which they feed back to shut off their own genes. That causes the levels of the proteins to drop, and the genes to turn back on. This oscillator, controlled by rising and falling protein levels, could be how the clock keeps time, but it also needs the equivalent of a power source: a gene activator that drives the expression of genes such as *per*, *tim*, and *frq* when the proteins aren't shutting them off. Such a gene driver might be part of the oscillator itself if its activity is repressed each day when the other proteins turn their genes off.

Loros and Dunlap's team at Dartmouth has shown that WC-1 and -2 drive the *frq* gene, and there is new evidence suggesting that a CLOCK-like protein may activate *per* in fruit flies. Paul Hardin's team at the University of Houston recently found that the *per* gene includes a DNA sequence known to serve as the binding site for a still-unidentified protein with a bHLH motif—the same motif found in CLOCK. That suggests, says Hardin, that there could be a mouse counterpart of CLOCK driving *per* expression. That, in turn, has fueled speculation that CLOCK may drive a *per*-like gene in mice.

That's just one of the speculations fueled by the new results. There is also the issue of the PAS sequence, which has now been found in more than a dozen proteins, most of them transcription activators and some of them clock genes. It has several apparent functions, and it isn't clear which of them is crucial in clocks. But its presence points to a possible evolutionary link, suggesting that clock mechanisms—which evolved to deal with daily light-dark cycles—may have arisen from light-responsive proteins in primitive organisms. Besides their role in *Neurospora*'s clock, WC-1 and WC-2 are regulators of all light-responsive genes in the mold; moreover, a number of light-responsive proteins with no known clock function—found in algae, bacteria, and higher plants—have PAS-like sequences, suggesting they share a common ancestor with clock proteins (*Science*, 2 May, p. 753).

Beyond all this speculation, researchers are looking forward to using the new genes as an opening for testing their hypotheses. With *Clock* in hand, researchers finally have a handle on the mammalian clock; they can now search for other components by looking for proteins that CLOCK interacts with and genes that it activates. Takahashi notes that there is no proof yet that CLOCK is a central part of the oscillating mechanism of a mouse's timepiece; by checking whether CLOCK activity levels rise and fall, and how manipulations of it affect mouse rhythms, researchers will learn whether it is a key component. And perhaps one day, when the molecular parts of the mammalian clock have all been discovered, jet-lagged travelers will know which molecular knob to turn to reset it.

–Marcia Barinaga

MALARIA RESEARCH

How the Parasite Gets Its Food

Malaria is a notoriously tenacious infection. One reason is the *Plasmodium* parasite's ability to sequester itself inside red blood cells, where it is protected from attack by the immune system and many drugs. Once there, however, the parasite faces a problem common to fugitives: how to get food. Red blood cells, which are little more than sacks of hemoglobin, cannot provide all the nutrients *Plasmodium* needs. But new results are helping to explain exactly how the parasite imports sustenance from outside the cell.

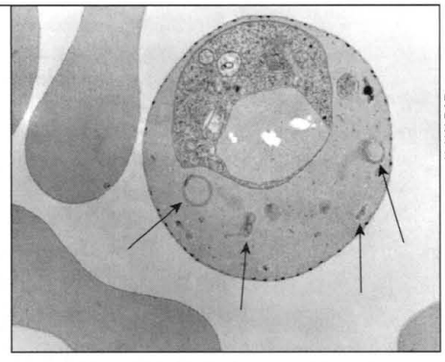
Researchers have suspected for several years that *Plasmodium* acquires at least some of its nutrients through a complex series of membranous tubules and vesicles that it constructs throughout the red blood cell shortly after taking up residence there. But while the structure of this network suggested that it might be a transport system, direct evidence for that had been hard to come by—until now, that is.

In work described on page 1122, biochemists Kasturi Haldar, Sabine Lauer, and Nafisa Ghori of Stanford University, with Pradipsinh Rathod of the Catholic University of America in Washington, D.C., have found that a chemical that disrupts the membrane network prevents the parasite from importing vital nutrients such as protein-building amino acids. The result is "the best evidence so far" that the membranes are an import system, says malaria researcher Barry Elford of Oxford University in the United Kingdom. The finding also suggests that drug researchers might take advantage of the system by designing antimalarial compounds that can sneak in with the essential nutrients.

The current work is an outgrowth of a previous discovery by Haldar and her colleagues. Almost 2 years ago, they showed that a chemical called PPMP, which prevents the parasite from forming a membrane component called sphingomyelin, disrupts the formation of the entire network—causing the tubules to become fragmented or constricted. To see whether this breakdown interferes with the network's proposed transport function, the team exposed both normal and PPMP-treated infected red blood cells to a dye called Lucifer yellow. In the control cells, the dye was distributed throughout the membrane network and in the parasite itself, but the PPMP-treated cells took up very little dye.

The researchers then went on to probe whether the chemical has a similar effect on the transport of nutrients. In a series of experiments, they exposed control cells and treated cells to several building blocks of nucleic acids and to glutamate, an amino acid used to build proteins—all with radioactive labels. When they measured how much radioactivity appeared in the two types of cells, they found that PPMP reduced accumulation of the nutrient molecules by as much as 91%. The team also found an even larger drop-off—up to 98%—in the amount of the imported substances actually used by the parasite to build DNA or proteins. The difference between the two figures suggests that while PPMP-treated cells were able to take up some of the molecules, they were unable to deliver them to the parasite, says Haldar.

Although the membrane-blocking compound itself might seem like an obvious drug candidate, Haldar says cutting the supply lines would kill the parasite slowly, giving it time to find alternate import routes and develop resistance. A better strategy might be to take advantage of the network to deliver drugs to the parasite. Indeed, while the network may block some drugs, a few compounds do seem to travel through it. The team found that blocking the network with PPMP also blocked the uptake of an experimental drug—a slightly modified nucleotide precursor that disrupts *Plasmodium*'s DNA synthesis. PPMP seemed to block uptake of the lethal compound by about 90%, enabling many cells to survive treatment with the drug.



K. HALDAR

The fugitive. The malaria parasite's network of tubules (small arrows) may import nutrients.

In fact, the new findings may help explain some drug-related mysteries, says Rathod: "It's always been puzzling why some modified nutrients are effective and why some very close analogs are ineffective." Some sort of selection mechanism in the membrane network may protect the parasite from certain drugs, he says. The team hopes to figure out those mechanisms in future experiments. "If you understand the permeability and specificity," says Rathod, "you can design drugs that take advantage of them."

–Gretchen Vogel