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Immune Control of Gut Microbiota Prevents Obesity and the Effect of Antibiotic on Microbial Population

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ABSTRACT

Gut microbiota have gained increasing recognition for their vital role in human health, particularly in their interactions with the immune system, including their involvement in obesity prevention through the production of IgA antibodies. These microbiotas are instrumental in lipid breakdown, utilizing lipases to break down phospholipids and triglycerides into polar head groups and free lipids. The loss of these beneficial microbes has been suggested as a potential cause for disruptions in various homeostatic mechanisms within our bodies. Factors contributing to this loss may encompass antibiotic usage, heightened sanitation practices, and low-fiber diets. Obesity, more prevalent in developed nations, is linked to the diminished regulatory immune responses associated with specific beneficial microbial species. This review article aims to provide a comprehensive exploration of how gut microbiota influence lipid metabolism, considering T-cell-mediated regulation, and examines the effects of antibiotics on the gut microbial population.

Key words: Immunoglobulin A, GutMicrobiota, Obesity, Antibiotic, Immune control

INTRODUCTION

The human body is a host to an extensive array of microorganisms, with the majority of them taking up residence in the gut. These microorganisms serve various vital functions, including the production of biologically active signaling molecules that interact with the host's metabolism [1]. Moreover, they are responsible for synthesizing essential vitamins like biotin, folate, and vitamin K, as well as contributing to the metabolism of foreign substances and the development of the immune system, among other roles [2]. The gut microbiome significantly impacts immune system regulation, body weight control, and the development of metabolic diseases [3], [4].

While the gut microbiome relies on the host, it can be influenced by external factors such as the environment, antibiotics, and, most notably, diet [3]. Maintaining these microorganisms within a healthy balance is crucial for preventing diseases like obesity, which has become a global health issue closely tied to gut microbes. Given that a substantial portion of these microorganisms resides in the gut, extensive research is underway to fully comprehend their functions. One approach involves analyzing stool samples from both lean and obese individuals, revealing differences in microbial populations [2],[39],[5]. While this method

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may not be entirely precise, it has shed light on the relationship between gut-dwelling microbes and factors that may contribute to metabolic diseases.

In this regard, this paper seeks to investigate the role the immune system plays in regulating the gut microbiome for obesity reduction, the impact of beneficial gut microbes, and how various factors such as fatty diet, environment, and antibiotic can affectthese microbes.

INTERACTIONS BETWEEN THE IMMUNE SYSTEM AND THE GUT MICROBES

While the primary role of the immune system is to combat pathogens such as bacteria, viruses, and fungi, the gut's immune system has a unique function in nurturing and cultivating beneficial microbes [6]. Immune cells residing in the gut are strategically positioned in both the epithelial surface and the lamina propria, working in close collaboration with epithelial cells [7]. Together, they form a defensive alliance with the gut microbiota to ward off invasive particles, including pathogens, and aid in the breakdown of complex molecules. These immune cells exert regulatory control over the gut microbiota, directing their actions towards specific substances. In cases of obesity, their focus shifts towards processing a high-fat diet and storing excess fats.

A notable study conducted by Wang and Hooper[8] in 2019 revealed intriguing findings. They observed that germ-free mice, which lack a microbiota, accumulate less body fat compared to conventionally reared mice with a microbiota that promotes fat storage. Additionally, when fecal microbiota from obese mice or humans was transplanted into germ-free mice, these mice gained weight. Conversely, transplantation of fecal microbiota from lean mice or humans to germ-free mice resulted in leanness. These discoveries highlight the pivotal role of different bacteria in the gut, either preventing or inducing obesity. This raised a perplexing question: "Who regulates the gut-residing microbiota?"

Also, according to Peterson et al[39], and supported by previous studies [9], [5] it is the immune cells in the intestine that exert control over the microbiota. The intestine comprises B cells and T follicle cells, with B cells originating in the bone marrow and maturing in lymph nodes. These B cells produce substantial amounts of immunoglobulin A antibodies (IgA). The secreted IgA in the gut binds to bacteria, guiding them to take up residence in the gut while constraining others. While the precise mechanisms remain incompletely understood, this process has demonstrated the potential to prevent obesity in mice [8]. However, it's worth noting that changes in IgA binding can alter the immune response, potentially leading to metabolic diseases like obesity.

