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Review Article

Microbiome Components, Functions and Uses

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Abstract

We carried out a comprehensive analysis of the microbiome and its components. This analysis includes all the microorganisms that make it up and the relationships between them and as a whole. Here we also highlighted the importance of viruses, in that they are the largest group, although it's currently the least known. The final piece of our analysis contained the determinants for the different bacterial phylos.

Incorporated in the review are bacteriophages, eukaryotic and giant viruses, as well as archaea, parasites and fungi.

We also concluded on the rational use of the microbiome, as well as its different units. Within these units are probiotics, prebiotics, symbiotics, postbiotics, paraprobiotics, FIF, microbiota transplantation and inactive bacterial cells.

Pointed out is the future that bacteriophages possess as a therapy in different ailments and the substitution that can be made of antibiotics for them, along with giving a turn to the constant resistance that these drugs produce.

Keywords: *Microbiome (Mic); Intestinal Microbiota (IM); Fecal Microbiota Transplant (FMT); Intestinal Microbiota Transplant (IMT)*

Introduction

Microbiome

On April 1, 2001, Joshua Lederberg introduced the world of Microbiome (Mic), defining it as the ecological community of commensal, symbiotic and pathogenic microorganisms that share our body space and have been ignored as determinants of health or disease [1]. Human microbiota presents itself as around 900 or 1000 different species of microorganisms (Extraordinary diversity of genomes) [2]. In the intestinal microbiota (IM), the most important component of the microbiota, located in the colon and rectum, inhabit microorganisms that exceed 101414 [3]. The Mic has been related to a significant series of functions in a new organ, which affects health and immunological functions [4]. Neurological metabolism [5] connects to the "gut-brain axis" through many different systems.

Gut microbiota

Gut microbiota is the most important of all microbiota given its volume in microorganisms. It is defined as the set of microorganisms that live in the intestine, especially the colon and rectum. Among the most significant processes of IM are inflammatory bowel disease

[7], gastric cancer [8], colorectal cancer [9], cardiovascular disorders [10], cutaneous manifestations, such as psoriasis, acne and atopic dermatitis [11]. These conditions count be developed though lifestyle, stress, antibiotics, certain nutrients in diets, and obesity due to its generation of microorganisms (dysbiosis) [12] and viruses.

Virus

Microorganisms are composed of genetic material protected by packaging protein. This can lead to various diseases by introducing itself as a parasite in the cell or microorganisms, to reproduce in them [13]. The respiratory system is the system most affected by these viruses, although patients generally have minimal symptoms. Microorganisms are mentioned as the second largest group that makes up the Mic [14].

Virome

(Set of all viruses found in the human body). Like Mic, the virome is influenced by genetics, diet, stress, obesity, and the administration of antibiotics [15]. The virome's interaction with the Mic is so complex because of how harmful and beneficial it can be. The DNA and RNA viruses that collectively form the intestinal virome outnumber bacterial cells by up to 10 to 1 and include eukaryotic viruses (infected eukaryotic cells), endogenous retroviruses, bacteriophages, and archaeal viruses that infect them [16]. Those viruses are equivalent to bacteria [17]. Their various genomes can consist of linear or circular double-stranded or single-stranded DNA or RNA, while RNA genomes can be positive-sense (translated directly into protein, similar to mRNA) or negative-sense [18]. For their classification, the Baltimore scheme is useful, where they are grouped according to the composition of their genomes and their method for genome replication. This scheme is particularly useful, as the viral genome will often be reflected in its method for replication, gene expression, and life cycle [19].

Bacteriophages

Bacteriophages are viruses that most frequently infect prokaryotic organisms (bacteria and archaea) [20]. They are the predominant biological organisms on earth: Prokaryotes, archaea and bacteria, hence their enormous importance [21]. Many of them have an icosahedral head composed of repeating protein subunits known as capsids. These viruses contain this viral genome [22]. Their main difference is the presence or absence of a "tail" structure [23]. Phages, like other eukaryotic viruses, have two distinct life cycles. These are the lytic cycle: a productive process leading to the synthesis of new phage particles, and the lysogenic cycle: a "silent" stage in which the phage genome integrates with the host chromosome [24]. It remains there for many generations and can return to the lytic cycle through the stimulation of gene expression [25]. Currently, around 5,500 different phages that can infect one or several types of bacteria have been discovered [26]. In the lithic cycle, they are represented by three families: Caudovirales, Myoviridae and Siphoviridae [27]. There are also intestinal localization phages and pseudolysogenic phages.

