Scientists sever molecular signals that prolific parasite uses to puppeteer cells

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Scientists studying a cunning parasite that has commandeered the cells of almost half the world's human population have begun to zero in on the molecular signals that must be severed to free the organism's cellular hostages.

While *Toxoplasma gondii* is not as widely known by the public as some of its more notorious parasitic brethren, it has been hijacking the cells of human and animal hosts for eons and is particularly dangerous to those with compromised and/or underdeveloped immune systems.

"We have understood for some time now that *Toxoplasma* can co-opt the biological processes of its host cell, but there's still a lot we don't know about how this happens and what benefit the parasite derives," said Dr. Amos Orlofsky at Albert Einstein College of Medicine of Yeshiva University, one of the co-authors of a new paper in the *Journal of Biological Chemistry* that reveals how blocking certain signals within a cell can liberate it from its captor.

Toxoplasma is a crafty single-celled organism that typically begins its life cycle in the warm body of a small mammal, such as a rat. While there, it reprograms the rat's gut instinct to avoid cats and, thus, makes the rat far more likely to get gobbled up. *Toxoplasma*'s ultimate goal is, in fact, to get eaten by a cat, because, once it settles into the feline's gastrointestinal tract, it begins the second stage of its life cycle: laying the next generation of eggs that will be shed in feces and acquired by the next rat.

Seeing as how humans usually aren't eaten by cats, *Toxoplasma* doesn't seek them out as hosts. But, humans are exposed to the parasite at a fairly high rate, usually while changing cat litter or eating unwashed vegetables or undercooked meat.

"*Toxoplasma* is a major cause of mortality in AIDS patients worldwide, and it's also a serious problem for transplant recipients and for infants whose mothers became infected during pregnancy. There is also some reason to be concerned about possible neurologic effects in those who are infected but apparently healthy," Orlofsky explained. "Current medications are limited by side effects, and new approaches to dealing with this highly sophisticated and successful microbe are urgently needed."

In collaboration with colleague Louis M. Weiss and then-graduate-student Yubao Wang, who is now a postdoctoral fellow at Harvard University, Orlofsky set out to identify which cellular signals are used by *Toxoplasma* to capture and rearrange key structures in the host cell. He described those cellular signals as, essentially, the strings used by the parasite-puppeteer to manipulate the behavior of the cell.

They focused on one particular cellular structure known as the centrosome, which serves as the networking hub for fibers that direct traffic within the cell. The centrosome also controls the direction in which the cell moves within the body, but, when infected with *Toxoplasma*, it doesn't take its normal routes.

Orlofsky said this suggests that *Toxoplasma* disables the steering of the host cell by taking hold of the cell's "rudder."

"We infected cells in a Petri dish with *Toxoplasma* and then scratched the dish to create a 'wound.' Normally, cells next to the wound sense the new emptiness next to them and respond by trying to fill the wound, and

the cell then starts moving in that direction," Orlofsky said. "We discovered that *Toxoplasma*-infected cells don't do this: Their captured centrosomes fail to move toward the wound, and the entire cell fails to move as well."

When the team "liberated" the centrosome of the infected cell, by inhibiting certain signals, it re-oriented itself toward the wound and was able to move in the proper direction.

"These results give us some insight into what the parasite may be trying to accomplish. That is, it seems to be crippling the ability of host cells to respond to signals that say 'move over here'. That could make all the difference for the body's ability to make a quick immune response, which may depend on infected cells and immune-response cells moving toward each other and interacting."

Orlofsky's team hopes learning more about these signals and how to manipulate them may yield tools for protecting multiple host-cell functions from total parasite takeover. These tools could lead to improved treatments or preventive measures.

"If our speculation is correct about the effects of the parasite on the immune response, then one could envisage a live vaccine based on disabled *Toxoplasma* that, among their other engineered defects, lack the ability to hold the cell's rudder and so elicit a stronger immune response," Orlofsky said.

The team's research was carried out at the departments of medicine and pathology at Albert Einstein College of Medicine and was funded by the National Institutes of Health. The resulting paper was published on the Journal of Biological Chemistry's Web site March 17 and will appear in a forthcoming print issue.