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Bacteriophage - Mediated Micro Biome Manipulation: A Novel Venture in Fostering Infant Gut Health

Review Article

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Abstract

The incidence of Antimicrobial Resistance (AMR) has been growing globally, posing threat to medical practice. Around this instance, environmental enteropathy remains one of the major causes of infant mortality. In the past few decades, great efforts have been laid to foster gut health. Efforts have been focused on understanding the role of exogenous factors such as sanitation, exclusive breast feeding, consumption of probiotic nutrition, etc. Antibiotics, while treating the disease successfully, diminishes the gut micro biome and possess the threat of developing resistance. A complementary way of enhance gut health is to build a healthy gut micro biome environment which requires a great insight in understanding the host-microbiome interactions. Precise engineering of bacteriophages to develop novel models to understand, describe, probe and modify gut function by building a healthy micro biome environment will yield decade's worth progress in the field of biotechnology. The objective of this article is to introduce the hypothesis of tuning gut microbiota using bacteriophages and to familiarize the physiology of a bacteriophage, to elaborate its current implications, challenges faced on its application, future scope and to motivate new researchers to bring out novel strategies to mitigate the burden and spread of Environmental Enteric Dysfunction (EED) by establishing a healthy micro biome using bacteriophage- mediated micro biome engineering which proves complementary to nutritional and chemotherapeutic approaches.

Keywords: Bacteriophage; Environmental; Enteropathy; Gut Health; Gut Micro Biome.

List of Abbreviations: AMR - Antimicrobial resistance; WHO- World Health Organisation; EED- Environmental Enteric Dysfunction; DNA- Deoxyribo Nucleic Acid; dsDNA- Double stranded Deoxyribo Nucleic Acid; ssDNA- Single stranded Deoxyribo Nucleic Acid; ssRNA- Single stranded Ribo Nucleic Acid; CRISPR- Clustered, Regularly Interspaced Short Palindromic Repeats; CAS- CRISPR Associated Sequences; SiRNA- Silencing RNA; HMC- Hydroxy Methyl Cytosine PCR- Polymerase Chain Reaction.

Introduction

Emergence of antimicrobial resistance (AMR) and drug resistant infections are identified as a great threat to the global health. WHO has recorded an increasing incidence of drug resistance in a variety of organisms in all levels of clinical settings which threatens our progress in effective prevention and control of high-priority infectious diseases such as multidrug-resistant TB, artemisinin resistance in malaria, and antibiotic resistance in the most common bacterial agents causing pneumonia, diarrheal disease, neonatal sepsis, enteric fever, sexually transmitted diseases, maternal infections, and other syndromic infections. Virtually, all microbes have developed resistance to antimicrobials. Progressing towards the same lane, the day is soon approaching, the day when organisms become resistant to all known antimicrobial agents. It will be that very day making its mark on history as the 'Doomed day' of medical practice. Lets just imagine a day when the mankind has reached the wits end, no more antimicrobials left on stock to be prescribed! Therapeutic failure, death, sorrow and darkness across the globe! Will that be the moment of extinction of mankind? What will our next hope?

Diarrheal diseases constitute a major cause of morbidity and mortality worldwide; especially in developing countries. The global burden of pediatric diarrhea is estimated to be 1.5 billion episodes with 1.5 to 2.5 million deaths under 5 years of age per year. A growing body of evidence suggests that healthy gut function early in life plays significant role in adult well being. Recurrent

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colonization and infection by enteropathogens and chronic malnourishment serve as a major aetiology for environmental enteropathy and growth retardation especially in children living in developing countries [1, 2]. Environmental enteropathy, also being referred as Environmental Enteric Dysfunction (EED), is defined as any derangement in gut physiology causing intestinal inflammation, reduction in epithelial surface area and absorptive capacity, and blunting of intestinal villi due to feco-oral contamination an is often asymptomatic. This condition, generally characterized by a reduced linear growth rate, is disproportionally prevalent in developing countries, and is associated with numerous pathologies including lack of response to oral vaccines, cognitive impairment, metabolic diseases, and trans-generational perinatal morbidity [1, 3, 4].

