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GENERAL INFORMATION

The human microbiome. Its role in health and in some diseases

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KEYWORDS
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Abstract
The human microbiome is formed by microorganisms, their genetic elements and their interactions with the environment. Microbiota is essential for the normal functioning of some organs. Recently the microbiome has been implicated in the pathogenic mechanisms of certain diseases such as obesity, diabetes and digestive functional disorders. The study of these complex elements will allow a better understanding of the microbiome as well as that of related diseases.

PALABRAS CLAVE
Microbioma;
Obesidad;
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Prebióticos;
Probióticos;
Nutrición

El microbioma humano. Su papel en la salud y en algunas enfermedades

Resumen
El microbioma humano representa a los microorganismos con sus elementos genéticos y las interacciones que establecen con el medio ambiente en el que se encuentran. La microbiota es un elemento importante para el correcto funcionamiento de algunos órganos, pero recientemente se ha demostrado que está participando en la patogenia de algunas enfermedades. En el presente escrito se revisa el concepto de microbioma y se realiza un breve análisis de su relación con algunas enfermedades como: obesidad, diabetes y algunos trastornos del aparato digestivo. El mejor conocimiento de esta condición va a permitir comprender mejor la fisiología y la fisiopatología del microbioma, así como de las enfermedades y trastornos que se encuentran vinculados con la microflora que habita en el ser humano.

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"All levels of biological diversity are closely related. This relationship is the product of organic evolution process. You can build trees of life similar to those expressing genealogical relationships between each-other and groups of species".

José Sarukhán

Background

Man as a species has evolved in close and constant contact with a complex microbial flora. Experiments have shown that animals from high biological levels require the influence of certain microorganisms for the proper functioning of certain organs. We can say with almost complete certainty that some of man's physiological needs have been partly determined or influenced by the microbiota that have prevailed during their adaptation and evolution.

Joshua Lederberg, who received the Nobel Prize for Physiology and Medicine in 1958, introduced the concept of microbiome to show that commensal bacteria maintain an intense genetic exchange between them and the host cells; later the term *microbioma* was suggested to refer to all microorganisms, their genetic elements (genomes) and the interactions that they establish with their environment (epigenetics)[1]. This relationship is so intense that Lederberg himself came to believe that the genetic material of microbes should be considered part of the human genome. Recently, the human microbiome has been the subject of intense research, not only because it is involved in the functioning of organs, but because there is also evidence suggesting its involvement in some diseases. The purpose of this paper is to present a brief analysis of the human microbiome and comment on its role in the pathogenesis of certain conditions.

It has been shown that the human body is a complex ecosystem with trillions of bacteria that inhabit the skin, genitals, mouth, airways, and especially the digestive tract. It has been estimated that the total genetic material of the microbiome is 100 times higher than the human genome[2], so that paradoxically the genetic content of microorganisms that inhabit the human being is significantly higher than the humans who house them.

The gastrointestinal tract's "native" microbial flora

Bacteria that are present in the digestive tract of newborns come from the newborn's mother. In the first days of life, the population of *Lactobacillus* is very large, especially in breastfed children. Also, in very early life the gastrointestinal tract is colonised with *Clostridium perfringens* and *Escherichia coli*, the latter in very high values, to then rapidly decline, indicating that the human has mechanisms to eliminate, or at least control, microorganisms of various species, which were symbiotic during the evolutionary development[3]. It has been observed that intestinal microbiota usually stabilises at 4 years of age and remains relatively stable until the seventh decade of life[4].

Intestinal microflora have been studied extensively in the last 50 years and, although it appears that there are still species that have not been identified, these are classified into two divisions, Firmicutes (gram-positive) and Bacteroidetes (gram-negative). These two divisions represent 90% of the intestinal flora[5]. The predominant genera are noted in Table 1. Recently, metagenomics studies (studies of microorganisms in their natural environment without the need to isolate them) has confirmed the communication between commensal bacteria and identified in each species of commensal bacteria the 16S ribosomal gene, which has been useful for classification and identification. In 2010, the European group responsible for studying the human microbiome reported that the genes of intestinal microbiota total 3.3 million genes from >1,000 species of bacteria, which is about 150 times more than human genes[6].

