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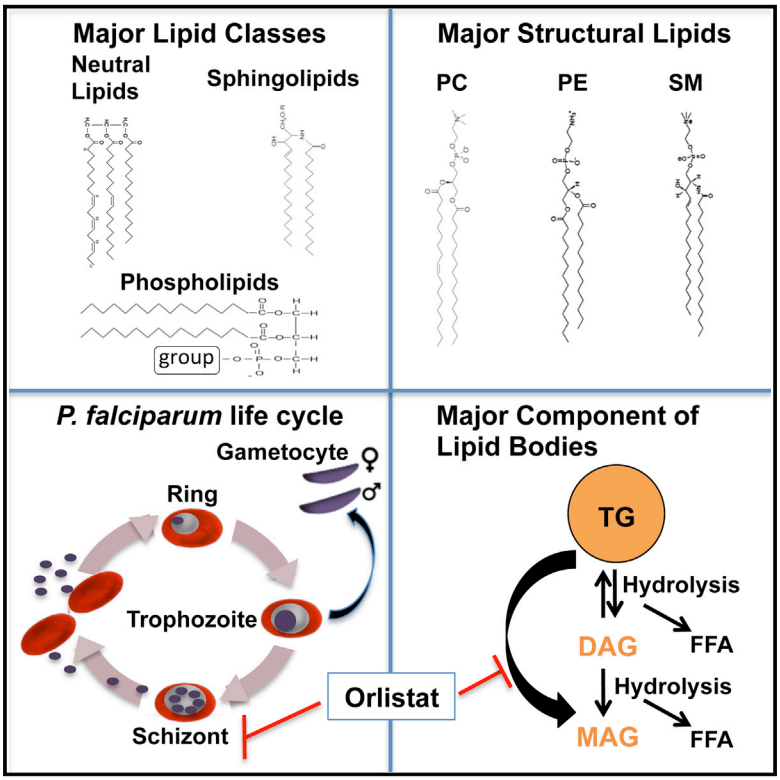
Profiling the Essential Nature of Lipid Metabolism in Asexual Blood and Gametocyte Stages of *Plasmodium falciparum*

Graphical Abstract



Highlights

- 300 lipids in *Plasmodium falciparum* asexual blood stages and gametocytes were profiled
- Identified lipid classes were synthesized de novo or scavenged from the host
- Triacylglycerols play a key role in asexual parasite maturation
- The identified lipid metabolic pathways are potential targets for future drug discovery

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In Brief

Plasmodium falciparum malaria parasites undergo rapid proliferation that is fueled by both de novo synthesis and the acquisition of lipids from the host cell. Gulati et al. provide a comprehensive lipid analysis of the pathogenic asexual blood stages and the transmissible gametocyte stages and identify potential targets for drug discovery.

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Profiling the Essential Nature of Lipid Metabolism in Asexual Blood and Gametocyte Stages of *Plasmodium falciparum*

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SUMMARY

During its life cycle, *Plasmodium falciparum* undergoes rapid proliferation fueled by de novo synthesis and acquisition of host cell lipids. Consistent with this essential role, *Plasmodium* lipid synthesis enzymes are emerging as potential drug targets. To explore their broader potential for therapeutic interventions, we assayed the global lipid landscape during *P. falciparum* sexual and asexual blood stage (ABS) development. Using liquid chromatography-mass spectrometry, we analyzed 304 lipids constituting 24 classes in ABS parasites, infected red blood cell (RBC)-derived microvesicles, gametocytes, and uninfected RBCs. Ten lipid classes were previously uncharacterized in *P. falciparum*, and 70%–75% of the lipid classes exhibited changes in abundance during ABS and gametocyte development. Utilizing compounds that target lipid metabolism, we affirmed the essentiality of major classes, including triacylglycerols. These studies highlight the interplay between host and parasite lipid metabolism and provide a comprehensive analysis of *P. falciparum* lipids with candidate pathways for drug discovery efforts.

INTRODUCTION

Symptomatic infection by the malaria parasite *Plasmodium* is caused by asexual blood stage (ABS) intra-erythrocytic parasites that undergo cycles of invasion, maturation, replication, and egress. Intra-erythrocytic forms can also enter gametocytogenesis, the sexual differentiation pathway (Nilsson et al., 2015). Gametocytes progress through five morphologically distinctive stages (I–V) over 10–14 days to become transmissible to *Anopheles* mosquito vectors, wherein they undergo fertilization and produce infectious sporozoites. Transcriptomic and proteomic studies have revealed marked differences between gametocytes and ABS parasites (Pelle et al., 2015; Silvestrini et al., 2010).

Throughout its life cycle *P. falciparum* orchestrates a vast array of lipid-dependent processes, including intracellular signaling, protein trafficking, membrane biogenesis, and hemoglobin degradation. Studies have shown that lipid synthesis, uptake, and transport are essential for *P. falciparum* ABS viability (Ben Mamoun et al., 2010). Fatty acids (FAs), the building blocks of lipids, are typically taken up from the human host by ABS parasites, in contrast to mosquito-resident stages that require de novo FA synthesis (van Schaijk et al., 2014). Potent antimalarial activity has been observed with compounds that target membrane or signaling lipids such as phosphatidylcholine (PC), phosphoethanolamine (PE), or phosphatidylinositol (PI) 4-phosphate (Bobenchik et al., 2013; González-Bulnes et al., 2011; McNamara et al., 2013).

To delineate the repertoire and dynamics of *P. falciparum* lipid metabolism, we undertook a comprehensive lipidomics analysis of ABS parasites, microvesicles derived from infected red blood cells (RBCs), gametocytes, and host RBCs. This study identifies potential vulnerabilities that can be leveraged to target malaria infection and transmission and provides a resource for further studies of plasmodial lipids and membrane trafficking.

RESULTS

Comparison of Lipids in *P. falciparum* ABS and Host RBCs

We measured the relative abundance of 304 lipid species in highly synchronized Dd2 parasites, harvested every 8 hr post-invasion (hpi) throughout the 48 hr intra-erythrocytic developmental cycle (IDC). Parasites were isolated following saponin treatment, which lyses RBCs but leaves parasites intact within their plasma membrane. Pelleted parasite samples were washed extensively to remove RBC cytosol and membrane. Lipids were extracted from parasite samples, or control uninfected RBCs, and subjected to liquid chromatography-mass spectrometry (LC-MS). Individual lipid species were assigned to three classes: phospholipids, sphingolipids, and glycerolipids (also referred to as neutral lipids).