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Targeting kinases in *Plasmodium* and *Schistosoma*: Same goals, different challenges☆

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ABSTRACT

With respect to parasite-induced infectious diseases of worldwide importance, members of the genera *Plasmodium* and *Schistosoma* are top pathogens. Nearly half a billion people suffer from malaria caused by *Plasmodium* spp. and schistosomiasis (bilharzia) induced by *Schistosoma* spp. Resistance against essentially all drugs used for malaria treatment has been reported. For schistosomiasis justified fear of upcoming resistance is discussed against the background of only one widely used drug for treatment. Research of the recent decade has demonstrated that essential steps of the biology of these and other parasites are controlled by kinases, which represent attractive targets for new-generation antiparasitic compounds. This article is part of a Special Issue entitled: Inhibitors of Protein Kinases.

1. *Plasmodium* and *Schistosoma*, pathogens with devastating impact on human and animal health

Two of the most devastating diseases caused by eukaryotic parasites are malaria and schistosomiasis. These diseases are caused by organisms which, despite sharing the same human host, are phylogenetically extremely distant from each other: the etiological agents for malaria are unicellular, obligate intracellular parasites of the superphylum Alveolates, while the pathogen that causes schistosomiasis is a metazoan, and thus belongs to the same phylum as its human hosts. As discussed below, this has implications on the composition of the kinomes of these two organisms, and hence on the strategies to target kinases in the context of antimalarial and anti-schistosomiasis drug discovery.

1.1. Plasmodium

Malaria is an ancient scourge of mankind with a huge impact on our species: it is estimated that it has been a major force for evolutionary selection in the recent history of the human genome [1]. Five species of malaria parasites (genus *Plasmodium*) infect humans, with *P. falciparum* being the most virulent and causing the vast majority of lethal cases.

P. falciparum malaria is caused by the cyclical multiplication of asexual forms of the parasite within erythrocytes; the clinical symptoms range from uncomplicated fevers to life-threatening cerebral and placental malaria, both of which are caused by the adhesive properties of the infected erythrocytes, itself mediated by parasite-encoded proteins that are exported to the infected erythrocyte surface. After a period of asexual cycling in red blood cells, some parasites commit to gametocytogenesis, yielding the sexual cells (male and female gametocytes) that are essential for transmission to the arthropod vector, a female mosquito of the genus *Anopheles*. Gametocytes ingested by the mosquito develop into fertilization-competent gametes in the insect's midgut. After fertilization, the zygote transforms into a motile ookinete that exits the midgut lumen and establishes an oocyst at the midgut outer surface. In oocysts, sporogony occurs, generating several thousand sporozoites; these transit through the hemolymph and accumulate in the mosquito's salivary glands, where they are primed for infection of a human host. The sporozoites injected into the host during a blood meal access the circulation and are transported to the liver, where they infect hepatocytes. The parasite develops through schizogony (a proliferation mode whereby successive nuclear divisions occur in the absence of cytokinesis), with each schizont eventually producing up to 40,000 merozoites. The liver stage of infection is asymptomatic.

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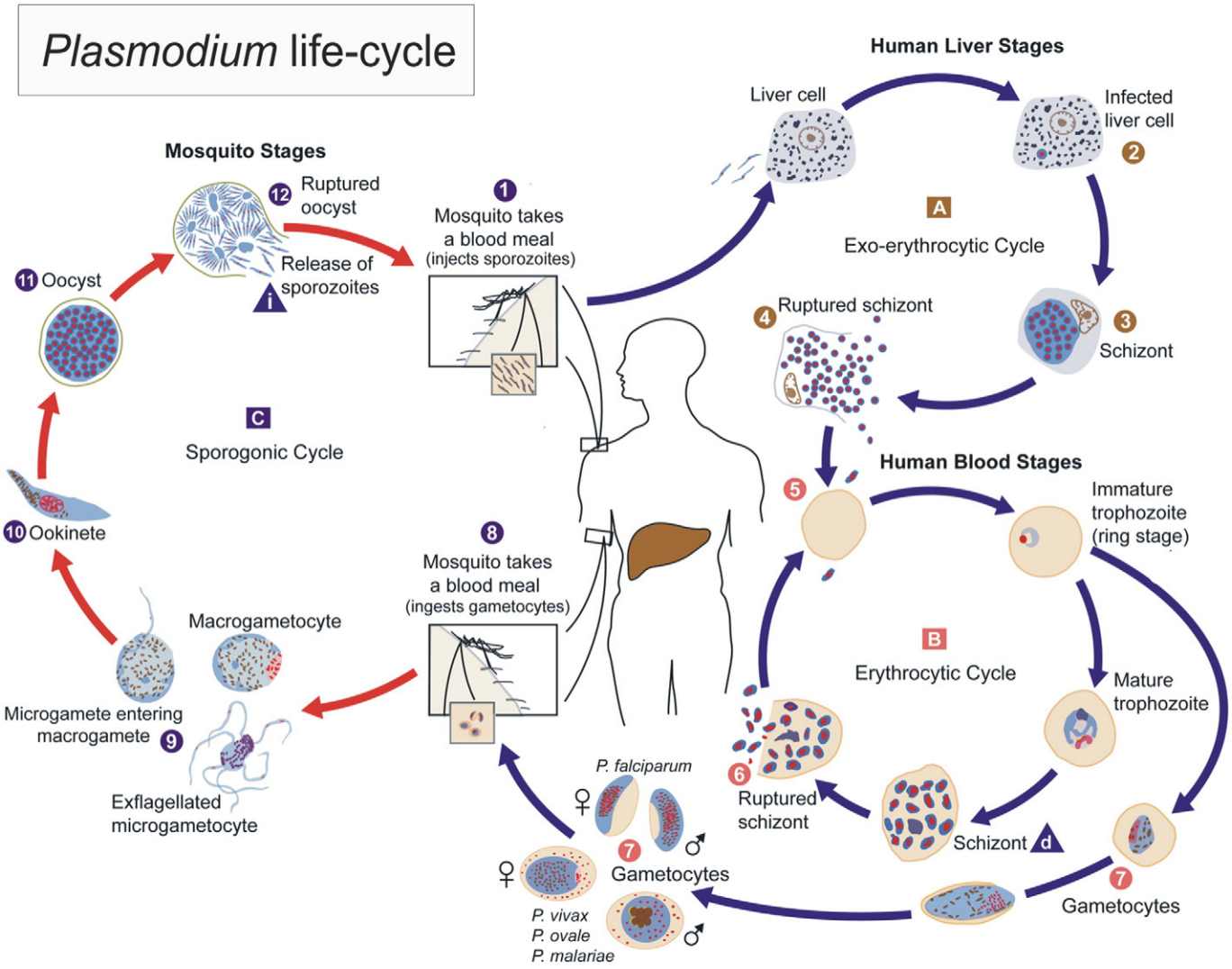

