DISCOVERY OF NEW TARGETS FOR ANTIMALARIAL CHEMOTHERAPY

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Summary:

The understanding of the biology and the biochemistry of malaria parasites has considerably increased over the past two decades with the discovery of many potential targets for new antimalarial drugs. The decrypted genomes of several *Plasmodium* species and the new post-genomic tools further enriched our "reservoir" of targets and increased our ability to validate potential drug targets or to study the entire parasite metabolism. This review discusses targets involved in calcium metabolism, protein prenylation and apicoplast functions that have emerged by different approaches.

KEY WORDS : antimalarials, drug targets, artemisinin, SERCA, apicoplast, isoprenoid, haem, farnesyltransferase.

Malaria, caused by the protozoa *Plasmodium*, is the most deadly parasitic infectious disease worldwide with 300-500 million cases and 2.7-3 million death per year, in majority among children (< 5 years old). Today, the chemotherapeutic arsenal for malaria treatments is limited to three main families of compounds: the quinolines (quinine, chloroquine, mefloquine...), the antifolates (sulfadoxine, pyrimethamine...) and the artemisinin derivatives. Widespread drug resistance resulted in the ineffectiveness of many antimalarials and chemotherapy now requires drug combinations. The understanding of the biology and the biochemistry of malaria parasites has increased considerably over the past two decades, as well as the understanding of the mechanisms of action and resistance of antimalarials (Woodrow & Krishna, 2006). Many potential targets for new drugs were identified (Table I). The decrypted genomes of several *Plasmodium* species further enriched the "reservoir" of putative targets either because they were homologous to validated targets in other organisms, or because they were species specific, with no homologous counterpart. Furthermore, recent advances in genetic manipulation of *Plasmodium* greatly increased the ability to validate potential drug targets and the access to transcriptome and proteome analysis offered new opportunities to study the entire parasite metabolism. High-throughput bioassays against these targets are becoming more accessible to the academic laboratories and allow to screen a large diversity of molecules issued either from pharmaceutical or natural product libraries, which may provide lead molecules for new antimalarial drugs (Mambu & Grellier, 2007). In this report, we review some of these newly identified targets for antimalarial chemotherapy.

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SARCOPLASMIC/ENDOPLASMIC RETICULUM CALCIUM PfATPase (SERCA)

Artemisinin and its derivatives are key antimalaria agents constituting the foundation of the ACT (artemisinin-based combination therapy) strategy developed by WHO against malaria. Understanding how artemisinins work is particularly important to prevent the emergence of resistant parasites. Indeed, there are accumulating evidences for increasing artemisinin resistance *in vitro* of *P. falciparum* isolates (Jambou *et al.,* 2005) and reduced *in vitro* susceptibility to dihydroartemisinin and recrudescence have been observed after artesunate monotherapy (Menard *et al.,* 2005). However and fortunately, no clear clinical resistance was reported. The mechanism(s) of action and the cellular target(s) for artemisinins remain controversial (Golenser *et al.,* 2006; Krishna *et al.,* 2006). Artemisinins are fast acting agents, the endoperoxide bridge being the key pharmacophore. It was commonly proposed that iron contained in parasite haem reacted with the peroxide moiety leading to production of free radicals, haem-artemisinin adducts and alkylation of proteins, resulting in parasite damage. This multiple-target mechanism of action of artemisinin was supported, until now, by the lack of evidence for artemisinin resistance. It was also suggested that the electron transport chain of *P. falciparum* might be a target for artemisinin. However, several reports supported that artemisinin activity was outside the parasite food vacuole that contains haem and in fact the sarco-endoplasmic reti-