Intestinal phages

Viruses located in the intestine exclusively infect prokaryotic organisms [28]. They are part of the intestinal virome and although they are generally enemies of bacteria, they can also help them seek health, an example of this, is *Clostridium* [29]. Since the discovery of intestinal phages by d'Hérelle in 1917, the understanding of their impact on IM structure remains weak [30]. Viruses, fundamentally bacteriophages, are found as intestinal virome, a component of the intestinal microbiota [31]. There is considerable diversity among phages, but 95% of them are non-enveloped-tailed dsDNA phages, or Caudovirales [32].

Pseudolysogenic phages

False state in which a phage with DNA genome maintains a latent or persistent, non-lytic relationship with the host bacterium [33]. This makes understanding bacteriophages a little more difficult. Next, we will analyze two of the three domains of living organisms (Archaea and Eukaryotes, attached to viruses), not including bacteria, which are analyzed last.

Archaeal viruses

Archaeal viruses are unicellular and ribosomal structured organisms. They differentiate from bacteria and eukaryotes due to some of their introns in the genome, as well as the different components of the membrane [34]. Introns along with exons are a series of nucleotides within a gene [35]. The archaeal virus phyllo is constituted by: Crenarchaeota, Euryarchaeota, Korarchaeota, Nanoarchaeota and Thaumarchaeota [36]. The Thaumarchaea are present in many habitats, where they carry out the aerobic oxidation of ammonia and are a key step in the nitrogen cycle [37]. The record of these microorganisms extends as far back as the geological pattern and the beginning of the organic origins of the Earth [38].

Eukaryotic viruses

(Bacteriophages or simply phages). They are the genes of viruses and bacteriophages that inhabit an ecosystem, either as microorganisms free or in the form of intracellular inclusions in the cytoplasm or integrated into chromosomes [39]. Within eukaryotic cells, dsRNA is a strong inducer of antiviral defense [40]. Each family of viruses has its own way of entering, replicating, and exiting the host cell [41]. Although many families use similar media at different stages of the replication cycle [42]. Eukaryotic RNA Viruses account for most of the diversity of the virome [43]. Double-stranded RNA viruses are derived from dsRNA bacteriophages or positive-stranded RNA viruses [44].

Giant viruses

There is still much more to know about viruses. For example, giant viruses are arbitrarily defined as microorganisms that infect eukaryotes with at least 500 protein-coding genes [45]. The first of them, *Acanthamoeba polyphaga* mimivirus, was discovered in 2003 [46]. It is considered that 19 eukaryotic giant viruses are its representatives [47] and that they were authentic living beings [48]. In the interrelation of giant viruses and Mic, it was observed that they encode a wide range of proteins, with putative functions in photosynthesis, as well as diverse processes in the transport of substrates. These viruses are surely associated with most eukaryotic lineages [49].

Bacteria

The first component of the Mic. is the prokaryotic, unicellular, and micrometric microorganisms with various shapes: rods (bacillus), spheres (coccus), helical rods (spirillum), or curved filaments [50]. Their genomes are double-stranded circular DNA [51]. They reproduce in a process known as binary fission [58]. Allowing them to be Gram-negative or positive [52]. The interrelation of bacteria with Mic is multiple, highlighting the impact that diet has in the first years of life [53], influencing metabolic changes, alterations of the immune system and metabolism [54], through MI metabolites and host receptors by the gut-brain axis [55]. In addition to that, if there is dysbiosis, there could be cognitive disorders [56]. As well as behavioral problems [57]. Molecular techniques have shown that the diversity of IM is much greater than that demonstrated in cultures [58]. The taxa range is between 100 and 300 and pyrosequencing thousands of phylotypes [59]. The most detected phyllo are *Bacteroidetes, Firmicutis, Proteobacteria* and *Actinobacteria*. The lesser extent *Verrucomicrobia, Tenericutes, Fusobacteria, Spirochaetes* and Cyanobacteria [60]. These phyllos can produce airborne spores that can infect another person [61].

