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Balancing Endothelial Training and Tolerance: Innate Immune Memory in Malaria Pathogenesis

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ABSTRACT

Malaria, predominantly caused by *Plasmodium falciparum*, remains a major global health challenge. While research has traditionally focused on adaptive immunity, emerging evidence highlights a critical role for innate immune memory in disease progression—particularly involving endothelial cells (ECs). Situated at the blood–tissue interface, ECs are not passive barriers but active participants in immune regulation, capable of developing memory-like responses through epigenetic and metabolic reprogramming. This review examines how repeated or chronic malaria exposure shapes EC behavior via trained immunity (a heightened, pro-inflammatory state) or trained tolerance (a hyporesponsive, anti-inflammatory state). Acute infections promote EC activation through pathogen recognition and cytokine signaling, whereas chronic or repeated infections induce tolerogenic adaptations that preserve vascular integrity and limit immunopathology. Malaria-derived molecules, such as hemozoin, glycosylphosphatidylinositols, and extracellular vesicles—modulate these memory states alongside cytokine cues like IL-1β and TGF-β. Despite growing recognition of EC plasticity, major gaps remain, particularly regarding the molecular distinction between trained and tolerized ECs, tissue-specific responses in organs like the brain and placenta, and the durability of memory states. The interplay of endothelial memory with malaria severity and tolerance has yet to be fully explored in human settings. Future research integrating single-cell profiling, spatial mapping, and clinical data is needed to clarify the immunoregulatory functions of ECs in malaria and assess their potential as therapeutic targets. This review highlights the importance of endothelial immune memory in shaping host–pathogen dynamics and underscores its relevance for understanding disease tolerance in malaria-endemic populations.

Keywords: Endothelial Cells, Trained Immunity, Trained Tolerance, Innate Immune Memory

INTRODUCTION

Malaria remains one of the most pressing global health concerns, particularly in sub-Saharan Africa and Southeast Asia, where *Plasmodium falciparum* is responsible for the majority of severe cases and deaths based on World Health Organization malaria report 2023.[1] The clinical spectrum of malaria ranges from mild febrile illness to life-threatening complications such as cerebral malaria, which is associated with vascular dysfunction, endothelial activation, and breakdown of the blood–brain barrier.[2] While significant research has focused on adaptive immunity and the role of circulating immune cells in controlling parasitemia, increasing evidence suggests that innate immune responses—including

those mediated by non-hematopoietic cells like endothelial cells (ECs)—play a pivotal role in determining disease progression and outcome.[3]

A growing body of literature has identified trained immunity as a form of innate immune memory whereby a primary stimulus induces long-lasting functional reprogramming through epigenetic, transcriptional, and metabolic changes.[4] Initially characterized in monocytes and macrophages, this phenomenon has since been observed in ECs, particularly in the context of chronic inflammatory or infectious stress.[5, 6] Trained ECs may exhibit enhanced pathogen recognition, cytokine production, and leukocyte recruitment during subsequent challenges. However, excessive or sustained activation may contribute to endothelial dysfunction and vascular pathology—features commonly observed in severe malaria.[7-9] In contrast, trained tolerance refers to a hyporesponsive state induced by similar primary stimuli, functioning as a regulatory mechanism to limit tissue damage in the context of persistent inflammation.[10-14] This tolerogenic adaptation is especially relevant in malaria-endemic areas, where individuals with repeated exposure often display reduced clinical symptoms despite ongoing parasitemia, a phenomenon attributed to disease tolerance.[15-18] ECs, given their position at the interface of blood and tissue, may act both as amplifiers of inflammation during acute infection [19, 20] and as regulators that restrain immune responses during chronic or recurrent exposure.[21, 22]

Despite growing interest in innate immune memory, the role of ECs in trained immunity and trained tolerance during malaria infection remains poorly defined. While trained immunity has been well characterized in myeloid cells and natural killer cells [4], less is known about how ECs contribute to long-term immune adaptation following *Plasmodium* exposure. This represents a critical gap, particularly because ECs are among the first cells to detect and respond to parasitic antigens, hemozoin, and inflammatory cytokines in the vascular environment. Although EC memory-like behavior has been described in models of sterile inflammation and bacterial sepsis,[23, 24] direct evidence from malaria contexts remains scarce. Current findings largely describe EC functions in terms of barrier integrity, cytokine secretion, and parasite sequestration,[25-27] without distinguishing whether these are outcomes of trained or tolerized states during repeated or secondary infection. In addition, there is no established consensus on the molecular markers that distinguish trained versus tolerized ECs in malaria. While several studies do not provide a direct comparison of EC immune memory across different vascular beds, they suggest that the immune responses and endothelial interactions in the brain, lungs, and potentially the placenta are distinct due to the unique structural and functional characteristics of these tissues.[28-30] Further research is needed to fully understand the variations in EC immune memory across these vascular beds. Few studies have integrated epigenetic and metabolic profiling to characterize how memory states are established, maintained, or reversed in ECs following malaria exposure. While recent work has implicated chromatin remodeling [31, 32] and metabolic reprogramming in endothelial responses,[33] the regulatory influence of specific malaria-derived stimuli—including parasite density, hemozoin, glycosylphosphatidylinositols (GPIs), and extracellular vesicles—has yet to be fully elucidated. Moreover, the downstream impact of trained EC phenotypes on disease severity, immune coordination, and vascular pathology remains speculative. Clarifying whether EC memory promotes immunopathology or facilitates host tolerance could have important implications for therapeutic strategies aimed at modulating vascular inflammation in malaria.

