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Neurovascular Interactions in Malaria

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Abstract
Malaria is caused by *Plasmodium* infection and remains a serious public health problem worldwide, despite control efforts. Malaria can progress to severe forms, affecting multiple organs, including the brain causing cerebral malaria (CM). CM is the most severe neurological complication of malaria, and cognitive and behavior deficits are commonly reported in surviving patients. The number of deaths from malaria has been reducing in recent years, and as a consequence, neurological sequelae have been more evident. Neurological damage in malaria might be related to the neuroinflammation, characterized by glia cell activation, neuronal apoptosis and changes in the blood-brain barrier (BBB) integrity. The neurovascular unit (NVU) is responsible for maintaining the homeostasis of the BBB. Endothelial and pericytes cells in the cerebral microvasculature and neural cells, as astrocytes, neurons, and microglia, compose the NVU. The NVU can be disturbed by parasite metabolic products, such as heme and hemozoin, or cytokines that can promote activation of endothelial and glial cells and lead to increased BBB permeability and subsequently neurodegeneration. In this review, we will approach the main changes that happen in the cells of the NVU due to neuroinflammation caused by malaria infection, and elucidate how the systemic pathophysiology is involved in the onset and progression of CM.

Introduction

Despite efforts to reduce malaria deaths and case incidence, an estimate of 228 million cases and 405,000 deaths worldwide occurred in 2018 [1]. Severe malaria includes metabolic, liver, and lung disorders; renal failure; anemia; and cerebral malaria (CM) [2]. *Plasmodium falciparum* infection is responsible for the most severe clinical conditions of malaria. However, infection with other species of *Plasmodium* can also lead to severe cases malaria, including CM [3–5]. In Brazil, it is a common disease in the Amazon region, and due to the progress of studies for its treatment, there has been a reduction in the number of deaths from malaria in recent years [1]. Despite this prog-

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ress, long-term cognitive and behavioral sequelae were reported in survivors even after effective resolution of the infection [6, 7].

During human CM, the course of infection can progress with increased parasitemia and deregulated inflammatory host response, leading to disruption of the blood-brain barrier (BBB). Cerebral edema and changes in the BBB integrity may be accompanied by microhemorrhages and necrosis of neighboring tissues [8]. The BBB comprises juxtaposed endothelial cells, surrounded by the basal lamina, astrocytes, and pericytes [9]. Together with neurons and microglia this structure is known as the neurovascular unit (NVU), responsible for the functional interface between the central nervous system (CNS) and the vascular system [10, 11]. The obstruction of the cerebral microvasculature by parasitized red blood cells (pRBC), perivascular monocytes, CD4+ and CD8+ T lymphocytes [12, 13], the exacerbated production of proinflammatory cytokines, and subsequent BBB dysfunction compromises the homeostasis of the NVU altering cellular functioning [14, 15], leading to a neuroinflammatory process [16].

Even though the BBB is widely addressed in experimental models involving cognitive and behavioral impairments, due to its involvement with the NVU, other barriers in the CNS have been described, such as the blood-cerebrospinal fluid barrier (BCSFB) and the blood-spinal cord barrier (BSCB). The BCSFB is defined by a single layer of epithelial cells enveloping the choroid plexus, a complex capillary network responsible for the production of the cerebrospinal fluid (CSF) [17, 18]. Beyond that, the secretions from the choroid plexus and the endothelial cells present in the BCSFB are the basis of the extracellular fluid for neurons, supporting their synapses [19]. In comparison to the BBB, BCSFB has an important role in providing the CNS with ions, micronutrients, proteins, and growth factors involved in hormone transport and fluid balance [20, 21]. However, due to the secretion of CSF, the BCSFB is more permeable, has lower electrical resistance between epithelial cells, and is more susceptible to diffusion from blood, creating a more favorable environment for the entry of pathogens [22, 23]. Thus, cytokines released during systemic infections can unbalance the neurochemistry as they diffuse through the BCSFB activating glia cells [19]. In addition, the communication between neurons, glia, and the brain interstitial fluid in cases of severe pathology can also alter the CSF chemical balance [18]. The CSF-altered composition have been described in cases of mental illnesses, such as schizophrenia, Alzheimer, and depression, and might be a result of a BCSFB dysfunction that leads to neurological impairment [24, 25]. During CM, lower white cell count, glucose levels below normal range – and even lower in fatal cases – and higher lactate can be found in the CSF [26, 27]. Despite the lack of further studies of the BCSFB in malaria, the disruption of this barrier integrity has already been assessed in CM [28, 29]. Additionally, the BSCB is composed of nonfenestrated endothelial cells, connected by tight junctions and involves other structures like pericytes and astrocytes [30]. Unlike the BCSFB, tight junctions from endothelial cells are even more sensitive to chemical imbalance in the surrounding environment [31–33]. Although not particularly studied in pathologies such as CM, the BSCB dysfunction is directly related to neurodegeneration and demyelination in diseases such as amyotrophic lateral sclerosis and spinal cord injuries caused by radiation therapy [30, 34]. The BSCB breakdown is also associated with an exacerbated immune response promoting the access of immune cells, like neutrophils and mast cells, to the CNS [35, 36] and exposure of the NVU to toxic compounds present in the blood [34, 37]. Taken together, more studies of other CNS barriers are important for a more comprehensive understanding of several pathologies and for new therapeutic approaches.

