A Plasmodium membrane receptor platform integrates cues for egress and invasion in blood forms and activation of transmission stages

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Critical events in the life cycle of malaria-causing parasites depend on cyclic guanosine monophosphate homeostasis by guanylyl cyclases (GCs) and phosphodiesterases, including merozoite egress or invasion of erythrocytes and gametocyte activation. These processes rely on a single GCalpha, but in the absence of known signaling receptors, how this pathway integrates distinct triggers is unknown. We show that temperature-dependent epistatic interactions between phosphodiesterases counterbalance GCalpha basal activity preventing gametocyte activation before mosquito blood feed. GCalpha interacts with two multipass membrane cofactors in schizonts and gametocytes: UGO (unique GC organizer) and SLF (signaling linking factor). While SLF regulates GCalpha basal activity, UGO is essential for GCalpha up-regulation in response to natural signals inducing merozoite egress and gametocyte activation. This work identifies a GC membrane receptor platform that senses signals triggering processes specific to an intracellular parasitic lifestyle, including host cell egress and invasion to ensure intraerythrocytic amplification and transmission to mosquitoes.
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