The intestinal microbiota has multiple functions. Some are well-known such as the synthesis of K and B_{12} vitamins or the digestion of complex carbohydrates found in plants and fruits, contribute to innate and adaptive immunity, to signalling and communication at a cellular level and, more recently, that they participate in metabolic pathways (Table 2). In addition, there is clear evidence that they are involved in the pathogenesis of several diseases such as functional gastrointestinal disorders, food intolerances, food allergies, inflammatory bowel disease, obesity, diabetes and atherosclerosis (Table 3).

Intestinal microbiota metabolism, obesity and diabetes

Excess weight and especially obesity cannot always be explained by hereditary factors and dietary habits. In experiments conducted in laboratory mice, it was found that germ-free animals (gnotobiosis) generated a lower amount of fat despite undergoing high caloric intake, but when their digestive tract was colonised with "normal" microbiota, mice significantly increased their weight and even developed insulin resistance and obesity[7]. Later, the same authors also demonstrated that transplanting intestinal

Table 1 Major divisions or phyla of the human digestive tract microbiota

Phylum	Most representative genus
Firmicutes	*Ruminococcus*
Enterococcus	
Clostridium	
Peptostreptococcus	
Lactobacillus	
Bacteroidetes	*Bacteroides*
Proteobacterias	*Desulfovibrio*
Escherichia	
Helicobacter	
Actinobacteria	*Bifidobacterium*
Actinomyces	
Verrucomicrobia	*Verrucomicrobium*

Modified from Mönckeberg and Corsini[21].

Table 2 Main functions of the intestinal microflora

Action	Example
Fermentation of indigestible substances	Fibres
Facilitates digestion	Lactose
Promotes absorption	Ca, Fe, Mg
Synthesises	Vitamin K and B_{12}, folic acid, biotin
Maintains intestinal permeability	
Barrier effect and prevents bacterial translocation	
Modulates gas production	
Regulates the proliferation and differentiation of epithelial cells	
Participates in the innate and adaptive immune system	

Table 3 Diseases related to changes in intestinal microbiota and/or that have been treated with prebiotics, probiotics and antibiotics

- Traveller's diarrhoea
- Diarrhoea cause by antibiotics
- Rotavirus diarrhoea
- Necrotising enterocolitis
- Pseudomembranous colitis
- Lactose intolerance
- Atopic dermatitis
- Food allergy
- Irritable bowel syndrome
- Prevention of bacterial translocation
- Inflammatory bowel disease
- Diabetes
- Obesity

microbiota from genetically obese mice (ob/ob) to thin mice also resulted in an increase in their weight[8], such that the term "obesogenic microbiota" was proposed. This microflora increases hepatic glucose production and promotes the deposition of triglycerides in the liver. There are at least three mechanisms that could explain this:

1. Suppression of fasting-induced adipocyte factor (FIAF), also known as angiopoietin-like 4 (Angptl4) protein. FIAF is a circulating inhibitor of lipoprotein lipase and by preventing the blocking of the latter, an increased incorporation of fatty acids into the cell and triglycerides to the adipose tissue occurs.
2. Alteration in the function of the activated protein kinase (AMPK), which functions as an "energy gauge"[9].
3. Energy production through fermentation of complex carbohydrates by the bacteria that transforms them into monosaccharides and short-chain fatty acids[10].

Studies on humans found that there is a larger population of Firmicutes and fewer Bacteroidetes in the faeces of obese subjects, and when these individuals embark on low-calorie diets the Bacteroidetes population increases and the Firmicutes population decreases[11]; however, this finding has not been confirmed by other authors such as Duncan et al.[12] who found no difference between the faeces of obese and slim people.

