Chapter

Introductory Chapter: *P. falciparum* Modulates Dendritic Cell Functions to Circumvent the Host Immune Response

Nikunj Tandel, Mansi Thakkar, Prakriti Sharma and Rajeev K. Tyagi

1. Introduction

Malaria, a human parasite infectious disease, has been a cause of mortality and morbidity across the world. Significant advancements toward the vaccine development have been made, yet half of the world's population survives under the threat of malaria infection, particularly young children residing in South East Asia (SEA) and Sub-Saharan Africa. As per the latest World Malaria Report 2022, 247 million cases of malaria were registered in 2021, slightly higher as compared to 245 million in 2020. Additionally, malaria death increased by 10% and reached an estimated number of 6,25,000 [1]. Malaria occurs due to the bite of female *Anopheles* mosquito which carries the infectious sporozoites of *Plasmodium* species. According to geographical location and environmental conditions, from the range of *Plasmodium* species, there are mainly four species that cause malaria infection in humans; *P. falciparum, vivax, malariae, and ovale* [2]. *P. falciparum* is the most fatal and leading cause of death in humans. Also, it leads to the development of cerebral malaria. *P. vivax* remains in the dormant stage for a prolonged period and develops an infection in the later stages.

The tens of millions of non-immunes from areas where malaria is not transmitted visit malaria-endemic areas, and face risks of malaria infection. The two major weapons against malaria are vector control and chemoprophylaxis/chemotherapy. Unfortunately, attempts to eradicate the disease based on these methods have had only limited success due to widespread development of drug resistance by the parasite and insecticide resistance by the mosquito vector [3]. Therefore, there is an urgent need to develop newer drugs and therapeutic approaches. There is no single effective malaria vaccine available due to the complex life cycle of malaria parasite; a number of approaches to malaria vaccine development based on attenuated sporozoite, synthetic and recombinant immunogenic peptide is available. However, these approaches suffer from the drawbacks of safety and short-lived species & stage-specific immunity [3].

There are antimalarial drug(s) available to treat human malaria infection, but continuous drug pressure to clear *P. falciparum* led to the development of drug pressure endurance to tolerate the therapeutic effects of the drugs. There have been many

mechanisms of action that parasites may have employed to escape the drug pressure. The emergence of resistance against frontline antimalarials and their combinations by *P. falciparum* is worrisome as it threatens to make malaria practically untreatable in SEA. This will have severe implications as it would hinder the global attempts to eliminate this deadliest human disease. A recent series of clinical trials, *in vitro*, genomics, and transcriptomic studies in SEA have defined *in vivo* and *in vitro* phenotypes of artemisinin resistance; identified its causal genetic determinant; explored its molecular mechanism; and assessed its clinical impact [4]. The artemisinin-based combination therapy (ACT) is the only remaining remedy to clear the parasite infection. However, tolerance shown by the parasite toward the combination of drugs and issue of co-resistance led researchers to develop an understanding of how do parasites escape the therapeutic effect of drugs.

Malaria life cycle begins with the bite of *Anopheles* mosquito which transmits the infectious motile sporozoites. Once it enters the human host, by escaping the host immune system it reaches the liver and develops into the liver stage. Following propagation in the liver, it comes out into the bloodstream where its prime targets are the circulating red blood cells (RBCs). Subsequently, these infected RBCs (iRBCs) further infect other healthy RBCs and result in the development of blood-stage infection which showcases the symptoms of fever, shivering, and others. During this continuous cycle, certain iRBCs convert into the male and female gametocytes. These sexual forms of parasites are taken up by the mosquito during the biting and further develop into the mosquito gut followed by becoming sporozoites and reside in the salivary glands of the mosquito and are further injected into the healthy human. With the progression of time, studies have revealed the different stages of malaria infection (in human and mosquito host) which helps in understanding the host-pathogen interaction. The malaria life cycle of *P. falciparum* has been shown in **Figure 1**.

2. Modulation of host immune system

The malaria life cycle in the human host initiates in the liver followed by symptomatic blood stage infection. Different experimental studies of humans and mice have confirmed the role of immune system to fight against the infection [2]. Further, studies have shown the importance of T cells, mainly IFN-γ producing $CD8^+$ T cells which have a prominent role in providing sterile protection during the infectious challenge. Moreover, other cells such as IFN-γ producing $CD4^+$ T cells and follicular helper T cells (T_{fh}) also play an important role in killing iRBCs and generation of antibody-producing B cells, respectively [2]. Additionally, different immune cells of innate immunity also support augmenting the immune response to the malaria infection [2]. It has been well-established that among the different immune cells, distinct mononuclear phagocytic cells known as dendritic cells (DCs) are consider as professional antigen-presenting cells (APCs). DCs have been well-known APCs to identify antigens, capturing, processing, and presentation to the T cells as well as activating B cells directly [6]. Furthermore, it also stimulates the innate immune system (activation of NK cells). The role of DCs is well-defined. These cells work in coordination with other immune cells and bridge the gap between adaptive and non-adaptive immunity (**Figure 2**).

