BACTERIAL PATHOGENESIS

Targeting SUMO

> *L. monocytogenes* inhibits host protein sumoylation to promote efficient infection.

One of the mechanisms by which intracellular bacteria, such as *Listeria monocytogenes*, subvert host cell functions is to interfere with host protein post-translational modifications such as ubiquitylation, which alter protein function and stability. Cossart and colleagues now show that *L. monocytogenes* also affects sumoylation, a post-translational modification that involves the attachment of small ubiquitin-like modifier (SUMO) onto target proteins.

To assess the effect of *L. monocytogenes* on host protein sumoylation, the authors examined the levels of SUMO-conjugated proteins in infected cells and observed a reduction in protein sumoylation 3 hours after infection. This effect was not seen following infection with bacteria lacking the pore-forming toxin listeriolysin O. Furthermore, incubation of host cells with purified listeriolysin O led to decreased levels of sumoylated proteins, indicating a direct role for the toxin in inhibiting this process. Indeed, listeriolysin O was found to mediate a decrease in the levels of the E2 SUMO enzyme UBC9, which, along with the E1 and E3 SUMO enzymes, makes up the SUMO conjugation machinery. This decrease occurred in a proteasome-independent manner involving an unknown aspartyl protease, as treatment with an aspartyl protease inhibitor partly impaired the UBC9 decrease. Moreover, incubation of listeriolysin O with an antibody that prevents its binding to the cell membrane impaired the decrease in UBC9 levels, indicating that membrane binding is integral to this process.

The transforming growth factor-β (TGFβ) signalling pathway is an important part of the host cell defence mechanism against infection with intracellular bacteria. Infection of host cells with *L. monocytogenes* or incubation with listeriolysin O triggered a decrease in the levels of SMAD4, a TGFβ signalling mediator that is stabilized by sumoylation. This was counteracted by SUMO overexpression in host cells, indicating that *L. monocytogenes* may impair TGFβ signalling, at least in part, by inhibiting SMAD4 sumoylation. SUMO overexpression in host cells also resulted in significantly reduced numbers of intracellular bacteria following infection compared with control cells, highlighting the importance of sumoylation in efficient infection. Finally, the *in vitro* findings were confirmed *in vivo*: mice infected with *L. monocytogenes* showed a significant reduction in the levels of UBC9 in the liver.

Taken together, these findings show for the first time that *L. monocytogenes* inhibits host protein sumoylation to promote efficient infection. As pore-forming toxins from other bacteria, such as perfringolysin O and pneumolysin, were also found to induce UBC9 degradation, inhibition of sumoylation might be a general mechanism used by pathogenic bacteria to subvert host defence pathways.

GETTY

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ORIGINAL RESEARCH PAPER Ribet, D. *et al.* *Listeria monocytogenes* impairs SUMOylation for efficient infection. *Nature* **464**, 1138–1139 (2010)