Parasites

An organism that lives on or in a host and feeds at its expense [62]. There are three major classes: protozoa, helminths, and ectoparasites [63]. Examples of protozoa are the *Amoeba* and *Plasmodium* [64]. Helminths are simple invertebrates, some of them infectious parasites. Schistosoma causes severe disease [65]. Although hepatic or splenic involvement is not common, it is a concern [66]. Another example is *Trichinella spiralis*, which can trigger heart failure and respiratory paralysis [67]. The relationship between gastrointestinal parasites and the gut microbiota may have an impact on health [68]. This occurs through changes in the environment, which determines

alterations in the composition of the IM [69]. And it is demonstrated, in gorillas, by significant differences after MI characterization by pyrosequencing [70].

Ectoparasites

They live on the surface of a host [71]. Examples: flies, ticks, lice, mange mites [72]. Behavioral alterations due to infection by ectoparasites such as louse flies (Diptera: Hoppoboscidae) are known [73]. And migratory taxa can influence the spread of long-term survival as well as reproductive success in birds [74]. The louse fly microbiome is dominated by primary endosymbionts, host species, that can affect both insect vectors and their avian hosts [75]. Due to their enormous resemblance to viruses and bacteria, although with substantial differences, we include Prions (infectious protein particles) [76]. Their misfolded protein is capable of transmitting its morphology to another protein and producing transmissible spongiform encephalopathies [77]. They are considered infectious agents that destroy nucleic acids in contrast to bacteria and viruses [78].

Wild type proteins in abnormal and misfolded β-sheet shapes such as cellular prion protein or amyloid beta are considered to be disease-causing [79]. The seeding of protein aggregates has been adduced as a producer of neurodegenerative disorders, including Parkinson's [80].

Fungus

Eukaryotic heterophobic organisms with rigid cell walls made of cellulose or chitin. They reproduce by forming spores [81]. Some of them are unicellular, although most are multicellular [82]. Fungi and bacteria decompose the environment [83]. Example diseases of its infection are histoplasmosis, vaginal candidiasis and some thrush [84]. The use of antibiotics causes the yeast to grow uncontrollably [85]. Sequencing has also allowed the study of the Mycobiome, which influences health and susceptibility to diseases and immunity [86]. Well, all the organisms described must be evaluated at the same time, considering their ways of acting, as well as their interactions, in order to reduce the impact that all of them cause; which is not always harmful [87]. The Intestinal Microbiota is very sensitive in the contact and communication between the individual and the external environment. For perfect homeostasis to exist, it must clearly distinguish between pathogens or potential pathogens, on the one hand, and commensal microorganisms in symbiosis with the host, on the other. In the first case, the IM must employ adequate defense elements and in the second case, it has to learn to tolerate, in order to obtain the benefit of the symbiosis [88]. Although some microorganisms stand out in importance in their functions such as the Intestinal Microbiota with its bacteria carrying viruses, they all count.

Probiotics, prebiotics and synbiotics

They have been tested in many circumstances for their good effects [89]. For example, Bifidobacteria, as beneficial organisms and with a large presence in the gut microbiota, are associated with the non-persistent lactase phenotype, helping to digest lactose, immersed in milk [90]. On the other hand, probiotics have been used in viral diarrhea; specifically, *Lactobacillus rhamnosus* GG, affecting rotavirus attenuation [91]. Psychological stress can be reversed with the use of probiotics [92]. *Saccharomyces boulardii* is one of the most studied probiotics; reduces the risk of diarrhea due to antibiotics, both in children and in adults [93]. It reduces diarrhea due to *Clostridium difficile* and its use is moderately evidenced, trying to be administered together with antibiotics, at doses of 250 to 1000 milligrams in adults and a maximum of 500 milligrams in children [94]. *Lactobacillus*, combined with enterococci or *Saccharomyces boulardii* or alone, reduces antibiotic-induced diarrhea [95]. In relation to the use of probiotics in *C. difficile* disorder, it has been argued that *Saccharomyces boulardii* reduces its incidence [96], although there is no unanimous opinion among the different authors [97]. The European Society for Pediatric Gastroenterology, Hepatology and Nutrition recommends *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii* in children with acute gastroenteritis [98]. The administration of *Lactobacillus acidophilus* or *Lactobacillus casei* improves the eradication of *Helicobacter pylori*, simultaneously using antibiotics [99].

