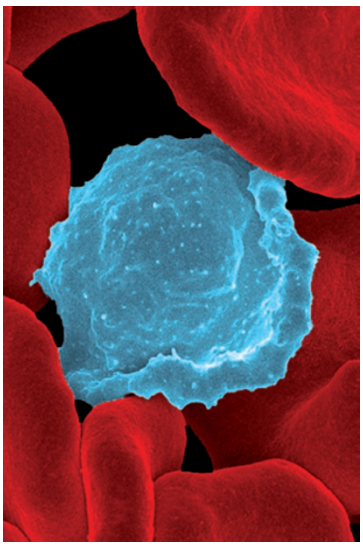
PARASITOLOGY

The malaria food channel

To survive within erythrocytes, malaria parasites modify the permeability of the host membrane to increase nutrient uptake. Although one or more ion channels were thought to be involved, the precise uptake mechanism and its genetic basis were unknown. Now, Desai and colleagues report that proteins encoded by the *clag3* genes of the human malaria parasite *Plasmodium falciparum* have a central role in nutrient uptake in infected erythrocytes.

Desai and co-workers used high-throughput screening as well as patch clamp experiments to identify ISPA-28, a highly specific small-molecule inhibitor that blocks nutrient uptake in erythrocytes infected with the *P. falciparum* line Dd2 but not in those infected with the *P. falciparum* line HB3. The authors then tracked the inheritance of ISPA-28 inhibition in the progeny of a Dd2 × HB3 cross and used microsatellite markers to identify a region in the parasite's chromosome 3. Fourteen genes from this locus in HB3 were separately transfected into Dd2. Only two related genes, *clag3.1* and *clag3.2* (named for previously assumed roles as cytoadherence-linked antigens), reduced ISPA-28 efficacy. The authors found that malaria parasites express either *clag3.1* or *clag3.2* but not both genes simultaneously, and used this observation to correlate *clag3* expression levels with ISPA-28 inhibition of nutrient uptake. Finally, protease treatment and confocal microscopy revealed that the *clag3*-encoded proteins are exposed at the erythrocyte surface, as expected for a nutrient channel.



Human erythrocytes infected with malaria parasites (blue) have altered morphology and permeability when compared with uninfected erythrocytes (red). Colourized electron micrograph courtesy of A. Mora, National Institute of Allergy and Infectious Diseases, Rockville, Maryland, USA.

Taken together, these results indicate that the plasmodial *clag3*-encoded proteins have a key role in the increased permeability of infected erythrocytes to nutrients and other solutes and, thus, constitute potential targets for future antimalarial drugs. As these proteins lack conventional ion channel domains, some as-yet-unknown interacting proteins could be required to form a functional channel.

Cesar Sanchez

> "the *clag3* genes of … *Plasmodium falciparum* have a central role in nutrient uptake in infected erythrocytes"

ORIGINAL RESEARCH PAPER Nguitragool, W. *et al.* Malaria parasite *clag3* genes determine channel-mediated nutrient uptake by infected red blood cells. *Cell* **145**, 665–677 (2011)
FURTHER READING Maier, A. G., Cooke, B. M., Cowman, A. F. & Tilley, L. Malaria parasite proteins that remodel the host erythrocyte. *Nature Rev. Microbiol.* **7**, 341–354 (2009)