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Host Metabolic Reprogramming During Plasmodium Infection: Implications for Biomarker Discovery and Therapeutics

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ABSTRACT

Plasmodium infection triggered profound alterations in host metabolic pathways affecting glucose metabolism, lipid homeostasis, amino acid catabolism, and mitochondrial function across multiple organ systems. These metabolic perturbations represented adaptive host responses aimed at limiting parasite replication and survival, while simultaneously reflecting pathological processes that contributed to disease severity and complications. Understanding the intricate interplay between parasite-induced metabolic reprogramming and clinical outcomes offered opportunities for identifying novel biomarkers and therapeutic targets. This review examined the mechanisms of host metabolic reprogramming during Plasmodium infection and evaluated the translational potential of metabolic signatures for biomarker discovery and development of host-directed therapies. A comprehensive analysis of metabolomic studies, mechanistic investigations, and translational research examining host metabolic responses to malaria across experimental models and human populations was conducted. Plasmodium infection induced glycolytic reprogramming, impaired oxidative phosphorylation, altered lipid metabolism, accelerated amino acid catabolism, and systemic inflammation-driven metabolic dysfunction. Distinct metabolic signatures correlated with disease severity, treatment response, and clinical outcomes, offering potential diagnostic and prognostic utility. Host-directed therapeutic strategies targeting metabolic pathways showed promise in preclinical models but required careful validation to avoid compromising protective immunity. Host metabolic reprogramming represented a critical determinant of malaria pathogenesis and clinical outcome, with emerging applications in precision diagnostics and innovative therapeutic interventions that complement conventional antimalarial drugs.

Keywords: Metabolic reprogramming, Plasmodium infection, Metabolomics, Biomarker discovery, Host-directed therapy.

INTRODUCTION

Malaria remains a leading cause of morbidity and mortality in tropical and subtropical regions, with an estimated 249 million clinical cases and 608,000 deaths reported globally in 2022, predominantly affecting children under five years and pregnant women in sub-Saharan Africa [1]. The disease is caused by intracellular protozoan parasites of the genus Plasmodium, with Plasmodium falciparum accounting for the majority of severe disease and mortality [2, 3]. The complex life cycle of Plasmodium species involves hepatic infection followed by repeated cycles of erythrocytic invasion, intracellular replication, and rupture, releasing merozoites that infect new erythrocytes. This asexual blood stage replication drives clinical manifestations ranging from uncomplicated febrile illness to life-threatening complications including cerebral malaria, severe anemia, metabolic acidosis, and multiorgan dysfunction. Despite substantial reductions in malaria burden achieved through vector control and artemisinin-based combination therapy, emerging parasite resistance to frontline antimalarials and insecticide resistance in mosquito vectors threaten these gains, necessitating innovative approaches to diagnosis, treatment, and disease management.

Host metabolic responses to Plasmodium infection extend beyond simple substrate depletion by replicating parasites to encompass comprehensive reprogramming of cellular and systemic metabolism. Infected erythrocytes exhibit dramatically increased glucose consumption, upregulated glycolytic flux, and altered membrane lipid composition to support parasite growth and immune evasion [4]. Simultaneously, systemic metabolic perturbations affect hepatic gluconeogenesis, adipose tissue lipolysis, skeletal muscle protein catabolism, and mitochondrial oxidative capacity across multiple organs. These metabolic alterations serve dual and sometimes conflicting purposes: supporting host immune responses and tissue repair while inadvertently providing nutrients and metabolic intermediates that parasites can exploit. The host immune response, particularly the production of proinflammatory cytokines including tumor necrosis factor alpha, interferon gamma, and interleukin-6, directly modulates metabolic enzyme expression and pathway activity, creating a complex feedback loop linking immunity and metabolism. Understanding these metabolic networks offers mechanistic insights into disease pathogenesis and identifies potential points of therapeutic intervention. The objective of this review is to critically evaluate current understanding of host metabolic reprogramming during Plasmodium infection, examine the utility of metabolic signatures as diagnostic and prognostic biomarkers, and assess the therapeutic potential of targeting host metabolic pathways to improve clinical outcomes in malaria.