THE ROLE OF INTESTINAL IGA IN REGULATING GUT MICROBES

Immunoglobulin A antibodies, despite being produced in smaller quantities in the serum, stand out as the most abundant antibodies in both humans and mice. In serum, they predominantly exist as monomers, although polymeric forms also occur. Secretory IgA primarily takes the form of a dimer, accompanied by J chain and secretory component polypeptides. It's worth noting that the secretory component is responsible for facilitating the transport of secretory IgA across membranes within the human body [10].

As with other antibodies, IgA is T cell independent, requiring activation signals from naive B cells [39], which are prompted by interactions with T cells through CD40 and cytokines following antigen exposure. Activated B cells subsequently undergo proliferation and generate memory cells and plasma cells within germinal center patches [11]. The IgA produced by plasma cells then ventures to sub-epithelial tissues and binds to the polymeric immunoglobulin receptor. Following this binding event, secreted IgA makes its way to the gut lumen [10], [11].

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Within the gut lumen, the interaction between the immune system and the gut microbiota heavily relies on IgA production. IgA plays a pivotal role in maintaining homeostasis by binding to commensal bacteria, preventing the invasion of pathogenic microbes into the epithelial layers, and directing them to interact with dietary fats [11], [12]. However, diet-induced obesity can reduce IgA production and disrupt the balance of beneficial microbiota, leading to dysbiosis. This alteration has a ripple effect on the immune system and can trigger disturbances in homeostasis, potentially resulting in inflammation. This evidence strongly suggests that IgA plays a central role in mitigating obesity. Supporting this assertion, studies have demonstrated that obese mice exhibit reduced IgA production and shifts in their microbial populations [13]. Although the precise mechanism through which diet-induced obesity diminishes IgA production remains unclear, this reduction has been linked to other metabolic disorders and inflammation in both humans and mice [39], [5].

Furthermore, additional research conducted by Kubinak et al [5]. has unveiled a fascinating pathway in mice that regulates IgA. MyD88 signaling in the T follicle process significantly influences IgA production, and the loss of this pathway can lead to reduced IgA levels, potentially contributing to the development of metabolic syndrome.

INFLUENCE OF GUT MICROBIOTA ON BREAKING DOWN OF LIPIDS IN THE GUT

Dietary lipids undergo not only host enzyme metabolism but also enzymatic breakdown by bacteria. Microbes have the capacity to produce distinctive lipid metabolites, including hydroxy fatty acids, conjugated linoleic acids, and oxo fatty acids, which exhibit bioactivity in the context of both host health and disease [14].

A mere 5% of the total dietary fat ultimately reaches the colon, where gut microorganisms, equipped with lipases, can break down phospholipids and triglycerides into their polar head groups and free lipids. While triglycerides constitute 95% of the dietary fat, phospholipids, often in the form of phosphatidylcholine, form a smaller fraction and can also originate endogenously from bile acids. Specific bacteria in the gastrointestinal tract, including enterococci, clostridia, lactobacilli, and Proteobacteria, can utilize the backbone of triglycerides as an electron sink, leading to the reduction of glycerol to 1,3-propanediol. This process generates an intermediate known as Reuterin or 3-Hydroxypropanal, which, when accumulated extracellularly in cultures of Enterococcus and Lactobacillus spp., exhibits antimicrobial properties against both pathogens and commensals. Importantly, Reuterin can spontaneously dehydrate into acrolein, a highly reactive genotoxin with mutagenic potency equivalent to that of formaldehyde. Additionally, gut microbes, such as species of Clostridia and Proteobacteria, can break down choline into trimethylamine [15].

As far back as the 1930s, it was demonstrated that intestinal microbiota could convert cholesterol into coprostanol. This cholesterol breakdown follows a two-mode distribution in humans, with the majority being efficient converters and a minority being inefficient converters. Two main pathways for this conversion were proposed, and a unique human-origin cholesterol-reducing bacterium, belonging to the phylum Bacteroidetes and named Bacteroides sp. strain D8, was isolated and characterized. Bioinformatic and biochemical studies also found that cholesterol dehydrogenases produced by gut microbiomes contribute to cholesterol breakdown into coprostanol [16].

