Cancer drugs may help stop major parasite

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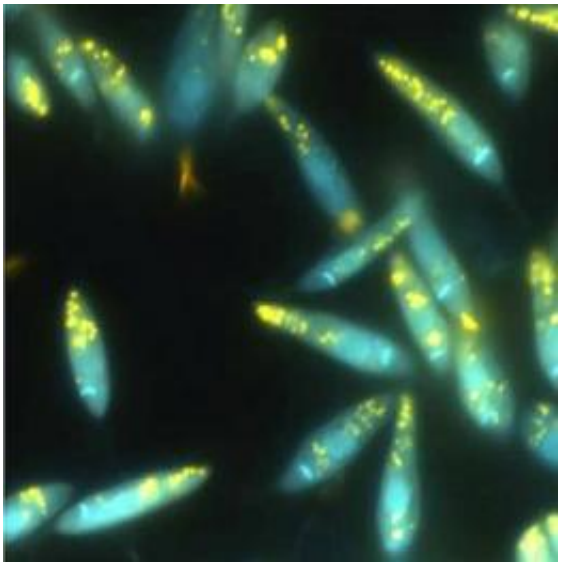

Scientists at Washington University School of Medicine in St. Louis recently showed that when a key protein was genetically disabled, the parasite *Leishmania* couldn't start infections in cell cultures and animals. Parasites in this picture have been stained so that compounds known as polyphosphates appear yellow. The structures where the parasite normally stores these compounds are misshapen and empty in mutant parasites that lack the TOR kinase 3 protein. Credit: Washington University School of Medicine in St. Louis

A parasite estimated to afflict as many as 12 million people worldwide relies on a family of genes that should make it vulnerable to compounds developed to treat cancer and other disorders, researchers at Washington University School of Medicine in St. Louis have found.

Scientists searched the genome of the parasite *Leishmania* to determine that it has three kinds of TOR kinases, proteins that are linked to cell growth and cancer and have been longstanding targets for drug development. When they removed the proteins individually, they found that all three were critical either to the parasite's ability to survive or its ability to cause infections.

"If we can hit any of these proteins with a drug that will inhibit them, we should be able to strike a significant blow against *Leishmania*," says senior author Stephen Beverley, PhD, the Marvin A. Brennecke Professor and head of Molecular Microbiology. "Given the numerous inhibitors already available, I think there's a pretty good chance that we'll be able to identify a compound that specifically inhibits one of *Leishmania*'s TOR kinases."

The finding appears online in The Proceedings of the National Academy of Sciences.

Infection with the *Leishmania* parasite, or leishmaniasis, is mainly spread by sand fly bites and is a major public health problem in Asia, Africa, the Middle East and other parts of the developing world. Symptoms include large skin lesions, fever, swelling of the spleen and liver, and, in more serious forms of the disease, disfigurement. The most severe form of leishmaniasis, a condition sometimes called black fever, is fatal if left untreated and is estimated to kill more humans than any other parasite except Plasmodium falciparum, the malaria parasite.

Mammals have only one TOR kinase protein, and drug developers have targeted it to block immune system rejection of transplanted organs, to treat certain forms of cancer and, more recently, to prevent some age-related illnesses.

When Beverley's lab separately deleted each of the first two TOR

kinases from *Leishmania*'s genome, the parasite could not survive. Deleting the third TOR kinase led to a parasite that survived the initial stage of its lifecycle, which normally occurs in sand flies. But the modified parasite died when it tried to infect animals or cell cultures.

Closer study of how loss of TOR kinase 3 affected *Leishmania* revealed that structures inside the parasite known as acidocalcisomes were defective. They were unusual in size and shape and did not carry their usual cargo, high-energy molecules known as polyphosphates.

The study provides the first proof that acidocalcisomes are essential for infection. The properties of the parasite with mutated TOR kinase 3 confirmed prior research that suggested the acidocalcisome may help cells regulate the flow of fluids across the cell membrane or cope with stress and loss of access to the sugar glucose.

"Entry into the host is one of the most stressful times in a parasite's lifecycle," says first author Luciana Madeira da Silva, PhD, a former postdoctoral researcher. "Having fewer ways to cope with stress at that point could be a real problem for *Leishmania*."

Beverley has begun working with another group that repurposes human TOR kinase inhibitors, adapting them for other uses. They plan to see if existing drugs might disable or kill the *Leishmania* parasite by inhibiting one of its three TOR kinases.

More information: da Silva LM, Beverley SM. Expansion of the target of rapamycin (TOR) kinase family and function in Leishmania shows that TOR3 is required for acidocalcisome biogenesis and animal infectivity. Proceedings of the National Academy of Sciences, online.