The aim of this literature review is to critically evaluate current evidence on the role of endothelial cells in trained immunity

and trained tolerance during malaria infection and to explore how these processes influence disease progression and host–pathogen interactions. Specifically, this review will (1) Mechanisms and Regulation of Trained Immunity and Tolerance in Endothelial Cells; (2) assess how repeated or chronic *Plasmodium* exposure modulates endothelial responses in malaria, particularly in relation to vascular inflammation, immune activation, and barrier dysfunction; and (3) identify gaps in current understanding and propose future research directions to clarify the immunoregulatory role of the endothelium in malaria tolerance and severity. By integrating insights from immunology, vascular biology, and infectious disease research, this review aims to contribute to a more nuanced understanding of endothelial function in malaria pathogenesis.

Mechanisms and Regulation of Trained Immunity and Tolerance in Endothelial Cells

Endothelial cells (ECs), once viewed as passive structural components of the vasculature, are now recognized as key immunoregulatory players capable of developing memory-like properties. Through a process resembling trained immunity or trained tolerance, ECs can be reprogrammed to mount either heightened or suppressed responses upon repeated stimulation. This reprogramming is orchestrated through complex epigenetic and metabolic pathways. Histone modifications—particularly methylation and acetylation—play a pivotal role in shaping transcriptional accessibility and responsiveness without altering the genetic code.[4] For instance, exposure to pro-inflammatory cytokines such as IL-1β or microbial ligands like β-glucan enhances trimethylation of histone H3 at lysine 4 (H3K4me3), priming genes associated with adhesion molecules and cytokines for faster reactivation.[34] In contrast, trained tolerance is marked by repressive modifications, including H3K9me2 and H3K27me3, which silence inflammatory gene expression.[11] These epigenetic shifts are tightly linked to metabolic reprogramming. In trained immunity, ECs typically transition from oxidative phosphorylation to glycolysis and glutaminolysis—metabolic profiles that support rapid ATP generation and feed epigenetic enzymes like histone acetyltransferases.[35] Conversely, tolerized ECs maintain mitochondrial metabolism and NAD^+ flux, favoring sirtuin-mediated histone deacetylation and suppression of inflammatory transcription.[36, 37] These metabolic–epigenetic feedback loops stabilize the trained or tolerant phenotype and guide the endothelial response during infection.

In malaria, external cues particularly *Plasmodium* burden and immune signaling—play a major role in dictating EC immune programming. Acute *P. falciparum* infections with high parasitemia drive EC activation via engagement of pathogen- and damage-associated molecular patterns (PAMPs and DAMPs) through receptors like TLRs and NLRs.[38-40] This results in the upregulation of ICAM-1, VCAM-1, TNF-α, and IL-6, supporting a trained immunity phenotype.[41-44] However, chronic or repeated low-level infections, common in malaria-endemic regions, are more likely to induce trained tolerance, enabling ECs to suppress excessive inflammation, reduce leukocyte adhesion, and maintain vascular stability. [45, 46] Several parasite-derived molecules further modulate these memory states. Hemozoin, a by-product of hemoglobin digestion, induces inflammasome activation and pro-inflammatory cytokine release during acute infection,[47-49] but chronic exposure leads to NF-κB suppression and repressive histone modifications, promoting tolerance.[50, 51] Glycosylphosphatidylinositol anchors, potent ligands for TLR2–TLR6, trigger trained immunity via MAPK and NF-κB activation and associated chromatin remodeling.[52-56] Yet repeated or high-dose exposure shifts the response toward tolerance by upregulating the NF-κB

