



Monocyte-derived dendritic cells in malaria

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The pathogenesis of malaria is a multifactorial syndrome associated with a deleterious inflammatory response that is responsible for many of the clinical manifestations. While dendritic cells (DCs) play a critical role in initiating acquired immunity and host resistance to infection, they also play a pathogenic role in inflammatory diseases. In our recent studies, we found in different rodent malaria models that the monocyte-derived DCs (MO-DCs) become, transiently, a main DC population in spleens and inflamed non-lymphoid organs. These studies suggest that acute infection with *Plasmodium berghei* promotes the differentiation of splenic monocytes into inflammatory monocytes (iMOs) and thereafter into MO-DCs that play a pathogenic role by promoting inflammation and tissue damage. The recruitment of MO-DCs to the lungs and brain are dependent on expression of CCR4 and CCR5, respectively, and expression of respective chemokine ligands in each organ. Once they reach the target organ the MO-DCs produce the CXCR3 ligands (CXCL9 and CXCL10), recruit CD8⁺ T cells, and produce toxic metabolites that play an important role in the development of experimental cerebral malaria (ECM) and acute respiratory distress syndrome (ARDS).

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Introduction

According to the World Health Organization (WHO 2017), in 2017, 216 million malaria cases were reported in 91 countries.

Amongst those cases, 445 000 resulted in death, primarily in children under five years old. The clinical outcome of the disease is affected by factors such as parasite and host genetics, previous exposure to infection, age, nutritional, geographic and socioeconomic factors. The most common early signs and symptoms of malaria in non-immune individuals, such as fever (paroxysm), nausea, headache and lethargy, are associated with rupture of schizonts and consequent inflammatory response. Activation of immune cells and systemic inflammation in response to the infection also lead to tissue damage and severe clinical manifestations such as anemia, jaundice, metabolic acidosis, respiratory distress, cerebral malaria, multiple organ failure and death.

The clinical manifestations of malaria result from three main events: excessive inflammation, destruction of red blood cells (RBCs) and cytoadherence of infected RBCs (iRBCs). The pro-inflammatory cytokines produced by the host stimulate the expression of adhesion molecules in endothelial cells. This promotes cytoadherence of iRBCs to the small capillary veins, formation of blood clots, edema, and leukocytes diapedesis to the inflamed areas. These inflammatory mediators also contribute to anemia by augmenting the phagocytosis of altered RBCs and inhibition of erythropoiesis [1,2].

In this review, we will discuss the importance of monocytes (MOs) and MO-derived dendritic cells (MO-DCs) as the main source of pro-inflammatory cytokines during acute infection with *Plasmodium* and their role on malaria pathogenesis.

Monocyte progenitors and differentiated effector cells

MOs are highly plastic cells that, when activated by microbial components and pro-inflammatory cytokines, can differentiate to more specialized cell types. MOs, macrophages and dendritic cells (DCs) are heterogeneous cell populations that have a critical role in sensing the presence of invading microorganisms and initiating protective immune responses. While presenting overlapping characteristics, MOs, macrophages and DCs can be distinguished based on specific surface markers, transcriptional signatures and certain specialized functions [3–6].

MOs originate from the myeloid lineage and are found in a resting stage in the bone marrow (BM), blood and peripheral lymphoid organs. Once activated by cytokines, such as IFN γ and TNF α , or pathogen associated microbial patterns (PAMPs), MOs differentiate into inflammatory MOs (iMOs)

that migrate to non-lymphoid and lymphoid tissues, where they further differentiate into macrophages or MO-DCs. Additionally, iMOs may also act as effector cells by producing pro-inflammatory mediators and toxic metabolites that effectively kill microbes. MOs can be also activated by IL-4 and differentiate into alternative macrophages (aMacs). This pathway is of particular relevance in worm infections, where aMacs play distinct roles in the immune response as well as on tissue homeostasis and repair [7]. In addition, both the iMOs and aMacs have distinct regulatory activities that protect the host from an excessive and a deleterious inflammatory reaction [8,9].

Each tissue has its own reservoir of embryonically developed cells that maintain the pool of tissue resident macrophages, without a major input of hematopoietic cells [4,6,10]. These resident phagocytes and aMacs have an important role on tissue homeostasis by clearing dead and senescent cells, as well as acting on tissue repair. Moreover, in the presence of invading microbes, these macrophages produce chemokines and pro-inflammatory cytokines that recruit myeloid and lymphoid cells, thus promoting local inflammation. Under these highly inflammatory conditions, the resident macrophages undergo cell death, which makes a niche accessible to the circulating MOs. The MOs rapidly replenishes the emptied space and differentiate into macrophages that, over time, assume similar phenotype and functional properties of the resident macrophages [4,6,10]. Furthermore, there is an intense infiltration of iMOs from the bone marrow (BM) and other lymphoid organs to the site of infection, enhancing the local inflammatory response.

DCs are professional antigen presenting cells (APCs) for T cells that regulate the acquired immune response. Depending on their stage of differentiation and tissue location, DCs play a central role in initiating immune responses and leading the development of immunologic memory or, alternatively, mediating immune tolerance [11]. In healthy individuals, most DC progenitors found in peripheral tissues at homeostasis are not derived from MOs. MOs are, however, more abundant than DC progenitors both in the bone marrow and in the blood stream. Thus, the *in vivo* mobilization of the MO reservoir to generate competent antigen-presenting DCs is of central importance during acute microbial insults. The MO-DCs share many morphological and functional characteristics with conventional DCs (cDCs), such as high efficiency in antigen capture and processing, expression of co-stimulatory molecules, and the ability to present microbial peptides to CD4⁺ T cells or to cross-present to CD8⁺ T cells [12–17,18^{**},19,20^{**}].

Understanding the origin, dynamics and emergence of MO-derived cells in lymphoid and non-lymphoid organs, as well as their roles, is essential for developing new strategies for immunological-based interventions to treat or prevent *Plasmodium* infection and disease.

DCs bridge the gap between innate and acquired immunity

DCs have the primary role of bridging innate and acquired immunity [3], playing an important role in host resistance to *Plasmodium* infection and in malaria pathogenesis [21,22]. After the infectious mosquito bite, CD11c⁺ as well as CD8α⁺CD11b⁻ DCs located in the draining lymph nodes elicit a protective CD8⁺ T cell response *in vivo* against the *Plasmodium yoelii* (*P. yoelii*) liver stage [23–25]. In the blood stage, splenic DCs efficiently phagocytize iRBCs, contributing to the removal of iRBCs from the circulation [26^{*}]. Once internalized, the schizonts are destroyed and parasite components are released, which activate both CD8α⁻CD11b⁺ and CD8α⁺CD11b⁻ DCs. Those cells then migrate from the marginal zone to the T cell area and enhance expression of MHC II, co-stimulatory molecules, IL-12 and present antigens to CD4⁺ T and CD8⁺ T cells [27–29].

