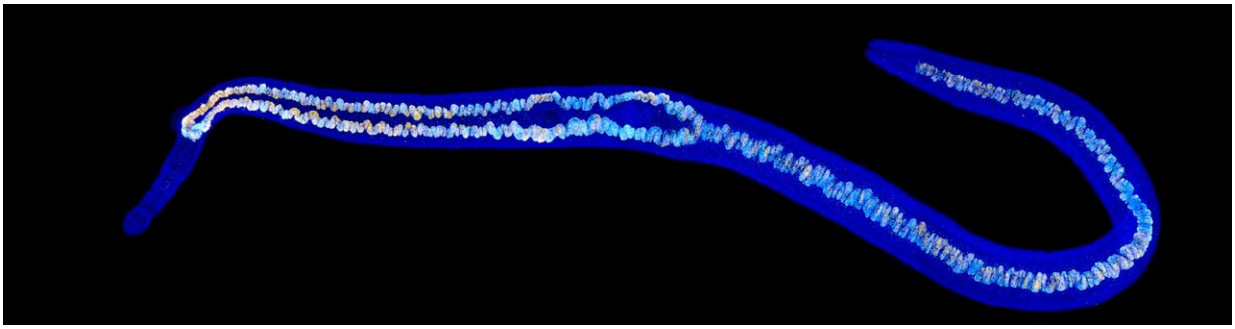
The big gulp: Inside-out protection of parasitic worms against host defenses

July 27 2020



This confocal image shows a juvenile female schistosome, a parasitic flatworm that infects hundreds of millions of people globally, causing the disease schistosomiasis. The species shown here, Schistosoma mansoni, lives inside host blood vessels, where it takes up nutrients that fuel its growth and reproduction. This individual is labeled with a fluorescent probe that allows us to visualize gene expression in the parasite's gut. Credit: Jayhun Lee, Newmark Lab, Morgridge Institute for Research

A team of developmental biologists at the Morgridge Institute for Research has discovered a means by which schistosomes, parasitic worms that infect more than 200 million people in tropical climates, are able to outfox the host's immune system.

Morgridge postdoctoral fellow Jayhun Lee and colleagues reported in today's issue of *Proceedings of the National Academy of Sciences (PNAS)*

that the parasite's esophageal gland, an accessory organ of the digestive tract, mediates an immune-evasion mechanism that is essential for survival in the host.

Schistosomiasis, the neglected tropical disease caused by schistosome infection, remains one of the major parasitic diseases affecting developing countries, according to the World Health Organization. It is especially impactful in children, resulting in anemia, stunting, and learning disorders. Despite its enormous impact on human health and the resulting socioeconomic losses, it remains an understudied and neglected disease.

Schistosomes have a complex life cycle, which begins in freshwater that is contaminated with human excrement. The parasites hatch from eggs released via human waste and infect a specific species of snail. In the snail, the parasite produces massive numbers of larval offspring, called cercariae. Once released from the snail, these fast-swimming, fork-tailed larvae burrow through human skin and cause infection.

After penetrating the host's skin, the parasites migrate into blood vessels and find their way to the vein that supplies the liver. Here, they pair with a mate and grow into mature adults, living for over a decade while releasing hundreds of eggs daily. Many of these eggs get lodged in host organs, such as the liver, resulting in chronic tissue damage.

Currently, only a single drug, praziquantel, is used to fight schistosomiasis, but it only works on adult worms, does not protect from reinfection, and some strains have developed resistance to the drug. Thus, it is critical to devise new strategies for targeting these parasites.

"One big question we're interested in is how these parasites can thrive for decades in the bloodstream, while avoiding the host immune system," says Lee.

Lee works in the lab of Phillip Newmark, a Morgridge investigator, Professor of Integrative Biology at the University of Wisconsin-Madison and investigator of the Howard Hughes Medical Institute (HHMI). The Newmark lab has primarily studied planarians, flatworms with an almost limitless capacity for regeneration. About 10 years ago, the lab began applying their knowledge of planarian biology to understand the planarian's parasitic cousin, the schistosome. By understanding how schistosomes develop inside the host, the lab hopes to find new ways to combat this disease.

In the new study, the team investigated a handful of stem cells that are inherited from the larval stage of the parasite. Stem cells in the parasite are necessary for their survival and reproduction, but their role during the early stages inside the mammalian host has been unclear. They found that the stem cells generate a specialized gland associated with the parasite's digestive tract called the esophageal gland—weeks before the animals start feeding on blood.

Why would the stem cells need to make this gland so early?

Suspecting that the esophageal gland might be important for the survival of the parasites, the team disrupted a gene critical for making the esophageal gland and cultured the parasites in a dish. Despite now lacking an esophageal gland, the viability and behavior of the parasites were not affected when cultured outside the host.

"I think this is normally where you would consider dropping the project," Lee says, since the esophageal gland appeared to have no function in the parasites cultured in vitro.

However, since current culture conditions do not fully reflect the in vivo environment of the host vasculature (such as the lack of host immune cells and blood flow), the team decided to take the project further by

examining the function of the gland when the parasite is living inside the mammalian host.

The next experiments were made possible by a technique pioneered by Donato Cioli in the 1970s in which schistosomes are surgically transplanted into the mesenteric veins of rodent hosts.

"This technically challenging experiment is the only way to introduce experimentally manipulated adult schistosomes back into the mammalian host, as only the larval stage of the parasite is able to penetrate the host skin," says HHMI research specialist Tracy Chong, who performed the surgical transplantations.

Chong transplanted parasites lacking the esophageal gland into mice. In contrast to parasites cultured in a dish, lack of the esophageal gland led to lethality in the mammalian host.

"Based on clues from previous studies, we hypothesized that the esophageal gland of the parasite was acting as a barrier to prevent host immune cells from infiltrating the parasite," says Lee.

To test this idea, the team surgically transplanted parasites lacking the esophageal gland into immunocompromised mice. The gland-lacking parasites were able to survive in immunocompromised mice, just like they did in culture dishes. Follow-up experiments in which the parasites were fed fluorescent immune cells showed that gland-lacking parasites were unable to destroy immune cells before they entered the parasite's gut.

"Our results show that the esophageal gland is an important barrier that needs to be in place before these parasites start feeding and ingesting immune cells," Lee adds. "We are hopeful this research will lead to new targets to fight these parasites."

Lee says the next chapter in this ongoing work will be to define the hundreds of different proteins that make up the esophageal gland.

"When we characterize these proteins, we might be able to find a way to block or disable their function, which would then allow immune cells to get inside the parasites and kill them," he says.

More information: The esophageal gland mediates host immune evasion by the human parasite Schistosoma mansoni, *Proceedings of the National Academy of Sciences* (2020). www.pnas.org/cgi/doi/10.1073/pnas.2006553117

Provided by Morgridge Institute for Research

Citation: The big gulp: Inside-out protection of parasitic worms against host defenses (2020, July 27) retrieved 3 May 2024 from https://phys.org/news/2020-07-big-gulp-inside-out-parasitic-worms.html

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