Super-resolution Imaging of *Salmonella* SPI-2 regulation: A View from 30,000 feet to 20 nm

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In bacteria, one paradigm for signal transduction is the two-component regulatory system, consisting of a sensor kinase and a response regulator. In *Salmonella*, the EnvZ/OmpR system responds to acid/osmotic stress and also positively regulates the *Salmonella* Pathogenicity Island 2 (SPI-2)-encoded type III secretion system required for its survival in the macrophage vacuole. EnvZ/OmpR acidifies the *Salmonella* cytoplasm in response to the acidified vacuole, driving virulence factor secretion into the host cytosol. Acidification is required for the secretion of virulence factors, blocking acidification results in a neutralized cytoplasm that is defective for SPI-2 secretion. Using super-resolution microscopy, we visualize the emergence of *Salmonella*-secreted effectors into the host cytoplasm and follow the resulting endosomal tubulation. Our results suggest a mechanical role in needle elongation of the type three secretory apparatus and subsequent gating of effector secretion. An invasive strain of *S.* Typhimurium has recently emerged in Vietnam that causes high mortality in HIV+ populations. Imaging analysis provides evidence for its invasive properties. Our work challenges existing views that bacteria regulate their pH to maintain neutrality, and provides a new model for *Salmonella* virulence factor secretion and infection. Supported by the Research Center of Excellence in Mechanobiology from the Ministry of Education, Singapore, VA 5I01BX000372 and NIH AI123640 to LJK.