Glycolytic Reprogramming and Energetic Alterations in Infected Erythrocytes

Plasmodium-infected erythrocytes undergo a profound metabolic transformation characterized by markedly increased glucose uptake and glycolytic flux compared to uninfected erythrocytes [5]. The parasite, which lacks a functional tricarboxylic acid cycle and relies almost exclusively on glycolysis for adenosine triphosphate generation, induces expression and insertion of additional glucose transporters into the erythrocyte membrane, increasing glucose permeability up to 75-fold. This metabolic reprogramming transforms the normally quiescent mature erythrocyte into a highly active metabolic factory supporting parasite replication. Parasite-encoded hexose transporters localize to the parasitophorous vacuole membrane and parasite plasma membrane, creating a continuous pathway for glucose delivery from the extracellular space to the parasite cytoplasm [6]. The resulting glycolytic flux generates lactate as the primary end product, contributing to the metabolic acidosis frequently observed in severe malaria.

Beyond simple upregulation, the glycolytic pathway in infected erythrocytes exhibits qualitative differences compared to uninfected cells. Metabolomic profiling reveals accumulation of specific glycolytic intermediates, including glucose-6-phosphate, fructose-1,6-bisphosphate, and phosphoenolpyruvate, reflecting bottlenecks at particular enzymatic steps and potential regulatory checkpoints [7, 8]. The parasite exports several of its own glycolytic enzymes, including lactate dehydrogenase and enolase, into the host erythrocyte cytoplasm, potentially modulating host glycolytic flux and diverting carbon flow toward pathways beneficial for parasite survival. Pentose phosphate pathway activity is similarly enhanced in infected erythrocytes, generating ribose-5-phosphate for nucleotide biosynthesis and nicotinamide adenine dinucleotide phosphate for maintaining reduced glutathione pools necessary for oxidative stress defense. The interdependence of glycolysis and the pentose phosphate pathway flux creates metabolic vulnerabilities that have been explored as potential therapeutic targets.

The energetic demands of Plasmodium infection extend beyond infected erythrocytes to affect systemic glucose homeostasis. Hypoglycemia represents a well-recognized complication of severe malaria, particularly in children and pregnant women, arising through multiple mechanisms, including increased glucose consumption by high parasite biomass, impaired hepatic gluconeogenesis due to organ dysfunction, depletion of glycogen stores, and quinine-induced hyperinsulinemia when this drug is used for treatment [9]. Metabolic modeling studies estimate that high-density parasitemia can increase whole-body glucose consumption by 40 to 75 percent, imposing substantial metabolic stress on the host. Conversely, some patients develop hyperglycemia and insulin resistance during acute infection, reflecting stress-induced counter-regulatory hormone secretion and inflammatory cytokine-mediated disruption of insulin signaling pathways. These opposing dysregulations of glucose homeostasis correlate with distinct clinical phenotypes and outcomes, suggesting that personalized metabolic management strategies may improve survival in severe malaria, though prospective interventional trials are lacking.

Lipid Metabolism Alterations and Membrane Remodeling

Lipid metabolism undergoes extensive reprogramming during Plasmodium infection, affecting both infected erythrocyte membrane composition and systemic lipid homeostasis [10, 11]. The parasite extensively remodels the host erythrocyte membrane through insertion of parasite-derived proteins, modification of lipid composition, and formation of novel membranous structures, including Maurer's clefts and knob-associated histidine-rich protein complexes that mediate cytoadherence. Lipidomic analyses reveal substantial increases in phosphatidylcholine, phosphatidylethanolamine, and neutral lipid content within infected erythrocytes, supporting the massive membrane biogenesis required for parasite organellar development and daughter merozoite formation [12]. The parasite acquires phospholipid precursors through multiple routes, including de novo synthesis via parasite-encoded enzymes, salvage of host phospholipids, and uptake of serum lipoproteins through receptor-mediated endocytosis.

