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Type 1 interferon-dependent repression of NLRC4 and iPLA2 licenses down-regulation of *Salmonella* flagellin inside macrophages

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Abstract

Inflammasomes have been implicated in the detection and clearance of a variety of bacterial pathogens, but little is known about whether this innate sensing mechanism has any regulatory effect on the expression of stimulatory ligands by the pathogen. During infection with *Salmonella* and many other pathogens, flagellin is a major activator of NLRC4 inflammasome-mediated macrophage pyroptosis and pathogen eradication. *Salmonella* switches to a flagellin-low phenotype as infection progresses to avoid this mechanism of clearance by the host. However, the host cues that *Salmonella* perceives to undergo this switch remain unclear. Here, we report an unexpected role of the NLRC4 inflammasome in promoting expression of its microbial ligand, flagellin, and identify a role for type 1 IFN signaling in switching of *Salmonella* to a flagellin-low phenotype. Early in infection, activation of NLRC4 by flagellin initiates pyroptosis and concomitant release of lysophospholipids which in

turn enhance expression of flagellin by *Salmonella* thereby amplifying its ability to elicit cell death. TRIF-dependent production of type 1 IFN, however, later represses NLRC4 and the lysophospholipid biosynthetic enzyme iPLA2, causing a decline in intracellular lysophospholipids that results in down-regulation of flagellin expression by *Salmonella* These findings reveal a previously unrecognized immune-modulating regulatory cross-talk between endosomal TLR signaling and cytosolic NLR activation with significant implications for the establishment of infection with *Salmonella*.