They are classified into different subsets and majority of them are divided according to the expression of certain defined phenotypic markers and location [6]. They reside in lymphoid and non-lymphoid organs and mainly classified as conventional/myeloid dendritic cells (cDCs/mDCs) ($CD3^-CD14^-CD19^-CD20^-CD56^-HLA\text{-}DR^+DC11c^+$)

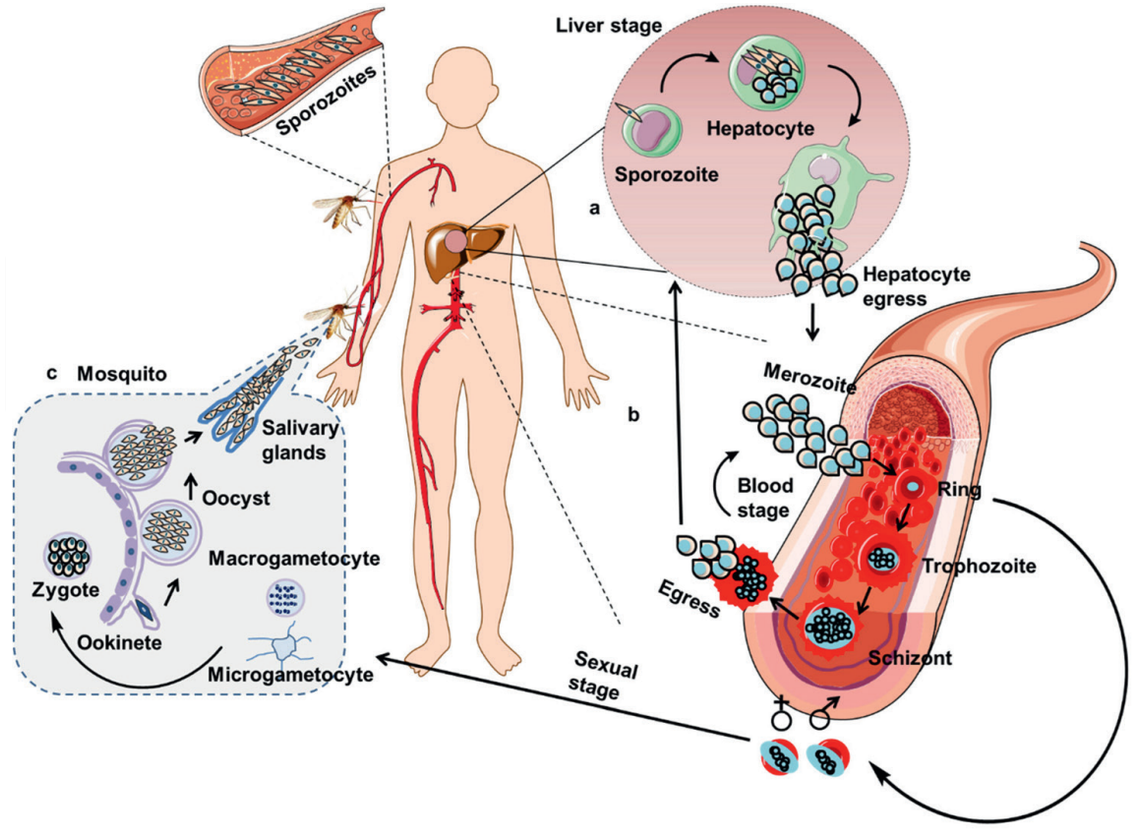

Figure 1.
Complex life cycle of P. falciparum. The life cycle has 3 stages: The pre-erythrocytic and erythrocytic stages in humans (host) and the sexual process in the mosquito vector a) pre-erythrocytic stage b) Erythrocytic stage, and c) mosquito/sexual stage. (adapted with permission from [5]).

and plasmacytoid dendritic cells (pDCs) ($CD3^-CD14^-CD19^-CD20^-CD56^-$HLA-$DR^+DC11c^+CD303(BDCA2)^+CD304(BDCA4)^+$). These mDCs in blood and lymphoid tissues can be further divided into two more subsets which express CD1c (BDCA1) or CD141 (BDCA3). pDCs are the major reservoir for antiviral immune response (IFN-α) which consist of 0.35% of PBMC whereas cDCs have a captive role in priming of T cells and account for 0.65% of PBMCs [7].

