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Human gut virome and microbiome and their role and importance for health: a mini-review

Abstract

Microbiome problematics and its impact on man´s health is today in the center of unprecedented interest of both professionals and lay people. The viral and bacterial species inhabiting especially the internal surfaces of the organism are directly or indirectly important for the activity of the main body organs and organ systems, especially of immune ones. This mini-review provides basic overview of the importance of viral and bacterial microbiomes in healthy humans and their impacts on our well-being.

Keywords: healthy human gut, virome, microbiome

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Clarification of terms "microbiome" and "virome"

In recent years, the problem of microbiome and its direct and indirect effects on overall health as well as on the activity of other organ systems, especially the immune, has attracted increasing attention. At present, there is a significant shift in views on the overall concept of the role of microorganisms colonizing external and namely internal surfaces of the macroorganisms. In the human body, they are located on the skin and on the internal mucosal interfaces of gastrointestinal, genitourinary, and respiratory tracts), and conjunctiva.[1] These highly complex viral and microbial communities, which include commensal, pathogenic and non-pathogenic viruses, prokaryotic bacteria and *Archaea*, and eukaryotic microorganisms such as protozoa and fungi (yeasts and molds) are referred to as the "microbiota" or relatively less accurately the "microflora". Today, the more exact term the "microbiome" is used. In a row of research papers even in materials originated from Human Microbiome Project is very often claimed that terms "microbiota" and "microbiome" were introduced in 2001 by J. Lederberg (1925-2008),[2] the Nobel Prize laureate (1958) for the discovery of the conjugation of bacteria.[3] However, this statement does not correspond to the historical truth. Lederberg never used these terms.[4,5] Microbiota as a basic term is used at least more than a half of the century since the first germfree animal experimental models were commonly used.[6]

The term "microbiome" therefore includes the set of genomes of all above-mentioned microbial communities inhabiting the aforementioned specific niches. Similarly, the term "virome" refers to the community of different virus species found in the microbiota (microbiome).

Virome

Viruses play an important role in evolution and homeostasis of biosphere and its connection with inorganic matrix. They participate on persistent exchanges of genes in planetary genetic milieu (pangenome or common genetic content of all living organisms). Viruses are the most abundant biological units with total number probably as high as 10^{31} particles.[7] They are omnipresent in all organisms and biotopes – atmosphere, soil and water including arid and polar areas (e. g. deserts, permafrost) and hot thermal waters. Some of them are very sophisticated biological entities as giant DNA viruses with specific immunity similar to bacterial CRISPR and directed against own viral parasites known as virophages. Dense viral habitat is present in bottom oceanic sediments but the highest densities of viruses are present on the epithelia of animal body organs, mainly intestines (and feces).

The human gut virome is composed from vast number of different viral species may be further subdivided into viruses infecting bacteria (bacterial virome or phageome), which is the most numerous community of viruses (reaching up to 10^{13} bacteriophages), other viruses infecting eukaryotic cells (eukaryotic virome), viruses that infect *archaea* (*archaea*l virome), and virus-derived genetic elements incorporated in host chromosomes, which may have potency to change host gene expression and even generate infectious endogenous viral elements like prophages, and endogenous retroviruses. It is estimated that more than three thousand human endogenous retroviruses are integrated into the host genome, comprising about 8% of human DNA.[8]

Despite of these facts and compared to bacterial component of the intestinal human microbiome, the role of the virome and the effects of viral activity on human health have been practically ignored and still remains one of the least understood components of the gut microbiota. Up-to-the present, only around 1% of human virome has been sequenced.[9,10] In present, it is quite clear that virome and bacterial microbiome interact with each other in both health and disease.

The common coevolution for billions of years formed specific DNA and RNA viruses, which outnumber bacterial cells by as much as 10:1. Fecal samples contain sequences of plant and animal viruses from the food or viruses of commensal or pathogenic protists, and other eukaryotic organisms living in the intestines. The diet is therefore an important and constant environmental factor that can camouflage and change the results of metagenomic studies of stool samples. The pepper mild mottle 138 virus (PMMoV), one of the genus *Tobamovirus* commonly found in pepper, is the most frequent phytovirus in human stool and it retains infectivity after passing through the human alimentary tract. Due to its stability, it can be used as a marker of fecal contamination of water.[11]

Viruses colonize the gut immediately after birth. Meconium did not contain any viral particles. Within a week after birth, numbers of virus-like particles reach $10^{8}.g^{-1}$ in feces, with the initial colonizers originating from a combination of dietary, maternal and/or environmental sources.[12] Different species of viruses were found

in fecal samples of healthy humans. The majority of them are phages and viruses of eukaryotic organisms, but some of them are human pathogens. By no means do all pathogenic viruses found in feces cause disease. Some cause silent infections of the gastrointestinal tract. SARS-2 coronavirus RNA positivity in feces can be observed in covid-19 and can last even after viral clearance in the respiratory tract.[13]

Differences in viral composition of stool and nasal mucus samples in healthy children are shown in Table 1.

