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Host Immune Modulation by Plasmodium-Derived Epigenetic Factors in Severe and Cerebral Malaria

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ABSTRACT

Plasmodium falciparum infection triggered complex host immune responses that determined disease severity, with cerebral malaria representing the most lethal complication characterized by profound neuroinflammation, endothelial dysfunction, and blood-brain barrier disruption. Emerging evidence indicates that parasite-derived epigenetic factors, including histones, nucleosomes, extracellular vesicles, and microRNAs, actively modulate host immune signaling pathways and contribute to immunopathology. This review examined the mechanisms by which Plasmodium-derived epigenetic factors influenced host immune responses and evaluated their contribution to the pathogenesis of severe and cerebral malaria. A comprehensive analysis of recent literature focused on parasite epigenetic regulators, host immune modulation, inflammatory pathways, and cerebral malaria pathophysiology was conducted. Plasmodium releases histones, DNA complexes, and extracellular vesicles during schizont rupture that activate toll-like receptors, induce proinflammatory cytokine cascades, promote endothelial activation, and trigger neutrophil extracellular trap formation. Parasite-derived microRNAs transferred via extracellular vesicles reprogrammed host gene expression, suppressing antimalarial responses while enhancing inflammatory pathways. Epigenetic modifications in host immune cells, including altered histone acetylation and DNA methylation patterns, establish persistent immune dysfunction and contribute to cytokine storm generation. These mechanisms collectively drove severe malaria complications, including cerebral pathology, respiratory distress, and metabolic acidosis. Plasmodium-derived epigenetic factors represented critical mediators of immunopathology in severe malaria through multifaceted modulation of innate and adaptive immunity. Understanding these molecular interactions provided opportunities for developing host-directed therapies that mitigated excessive inflammation while preserving antimalarial immune responses and improving clinical outcomes in life-threatening malaria.

Keywords: Cerebral malaria, Plasmodium falciparum, Epigenetic regulation, Immune modulation, Extracellular vesicles.

INTRODUCTION

Plasmodium falciparum employs sophisticated molecular strategies to manipulate host cellular environments, with increasing recognition that parasite-derived epigenetic factors constitute powerful modulators of human immune responses [1–3]. Epigenetic regulation encompasses diverse mechanisms, including DNA methylation, histone modifications, chromatin remodeling, and noncoding RNA expression, that collectively determine gene transcription patterns without altering underlying DNA sequences [4]. The malaria parasite exhibits remarkable epigenetic plasticity, utilizing variant histone proteins, specialized chromatin-modifying enzymes, and unique regulatory RNAs to control virulence gene expression, facilitate immune evasion, and coordinate developmental transitions throughout its complex life cycle. During blood stage replication, Plasmodium parasites extensively remodel host erythrocyte architecture, export hundreds of proteins into the host cell compartment, and release molecular cargo including nucleic acids, histones, hemozoin, and membrane-bound vesicles that interact directly with host immune surveillance systems.

The progression from uncomplicated malaria to life-threatening severe disease involves dysregulated immune activation characterized by excessive proinflammatory cytokine production, systemic endothelial dysfunction, microvascular sequestration of parasitized erythrocytes, and organ-specific pathology. Cerebral malaria, affecting predominantly children in sub-Saharan Africa and non-immune travelers, manifests as impaired consciousness,

seizures, and neurological sequelae, with mortality rates approaching twenty percent despite antimalarial treatment [5]. Pathophysiological mechanisms involve cytoadherence of infected erythrocytes to brain microvasculature, localized inflammation, blood-brain barrier compromise, and neuronal injury mediated by inflammatory mediators, metabolic derangements, and microvascular obstruction. Emerging evidence demonstrates that parasite-derived epigenetic factors, released during schizont rupture or secreted via extracellular vesicles, serve as potent immunomodulatory signals that shape both protective immunity and damaging immunopathology. This review critically examines the mechanisms by which Plasmodium-derived epigenetic factors modulate host immune responses and evaluates their specific contributions to the pathogenesis of severe and cerebral malaria.

