



International Journal of
Virology

ISSN 1816-4900



Academic
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Virus, Parasite May Combine to Increase Harm to Humans

A parasite and a virus may be teaming up in a way that increases the parasite's ability to harm humans, scientists at the University of Lausanne in Switzerland and Washington University School of Medicine in St. Louis recently reported in Science.

When the parasite *Leishmania* infects a human, immune system cells known as macrophages respond. However, some *Leishmania* strains are infected with a virus that can trigger a severe response in macrophages, allowing the parasite to do more harm in animal infections. In humans, the parasite's viral infection may be why some strains of *Leishmania* in Central and South America tend to cause a disfiguring form of disease that erodes the soft tissues around the nose and mouth.

"This is the first reported case of a viral infection in a pathogen of this type leading to increased rather than reduced pathogenicity," says Stephen Beverley, PhD, the Marvin M. Brennecke Professor and Head of the Department of Molecular Microbiology at Washington University School of Medicine. "It raises a number of important questions, including whether we can use antiviral strategies to reduce the damage caused by forms of *Leishmania* that carry viruses."

Leishmania infection, known as leishmaniasis, affects an estimated 12 million people worldwide. It is mainly spread by sand fly bites and is a major public health problem in the Mediterranean basin, Asia, Africa, the Middle East, Central and South America and a potential hazard to travelers and military personnel. Symptoms include large skin lesions, fever, swelling of the spleen and liver, and, in more serious forms of the disease, disfigurement and death.

The study brought together two different lines of investigation in Europe and the Americas.

Nicolas Fasel, PhD, Professor of Biology and Medicine at the University of Lausanne, and Nancy Saravia, PhD, of the International Center for Medical Training and Investigation in Cali, Columbia, have been studying the causes of

mucocutaneous leishmaniasis, a particularly harmful form of the disease that destroys the soft tissues of the nose and mouth. This type of infection is frequently associated with *Leishmania Viannia*, a subgenus of *Leishmania* strains prevalent in Central and South America.

In tests in mice and hamsters using parasite strains taken from the wild, Fasel and Saravia showed that only some *Viannia* strains spread rapidly and cause high levels of inflammation and damage similar to that seen in mucocutaneous leishmaniasis.

A breakthrough came when researchers realized that the rapid, highly damaging form of infection relied on an immune system sensor protein called TLR3. This protein is found in intracellular vesicles, which are compartments inside macrophages also known to host the parasite.

"Those vesicles are where the rendezvous between host, parasite and virus takes place," Fasel says. "TLR3 normally helps the immune system fight infections, but when we deleted it in mice and repeated the experiment, infections with virus-infected *Leishmania* were less harmful."

Researchers sorted the *Leishmania* into viral-infected and non-infected strains and found that the more serious infections in laboratory animals were much more likely to be caused by viral-infected *Leishmania*.

Beverley's group has been exploring the role of viral infections of *Leishmania* in the evolution of the RNA interference pathway, which can help fight viruses.

"Surprisingly many *Leishmania* species have lost the RNAi interference pathway, and one force contributing to this loss could be the successful infection of the parasite by viruses," he says. "This hints at the possibility of an evolutionary trade-off, suggesting that the loss of RNAi

could be balanced if the parasite gained some type of advantage when infected by a virus.”

To ensure that genetic differences in the wild strains weren’t interfering with the results, Lon-Fye Lye, PhD, staff scientist, and Suzanne Hickerson, senior research technician, both of Beverley’s lab, supplied lines of genetically identical Leishmania with and without the virus. As in the prior comparisons, virally-infected Leishmania caused more disease and provoked a stronger response from macrophages.

According to Beverley, the results suggest that some viral infections in Leishmania may be improving the parasite’s chances to infect the mammalian host’s immune cells. He speculates that this increased pathogenicity may be one evolutionary trade-off that makes losing the RNAi pathway worthwhile for Leishmania and other microbes.

“How the virally increased pathogenicity arises is now a fascinating question in its own right,” Beverley says. “It could teach us a great deal about how Leishmania causes a severe form of the disease and potentially offer new opportunities for its cure.”

Funding from Swiss National Science Foundation, Foundation Pierre Mercier and the National Institutes of Health supported this research.

Source: A. Ives, C. Ronet, F. Prevel, G. Ruzzante, S. Fuertes-Marraco, F. Schutz, H. Zangger, M. Revaz-Breton, L.-F. Lye, S. M. Hickerson, S. M. Beverley, H. Acha-Orbea, P. Launois, N. Fasel, S. Masina. Leishmania RNA Virus Controls the Severity of Mucocutaneous Leishmaniasis. *Science*, 2011; 331 (6018): 775 DOI: 10.1126/science.1199326