Title:

Malaria Heat Shock Protein 101 (HSP101) is a Substrate of Plasmodium falciparum Signal Peptide Peptidase; Identification of a Novel Therapeutic Target

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Abstract:

Previously we described the identification of a Plasmodium falciparum signal peptide peptidase (PfSPP), thought to localize to the micronemes and apical regions, where it plays a functional role at the blood stage of malaria infection. This single gene encoded enzyme, with no other paralogs, is conserved in other apicomplexan parasites, and expressed during the merozoite, gametocyte, and sporozoite stages of the malaria parasite life cycle. Our previous studies demonstrated the pharmacological inhibitors of mammalian SPP prevent malaria parasite growth at the late-ring/early trophozoite stage of intraerythrocytic development. Eukaryotic SPPs are generally expressed in the endoplasmic reticulum (ER), and play an important role in development. Consistent with its role in development, PfSPP functions at the ER in Plasmodium falciparum where it cleaves membrane-bound signal peptides, generated following the activity of signal peptidase. We co-localized PfSPP to the ER with a known ER-marker using immunofluorescence microscopy, and confirmed its ER localization by immunogold electron microscopy. An antibody raised against the C-terminus of PfSPP enabled its isolation from parasite lysate, and demonstrated its existence as both a monomer and dimer. We performed a bioinformatics screen and identified several candidate PfSPP substrates in the parasite genome. Using an established transfection-based luminescence assay, we demonstrate that malaria heat shock protein 101 (HSP101) functions as a substrate of PfSPP. This finding reveals the first known substrate of PfSPP, and may provide a novel pharmacological target for use in a multi-targeted antimalarial therapy.