There is multiple evidence that both diabetes and obesity are associated with a state of chronic low-grade inflammation, whose origin is not fully defined, but largely due to the cytokines produced in adipose tissue. Animal models and in vitro experiments found an increase of proinflammatory cytokines such as tumour necrosis factor alpha (TNFα), which can generate insulin resistance[11]. Cani et al.[13] successfully demonstrated that the lipopolysaccharide found on the wall of intestinal bacteria is able to release proinflammatory cytokines. Lipopolysaccharide could move from the portal and systemic circulation by alteration of the permeability of the intestinal barrier and produce a state of "metabolic endotoxemia" (Fig. 1).

Cani et al.[13] also showed that a high fat diet reduces the number of bifidobacteria and increases the plasma levels of lipopolysaccharide. In addition it also found that, at least in experiments on animals, intestinal flora can be modulated by antibiotic treatment or a diet of oligofructose, which also improves glucose tolerance, decreases weight and inhibits inflammation[11,13]. The authors suggest that changes in intestinal microbiota could generate the metabolic endotoxemia state that occurs in response to a high fat diet.

Another avenue that could associate microbiota with chronic inflammation is the reduced availability of butyrate because, apart from its well-known role as an energy source for colonic epithelial cells, butyrate also has anti-inflamma-

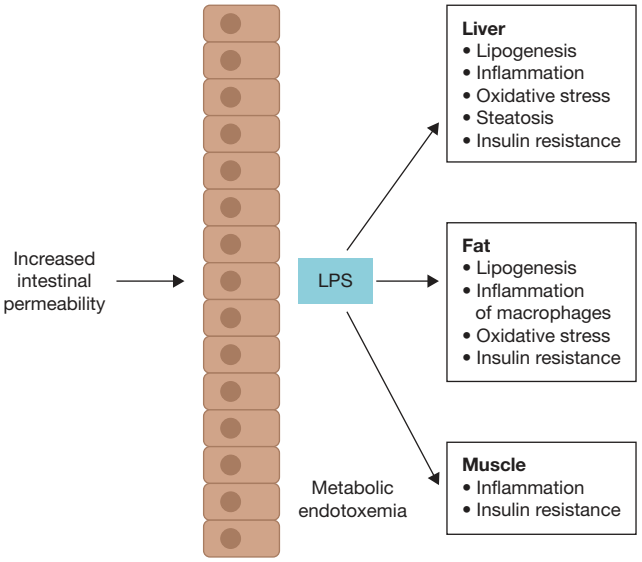

Figure 1 Intestinal lipopolysaccharide permeability and metabolic endotoxemia. Taken from Gravitz[18].

tory properties. It has been found that an intake of fermentable carbohydrates can influence the production of butyrate, particularly diets that contain a high amount of non-digestible carbohydrates, which stimulate the production of butyrate-producing bacteria and their values thus rise. Recent publications have shown that butyrate improves insulin sensitivity[14] (Fig. 2).

Helicobacter pylori and weight gain

Ghrelin is a peptide produced by gastric mucosa cells and to a lesser extent by pancreatic cells, duodenum, small intestine and cecum. One of its main activities is controlling appetite through intestine-hypothalamic, afferent and efferent neural pathways. This gastrointestinal hormone stimulates appetite and its values are elevated before food intake and decreases in the postprandial state[15]. In a study where subjects or patients with and without the presence of *Helicobacter pylori* were compared, it was found that those who had the bacteria in their stomach had decreased postprandial ghrelin, which was lost when *H. pylori* was eradicated, such that stimulation of appetite was undiminished. At least one study has reported that there is weight gain after treatment for eradication of *H. pylori*. It has been proposed that the bacteria is involved in the regulation of ghrelin[6].