Plasmodium Epigenetic Machinery and Host-Parasite Molecular Interactions

Plasmodium falciparum possesses a distinctive epigenetic regulatory apparatus adapted to its parasitic lifestyle and complex developmental program [6]. The parasite genome encodes variant histone proteins, including histone H2A.Z, H2B.Z, H3.3, and centromeric H3 variants that exhibit substantial structural divergence from canonical human histones, conferring unique chromatin properties that facilitate antigenic variation and stage-specific gene regulation [7, 8]. Plasmodium histone-modifying enzymes, including histone acetyltransferases, deacetylases, methyltransferases, and demethylases, establish distinct chromatin landscapes that partition the genome into transcriptionally active euchromatin and silenced heterochromatin domains. Notably, virulence genes encoding erythrocyte membrane protein 1 variants, which mediate cytoadherence and immune evasion, undergo epigenetic switching through histone modifications and heterochromatin protein recruitment, enabling sequential expression of antigenically distinct proteins that prevent immune clearance.

During intraerythrocytic development, parasites extensively modify host cell properties through protein export via the Plasmodium translocon of exported proteins and establishment of membranous structures that facilitate nutrient acquisition and waste disposal [9]. Schizont rupture, occurring synchronously every 48 hours, releases merozoites alongside substantial quantities of parasite-derived danger-associated molecular patterns, including glycosylphosphatidylinositol anchors, hemozoin crystals, genomic DNA, histones, and extracellular vesicles [10]. These molecular entities engage pattern recognition receptors on innate immune cells, particularly toll-like receptors 2, 4, and 9, triggering nuclear factor kappa B activation and proinflammatory cytokine production. Parasite histones, released extracellularly during schizont rupture, exhibit particularly potent immunostimulatory properties, activating toll-like receptor 2 and 4 signaling pathways and inducing robust tumor necrosis factor alpha, interleukin 1 beta, and interleukin 6 secretion from monocytes and macrophages.

Extracellular vesicles represent another critical vehicle for host-parasite communication, with infected erythrocytes releasing abundant microvesicles and exosomes containing parasite proteins, nucleic acids, and regulatory RNAs [11]. These vesicles traffic parasite-derived cargo to recipient cells, including endothelial cells, platelets, monocytes, and uninfected erythrocytes, transferring functional molecules that reprogram cellular behavior. Proteomic and transcriptomic analyses reveal that Plasmodium-derived extracellular vesicles contain hundreds of parasite proteins involved in metabolism, protein trafficking, and virulence, alongside diverse RNA species including messenger RNAs, transfer RNAs, ribosomal RNAs, and regulatory microRNAs [12]. The molecular cargo exhibits stage specificity, with distinct profiles characterizing ring, trophozoite, and schizont-derived vesicles, suggesting developmentally regulated communication strategies. These findings establish that Plasmodium deploys multifaceted epigenetic and molecular strategies to interface with host immune systems, setting the stage for understanding their role in severe disease pathogenesis.

Mechanisms of Immune Activation by Parasite-Derived Epigenetic Factors

Plasmodium-derived histones and nucleosomes constitute particularly potent immunostimulatory factors that drive pathological inflammation during severe malaria [13, 14]. Extracellular histones, released during schizont rupture or parasite killing by immune effectors, bind directly to toll-like receptor 2 and 4 on innate immune cells, triggering MyD88-dependent signaling cascades that activate nuclear factor kappa B and mitogen-activated protein kinase pathways. This engagement induces rapid transcription of proinflammatory cytokine genes, resulting in massive secretion of tumor necrosis factor alpha, interleukin 1 beta, interleukin 6, and interleukin 8 that collectively orchestrate systemic inflammatory responses. Circulating histone levels correlate strongly with disease severity, parasitemia burden, and mortality risk in pediatric cerebral malaria cohorts, establishing histones as both pathogenic mediators and potential biomarkers. Beyond direct immune cell activation, extracellular histones exert cytotoxic effects on endothelial cells, inducing calcium influx, reactive oxygen species generation, and cell death pathways that compromise vascular integrity.

