

Human Virome

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Abstract

Microorganisms found upon and within the human body play an important role in health and disease. The human virome refers to a whole genome of the human viruses living on and inside us. The genetic material of viruses includes both DNA and RNA because viruses lack a universal sequence platform, which makes it difficult to detect them or analyse their composition. By Entrance of next-generation sequencing (NGS), technology allowed the researcher to determine all viral sequences in a given sample, through an expanding field called viral metagenomics. Several factors affect on virome variation between individuals such as disease exposure to it, diet, immune status and birth mode. The gut virome consist of prokaryotic and eukaryotic viruses. However, prokaryotic viruses have an impact on human health by affecting the bacterial community function and structure. Bacteriophages are the most abundant enteric viruses. There is an interaction between virome and other members of the microbiome.

Keywords: Virome; Microbiome; Gut Virome; Viruses; Bacteriophage***Correspondence to:** Sana G AlAttas, Department of Biological Sciences, Faculty of Sciences, King Abdulaziz University, Jeddah, Saudi Arabia.**Citation:** AlAttas SG, Bahieldin A, Alotibi A, et al. (2020) Human Virome. *Prensa Med Argent*, S2:014. DOI: <https://doi.org/10.47275/0032-745X-S2-014>.**Received:** June 20, 2020; **Accepted:** July 31, 2020; **Published:** August 04, 2020

Introduction

All microorganisms and their genes can form essential part of human body [1-3]. In recent years, the number of viruses, bacteria, fungi, protists and archaea staying upon and within the human body have been increasingly discovered. All these microorganisms play important roles in human health and disease, including inflammatory bowel disease (IBD), age, diabetes, diet and weight [4-10]. In 2003, the first article about 'virome' was published [11]. The article indicated that viruses are presented in the human microbiome. The first sequenced bacteriophages from faeces was published for an infected patient in the same year [12]. Intestines considered the most infected organ with viruses, and their number reach up to 10^9 per gram [13]. The term 'mammalian virome' refers to both eukaryotic virome that infects eukaryotic cells, bacterial virome or bacteriophages that infects bacteria and archaeal virome that infects archaea [14]. The genetic material of viruses includes both DNA and RNA because viruses lack a universal sequence platform, which makes it difficult to detect them or analyze their composition [15]. The huge development in sequencing technology and assembly of information in sequence databases made recent researchers to reveal that viruses and their genomes (virome) play important role in human health and disease [16-18]. Entrance of next-generation sequencing (NGS), technology allowed the researcher to determine all viral sequences in a given sample, through an expanding field called viral metagenomics [19]. Previous studies discovered that gut viruses had a beneficial role in normal microbial homeostasis despite pathogenic effects [19]. Eukaryotic viruses are capable to produce transient or stable infection and diseases in host cells. However, beneficial aspect of these viruses in health is rare [19]. Bacteriophages revolved around the concept that they are the most abundant entities

on earth and also expand to the gut where they constitute the most abundant inhabitants [19]. The effect of gut bacteriophages on prokaryotic communities either by direct lysis of their host (lytic phages) or by integrating their genomes into the host (lysogenic phages or prophages) which result in changing the phenotype and fitness of the host cells [20]. When bacteriophages interact with their hosts, they compromise impacts on the biogeochemical cycling, composition of microbial communities and microbial abundance [21,22].

The Definition of Virome and its Components

The human microbiome refers to a whole genome of the human microbiota living on and inside us, encompassing fungi, bacteria, parasite, archaea and viruses [23]. Therefore, "microbiome" includes bacteriome, virome and mycobioime. However, researchers worked hard to study the human microbiome in different environments for example in animals, oceans or soil [23-25].

Recently, viruses have obtained their own "-omics" and "-ome" (meta) viromics and the virome. These terms include all viruses and their genomes that inhabit particular ecosystem and the study of them [26]. Human virome constitutes part of the microbiome which represent the most genetically diverse and ubiquitous fraction [27]. Because, virome plays a role on the biogeochemical cycling of nutrients, hence cause host diversification and breakdown trophic structures [28,29].

