

Hepatocystis

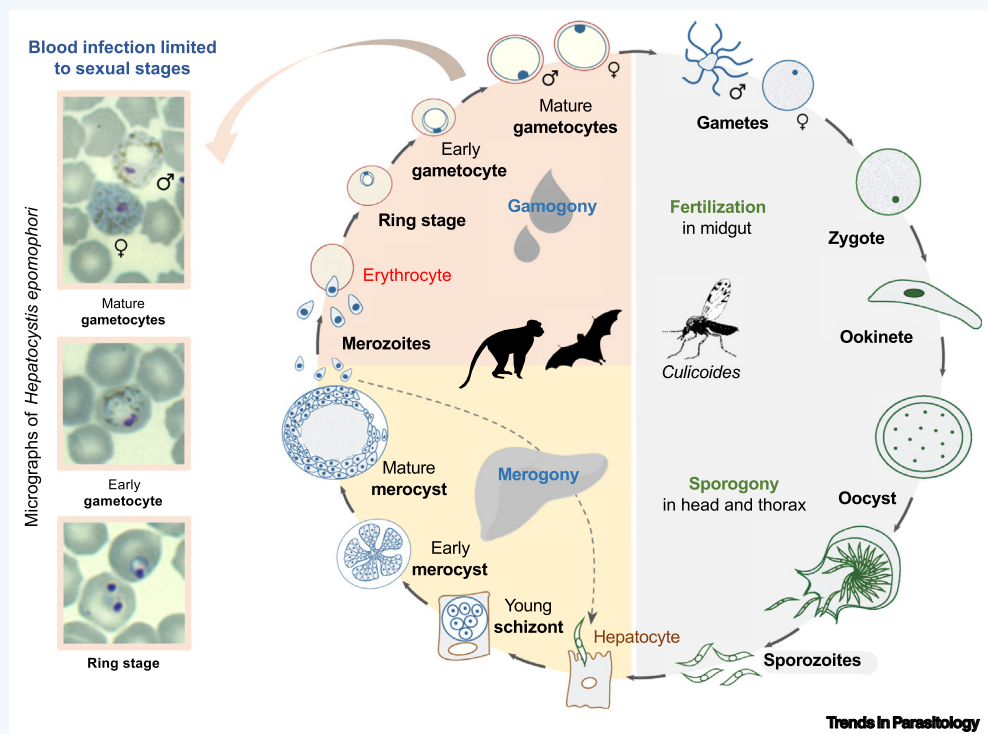
Imran Ejotre,^{1,2} DeeAnn M. Reeder,³ Kai Matuschewski,¹ and Juliane Schaer^{1,4,*}

¹Department of Molecular Parasitology, Humboldt University, Berlin, Germany

²Muni University, Arua, Uganda

³Department of Biology, Bucknell University, Lewisburg, PA, USA

⁴Department of Biological Sciences, Macquarie University, North Ryde, NSW, Australia



KEY FACTS:

Hepatocystis is phylogenetically nested within (paraphyletic) mammalian *Plasmodium* clades.

Vector *Culicoides adersi* has been confirmed for primate-infecting species *Hepatocystis kochi*; experimental infection of *Culicoides nubeculosus* was reported with *Hepatocystis* of Australian bats.

Liver merocysts differ in size and structure among *Hepatocystis* species and mature within 2 months.

Merozoites are discharged into sinusoids, while a small proportion likely reinvades hepatocytes for a secondary merogony.

Ookinetes penetrate the midgut and transform to oocysts in the thorax and head of *Culicoides*. Sporozoites accumulate in the hemocoel.

Three genomes in the nucleus (19.95 Mb encoding 5341 genes), mitochondrion (6.6 kb), and apicoplast (27 kb).

Hepatocystis parasites are the closest relatives of *Plasmodium* species of mammals. They infect monkeys, bats, squirrels, and ungulates in Africa, Asia, and Australia. A prevalence of up to 100% has been documented in fruit bats and monkeys. Twenty-five morphospecies have been described, and cross-species transmission, divergent *Hepatocystis* lineages, and species complexes are reported in primate and bat hosts. Biting midges (*Culicoides*) are the only known vectors. In the vertebrate, merogony occurs exclusively in the liver, resulting in formation of macroscopic merocysts. Merozoites invade erythrocytes and transform directly into sexual gametocytes, thereby omitting asexual replication and associated health conditions. Gametocytes can persist for several weeks and fertilize after a bloodmeal in the *Culicoides* midgut. The *Hepatocystis* genome features unique gene families, a low number of *Plasmodium* interspersed repeat (*pir*) genes, and an absence of the reticulocyte-binding protein family.

Adaptations to the *Culicoides* vector are recognizable in the genome/transcriptome.

DISEASE FACTS:

Infections rarely cause disease, but anemia has been documented.