Specific lipid species play critical roles in parasite biology and host-pathogen interactions. Phosphatidylinositol-4-phosphate, generated by parasite phosphatidylinositol 4-kinase, localizes to the parasite plasma membrane and parasitophorous vacuole membrane, serving as an essential signaling lipid that regulates protein trafficking and nutrient acquisition [13, 14]. Inhibitors targeting this kinase have shown potent antimalarial activity in preclinical studies, validating lipid metabolism as a therapeutic target. Cholesterol homeostasis is similarly perturbed, with infected erythrocytes exhibiting increased cholesterol content derived primarily from serum low-density lipoprotein uptake. Parasite-encoded Niemann-Pick Type C1-related proteins mediate cholesterol transport from the parasitophorous vacuole to the parasite plasma membrane, and genetic or pharmacological disruption of these transporters impairs parasite development [15]. The dependence on host lipid acquisition creates vulnerabilities that can be exploited therapeutically, though concerns about toxicity from global lipid pathway inhibition require careful target selection and validation.

Systemically, Plasmodium infection induces hypolipidemia characterized by decreased total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride concentrations [16]. These changes reflect multiple mechanisms including sequestration of lipids by infected erythrocytes and organs harboring sequestered parasites, impaired hepatic lipoprotein synthesis, accelerated lipoprotein clearance, and inflammatory cytokine-mediated suppression of lipogenic enzyme expression. Epidemiological studies have identified inverse correlations between baseline lipid levels and malaria risk, with individuals having genetically determined low cholesterol exhibiting reduced susceptibility to severe disease. Conversely, extremely low lipid levels during acute infection correlate with poor outcomes, potentially reflecting severe hepatic dysfunction or consumptive processes. The relationship between lipid metabolism and malaria pathogenesis appears nonlinear and context-dependent, complicating efforts to therapeutically modulate lipid pathways. Nonetheless, the profound alterations in lipid metabolism provide potential biomarker candidates, with specific lipid species showing promise for distinguishing severe from uncomplicated malaria and predicting treatment response.

Amino Acid Catabolism, Nitrogen Balance, and Metabolic Acidosis

Amino acid metabolism undergoes substantial perturbation during Plasmodium infection, reflecting both parasite nutritional requirements and host inflammatory responses [17, 18]. The parasite requires exogenous amino acids for protein synthesis, as it possesses limited capacity for de novo amino acid biosynthesis. Hemoglobin degradation within the parasite digestive vacuole provides a rich source of amino acids, generating approximately 2 to 3 billion amino acid molecules per parasite replication cycle. However, the composition of hemoglobin-derived amino acids does not match parasite biosynthetic needs, necessitating the selective import of particular amino acids from the extracellular environment [19]. Metabolomic studies consistently demonstrate depletion of isoleucine, arginine, tryptophan, and methionine in plasma from malaria patients, reflecting accelerated consumption by parasites and activated immune cells.

Arginine metabolism represents a particularly critical pathway linking amino acid catabolism to disease pathogenesis. Arginine serves as a substrate for two competing enzymatic pathways: nitric oxide synthase, which generates nitric oxide and citrulline, and arginase, which produces ornithine and urea [20]. During malaria infection, both pathways are upregulated, creating competition for the limited arginine substrate. Nitric oxide plays complex and context-dependent roles in malaria, exhibiting antiparasitic effects through inhibition of parasite mitochondrial respiration while potentially contributing to pathology through vascular dysfunction and tissue damage at high concentrations. Arginase activity is markedly elevated during infection, released from hemolyzed erythrocytes, and upregulated in myeloid cells responding to inflammatory stimuli. The resulting arginine depletion impairs endothelial nitric oxide production, contributing to endothelial dysfunction, impaired microvascular blood flow, and potentially cerebral malaria pathogenesis. Clinical trials examining arginine or citrulline supplementation have shown mixed results, with some studies demonstrating improved endothelial function but no significant impact on mortality, highlighting the complexity of therapeutic manipulation of this pathway.