Changes in the NVU and Impacts in the CNS Pathophysiology during Malaria Infection

Many substances that circulate without causing damage to the periphery can be toxic to the CNS and may cause neural damage. The BBB provides this protection, controlling the passage of molecules and cells that cross from the vascular endothelium into the cerebral parenchyma. Changes in the properties of the BBB and the NVU are important components of the pathophysiology and neurological progression of different infectious diseases, including CM [38] (Fig. 1).

Endothelial Cells

Endothelial cells have a significant role in the inflammatory response, with an active phenotype and having persistent effects [39]. In malaria infection, systemic inflammation and the presence of molecules such as heme and hemozoin promote endothelial cell activation [40–42] and increase the expression of the adhesion molecules CD36, intercellular adhesion molecule (ICAM)-1, vascular cell adhesion protein-1, and E-selectin [43]. Erythrocyte sequestration involves the interaction of adhesion molecules present in endothelial cell surface and antigens

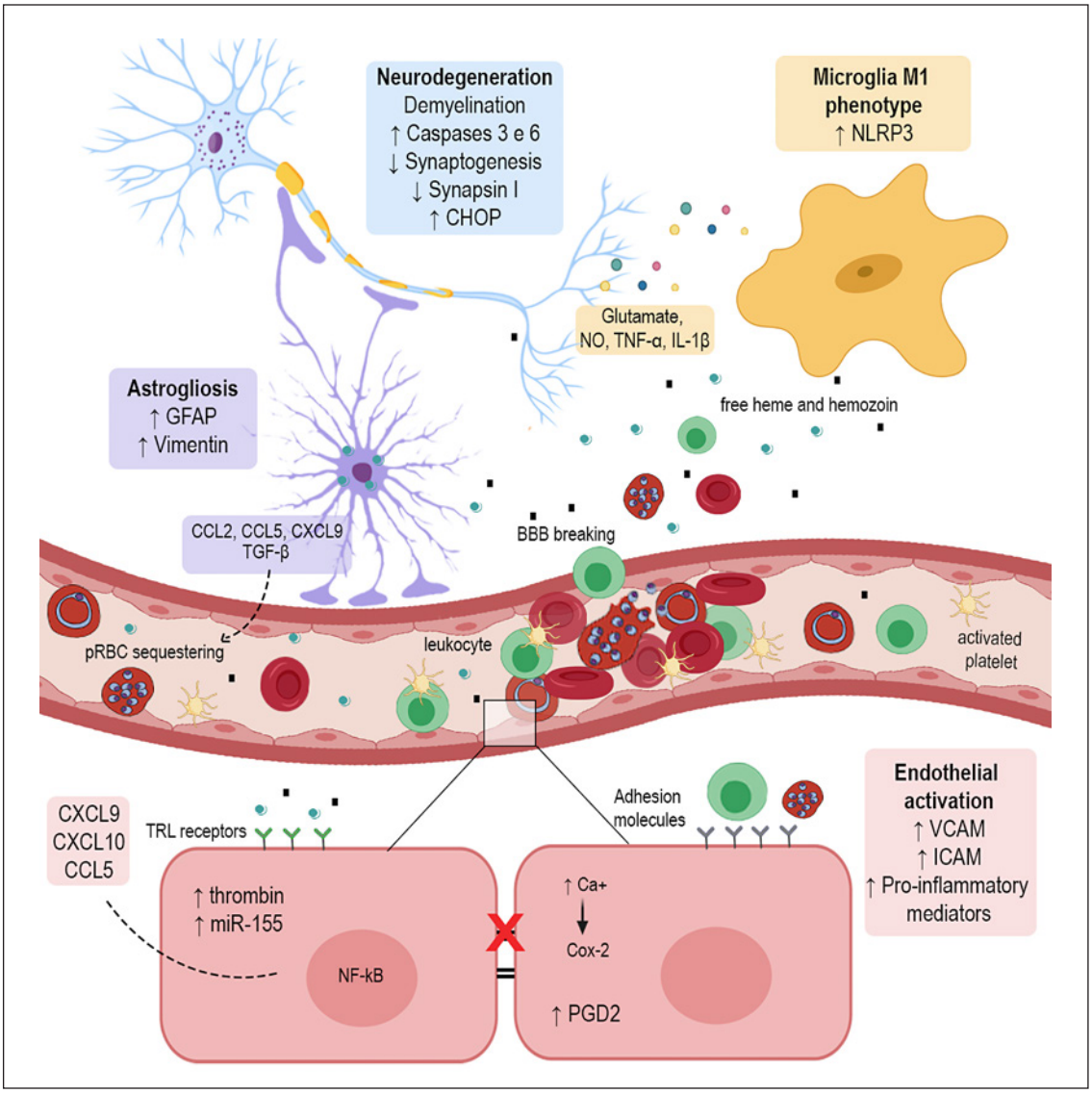

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Fig. 1. Neurovascular interactions after *Plasmodium* infection. Malaria infection leads to systemic production of inflammatory mediators that promote the activation of endothelial cells. Molecules related to the parasite's metabolism, such as heme and hemozoin, are recognized by TRL and promote the translocation of the transcription factor NF-κB to the nucleus and increased inflammatory response. The increase in intracellular Ca^{2+} levels is also related to the endothelial activation process, which culminates in the increase of PGD2, contraction in the actin cytoskeleton, promoting the rearrangement of the occludent and