Bacteriophages treatment

The idea of using bacteriophages to treat Infections has been known since Frederik Twort [100] and Felix d´Hérelle [146] discovered bacterial viruses. Phages infect bacteria and not eukaryotic cells [101]. There are several countries that use bacteriophages as a treatment for bacterial infections, including Georgia, Russia and Poland [102]. Currently, lytic bacteriophages are making a comeback, especially in multiresistant infections [103]. Phages are commonly used in cocktails [104]. Their usage has decreased the presence of *Staphylococcus, Pseudomonas, Escherichia, Klebsiella* and *Proteus* in Eastern countries [105]. The proteins that the phages encode (endolysins, exopolysaccharides and holins) are promising antibacterials [106].

Post-biotics

Bioactive compounds can be used to promote health and are generated in a matrix during fermentation [107]. Either probiotic metabolites or components resulting from the fermentation of probiotics in the intestine [108]. Some foods that can help increase the concentration of post-biotics in the gut: Sauerkraut, kefir, sourdough bread, pickles, soft cheeses, millet soup, buttermilk, tempeh and yogurt [109].

Pili

Pili are mainly composed of oligomeric pilin proteins, they are arranged helically to form a cylinder [110]. There is a conviction of the beneficial effect of postbiotics, even in healthy people [111]. They relieve infant colic, different types of diarrhea and atopic dermatitis.

Para-probiotics

Inactivated (non-viable) microbial cells that confer health benefits to consumers. They regulate adaptive and innate systems, being anti-oxidant, anti-proliferative, and anti-inflammatory. They are safe and can be used on the disabled or elderly. They are included in the group of nutraceuticals [112].

FIF or fortified food formula

It has been suggested that they can be very suitable for children around 5 years, however, we must not forget the dietary diversity, based around vegetables [113].

Dormant bacterial cells

Bacteria can exist in states metabolically inactive, allowing them to survive conditions that are not conducive to growth. Such dormant bacterial cells can feel when conditions have improved and restart growth, otherwise, they would be affected by their neighbors. We will soon see a new therapy, that of inactive bacterial cells, as has already been tested in some types of cancer [114].

Fecal microbiota transplant (FMT)

Its effectiveness in infection have been proven in recurrence due to *Clostridium difficile*, with successes of up to more than 90% [115]. In inflammatory bowel disease, especially chronic ulcerative colitis nonspecific improvement has also been noted with the IMT, as in the irritable bowel syndrome and neurodevelopmental disorders [116]. For perform the TMI, we must not forget the recommendations of the FDA, in relation to with the great COVID-19 pandemic [117].

Conclusion:

- Further investigation of the interconnectivity of the virome with other elements of the microbiome is essential to fully define the role of the gut virome in human health.

- The current therapeutic arsenal to modulate the microbiome is broader every day since we have: probiotics, prebiotics, symbiotics, bacteriophages (phages), postbiotics, paraprobiotics, FIFs, intestinal microbiota transplant, and inactive bacterial cells.
- If someone manages to get different experts from the Microbiome to work together, such as virologists, microbiologists, parasitologists, geneticists, immunologists, gastroenterologists, neurologists, etc. We will not only be able to achieve substantive progress, but we will also achieve new knowledge in favor of not only human health.
- It is useful to reduce the intake of carbohydrates and fats; and, if possible, swallow precursors of intestinal postbiotics.
- Administer antibiotics only rationally.
- Learn to manage your stress, either with physical exercise, according to your circumstances, or with specific mental activities.
- Help decrease the number of cesarean sections.

Conflicts of Interest

The authors declare that do not have affiliation or participation in organizations with financial interests.

Ethical Approval

This report does not contain any study with human or animal subjects carried out by the authors.

Informed Consent

The authors obtained informed written consent from the patients, in order to develop this article.

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