Review Article

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# The Role of Myeloid Cells in Immunity to Malaria: A Review

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## Abstract

Malaria has continued to be a major cause of morbidity and mortality in the Tropical World. Research on its complex immunology has focused more on the host adaptive immunity to the plasmodium parasite. The role of innate immune mechanisms involving myeloid cells has not been given adequate attention. This review highlights the key role of myeloid cells in immunity to malaria through such mechanisms as parasite sensing and elimination, pro inflammatory activities and activation of other immune components.

**Keywords:** Malaria; Myeloid cells; Immunity

## Introduction

Advances in immunology research have given some insight into the nature and functions of myeloid cells. Most of this information majorly concerns the role of these cells in the promotion of tumor and other cancers as well as in enhancing pathogenicity of infectious disease agents. However, due to the cellular complexity of the innate immune system, the contribution of these cells in immunity against malaria has remained elusive.

Malaria remains the most important infectious disease in the tropical World where it is responsible for 198 million cases and 584,000 deaths [1]. *Plasmodium falciparum* is the parasite responsible for the majority of morbidity and mortality due to malaria. This parasite is transmitted by the female anopheles mosquitoes in regions where it breeds in favourable climatic conditions. The human acquires infections through injection of sporozoites during a blood meal by the female anopheles mosquito. These sporozoites replicate in the hepatocytes and are released as merozoites into the circulation where they multiply within the erythocytes. While the parasite multiplies, the human body tries to exert some immune reaction to the invading parasite. Human immunity to malaria is a complex system. However it is thought that partial immunity is developed over years of exposure especially among adults, and while it never provides complete protection, the risk of progression to severe disease is reduced. This the possible reason why most malaria deaths in high transmission areas such as Sub Saharan Africa occur mainly in young children while in low transmission areas accompanied with low immunity, it is usually across all age groups [1,2].

Several studies have focused on the pattern and dynamics of human immunological reactions to the malaria parasite with the aim of finding a suitable target for a sustainable vaccine against the disease. The parasite genome has also evolved to maximise the array of immunogenic proteins to its advantage especially through its ability to produce several antigenic variants [3]. Continuous evaluation of all aspects of the human immune system as regards the malaria parasite is very important towards finding an effective target for a sustainable malaria vaccine as well as for therapeutic purposes.

Apart from the malaria parasites, the environment contains so many other potentially infectious agents which can cause a lot of damage if they multiply unchecked. However most times the immune system ensures that most of these infectious agents are of limited duration in the human body and that they do not cause very permanent damage. The immune system is made up of different types of cells including developed from pluripotent stem cells of the bone which include tissue cells and white blood cells or leucocytes. Two pathways are responsible for the production of leucocytes; (1). The lymphoid lineage producing the T lymphocytes, B lymphocyte and the Natural killer cells (2). The Myeloid pathway producing the Mononuclear phagocytes, Monocytes and Macrophages, Neutrophils, Eosinophils, Basophils, Mast cells and Dendritic Cells. These cells are collectively called myeloid cells.

Myeloid cells are very important elements of the innate immune system because of their roles in inflammatory response as well as in sensing and eliminating invading parasites [4,5]. Most studies on immunity to malaria have focused on the adaptive immune system. The importance of myeloid cells as agents of tumor promotion has also been widely reported [6-10]. In this paper however, we focus on the role of some myeloid cells in immunity to malaria.

## Malaria Pathogenesis

Malaria causes disease through a number of pathways, which depend to a certain extent on the species. The five plasmodium species implicated in malaria infections namaely; *Plasmodium falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi* are introduced into the human blood stream through the bite of an infected mosquito. This infectious stage is known as the "sporozoite", and they pass first to the liver, where they undergo an initial stage of replication (called "exo-erythrocytic replication"), before passing back into the blood and invading red blood cells (called "erythrocytes", hence this is the "erythrocytic" part of the cycle) [11]. The malaria parasites that invade

red blood cells are known as merozoites, and within the cell they replicate again, bursting out once they have completed a set number of divisions. It is this periodic rupturing of the red blood cells that causes most of the symptoms associated with malaria, as the host's immune system responds to the waste products produced by the malaria parasites and the debris from the destroyed red blood cells [12].