Bacteriophage

Bacteriophages are viruses that utilise bacterial cells as their host. It was observed in 1917 by d'Herelle that filtrates of feces culture from dysentery patients induced transmissible lysis of broth culture of dysentery bacillus and he named it bacteriophage. The growing interest on bacteriophage- mediated micro biome engineering deems a great insight in understanding the viral physiology which will be extensively discussed in this review. Few bacteriophages known till today of greater significance are fd phage, T- even phages (T2, T4, T6), MS2 phage, P1 phage, Pf1 phage, QB phage, ƛ (lambda) phage, Ø6 phage and ØX174 phage. The interaction between a myriad of phages with *E. coli* have been extensively studied [5].

Among these phages T- even phages, ØX174 phage, fd phage, ƛ (lambda) phage and P1 phage are known to infect *E.coli*. T- even phages (especially T2 and T4) have been exploited widely in the field of genetic engineering as cloning vectors. A brief discussion about each phage is given below [6]:

T4 phage is a virulent dsDNA phage. They produce two proteins namely holing and T4 lysozyme. Holin creates holes on the host cell membrane while T4 lysozyme degrades the peptidoglycan coat. Thus, both aid in cytolysis and release of daughter virions.
ØX174 phage is a ssDNA virus. Host is lysed by Enzyme E. This enzyme inhibits the activity of *Mray* protein which catalyses the transfer of peptidoglycan precursors to lipid carriers. As a result of this, the cell wall is weakened, enabling cytolysis.
fd phage is a ssDNA phage that enters into a F^+, F' or Hfr cell through the tip of tip of sex pili. It does not lyse the host but establishes a relationship in which new virions are continually released by secretory process.
MS2 and **Qβ** phages are the simplest of all known phages due to their simple morphology. Their genome is composed of a positive sense ssRNA and it enters the bacterial cell through the side of sex pili.
Other phages gaining greater attention today are Ø6 and Pf1 phages which infect *Psuedomonas syringase* and *Pseudomonas aeruginosa respectively*.

Life cycle

Phages exhibit two kinds of life cycles. In the virulent or lytic cycle, intracellular multiplication of the phage culminates in the lysis of the host bacterium and release of progeny virions. In temperate or lysogenic cycle, the phage DNA becomes integrated with the bacterial genome, replicating synchronously with it, causing no harm to the host cell. Any virus undergoing lysogenic cycle can be reverted back to lytic cycle and this is called induction.

Regulation of life cycle

Phages can be lytic or lysogenic. All virulent phages such as T4 phage are purely lytic i.e. they follow only lytic cycle whereas, ƛ (lambda) phage is both lytic and lysogenic i.e. it has the ability to undergo both lytic and lysogenic cycles. Considering such an instance, a complex integrated sequence of genomic and proteomic alterations makes them decide which cycle to follow, either lytic or lysogenic cycle. Understanding this complex sequence of genomic, transcriptional and proteomic molecular modifications is of prime importance in resolving the viral physiology. The mechanism of life cycle regulation has been demonstrated in ƛ (lambda) phage. Phage adsorbs to the surface of *E.coli* with its end plate and tail fibres. Introduction of the viral genome into the cytoplasm of host follows. In the host cytoplasm, linear genome of the virus is circularised and sealed by host cell's DNA ligase. In the circularised genome, genes are clustered according to their function as head synthesis, tail synthesis, lysogeny, lysis and replication. Clustering and circularised configuration of the viral genome has a major influence over the regulation of life cycle. This regulation comes into act by the production of regulatory proteins such as protein CI, protein CII, protein CIII, Cro protein, Q protein and Rec A protein [7].

