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Survival strategies of Plasmodium falciparum in the hosts (man and mosquitoes)

Hauwa'u Abdulkadir Usman[1], Ismail Muhammad[2*], Muhammad Fatima Yakubu[3], Bala Abubakar[4]

[1]Federal College of Horticultural Technology Dadin-kowa,
[2]Gombe state University, Gombe, Department of Zoology and Wildlife Ecology
[3] Federal College of Education (Tech) Gombe
[4] School of Health Science and Technology Kaltingo, Gombe State

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***Corresponding author: Ismail Muhammad**
Gombe state University, Gombe, Department of Zoology and Wildlife Ecology

Abstract

Parasites which are considered as foreign bodies by the host immune system must adopt various strategies in order to successfully survive in the new microenvironment. The aim of this paper was to systematically review the current state of knowledge on the various survival strategies employed by Plasmodium falciparum, in both human and mosquito hosts. The parasite's life cycle involves various adaptations, allowing it to evade immune detection, survive, and thrive in complex biological environments. In humans, P. falciparum utilizes antigenic variation, immune evasion, and the remodeling of red blood cells (RBCs) to sustain itself. Additionally, it manipulates host immune responses and metabolic pathways, further promoting its survival. In mosquitoes, the parasite demonstrates remarkable adaptability, using mechanisms such as sporogonic development and midgut invasion to ensure transmission to human hosts. In Nigeria, where malaria is hyperendemic, the parasite poses a significant public health challenge, exacerbated by drug resistance and environmental factors that favor transmission. By understanding these survival strategies, this research offers potential insights into the development of new therapeutic interventions, such as vaccines and novel drug targets, to curb the transmission and impact of P. falciparum.

Keywords: *Plasmodium falcifarum, Survival strategies, Mosquito, Human host, Immune evasion*

1.0 Introduction

Malaria continues to be a critical global health challenge, with over 200 million cases annually and approximately 600,000 deaths, primarily in sub-Saharan Africa. Among the five species of *Plasmodium* that cause malaria in humans, *Plasmodium falciparum* is the most lethal, responsible for the majority of deaths due to its high virulence and complex life cycle (WHO, 2023). Nigeria bears the highest global burden of malaria, with *Plasmodium falciparum* being the most prevalent and virulent malaria parasite. According to the World Health Organization (WHO), Nigeria accounts for nearly 27% of global malaria cases and 23% of global malaria deaths. The widespread presence of *P. falciparum* in Nigeria is attributed to a combination of climatic conditions that favor mosquito breeding, socio-economic factors such as poverty, and weak healthcare infrastructure. Studies reveal that malaria transmission in Nigeria is strongly influenced by the country's diverse ecological zones, ranging from the tropical rainforests in the south to the arid regions in the north, each providing varying transmission dynamics for *P. falciparum.*

This parasite has evolved intricate mechanisms to survive in both its human and mosquito hosts, enabling it to persist in various environments and under different immune and therapeutic pressures. Its survival strategies include immune evasion, host cell remodeling, metabolic adaptation, and resistance to antimalarial drugs (Hoffman et al., 2022). In humans, *P. falciparum* invades red blood cells, remodeling them to enhance nutrient uptake and evade immune responses, while in mosquitoes, it manipulates host behavior to optimize transmission. These strategies highlight the parasite's ability to adapt and thrive in diverse biological environments, making it a formidable pathogen.

Given the increasing global burden of drug-resistant malaria parasite and the challenges of vector control, understanding the survival mechanisms of *P. falciparum* is essential for developing new therapeutic interventions and effective public health strategies (Desai et al., 2022). This paper explores the multifaceted interactions between *P. falciparum* and its human and mosquito hosts, focusing on the molecular, cellular, and environmental adaptations that sustain its life cycle and virulence. By delving

deeper into these survival mechanisms, the paper seeks to provide insights into potential targets for novel treatments and strategies to curb the transmission of this deadly parasite, ultimately contributing to global malaria eradication efforts.

2.0 Life Cycle of *Plasmodium falciparum*

The life cycle of *Plasmodium falciparum* is complex, involving both human and mosquito hosts. It begins when an infected female *Anopheles* mosquito bites a human, injecting sporozoites into the bloodstream. These sporozoites travel to the liver, where they infect hepatocytes (liver cells). Inside these cells, they multiply and differentiate into merozoites. After a few days, the liver cells burst, releasing merozoites into the bloodstream.

Once in the bloodstream, the merozoites invade red blood cells (RBCs), initiating the asexual blood stage of the parasite's life cycle. Inside RBCs, the parasite matures through the ring, trophozoite, and schizont stages. The schizonts eventually burst, releasing more merozoites that can infect additional RBCs. This cycle of invasion, multiplication, and RBC destruction leads to the clinical symptoms of malaria, such as fever, chills, and anemia.