It has been established that protection against the malaria infection (liver/blood stage infection) is initiated when the DCs or macrophages capture the malaria antigen followed by processing and presenting them to T cells through MHC-I or II pathway. During the antigen presentation, several signaling mechanisms resulted in the secretion of pro-inflammatory cytokines such as IFN-γ, IL-12, and TNF-α. It further activates/stimulates the other immune cells and results in the direct/indirect killing of infected cells. Experimental studies have confirmed that DCs play a dual role by producing cytokines against the respective pathogen and creating tolerogenic conditions [6, 7].

2.1 Functional DCs during malaria infection

Role of DCs during malaria infection has been recently reviewed showing contradictory outcomes. However, it could be reasoned due to the use of different species and a subset of DCs. Therefore, our main focus is on understanding the mechanism of *P. falciparum* that modulates the DCs function and results in the exacerbated infection. Further, it is proven that interaction between DCs and *Plasmodium* parasites

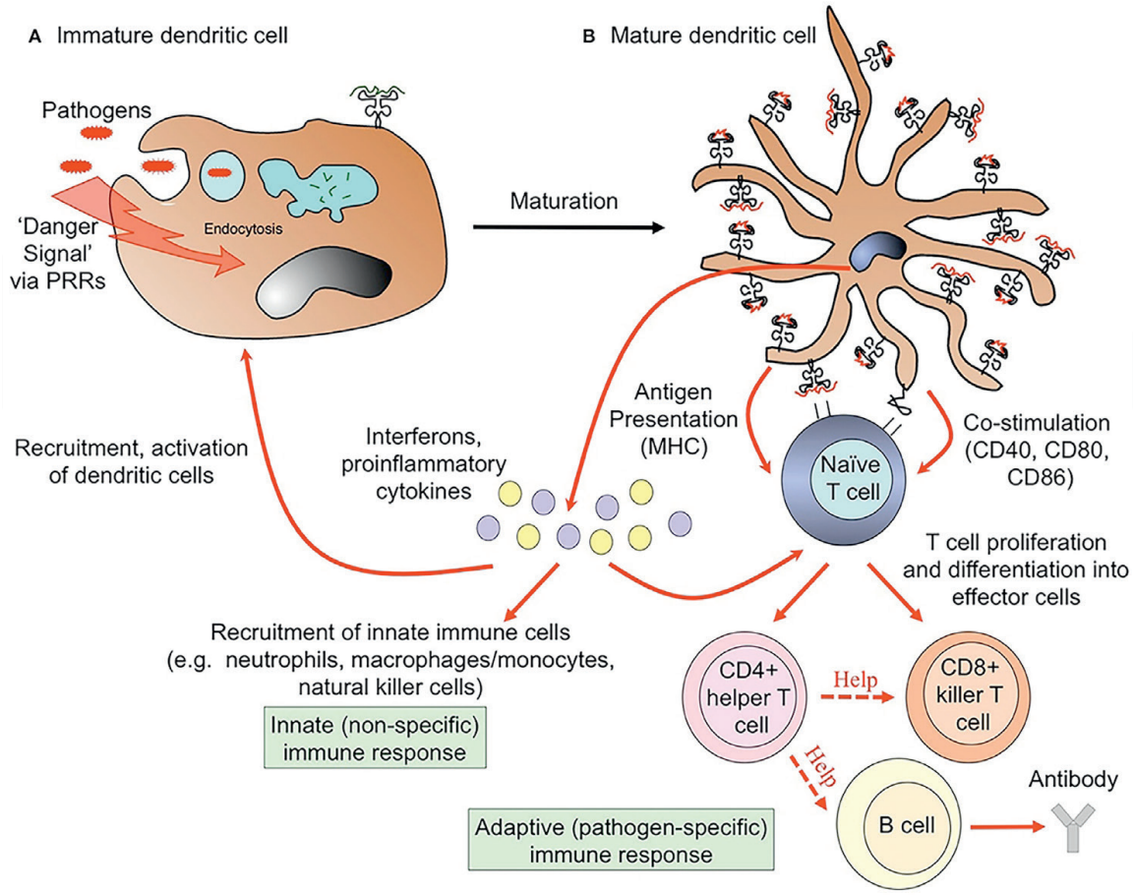

Figure 2.
Dendritic cells link innate and adaptive arms of the immune system (a) uptake of pathogens and recognition of pathogen-associated "danger signals" by pattern recognition receptors (PRRs) triggers dramatic morphological and functional changes in DCs, termed maturation. These changes involve the formation of dendrites, downregulation of antigen uptake, and redistribution of the major histocompatibility complex (MHC) molecules from intracellular endocytic compartments to the cell surface (b) mature DCs migrate to draining lymph nodes and present information about the invading pathogen in the form of processed peptides loaded onto MHC molecules to naïve T cells. Upregulation of MHC and co-stimulation molecules enables activated DCs to initiate adaptive T and B cell immune responses, the nature of which is determined by the cytokine milieu. This initiates the cascade to an adaptive immune response, leading to the clearance of infected cells, and the extracellular pathogens. Activated mature DCs also secrete interferons and pro-inflammatory cytokines that recruit circulating innate immune cells to provide rapid defense against infection (adapted with permission from [7]).