Table 1 Main viral taxa found in healthy children

Viruses in fecal samples[14]	Viruses in nasal samples[15]
Picobirnaviridae	adenovirus
Adenoviridae	human coronavirus
Anelloviridae	human bocavirus
Astroviridae	human parechovirus
bocaviruses	human metapnerumovirus
sapoviruses	human parainfluenzavirus
rotaviruses	human rhinovirus
enteroviruses	respiratory syncytial virus

Anelloviruses and picobirnaviruses found in fecal samples of healthy children are probably viruses that have other hosts than human and represent commensal viruses in the meantime (as the phages). Anelloviruses were found in serum, saliva and gut shortly after birth. A typical representative of anelloviruses is TTV (Torque teno virus). This human virus was observed as a circular single-negative-strand DNA in various tissues and biological samples, notably in the gut, blood serum and lymphocytes. It was discovered by DNA sequencing of transfusion blood and is considered as a commensal human virus - similar to some circoviruses in the skin and picobirnaviruses in human stool. TTV has no apparent clinical significance, although it might be very useful as a prospective tool for gene delivery or as an epidemiological marker. Human populations are ubiquitously infected with TTV - the prevalence may reach 100%. The majority of babies become spontaneously infected with TTV, so that by the end of the first year of life, the prevalence reaches adult values. TTV positivity in healthy early infancy and the presence of TTV in umbilical cord blood samples have been reported. The mechanism of infection and the dynamics of TTV prevalence in infants with age remain understudied. Meanwhile, the potential diagnostic and prognostic value of TTV as a marker deserves special attention and study, along with the possibility, causes and consequences of placental transmission of TTV under normal or pathological conditions.[14]

Picobirnaviruses (PBVs) have been widely reported in fecal samples/gut contents of humans and various animal species with or without diarrhoea. These opportunistic mammals or avian enteric pathogens occur also in invertebrates or environmental samples. PBVs can be prokaryotic or fungal viruses. True hosts are still unknown, but many viruses are present in silent infections. The gut virome of healthy individuals include herpesviruses, anelloviruses, papillomaviruses, polyomaviruses, adenoviruses, parvoviruses and pegivirus.[16]

Statoviruses (stool-associated tombus-like viruses), recently defined a novel taxon of RNA viruses, which are phylogenetically related to other RNA viruses such as tombusviruses or flaviviruses, were also demonstrated in man, macaque, mouse, and cow feces. There were identified five distinct statovirus types in humans (statovirus C1) in a child suffering fever and rash. These RNA viruses could be parasites of accompanying intestinal protist symbionts or pathogens.[17]

Parvoviruses as human bocaviruses, dependoviruses (adeno-associated viruses whose genome persists in infected cell infinitely until the time of rescuing by new infection with an adenovirus) and human parvovirus 4 were found in different stool samples of apparently healthy individuals. Sequences of giant DNA virus similar to them, originally found in amoebae, were also detected in healthy human stool. These findings which can be caused by laboratory contamination have started studies of human megavirome.

Other organs of healthy humans than the intestine contain many different viruses too. Almost all individuals are seropositive against tens of polyoma viruses, e.g. BK and JC (John Cunningham) viruses and herpesviruses (e.g. herpes simplex virus 1, cytomegalovirus, Epstein-Barr virus or varicella zoster virus), many of them forming persistent latent infection which can change in disease in immunocompromised humans or individuals after anti-immune therapy (e. g. natalizumab in biological therapy of multiple sclerosis with activation of JC viruses in some patients). The blood virome of healthy individuals include herpesviruses, anelloviruses, papillomaviruses, polyomaviruses, adenoviruses, parvoviruses and pegivirus.[14]

