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Cellular and Molecular mechanisms for invasion, growth and pathogenesis of *Plasmodium* species in human

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REVIEW
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ABSTRACT: Malaria is a disease of humans caused by protozoan parasites of the genus ***Plasmodium*** with a complex life cycle. Invasion is initiated when merozoites invade circulating erythrocytes. Many proteins, parasite ligands, and host receptors are involved in signaling and erythrocyte membrane fusion. The tight junction and formation of the parasitophorous vacuole membrane must fuse to seal the invasion process. The development of intracellular parasites in conjunction with human evolution has resulted in the establishment of intricate molecular contacts between the parasite and the host cell. These interactions serve the purpose of invading host cells, facilitating migration across different tissues, evading the host immune system, and undergoing intracellular replication. The occurrence of cellular migration and invasion events is crucial for both growth and the development of disease pathogenesis. To review literature written on cellular and molecular mechanisms for invasion, growth, and pathogenesis of ***Plasmodium*** species in humans. Literature written on cellular and molecular mechanisms for invasion, growth, and pathogenesis of ***Plasmodium*** species in humans was systematically reviewed from 2000–2021 years on Google Scholar sources, Pub Med, and Medline. The key words used to search were erythrocyte, growth, invasion, malaria, and molecular mechanism Pathogenesis, Plasmodium, Red Blood Cell, and Host-parasite Interaction. Malaria is a major health problem caused by protozoan parasites of the genus ***Plasmodium,*** whose obligate intracellular life cycle is complex. They use molecular mechanisms to gain access to the host cell and multiply; their apical organelles integrate secretary functions. These secretary organelles, which are proteins in nature, are responsible for successful attachment, reorientation, and invasion of host cells and use Hgb as a nutrient for growth and development. Hgb degradation occurs in an acidic digestive vacuole. During growth, three morphologically distinct phases are observed, and pathogenesis is due to several mechanisms, such as the production of toxins, the sequestration of infected RBC in different organs, the production of inflammatory mediators by the innate and adaptive immune responses, and the hemolysis of RBC. This review was an overview of the molecular and cellular mechanisms for invasion, growth, and pathogenesis of ***Plasmodium*** parasites in various aspects of parasite biology and host cell tropism and indicated opportunities for malaria control and the development of an effective vaccine.

KEYWORDS: Cellular, Molecular, invasion, growth, pathogenesis, Plasmodium

INTRODUCTION

The genus *Plasmodium* is a blood parasite of the family plasmodia in the suborder Haemosporina that causes a disease called malaria. There are around 156 species of *Plasmodium* that infect various species of vertebrates. Five are known to infect humans, namely *P. falciparum, P. vivax*, *P. ovale*, *P. malariae,* and the recently described species (*P. knowlesi)* [1]. Among these malarial parasites, *P. falciparum* remains the most extremely severe and devastating human parasitic infection [2].

Malaria is one of the most fatal diseases and remains an important cause of morbidity and mortality worldwide. It has a broad distribution in both the subtropics and tropics, with many areas of the tropics endemic to the

disease. The countries of sub-Saharan Africa account for the majority of all malaria cases, with the remaining cases mostly clustered in India, Brazil, Afghanistan, Sri Lanka, Thailand, Indonesia, Vietnam, Cambodia, and China[3]. According to the WHO 2021 report, in 2020 there will be around 241 million new cases, compared to 229 million cases in 2019 and 627 000 deaths in 2020, an increase of 69 000 deaths over the previous year. Malaria reported in children aged less than 5 years accounts for 80% of all malaria deaths worldwide. From the total, the WHO African region accounted for most of the global cases of malaria (94% of malaria cases and deaths). Nigeria, the Democratic Republic of the Congo, the United Republic of Tanzania, and Mozambique were responsible for slightly more than half of the global malaria deaths: 31.9%, 13.2%, 4.1%, and 3.8% respectively [4].

In Ethiopia, the burden of malaria continues to cause a large number of morbidities and deaths. Malaria has been one of the main causes of death in the country. About 68–70% of the population lives in malaria-risk areas. *Plasmodium falciparum* and *P. vivax* are the dominant parasites, accounting for 60% and 40% of malaria cases, respectively, in Ethiopia [5]. The female Anopheles mosquito spreads Plasmodium species through a two-host life cycle that must go back and forth between the final female Anopheles mosquito host and the intermediate human host[6].Humans are the intermediate hosts for asexual reproduction, which occurs in the liver and RBC, whereas mosquitoes are the definitive hosts, in which sexual reproduction takes place in the stomach of mosquitoes[7]. During infection, sporozoites leave Anopheles' salivary glands and enter the human host. They then find hepatocytes and grow into schizonts and then merozoites, which is known as the exoerythrocytic stage of infection. Rhoptries, micromeres, dense granules, and specialized secretary organelles in the parasite's apical complex mediate the merozoites' egress and entry into specific host cell types [8]. Polarized merozoites initially attach to the surface of red blood cells (RBCs) through a ligands-receptor-mediated process, allowing them to invade and escape from host cells. Inside the red blood cells, the parasite copies itself and grows into schizonts. These break open to release new merozoites and finish the blood stage cycle [9]. The human host immune system exposes merozoites antigens, such as merozoites surface proteins -1 and -2 (MSP-1 and -2) and apical membrane antigen-1 (AMA-1) [10], making them potential vaccine candidates. During the invasion, the parasite proteolytically sheds these membrane-bound proteins (adhesions), resulting in the disengagement of interactions between parasite ligands and the host cell surface [11] .