Various parasite [e.g. glycosylphosphatidylinositol anchors (GPI-anchors), DNA, RNA and hemozoin (Hz)] and host components (e.g. heme and uric acid) released from bursting iRBCs activate DCs during malaria [2]. Much attention has been given to the pro-inflammatory activity of Hz, the β-hematin crystals that are formed to detoxify the free heme generated from hemoglobin digestion by the parasites [30]. Hz is constantly released during malaria and is promptly internalized by phagocytic cells including DCs. Internalized Hz crystals rupture phagolysosome membranes, which releases its content in the cytosol, resulting in NLRP3 inflammasome assembly, caspase-1 activation and IL-1β release [31–33]. In addition, Hz acts as a carrier of nucleic acids from the parasite. This material activates multiple innate cognate receptors, such as TLR7 [34,35] and TLR9 [34,36–39], AIM2 [33,39], and other DNA/RNA sensing cytosolic receptors [35,40]. Among the cytosolic receptors that are activated by *Plasmodium* DNA is cGAS [41], which stimulates DCs to produce type I IFN. The TLR activation leads to IL-12 production by iMOs and DCs, which in turn activates NK cells, CD8⁺ T cells and promotes polarization of CD4⁺ T helper 1 (Th1) lymphocytes, all important sources of IFNγ [42,43].

IFNγ is a pleiotropic cytokine that promotes host resistance to infection in multiple ways, including: (i) differentiation of MOs to macrophages and MO-DCs, which have enhanced phagocytic activities; (ii) amplification of pro-inflammatory cytokines and toxic molecules release by macrophages, MO-DCs, and neutrophils that contribute to parasite killing; (iii) differentiation and activation of Th1 lymphocytes and cytotoxic T cells; and (iv) IgG switching and production of IgG isotypes that block parasite invasion, enhance the efficiency of phagocytosis and mediate cytotoxicity of opsonized iRBCs. The DCs have been shown to impact effector functions, maintain the pool of effector memory T cells,

Table 1

Cell surface markers and classification of monocytes and dendritic cells in malaria patients^a

Author, year, [ref]	Strain ^b	Tissue	Population ^c	Cell surface markers
Pinzon-Charry, 2013 [72]	<i>Pf, Pv</i>	Blood	mDCs	Lin ⁻ (CD3, CD14, CD19, CD20, CD56, CD34) HLA-DR ⁺ CD11c ⁺
Pinzon-Charry, 2013 [72]	<i>Pf, Pv</i>	Blood	mDCs subset	Lin ⁻ (CD3, CD14, CD19, CD20, CD56, CD34) HLA-DR ⁺ CD11c ⁺ CD141 ⁺
Pinzon-Charry, 2013 [72]	<i>Pf, Pv</i>	Blood	mDCs subset	Lin ⁻ (CD3, CD14, CD19, CD20, CD56, CD34) HLA-DR ⁺ CD11c ⁺ CD1c ⁺
Pinzon-Charry, 2013 [72]	<i>Pf, Pv</i>	Blood	mDCs subset	Lin ⁻ (CD3, CD14, CD19, CD20, CD56, CD34) HLA-DR ⁺ CD11c ⁺ CD16 ⁺
Pinzon-Charry, 2013 [72]	<i>Pf, Pv</i>	Blood	pDCs	Lin ⁻ (CD3, CD14, CD19, CD20, CD56, CD34) HLA-DR ⁺ CD11c ⁺ CD123 ⁺
Franklin, 2009 [37]	<i>Pf</i>	Blood	MOs	CD14c ⁺
Franklin, 2009 [37]	<i>Pf</i>	Blood	DCs	CD11c ⁺
Urban, 2006 [68]	<i>Pf</i>	Blood	mDCs	Lin ⁻ (CD3, CD14, CD19) HLA-DR ⁺ CD11c ⁺ CD1c ⁺
Urban, 2006 [68]	<i>Pf</i>	Blood	mDCs	Lin ⁻ (CD3, CD14, CD19) HLA-DR ⁺ CD11c ⁺ BDCA3 ⁺
Urban, 2006 [68]	<i>Pf</i>	Blood	pDCs	Lin ⁻ (CD3, CD14, CD19) HLA-DR ⁺ CD123 ⁺ BDCA2 ⁺
Urban, 2006 [68]	<i>Pf</i>	Blood	MOs	CD14 ⁺ HLA-DR ⁺
Leoratti, 2012 [65]	<i>Pv</i>	Blood	MOs	CD14 ⁺ CD16 ⁻ CD66b ⁻
Osier, 2014 [64]	<i>Pf</i>	Blood	MOs	CD14 ⁺
Zhou, 2015 [56]	<i>Pf</i>	Blood	cMOs	CD14 ^{hi} CD16 ⁻
Zhou, 2015 [56]	<i>Pf</i>	Blood	intMOs	CD14 ^{hi} CD16 ⁺
Zhou, 2015 [56]	<i>Pf</i>	Blood	ncMOs	CD14 ^{lo} CD16 ⁺
Dobbs, 2017 [57]	<i>Pf</i>	Blood	cMOs	CD14 ⁺⁺ CD16 ⁻
Dobbs, 2017 [57]	<i>Pf</i>	Blood	intMOs	CD14 ⁺⁺ CD16 ⁺
Dobbs, 2017 [57]	<i>Pf</i>	Blood	ncMOs	CD14 ⁺ CD16 ⁺⁺
Jangpatarapongsa, 2008 [71**]	<i>Pv</i>	Blood	pDCs	HLA-DR ⁺ CD123 ⁺ Lin ⁻ (CD3, CD14, CD19, CD20, CD56, CD66b)
Jangpatarapongsa, 2008 [71**]	<i>Pv</i>	Blood	mDCs	HLA-DR ⁺ CD11c ⁺ Lin ⁻ (CD3, CD14, CD19, CD20, CD56, CD66b)
Antonelli, 2014 [61**]	<i>Pv</i>	Blood	cMOs	CD14 ⁺ CD16 ⁻
Antonelli, 2014 [61**]	<i>Pv</i>	Blood	iMOs	CD14 ⁺ CD16 ⁺
Antonelli, 2014 [61**]	<i>Pv</i>	Blood	pMOs	CD14 ^{lo} CD16 ⁺
Ataide, 2014 [52]	<i>Pf, Pv</i>	Blood	MOs	CD14 ⁺ CD16 ⁻
Ataide, 2014 [52]	<i>Pf, Pv</i>	Blood	iMOs	CD14 ^{dim} CD16 ⁺
Ataide, 2014 [52]	<i>Pf, Pv</i>	Blood	mDCs	CD1c ⁺ CD19 ⁻
Gonçalves, 2010 [70]	<i>Pf, Pv</i>	Blood	mDCs	HLA-DR ⁺ CD11c ⁺ Lin ⁻ (CD3, CD14, CD16, CD20, CD56,)
Gonçalves, 2010 [70]	<i>Pf, Pv</i>	Blood	pDCs	HLA-DR ⁺ CD123 ⁺ Lin ⁻ (CD3, CD14, CD16, CD20, CD56,))
Kho, 2016 [76]	<i>Pf, Pv</i>	Blood	pDCs	CD303 ⁺ (BDCA-2) ⁺
Kho, 2016 [76]	<i>Pf, Pv</i>	Blood	mDCs	CD1c ⁺ (BDCA-1) ⁺
Kho, 2016 [76]	<i>Pf, Pv</i>	Blood	mDCs	CD141 ⁺ (BDCA-3) ⁺
Woodberry, 2017 [75]	<i>Pv</i>	Blood	pDCs	Lin ⁻ (CD3, CD14, CD19, CD20, CD56, CD34) HLA-DR ⁺ CD123 ⁺
Woodberry, 2017 [75]	<i>Pv</i>	Blood	mDCs	Lin ⁻ (CD3, CD14, CD19, CD20, CD56, CD34) HLA-DR ⁺ CD11c ⁺
Woodberry, 2017 [75]	<i>Pv</i>	Blood	mDCs subset	Lin ⁻ (CD3, CD14, CD19, CD20, CD56, CD34) HLA-DR ⁺ CD11c ⁺ CD141 ⁺
Woodberry, 2017 [75]	<i>Pv</i>	Blood	mDCs subset	Lin ⁻ (CD3, CD14, CD19, CD20, CD56, CD34) HLA-DR ⁺ CD11c ⁺ CD16 ⁺
Woodberry, 2017 [75]	<i>Pv</i>	Blood	mDCs subset	Lin ⁻ (CD3, CD14, CD19, CD20, CD56, CD34) HLA-DR ⁺ CD11c ⁺ CD1c ⁺
Loughland, 2017 [73]	<i>Pf</i>	Blood	pDCs	Lin ⁻ (CD3, CD14, CD19, CD20, CD56, CD34) CD11c ⁻ HLA-DR ⁺ CD123 ⁺
Loughland, 2019 [74]	<i>Pf</i>	Blood	mDCs	Lin ⁻ (CD3, CD14, CD19, CD20, CD34, CD56) CD11c ⁻ HLA-DR ⁺ CD123 ⁺ CD16 ⁺

