

Bacteriophage Therapy in Modern Medicine

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Antibiotic resistance in pathogenic bacteria has become a growing problem in medicine. Through mutation bacteria are able to become immune to antibiotics and pass on their resistance to other bacteria via gene transfer. Antibiotic resistant bacteria are able to thrive in the presence of antibiotics, rendering some medical treatments for pathogenic infections ineffective. A possible solution to this problem is the use of bacteriophages, viruses that attack bacteria. In past years, phage therapy has been neglected as a viable treatment option, but has been gaining more popularity because of the recent issue with antibiotic resistance. One experiment in particular performed by Vinodkumar et al. (2008) demonstrated that phage therapy is effective in treating bacteria caused illness. The results proved that phages can eradicate antibiotic resistant bacteria if given in the appropriate dose and time. Furthermore, phage therapy can overcome bacterial resistance. If a bacterium becomes resistant to its phage, the phage can adapt to continue its antibacterial action as demonstrated by Kashiwagi and Yomo (2011). Research on phages to this point has not revealed any major problems with phage therapy, but some minor challenges exist. One such issue is the narrow host range utilized by Schofield et al. (2011) in the test they modified for identifying bacteria. This is a problem that limits phage therapy to only being useful if the bacteria responsible are identified but that can be solved with further research.

Introduction

Although most bacteria play a distant role in the lives of humans, the small percentages that do affect us can be a source of help or harm. In the field of medicine, much work goes into dealing with the harmful, or pathogenic, bacterial strains. Usually cures for pathogens are in the form of antibiotics. Antibiotics act against microorganisms through a variety of mechanisms, for example: inhibiting important processes in metabolism or disrupting major structural units. This diversity in antibiotic pathways is important for their ability to work against many different pathogens as well as presenting opportunities to overcome bacterial resistance to certain antibiotics. Antibiotic resistance in bacteria is one of the major growing concerns regarding antibiotics at this time (Vinodkumar, et al., 2008).

Antibiotic resistance has been gradually increasing over the years due to the amount of exposure to

them bacteria encounter. Genetic transfer of the genes responsible for antibiotic resistance, from bacteria with resistance to those without, is another cause of the rapidly decreasing effect of antibiotics on bacteria. Because of the looming threat of an uncontrollable strain of bacteria that cannot be controlled by antibiotics, other methods of dealing with pathogenic bacteria are being sought out (Vinodkumar, et al., 2008).

Bacteriophages are viruses that target and kill bacteria. Using the same mechanisms that harm us when humans are the host, these viruses use bacteria as a means to reproduce and lyse them in the process. Although the concept of phage therapy has been in existence for many years, it has received little attention because of the prima facie fear of viruses and mishandled experiments when the idea was conceived (Vinodkumar, et al., 2008). The result of the disregard of bacteriophages has resulted in a deficiency of knowledge in a potentially very promising

branch of medicine. The articles represented reveal some of the work that is currently being done to bridge the gap in utilizing this underdeveloped medicine.

Recent Progress

Effectiveness of Phage Therapy

Vinodkumar et al. (2008) demonstrated phage therapy effectiveness against a bacterial strain that had become resistant to a number of antibiotics. Mice were exposed to the antibiotic resistant bacteria *P. aeruginosa* at a dose that was lethal within 48 hours. The infected mice were then treated with a phage that was found to have antibacterial effects on *P. aeruginosa* at varying doses and times between administration of the bacteria and phage.

The results revealed that the bacteriophage was an excellent treatment against *P. aeruginosa*. At appropriate doses, all mice that were given the treatment within five hours of being inoculated with the bacteria fully recovered. Even when treatment was delayed 24 hours, well after visible signs of infection were present, about half of the mice recovered. Additional testing to insure that the phage, and not the mouse immune system, was the source of reduction of *P. aeruginosa* confirmed that the phage therapy was responsible for the mice's recovery.

While this only gives evidence for the effectiveness of phage therapy in one situation, it has important implications that can be extended to all bacteriophages. This experiment proves that phages efficiently work against bacteria and are a viable treatment method. No harmful side-effects were observed in the mice as a result of being exposed to a virus, and heavily antibiotic resistant bacteria were eliminated.

