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PARASITE DEVELOPMENT

Master regulator of sex

> AP2-G triggers sexual development by activating the transcription of early gametocyte genes

Differentiation of *Plasmodium* parasites into gametocytes is essential for their transmission from the human host to the mosquito vector; however, the molecular mechanisms that trigger commitment to sexual development have been unknown. Now, two studies identify the highly conserved transcription factor AP2-G as a master regulator of gametocytogenesis.

Plasmodium spp. have a complex life cycle that involves several distinct developmental stages. In red blood cells, asexual parasites stochastically produce non-replicative male and female gametocytes, which are taken up by female anopheline mosquitoes during a blood meal. As gametocytes are required to infect mosquitoes, this developmental transition is crucial for the parasite to complete its life cycle and transmit to the next human host.

Members of the apicomplexan AP2 (ApiAP2) family of DNA-binding proteins are associated with developmental transitions in *Plasmodium* parasites. Interestingly, Kafsack *et al.* found that *pfap2-g* (which encodes an ApiAP2 protein) transcript levels and gametocyte formation were positively correlated in *Plasmodium falciparum*, and deletion of *pfap2-g* abolished the production of gametocytes. In the second study, Sinha *et al.* found that the rodent parasite *Plasmodium berghei* also failed to produce gametocytes, owing to inactivating mutations in the same gene (known as *pbap2-g*). Replacement of the mutated gene with a wild-type copy of *pbap2-g* restored gametocyte production and enabled transmission through mosquitoes. Together, these findings confirm that AP2-G is essential for gametocytogenesis in both *P. falciparum* and *P. berghei*.

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Consistent with its putative role as a transcriptional regulator, Kafsack *et al.*, showed that PfAP2-G localizes to the parasite nucleus, and global transcriptional profiling during the intra-erythrocytic cycle revealed that — compared with the ancestral parasite — levels of early gametocyte markers were reduced in cells that were infected with the *pfap2-g*-null mutant. Similarly, gametocyte-specific genes were among the most downregulated genes in the *pbap2-g*-null mutant. Thus, these data indicate that AP2-G triggers sexual development by activating the transcription of early gametocyte genes.

Sinha *et al.* found that PbAP2-G recognizes the DNA motif that was previously identified for PfAP2-G, and both studies showed that PbAP2-G and PfAP2-G interact with the promoters of gametocyte-specific genes in a motif-dependent manner. Importantly, the motif that is recognized by PbAP2-G is present upstream of its own coding gene and deletion of the motif resulted in loss of gametocyte formation, which suggests that commitment to sexual development requires a positive-feedback loop that is driven by AP2-G.

Previous studies had shown that the *pfap2-g* locus is subject to silencing by heterochromatin modification, which led Kafsack *et al.* to suggest that the inactivation of epigenetic silencing in a subset of asexual parasites might provide an elegant mechanism for the stochastic production of gametocytes. Indeed, immunofluorescence experiments showed that only a small fraction of asexual parasites produce PfAP2-G, and its production is highly predictive of subsequent gametocyte formation. Finally, Sinha *et al.* also identified a second member of the ApiAP2 family (known as PbAP2-G2) that also seems to be involved in modulating gametocytogenesis, which suggests that a cascade of transcriptional regulators is responsible for sexual development.

Collectively, these studies provide the first mechanistic insights into the sexual development of malaria parasites and define AP2-G as a key developmental switch that triggers gametocytogenesis.

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ORIGINAL RESEARCH PAPERS

Kafsack, B. F. C. *et al.* A transcriptional switch underlies commitment to sexual development in malaria parasites. *Nature* http://dx.doi.org/10.1038/nature12920 (2014) | Sinha, A. *et al.* A cascade of DNA-binding proteins for sexual commitment and development in *Plasmodium*. *Nature* http://dx.doi.org/10.1038/nature12970 (2014)