Inhibiting the *Plasmodium* elf2α Kinase PK4 Prevents Artemisinin-Induced Latency

**Highlights**

- *Plasmodium* elf2α kinase PK4 is activated upon artemisinin treatment

- elf2α phosphorylation by PK4 leads to latency and recrudescence post artemisinin therapy

- Inhibiting PK4 abolishes recrudescence after artemisinin therapy

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**In Brief**

The antimalarial drug artemisinin is associated with a high frequency of recrudescent infection. Zhang et al. identified that artemisinin induces latency through *Plasmodium* eukaryotic initiation factor 2α (elf2α) phosphorylation. Inhibiting the *Plasmodium* elf2α kinase PK4 blocks parasites from entering latency and abolishes recrudescence after artemisinin therapy.
Inhibiting the *Plasmodium* eIF2α Kinase PK4 Prevents Artemisinin-Induced Latency

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**SUMMARY**

Artemisinin and its derivatives (ARTs) are frontline antimalarial drugs. However, ART monotherapy is associated with a high frequency of recrudescent infection, resulting in treatment failure. A subset of parasites is thought to undergo ART-induced latency, but the mechanisms remain unknown. Here, we report that ART treatment results in phosphorylation of the parasite eukaryotic initiation factor-2α (eIF2α), leading to repression of general translation and latency induction. Enhanced phosphorylated eIF2α correlates with high rates of recrudescent following ART, and inhibiting eIF2α dephosphorylation renders parasites less sensitive to ART treatment. ART-induced eIF2α phosphorylation is mediated by the *Plasmodium* eIF2α kinase, PK4. Overexpression of a PK4 dominant-negative or pharmacological inhibition of PK4 blocks parasites from entering latency and abolishes recrudescent after ART treatment of infected mice. These results show that translational control underlies ART-induced latency and that interference with this stress response may resolve the clinical problem of recrudescent infection.

**INTRODUCTION**

The malaria parasite *Plasmodium* spp. was estimated to cause 212 million new cases and over 0.4 million deaths in 2015 (World Health Organization, 2015). Artemisinin and its derivatives (ARTs) are the most potent antimalarial drugs to date (Chen, 2016; O’Neill et al., 2010; Tu, 2011), but their use is stymied by recrudescent rates as high as 60% (Codd et al., 2011; de Vries and Dien, 1996; Meshnick et al., 1996). Malaria recrudescence, defined as the reappearance of the original strain of the parasite after antimalarial medications, is considered as treatment failure (Shaukat et al., 2012). To minimize this problem, the World Health Organization recommends against monotherapy in favor of ART-based combination therapy. Nevertheless, recrudescent *P. falciparum* infections have still been reported (Ndoungha et al., 2015; Yeka et al., 2005).

Most clinical antimalarials are schizonticidal drugs, targeting blood-stage parasites that are responsible for the clinical symptoms associated with malaria. Within blood cells, merozoites develop to form either gametocytes or schizonts. *Plasmodium* schizonts release daughter merozoites and the free merozoites re-invoke erythrocytes and differentiate into rings, trophozoites, and schizonts. Recrudescence following antimalarial therapy has been thought to occur as a result of drug-resistant parasites (O’Brien et al., 2011). However, recrudescent parasites isolated from patients remain sensitive to ARTs (Dondorp et al., 2009; Noedl et al., 2008; Phyo et al., 2012). As the in vivo half-life of ARTs is short (Li et al., 2014), it has been proposed that the concentration of the drug in plasma was insufficient to suppress all parasites (White, 2013). Consequently, longer courses of therapy or twice-a-day dosing intervals are recommended to efficiently clear the infection (Dogovski et al., 2015). Recent studies also indicate that ARTs induce transition of a subset of parasites into latent rings that are responsible for recrudescence (Codd et al., 2011; Grobler et al., 2014; LaCrue et al., 2011; Teuscher et al., 2010, 2012). Despite its clinical importance, the molecular mechanism of ART-induced parasite latency remains unknown.

We have previously demonstrated that latent stages of apicomplexan parasites, including *Toxoplasma* and *Plasmodium*, coincide with increased phosphorylation of the α subunit of eukaryotic translation initiation factor-2 (eIF2), which delivers initiator tRNA to ribosomes. Phosphorylation of eIF2α, which occurs during cellular stress, results in a reduction of general protein synthesis, accompanied by preferential translation of mRNAs encoding products that are important for recovery from the stress (Young and Wek, 2016). We hypothesized that translation control through parasite eIF2α phosphorylation contributes to ART-induced latency. Consistent with this idea, RNA sequencing and microarray studies have shown that ribosomal protein genes are downregulated in response to ART in the human malaria parasite, *P. falciparum*, and the rodent malaria parasite, *P. berghei* (Shaw et al., 2015). Furthermore, proteins involved in the translation process were among the
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