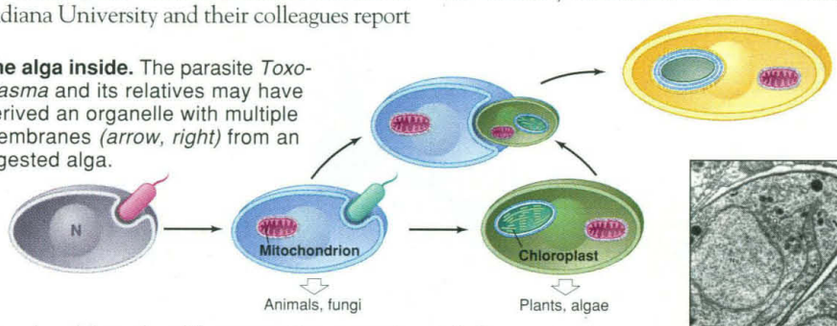
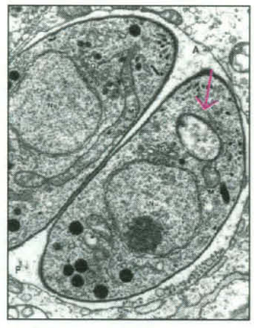
Parasites Shed Light on Cellular Evolution

By now, it's well established that the cells of higher organisms acquired some of their most important components—the energy-producing mitochondrion and the photosynthesizing chloroplast—when they engulfed much simpler bacterial cells, which then took up residence and now provide those key services. But now, it seems that even a complex cell can be engulfed by another cell and become an essential part of it.

On page 1485, molecular parasitologists Sabine Köhler and David Roos of the University of Pennsylvania, molecular evolutionist Jeff Palmer, and botanist Charles Delwiche of Indiana University and their colleagues report that the chloroplast-like organelles recently found in an important group of single-celled parasites apparently arose when one of the parasites' ancestors engulfed, and then retained, a chloroplast-containing algal cell. The work adds to the growing evidence suggesting that secondary endosymbiosis, as it is called, may have been a relatively common event in evolution: There is already strong evidence that it occurred in some of the commonest types of algae, perhaps on several different occasions.



The alga inside. The parasite *Toxoplasma* and its relatives may have derived an organelle with multiple membranes *(arrow, right)* from an ingested alga.



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SOURCE: KÖHLER *ET AL.*

While no one yet knows exactly what function the plastids have in the parasite group—which includes *Toxoplasma*, a common cause of infections in AIDS patients, and the malaria-causing *Plasmodium*—the fact that they have been retained through evolutionary history suggests that they are essential. That would make them tempting targets for drug therapies, because humans and other mammalian hosts of the parasites don't have such organelles. Indeed, says molecular parasitologist Jean Feagin of the Seattle Biomedical Research Center, researchers are attracted "almost like flies to the potential that this could have."

The first clue that the parasites carry plastids came when researchers found that *Plasmodium* and its relatives carry three distinct sets of genetic material: the usual nuclear DNA, a small circular molecule, and an even shorter linear fragment. Scientists at first thought the circular piece belonged to the cells' mitochondria, which typically have circular remnants of the original bacterial genome. But on closer examination, they found that the circular DNA's sequence contained some key features of the plastid DNA of plants and algae, while the linear piece turned out to be the mitochondrial DNA. That was very puzzling, says Roos. "Here, we have a genome without a known function and without a known home [in the cell]," he says.

Last year, while studying *Toxoplasma*, botanist Geoffrey McFadden of the University of Melbourne in Australia and his colleagues provided the first solid evidence for the misfit genome's home. They selectively tagged the plastidlike DNA and found that it indeed resides in a small membrane-bound organelle that had no obvious function. That finding only deepened the puzzle, says Roos: "Its DNA looks more like a chloroplast's than a mitochondrion's, but these are not plants. So, what are they doing with a chloroplast?"

The current work, says McFadden, "provides that missing piece of the puzzle." The team presents two lines of evidence that the parasites obtained their plastid when one of their ancestors attempted to eat a chloroplast-containing algal cell. First, electron-microscope images revealed that the *Toxoplasma* organelle is surrounded not just by two membranes, as chloroplasts and mitochondria normally are, but by four. The inner two, the researchers reason, are from the double-membraned plastid that existed inside the engulfed cell. The third derives from the outer membrane of the algal cell, while the outermost membrane came from the vacuole formed when the host cell surrounded and engulfed the potential prey. Second, a phylogenetic analysis of one of the plastid genes suggested that it is more closely related to a gene in the plastids of green algae than to the comparable gene in the photosynthetic bacteria that were the original source of chloroplasts.

The scientists acknowledge that neither line of evidence is strong enough to stand alone. "I wouldn't bet my life on there being four membranes there," says Roos, who notes that it is sometimes difficult to see all four clearly. And Palmer, whose laboratory conducted the phylogenetic analysis, acknowledges that the data, which apply to only one gene, do not yield "a strong answer." But the two lines of evidence taken together, says McFadden, "provide the first explanation of parasite plastid origin," one consistent with secondary endosymbiosis.

The parasites' plastids add to growing evidence that endosymbiosis may have happened "at least a half-dozen times" during the early evolution of cells, says Palmer. Other researchers have found not only multiple membranes, but also the remnants of an engulfed cell's nucleus, in two groups of algae, the red *Cryptomonas* and the green chlorarachniophytes, implying that they got their chloroplasts in the same way. And based on an as-yet-unpublished genetic analysis of red and green algae, University of Washington botanists Benjamin Hall and John Stiller suggest that green algae themselves may have arisen from a cell that engulfed a plastid-containing alga.

But even though the new results help explain how the plastid got into *Toxoplasma* and its relatives, they do not explain what it is doing there today. It apparently does not carry out photosynthesis, having lost the genes required to obtain energy from sunlight, as well as its chlorophyll. It does, however, retain genes that may be involved in such crucial metabolic processes as the manufacture of amino acids, which are the building blocks of proteins, and the breakdown of lipids, which produces energy needed by the cell.

Biomedical researchers would like to pinpoint the plastid's critical functions, because it might be possible to design drugs that block them with minimal side effects for humans. Indeed, several drugs used to treat malaria and toxoplasmosis may already be targeting the plastids. The drugs are thought to inhibit protein synthesis, but researchers find no sign of inhibition in the usual places—the cytoplasm or the mitochondria. The plastid, therefore, may be the target, says Roos. To date, direct evidence that such drugs attack the plastid has not surfaced, he says, "but it sure smells like it. It's very close." If researchers have their way, whatever benefits the ancestral cell derived from its potential dinner will end up as its Achilles' heel.

–Gretchen Vogel