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BACTERIOPHAGES: DISCOVERY AND THERAPEUTIC USES IN HUMANS AND ANIMALS

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ABSTRACT

Viruses are particles which can specifically infect many kinds of organisms such as bacteria, plants, animals and humans. These organisms are called host cells. Recently, bacteriophages, viruses specifically infecting bacteria, have become interesting to replace antibiotics to treat diseases in animals and humans caused by pathogenic bacteria infections. This article briefly describes about the discovery of bacteriophages, and their therapeutic uses in animals and humans

Key words: Bacteriophage, bacteriophage therapy, discovery

INTRODUCTION

A bacteriophage, or phage for its shortened name, is the collective name for viruses that infect bacteria. The name is derived from two words, bacteria and phagein (a Greek word for "to eat"). Generally, bacteriophages consist of an outer protein coat enclosing genetic material. The genomes of bacteriophages can be single stranded (ss) RNA, double stranded (ds) RNA, ssDNA or dsDNA between 5 and 500 kb long with either circular or linear arrangement. The phages, which are much smaller than their hosts, are usually between 20 to 200 nm in size. They are ubiquitous and can be found in all places populated by bacterial hosts such as soil, sea, food and gastro-intestinal tracts of animals and human. Although bacteriophages are infamous for their destructive activity against useful bacteria such as bacterial starter cultures used in fermented food industries, they show potentials to be used as an alternative way to kill pathogenic bacteria resistant to antibiotics. Recently, many research groups have tried to develop a new way of treatment based on bacteriophages which is called bacteriophage therapy for fighting animals and human diseases caused by multi drug resistant strains of many bacteria.

Discovery of bacteriophages

The history of bacteriophage discovery can be divided into two eras. The first era began in 1986. Ernest Hankin, a

British bacteriologist observed the presence of antibacterial activity against *Vibrio cholerae* in the waters of the Gange and Jumna rivers in India[1]. He reported that an unidentified substance (which passed through fine porcelain filters and was heat labile) was responsible for this phenomenon. Later on, several investigators found evidence related to the finding of Hankin[2]. However, none of them further explored their findings until Frederick Twort, a British medically trained bacteriologist, reintroduced the subject almost twenty years after Hankin's observation by reporting a similar phenomenon and advancing the hypothesis that it may have due to a virus[3, 4]. However, he did not pursue his finding because of various reasons including financial difficulties.

Felix d'Herelle, French-Canadian microbiologist at the Institute of Pasteur, Paris, was the most important person in the second era of bacteriophage discovery. Besides being the first man who used the word "bacteriophage", his works have been the strong foundation for modern researches on bacteriophages[5]. The first report of d'Herelle on bacteriophage phenomenon was in 1910 while he tried to develop microbiological means of controlling epizootic of locusts in Mexico. His work on bacteriophage continued until 1916 he proposed the name "bacteriophage" to call viruses capable of parasitizing bacteria. The name was formed from "bacteria" and "phagein" (to eat or devour, in Greek). In 1915, d'Herelle discovered plaques, although they were not initially called plaques. The discovery of plaques by d'Herelle was associated with an outbreak of hemorrhagic dysentery among French troops stationed at Maisons-Laffitte (on the outskirts of Paris) in 1915. Several soldiers were hospitalized, and d'Herelle was assigned to conduct an investigation of the outbreak. During this study, he made bacterium-free filtrates of the patients' fecal samples and mixed and incubated with *Shigella* strains isolated from the patient. A portion of the mixtures was inoculated into experimental animals and a portion was spread on agar medium in order to observe the growth of the bacteria. It was on these agar cultures that d'Herelle observed the appearance of small, clear areas, which he initially called taches, then taches vierges, and later, plaques. His findings were presented in the meeting of the Academy of Sciences in 1917[6].

