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Evading Antibody Mediated Inactivation of Bacteriophages Using Delivery Systems

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Abstract

The emergence of drug resistance among bacterial pathogens has prompted scientists to develop strategies for their effective elimination. In this regard, phage therapy is considered as an alternative approach to target these pathogens. To make this line of treatment effective, a number of steps are being taken to increase their effectiveness *in-vivo*.

Keywords: Antibiotic resistance; Bacteriophage therapy; Delivery systems; Liposomes

Abbreviations: WHO: World Health Organization; MDR: Multi-Drug Resistant

Introduction

In early 1900's, discovery of bacteriophages (phages) suddenly prompted their use as a potent anti bacterial agents because of their higher specificity and easy availability. Ernest Hankin was the first to report their antibacterial activity against *Vibrio cholerae* in the water of Indian rivers [1]. Subsequently phages were considered as one of the most effective therapeutic agents against deadly bacterial infections. However, discovery of antibiotics negated the application of phage therapy [2]. The reasons behind failure of phage therapy during antibiotic era were multifold for example, sudden increase in the titre of anti phage antibodies upon hypodermic inoculation, bacterial resistance towards phages and inability to target intracellular pathogens were some of the reasons that led to the failure of phage therapy [3-5]. The scope of using another antibacterial agent for many decades did not arise. However, in recent years emergence of antibiotic resistance among bacterial strains has posed a serious threat to medical community where a small cut can lead to deadly infection. According to WHO report 2016 patients infected with MRSA (methicillin-resistant *Staphylococcus aureus*) are expected to be 64% more prone to death than people with a non methicillin-resistant type of infection. In many countries, presence of carbapenem resistance has been shown in more than 50% clinical isolates of *Klebsiella pneumoniae* [6]. A recent report (2017) highlighted the consequences of bacterial drug resistance. A woman who travelled from India to United States was killed by *K. pneumoniae* which was resistant to 26 antibiotics including colistin, which is recognized as an antibiotic of last resort [7]. WHO estimated that, only in 2014, 480000 new cases of multidrug-resistant tuberculosis (MDR-TB) were recorded. Increased antimicrobial resistance has prompted the scientists to look back at the old therapies including phage therapy. In western countries, phage therapy was neglected after discovery of antibiotics but former Soviet Union still relied on phage therapy and even today it is being practiced in these countries. Phage preparations were also prepared in Pasteur Institute against various bacterial pathogens including Staphylococcus, Escherichia, Pseudomonas, Serratia until 1974.

However, in recent years the interest in phage therapy has been rekindled the world over. Various studies have shown that phages can efficiently eliminate bacteria especially those that have acquired resistance to antibiotics and cause life-threatening infections such as *K. pneumoniae, methicillin* resistant ***staphylococcus aureus***, *Pseudomonas aeruginosa* and vancomycin-resistant *Enterococcus faecium* [4-10]. Bacteriophages can also distrupt bacterial biofilm alone and in conjunction with antibiotics, which are associated with most of the chronic infections [11,12]. The ability of bacteriophages to rapidly kill or lyse infected bacteria, their specificity and their proven clinical safety makes them ideal, robust, safe and effective self replicating antimicrobial drugs of the future [1]. Inspite of many advantages, one of the major threat to phage

therapy is development of immune response to antigenic phage, which can induce production of phage neutralizing antibodies. The antibodies can mediate inactivation of phage on repeated administration [5,13]. One of the means of protecting phages from the developed immune response could be by shielding them. Antibody mediated inactivation of phages can be countered by using suitable delivery systems which can mask phages from immune surveillance. Limited reports of use of delivery systems to keep phages concealed from immune response are available. In one of the reports, phage entrapped liposomal formulation has been sucessfully used for the treatment of *K. pneumoniae* induced respiratory tract infection in mice. The liposomal entrapped phages were also protected from anti phage antibodies as compared to un-entrapped phages [14]. Phages showed antibody mediated inactivation after 3 hour of incubation with antiserum, containing phage specific antibodies when used without delivery system. The liposomal delivery system provided 100% immune protection from anti phage antibodies as no lowering of phage titre also seen. Incubation of bacteria along with liposomal phage preparation showed significant log reduction in bacterial population, confirming the presence of active phage in liposomes. Not only entrapped phages in liposomes blocked the antibody mediated phage inactivation but it also showed that phages were delivered inside macropahges, leading to killing of intracellular *K. pneumoniae* as well as into the interior matrix of biofilms [14]. In earlier studies antibody mediated phage neutralization and inability of phages to target intracellular bacterium have been considered as one of the major drawbacks of phage therapy. However, use of liposomal delivery system can evade the circulating antibodies as well as delivers the phage inside the macrophages, where bacterium may escapes the phage interaction [14].

Conclusion

Another more specific delivery system than liposomes can be evaluated which not only protects phages from antibody mediated phage inactivation but also provides better delivery of phages at or across the specific tissues, at specific pH or at specific temperature.

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