

Successful elimination of bacteria in phagocytes occurs in the phago-lysosomal system, but also depends on mitochondrial pathways. Yet, how these two organelle systems communicate is largely unknown. Here we identify the lysosomal biogenesis factor transcription factor EB (TFEB) as regulator for phago-lysosome-mitochondria crosstalk in macrophages. By combining cellular imaging and metabolic profiling, we find that TFEB activation, in response to bacterial stimuli, promotes the transcription of aconitate decarboxylase (*Acod1*, *Irg1*) and synthesis of its product itaconate, a mitochondrial metabolite with antimicrobial activity. Activation of the TFEB–*Irg1*–itaconate signalling axis reduces the survival of the intravacuolar pathogen *Salmonella enterica* serovar Typhimurium. TFEB-driven itaconate is subsequently transferred via the *Irg1*–Rab32–BLOC3 system into the *Salmonella*-containing vacuole, thereby exposing the pathogen to elevated itaconate levels. By activating itaconate production, TFEB selectively restricts proliferating *Salmonella*, a bacterial subpopulation that normally escapes macrophage control, which contrasts TFEB's role in autophagy-mediated pathogen degradation. Together, our data define a TFEB-driven metabolic pathway between phago-lysosomes and mitochondria that restrains *Salmonella* Typhimurium burden in macrophages in vitro and in vivo.