Article

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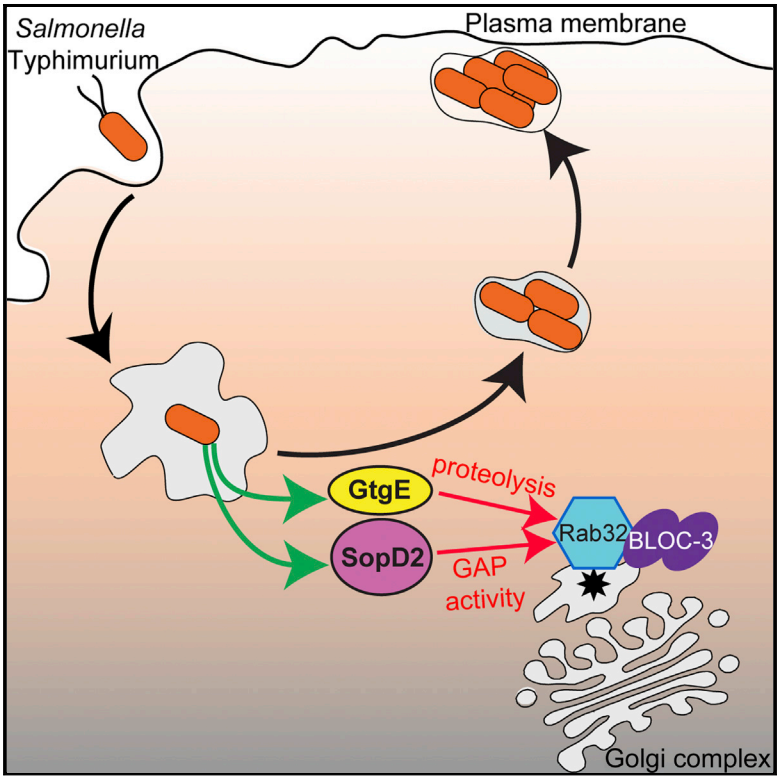
A Bacterial Pathogen Targets a Host Rab-Family GTPase Defense Pathway with a GAP

Graphical Abstract



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In Brief

Microbial pathogens have evolved mechanisms to counter host defense pathways that limit their replication. Spanò et al. show that a cell-autonomous, Rab32-dependent mechanism of defense restricts the replication of the intracellular pathogen *Salmonella*, which counters it by delivering a GAP and protease that target this Rab GTPase.

Highlights

- A Rab32-dependent mechanism of defense restricts the replication of *Salmonella*
- *Salmonella* counters this host defense pathway with the effectors SopD2 and GtgE
- SopD2 is a GAP and GtgE a protease, which both target Rab32
- A mutant lacking these effectors exhibits drastic virulence reduction

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A Bacterial Pathogen Targets a Host Rab-Family GTPase Defense Pathway with a GAP

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SUMMARY

Cell-autonomous defense mechanisms are potent strategies that protect individual cells against intracellular pathogens. The Rab-family GTPase Rab32 was previously shown to restrict the intracellular human pathogen *Salmonella* Typhi, but its potential broader role in antimicrobial defense remains unknown. We show that Rab32 represents a general cell-autonomous, antimicrobial defense that is counteracted by two *Salmonella* effectors. Mice lacking Rab-32 or its nucleotide exchange factor BLOC-3 are permissive to *S.* Typhi infection and exhibit increased susceptibility to *S.* Typhimurium. *S.* Typhimurium counters this defense pathway by delivering two type III secretion effectors, SopD2, a Rab32 GAP, and GtgE, a specific Rab32 protease. An *S.* Typhimurium mutant strain lacking these two effectors exhibits markedly reduced virulence, which is fully restored in BLOC-3-deficient mice. These results demonstrate that a cell-autonomous, Rab32-dependent host defense pathway plays a central role in the defense against vacuolar pathogens and describe a mechanism evolved by a bacterial pathogen to counter it.

INTRODUCTION

Microbial pathogens encounter a variety of host innate immune mechanisms that restrict their survival and growth. Pathogens are most often sensed by the host through pattern-recognition receptors, which can detect microbial products or microbial-induced tissue injury (Broz and Monack, 2013; Dixit and Kagan, 2013; Medzhitov, 2007). Pathogen recognition is then followed by host defense responses that, when successful, limit pathogen replication (Yang et al., 2013; Jarczak et al., 2013; Nairz et al., 2014; Nish and Medzhitov, 2011; Voehringer, 2013). In turn, and as part of the everlasting evolutionary "arms race," pathogens have evolved mechanisms to avoid their detection or to survive the defense responses (Diacovich and Gorvel, 2010; Reddick and Alto, 2014). Although much is known about host-sensing mechanisms to detect microbial pathogens, much less is known about host-effector mechanisms to control microbial infections or the microbial virulence factors that may have specifically evolved to counter them. Greater emphasis has been placed on the role of immune cells in pathogen defense. However, the first, and evolutionarily the oldest, line of defense against microbial infection is composed of cell-intrinsic or cell-autonomous mechanisms that operate in most cells of the body (Deretic, 2011; Randow et al., 2013). These mechanisms, which tend to be conserved across phyla, provide protection to individual cells in the body and, in metazoan, synergize with the immune system to confer whole-body protection against pathogens. Some of these cell-autonomous mechanisms have adapted to operate in a rather specific manner. For example, members of the tripartite motif (TRIM) protein family, such as TRIM5α (Rajsbaum et al., 2014) and the single-stranded DNA cytosine deaminase APOBEC3 (Harris and Dudley, 2015), have evolved to restrict the replication of retroviruses. Others, however, have the capacity to restrict the growth a broad range of pathogens. For example, a family of interferon-inducible GTPases has been found to restrict the growth of a variety of intracellular microbial pathogens (Hunn et al., 2011; Kim et al., 2012).

The bacterial pathogen *Salmonella enterica* comprises many serovars that can infect a large and diverse number of vertebrate species (Grassl and Finlay, 2008; Ohl and Miller, 2001). While some serovars such as *Salmonella enterica* Typhimurium (*S.* Typhimurium) can infect a broad range of hosts, others are extremely host specific. *Salmonella enterica* Typhi (*S.* Typhi), for example, can only infect humans, where it causes typhoid fever, a systemic disease that results in ~200,000 deaths worldwide, mostly children in developing countries (Crump and Mintz, 2010; Parry et al., 2002; Raffatellu et al., 2008). We recently discovered that expression of a single gene from *S.* Typhimurium in *S.* Typhi allows this bacterium to replicate in cells and tissues of a nonpermissive host (Spanò and Galán, 2012). This gene, *gtgE*, encodes for a protease that targets the Rab-family GTPase Rab32 (Spanò and Galán, 2012; Spanò et al., 2011). In specialized cells, these GTPases are known to orchestrate the maturation and assembly of lysosome-related organelles such as melanosomes and T cell granules (Dell'Angelica, 2004; Luzio et al., 2014; Raposo and Marks, 2007; Wasmeier et al., 2006). However, the potential role of these GTPases in other cells has not been investigated. Removal of Rab32 or its exchange factor, the biogenesis of lysosome-related organelle complex 3 (BLOC-3) (Gerondopoulos et al., 2012), allowed the replication of human-specific serovar *S.* Typhi in mouse macrophages (Spanò and Galán, 2012). We report here that the