Protein CII is a regulatory active protein. It is produced during the early infection by the phage. Intracellular raise in the levels of CII protein maintains lysogeny and when it does not reach critical levels, lytic cycle proceeds. This protein activates the *int* gene, the transcription of which produces integrase, responsible for integration of viral genome with the host genome. There exist unique sequences on both phage and bacterial chromosomes called attachment sites where the cross over occurs. The phage attachment site is called *attP* and the bacterial site on *E.coli* chromosome between galactose and biotin operons, is called *attB*. The recombination reaction is catalysed by integrase in conjunction with two host proteins and occurs by a highly concerted reaction that requires no new DNA synthesis [8]. But in phage P1 lysogen, the viral genome exists extra chromosomally as an autonomous single- copy plasmid. Protein CII also enhances the transcription of CI gene which produces ƛ (lambda) repressor. This protein causes the repression of all phage genes but increases the expression of its own. Thus, lysogeny is established between the host and the virus. Occasionally, one or more phage genes, in addition to the gene coding for the repressor protein, are expressed in the lysogenic state. If expressed protein confers a new phenotypic property on the cell, then it is said that lysogenic conversion has occurred. Diphtheria, scarlet fever and botulinum are all caused by exotoxins produced by bacteria that have been converted by temperate phage. In each case, the gene that codes for the toxin resides in the phage DNA and is expressed along with the repressor gene in the lysogenic state. It remains a mystery as to how these toxin genes were acquired by the phage; it is speculated that they may have been picked up by a mechanism similar to specialised transduction [8]. Protein CII is protected by protein CIII from degradation by host enzyme HflB. If not protected by CIII, the levels of Cro protein which acts as both repressor and activator. This Cro protein inhibits CIII and CI expression, further

reducing the levels of CII and λ repressor levels. It also increases the synthesis of Q protein which intern increases the expression of all viral genes. The reduced levels of CII, λ repressor proteins and enhanced transcription of viral genes enters the lytic cycle. Induction is the process of reversal of lysogeny. Induction by UV rays or chemical mutagens increase the transcription of Rec A protein. This protein interacts with the λ repressor and makes it to cleave itself. This leads to enhanced transcription of *xis, int* and *Cro* genes, intern unceasing the levels of Q protein. The combined activities of these two proteins catalyse sit- specific recombination between the two attachment sites that flank the prophage DNA, attL, attR [8]. Early after infection, when integration is to occur in the cells destined to become lysogens, synthesis is Xis protein is blocked. Otherwise, the integrated prophage DNA would excise soon after integration, and stable lysogen would be impossible. However, after induction of a lysogen, both the integrate and the Xis proteins are synthesised and catalyse the excision event that releases prophage DNA from the chromosome. This reverts lysogenic cycle back to the lytic cycle.

Host resistance to a phage infection

Host cell offers resistance to infection by the phage by various mechanisms. Restriction endonuclease system and CRISPR system play a major role in the evolution of resistance. Hence, whenever strategies are developed to foster gut health using phages, micro biome dynamics, evolution of resistance and gut function consequences have to be taken into consideration. Restriction is a process by which bacteria develop resistance against a phage by production of restriction enzymes. Recently, it has been brought into light that the bacteria express a group of proteins called CRISPR system which makes the bacteria immune to phage infection.

CRISPR system

CRISPR system incorporates repeated genomic sequences separated by spacers. It refers to *Clustered, Regularly Interspaced Short Palindromic Repeats*. The expression of CRISPR proteins is regulated by *CRISPR- associated sequences (CAS)* gene [9]. This helps in determining the history of viral infection in a bacteria similar to the circular whorls on the trunk of a tree that help in assessing its age. Oldest infection is located at the 3' end of the CRISPR region while the most recent infection lies closer to the *CAS* gene. *CAS* genes are always associated with small RNA molecules called CrRNA. These CrRNA have a single repeat and a single spacer which are formed by the degradation of long strand RNAs. The CAS-CrRNA complex associate with the DNA or mRNA of the virus and cause its destruction [10]. Thus, the viral infection is thawed. Interestingly, recent evidences say that analogous to CrRNAs the mammalian cells have SiRNAs (Silencing RNAs) which silence the expression of specific genes. Extensive researches are being carried out towards the utility of SiRNAs in oncology.

Even bacteriophages offer a minor degree of resistance to the host defences. The mechanism of this differs from each phage. For example, in T4 even phages, cytosine in their nucleic acid is replaced by hydroxymethyl cytosine (HMC). The phage is protected from the endonucleases of *E.coli* by glucosylated HMC residues [11].