A child's age, the level of parasitemia, their parents' or guardians' lack of attention to fevers, their parents' or guardians' busy work schedules or other healthy children and their refusal to use available health facilities, the host's innate and acquired immunity, and the timing and effectiveness of effective treatment [12] were all things that led to the rapid progression of simple malaria to severe malaria. Plasmodium parasites have a good way of getting into cells that don't get eaten by other cells. They challenge their hosts by infecting tissues that don't have strong immune systems. Plasmodium needs to be able to glide in order to enter the invasive stage, which lets it move through tissues and actively enter and leave host cells [1, 13]. The aim of this review is to provide an overview of what is currently known about cellular and molecular mechanisms for invasion, growth, and pathogenesis of *Plasmodium* species in humans and to highlight directions that are likely to lead to malaria control and the development of an effective vaccine.

To review literature written on cellular and molecular mechanisms for invasion, growth, and pathogenesis of *Plasmodium* species in humans

METHODS

Literature written on cellular and molecular mechanisms for invasion, growth, and pathogenesis of *Plasmodium* species in humans was systematically reviewed from 2000–2021 years on Google Scholar sources, PubMed, and MedLine. The terms used to search were erythrocyte, growth, invasion, malaria, and molecular mechanism. Pathogenesis, Plasmodium, red blood cells, host-parasite interaction.

LITERATURE REVIEW

Molecular mechanisms of *Plasmodium* species invasion in human cells

Invasion of host cells by Apicomplexa parasites, including *Plasmodium* species is essential and stepwise process in the life cycle of obligate intracellular pathogen. Following invasion, a tight junction is established, serving as an aperture within the host cell that facilitates the parasite's self-retraction prior to its establishment into a newly created parasitophorous vacuole.

Two protein groups secreted from different secretary organelles, the micronemal protein apical membrane antigen 1 (AMA 1) and rhoptry proteins form part of this structure. Association between *Pspecies, parum* AMA 1 and the rhoptry neck (RON) complex occurs after reorientation, and engagement of the actinomycin motor results in rhoptry release. The establishment of parasite infection within the parasitophorous vacuole is facilitated by the creation of the AMA1-RON complex, which is crucial for the rhoptry contents [14, 15].

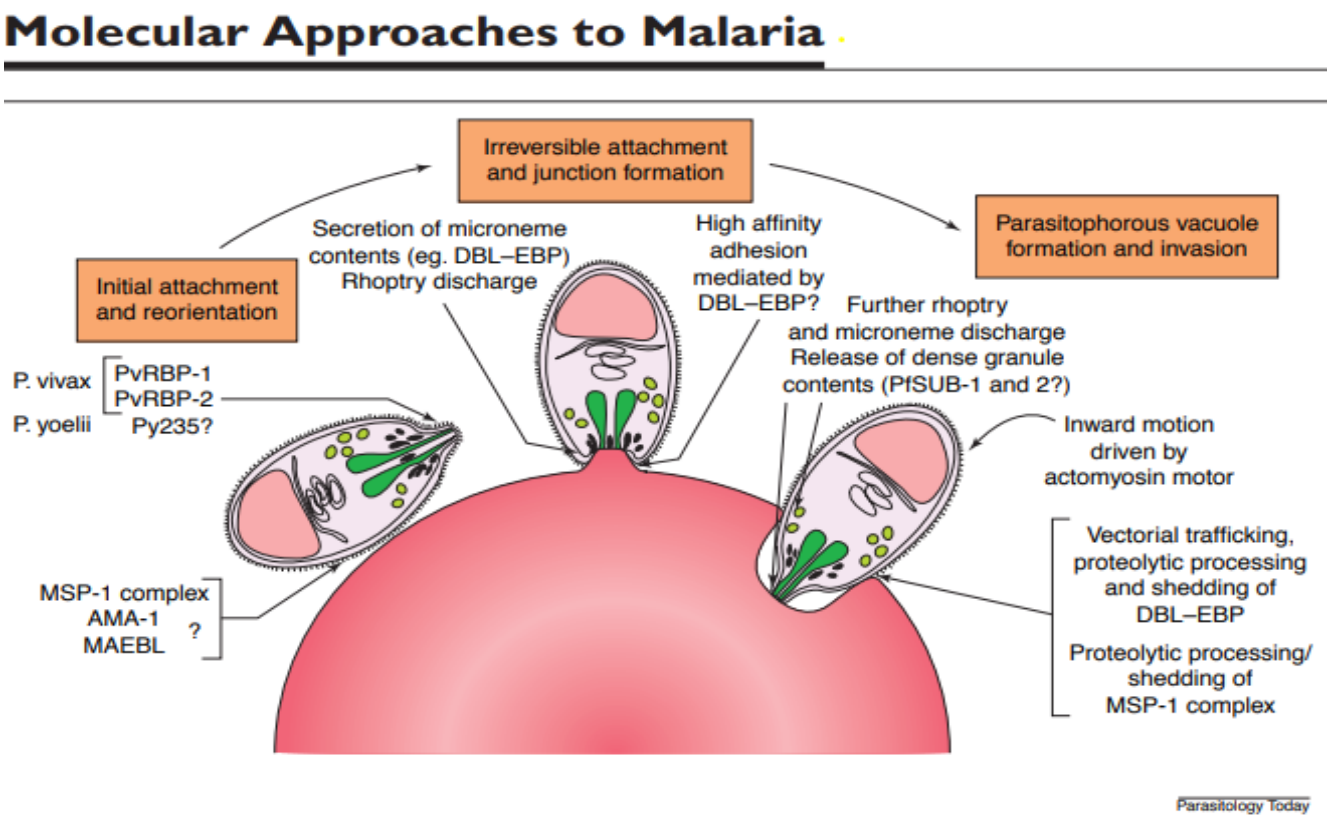

Figure 1. Red blood cell invasion by the malaria merozoites and the roles of protein and secretary organelles of the merozoites [16].