Tryptophan catabolism through the kynurenine pathway is similarly enhanced during malaria, driven by interferon gamma-induced expression of indoleamine 2,3-dioxygenase in immune cells and potentially within infected tissues [21, 22]. This pathway generates multiple bioactive metabolites, including kynurenine, kynurenic acid, and quinolinic acid, which modulate immune responses and neurotransmitter signaling. Elevated kynurenine to tryptophan ratios correlate with disease severity and have shown promise as prognostic biomarkers. However, the functional significance of kynurenine pathway activation remains debated, with evidence supporting both protective immunoregulatory roles that prevent excessive inflammation and detrimental effects through the generation of neurotoxic metabolites that may contribute to cerebral complications. The accelerated amino acid catabolism and nitrogen mobilization contribute to the negative nitrogen balance frequently observed in severe malaria, manifesting as muscle wasting and hypoalbuminemia. These metabolic perturbations impair wound healing, compromise immune function, and delay convalescence, representing important contributors to post-infection morbidity that persist even after parasite clearance.

Mitochondrial Dysfunction and Oxidative Stress Responses

Mitochondrial function is profoundly impaired during Plasmodium infection across multiple tissues and cell types, contributing to lactate accumulation, metabolic acidosis, and multiorgan dysfunction characteristic of severe disease [23]. Although mature erythrocytes lack mitochondria, infected erythrocytes experience oxidative stress from parasite metabolic byproducts, particularly reactive oxygen species generated during hemoglobin digestion and heme detoxification. The parasite defends against oxidative damage through multiple antioxidant systems, including superoxide dismutase, glutathione peroxidase, and thioredoxin reductase pathways, but accumulation of oxidized membrane lipids and proteins nonetheless occurs. This oxidative damage increases erythrocyte membrane rigidity, impairs deformability, and promotes recognition and clearance by splenic macrophages, contributing to malarial anemia.

Beyond infected erythrocytes, mitochondrial function is impaired in hepatocytes, skeletal muscle, and immune cells during malaria infection. Hepatic mitochondria exhibit decreased oxidative phosphorylation capacity, reduced adenosine triphosphate synthesis, and increased reactive oxygen species generation, contributing to hepatic dysfunction manifesting as hypoglycemia, hypoalbuminemia, and coagulopathy in severe cases [24, 25]. The mechanisms underlying hepatic mitochondrial dysfunction include direct effects of sequestered parasites and infected erythrocytes in hepatic sinusoids, inflammatory cytokine-mediated downregulation of mitochondrial gene expression, and mitochondrial damage from systemic oxidative stress and circulating heme. Similar mitochondrial impairments occur in skeletal muscle, manifesting as reduced exercise capacity and accelerated fatigue during acute infection and convalescence. Metabolomic signatures of mitochondrial dysfunction, including elevated lactate to pyruvate ratios, accumulation of tricarboxylic acid cycle intermediates, and altered acylcarnitine profiles indicating impaired fatty acid oxidation, correlate strongly with disease severity and predict mortality in pediatric cerebral malaria cohorts.

The relationship between mitochondrial dysfunction and metabolic acidosis, a cardinal feature of severe malaria and a strong predictor of fatal outcome, remains incompletely understood. Traditional explanations emphasizing inadequate tissue oxygen delivery due to microvascular obstruction by sequestered parasites have been challenged by observations that arterial and venous oxygen content differences are often preserved in acidotic patients [26]. Alternative or complementary mechanisms include impaired cellular oxygen utilization due to mitochondrial dysfunction, accelerated glycolytic flux overwhelming oxidative capacity, and accumulation of unmeasured anions beyond lactate. Recent metabolomic studies have identified multiple organic acids, including ketone bodies, branched-chain keto acids, and tricarboxylic acid cycle intermediates, contributing to acidosis, suggesting that comprehensive metabolic profiling rather than lactate measurement alone may better characterize the metabolic derangements underlying this critical complication. Therapeutic strategies aimed at supporting mitochondrial function or enhancing lactate clearance remain largely unexplored in malaria, representing potential avenues for adjunctive interventions that could improve outcomes in patients with severe metabolic acidosis.