Parasite genomic DNA complexed with histones forms nucleosomes that engage toll-like receptor 9 in endosomal compartments following internalization, providing an alternative immunostimulatory pathway [15]. These DNA-histone complexes exhibit greater inflammatory potency than isolated components, suggesting synergistic activation mechanisms. Furthermore, extracellular histones promote neutrophil extracellular trap formation, wherein activated neutrophils release decondensed chromatin decorated with antimicrobial proteins into the extracellular space. While initially conceived as antimicrobial defense mechanisms, neutrophil extracellular traps

contribute to immunopathology by promoting microthrombus formation, damaging endothelial cells, and amplifying inflammatory cascades through the release of additional danger signals.

Parasite-derived microRNAs represent sophisticated regulatory molecules that reprogram host cell gene expression profiles. Plasmodium falciparum expresses a limited repertoire of canonical microRNAs but generates abundant small noncoding RNAs through alternative biogenesis pathways. These regulatory RNAs are packaged into extracellular vesicles and delivered to host cells, where they integrate into recipient RNA-induced silencing complexes and direct sequence-specific messenger RNA degradation or translational repression. Functional studies demonstrate that parasite-derived microRNAs target host immune signaling pathways, suppressing interferon responses, attenuating natural killer cell activation, and modulating cytokine production profiles. Additionally, parasite small RNAs influence erythropoiesis, angiogenesis, and coagulation pathways, contributing to the multiorgan dysfunction characteristic of severe malaria [16]. These diverse mechanisms establish that Plasmodium-derived epigenetic factors orchestrate widespread immune dysregulation that transitions protective responses into damaging immunopathology.

Epigenetic Reprogramming of Host Immune Cells During Malaria Infection

Plasmodium infection induces substantial epigenetic remodeling in host immune cells that fundamentally alters their functional capabilities and contributes to both acute immunopathology and long-term immune consequences. Genome-wide chromatin immunoprecipitation studies reveal dramatic alterations in histone modification patterns across innate and adaptive immune cell populations during acute malaria, with particular enrichment of activating marks, including histone H3 lysine 4 trimethylation and histone H3 lysine 27 acetylation at proinflammatory gene loci [17, 18]. These epigenetic changes facilitate rapid transcriptional responses to parasite-derived signals, effectively priming immune cells for exaggerated inflammatory output. Conversely, regulatory genes encoding anti-inflammatory mediators and immune checkpoint molecules exhibit enrichment of repressive histone marks, including histone H3 lysine 27 trimethylation, contributing to impaired regulatory mechanisms that normally constrain excessive inflammation.

DNA methylation patterns undergo similarly profound alterations, with widespread hypomethylation at inflammatory gene promoters accompanied by hypermethylation at immunosuppressive gene loci [19]. These methylation changes exhibit surprising persistence, remaining detectable weeks after parasite clearance and potentially contributing to altered immune responsiveness in convalescent individuals. Monocytes isolated from severe malaria patients display epigenetic signatures consistent with trained immunity, wherein initial pathogen exposure establishes long-lived epigenetic modifications that enhance responses to subsequent challenges. However, this training appears maladaptive in malaria contexts, predisposing toward hyperinflammatory responses that exacerbate immunopathology during repeated infections.

