Parasite helps itself to sugar

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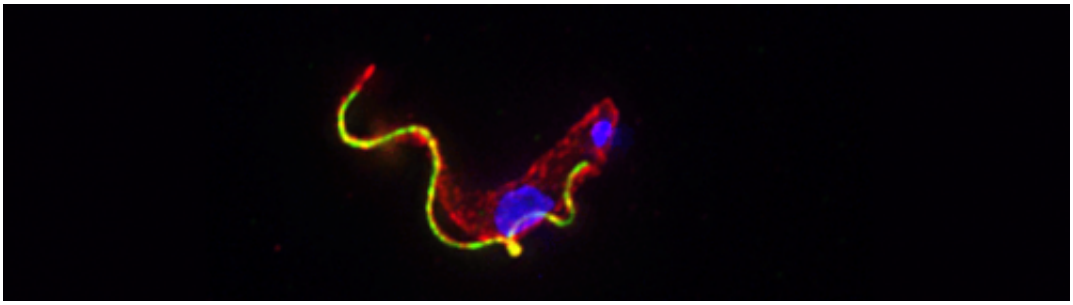

Trypanosoma brucei: The fluorescence micrograph shows the cell nucleus and the kinetoplast (top right) in blue, the flagellum (green) and the cytosol (red).

Trypanosoma brucei, the parasite that causes sleeping sickness, is transmitted to mammals by the tsetse fly, and must adapt to the divergent metabolisms of its hosts. A new study shows how it copes with the frugal diet offered by the fly.

Sleeping sickness is a deadly human disease in tropical Africa, caused by the unicellular parasite *Trypanosoma brucei*. Many species of mammals, including humans, are susceptible to the pathogen, which is transmitted by the tsetse fly. In the course of its life cycle, the parasite must adapt to very different physiological environments and food sources, and has therefore evolved a highly flexible form of energy metabolism.

LMU biologist Professor Michael Boshart, in collaboration with his French colleagues Drs. Frédéric Bringaud (CNRS, Bordeaux University) and Jean-Charles Portais (INSA, Toulouse University), has now looked

at how T. brucei manages to adapt to the diverse environments it encounters in its hosts. "We were especially interested in learning more about the metabolic capabilities that help T. brucei to negotiate the bottlenecks it meets during its development in the tsetse fly," says Boshart.

Surviving in hostile territory

The first metabolic challenge faced by T. brucei in its insect host is the relative scarcity of glucose. In the bloodstream of infected mammals, the pathogen can feast on an abundance of the sugar, but conditions in the fly are very different. It must reconfigure its metabolism to exploit amino acids as its primary energy source. – But that's not all. "The so-called proventriculus represents an even more threatening bottleneck. This is a region at the head of the fly's midgut which forms a constriction that functions like a valve, and the trypanosomes have to get past it to reach the salivary glands, so that they can be transferred to their next mammalian host," as Stefan Allmann, first author of the new study, explains.

The proventriculus is also characterized by a very basic pH and it is rich in reactive oxygen species (ROS). In order to survive the resulting oxidative stress, T. brucei must neutralize the noxious chemicals, and this would appear to pose a problem. As Allmann points out: "Detoxification of ROS depends on the availability of the coenzyme NADPH, but regeneration of NADPH normally requires glucose metabolism."

Do-it-yourself glucose

However, the researchers have now shown that several metabolic pathways contribute to the regeneration of NADPH by T. brucei in the

fly. And, as it turns out, glucose is dispensable for one of them, which can thus supply the essential coenzyme for the detoxification of ROS. Moreover, the scientists discovered – to their surprise – that T. brucei is not actually forced to do without glucose altogether during its residence in the tsetse fly. The protozoan can itself synthesize glucose-6-phosphate – and this too can be used for the production of NADPH.

In cooperation with their French colleagues, the LMU researchers now plan to extend their experiments to gain deeper insights into the mechanisms that enable the parasites to adapt to, and survive in, their insect host. The hope is that their findings will allow them to manipulate the parasite's metabolism to enable them to interrupt its life cycle – in domestic animals, for instance – and thus prevent its propagation.

More information: *JBC* 2013: www.ncbi.nlm.nih.gov/pubmed/23665470

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