Metabolomic Biomarkers for Diagnosis, Prognosis, and Treatment Monitoring

The comprehensive metabolic perturbations induced by Plasmodium infection generate distinct metabolomic signatures that hold substantial promise for clinical applications spanning diagnosis, severity assessment, prognostication, and treatment response monitoring [27]. Untargeted metabolomic profiling using mass spectrometry or nuclear magnetic resonance spectroscopy platforms has identified hundreds of metabolites with significantly altered concentrations in malaria patients compared to healthy controls or patients with other febrile illnesses [28, 29]. Multivariate statistical approaches, including principal component analysis and partial least squares discriminant analysis, reveal that malaria patients cluster distinctly from controls in metabolomic space, with discrimination accuracy exceeding 90 percent in some studies. Specific metabolite panels comprising glucose, lactate, lipid species, amino acids, and inflammatory mediators can distinguish malaria from bacterial sepsis, viral infections, and other tropical diseases that present with similar clinical features, potentially improving diagnostic accuracy in resource-limited settings where laboratory confirmation is unavailable.

For severity stratification and prognostication, metabolomic signatures demonstrate superior performance compared to conventional clinical and laboratory parameters in multiple cohorts [30, 31]. Studies in pediatric populations have identified metabolite panels that predict cerebral malaria development, fatal outcome, and neurological sequelae with area under receiver operating characteristic curves ranging from 0.85 to 0.95, substantially exceeding the discriminatory capacity of parasite density, lactate, or clinical severity scores alone. Key metabolites consistently associated with poor outcomes include elevated lactate, reduced arginine and arginine bioavailability ratio, elevated kynurenine to tryptophan ratio, specific acylcarnitine species indicating mitochondrial dysfunction, and altered phospholipid profiles. Integration of metabolomic data with clinical, parasitological, and host genetic information through machine learning algorithms has achieved even higher prognostic accuracy, identifying high-risk patients who might benefit from intensified monitoring or adjunctive therapies.

Treatment response monitoring represents another promising application, as metabolomic signatures evolve dynamically during antimalarial therapy and convalescence. Rapid clearance of parasite-associated metabolites

following effective treatment contrasts with slower normalization of host metabolic pathways, particularly those reflecting immune activation and tissue damage. Persistent metabolic abnormalities despite parasite clearance may identify patients at risk for prolonged recovery, post-treatment complications, or recrudescence [32]. Pharmacometabolomic approaches that examine relationships between drug concentrations, metabolomic profiles, and treatment outcomes could enable precision dosing strategies, particularly for special populations including pregnant women, young children, and individuals with comorbidities. However, translating these research findings into clinical tools requires validation across diverse populations and transmission settings, development of simplified assays compatible with point-of-care platforms, and demonstration of clinical utility through implementation trials that assess whether metabolomic-guided management improves outcomes compared to standard care.

Host-Directed Therapeutic Strategies Targeting Metabolic Pathways

The recognition that host metabolic pathways critically influence malaria pathogenesis has stimulated interest in host-directed therapies that complement conventional antimalarial drugs by targeting human rather than parasite proteins [33]. This approach offers potential advantages, including reduced likelihood of parasite resistance development, applicability across Plasmodium species, and potential benefits in treating severe manifestations driven primarily by host responses rather than parasite replication. However, host-directed therapies also pose unique challenges, as metabolic pathways targeted for therapeutic intervention often serve essential physiological functions, raising concerns about on-target toxicity and impairment of protective immune responses.