Viruses infecting prokaryotes or eukaryotes are present in the microbiota referred to virome [30]. Prokaryotic and eukaryotic viruses can cause latent or lytic life cycle which leads to virus evolution and survival (Figure 1) [31]. Consequently, when human eukaryotic viruses integrated into host chromosomes, then it can affect the host

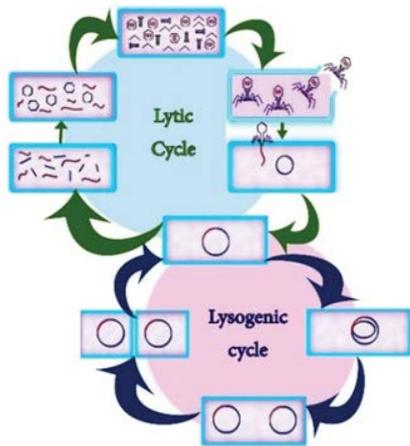


Figure 1: In the case of the lytic cycle, the virus infects a host and use their cellular machinery to produce millions of progeny, this end with the death of host but in the lysogenic, genetic material of virus integrate with DNA of the host and replicate.

physiology, especially when particular site gets infected with chronic infection and virus-derived genetic elements can modify protein expression and host gene [14,32,33].

Few studies recorded on archaeal viruses of the family Lipothrixviridae [22]. On Earth, bacteriophages are considered the most abundant entities but also, inside the gut it is dominant than other viruses [34]. The majority of bacteriophage genome were sequenced from feces or gut samples belongs to ssDNA family Microviridae and dsDNA families Myoviridae, Siphoviridae, and Podoviridae [4,9,35]. The introduction of next-generation sequencing (NGS) technology caused a revolution in the discovery of novel viruses in animals and human in different environments [36-38]. In spite of massive recent efforts have been made to study the critical role of viruses in Acquired Immune Deficiency Syndrome, Inflammatory Bowel Disease and diabetes patients. However, the role of virome in human diseases have been less described [8,39-41].

There is an absence of validated methods that enable reproducible virome analysis and high throughput, hence constitute huge limitation in understanding the presence of human gut virome in disease and health [27]. One of these limitations, is that most of the genetic material in a sample is the non-viral origin, which causes precisely makes studying of the virome becomes more difficult than studying other microbiomes [42]. Viruses are considered the most morphologically and genetically diverse and lack universally preserved genomic regions [30].

Human Virome Diversity in Health and Disease

The human body in each compartment harbours distinctive viral population, here we discuss this separately. Several factors effect on virome variation between individuals such as disease exposure to it, diet, immune status and birth mode [34,43].

However, characterization of virome from different people around the world has revealed the role of the environment on its composition. Healthy people not showing any signs of disease and individuals that recently recover from acute infections harbor different viruses [44].

In Addition, the number of viruses varies according to the site that is occupied from, 10^6 per $[\text{cm}]^2$ on the skin, up to 10^8 per

milliliter of saliva fluids, nasal, oral and pharynx, and 10^5 in the blood, 10^9 per gram in the intestinal and 10^7 in the urine (Figure 2) [45,46]. Bacteriophages were the most abundant ones among them. The size of the human virome is poorly understood. As mentioned by Mokili JL, et al. (2012). Our cells exceed about 10-fold by our bacterium. Previously thought the number of viruses could be 10-fold higher still. And with the emerging of new RNA viruses that were unknown before the entrance of sequencing platforms, the number of eukaryotic virome may be larger than this thought [48].

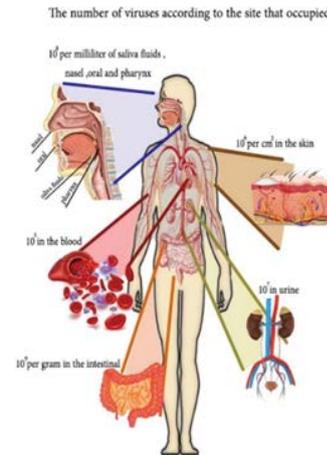


Figure 2: Number of viruses in the body according to site.