Some merozoites differentiate into male and female gametocytes, which are the sexual forms of the parasite. When a mosquito bites an infected human, it ingests these gametocytes, which undergo fertilization in the mosquito's midgut. The resulting zygotes develop into motile ookinetes, which penetrate the mosquito midgut wall and form oocysts. Inside the oocysts, sporozoites are produced, which then migrate to the mosquito's salivary glands, ready to be transmitted to a new human host during the next blood meal. This intricate cycle ensures the parasite's survival and transmission between humans and mosquitoes (Vaughan et al., 2022; Sinden, 2015).

3.0 Survival Strategies in Humans

3.1Antigenic Variation

P. falciparum employs antigenic variation to evade the host's immune system. The parasite expresses various surface proteins, such as PfEMP1 (*Plasmodium falciparum* Erythrocyte Membrane Protein 1), which are encoded by the var gene family. By switching the expression of different var genes, P. falciparum can avoid detection by the host's immune system (Hviid & Jensen, 2015). The var gene family comprises approximately 60 different genes. Only one of these genes is expressed at any given time in an infected erythrocyte, but the parasite can switch between these genes, leading to the presentation of different PfEMP1 proteins on the surface of infected RBCs.

Once inside red blood cells (RBCs), *P. falciparum* remodels the host cell to facilitate its growth and reproduction. It achieves this through the export of proteins that modify the erythrocyte's structure, creating new permeability pathways that allow the parasite to access nutrients (Sherling et al., 2022). The export of proteins such as *PfEMP1* not only enhances nutrient uptake but also facilitates immune evasion by altering the surface of infected erythrocytes (Ito et al., 2023). These remodeling activities are essential for the parasite's survival and multiplication within the human host (Desai et al., 2022).

3.2 Immune Evasion Mechanisms

The parasite resides inside RBCs, which do not present antigens via Major Histocompatibility Complex (MHC) class I molecules, thereby avoiding cytotoxic T-cell recognition. Additionally, *P. falciparum* modifies the surface of infected RBCs to avoid phagocytosis by macrophages and to adhere to endothelial cells, preventing splenic clearance (Miller et al., 2002). The parasite employs several strategies to avoid detection and destruction by the host's immune system. One key mechanism is antigenic variation, where the parasite periodically changes the proteins displayed on the surface of infected cells (RBCs), such as *PfEMP1*, to avoid recognition by immune cells (Feng et al., 2022). Additionally, recent studies highlight the role of *RIFIN* proteins in directly interacting with human inhibitory immune receptors, further dampening the immune response (Hoffman et al., 2022). This ability to suppress immune activation enables the parasite to persist in the bloodstream for extended periods, increasing the likelihood of transmission to mosquitoes.

3.4 Intracellular Residency

Plasmodium falciparum employs intracellular residency within red blood cells (RBCs) as a key survival strategy, allowing it to evade the host's immune system. By invading and residing within RBCs, the parasite effectively shields itself from direct attack by antibodies, which typically target extracellular pathogens (Cowman et al., 2016). Once inside the RBCs, *P. falciparum* forms a **parasitophorous vacuole membrane (PVM)**, an additional layer of protection that insulates it from the host's intracellular defense mechanisms, such as lysosomal degradation (de Koning-Ward et al., 2022). The PVM not only provides physical separation from host defenses but also facilitates the export of parasite proteins that modify the RBC's structure, enhancing nutrient uptake and contributing to immune evasion (Birnbaum et al., 2020). This process is critical for the parasite's development and replication, as the RBC environment offers both a nutrient-rich habitat and protection from immune surveillance (Scully et al., 2019).

3.5 Knobs Formation

During the asexual blood stage of infection, *Plasmodium falciparum* induces significant modifications in the red blood cells (RBCs), leading to the formation of knob-like structures on the surface of infected erythrocytes. These knobs are rich in the parasite-derived protein **PfEMP1 (*Plasmodium falciparum* erythrocyte membrane protein 1)**, which plays a key role in the parasite's survival strategy. These protrusions enable infected RBCs to adhere to endothelial cells lining blood vessels, a process known as **cytoadherence**. This adhesion occurs in various organs, most notably in the brain, contributing to severe complications like **cerebral malaria** (Hviid & Jensen, 2015; Maier et al., 2022).

The formation of these knobs and the interaction between PfEMP1 and endothelial receptors such as **ICAM-1** (intercellular adhesion molecule-1) and **CD36** allow infected RBCs to avoid being filtered and destroyed by the spleen, a process known as **splenic clearance**. This sequestration is critical for the parasite, as it prolongs the lifespan of infected RBCs, enabling the parasite to continue its replication cycle (Turner et al., 2018). Studies have also shown that the mechanical properties of these knobs enhance the cytoadherence ability, contributing to the severity of malaria by obstructing blood flow, particularly in small capillaries, thereby exacerbating complications (Abdi et al., 2022).

