UC Riverside

UC Riverside Previously Published Works

Title

Sex in Plasmodium falciparum: Silence Play between GDV1 and HP1

Permalink

https://escholarship.org/uc/item/5kt8k7nt

Journal

Trends in Parasitology, 34(6)

ISSN

1471-4922

Authors

Rea, Edward
Le Roch, Karine G
Tewari, Rita

Publication Date

2018-06-01

DOI

10.1016/j.pt.2018.04.006

Peer reviewed

eScholarship.org Powered by the California Digital Library
University of California

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Trends Parasitol. Author manuscript; available in PMC 2018 September 04.

Published in final edited form as:

Trends Parasitol. 2018 June ; 34(6): 450–452. doi:10.1016/j.pt.2018.04.006.

Sex in *Plasmodium falciparum:* Silence Play between GDV1 and HP1

Edward Rea[1], **Karine G. Le Roch**[2], and **Rita Tewari**[1,*]

[1]School of Life Sciences, Queens Medical Centre, University of Nottingham, Nottingham, UK

[2]Department of Molecular, Cell and Systems Biology, University of California Riverside, Riverside, CA 92521, USA

Abstract

Understanding how malaria parasites commit to sexual development is key to the development of transmission-blocking strategies. Recent work by Filarsky and colleagues extends our understanding of the molecular mechanisms driving this process by characterizing an early factor in gametocytogenesis, and showing how this fits neatly into our current knowledge of sexual commitment.

Malaria, caused by apicomplexan parasites of the *Plasmodium* genus, is a vector-borne disease that affects 216 million people and leads to approximately 445 000 deaths annually, as reported by WHO in 2017. Whilst the rapid asexual proliferation of malaria parasites within the erythrocytes of vertebrate hosts leads to the pathology and clinical symptoms of the disease, it is the sexual stages that are responsible for the transmission between vertebrate host and mosquito vector and the spread of the parasite. Hence, understanding the molecular mechanisms controlling gametocytogenesis, the formation and maturation of male and female gametocytes in the vertebrate bloodstream, will be essential if we want to develop novel intervention strategies to eradicate the disease.

Until recently little was known of the molecules that trigger or regulate sexual commitment in the parasite life cycle. In 2012, Eksi *et al*. showed that gametocyte development 1 (GDV1), a perinuclear *Plasmodium falciparum* protein, plays a role in gametocytogenesis [1]. GDV1 overexpression enhanced gametocyte formation, whereas *gdv1*-deleted parasite lines were gametocyte deficient. Further seminal papers in both *P. falciparum* and *Plasmodium berghei* identified the master regulator of gametocytogenesis: AP2-G, a member of the apiAP2 transcription factor family that was found to control the switch between asexual and sexual development [2,3]. Additional studies identified heterochromatin protein 1 (HP1) and histone deacetylase 2 (HDA2) as epigenetic regulators of sexual commitment that control AP2-G expression, strongly suggesting that gametocytogenesis is under epigenetic control [4,5]. Despite these discoveries, the function of GDV1, and how it works in concert with HP1, remained unclear.

*Correspondence: rita.tewari@nottingham.ac.uk (R. Tewari).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

In a new study in *Science*, Filarsky *et al.*[6] dissected the function of GDV1 in *P. falciparum* using elegant and complementary methodologies, including conditional CRISPR-Cas9 gene editing and ChIP-seq experiments. The authors showed that GDV1 evicts HP1 from H3K9me3 sites in the parasite genome, thereby depressing AP2-G expression and inducing gametocytogenesis. Intriguingly, they provide evidence that GDV1 expression is controlled by a GDV1 antisense RNA, and that GDV1 protein acts by antagonising epigenetic silencing of HP1 (Figure 1).

Filarsky *et al.* [6] show that GDV1 binds HP1, both *in vivo* and *in vitro*, through reciprocal immunoprecipitation and cellular colocalization studies, suggesting that they form a regulatory complex that functions to activate gametocytogenesis. Using an FKBP/Shield-1 conditional expression system, the authors revealed that GDV1 expression titrates sexual commitment and gametocytogenesis. These data, combined with those of earlier GDV1 knockdown experiments showing abrogation of sexual commitment, provide evidence that GDV1 is both necessary and sufficient to promote gametocytogenesis in *Plasmodium*. Furthermore, by using choline as an inhibitor of sexual commitment, the authors confirm that GDV1 operates in a dose-dependent manner, and show that environmental factors can trigger gametocytogenesis. These data further substantiate the earlier finding by Eksi *et al.* [1] that overexpression of *Pfgdv1* modulates gametocytogenesis in a dynamic fashion.

