Aimless proteins crucial to disease, research suggests

March 31 2011

Researchers from the University of Pittsburgh and Stanford University discovered that a supposedly inactive protein actually plays a crucial role in the ability of one the world's most prolific pathogens to cause disease, findings that suggest the possible role of similarly errant proteins in other diseases.

The team reports in the Proceedings of the National Academy of Sciences (*PNAS*) that Toxoplasma gondii—the parasitic protozoa behind toxoplasmosis—attacks healthy cells by first injecting them with pseudokinases, which are enzymes that have abandoned their original function of transferring phosphates. When the researchers engineered strains of *T. gondii* without a particular pseudokinase gene cluster called ROP5, the pathogen was subsequently unable to cause disease in mice—a notable loss of potency in an organism that can infect nearly any warm-blooded animal.

These results are among the first to implicate pseudokinases as indispensible actors in pathogen-based disease, said senior author Jon Boyle, a professor in the Department of Biological Sciences in Pitt's School of Arts and Sciences. Boyle coauthored the paper with John Boothroyd, a professor of microbiology and immunology in the Stanford School of Medicine. Boyle and Boothroyd worked with Michael Reese, a postdoctoral researcher in Boothroyd's lab, as well as Gusti Zeiner and Jeroen Saeij, former postdoctoral researchers under Boothroyd.

The Pitt-Stanford project suggests that the significance of these aimless

enzymes to
T. gondii could apply to pseudokinases in other pathogens, Boyle said, including the parasite's close relative Plasmodium, which causes malaria.

"Our work shows that just because these proteins have lost their original function does not mean they don't do anything," Boyle said. "*T. gondii* cannot cause disease without them, and if one is trying to understand how pathogens work, the role of these proteins should obviously be considered."

The ROP5, or rhoptry protein 5, gene cluster—so named for the specialized organelle rhoptry, which secretes them—belongs to a larger family of approximately 40 pseudokinases present in *T. gondii*. Once *T. gondii* injects ROP5 into the host cell, the parasite enters the cell and forms a protective membrane pocket, or vacuole, around itself to which ROP5 and other proteins attach. While the other secreted kinases are known to help disable or disrupt activity in the host cell, the ROP5 cluster, a kind of infectious ringleader, appeared to have a more dominant role in causing severe disease in mice than other virulence factors, Boyle said.

The team plans to further investigate the significance of ROP5 to *T. gondii*'s survival within the host, Boyle said. In the *PNAS* paper, the researchers suggest that ROP5 has undergone multiple rounds of gene duplication followed by mutation of the individual copies. Thus, the authors propose, the ROP5 cluster may act like a genetic Swiss Army Knife, a multipurpose tool that allows *T. gondii* to adapt to and infect its famously wide variety of hosts.

More information: www.pnas.org/content/early/201 … /1015980108.abstract

Provided by University of Pittsburgh