Researchers advance understanding of schistosome reproduction

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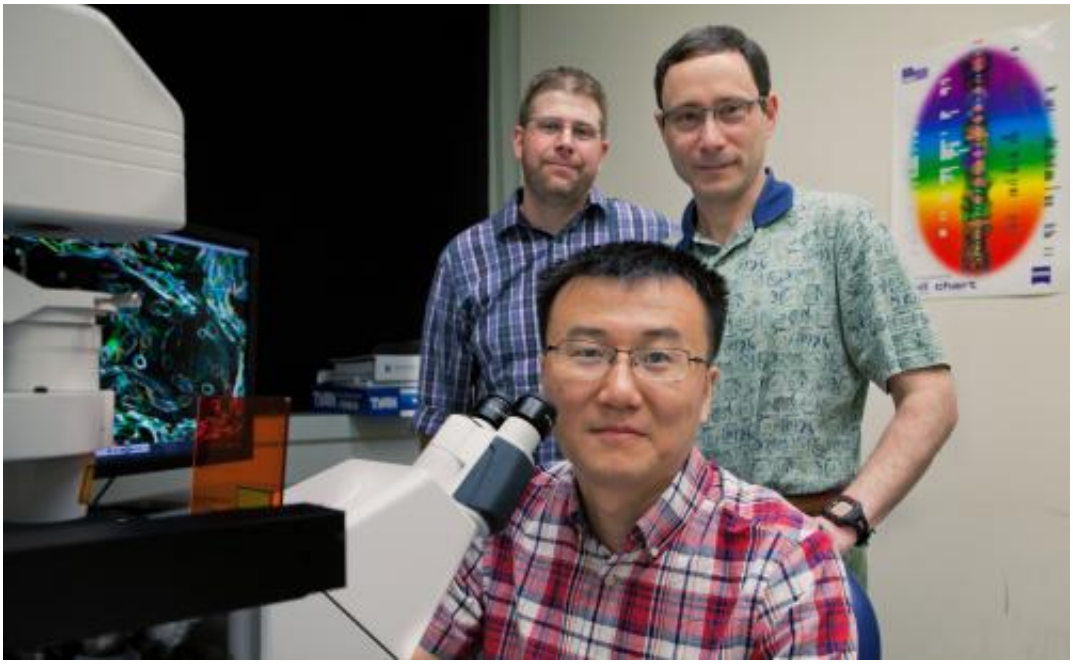

Institute for Genomic Biology Fellow Bo Wang (front), with Professor of Cell and Developmental Biology Phil Newmark (right) and postdoctoral researcher in Cell and Developmental Biology James Collins (left) from the University of Illinois at Urbana-Champaign are studying the unique mechanisms that allow schistosomes' germinal cells to create thousands of clonal larvae that can then infect humans. Credit: Kathryn Coulter, provided by Institute for Genomic Biology

Ancient Egyptian mummies revealed that humans have been hosting parasitic flatworms called schistosomes for more than 5,000 years.

Today the parasites continue to plague millions of people across the world, causing roughly 250,000 deaths each year.

The schistosome reproductive cycle results in exponentially more schistosomes each generation. Not only do the adults lay hundreds to thousands of eggs each day but the larval schistosomes are able to clone themselves thousands of times, with each clone capable of developing into an egg-producing adult.

Researchers at the University of Illinois quickly realized that one key to controlling schistosomes is being able to control their incredibly prolific life cycle. In a recent study published in the journal eLife, Illinois researchers have come one step closer to understanding the unique mechanisms that allow schistosomes' germinal cells, stem cells that multiply into other types of cells, to create thousands of clonal larvae that can then infect humans.

The Disease

This work adds to our understanding of the basic biology of schistosomiasis, a chronic disease caused by schistosome parasites, that robbed at least 243 million people of their productivity in 2011.