Scientific implications and Challenges

In the recent times, an extensive knowledge about exogenous factors such as environmental sanitation, breastfeeding, general nutrition and probiotic supplementation has been acquired and are accordingly promoted. But this knowledge possess no hope in performing hypothesis-based, robust, specific perturbations and manipulation of gut micro biome. Hence, it requires a specific, more accurate means for which bacteriophages can possess utility. The use of antibiotics, while successful intreating the progression of many acute pathogenic bacterial infections, can lead to antibiotic resistance and therapeutic failure, is challenging to deliver to low-resource settings, and often kills probiotic gut microbes as well. Innovative ways to manipulate and evaluate the gut micro biome in new borns and infants, with a particular focus on reducing the incidence and burden environmental enteropathy in low-resource settings have to be developed. In Russia, they use Bandages saturated with phage solutions and phage mixtures. Phage delivery systems have immense potential in the management of bacterial infections in a medical and veterinary setting. In addition to using phage in the prophylaxis and treatment of bacterial infections in humans, lethal-agent delivery systems also have immense potential at the preharvest stage in the biocontrol of *E. coli* in animals and fresh foods [12] and could play a role in preventing transmission of fish patho-gens [13]. Efforts to deliver antimicrobial agents using genetically engineered bacteriophages in bacterial infections have been proved to possess an immense potential [14]. Williams Smith [15] et al., demonstrates that the *in vivo* activity of phages show a wide variation with their *in vitro* activity due to spontaneous development of resistance to phage infection. This in fact can be ascribed as the major challenge faced in implementation of bacteriophage-based strategies in fostering gut health.

Gut Microbiota

The normal flora inhabiting in the skin and mucous membranes of the human body are collectively called microbiota. The complete genomic incorporation of the microbiota is referred to as micro biome. It has been described that microbiota exist as two forms- Resident and Transient microbiota. Though the normal microbiotas are not essential for life, they enhance the immunity of skin and mucous surfaces. Recent evidences suggest that, these microbiota form the first line of defence against any invading pathogens. Interestingly, advanced molecular studies of Host-Microbiome interaction by PCR amplification and sequencing of small 16s ribosomal RNA have revealed the role of these interactions in development of obesity. Human gut comprises of the microbiota-rich intestinal environment and acidic microbiota-scarce gastric environment. In the gut of a normal infant, there exists an balance between the body's immunity, pathogenic microbes and normal intestinal flora. Any disruption in the pre-existing balance between these three domains causes physiological instability of gut. Disruption of normal barrier of microbiota enhances the risk of invasion of pathogenic bacteria while the imbalance between immunity and microbiota leads to opportunistic infections or hypersensitivity to microbial antigens as suggested in case of inflammatory bowel disease. Gut micro biome in newborn and infants possess a direct influence on their gut health, growth and development. Furthermore, the micro biome influences the gut health by a myriad of mechanisms and

host-biome interactions inclusive of immune signalling, toxin release, nutrient use, and modulation of the physical nature of the gut wall (including mucosal barrier function and wall integrity) [16, 17].

Growth, development and Gut micro biome

In 2007, the Human Microbiome Project [18] was launched by the National Institutes of Health (NIH) to decipher the influence of normal flora on health and disease. Gut micro biome comprises a complex ecosystem of diverse microbial population including eubacteria, archaebacteria, viruses and protozoans the proportion of which varies in accordance to time and space [19]. The gut of a new born (almost 90%) is sterile while they acquire organisms from the maternal vaginal tract during delivery, breast milk and by the downward invasion of pharyngeal microbiota which is acquired from atmospheric air. Intestinal flora gets established within 4- 24 hours of birth depending upon the mode of delivery, time at which breast feeding was initiated and the surrounding environment of birth. Few studies earlier reported that *Bifidobacteria* forms the major part of intestinal flora in a breast fed newborn but now studies using quantitative PCR have shown that it appears several months after birth and are quantitatively limited. According to the recent evidences, the gut of a new born mainly comprises of bacteria such as *Klebsiella, Citrobacter and Enterobacter* which belong to the family *Enterobacteriaceae*. It has been established that the gut of a bottle-fed infant has a wider diversity of mixed flora than does a breast-fed infant. As the child matures, the compartment of anaerobic bacteria proportionally grows wider and so the an adult gut contains almost 90% of anaerobic bacteria. The anaerobic population in an adult gut is made up of bacteria belonging to the phyla *Bacterioidetes, Firmicutes, Actinobacteria, Verrucomicroviota, Fusobacteria* and *Propiobacteria*. The archaebacterial diversity comprises *Methanobrevia stadmanae* and *Methanosphaera stadmanae* which are methane producers while the viral population mainly contains phages [20].

