



## BACTERIOPHAGES AS BENEFICIAL REGULATORS OF THE MAMMALIAN MICROBIOME

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### ABSTRACT

Much of the research on viruses has concentrated on their disease causing ability. The creation model biomatrix theory predicts that viruses play a beneficial role in cells and organisms. In this report we present a new theory which proposes that mammalian phages (bacteriophages), the most abundant organism associated with mammals, guard and regulate growth of the mammalian microbiome. We base this theory on nearly a century of published evidence that demonstrates that phage can insert into the bacterial genome and cover the surface of bacteria. We propose that this “cloaking” of the bacterial cell surface is an elegant mechanism whereby the normal flora bacteria are protected from immune detection and pathogenic bacteria can be directly lysed by the same phage. Additionally, both phage genome integration and cloaking can be used to prevent normal flora bacteria from conversion to a pathogenic state. Further support for the phage cloaking aspect of our theory has been demonstrated in recent studies which show that phage proteins bind specifically to microbial-associated molecular patterns (MAMPs), which are known to be the major ligands that activate the mammalian immune system. Although these phenomena have been documented separately over decades, we postulate for the first time that these functions work together to promote the integrity of the mammalian microbiome.

### KEY WORDS

virus, bacteriophage, virome, microbiome, biomatrix, bacteriome, phage

### INTRODUCTION

Creationists have noted that the exquisite design in structural composition, life-cycle and genetic control within viruses suggests that they were created as part of God's original good creation (Bergman 1999, 2002; Davidheiser 1965; Coppedge 2011; Doyle 2008; Francis 2003, 2008; Greunke 2004; Kim 2006, 2007, 2008; Liu and Soper 2009; Liu 2007, 2015; Larson 2000; Wood 2003; Peet 2006; Sarfati 2008). Relatedly the biomatrix theory is a creation theory postulating that the microbes (including viruses) that exist on earth perform beneficial activities consistent with their good creation, with most bacteria involved in life sustaining biogeochemical cycles (Francis 2003). Instances of beneficial viral activity however are more difficult to document. Although viruses display design features at the molecular-genetic level, they are often viewed as parasitic (Lucas and Wood 2006) and there is a lack of in-depth analysis and theory building in the creationist literature regarding viral function within the biomatrix.

A fruitful approach to determining viral function within the biomatrix may be to assess animal associated viruses because animals possess some of the most densely populated biomatrix communities. Furthermore, the biblical creation model suggests that community is an important part of the living world, and assessing viral function within the larger community of multicellular organisms may aid in determining the “good” function of viruses (Francis 2009).

In this report we analyze the role of bacteriophages associated with mammalian commensal bacteria (the microbiome).

### PHAGES AND THE BIOMATRIX

Biomatrix theory predicts that all prokaryote and eukaryote cells

possess multiple viral symbionts or parasites. One major function of phages in the biomatrix appears to be the control of bacterial populations (Francis 2003, Gruenke 2004). Two examples of population control by phages in the marine biomatrix are instructive and may help to formulate hypotheses about the role of phages in the mammalian microbiome.

In one example, a vibriophage is known to decrease the population of *Vibrio cholerae* bacteria in the ocean, the causative agent of cholera. Cholera is often associated with weather patterns that produce monsoon rains, which are postulated to lower the vibriophage populations and correspondingly increase *Vibrio cholerae* populations (Francis 2013; Faruque 2005). Secondly, cyanophages can influence the population of cyanobacteria which are one of the most populous carbon fixers on earth (Shestakov and Karbysheva 2015).

Given that phages control populations of the free living microbiome we predict that mammalian associated phages may play a similar role in the mammalian microbiome.

### PHAGES AND THE MAMMALIAN MICROBIOME

The human bacteriome is composed of at least 50 trillion cells (current theory predicts that there are about one bacterium associated with each human body cell) and each bacterial cell may be associated with at up to 10 viral partners (Dewart 2016; Virgin 2014). Thus we predict that there may be greater than 500 trillion viruses on the adult human body.