The role of malaria merozoite proteases in red blood cell invasion

Protease activity is needed for effective invasion to separate interactions between parasite adhesin proteins and receptors that are found in host cells [17]. Throughout the invasion process, the parasite continuously releases at least two crucial surface proteins from the merozoites when it enters the parasitophorous vacuole. The process of shedding is executed by the cleavage of the juxtamembrane and is facilitated by the enzyme sheddase, which is classified within the subtilisin-like superfamily [18, 19].

Cleavage of microneme proteins

The photolytic cleavage of microneme proteins, including members of the thrombospondin-related apical membrane antigen family (TRAP) and AMA-1, is a key event for successful host cell invasion[1]. The merozoite surface is covered uniformly with a protein complex comprising four polypeptides derived from the MSP-1 precursor, in association with two other proteins encoded by distinct genes 1 and 2. During erythrocyte invasion, the bulk of this complex is released from the merozoite surface as a result of an essential proteolytic cleavage of the single membrane-bound component of the complex [20]. Another family of intramembrane serine proteases called rhomboids found in *plasmodium* plays a vital role in invasion by the malaria parasite and in capping proteolysis [17]. *Plasmodium* invasion is completed within 30 seconds in four separate steps: 1). Reversible initial low-affinity interaction between the merozoite and the host cell surface; 2). Reorienting the merozoites to allow its apical prominence to contact the host cell; 3). Irreversible attachment and formation of an electron-dense junction between the apical prominence and the host cell; 4). Appropriate invasion, in which the junction is translocated back over the parasite circumference as it is propelled forward into an invagination in the host cell membrane called the parasitophorous vacuole, entry into the vacuole by movement of the junction, and eventually resealing of the vacuolar and erythrocytic membranes [18, 21].

The initial low-affinity interactions occur between the hosts and the resident parasite surface molecules (MSP1). Reorientation and junction formation are mediated by higher-affinity transmembrane adhesins released from a set of secretory organelles called micronemes, which are located at the apical end of the parasite [22]. These adhesins bind host cell surface receptors through their ectodomains and engage with a cortical actinomyosin motor through their cytoplasmic domains. Myosin-driven capping of the adhesins then draws the junction around the parasite and provides the attraction to drive invasion. Successful completion of invasion requires the eventual detachment of all these adhesin-receptor interactions by proteolytic enzymes, which is accomplished by the shedding of the adhesins [23-25]

A total of ten merozoite surface proteins (MSP1–MSP10) are found on the merozoite surface. MSP1 is important because it is one of the most abundant constituents of the merozoite surface and it induces protective antibody responses (giving it potential as a vaccine). MSP1 is synthesized as a 200 kDa precursor protein that is subject to proteolytic processing soon after transport to the plasma membrane of the intracellular developing parasite[26]. On the surface of the released merozoites, MSP exists as a non-covalently associated complex of proteolytic fragments, and it is this complex that mediates the primary low-affinity interactions between merozoites and RBCs. During invasion, the membrane-bound fragment of the complex is further cleaved at a single juxtamembrane site. The C-terminal domain, which is called MSP-119, remains bound to the invading parasite surface while the rest of the MSP1 complex (like fragments of MSP6 and MSP7) becomes shed. The parasite protease responsible for shedding is a membrane-bound calcium-dependent serine protease that is probably released onto the merozoite surface at the point of invasion and is positioned at the moving junction as it tracks back over the parasite surface [27]. This protease is termed merozoite surface sheddase (MESH). Merozoite Surface Protein 1 is also essential for blood-stage growth and is expressed and processed in all *Plasmodium* species. Shedding MSP1 is a prerequisite for invasion. Merozoite surface sheddase also mediates the shedding of other MSPs during invasion [10, 28]

DISCUSSION

The role of *plasmodium* apical membrane antigen-1 in host cell invasion

The asexual blood-stage protein known as Apical Membrane Antigen 1 (AMA1) is found in the invasive merozoite form of plasmodia species. AMA1 has an important role in the invasion of RBCs by *plasmodium* species [29]. Before invasion, an integral membrane protein called apical membrane antigen-1 (AMA1) is secreted from micronemes onto the merozoite surface [30]. The micromeres emerge from the Golgi, translocate along the subpellicular microtubules, and eventually dock with the rhoptry tips. AMA1 has the following roles in the invasion of host cells: 1) Like MSP1, antibodies to AMA1 can prevent invasion and can protect against blood stage parasitemia in vivo; 2). both blood-stage growth and sporozoites express AMA1, which plays a similarly important role in invasion; 3) AMA1 plays a role in the reorientation of the parasite or in junction formation; 4) AMA1 or its sub domain has RBC-binding activity; 5) Like MSP1, shedding of AMA1 is required for productive invasion, as Abs that interfere with shedding also inhibit invasion [28].

