Metabolic Modulation in Macrophages During *Leishmania* Infection: Impacts on Parasite Survival and Therapeutic Potential

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Macrophages are crucial players in innate immunity, recognizing and responding to pathogens. *Leishmania* spp. infections trigger significant metabolic alterations, increasing the energy demands of infected cells in a process closely linked to host mitochondrial integrity. However, the mechanisms by which different *Leishmania* species manipulate host cell metabolism remain unclear. In this study, we investigated key metabolic processes essential for *Leishmania* persistence in macrophages, focusing on pathways exploited by the parasite.

Bone marrow-derived macrophages (BMDMs) from C57BL/6 mice were infected with *Leishmania* spp., and metabolic activity was assessed through extracellular acidification rate (ECAR) and oxygen consumption rate (OCR) using the Seahorse system. Mitochondrial function was analyzed with MitoTracker probes, and parasite burden was quantified after treatment with metabolic inhibitors. Additionally, we examined parasite adhesion, phagocytosis, and mitochondrial reactive oxygen species (ROS) production using MitoSOX. Our findings reveal that despite distinct immune evasion mechanisms, *L. amazonensis* and *L. braziliensis* induce similar metabolic changes in macrophages. Infected cells displayed increased glycolysis and oxygen consumption, accompanied by enhanced proton leak and decreased ATP production. Infection also led to elevated mitochondrial mass and membrane potential.

Notably, inhibitors of oxidative phosphorylation and glycolysis significantly reduced parasite burden, reinforcing the crucial role of metabolic pathways in host-parasite interactions. Collectively, our results suggest that *L. amazonensis* and *L. braziliensis* exploit host metabolism in a similar manner to ensure intracellular survival. Despite species-specific immune evasion strategies, both parasites consistently impact host bioenergetics. Importantly, targeting these metabolic pathways pharmacologically significantly impairs parasite survival, offering promising therapeutic strategies against leishmaniasis. This study advances our understanding of host-parasite interactions and provides valuable insights for developing novel treatments for this neglected disease.

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