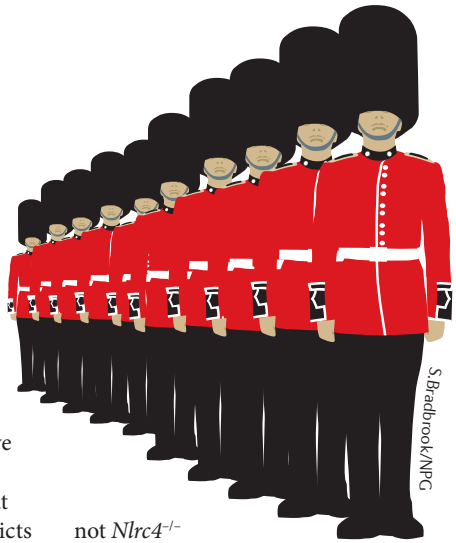
INFLAMMASOME

Stiffening up defences against *Salmonella*



S.Bradbrook/NPG

The activation of inflammasome signalling pathways has a central role in innate immunity to *Salmonella* infection. However, the mechanisms by which inflammasome activation mediates intracellular bacterial killing remain unknown. Bryant and colleagues now show that actin polymerization induced by NOD-, LRR- and CARD-containing 4 (NLRC4) inflammasome activation results in cellular stiffness and limits bacterial uptake and growth following infection with *Salmonella enterica* subsp. *enterica* serovar Typhimurium.

Previous studies have shown that the NLRC4 and NLRP3 (NOD-, LRR- and pyrin domain-containing 3) inflammasomes, as well as caspase 11, control *S.* Typhimurium infection *in vivo*. In this study, the authors infected wild-type bone marrow-derived macrophages (BMMs) or BMMs deficient for various inflammasome components with *S.* Typhimurium. They found that infected BMMs lacking NLRC4 or caspase 1, but not those lacking NLRP3, ASC or caspase 11, had a significantly higher bacterial burden than wild-type cells. Unlike wild-type and *Nlrp3*$^{-/-}$ BMMs, *Nlrc4*$^{-/-}$ and *Casp1*$^{-/-}$ BMMs failed to produce the antimicrobial molecules mitochondrial reactive oxygen species and hydrogen peroxide. These data suggest that the NLRC4 inflammasome restricts intracellular bacterial numbers in macrophages.

Using live-cell imaging, the authors observed that unlike wild-type BMMs, *Nlrc4*$^{-/-}$ BMMs remained readily susceptible to infection over time; therefore, NLRC4 activation might alter cytoskeletal functions to reduce bacterial uptake. Indeed, inhibition of actin polymerization in wild-type BMMs using cytochalasin D reduced bacterial uptake and also inhibited *S.* Typhimurium-induced NLRC4-dependent pyroptosis. Furthermore, cytochalasin D inhibited the formation of ASC inflammasome specks and NLRC4-dependent interleukin-1β production following *S.* Typhimurium infection. Thus, changes in actin polymerization are crucial for *Salmonella*-induced NLRC4 inflammasome activation and reduce bacterial uptake.

Next, the authors determined how *S.* Typhimurium-induced NLRC4 activation results in changes in cytoskeletal functions. They found that infected wild-type BMMs but not *Nlrc4*$^{-/-}$ BMMs exhibited a change in their viscoelastic properties and had increased cellular stiffness. In addition, the cellular movement of wild-type BMMs ceased rapidly following infection, whereas the movement of *Nlrc4*$^{-/-}$ BMMs was unaffected. Reduced macrophage movement might help to control bacterial dissemination in tissues; indeed, a higher number of infectious foci was observed in the liver of infected *Nlrc4*$^{-/-}$ mice compared with wild-type mice.

This study shows that NLRC4 inflammasome activation by *Salmonella* infection changes cytoskeletal dynamics, resulting in increased cellular stiffness, reduced cellular movement, decreased bacterial uptake and the production of antimicrobial molecules, all of which result in reduced intracellular bacterial burden.

Olive Leavy

> “actin polymerization is crucial for *Salmonella*-induced NLRC4 inflammasome activation”

ORIGINAL RESEARCH PAPER Man, S. M. *et al.* Actin polymerization as a key innate immune effector mechanism to control *Salmonella* infection. *Proc. Natl Acad. Sci. USA* **11**, 17588–17593 (2014)