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Researchers discover potential new mechanisms of drug resistance in Toxoplasma

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Scientists have for years been puzzled by why drugs are sometimes effective in treating parasitic diseases, while other times they have little or no effect.

In research just published in the Journal of Experimental Medicine, a team of scientists, led by Boris Striepen at the University of Georgia, provides both physiological and genetic explanations for the disparities.

Striepen and his team study Apicomplexa, a large group of parasitic microorganisms that includes the causative agents for malaria, cryptosporidiosis and toxoplasmosis, three important infectious diseases worldwide. Most of these parasites have an apicoplast, a remnant chloroplast. Chloroplasts are the green cellular structures that plants and algae use to harvest the energy of sunlight. Striepen said the remnant apicoclast suggests that these dangerous parasites had a benign past as photosynthetic algae in the ocean.

“Today, the apicoplast makes an excellent drug target, because the parasites have it, but humans don’t,” said Striepen, who is a Georgia Research Alliance Distinguished Investigator and a professor in UGA’s cellular biology department. Researchers in his lab have been studying the apicoplast’s functions while trying to determine which are essential to parasite survival.

The study confirms that the ability of the apicoplast to produce certain lipids called isoprenoids is likely its most important function and a drug target in a broader group of pathogens than initially thought. It also points to potential mechanisms of future drug resistance in malaria, a mosquito-borne infectious disease that infects millions of people a year worldwide.

Striepen's team demonstrated that the critical difference in the effectiveness of some drugs acting on the apicoplast lies in their uptake (or not) by the parasite. The antibiotic fosmidomycin is effective against malaria, but surprisingly, fosmidomycin is not effective against most other apicomplexan parasites, including Toxoplasma.

By using Toxoplasma as a model, Stripen's team determined that the process poisoned by fosmidomycien, the synthesis of isoprenoids in the apicoplast, is critical even in parasites that are fosmidomycin-resistant. The research defined the molecular basis of resistance and susceptibility by experimenting with various host-parasite contributions using both Toxoplasma and malaria parasites. The scientists determined that the parasite plasma membrane is a critical barrier to drug uptake in some parasites.

"It's difficult to prove a negative like lack of drug uptake," said graduate student and author Sethu Nair. "However, we introduced a transporter by genetic engineering, and this turned drug-resistant parasites into drug-sensitive parasites." The researchers believe that the varied extent of metabolite exchange between host and parasite is a critical determinant—not only of the susceptibility of drugs—but also as a predictor of future drug resistance.

Provided by University of Georgia