^a We used the cell population classification provided by the authors in the original manuscript.

^b *Pf, P. falciparum; Pv, P. vivax.*

^c MOs, monocytes are equivalent to classical monocytes (cMOs); iMOs, inflammatory monocytes are equivalent to intermediate monocytes (intMOs); pMOs, patrolling monocytes are equivalent to non-classical monocytes (ncMOs); DCs, dendritic cells; pDCs, plasmacytoid dendritic cells; mDCs, myeloid dendritic cells are equivalent to monocyte-derived dendritic cells (MO-DCs) [76,77].

and promote long-term immunity to *Plasmodium* infection [29,38,44–49]. Importantly, in mice, virulent *Plasmodium* strains subvert the function of DCs, and thereby impair IL-12 production and the development of T cell-mediated immunity [50,51].

IFN γ is, however, the classic ‘double-edged sword’. While IFN γ -priming of innate immune cells enhances the capacity of fighting an ongoing infection, it makes innate immune cells hyper-responsive to microbial challenge. Thus, IFN γ also mediates the cytokine storm and a septic shock-like syndrome observed during malaria [37,52].

MO and DC subsets in malaria patients

On the basis of their function, human monocytes can be classified into at least three subsets that are defined by the level of CD14 and CD16 expression [53,54,55**]. Classical MOs (cMOs) are CD14⁺CD16⁻, whereas intermediate MOs (intMOs) are CD14⁺CD16⁺, and patrolling MOs (pMOs) express low levels of CD14 and high levels of CD16 (CD14^{low}CD16⁺). In other studies, based on the pattern of CD14 and CD16 expression, intMOs and pMOs are defined as iMOs and non-classical monocytes (ncMOs), respectively [56,57]. In addition to the differential expression of CD14 and CD16, these MOs subsets vary on expression of molecules associated with cell

Table 2

Cell surface markers and classification of monocytes and dendritic cells in rodent malaria models^a

