-CSF-1), causing an increased influx of monocytes from bone marrow-derived precursors and regulating macrophage differentiation and survival (4, 5). The expanded WAT also secrets pro-inflammatory and prothrombotic factors such as interleukin (IL)-1β, IL-6, tumoral necrosis factor (TNF), monocytes and macrophages chemoattractant protein (MCP-1/CCL2), C-reactive protein (CRP), tissue factor and factor VII, plasminogen activator inhibitor type-1 (PAI-1) (6). This pro-inflammatory, prothrombotic environment contributes to the onset of obesity-related complications such as metabolic syndrome, insulin resistance, hypertension, and systemic sterile inflammation.

One of the first studies linking obesity and microbiota was conducted by Ley et al. (7), showing that obesity is associated with a specific microbiota profile. The gut microbiota of healthy individuals is mostly composed of *Firmicutes* (70%) and the *Bacteroidetes* (30%). Other minor phyla are *Actinobacteria, Proteobacteria*, *Fusobacteria,* and *Verrucomicrobia* (8). The genetically obese ob/ob mice have in their microbiota 50% fewer *Bacterioidetes* and a higher proportion

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of *Firmicutes* when compared to lean mice. This altered ratio between *Firmicutes* and *Bacteroidetes* (F/B ratio) has also been described in obese individuals (9). Nonetheless, obesity in adulthood is influenced by several factors besides the different profiles of gut microbiota and, until now, studies have not found enough consistency to point out specific obesogenic bacteria (10). However, preclinical studies revealed that the obesogenic microbiota profile could be transmitted from twins discordant for obesity to germ-free (GF) mice. When the fecal microbiota of the obese twin is transplanted to GF mice, the mice eventually become obese, the same occurring with the transplantation of microbiota from the lean twin to GF mice. Moreover, obesity was prevented when mice carrying the obese twin's microbiota were kept in the same cage with mice carrying the lean twin's microbiota (11).

SINCE CHANGES IN MICROBIOTA PREDISPOSE TO OBESITY, WHAT DETERMINE THE TYPES OF BACTERIA THAT INHABIT THE GUT?

The influence of microbiota on obesity development and low-grade inflammation seems to occur even before or immediately after birth. The gut-associated lymphoid tissues (GALT) are formed during embryogenesis and become mature during the microbial colonization, after birth. Bacterial antigens were recognized by the intestinal epithelium via pattern recognition receptors (PRR), such as Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain 1 (NOD-1) (12, 13). Changes in the microbial composition, which occur in the presence of obesity, disrupt the barrier integrity promoted by GALT, increase the intestinal permeability, favor bacterial translocation that triggers the inflammatory process (14).

Maternal obesity, caesarian section (CS), infections, and antibiotic utilization were described as factors influencing obesity (15) (**Figure 1**). Antibiotic therapy in the perinatal period is associated with intestinal microbiota disruption and metabolic changes sufficiently strong to affect body composition in late childhood (16, 17). Indeed, babies from mothers receiving antibiotics during the last gestational trimester presented an 84% higher risk of obesity (16). Moreover, CS is associated with the reduction in *Bacteroidetes* abundance and microbiota diversity in the first 2 years of life. Systemic levels of CXCL10 and CXCL11 chemokines were also reduced in children born by CS (17). Young adults born by CS have a higher risk for increased central and peripheral adiposity than those born by vaginal delivery (18). These associations are stronger in children whose mothers were obese compared to children of non-obese mothers (19).

WHAT IS THE PARTICIPATION OF THE INFLAMMATION IN THIS SCENARIO?

Previous studies clarified the crosstalk between the immune system and microbiota in obesity (20). The IgA is produced by intestinal B cells after interaction with T follicular helper cells (TFH) and secreted into the gut lumen covering bacteria membrane and reducing gut colonization (20, 21). Although bacteria-IgA binding participates in hosting defense against pathogens, IgA can also regulate the gene expression of

