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BACTERIAL PATHOGENESIS

Opening the gates of type III secretion

Bacterial pathogens subvert host cell pathways by using type III secretion systems (T3SSs) to deliver bacterial effectors through a translocon pore into the host cytosol. Three studies, each investigating a different organism, now show that type III secretion is controlled by changes in the oxygen level and by the pH in the host cell.

In the first study, Schüller and Phillips used an *in vitro* model to show that binding of enterohaemorrhagic *Escherichia coli* (EHEC) to epithelial cells increases at low oxygen levels, as does the production of T3SS effectors. Furthermore, using strains that lack specific T3SS substrates, they found that the increased adherence is due to elevated secretion of EspA, which forms a filamentous structure on the bacterial surface that mediates adherence to host cells.

Type III secretion by *Shigella flexneri* is also regulated by oxygen levels, as shown by Marteyn and colleagues in the second study. The authors screened for mutants that failed to colonize the gut and identified mutations in *fnr*, which encodes a transcriptional regulator that is active at low oxygen levels. Two T3SS genes, *spa32* and *spa33* (also known as *spaN* and *spaO*, respectively), were upregulated in the *fnr* mutant. Spa32 regulates needle length, and Spa33 is required for the secretion of effectors.

How, then, does type III secretion occur in the supposedly anaerobic environment of the intestine? Marteyn *et al.* showed that the area immediately adjacent to the mucosa is sufficiently oxygenated to inactivate Fnr and allow expression of *spa32* and *spa33*. Indeed, using microelectrodes in their cell culture model and reporter bacteria in an *in vivo* model, they found that there is a small zone of oxygenation immediately above the epithelial cell layer. The authors speculate that bacteria accumulate effectors and translocon proteins in the anaerobic conditions of the intestinal lumen, priming themselves for when they reach the epithelium, which would be signalled through the presence of oxygen and regulated through the loss of Fnr repression.

In the final study, Yu and colleagues investigated the pH dependency of secretion from the T3SS encoded by the *Salmonella* pathogenicity island 2 (SPI-2) in *Salmonella enterica* subspecies *enterica* serovar Typhimurium. This T3SS is active when the bacteria reside in an acidic, intracellular, membrane-bound compartment. *In vitro*, SPI-2 translocon proteins are produced at pH 5, but effector secretion occurs at neutral pH; this pH-dependent secretion requires the proteins SsaL, SsaM and SpiC. Showing that this reflects the situation *in vivo*, the authors found that reducing the pH of the host cell cytosol reduces translocation of SPI-2 effectors and that this pH-dependence requires SsaL, SsaM and SpiC. The authors propose a model in which the T3SS is formed and translocon proteins are secreted at low pH, but effector secretion is prevented by the SsaL–SsaM–SpiC complex until a sensor detects the neutral pH of the cytosol. Then, the complex disassembles and is degraded, allowing effector delivery. It is unclear what senses the pH signal, although the authors speculate that it may be the needle itself.

These three studies provide examples of the different ways in which pathogens prime T3SSs for secretion by making effectors in advance to release them rapidly when the appropriate signal is detected.

Christiaan van Ooij

ORIGINAL RESEARCH PAPERS Schüller, S. & Phillips, A.D. Microaerobic conditions enhance type III secretion and adherence of enterohaemorrhagic *Escherichia coli* to polarized human intestinal epithelial cells. *Environ. Microbiol.* 7 Apr 2010 (doi:10.1111/j.1462-2920.2010.02216.x) | Marteyn, B. *et al.* Modulation of *Shigella* virulence in response to available oxygen *in vivo*. *Nature* 2 May 2010 (doi:10.1038/nature08970) | Yu, X.-J. *et al.* pH sensing by intracellular *Salmonella* induces effector translocation. *Science* 15 Apr 2010 (doi:10.1126/science.1189000)