How Salmonella survives the macrophage's acid attack

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Salmonella Saintpaul bacteria (dark red)

Macrophages destroy bacteria by engulfing them in intracellular compartments, which they then acidify to kill or neutralize the bacteria. However, some pathogenic bacteria, such as *Salmonella enterica*, have evolved to exist and even grow while within these acidified compartments. Yet, how *Salmonella* responds to the acidic environment and how that environment affects the virulence of this pathogen are unclear. New research reveals that *Salmonella* fights acid with acid, by lowering the pH of its own interior in response to the acidification of the *Salmonella*-containing compartment by the macrophage, and by using that low pH as a signal to turn on genes needed to establish an infection.

"The question that we are addressing is: what is the signal that

Salmonella senses when it is in the macrophage vacuole that turns on virulence gene expression and enables *Salmonella* to replicate and disseminate," says Linda J. Kenney, senior author and professor of the Mechanobiology Institute, National University of Singapore and at the University of Illinois at Chicago. Research from her group, publishing on April 14th in the Open Access journal *PLOS Biology*, demonstrates that the acidic cytoplasm then acts as a signal to stimulate the secretion of a particular class of *Salmonella* virulence proteins. These virulence proteins, or effectors, are released into the host cell, where they are able to perturb the immune response.

To investigate the effect of the acidic environment on *Salmonella*, the authors used a biosensor, called an I-switch, which allowed for measurements of pH within a single cell. Using the I-switch, the authors found that the *Salmonella* cytoplasm acidifies rapidly after being engulfed and exposed to the acidic environment of the macrophage interior. Interestingly, they found that the *Salmonella* actively, as opposed to passively, acidify their cytoplasm.

According to Professor Kenney, scientists who study more complex organisms are "astonished to find that bacteria can survive a cytoplasmic pH of 5.6 and that they even use this to signal expression of virulence genes." Their research shows that low pH activates an intracellular signaling cascade, which induces the formation of a nanomachine called the type III secretion system. This nanomachine is composed of a needle complex used to inject bacterial virulence proteins into the host cell.

"Understanding that signals previously thought to be external, but now shown by us to be internal, changes our thinking about mechanisms of signal transduction," reports Professor Kenney. This work also identifies new potential therapeutic targets, which could be exploited to prevent the expression of the virulence proteins, thus blocking the ability of *Salmonella* to survive and flourish within the macrophage.

More information: Chakraborty S, Mizusaki H, Kenney LJ (2015) A FRET-Based DNA Biosensor Tracks OmpR-Dependent Acidification of Salmonella during Macrophage Infection. *PLoS Biol* 13(4): e1002116. DOI: 10.1371/journal.pbio.1002116