Beyond the conversion of dietary lipids, the gut microbiota generates bioactive lipids that may traverse the epithelial barrier and interact with host metabolism. An example is sphingolipids produced by gut bacteria of the Bacteroides genus, which increase the pool of sphingolipids available to the host and modulate bioactive lipid levels in the liver [17].

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One mechanism through which gut microbiota influence lipid metabolism involves the fermentation of non-digestible carbohydrates. While the human gut cannot break down many forms of carbohydrates like pectins, gums, and hemicelluloses, certain anaerobic gut bacteria can ferment these compounds. This fermentation yields short-chain fatty acids, including butyrate, propionate, and acetate, which traverse the small intestine unchanged, only to be metabolized by anaerobic bacteria in the proximal colon and cecum. These short-chain fatty acids influence cholesterol and lipid metabolism and provide a significant energy source for the host, among other effects.

In addition to short-chain fatty acids, the gut microbiome can affect lipid levels through the production of conjugated linoleic acids and the metabolism of bile acids. Conjugated linoleic acids result from the action of microbes such as *Roseburia*, *Bifidobacteria*, and *Lactobacillus* on polyunsaturated fatty acids fromomega-3-rich food sources. Short-chain fatty acids impact lipid breakdown by activating peroxisomeproliferator-activated receptor isoforms, leading to increased lipolysis, mitochondrial biogenesis, reducedlipid levels, and increased β-oxidation. Bile acids primarily assist in the breakdown of dietary fats in the small intestine and regulate cholesterol homeostasis. Evidence indicates that colonic bacteria generate secondary bile acids from secreted bile salts in the intestine [18].

THE IMPACT AND EFFECTS OF HIGH FAT DIET ON THE GUT MICROBES

Gut microbes have emerged as crucial participants in the host intestine, influencing a wide range of factors including intestinal epithelial integrity, immune responses, disease susceptibility, and the digestion and metabolism of nutrients [1],[19],[20]. The abundant bacteria residing in the gut can be categorized into three primary phyla: *Firmicutes* (e.g., *Ruminococcus, Clostridium, Eubacteria*, etc.), *Bacteroidetes (e.g., Porphyromonas, Prevotella*, etc.), and *Actinobacteria* (such as *Bifidobacterium*). Additionally, bacteria like Lactobacilli, Streptococci, and Escherichia (E. coli) have been identified in the small intestine [21–23].

Disruptions to this delicate balance of gut microbes can lead to chronic diseases, including inflammation, obesity, and obesity-related conditions such as cardiovascular disease, diabetes, and cancer. One significant factor capable of reshaping the composition of gut microbes is a high-fat diet, which can have detrimental effects on the host. The gut microbiota plays a pivotal role in digesting substances that profoundly impact the host's health. As previously mentioned, short-chain fatty acids like acetate and butyrate are metabolized by gut microbes, and their levels have notable effects on host health [23], [24].

Numerous studies [20], [25], [26] have demonstrated that an increase in high-fat diet consumption reducesthe abundance of *Bacteroidetes* and increases *Firmicutes* in both mice and humans' gut microbiota. These findings suggest that gut microbes exert a degree of control over how individuals respond to specific dietary patterns. Researchers have embarked on various therapeutic approaches, such as the use of probiotics, to restore and maintain a healthier microbial balance [30]. For instance, Bifidobacterium animalis ssp. lactis420 was employed to treat mice fed a high-fat diet, resulting in decreased fat mass, improved glucose tolerance, reduced levels of LPS (lipopolysaccharides), and a decrease in inflammation (LK, Angela). Additionally, probiotic yeast like *Saccharomyces boulardii* has shown promise in reducing body weight, fat mass, and altering the composition of the gut microbiota.