"People don't feel well, and so they are not productive in their work," said James Collins III, a postdoctoral researcher in the Department of Cell and Developmental Biology (CDB) at Illinois. "This disease keeps them from being able to realize their full potential, and in turn, they remain poor and are exposed to more diseases like schistosomiasis, which are ultimately diseases of sanitation. It's a disease of poverty that also perpetuates poverty."

Schistosomiasis can result in abdominal pain, diarrhea, and blood in urine or feces. The parasite's eggs, and not the parasite itself, cause these

symptoms and others. The bloodstream carries many of the eggs to the liver and other areas of the body where they can trigger a massive immune response.

"When you look at people who have a high level of infection, you see many holes in their liver," said Phillip Newmark, a Professor of Cell and Developmental Biology at Illinois, an Investigator of the Howard Hughes Medical Institute, and an affiliate of the Regenerative Biology and Tissue Engineering research theme at the Institute for Genomic Biology (IGB). "Where there was an egg, a hole is formed where the tissue has been destroyed by the host immune system's inflammatory response."

The Life Cycle

Every day for decades, adult schistosomes can lay hundreds to thousands of eggs. Their life cycle starts over when the eggs are excreted from the human host through urine or feces. When the eggs contact water, they hatch out "miracidia" that seek out the snail intermediate hosts.

Inside the correct species of snail, the miracidia become sporocysts, essentially sacs filled with germinal cells, that undergo clonal expansion, making tens to hundreds of thousands of copies of themselves in the form of "cercariae." The fast-swimming cercariae are shed from the snail, and search for human hosts who find themselves in cercariae-infested fresh water.

"They are attracted by the fatty acids in your skin," said Collins. "In the lab, you can leave your thumbprint on a plastic petri dish, and all the cercariae will swarm to your thumbprint and try to penetrate the plastic."

Once they find a host, they are able to burrow through the skin and enter the bloodstream. Inside the body, they migrate to specific sites in the human host, mature into male or female worms, and find mates with

whom they will live, paired together "in copula." If left undetected, they will continue mass producing eggs for decades.

The Research

Illinois researchers are approaching this important problem from a unique perspective, using developmental biology (the study of how organisms grow and develop) and applying the lessons they have learned from studying planarians, non-parasitic relatives of schistosomes.

"When researchers are just focused on targeting diseases and developing drugs, they may wind up limiting their opportunities by not really understanding the biology of the system," Newmark said. "I think fundamental, curiosity-driven research is still vital for developing long-lasting solutions. If anything comes of this, it will be because we were asking very fundamental questions about these parasites, based upon our knowledge of their free-living cousins, the planarians."

The team's research was motivated by the idea that stem cells seem to be key to schistosomes' ability to live within humans, but also to their ability to live and clone themselves within their snail hosts.

They discovered that germinal cells possess a molecular signature—a collection of expressed genes—that is similar to that of neoblasts (adult stem cells) that allow planarians to regrow missing body parts. Among these genes, they identified some that are required for maintaining the germinal cell population.

This evidence suggests that schistosome larvae may have evolved by adapting a developmental program used by non-parasitic flatworms in order to rapidly increase their population—essentially giving them the opportunity to reproduce twice within their life cycle, once asexually inside snail hosts and once sexually inside human hosts.

Illinois researchers believe they can apply this newfound developmental knowledge to future studies that may lead to ways to control, or even eradicate, schistosomes. They have already discovered that they can make the reproductive system of a planarian disappear by removing the function of a neuropeptide; eventually, they hope to do the same in schistosomes.

Still, there's much to still be learned, says Collins. "We have really only scratched the surface of understanding the basic biology of these organisms. In order to be able to treat this disease, we need to know more about the organisms that cause it. That's one of our main motivations for this work."

First author Bo Wang, a postdoctoral fellow at the IGB, said the obvious next step will be to further characterize these schistosome cells on a genomic level. "We really need to improve our understanding of schistosome stem cells," Wang said. "We still don't understand all the mechanisms that really make them unique, that really make them have this tremendous capacity to proliferate, or reproduce."

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