Trends in Parasitology

CellPress

Review

The Role of Chromatin Structure in Gene Regulation of the Human Malaria Parasite

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The human malaria parasite, *Plasmodium falciparum*, depends on a coordinated regulation of gene expression for development and propagation within the human host. Recent developments suggest that gene regulation in the parasite is largely controlled by epigenetic mechanisms. Here, we discuss recent advancements contributing to our understanding of the mechanisms controlling gene regulation in the parasite, including nucleosome landscape, histone modifications, and nuclear architecture. In addition, various processes involved in regulation of parasite-specific genes and gene families are examined. Finally, we address the use of epigenetic processes as targets for novel antimalarial therapies. Collectively, these topics highlight the unique biology of *P. falciparum*, and contribute to our understanding of mechanisms regulating gene expression in this deadly parasite.

Trends

Chromatin organization within the parasite nucleus plays a role in gene regulation.

Parasite-specific genes involved in pathogenesis, immune evasion, and host cell invasion are regulated at the epigenetic level.

Histone variants and the nucleosome landscape of the parasite genome are associated with gene expression.

Most of the parasite's genome is maintained as euchromatin, while only a small subset of genes are maintained in heterochromatin clusters.

Mediators of epigenetic control and nuclear remodeling could be promising targets for antimalarial drugs.

The Malaria Parasite

The human malaria parasite remains one of the deadliest infectious agents worldwide. In 2015, an estimated 214 million cases of infection and 438 000 malaria-related deaths were reported [1] (http://www.who.int/malaria/publications/world-malaria-report-2015/report/en/). Most malaria infections occur in sub-Saharan Africa; however, developing countries in South East Asia and South America are also affected. Children under the age of five and pregnant women are most susceptible to the disease, and in 2015 children under the age of five accounted for approximately 70% of all malaria-related deaths.

P. falciparum, one of five *Plasmodium* species that can infect humans, is responsible for the most severe disease symptoms and the highest mortality rate in humans. The parasite develops through a complex life cycle that involves two hosts: the *Anopheles* mosquito and the human host (Figure 1). The parasite's life cycle begins as an infected *Anopheles* mosquito takes a blood meal from a human and in the process injects sporozoites into the host's bloodstream. The sporozoites translocate to the liver, invade liver cells (hepatocytes), and replicate multiple times for a 2-week period, producing thousands of merozoites that leave the liver and invade red blood cells (erythrocytes) [2,3].

During the intraerythrocytic developmental cycle (IDC), the parasite develops asexually through ring, trophozoite, and schizont stages and multiplies by a process of replication termed schizogony. As the parasite progresses through the three distinct developmental stages, it undergoes multiple rounds of nuclear replication and cytokinesis to produce 16–32 daughter cells at the end of each IDC. The daughter merozoites then burst out of the host red blood cell and invade new healthy red blood cells. During the IDC, environmental stress can trigger the

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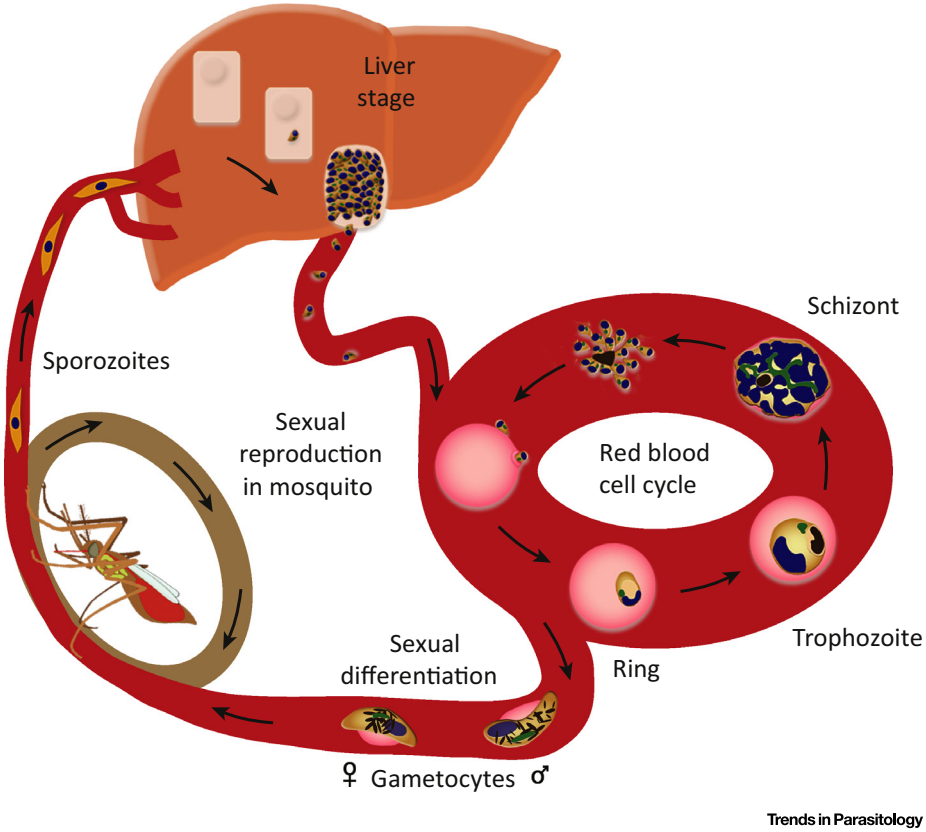

Figure 1. Schematic Representation of the Life Cycle of the Malaria Parasite. In the human host, the parasite first develops through the liver stage, followed by subsequent 48-h replication cycles inside red blood cells, which is the stage responsible for symptomatic disease. During this replication cycle, a small proportion of parasites will commit to sexual differentiation into male and female gametocytes that can be taken up by a mosquito. Sexual reproduction takes place inside the mosquito midgut and ultimately results in the formation of sporozoites that can be transmitted to a new human host.

parasites into committing to sexual development, resulting in differentiation into male and female gametocytes. The mature gametocytes can be ingested by a feeding mosquito, undergo sexual replication in the mosquito midgut, and develop further into salivary gland sporozoites to be transmitted to a new human host as the mosquito takes the next blood meal. This multistage life cycle of the parasite is tightly regulated, most likely by strict control of stage-specific gene expression. In eukaryotes, stage-specific regulation of gene expression can be a combined effect of transcriptional, post-transcriptional and translational control. In *P. falciparum*, the nature and the contribution of mechanisms regulating gene expression at the transcriptional level, including the role of chromatin structure, are starting to emerge. In this review, we summarize the current knowledge on the role of chromatin structure and epigenetics in gene regulation of the human malaria parasite and its potential to identify much-needed new therapies.

P. falciparum Genome

The human malaria parasite *P. falciparum* has a relatively compact genome of twenty three million base pairs that is organized into 14 chromosomes (per haploid genome) [4]. The *P. falciparum* genome is the most AT-rich eukaryotic genome sequenced to date, with an overall AT composition of ~80%, rising to 90–95% in introns and intergenic regions. The distinct developmental stages of the *P. falciparum* life cycle (Figure 1) are characterized by coordinated changes in gene expression [5–10]. In eukaryotes, gene expression is partly controlled by transcription factors that bind to cell- or tissue-specific promoters to regulate transcription [11].