Phages are the most abundant virus associated with mammals and yet they are largely ignored as members of the mammalian

virome. We can readily postulate that each bacterial species in the mammalian microbiome is infected or associated with multiple species of phage (Youle 2017). Given that there are thousands of bacterial species in the mammalian microbiome we could then postulate that there are tens of thousands of mammalian associated phage species and strains (Dutilh 2014; Kahrstrom 2013; Mirzaei 2017; Pride 2012).

We would like to propose in this communication, for the first time, that phages play a role in maintaining the mammalian microbiome in several ways including protecting the microbiome genome, shielding the microbiome from the mammalian immune system, and protecting the mammalian host from pathogens and life-threatening virulence factors harbored in the microbiome itself.

### **1. Phages guard mammalian microbiome genomes, a recently derived concept consistent with biomatrix theory**

*E.coli* phages were the first phages studied, and hundreds of species have now been identified.

Among the first phages discovered was the *E.coli* lambda phage discovered in 1950 by Esther Lederberg (Lederberg 1953). The lambda phage was discovered when bacteria growing as a lawn on a plate were lysed (viewed as a clear spot or plaque on the plate) when the bacterial plate culture was exposed to ultraviolet light. This is a fascinating temperate (lysogenic) phage system which involves insertion of the phage DNA into the mammalian *E.coli* DNA leaving the bacterial lifecycle largely undisturbed, but lyses bacteria when they are stressed by agents which in some cases can cause genetic alteration. Thus, lysogenic lambda phage can be viewed as acting like a guardian of the genome in some respects, helping to maintain the microbiome from collecting threatening mutations and genetic alteration similar in some ways to the endogenous protein guardians of the genome in eukaryotic cells. In addition, when a phage establishes lysogeny by integrating into the host genome, that bacterium becomes immune to lysis by identical and similar phages, helping to preserve the microbiome bacteria (Youle 2017).

The lambda phage was not known in the 1950s for being involved with the microbiome. Since little was known about the microbiome as being a beneficial system, the focus on the lambda phage involved its temperate lifecycle and the genetic mechanisms at the molecular level. Indeed, it was a model system that helped start the field of molecular genetics leading to early discovery of gene expression mechanisms. In fact, to this day, it appears that lambda phage is known for its genetic mechanisms which help determine genetic function in other organisms rather than as a phage which may protect the microbiome (Gottesman, 2004). A search of databases like PubMed and others with the terms “lambda phage” and “microbiome” do not show any publications related to maintenance or protection of the mammalian microbiome. There is some indication however that phages may play a role in the microbiome as agents of bacterial innovation via gene transfer mechanisms (Kahrstrom 2013), but their role as protectors of the microbiome is not stressed. A recent text on phages suggests that phages may play a role in genome stability and change in the bacterium host, but does not refer to how this influences the microbiome at the ecological or organismal level (Youle 2017).

### **2. Mammalian associated phages possess mechanisms to shield bacteria from the immune system, phage cloaking theory**

It is well established that phages known to invade *E.coli* and other mammalian normal flora bacteria begin their infection process by binding to microbe associated molecular patterns (MAMPs) (Datta 1977; Simpson 2016). MAMPs are molecular patterns found in bacterial macromolecules, for example lipopolysaccharide (LPS) or peptidoglycan (PG). MAMPs are located on all known bacteria (Owen et al. 2013). When released during cell death or present within dense concentrations of bacteria during infection, MAMPs are recognized by the pattern recognition receptors (PRRs) of the innate immune system (Owen et al. 2013). The innate immune system is now known to play a vital role in activating major pathways of the immune system (Owen et al. 2013). In some cases, instead of causing host protection, the immune response causes a life threatening reaction called sepsis. For example, gram-negative sepsis, a bacterial induced mechanism causes the death of hundreds of thousands of human patients each year, and is largely caused by pathogen released LPS and other MAMPs (Mossie 2013). One question raised by these facts is why the large numbers of normal flora bacteria, which all contain MAMPs, do not cause constant activation of the immune system and pose an ongoing threat of sepsis? We propose that phages possess mechanisms which allow them to coat bacteria and bind to cell free MAMPs thus shielding them from activating the mammalian immune system.