Host-cell-binding proteins found in *plasmodium* species

Proteins used for host cell attachment and invasion in *P. vivax* and *P. knowlesi*

There are two host cell binding proteins for *Plasmodium vivax: P. vivax* reticulocyte binding protein-1 (PvRBP-1) and *P. vivax reticulocyte* binding protein-2 (PvRBP-2). These RBPs are highly expressed on the surface of the merozoite apical prominence. They are involved in selective binding and invasion of reticulocytes. The reticulocyte binding proteins 1 and 2 of *P. vivax* are situated at the apical end of the merozoites in *P. vivax*. These proteins have a crucial function in attaching to host cell receptors during reorientation. This protein family is required in the different *plasmodium* species for sensing of the host erythrocyte, activation of the invasion process, and development of the rigid junction [31, 32]. The human malaria parasite, *P. vivax,* and the related simian parasite, *P. knowlesi,* invade human erythrocytes using the Duffy blood group antigen as the receptor [33]. The *P. vivax* and *P. knowlesi* Duffy antigen-binding proteins are members of another group of merozoite proteins that function in adhesion to RBC surface receptors. These proteins belong to a large family called the Duffy binding-like erythrocyte binding protein (DBL-EBP) family, which includes the *P. knowlesi* b and g proteins [34]. The N-terminal Cystine-rich domains of the EBP, also known as Duffy-binding-like (DBL) domains, are within region II of the molecule and possess receptor-binding activity. The adhesive domains of *P. vivax* are being developed as vaccines for malaria. *Plasmodium vivax* is completely dependent on the Duffy antigen for RBC invasion. The proper functioning of these adhesion proteins requires their appropriate proteolytic shedding as they cap to the posterior of the parasite [35, 36].

Proteins used for host cell attachment and invasion in *P. falciparum*

Host cell invasion is essential for the survival of obligate intracellular parasites; *P. falciparum* is known to invade RBC by several pathways. Creating multiple pathways makes sure that the host cell can enter even when the host's immune system reacts in certain ways and has different receptor types. In fact, P. falciparum merozoites get into erythrocytes through more than one ligand-receptor interaction, and there are duplicates in each pathway [36]. The *P. falciparum* merozoite expresses several members of the EBL family, which includes EBA-175, EBA-140, and EBA-181 [37]. The proteins attach to particular glycoproteins on the erythrocyte's surface and contribute to the invasion mechanism. The binding of EBA-175 to glycophorin A has been observed to play a significant role in the ligand-receptor interaction across many strains of *P. falciparum*. Certain antibodies have the ability to impede the process of invasion. The available evidence suggests that recombinant parasites that do not express this ligand have the ability to penetrate and exhibit normal growth. Indeed, some parasites are capable of switching reliance to other ligand-receptor interactions for merozoite invasion to compensate for the loss of EBA-175 function. EBA-140 specifically binds to glycophorin C on RBCs, and this interaction contributes to invasion as Abs to the ligand can partially inhibit the process [38]. Glycophorin C is responsible for the Gerbich (Ge) blood group system. EBA-140 does not bind to the altered form of glycophorin C in Ge-negative erythrocytes, nor can *P. falciparum* invade these cells using this invasion pathway [39]. The *P. falciparum* reticulocyte-binding-like proteins (Pf RBLP) family of proteins is a second family of proteins in *P. falciparum*. There is a protein that looks a lot like PvRBP in P. vivax that seems to be very important for merozoite invasion. There are two *P. falciparum* merozoite proteases important for shading, both of which localize to organelles within the apical complex called *P. falciparum* subtilisin like proteases 1 and 2 (PfSUB-1 and PfSUB-2). The enzymes belong to the subtilisin-like superfamily of serine proteases and are subjected to a complex post-translational maturation process [40]. The expression of Thrombospondin-related apical merozoite protein (TRAP) varies across different invasive stages of Plasmodium Micronemes. These proteins are stored in the TRAP family and are released onto the surface of the parasite during invasion. Upon reaching the host cell receptors, these proteins bind to host cell receptors, thereby facilitating the motility and invasion of the parasite. The proteins Thrombospondin-related apical merozoite protein (CSP), Circumsporozoite protein (CSP), and Circumsporozoite and TRAP-related protein (CTRP) play significant roles in the invasion of host cells by both sporozoites (TRAP and CSP) and ookinetes (CTRP) [41].

Redundancy in the invasion of *Plasmodium falciparum*

Malarial merozoites, especially those from *P. falciparum* and *P. knowlesi*, have the ability to invade erythrocytes through several invasion pathways. Evidence for alternative invasion pathways was provided by *P. falciparum* strains that invaded glycophorin A-deficient erythrocytes and sialic acid-deficient erythrocytes [42]. Unlike *P. vivax*, which invades only Duffy blood group-positive reticulocytes, *P. falciparum* exhibits redundancy in erythrocyte invasion and invades all-age human erythrocytes. Using different enzymatic treatments on target erythrocytes showed that P. falciparum does not only need sialic acids or glycophorin A to invade. The alternative invasion pathways are classified on the basis of the nature of the erythrocyte receptor involved in invasion, which in turn is defined by the enzymatic treatments and erythrocytes being null for specific surface proteins [43].

Mechanisms of host cell invasion, parasitophorous vacuole formation, and egress/exit

Invasion by sporozoites is the most versatile invasive form of plasmodium and is capable of gliding, migration, host cell invasion, and egress. The parasites can enter liver cells either by disrupting the plasma membrane and migrating through the cells, or by forming vacuoles and then dividing. Migration through cells has an effect on both sporozoite infectivity by inducing the exocytosis of sporozoite apical organelles and on the permissiveness of the surrounding hepatocytes through the secretion of hepatocyte growth factor (HGF), which increases their susceptibility to infection [44]. Sporozoites microneme protein essential for cell traversal (SPECT) sheds new light on migration into the liver. This protein helps sporozoites gain access to hepatocytes by crossing the liver sinusoidal cell at the level of the Kupffer cells [45, 46].