occurs at each stage of infection in human host led by the spleen and blood [7]. Further, tissue-residential DCs also have the capacity to phagocyte the parasitic components and generate the adaptive immune response. However, DCs in all these tissues have different levels of maturation and varying activation and generation of adaptive and innate immunity. DCs play a tolerogenic role to halt the immunopathology of infection in liver, whereas in peripheral blood it provokes an intermediate immune response than the potent responses seen in spleen [8].

DCs have a different role to play based on location specificity. The liver resident DCs are less mature and express lower costimulatory molecules compared to the blood DCs which accounts for their poor antigen presentation [9]. Additionally, their allogenic T cell response is also lower compared to their blood counterpart which results in less T cell-based response against the subsequent stimulation [10]. Whereas liver DCs are prominent IL-10-producing cells which favor the survival of sporozoites in the liver and hence fail to generate sterile immunity against natural infection [9]. Thus, after successfully invading the immune system by marginally around 30% of

sporozoites, the tolerogenic nature of liver DCs is the first step for the development of malaria infection which could further progress and develop immunopathology. In this context, developed humanized mice may be a valuable tool to explore and study the role of DCs in liver-stage malaria infection [11].

Once the malaria infection reaches to blood stage, it allows the host immune system to activate and respond accordingly as a range of innate and toll-like receptors (TLRs) get activated. *P. falciparum* infection attacks the mature RBCs which do not express surface MHC and hence support the invasion from the host-immune response. Once the parasite matures in iRBCs they rupture and release thousands of merozoites in the circulation. If merozoites fail to infect healthy RBCs, they could be phagocytosed or reached to the spleen for clearance [12]. Later on, it was shown that *Pf*EMP1 molecule, expresses on iRBCs, plays a dual role during the blood-stage infection. It is the prime source for antibodies in the initial stage of infection whereas a study shows that it modulates the expression of CD36 by binding on APCs including DCs [13]. Further, it has shown that the modulated DCs have the capacity to express TNF-α, yet it fails to activate T cells and produce IL-10.

Role of DCs in human malaria infection has been studied mainly in two ways. One in which peripheral DCs of infected or pre-and-post infection DCs and in another way *in-vitro* isolated and stimulated DCs (via IL-4 and GM-CSF) and their interaction with different *Plasmodium* stimuli (pRBCs, synthetic hemozoin, *P. falciparum* merozoites) [7].

2.1.1 DCs and P. falciparum interaction

P. falciparum being the reason for greater mortality and morbidity, mainly targets children and pregnant women leading to death if goes undiagnosed and not treated. The studies conducted on children (in Kenya) depicted that irrespective of disease severity, it mainly reduces the expression of HLA-DR on cDCs not on pDCs alongside DCs numbers [14, 15]. Later on, it was found that increasing infection directly correlated with an elevated number of BDCA-3^{+}cDC1s. Interestingly, this effect persists for around two weeks after the discharge of patients suggesting that despite the clearance of parasites the immunosuppressive effect has not weakened [15]. Similar results were found when the study was conducted on children of 2–10 years in Mali between infected and non-infected once. The reduced expression of HLA-DR, an elevated number of BDCA-2^{+}pDC1 and BDCA-3^{+}cDC1, and less expression of CD86 were noticed after the malaria infection [16]. Furthermore, study carried out by Guermonprez and colleagues has also found similar results about the increased number of BDCA-3^{+}cDCs [17]. Other studies confirmed that it correlates with enhanced serum DCs growth factor, Flt3-L (Fms-like tyrosine kinase receptor 3 ligand), which provokes cDC1 and pDCs *in vivo* [18, 19]. This receptor is a product of uric acid metabolism driven by *Plasmodium* species and generated by the mast cells.

Studies conducted on DCs role in pregnant women have shown contradictory results. Out of four studies, two studies have shown the overall decrease in DCs population in *P. falciparum*-infected pregnant women in comparison to the uninfected pregnant women [20, 21]. Whereas a study conducted by Mamadou and colleagues only observed a decrease in the number of pDCs in infected once [22]. However, study of Fievet *et al*., on Beninese pregnant infected/uninfected women did not see any alteration in the number of DCs [23]. The discrepancies in the results could be due to several reasons such as gating strategies and source of DCs, stages of pregnancy, and inclusion of controls. Studies conducted on Papua, Thailand, and Brazilian people

have shown the role of DCs in low-transmission settings. The reduced circulating pDCs were observed in both types of infected people (mild and severe) [24].

