In the successful elimination of bacteria within phagocytes, the phago-lysosomal system plays a crucial role, but this process also relies on mitochondrial pathways. However, the communication between these two organelle systems is not well understood. This study identifies the lysosomal biogenesis factor transcription factor EB (TFEB) as a regulator for the crosstalk between phago-lysosomes and mitochondria in macrophages. Through a combination of cellular imaging and metabolic profiling, the research reveals that TFEB activation, triggered by bacterial stimuli, induces the transcription of aconitate decarboxylase (Acod1, Irg1) and the synthesis of its product itaconate. Itaconate is a mitochondrial metabolite with antimicrobial activity. The activation of the TFEB–Irg1–itaconate signaling axis proves effective in reducing the survival of the intravacuolar pathogen Salmonella enterica serovar Typhimurium. Subsequently, TFEB-driven itaconate is transferred via the Irg1-Rab32–BLOC3 system into the Salmonella-containing vacuole, exposing the pathogen to elevated itaconate levels. By activating itaconate production, TFEB selectively restricts the proliferation of Salmonella, a bacterial subpopulation that typically evades macrophage control. This contrasts TFEB's role in autophagy-mediated pathogen degradation. The data from this study define a TFEB-driven metabolic pathway between phago-lysosomes and mitochondria that effectively restrains the burden of Salmonella Typhimurium in macrophages both in vitro and in vivo.