There are also several novel genes involved in motility and invasion. These include proteins involved in signaling cascades, adhesive molecules involved in recognition and attachment to host cells, proteases acting on parasite or host proteins, and components of the myosin motor complex [47]. Throughout their life cycle, malaria parasites are required to identify and infiltrate several cells. The invasion of erythrocytes by merozoites is a multifaceted and intricate process that relies on a sequence of distinct molecular interactions. Hence, it is imperative to possess a comprehensive comprehension of the molecular interactions that underlie the invasion process. Survival and transmission depend on the ability of the invasive stages of the parasite to recognize and invade the appropriate host cell types. Numerous molecules that participate in the invasion process are found in

apical organelles (Rhoptries, micromeres, and dense granules) in the invasive stages of plasmodia species. The sequence of invasive steps is similar for all *plasmodium* species [44]. Invasive stages of plasmodium species are made up of very polarized, moving cells that use their ability to glide on substrate to get into and out of host cells and cross biological barriers. The process by which these invasive forms are expelled from host cells, typically following parasite reproduction, is referred to as egress. The merozoites exhibit an apical complex consisting of specialized secretory organelles such as rhoptries, micronemes, and dense granules. Additionally, they possess an inner membrane complex constituted of flattened vesicles that are connected to the subpellicular microtubules [48, 49]. Host cell invasion typically leads to the formation of a parasitophorous vacuole. The malaria parasite elaborates a tubulovesicular network that can extend into the erythrocyte cytoplasm, and these extensions may be important for the transport of solutes [50]. Other membranous structures, such as Maurer's clefts, are formed in the host cell cytoplasm and are important in protein trafficking. Merozoite release (egress) involves a primary rupture of the parasitophorous vacuole membrane, followed by a secondary rupture of the erythrocyte plasma membrane. Both steps rely on the action of distinct proteases. Falcipain-2 has a role in the release of merozoites from RBCs and in Hgb degradation [51, 52].

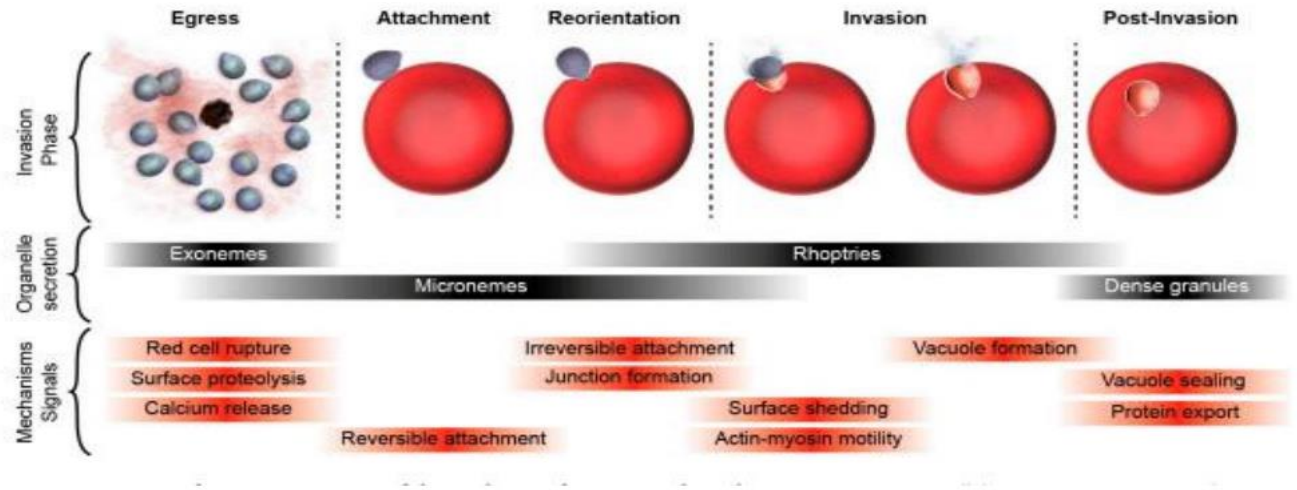

Figure 2. Merozoites invasion of the erythrocyte from egress through post-invasion [53].

The role of calcium in signaling during invasion

In all eukaryotic cells, including protozoan parasites, calcium (Ca2+) serves as a prominent signaling molecule. Its primary function is to facilitate motility and host cell entrance by promoting the release of adhesion proteins. The feeding vacuole in *P. falciparum* serves as a significant storage site for Ca2+ ions. The application of Ca2+ indicator dyes has provided evidence of increased Ca2+ levels within the parasitophorous vacuole of infected erythrocytes. The second source of Ca2+ is likewise expected to have a role in the accumulation of intracellular Ca2+ stores in parasites, which is necessary for the functioning of a Ca2+-dependent signaling system [54, 55].

Cellular mechanisms for invasion of *plasmodium* species

The cellular steps of invasion

Sporozoites cross the cytosol of several cells before invading hepatocytes by the formation of a parasitophorous vacuole, in which they develop into merozoites. Sporozoites migration through several cells in the mammalian host appears to be essential for the completion of the life cycle [56]. Upon egress, the bursting schizonts release the mature merozoites, which then associate with erythrocytes. The initial encounter entails a notable displacement of the merozoite and alteration of the surface of the erythrocyte, which is subsequently followed by an aggressive process of reorientation that positions the apex of the parasite in close proximity to the membrane of the host cell. Subsequently, the erythrocyte cytoskeleton undergoes remodeling driven by the parasite, leading to the final entry of the parasite into the erythrocyte. Following the process of sealing at the posterior region of invasion, there is a subsequent brief phase characterized by echinocytosis of the red blood cell. This morphological phenomenon is triggered by the efflux of potassium and chloride ions, resulting in the erythrocyte returning to its original shape within a time frame of 10 minutes. Subsequently, the internalized parasite undergoes a phase of ring formation and experiences swift and significant alterations in its morphology [57] [58].