Human studies confirmed that functional impairment of DCs in malaria is common. The endemic and higher transmission showed the parasite load and higher chances of re-infection. Furthermore, studies of co-infection with two *Plasmodium* species showed similar results and overall reduction in DCs in peripheral blood [25, 26]. The correlation between malaria infection and impairment functional activity of DCs is yet to be established. Interestingly, expression of HLA-DR on DCs was positively correlated with parasitemia in children having asymptomatic *P.vivax* infection, whereas negatively associated with parasitemia in adults having asymptomatic *P. falciparum* infection. Based on these data, distinct mechanism played by individual parasites and age-factor does play a dominant role in endemic area for considering the risk factor.

2.1.2 P. falciparum modulates TLRs present on DCs

The study conducted by Loharungsikul and colleagues has detailed the role of *P. falciparum* modulation of TLRs on DCs [24]. The comparison of infected (mild/severe) and non-infected people has shown the reduction of TLR9 expression on pDCs, whereas increased TLR2 expression on cDCs was seen. Additionally, no changes were observed in TLR4 expression [24]. However, there was no evidence found for the correlation between disease severity and alteration in TLR expression. Experimental studies have proven the important role of TLR2, 4, and 9 in sensing the *Plasmodium* species. It was confirmed later on that TLR 2 and 4 help recognize the GPI anchor for merozoite surface proteins [27], and TLR9 is known to identify the DNA of *Plasmodium* [28]. Detailed investigations are indeed needed to confirm the role played by TLRs in modulating the host response by the alteration of DCs function.

2.1.3 In vitro modulation of DCs

Earlier studies have shown the role of TLRs during malaria infection. To study more in detail, isolated peripheral blood mononuclear cells (PBMCs) of pregnant women (naturally exposed to *P. falciparum*) were stimulated with TLR3 (poly (I:C)), TLR4 (LPS) and TLR9 (CpG-A ODN) ligand [23]. Additionally, they were also stimulated with synthetic hemozoin products of haemin chloride. There was no difference in HLA-DR expression in infected or uninfected controls irrespective of any stimuli were seen. Whereas, enhanced production of TNF-α, IFN-γ, and IL-10 and TNF-α was measured against the PBMCs stimulated (of infected women) with hemozoin, poly(I:C), and CpG-A, respectively [23]. In another recent study, DCs were purified from the blood of adults residing in Mali and stimulated with parasitized red blood cells (pRBC) during the end season of transmission [29]. The stimulation of pRBCs with DCs (3:1 ratio) has upregulated the expression of CD86 and HLA-DR whereas expressed CXCL10, CCL2, and CXCL9. However, they failed to produce IL-10, TNF-α, IL-6, or IL-1β [29]. This data indicates that DCs can restore functional characteristics during the reduction in transmission.

Only fewer studies have been carried out using the *bonafide* population of DCs and the majority of the work done using BDCA-1^{+} cDC2 and pDCs. Upregulation of co-stimulatory molecules alongside secretion of IFN-α during the incubation of peripheral DCs with pRBCs and merozoites suggest that *P. falciparum* has the capacity

to induce naïve DCs [29–31]. The detailed analysis showed contradictory results with moDCs studies and controlled human malaria infection (CHMI) studies that pointed out the cross-talk between different populations of DCs in the generation of immune response against *P. falciparum* infection [7].

2.1.4 Modulation of DCs from controlled human malaria infection (CHMI) studies

The controlled human malaria infection model (CHMI) is one of the successful models developed for understanding host-pathogen interaction. This has provided us with significant insights into antimalarial immunity. Woodberry and colleagues carried out a study to understand the role of DCs in malaria by inoculating the ultra-low or low numbers of *P. falciparum* pRBCs [32]. Drug treatment was given on day 6 post-inoculation or parasitemia reached 1000/ml. They found the curtailed down population of DCs due to the apoptosis, mainly DCs expressing HLA-DR$^+$. It was also found to be correlated with symptomatic malaria. The number of cDCs was found to be recovered in comparison to the pDCs which remains at the base level of around 47% 60 hr. post-treatment [32]. Despite the overall recovery of DCs, phagocytic activity was found to be impaired after 36 hr. of treatment. Overall, this study depicts that a specific number of sporozoites are required for the functional impairment of DCs. However, treatment in the ultra-low dose group before any symptoms has raised the question about the said correlation.