THE IMPACT OF GUT MICROBIOTA ON OBESITY REDUCTION

Obesity can arise from genetic predisposition or an obesogenic environment and has become a global health crisis, often accompanied by other diseases such as type 2 diabetes, cardiovascular disease, and cancer. While Genome Wide Association studies have linked approximately 3,000 single-nucleotide polymorphisms to obesity, the genetic contribution to obesity is relatively low [7], [27]. In contrast,

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obesogenic environmental factors play a significant role in weight gain, indicating that obesity is potentially preventable.

The gut microbiota, primarily through its interaction with IgA, has been identified as a critical player in regulating obesity, whether reducing or exacerbating it. These microorganisms extract energy from food and utilize it to promote overall health. For instance, they metabolize polysaccharides and complex carbohydrates, indigestible by the host, into short-chain fatty acids (SCFA), including butyrate (an energy source for colonic epithelial cells), propionate, and acetate (used in liver lipogenesis and gluconeogenesis) [2],[28].

Numerous studies have shed light on how gut microbes contribute to obesity reduction, with a focus on mice subjects, but with implications for humans. Peterson et al [39]. conducted pivotal research using T-myd88 mice. Their studies revealed that as T-myd88 mice aged, they became obese and developed metabolic syndromes akin to those observed in humans. This led to the insight that obesity is triggered by a high-fat diet, resulting in alterations in the gut microbial population. Beneficial microbes were depleted, while those promoting obesity proliferated. To counter this, the researchers employed broad-spectrum antibiotics to target the harmful microbes, and they observed that the mice became lean. These findings underscore the notion that certain microbes either contribute to obesity or aid in its reduction.

So, what specific microbiota is associated with T-myd88? Beneficial Clostridium, a spore-forming bacterium, is abundant in lean myd88 mice, whereas *Desulfovibrio*, a motile bacterium that produces hydrogen sulfide, is found in obese T-myd88 mice.

To delve deeper into this, Peterson et al [39]. fed T-myd88 mice with Clostridium and observed that the mice became lean, supporting their hypothesis that the loss of Clostridium leads to obesity in T-myd88 mice. Introducing Clostridium to these mice repressed the expression of genes in the intestine responsible for the absorption and processing of dietary lipids. Conversely, introducing Desulfovibrio led to gene expansion and increased expression, resulting in obesity. Other motile bacteria such as *Salmonella typhi* and *E. coli* were also identified in activating these expression genes. These findings are transferable to humans since both Clostridium and Desulfovibrio are present in the human intestine, suggesting that a reduction in Clostridium may contribute to obesity [8]

THE SIGNIFICANCE OF GUT MICROBES IN FOSTERING HEALTH

Within a single individual, there exists a staggering 40 to 100 trillion microbial cells, categorized into four main groups: Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria. However, it is Firmicutes and Bacteroidetes that predominantly populate the gut [29]. These gut-dwelling bacteria serve a multitude of vital functions encompassing physiology, metabolism, regulation of the immune system, developmental support, defense against pathogenic bacteria, detoxification of chemical toxins, and the synthesis of essential vitamins and amino acids [28], [30].

When maintained in the proper balance, there are no inherently good or bad microbes; however, alterations induced by antibiotics, dietary choices, lifestyle, environmental factors, and microbial competition for dominance can have detrimental consequences [31]. Numerous studies have emphasized the benefits of preserving a balanced microbial population, given their ability to influence the activation and deactivation of genes. As previously mentioned, gut microbes break down complex molecules into short-chain fatty acids like butyrate, propionate, and acetate. Butyrate, recognized as the primary energy source for colonic epithelial microbes, while propionate and acetate contribute to lipid and glucose synthesis. The production of vitamin K by these microbes is pivotal in activating proteins that regulate calcium levels in the body, and a decrease in vitamin K production can be linked to heart disease [32], [33]. Additionally, vitamin B production plays a crucial role in supporting health by aiding in hormone synthesis, DNA maintenance, and

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energy extraction from food.

Recent research has uncovered links between alterations in gut microbes and several autoimmune diseases, including diabetes, rheumatoid arthritis, muscular dystrophy, obesity, and multiple sclerosis [32]. This body of evidence underscores the essential role of microbes in our bodies and highlights the paramount importance of maintaining them in a balanced state.

