Researchers reveal secrets of parasite that causes African sleeping sickness

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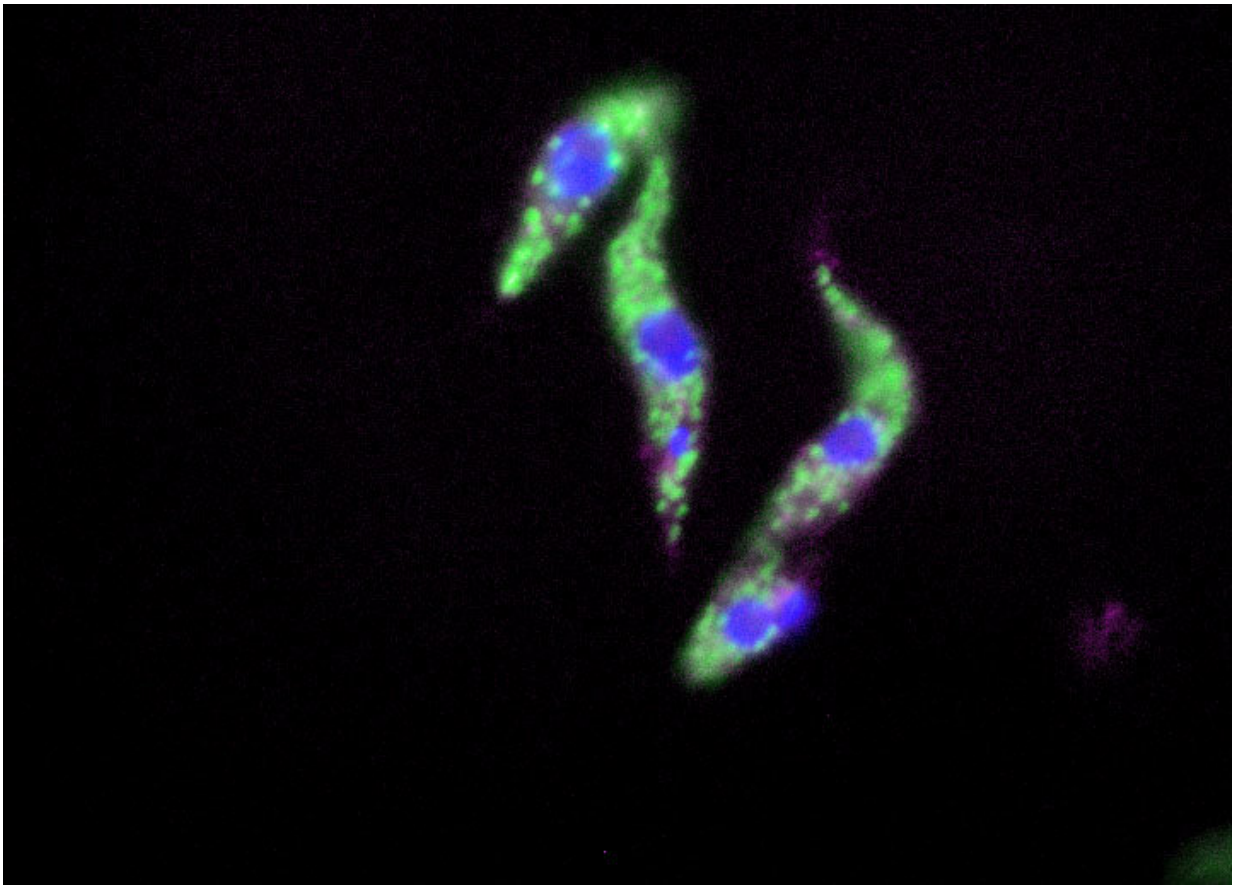

The parasite that causes African sleeping sickness can cause death in humans if not treated. Credit: College of Science

A team of Clemson University researchers wants to protect humans and

other mammals from the debilitating and even deadly effects of African sleeping sickness.

James Morris, a Clemson professor in the College of Science's department of genetics and biochemistry, said that studying the cause of the disease is vital because, although the transmission of African sleeping sickness by tsetse flies has been studied for more than 100 years, the secret to the underlying parasite's success remains largely a mystery.

"There are a number of questions about how the parasite grows and develops in the fly and then gets transmitted to humans and other mammals," said Morris, who is on the faculty of Clemson's Eukaryotic Pathogens Innovation Center.

A paper titled "Glucose Signaling is Important for Nutrient Adaptation During Differentiation of Pleomorphic African Trypanosomes" was recently published on the American Society of Microbiology's *mSphere* site. It focuses on the biological cues that "tell" the parasite—the African trypanosome (Trypanosoma brucei) - to change life cycle stages as it moves from host to host.