Author, year, [ref]	Strain ^b	Tissue ^c	Population ^d	Cell surface markers
Schumak, 2015 [82]	<i>PbA</i>	Sp	MOs	Ly6C ^{hi} F4/80 ⁺
Schumak, 2015 [82]	<i>PbA</i>	Sp	MOs	Ly6C ^{int} F4/80 ⁺
Pai, 2014 [81 [*]]	<i>PbA</i>	Br	MOs	CD11b ⁺ Ly6G ⁻ Ly6C ^{hi}
Pai, 2014 [81 [*]]	<i>PbA</i>	Br	MOs	Ly6C ^{lo}
Franklin, 2007 [38]	<i>Pc</i>	Sp	MOs	CD11b ⁺
Haque, 2014 [105]	<i>PbA</i>	Bl	MOs	CD11b ⁺ Ly6C ^{hi}
Hirako, 2016 [20 ^{**}]	<i>PbA</i>	Sp	MOs	F480 ⁺ CD11b ⁺ Ly6C ⁻ MHCII ⁻
Ataide, 2014 [52]	<i>Pc</i>	Sp	MOs	CD11b ⁺ F4/80 ⁺
Lai, 2018 [84 ^{**}]	<i>Py17</i>	Sp, Lv, Lg	MOs	F4/80 ^{int} CD11b ^{hi}
Galvão-Filho, 2018 [85 [*]]	<i>PbN</i>	Lg	MOs	CD11b ⁺ F4/80 ⁺ Ly6C ⁻ CD11c ⁻ DC-SIGN ⁻ CD80 ^{int} CD86 ^{int}
Lagasse, 2015 [89 ^{**}]	<i>PbA</i>	Lg	iMOs	F4/80 ⁺ CCR2 ⁺ CD11b ⁺ Ly6C ^{hi}
Schumak, 2015 [82]	<i>PbA</i>	Br	iMOs	Ly6C ^{hi} Ly6G ⁻
Sorensen, 2018 [83 [*]]	<i>PbA</i>	Br	iMOs	CD45 ⁺ CD11b ⁺ CD11c ⁻ Ly6C ^{hi}
Tamura, 2011 [107]	<i>PbA</i>	Sp	iMOs	CD11c ⁻ Ly6C ⁺
Hirako, 2016 [20 ^{**}]	<i>PbA</i>	Sp	iMOs	F480 ⁺ CD11b ⁺ Ly6C ⁺ MHCII ⁻
Sponaas, 2009 [80 [*]]	<i>Pc</i>	Sp	MO-DCs	CD11b ⁺ Ly6C ⁺ F4/80 ⁺ CD68 ⁺ CD11c ⁺ MHCII ⁺ CD40 ⁺ CD86 ⁺
Lai, 2018 [84 ^{**}]	<i>Py17</i>	Sp, Lv, Lg	MO-MACs	F4/80 ^{int} CD11b ^{hi} Ly6C ^{hi} MHCII ⁻
Lai, 2018 [84 ^{**}]	<i>Py17</i>	Sp, Lv, Lg	MO-MACs	F4/80 ^{int} CD11b ^{hi} Ly6C ^{hi/int} MHCII ⁺
Lai, 2018 [84 ^{**}]	<i>Py17</i>	Sp, Lv, Lg	MO-MACs	F4/80 ^{int} CD11b ^{hi} Ly6C ⁻ MHCII ⁺
Lai, 2018 [84 ^{**}]	<i>Py17</i>	Sp, Lv, Lg	rMACs	F4/80 ^{hi} CD11b ^{lo}
Lai, 2018 [84 ^{**}]	<i>Py17</i>	Sp, Lv, Lg	Act-rMACs	F4/80 ^{hi} CD11b ⁺ CD11c ⁺
Chakravarty, 2007 [24]	<i>Py</i>	ALN, CLN, Sp	DCs	CD11c ⁺
Seixas, 2001 [27]	<i>Pc</i>	Sp	DCs	CD11c ⁺ MHCII ⁺
Leisewitz, 2004 [28]	<i>Pc</i>	Sp	DCs	CD11c ⁺
Ing, 2006 [29]	<i>Pc</i>	Sp	DCs	CD11c ⁺
Franklin, 2007, [38]	<i>Pc</i>	Sp	DCs	CD11c ⁺ CD40 ⁺ CD86 ⁺
da Silva, 2013 [44]	<i>Pc</i>	Sp	DCs	CD11c ⁺ MHCII ⁺
Perry, 2005 [51]	<i>Py</i>	Sp	DCs	CD11c ⁺ CD11b ⁻ MHCII ⁺
Perry, 2005 [51]	<i>Py</i>	Sp	DCs	CD11c ⁺ CD11b ⁺ MHCII ⁺
Ataide, 2014 [52]	<i>Pc</i>	Sp	DCs	CD11c ⁺ MHCII ⁺
Guermontprez, 2013 [69]	<i>Pc</i>	Sp	DCs	CD8α ⁺ CD103 ⁺
Piva, 2012 [106]	<i>PbA</i>	Sp	DCs	CD11c ^{high} CD8 ⁺
Piva, 2012 [106]	<i>PbA</i>	Sp	DCs	CD11c ^{high} CD8 ⁻
Tamura, 2011 [107]	<i>PbA</i>	Sp	DCs	CD11c ^{high} CD8 ⁺ CD3e ⁻ CD19 ⁻ DX5 ⁻
Gowda, 2012 [45]	<i>Py17</i>	Sp	DCs	CD11c ⁺
Haque, 2014 [105]	<i>PbA</i>	Sp	DCs	CD8 ⁺ CD11c ^{hi} MHCII ^{hi} CD86 ⁺ TCRb ⁻ B220 ⁻
Haque, 2014 [105]	<i>PbA</i>	Sp	DCs	CD8-CD11c ^{hi} MHCII ^{hi} CD86 ⁺ TCRb ⁻ B220 ⁻
deWalick, 2007 [88 [*]]	<i>PbA</i>	Sp	DCs	CD11c ⁺
Radtke, 2015 [25]	<i>Py spr</i>	LT	pDCs	B220 ⁺
Piva, 2012 [106]	<i>PbA</i>	Sp	pDCs	CD11c ^{int} Siglec-H ⁺
deWalick, 2007 [88 [*]]	<i>PbA</i>	Sp	pDCs	B220 ⁺ mPDCA-1 ⁺
Sorensen, 2018 [83 [*]]	<i>PbA</i>	Br	MO-DCs	CD45 ⁺ CD11b ⁺ CD11c ⁺ Ly6 ⁺ F4/80 ⁺ DC-SIGN ⁺
Hirako, 2016 [20 ^{**}]	<i>PbA</i>	Sp	MO-DCs	F480 ⁺ CD11b ⁺ DC-SIGN ⁺ MHCII ⁺ CD11c ⁺ CD80 ⁺ CD86 ⁺
Hirako, 2016 [20 ^{**}]	<i>PbA</i>	Br	MO-DCs	CD45 ⁺ CD8 ⁻ CD3 ⁻ Ly6C ⁺ CD11b ⁺ CD11c ⁺ DC-SIGN ⁺
Galvão-Filho, 2018 [85 [*]]	<i>PbN</i>	Lg	MO-DCs	CD11b ⁺ CD11c ⁺ F4/80 ⁺ Ly6C ⁺ DC-SIGN ⁺ CD80 ⁺ CD86 ⁺
Galvão-Filho, 2018 [85 [*]]	<i>PbN</i>	Lg	Tip-DC	CD11b ⁺ CD11c ⁺ F4/80 ⁺ DC-SIGN ⁺ TNF ⁺ iNOS ⁺

^a We used the cell population classification provided by the authors in the original manuscript.