inhibitor A20 (TNFAIP3) and reinforcing gene silencing.[57-60] Other malaria-derived antigens, such as histidine-rich protein II (HRPII) and parasite-derived extracellular vesicles (EVs), also influence EC function. HRPII enhances endothelial permeability and inflammasome activation, promoting trained responses.[33, 61, 62] However, prolonged exposure to HRPII or EVs induces immunosuppressive signaling, including PD-L1 expression and histone deacetylation, indicative of trained tolerance.[63-66] In the other hand, parasite-derived extracellular-vesicles (EVs) contain the *PfEMP1* protein and induce significant transcriptional changes in human monocytes, thereby influencing the inflammatory response and endothelial permeability. Others also indicate a direct effect of parasite EVs on endothelium dynamics and immune modulation influence inflammatory EC function.[67-69] The cytokine environment further modulates endothelial memory. Pro-inflammatory cytokines like IL-1β and IFN-γ facilitate trained immunity through chromatin activation and transcriptional upregulation,[70-72] while IL-10 and TGF-β foster tolerance by silencing inflammatory gene loci and inhibiting NF-κB signaling.[73, 74] In malaria, the immune system cycles through phases of activation and resolution, creating a dynamic cytokine milieu that reprograms ECs throughout the infection course. Recent single-cell and epigenomic studies have confirmed the durability of these trained states. ECs exposed to *Plasmodium* antigens retain specific chromatin marks—such as H3K4me3 in activated genes and H3K27me3 in silenced loci—long after initial exposure. The effects of *Plasmodium* infection on brain endothelial cells (BECs) highlight that prolonged exposure to *Plasmodium* antigens, such as those from the infected erythrocytes, alters the transcriptional landscape of BECs, indicating the presence of specific chromatin modifications that facilitate antigen presentation and inflammatory responses. This study underscores the connection between chromatin marks and the retention of a memory state in endothelial cells.[46] These epigenetic patterns are stabilized by chromatin remodelers and reinforced by metabolic shifts, effectively locking ECs into their trained or tolerant phenotype. In summary, endothelial immune memory in malaria is shaped by the interplay of parasite-derived molecules, cytokine signals, and intrinsic metabolic–epigenetic programs. This balance between trained immunity and tolerance equips ECs to respond rapidly to acute infection while mitigating vascular damage during persistent or recurrent exposure—contributing to disease outcome and host survival in malaria-endemic settings.

Endothelial Modulation by Repeated or Chronic Plasmodium Exposure

Chronic or repeated *Plasmodium* exposure, especially in malaria-endemic regions, leads to long-term changes in endothelial cell (EC) function that fundamentally alter the vascular response to infection. Unlike acute infections that induce robust pro-inflammatory activation, chronic exposure drives a more complex, adaptive phenotype marked by a balance between immune activation and vascular protection. This modulation is critical for host survival in environments where reinfection is frequent and unavoidable. Repeated parasitemia causes vascular inflammation that is initially driven by the upregulation of endothelial adhesion molecules (e.g. ICAM-1, VCAM-1) and pro-inflammatory cytokines (e.g. TNF-α, IL-6) in response to circulating *Plasmodium* components.[75-77] However, with sustained or cyclical exposure, ECs adapt by limiting the magnitude of these responses. This is mediated by epigenetic and metabolic reprogramming that suppresses excessive cytokine release and reduces leukocyte recruitment to the vascular wall.[78-83] For instance, tolerized ECs exhibit increased expression of anti-inflammatory regulators and reduced chromatin accessibility at key inflammatory

loci, dampening vascular inflammation over time.[84-87] In terms of immune activation, chronic *Plasmodium* exposure leads to what is often referred to as "immune exhaustion" or tolerance in endothelial and innate immune compartments. While ECs retain the ability to detect parasitic ligands through PRRs such as TLR2 and TLR4, their downstream signaling is blunted during chronic infection phases. This attenuation helps prevent immunopathology, such as cerebral edema and vascular occlusion, which are typically driven by exaggerated endothelial responses.[88, 89] Moreover, repeated exposure alters the cytokine milieu, increasing levels of IL-10 and TGF-β, which further promote a regulatory cell phenotype through repression of NF-κB and induction of tolerance-associated epigenetic marks.[90-93] These support study has been done in ECs shows TGF-β interacts with endothelial junctions, helping to prevent the activation of the endothelium under flow conditions, which is critical for maintaining a regulatory phenotype in ECs amidst inflammatory challenges.[94] Barrier dysfunction is a hallmark of severe malaria but becomes less pronounced with repeated infections. In naïve hosts, *Plasmodium* infection disrupts endothelial tight junctions and increases permeability, contributing to complications such as cerebral and pulmonary edema.[25, 95-97] However, studies in other diseases open possibility that in semi-immune individuals, ECs exposed to chronic low-level infections have partial restoration of barrier integrity, possibly due to metabolic and transcriptional adaptations that stabilize junctional proteins.[98, 99] These changes are supported by observations that ECs in chronically exposed individuals show reduced expression of permeability-inducing molecules and greater resilience to inflammatory stress. Overall, repeated or chronic *Plasmodium* exposure reprograms endothelial responses to prioritize vascular stability and controlled immune activation. This modulation reflects a form of trained tolerance that plays a protective role in host survival and limits severe pathology in populations with long-term malaria exposure.

