Abstract

Discerning the role of a lysosomal tethering factor in promoting intravacuolar replication of *Salmonella*.

Salmonella (Salmonella enterica serovar *typhimurium)* is a successful intracellular pathogen that extensively manipulates the host membrane trafficking machinery as it strives to establish its replication-competent vacuolar microenvironment within host cells; also known as ***S****almonella* **C**ontaining **V**acuole **(SCV)**. To maintain the integrity of its phagosome, *Salmonella* translocates several virulence determinants into the host cytoplasm that intercept and instigate dynamic membrane exchanges with the endo-lysosomal compartments including late endosomes and lysosomes, ultimately leading to metamorphosis of these endocytic membranes into an extensive tubular network emanating from and interconnecting the SCVs (***S****almonella* **I**nduced **F**ilament**s, SIFs**). This fusogenic activity is essential for the procurement of nutrients to mediate intracellular survival and proliferation of this pathogen inside the vacuole. However, the mechanism by which *Salmonella* constantly acquires these host membranes and endocytosed nutrients has been poorly characterized.

Here in this study, we have uncovered an important aspect of *Salmonella*'s intracellular survival strategy that involves recruitment of a multi-subunit lysosomal tether, **HOPS (HO**motypic fusion and **P**rotein **S**orting**)** complex to *Salmonella*-modified membranes in a temporal manner. Once recruited, HOPS functions as a molecular bridge linking the phagosomal membranes to the late endo-lysosomal compartments, thereby promoting SCV maturation, SIF biogenesis and nutrient acquisition for intravacuolar replication of this pathogen. Notably, in the absence of HOPS complex subunits we observed a significantly reduced bacterial load in cultured cell lines as well as in a mouse model of *Salmonella* infection. We also found that HOPS complex was required for nutrient access to the SCV membranes. Finally, we identified that bacterial effector SifA in complex with host protein SKIP recruits HOPS complex to SCV membranes. Taken together, our findings suggest that *Salmonella* modifies its vacuole by recruiting a critical component of host vesicle fusion machinery, HOPS complex, ensuring a constant retrieval of nutrients to promote its intracellular replication inside the host cells.