A Genome-Wide siRNA Screen Implicates Spire1/2 in SipA-Driven Salmonella Typhimurium Host Cell Invasion

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Salmonella Typhimurium (S. Tm) is a leading cause of diarrhea. The disease is triggered by pathogen invasion into the gut epithelium. Invasion is attributed to the SPI-1 type 3 secretion system (T1). T1 injects effector proteins into epithelial cells and thereby elicits rearrangements of the host cellular actin cytoskeleton and pathogen invasion. The T1 effector proteins SopE, SopB, SopE2 and SipA are contributing to this. However, the host cell factors contributing to invasion are still not completely understood. To address this question comprehensively, we used Hela tissue culture cells, a genome-wide siRNA library, a modified gentamicin protection assay and S. TmSipA, a sopBsopE2sopE mutant which strongly relies on the T1 effector protein SipA to invade host cells. We found that S. TmSipA invasion does not elicit membrane ruffles, nor promote the entry of non-invasive bacteria ”in trans”. However, SipA-mediated infection involved the SPIRE family of actin nucleators, besides well-established host cell factors (WRC, ARP2/3, RhoGTPases, COPI). Stage-specific follow-up assays and knockout fibroblasts indicated that SPIRE1 and SPIRE2 are involved in different steps of the S. Tm infection process. Whereas SPIRE1 interferes with bacterial binding, SPIRE2 influences intracellular replication of S. Tm. Hence, these two proteins might fulfill non-redundant functions in the pathogen-host interaction. The lack of co-localization hints to a short, direct interaction between S. Tm and SPIRE proteins or to an indirect effect.
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