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Drug targets for resistant malaria: Historic to future perspectives

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ABSTRACT

New antimalarial targets are the prime need for the discovery of potent drug candidates. In order to fulfill this objective, antimalarial drug researches are focusing on promising targets in order to develop new drug candidates. Basic metabolism and biochemical process in the malaria parasite, i.e. *Plasmodium falciparum* can play an indispensable role in the identification of these targets. But, the emergence of resistance to antimalarial drugs is an escalating comprehensive problem with the progress of antimalarial drug development. The development of resistance has highlighted the need for the search of novel antimalarial molecules. The pharmaceutical industries are committed to new drug development due to the global recognition of this life threatening resistance to the currently available antimalarial therapy. The recent developments in the understanding of parasite biology are exhilarating this resistance issue which is further being ignited by malaria genome project. With this background of information, this review was aimed to highlights and provides useful information on various present and promising treatment approaches for resistant malaria, new progresses, pursued by some innovative targets that have been explored till date. This review also discusses modern and futuristic multiple approaches to antimalarial drug discovery and development with pictorial presentations highlighting the various targets, that could be exploited for generating promising new drugs in the future for drug resistant malaria.

1. Introduction

Malaria is a disease caused by parasite of the genus *Plasmodium* and it is transmitted *via* the bites of infected female mosquitoes of *Anopheles* species. *Plasmodium falciparum*and *Plasmodium vivax*are the rampant species, but the infection caused by the former is the deadliest. In 2016, there are around 216 million cases of malaria worldwide. The majority of cases (90%) are prevalent in the African zone, South-East Asia and Eastern Mediterranean zones [1]. The children and the pregnant women are the individuals who are most at risk of morbidity and death on account of malaria [2,3].

The term “malaria” derived from the Italian words ‘mala’ meaning bad and aria - meaning ‘air’, was used by Dr. Francisco Torti, when people associated the disease with foul air of marshy land. It was later in 1880 that a French Army Physician, Laveran showed that malaria is caused by *Plasmodium* protozoan. Later, Ronald Ross, a British Army Surgeon in India, demonstrated that the parasitic disease is transmitted by ‘anopheles’ mosquito [4].

The increase in morbidity caused by drug resistant malaria has inspired the scientists to search for suitable drug inhibitors, genetic basis of drug resistance and the new approaches to overcome drug resistant [5]. The progress over the last years and the awareness about sanitation has led to the eradication of malaria, but there is no such vaccine or technique available which can eradicate it completely. The parasite has a complex life cycle, therefore every stage should be considered in order to eradicate the disease (Fig. 1).

All *Plasmodium* species have two hosts, vertebrate and mosquito. Malaria is caused by the parasites (sporozoites), passed into the human circulation by the bite of infected Anopheles mosquitoes. The sporozoites get lodged into parenchymal cells of the liver, where they multiply and develop into tissue schizonts. This forms the primary erythrocytic or preerythrocytic phase of infection depends on species of *Plasmodium* and last for 5–16 days. Thousands of merozoites are released upon rupturing of tissue schizonts. These merozoites start erythrocytic phase or blood cycle once enter into circulation and invading erythrocytes.

The secondary exoerythrocytic phase involves a portion of these parasites infecting more liver cells. Some tissue parasites may remain dormant (hypnozoites) in *P. vivax* and *P. ovale* infections, but not in *P. falciparum* and *P. malariae* infections. The dormant parasites may result in relapse months or years later in the infected patient. Most parasites undergo asexual development in erythrocytes through trophozoites and finally mature into schizonts. The schizont-containing erythrocytes on rupturing release 6–32 merozoites. There is a feeling of chill and fever

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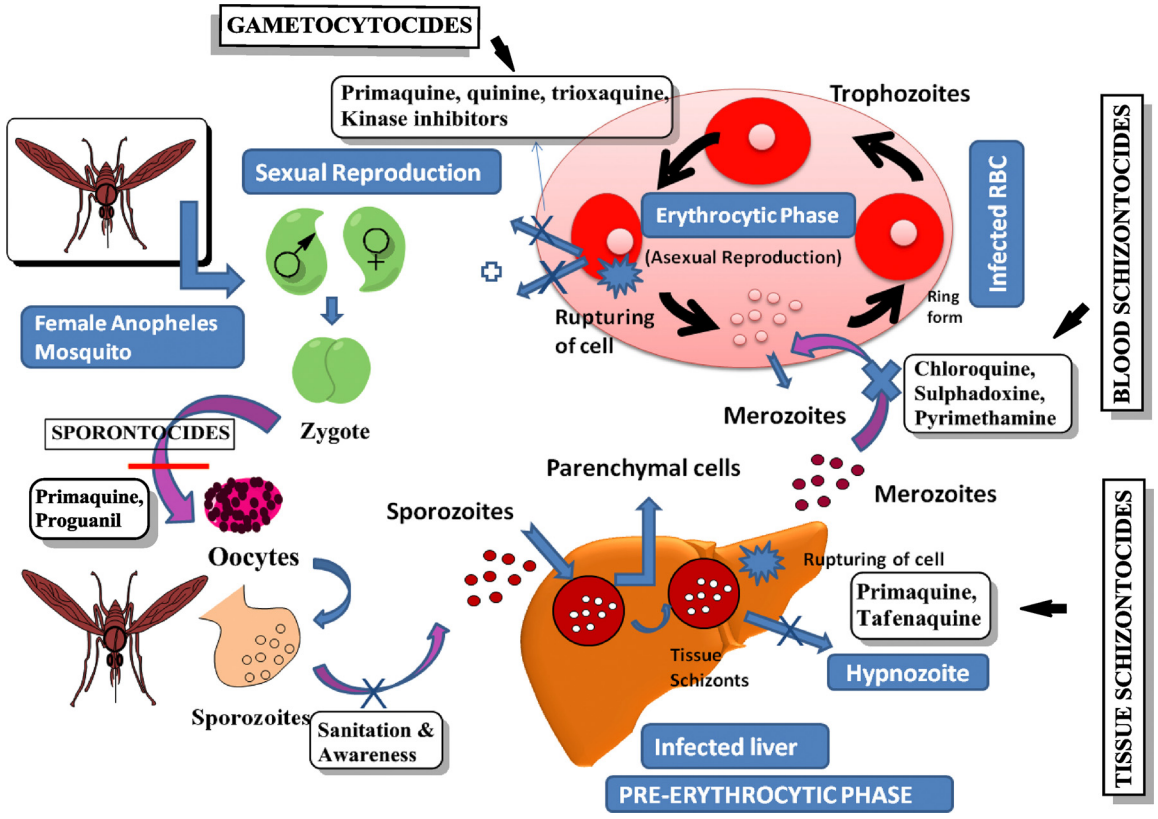

