Environmental and host determinants of Plasmodium falciparum sexual conversion

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Malaria transmission depends on the differentiation of Plasmodium falciparum asexual blood-stage parasites into transmissible sexual stages, the gametocytes. At each intraerythrocytic replication cycle, a small proportion of parasites undergoes sexual conversion (SC), a process initiated through epigenetic activation of the master regulator pfap2-g. Increasing evidence indicates that SC is dynamically regulated by environmental and host-derived signals, allowing parasites to balance replication and transmission investment. Recent studies have shown that parasite metabolic sensing pathways linked to choline and lysophosphatidylcholine metabolism modulate pfap2-g activation and SC rates, supporting the idea that P. falciparum adapts its reproductive strategy to changes in the host environment. In our work, we investigate how host and environmental factors shape parasite sexual commitment and transmission potential. We first assessed the impact of artemisinin (ART) exposure on SC both in vitro and in natural infections. Using gametocyte-reporter parasite lines, we showed that subcurative dihydro-ART exposure at the trophozoite stage induced a fourfold increase in SC rates in vitro. Consistently, malaria patients receiving ARTbased treatment displayed increased expression of early sexual-stage biomarkers following treatment. We also explored how host erythrocyte genetics influence sexual differentiation. Parasites infecting haemoglobin S and C erythrocytes showed significantly higher SC rates than parasites growing in HbAA erythrocytes. Using a novel SC assay, we are currently investigating how host immune and metabolic factors regulate parasite transmission investment. We show significantly higher SC in patients with severe malaria compared to uncomplicated and asymptomatic infections. Understanding the mechanisms regulating SC may open new avenues for transmission-blocking interventions.