Abstract

Recent studies highlight a critical role for metabolic adaptation in various immune cells during activation. Innate immune cells such as macrophages increase glycolysis when stimulated with pathogen-associated molecular patterns (PAMPs); pathogens also target these metabolic pathways for their own benefit. Yet, how the rewiring of metabolic pathways influence pathogenicity is not well understood. To unravel these interactions in an unbiased fashion, we employed integrative omics approaches to identify key changes in the metabolome and transcriptome of infected macrophages.

We found that *S.* Typhimurium abrogates glycolysis and its modulators such as insulin-signaling to derail the innate defense response. Downregulation of glycolysis leads to reduced acidification of phagosomes resulting in impaired bacterial clearance and antigen presentation. Furthermore, induction of glycolysis facilitates v-ATPase assembly and the acidification of phagosomes by mobilizing aldolase A to the v-ATPase complex. Our results highlight a previously unknown molecular link between metabolism and phagosome maturation, which is targeted by *S.* Typhimurium to evade cell-autonomous defense.