PLEKHM1 Regulates Salmonella-Containing Vacuole Biogenesis and Infection

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The host endolysosomal compartment is often manipulated by intracellular bacterial pathogens. Salmonella (Salmonella enterica serovar Typhimurium) secrete numerous effector proteins, including SifA, through a specialized type III secretion system to hijack the host endosomal system and generate theăSalmonella-containing vacuole (SCV). To form this replicative niche, Salmonella targets the Rab7 GTPase to recruit host membranes through largely unknown mechanisms. We show that Pleckstrin homology domain-containing protein family member 1ă(PLEKHM1), a lysosomal adaptor, is targeted by Salmonella through direct interaction with SifA. By binding the PLEKHM1 PH2 domain, Salmonella utilize a complex containing PLEKHM1, Rab7, and the HOPS tethering complex to mobilize phagolysosomal membranes to the SCV. Depletion of PLEKHM1 causes a profound defect in SCV morphology with multiple bacteria accumulating in enlarged structures and significantly dampens Salmonella proliferation in multiple cell types and mice. Thus, PLEKHM1 provides a critical interface between pathogenic infection and the host endolysosomal system.
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