Molecular mechanisms for the growth of *plasmodium* species in humans

Parasite growth starts after the entry of *plasmodium* merozoite into RBCs, and it starts to develop to the ring stage (immature trophozoite) to continue development. This growth is mainly accomplished by HGB degradation. AMA1 and MSP1 are essential for blood stage growth in addition to invasion and are expressed and processed in all *plasmodium* species [59]. Being intracellular is important because it leads to easy access to Hgb. The merozoite exhibits a heightened commitment to the processes of invasion and the development of parasitophorous vacuoles, both of which play a crucial role in the subsequent differentiation of the parasite within the host erythrocyte. Late schizonts transcribe the genes required for differentiation into an invasive parasite, in accordance with their intended purpose [60, 61].

Hemoglobin ingestion

Hemoglobin consumption during the ring, which is the early stage of growth known as the young trophozoite stage, seems to be restricted. Nevertheless, the presence of hemozoin in early-stage parasites indicates the existence of cellular mechanisms involved in ingestion and proteolysis [62]. Micropinocytosis takes up small portions of cytoplasm early in development. Sometimes, one can see vesicles containing a tiny hemozoin crystal. The maturation process of the parasite involves the invagination of both the parasitophorous vacuolar membrane and the parasite plasma membrane, resulting in the formation of a cytostomal system that facilitates the uptake of a greater quantity of hemoglobin. The cytosome is a membrane-spanning structure that separates the cytoplasms of parasites and erythrocytes. The cytosome in P. falciparum is a sizable double membrane encapsulated within a pear-ear shaped composition [63].

Digestive Vacuole and Hemoglobin Degradation

After the formation of the digestive vacuole, it becomes evident that it serves as the principal location for the breakdown of Hgb. The vesicle is subsequently broken down, and Hgb undergoes hydrolysis. Phospholipase activity is the agent responsible for vesicular lysis. The digestive vacuoles seen in *P. falciparum* are characterized by their acidic nature, with an estimated pH range of 5.2–5.3. The defining features of lysosomes and yeast vacuoles include their degradative capability and acidic pH. In *P. falciparum*, acid phosphatase is found in endocytic vesicles but not in digestive vacuoles [64]. Throughout the intraerythrocytic cycle, the cytoplasm of the host cell is used and approximately 60-80% of the Hgb undergoes degradation. Proteolysis of hemoglobin results in the liberation of heme and the production of amino acids. The metabolic and recycling processes do not involve the heme component, instead it is kept as an inert polymer referred to as the malaria pigment hemozoin. Parasite proteins include amino acids produced from globin hydrolysis, which also seem to be accessible for energy metabolism. The process of hemoglobin proteolysis plays a crucial role in the proliferation and survival of the plasmodium parasite due to its restricted ability to synthesize amino acids from scratch [65]. Nevertheless, the process of hemoglobin degradation in isolation seems inadequate to meet the metabolic requirements of the parasite due to its limited availability of essential amino acids such as methionine, cysteine, glutamine, and glutamate, as well as its complete absence of isoleucine. Additional amino acids are produced by the breakdown of Hgb, which are then utilized for protein synthesis. This leads to the diffusion of certain amino acids derived from Hgb into the host cell. This observation suggests that the process of Hgb catabolism may include supplementary roles. The digestion of host cell cytosol content by parasites serves the purpose of preventing premature red blood cell (RBC) lysis, which may potentially occur if parasite development were not offset by a reduction in host cell volume [64, 66].

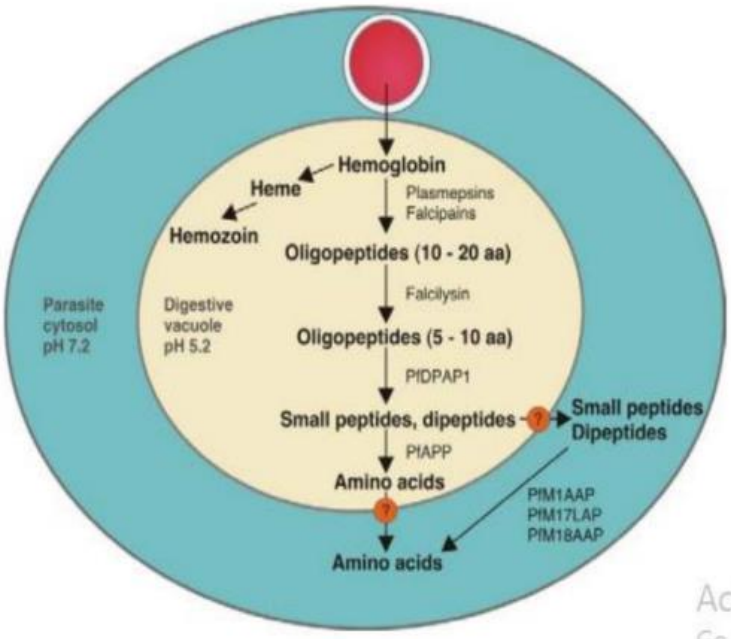

Figure 3. HGB degradation in malaria parasites [67].

