Instituto de Medicina Molecular João Lobo Antunes

Master Project Proposal

Title: Investigating the role of transcription factors in Plasmodium nutrient sensing

Synopsis:

Malaria remains a global health problem with over 600,000 malaria deaths in 2021, mostly in children under 5 years[1]. The blood-stage infection, responsible for the onset of disease, is initiated when *Plasmodium* merozoites derived from infected hepatocytes enter the blood stream and infect red blood cells. As a rapidly multiplying obligate intracellular parasite, *Plasmodium* has high nutritional needs and depends on the nutrients provided by its host.

We have shown that the parasites can sense, adapt and respond to alterations in calorie intake by the host. Mice fed on a calorie restricted diet (30-40% reduction in calorie intake) and infected with the rodent malaria parasite, *P. berghei*, were protected from severe malaria and had reduced replication compared to those fed *ad libitum*[2]. Our data revealed that a *Plasmodium* kinase, KIN, acts as a critical regulator of the parasite energy-sensing pathway. Yet, we are only now beginning to understand exactly how malaria parasites sense and adapt to nutrient availability. In many organisms, master nutrient sensors regulate transcription factors, which in turn modulate the expression of genes in response to nutrient availability. Our preliminary data has identified 11 members of the multigene family of apicomplexan apetala2 (AP2) transcription factors, to be involved in sensing calorie restriction in *Plasmodium*.

In this project the student will (i) determine the pathways of transcriptional response to nutrient sensing using genetic screens, ChIP-seq and calorie restriction mimetics (e.g. salicylate) and (ii) determine the impact of transcriptional regulation during calorie restriction on virulence by assessing parasite sequestration and biomass in a rodent malaria model. The findings generated by this proposal will unlock a new area of the biology of the malaria parasite and also provide new opportunities to design intervention strategies against malaria.

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Bibliography

1. Geneva: World Health Organization. *World malaria report 2022*. (2022).
2. Mancio-Silva, L. *et al.* Nutrient sensing modulates malaria parasite virulence. *Nature* **547**, 213–216 (2017).