ABSTRACT

Salmonella enterica serovar Typhimurium (*S.* Typhimurium) is a facultative intracellular, gram negative bacterium that invades various types of cells. *S.* Typhimurium replicates in the phagosomes of epithelial cells, induces severe inflammation and cell death. Cell death is associated with mitochondrial dysfunction and drop in ATP. Our data reveal that *S.* Typhimurium infection causes mitochondrial dysfunction, despite an increase in mitochondrial mass. These changes are accompanied by a significant drop in energy levels and a striking increase in mitochondrial reactive oxygen species.

Sirtuins are NAD^+-dependent enzymes, which respond to changes in energy status by conferring post-translational modifications on their targets and altering their activities. Out of seven sirtuins Sirtuin 3, 4 and 5 have been reported to localize in the mitochondria and Sirtuin 1 is a nuclear regulator of mitochondrial biogenesis. Our results reveal that Sirtuin 4 (SIRT4) levels are dramatically increased upon *S.* Typhimurium infection.

SIRT4 is a multifunctional enzyme that targets metabolic entry points of the TCA cycle, thereby inhibiting mitochondrial metabolism. We could show that depletion of SIRT4 restores mitochondrial morphology and fusion and fission dynamics in the infected cells. Furthermore, loss of SIRT4 results in reduced inflammation and cell death, which are the hallmarks of *S.* Typhimurium-induced pathogenicity. A similar decrease in inflammation was also observed in Sirt4-deficient mice infected with *S.* Typhimurium.

Taken together, our data suggest that SIRT4 plays a key role in *S.* Typhimurium-induced mitochondrial dysfunction and thereby controls cell-intrinsic immune responses.