Dengue and Zika viruses make infected hosts more delicious to mosquitoes

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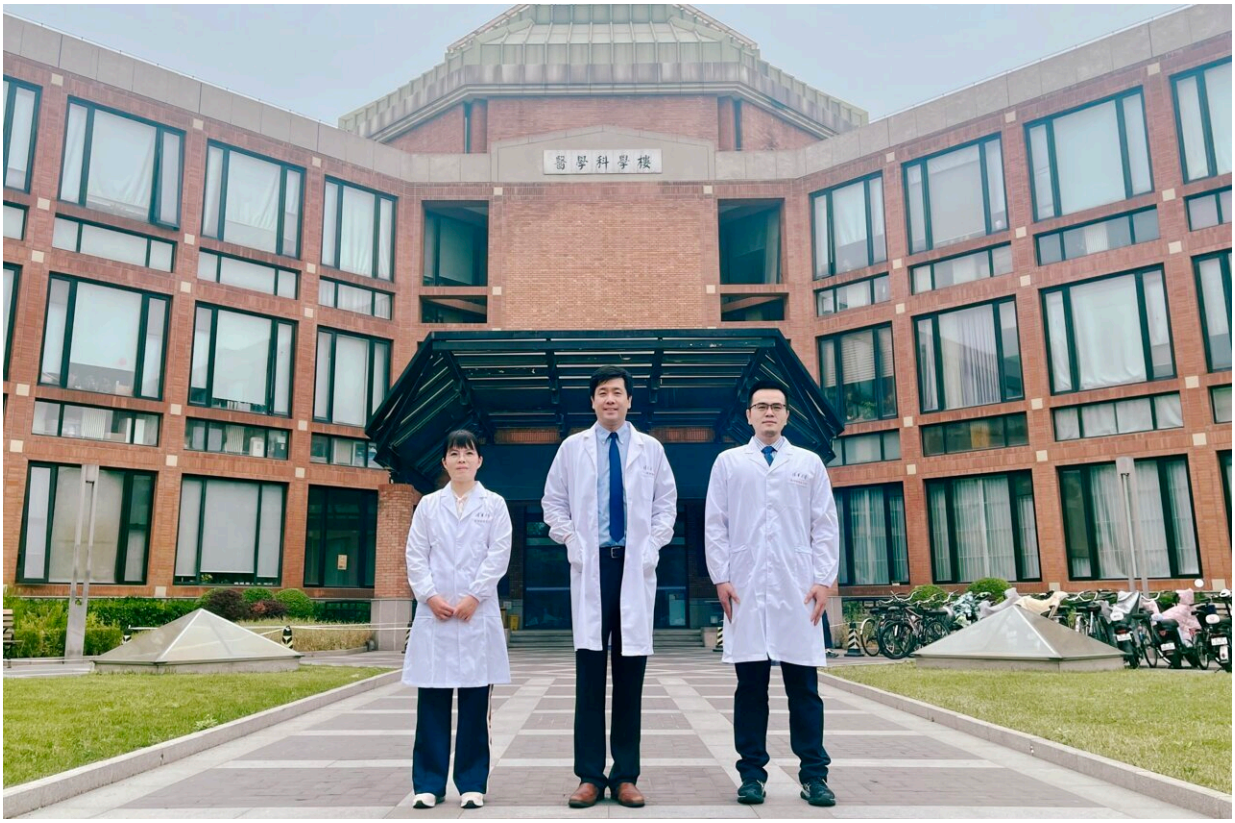

Group photo of investigators in front of the Medical Building, Tsinghua University. Credit: Xi Yu

A study published in the journal *Cell* on June 30 shows that when humans and mice are infected with dengue or Zika viruses, they secrete

a chemical that may make them more attractive to mosquitoes, the vector that transmits the virus. Almost half of the world's population lives in an area at risk of dengue fever, and with a lack of treatments, many dengue-affected regions see high morbidity and mortality rates as a result. Now, with the identity of the chemical attractant in hand, the researchers found a way to reduce its release in mice and make mosquito bites less frequent: treatment with a commercially available acne medication.

Dengue and Zika viruses rely on mosquitoes to survive in nature. When healthy mosquitoes take a bite from an infected host, they can become infected themselves and spread the viruses to other animals they feed on in the future. "Mosquitoes rely on their sense of smell to detect hosts and guide fundamental behaviors of survival," says Gong Cheng, the lead scientist of the project at Tsinghua University. "At the beginning of this study, we found that the mosquitoes preferred to seek and feed on dengue- and Zika-infected mice."

To investigate why mosquitoes preferred infected hosts, the team performed a chemical analysis on odor samples from infected mice and humans. The group identified the culprit that makes them smell more "delicious" as acetophenone, which was present at an abnormally high level in infected individuals. This compound can also be found in many fruits and some cheeses.

"We found that flavivirus [like dengue and Zika] can utilize the increased release of acetophenone to help itself achieve its lifecycles more effectively by making their hosts more attractive to mosquito vectors," says Cheng.

Cheng and colleagues then investigated exactly how dengue and Zika viruses increase the level of acetophenone and described it as "a sophisticated interplay between hosts' skin microbiota, flaviviruses, and

mosquitoes."

When a flavivirus invades a host, the virus enters a tug-of-war with the cells in the host's body for control of the level of a key protein that regulates the composition of the skin microbiome—RELMα. If the cells are winning, RELMα keeps the acetophenone-producing bacteria in check.

"Intriguingly, both dengue and Zika viruses promoted the proliferation of acetophenone-producing skin bacteria by suppressing the RELMα expression," Cheng says. As a result, some bacteria over-replicate and produce more acetophenone. Suddenly, these sick individuals smell as delicious to mosquitoes as a tray of freshly baked cookies to a group of five-year-old children.

With a clearer understanding of how flavivirus affects the skin microbiome, the team set out to find a way to help the cells to win the tug-of-war. After examining existing RELMα literature, the group decided to test whether isotretinoin—a vitamin A derivative commonly used as acne medicine—may suppress the production of acetophenone.

The experiment was simple: feed the mice with isotretinoin and put them in a cage with mosquitoes. The results were encouraging. The authors found that mosquitoes did not feed on isotretinoin-treated infected mice any more than those feeding on uninfected animals. "Dietary administration of isotretinoin, in flavivirus-infected animals, reduced acetophenone volatilization by reshaping resident commensal bacteria on the host skin," Cheng says.

In the future, Cheng and his team are setting out to apply their findings in the real world. "We plan to dietarily administer isotretinoin in dengue patients to reduce acetophenone-mediated mosquito activity," says Cheng.

They are attacking the issue from the mosquito side as well. "We plan to identify specific olfactory receptors for acetophenone in mosquitoes and remove the genes from the mosquito population by a gene drive technology," Cheng explains. Without the receptors, mosquitoes will no longer be able to smell the acetophenone that they love so much, which will possibly mitigate the spread of dengue and other flaviviruses.

More information: Gong Cheng, A volatile from the skin microbiota of flavivirus-infected hosts promotes mosquito attractiveness, *Cell* (2022). DOI: 10.1016/j.cell.2022.05.016. www.cell.com/cell/fulltext/S0092-8674(22)00641-9

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