Intracellular pathogens have evolved complex strategies to neutralize host antimicrobial defences, exploit host cell resources, and reprogram host metabolism to ensure their survival and replication. The protozoan parasite *Leishmania*, an obligate intracellular pathogen of macrophages, provides a unique model to investigate these immune–metabolic subversion mechanisms. Despite extensive research into the parasites immunopathological potential, the molecular processes underlying *Leishmania*-mediated reprogramming of macrophage (Mφ) immune and metabolic functions remain poorly understood. Here, we delineate three interlinked host-cell functions that are subverted by *Leishmania amazonensis* to promote chronic infection: regulation of cell death, epi-transcriptomic control, and epigenetic modification.

First, we demonstrate that *Leishmania* suppresses macrophage regulated cell death (RCD) pathways, enabling long-term survival of infected cells despite heavy parasitic loads. Transcriptomic profiling of *L. amazonensis*-infected macrophages (LIMs) revealed a dichotomic dysregulation of more than 60% of RCD-associated genes, characterized by upregulation of anti-RCD markers and repression of pro-RCD mediators, including *CASP8, FADD, TRADD, TNFAIP3, TAX1BP1, BIRC3,* and *ITCH*. These changes were associated with altered activity of transcription factors from the AP-1, NF-κB, PPARγ, and C/EBPβ families, resulting in remarkable macrophage longevity in culture for over 50 days, sharply contrasting with the rapid decline of non-infected controls. Functionally, LIMs exhibited strong resistance to intrinsic, extrinsic, and pyroptotic death stimuli. The anti-RCD phenotype was also observed in ex vivo macrophages from infected lesions and was rapidly reversed following pharmacological parasite clearance, demonstrating that *Leishmania* actively maintains host cell survival to support its persistence.

Second, we identify an unanticipated layer of macrophage subversion mediated through epi-transcriptomic regulation. *Leishmania* infection selectively manipulates the m6A reader protein IGF2BP2, establishing a unique macrophage phenotype that integrates elements of both M1 and M2 polarization. Early infection stages are characterized by oxidative energy metabolism typical of M2 macrophages, whereas chronic infection induces a glycolytic, M1-like phenotype reliant on IGF2BP2-dependent stabilization of *hexokinase 2* (HK2) mRNA. This glycolytic reprogramming occurs independently of HIF-1α and supports both macrophage and parasite viability. IGF2BP2 knockdown markedly reduced glycolytic capacity and cell survival, effects rescued by exogenous lactate, highlighting the central role of IGF2BP2-mediated metabolic rewiring in sustaining chronic infection.

Finally, we revealed an epigenetic subversion strategy in *Leishmania*-infected macrophages. Using pharmacological inhibition, transcriptomic analysis, and protein interaction studies, we show that the lysine demethylase LSD1 (KDM1A) plays a pivotal role in supporting intracellular parasite survival. LSD1 inhibition restored antimicrobial gene expression in infected macrophages, reduced cholesterol biosynthesis, and dramatically decreased parasite load, linking host demethylase activity to parasite persistence. Infection altered the composition of LSD1 complexes without affecting LSD1 expression or localization, revealing the LSD1 scaffolding function rather than its enzymatic activity as an interesting novel target for host-directed, anti-leishmanial intervention.

Together, these findings reveal that *Leishmania* orchestrates a multi-layered strategy of host-cell subversion encompassing transcriptional, epi-transcriptomic, and epigenetic control of macrophage survival and metabolism. By suppressing cell death, rewiring energy production, and co-opting chromatin regulators, *Leishmania* ensures a stable intracellular niche for its

proliferation. This integrative understanding of immune–metabolic manipulation identifies novel host-directed therapeutic targets, including RCD regulators, IGF2BP2, and LSD1, offering new avenues for combating chronic leishmaniasis.