adherent junctions, such as claudin-5 and cadherin. The increase in the production of chemokines by endothelial cells promotes the recruitment of leukocytes. Endothelial activation also promotes the increase of adhesion molecules, such as ICAM and VCAM, which promotes the adhesion of pRBC, RBC, and leukocytes into the brain microcirculation. Platelet activation and deregulation of the coagulation pathway is associated with the interaction of thrombin with thrombomodulin in endothelial cells, leading to obstruction of the vessels, breakage of the BBB, and leakage of the contents of the vessel into the cerebral parenchyma. miR, such as miR-155, have an important role in endothelial cells activation and permeability of the BBB. Heme and hemozoin can also be recognized by neural cells, and promote inflammatory responses. Microglial cells switch to an activated phenotype (M1) with an increase of NLRP3 expression and activation of the NLRP3 inflammasome. Microglial cells secrete inflammatory mediators such as glutamate, NO, TNF-α, and IL-1β that are recognized by neurons and promote neurodegeneration and neurotoxicity. Neurodegeneration involves demyelination, loss of synapses, and neuronal apoptosis involving caspases 3 and 6. Astrocytes become reactive, increase GFAP and vimentin expression, and secrete chemokines (CCL2, CCL5, and CXCL9) and growth factors (TGF-β). These molecules modulate the response of endothelial cells and are more specifically related to increased pRBC sequestration. TRL, Toll-like receptors; BBB, blood-brain barrier; pRBC, parasitized red blood cells; miR, micro RNAs; GFAP, glial fibrillary acidic protein; TGF-β, transforming growth factor-β; ICAM, intercellular adhesion molecule; VCAM, vascular cell adhesion protein; NF, nuclear factor; PGD2, prostaglandin D2; TNF, tumor necrosis factor; NO, nitric oxide.

