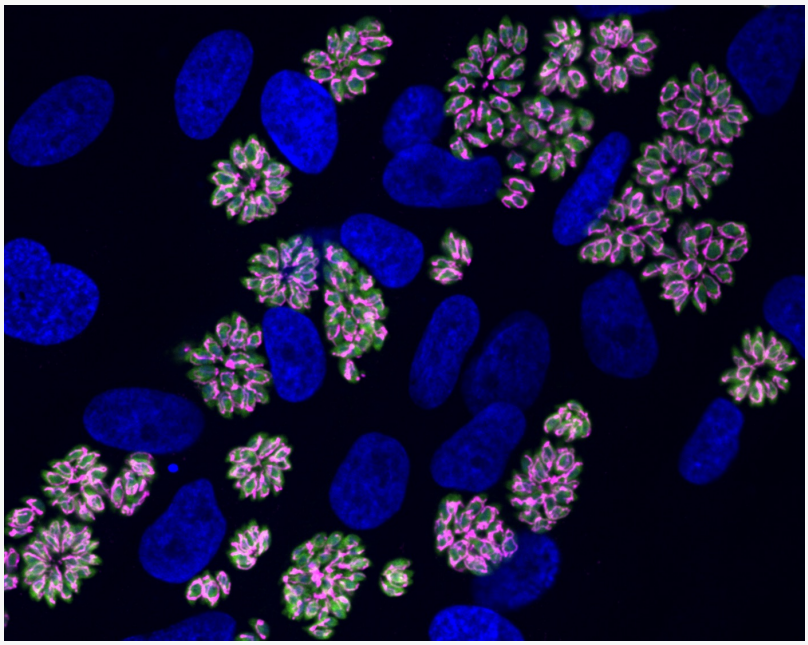
New study shows how Toxoplasma parasite evolved to adapt to crowded conditions in host cells

MA, UNITED STATES, August 11, 2026 /EINPresswire.com/ -- Toxoplasma gondii, or Toxoplasma, is a parasite that infects hundreds of millions of people around the world. Although cases are often mild, it can cause severe symptoms in in people with weakened immune systems and developing fetuses. It can also persist for years by forming long-lived cysts in tissues, allowing infection to become chronic.



Toxoplasma parasites shown in green, with host and parasite nuclei in blue. The iron-sulfur cluster assembly protein ISCU, shown in magenta, localizes to the parasite mitochondria. ISCU is one of the targets regulated by TgPRO. Credit: Lourido Lab/Whitehead Institute

During chronic infection, hundreds of Toxoplasma parasites can pack into a tissue cyst inside a brain or muscle cell. That crowded life carries a cost: nutrients become harder to obtain, waste accumulates, and energy-producing reactions can become damaging. How Toxoplasma reshapes its metabolism to keep growing under such strained conditions has been unclear.

A new study from the lab of Whitehead Institute Member Sebastian Lourido, also an Associate Professor of Biology at the Massachusetts Institute of Technology (MIT), identifies a parasite-specific protein that helps coordinate this response. The protein, named TgPRO, allows Toxoplasma to manage oxidative stress—the buildup of reactive oxygen molecules that can damage cells—by controlling genes involved in energy production and iron use.

The findings, published on August 11 in the journal Cell, reveal the first dedicated regulator of metabolic gene expression identified in apicomplexans, the group of parasites that includes

Toxoplasma and the organisms that cause malaria. The study, led by co-first authors Christopher Giuliano, a former graduate student, and current graduate student Chinmay Kalluraya in the Lourido lab, reveals a previously unknown way that parasites regulate metabolism. The findings also point to a possible therapeutic strategy: inhibiting pathways controlled by TgPRO could make Toxoplasma more vulnerable to antiparasitic drugs that induce oxidative stress, though this approach remains to be tested.

To discover the genes that support Toxoplasma's ability to live in crowded cells, the researchers used a genome-wide CRISPR screen to compare Toxoplasma growing at low and high densities. The screen tests the effects of turning off genes one by one at both population densities in order to determine which genes are essential specifically in crowded conditions. It highlighted pathways that make or recycle NAD and NADP, molecules important for energy production and defending against oxidative damage. It also pointed to TgPRO, a previously unstudied protein that was especially important when parasites became crowded.

"A genome-wide screen was a powerful way to ask how crowding affects parasite fitness," Kalluraya says. "TgPRO emerged as very important at high density. Because almost nothing was known about it, we wanted to understand what it was doing."

Parasites lacking functional TgPRO accumulated more reactive oxygen molecules and struggled to compete at high density. Experiments showed that the loss of TgPRO disrupted the mitochondrion—the structure that supplies much of a cell's energy—and changed how parasites processed glucose and other nutrients. Providing additional iron or restoring an important chemical balance inside the mitochondrion improved parasite growth, connecting TgPRO's effects to iron-dependent energy metabolism.

The team then traced the response to a molecular mechanism. TgPRO is an RNA-binding protein, meaning it attaches to the molecular messages (RNAs) that cells use to make proteins. The researchers found that it binds and stabilizes a select set of messages involved in nutrient use, mitochondrial activity, and the assembly of iron-sulfur clusters, small structures that many enzymes need to function. The experiments connected the original observation—that some parasites faltered only when crowded—to a precise interaction between a regulatory protein and its RNA targets.

"One of the really nice elements of the story is our ability to connect it all the way through—from the original observation and genome-wide screen to the metabolic consequences and the direct interaction between TgPRO and its target RNAs," Lourido says.

The researchers found that lowering oxygen levels also reduced oxidative stress and partially restored the growth of parasites without TgPRO. Toxoplasma is commonly grown in laboratories at atmospheric oxygen levels, which are considerably higher than those found in most animal tissues. The result suggests that oxygen conditions can strongly shape parasite metabolism, and the researchers caution others studying Toxoplasma to take this into consideration.

Connecting TgPRO to chronic infection

After testing the role of TgPRO in artificially crowded settings, the team also tested whether TgPRO matters during chronic infection, when Toxoplasma forms cysts in the brain. Mice infected with parasites lacking functional TgPRO developed smaller brain cysts, suggesting TgPRO supports parasite growth in the naturally dense environment of a chronic-stage cyst.

“The chronic stage is still somewhat elusive,” Giuliano says. “Showing that TgPRO affects cyst growth suggests that these same metabolic changes are needed in the brain and gives us clues about how the parasites persist there for months or years.”

TgPRO bears little resemblance to the proteins that regulate similar metabolic programs in mammals, yeast, and bacteria, yet it controls many of the same kinds of genes that these organisms adjust when cells face oxidative stress or changing nutrient conditions. This is an example of convergent evolution: distantly related organisms evolved different molecular machinery to solve a similar biological problem.

That convergence suggests that coordinating these metabolic pathways may be a fundamental requirement for cells adapting to stress.

Altogether, the study establishes a new paradigm for how apicomplexan parasites regulate their metabolism and advances the foundation for investigating how Toxoplasma persists inside its hosts.

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