Molecular and cellular mechanisms of pathogenesis in *Plasmodium* species

The different manifestations of severe malaria morbidity arise from the interaction of a limited number of pathogenic processes like red cell destruction, toxin-mediated activation of cytokine cascades, and infected cell sequestration in tissue microvascular beds. The asexual erythrocytic phase of the *plasmodium* life cycle is responsible for producing the clinical features and pathology associated with malaria [68]. The clinical manifestations of malaria also result from schizont rupture and, additionally, in the case of *P. falciparum*, from mature trophozoite adherence to endothelial cells [69]. During infection by *P. falciparum*, the surface of the erythrocyte undergoes many changes. The aforementioned alterations have a crucial role in the development of severe diseases and the establishment of host immunity by influencing the interactions between the host and the parasite, as well as in the variety of antigenic markers. The most well-known protein on the surface of the infected erythrocyte is *P. falciparum* erythrocyte membrane protein-1 (PfEMP1). *Plasmodium falciparum* is the only human malaria that exhibits cytoadherence of mature trophozoite and schizont forms. On the other hand, almost all cells infected with mature forms of *P. vivax*, *P. ovale,* and *P. malariae* pass through the spleen [70]. *Plasmodium falciparum* is capable of invading erythrocytes of all agesOnce again, this is a crucial virulence component, as the parasite's capacity to achieve elevated levels of parasitemia is frequently linked to severe disease and morbidity [69].

Immunological processes in malaria pathogenesis

The host's adaptive immune responses play a crucial role in mitigating the clinical consequences of infection and offer limited yet inadequate protection against plasmodium reproduction due to its intricate life cycle. However, it is important to note that these intricate immunological reactions can also contribute to the progression of disease and associated mortality. The prudent control of immunological responses to malaria has significant implications for worldwide public health [71]. The inoculated sporozoite stage is transient and does not induce any pathological effects. The virus invades hepatic cells within a time frame of 30 minutes and subsequently experiences a phase of intracellular reproduction, which remains asymptomatic in clinical manifestations. Following the completion of liver stage replication, the parasite proceeds to establish blood stage infection, which is the primary etiology of the disease. The infection caused by *Plasmodium vivax* and ovale is generally considered to be rather benign. *Plasmodium malariae* often remains asymptomatic in clinical settings, although persistent infection can lead to the development of immune complex-related glomerulonephropathy, which is infrequently linked with mortality. *Plasmodium vivax* is a prevalent inducer of sudden fever, particularly in Asia, South America, and Oceania, and is a contributing factor to the development of anemia. Nevertheless, the majority of severe cases and fatalities are attributed to the blood stage cycle of P. f., which is prevalent in the majority of sub-Saharan Africa and most tropical regions [72].

The release of bioactive parasite molecules and an inappropriately regulated host immune response are therefore the main causes of malaria's fatal pathogenesis. The presence of metabolic acidosis, cerebral malaria (CM), and severe malarial anemia are commonly observed as life-threatening conditions in this particular context. In regions with lower transmission rates, primary infections may manifest into adulthood, wherein severe illness often entails comorbidities such as renal failure, pulmonary edema, shock, and jaundice. Transmission dynamics and host age are significant factors that contribute to the development of diseases, alongside host genetics and immune responses [73]. The parasite growth cycle in RBCs relates to malaria fever. After a fixed period of replication, a schizont causes the infected RBCs to rupture, releasing progeny that quickly invades other RBCs. A simultaneous rupture of a large number of schizonts stimulates a host fever response. Febrile temperatures are damaging to *P. falciparum,* particularly in the second half of its 48-hour replicative cycle. The site-specific localization of parasitized red blood cells (PRBCs) among target organs, the local and systemic action of bioactive parasite products like toxins on host tissues, the local and systemic production of proinflammatory and regulatory cytokines and chemokines by the innate and adaptive immune systems in response to parasite products, and the activation, recruitment, and infiltration of inflammatory cells are generally underlined causes of *plasmodium* pathogenesis [61, 73].

A critical event in the pathogenesis of severe malaria is the sequestration of *P. falciparum*-infected erythrocytes in small blood vessels. A range of receptor-ligand interactions causes parasitized erythrocytes to stick to cells of the endothelium. This is thought to be an immune invasion strategy that allows the parasite to stay within the vascular compartment but to avoid circulating through the spleen [74]. On the parasite side, the major ligand is *P.* erythrocyte-membrane protein-1 (PfEMP-1) encoded by a variable gene family called the var gene. On the host side, a range of different adhesion molecules expressed on the endothelium, platelets, macrophages, and other erythrocytes serve as binding receptors for different forms of PfEMP-1. Oxidative stress is believed to have a

significant impact on numerous catastrophic outcomes. Simultaneously, oxidative stress gives a highly promising justification for the use of anti-malarial treatment [75].

Progression to cerebral malaria

The histopathology of cerebral malaria is related to the accumulation of mature parasitized or infected RBCs in cerebral microvessels through sequestration. This results in CM pathogenesis. PRBCs are sequestered in brain capillaries and postcapillary venules [75, 76]. They induce flow perturbations that result in obstruction and hypoxia of the surrounding brain parenchyma and hemorrhages. Patients infected with *P. falciparum* do not exhibit the presence of mature-stage parasites in their peripheral blood. It is evident that the sequestration of peripheral red blood cells (PRBCs) in deep microvascular beds is a common occurrence among all patients, albeit with a mere 1% of these individuals experiencing cerebral malaria. While PRBC sequestration alone is not enough to induce cerebral malaria, it is essential [77].

In humans with CM, in addition to PRBCs, other cells such as leukocytes or platelets can also be sequestered in brain microvessels. Thus, these host cells can contribute to the development of CM either by local effects in brain microvessels or through distant impacts facilitated by the creation of potentially toxic or damaging mediators, such as pro-inflammatory cytokines, which can be detected in the bloodstream. Parasite toxins, such as glycosylphosphatidylinositols (GPI) and haemozoin, elicit acute-phase immune responses characterized by the local activation of monocytes and the vascular endothelium. Generally, cerebral malaria is due to the accumulation of intravascular infiltrates and microvascular obstruction [59, 78].