3.6 RBC Surface Alteration

Plasmodium falciparum has evolved mechanisms to modify the surface of infected red blood cells (RBCs), primarily through the display of adhesive proteins such as **PfEMP1 (*Plasmodium falciparum* erythrocyte membrane protein 1)**. These proteins bind to endothelial receptors like **ICAM-1** (intercellular adhesion molecule-1), **CD36**, and **E-selectin**, which enables infected RBCs to adhere to the walls of blood vessels, particularly in the microvasculature (Maier et al., 2022). This cytoadherence prevents the infected RBCs from passing through the spleen, where they would otherwise be filtered and destroyed by splenic macrophages (Turner et al., 2018). The sequestration of infected RBCs in various organs, including the brain, lungs, and placenta, is closely associated with severe clinical manifestations of malaria, such as cerebral malaria (Abdi et al., 2022). The binding of PfEMP1 to multiple endothelial receptors also exacerbates microvascular obstruction, contributing to complications like hypoxia and organ failure (Schmidt et al., 2021).

3.7 Modulation of Host Immune Response

Plasmodium falciparum secretes various molecules that actively modulate the host's immune response, allowing the parasite to survive within the human host for extended periods. One such mechanism involves the inhibition of macrophage activation, which is critical for the early immune response to infection (Ockenhouse et al., 2022). The parasite interferes with the production of pro-inflammatory cytokines such as TNF-α and IL-12, which are essential for coordinating a robust immune response (Sewell et al., 2023). In addition, the parasite releases **hemozoin**, a by-product of hemoglobin digestion, which has been shown to disrupt cytokine signaling and diminish the antigen-presenting capabilities of dendritic cells (Wykes & Horne-Debets, 2022). These modulations of the host immune system are crucial for enabling parasite replication and facilitating the chronic nature of *P. falciparum* infection.

Nutrient Acquisition

Once inside the red blood cells, *P. falciparum* heavily relies on the modification of the host cell's membrane permeability to ensure its metabolic needs are met. The parasite induces the formation of **new permeability pathways (NPPs)** that allow for the influx of essential nutrients like glucose, amino acids, and ions, while simultaneously facilitating the efflux of waste products such as lactate and ammonia (Martin et al., 2023). The parasite's ability to hijack host cell transport mechanisms is critical for its survival, as *P. falciparum* is unable to synthesize certain nutrients de novo. In addition, the parasite utilizes host hemoglobin as a major source of amino acids, breaking it down within the parasitophorous vacuole (Kirk et al., 2022). This metabolic reprogramming not only ensures the parasite's growth but also contributes to the pathological effects seen in malaria, such as anemia and metabolic acidosis.

Haemoglobin Digestion as a Survival Strategy in *Plasmodium falciparum*

One of the essential survival strategies of *Plasmodium falciparum* during its asexual blood stage is its ability to digest host hemoglobin within the red blood cells (RBCs). Hemoglobin, the oxygen-carrying protein in RBCs, serves as a crucial source of amino acids for the parasite, which lacks the metabolic pathways to synthesize many essential nutrients. Inside the parasitophorous vacuole, the parasite degrades hemoglobin using a set of specialized proteases, such as **plasmepsins**, **falcipains**, and **metalloenzymes** (Kirk et al., 2022).

Hemoglobin digestion occurs in a stepwise process. Initially, hemoglobin is broken down into globin chains, which are further hydrolyzed into free amino acids (Martin et al., 2023). These amino acids are then used for the parasite's protein synthesis, supporting its rapid growth and replication. However, this process generates a toxic by-product, **heme**, which is converted into an inert crystalline form called **hemozoin**. The formation of hemozoin is critical for the parasite's survival, as free heme can cause oxidative damage to the parasite (Wang et al., 2022).

Hemoglobin digestion not only meets the parasite's nutritional needs but also contributes to the pathophysiology of malaria, particularly through hemolysis and the resulting anemia in the host (Maier et al., 2022). This survival strategy is thus an attractive target for antimalarial drugs, such as **chloroquine**, which interferes with hemozoin formation, leading to the accumulation of toxic free heme (Kirk et al., 2022).

4.0 Survival Strategies in Mosquitoes

4.1 Adaptation to Mosquito Midgut Environment

Upon ingestion by a mosquito, *Plasmodium falciparum* gametocytes transform into male and female gametes within the midgut. These gametes fuse to form zygotes, which then develop into motile **ookinetes**. To survive and progress within the hostile environment of the mosquito midgut, ookinetes secrete enzymes such as **chitinases** that help degrade the **peritrophic matrix**, a protective barrier in the mosquito gut. This degradation allows the ookinetes to pass through the midgut epithelium (Sinden, 2015; Vaughan et al., 2022). Additionally, ookinetes express surface proteins such as **P25 and P28** that aid in adhesion to and penetration of the midgut wall, a critical step for further development (Ghosh et al., 2022). The ability of *P. falciparum* to navigate this challenging environment is essential for completing its life cycle and achieving transmission to the next human host.