Several proof-of-concept studies have demonstrated the therapeutic potential of metabolic pathway modulation in experimental malaria models. Inhibition of host fatty acid synthesis using TOFA (5-tetradecyloxy-2-furoic acid) or genetic deletion of fatty acid synthase reduced parasite replication and improved survival in rodent models, supporting the feasibility of targeting host lipid metabolism [34]. However, concerns about hepatotoxicity and effects on host lipid-dependent processes have limited clinical translation. Glucose metabolism modulation represents another area of investigation, with studies examining the effects of dietary interventions, insulin, and glycolytic inhibitors on malaria outcomes. Moderate caloric restriction and ketogenic diets have shown protective effects in some animal studies, potentially by limiting glucose availability to parasites while enhancing host ketone metabolism, though applicability to malnourished children in endemic areas is questionable. Conversely, aggressive glucose supplementation to prevent hypoglycemia requires careful titration to avoid exacerbating hyperparasitemia through increased substrate availability.

Amino acid supplementation strategies, particularly arginine and citrulline, have progressed furthest toward clinical implementation [35, 36]. Multiple small clinical trials have examined oral or intravenous arginine or citrulline administration in severe malaria patients, with some studies demonstrating improved endothelial function, reduced pulmonary injury, and trends toward mortality reduction. However, definitive evidence of clinical benefit remains lacking, and concerns have been raised about potential adverse effects, including enhanced nitric oxide production contributing to hemodynamic instability or neurotoxicity in cerebral malaria. Broader targeting of inflammatory metabolism through drugs that modulate macrophage metabolic reprogramming, inhibit aerobic glycolysis, or enhance oxidative metabolism represents an emerging area with limited clinical data but substantial conceptual appeal [37]. As understanding of immunometabolism advances, rational selection of metabolic targets that impair pathological processes while preserving or enhancing protective immunity may enable the development of safe and effective adjunctive therapies that reduce malaria mortality and morbidity when combined with artemisinin-based combination therapy.

CONCLUSION

Host metabolic reprogramming during Plasmodium infection encompasses profound alterations in glucose metabolism, lipid homeostasis, amino acid catabolism, and mitochondrial function that collectively determine disease severity and clinical outcome. Infected erythrocytes exhibit dramatically upregulated glycolytic flux and altered membrane lipid composition to support parasite replication, while systemic metabolic perturbations, including hypoglycemia, hypolipidemia, amino acid depletion, and mitochondrial dysfunction, contribute to complications, including metabolic acidosis and multiorgan failure. These metabolic changes reflect complex interactions between parasite nutritional demands, host immune responses, and tissue damage, creating a metabolic landscape that both constrains and enables parasite survival. Comprehensive metabolomic profiling has revealed distinct signatures that discriminate malaria from other febrile illnesses, stratify disease severity, predict clinical outcomes, and monitor treatment response with accuracy exceeding conventional biomarkers. Specific metabolite panels incorporating markers of glycolytic flux, mitochondrial function, amino acid catabolism, and lipid metabolism show particular promise for clinical translation as point-of-care diagnostic and prognostic tools. The therapeutic potential of targeting host metabolic pathways offers innovative approaches to improving malaria outcomes, though careful validation is required to ensure that metabolic interventions enhance rather than compromise protective immunity. Current evidence supports continued investigation of arginine supplementation, metabolic support during severe acidosis, and modulation of inflammatory metabolism, while emerging targets, including lipid synthesis and mitochondrial function, require extensive preclinical optimization before clinical evaluation. Advancing this field

toward clinical impact requires integration of metabolomic discovery with mechanistic studies, validation across diverse populations and transmission settings, and rigorous clinical trials demonstrating that metabolism-informed diagnostics and therapeutics improve patient outcomes.

Future research should prioritize multicenter clinical trials validating metabolomic biomarker panels for severity stratification and outcome prediction, coupled with mechanistic studies identifying specific metabolic targets amenable to safe and effective host-directed therapeutic intervention that complements antimalarial chemotherapy in reducing malaria mortality and long-term sequelae.

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