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Study suggests new way to help the immune system fight off sleeping sickness parasite

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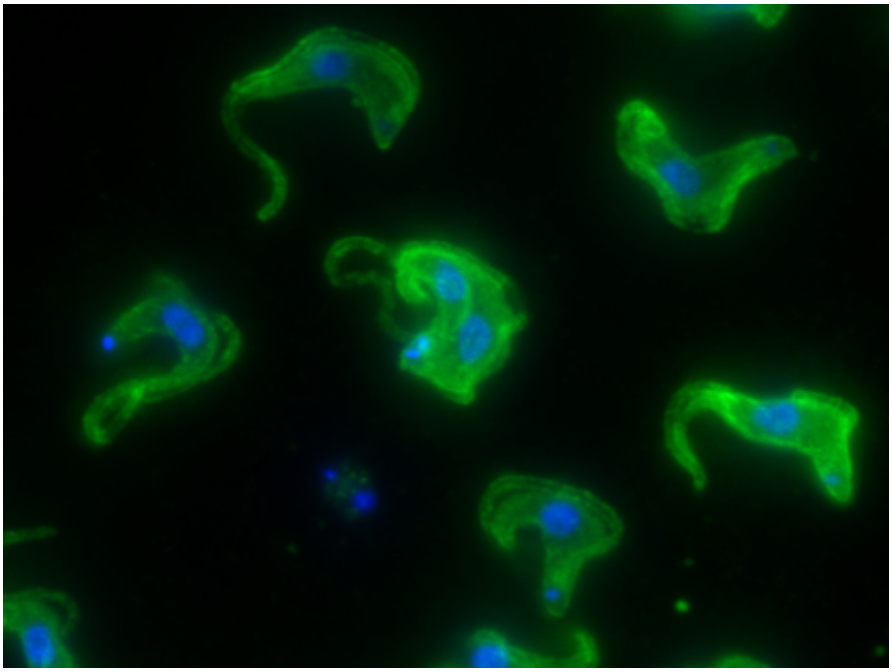

Trypanosomes are able to flourish in the bloodstream by continually changing their protein coat. The inhibition of bromodomains causes the protein coat to stick, shown in green, giving the host immune system enough time to recognize and eliminate the parasite. Credit: Laboratory of Lymphocyte Biology at The Rockefeller University

Some infectious diseases are particularly difficult to treat because of their ability to evade the immune system. One such illness, African sleeping sickness, is caused by the parasite *Trypanosoma brucei*, transmitted by the tsetse fly, and is fatal if left untreated. The

trypanosome parasite is transmitted to mammals through fly bites and eventually invades major organs such as the brain, disrupting the sleep cycle, among other symptoms.

Trypanosomes exist in different forms. When inhabiting a fly, they are covered with proteins called procyclins. But upon entering the bloodstream of a mammal, they acquire a dense layer of glycoproteins that continually change, allowing the parasite to dodge an attack from the host's immune system.

Now, new research from postdoctoral scientists Danae Schulz and Erik Debler, working in Nina Papavasiliou's and Günter Blobel's labs at Rockefeller University, reveals a method to manipulate trypanosomes in the mammalian bloodstream to acquire fly stage characteristics, a state that makes it easier for the host immune system to eliminate the invader. The findings suggest that inhibiting specific proteins that interact with chromatin—the mass of DNA and proteins that packages a cell's genetic information—can "trick" the parasite into differentiating to a different stage of its lifecycle. The study was published on December 8 in *PLOS Biology*.

"By blocking these chromatin-interacting proteins, we have found a way to make the parasite visible to the immune system," says Nina Papavasiliou, head of the Laboratory of Lymphocyte Biology. "The bloodstream form of the parasite is constantly switching protein coats, so the immune system can't recognize and eliminate it. This new method makes the parasite think it's in the fly, where it doesn't need to worry about the immune system attacking it."

Epigenetic regulation

Regulatory proteins interact with chromatin to either unwind it or package it more tightly, affecting which genes are expressed. Some of

these regulatory proteins contain a region called the bromodomain, which recognizes a specific signal on chromatin and induces changes in gene expression.

Recent findings in mice have indicated that bromodomains are involved in cell differentiation, which led Papavasiliou and colleagues to hypothesize that such epigenetic mechanisms may drive the trypanosome to change from one form to another.

"The changes in gene expression that accompany the transition between the different parasite forms had been well established," said Schulz, the lead author of the study. "But we didn't understand if there was some type of regulation happening at DNA, at the level of chromatin. Whether chromatin-altering mechanisms might be important for differentiation hadn't really been studied before."

To investigate this, the researchers inhibited bromodomain proteins in cells by introducing genetic mutations in their DNA or by exposing the cells to a small-molecule drug called I-BET151, which is known to block bromodomains in mammals. When these perturbations were made, the investigators observed changes in gene expression levels that resembled those seen in cells differentiating from the bloodstream form to the fly form. They also saw that the parasites developed a procyclin coat normally found on the fly form.

Based on these findings, Papavasiliou and colleagues suggest that proteins with bromodomains maintain the bloodstream form of trypanosomes, and inhibiting them causes the parasite to progress in its development toward the fly form. They believe bromodomains could serve as a potential therapeutic target to treat African sleeping sickness.

Harnessing the natural immune system

To explore whether I-BET151 could be used to combat the disease, the researchers used drug-treated trypanosomes to infect mice. The mice infected with drug-treated trypanosomes survived significantly longer than those infected with untreated trypanosomes, indicating that the virulence of the parasite—its ability to invade the host—was diminished in the presence of I-BET151.

"When bromodomains are inhibited, the variant protein coat is replaced with an unvarying coat on the surface of the trypanosome cell," says Schulz. "This means that the parasite surface is no longer a moving target, giving the immune system enough time to eliminate it."

I-BET151 is not effective enough to be used in the clinic, but a crystal structure determined by Debler and published as part of this study provides direct clues for how an optimized drug could be designed to bind parasite bromodomains in a highly specific manner, limiting side effects.

"Current treatments for this disease are limited and they have substantial side effects, including very high mortality rates," says Papavasiliou. "This study, and recent work by others, demonstrates that targeting chromatin-interacting proteins offers a promising new avenue to develop therapeutics."

This could apply not only to African sleeping sickness, she adds, but to a number of related parasitic diseases like Chagas or malaria, with disease burdens that are far more substantial than those caused by *Trypanosoma brucei*.

More information: Schulz D, Mugnier MR, Paulsen E-M, Kim H-S, Chung C-wW, Tough DF, et al. (2015) Bromodomain Proteins Contribute to Maintenance of Bloodstream Form Stage Identity in the African Trypanosome. *PLoS Biol* 13(12): e1002316.

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