Additional microarray analysis [6] confirmed that, following ectopic expression of GDV1, AP2-G expression is immediately and significantly upregulated, and that other markers of gametocytogenesis were also differentially regulated. In the F12 parasite line, which has a loss-of-function mutation in *ap2g*, no downstream effectors were affected (even though AP2-G protein is still upregulated). In addition to AP2-G, eight other genes, not under the control of AP2-G, were upregulated in response to GDV1 expression in the F12 line, all of which are known to be marked by HP1 [6]. This result, combined with the upregulation of AP2-G, suggests that GDV1 activates sexual commitment by antagonizing HP1-dependent silencing of the AP2-G gene.

The results of ChIP-seq experiments indicated that GDV1 and HP1 occupancy of heterochromatin is correlated, and this occupancy begins to decrease 6 h after induction of GDV1 expression. A simultaneous decrease in HP1 occupancy was observed, although this was not homogeneous: some loci showed a marginal decrease; however, gametocytogenesis-specific loci demonstrate a more substantive, up to 40%, reduction in HP1 occupancy. Although the mechanism determining this specificity is not currently obvious, it is abundantly clear that expression of GDV1 antagonizes HP1-dependent silencing of early gametocytogenesis genes.

How do parasites limit GDV1 expression in the asexual stage to prevent uncontrolled commitment to the sexual pathway? A recent study [7] identified a number of noncoding RNAs present in the *Plasmodium* transcriptome, including *asgdv1*, a multiexon antisense transcript from the GDV1 locus. When Filarsky *et al.* [6] generated an *asgdv1* knockout in the F12 line, they observed almost identical changes in gene expression as those resulting from ectopic *gdv1* expression, confirming that this antisense transcript is a negative regulator

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

of GDV1 expression. How this antisense transcript transduces the environmental signals that promote sexual commitment remains unanswered (Figure 1).

Interestingly, there is no syntenic GDV1 locus in rodent malaria genomes, including *P. berghei* [1], suggesting that this mechanism is not conserved in all species. Alternatively, another gene with similar function may fulfil this role. In either case this observation opens another avenue of research to improve our understanding of how environmental factors may influence gametocytogenesis.

Fraschka *et al.* [8] have demonstrated that heterochromatin features marked by HP1 are conserved in the differentiating gametocytes of several *Plasmodium* species, and showed that epigenomic patterns are linked to various stages of parasite development. A similar analysis by Bunnik *et al.* [9] identified both specific changes in heterochromatin throughout the parasite life cycle, as well as changes in 3D genome structure in *P. falciparum* and *Plasmodium vivax*. These features seem to be essential and connected with transcription of several gene families, including those involved in pathogenesis, liver-cell invasion, erythrocyte remodeling, and regulation of sexual differentiation.

Despite all the studies described above, it remains to be seen whether commitment to gametocytogenesis can be controlled by molecules at the interface of host–parasite genetics or by various environmental conditions in the host red blood cell milieu. Recent studies on lysophosphatidylcholine and sexual differentiation are an initial step in this direction [10].

Acknowledgments

ER and RT were funded by MRC Investigator Award and MRC and BBSRC project grants (G0900109, G0900278, MR/K011782/1, and BB/N017609/1). KLR is supported by the National Institutes of Health (R01 AI06775–01) and the University of California, Riverside (NIFA-Hatch-225935). We would like to thank David Guttery and Tony Holder for their assistance in reading this manuscript.

