Malaria is a major health problem in various parts of the world especially affecting the tropical countries. It affects the vital organs causing severe complicated malaria. Clinical syndromes like severe cerebral anaemia, coagulation abnormalities, respiratory distress and severe anaemia can increase the mortality of malaria infected cases. Variation in individual susceptibility and severity and type of clinical presentations of malaria raises the need for study of both the parasite and host immune reactions as well as the contribution of inflammatory cytokines in malaria pathogenesis. This study explored the immunopathological basis and advances of severe malaria and their importance in pathogenesis of malaria and its complications. Previous and ongoing studies indicate that changes in endothelium during the sequestration of parasites in organs causes disruption of endothelial barrier function leading to serious effects of malaria. Parasite and host factors contribute to disturbance of cytokine regulation and escape of parasites from the immune system of the host. Immunopathological changes and dysregulation of cytokine production play central role in pathogenesis and disease severity in malaria.

INTRODUCTION

Malaria caused by the intracellular parasite Plasmodium, affects many people in the world especially those living in tropical countries. It affects the vital organs causing severe complicated malaria. Life-threatening complications such as cerebral malaria,
coagulation abnormalities, respiratory distress and severe anaemia can increase the mortality of malaria infected cases. Variation in individual susceptibility and severity as well as type of clinical presentations of malaria raises the need for study of both the parasite and host immunopathological mechanisms. Cytokines released by the host cells upon induction by parasite surface antigens play important role in tissue damage and red cell sequestration seen in severe malaria. Immunopathological basis of severe malaria and their importance in outcome prediction and success of management should be explored.

Endothelial Activation and Parasite Cytoadherence

Endothelial activation is a major pathogenetic mechanism in malaria pathogenesis. Plasmodium falciparum erythrocyte membrane protein-1 from parasites (PfEMP) is a product of diverse var gene. PfEMP forms knobs on the parasitized red cell surface and binds ligands including CD36 and E-elastin on the endothelial cells which are then activated. Increased expression of adhesion molecules on endothelial surfaces occur and result in sequestration of red blood cells leading to ischaemia of the organ affected. Endothelial permeability is augmented by cytokine cascade. The sequestration process results in firm adhesion of IEs to endothelial cells (ECs), monocyte recruitment, microcirculatory changes and induction of cytokine cascade causing local injury and dysfunction. Endothelial surface expression of intercellular adhesion molecule-1 (ICAM-1), endothelial protein C receptor (EPCR) and PECAM-1 are augmented in severe cases of falciparum malaria. These augment the inflammation around the minute vessels and lead to tissue and endothelial injury of pulmonary and brain microvasculature causing acute lung injury and disruption of blood brain barrier in cerebral malaria.

ICAM-1 and EPCR are receptors involved in cerebral malaria. Studies showed that some haemoglobinopathies cause limited red cell invasion by the parasites. Haemoglobin S causes sickling of parasitized red cells rendering protection of malaria. Homozygous (HbSS) and heterozygous (HbAS) states have host microRNA (mRNA) profiles which after fusion with parasite mRNA render inhibition of parasite growth intracellularly. Host polymorphism that affects P. falciparum erythrocyte membrane protein-1 (PfEMP-1) may protect against malaria by impairing the parasite’s ability to cytoadherence to microvessels. Spleen is a major organ to remove malaria parasites from the circulation. Cytoadherence of malaria parasites is vital to the parasite survival to escape from splenic removal. Virulence of the parasites differs according to the ability of cytoadherence through several parasite receptors such as plasmodium EMP1 (PfEMP1). PfEMP1 proteins mediate cytoadhesion of parasitized red cells lining cells of the organ microvasculature. PfEMP1 has dual binding specificity and these structures can be divided into group A (EPCR binders) and group B (CD 36 binders). Cerebral malaria is caused by dual binding of PfEMP to ICAM-1 and endothelial protein C receptor (EPCR) and this fact can be implicated in prevention of cerebral malaria in future.

