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INNATE IMMUNITY

Coated for destruction in new defence strategy

The innate immune response against bacteria that reside in the mammalian cell cytoplasm is poorly understood. Previous studies have shown that cytoplasmic bacteria are coated with ubiquitin and that bacterial growth is restricted by TANK-binding kinase 1 (TBK1), but the biological significance of these findings remained unclear. Now, new research published in *Nature Immunology* identifies nuclear dot protein 52 kDa (NDP52; also known as CALCOCO2) as a new innate immune receptor that links the host autophagy and ubiquitin systems by recruiting TBK1 to stop ubiquitin-coated bacteria proliferating in the cytoplasm.

Salmonella enterica subspecies *enterica* serovar Typhimurium normally resides intracellularly within a *Salmonella*-containing vacuole (SCV). Thurston *et al.* studied the fate of *S.* Typhimurium that escape the SCV and enter the cytoplasm and showed that ubiquitin-coated *S.* Typhimurium indirectly recruited the TBK1 adaptor proteins NAP1 (also known as AZI2) and SINTBAD (also known as TBKBP1). Analysis of TBK1 complexes in cell extracts identified NDP52 as the cytoplasmic receptor that recruits TBK1 and its adaptors to ubiquitin-coated *S.* Typhimurium. Depletion of either TBK1 or NDP52 led to an increase in intracellular bacterial numbers, confirming the role of these proteins in preventing bacterial growth in the cytoplasm. Finally, it was shown that NDP52 limits bacterial growth by acting as a cytoplasmic autophagy receptor. It delivers ubiquitin-coated bacteria into autophagosomes, where the bacteria are presumably degraded, by binding directly with the autophagosome marker LC3; knockdown of NDP52 led to a decrease in the percentage of ubiquitin-coated bacteria present in LC3-positive autophagosomes.

Previous work has identified a key role for TBK1 in antiviral innate immunity. This work reinforces the role for TBK1 and identifies NDP52, a new innate immune receptor, in the response to cytoplasmic bacteria. Further work will be required to determine how NDP52 detects ubiquitin and to clarify the role of TBK1 in autophagy. Also, more work is needed to establish the host mechanisms for ubiquitin coating of bacteria in the cytoplasm and how bacteria specifically adapted for growth in the cytoplasm, such as *Shigella flexneri*, manage to avoid this.

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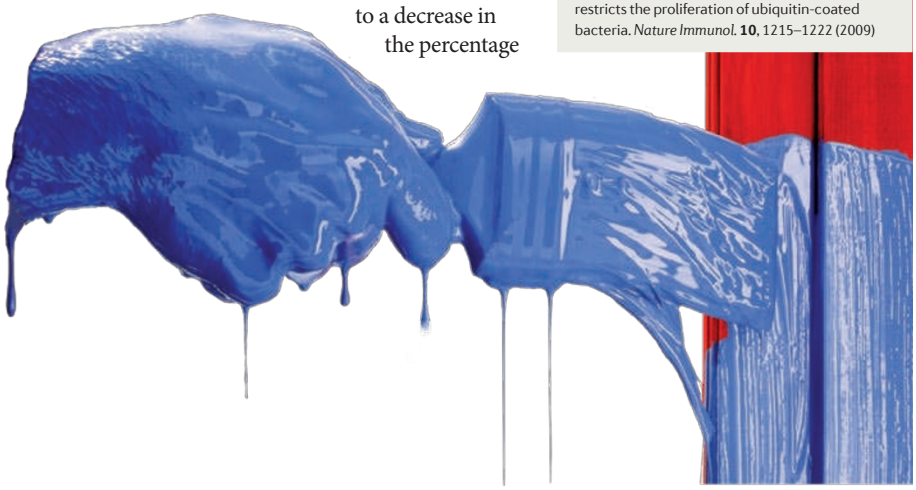
ORIGINAL RESEARCH PAPER Thurston, T. L. M., Ryzhakov, G., Bloor, S., von Muhlinen, N. & Randow, F. The TBK1 adaptor and autophagy receptor NDP52 restricts the proliferation of ubiquitin-coated bacteria. *Nature Immunol.* **10**, 1215–1222 (2009)



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