References

1. Eksi S et al. (2012) *Plasmodium falciparum* gametocyte development 1 (Pfgdv1) and gametocytogenesis early gene identification and commitment to sexual development. PLoS Pathog. 8, e1002964 [PubMed: 23093935]
2. Kafsack BF et al. (2014) A transcriptional switch underlies commitment to sexual development in malaria parasites. Nature 507, 248–252 [PubMed: 24572369]
3. Sinha A et al. (2014) A cascade of DNA-binding proteins for sexual commitment and development in *Plasmodium*. Nature 507, 253–257 [PubMed: 24572359]
4. Brancucci NMB et al. (2014) Heterochromatin protein 1 secures survival and transmission of malaria parasites. Cell Host Microbe 16, 165–176 [PubMed: 25121746]
5. Coleman BI et al. (2014) A *Plasmodium falciparum* his-tone deacetylase regulates antigenic variation and game-tocyte conversion. Cell Host Microbe 16, 177–186 [PubMed: 25121747]
6. Filarsky M et al. (2018) GDV1 induces sexual commitment of malaria parasites by antagonizing HP1-dependent gene silencing. Science 359, 1259–1263 [PubMed: 29590075]
7. Broadbent KM et al. (2015) Strand-specific RNA sequencing in *Plasmodium falciparum* malaria identifies developmentally regulated long non-coding RNA and circular RNA. BMC Genomics 16, 454 [PubMed: 26070627]
8. Fraschka SA et al. (2018) Comparative heterochromatin profiling reveals conserved and unique epigenome signatures linked to adaptation and development of malaria parasites. Cell Host Microbe 23, 407–420 e8 [PubMed: 29503181]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

9. Bunnik EM et al. (2018) Changes in genome organization of parasite-specific gene families during the *Plasmodium* transmission stages. bioRxiv 10.1101/242123 Posted online January 3, 2018

10. Brancucci NMB et al. (2017) Lysophosphatidylcholine regulates sexual stage differentiation in the human malaria parasite *Plasmodium falciparum*. Cell 171, 1532–1544.e15 [PubMed: 29129376]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

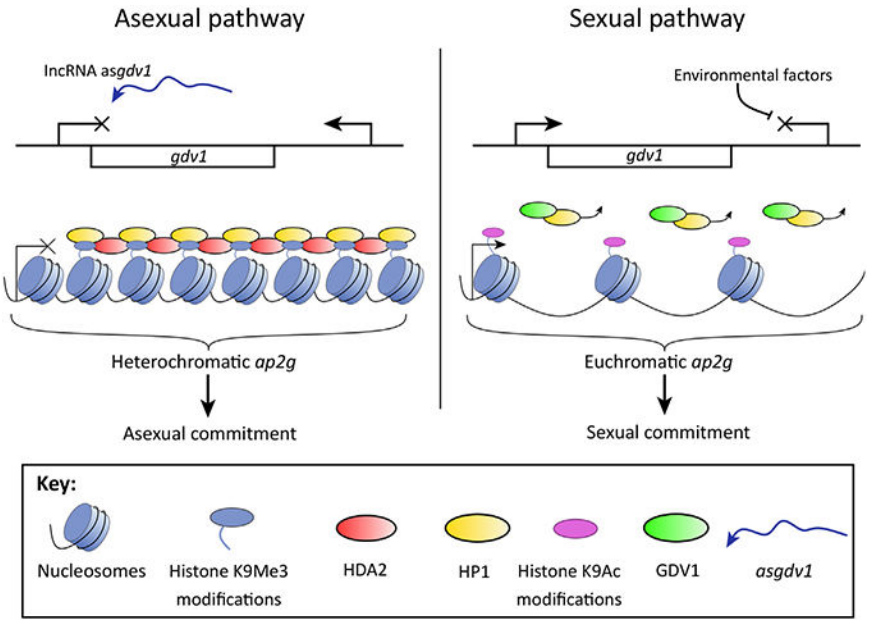

Figure 1. Regulation of Sexual Commitment in Human Malaria.

In parasites undergoing asexual development, the long noncoding *gdv1* antisense RNA *asgdv1* acts as a negative regulator of GDV1 expression. The lack of GDV1 allows HP1 and HDA2 to maintain a repressed chromatin state through H3K9 methylation and deacetylation at many loci, including that of AP2G. This prevents expression of AP2G, allowing continued asexual development. In a small subset of parasites, *asgdv1* is somehow inactivated, either stochastically or following the transduction of various environmental signals, allowing expression of GDV1 and therefore eviction of HP1 from specific loci, including AP2G. Without HP1 to maintain H3K9 methylation, the chromatin returns to a euchromatic state, leading to the expression of AP2G and a resultant commitment to sexual development.