Fig. 1. The Plasmodium life-cycle. The Plasmodium life-cycle involves two hosts. During a blood meal, a malaria-infected female Anopheles mosquito inoculates sporozoites into the human host (1). Sporozoites infect liver cells (2) and mature into schizonts (3), which rupture and release merozoites (4). (Of note, in *P. vivax* and *P. ovale* a dormant stage [hypnozoites] can persist in the liver and cause relapses by invading the bloodstream weeks, or even years later.) After this initial replication in the liver (exo-erythrocytic schizogony, A), the parasites undergo asexual multiplication in the erythrocytes (erythrocytic schizogony, B). Merozoites infect red blood cells (5). The ring stage trophozoites mature into schizonts, which rupture releasing merozoites (6). Some parasites differentiate into sexual erythrocytic stages (gametocytes) (7). Blood stage parasites are responsible for the clinical manifestations of the disease. The gametocytes, male (microgametocytes) and female (macrogametocytes), are ingested by an Anopheles mosquito during a blood meal (8). The parasites' multiplication in the mosquito is known as the sporogonic cycle, C. While in the mosquito's stomach, the microgametes penetrate the macrogametes generating zygotes (9). The zygotes in turn become motile and elongated (ookinetes) (10) which invade the midgut wall of the mosquito where they develop into oocysts (11). The oocysts grow, rupture, and release sporozoites (12), which make their way to the mosquito's salivary glands. Inoculation of the sporozoites into a new human host perpetuates the malaria life cycle. Figure and legend are slightly modified versions of those provided by the US Centers for Disease Control and Prevention (CDC) (http://www.cdc.gov/dpdx/malaria/index.html).

The merozoites are released into the bloodstream and are able to infect erythrocytes, where a second round of schizogony occurs, causing disease (see Fig. 1 for a depiction of the parasite's life cycle).

1.2. Schistosoma

Schistosome parasites cause schistosomiasis (bilharzia), an infectious disease spread mainly in sub-Saharan Africa, the Middle East, South America, the Caribbean and parts of Asia including the Philippines. As members of the platyhelminths, schistosomes belong to the class trematode, and species such as *Schistosoma mansoni*, *Schistosoma haematobium*, *Schistosoma japonicum*, *Schistosoma intercalatum*, and *Schistosoma mekongi* are of high relevance for human and animal health [2–4].

The complex biology of schistosomes (Fig. 2) starts with eggs, which are released with feces or urine (in case of *S. haematobium*) of human or animal hosts into water. Miracidia hatch from the eggs and swim through the aquatic environment to find a species-specific intermediate host snail. Following penetration, the miracidium transforms into a mother sporocyst, which multiplies asexually to produce daughter sporocysts. They continue reproduction and finally differentiate into cercariae, which leave the snail to become the infectious stage of the life-cycle. Cercariae swim through the water to get contact to a final host. Following skin penetration, carcariae transform into schistosomula, a juvenile schistosome stage drifting via the bloodstream through lungs and heart to the liver. On their journey schistosomula have developed into adult worms, which pair in the portal vein of the liver. As couples they start egg production and migrate to the mesenteric veins of the gut, where they survive for decades defying attacks of the host´s immune system.

As the only members of the trematodes schistosomes have evolved separate sexes. Another, nearly unique feature of schistosome biology is the pairing-dependent sexual maturation of the female. Pairing is a prerequisite for the induction and maintenance of mitotic and