Review

Molecular Bases and Role of Viruses in the Human Microbiome

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Abstract

Viruses are dependent biological entities that interact with the genetic material of most cells on the planet, including the trillions within the human microbiome. Their tremendous diversity renders analysis of human viral communities ("viromes") to be highly complex. Because many of the viruses in humans are bacteriophage, their dynamic interactions with their cellular hosts add greatly to the complexities observed in examining human microbial ecosystems. We are only beginning to be able to study human viral communities on a large scale, mostly as a result of recent and continued advancements in sequencing and bioinformatic technologies. Bacteriophage community diversity in humans not only is inexorably linked to the diversity of their cellular hosts but also is due to their rapid evolution, horizontal gene transfers, and intimate interactions with host nucleic acids. There are vast numbers of observed viral genotypes on many body surfaces studied, including the oral, gastrointestinal, and respiratory tracts, and even in the human bloodstream, which previously was considered a purely sterile environment. The presence of viruses in blood suggests that virome members can traverse mucosal barriers, as indeed these communities are substantially altered when mucosal defenses are weakened. Perhaps the most interesting aspect of human viral communities is the extent to which they can carry gene functions involved in the pathogenesis of their hosts, particularly antibiotic resistance. Persons in close contact with each other have been shown to share a fraction of oral virobiota, which could potentially have important implications for the spread of antibiotic resistance to healthy individuals. Because viruses can have a large impact on ecosystem dynamics through mechanisms such as the transfers of beneficial gene functions or the lysis of certain populations of cellular hosts, they may have both beneficial and detrimental roles that affect human health, including improvements in microbial resilience to disturbances, immune evasion, maintenance of physiologic processes, and altering the microbial community in ways that promote or prevent pathogen colonization.

Introduction

Microorganisms and their viruses inhabit every surface of the human body and are recently widely recognized to be a major factor shaping human health. Cellular microbes, including bacteria, archaea, and fungi colonizing human body surfaces, outnumber human host cells by approximately 10 is to 1 and play crucial roles in human health by several means including contributions to nutrition, inflammation, and immunity [1–4]. Bacteria are the most populous cellular microbes inhabiting body surfaces, and their viruses (bacteriophage) are significantly more prevalent in humans than their eukaryotic counterparts [5,6]. There is now increased interest and research on the community of viruses (virobiota) and bacteria (microbiota) afforded by the advances in next-generation sequencing technologies and analysis tools that have improved our capabilities in the field of metagenomics. Recognizing the complexity and diversity within these dynamic viral communities has given new perspective on the human body as an ecosystem, reestablishing the role of microbes in human health and disease at the start of the 21st century.

Viruses are parasitic biologic entities that require host cells for replication. They are made up of single- or double-stranded DNA or RNA and a protein capsid, which form a structure called a virion. Some viruses may also have a lipid envelope modified from their host cell membrane. They are considered ubiquitous in that they infect nearly every type of cell (including eukaryotes, bacteria, archaea, and fungi) and are found in every ecosystem previously described [7]. Despite the large presence of phage on the planet, they were not discovered until 1915 due to their predominantly sub-microscopic existence. To this day, we remain in an age of viral discovery; most of the viruses currently being described using deep sequencing methods have not been described before and have no homologous sequences in current virus sequence databases [6,8,9]. Equally important to the next-generation sequencing are advancements in informatics allowing us to make more meaningful analyses of viromes. Tools such as the bioinformatic pipeline VIROME (Viral Informatics Resource for Metagenome Exploration) and OptItDBA (Optimized Iterative de Bruijn Graph Assembly) have greatly improved the breadth and accessibility of virome analysis by improving assembly and annotating viromes against multiple annotated sequence databases, which improves the analytic capabilities beyond the constraints of individual sequence databases [10,11]. Some molecular interactions between viruses and their hosts can be deduced from analysis of metagenomic data, which add substantially to knowledge gained from studies of laboratory-adapted host-virus model systems.

While historically many viruses in humans have been identified based on their direct pathogenic effects, we now know that there is a vast viral community in the human body that does not directly cause human disease. In fact, a large portion of the viruses identified thus far in the human virome are bacteriophage rather than eukaryotic viruses [5,6]. We will now review the current data available from studies of the human virome. Despite the current limitations in virome analysis such as the lack of available homologous sequences to identify viral community constituents, the relative dearth of information about RNA viruses in human microbial communities, and potential methodological limitations that may limit recovery of eukaryotic viruses, the continually growing number of studies focusing on viruses as members of the human microbiome provide numerous insights into the role and molecular basis of viral contributions to the human microbiome.

Bacteriophage and Bacterial Coevolution

Bacteria and their viruses have coexisted and coevolved for approximately 3–5 billion years [12] but have been only recently shown to coexist in great abundance as members of the human microbiome. For perspective, the origin of mammals traces back to only 225 million years ago [13]; primates, to about 65 million years ago [14]; and *Homo sapiens sapiens* ancestry, to 200,000 years ago. There are an estimated 10^{31} phage on earth, based on calculations of 10^{30} bacteria on the planet [15] and approximately 10 phage that exist for every bacteria [16]. Comparatively, there are only 10^{22}–10^{24} stars estimated to exist in the entire universe [17]. Phage are a component of virtually all molecular communities described thus far on the planet [18,19]. They are an important vehicle for exchange of genetic materials among living organisms and are likely a means by which gene functions are exchanged in the human microbiome [20–22].

Phage have been shown to be a major stimulus for evolutionary change among bacteria [16,23] and thus are dominant players in shaping the microbiota of all metazoans. They have classically been regarded as having high host specificity as an important aspect of their ecology, as many have been shown to only parasitize within a certain species and even within a subset of that species [24–28]. The increased fitness of phage with high host specificity has been largely explained by two major observations: (1) decreased efficiency for infection with broader host range [29] and (2) antagonistic pleiotropy in which an adaptation is beneficial for certain hosts but deleterious to others [30]. However, with such diversity in bacteria communities, a broader host range could be advantageous by increasing the chances of a phage encountering a suitable host cell, particularly in the setting of rare bacteria [31]. More recently, the classic view of phage host specificity has been challenged as a potential artifact from observations made on phage selected for the laboratory setting [7,32]. Instead of specificity always being advantageous over a more generalist approach, there likely exists a spectrum of viral tropism that is dependent on environmental, bacterial, and phage characteristics [33].

Phage provide great evolutionary pressure on bacteria, spurring mutations and adaptations and changing the existing gene pool. *In vitro* studies of *Pseudomonas fluorescens* and its phage have demonstrated a 10- to 100-fold increase in mutation rates over 200 bacterial generations compared to bacteria grown in the absence of phage [34,35]. Although the *in vitro* scenario of one bacteria evolving with one phage does not reflect *in vivo* evolutionary conditions, coevolution has also been shown to occur rapidly in an *in vivo* study using a "mark-recapture" strategy with *P. fluorescens* and its lytic bacteriophage [36]. The demonstration of the stimulus for evolution importantly demonstrates the significant impact that communities of phage may have as members of the human microbiome. In the setting of increased variables such as competition