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Keeping parasites from sticking to mosquito guts could block disease transmission

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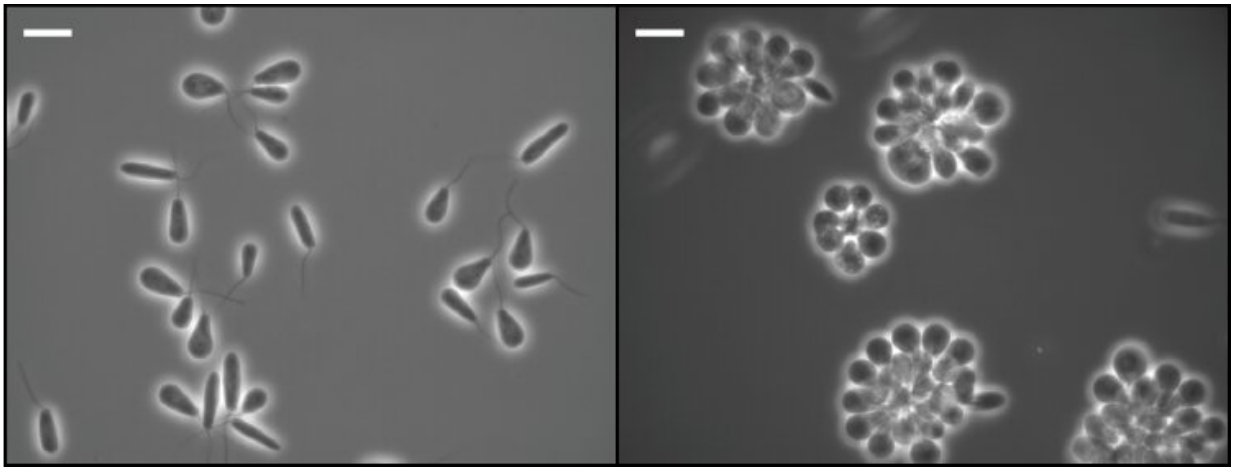

Researchers were able to replicate two forms of Crithidia parasite in the lab. On the left, with flagella, or tails, are "swimming" cells, and on the right are stationary cells growing in rosettes, similar to how the parasites grow in the hindgut of their mosquito insect host. Credit: Michael Povelones

A group of microorganisms known as kinetoplastids includes the parasites that cause devastating diseases such as African sleeping sickness, Chagas disease, and leishmaniasis. They share an ability to adhere to the insides of their insect hosts, using a specialized protein structure. But what if scientists could prevent the parasite from adhering? Would the parasites pass right through the vectors, unable to be passed on to a human?

That's the idea behind a new study led by Michael Povelones of Penn's School of Veterinary Medicine and Megan L. Povelones of Penn State Brandywine. Using a non-disease-causing kinetoplastid species called Crithidia fasciculata, this husband-wife duo and their research team identified a number of genes involved in adherence in its mosquito host.

"The parasite has to hold on so it won't pass right through," says Michael Povelones, an assistant professor of pathobiology at Penn Vet. "It needs to get retained in the gut in order to multiply and eventually get transmitted. These mechanisms of adherence seem to be [shared] across kinetoplastid species, so the hope is that our insights about Crithidia will tell us something about adherence in the medically relevant species."

The study appears in the journal *PLOS Neglected Tropical Diseases*.

Scientists had long turned to Crithidia fasciculata as a biochemical model to understand features of parasitic disease, as it is easily grown in the lab. Megan Povelones, whose specialty is African trypanosomiasis, was familiar with it from her doctoral studies at Johns Hopkins University, and the subject came up in conversations with her spouse.

"We talk shop at home sometimes," says Michael Povelones, whose own research has focused on ways to harness the power of the mosquito's own immune defenses to stop them from transmitting disease. "I was intrigued by the fact that Crithidia infects mosquitoes but isn't a human or animal pathogen, that little was known about its life cycle, and that there had been some electron microscope studies done that show the parasite is actually adhering to the mosquito gut with a very specific type of structure that people had described as a hemidesmosome. I felt like there was some fascinating cell biology there to explore."

Together they set out to investigate what happens to enable the parasite to "hold on" to the inside of the mosquito, a trait believed to be critical

for disease transmission.

In the lab, the researchers were able to replicate what other scientists had found previously: That Crithidia parasites exist in both a swimming form, with a tail-like appendage called a flagellum, and an adhering form, that even sticks to the surface of the plastic dishes in which they were grown in the lab. The swimming form was favored when the culture dishes were placed on a shaker, while the adherent form, which divided to form rosette structures, was more likely to develop when the dishes were kept stationary. Interestingly, they observed that the adherent parasites in the rosettes would occasionally give rise to swimming versions.

To focus on the adherent parasites, the researchers would wait to see rosettes appear and would then wash away the swimming parasite. They could then focus on probing the genetics of the two types.

"One question we had was really simple," says Michael Povelones, "which was, 'What were the transcriptional differences between the swimming cells versus those allowed to grow as rosettes.'"

Remarkably, for two forms of the same species growing in the same medium, the researchers found a significant amount of variation in gene expression between the two.

"The process of adhesion transformed their transcriptome in a really dramatic way," says Michael Povelones.

When the researchers infected laboratory mosquito strains with Crithidia, they found that the parasites adhering to the mosquitoes, primarily in their hindgut region, resembled the adherent form they were culturing in the lab, giving them confidence that studying their lab strains could reveal important information about what was going on in the

parasites' insect hosts.

Among the genes with enhanced expression were a group known as GP63s that have been implicated in adhesion to immune cells in the Leishmania parasite.

The team is hoping to pursue further investigations of adhesion using Crithidia as a tool, looking specifically at genes involved in the process that are known to be shared across kinetoplastid species and that could perhaps one day serve as a target for blocking transmission of vector-borne diseases.

More information: John N. Filosa et al, Dramatic changes in gene expression in different forms of Crithidia fasciculata reveal potential mechanisms for insect-specific adhesion in kinetoplastid parasites, *PLOS Neglected Tropical Diseases* (2019). DOI: 10.1371/journal.pntd.0007570

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