^b *PbA*, *P. berghei* ANKA; *Pc*, *P. chabaudi*; *PbN*, *P. berghei* NK65; *Py17*, *P. yoelii* 17XNL; *Py*, *P. yoelii*; *spr*, sporozoite.

^c Bl, blood; Br, brain; Lv, liver; Lg, lung; Sp, spleen; LT, lymphoid tissue.

^d MOs, monocytes; iMOs, inflammatory monocytes; MO-MACs, monocyte-derived macrophages; rMACs, resident macrophages; Act-rMACs, activated-resident macrophages; DCs, dendritic cells; pDCs, plasmacytoid dendritic cells; MO-DCs, monocyte derived-dendritic cells; Tip-DCs, TNF/iNOS producing dendritic cells; ALN, auricular lymph node; CLN, celiac lymph node.

adhesion, migration, innate immune response and phagocytosis [55^{**},58]. In studies with human DCs, the term MO-DCs is used for DCs that are differentiated from monocytes *in vitro*, whereas term myeloid DCs (mDCs) is used for the equivalent DCs differentiated *in vivo*. Although some functional differences have been described between human MO-DCs and

mDCs, they show high similarity in the pattern of cell surface markers expression [59,60]. Table 1 lists the nomenclature and cell surface markers of MOs and DCs used in various studies employing the peripheral blood mononuclear cells (PBMCs) from malaria patients. For better comparison with studies performed in rodent malaria models (Table 2), please notice that human

mDC is the equivalent human DC subset to mouse MO-DC.

Studies performed in our lab and elsewhere show that iMOs are the most efficient subset in phagocytizing both *Plasmodium vivax* and *Plasmodium falciparum*-infected RBC. Along with neutrophils, iMOs exposed to iRBC produce significantly higher levels of both intracellular ROS and mitochondrial ROS than the other MO subpopulations [56,61^{**},62]. Additionally, antibody-dependent phagocytosis of iRBC, complement, and adhesion molecules are also known to contribute to protection against malaria caused by *P. falciparum* [57,63,64]. MOs are also an important source of pro-inflammatory cytokines during acute malaria episodes [2]. In children infected with *P. falciparum* there is an expansion mainly of iMOs (CD14⁺CD16⁺) from the pool of circulating MOs. This parallels the higher levels of circulating CXCL10, TNF α , IFN γ and IL-6 [57]. Either in *P. vivax* or *P. falciparum* malaria, the CD14⁺CD16⁺ monocytes produce high levels of the pro-inflammatory cytokines IL-1 β , IL-6 and TNF α , upon stimulation with TLR agonists [37,52,61^{**},65].

MOs also give rise to mDCs, which are important players in the immune response in *Plasmodium*-infected patients [21,66,67]. CD141 expressing mDCs (BDCA3⁺: Lineage⁻HLA-DR⁺CD11c⁺), but not CD1c⁺ expressing mDCs, are expanded in children infected with *P. falciparum* [68,69]. In contrast, adults infected with *P. vivax* and *P. falciparum* show a decrease in the ratio of mDCs (BDCA2/CD303)⁺ to plasmacytoid DCs (pDCs) (HLA-DR⁺CD11c⁺) [70,71^{**}]. The reduction of both mDCs and pDCs in the circulation of *P. falciparum* and *P. vivax*-infected patients is associated with an impairment of DCs maturation and antigen presentation to T cells [72]. In another study, it was shown that expression of the co-stimulatory molecules CD86, CD80 and CD40 were not upregulated and the surface expression of HLA-DR and CD123 (IL-3R- α) was reduced in pDCs during early infection, suggesting that they are not activated [73]. Indeed, it was shown that the CD16⁺ mDCs is the main subset activated during subpatent infection with *P. falciparum*. The CD16⁺ mDCs produce TNF α and IL-10 and are potentially involved on both inflammatory as well as regulatory immune processes [74^{*}]. In addition, it was shown that during primary *P. vivax* infection, the number of cells and HLA-DR expression are decreased in CD1c(+) mDCs, while increased in CD16⁺ mDCs [75]. Importantly, in asymptomatic malaria patients with sub-microscopic parasitemia, the function of the DCs is not affected [76]. *In vitro*, high concentrations of iRBCs or Hz impair monocyte differentiation. In contrast, smaller concentrations of iRBCs or under certain conditions Hz activate DCs leading to cytokine production, expression of adhesion and co-stimulatory molecules favoring antigen presentation [77–79].