in pRBC [44]. In *P. falciparum* infection, one of the main molecules expressed on the surface of pRBC is *P. falciparum* erythrocyte membrane protein 1 [45]. In addition, endothelial cells incubated with pRBC increased expression of chemokines responsible for leukocyte recruitment such as CXCL8, CXCL1, CXCL2, CXCL20, and CXCL10 [46, 47]. CX3CL1 participates in the cytoadherence of pRBC [48–50], and CXCL10 participates in the adhesion process of T cells to the endothelium, mainly CD8+ T cells [51]. Furthermore, CXCL10 is present in high concentrations in plasma and brain tissue of CM patients [52] and can be used as a marker of mortality in CM [53].

Endothelial and platelet activation have been associated with downregulation of endogenous anticoagulant pathways [54–56]. Coagulatory alterations and local microvascular lesions in severe malaria may be associated with thrombin [57]. Despite its main function to convert fibrinogen into fibrin, thrombin can act as a potent mediator of pro- and anti-inflammatory pathways depending on the context of endothelial signaling [58, 59]. When thrombin interacts with thrombomodulin in the endothelial cell, it activates protein C that has a pivotal role in regulating coagulation and fibrinolysis and exhibits cytoprotective properties that may modulate pathological processes [60]. However, *P. falciparum* erythrocyte membrane protein 1 competes with the activated protein C interaction with its endothelial cell protein C receptor, leading to disruption in the BBB and vasogenic cerebral edema [58]. During CM, pRBC leads to BBB disruption, regardless of the parasite's stage, as a result of the interaction of the ligands present on the surface of pRBC with their receptors on immune cells (such as lymphocytes and macrophages that are increased in CM), leading to a series of events that culminate with local inflammation and BBB breakdown [49] (Fig. 1). However, the schizont stage causes higher endothelial dysfunction and is also associated with a delayed thrombin-induced barrier recovery [61]. Similarly, coculture of cerebral microvasculature endothelial cells (HBMEC) and RBC infected with schizont-stage parasites causes higher barrier disruption than trophozoite-stage parasites. Circulating plasmodial histones are significantly elevated in CM and are associated with the development of CM as they promote endothelial activation, deregulated coagulation, and consequently thrombosis [62].

The inflammatory endothelial response differs in different regions of the body as the cells of the cerebral microvasculature are more sensitive to the inflammatory stimulus [63, 64], which may be related to the development of CM. Endothelial cells of the cerebral microvasculature have increased zonula occludens-1, but not CD36, expression after the stimulation that may play a crucial role in BBB permeability [65]. In addition, cells from CM patients have higher levels of ICAM-1, vascular cell adhesion protein-1, CD61, MCP-1, and IL-6 and are more likely to undergo apoptosis when compared to cells from uncomplicated malaria patients [65]. Hemozoin and pRBC promotes endothelial activation through the nuclear factor (NF)-κB pathway [47, 66], whose target genes include those with apoptosis function, expression of adhesion molecules, and proinflammatory cytokines and chemokines [47, 66] (Fig. 1). Immunohistochemistry analyses of the brain of CM patients showed activation of NF-κB in endothelial cells and intravascular leukocytes [67]. Interestingly, the blocking of NF-κB pathway in vitro can prevent the inflammatory activation of endothelial cells [66].

Endothelial activation promotes an increase in calcium secretion by the endoplasmic reticulum, increasing the concentration of this ion in the cytoplasm [68]. Elevated levels of cytoplasmic calcium may promote the activation of intracellular signaling pathways [68], including the activation of the phospholipase enzyme, responsible for increasing the synthesis of arachidonic acid (AA). Pediatric CM brain swelling is associated with activity of phospholipase A2 metabolites fatty acid products, such as AA [69]. The enzymes cyclooxygenase I and cyclooxygenase II (COX-2) convert AA into prostaglandins [70, 71]. Brains of CM patients show elevated levels of COX-2 in endothelial cells and astrocytes [70]. In the ECM model, the increase in the level of COX-2 mRNA was related to the activation of the NF-κB pathway and to the increase in proinflammatory cytokines [72]. Platelet-derived extracellular vesicles (EV) can alter the metabolism of endothelial cells, inducing the production of COX-2 and prostaglandins, which can affect vascular permeability and induce endothelial cell apoptosis [73].

