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Horizon of New Hope towards a Robust Infantile Gut: Advent of Bacteriophages in Tuning Gut Microbiome

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Abstract

The human gut is blessed with a complex ecosystem of micro biota the organization and integrity of which has not been explained though huge loads of resources and energy have been invested in achieving it. But it has been well understood that this unexplainable integrity of the gut micro biota is a major factor which maintains the stability of gut health. In the recent years, many efforts have been initiated by bodies working on global health to improve the gut health by building a strong microbial immunity due to which probiotic nutrient supplementation has been widely accepted for tackling the burden of Enteric Environmental Dysfunction (EED) in infants and children. EED was recognized as a global health issue when it was known to impair the quality of life in adulthood. Bacteriophages are known to be viruses that infect bacteria. Making use of this knowledge, one can use these bacteriophages in manipulating the gut micro biota and thus the gut health. Due to their property of host-specificity, lytic phages can be used to clear a specific clone of pathogenic bacteria while lysogenic phages can be used to tune the genome of host bacteria. Though promising, major obstacles for the acceptance of this new technique are the development of resistance by the bacteria to phage infection, insufficient knowledge about Microbiome interactions and non-availability of prototypes for pharmacological testing. Moreover, no efforts have been laid in evaluating the utility of this new technique over the existing techniques which is again a major cause for the dormancy of this novel venture. In the days to come scientists can work on modalities to hamper the development of bacterial resistance to phage infection and can introduce evaluated, titrated mixture of lytic and genetically modified lysogenic phages to build a healthy gut especially in children.

Keywords: Pediatric gut health; Gut micro biota; Bacteriophages

Introduction

In the past few decades, the World Health Organization (WHO), its associated partner bodies and other such

organizations have thrown tremendous efforts and funds towards reduction of the burden of childhood diarrheal diseases. Even today, diarrheal diseases rank as a major cause of infant morbidity but it should be noted that we have recorded a remarkable progress in reduction of his burden in the few recent years. Owing to the implementation of numerous community-based approaches, active and passive surveillance services, the load of Diarrhea-associated infant mortality has faced intense and significant downfall. Having documented this imperative milestone, have we reached the stint of relaxation? The riposte is a huge 'NO'. Reduction in diarrhea-associated infant mortality being at one end of the spectrum, recurrent pathogenic infections by enteropathogens that often go in hand with chronic malnourishment pave way for stunting of growth [1,2]. This end of the spectrum involves a myriad of pathognomic histo-morphological alterations in the integrity of gut mucosa. These microscopic features noted are mucosal inflammation and blunting of mucosal villous projections which result in a greater reduction in the surface area of nutrient absorption. These vignettes of features have been termed as Environmental Enteropathy or Environmental Enteric Dysfunction (EED) [2]. The onset of EED marks the initiation of a vicious cycle of progression between physiological instability of gut and malnourishment. EED has been commonly documented to be asymptomatic but ultimately brings about growth stunting, impairment of cognitive skills and development of lifestyle-related metabolic diseases in their later span [1,3]. These expected adverse outcomes are seconded by Barker's hypothesis according to which stressful events especially those disturbing the gut physiology transpiring in infancy possess a negative impact on adult wellbeing [4]. With a motive to culminate this clause of illness, immense reforms such as promotion of exclusive breast feeding, improvement of sanitation facilities, providing safe drinking water and supplementation of probiotic nutrition have been incriminated.

Gut micro biota have been designated to be the 'First line of gut defense'. A normally functioning gut is an upshot of functional and metabolic equilibrium between gut micro biota, pathogenic microbial population and gut immunity [5]. Any derangement in this well-established and complex balance results in some pathological state. Remarkable role of gut micro

biota in the development and effective physiological operation of gastrointestinal immunity has been established beyond queries [6-8]. Comprehending the significance of this factor, scientists have been working on the valuable applicability and utility of normal intestinal flora in fostering the gut health of children. And consequently, probiotic and prebiotic nutrition modalities have been ushered in.

The Postulate

The first decade of 21st century ran with a wide accepted norm of antibiotic therapy for environmental enteropathy and associated symptomatic infective gastrointestinal dysfunctions. Far long, in the recent years, a devastating outcome of eclectic and irrational use of antimicrobial agents, development of drug resistance was brought into the lime light which creates an unreliable line of attack to be adopted in backdrops with a truncated reserve. Additionally, the radical 'wash off' effect of these antibiotic agents is still more perilous in clearing of the normal gut micro biota that prompts in development of intimidating antibiotic-associated colitis. In the wake of this circumstance, the era of extensive probiotic administration emerged and is being exercised till this day. *Lactobacillus acidophilus*, the most commonly used probiotic organism speaks by fortifying the existing population of micro biota and by minimizing the plausibility of pathogenic invasion [9].