Viruses don't have universally conserved genes because they are highly genetically diversity such as 16S rRNA in prokaryotes or 18S rRNA in eukaryotes. Consequently, cannot use metataxonomic approaches to characterize viruses. They relied upon classical approaches such as cultivation and microscopy to characterize gut viruses [49]. Nowadays researchers use bioinformatics tool to identify unknown viruses through massive search in database references (e.g. NCBI viral RefSeq) about homologous sequences [50]. This provides precise prediction about the desired viruses [45,46].

Virome was associated with different disease as shown in these studies which revealed a relationship between bacteriophages and eukaryotic virome with inflammatory bowel disease (IBD) infection [8,51,52]. Moreover, gut phageome is associated with colorectal cancer and type I diabetes [53,54]. While diarrhoea in AIDS and infants had been linked to eukaryotic virome [55].

One recent study was conducted in 2018, found that bacteriophages diversity in patients gut with colorectal cancer (CRC) was significantly increased compared with healthy people [56]. Data from this study can be used to identify all patients with predicted outcomes or CRC [56].

Another study was conducted with HIV patients showed that the most frequently sequences assigned to bacteriophages of Microviridae family or Caudovirales order along with several eukaryotic virus families and other viral families were defined as "unclassified" in the NCBI Taxonomy Database. Also, it was found that there were no significant differences between HIV-negative and HIV-positive for Papillomaviridae, Adenoviridae, Circoviridae and Anelloviridae [57].

Gastrointestinal Tract

The concept of viral infection has changed since mucosal viruses exist in healthy people. Viruses are abundant in the gastrointestinal



tract even without showing any symptoms, in the healthy gut mucosa described by frequent infections which become part of virome and in turn promote damaging and/or beneficial impact on the host [1].

The intestinal human virome is more than 10^9 viral particles per gram of faeces [1,35]. The gut virome consist of prokaryotic and eukaryotic viruses. Moreover, prokaryotic viruses have an impact on human health by affecting the bacterial community function and structure [9,35,52]. While bacteriophages are the most abundant enteric viruses, which can harbour up to 10^{14} bacterial cells according to sequencing from the faecal sample [58]. Until now there are many bacteriophages have not been classified yet, currently the most prevalent prokaryotic viruses belong to the order Caudovirales (Myoviridae, Podoviridae and Siphoviridae) in which they were characterized as tailed and double-stranded DNA viruses together with (Microviridae) which have tailless cubic, or filamentous single-stranded DNA viruses [59].

In fact the number of eukaryotic viruses is less than bacteriophages inside the gut [4,9,60]. Moreover, a faecal sample from healthy children has discovered several families of viruses which includes Astroviridae, Picobirnaviridae, Anelloviridae, Adenoviridae and species such as sapoviruses, bocaviruses, rotaviruses and rotaviruses [43].

Although they show few numbers, these viruses play a critical role in health and immune compromised subjects, which give rise to colitis, acute gastroenteritis or acute enteritis [43,61, and 62]. For example, in the fecal sample of individuals suffered from diarrhea of unknown aetiology, Picobirna viruses have been found [63-65]. In addition to that, RNA viruses were found (plant viruses) in the gut which has been introduced in the diet [4,9,35,52,59,66].

In the gastrointestinal tract, there is a dynamic community structure described by prey-predator interactions which provide horizontal gene transfer [66]. A recent study revealed that the development of symbiotic relationships between virome and the host at a young age with variation occurs at the first two years, and that is according to dietary and environmental changes. In contrast, people on the same diet system have a similar composition of gut virome [4,35]. The imbalances between pathobionts and symbiotic bacteria (dysbiosis) may contribute to the transmission from healthy state to disease, which caused by intestinal bacteriophage [67]. However, there are continuous changes in the function, structure and diversity of the gut microbial communities (dysbiosis) which are mainly contributed to the emergence and maintenance of several diseases [68-70]. Such as cancer, colon cancer, inflammatory bowel disease (IBD), Crohn's Disease (CD) and obesity [71-75].

The complex interplay between environmental factors, cognate microbiota and the host can help in the gut dysbiosis development [50,76]. Recent studies revealed that the gut virome have a critical role in disease progression and homeostatic regulation over multiple interaction paths with human immune system component or with bacteriome [76].