Micro RNAs (miR) are involved in the activation of endothelial cells in the BBB dysfunction that occurs in CM. miR-155 deficiency is associated with decreased endothelial activation during ECM, and anti-miR-155 therapy was able to increase survival, maintain the BBB integrity, while decreasing endothelial activation and proinflammatory cytokine levels [74]. EV from pRBC (EV-pRBC) are rich in miRNAs [75], including miR-451a and let-7b that are associated with the argonaut-2, a molecule that plays a central role in RNA silencing processes, forming an active regulatory complex [76]. HBMEC cells internalized EV-pRBC containing miRNA 451A, which targets the activating transcription factor 2 and caveolin-1, involved in vascular permeability [76].

Astrocytes

Astrocyte end-feet encircling endothelial cells have an important role in maintaining the BBB integrity [77, 78]. In CM, astrocytes retract their processes and distribute themselves unevenly in the vessel which is associated with increased BBB permeability [79]. In situations of BBB injury, astrocytes become reactive, a process known as astrogliosis that involves proliferation and changes in cell morphology, increased expression of glial fibrillary acidic protein and vimentin, and secretion of proinflammatory mediators and growth factors [80]. Astrogliosis has been associated with the BBB dysfunction observed in CM and ECM [81–83]. Astrocytes stimulated with pRBC regulates CXCL10 positively [84]. Moreover, if stimulated with TNF-α, interferon (IFN)-γ, IL-1β, and IL-6, which are related to the pathophysiology of malaria, astrocytes increase the production of CCL2, CCL5, CXCL9, and CXCL10 [85] that can exacerbate the disease by recruiting leukocytes (Fig. 1). Astrocytes increased expression of transforming growth factor-β in pRBC sequestering areas has also been observed in CM and ECM [86, 87].

Astrocytes are activated 2–3 days before the onset of clinical symptoms in ECM and are related to the progression of the BBB dysfunction that begins along the rostral migratory pathway initiated in the olfactory bulb and in the retina [79, 88–91]. pRBC sequestered in the cerebral microvasculature can make contact with the cells of the brain parenchyma, including astrocytes, leading to the activation of these cells [92]. EV from red blood cells infected with *Plasmodium berghei* ANKA can be internalized by astrocytes in vitro [84]; thus, the transfer of EV-pRBC can be an important process in the loss of the BBB integrity. Prostaglandins are lipid inflammatory mediators, which can affect the nervous system and play a significant role in neurodegenerative disorders and in parasitic diseases, including malaria [93–95]. Human astrocyte CCF-STTG1 cell line treated with prostaglandin D2 showed increased expression of hemoxygenase-1 in a dose- and time-dependent manner, indicating the involvement of these molecules in the pathogenesis of CM [96]. Stimulation of human astrocytes with purified hemozoin results in cellular dysfunction and cytotoxicity to these cells [97], suggesting a role of hemozoin in the neuropathogenesis of CM.

Microglial Cells

Microglial cells are immune cells of the myeloid lineage that reside in the CNS. They play a role in homeostatic maintenance and protection of the CNS, releasing neurotrophic substances and modulating processes such as neurogenesis [98], oligodendrogenesis, and synaptic activity and plasticity [99, 100]. Microglia are ramified cells that express many receptors and molecules on its surface and act in a bidirectional manner, being in constant contact with other CNS resident cells, such as neurons, astrocytes, and endothelial cells from the BBB, contributing for the surveillance of this structure [11, 101].

Microglial cells are the first to respond to the inflammatory process resulting from malaria infection. Microglial activation has already been demonstrated in postmortem brains from patients with CM and in ECM. The secretion of chemokines and cytokines by microglia can contribute to the progression of neuroinflammation in the more severe cases of malaria.

