Virus Research 240 (2017) 47–55

Contents lists available at ScienceDirect

Virus Research

journal homepage: www.elsevier.com/locate/virusres

Review

Bacteriophages in the human gut: Our fellow travelers throughout life and potential biomarkers of heath or disease

Babak Bakhshinejad[a], Saeedeh Ghiasvand[b,*]

[a] Department of Genetics, Faculty of Biological Sciences, Tarbiat Modares University, Tehran, Iran
[b] Department of Biology, Faculty of Sciences, Malayer University, P.O. Box: 65719-95863, Malayer, Iran

ARTICLE INFO

Keywords:
Gut
Phage
Phageome
Prophage
Biomarker

ABSTRACT

The gastrointestinal (GI) tract is populated by a huge variety of viruses. Bacterial viruses (bacteriophages) constitute the largest and the most unrecognized part of virome. The total bacteriophage community of the human gut is called phageome. Phages colonize the gut from the earliest moments of life and become our fellow travelers throughout life. Phageome seems to be unique to each individual and shows a high degree of interpersonal variation. In the healthy gut, a vast majority of phages have a lysogenic lifestyle. These prophages serve as a major respository of mobile genetic elements in the gut and play key roles in the exchange of genetic material between bacterial species via horizontal gene transfer (HGT). But, imbalance in the gut microbial community during dysbiosis, caused by diseases or environmental stresses such as antibiotics, is accompanied by induction of prophages leading to a decreased ratio of symbionts to pathobionts. Based on this, a diseased gut is transformed from an environment predominantly occupied by prophages to an ecosystem mostly inhabited by lytic phages. A growing body of evidence has provided support for the notion that phageome structure and composition change dependent on the physiological or pathological status of the body. This has been demonstrated by pronounced quantitative and qualitative differences between the phageome of healthy individuals and patients. Although many aspects of the contribution made by phages to human biology remain to be understood, recent findings favor the suggestion that phageome might represent potential to serve as a biomarker of health or disease.

1. Introduction

Microbiome is defined as different microbial communities that inhabit various niches of the body (Ursell et al., 2012). These microbial populations colonize the human body from the early moments after birth and live with us throughout our lifetime (Palmer et al., 2007). The viral component of human microbiome is known as virome. This viral metagenome is made up of all viruses that live in or on our body, including endogenous viral genetic elements in chromosomes, eukaryotic viruses (eukaryotic virome) and bacterial viruses (Fig. 1). Recent breakthroughs in mass sequencing methodologies and growing epidemiological evidence have indicated that virome members are the most abundant and quickest mutating genetic elements of the human body and show a high degree of inter-individual and temporal variations (Ogilvie and Jones, 2014). Also, it is estimated that the major part of virome still remains unidentified. Viruses have been recognized to populate numerous ecological niches of the body, in particular mucosal surfaces. Studies have shown that the gastrointestinal (GI) tract has the richest concentration of viruses in the body (Cadwell, 2015; Columpsi et al., 2016). Non-invasive and convenient sampling from the GI tract allows researchers to analyze and monitor the composition and dynamics of gut viral population during the life span of an individual (Popgeorgiev et al., 2013).

The human virome has a complex network of diverse interactions with other components of microbiome. These are called “trans-kingdom interactions” (Virgin, 2014). Different components of microbiome and virome have also extensive cross-talks with human cells. These interconnections indicate that the human body is like a metagenomic universe with our metagenome at the center and microbial metagenomes revolving around this core metagenome. Although the study of our inner metagenomic universe is still in its infancy, recent advances in building very large sequence data sets and using cutting-edge bioinformatic tools have yielded valuable insights into the microbial world within our body, as well as the role of trans-kingdom relationships in human health and disease (Angly et al., 2005; Lysholm et al., 2012). Within the last several years, an accumulating body of evidence collected by investigating the human microbiome and virome has suggested that both physiological and pathological processes are ecological

* Corresponding author.
E-mail addresses: biologicalresearchmm@gmail.com, s.ghiasvand@malayeru.ac.ir (S. Ghiasvand).

http://dx.doi.org/10.1016/j.virusres.2017.07.013
Received 12 March 2017; Received in revised form 11 July 2017; Accepted 12 July 2017
Available online 22 July 2017
0168-1702/

