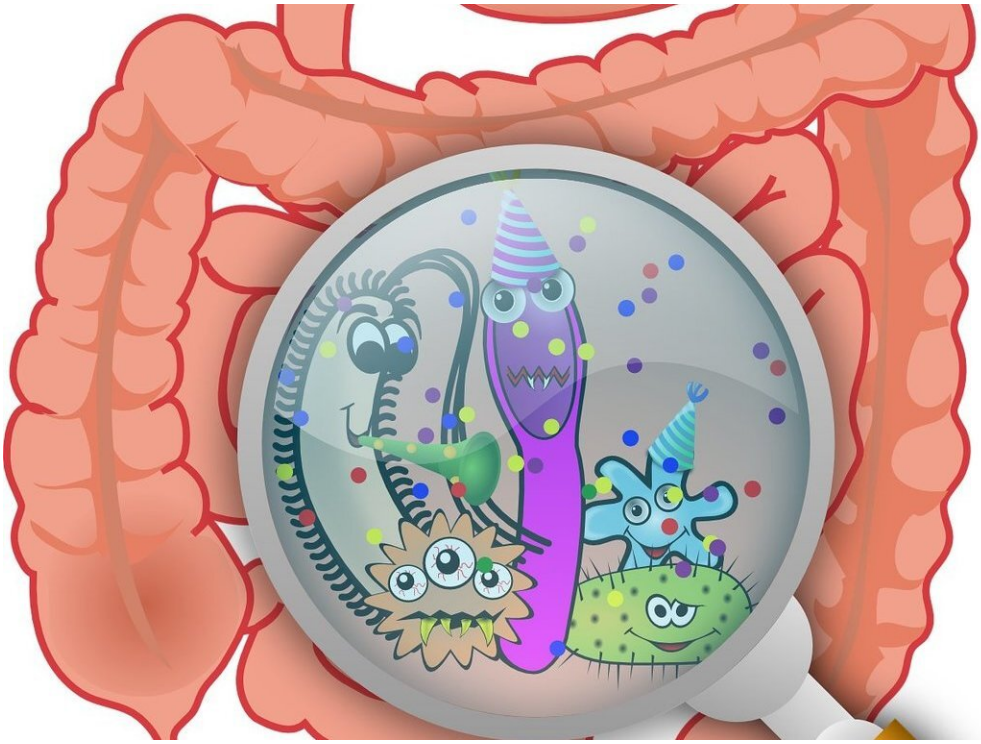
Gut bacteria protect against mosquito-borne viral illness

July 14 2020



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Chikungunya virus, once confined to the Eastern Hemisphere, has infected millions of people in the Americas since 2013, when mosquitoes carrying the virus were discovered in the Caribbean. About half of all people infected with chikungunya virus never show symptoms, while some develop fever and joint pain that lasts about a

week, and 10% to 30% develop debilitating arthritis that persists for months or years.

Scientists have understood little about why the severity of the illness varies so widely. A study from researchers at Washington University School of Medicine in St. Louis indicates, in mice, that gut bacteria may play a role. The research shows that mice with faulty gut microbiomes were less able to control chikungunya virus infection. Further, giving the mice a single species of bacteria—or a chemical compound produced by that species—improved the mice's immune responses, lowered levels of the virus in their blood and reduced the chances that a mosquito that fed on blood from infected mice would acquire the virus.

The findings, published July 14 in the journal *Cell*, suggest that a healthy microbiome could help reduce the chance of severe chikungunya disease and possibly even reduce community spread by disrupting the transmission of virus from person to mosquito to another person.

"In many viral diseases, only a subset of the people who get infected become symptomatic, and we don't really understand why," said senior author Michael S. Diamond, MD, Ph.D., the Herbert S. Gasser Professor of Medicine. "There might be things that happen during your lifetime that shape your immune system and influence whether you can stop the infection early and have minimal symptoms, or fail to stop it and develop severe disease. We found that when mice don't have a healthy gut microbiome, not only do they get sicker, but mosquitoes that sample their blood are more likely to get infected. Promoting a healthy microbiome could be important not just for individuals who might get infected but for the whole community in breaking or reducing the cycle of transmission."

The gut microbiome is the community of bacteria that live in the intestines. Gut bacteria metabolize and chemically modify some of the

material that comes through the digestive tract, generating vitamins and other compounds as byproducts that then are absorbed by cells or other microbes, and help regulate inflammation and the body's response to infection.

To find out if the gut microbiome affects the severity of chikungunya infection, Diamond, first author Emma Winkler, a graduate student in Diamond's lab, and colleagues studied mice without normal gut microbiomes. They used two kinds of mice: germ-free mice, which had been kept under sterile conditions since birth and therefore never developed a gut microbiome, and ordinary laboratory mice treated with a cocktail of two commonly used antibiotics to reduce the complexity of their gut microbiomes.

The researchers infected groups of germ-free and antibiotic-treated mice with chikungunya virus, as well as a group of laboratory mice with normal microbiomes for comparison. The virus multiplied and spread rapidly in the mice that lacked gut microbes, reaching high levels in the blood and in tissues far from the site of infection. Further experiments showed that key immune cells were impaired in the mice without a normal gut microbiome.

Introducing just one bacterial species—a normal member of the human gut microbiome known as Clostridium scindens—rescued the mice's ability to fight the infection. C. scindens is not typically found in mice. But it is common in people, where it modifies a bile acid produced in the liver, generating a compound that affects immune cells. When the researchers gave the modified bile acid alone to mice that lacked normal microbiomes, it improved their immune responses and reduced viral levels in the blood and tissues.

"If having an unhealthy microbiome affects the virus levels in your blood, that raises an interesting question for a blood-borne pathogen:

Does the health of your microbiome impact transmission?" said Diamond, who is also a professor of molecular microbiology, and of pathology and immunology. "It stands to reason that if there is more virus in the blood, a mosquito would be more likely to get infected when it takes a blood meal."

To test this idea, Diamond and Winkler infected three groups of mice with chikungunya virus. One group was treated with antibiotics to eliminate their gut bacteria, a second was treated with antibiotics and later given C. scindens to repopulate such bacteria in their intestines, and the third group didn't receive antibiotics at all, leaving them with normal gut microbiomes. The researchers drew blood one day after infection and offered the blood to mosquitoes to feed on. More than half of the mosquitoes that sampled the blood of the antibiotic-treated mice became infected, compared with less than a third of the mosquitoes that fed on blood from the mice with normal microbiomes or with only C. scindens.

"There are plenty of people walking around with unhealthy microbiomes and varying levels of conjugated bile acids in their guts," said Diamond. "There may be other bacteria that might be even better than C. scindens at modifying bile acids that could be used to rebalance microbiomes. If a probiotic like that were created, it might be one way to not only minimize disease in individuals, but reduce community spread at the same time."

Provided by Washington University School of Medicine