ABSTRACT

Title of the thesis: "A study on the phagosomal survival mechanisms of *Salmonella* enterica Serovar Typhi in macrophages: focus on type III secretion system 2 (T3SS-2)-independent mechanisms".

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Intracellular bacterial pathogens, including *Salmonella* Typhimurium, employ intricate strategies to survive and replicate within host cells, exploiting various cellular processes to create a hospitable environment. These pathogens, also known as "professional intracellular parasites," can manipulate phagosomal maturation, acidification, and lysosomal fusion, thereby evading the host's immune response. For instance, *Salmonella* Typhimurium utilizes its type III secretion system (T3SS) to inject effector proteins into the host cell cytoplasm, modulating phagosomal trafficking and avoiding lysosomal degradation. The fate of *Salmonella*-containing phagosomes remains a topic of debate, with conflicting evidence suggesting that *Salmonella* Typhimurium can survive within lysosomal compartments by delaying acidification or inhibiting phagosome/lysosome fusion, thereby preferentially dividing in unfused phagosomes. Notably, *Salmonella* Typhimurium-containing vacuoles acquire lysosomal molecules and acid phosphatases while evading lysosomal markers. In contrast, research on *Salmonella* Typhi's phagosomal survival is limited, despite sharing of 90% of its DNA with *S.* Typhimurium. The primary distinction between these serovars lies in the diversity of their effector contents, which influences host adaptation. Specifically, *S.* Typhi lacks several SPI-2 effectors present in *S.* Typhimurium, including sseI and gogB, which mediate long-term systemic infection in mice. Furthermore, the SPI-2 T3SS-2 of *S.* Typhi is dispensable for survival in human macrophages, underscoring the disparate survival strategies employed by these closely related serovars. Elucidating these complex mechanisms is essential for developing effective therapeutic strategies against Salmonella Typhi and other intracellular bacterial pathogens.

This laboratory previously reported that a eukaryotic-like serine threonine kinase (T4519), exclusively present in typhoidal Salmonellae is responsible for intracellular survival of *S.* Typhi and pathogenicity in a mouse model. This study elucidates the molecular mechanisms underlying the intracellular survival of *Salmonella* Typhi, with a specific focus on the eukaryotic-like serine-threonine kinase (T4519). Notably, T4519 was found to increase vacuolar pH by inducing lysosomal membrane permeabilization (LMP), thereby creating a conducive environment for bacterial survival. The T4519-mediated LMP pathway involves the binding of T4519 to Toll-like receptor 2 (TLR-2), leading to decreased cystatin B expression, activation of cathepsin B in the cytosol of infected human macrophages, and subsequent translocation of p65 to the nucleus. This cascade of events triggers excessive reactive oxygen species (ROS) production, ultimately culminating in LMP. Furthermore, the LMP enhances bacterial numbers by decreasing lysosomal degradation. Interestingly, in another separate study, it was shown that exposure of wild-type Ty2 to increasing concentrations of ampicillin resulted in the formation of a cell-wall-less L-form *Salmonella* Typhi, designated as A200, which retained its infectivity in human and murine macrophage cell lines and mice, highlighting the remarkable adaptability of this pathogen.

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