IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 15, Issue 3 Ver. I (Mar. 2016), PP 134-138
www.iosrjournals.org

Host and Parasite Immunopathogenesis of Malaria

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Abstract: *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 malaria,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. Disturbance of cytokine regulation and escape of parasites from the immune system of the host also contribute to pathogenesis of severe malaria. Immunopathological changes and dysregulation of cytokine production play central role in pathogenesis and disease severity in malaria.*

Keywords: *Malaria, Immunopathology, Host, Parasites*

I. Introduction

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 malaria, coagulation abnormalities, respiratory distress and severe anaemia can increase the mortality of malaria infected cases [1]. Variation in individual susceptibility and severity and type of clinical presentations of malaria raises the need for study of both the parasite and host immunopathological mechanisms as well as the contribution of inflammatory cytokines in malaria pathogenesis. Immunopathological basis of severe malaria and their importance in outcome prediction and success of management should be explored.

Endothelial Activation And Vasoconstriction

Endothelial activation plays an important role in malaria pathogenesis. There is increased expression of adhesion molecules, augmented chemokine/cytokine cascade and endothelial permeability by inflammatory cytokines. In *plasomodium falciparum* infection, infected erythrocytes (IEs) and monocytes are sequestered in the cerebral vessels by endothelial cells by attaching to the endothelial receptors [2-5]. IEs displayed Plasmodium Falciparum Erythrocyte Membrane Protein (Pfemp), a product of diverse *var* gene, on their surface to bind to the endothelial cell receptors mainly CD36 and intercellular adhesion molecule -1 (ICAM -1) [3]. 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. In Falciparum Malaria, there are increased expression of intercellular adhesion molecule-1 (icam-1), urokinase plasminogen activator receptor (Upar), CD23 and chemokine receptor 5 (CCR5) [2]. These augment the inflammation around the minute vessels and leads to tissue and endothelial injury in acute lung injury and disruption of blood brain barrier in cerebral malaria.

Parasite Cytoadherence

Some endothelial receptors are able to bind infected erythrocytes: thrombospondin, CD36(Platelet glycoprotein Iiib Or V) , intercellular adhesion molecule (ICAM -1), vascular cell adhesion molecule -1 and endothelial leucocyte adhesion molecule -1 [6]. Hemoglobinopathy C and the 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 [7, 8]. CD-36 is the surface receptor adhesion of irbc to endothelial cells [9]. 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 [10]. Cytoadhesion causes obstruction of the microcirculatory blood flow, tissue hypoxia and organ dysfunction. Virulence of the parasites Differs

according to the ability of cytoadherence through several parasite receptors such as plasmodium EMP1 (Pfmp1). PFEMP1 family mediates cytoadhesion of infected erythrocytes to human endothelium. Antibodies blocking cytoadhesion are important mediators of malaria immunity acquired by endemic populations [11]. Platelet-derived microparticles regulate the pro-inflammatory cytokine production and increase the endothelium permeability [12].

Role Of Host Immunity

TNF alpha, IL-3.granulocyte colony stimulating factor (GM-CSF) are responsible for onset of neurological symptoms [6, 13]. Malaria toxin GPI (Glycophosphoinositol) binds to receptors and activates T cells and monocytes to secrete proinflammatory cytokines including interleukin (IL)-1, IL-6, IL-12, macrophage colony-stimulating factor (M-CSF),TNF α, lymphotoxin (LT), and superoxide and nitric oxide (NO) [14]. GPI may be non-self in humans, and antibodies to GPI lipid domains may be associated with protection against disease [15, 16]. Elevated levels of interferon gamma inducible chemokine, CXCL10, plasma CXCL10 and CXCL4 are associated with mortality of cerebral malaria [17, 18]. Cytokine cascade is augmented by some chromosomal proteins such as high mobility group box chromosomal protein 1 (HMGB1) which is released from damaged cells. Human HMGB1 has been shown to induce permeability in endothelial cells, induce proinflammatory responses in macrophages through activation Oftlr2, TLR4, Or Receptor For Advanced Glycation Endproducts (RAGE) [19]. Elevated levels of HMGB1 can be used as a prognostic marker of disease severity in human severe malaria [20, 21]. IFN gamma plays a crucial role in the clearance of intracellular pathogen by inducing the MHC molecules. 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 levels of qa is implicated in the causation of hyperexcitability, dementia and neurological dysfunctions seen in complicated malaria [22, 23]. CD 40- CD40 ligand binding is important for binding of TNF activated platelets to the endothelial cells [24, 25]. IL-1 which increases the expression of ICAM1 and the production of cytokines (such as IL-6) by endothelial cells [24]. 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 [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 [27, 28]. They help to produce ifn γ and help b cells in control of malaria. People living in endemic areas of malaria possess IFN γ and IL-10 secreting CD4 + T cells [28].

Haematological Abnormalities Contributing Disease Severity

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 [29]. Severe anaemia in malaria can be caused by lysis of infected and uninfected RBCs, splenic sequestration of RBCs [30] dyserythropoiesis and bone marrow suppression [31], erythrophagocytosis [32] and chronic transmission of malaria in endemic regions. *P. Falciparum*-derived haempozoin pigment (*Pf*hz) and cytokines (TNF And IFN) promotes the host immune response and potentially Causes suppression of the erythropoietic response [32].

Role Of Microglial Cells And Apoptosis In Malaria

Plasmodium apoptosis-linked pathogenicity factors (PALPF), PALPF-2, PALPF-5 can induce endothelial cell death in pulmonary and brain endothelial cells in severe malaria [33]. These factors contribute to the development of respiratory distress and neurological dysfunction in severe malaria. $CD8^+$ 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 can produce matrix enzyme, metalloproteinase, 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 [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 haempozoin pigment (*Pf*hz) 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 [38].

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 and cell death, activate TLR2 and other receptors, leading to the induction 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. Genetic disorders causing A and B-Thalassemias, southern asian ovalocytosis (SAO), glucose-6-phosphate dehydrogenase (G6PD) reduce parasite growth rate into erythrocytes or by causing a more efficient phagocytosis of infected red cells at an early stage of parasite maturation. There is an increased risk with icam-1 polymorphism resulting in severe malaria [42- 44]. Individuals with a variant of the tnf gene promoter region [45] and mutation in TLR gene (TLR4 Asp299Gly) have increased risk of neurological and other fatal complications[46].

Host And Parasite Macropahge Inhibitory Factors (Mif)

Macrophage migration inhibitory factor (MIF) is a cytokine produced mainly by host macrophages. It regulates the expression of TNF α, nitric oxide and cyclooxygenase 2 (COX 2) [47]. Plasmodium MIF (Pmif) is secreted when the parasites ruptured in schizont stage and they are exposed to immune cells in the blood. Plasmodium MIF (Pmif) are positively correlated with paarsitemia, TNF A and IL-10. Pmif attenuates plasmodium virulence by modulating functions of monocytes in host immune responses [48-52].

Vector –Parasite Association Affecting The Parasite Virulence

Studies have shown that vector mortality varies significantly among the different genotypes of parasites and environmental conditions [53]. Mosquitoes can not only act as vectors but also modify the virulence of paarsites. Mosquito transmission modify the diversity and magnitude of genes such as *Rifin* and *Var* [54] in malaria parasite which progress through each step of the life cycle in both vector and host [55, 56].

II. 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.

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