Segmental gut anatomy and Floral diversity

Human gut is anatomically divided into various segments. The quantity and proportion of microbial flora differs in relation to each anatomical segment [21]. This variation is encountered owing to the difference in pH and composition of secretions in various segments along the gastrointestinal tract. Anatomically gut comprises of an acid-rich environment, the stomach followed by intestine with an alkaline environment. Quantitative bacterial assays have proved that the quantity of intestinal flora in proportional to the alkalinity of the environment. The acidity of stomach makes it unfit for growth and proliferation of pathogenic as well as normal flora expect for *Helicobacter pylori* which forms the major component and has a minimal flora of 10^2 to 10^3 organisms per millilitre of gastric fluid. Microbial rich environment is encountered while moving down along the gut and maximum quantity and diversity is seen in the cecum and colon with 10^{11} organisms per millilitre of the effluent. The duodenum contain 10^3 to 10^4 organisms per millilitre of the effluent, 10^8 per millilitre in ileum. The mucosal lining of the upper intestine is lined by a biofilm of bacterial population which belong to phyla *Bacteriodetes* and *Clostridia* while the lumen contains *Enterobacteriales* and *Enterococci*.

Gut microbiome in physiology

As previously mentioned, a normally functioning gut is the outcome of a state of equilibrium between the gut microbiome, pathogenic microbes and the host immunity. Hence, the gut microbial ecosystem plays an imperative role in maintenance of physiologically healthy state of the host. O'Hara and Shanahan [22] have mentioned about three roles of gut micro biome. They are as follows:

Defensive role: The component bacteria forming the microbial flora provide immunity to the host by secreting bacteriocins which are bactericidal, lactate production which lowers the pH of gut making it unsuitable for pathogenic bacterial growth and competing with the pathogenic bacteria for nutrition and receptors. Hence, they are termed as the first line of gut immunity.

Stimulatory role: Normal intestinal flora influence the development of mucosa associated innate immunity. They induce the secretion of secretory IgA, development of intestinal humoral immunity, modulate T cell response and modulate the profile of cytokines release.

Metabolic role: Normal intestinal flora possess a wide range of metabolic utility. They synthesise short chain fatty acids which are essential for the growth and differentiation of intestinal cells, increase electrolyte absorption, synthesise micronutrients such as Vitamin K, biotin and folate, metabolise ingested carcinogens into non-toxic forms and ferment non-digestible dietary residues.

Gut micro biome, Clinical and Pathological states

Stomach is known to have scanty microbial flora and diversity but proliferation of Gram positive bacteria has been documented in case of pyloric obstruction. Administration of antacids, H2 blockers and proton pump inhibitors enhances the microbial flora by reducing the acidity of gastric compartment. Diarrhoea quantitatively reduces the decal mass of microbial excretion while it is counteracted in constipation and intestinal stasis [23]. Minor iatrogenic trauma to the intestinal wall in procedures like sigmoidoscopy and barium enema most likely induces a transient bacteraemia and need prophylactic antimicrobial therapy. Prescription of broad spectrum potent antibiotics like clindamycin and doxycycline can cause a spectrum of diseases from self limiting diarrhoea to life threatening pseudomembranous colitis due to loss of immunity provided by the microbial biofilm and other component organisms of gut microbiota. Preoperative antibiotic therapy with neomycin, erythromycin and metronidazole for two days in lower bowel surgeries is provided to intentionally suppress the gut microbiota with a view of preventing accidental spill because the it has been established that the incidence of postoperative infections in lower bowel surgeries reduced with lower microbial count [24]. Following the procedure, the gut microbial population regrows and this time is it replaced by microbial community such as *Staphylococci, Enterobacter, Enterococci, Protei, Pseudomonas, Clostridium difficile* and *yeasts*. which exhibit drug resistance [25]. Supplementation with probiotic *Lactobacillus acidophilus* leads to temporary dominance and partial suppression of other organisms an thus reducing the probability of growth, proliferation and survival of pathogenic bacteria. Abscess formation in perforated wounds is communal

caused by *Bacillus fragilis, Clostridia* and *Peptostreptococci*. Turnbaugh PJ et al., demonstrates that the gut micro biome also influences fat deposition which causes obesity [26]. It is recently hypothesised that inflammatory bowel disease results due to the hypersensitivity to microbial antigens in genetically susceptible individuals. Thus, the gut micro biome possess an integral influence on the general health, gut health, various clinical and pathological states. The objective of this article is to establish a hypothesis of manipulating the gut micro biome in order to build a healthy gut especially in infants.