Parasite multiplication in the red blood cells results in all the pathology of malaria. The primary attack of the disease begins with headache, fever, anorexia, malaise, and myalgia. This is followed by paroxysms of chills, fever, and profuse sweating. There may be nausea, vomiting, and diarrhea. The paroxysms tend to assume a characteristic periodicity depending on the infecting parasite specie. In *P. vivax, P. ovale* and *P. falciparum* the periodicity is 48 h and for *P. malariae* the periodicity is 72 h. The fever actually corresponds to the rupture of the red cell as merozoites are released from the schizont-infected cell. If the infection is not synchronous and there are several broods of parasites the periodicity may occur at 24 h intervals [13]. Anemia is the most immediate pathologic consequence of parasite multiplication and destruction of erythrocytes and there can also be suppression of red cell production in the bone marrow. During the first few weeks of infection, there is accumulation of parasitized red cells and proliferation of white cells which result in the spleen becoming swollen and palpable [14]. At this time it is soft and easily ruptured. The spleen returns to normal size if the infection is treated but, in chronic infections the spleen continues to enlarge, becoming hard and blackened in colour due to the accumulation of malaria pigment, hemozoin [13].

The clinical manifestations of *Plasmodium falciparum* infection are induced by the asexual stages of the parasite that develop inside red blood cells (RBCs). Because splenic microcirculatory beds filter out altered RBCs, the spleen can innately clear subpopulations of infected or uninfected RBC modified during falciparum malaria [14,12]. The spleen appears more protective against severe manifestations of malaria in naïve than in immune subjects [14,15]. The spleen-specific pitting function accounts for a large fraction of parasite clearance in artemisinin-treated patients [16]. RBC loss contributes to malarial anemia, a clinical form associated with subacute progression, frequent splenomegaly, and relatively low parasitemia. Stringent splenic clearance of ring-infected RBCs and uninfected, but parasite-altered, RBCs, may altogether exacerbate anemia and reduce the risks of severe complications associated with high parasite loads, such as cerebral malaria [17]. The age of the patient directly influences the risk of severe manifestations too. In addition, the unique pathological features produced by *Plasmodium falciparum* are due to its manipulation of the host's physiology. It has been observed that when it infects red blood cells, it makes them stick to the walls of tiny blood vessels deep within major organs, such as the kidneys, lungs, heart and brain [18,14]. This is called "sequestration", and results in reduced blood flow to these organs, causing the severe clinical symptoms associated with this infection, such as cerebral malaria. Falciparum infections are more severe and when untreated can result in a death rate of 25% in adults. The complications of the infection are as a result of what has been called the pathology cascade. Some of them include renal insufficiency, renal failure, pulmonary edema, neurologic symptoms and severe hemolytic anemia [19,11]. In the pregnant female falciparum malaria may result in stillborn, lower than normal birth weight, or abortion. Non-immunes and children may develop cerebral malaria which is a consequence of the mechanical blockage of microvessels in the brain, or organ infarcts, due to sequestration of infected red cells *via* protuberances called knobs [20]. If relapse occurs in falciparum malaria it is due to the increase in numbers of pre-existing erythrocytic forms, which were too low to be detected microscopically; this type of relapse is termed recrudescence.

## Host Immunity to Malaria

Malaria infection gives rise to host responses which are regulated by both the innate and adaptive immune system as well as by environmental factors. Immunity against malaria can therefore be classified into acquired or adaptive immunity and innate or natural immunity.

Acquired or adaptive immunity against malaria arises after infection and the protection it confers depends on the characteristics of the host, place of stay, number of infections suffered etc. It has been graded as anti-disease immunity (that protects against clinical disease), anti-parasite immunity (protects against high parasitemia), and sterilizing immunity (protects against new infections by maintaining a low-grade, asymptomatic parasitemia; also called premunition) [21]. An initial infection with malaria parasites commonly induces clinical illness in a non-immune individual with very low levels of parasitemia and the infection may progress to severe disease and death. What is referred to as anti-disease immunity develops after a couple of more infections. This causes suppression of clinical symptoms even in the presence of heavy parasitemia and also reduces the risk of severe disease. Further infections slowly lead to the development of anti-parasite immunity those results in very low or undetectable parasitemia. Sterilizing immunity, though never fully achieved, results in a high degree of immune responsiveness, low levels of parasitemia, and an asymptomatic carrier status. Premunition suggests an immunity mediated directly by the presence of the parasites themselves and not as much the result of previous infections [22,23].