Gaps in Understanding and Future Directions

Despite growing recognition that endothelial cells (ECs) contribute actively to the immune landscape of malaria, significant gaps remain in our understanding of how they modulate disease tolerance and severity. Research has demonstrated that after exposure to Plasmodium falciparum—particularly through controlled human malaria infection—monocytes show long-term functional alterations that resemble a state of innate immune memory, which is akin to trained immunity. This indicates that not only monocytes but potentially endothelial cells may undergo similar reprogramming, allowing them to react more robustly to subsequent infections or inflammatory insults.[55, 100] The ability of human ECs to adapt their responses to repeated parasitic exposure suggests an evolving understanding of their role in immunity, where they may not just act as passive participants, but rather exhibit a type of functional "memory" in response to malaria.[101] Additionally, it has been noted that certain cytokines and signaling pathways activated during malaria infections foster an environment where ECs might develop these memory-like responses. The investigation into IL-27's role, for example, indicates that while it can enhance certain inflammatory responses in ECs, it may also downregulate others, showing a balance that is crucial for modulating the overall immune response during plasmodial infections.[101] Although studies have shown that ECs exhibit memory-like responses to inflammatory and parasitic stimuli, the specific epigenetic and metabolic pathways that distinguish trained immunity from trained tolerance in ECs remain poorly defined, especially in human tissues. Another critical knowledge gap lies in the temporal dynamics of endothelial reprogramming across repeated malaria infections. exposure to *Plasmodium*

falciparum leads to significant epigenetic reprogramming in human monocytes, resulting in a regulatory phenotype that impacts their inflammatory response. The study indicates that monocytes derived from children with cumulative malaria exposure exhibit traits suggesting a form of immune tolerance, characterized by alterations in inflammatory cytokine profiles.[102] These findings suggest that cumulative exposure to the malaria parasite not only affects monocytes but may also influence the endothelial cells they interact with, potentially leading to enhanced tolerance. The repeated malaria infections can lead to a distinct immune profile characterized by tolerance and adaptations in innate immune cells. The study implies that this immune configuration can change when there is a lack of reinfection, hinting at the potential for re-establishing baseline immune responses.[88] There is limited understanding of how long these memory states persist. Furthermore, much of the current evidence is derived from in vitro models or animal studies, which may not fully capture the heterogeneity of endothelial responses in humans across different vascular beds—particularly the brain, lungs, and placenta, where malaria pathology is most severe.[7] The spatial dimension of endothelial immune programming also remains understudied. Emerging technologies such as single-cell and spatial transcriptomics could provide crucial insights into how endothelial subsets within distinct tissue microenvironments contribute differentially to disease tolerance or progression.[103, 104] The exploration of the role of parasite-derived extracellular vesicles (EVs) in reprogramming the endothelium is still in its emerging stages, indicating a significant avenue for research on how Plasmodium modulates vascular immunity without necessitating direct cellular invasion. Recent studies have begun to elucidate the mechanisms through which these vesicles influence endothelial function.[105, 106] Future research should also address how host factors—including age, co-infections, and comorbidities such as malnutrition or HIV—influence endothelial training and tolerization during malaria. This is especially relevant for populations in endemic regions, where individuals are often exposed to multiple immunological challenges. Furthermore, interventional studies are needed to test whether modulating endothelial training (e.g., via metabolic modulators or epigenetic drugs) can enhance tolerance without compromising pathogen control, potentially opening new therapeutic avenues. In summary, advancing our understanding of endothelial immunoregulation in malaria will require integrative, longitudinal, and tissue-specific studies that bridge molecular mechanisms with clinical outcomes. This could transform how we assess disease severity, monitor immune adaptation, and design interventions aimed at reducing malaria mortality in high-burden regions.

CONCLUSION

Understanding the dynamic role of endothelial cells in trained immunity and tolerance is crucial for unraveling malaria pathogenesis and could pave the way for novel therapeutic strategies aimed at modulating vascular inflammation to improve disease outcomes in endemic regions.

Declaration by Authors

Declaration of generative AI in scientific writing: During the preparation of this work, the authors used ChatGPT to enhance the clarity of the writing. After using the ChatGPT, the authors reviewed and edited the content as needed and take full responsibility for the publication's content.

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