CD4 T lymphocytes exhibit particularly extensive epigenetic reprogramming, with severe malaria patients showing enriched histone acetylation at T helper 1 response genes alongside reduced accessibility at T helper 2 and regulatory T cell signature loci [20, 21]. These changes correlate with skewed cytokine production profiles, excessive interferon gamma secretion, and impaired regulatory T cell function that collectively drive immunopathology. B lymphocytes similarly undergo epigenetic modifications that influence antibody responses, with alterations in immunoglobulin class-switch recombination and plasma cell differentiation programs. Importantly, epigenetic dysregulation contributes to immune exhaustion during chronic or repeated malaria exposure, with progressive accumulation of repressive chromatin marks at effector gene loci and upregulation of inhibitory receptor expression. These findings establish that parasite-induced epigenetic reprogramming represents a central mechanism driving immune dysfunction, with implications extending beyond acute disease to influence long-term immunological memory and susceptibility to secondary infections.

Contribution of Epigenetic Immune Modulation to Cerebral Malaria Pathogenesis

Cerebral malaria pathophysiology involves intricate interactions between sequestered parasitized erythrocytes, activated endothelium, infiltrating leukocytes, and disrupted blood-brain barrier function, with parasite-derived epigenetic factors serving as critical orchestrators of this pathological cascade [22, 23]. Infected erythrocytes expressing particular erythrocyte membrane protein 1 variants adhere to brain microvascular endothelium via interactions with intercellular adhesion molecule 1, endothelial protein C receptor, and other adhesion receptors, establishing intravascular sequestration that obstructs blood flow and creates localized hypoxic microenvironments. Concomitantly, parasite-derived histones and extracellular vesicles activate brain microvascular endothelial cells, inducing upregulation of adhesion molecule expression, disruption of tight junction proteins, including occludin and claudin 5, and increased permeability that permits inflammatory mediators to access the central nervous system parenchyma.

The blood-brain barrier disruption facilitated by epigenetic immune modulators enables infiltration of activated monocytes, neutrophils, and T lymphocytes into perivascular spaces and brain parenchyma [24]. These infiltrating cells, themselves epigenetically reprogrammed toward hyperinflammatory phenotypes, release abundant proinflammatory cytokines, reactive oxygen species, proteolytic enzymes, and additional danger signals that amplify

local inflammation and directly injure neurons and glial cells. Parasite histones promote formation of neutrophil extracellular traps within cerebral microvasculature, creating prothrombotic microenvironments that exacerbate microvascular obstruction and contribute to localized ischemia. Additionally, extracellular histones exhibit direct neurotoxicity, inducing neuronal calcium dysregulation, mitochondrial dysfunction, and apoptotic cell death pathways.

Neuroimaging and postmortem studies reveal that cerebral malaria involves substantial astrocyte and microglia activation, with these glial populations contributing to neuroinflammation through cytokine production and glutamate excitotoxicity [25]. Parasite-derived extracellular vesicles cross the compromised blood-brain barrier and deliver cargo directly to glial cells, inducing epigenetic modifications that sustain inflammatory activation and impair neuroprotective functions. MicroRNAs transferred via these vesicles target neuronal survival pathways, synaptic plasticity genes, and neurotrophic factor signaling, potentially contributing to the cognitive deficits and neurological sequelae observed in cerebral malaria survivors. Metabolic consequences of severe inflammation, including hypoglycemia, lactic acidosis, and impaired cerebral perfusion, synergize with direct immune-mediated injury to produce the devastating neurological syndrome. Collectively, these mechanisms establish that parasite-derived epigenetic factors serve as central mediators connecting intravascular parasite sequestration to immunopathological cascades that culminate in cerebral malaria, highlighting potential therapeutic intervention points.

Therapeutic Implications and Future Research Directions

Recognition that parasite-derived epigenetic factors drive immunopathology in severe malaria has catalyzed exploration of host-directed therapeutic strategies targeting these pathways. Extracellular histone neutralization represents a particularly promising approach, with several experimental strategies demonstrating efficacy in preclinical models [26]. Activated protein C, an endogenous anticoagulant with cytoprotective properties, binds and neutralizes extracellular histones while simultaneously protecting endothelial barrier function and attenuating inflammation [27, 28]. Administration of recombinant activated protein C or small molecule protein C pathway activators reduces mortality and neurological injury in murine cerebral malaria models, suggesting translational potential. Similarly, heparin and heparin derivatives sequester histones through electrostatic interactions, preventing toll-like receptor engagement and cytotoxic effects, though bleeding risk considerations complicate clinical implementation.