#### **A. Phage receptor binding proteins bind to MAMPs possibly hiding them from the mammalian immune system**

Phages bind to the MAMPs using receptors known as receptor binding proteins (RBPs) (Datta 1977; Rakhuba 2010; Simpson 2016). Fascinatingly, in databases of known RBPs, we have calculated that up to 90% of the documented RBPs bind known MAMPs (Silva 2015). Phages are known to quickly destroy their host bacterium, breaking open the cell (lysis) such that the cell becomes unrecognizable. However, we have found that many photographs of phage infection appear to show that phage bind to the surface of the bacterium in great abundance (Figure 1) (Caro 1966; Luria 1978). If the cell were rapidly and completely lysed, few of these photos could be obtained suggesting that phages can coat their bacterial hosts for a time before the lytic event occurs supporting the idea that phages are designed to continuously coat bacteria. In addition, there are primary and secondary binding sites for RBPs. The RBPs often bind in a reversible manner to the primary sites on the surface of the bacterium, allowing for movement of the phage on the bacterial surface and most likely promoting their tight packing on the surface (Youle 2017). On tailed phages the RBPs are often located on several phage tail fibers such that as one tail fiber becomes detached another can be attaching allowing for a “walking” type movement across the cell surface (Youle 2017). A secondary receptor can then be found and the phage binds irreversibly to this receptor. The secondary receptor serves as the site of infection whereby the phage can inject its DNA or RNA into the cell (Youle 2017). This can result in lysis or lysogeny. Curiously there are few secondary binding sites compared to the primary binding sites and they are often located at distinct sites on the cell surface (Youle 2017). We postulate that this design, which causes a time delay in lysis, is to promote coating of the bacteria prior to lysis, and to coat the MAMPs prior



**Figure 1.** Tailed phages bind to the surface of bacteria. In some photos, the phages appear to saturate the bacterial surface. Some phages also bind to pili and flagellum which extend from the bacteria surface. We propose that this evidence supports the theory that phages can coat MAMPs on normal flora bacteria protecting them from the mammalian immune system. Courtesy of Graham Beards, WikiCommons. Retrieved from the web <https://commons.wikimedia.org/wiki/File:Phage.jpg>, Feb 13, 2018.

to their release from the cell to effectively shield them from PRRs preventing immune system activation. It may be argued that this coating only occurs for a short time as phage binding to the bacterial surface typically results in cell lysis. However, it has been demonstrated in several studies that lysogeny instead of the lytic lifestyle is the preferred lifestyle in the mammalian microbiome (Kim and Bae 2018). This is intriguing because lysogeny promotes the long term survival of bacteria by preventing phage invasion of the intracellular environment, and therefore would complement the protective effect of cell surface phage binding.

### **B. Multiple phage bind to microbiome bacteria and may collaborate in phage cloaking and protection of the microbiome and host**

Several hundred phage are now known to infect *E.coli* and single *E.coli* strains can be simultaneously infected with multiple phage species. It's striking that each phage species which infects *E.coli* has different length tails. This could in theory allow for the packing of multiple icosahedral and other shaped heads to fit in layers on the bacterial surface effectively blocking the access of PRRs to the MAMPs on the surface of the cells. Currently, there is no known evolutionary explanation for phage tail length (Youle 2017). Cloaking theory would predict that tail length would be important for effective phage packing of multiple phage species and phage blocking of PRR receptor engagement. For instance, the

extracellular component of the Toll-like-receptors (TLR) immune receptors, which are the primary receptors of the immune system that bind to MAMPs, are arranged in a horseshoe like shape with a 9 nm diameter suggesting that they project at least 9 nm from the surface of the immune cell (Francis 2007; Owen et al. 2013; Yong 2005). Phage tails of some of the well known T-phages range from 90-230 nm and thus we predict that they can effectively block TLRs from binding to microbiome bacteria MAMPs (Rowher 2014).

