A Role for the VPS Retromer in Brucella Intracellular Replication Revealed by Genomewide siRNA Screening

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Author(s) Casanova, Alain; Low, Shyan Huey; Québatte, Maxime; Sedzicki, Jaroslaw; Tschon, Therese; Ketterer, Maren; Smith, Kevin; Emmenlauer, Mario; Ben-Tekaya, Houchaima; Dehio, Christoph
Author(s) at UniBasel Dehio, Christoph ; Québatte, Maxime ; Sedzicki, Jaroslaw ; Ketterer, Maren ;
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Brucella, the agent causing brucellosis, is a major zoonotic pathogen with worldwide distribution. Brucella resides and replicates inside infected host cells in membrane-bound compartments called Brucella-containing vacuoles (BCVs). Following uptake, Brucella resides in endosomal BCVs (eBCVs) that gradually mature from early to late endosomal features. Through a poorly understood process that is key to the intracellular lifestyle of Brucella, the eBCV escapes fusion with lysosomes by transitioning to the replicative BCV (rBCV), a replicative niche directly connected to the endoplasmic reticulum (ER). Despite the notion that this complex intracellular lifestyle must depend on a multitude of host factors, a holistic view on which of these components control Brucella cell entry, trafficking, and replication is still missing. Here we used a systematic cell-based small interfering RNA (siRNA) knockdown screen in HeLa cells infected with Brucella abortus and identified 425 components of the human infectome for Brucella infection. These include multiple components of pathways involved in central processes such as the cell cycle, actin cytoskeleton dynamics, or vesicular trafficking. Using assays for pathogen entry, knockdown complementation, and colocalization at single-cell resolution, we identified the requirement of the VPS retromer for Brucella to escape the lysosomal degradative pathway and to establish its intracellular replicative niche. We thus validated the VPS retromer as a novel host factor critical for Brucella intracellular trafficking. Further, our genomewide data shed light on the interplay between central host processes and the biogenesis of the Brucella replicative niche.; IMPORTANCE; With >300,000 new cases of human brucellosis annually, Brucella is regarded as one of the most important zoonotic bacterial pathogens worldwide. The agent causing brucellosis resides inside host cells within vacuoles termed Brucella- containing vacuoles (BCVs). Although a few host components required to escape the degradative lysosomal pathway and to establish the ER-derived replicative BCV (rBCV) have already been identified, the global understanding of this highly coordinated process is still partial, and many factors remain unknown. To gain deeper insight into these fundamental questions, we performed a genomewide RNA interference (RNAi) screen aiming at discovering novel host factors involved in the Brucella intracellular cycle. We identified 425 host proteins that contribute to Brucella cellular entry, intracellular trafficking, and replication. Together, this study sheds light on previously unknown host pathways required for the Brucella infection cycle and highlights the VPS retromer components as critical factors for the establishment of the Brucella intracellular replicative niche.
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