One such harmonizing attitude would be to maneuver the normal microbial residents of the paunch. Owing to the maximal inhabitation of the gut by bacterial population, tools can be expounded to manipulate this bacterial population with an ultimate intention of building a healthy gut. Manipulation of gut micro biota calls for a cavernous and unfathomable insight on the metabolic functioning, inter-microbial signaling and gut immunity-microbial interactions in the course of stable gut health and in a state of homeostatic disruption of gut health. Host specificity of bacteriophages holds a prodigious potential for this accord. Bacteriophage-based strategies can enable us to carry out specific-microbe labeled exploration of interactions, to amend performance of gut micro biota by altering the album of microbiome and also to be exploited as tool for the clearance of specific pathogenic microbial population.

Hopes and Hindrances

Recently acquired ability of the human scientific skills to amplify, refashion and to engineer any piece of nucleic acid with the succor of advanced gears of sequencing and manipulation reclines as the core principle of this novel venture. Evidences have demonstrated the utility of genomically altered bacteriophages in provision of antibiotic agents and in the preservation of food quality [10-12]. A key contest in exploiting bacteriophage-based strategies is the development of bacterial resistance to phage infection [13]. In retort to phage infection, the host bacteria fabricate restriction enzymes and CRISPR proteins that render them resilient to phage infection [5,14,15]. Scientific efforts focused on approaches to mitigate the elaboration of such resistance can be rewarding. Even if such efforts fail, selecting, engineering and screening a new type of

phage would be relatively trouble-free over developing a novel anti-microbial agent [16].

Another spectacular marvel with the survival of bacteriophages is their aptitude to establish two genres of living-lytic and lysogenic modes. Lytic phages can be used for clearance of particular group of pathogenic organisms while lysogenic phages can be used in manipulating the microbial genome and thus altering their rules of existence. Targeted clearance of specific clones of pathogenic bacteria requires an extensive knowledge about the colonization and residence of the pathogenic bacteria to ensure accessibility of phages to all niches of bacterial dwelling [17]. For example, phage therapy can be used only as an adjuvant to chemotherapy for absolute eradication of *H. pylori* infection since bacteriophages do not possess accessibility to the intracellular organisms. Copious efforts have been invested in establishing the utility of lytic phages while the blessed virtue of lysogeny is still unexploited. A more appreciated reform would be to formulate a cocktail of lytic and lysogenic phage mixture. Coherent formulation of such cocktails requires operative computational or animal replicas to authenticate their pharmacological topographies which have not yet been developed [18]. Hence, initiatives concentrated on assembling and manufacturing such mockup should be encouraged. Despite the fact that this innovative technique is superior to the use of antibiotics, their dominance over the niftiness of probiotic nutrition is yet to be documented.

Table 1 Challenges Encountered in Instigation and Utilization of Gut Microbiome Manipulation Strategies for Strengthening Gut Integrity of Infants

S. No	Challenges Encountered in Instigation and Utilization of Gut Microbiome Manipulation Strategies for Strengthening Gut Integrity of Infants
1	Spontaneous emergence of bacterial resistance to bacteriophage infection
2	Inaccessibility of phages to all niches of habitation of pathogenic bacterial clones that were desired for absolute elimination
3	Deficiency of prescribed techniques to engineer bacteriophages so as to tune the gut microbiota accordingly
4	Non availability of tools to ascertain and validate pharmacological (pharmacokinetic and pharmacodynamics) characters of bacteriophage mixtures
5	Knowledge gap in understanding the complete set physiological, metabolic and immunological interactions within the gut microbial ecosystem and with the host immune system
6	Lack of evidences that demonstrate the superiority of bacteriophage-based approaches over the reforms that are already under practice

Asphyxiation of above hindrances will result in developing oral formulation of phage cocktail preparation. Another glitch in oral administration would be to withstand gastric acidity. Gastric pH is known to vary between 4 and 6.5 [19]. Most of the phages are known to lose their activity as a consequence of this pH range [20] and thus staunching the desired upshot (either lytic phage mediated elimination or establishment of engineered phage-mediated lysogeny). Yet this can be overcome either by microencapsulation for acid protection or by co-administration of antacids [21]. Oral microencapsulation has been

experimented in animals and has been recorded to be efficient [22] but might work out to be expensive. Co-administration of antacids, though hypothetically sound, requires reliable evidence and documentation for implementation.

Conclusions

The strategy of microbiome manipulation using bacteriophages is a promising unique technology to promote gut health in new born and infants. They also possess an inordinate prospect in enhancing the quality of adulthood living by establishing and conserving the stable ecosystem of gut physiology. The instinctive or innate virtue of dual mode of survival of the bacteriophages poses immense potential in manipulating and fostering gut health. Building or designing animal or computational models to elucidate the pharmacological properties of phage therapeutics and filling the knowledge gaps to unravel the integrity of complex gut microbial community to throw light on desired persuasions would be the valuable initial phases of progress in the furtherance of this strategy.

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