Bacteria-Killing Viruses May Provide New Treatments for Liver Disease

A pair of studies found that bacteriophage therapy may treat alcoholic hepatitis and primary sclerosing cholangitis.

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Bacteriophage therapy, in which bacteria-killing viruses are used to treat disease, showed promise as a treatment for both alcoholic hepatitis and primary sclerosing cholangitis (PSC) in a pair of recent studies.

Known as phage therapy for short, this treatment relies on bacteriophages that penetrate and inject their DNA into bacteria. This gives rise to replication of the virus within the bacterial cells, which ultimately kills them.

Phage therapy may hold particular promise as a new avenue for treating drug-resistant bacteria as the overuse of antibiotics in humans and livestock has led to mutated bacterial strains that can evade such treatments.

Phage therapy was used to treat an overgrowth of the bacteria Klebsiella pneumoniae (K. pneumoniae) in people with PSC and Enterococcus faecalis (E. faecalis) in individuals with alcoholic hepatitis. Each of these bacteria are associated with worsening of the respective liver diseases.

Findings from the PSC study were presented by BiomX, an Israeli biotech company, at The Liver Meeting, the Annual Meeting of the American Association for the Study of Liver Diseases, in Boston this month. The alcoholic hepatitis study, which was funded in part by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), a division of the National Institutes of Health (NIH), was published in the journal Nature.

PSC, a rare liver disease affecting about 30,000 people in the United States, is characterized by liver inflammation and fibrosis (scarring) within the bile ducts of the liver. The disease eventually leads to cirrhosis and often the need for a liver transplant. There are no approved treatments for PSC.

Scientists have linked an individual's microbiome—the specific bacterial colonies within the body—with PSC. In particular, changes in the microbiome that compromise the intestinal lining may expose the bile ducts and liver to harmful bacteria and give rise to inflammation.

In previous research, BiomX investigators found that K. pneumoniae induces a particular inflammatory response in the liver and disrupts the intestinal lining in mice. This finding suggested that targeting K. pneumoniae with phage therapy—with viruses that kill the bacterium—may have therapeutic effects for people with PSC.

In the study presented at The Liver Meeting, scientists collected stool samples from more than 350 people with PSC and healthy control subjects in Germany, France and Israel. The investigators conducted genetic sequencing of these samples and found that the prevalence and abundance of K. pneumoniae is higher in people with PSC compared with controls. Furthermore, abundance of K. pneumoniae was associated with progression of liver fibrosis and longer duration of disease.

The investigators then searched for phages that would target K. pneumoniae and came up with more than 20, which they arranged into 100 different combinations. They assessed these phage cocktails for their ability to eradicate the bacteria in laboratory tests. Based on those experiments, they identified a phage cocktail that in mice was able to reduce the K. pneumoniae burden by more than 1,000-fold while also minimizing the emergence of mutated bacteria resistant to the treatment.

BiomX intends to move this therapy into clinical trials during the first half of 2021.

The Nature paper about alcoholic hepatitis focused on the E. faecalis bacterium, which is found in most people with the disease—specifically, at high levels in the gut—and is associated with worse liver disease severity as well as a higher risk of death.

A team of researchers led by Bernd Schnabl, MD, of the University of California, San Diego, analyzed stool samples from individuals with and without alcoholic hepatitis and found that those with the disease had about a 2,700-fold greater burden of E. faecalis compared with healthy control subjects without alcohol use disorder (AUD).

Further investigation found that a toxin that E. faecalis excretes known as cytolysin killed liver cells and damaged the organ in mice with alcohol-associated liver disease.

“We detected cytolysin-positive E. faecalis in fecal samples from 30% of patients with alcoholic hepatitis and in none of the fecal samples from non-AUD controls,” Schnabl said in a press release. “Importantly, 89% of cytolysin-positive patients with alcoholic hepatitis died within 180 days after admission compared to only about 4% of cytolysin-negative patients.”

The scientists then transplanted feces containing E. faecalis from the intestines of people with alcoholic hepatitis into mice, which gave rise to severe liver disease in the animals. Next, they investigated phages that target the bacterium as a treatment for the liver disease. A cocktail of such phages mitigated liver injury and inflammation in the mice compared with control animals that did not receive the therapy. The treatment also reduced levels of cytolysin in the liver.

“Taken together, our findings link cytolytic E. faecalis with worse clinical outcomes and mortality in humans with alcoholic hepatitis, and that bacteriophages can specifically target cytolytic E.

faecalis in a mouse model of alcohol-induced liver disease," said Schnabl. "A prospective clinical trial is required to validate the human relevance of our findings and to test whether this new therapeutic approach is effective for patients with alcoholic hepatitis."

"This is a hopeful advance against a potentially life-threatening disease for which few effective treatments are available," said NIAAA director George F. Koob, PhD. "Alcoholic hepatitis has a mortality rate of more than 50% within the first 60 days of diagnosis in severe cases and is a particularly important area of focus for NIAAA. The current findings warrant further investigation as a potential novel treatment for people with alcoholic hepatitis."

To read the liver conference abstract, click here.

To read a press release about the PSC study, click here.

To read a press release about the alcoholic liver disease study, click here.

To read the Nature abstract, click here.

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