ISSN: 2279 - 0594

Available Online at www.jbpr.in

Journal of Biomedical and Pharmaceutical Research 2 (3) 2013, 143-145

REVIEW ARTICLE

PHAGE THERAPY: THE USE OF BACTERIOPHAGES AGAINST INFECTIONS

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Received 28 May 2013; Revised 05 June 2013; Accepted 13 June 2013

ABSTRACT

Phages are a kingdom of viruses that infect bacteria, and are distinct from the animal and plant viruses. Phages can have either a "lytic" or a "lysogenic" life cycle. After their discovery early in the 20th century, phages were widely used to treat various bacterial diseases in people and animals. The worldwide increase of pathogenic bacteria resistant to antibiotics makes it an imperative to exploit alternative strategies to combat this threat. This review discusses the potential of phage therapy for detection and control pathogens.

KEYWORDS: Phage therapy, Pathogens, Bacteriophage, Antibiotic Resistance

INTRODUCTION:

The application of bacteriophages (phages) as antibacterial agents first began in the early1920, following their discovery by English bacteriologist Fredrick Twort in 1915 and also by French Canadian scientist Felix D'Herelle in 1917 [1]. Viruses are small infectious particles, typically 20-200 nm consisting of a nucleic acid core (single or double stranded RNA or DNA) enclosed by a protein coat (capsid) and in some cases a lipid envelope. Bacteriophages (phages) are viruses that infect prokaryotes. Most bacteriophages have dsDNA, however, some have ssDNA, dsRNA or ssRNA. Phage adsorption and entry are mediated by specific receptors such as carbohydrates, proteins and lipopolysaccharides on the surface of the host cell [3]. Bacterial cells can undergo one of two types of infections by viruses termed lytic infections and lysogenic (temperate) infections [3, 4]. Two categories of bacteriophages are recognised; temperate and virulent. During lytic infection, virulent phages inject their nucleic acid into the host cell following attachment. Expression of the phage genome directs the cellular machinery of the host to synthesise new phage capsule material. The resulting phage progeny are released by fatal cell lysis enabling the lytic cycle to continue as new cells are infected. The number of progeny released (burst size) varies from 50-200 new phage particles. In contrast, during lysogenic infection temperate phage nucleic acid recombines with the host cell genome forming a dormant prophage. The prophage is reproduced in the host cell line and confers immunity from infection by the same type of phage. Stress conditions such as ultraviolet light or chemical mutagens can induce a switch to the lytic cycle [5, 6]. Problems of phage therapy: Host range, Bacterial debris present in the phage preparations, Attempts to remove host bacteria from therapeutic Preparations, Rapid clearance of phages Lysogeny, Anti-phage antibodies, Failure to establish scientific proof of efficacy,The scientific style of phage investigators in the historical era [7]. Advantages of Phages: They are self-replicating but also self-limiting because they multiply only as long as sensitive bacteria are present, They can be targeted far more specifically than most antibiotics to the problem bacteria, causing much less damage to the normal microbial balance in the gut, Phages can often be targeted to receptors on the bacterial surface that are involved in pathogenesis, so any resistant mutants are attenuated in virulence, Few side effects have been reported for phage therapy, Phage therapy would be particularly useful for people with allergies to antibiotics, Appropriately selected phages can easily be used prophylactically to help prevent bacterial disease at times of exposure or to sanitize hospitals and help protect against hospital-acquired (nosocomial) infections, Especially for external applications, phages can be prepared fairly inexpensively and locally, facilitating their potential applications to underserved populations, Phages can be used either independently or in conjunction with other antibiotics to help reduce the development of bacterial resistance [7, 8]. This review discusses the potential of phage therapy for detection and control pathogens.

APPLICATION OF PHAGES:

Phage typing is a popular tool to differentiate bacterial isolates, and is used in epidemiological studies with the aim of identifying and characterizing outbreak-associated strains. Although more sophisticated systems for differentiation are available, such as ribotyping, random amplified polymorphic DNA-PCR fingerprinting, or pulsed

