Molecular Basis of Oxidative Stress Responses in Malaria Parasite Survival

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Oxidative stress is a central pressure shaping parasite survival during malaria infection. During the blood stage, *Plasmodium falciparum* is exposed to reactive oxygen species generated by host immune responses, febrile episodes, hemoglobin variants, and antimalarial drugs such as artemisinin. In malaria-endemic regions, hemoglobinopathies (e.g., sickle cell, thalassemia, HbE, HbC) are highly prevalent and confer strong protection against severe malaria. This protection is thought to arise partly from the pro-oxidative environment generated within hemoglobinopathic red blood cells. Also, oxidative stress is central to the mechanism of action of artemisinin drugs, the cornerstone of frontline antimalarial therapy. Thus, parasites in endemic regions experience overlapping oxidative pressures arising from both host genetics and antimalarial treatment. Despite this mechanistic and geographic overlap, how hemoglobinopathy-associated oxidative stress influences parasite adaptation and artemisinin efficacy remains poorly understood. To address this question, we used a physiologically relevant *in vitro* model of oxidized erythrocytes that mimics the redox environment of sickle red blood cells. Using this system, we observed that parasites grown under oxidative conditions display reduced sensitivity to the artemisinin derivative dihydroartemisinin, suggesting that prolonged exposure to oxidative microenvironments may predispose parasites to increased drug tolerance. To investigate the mechanisms underlying this phenomenon, we performed large-scale forward genetic screens using a *P. falciparum piggyBac* mutant library to identify genes associated with altered sensitivity to oxidative stress. Comparison with previous *piggyBac* screens for dihydroartemisinin exposure, heat shock, and growth in sickle-trait cells revealed overlapping genetic pathways linked to lipid metabolism, exported protein functions, and RNA metabolism. Together, these findings suggest that host-derived oxidative environments reshape parasite growth dynamics and modulate antimalarial drug responses.