Host Immunopathogenesis

In endemic areas of malaria, there is development of immunity by forming acquired antibodies against variant surface antigen (VSA) such as PfEMP, MSP3 and GLURP (RO). Microparticles derived from platelets or parasitized RBC are seen in association with cerebral malaria in the sites of inflammation. Platelet-derived microparticles activate the capillary endothelium and regulate the pro-inflammatory cytokine production leading to increased vascular permeability. Overproduction of TNFα, IL-1β and chemokines induced by plasmodium glycophosphoinositol
(GPI) are responsible for disease mortality and deterioration\textsuperscript{6, 16}. Antibodies to GPI is closely correlated with parasitaemia and disease severity\textsuperscript{15 – 18}. Cytokine cascade is augmented by some chromosomal proteins called high mobility group box chromosomal protein 1 (HMGB1) which is secreted by activated mononuclear cells and passively through damaged cells. Levels of HMGB1 has been shown to parallel with disease severity and to induce permeability in endothelial cells, induce proinflammatory responses in macrophages through activation of TLR2, TLR4, or receptor for advanced glycation end products (RAGE)\textsuperscript{19, 20}. Elevated levels of HMGB1 can be used as a prognostic marker of disease severity in severe malaria\textsuperscript{20, 21}. IFN\textgreek{g} plays a crucial role in the clearance of intracellular pathogen by inducing the MHC molecules\textsuperscript{22}. It also causes expression of gene encoding IDO (indoleamine 2, 3-dioxygenase), a rate limiting enzyme of tryptophan metabolism that can generate quinolinic acid (QA). Increased central level of QA is implicated in the causation of hyperexcitability, dementia and neurological dysfunctions seen in complicated malaria\textsuperscript{23}. CD40/CD40 ligand binding is important for binding of TNF activated platelets to the endothelial cells\textsuperscript{24, 25}. IL-1 increases the expression of ICAM1 and the production of cytokines (such as IL-6) by endothelial cells\textsuperscript{26}. Microparticles or moieties derived from blebbing of membranes of platelets and other cells during malaria infection. Platelet-derived microparticles can modulate the macrophage pro-inflammatory cytokine production and increase the endothelium permeability\textsuperscript{26}. Cell mediated immunity contributed by CD4+ T cells has a major role in immunity against malaria infection, both in pre-erythrocytic and erythrocytic stage\textsuperscript{27, 28}. They help to produce IFN\textgreek{g} and help B cells in control of malaria. People living in endemic areas of malaria possess IFN\textgreek{g} and IL-10 secreting CD4+ T cells\textsuperscript{28}.  

**Cytokines-Enhanced Haematological Abnormalities**

Disseminated intravascular coagulation (DIC) is a life-threatening disorder occurring as a secondary to malaria. Expression of tissue factor (TF) is essential in initiation of blood coagulation. It occurs when the endothelial cells (EC) are exposed to pRBC. Initial stage of coagulation cascade after TF expression is escalated by amplification, propagation, and consolidation contributed by active role of sequestered pRBC and activated platelets at the sequestered sites\textsuperscript{29}. Severe anaemia in malaria can be caused by lysis of infected and uninfected RBCs, splenic sequestration of RBCs\textsuperscript{30} dyserythropoiesis and bone marrow suppression\textsuperscript{31}, erythrophagocytosis\textsuperscript{32} and chronic transmission of malaria in endemic regions. \textit{P. falciparum}-derived haemopozoin pigment (PfHz) and cytokines (TNF and IFN) promotes the host immune response and potentially causes suppression of the erythropoietic response\textsuperscript{32}.