Intestinal microbiota and incretins

Intestinal hormones are produced by enteroendocrine cells distributed throughout the digestive tract, from the stomach to the distal colon. Incretins are intestinal hormones that potentiate insulin secretion after ingesting food. The two main incretins are gastric inhibitory peptide (GIP) and glucagon-like peptide 1 (GLP-1). GIP is secreted by K cells and released into the duodenum and proximal jejunum in response to oral intake of carbohydrates and lipids. GLP-1 is produced by L cells located in the ileum and colon. Secretion of both hormones in type 2 diabetes is poor and delayed. These changes have also been observed in obese subjects. Experiments on rats found that ingestion of probiotics leads to increased GIP[11]; prebiotics as oligofructose also favour the release of GLP-1. In rats with induced diabetes, administration of prebiotics and probiotics improved glycemic control[16,17].

Furthermore, in genetically obese mice, the administration of antibiotics that alter intestinal microflora caused a reduction in weight and improved blood glucose and glucose tolerance.

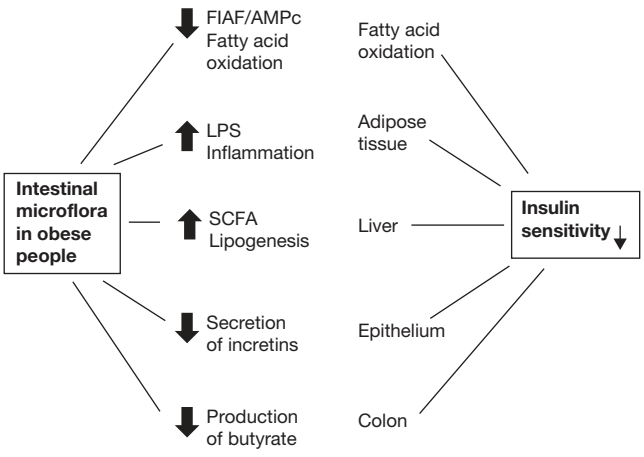

Figure 2 Mechanisms of insulin resistance by the intestinal microbiota. Taken from Vrieze et al.[11].

Therapeutic approaches

Although there have been no controlled clinical trials, the restoration or rebuilding of the intestinal microbiota has not yet found a place in medical therapy. The use of prebiotics, probiotics, antibiotics and even surprising treatments such as the transplanting of faecal material with normal microbiota into the colon of patients has been recommended. Vrieze et al.[11] conducted a study in 18 men who had been recently diagnosed with metabolic syndrome; nine of them received "faecal transplants" of lean individuals with normal microbiota. After 6 weeks of faecal transplants there was an improvement in insulin sensitivity; however, after 1 year the increase in insulin sensitivity decreased again. The study does not clearly state whether other therapeutic interventions that may have influenced insulin sensitivity were performed[18].

In addition, and as part of nutritional support, symbiotic foods (blends of probiotic and prebiotic) have also been used in trauma patients in critical condition. These treatments have found that nutritional support with symbiotic food is associated with less intestinal permeability and fewer infections[19].

Infusion of faeces into the duodenum and faecal transplants have been employed in cases of recurrent *Clostridium difficile* infection. A study has recently been published on patients with recurrent colitis due to *C. difficile infection*. They were distributed randomly and received one of the following treatments: vancomycin, vancomycin and intestinal lavage and oral vancomycin for 4 days and subsequent to that an infusion of faeces from healthy individuals who were free of parasites and pathogens through a duodenal probe. Of the 16 patients treated with faecal infusion, the medical profile of 81% had a resolution of symptoms with the disappearance of *C. difficile* compared to a significant difference with the other groups. The variety of faecal flora of these patients was similar to that of the donors, with an increase in bacteroidetes and a decrease of proteobacteria[20].

There are few human clinical studies, especially controlled clinical trials, where the intestinal flora is modified to treat diseases related to nutrition. The most studied medical problems that have shown the most promising results have been diarrhoea cause by antibiotics and functional disorders of the colon, which have been treated with probiotics and prebiotics.

Although the microbiome has sparked growing excitement among the scientific community and resulted in a large number of published studies, most research has been conducted on experimental animals. There is no doubt that mi-

crobiota is involved in the pathogenesis of some metabolic diseases and digestive system; however, its role in health and human disease remains to be defined. The answer will most likely present itself in the coming years.

Conflict of interest

The authors declare no conflict of interest.

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