Fig. 1. The life cycle of *Plasmodium*. The *Plasmodium* life cycle involves two hosts: female Anopheles mosquito and human host. Anopheles mosquito inoculates sporozoites into the human host where they infect liver cells and mature into schizonts, which ruptures and release merozoites. Merozoites infect red blood cells where ring stage trophozoites are formed which mature into schizonts. Schizonts rupture releasing more merozoites. This blood stage cycle is responsible for the clinical manifestation of the disease. Some of the parasites differentiate into sexual erythrocytic stages (male and female gametocytes) which are infested by an Anopheles mosquito during blood meal.These gametocytes can undergo sporogony (sexual cycle) in the gut of female mosquitoes. The resulting zygote develops in the gut wall as oocysts and ultimately gives rise the infective sporozoites, which infect the salivary gland of the mosquito. Inoculation of the sporozoites into a new human host repeat the malaria life cycle.

follows, and liberated merozoites infect more red-blood cells and start the cycle afresh. The cycle continues until the death of the host or modulation by drug or acquired immunity. Some of the merozoites differentiate into male and female parasites known as gametocytes. The gametocytes (male and female) are ingested by an Anopheles mosquito during a blood meal and undergo sexual cycle call sporogony generating zygotes. The zygotes invade the midgut wall of the mosquito where they develop into oocysts. The oocysts grow, rupture and release sporozoites which infect the salivary gland of the mosquito. Inoculation of the sporozoites into a new human host repeats the malaria life cycle.

The parasite undergoes cell differentiation and metamorphosis multiple times throughout its life cycle. This transformation requires degradation of unnecessary proteins and organelles within host cells. Knowing the mechanism of this degradation pathway may open new doors for the advancement of new antimalarial drugs.

2. Currently usedantimalarial drugs and their limitations

Currently available antimalarial drugs, according to their chemical structure and mechanism of action divides into three broad categories Fig. 2.

A Aryl aminoalcohol compounds: quinine, quinidine, halofantrine, lumafantrine, chloroquine, amodiaquine, mefloquine, cycloquine *etc.*
B Antifolate compounds: proguanil, pyrimethamine, trimethoprim *etc.*
C Artemisinin compounds (artemisinin, dihydroartemisinin, artesunate, artemether, arteether *etc.*).

Most of the antimalarial drugs target the asexual erythrocytic stages of the parasite, hence called as blood schizonticidal drugs. Tissue schizonticidal drugs target the hypnozoites (dormant stage of the parasite) in the liver whereas gametocytocidal drugs destroy sexual erythrocytic forms of the parasite in the bloodstream and thus prevent transmission of the malaria to mosquito. Sporontocides prevent or inhibit formation of malarial oocysts and sporozoites in infected mosquito. Chloroquine, quinine and mefloquine are typical fast acting schizonticidal drugs. Pyrimethamine, sulphonamides and sulphone also possess schizonticidal activities, but the action is slow. Primaquine, Tafenoquine and other novel kinase inhibitors have gametocidal activities. The main sporontocidal drugs are primaquine and praguanil. These antimalarial drugs were designed based on major metabolic differences of malaria parasite with its host. Nucleic acid metabolism, heme toxification, oxidative stress and fatty acid biosynthesis are some of the major pathways that were targeted mostly for antimalarial drug design. However, in the chemotherapy of malaria, the emergence of resistance to the available drugs is the major obstacle [6]. Most of the available antimalarial drugs have been used for decades and now, their use is restricted by the emergence of drug resistance. According to the literatures, there are no existing anti-malarial drugs which were developed in a fully rational manner, with a focused attempt to inhibit a known drug target. Instead, in all cases, anti-malarial potency has been identified in animal or *in vitro*model studies. Therefore, the target of action for most available agents within the malaria parasite remains uncertain [7,8]. In addition, the mechanisms of emergence of resistance are poorly understood for most of the drugs. Genetic, molecular and pharmacological approaches have shown that different targets of older