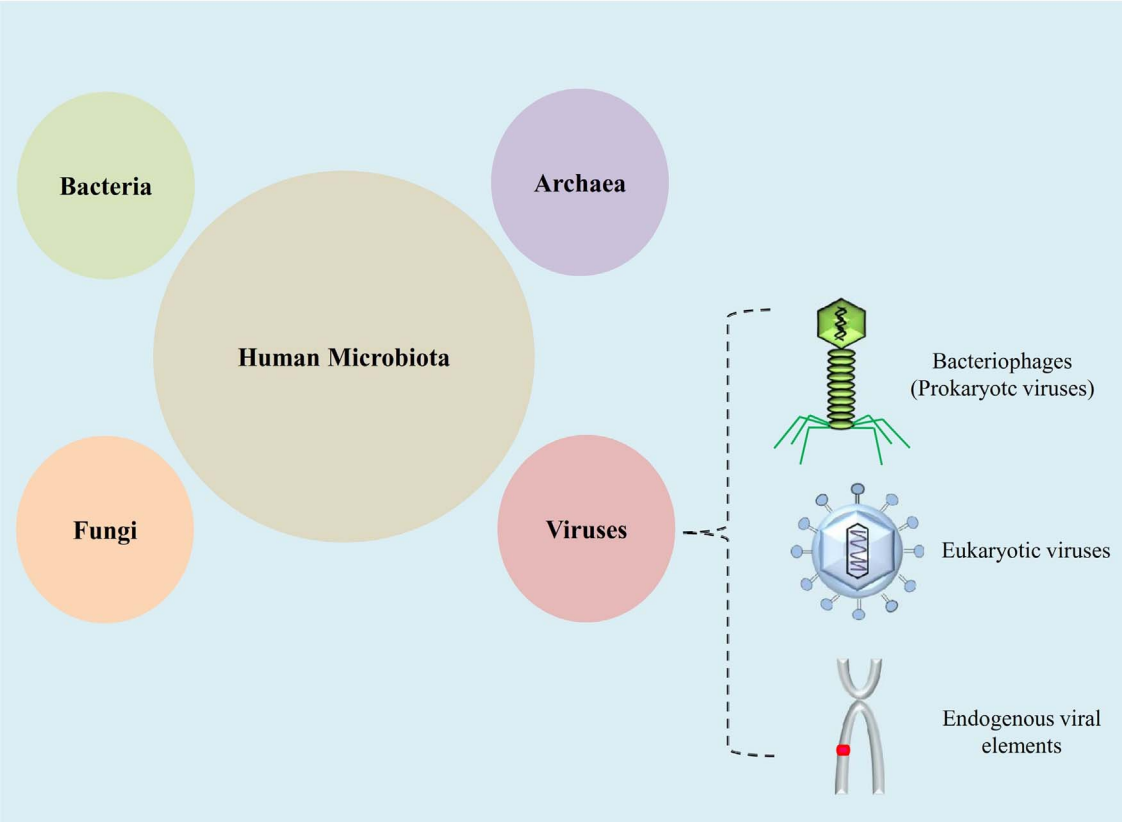

Fig. 1. Different components of microbiota.
The human microbiota is composed of all microorganisms that live within or on the body and contains bacteria, fungi, archaea, and viruses. Virome is known as the largest, the most diverse and the most dynamic part of microbiome and includes all viruses residing in various tissues and fluids of the body. Virome consists of bacterial viruses (bacteriophages), eukaryotic viruses, and virus-derived genetic elements residing endogenously in the human genome.

issues of interaction between groups of microorganisms within the body and also between microorganisms and their internal/external environment (Virgin, 2014).

Previously, the study of viruses in particular human-associated viruses was, to a great degree, limited to uncovering their roles in the emergence of pathologies. This may be attributed mainly to the simplified monodimensional view of viruses as pathogens that cause a wide variety of diseases ranging from mild infections to life-threatening conditions (Popgeorgiev et al., 2013). This standpoint was a major barrier to understand the true role of viral agents in the human body. The occurrence of some horrible viral outbreaks during recent centuries that killed many people (sometimes up to thousands) was also very important to reinforce the pathology-centered view of viruses. But, the discovery that the human body is also inhabited by a diversified collection of viral species under non-pathological status led to a paradigm shift in our understanding of the role of viruses in human biology. Bacteriophages are an important category of viruses whose contribution to human biology has gained growing attention in recent years. These bacterium-specific viruses were first attracted broad interest for clinical purposes in the earliest years of the previous century due to their capacity for fighting bacterial infections, a procedure known as phage therapy (Carlton, 1999). However, today it has been revealed that these viral agents also play important roles in the human body. It is of interest to note that with increasing attention directed toward the role of phages in human biology, these viral entities have also found different applications in modern medicine for the development of a variety of prophylactic, diagnostic, and therapeutic platforms. These platforms are intricate systems that merge the natural biology of phages with their genetic/chemical engineering, which can lead to the formation of novel clinically relevant characteristics in phage particles. Over the recent several decades, phages have been used for detection of disease-associated biomarkers (Wang et al., 2015; Zhou et al., 2015), construction of scaffolds/matrices with potential application in tissue engineering and regenerative medicine (Wang et al., 2014a; Wang et al., 2014b), synthesis of biosensors able to detect human diseased cells (Souza et al., 2006) or microbial contaminations in environmental samples (Vinay et al., 2015), design of vaccines against different pathogenic agents including nematodes (Cui et al., 2013), protozoa (Melzer et al., 2002), bacteria (Malito et al., 2013), and viruses (Giang et al., 2012), development of therapeutic vaccine delivery vehicles for neurodegenerative disorders (Frenkel et al., 2003; Solomon, 2008), and generation of targeted drug carriers for the eradication of emerging antibiotic-resistant bacterial infections (Yacoby et al., 2006). Phages have also been investigated extensively in anticancer precision medicine for ultrasensitive diagnosis and targeted treatment of different malignancies. In line with this, the efficacy of phage-based platforms have been shown in the development of diagnostic imaging approaches for early cancer detection (Cho et al., 2017; Hsiung et al., 2008; Yeh et al., 2016) and formulation of malignant cell-specific targeted gene/drug delivery systems for cancer therapy (Bedi et al., 2013; Bedi et al., 2011; Gandra et al., 2013; Janardhanan et al., 2010; Suthiwangcharoen et al., 2011).

In the current review, we aim to delve deeply into the role of phages in the gut and describe interplay between the structure of gut phages and disease/health states. After an overview of phage diversity and the intra- and interpersonal variability of phages, we discuss different types of interactions between phages and their bacterial hosts in the healthy and diseased gut and address the physiological and pathological implications of following different lifestyles by phages for the human body. We also shed light on the potential capacity of gut phages to serve as a biomarker of health or disease in the body.