"One of the key things that happens is that, as the parasite is floating around in (mammalian) blood, it perceives its neighbors and says 'oh, there are a lot of us,' and becomes a different form that is ready to go into a fly, if the fly were to happen to bite that person," Morris said. "That form that's ready for life in the fly doesn't grow—it's not a growing form—it's really sitting there, waiting to be taken up by a fly. Once it passes into the fly, though, it begins to grow again. It becomes a form that can live in the fly, and that's the insect-stage form, or procyclic form."

The team worked to unravel the mechanism by which the parasite knows

when to grow and when not to grow.

"What has been a mystery, and still is a mystery, is how the parasite really knows where it is," Morris said. "It turns out that if you take the form that lives in the fly and inject it into a mammal, it is killed instantly by the mammal's immune system. So, the parasite really has to do an excellent job of recognizing its environment."

As the study's name suggests, the team focused on sugar, or glucose, as a possible cue for the parasite's changing ways.

"We've always suspected the sugar was the cause, but it's been hard to prove," Morris said, so the team looked at the possibility that the parasite was somehow monitoring the glucose in its environment.

"We felt, wouldn't it be interesting if the parasite is monitoring that sugar to know when it has moved into a fly, because when there's lots of sugar, the parasite thinks 'I'm in a mammal,' and when there's no sugar, the parasite thinks 'oh, I'm in a fly'," Morris said. "We found that if you take the parasites and remove glucose nearly completely, they're still alive, which was: A, very surprising because they're so reliant on the sugar; but B, they also then quickly changed into the form that can live in the fly."

That discovery opens the possibility for treatment that can defuse an outbreak of the potentially deadly African sleeping sickness in humans.

"That's the first step in understanding that pathway and trying to confuse the parasite with drugs later," Morris said, "so that when they're in your blood, perhaps you could give them a drug and make them think 'oh, there's no glucose around, I should become the insect stage,' and they would be killed."

Yijian Qiu, who was a doctoral student in Morris' lab before recently becoming a post-doctoral associate at the University of Buffalo, was the lead author of the paper. Qiu's research focus is in organism-environment interaction and interaction between different organisms.

"This is why I found my Ph.D. project on how T. brucei communicates with its environment so fascinating," Qiu said. "I think the most exciting part of the results is that we found that glucose, the most common energy source for the majority of organisms, could actually become a signal for cell development or an inhibitor for proliferation in different stages of a lethal parasite. We discovered this during the process of addressing a long-standing debate in the parasite field: whether environmental glucose plays a role in the differentiation of T. brucei during its traveling from mammalian host to insect vector."

Although there have been no recent outbreaks of African sleeping sickness among humans, Morris said it's important that scientists continue to unlock the disease's secrets.

"Currently, I'd say there are certainly less than 10,000 cases of the sickness on the planet each year, but certainly in our lifetime there have been epidemic levels of the stuff, and so it comes and goes," he said.

In humans and animals, African sleeping sickness entails bouts of fever, headaches, joint pains and itching. The parasite can eventually enter the brain, causing changes of behavior, confusion and poor coordination. It also can disturb the sleep cycle, hence its name. Without treatment, sleeping sickness is usually fatal.

But while the disease numbers aren't currently at epidemic levels in humans, the same is not true for other mammals.

"The problem really is that in animals it's unchecked, and it has a really

catastrophic effect on agriculture and those pursuits in sub-Saharan Africa," Morris said.

Morris has worked on the mysteries surrounding African sleeping sickness for 26 years, and he said that many questions still remain unanswered.

"We want to exploit this new understanding," Morris said. "The question then becomes, how does the parasite measure glucose, how does it know it's going away? There are a couple of possibilities—more than a couple, probably—but we think one thing that's happening is that the parasite has a receptor for the sugar somewhere on its surface where it can assess what's out there, sort of sample it and say okay, there's sugar out there or there's not. And all those pieces are missing right now.

"I think we have the genetic tools to understand how all that's connected," he added, "so I think that's the next big step."

In addition to Morris and Qiu, the authors were Jillian Milanes, Jessica Jones, Rooksana Noorai and Vijay Shankar, all of whom were affiliated with Clemson during the research and writing of the paper. Morris credited Noorai's and Shankar's work at Clemson's Genomics and Computational Biology Lab, without which "we wouldn't have the depth of insight that we do."

More information: Yijian Qiu et al, Glucose Signaling Is Important for Nutrient Adaptation during Differentiation of Pleomorphic African Trypanosomes, *mSphere* (2018). DOI: 10.1128/mSphere.00366-18

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