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Targeting Plasmodium oocyst rupture for antimalarial strategies development

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Abstract

Malaria caused by *Plasmodium* parasites is a complex and tremendous disease, with about 405000 deaths per year in the world (OMS). An infected *Anopheles* mosquito, able to transmit malaria parasites to humans, contains several oocysts in its midgut. Oocysts are formed after the passage of the motile zygote, the so called ookinete, through the midgut epithelium. The ookinete rounds up to form the oocyst beneath the epithelial cells and surrounded by the basal lamina. Oocysts remain attached to the mosquito gut basal lamina during their development, a process taking about two weeks, and which leads to the formation of sporozoites, the infectious forms of the malaria parasite able to be transmitted to humans. Despite the oocyst represents the longest stage of the parasite life cycle it is poorly understood due to the difficulties to manipulate infected midguts.

Two proteins containing a histone fold domain (HFD), named ORPs (Oocyst Rupture Proteins), play a fundamental role in the sporozoite release through the HFD interaction, since deletion of either ORP1 or ORP2 HFD resulted in a block of oocyst rupture.

Sequence analysis indicated that the ORP1 and ORP2 HFDs are homologous to those found in the transcription factor NF-YB and C, respectively. From the structural viewpoint, NF-Y is composed of three subunits: NF-YA, NF-YB and NF-YC. Heterodimerization of NF-YB and NF-YC results in the formation of a surface for the association of the third subunit, NF-YA, allowing the resulting trimer to bind DNA with high affinity for the CCAAT box in promoters.

We identified a third protein, with domains similar to the NF-YA, named ORP3. KO parasites formed normal oocysts which failed to rupture, suggesting that the three ORPs may act as a trimer as well. Live oocysts imaging shows a partial co-localization of these proteins at the oocyst wall. The application of techniques such as EM and Mass Spectrometry is limited due to the mosquito tissue contamination. We recently developed a method for oocyst purification from the mosquito midgut cells which will implement the study of protein interactions occurring at this stage. Structural biology and molecular methods applied to the study of ORP interactions, or their specific domains, could lead to new possible target identification for anti-malarial strategies development to stop malaria transmission to the vertebrate host.