

# Deciphering mitochondrial complex III in *Plasmodium falciparum*: the role of PfC3AP1

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The mitochondrial electron transport chain (mETC) is essential for *Plasmodium falciparum*, supporting both energy production and *de novo* pyrimidine biosynthesis. Complex III (cytochrome *bc*<sub>1</sub>, CIII) is central to this pathway and a validated antimalarial target, as exemplified by the clinical use of atovaquone. Previous complexome studies by our group and others have identified divergent components of apicomplexan CIII (Maclean et al., PLoS Pathog., 2021; Evers et al., Nat. Commun., 2021). Some of these parasite-specific subunits have been characterised, highlighting differences from the human counterpart and offering opportunities for selective therapeutic intervention (MacLean et al., PLoS Pathog., 2021; Sheokand et al., Int. J. Mol. Sci., 2024; MacLean et al., Nat. Struct. Mol. Biol., 2025).

Here, we characterise PfC3AP1, a mitochondrially localised, apicomplexan-specific protein, as a critical component of PfCIII. Using the DiCre inducible knockout system, we show that PfC3AP1 is essential for asexual blood-stage growth, with its loss arresting trophozoite development, thereby preventing schizont formation. Importantly, addition of the electron acceptor decylubiquinone mitigates this growth defect, suggesting a role for PfC3AP1 in mETC function, potentially in complex assembly or stability. Interestingly, PfC3AP1-deficient parasites can still initiate gametocytogenesis, indicating stage-specific metabolic requirements.

Together, these findings establish PfC3AP1 as an essential, parasite-specific PfCIII subunit, providing mechanistic insights into apicomplexan mitochondrial biology and identifying a promising target for selective antimalarial therapy.

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