Tuning Gut Microbiota- A Hypothesis

In the recent years, administration of probiotic nutrition has been implicated in the management of environmental enteropathy. Probiotic act by reinforcing the gut microbiota. Precise engineering of the gut micro biome calls for a great insight in host-microbiome interactions such as signalling, population dynamics, stability and nutrient use with respect to physiology and acute malfunction. Bacteriophage-based strategies may aid us in specific robust perturbations of this complex ecosystem with no negative impact on host. Bacteriophages-based strategies being pathogen-specific are novel promising tools to probe, manipulate and ultimately foster gut health by establishing a healthy gut micro biome. These strategies are more promising than chemotherapeutic approaches since they possess no risk of development of AMR and opportunistic infections due to destruction of normal intestinal flora. The ability to clone and manipulate almost any given piece of DNA, together with our present knowledge of phage genetics, may make it possible to adapt this technology for a multitude of bacterial pathogens.

Future Scope

Efforts to study and investigate all stages of development of bacteriophage-mediated strategies for micro biome engineering in children under five years of age, as an approach to reduce the burden of environmental enteropathy in low-resource settings should be promoted. A basic early-stage approach would be to develop a model on the properties of bacteria which determine gut health using bacteriophages, such as targeted elimination of specific bacterial strain and recording the response of microbial community to an acute disruption as in EED. An advanced initiative would be to bring out an innovative computational model which allows us to develop novel treatment modalities based on factors such as pharmacokinetics, delivery characteristics, micro biome dynamics, chemical signalling, response of gut immunity, etc.

Efforts with regard to possess a great significance may be:[27]

- Approaches which are aimed at establishing the pharmacodynamic (efficacy to eliminate the specific pathogen) and pharmacokinetic (time taken for elimination of phage mixtures) properties of phage therapies.
- Efforts to bring-forth simulated, computational or animal models to understand the disruption in the integrity of microbial community, immunogenic response of the host, chemical signalling within the gut microbiota and between the host and microbiota.
- Studies which demonstrate the principles of healthy host-microbime interactions and during physiological instability.
- Strategies to mitigate the evolution of resistance of microbial pathogens to introduced bacteriophage.
- Efforts that demonstrate the challenges faced and modifications necessary from adult gut on implementation of bacteriophage-based strategies on neonates and infants.
- Efforts to develop animal models for dose titration of phage mixtures and to test their efficacy.
- Approaches with a motive of identifying and understanding the risks involved in the utility of bacteriophage-based therapeutic strategies and propose scientific solutions to overcome them.
- Selective approaches to engineer pathogen-specific phages or phage cocktails.

Conclusions

Environmental enteropathy, being an expanding health problem in infants of developing and under developing countries, needs special attention for effective reduction in incidence. Bacteriophage-based strategies may address many of the challenges being faced today in the management of environmental enteropathy, as they are pathogen-specific and not directly interact with eukaryotic cells. Further efforts are needed to develop a bacteriophage-based tool to probe, modify and ultimately foster healthy gut function through a healthy gut micro biome by integrating modern biotechnological methods on gene synthesis and sequencing. A major challenge encountered on the advent of above described approach is to develop ways to mitigate bacterial resistance to phage infection. Though the scope of manipulating gut health by tuning the gut microbiota using pathogen-specific and genetically engineered phages, appear to worthwhile and fruitful in relation to antibiotic use, further evaluation of feasibility and superiority of this novel technology over pre-existing probiotic nutrition utility has to be established. Being a hypothesis, no efforts have been laid and no much literature is available in regard to this new venture. Tremendous efforts and works with a motive of implementation and evaluation of this new technology over the pre-existing approaches is essential.

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