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field gel electrophoresis of enzyme-digested DNA, the variable sensitivity to a set of bacteriophages (phage typing) remains a useful method because of its speed, relative simplicity, and cost-effectiveness. Studies on enterohemorrhagic *E. coli* (EHEC) and Campylobacter showed that phage typing can be highly useful, especially because any one typing method alone fails to produce all the relevant data pertaining to epidemiological relatedness [9, 10]. Phage therapy is the therapeutic use of lytic bacteriophages to treat pathogenic bacterial infections. Phages were used widely in the early 20th century to treat human and animal illness with varying degrees of success [11]. Before attempting phage therapy several, sometimes rather demanding, prerequisites should be met: 1. Phage therapy should not be attempted before the biology of the therapeutic phage is well understood. Since the phage–host systems are extremely complicated, this prerequisite has to be faced with some common sense. 2. Phage preparations should meet all the safety requirements; the preparations should be free of bacteria and their components. 3. Phage preparations should contain infective phage particles, thus storage of the preparations should be validated. 4. The phage receptor should be known. In a bacterial population of 106–108 bacteria there is a high possibility of spontaneous phage-resistant mutants deficient in the receptor or with an altered receptor. It can be assumed that a mutation eliminating the receptor that functions as a virulence factor of a pathogen (such as LPS) would attenuate the bacterium and then it would be easier for the host immune system to eliminate the bacteria. 5. The efficacy of phage therapy should be tested in an animal model.

BACTERIOPHAGE TREATMENT OF *CAMPYLOBACTER* AND *SALMONELLA:*

Campylobacter jejuni and *Campylobacter coli* are major causes of acute bacterial enteritis in the developed world. Domestic poultry have been identified as the primary reservoir for these organisms and their presence in undercooked poultry is implicated as the natural source of human infection. In study wagenaar et al, conclude that phage treatment is a promising alternative for reducing *C. jejuni* colonization in broilers. Goode et al. were able to achieve a 95% reduction in *C. jejuni* counts on artificially contaminated chicken skin [12, 13]. *Salmonella* is a Gram-negative bacterium. Its cell envelope includes a lipopolysaccharide (LPS) layer (the outer membrane), which can protect it from the lysis caused by lytic enzymes. Phage biocontrol measures have been reported both in vivo and on food. Goode et al, observed eradication of phage-susceptible Salmonella strains. Whichard et al, tested the broad host range Salmonella phage Felix-O1 in biocontrol experiments with *Salmonella typhimurium* on sausages, and reported a 2 $\log_{10}$ reduction of viable cells [14].

BACTERIOPHAGE TREATMENT OF *LISTERIA MONOCYTOGENES* AND *ENTEROBACTER:*

Listeria monocytogenes has only recently emerged as a serious food-borne pathogen that can cause abortion in pregnant women and meningitis, encephalitis and septicaemia in newborn infants and immunocompromised adults [15]. Pasternack and Sulakvelidze, patented six *Listeria monocytogenes* phage strains (ATCC Deposit Accession Nos. PTA-5372, PTA-5373, PTA-5374, PTA-5375, PTA-5376 and PTA-5377), which are capable of con-trolling the contamination of food products by *L. monocytogenes* [16]. In study, Carlton et al, which also evaluated in vivo feeding toxicity and addressed the issue of potential allergenicity by an in silico approach, the effect of the broad host range, virulent phage P100 on growth of Listeria in soft cheese was studied. Complete eradication of target cells was achieved, depending on dosage and treatment schedule [17]. Nosocomial infections are caused by *Enterococcus faecalis* and *Enterococcus faecium*, two gram-positive bacteria that normally colonize the lower intestinal track. A PlyV12 phage virolysin has been discovered to have lytic effect on those *enterococcus* species as well as on two vancomycin-resistant *E. faecalis* strains (VRE) and three vancomycin-resistant *E. faecium* strains. Vancomycin is an antibiotic that is considered as the last line of defense against a bacterial pathogen that is already resistant to the other antibiotics [16].

BACTERIOPHAGE TREATMENT OF *E. COLI:*

Escherichia coli is the cause of a third of cases of childhood diarrhoea in developing and threshold countries and is also the most prominent cause of diarrhoea in travellers to developing countries [18]. *E. coli* O157:H7 is a highly virulent foodborne pathogen naturally found in the gastrointestinal tract of ruminants and other mammals. *E. coli* phages are commonly isolated from sewage, hospital waste water, polluted rivers and faecal samples of humans or animals. Merril et al, demonstrated in1996 that mice with fulminant *E. coli* bacteremia could be rescued by phages [19]. Raya et al, demonstrated that a single oral dose of bacteriophage specific to *E. coli* O157:H7 given to sheep resulted in a two-log reduction (% 99) of the pathogen [20].

CONCLUSIONS:

Numerous inventions have been disclosed in the last two decades regarding the production and application of phages into practical alternatives to antibiotics.

Applications of phages and virolysins include treatment and prevention of bacterial infections, detection of pathogens in foods and other samples, and decontamination of foods and medical devices. Phages can also be utilized for a diversity of other applications such as in targeted drug delivery and in preventing biofilm formation in industrial processes.

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