Virome richness in the intestine parallel development and diversification of bacterial microflora. The composition of bacterial colonizers is changing with age and diet. Also disease and application of antibiotics, and especially fecal microbial therapy (FMT) induce substantial changes of viral species and their contents within the gut. The effect of the virome on the success of FMT therapy has been appreciated only recently (fecal phage therapy). Phages modulate composition of bacterial communities and can influence their human host. Thus, phage transcription factor Cro can activate the enterohemorrhagic *Escherichia coli* type III secretion system enhancing the virulence of EHEC.[12]

Conclusively, our understanding of the intestinal virome is fragmented and requires standardized methods for virus isolation and sequencing to provide a more complete picture of the virome, which is a key to explaining how viruses can contribute to the etiology of diseases and how could be rationalized as targets for interventions.[18,19]

General importance of gut microbiome

It is estimated that on planet Earth are more than 100 bacterial phyla. So far, only a few taxa have been identified in the human gut microbiome. On the other hand, the intestinal microbiome represents one of the most complex ecosystems in nature and plays a prominent role in maintaining health.[20] The composition and activity of gut microbiota is also involved in digestion and food processing, and producing vitamins and other important substances. All it affects the course of many diseases ranging from gastrointestinal dysfunctions through diabetes 2, cardiovascular and cancer diseases to neuropsychological manifestations.[7,21–26]

Already Hippocrates of Kos (c. 460 – c. 370 BC), the Father of the medicine, taught that: "... all diseases begin in the intestine." However, the intense interest in this issue only occurred in the early 20th century and is associated with the name of I. I. Metchnikoff (1845-1916), among others, the discoverer of phagocytosis (Nobel Prize 1908), who recommended using lactic acid microbes to prolong human life and hence the treatment of infections. Some sporadic papers have reported that the type of diet may be directly reflected in composition and metabolism of intestinal microorganisms, later called the intestinal microflora.

Only at the beginning of the 21st century, did many researchers pursue a deeper understanding of the microbiome's composition

and the consequences of its manifestations.[27] Twenty years ago, J. Lederberg estimated that a microbiome has a 150-fold genome greater than that of a human. It is commonly reported in the literature that the number of prokaryotic species is about 10^3–10^4, it means 10 microbes 1 eukaryotic cell of the body, and that the microbiome has about 3.10^5 genes, while humans have only about 2.10^4. The myth 10:1 has continued since the early 1970s.[3] As some recent authors criticize, this ratio should not be taken literally, that is, that our bodies have more bacteria than body cells.[28,29] Rather than sticking to these numbers, it is important to keep in mind that the number of human microbiota cells is highly variable. It depends on a number of factors, in particular the age of the individual and his or her ethnic origin, cultural habits and lifestyle determining the intake and type of nutrition, as well as the geographical environments, i. e. climate zones and high-altitude conditions (for rev. see [30,31]).

Sender et al.[32] estimate that the total number of bacteria in a 'reference man' (70 kg) is $3.8.10^{13}$ and the body cell count is $3.0\ 10^{13}$. Therefore, in reality, the number of bacteria in the body is essentially the same, as the number of human cells. Average range of areas in the human body and corresponding numbers of bacterial species found in them is shown in Table 2.

Table 2 Average estimates of organ area and approximate numbers of microbial species that populate them[29,32]

Organ surface	Area in m^2	No. of species
oral cavity	0.215	2600
gastrointestinal tract	300-400	1180-3180
respiratory tract	160	314
urinary tract	0.35	20-500
vaginal cavity	0.090	280
skin	1.8	110

Individual species of microorganisms respond to environmental changes and exchange information not only among themselves, but also with the cells of the macroorganism using a number of chemically diverse signal molecules. This mutual communication has been referred to as "quorum sensing" (QS).[33] By QS, bacteria monitor their numbers and reactivity within the environment[34] and control synthesis of secondary metabolites, mechanisms of stress adaptation, and bacterial secretion systems (SS), which are important for communication among bacteria. Eight main types of SS involving in bacterial communication are known for now.[35]

QS induces changes in gene expression of bacterial species occurring in the microbiome, resulting in the production of a row of signaling molecules, which differ both in structure, and in mechanism of their action[36] that influence both the numbers of microbial and viral individuals, and the representation of individual species in the microbiome, including their functional activity, which ultimately affects the cells of the macroorganism.[37] Regulatory molecules transfer of QS signals, bind QS signals, and reprogram gene expression. The so-called autoinducers like acylhomoserine lactones (AHLs) (in G-negative bacteria), auto-inducing peptides (AIPs), and auto-inducer 2 (AI-2) (in *Vibrio harveyi*), can be cited as the most studied. In general, QS contributes to regulation of genes controlling virulence, competition, pathogenicity, resistance, and also such processes as bioluminescence, biofilm formation and horizontal gene transfer.[38,39]