In the mosquito host, *P. falciparum* demonstrates remarkable adaptability to ensure successful transmission. Research by O'Donnell et al. (2023) reveals that the parasite manipulates mosquito feeding behavior, increasing the frequency and duration of feeding to enhance transmission potential. Additionally, the parasite undergoes sexual reproduction in the mosquito midgut, where it evades the mosquito's immune defenses by exploiting midgut enzymes and proteins that facilitate its development into sporozoites (Sinden et al., 2023). These adaptations ensure that infectious sporozoites reach the mosquito's salivary glands, ready for transmission to the next human host.

4.2 Sporogonic Development

After successfully penetrating the midgut epithelium, ookinetes embed themselves in the midgut wall and transform into **oocysts**. These oocysts undergo **sporogonic development**, a process during which thousands of infectious **sporozoites** are produced within each oocyst. The oocysts take 10-14 days to mature, after which they rupture, releasing sporozoites that migrate to the mosquito's **salivary glands** (Sinden, 2015; Smith & Boyer, 2023). The timing of this development is synchronized with the mosquito's feeding cycle, ensuring that sporozoites are ready for transmission during

the mosquito's next blood meal. This intricate synchronization enhances the parasite's ability to infect new human hosts efficiently and ensures successful continuation of the life cycle (Kaushal et al., 2023).

5.0 Role of Host Factors in Parasite Survival

As stated above, host factors play a crucial role in the survival and proliferation of *Plasmodium falciparum* during malaria infection. These factors include the immune response, genetic traits, metabolic pathways, and environmental conditions provided by the host, all of which impact the parasite's ability to thrive.

5.1 Immune Modulation: *P. falciparum* exploits several host immune mechanisms to evade destruction. The immune system initially responds to the parasite's presence through both innate and adaptive pathways. However, the parasite uses strategies like antigenic variation, which alters the proteins displayed on infected red blood cells (such as PfEMP1), to evade detection and neutralization by the host's immune cells (Hoffman et al., 2022). In some cases, *P. falciparum* produces proteins like RIFIN that inhibit macrophage activation, further dampening immune responses (Desai et al., 2022).

5.2 Genetic Traits: Host genetic factors such as sickle cell trait (HbS), thalassemia, and G6PD deficiency are known to influence parasite survival. In individuals with these genetic traits, red blood cells are less hospitable to the parasite, often impeding its replication. For example, sickle-shaped RBCs have a shorter lifespan, preventing the parasite from completing its asexual cycle, thus reducing the severity of malaria in individuals with the sickle cell trait (Miller et al., 2002).

5.3 Metabolic Adaptation: *P. falciparum* heavily relies on the host's metabolic environment, particularly the availability of glucose and hemoglobin. Inside red blood cells (RBCs), the parasite modifies host cell permeability to access these nutrients. The host's ability to supply essential nutrients, such as glucose, facilitates the growth of the parasite, as it cannot synthesize key nutrients independently (Martin & Kirk, 2023). Moreover, the host's stress responses, such as the production of reactive oxygen species (ROS), can influence parasite development, with *P. falciparum* adapting its antioxidant defenses to neutralize these harmful compounds (Wang et al., 2022).

5.4 Cytokine Response and Pathology: Host cytokine responses, such as the production of TNF-α, IL-12, and IFN-γ, are crucial in controlling parasite load, but excessive production can lead to severe immunopathology. The parasite has evolved mechanisms to manipulate these cytokine responses to prevent an overzealous immune reaction, ensuring its survival. For instance, the secretion of hemozoin disrupts the function of dendritic cells and antigen-presenting cells, weakening the host's adaptive immune response (Ockenhouse et al., 2022).

5.6 Cellular and Tissue Environment: The physical properties of host tissues and cells play a significant role in parasite survival. The ability of *P. falciparum* to alter RBC deformability aids its sequestration in tissues like the brain, lungs, and placenta, which facilitates immune evasion. Host endothelial cells provide receptors, such as ICAM-1 and CD36, that enable the cytoadherence of infected RBCs to avoid clearance by the spleen (Maier et al., 2022). These interactions between the parasite and host cells not only support parasite survival but also contribute to severe clinical outcomes like cerebral malaria.

Conclusion

Overall, host factors, ranging from immune system modulation to genetic traits and metabolic adaptation, significantly influence *Plasmodium falciparum*'s ability to survive and propagate. The intricate interplay between the host and the parasite offers insights into potential therapeutic strategies, such as targeting host-parasite interactions, to disrupt the survival mechanisms of the parasite.

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