Targeting Protein Prenylation for Malaria Therapeutics: A Piggyback Approach

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Antimalarial drugs are the only means for the clinical treatment of over 300 million annual global malaria cases. Because of the prevalence of drug resistant strains of *Plasmodium falciparum*, which mitigates the efficacy of existing drugs, there is an urgent need to identify new drug targets. An approach to accelerate the development of new antimalarial therapeutics is to identify targets that have been selec ted as a major focus for drug development for other human diseases (Piggy Back Approach). One such target is the enzyme catalyzing protein prenylation, protein farnesyltransferase, which has been validated for anticancer therapeutics development. Research done in our laboratory provided the first proof-of-principle that farnesyltransferase inhibitors (FTI) could potentially be developed as antimalarials, as they exhibit significant inhibition of the intraerythrocytic maturation of *P. falciparum* (1). We have shown the evidence for the existence of farnesylated and geranylgeranylated malaria parasite proteins and have shown that the prenylation of *P. falciparum* proteins is inhibited by FTIs (2). We have also demonstrated several unique features of protein prenylation in *Plasmodium* compared to the human host (2). Tetrahydroquinoline-based FTIs were developed that exhibited low nanomolar potency against the malarial farnesyltransferase (PfPFT) enzyme and the in vitro growth of the parasite. One of the lead compounds was able to cure malaria infection in rodents (3). Because of pharmaocokinetic issues with tetrahydroquinolines, 2-oxo-tetrahydro-1,8-naphthyridines (4) and ethylenediamine-based compounds (5) have been synthesized recently. To understand the physiological function of prenylated proteins of malaria parasites, that are targets of prenyltransferase inhibitors, we searched the PlasmoDB database for proteins containing the C-terminus prenylation motif (CAAX) and have identified 13 proteins that are most likely to be farnesylated. Two of these proteins, a protein tyrosine phosphatase of the PRL subfamily (PfPRL) and the Ykt6 (PfYkt6) SNARE have been shown to be farnesylated in other organisms. We have shown that the recombinant *P. falciparum* PRL can be farnesylated in vitro and a heptapeptide corresponding to the C-terminus (CAAX terminus) of PfPRL inhibits the PfPFT activity (6). Likewise, a heptapeptide corresponding to the PfYkt6 C-terminus can inhibit PfPFT in vitro. We have observed that the subcellular distribution PfYkt6 is prenylation-dependent. The GFP-PfYkt6? CAAX mutant protein does not show the diffused pattern of localization seen with the wild type GFP-PfYkt6, instead accumulates in the Golgi. The implication of our work is that protein prenylation is an important post-translational modification in malaria parasites, which can be targeted for the development of novel antimalarials.

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