Leishmania virulence strategy unveiled

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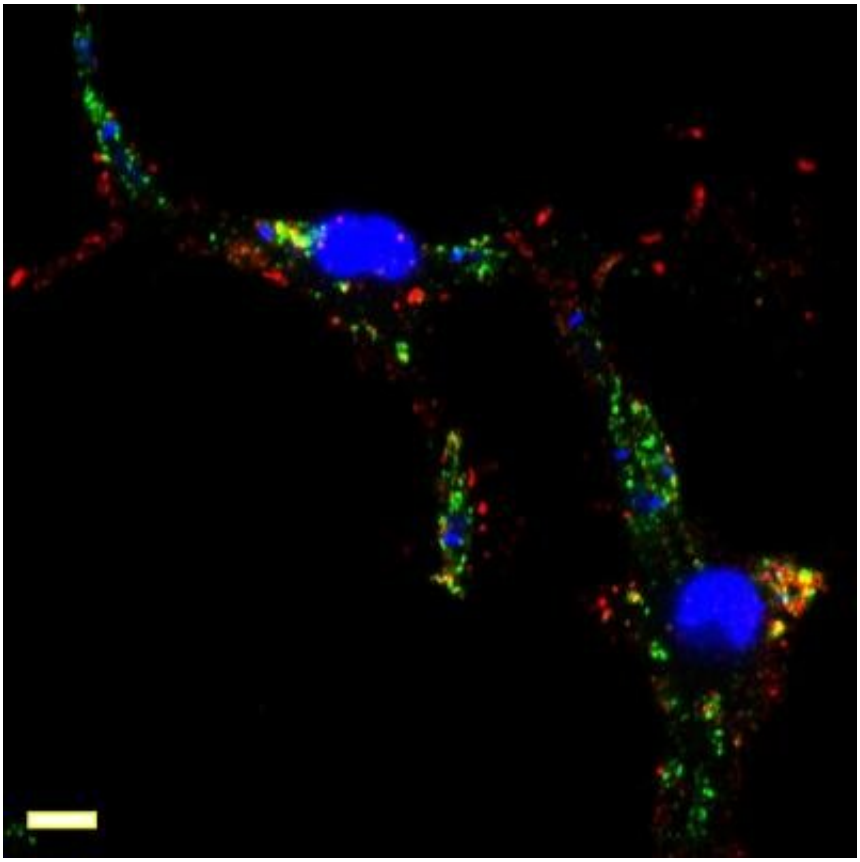

Intracellular redistribution of Leishmania virulence factors (GP63 and LPG) in host macrophages. GP63 is shown in green, lipophosphoglycan (LPG) in red and DNA in blue. Credit: Guillermo Arango Duque, Institut National de la Recherche Scientifique (INRS)

A team from the Institut National de la Recherche Scientifique (INRS) has made a scientific breakthrough regarding the virulence strategy

employed by the Leishmania parasite to infect cells of the immune system. This microorganism is responsible for Leishmaniasis, a chronic parasitic disease that affects more than 12 million people worldwide.

The Leishmania parasite was already known to conquer its host—human or animal—by sabotaging the macrophage defence system, macrophages being a type of white blood cell active in the body's frontline immune response. The mechanics of Leishmania virulence strategies, however, remained unclear.

INRS professor Albert Descoteaux and his team, in collaboration with researchers from McGill University, Université de Montréal, and Tohoku University, have discovered that Leishmania exploits an intracellular transport mechanism already present in macrophages to spread its virulence factors. The results of the team's research were published in the journal *PLOS Pathogens*.

"It's like there's a train travelling among the different intracellular compartments that the parasite boards to deliver its virulence factors inside the infected cell," says Professor Descoteaux, the study's lead author. "Our study sheds new light on the pathogenesis of infection."

Explanations

Leishmania is transmitted to the mammalian host through a bite from an infected phlebotomine sand fly. The parasite has two key molecules on its surface that allow it to infect the host cell's interior: The GP63 metalloprotease and lipophosphoglycan (LPG). These are known as virulence factors.

Upon infecting the macrophage, Leishmania enters a parasitophorous vacuole that it hijacks with the help of virulence factors. This vacuole acts as a sort of "protective bubble" against the host cell's immune

defences. Leishmania creates a compartment in the host cell where it can replicate.

Researchers wanted to understand how the parasite's molecules reach their targets inside the infected cells and what mechanisms they employed.

"Most research teams study the impacts of virulence factors, but until now no one understood how Leishmania was able transfer virulence factors from the vacuole to the cytoplasm of the infected cell. That's what we've just shown with our work," says the study's first author, Guillermo Arango Duque, who recently received his Ph.D. in virology and immunology supervised by Professor Descoteaux.

"We discovered that Leishmania co-opts the macrophage's membrane fusion machinery to export virulence factors out of the vacuole," he adds.

Interconnected cellular compartments

Since the parasite successfully transfers its virulence factors (GP63 and LPG molecules) to the other side of the vacuole's membrane, it was necessary to determine what other compartment of the infected host cell contained these factors.

The researchers observed that most of the virulence factors were found in a compartment called the endoplasmic reticulum (ER). This compartment takes up the most space in the host cell and is connected with all other intracellular compartments. They concluded that this facilitated the spread of virulence factors within the cell.

They then used the latest genetic technology to identify the molecules involved in intracellular trafficking that are needed to spread Leishmania

virulence factors in the infected host cell. The team found that by decreasing the expression of two host cell molecules, sec22b and syntaxin-5, that are responsible for regulating intracellular traffic in the ER—they could block the spread of virulence factors in the infected cell and interfere with their actions.

"To fully understand what enables the compartment where Leishmania replicates to connect with other compartments of the infected host cell is a major step forward," Professor Descoteaux says. "This pathway could also be exploited by other intracellular microorganisms such as Mycobacterium tuberculosis, which is the agent of tuberculosis, or Legionella pneumophila, which causes Legionnaires' disease."

The next step will be to find out to what extent, by manipulating or blocking this pathway over the long term, researchers could interfere with parasite replication without significantly altering how the cell functions.

More information: Guillermo Arango Duque et al, The host cell secretory pathway mediates the export of Leishmania virulence factors out of the parasitophorous vacuole, *PLOS Pathogens* (2019). DOI: 10.1371/journal.ppat.1007982

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