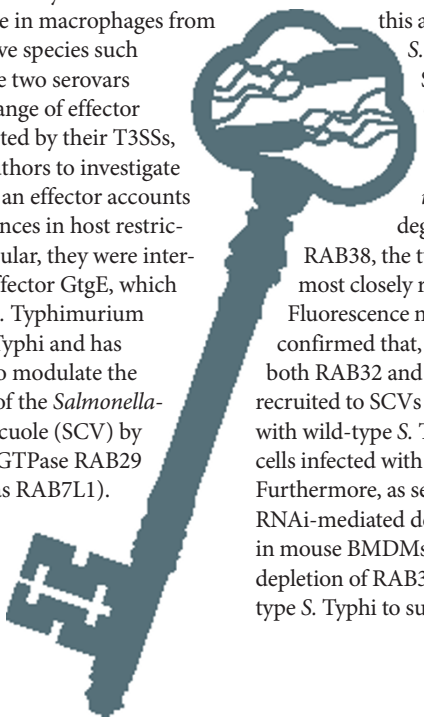
BACTERIAL PATHOGENESIS

Salmonella's skeleton key

> GtgE-mediated degradation of RAB32 allows *S.* Typhi to survive in a non-permissive host.

The species *Salmonella enterica* comprises distinct serovars, some that can infect a broad range of hosts, and others that have a narrow host range. Writing in *Science*, Spanò and Galán show that a single type III secretion system (T3SS) effector from the broad-host-range *Salmonella enterica* subsp. *enterica* serovar Typhimurium can expand the narrow host range of *Salmonella enterica* subsp. *enterica* serovar Typhi by targeting the RAB32-dependent trafficking pathway.

Unlike *S.* Typhimurium, which infects both humans and mice, *S.* Typhi infects only humans and cannot survive in macrophages from non-permissive species such as mice. These two serovars differ in the range of effector proteins secreted by their T3SSs, leading the authors to investigate whether such an effector accounts for the differences in host restriction. In particular, they were interested in the effector GtgE, which is present in *S.* Typhimurium but not in *S.* Typhi and has been shown to modulate the composition of the *Salmonella*-containing vacuole (SCV) by targeting the GTPase RAB29 (also known as RAB7L1). The authors found that compared with wild-type *S.* Typhi, engineered *S.* Typhi expressing GtgE showed enhanced survival in mouse primary bone marrow-derived macrophages (BMDMs), with the number of bacteria recovered after 48 hours being equivalent to the numbers seen during *S.* Typhimurium infections. Furthermore, infection of mice with *S.* Typhi expressing GtgE led to more bacteria in tissues than were seen in infections with wild-type bacteria.



To investigate the mechanism by which GtgE allows *S.* Typhi to survive in mouse macrophages, the authors used RNAi to deplete RAB29 from BMDMs and tested whether this allowed wild-type *S.* Typhi to grow. Surprisingly, RAB29 depletion had no effect. However, both *in vitro* and *in vivo*, GtgE could degrade RAB32 and RAB38, the two RAB GTPases most closely related to RAB29. Fluorescence microscopy confirmed that, like RAB29, both RAB32 and RAB38 were recruited to SCVs in cells infected with wild-type *S.* Typhi but not in cells infected with *S.* Typhimurium. Furthermore, as seen with RAB29, RNAi-mediated depletion of RAB38 in mouse BMDMs had no effect, but depletion of RAB32 allowed wild-type *S.* Typhi to survive, suggesting that GtgE-mediated degradation of RAB32 allows *S.*Typhi to survive in a non-permissive host.

Together with components of BLOC1 (biogenesis of lysosome-related organelle complex 1), BLOC2 and BLOC3, RAB32 and RAB38 had previously been shown to coordinate the delivery of specific cargoes, including enzymes and antimicrobial proteins, to lysosome-related organelles, which share a number of properties with SCVs. Accordingly, the authors found that depletion of an essential component of BLOC3, but not BLOC1 or BLOC2, allowed *S.*Typhi to survive in mouse BMDMs.

Taken together, these data suggest that the T3SS effector GtgE can act as a skeleton key that 'unlocks' the normally non-permisive mouse host, allowing *S.*Typhi to survive and grow in macrophages by preventing the RAB32–BLOC3-dependent delivery of antimicrobial proteins to the SCV. RAB32 polymorphisms have been linked with susceptibility to several other intracellular pathogenic bacteria, suggesting that this constitutes a conserved host defence pathway.

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ORIGINAL RESEARCH PAPER Spanò, S. & Galán, J. A Rab32-dependent pathway contributes to *Salmonella* Typhi host restriction. *Science* **338**, 960–963 (2012)
FURTHER READING Mathur, R. *et al.* A mouse model of *Salmonella* Typhi infection. *Cell* **151**, 590–602 (2012)