The host mounts specific immune response in the presence of genetically and antigenically distinct strains of the parasites in a given locality and the occurrence of clonal antigenic variation during the course of an infection [21]. In this case, the acquisition of immunity against malaria is, therefore, very slow and not very effective and remains species specific and strain specific. However, in areas with stable endemic malaria and intense malaria transmission, such as sub-Saharan Africa acquired immunity develops at a very early age [24-26]. In these areas, children born to immune mothers are protected against disease during their first half year of life by maternal antibodies. This passive immunity is followed by 1 or 2 years of increased susceptibility before acquisition of active immunity. On the other hand, people living in unstable endemic areas tend to acquire only partial immunity [22,23,27,28]. Thus, the level of antimalaria immunity influences the clinical outcome of the disease in different locations and age groups.

The underlying mechanisms and antigenic specificity of protective immunity against malaria are the focus of several studies. The acquired anti malaria immunity has been demonstrated to be strain specific and stage specific, with cross reactivity [29]. Immune response has been documented against the various parasite antigens in pre-erythrocytic (sporozoite), asexual erythrocytic (merozoite) and sexual stages (gametocyte) [23]. Natural exposure to sporozoites does not guarantee complete antiparasite and antidisease immunity but only limit the density of parasitemia and decrease the malaria-associated morbidity and mortality. The acquired immunity is directed predominantly against the asexual erythrocytic stage, the primary targets being the extracellular merozoites in circulation. Although the preerythrocytic stage is also targeted by protective immune responses, it does not

effectively block sporozoite invasion or intrahepatic development of the parasite [22,23].

The acquired anti malaria immunity is typically not long lasting. In the absence of re-infection over a period of time, for instance when the person leaves a malarious area for some time, the acquired immunity becomes ineffective and the individual is once again vulnerable to the full impact of a malarial infection. The immunity is also rendered less effective during pregnancy, particularly during the first and second pregnancies, due to the physiological immunosupression as well as the cytoadherence of erythrocytes to the newly available Chondroitin Sulfate A receptors on the placenta. Such loss of acquired immunity makes the pregnant woman more susceptible to malaria and its complications [22,23]. Immunosuppression such as in HIV/AIDS also increases the risks of clinical malaria, its complications and death [30].

Innate or natural immunity to malaria is an inherent proactive system of the host that prevents the establishment of the infection or an immediate inhibitory response against the introduction of the parasite. The innate immunity is naturally present in the host and does not depend on any previous infection. Alterations in the structure of hemoglobin or in certain enzymes have been found to confer protection against either the infection or its severe manifestations [22]. These traits are often found in areas of high malaria transmission. Certain thalassemias (50% reduction in infection), homozygote hemoglobin C (90% reduction), hemoglobin E, and ovalocytosis carrier status have been reported to confer protection against *P. falciparum* or *P. vivax*. Glucose 6 phosphate dehydrogenase deficiency (50% protection) and sickle cell hemoglobin (90% protection) confer protection against severe malaria and related mortality [22,23].

Acute malarial infection also induces immediate, non-specific immune response that tends to limit the progression of disease. Even though the mechanisms of this non-specific defence are poorly defined, the myeloid cells appear to play very important roles in this respect. Related cell types probably playing a role in innate malaria immunity are the Natural Killer T cells (NKT cells) which in mice carry both the NK1.1 surface marker and T-cell receptors (TCR) [31]. NK cells in peripheral blood produce Interferon-gamma in response to Plasmodium infected erythrocytes, leading to activation of myeloid cells such as the parasiticidal macrophage [2], and this may be of greater importance for innate malaria immunity than their potential to lyse infected host erythrocytes. These cells are also important in the initiation and development of adaptive immune responses. Other myeloid cells such as the dendritic cells also sense the presence of the parasite and participate in the immune response. Malaria infection gives rise to strongly elevated blood concentrations of non-malaria-specific immunoglobulin, but understanding of importance of the underlying activation and functions of these cells in innate immunity remains insignificant [31-34].

## Myeloid Cells Involved In Immunity to Malaria

Myeloid cells are differentiated descendants from common progenitors derived from hematopoietic stem cells in the bone marrow. Commitment to either lineage of myeloid cells is controlled by distinct transcription factors followed by terminal differentiation in response to specific colony-stimulating factors and release into the circulation [5]. Upon pathogen invasion, myeloid cells are rapidly recruited into local tissues *via* various chemokine receptors, where they are activated for phagocytosis as well as secretion of inflammatory cytokines, thereby playing major roles in innate immunity.