Overcoming Bacterial Resistance

For the time being, phage therapy offers an alternate mode of attack against pathogenic bacteria, but eventually the target bacteria will build up a resistance to this treatment. Fortunately, because viruses are not merely chemicals, as is the case with antibiotics, they can also adapt to their environment. The ability of phages to respond to bacterial mutations that gave them favorable resistance was studied by Kashiwagi & Yomo (2011). The bacteria *E. coli* was grown in the presence of a bacteriophage labeled Q β to which it was a host.

Both the bacteria and phage went through multiple mutations throughout the observation. *E. coli* would first mutate to become partially resistant to Q β . However, the bacteriophage would then quickly mutate advantageously, allowing it to better act against *E. coli*. This arms race, or Red Queen hypothesis, causes these two organisms to continue to adapt to each other in order to improve their situation.

Challenges to Phage Therapy

An alternate use of bacteriophages developed by Schofield et al. (2011) determines if certain bacteria are present in a sample by making use of the high degree of specificity that is demonstrated by bacteriophages. In the past, phages of certain bacteria were introduced to a sample of unknown bacteria, and their activity was observed after a period of time. In the cases that a plaque was visible after 24-36 hours, the bacteriophages had lysed their host bacteria, accurately indicating that the bacteria in question were present in the sample because phages have predictably narrow host ranges.

This experiment was able to improve on the described test to introduce a faster and more easily implemented method. The phages were genetically engineered to more rapidly infect their host bacteria and insert a gene that was fluorescent. Because the luminescent bacteria were detected faster, these modifications allow for a better response time to take action against especially harmful and contagious bacteria.

A key feature of bacteriophages that is divulged by this test is high specificity, which phages have toward their host. A bacteriophage will usually have a host range that is reliably narrow. This feature of phages was essential to the study because it allowed for accuracy in making conclusions on the bacteria present in a sample. This narrow host range is problematic for phage therapy because different phages are required to treat each pathogenic bacterium. Especially in cases in which the symptoms of an illness are not sufficient to properly identify the bacteria responsible, the efficiency of phage therapy would be decreased.

Discussion

Due to the increasing danger of antibiotic resistance in pathogenic bacteria, it is becoming more important to consider alternate methods of controlling bacteria (Vinodkumar, et al., 2008). Phage therapy is one possible solution to the problem in which we currently find ourselves. The experiment done by Vinodkumar et al. is one in many that demonstrates the effective process by which bacteriophages eliminate their bacterial host, but it provides compelling evidence in support of phage therapy.

Phage therapy is an easy and obvious solution to the problem of antibacterial resistance. The phages used in the experiment, after being identified, were merely purified before they were ready to be used to treat the infected mice. Although genetic engineering is an option for improving phage therapy, no such measures were necessary for the bacteriophages to completely cure many of the infected mice. The treatment was more effective if a larger dose was administered after a short delay between exposure to the bacteria and phage. These factors are similar to antibiotics, making it clear that levels of phage

doses to use and the severity of the bacterial infection will need to be accounted for in phage therapy.

In addition to phage therapy offering an elegant solution to antibiotic resistance, it can continue to treat pathogenic bacteria without the eventuality of resistant bacterial strains. The findings Kashiwagi and Yomo made in their study have important implications to the future of phage therapy in medicine. If bacterial resistance to its phage occurs, merely exposing the phage to its bacteria for a period of time eventually results in a mutation that adapts the phages to the changes in their host.

Without the threat of bacterial resistance, phage therapy would not have to be monitored as closely as antibiotics are. Conflicts that have arisen over the use of antibiotics in medicine and agriculture could be resolved with the existence of an antibacterial agent that can overcome resistance. The lack of restrictions that bind antibiotics would allow for a liberal use of bacteriophages on patients suffering from pathogenic bacterial infections.

So far, research of bacteriophages has not yielded any evidence of major drawbacks or negative effects of phage therapy. However, some minor challenges exist. The identification test described in the experiment done by Schofield et al. gives insight to the great amount of specificity phages have for their hosts. This feature of phage therapy could be problematic because phages will not be able to treat bacterial infections in the generalized manner that is exhibited by antibiotics. Although this is true, it is not an obstacle that cannot be surmounted. Some methods that could be used to form a general phage treatment are to combine multiple phages into one treatment, or to genetically engineer phages for a broader host range. Whether or not a solution to this problem is easily attainable, it is not a major vice to phage therapy because it simply means that phage therapy is not yet suited to replace antibiotics in medicine.

References

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