THE IMPACT OF ANTIBIOTICS ON GUT MICROBIOTA AND ITS POTENTIAL ROLE IN OBESITY ONSET

Antibiotics wield a dual-edged sword, offering both assistance and potential harm. Their actions, which encompass inhibiting cell wall synthesis, protein synthesis, nucleic acid synthesis, metabolic pathways, and cell membrane integrity, vary based on an individual's genetic makeup [29]. Antibiotics are broadly classified into two types: broad-spectrum antibiotics, which act against both gram-positive and gram-negative bacteria, and narrow-spectrum antibiotics, which target either gram-negative or gram-positive bacteria.

When antibiotics come into play, particularly concerning anaerobic bacteria, they exert an influence on the gut microbiome. Both broad-spectrum and narrow-spectrum antibiotics can lead to alterations in the gut microbiota, but broad-spectrum antibiotics are notably implicated in causing substantial disruptions [30]. These alterations, or depletions, within the gut microbiota not only eliminate beneficial bacteria but also inflict damage upon or destroy epithelial cells. This damage carries significant consequences, as epithelial cells play vital roles in nutrient absorption and the prevention of bacterial translocation from the gut into the bloodstream. Moreover, the diversity within the gut microbiota influences the repression of genes associated with adipogenesis while also serving as a barrier against pathogenic microbes.

A striking observation pertains to the impact of broad-spectrum antibiotics on gram-positive bacteria, particularly Clostridium. Clostridium species are recognized for their pivotal role in calibrating the immune system, and their reduction due to antibiotics may lead to inflammation [35]. A noteworthy example is *Clostridium difficile*, an opportunistic microbe. The prevalence of this bacterial infection arises when the competitive balance among gut microbes is disrupted, often due to the use of broad-spectrum antibiotics [36]. The treatment for this infection involves the transfer of fecal material from a healthy donor to an infected patient, aiming to restore the normal microbial population that has been decimated by broad-spectrum antibiotics [37].

It is important to note that the microbial composition differs between obese and lean individuals [29]. This distinction prompts speculation that antibiotic use may contribute to obesity. Substantiating this claim, a study conducted on mice involved transferring the microbiota from 18-week-old control mice and mice treated with penicillin to germ-free mice, shedding light on the impact on body composition and metabolism [38]. Mice whose mothers received penicillin treatment before giving birth to the pups and throughout the weaning period exhibited alterations in adulthood, including weight gain, increased hepatic expression of genes linked to adipogenesis, reduced bone mineral content, and increased bone surface area [38)].

CONCLUSIONS

It is undeniable that the gut microbiota plays a crucial role in fostering overall health, and maintaining them in a balanced state is of paramount importance. Emphasizing their significance, microbial composition can be upheld through the transfer of fecal material from lean individuals to those who are obese. This innovative approach has not only enabled obese individuals to preserve their microbial equilibrium but has also resulted in weight reduction. Additionally, this method has proven effective in curing *Clostridium*

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difficile infections. Furthermore, the utilization of probiotics, symbiotics, and supplements like Akkermansia muciniphila has demonstrated effectiveness in maintaining gut health.

The revelation of the immune system's control over gut microbes through the production of immunoglobulin A antibodies has illuminated the pathway to understanding that metabolic diseases such as obesity are preventable. While the precise mechanisms underlying this interaction remain enigmatic, it provides a solid foundation for more robust research endeavors. While many of the studies mentioned herein were conducted on mouse subjects, some findings have translated to human contexts. In this age of advanced technology, it is imperative that we investigate how dietary factors induce obesity, impacting IgA production and altering microbial composition.

Furthermore, while antibiotics were initially developed to combat pathogenic microbes, their widespread use has unintentionally led to the depletion of beneficial microbes. Consequently, it is imperative for researchers to focus on innovative and effective strategies for targeting pathogenic microbes while preserving the beneficial ones, with the aim of preventing metabolic diseases. Although such efforts may require considerable time and collective dedication, they hold the potential to address significant challenges in human health.

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