Getting a virus to do an antibiotic's job

By Nicholas Staropoli — June 26, 2015

It is an understatement to say that antibiotic resistance is a major problem facing our healthcare system. Every year 2 million Americans are infected with resistant bacteria and at least 23,000 people die each year from these infections. Each year MRSA [2] kills about as many people as HIV [3]. Compounding this problem is the fact that some companies are feeding antibiotics to their livestock, a practice our adviser [4] Dr. David Shlaes has frequently railed [5] against as a source of resistance.

Furthermore, there has been a severe lack of progress in making [6] new antibiotics, mostly due to depleted funding from the NIH. Additionally, changes in the 1990s to how the FDA treats new antibiotic discoveries have discouraged many drug companies from developing new antibiotics. The struggle has made some researchers start to think about new ways to fight infections. One idea that is being attempted is using viruses to fight infections.

When we think about viruses, we generally think of them as human contagions. The flu, HIV, and the common cold all come to mind quickly. However, all organisms have viruses that infect them, including bacteria. Bacteriophage (or just phage) is the special name given to these viruses. These phages interact with bacteria in the same way they do with human cells (or any other cell for that matter): they enter the cell, take control of the host’s cellular machinery, trick the cell into making more of copies of the virus, burst the cell open to release these new copies, and then the cycle repeats. The phages are also species specific, and sometimes even strain specific; a phage that attacks MRSA is not a threat to a human cells, nor an E. coli cell.

You maybe thinking this sounds like a great way to treat infections and you wouldn’t be the first. In fact during the Cold War [7], antibiotics rarely reached countries behind the iron curtain. This led to a boom in phage therapy research there and it’s still used today as a successful treatment in countries like Russia and Georgia.

One of the benefits of phage therapy over traditional antibiotic therapy is the specificity of the treatment. A major adverse effect of antibiotics is that they wipe out a significant portion of a
person's healthy microbiome. This contributes to the creation of antibiotic resistant bacteria and leaves a person susceptible to even worse infections like colitis from *Clostridium difficile* (aka *C. diff* [8]). However, a properly selected phage can only attack the bacteria causing the infection, while leaving the healthy ones untouched. Furthermore, the self replicative property of viruses means the response would get stronger the more bacteria the viruses killed.

There is still some worry about the bacteria becoming resistant to the phages, however, researchers can develop ways to handle this issue. Most phages, even those that attack the same strain of bacteria, are genetically distinct. Therefore, researchers can administer cocktails of phages, so that if the human contagion evolves resistance to one phage, other phages are around that the bacteria is still susceptible to.

Another concern is that when the bacteria burst open, they release a myriad of toxins, which can lead to sepsis and even death. Scientists at MIT [9] have a now have a solution to this. The researchers there have bioengineered what they have named phagemids,” which are phages that carry a very small piece of DNA called a plasmid (the mids in phage-mids). Instead of entering the cell, these phagemids, insert the plasmid into the bacteria. The plasmid codes for proteins that kill the bacteria without bursting the cell open and releasing the dangerous toxins.

The researchers are already having ample success with the technique. In a paper they recently published [10] in *Nano Letters*, the researchers reported having excellent success treating peritonitis in mice *in vivo*. Not only did they have a high degree of success in these trials, they also did not witness any bacterial resistance to the treatment.

It still remains to be seen what role phage therapy or phagemids might play in treating infectious disease in this country, however, with the growing threat of antibiotic resistance, any help we can get is important. It maybe that phages should be given alongside traditional antibiotics to augment traditional therapy. This combination with antibiotics might be the solution in the short term as phage therapy requires the identity of the contagion to be known before treatment, which currently can takes days to determine. But as detection techniques for bacteria become quicker, the use of phage therapy or phagemids might be able to stand on its own.

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