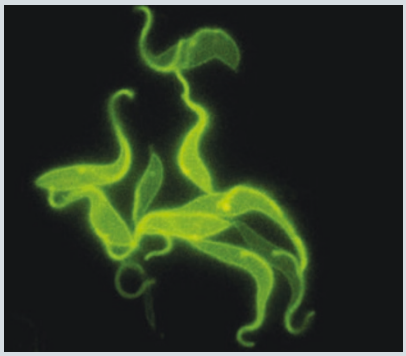
GENE REGULATION

How parasites do it

A screen to rapidly identify regulatory regions in trypanosome's RNA yields sequences necessary and sufficient for the regulation of mRNA stability, giving insights into the parasite's ability to control gene expression during different life cycle stages.



Trypanosomes in procyclic form expressing EYFP.

Trypanosomes don't rank very high in public opinion, being insect-borne eukaryotic parasites. And yet, scientists like Mark Carrington at Cambridge University will attest to their usefulness as model systems to understand basic molecular processes. "The regulation of gene expression in trypanosome is predominantly post-transcriptional", he says, "and so it is a very good model system for looking at the regulation of mRNA levels."

RNA in trypanosomes is first constitutively transcribed as polycistrons—one strand of RNA contains many transcripts and is subsequently processed by splicing into single transcripts. The stability of some mRNAs, and consequently the expression of these genes, changes as the parasite goes through various life cycle stages; two of these, the bloodstream form in mammals and the procyclic form in the tse tse fly, can be easily cultured *in vitro*. Carrington explains, "The reason we use these two forms is because they represent a shift in hosts. You can do the differentiation *in vitro*, and those are the two forms that are most readily cultured."

As a proof of concept, they targeted glycophosphoinositol–phospholipase C (*GPI-PLC*), a tightly regulated gene expressed only in the bloodstream stage. Taking advantage of trypanosome's propensity for homologous recombination, Carrington's team replaced the *GPI-PLC* 5′ and 3′ untranslated regions (UTRs) with the equivalent sequences from tubulin, which is not differentially regulated. They demonstrated that the 3′ UTR of *GPI-PLC* alone is necessary and sufficient to confer differential stability to the mRNA: its replacement led to *GPI-PLC* expression in both the bloodstream form and the procyclic form. An attractive feature of the screen is its amenability to higher throughput.

This screening strategy is not limited to trypanosomes but can be applied to any organism with polycistronic RNA and high homologous recombination rates, including many other kinetoplastid protozoa. As Carrington points out, "[The screen] provides a very rapid way in these organisms for analyzing where the regulatory sequences lie within any gene. It could be widely used combined with the results of microarrays to see which genes are regulated in one life cycle stage and not the other."

Knowing more about the differential expression of genes in a parasite will be valuable to understanding basic biology. In the case of trypanosomes, which cause serious illness such as sleeping sickness in equatorial Africa, this may also lead to improved therapy down the road. Unfortunately preventing trypanosome-borne disease is not only a question of science. "We could still do with better treatments, they have a lot of side effects, but this is really a disease of poverty, the problem is having access to the treatments," highlighting the fact that eliminating this threat will take more than a perfect understanding of the biology.

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RESEARCH PAPERS

Webb, H. *et al.* A novel strategy to identify the location of necessary and sufficient *cis*-acting regulatory mRNA elements in trypanosomes. *RNA*; published online May 31, 2005.