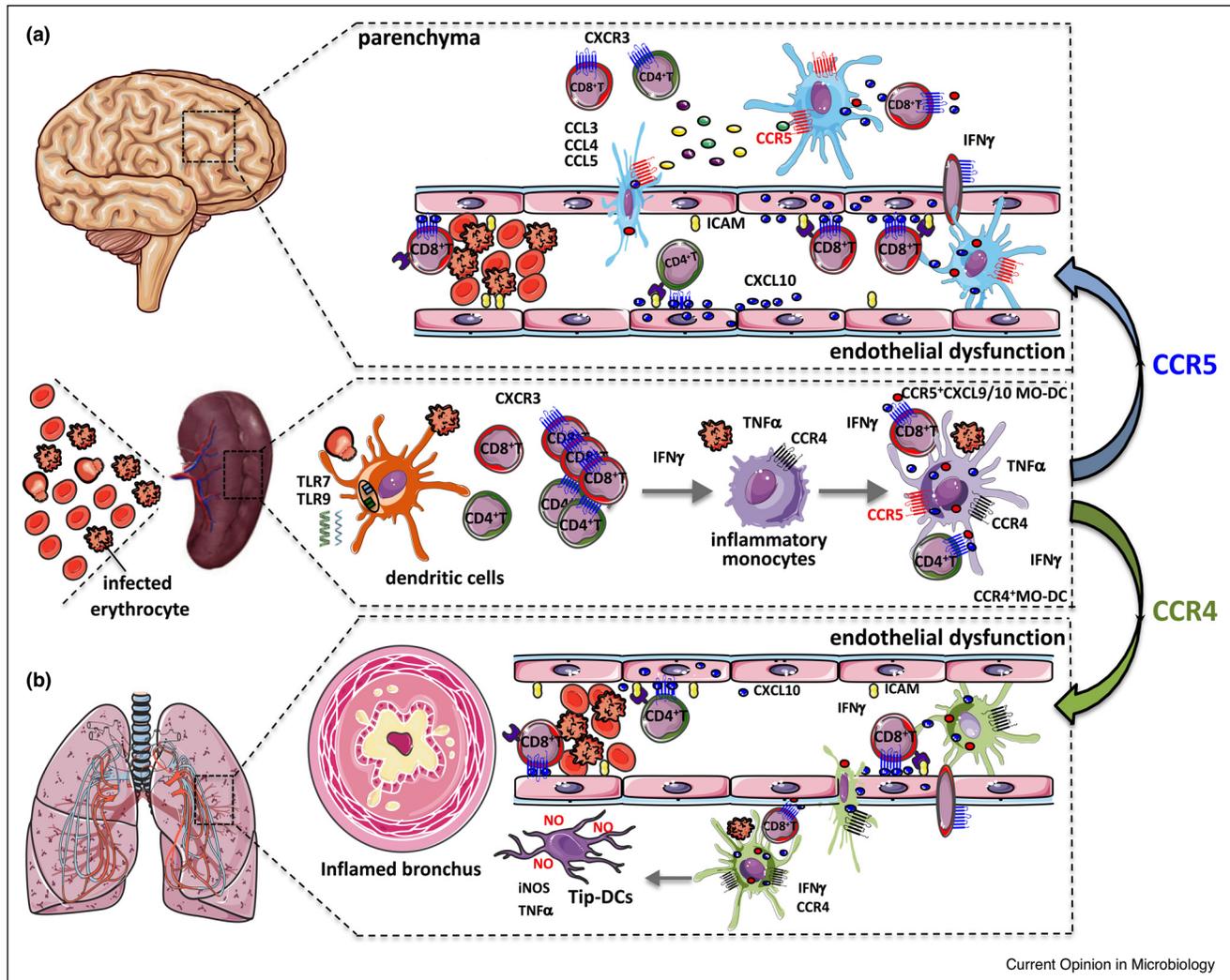
MO-DCs in rodent malaria models

During acute *Plasmodium* infection in mice, the cellularity of spleen, blood, as well as non-lymphoid organs such as brain, liver, and lungs, changes drastically. An enhanced frequency of iMOs, activated macrophages, and MO-DCs is observed [20^{**},80^{*},81^{*},82,83^{*},84^{**},85^{*}]. The aforementioned studies addressed the role of iMOs during malaria. Only few studies have suggested that aMacs have an anti-pathology effect and that they should be explored as potential therapeutic targets during malaria [86,87]. Hence, in this review we focus our discussion on the role of iMOs and MO-DCs during malaria.

In a study performed by Lai *et al.* [84^{**}], it was shown that at early stage of *Plasmodium* infection, there is a rapid disappearance of resident macrophages (F4/80^{hi}CD11b^{lo}) in different organs, such as spleen, liver, and lungs and the distribution of MO subsets undergoes striking changes. In all these organs there is a transient emergence of activated MOs that express F4/80^{int}CD11b^{hi}MHCII^{hi}Ly6C^{hi}. During the healing process, these monocytic cells disappear and the splenic red pulp and kupffer cell compartments are restored, presumably by circulating MOs (F4/80^{hi}CD11b^{lo}) that assume similar characteristic of the embryonic resident macrophages [84^{**}]. In the *Plasmodium chabaudi*-infected mice, CD11b⁺Ly6C⁺ cells are important sources of inflammatory cytokines, reactive oxygen species, and nitric oxide that effectively phagocytize and destroy iRBCs, thus mediating resistance to infection [80^{*}]. In addition, both CD11c⁺ and Ly6C⁺ cells have been shown to play important roles in the development of experimental cerebral malaria (ECM) in *P. berghei*-infected mice [81^{*},82,83^{*},88^{*}]. Likewise, it has been shown that CCR2⁺CD11b⁺Ly6C⁺ cells mediate malaria-induced lung injury in a rodent malaria model [89^{**}]. However, the role of MO-DCs in rodent malaria models had not been explored.

Traditionally, iMOs are defined as F4/80^{int}, CD11b^{hi}, MHC II⁻, Ly6C^{hi} and CCR2⁺, whereas MO-DCs are supposedly Ly6C⁻ [18^{**},19,90]. In the studies described below, we defined F4/80^{int}CD11b^{hi}MHC II^{hi}Ly6C⁺ cells as MO-DCs, because they express high levels of CD11c, DC-Sign, MHC-II^{hi} and co-stimulatory molecules (CD86 and CD80), display large dendrites, are highly phagocytic, and efficiently present antigens to CD8⁺ T cells [20^{**}]. Similarly, in a second study by our group, F4/80^{int}CD11b^{hi}MHC II^{hi}Ly6C⁺ cells also showed all the characteristic markers of DCs [85^{*}] and a subset of them simultaneously expressed TNF α and iNOS, suggesting that they are the TNF/iNOS producing DCs (Tip-DCs) subset. It is noteworthy that the MO-DCs defined in our studies showed a gradient of Ly6C expression, suggestive of a population that includes cells transitioning from iMOs to MO-DCs [20^{**},85^{*}]. Hence, we believe that the role of MO-DCs in rodent malaria models has been underestimated. Most of the studies that addressed the role of DCs in rodent malaria have used a limited number

Figure 1



MO-DC and Tip-DCs mediate cerebral malaria and ARDS in *P. berghei*-infected mice.

The systemic increase of circulating cytokines, elicited during malaria, induce the expression of adhesion molecules by endothelial cells, which mediate parasite sequestration. The sequestration of infected RBCs disrupts blood flow, promotes blood clots, injures endothelial cells and ruptures vascular walls, leading to the extravasation of vascular content and local tissue inflammation. These mechanisms contribute to the ECM and the acute respiratory distress in experimental malaria. **(a)** Infection with *P. berghei* ANKA leads to an IFN γ -dependent differentiation of inflammatory monocytes into splenic MO-DCs (CD45^{high}CD8⁻CD11b⁺Ly6C⁺CD11c⁺MHCII^{high}CCR5⁺CXCL9⁺CXCL10⁺). After differentiation, these MO-DCs migrate to the CNS in response to CCR5 ligands and amplify recruitment of CD8⁺ T lymphocytes, initiated by endothelial cells producing CXCL10 and promote development of ECM. **(b)** Infection with *P. berghei* NK65 leads to differentiation of inflammatory monocytes into MO-DCs that migrate to the lung. In the lung these cells are further activated by IFN γ locally produced by CD8⁺ T cells and differentiate into Tip-DCs (CD45^{high}CD8⁻CD11b⁺Ly6C⁺CD11c⁺MHCII^{high}CCR4⁺TNF α ⁺iNOS⁺). The nitric oxide produced by the Tip-DCs is the main cause of lung damage. This figure is adapted from Figure 10 of Hirako *et al.* [17], which now includes the path of MO-DCs to the lungs and their differentiation to Tip-DCs during MA-ARDS. This image was prepared using the Medical ART (<https://smart.servier.com/>).

of cell surface markers and have defined CD11c as a specific marker for cDCs. In addition, multiple studies have defined iMOs regarding the expression of CD11b, F4/80, and Ly6C, but did not evaluate CD11c [5]. This is of particular importance during the acute stage of infection, when the MO-DCs transiently emerge as a main population in the spleen and non-lymphoid organs [20^{••},84^{••},85[•]]. Table 2 lists the nomenclature and cell

surface markers used for iMOs and DCs employed in various studies using mouse malaria models.