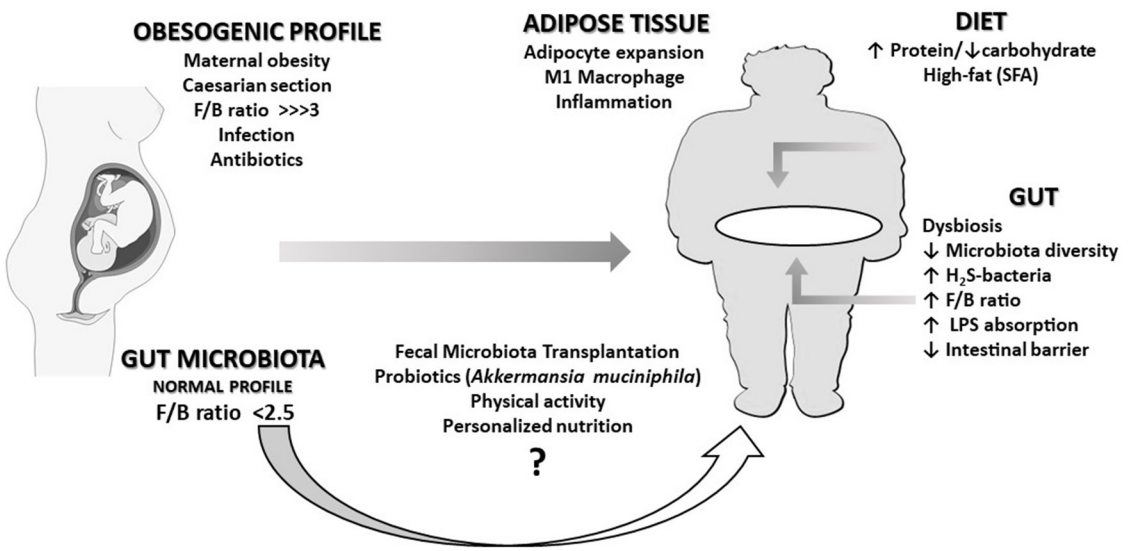

FIGURE 1 | An overview of the relationships described in this opinion paper. An obesogenic profile (characterized by a very high *Firmicutes*/*Bacteroidetes* ratio, F/B) can be caused in the fetus by conditions such as maternal obesity, caesarian section, infections, or antibiotics treatments during pregnancy. The immune and pro-inflammatory response caused by intestinal dysbiosis over life can eventually lead the individual to obesity in adulthood. This scenario can be worsened by the chronic intake of a high-fat diet, responsible for the increase of bacteria producing hydrogen disulfide (H_2S-bacteria) and pathogenic bacterial lipopolysaccharide (LPS) translocation. A healthy dietary pattern and physical activity may contribute to revert dysbiosis. Although probiotics and fecal microbiota transplantation could eventually improve this condition, presently, there is not enough clinical evidence supporting the adoption of such intervention.

some gut bacteria population and intestinal cells. It has been proposed that IgA promotes colonization of a healthy microbiota reducing dysbiosis (22). It was tested in MyD88$^{-/-}$ mice that develop obesity faster than controls and are defective in TFH and IgA (23). The expansion of WAT in MyD88$^{-/-}$ is associated with the increase of *Desulfovibrio* and the loss of *Clostridia* populations. When mice were treated with antibiotics or replacement of *Clostridia*, the weight gain was reduced, confirming a cause-effect interaction (20). It suggests that by regulating IgA production, TFH cells maintain the intestinal *Clostridia* population, reducing fatty acids (FA) absorption and protecting the host against obesity.

Previous studies addressed the interaction of microbiota, and pro-inflammatory markers (24) showed that *Bifidobacterium, Faecalibacterium*, *Ruminococcus,* and *Prevotella* genus abundances were inversely associated with blood levels of CRP or pro-inflammatory cytokines (14, 25–29). Besides the abundance of a specific genus, gut microbial diversity has also been related to obesity. Individuals with low microbial diversity presented higher blood leukocyte count and CRP level that is related to higher triglyceridemia and lower high-density lipoprotein (HDL) levels, insulin resistance and increased risk of atherosclerosis-associated disorders (30).

The decrease in commensal bacteria levels and diversity (dysbiosis) permit the establishment of foreign bacteria, increasing the lipopolysaccharide (LPS) concentration in the gut lumen (**Figure 1**). LPS can reach systemic circulation by crossing the intestinal mucosa through altered tight junctional complex or linked to dietary fat incorporated into chylomicrons. In the plasma, LPS is transported bound to lipoproteins. Initially, LPS is transported in chylomicrons and then distributed to the other lipoproteins, mainly HDL (31). LPS increases the scavenger receptor binding to lipoproteins, as well as the endocytoses in endothelium and adipocytes. The expanded adipocytes and activated macrophages internalize LPS-rich lipoproteins (32), perpetuating the expansion and inflammation of the WAT. Indeed, LPS triggers the innate immune response on macrophages and adipocytes via TLR4 signaling, resulting in nuclear factor-kappa B (NF-κB) release and pro-inflammatory cytokine production (14, 33).

HOW CAN THE DIET FAVOR THE OBESOGENIC MICROBIOTA?

Previous studies have demonstrated the effect of high-fat diets (HFD) in increasing *Firmicutes/Bacteroidetes* ratio and in inducing dysbiosis (34–40) (**Figure 1**). Not only the amount of fat but also the type of FA may influence microbiota. Saturated FA (SFA) promotes dysbiosis by increasing H_2S-bacteria, which results in the disruption of epithelial integrity by suppression of the tight junction proteins (41). Comparing the effects of HFD with different FAs, SFA quickly and persistently increased the proportion of H_2S-bacteria over time. When SFA was replaced by ω6-polyunsaturated FAs (ω6-PUFA), the proportion of H_2S-bacteria remained stable, while replacing SFA for ω3-PUFA, the proportion of H_2S-bacteria was reduced. This result aggregates beneficial effects to ω3-PUFA, a well-known systemic anti-inflammatory agent.