In addition, in support of the idea that phages possess design features which promote their effective collaborative binding on the bacterial surface, T3 phages are known to plug leaking holes in the membrane/cell wall of bacteria which are simultaneously infected by T7 (Villarreal 2009).

### **3. Phage lysis of mammalian associated bacteria promotes a stable population of microbiome bacteria**

How then do we reconcile the idea that phages may protect the microbiome with the fact that phages lyse bacteria? We postulate, based on published evidence, that the microbiome bacteria and phage populations achieve a dynamic equilibrium such that each can exist long term in the mammalian host (Youle 2017). The population equilibrium between bacteria and phage involves several defense mechanisms employed by both (Youle 2017). Bacteria possess mechanisms to control phage infection including changing their surface antigens, use of restriction enzymes, and the presence of an immune system known as Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR). CRISPR is a system which involves obtaining small segments of nucleic acid from infecting viruses (Rowher 2014). These small snippets of DNA or RNA can then be used to identify invading viruses during subsequent infection of the same viral species. In turn, phages can adapt to bacterial MAMP alteration by changing their RBPs. RBPs are known as the fastest evolving genes in a phage genome (Youle 2017). In addition, phages can modify their nucleic acids or delay the entry of their DNA into the cell while making defensive proteins from the initial inserted DNA to defend against the anti-nucleic acid bacterial host defense mechanisms. The end result of this back and forth defensive posturing results in the modulation of both bacterial and phage growth and maintenance of populations of both (Youle 2017).

Furthermore, the ability of RBP to bind to MAMPs can inhibit immune activation even after cells lysis, because there is evidence that RBPs can bind to soluble MAMPs (Gorski et al. 2012).

### **4. Mammalian associated phage possess specific mechanisms to protect both of its hosts from pathogenic bacterial invaders**

How then do the protective mammalian associated phage recognize and lyse foreign pathogenic bacteria if they have become less able to cause lysis in their host bacteria? We speculate that the pathogen invader may not be immune to the phages which have been diversifying and becoming more resistant to bacterial defense mechanisms within the mammalian microbiome so the pathogen invader in fact may be initially more susceptible to the mammalian microbiome phage. We would also speculate that the invading pathogen would be present in small populations and be susceptible to complete lysis before establishing resistance to the phages. Phages also possess design features to complement the

mammalian immune system as they have been known to contain immunoglobulin like proteins which allow them to stick and hide in mucosal surfaces of the human body (Gorski and Miedzybro 2017). In addition, some bacteria appear to have co-opted genes for the tails of tailed phages and can use these tailocins placed in their outer surface to lyse competing bacteria (Youle 2017; Ghequire and De Mot 2015). It would be interesting to see if microbiome bacteria use these antibacterial weapons. Recent studies have also shown that RBPs can recognize multiprotein complexes which are involved in exchange of antibiotic resistance genes by bacterial conjugation (Huiskonen, J. 2007) and prevent the development of antibiotic resistance. These RPBs could be used as “novel bactericides against antibiotic-resistant bacteria” as noted by Huiskonen 2017.