Monoclonal antibodies targeting specific histone epitopes or histone-binding proteins offer alternative neutralization strategies with potentially improved safety profiles [29, 30]. DNase treatment to degrade neutrophil extracellular traps and associated DNA-histone complexes has shown promise in reducing inflammation and improving outcomes in experimental models, though optimal dosing and timing remain undefined [31]. Epigenetic enzyme inhibitors, including histone deacetylase inhibitors and DNA methyltransferase inhibitors, represent another therapeutic avenue by preventing or reversing pathological epigenetic reprogramming in host immune cells. Preliminary studies demonstrate that histone deacetylase inhibitors attenuate inflammatory responses, reduce parasitemia, and improve survival in rodent malaria models, potentially through combined effects on both parasite and host cell gene expression.

Targeting extracellular vesicle biogenesis, release, or uptake could theoretically interrupt parasite-host communication and prevent transfer of immunomodulatory cargo [32]. Inhibitors of vesicle formation pathways, including neutral sphingomyelinase inhibitors and Rab GTPase inhibitors, reduce extracellular vesicle production and attenuate disease severity in experimental systems. However, the ubiquity of extracellular vesicle-mediated communication across human physiology raises concerns regarding off-target effects and tolerability. Oligonucleotide-based approaches to neutralize parasite-derived microRNAs, including antagomirs or competitive inhibitors, represent conceptually attractive but technically challenging strategies given delivery obstacles and potential for immune activation by exogenous nucleic acids.

Critical knowledge gaps persist regarding the relative contributions of different epigenetic factors to severe malaria pathogenesis, optimal therapeutic intervention timing, and potential interactions between host-directed therapies and standard antimalarial treatments. Comprehensive biomarker studies correlating circulating levels of specific epigenetic factors with disease severity, treatment responses, and clinical outcomes could guide patient stratification and personalized therapeutic approaches [33]. Furthermore, investigating whether epigenetic immune modulation contributes to post-malaria immunological consequences, including increased susceptibility to bacterial infections and altered vaccine responses, represents an important research priority with implications extending beyond acute disease management.

CONCLUSION

Plasmodium-derived epigenetic factors, encompassing histones, nucleosomes, extracellular vesicles, and regulatory RNAs, represent powerful modulators of host immunity that critically influence malaria disease severity and progression to life-threatening complications. These molecular mediators engage pattern recognition receptors on innate immune cells, trigger proinflammatory signaling cascades, induce widespread epigenetic reprogramming of

host immune cell populations, compromise endothelial barrier function, and promote formation of prothrombotic neutrophil extracellular traps. In cerebral malaria specifically, parasite-derived epigenetic factors orchestrate the pathological sequence connecting intravascular parasite sequestration to blood-brain barrier disruption, neuroinflammation, and neuronal injury. Current evidence derives predominantly from experimental models with supporting correlative data from human studies, necessitating cautious interpretation and highlighting the need for mechanistic human studies employing advanced genomic and proteomic approaches. The translational potential of targeting these pathways through histone neutralization, epigenetic enzyme inhibition, or extracellular vesicle disruption appears substantial, though clinical development remains nascent. Integration of host-directed therapies targeting pathological immune responses with conventional antimalarial treatments offers promise for reducing severe malaria mortality and morbidity, particularly if interventions can be optimally timed and personalized based on patient-specific immunological profiles and disease trajectories. Clinical trials should prioritize evaluation of extracellular histone neutralization strategies, particularly activated protein C pathway modulators, in pediatric severe malaria populations with integrated pharmacokinetic, immunological, and neurological outcome assessments to establish safety, optimal dosing, and efficacy of this host-directed therapeutic approach.

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