After the rupture of the BBB, pRBC, EV-pRBC, and molecules such as heme [102] and hemozoin can invade the brain parenchyma and be recognized by microglia [84, 103, 104]. In ECM, a rapid response of microglial cells occurs with morphological alteration characteristic of microglial activation [90, 105, 106]. The microglial cells start to present a M1 phenotype, dependent on the type I IFN signaling pathway [107]. In vitro experiments demonstrate that microglial cells stimulated with synthetic hemozoin are activated via the NF-κB pathway [102, 104], with activation of the NLRP3 inflammasome and increased production of TNF-α IL-6, iNOS, and IL-1β [104] (Fig. 1). Additionally, microglial cells are able to internalize the EV-pRBC and switch to an activated profile, secreting TNF-α [103].

The receptor CX3CR1 present in microglial cells recognizes CX3CL1 (fractalkine) that is present in the mature neurons of the hippocampus. Mice infected with *P. chabaudi* showed a reduction in the levels of CX3CL1 in the hippocampus and alterations in social and anxiety-like behaviors [106]. In addition, CCL5 is increased in the brain of patients with CM and in ECM [108, 109]. During a systemic inflammation, endothelial cells secrete CCL5, causing the microglia to express the CCL5 receptor and infiltrate the NVU, in order to protect the BBB. However, with the progression of the inflammation, the microglia assume an activated phenotype and phagocyte components of the BBB [110]. This phagocytosis is facilitated due to microglial cell expression of the proteolytic enzyme matrix metalloproteases. These enzymes are increased in CM [83] and are responsible for the degradation of the extracellular matrix. Thus, there is a further increase in the permeability of the BBB and consequently the passage of substances from the vessels into the cerebral parenchyma [98]. In CM patients, there is an increase

in transforming growth factor-β levels [111] secreted by astrocytes, which may modulate microglial phagocytic activity [112].

Neurons

During the process of neuroinflammation, nitric oxide (NO) produced during cytokine-stimulated blood vessel inflammation may diffuse through the BBB, leading to interferences in synapses and contributing to neurodegeneration [113]. Cocultures of neurons and immune-stimulated microglial cells increased the production of NO and neurotoxicity [114]. This adverse effect indicates a conflicting consequence of glial activation since, as an immune cell, neuroprotection would be expected, instead of neurodegeneration. Even though not yet fully explained in CM models, studies have shown the microglia's ability to induce apoptosis in neurons, through diffusible molecules, such as glutamate, TNF-α, NO, and IL-1β, and synaptogenesis, mediated by the release of cytokines and neurotrophins, such as the brain-derived neurotrophic factor (BDNF) [115] (Fig. 1). Furthermore, SK-N-SH cells were able to internalize hemozoin dysregulating proapoptotic proteins, resulting in apoptosis. Hemozoin was already described to activate microglial cells in coculture with differentiated neural progenitor human cells. Microglial cells induce neurotoxicity in neurons, increasing the activity of reactive oxygen species and caspase-6, related to apoptosis-mediated neurodegeneration [97, 104]. Likewise, the activation of caspase-3 has been investigated during ECM and showed increased levels specially in the cerebellum and brainstem [116].

In CM, neurotoxicity has previously been addressed in analyses of brain tissues of infected children, which revealed the presence of diffuse myelin and axonal injury associated with sequestration of pRBCs in the microvessels [117], as well as the suggestion of a link between the axonal injury and impaired consciousness and duration of coma [118]. CM patients presented demyelination of the nerve fiber sheath due to the production of NO by surrounding immune cells [119] and exhibited elevated and heterogeneous axonal injury independently of hemorrhages or immune responses, and to other neuropathological features [120]. In ECM, axonal demyelination and neurodegeneration of optic nerves of infected mice have been associated with compromised blood-nerve barrier [89], indicating a similar development of CM and neurological damage in human and mice. Besides, ECM also leads to alterations in the gene and protein expression of LIMK-1, cofilin-1, and β-actin, involved in the LIMK-1/cofilin-1 pathway, related to the maintenance of actin cytoskeleton, neuronal morphology, synaptic plasticity, and axonal outgrowth [121].