HFD may also favor obesity not only by promoting dysbiosis but directly by favoring the entry of bacterial components such as LPS (42) (**Figure 1**). As mentioned before, the absorption of dietary fat facilitates the absorption of LPS since both are transported by chylomicron (43). In the WAT, LPS and palmitic acid increase expression of chemokines and cytokines such as MCP-1 and IL-1β, and inflammation-related enzymes such cyclooxygenase-2, inducing macrophages infiltration and adipocyte expansion. In the liver, palmitic acid also increases the ceramide synthesis of CD36 and free-fatty-acid receptor-1 (FFA1/Gpr40) (41).

Protein-rich/carbohydrate-poor diet may also lead to dysbiosis, changes in barrier integrity and inflammatory activity. Unabsorbed proteins reach the colon, where microbiota exchanges fermentation substrate from carbohydrates to proteins, increasing colonic transit time and pH (41, 44). Protein fermentation increases H_2S, reactive oxygen species and ammonia production and reduces butyrate and *Roseburia/Eubacterium* abundance, suggesting a worse microbiota profile (45–47). Nonetheless, microbial metabolites from the proteolysis of the essential amino acid tryptophan also influence and modulate host microbiota. Indole groups bind aryl hydrocarbon receptor (AHR) that interfere with several metabolic steps, activate the immune system and reduce intestinal permeability (48).

The presence of non-digested carbohydrates in the colon increases the short-chain FAs produced by microbiota fermentation. These FAs can be absorbed and contribute to the host energy input. In addition to the additional energy absorption caused by short-chain FAs absorption, dysbiosis decreases the expression of FIAF (a lipase lipoprotein inhibitor), stimulating fat deposition in the WAT (33).

HOW ARE WE FIGHTING OBESITY-RELATED DYSBIOSIS?

Changing in diet and physical activity are crucial points in the treatment of obesity. Some studies suggest that such changes can alter not only bodyweight but also the microbiota in those individuals. The effects of physical activity modifying microbiota composition and metabolism have been studied, but the results are still controversial (49). Previous studies (50, 51) observed in HFD-fed animals that moderate and high-intensity exercise induced an abundance of *Bacteroidetes* in the colon. Nonetheless, an abundance of *Firmicutes* after physical exercise was also observed in animals with and without diabetes compared to sedentary ones (52). Thus, the influence of exercise on microbiota needs to be carefully evaluated.

Some of the well-established approaches, such as adopting a healthy dietary pattern (53–55), by reducing saturated fat and increasing fiber and antioxidant compounds intake (56, 57) have partially reverse dysbiosis and obesity in experimental studies. Nonetheless, it seems not to be enough to control obesity

epidemy. Furthermore, new insights using pre and probiotics and fecal microbiota transplantation (FMT) have now been tested in humans (**Figure 1**).

Akkermansia muciniphila, which is a mucin-degrading bacterium that resides in the mucus layer, has been the most studied, mainly in animal models (58, 59). Clinical studies (60, 61) showed that, in overweight/obese individuals, the oral supplementation of *A. muciniphila* reduced insulin resistance and plasma total cholesterol and levels of blood markers for liver dysfunction and inflammation. However, there was only a modest effect on body weight and composition with *A. muciniphila* supplementation.

Although FMT could be a rational strategy to treat obesity-linked dysbiosis (62), few clinical studies have assessed FMT in individuals with metabolic syndrome or obesity (63–67). Results are until now disappointing, despite the improvement in insulin sensitivity seen in two studies (66, 67), none of them presented promising results in terms of weight loss or reduction in the inflammatory profile. It is confirmed by recent reviews (68, 69) reinforcing the need for studies evaluating the mechanisms by which FMT affect host metabolism and its long-term effects. Moreover, the best preparation, concentration and form of administration of FMT should be defined.

In summary, the study of the complex network formed by gut microbiota, obesity, and inflammation are only in its first steps. The role of the dysbiosis in the genesis of obesity has been progressively uncovered, and the infectious component of this disease has gained more interest. However, up to date, no intervention based on microbes was able to reduce body weight effectively and persistently. Considering the relatively well-established relationship between microbiota and obesity in preclinical studies, additional efforts are necessary for the development of clinical interventions that support the microbiota manipulation as a realistic alternative to combat obesity.

AUTHOR CONTRIBUTIONS

PL and JA-L wrote the paper. MC-L and RO revised the paper.

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