Some of the myeloid cells that play these very important roles in innate immunity to malaria include eosinophils, macrophages and dendritic cells.

## Eosinophils

Eosinophils or 'eosinophilic granulocytes' are multifunctional cells which comprise about 1-5% of peripheral-blood leucocytes in a normal person. They are terminally differentiated cells which are constitutively released from the bone marrow where they are produced [35] and may remain in circulation for several days under normal physiological conditions [36]. Eosinophil counts in the blood or tissue are strictly regulated however, in certain disease conditions, eosinophils may selectively accumulate in the peripheral blood or any tissue in the body resulting in eosinophilia with accompanied profound clinical effects [37]. Eosinophils are recruited to sites of inflammation in response to stimuli such as IL-5 and eotaxin family of chemokines [38] where they participate in diverse immune response mechanisms. Activated eosinophils secrete various molecules including the proinflammatory cytokines like IL-2, IL-4, IL-5,IL-10, IL-12, IL-13, IL-16, IL-18, and TGF -α/β, the chemokines (RANTES and eotaxin-1) and lipid mediators such as platelet-activating factor(PAF) and leukotriene C4 (LTC4) [39].

In addition, eosinophils have granules which contain highly potent cytotoxic cationic proteins [major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil peroxidase (EPO), and eosinophil derived neurotoxin/eosinophil protein X (EDN/EPX)] capableof inducing tissue damage and dysfunction [40]. These granule proteins are the major components responsible for eosinophil mediated pathological processes. The involvement of eosinophils in the pathogenesis of inflammatory processes such as parasitic helminth infections and allergic diseases has been extensively studied [37,41]. However, although not as well studied, accumulating evidence suggest eosinophils may function as 'double-edged' swords in *P. falciparum* infection by contributing both to *in vivo* parasite clearance and severe malaria pathogenesis, particularly cerebral malaria [42]. Eosinophilia is a hallmark of helminth infection and it has been suggested that concomitant infection in malaria patients may contribute to decreasing disease severity [43]. Eosinophil secretory products were 35 found to be highly toxic to late stage intra erythrocytic *P. falciparum* parasites with ECP being a significant mediator [44], suggesting a positive contribution of eosinophils in controlling malaria infection.

## Macrophages

Mature macrophages are derived from monocytes, granulocytes, stem cells, or the cell division of pre-existing macrophages. Macrophages do not have granules, but contain many lysosomes. They are found throughout the body in almost all tissues and organs. The importance of macrophages in the clearance of iRBC and control of parasitemia has been shown in experiments with lethal and non-lethal strains of *P. yoelii*, where depletion of monocytes/macrophages exacerbated parasite growth and anemia [45]. Macrophages can phagocytose iRBCs through two different mechanisms. One mechanism does not require opsonizing antibodies; upon activation mediated by inflammatory cytokines such as TNF and IFN-γ, macrophages can bind to parasite antigens expressed on iRBCs *via* receptors on their surface [46]. In particular, in human malaria binding of the scavenger receptor CD36 to the *P. falciparum* erythrocytes membrane protein-1 (PfEMP-1) seems to be involved in this mechanism [47]. In the *P. chabaudi* murine model, CD36 is also

believed to mediate non-opsonin dependent phagocytosis [48]. This mechanism may be important during early infection; however macrophages are also important for parasite clearance during adaptive immunity, when the second mechanism, the antibody-dependent phagocytosis, becomes prevalent. Indeed, in rodent models immune animals showed a more efficient clearance of iRBCs compared to non-immune animals [49]. Beside spleen resident macrophages, in the *P. chabaudi* infection model a population of CD11b$^{high}$Ly6C$^+$ monocytes arising from the BM has been shown to appear in the spleen and to be actively involved in control of acute parasitemia [50].

