New research shows how disease-causing parasite gets around human innate immunity

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Trypanosomes are parasites responsible for many human and animal diseases, primarily in tropical climates. One disease these parasites cause, African sleeping sickness, results from the bite of infected tsetse flies, putting over 60 million Africans at risk in 36 sub-Saharan countries. The recent 1998-2001 sleeping sickness epidemics in South Sudan, Angola, Democratic Republic of Congo and Uganda killed tens of thousands of people and resulted in over a half million infected individuals.

A team of researchers at the University of Georgia and Glasgow University has now shown, for the first time, just how one species of these parasites evades the human innate defenses. The finding could open the way for new classes of drugs and more in-depth studies about how parasites manage to kill so many and cost governments billions of dollars to fight.

"We believe this research represents a paradigm shift and causes us to think more broadly about how pathogens avoid host defense mechanisms," said Stephen Hajduk, professor and head of the department of biochemistry and molecular biology at UGA and one of the leaders of the research. "It turns out that African trypanosomes have evolved a diversity of ways to avoid human innate and acquired immune systems."

The research, published today in the Proceedings of the National Academy of Sciences, was a joint effort between UGA and a group led

by Annette Macleod at the University of Glasgow in Scotland. Other authors of the paper include Rudo Kieft, a research professional in Hajduk's lab at UGA; Paul Capewell and Nicola Veitch in the Macleod lab in Wellcome Center for Molecular Parasitology in Glasgow; and Michael Turner of the Biomedical Research Center at the University of Glasgow. The department of biochemistry and molecular biology at UGA is part of the Franklin College of Arts and Sciences. Hajduk also is a member of the Center for Tropical and Emerging Global Diseases at UGA.

The need for a clearer understanding of how these parasites evade human immune systems is at the heart of a serious public health problem, Hajduk said. During the recent epidemics of African sleeping sickness, as many as half the occupants in some African villages were infected with trypanosomes. The geographical isolation of these villages and ongoing civil wars contributed to what many believe were the worst epidemics of sleeping sickness in five decades.

This led to the realization that many of the existing therapies now available to fight African sleeping sickness are often ineffective and have extreme toxicity, frequently causing death. Additionally, there is increasing evidence that while new therapeutics may cure the disease, long-lasting neurological damage can be caused by infection.

The World Health Organization reports that the recent introduction of aggressive population screening in rural areas and distribution of more effective drugs has dramatically reduced the number of deaths, however.

Several species of African trypanosomes infect non-primate mammals and cause important veterinary disease yet are unable to infect humans. The trypanosomes that cause human disease, Trypanosoma brucei gambiense and T. b. rhodensiense, have evolved mechanisms to avoid the native human defense molecules in the circulatory system that kill

the parasites that cause animal disease.

Two of the major challenges faced by scientists studying human sleeping sickness have been the identification of the naturally occurring human defense molecules that are active against the trypanosomes causing animal disease, and the identification of the strategies used by the human sleeping sickness parasites to avoid the action of these molecules.

Human innate immunity against most African trypanosomes is mediated by a subclass of HDL (high density lipoprotein, which people know from blood tests as "good cholesterol") called trypanosome lytic factor-1, or TLF-1. This minor subclass of human HDL further contains two proteins, apolipoprotein L-1 and haptoglobin-related protein, which are only found in primates. These proteins work together, in the lipid environment of the HDL particle, as a specific and highly active toxin against the trypanosomes that infect non-primate mammals. Despite its activity against some African trypanosomes, the toxin is completely nontoxic to the human sleeping sickness parasites.

The parasite that causes fast-onset, acute sleeping sickness in humans, T. b. rhodensiense, is able to cause disease because it has evolved an inhibitor of TLF-1 called Serum Resistance Associated (SRA) protein. Another species, T. b. gambiense, causes slow onset, chronic sleeping sickness and is responsible for over 95 percent of the human deaths caused by these parasites. Until the just-published research by Hajduk, Macleod and their colleagues, nothing was known about TLF-1 resistance in T. b. gambiense. Hajduk and Macleod report, for the first time, that T. b. gambiense resistance to TLF-1 is caused by a marked reduction of TLF-1 uptake by the parasite.

So how is this happening?

To survive in the bloodstream of humans, these parasites have apparently

evolved mutations in the gene encoding a surface protein receptor. These mutations result in a receptor with decreased TLF-1 binding, leading to reduced uptake and thus allow the parasites to avoid the toxicity of TLF-1.

"Humans have evolved TLF-1 as a highly specific toxin against African trypanosomes by tricking the parasite into taking up this HDL because it resembles a nutrient the parasite needs for survival," said Hajduk, "but T. b. gambiense has evolved a counter measure to these human 'Trojan horses' simply by barring the door and not allowing TLF-1 to enter the cell, effectively blocking human innate immunity and leading to infection and ultimately disease."

The parasite may pay a price for blocking the uptake of a nutrient, but still the strategy works and the parasite can infect humans. Now that researchers know how the parasite survives, this may provide an intervention target that could keep the parasites from evading the human defense system. The result could be a newly strengthened innate defense system that halts the parasites in their paths.

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