MO-DCs in malaria acute respiratory distress syndrome (MA-ARDS)

MA-ARDS is a severe and often fatal complication of *P. falciparum* and *P. vivax* infection that is related to the sequestration of iRBCs into the pulmonary

microvasculature [91–95]. The lung inflammatory process and injury, both in humans and mice, are linked with the presence of Hz. This crystal induces the expression of various inflammatory mediators, such as chemokines (e.g. CXCL10 and CCL2), cytokines (e.g. IL-1 β , IL-6, IL-10 and TNF α) and metabolic enzymes (e.g. iNOS and heme-oxygenase) [85*,96]. In infections caused by *P. berghei* NK65 (*PbN*), the inflammatory infiltrate in the lungs is characterized by a Th1 response and a predominance of CD8⁺ T lymphocytes expressing Tbet and high levels of IFN γ [85*,97,98].

Our recent study [85*] demonstrated that development of murine MA-ARDS is dependent on a functional CCR4. This chemokine receptor is involved in lung pathologies, but is normally responsible for mediating the recruitment of Th2 and regulatory T cells. CCR4^{-/-} mice infected with *PbN* are protected from lung damage and present less hemorrhagic lesions and edema. A deeper analysis of leukocyte subsets in the lung of MA-ARDS mice showed a high frequency of MOs. Most of these cells express MO-DC markers such as CD11c and DC-Sign, stimulatory molecules MHCII, CD80, and CD86, and did not express specific markers for blood MOs (CD115), macrophages (CD68) or cDCs (CD135). In addition, a significant proportion of these MO-DCs are Tip-DCs. Importantly, MOs from control mice constitutively express CCR4, and we found that the recruitment of MO-DCs to the lungs, and not of T lymphocytes, is profoundly impaired in CCR4^{-/-} mice infected with *PbN*.

As observed in other models, the differentiation of MO-DCs in *PbN* infection is highly dependent on endogenous IFN γ [85*,97–99]. It is also known that during experimental MA-ARDS, CD8⁺ T cells are the main source of IFN γ in the lungs. In fact, our studies suggest that the differentiation of MO-DCs into Tip-DCs that occurs in the lungs of *PbN*-infected mice is dependent of locally produced IFN γ by CD8⁺ T cells. Additionally, we found that Tip-DCs are the most important nitric oxide synthase 2 (NOS2) expressing cells in the MA-ARDS model and that NOS2^{-/-} mice have attenuated pathology [85*]. Thus, these results indicate that Tip-DCs are important effector cells mediating lung tissue damage and MA-ARDS (Figure 1).

MO-DCs in experimental cerebral malaria (ECM)

Cerebral malaria is a severe and often fatal neurological complication of *P. falciparum* infection [100–102]. It is characterized by cerebral dysfunctions that includes different degrees of impaired consciousness, delirium, abnormal neurological signs, as well as focal and generalized convulsions. The most studied ECM model is the infection of C57BL/6 mice with *P. berghei* ANKA (*PbA*). ECM develops within 6–12 days of infection and is characterized by ruffled fur, hunching, unbalancing, limb

paralysis, convulsions, coma and death. The development of ECM is highly dependent on the inflammatory response, in particular of TNF α , IFN γ , Th1 and CD8⁺ T lymphocytes [103,104]. Intriguingly, it has been shown that Type I IFN promotes development of ECM by regulating the production of IFN γ by Th1 lymphocytes [105].

Different studies have demonstrated an intense infiltrate of blood iMOs in the CNS of *PbA*-infected mice [81*,82,83*]. In addition to iMOs, CD11c⁺DCs are also important for the development of ECM [88*,106]. In contrast, it was shown that treatment with Flt3, a potent differentiation factor for DCs, promoted the expansion of CD8⁺ DCs resulting in lower levels of parasitemia and protection against ECM [107]. However, these studies have used a limited number of cell surface markers to define iMOs and DCs, and the precise subpopulations are not defined. Our recent study indicates that MO-DCs (CD45^{high}CD8-CD11b⁺Ly6C⁺CD11c⁺MHCII^{high}CCR5⁺) are pivotal cells in mediating *PbA*-induced neuroinflammation [20**]. At five days post-infection, MO-DCs become a dominant DC population during the period of ECM development. Amongst CD11b⁺F480⁺ cells, the frequency of splenic MO-DCs increases from 18% in uninfected controls to 74% in *PbA*-infected mice. These MO-DCs are highly phagocytic, when compared to splenic MOs and iMOs. They express high levels of CD80 and CD86 and cross-present soluble antigens, suggestive of a role in activating CD8⁺ T lymphocytes. Among members of chemokine family, the enhanced production of CXCL9, CXCL10, and expression of CCR5 by the differentiated MO-DCs stands out [20**]. It is noteworthy that CXCL9 and CXCL10 play important roles on ECM [108**,109]. Importantly, IFN γ or IFN γ R deficiency leads to an impairment in the differentiation of iMOs into CXCL9/CXCL10-expressing MO-DCs. Furthermore, treatment with E6446 (a TLR7 and TLR9 antagonist) inhibits the expression of IFN γ by both CD4⁺ T and CD8⁺ T cells, CXCL9 and CXCL10 by MO-DCs, and prevents development of ECM [20**,34].

Soon after their differentiation in the spleen, MO-DCs emerge in the CNS of *PbA*-infected mice. While endothelial cells express high levels of CXCL10, MO-DCs are the main hematopoietic source of CXCL9 and CXCL10 in the brain of *PbA*-infected mice undergoing ECM [83*]. Importantly, the emergence of MO-DCs in the CNS is highly compromised in *PbA*-infected CCR5^{-/-} mice, which are resistant to ECM. Different CCR5 ligands (i. e. CCL3, CCL4 and CCL5) are expressed in the brain of *PbA*-infected mice and CCL5 is highly efficient in mediating MO-DC migration *in vitro* [20**].

