L-lactate as a regulator of gametocytogenesis in *Plasmodium falciparum*

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Epigenetic processes play important roles in the biology of the malaria parasite *Plasmodium falciparum*. We recently showed for the first time that *Plasmodium* histones are not only acetylated and methylated, but also lactylated[1]. This new epigenetic mark could serve as an important axis of host-parasite signalling because severe malaria is often characterised by hyperlactataemia, causing potentially-fatal respiratory distress syndrome. For the malaria parasite, it could be advantageous to sense this state of pathology and respond by modulating virulence.

Virulence processes under epigenetic control in *P. falciparum* include antigenic variation, invasion-switching and conversion to sexual gametocytes. One publication has already reported that gametocytogenesis can be boosted by adding lactic acid to cultured parasites[2]. Here, we pursued this finding, using defined, physiological concentrations of the biologically-relevant metabolite, L-lactate. Hyperlactataemia in malaria patients is designated at ≥ 5 mM blood lactate. We confirmed that this level of L-lactate boosted conversion to gametocytes in culture. We also showed that it rapidly induced histone lactylation. The mechanism by which gametocytogenesis is induced probably involves increased expression of the 'master regulator' genes *GDV-1* and *AP2-G*, and hence increased developmental switching. Expression of these genes increased within one cell cycle of exposure to 5mM L-lactate (and within just 12 h of exposure to 25 mM L-lactate). In the same parasites, the chromatin in the *AP2-G* gene was inducibly lactylated. Thus L-lactate joins S-adenosylmethionine as a metabolite that can epigenetically regulate sexual conversion in *P. falciparum.*

1. Jabre, I., Andoh, N.E., *et al.* Histone lactylation: a new epigenetic mark in the malaria parasite *Plasmodium*. *Plos Genetics* 2025; doi.org/10.1371/journal.pgen.1011991.

2. West R, Sullivan DJ. Lactic acid supplementation increases quantity and quality of gametocytes in Plasmodium falciparum culture. *Infection and immunity*. 2020;15(89(1)):e00635-20.