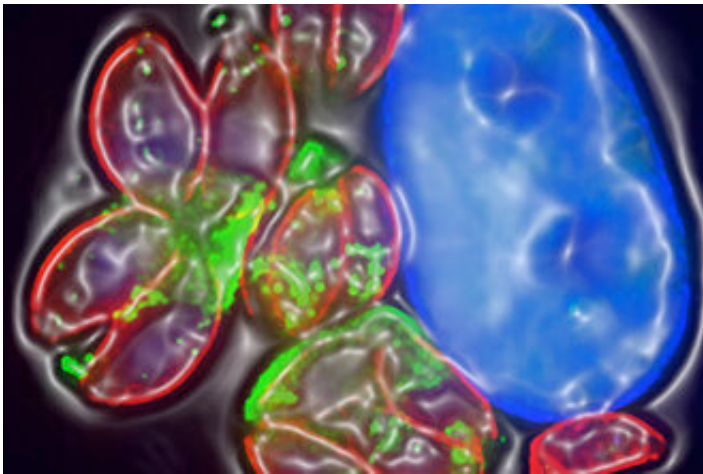


Toxoplasma parasites manipulate brain cells to survive

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A Toxoplasma-infected human cell moments before it bursts. Credit: Walter and Eliza Hall Institute of Medical Research

WEHI researchers have discovered how dormant Toxoplasma parasites in the brain manipulate their host cells to ensure their own survival.

The researchers showed that the parasites were able to lay dormant and undetected inside neurons ([brain cells](#)) and [muscle cells](#) by releasing proteins that switch off the cells' ability to alert the immune system. With expertise and technologies from WEHI's Advanced Genomics facility and Centre for Dynamic Imaging, they were able to visualize the parasites in real-time.

The discovery provides a better understanding of how *Toxoplasma* parasites can hide in the brain and what triggers them to reactivate and cause [disease](#). It could pave the way for new drug targets to treat patients suffering from chronic toxoplasmosis infections.

The research, led by Dr. Simona Seizova, Ph.D. student Ms Ushma Ruparel, Associate Professor Chris Tonkin and colleagues from WEHI, was published in the journal *Cell Host & Microbe*.

A 'molecular battle' for survival

Toxoplasmosis is a parasitic [infection](#) that affects humans and other mammals. It is caused by eating undercooked or contaminated meat, and from exposure to infected cat feces.

Around one in five Australians have been infected with *Toxoplasma gondii*, the parasite that causes toxoplasmosis. *Toxoplasma* infections can cause congenital birth defects, blindness and neurological dysfunction in unborn children. In adults who are immunocompromised, it can cause blindness and even death.

Ph.D. student Ushma Ruparel said *Toxoplasma* parasites often lay dormant in the brain of the host animal, where they could reactivate to cause severe disease.

"We know that *Toxoplasma* parasites make their own molecules and proteins that it exports into the host cell to protect itself from detection by the immune system. While this is well-understood in the acute, initial stage of infection, how *Toxoplasma* hijacks its host cells in its dormant form was unknown," Ms Ruparel said.

"With our colleagues who have expertise in genomics and advanced imaging, we showed that the parasite exports proteins called Inhibitor of

STAT1 transcription (IST) to the [host cell](#) to suppress immune signals."

Associate Professor Tonkin said IST played a key role in limiting interferon signaling in bradyzoites, to protect host cells from immune-mediated cell death, which is essential to the body's fight against Toxoplasma.

"Interferon is the beacon molecule of the immune system. It gives off a blinking sign to notify the immune system that the body has been infected with a range of diseases, including Toxoplasma," he said.

"Interferon is crucial in the fight against disease. However, the cunning parasite tries to turn this signal off during the latent period, as this is the only way it can survive. While the immune system is determined to rid the infection from the body, the parasite only has survival on its mind. So, it's essentially a tug-of-war, a molecular battle."

Link to neurological disease

While the exact mechanism of why and how the pathogen is reactivated to create disease is little understood, there appears to be a correlation between people who have immune deficiencies and brain lesions.

The association of Toxoplasma with neuropsychiatric conditions over the past decade is another curious element to this disease, said Associate Professor Tonkin.

"While there is a correlation between Toxoplasma infection and schizophrenia, bipolar disorder and other neurodegenerative conditions like Alzheimer's disease, there's no causation yet as we don't know the cause and effect," Associate Professor Tonkin said.

"The way this parasite resides in our brains during chronic infection and

the way that it shuts down our innate [immune system](#) to survive is quite unique. While this work was all done in the laboratory, it will lay the foundation to bring us closer to understanding these age-old questions about how these pathogens interfere in our neural pathways and what their exact role is.

"Our next step is to figure out what it is about chronic infections that make those changes really unique to chronic infections. We have found one specific parasite protein that seems to have a role, but it doesn't seem to account for all changes, and we want to explore if there are any others."

Tackling a key health burden

The findings have started to unravel the molecular players that help pathogens create latency, which could pave the way for a better understanding of the impact of [parasites](#) on the brain.

Associate Professor Tonkin said latent infections were one of the biggest global health burdens.

"Diseases such as HIV, hepatitis, malaria and tuberculosis are all examples of chronic or latent infections that cause significant disease, disability and economic impact. If we can understand what causes these latent infections to reactivate and their control over our [cells](#) and brain, we will be on the pathway to finding new treatments that diminish this burden for some of the most underprivileged people around the world."

More information: Simona Seizova et al, Transcriptional modification of host cells harboring *Toxoplasma gondii* bradyzoites prevents IFN gamma-mediated cell death, *Cell Host & Microbe* (2021). [DOI: 10.1016/j.chom.2021.11.012](https://doi.org/10.1016/j.chom.2021.11.012)

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