In this direction, another two studies were done to study more about BDCA-1$^+$ cDC2 activation [33] and the function of pDC [34]. The results of both studies were found to be similar. Moreover, elevated apoptosis in DCs with a reduction in number and its decreased phagocytic activity was found only in the higher-dose group. Additionally, Loughland *et al.,* have also analyzed the DCs population followed by TLR stimulation (TLR4, TLR7, and TLR1/2) [33]. They have seen that BDCA-1$^+$ cDC2 population failed to express CD86 and HLA-DR after TLR stimulation whereas upregulation of IFN-γ, HLA-DR, and CD123 was observed on pDCs upon stimulation with TLR7 and TLR9. Consistent with earlier findings, studies were carried out on the stimulation of DCs with CpG-A isolated from pregnant women. In summary, it is concluded that even a small number of infected sporozoites may lead to impairment in the function of cDCs whereas not affecting the pDCs population.

2.1.5 Interaction between DCs and parasite-generated metabolic products

Parasite progresses inside the human host and mainly relies on the nutrient available in the vicinity. Hemoglobin, the major target of the parasite, is the key product as it metabolite and results into the formation of heme which is further neutralized by parasites and converted into hemozoin [35]. It plays a dual role in the activation and suppression of DCs. Later on, it has been confirmed that hemozoin serves as a carrier for *Plasmodium* DNA and presents to TLR9 [36]. Similarly, uric acid, a toxic product of *P. falciparum*, also accounts for the up-and-down regulation of co-stimulatory molecules (CD86, CD80, and CD11c) and HLA-DR, respectively of human peripheral DCs [37]. Later on, it has revealed that uric acid was responsible for the inflammation during *Plasmodium* infection by activating the inflammasome. However, its role in antimalarial DCs response needs to be investigated [38]. Collectively, these studies suggest that *P. falciparum* DNA is responsible for the activation of TLR ligands, especially TLR9 on pDCs as it is the only TLR ligand expressed by human pDCs.

3. Conclusions

The role of DCs in malaria infection failed to understand the immunopathology due to several factors in-and-out of experiments. Similarly, the studies which had a focus on direct interaction between *Plasmodium* species and DCs have used human monocyte-derived DCs (moDCs) due to their easy *ex-vivo* generation. However, recent studies have confirmed that moDCs are distinct from blood and cDCs populations and may not represent the true DCs population. Additionally, it has been also hypothesized that inflammatory moDCs are similar to the macrophages and not *bonafide* population of DCs. Further, the relationship between pRBCs and moDCs for their inhibition or activation and how particular stimuli play a cascade role in it is still elusive. Therefore, understanding how malaria infection modulates DCs functions followed by their suppression is not fully studied. Also, whether it can happen directly through interaction with DCs or the involvement of other mediators such as cytokines or metabolites play a crucial role warrants further detailed investigations.

Acknowledgements

Rajeev K. Tyagi would like to express his gratitude to DBT, New Delhi, Ramalingaswami Re-entry Fellowship Project (No. BT/RLF/Re-entry/27/2018) and Indian Council of Medical Research (ICMR), New Delhi extramural grant (35/1/2020-Nano/BMS) for generously supporting this study. Rajeev K. Tyagi would like to express his thanks to the central MIL facility of CSIR-IMTECH, Chandigarh. Nikunj Tandel would like to thank the Nirma University and the Indian Council of Medical Research (ICMR) for providing the fellowship to carry out his research (ICMR award letter No.: 2020-7623/CMB-BMS).

Conflict of interest

The authors declare no conflict of interest.

Abbreviations

ACT	artemisinin-based combination therapy
APC	antigen-presenting cells
cDCs/mDCs	conventional/myeloid dendritic cells
CHMI	controlled human malaria infection model
DCs	dendritic cells
Flt3-L	Fms-like tyrosine kinase receptor 3 ligand
iRBCs	infected red blood cells
MHC	major histocompatibility complex
pRBC	parasitized red blood
PPR	pattern recognition receptors
RBCs	red blood cells
SEA	South-East Asia
TLRs	toll-like receptors

DOI: http://dx.doi.org/10.5772/intechopen.111476

Author details

Nikunj Tandel[1], Mansi Thakkar[1], Prakriti Sharma[2] and Rajeev K. Tyagi[2*]

1 Institute of Science, Nirma University, Ahmedabad, Gujarat, India

2 Division of Cell Biology and Immunology, Biomedical Parasitology and Nano-Immunology Lab, CSIR-Institute of Microbial Technology (IMTECH), Chandigarh, India

*Address all correspondence to: rajeevtyagi@imtech.res.in; rajeev.gru@gmail.com

References

[1] WHO. World Malaria Report 2022. Geneva, Switzerland: World Health Organization; 2022

[2] Nikunj T, Sarat KD. T cell-based vaccines: Hope for malaria elimination. In: Alfonso JR-M, editor. Current Topics and Emerging Issues in Malaria Elimination. IntechOpen: Rijeka; 2021. p. Ch. 15