In summary, our studies suggest that parasite nucleic acids activate cDCs to produce IL-12, which in turn

stimulates the production of IFN γ by NK cells and T cells. The circulating IFN γ induces the expression of CXCL10 by endothelial cells in the CNS and promotes the differentiation of MOs into CXCL9/CXCL10-producing MO-DCs in the spleen of *PbA*-infected mice. After differentiation, MO-DCs migrate to the CNS in response to CCR5 ligands and amplify the recruitment of CXCR3⁺CD8⁺ T lymphocytes, initiated by endothelial cells producing CXCL10 and promote the development of ECM. Finally, CD8⁺ T cells act as effector cells causing tissue damage and lethal encephalitis (Figure 1).

MO-DC precursors in rodent malaria

Myelopoiesis-induced inflammation is critical to replenish myeloid cells in the periphery and control infectious pathogens. It has been shown that IL-27 promotes expansion of lineage negative (LIN⁻) LIN-Sca-1⁺c-Kit⁺ (LSK) cells, especially the long-term repopulating hematopoietic stem cells, and the common myeloid progenitor (CMP) cells that preferentially differentiate into mDCs, but not pDCs or cDCs. Importantly, the *Plasmodium* blood stage infection in mice production of IL-27 is enhanced through the induction of IFN γ . IL-27 then promotes the expansion of LSK cells in the bone marrow (BM), their differentiation and mobilization to the spleen [110]. Our unpublished results indicate that during rodent malaria, BM-MOs (CD11b⁺CCR2⁺F4/80⁺MHC-II⁻DC-Sign⁻Ly6c^{lo}CD11c⁻CCR5⁻CXCL9-CXCL10⁻) differentiate into BM-iMOs (CD11b⁺F4/80⁺MHC-II⁺CCR2⁺DC-Sign⁺Ly6c^{lo}CD11c⁻CCR5⁻CXCL9-CXCL10⁻) that express some, but not all markers from MO-DCs (CD11b⁺F4/80⁺MHC-II⁺CCR2⁺DC-Sign⁺Ly6c⁺CD11c⁺CCR5⁺CXCL9⁺CXCL10⁺). These findings suggest that the BM-iMOs may migrate to the spleen and then differentiate into MO-DCs [20^{**},85^{*}]. In fact, it has also been observed a contraction in the population of LIN⁻ cells as well as the CMP and the granulocyte monocyte progenitor (GMP) cells in the BM of *P. chabaudi*-infected mice. This contraction of BM progenitor cells during rodent malaria is dependent on IFN γ and CCR2 [111,112]. These results are consistent with the findings that the egress of MOs from the BM and their emergence in the site of infection is CCR2-dependent [80^{*},113]. Altogether, these results support the hypothesis that myeloid precursors cells migrate out of the BM for extra-medullary myelopoiesis and lead to the generation of iMOs and MO-DCs in the spleen of *Plasmodium*-infected mice.

However, we found that the generation of splenic MO-DCs is only partially compromised, whereas the migration of MO-DCs to the CNS and the development of ECM are not affected in *PbA*-infected CCR2^{-/-} mice [20^{**}]. Furthermore, BM-iMOs do not express CCR5 and could not be recruited in a CCR5-dependent manner directly from the BM to the CNS in the ECM model. Importantly, our results also demonstrate that there is an accumulation of

iMOs in the spleen of IFN γ ^{-/-} mice infected with *PbA*, but these cells do not differentiate into MO-DCs. As a consequence, there is no emergence of MO-DCs in the brain and development of ECM in IFN γ ^{-/-} mice [20^{**}]. These results indicate that CCR2, and potentially the egress of precursor cells from the BM during *PbA* infection, is not strictly necessary for the generation of splenic iMOs and that the final differentiation of MO-DCs in the spleen is highly dependent on IFN γ .

By using adoptive cell transfer experiments, MOs (F4/80⁺CD11b⁺Ly6C⁻DC-SIGN⁻MHCII^{lo}) were enriched from spleens of uninfected CD45.2 C57BL/6 mice and transferred to either uninfected or *PbA*-infected CD45.1 congenic mice. Two days later, the frequencies of splenic CD45.2⁺ MOs, iMOs and MO-DCs were evaluated. In infected mice, like host cells (CD45.1⁺), most splenic CD45.2⁺ MOs differentiated into splenic MO-DCs (F4/80⁺CD11b⁺Ly6C⁺DC-SIGN⁺MHCII⁺). Thus, we favor the hypothesis that splenic MOs (F4/80⁺CD11b⁺Ly6C⁺DC-SIGN⁻MHCII⁻) [84^{**}] are the main precursors or, at least, sufficient to generate the pathogenic MO-DCs that then migrate and promote ECM.

Since MOs constitutively express CCR4, it is possible that they are being recruited directly from the BM to the lungs in the MA-ARDS model. However, the emergence of MO-DCs in the lungs and development of MA-ARDS is unaffected in the *PbN*-infected CCR2^{-/-} mice. Thus, we speculate that MO-DCs differentiate in the spleen and then are recruited to the lungs. Once they emerge in the lungs, the final differentiation to Tip-DCs occurs after interaction with IFN γ -producing CD8⁺ T cells. Both in the ECM and MA-ARDS one can propose that MO-DCs differentiate from brain and lung resident macrophages (F4/80⁺CD11b⁺Ly6C⁻DC-SIGN⁻MHCII⁻) [84^{**}]. However, the requirement of CCR5 and CCR4 for MO-DCs emergence in these organs must be taken into consideration [20^{**},85^{*}].

Conclusions

Our studies highlight an intense differentiation of MO-DCs during the MA-ARDS and ECM models. We emphasize the importance of endogenous IFN γ in mediating MO-DCs differentiation and their migration to the brain or lungs in a CCR5-dependent or CCR4-dependent manner, respectively. Once they migrate to the target organs, MO-DCs amplify the local inflammation causing tissue damage and consequent clinical manifestations. We hypothesize that MO-DCs amplify local tissue inflammation by serving as professional APCs and producing the chemokines CXCL9 and CXCL10 which recruit CD8⁺ T cells that mediate pathology. Therefore, the molecular steps involved on differentiation and migration of MO-DCs to the inflamed tissues may be

important targets for therapeutic intervention during malaria.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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