On the other hand, the term "quorum quenching" (QQ) represents mechanism when bacterial communication is interrupted by means of inhibition of synthesis of auto-inducers, their binding to the receptor, or by their degradation.[40] Generally, QQ blocks QS system and inhibits gene expression mediating bacterial communication, and activity. From this point of view, QQ system is currently offered as an alternative option to limit the spread of infections in certain environments, e. g. in aquaculture industry. It is can be used to control bacterial biofilms also in medicine, industry, and agriculture.[41]

The cooperative QS/QQ system is the basis of positive (from neutralism to commensalism) and negative (from antibiosis to parasitism) symbiotic relationships in the sense of how was defined it by A. de Bary as early as 1879[42], both within the microbiome/virome and between the microbiome/virome and the macroorganisms.

The biochemical activity of microbiome can have both positive and negative effects for the health of an organism. Health positively affects the condition when microbes live in mutual balance and their species distribution is also balanced. It is referred to as "eubiosis", or less often "normobiosis". A broken composition of microbiota, for whatever reason, or when this balance is upset because some part of microbes has grown out of the proportion to other species, which adversely affects health, is referred to as "dysbiosis".[43] There were described three types of dysbiosis: loss of beneficial microorganisms, the expansion of harmful groups, and a general loss of diversity[44], or similarly, bloom of pathobionts, loss of commensals, and loss of diversity.[45] Dysbiosis increases the risk of various diseases such as inflammations of the intestine, stomach and infectious diseases caused by agents such as rotaviruses or bacteria ranging from salmonella and yersinia to dangerous *Clostridium difficile* and *Helicobacter pylori*.

It is mentioned in many works as for example[46,47] that Metchnikoff originally used the term dysbiosis for describing an imbalance of commensal and pathogenic bacteria in the gut. However, he never mentioned this term. He only divided resident intestinal bacteria according to their effects into pathological and normal.[48] It is a similar historical mistake as mentioned above with the use of the term microbiome and microbiota by J. Lederberg. The first use of the term dysbiosis in today's sense appeared in 1920 when German nutritionist C. A. Scheunert studied the relationship between intestinal "flora" and inflammation in horses.[49,50]

Structure of intestinal microbiome

The initial composition of the intestinal microbiome depends primarily on whether the birth took place naturally or by caesarean section. During normal birth, lactobacilli and bifidobacteria occur mainly in the intestinal microbiome of the newborn. For example, facultative anaerobic *Escherichia coli*, strictly anaerobic *Bacteroides fragilis* and clostridia are missing. After birth by caesarean section the species abundance is poorer. It includes members of the taxa *Staphylococcus*, *Corynebacteria* and *Pripionibacteria*, but less is bifidobacteria (similar to premature babies). Such a less varied microbiota may, at a later age, be a cause of susceptibility to certain non-communicable diseases (such as obesity and celiac disease), but also to a higher incidence of allergic conditions and asthma, as well as autoimmune and metabolic diseases.[51] The microbial composition can be normalized by breastfeeding or by administering the mother's vaginal microflora.

The composition and amounts of intestinal microbiome species stabilize approximately since the age of 3 years, practically after the transition to solid food. In adulthood, besides *Firmicutes* and *Bacteroidetes* (99% of the identified species representing together 70% of the total microbiota)[52], also *Actinobacteria*, *Proteobacteria, Verrucomicrobia,* and *Fusobacteria* are still frequently found but in much smaller amounts, similarly as methanogenic *Archaea* (most frequently *Methanobrevibacter smithii*), *Eukarya* (mainly yeasts) and viruses (primarily phages).[53,54]

According to metagenomic analysis, the intestinal microbiome is divided into three main enterotypes, which of terms firstly appeared in 2011.[55,56] Individual enterotypes are differentiated according to the representation of bacterial species and the functions that these bacteria perform.

Main taxa of microbes in enterotypes and examples of their action is introduced in Table 3.