[3] Tandel N, Tyagi RK. Chapter 5 - Malaria. In: Misra G, Srivastava V, editors. Molecular Advancements in Tropical Diseases Drug Discovery. London, UK: Academic press is an imprint of Elsevier; 2020. pp. 95-116

[4] Fairhurst RM, Dondorp AM. Artemisinin-Resistant Plasmodium falciparum Malaria. Microbiology spectrum. 2016;**4**:3

[5] Bonam SR, Rénia L, Tadepalli G, Bayry J, Kumar HMS. Plasmodium falciparum Malaria Vaccines and Vaccine Adjuvants. Vaccine. 2021;**9**(10):1072

[6] Amorim KN, Chagas DC, Sulczewski FB, Boscardin SB. Dendritic cells and their multiple roles during malaria infection. Journal of Immunology Research. 2016;**2016**:2926436

[7] Yap XZ, Lundie RJ, Beeson JG, O'Keeffe M. Dendritic cell responses and function in malaria. Frontiers in Immunology. 2019;**10**:357

[8] Mittag D, Proietto AI, Loudovaris T, Mannering SI, Vremec D, Shortman K, et al. Human dendritic cell subsets from spleen and blood are similar in phenotype and function but modified by donor health status. Journal of Immunology (Baltimore, Md. : 1950). 2011;**186**(11):6207-6217

[9] Bamboat ZM, Stableford JA, Plitas G, Burt BM, Nguyen HM, Welles AP, et al. Human liver dendritic cells promote T cell hyporesponsiveness. Journal of Immunology (Baltimore, Md. : 1950). 2009;**182**(4):1901-1911

[10] Bosma BM, Metselaar HJ, Mancham S, Boor PP, Kusters JG, Kazemier G, et al. Characterization of human liver dendritic cells in liver grafts and perfusates. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2006;**12**(3):384-393

[11] Tyagi RK, Tandel N, Deshpande R, Engelman RW, Patel SD, Tyagi P. Humanized mice are instrumental to the study of plasmodium falciparum infection. Frontiers in Immunology. 2018;**9**:2550

[12] Trubowitz S, Masek B. Plasmodium falciparum: Phagocytosis by polymorphonuclear leukocytes. Science (New York, N.Y.). 1968;**162**(3850):273-274

[13] Urban BC, Willcox N, Roberts DJ. A role for CD36 in the regulation of dendritic cell function. Proceedings of the National Academy of Sciences of the United States of America. 2001;**98**(15):8750-8755

[14] Urban BC, Mwangi T, Ross A, Kinyanjui S, Mosobo M, Kai O, et al. Peripheral blood dendritic cells in children with acute plasmodium falciparum malaria. Blood. 2001;**98**(9):2859-2861

[15] Urban BC, Cordery D, Shafi MJ, Bull PC, Newbold CI, Williams TN, et al. The frequency of BDCA3-positive dendritic cells is increased in the peripheral circulation of Kenyan children

with severe malaria. Infection and Immunity. 2006;**74**(12):6700-6706

[16] Arama C, Giusti P, Boström S, Dara V, Traore B, Dolo A, et al. Interethnic differences in antigen-presenting cell activation and TLR responses in Malian children during plasmodium falciparum malaria. PLoS One. 2011;**6**(3):e18319

[17] Guermonprez P, Helft J, Claser C, Deroubaix S, Karanje H, Gazumyan A, et al. Inflammatory Flt3l is essential to mobilize dendritic cells and for T cell responses during plasmodium infection. Nature Medicine. 2013;**19**(6):730-738

[18] Maraskovsky E, Brasel K, Teepe M, Roux ER, Lyman SD, Shortman K, et al. Dramatic increase in the numbers of functionally mature dendritic cells in Flt3 ligand-treated mice: Multiple dendritic cell subpopulations identified. The Journal of Experimental Medicine. 1996;**184**(5):1953-1962

[19] Waskow C, Liu K, Darrasse-Jèze G, Guermonprez P, Ginhoux F, Merad M, et al. The receptor tyrosine kinase Flt3 is required for dendritic cell development in peripheral lymphoid tissues. Nature Immunology. 2008;**9**(6):676-683

[20] Ibitokou S, Oesterholt M, Brutus L, Borgella S, Agbowaï C, Ezinmègnon S, et al. Peripheral blood cell signatures of plasmodium falciparum infection during pregnancy. PLoS One. 2012;**7**(12):e49621

[21] Breitling LP, Fendel R, Mordmueller B, Adegnika AA, Kremsner PG, Luty AJ. Cord blood dendritic cell subsets in African newborns exposed to plasmodium falciparum in utero. Infection and Immunity. 2006;**74**(10):5725-5729

