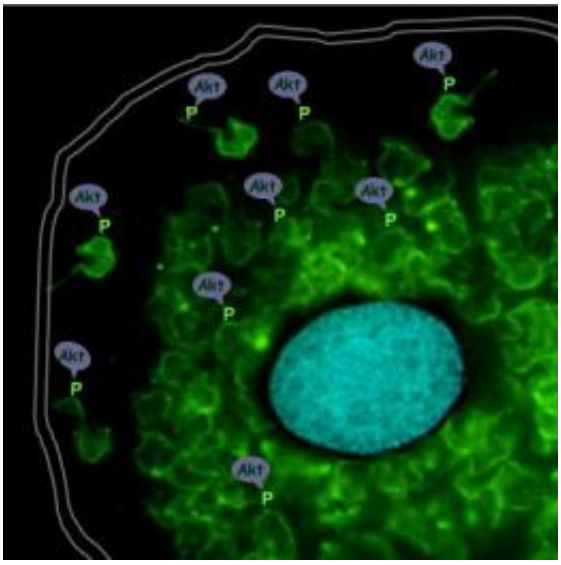
Parasite evades death by promoting host cell survival

December 8 2009



A human cell infected with *Trypanosoma cruzi.* Akt kinase (shown in purple) activates PDNF (shown in green) on the parasite surface. Credit: Tufts University

Researchers have discovered how the parasite Trypanosoma cruzi, which causes Chagas' disease, prolongs its survival in infected cells. A protein on the parasite activates the enzyme Akt, which blocks cell death signals, preventing cell destruction and parasite elimination. Chagas' disease affects some 8 to 11 million people throughout Latin America and even the United States.

The parasite *Trypanosoma cruzi* (or *T. cruzi*), which causes Chagas' disease, will go to great lengths to evade death once it has infected human host cells, researchers have discovered. In a study published in the November 17 online issue of *Science Signaling,* the researchers describe how a protein called parasite-derived neurotrophic factor (PDNF) prolongs the life of the T. cruzi parasite by activating anti-apoptotic (or anti-cell-death) molecules in the host cell. These protective mechanisms help to explain how host cells continue to survive despite being exploited by *T. cruzi* parasites.

"We asked ourselves, 'How is it possible that the host cells stay alive for so long with thousands of *T. cruzi* parasites consuming the host cell's vital resources?' We discovered that PDNF on the surface of the *T. cruzi* parasite essentially inhibits cell death signals and activates cell-protective mechanisms, ensuring *T. cruzi* sufficient time to develop and reproduce in the host cell," says senior author Mercio Perrin, MD, PhD, professor in the pathology department at Tufts University School of Medicine (TUSM) and member of the immunology program faculty at the Sackler School of Graduate Biomedical Sciences at Tufts.

Taking a multi-faceted approach, the researchers used bioinformatics, immunochemistry, intracellular colocalization microscopy, and in vitro enzymatic techniques to study *T. cruzi* survival in the host. Perrin and co-author Marina Chuenkova, PhD, a research instructor in the pathology department at TUSM and the Sackler School, demonstrated that PDNF is a substrate and activator of Akt kinase, an enzyme that promotes cell survival by inhibiting "cell death" proteins.

"Further investigation showed that within *T. cruzi*-infected cells, PDNF also activates increased production of Akt, prolonging its protective effects," says Chuenkova. "Akt is a key regulator of diverse cellular processes, and supports cell survival not only by inhibiting apoptotic molecules, but additionally by increasing nutrient uptake and

metabolism," she continued.

"In short, the *T. cruzi* parasite has a means of establishing life insurance once it has invaded the host. If we can fully understand the mechanisms behind this protection, we can begin to explore ways to undermine it with treatment," said Perrin.

Chagas' disease, typically transmitted to humans by blood-feeding insects, infects an estimated 8 to 11 million people throughout Mexico, and Central and South America. Although it is still rare in the United States, according to the Centers for Disease Control and Prevention (CDC), there are 300,000 people with Chagas' disease living in the United States, most of whom acquired the disease while living in other countries.

The acute phase of Chagas' disease can result in fever or swelling at the site of the insect bite, but many people do not experience symptoms at all. If left untreated, the disease enters an indeterminate phase in which no symptoms are present. During this phase, many people are not aware that they are infected, but approximately 30 percent will eventually develop life-threatening complications of the disease, including enlargement of the digestive tract and/or heart.

More information: Chuenkova MV and PereiraPerrin M. *Science Signaling*. 2009. (November 17); 2(97), ra74. "Trypanosoma cruzi targets Akt in host cells as an intracellular antiapoptotic strategy." Published online November 17, 2009, doi:10.1126/scisignal.2000374

Source: Tufts University