

# Molecular Basis of Acetylated Lysine Recognition by the *Plasmodium falciparum* Bromodomain Protein 1

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*Plasmodium falciparum* is a unicellular protozoan parasite that is commonly known to cause malaria in humans. The symptoms of malaria associated with repeated rounds of parasite replication, egress, and invasion into the red blood cells. During the red blood cell stage of malaria infection, PfBDP1 is shown to bind at the transcriptional start sites of invasion-related genes and regulates their expression. A recent spike in malaria infections may be attributed to drug-resistance in *P. falciparum*, thus we need a better understanding of the parasite's life cycle to produce more effective antimalarial drugs. The *P. falciparum* genome encodes for ten bromodomain-containing proteins. Previously, the bromodomain of PfBDP1 was shown to preferentially bind acetylated lysine marks on histones, effectively tethering the PfBDP1 transcriptional activator complex to modified nucleosomes within specific chromatin regions. However, the molecular mechanisms driving chromatin binding and recognition by PfBDP1 are not well understood. PfBDP1 contains a unique combination of seven ankyrin repeats (Ank) domain followed by a bromodomain (BRD). Bromodomains are evolutionary conserved protein-protein interaction modules (110 amino acids long) that recognize acetylated lysine (Kac) on histones and other proteins. We hypothesized that the bromodomain would modulate the interaction of PfBDP1 with a subset of acetylated histone modifications. We used a structure-function approach including X-ray crystallography, Nuclear Magnetic Resonance (NMR), and Isothermal Titration Calorimetry (ITC) to characterize the binding of PfBDP1 with specifically modified histone ligands. The crystal structure of PfBDP1-BRD at 2.0 Å shows that it has a conserved bromodomain fold, and an acetylated lysine binding pocket comprised of four alpha helices. As previously reported, PfBDP1 has been shown to interact with acetylated histone H3, but our *in vitro* binding experiments revealed that PfBDP1-BRD preferentially binds to tetra-acetylated histone H4. Our data indicate that PfBDP1 has a unique histone ligand binding mechanism that might be leveraged for the design novel therapeutic treatments, and suggest that PfBDP1 may have additional, yet unidentified roles in the *P. falciparum* life cycle.