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How some trypanosomes cause sleeping sickness while others don't

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Trypanosome parasites transmitted by tsetse flies cause devastating diseases in humans and livestock. Different subspecies infect different hosts: *Trypanosoma brucei brucei* infects cattle but is non-infectious to humans, whereas *T. b. gambiense* and *T. b. rhodesiense* cause sleeping sickness in humans. A study published on May 15th in *PLOS Pathogens* reveals how humans can fight off some trypanosomes but not others.

Sam Alsford, from the London School of Hygiene and Tropical Medicine, UK, and colleagues, undertook a comprehensive search for genes that make *T. b. brucei* sensitive to the innate (the first-line, non-specific) defenses of the human immune system. The hope is that understanding the molecular basis of sensitivity would enable the development of strategies to sensitize resistant trypanosome subspecies. And new drugs are badly needed because existing ones have serious side effects.

The researchers systematically inactivated *T. b. brucei* genes and looked for parasites which could survive exposure to human blood serum (factors in which can kill this subspecies, making it harmless to humans). Three genes thought to sensitize *T. b. brucei* to human defenses had been previously identified by other methods, and the researchers re-discovered all three—plus they found a previously unknown fourth gene in this study.

One of the known genes codes for a protein called inhibitor of cysteine peptidase (or ICP), and the researchers further analyzed its role. Using

chemical and genetic approaches, they show that ICP sensitizes *T. b. brucei* to human serum by dampening the activity of a specific cysteine peptidase (a protein that can cut other proteins) called CATL. In the absence of ICP, CATL is fully active and can counteract components of human serum responsible for killing trypanosomes.

Discussing the findings, Alsford commented: "CATL is under consideration as a potential drug target, and our results suggest that its inactivation could indeed support the human defense system in fighting off disease-causing trypanosome strains. However, as CATL might also be involved in the generation or break-down of other factors involved in parasite-host interactions, it will be important to develop an improved understanding of the complex interplay of all of these factors in human-infective trypanosomes".

The researchers also plan work on the new (fourth) gene they discovered. It codes for a protein that appears to be a so-called transmembrane channel. Studying this channel (which is likely to be involved in the uptake of human defense factors by the parasite) should further improve the understanding of the interaction between the parasite and the anti-trypanosomal components of human serum.

More information: Alsford S, Currier RB, Guerra-Assunc¸a˜o JA, Clark TG, Horn D (2014) Cathepsin-L Can Resist Lysis by Human Serum in Trypanosoma brucei brucei. *PLoS Pathog* 10(5): e1004130. DOI: 10.1371/journal.ppat.1004130