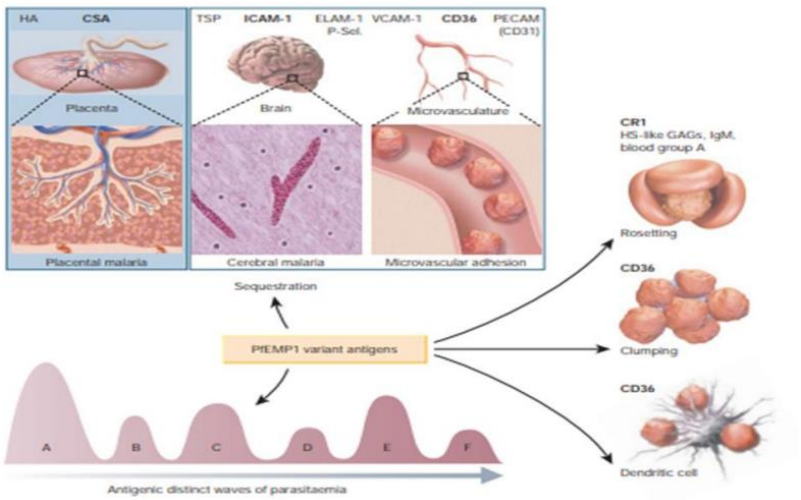

Figure 4. The variant antigen family of PfEMP1 is central to host-parasite interaction and pathogenesis [79].

Host-parasite interaction

The immune response of the host to malaria encompasses phagocytosis, along with the generation of nitric oxide and oxygen radicals. These components are crucial to the host's defensive mechanism and played a role in the development of the disease. The malaria parasite breaks down hemoglobin, resulting in the production of redox-active substances such as free hemoglobin and H2O2. This process causes oxidative damage to the host cell. Nevertheless, the parasite also provides antioxidant compounds to the host and has a highly effective enzymatic antioxidant defense mechanism, which encompasses glutathione and thioredoxin-dependent proteins [80]. The process of detoxifying reactive oxygen species (ROS) is a significant difficulty for erythrocytes that have been infected with Plasmodium. The parasite's rapid growth and multiplication lead to the production of significant amounts of hazardous redox products due to its high metabolic rate. At the core of the induction of oxidative stress lies the process of host hemoglobin breakdown facilitated by the parasite [9]. Haemoglobin serves as the primary amino acid supply for Plasmodium. However, when it is broken down in an acidic food vacuole, it leads to the generation of harmful free hemoglobin and reactive oxygen species (ROS). In addition to the metabolically induced oxidative stress, the host immune system's generation of reactive oxygen species (ROS) contributes to the overall oxidative load experienced by the parasitized cell. Malaria parasites possess a variety of low-molecular-weight antioxidants, with the tripeptide glutathione (GSH) antioxidant enzymes and superoxide dismutase being the most notable, in order to uphold a redox equilibrium. It is worth mentioning that Plasmodium species lack a conventional catalase or a conventional glutathione peroxidase, instead acquiring these enzymes from red blood cells (RBCs) [81, 82].

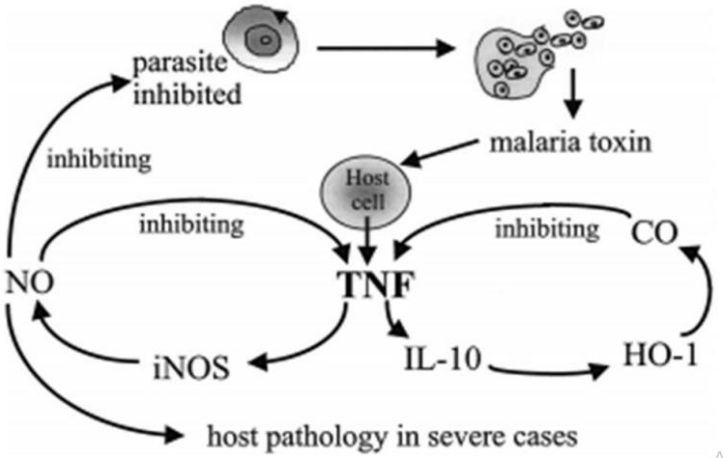

Figure 5. The ability of cytokine-induced NO and CO to inhibit TNF production [83].

CONCLUSIONS AND RECOMMENDATIONS

Malaria is a major health problem caused by protozoan parasites of the of the genus *Plasmodium*. *Plasmodium* parasites are obligate intracellular parasites and exhibit a complex life cycle. They use mechanisms to gain access to the host cell, multiply there, and have apical organelles incorporate secretory function. These secretory organelles, which are proteins in nature, are responsible for successful attachment, reorientation, and invasion of host cells and use Hgb as a nutrient for growth and development. Hgb degradation occurs in an acidic digestive vacuole. Proteases participate in this catabolic pathway. Three morphologically distinct phases are observed during *plasmodium* growth, and the occurrence of pathogenesis is due to several mechanisms, such as the production of toxins, the sequestration of infected RBC in different organs, the production of inflammatory mediators by the innate and adaptive immune responses, and the hemolysis of red blood cells. So cellular and molecular mechanisms for invasion, growth, and pathogenesis of *Plasmodium* species in human parasites on various aspects of parasite biology and host cell tropism indicate opportunities for malaria control, the development of an effective vaccine, an overview of what is currently known, and also highlight directions that are likely to see major advances.

DECLARATIONS

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Authors Contributions statement

E.Woldegerima designed and wrote the review; F.Getachew, M.Misganaw critically read and modified the review; E.Woldegerima, D.Belete performed literature revision and took care of the editing of the review; M.Aemiro, T.Sissy and N.Berhane performed final revision.

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Ethical approval

Not applicable

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