### 5. Design features of the mammalian innate immune system allow for discrimination between infectious pathogenic animal viruses and phages

We predict that phages cloak the mammalian bacteriome, but how do the cloaking phages themselves escape immune system detection of the mammalian host? Recent studies of phages being used to treat infections has shown mixed results regarding the recognition of phages by the human immune system (Navarro 2017). Fascinatingly, phages are largely ignored by the innate immune system by an elegant design feature which involves recognition of primarily internalized viruses. For instance, the TLR receptors which are the primary first-responder receptors to viruses are found on internal membranes of innate immune cells and not on the plasma membrane (Owen et al. 2013). Thus, viruses which engage and infect mammalian cells elicit an anti-viral immune response and because phages do not infect eukaryotic cells and are not typically internalized by them they are largely ignored by the immune system. This supports the idea that phages are meant to be long term agents which associate with the mammalian host and mammalian microbiome.

### CONCLUSION

We propose here for the first time that mammalian associated phages, the most abundant organism associated with mammals, protect the mammalian microbiome from attack by the mammalian immune system, minimize mutational decay of the microbiome, and protect both the mammalian host and its microbiome from pathogens. We base our theory on published facts about the association of phages with the microbiome. Our theory also flows from the biomatrix theory, a creation model concept (Francis 2003) which predicts that microbes including phages form a life supporting network on earth and among organisms. Here is a summary of the data and hypotheses which support the new theory presented in this paper. Here is a summary of the data which support the new theory presented in this paper.

- The lytic lifestyle of phages is uniquely capable of controlling fast-growing microbiome populations.
- There seems to be one or more phage species specific to each microbiome species which promote the survival of multiple species of microbiome bacteria and prevent any one species from displacing others by overpopulating.
- The lysogenic lifecycle of phages promotes long term

association of phages with the microbiome at the genome level and cell surface level.

- Phages can quickly adapt to the rapidly changing genomes and populations of the microbiome.
- Phage and microbiome symbionts adapt over time and the same mechanisms which promote recognition of microbiome bacteria also promote phage recognition of pathogenic bacteria.
- Phages possess exquisitely designed systems to protect the mammalian host including the ability to directly neutralize pathogenic invaders and possession of proteins which help them localize to mammalian tissues to effectively accomplish this task.
- Phages possess receptor binding proteins which allow them to engage microbiome bacterial MAMPs. MAMPs can activate the immune system. Binding of phages to MAMPs protects the microbiome from attack by the host immune system and also protects the host from an overwhelming life-threatening immune response.
- Tailed phages possess designs which may allow them to efficiently cover the bacterial surface. For instance, phage species differ in tail length allowing for the potential formation of layers of phage on the bacterial surface.
- The surface of bacteria contain different kinds of MAMPs. Some promote injection of DNA from the phage and some primarily promote binding of phage to the surface. The MAMPs which primarily promote surface binding are in the majority on many bacteria, allowing coating of the bacteria without immediate lysis supporting the hypothesis that phages are designed to block MAMPs.
- Phages are also known to bind to soluble MAMPs supporting the hypothesis that phages are designed to block MAMPs from activating the immune system.
- Phages are, in general, protected from the mammalian immune system because the immune system’s viral detection mechanisms are geared toward animal viruses and not phages.

We propose that the cloaking of the microbiome by phage be considered a new theory known as phage cloaking theory and is a part of the larger theory presented here which proposes that phages can protect the microbiome and mammalian host in general.

Perhaps the most interesting aspect of our observation is that the same mechanisms which lead to pathogen elimination by phages can be used to preserve the mammalian microbiome. It appears that it is the context of the relationship, i.e. the long term relationship of phage with microbiome bacteria, which helps determine whether the phage helps to preserve bacteria or eliminate them.

Few research groups have been working on these intriguing discoveries as being part of a mechanism to foster the health of the mammalian microbiome. We believe that this is an example of how the creation model can lead to novel insights into biological phenomenon.

Those groups who are working in this area have begun to see the

relevance of phage to the mammalian ecosystem and others (Youle 2017). One group in particular has been detecting phages within the human body. They have discovered that as illness occurs in the body, the microbiome can be affected early to the point that released phages may provide an early warning system of impending illness (Rohwer 2013). This certainly adds more support to the idea that microbiome phages are important partners in maintenance of the microbiome.

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