Characterizing the AP2-I/BDP1 complex as an antimalarial drug target

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Abstract

Invasion of red blood cells by Plasmodium falciparum parasites is essential for survival and proliferation and therefore constitutes an opportunity for therapeutic targeting. Expression of invasion genes are known to be under the control of both the PfAP2-I transcription factor and the bromodomain-containing protein PfBDP1 (1). To better understand the regulation of invasion, we have characterized the AP2-I/BDP1 complex .

Using co-expression and co-purification experiments, we found that PfAP2-I and PfBDP1 directly interact to form a stable complex. Both PfAP2-I and PfBDP1 contain large, disordered regions that impair further in vitro characterization of the native protein complex. Therefore, we produced targeted protein fragments to identify the minimal stable complex that could be used for structural characterization and to search for inhibitors of PfAP2-I:PfBDP1 complex formation.

PfAP2-I belongs to the apicomplexan AP2 (ApiAP2) subfamily of transcription factors that, in addition to containing an AP2/ERF DNA binding domain, also contain a unique Apicomplexan domain of unknown function called the AP2-Coincident Domain found mainly at the C-terminus (ACDC). Interestingly, AP2-I is the only ApiAP2 protein that contains an N-terminal ACDC domain. We have determined the crystal structure of this atypical N-terminal ACDC domain from both PfAP2-I and PvAP2-I and compared it to a canonical C-terminal ACDC domain of PfAP2-O5. These results revealed that both ACDC domains adopt a similar four-helix bundle fold that lacks similarity to other known 3D structures, suggesting that the ACDC domain, which is observed in all apicomplexan parasites, is a unique target for future antimalarial drug development. To test this, we performed a virtual screen of the Tres Cantos Anti-Malarial Set by docking calculations against our crystal structures and identified a potential ligand of ACDC domains from any apicomplexan species.

(1) Santos et al. Red Blood Cell Invasion by the Malaria Parasite Is Coordinated by the PfAP2-I Transcription Factor. (2017)