ScienceWatch – Mosquito-borne Diseases Make You More Attractive—to Mosquitoes

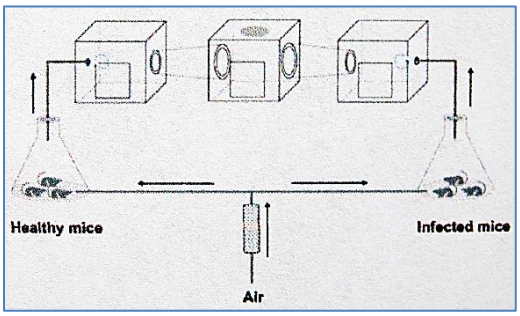
"At the beginning of this study, we found that the mosquitoes preferred to seek and feed on dengue and Zika-infected mice." – G. Chen

Mosquito-borne diseases kill about a million people annually. Malaria alone kills about 600,000, most of them children, while dengue fever results in 40,000 annual deaths. Zika virus cases are rarely fatal but about five percent result in birth defects.

Mosquitoes find us by a multitude of means. Body heat, exhaled CO_2, and the suite of smelly, volatile chemicals made by our skin bacteria can all be attractants and some of us are "loved" by mosquitoes because we emit more of these chemicals (see 2003, *How Attractive Are You?* at https://www.hras.org/past-sciencewatch-articles). In 2018 scientists showed that malaria-infected people emit higher levels of fruity-smelling aldehydes which attract the mosquito that transmits malaria. Thus, the malaria parasite promotes its spread by manipulating our physiology.

That knowledge prompted a team led by Gong Chen, Tsinghua University, Beijing, China, to investigate whether a similar phenomenon occurred with the RNA viruses (flaviviruses) that cause dengue and Zika fever. Their comprehensive study appears in the July 7, 2022 issue of *Cell*.

First the scientists established that the mosquitoes transmitting dengue and Zika, *Aedes aegypti* and *A. albopictus*, respectively, were more attracted to mice infected with the diseases. Using a "three-cage olfactometer" (see figure) they showed that mosquitoes placed in the central chamber preferentially flew to the chamber receiving air from infected mice compared to uninfected mice. The preference could be eliminated by passing the incoming air over a deodorizing device that removed the volatile chemicals given off by the mice.



Next, they characterized the volatile emissions from infected and uninfected mice and found 420 chemical compounds, eleven of which were emitted at higher levels by both Zika and dengue-infected mice.

They then tested each compound to see which could activate mosquito antennae to send an impulse to its brain. Three compounds caused a response, indicating that the mosquitoes could sense them, but only one, acetophenone, a sweet-smelling liquid used in perfumes and as a flavoring agent, attracted more mosquitoes than the control in the three-cage olfactometer assay.

The team next showed that infected mice emitted ten times more acetophenone into the air than uninfected ones, and they could make uninfected mice more attractive to the mosquitoes by

adding acetophenone to their skin. Similarly, dengue-infected patients were also more attractive to the mosquitoes and had higher emissions of acetophenone than healthy ones.

Suspecting skin bacteria were the source of acetophenone, the team disinfected the skin of infected mice and saw their attractiveness to mosquitoes disappear. *Bacillus* bacteria proved to be potent acetophenone producers and were 1.5 times more abundant on the skin of infected mice.

To complete the story Cheng *et al*. elucidated the mechanism by which the flaviviruses generate abnormally high acetophenone levels in infected mice. They showed that a protein (RELMα) made by mouse skin cells that normally limits the growth of skin bacteria was absent in infected mice because the gene making it was shut down. This resulted in higher levels of *Bacillus* bacteria and more acetophenone. "Intriguingly, both dengue and Zika viruses promoted the proliferation of acetophenone-producing bacteria by suppressing the RELMα [gene] expression," says Cheng.

Knowing that isotretinoin, a vitamin A derivative used to treat acne, increases levels of RELMα in human skin, the team fed it to infected mice to suppress the growth of the acetophenone-producing bacteria. As expected, levels of *Bacillus* bacteria were reduced and the attractiveness of infected mice to mosquitoes disappeared.

"We found that flavivirus can utilize the increased release of acetophenone to help itself achieve its life cycles more effectively by making their hosts more attractive to mosquito vectors," says Cheng.

Cheng believes they have found a way to reduce dengue fever transmission. "We plan to dietarily administer isotretinoin in dengue patients to reduce acetophenone-mediated mosquito activity," he says.

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