Neurological lesions, such as shrinkage of nucleus, vacuolization of the cytoplasm, chromatin clumping, disintegrated membrane, and structurally altered mitochondria associated with morphological changes such as parenchymal microhemorrhages, can be detected in CM patients [116, 122]. The infection activates the endoplasmic reticulum stress signaling pathway on neuronal cells, with increased levels of protein kinase R-like ER kinase, inositol-requiring enzyme 1, and activating the transcription factor 6, which converge to a higher C/EBP homologous protein expression, a key element in ER-stress-induced neuronal apoptosis [122, 123]. This form of programmed cell death has been detected in ECM in different areas of the brain and with no clear pattern, which could be associated with the neurocognitive damage present in mice surviving CM [124]. Stress induced actin-cofilin rods, detected in many neurodegenerative diseases, such as Alzheimer and Parkinson, are also present in the neurites of CM-infected brain tissues, which may contribute to impaired morphological aspects of neurons during infection and corroborate the neurological symptoms observer postinfection [121]. In ECM, increased levels of neuronal cell death in the hippocampus are observed, which associated with a reduction in the neurogenesis potential can indicate a loss of hippocampal function [125]. Moreover, protein expression levels of BDNF are decreased [126]. BDNF is important for synaptic plasticity, learning, and memory [127] and is critical for neuronal survival and function; thus, its downregulation may lead to irreversible neurodegeneration [128].

Malaria infection in patients leads to reduced synaptic densities [116] and increased levels of synapsin I in the glomerular synaptic complex of the cerebellum. Synapsin I regulates neurotransmitter release and synaptic formation, and its immunoreactivity is used as an indirect indicator of synapses in the CNS. Alterations in synapsin I expression leads to brain malfunction, which may link CM to ischemia, coma, and other neurological complications [129] (Fig. 1). Furthermore, focal swelling of dendrites has also been reported in animal models of CM, as well as alteration in the dendritic arborization of neurons [121].

Pericytes

Pericytes are part of the NVU and have a significant role in the development, maturation, and maintenance of BBB [130]. Pericytes are vascular mural cells embedded in the basement membrane of blood microvessels and

communicate with others cells of the NVU, such as endothelial cells and astrocytes [131]. Pericytes were described for having similar behavior and properties of stem cells, participating in the repair of the cerebral blood vessels and angiogenic processes as they were reported to differentiate into endothelial and neural cells [132, 133]. Recently studies described that pericytes cells have an important role in the BBB permeability and dysfunction, neuroinflammation, and changes on neural activity [131].

Pericytes stimulated with lipopolysaccharides, TNF-α, IL-1β, and IFN-γ had altered expression of alpha smooth muscle actin, the most prevalent pericyte marker, and of iNOS, reactive oxygen species, COX-2, and MHCII [134]. In addition, pericytes participate in the modulation of phagocytosis and in the support for ICAM-1-mediated neutrophil transmigration. Although, there is evidence that suggest the involvement of pericytes during an inflammatory response, their role in malaria infection has not yet been defined(Fig. 1).

Conclusion

Malaria is still classified as a highly lethal disease that leaves sequels to its survivors. It is known that the pathophysiology of CM involves the activation of endothelial cells due to molecules derived from the parasite's metabolism, like heme and hemozoin, leading to BBB dysfunction. Astrogliosis may contribute to the most serious conditions of the disease and the most aggressive sequelae, which includes neurological impairments. Nonetheless, microglial cells are the first CNS cells to respond, switching to an activated M1 phenotype. The aggressive inflammatory host response to malaria infection favors the occurrence of neurotoxicity and is related to reduced synaptic densities and axon's demyelination. Despite efforts, the pathophysiology of malaria needs further understanding. The alarming number of cases, deaths, and sequelae related to malaria around the world and the potential benefit that the advance in research can offer to the global society justify and reinforce the value of all the work still in progress in this area, related both to the search for more efficient therapeutic approaches and to a deeper understanding about the host-pathogen relation and its consequences.

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Conflict of Interest Statement

The authors declare that they have no conflict of interests.

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Author Contributions

M.N.L., H.C.C.-F.-N., and T.M.-G. made substantial contributions to the conception and design of the work and revised it critically. M.N.L., R.J.R.X.F., B.A.B.R.P., and A.M.G.D. wrote the manuscript and revised it critically. All authors gave final approval of the version to be published.

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