The merge between re-analysis of the virome data to establish consistent processing and extensive virus identification, gut metagenomes from 572 individuals were collected and an extensive metadata curation through literature mining and, as needed, direct communication with the original researchers contributed in the development of Gut Virome Database (GVD). This database includes 13,204 viral communities predominant by phages [77].

The Interaction between Virome and other Member of Microbiome

In adults, gut virome and bacterial microbiome are mainly stable and are resilient to change. While in the infant's gut virome and bacterial microbiome are highly dynamic in nature during early development [4,9,78]. The bacterial microbiome structure can change by bacteriophages through prey-predator relationships [8,79].

However, there are significant findings from previous studies that there is an interaction between bacteria and viruses which can make huge effect on disease and health status of the host [31,80]. The intestinal antiviral immunity relies on Gram-negative bacterial signaling [81]. In contrast, the mechanism of enteric virus infection is a defense line against pathogenic bacteria and intestinal damage [82]. Moreover, the replication of enteric viruses such as rotavirus, poliovirus, reovirus, and mouse mammary tumour virus and mouse norovirus can also be enhanced by the bacterial microbiome [82-87].

As mentioned previously, asymptomatic and symptomatic individuals can carry eukaryotic viruses. This results from either a direct interaction with the host or with the interplay with other members of the micro biota [1,19,88-91]. Most of these interactions are happening inside the gut. For example, when enteric viruses enter the human body they find a large number of inhabitant microorganisms inside the intestinal lumen, and the majority of them are commensal bacteria, but also another kind of microorganism such as viruses, archaea, protozoa and fungi, with which they enable to interact [19].

The interaction between them can also modulate viral infection [80,92,93]. The direct physical interaction between microbiome can enhance enteric viruses. Such as the interaction between commensal bacteria reovirus and poliovirus that increases the viral infectivity [84]. In the case of poliovirus, it binds to the bacterial surface polysaccharides, which promotes its binding and its stability to cells through its attachment to the cellular receptor [93]. Furthermore, recent findings have shown that bacteria can facilitate poliovirus infection and enhance virus genetic recombination [94].

Additionally, the enteric bacteria were shown to enhance the replication of rotavirus and diarrhoea in vivo [85]. Also, the microbiota has the ability to weaken the antiviral host immune response which stimulates a tolerogenic environment, and this results in an ease of the establishment of a chronic infection [83,92]. This weakening can be due to either modifying the virus-induced interferon (IFN) signaling [87,92], or by the antiviral antibody response suppression [85,92] All these examples have revealed the ability of commensal microbiota in enhancing many enteric viruses infection.

Besides, many positive effects, microbiota can also affect negatively on viral infection. The binding of rotavirus to a cell requires the interaction with the glycan layer on the cell surface. When inserting human intestinal cells into a culture made of bacterial soluble factors such as *L. casei* and *B. the taiotao* micron that increases cell-surface, it was found that it prevents the rotavirus infection [95]. In the neonatal mouse model, it was found that the duration of rotavirus diarrhoea was being lowered by probiotic bacteria *L. reuteri* [96].

Conclusion

Even though virome is a hot topic of research, luckily there are only few studies about it. Moreover, the limitations in virome studies are few in terms of patients and literature numbers, the absence of validated methods, the viral diversity and the lack of universally preserved



genomic regions. The role of virome in diseases has been less described despite the efforts in the study of the role of viruses in many diseases. There are several factors that has an effect on the virome variation. Researchers must study these factors in more details. The human body in each compartment harbor different viruses but until now the size of the virome body is still poorly understood. Most of the studied viruses belong to DNA viruses. RNA viruses need more study. Bacteriophages are the most abundant in the world and in the human body as well. There are interactions between viruses and microbiome. These interactions can result in either a positive or negative effect on the host. However, the microbiota members can modulate viral infectivity. Also, viruses can modulate bacterial infection in the gut. Consequently, it can help in the anti-microbial resistance. Briefly, virome has a significant role in health status and disease. It is important to study their role.

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