History of bacteriophage therapy

The first attempt to use bacteriophages therapeutically was conducted by d'Herelle. He used phages to treat dysentery at the Hopital des Enfants-Malades in Paris in 1919 under supervision of Professor Victor-Henri Huntinel, the hospital's Chief of Pediatrics[5]. The phage preparation was ingested by d'Herelle, Hutinel and several hospital interns in order to confirm its safety before giving it to a 12-year-old boy with severe dysentery. The patient's symptoms ceased after a single administration of the antidysentery phage, and the boy fully recovered within a few days. The

efficacy of the phage preparation was confirmed shortly afterwards. Three patients suffered from bacterial dysentery started to recover within 24 h after taking a dose of the phage preparation. However, the results of these studied were not immediately published and, therefore, the first report of bacteriophage therapy against bacterial infected diseases in human came in 1921 from Richard Bruynoghe and Joseph Maisin[7]. They used bacteriophages to treat staphylococcal skin disease. Several similarly promising studies followed and encouraged by these early results[8-10].

Bacteriophage therapy in human

The first report of application of phages to treat infectious diseases of human came from Bruynoghe and Maisin in 1912[7]. They used phages to treat staphylococcal skin disease. The phages were injected into and around surgically opened lesions and the regression of the infections was observed within 24 to 48 h. Phages have been used since that time for therapeutic purposes in the United States, in eastern Europe and in the former Soviet Union.

The international literature contains several hundred reports on phage therapy, with the majority of the publications coming from researchers in the former Soviet Union and eastern European countries[11-13]. Phages have been reported to be effective in treating skin infections caused by *Pseudomonas, Staphylococcus, Klebsiella, Proteus, and E. coli, staphylococcal* lung and pleural infections[14, 15]. *P. aeruginosa* infections in cystic fibrosis patients[16], neonatal sepsis[17], and surgical wound infections[18, 19]. The most detailed descriptions have come from the Institute of Immunology and Experimental Medicine of the Polish Academy of Sciences. Briefly, phage therapy was used on 550 patients, at 10 clinical and hospital departments in three different cities (Wrozlav, Lubin, and Kamienna Gora). The major infecting agents included *Staphylococcus, Pseudomonas, Escherichia, Klebsiella,* and *Salmonella* species. Phages were administered orally, applied directly to wounds, or given in eye drops. Reported success rates ranged from 75 to 100%, depending on the pathogen[20-26].

Recently, many strains of multi drug resistant bacteria have been discovered. Patients infected by these bacteria can be no longer treated with antibiotics. Bacteriophage therapy may be the answer for the diseases. The researches on bacteriophage therapy against multi drug resistant bacteria have been growing. In the future, many phage preparations will be come out to the public as new weapons for fighting the diseases that cannot be cured by antibiotics.

Bacteriophage therapy in animals

Many reports on bacteriophage therapy in animals have been published in scientific literature. One of the most detailed reports of the use of phages in veterinary medicine came from Smith and Huggin. In one of their early papers published in the Journal of General Microbiology, they reported the

successful treatment of experimental *E. coli* infections in mice using phages and claimed the advantages of phage therapy or antibiotics[27]. They also conducted experiments using phages to reduce diarrheagenic *E. coli* in the alimentary tracts of calves, lambs and piglets. In addition, they showed that diarrhea could be prevented in calves by simply spraying the litter in the calf rooms with an aqueous phage suspension[28, 29]. A group of investigators in England successfully used phages to prevent and treat experimental infections with *Psuedomonas aeruginosa* and *Acinetobacter* in mice and guinea pigs[30]. There was also a report of using *Salmonella* and *E. coli* phages to prevent death of experimentally infected chickens[31]. Examples mentioned above are a very small fraction of works on bacteriophage therapy in animals. The researches on the issue are increasing and they will be in this direction for many years ahead.

CONCLUSION

Much of the evidence presented in this review strongly shows that phage therapy is very effective for treatment and prevention of many kinds of bacterial infectious diseases. Currently, many pathogenic bacteria have acquired multiple drug resistance, which is a serious clinical problem. Future trend of the research concerning phage therapy will be associated with the use of phages to control diseases caused by the multiple drug resistant pathogenic bacteria. However, phage therapy still has some problems remained to be solved including (1) inactivation of administrated phages by immune response of the treated organisms, (2) appearance of mutants to phages and (3) transfer of bacterial antibiotic resistant genes by phages. Finding of solutions for these problems are also the hot issues for future research about phage therapy.

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