[22] Diallo M, Aldebert D, Moreau JC, Ndiaye M, Jambou R. Decrease of lymphoid dendritic cells in blood from malaria-infected pregnant women. International Journal for Parasitology. 2008;**38**(13):1557-1565

[23] Fievet N, Varani S, Ibitokou S, Briand V, Louis S, Perrin RX, et al. Plasmodium falciparum exposure in utero, maternal age and parity influence the innate activation of foetal antigen presenting cells. Malaria Journal. 2009;**8**:251

[24] Loharungsikul S, Troye-Blomberg M, Amoudruz P, Pichyangkul S, Yongvanitchit K, Looareesuwan S, et al. Expression of toll-like receptors on antigen-presenting cells in patients with falciparum malaria. Acta Tropica. 2008;**105**(1):10-15

[25] Kho S, Marfurt J, Noviyanti R, Kusuma A, Piera KA, Burdam FH, et al. Preserved dendritic cell HLA-DR expression and reduced regulatory T cell activation in asymptomatic plasmodium falciparum and P. vivax infection. Infection and Immunity. 2015;**83**(8):3224-3232

[26] Kho S, Marfurt J, Handayuni I, Pava Z, Noviyanti R, Kusuma A, et al. Characterization of blood dendritic and regulatory T cells in asymptomatic adults with sub-microscopic plasmodium falciparum or plasmodium vivax infection. Malaria Journal. 2016;**15**:328

[27] Nebl T, De Veer MJ, Schofield L. Stimulation of innate immune responses by malarial glycosylphosphatidylinositol via pattern recognition receptors. Parasitology. 2005;**130**(Suppl):S45-S62

[28] Coban C, Ishii KJ, Kawai T, Hemmi H, Sato S, Uematsu S, et al. Toll-like receptor 9 mediates innate immune activation by the malaria pigment hemozoin. The Journal of Experimental Medicine. 2005;**201**(1):19-25

[29] Götz A, Tang MS, Ty MC, Arama C, Ongoiba A, Doumtabe D, et al. Atypical activation of dendritic cells by plasmodium falciparum. Proceedings of the National Academy of Sciences of the United States of America. 2017;**114**(49):E10568-e10577

[30] Pichyangkul S, Yongvanitchit K, Kum-arb U, Hemmi H, Akira S, Krieg AM, et al. Malaria blood stage parasites activate human plasmacytoid dendritic cells and murine dendritic cells through a toll-like receptor 9-dependent pathway. Journal of immunology (Baltimore, Md. : 1950). 2004;**172**(8):4926-4933

[31] Wu X, Gowda NM, Kumar S, Gowda DC. Protein-DNA complex is the exclusive malaria parasite component that activates dendritic cells and triggers innate immune responses. Journal of immunology (Baltimore, Md. : 1950). 2010;**184**(8):4338-4348

[32] Woodberry T, Minigo G, Piera KA, Amante FH, Pinzon-Charry A, Good MF, et al. Low-level plasmodium falciparum blood-stage infection causes dendritic cell apoptosis and dysfunction in healthy volunteers. The Journal of Infectious Diseases. 2012;**206**(3):333-340

[33] Loughland JR, Minigo G, Burel J, Tipping PE, Piera KA, Amante FH, et al. Profoundly reduced CD1c+ myeloid dendritic cell HLA-DR and CD86 expression and increased tumor necrosis factor production in experimental human blood-stage malaria infection. Infection and Immunity. 2016;**84**(5):1403-1412

[34] Loughland JR, Minigo G, Sarovich DS, Field M, Tipping PE, Montes de Oca M, et al. Plasmacytoid dendritic cells appear inactive during sub-microscopic plasmodium falciparum blood-stage infection, yet retain their ability to respond to TLR stimulation. Scientific Reports. 2017;**7**(1):2596

[35] Boura M, Frita R, Góis A, Carvalho T, Hänscheid T. The hemozoin conundrum: Is malaria pigment immune-activating, inhibiting, or simply a bystander? Trends in Parasitology. 2013;**29**(10):469-476

[36] Parroche P, Lauw FN, Goutagny N, Latz E, Monks BG, Visintin A, et al. Malaria hemozoin is immunologically inert but radically enhances innate responses by presenting malaria DNA to toll-like receptor 9. Proceedings of the National Academy of Sciences of the United States of America. 2007;**104**(6):1919-1924

[37] van de Hoef DL, Coppens I, Holowka T, Ben Mamoun C, Branch O, Rodriguez A. Plasmodium falciparum-derived uric acid precipitates induce maturation of dendritic cells. PLoS One. 2013;**8**(2):e55584

[38] Gallego-Delgado J, Ty M, Orengo JM, van de Hoef D, Rodriguez A. A surprising role for uric acid: The inflammatory malaria response. Current Rheumatology Reports. 2014;**16**(2):401