Table 3 Enterotypes of human gut

Enterotypes	Main bacterial taxa	Involved mainly in metabolism of	Production of
enterotype 1	*Bacteroides*	carbohydrates, cell wall proteins	riboflavin (B2), biotin (B7), pantothenic acid (B5) vitamin C menaquinone (vitamin K2)
enterotype 2	*Prevotella, Desulfovibrio*	mucin glycoproteins	thiamine (B1), folic acid (B9)
enterotype 3	*Ruminococcus, Bacteroides*	carbohydrates, mucin, heme vascular wall proteins	menaquinone (vitamin K2)

Intestinal bacterial microbiomes by their activity and products influence the activity of organs and organ systems of the macroorganisms, which greatly contributes to ensuring of homeostasis of its internal environment, *i.e.* its health. To mention this topic in more detail here would exceed the scope of this minireview, as a plethora of studies have already been published on it. Therefore, the influence of the microbiome on the three basic homeostatic systems of the macroorganism is only briefly recalled in a following survey:

I. Gastrointestinal digestive system

Bacteria of intestinal microbiome are involved in a number of biochemical (metabolic) processes, including digestion (processing and energy utilization of food). They are producers of some important vitamins (see above) and other important substances such as antimicrobial peptides (bacteriocins), which inhibit the growth of pathogenic bacteria and participate directly in the degradation of xenobiotics.[36]

II. Immune system

As early as 1927, at a time when immunology was essentially a mere serology, it was suggested that mucosal surfaces must be accompanied by the immune system in order to protect the internal environment of the body.[57] It is in the close proximity to mucosal surfaces, especially the gastrointestinal tract, that the largest lymphoid structures, the so-called GALT (Gut Associated Lymphoid Tissue), are formed, which are also the body's largest immune organ on which the body's overall resistance depends. The composition of the intestinal microbiome (the representation of eubiotic and dysbiotic species) then affects the overall activity of the immune system, which directly or indirectly determines the occurrence and course of communicable and non-communicable diseases. Disruption of microbiome balance may also cause a variety of cancers, particularly colorectal cancer, as well as pancreatic tumors.

III. Neuroendocrine system

As mentioned, the action of intestinal microbiome affects many processes in the body, even in relatively distant tissues and organs. This also applies to CNS. There is even talk about the intestinal microbiome - CNS axis[58] and one of the main communication channels between the intestinal microbiome, and the CNS may be the vagus nerve.[59,60]. Intestinal bacteria produce a number of neurotransmitters and other activating factors that can stimulate GALT immunocytes and endocrine cells in the intestinal wall, in which they induce the production of bioactive substances such as peptides, cytokines, antimicrobial cationic peptides, gamma aminobutyric acid (GABA), serotonin, catecholamines, melatonin, histamine, acetylcholine, etc., which then act on nerves endings in the intestine wall. Many of these substances may be involved in attenuating inflammatory processes or mitigating the response to stressing factors (affecting emotional states, relieving depression, and *vice versa*, the stressing factors may cause changes in microbiome composition. Depression has been reported to reduce bacterial counts of *Bacteroidetes*, which is accompanied by increased pro-inflammatory marker formation (IL-6, TNF-α, C-reactive protein) and decreased brain-derived-neurotropic factor (BDNF) levels.[60,61] In this context, the importance of microbiome for the production of one of the most important neurotransmitters, serotonin (of which 70% is produced in the gut), which interferes with a plethora of psychoneuroendocrine processes, e.g. regulates vascular smooth muscle contractions, vascular permeability, heart rhythm, blood pressure, body temperature, taste, emotions, mood, response to stress, mobility, pancreatic secretion, etc.[62]

Conclusion

This paper provides a general overview of the importance of microbiome and highlights some of the latest findings on biological activity of the intestinal microbiome, which are of paramount importance to the health of the organism. Nevertheless, it has not been possible to mention some of the themes for their vastness, such as for instance the relationship between microbiome and nutrition, which is currently of unprecedented interest. It could be mentioned also the broad issue concerning the importance of recently discovered role of beneficial microbes, which could be used for therapeutic application as next generation of probiotics such as *Akkermansia muciniphila*).[63] There are so many published papers on microbiome that it is not in the power of one person to contain them. The references are therefore not and cannot be exhaustive, they are intended only for the basic orientation of the reader. The worst is (or the best?) that the numbers of publications are growing. The pessimistic point is that this information mass cannot be managed, but optimistic that new and more accurate knowledge is coming, which will certainly not only improve the quality of life but also extend it in the near future. At this point, it is important to realize that any treatise on the microbiome can only capture a narrowed view on individual topics and only the current "*status quo ante*", because tomorrow will bring new and perhaps even surprising, or even refuting discoveries.

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Conflicts of interest

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