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REVIEW

Phage therapy: Facts and fiction

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Abstract

Recent examples of the use of bacteriophages in controlling bacterial infections are presented, some of which show therapeutic promise. The therapeutic use of bacteriophages, possibly in combination with antibiotics, may be a valuable approach. However, it is also quite clear that the safe and controlled use of phage therapy will require detailed information on the properties and behavior of specific phage–bacterium systems, both in vitro and especially in vivo. In vivo susceptibility of bacterial pathogens to bacteriophages is still largely poorly understood and future research on more phage–bacterium systems has to be undertaken to define the requirements for successful phage treatments.

Keywords: Phage therapy; *Yersinia enterocolitica*; *Escherichia coli*

Contents

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Introduction

In the April 2003 issue of "New Scientist", James Randerson wrote an article "Virus cleans up food poisoning bug" (Randerson, 2003) where he reported observations presented by Andrew Brabban (Evergreen State College in Washington state) in the XXth Annual Meeting of the Society for General Microbiology in Edinburgh, UK. Brabban had wanted to test the effect of different antibiotics on *Escherichia coli* O157:H7 in infected sheep. However, the researchers faced an unexpected problem; the bacteria disappeared from the infected sheep very rapidly. It turned out that the sheep carried a bacteriophage specific for *E. coli* O157:H7 and the phage efficiently eliminated all the inoculated pathogens from the sheep tissues. This is an example of a number of observations made on the antibacterial potency of bacteriophages during the last 90 years after the independent discoveries of bacteriophages by d'Herelle and Thwort.

The prospect of phage therapy has stimulated a lot of discussion recently. The increase in interest can be explained in part by the publication of experiments conducted using phage lysins (Loeffler et al., 2001; Nelson et al., 2001; Schuch et al., 2002) and by animal experiments where the bacterial infections are challenged with live bacteriophage particles (Biswas et al., 2002; Broxmeyer et al., 2002; Cerveny et al., 2002; Loeffler et al., 2003; Merril et al., 1996; Sulakvelidze et al., 2001; Westwater et al., 2003).

Steve Projan (2004) presented a number of provocative arguments recently challenging the optimism regarding phage therapy. Apparently, Projan dislikes proponents of phage therapy since he puts forward such expressions like "a cult of phage therapy followers", "the little animal efficacy data there is in the literature can charitably be described as meager", "this silence (on animal efficiency data) speaks volumes" and "anecdotal testimonials of former patients".

We will not try to cover old literature in this review since there are excellent recent reviews on phage therapy available (Alisky et al., 1998; Anonymous, 1983; Bradbury, 2004; Bull et al., 2002; Cerveny et al., 2002; Dixon, 2004; Duckworth and Gulig, 2002; Inal, 2003; Levin and Bull, 2004; Merril et al., 2003; Nakai and Park, 2002; Payne et al., 2000; Pirisi, 2000; Projan, 2004; Schoolnik et al., 2004; Stone, 2002a, b; Sulakvelidze et al., 2001; Summers, 2001; Thacker, 2003; Thiel, 2004; Weber-Dabrowska et al., 2002, 2003; Weinberg, 2002). We will focus mainly on recent work carried out to exploit the therapeutic potential of phages and phage products to combat bacterial pathogens. Another interesting aspect of phage application is the use of whole phage particles to deliver vaccines in the form of immunogenic peptides attached to modified phage coat proteins or as delivery vehicles for DNA vaccines, which was recently reviewed by Clark and March (2004).

Principles of phage biology

Bacterial viruses (bacteriophages) occupy all those habitats of the world where bacteria thrive. It has been estimated that for each bacterial cell there are ten bacteriophage particles. Recently, the existence of viruses specific for archaebacteria (archeophages) has become evident also. Some phages are highly specific while others are extremely broad in their host range. Bacteriophage taxonomy is based on their shape and size as well as on their nucleic acid. Most bacteriophages have ds DNA, however, some have ss DNA, ds RNA or ss RNA.

Upon infection of the bacterial host different phages can have quite different fates. Some phages follow the lytic infection cycle whereby they multiply in the bacterial cell and lyse the bacterial cell at the end of the cycle to release newly formed phage particles. Some phages may use the lysogenic pathway where the phage genome will integrate as part of the host genome, replicate as part of the host genome and stay in a dormant state as a prophage for extended periods of time. If the host bacterium encounters adverse environmental conditions the prophage may become activated and turn on the lytic cycle, at the end of which the newly formed phage particles will lyse the host cell.

The following phases can be distinguished in the lytic bacteriophage developmental cycle:

1. Adsorption of the phage on the bacterial cell by binding to a specific receptor.
2. Injection of the nucleic acid into the bacterium.
3. Expression of the phage early genes, synthesis of early proteins, most involved in the shutting down of the host bacterium systems and phage genome replication.
4. Replication of the phage genome.
5. Expression of the phage late proteins involved in the formation of new phage particles and lysis of the host bacterium.
6. Assembly of the phage heads and tails and packaging of the genome.
7. Lysis of the host bacterium and release of the new phage progeny.

The ability of the phages to kill the bacterial cells at the end of the infectious cycle is the cornerstone of the idea of using phages as therapeutic agents. However, for a positive outcome of the therapeutic use of bacteriophages all the above listed steps in the phage infectious cycle need to take place. Bacteriophages have coevolved with their bacterial hosts. Already in the few thoroughly studied phage–bacterium systems many examples of intricate molecular mechanisms have been revealed. Therefore, one cannot expect that all the phage/host systems will behave identically under the conditions met