Insights into the pyrimidine biosynthetic pathway of human malaria parasite *Plasmodium falciparum* as chemotherapeutic target

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**ABSTRACT**

Malaria is a major cause of morbidity and mortality in humans. Artemisinins remain as the first-line treatment for *Plasmodium falciparum* (*P. falciparum*) malaria although drug resistance has already emerged and spread in Southeast Asia. Thus, to fight this disease, there is an urgent need to develop new antimalarial drugs for malaria chemotherapy. Unlike human host cells, *P. falciparum* cannot salvage preformed pyrimidine bases or nucleosides from the extracellular environment and relies solely on nucleotides synthesized through the *de novo* biosynthetic pathway. This review presents significant progress on understanding the *de novo* pyrimidine pathway and the functional enzymes in the human parasite *P. falciparum*. Current knowledge in genomics and metabolomics are described, particularly focusing on the parasite purine and pyrimidine nucleotide metabolism. These include gene annotation, characterization and molecular mechanism of the enzymes that are different from the human host pathway. Recent elucidation of the three-dimensional crystal structures and the catalytic reactions of three enzymes: dihydroorotate dehydrogenase, orotate phosphoribosyltransferase, and orotidine 5'-monophosphate decarboxylase, as well as their inhibitors are reviewed in the context of their therapeutic potential against malaria.

1. Introduction

Malaria remains as one of the most deadly diseases in tropical and subtropical endemic countries, with almost half of the world's populations at risk of infection, estimated at 515 million clinical cases and 1.3 million deaths annually [1–3]. Of the five *Plasmodium* species that infect humans, including *Plasmodium vivax* (*P. vivax*), *Plasmodium malariae*, *Plasmodium ovale*, and *Plasmodium knowlesi*, *Plasmodium falciparum* is the causative agent of the most lethal and severe form of malaria [1–4]. *P. vivax*, responsible for 25%–40% of the estimated annual cases of malaria worldwide, is seldom fatal but relapses often occur even after a primary infection has cleared [6]. Over the past 50 years, the parasites’ resistance to both chloroquine and sulphadoxine-pyrimethamine has rapidly emerged and is now widespread in the endemic countries [7].

Artemisinin and its derivatives, considered the most rapid acting and efficacious drug, are the first-line drugs for treatment of *P. falciparum* malaria [8]. However by 2009, resistance to the drug treatment has been reported (Figure 1) [9]. Thus, it is deemed necessary to develop novel antimalarial drugs for malaria chemotherapy [10,11]. Applying lessons learned from malaria research in the post-genomic era, together with increased understanding in genomics, transcriptomics and proteomics [12–16], this review highlights the candidate drug targets for antimalarial drug discovery [11,17–20].

2. Genomics and metabolomics of malaria parasite

Most of the biochemical knowledge on *P. falciparum* has focused on the intraerythrocytic life cycle of the parasite owing to over 60 years of research [21–24], as well the established cultivation method for these stages since 1976 by Trager and Jensen [25]. With the availability of complete genome sequences from various *Plasmodium* species such as, rodent