## Dendritic cells

Dendritic cells are specialized antigen-presenting cells that have long outgrowths called dendrites, which help to engulf microbes and other invaders. DCs play a central role during infection in activating and orchestrating both innate and adaptive immune responses. This is largely due to their presence in sites of pathogen entry, their unique ability to sample, uptake, process and present antigens, as well as their capacity to integrate and respond to microbial and other immune cells signals (Figure 1). The presence of a large variety of pattern recognition receptors on DC surface, like TLRs, which allow them to sense and interact with various conserved microbial molecules, is central in DC functions. The evidence that different DC subsets are equipped with different sensing receptors suggests specialized functions during various types of infection [51]. These characteristics of DCs make them an inviting target for malaria immunotherapy. Protective immunity to blood stage malaria requires high titres of neutralizing antibodies, as well as malaria specific CD4+ T cells to effectively contain and clear the parasite [51]. During blood stage malaria, DCs in the marginal zone of the spleen are ideally placed to sample the blood flowing through the marginal sinus and, upon activation, they can migrate to the white pulp were they can initiate acquired immune responses. In humans, studies by Urban and colleagues showed that monocyte-derived DCs could interact with *P. falciparum* iRBCs by binding of CD36 to PfEMP-1. However, this interaction resulted in inhibition of DC maturation, thus affecting their ability to stimulate T cells [52,53]. However, a subsequent study showed that this inhibition is dose dependent and does not require interaction between CD36 and PfEMP-1 [54]. *In vivo* studies in mice demonstrated that 6 days after infection with *P. chabaudi* DCs were fully functional [55,56], upregulated co-stimulatory molecules important for activating T cells such as CD40, CD86 and ICAM-1, and migrated from the marginal zone to the T cell area in the spleen within 5 days of infection [57]. However, other studies found that upon infection DCs exhibited an impaired immunostimulatory activity [58-60]. In studies aimed at understanding the effect of iRBCs on DCs, splenic CD11c+ cDCs were shown to be more efficient in uptaking iRBCs than RBCs and, *in vivo*, iRBCs induced DC maturation, production of IL-12 and IFN-γ, and CD4+ T cell maturation [61]. In particular, during *P. chabaudi* infection both CD8+ and CD8- cDCs could present parasite antigens, but only CD8- cDCs isolated during acute infection could activate antigen-specific CD4+ T cell responses [62]. Despite the contrasting results obtained by different groups, what has become evident is that the functional capacity of splenic DC subsets changes during infection, and that the antigen dose plays a part in such a modulation. Indeed, the amount of antigen is known to affect whether the generated immune responses are cell-mediated or antibody-mediated [63]. During early malaria infection, low parasite levels activate DCs to produce TNF-a and IL-12, which stimulate IFN-γ. Production by NK and naïve CD4+ T cells, and IL-12-associated protection has been observed as early as 6 days post infection [56,62]. As the infection progresses and parasitemia increases, DCs produce less IL-12 and, instead, begin to produce IL-10, but they are still able to activate naïve CD4+ T cells [64]. During the later phase of infection, the induced, widespread systemic activation of DCs renders them refractory to TLR stimulation, thus dampening their ability to phagocytose antigens and primimg T cells [64]. Apoptosis of CD8+ cDCs is observed at this phase in *P. chabaudi* infection, whereas the number of CD8- cDCs increases in the spleen [62], and IL-4 and IL-10 production by proliferating CD4+ T cells prevails, which corresponds to a switch from Th1 to Th2 immune responses. At this stage, protection is essentially antibody-mediated [65]. As high doses of *P. falciparum* iRBCs have been shown to induce apoptosis in monocyte-derived human DCs, while low doses activate them to stimulate CD4+ T cell proliferation [54], it has been proposed that CD8+ cDCs, which are the major producers of IL-12 [66], might be important in early infection, when parasitemia is low, to activate Th1 responses, whereas CD8- cDCs could have a major role during the acute phase to promote the switch from Th1 to Th2 immune responses [67].
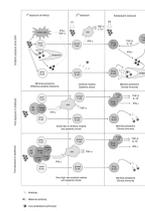


**Figure 1:** A Model for the development of clinical immunity to *P. falciparum* malaria, dependent on age at first exposure.

## Conclusion

Myeloid cells play critical roles in the development of malaria pathogenesis and protective immunity development. A deeper understanding of the molecular interactions by which these cells respond immunologically to malaria parasites and how these immune responses are regulated is crucial to identify targets for the development of immunomodulatory therapeutics to prevent/treat severe malaria and/or for enhancing the efficacy of malaria vaccine. The roles of these cells described in this review include functions in sensing and clearing parasites, pro inflammatory agent as well as intricate interaction with various other components of the immune system. It is therefore very important that the mechanism and dynamics of myeloid cells in conferring innate immunity to malaria be given more attention. This is because they may have useful implications for novel therapeutic design and advice as well as offer effective targets for malaria vaccine.

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