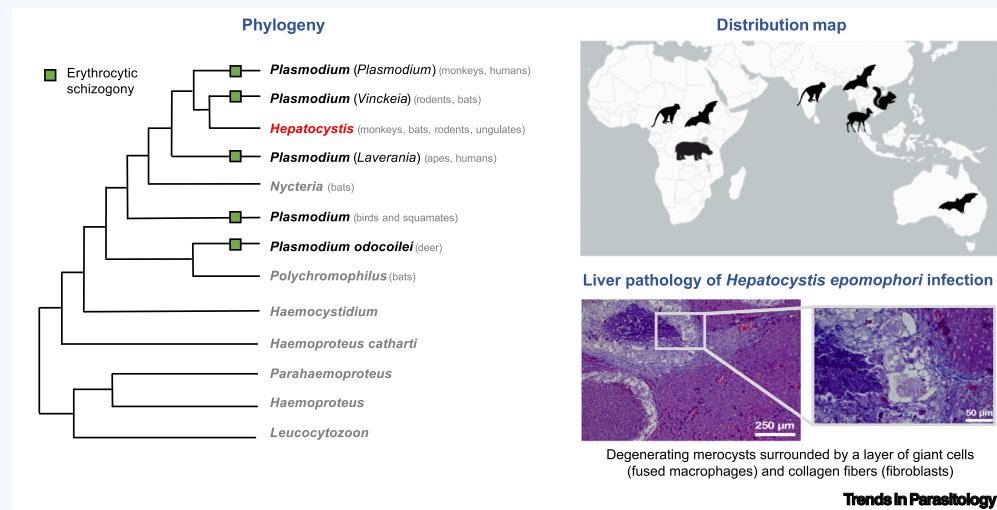
Cyclical fevers do not occur as blood stages are limited to gametocytes that do not provoke cytokine responses.

Liver merocyst maturation leads to cellular infiltration and inflammation, followed by granuloma formation.

Hemozoin pigment is deposited in liver and spleen.

Identification of apparent selection of resistance alleles in the promoter region of the Duffy blood group antigen/chemokine receptor DARC in *H. kochi*-infected monkeys.

*Correspondence: schaerju@hu-berlin.de (J. Schaer).



Acknowledgments

I.E. is supported by a PhD scholarship of the German Academic Exchange Service (DAAD). J.S. is funded by an individual research grant from the German Research Foundation (DFG; project number 437846632). We acknowledge Dr Werner Stenzel (Charité, Universitätsmedizin Berlin) for his contribution to the liver histology.

Resources

www.ebi.ac.uk/ena

<https://github.com/adamjamesreid/hepatocystis-genome>

Literature

1. Laveran, A. (1899) *Les hématozoaires endoglobulaires (haemocytozoa)*, Societe Paris, Volume jubilaire, pp. 124–133
2. Garnham, P.C.C. *et al.* (1961) The vector of *Hepatocystis* (= *Plasmodium*) *kochi*; the successful conclusion of observations in many parts of tropical Africa. *Trans. R. Soc. Trop. Med. Hyg.* 55, 497–502
3. Garnham, P.C.C. (1966) *Malaria Parasites and Other Haemosporidia*, Blackwell Scientific Publications
4. Tung, J. *et al.* (2009) Evolution of a malaria resistance gene in wild primates. *Nature* 460, 388–391
5. Thurber, M.I. *et al.* (2013) Co-infection and cross-species transmission of divergent *Hepatocystis* lineages in a wild African primate community. *Int. J. Parasitol.* 43, 613–619
6. Schaer, J. *et al.* (2017) Epauletted fruit bats display exceptionally high infections with a *Hepatocystis* species complex in South Sudan. *Sci. Rep.* 7, 6928
7. Schaer, J. *et al.* (2018) Phylogeny of *Hepatocystis* parasites of Australian flying foxes reveals distinct parasite clade. *Int. J. Parasitol. Parasit. Wildl.* 7, 207–212
8. Boundenga, L. *et al.* (2018) Extensive diversity of malaria parasites circulating in Central African bats and monkeys. *Ecol. Evol.* 8, 10578–10586
9. Galen, S. *et al.* (2018) The polyphyly of *Plasmodium*: Comprehensive phylogenetic analyses of the malaria parasites (order Haemosporida) reveal widespread taxonomic conflict. *R. Soc. Open Sci.* 5, 171780
10. Aunin, E. *et al.* (2020) Genomic and transcriptomic evidence for descent from *Plasmodium* and loss of blood schizogony in *Hepatocystis* parasites from naturally infected red colobus monkeys. *PLoS Pathog.* 16, e1008717

TAXONOMY AND CLASSIFICATION:

PHYLUM: Apicomplexa

CLASS: Aconoidasida

ORDER: Haemosporida

FAMILY: Plasmodiidae/Haemoproteidae

GENUS: *Hepatocystis*