**Role of Microglial Cells and Apoptosis in Malaria**

\textit{Plasmodium} apoptosis-linked pathogenicity factors (PALPF), PALPF-2, PALPF-5 can induce endothelial cell death in lining cells of microcapillaries in brain and lungs in severe malaria which are responsible for the development of acute respiratory distress and neurological abnormalities in severe malaria\textsuperscript{33}. CD8+ T cells act by direct cytotoxicity on endothelial cells by apoptosis or granzyme-induced lysis of cells. This can lead to disruption of blood-brain-barrier and development of cerebral malaria. Microglial cells are activated in human cerebral malaria and shown to produce matrix enzyme, metallopeptinase, and induce cytokines which can be applied in destruction of blood brain barrier and spread of infection to the central nervous system and neuron survival\textsuperscript{34, 35}.
Malaria Pigment: A Potential Prognostic Marker

Accumulation of haemozoin pigment (HZ) in the phagocytic cells of the immune system is used in the diagnosis and prognosis of malaria\(^{36}\). \(P. falciparum\)-derived haemozoin pigment (PfHz) promotes the host immune response by activating NOD-like receptor of macrophages and potentially causes suppression of the erythropoietic response\(^{37, 38}\). It can cause monocyte and macrophage dysfunction by impairing phagocytosis and the expression of MHC class II molecules and ICAM1, inhibiting dendritic cell (DC) maturation and proliferative responses by leucocytes\(^{39}\).

Role of Nuclear Histones

Histones are acid-soluble proteins found in chromatin complexes released on rupture of parasites and host cells. Level of circulating histones in patients with falciparum malaria is correlated positively with disease severity\(^{39}\). Histones can cause endothelial permeability and cytotoxicity by causing disruption of junctional proteins leading to cell death. Activation of toll like receptor (TLR2) and other receptors induces the release of IL-8 and other inflammatory mediators. Research is in progress to find out the potential uses of rhAPC that can cleave histones in hope to inhibit the cytokine induction and vascular permeability\(^{40, 41}\).

Host Susceptibility

Susceptibility and severity of malaria infection is determined by a variety of host factors. Red blood cells carrying haemoglobin S (HbAS), HbAE, G6PD deficiency and alpha and beta thalassemia have reduced risk of developing severe anaemia by various protective effects such as reduced red cell invasion or impaired multiplication of parasites\(^{42}\). There are increased susceptibility and risk of severe malaria in individuals with polymorphism of adhesion molecules and cytokine such as ICAM-1, PECAM1, TLR, CXCL10 and tumour necrosis factor (TNF)\(^{43 - 48}\).

Host and Parasite Macrophage Inhibitory Factors (MIF)

Macrophage migration inhibitory factor (MIF) is a cytokine produced mainly by host macrophages. It regulates the expression of TNF \(\alpha\) and inflammatory mediators such as nitric oxide and cyclooxygenase 2 (COX 2)\(^{49}\). Plasmodium MIF (pMIF) is secreted when the parasites ruptured in schizont stage and they are exposed to immune cells. Levels of plasmodium MIF (pMIF) are positively correlated with parasitaemia, TNF \(\alpha\) and IL-10. pMIF attenuates \(Plasmodium\) virulence by modulating functions of monocytes in host immune responses\(^{49 - 51}\).

Vector-Parasite Association Affecting the Parasite Virulence

Studies have shown that vector mortality varies significantly among the different genotypes of parasites and environmental conditions\(^{52}\). Mosquitoes not only act as vectors but also modify the virulence of parasites. Transcriptomic studies showed after several blood passages, there is an expression of PIR gene in blood-stage parasites and increased virulence\(^{53}\). Mosquito transmission modifies the diversity and magnitude of gene such as rifin and \(var\)\(^{54}\) in malaria parasite which progress through each step of the lifecycle in both vector and host\(^{55, 56}\).

CONCLUSION

Understanding of basic and advances in immunopathological processes that cause endothelial barrier dysfunction, sequestration of parasites, destructive effects of host and parasite factors and cytokine storm in malaria infection explains the need for defining clinical biomarkers of outcome. It also helps to identify possible new targets for management
in severe *falciparum* malaria such as trial of rhAPC to regulate the endothelial dysfunction and monoclonal anti-cytokine antibody or other drugs that block cytokine such as TNF to inhibit the activated macrophages.

**REFERENCES**


