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BACTERIAL VIRULENCE

SteC actin rearrangements, step by step

During intracellular growth of *Salmonella enterica* subsp. *enterica* serovar Typhimurium, the type III secretion effector kinase SteC induces major changes in the host cytoskeletal network. Here, Holden and colleagues elucidate the host cell signalling cascade that is activated by SteC, which ultimately leads to filamentous actin (F-actin) accumulation around the *Salmonella*-containing vacuole (SCV).

As the F-actin bundles induced by SteC resemble those induced by myosin II activation, the authors postulated that this molecule might be involved in *S.* Typhimurium-triggered actin reorganization. Indeed, SteC expression in fibroblasts induced the phosphorylation of myosin IIb light chain, which then colocalized with actin fibres. Moreover, there was decreased association of myosin IIb light chain with SCVs when cells were infected with bacteria lacking SteC. Further analysis revealed that depletion of myosin IIb, but not of myosin IIa, decreased the association of F-actin with SCVs in mouse embryonic fibroblasts expressing SteC.

Next, the authors sought to identify what occurs upstream of myosin light chain phosphorylation and F-actin accumulation at SCVs following triggering by SteC. Myosin light chain is known to be activated by myosin light chain kinase (MLCK); consistent with this, inhibition of MLCK or depletion of the encoding transcript by RNAi reduced the association of F-actin with SCVs. MLCK is itself activated by Ca^{2+}–calmodulin binding, and this is enhanced by phosphorylation mediated by the mitogen-activated protein kinase cascade, involving MEK and ERK. In agreement with this, F-actin accumulation at SCVs decreased when these kinases were inhibited. Furthermore, MEK phosphorylation was significantly higher in cells infected with wild-type bacteria than in those infected with SteC-null bacteria. Interestingly, structural analysis indicated that SteC phosphorylates MEK at Ser200, resulting in conformational changes that the authors propose facilitate MEK autophosphorylation and activation.

Finally, the authors confirmed that all these molecules function in the same, SteC-activated signalling cascade. Depletion of ERK or MEK led to a strong reduction in myosin IIb recruitment to SCVs, and inhibition of MEK or MLCK in fibroblasts expressing SteC interfered with myosin IIb phosphorylation and the formation of F-actin bundles. Thus, the authors conclude that SteC activates MEK, which in turn activates ERK, leading to MLCK-mediated phosphorylation of myosin IIb and the consequent formation of actin bundles at SCVs. Importantly, inhibition of the different components of the cascade did not completely abrogate F-actin accumulation at SCVs, which suggests that SteC activates a second pathway that is independent of these proteins.

Together, these findings reveal a signalling pathway used by *S.* Typhimurium to manipulate the host actin network. The authors also observed that a *steC* mutant grew significantly better than its wild-type counterpart *in vivo*, and from this they conclude that SteC functions to restrain bacterial growth, thereby regulating its virulence.

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> “a signalling pathway used by *S.* Typhimurium to manipulate the host actin network.”

ORIGINAL RESEARCH PAPER Odendall, C. *et al.* The *Salmonella* kinase SteC targets the MAP kinase MEK to regulate the host actin cytoskeleton. *Cell Host Microbe* **12**, 657–668 (2012)

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