UKE Paper of the Month August 2015
Cell Reports, 2015 Sept 22 (PMID 26344766)

ER-coordinated activities of Rab22a and Rab5a drive phagosomal compaction and intracellular processing of *Borrelia burgdorferi* by macrophages
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ABSTRACT:
Borrelia burgdorferi is the causative agent of Lyme disease, a multisystemic disorder affecting skin, joints and nervous system. Macrophages and dendritic cells counteract *Borrelia* dissemination through internalization and degradation of spirochetes. We now show that *Borrelia* internalization by primary human macrophages involves uptake and compaction into Rab22a-positive phagosomes that are in close contact with Rab5a-positive vesicles. Compaction of borreliae involves membrane extrusion from phagosomes, is driven by Rab22a and Rab5a activity, and coordinated by endoplasmic reticulum tubules forming contact sites of Rab22a phagosomes with Rab5a vesicles. Importantly, Rab22a and Rab5a depletion leads to reduced localization to lysosomes, and to increased intracellular survival of spirochetes. These data show that Rab22a- and Rab5a-driven phagosomal uptake is a crucial step in the vesicular cascade that leads to elimination of spirochetes by macrophages. Rab22a and Rab5a thus present as potential molecular targets for the modulation of intracellular pro-cessing of borreliae in human immune cells.

STATEMENT:
We show for the first time that uptake of borreliae in phagosomes is critical for their intracellular processing by macrophages. In consequence, interference with Rab22a or Rab5a activity results in increased intracellular survival of spirochetes, pointing to a potential strategy for persistence in the host. Our results also reveal a novel role for Rab22a as an early and important player in the phagocytic RabGTPase cascade in macrophages - a role preceding that of Rab5, which is generally assumed to be the inital RabGTPase in this cascade. Moreover, our data reveal how the activity of different RabGTPases that are present at discrete vesicular entities can be coordinated by the endoplasmic reticulum, which adds detailed new information to the current debate on the role of the ER in endocytic processes.

BACKGROUND:
This work was performed at the Institute for Medical Microbiology, Virology and Hygiene in the group of Stefan Linder, who holds a professorship at UKE since 2009. It was part of the PhD thesis of Xenia Naj within the DFG research training group “Sorting and interactions between proteins of subcellular compartments” (GRK1459). Both authors have strong research interests in the field of cytoskeletal regulation and intracellular trafficking, with a special focus on macrophage and Borrelia biology and pathophysiology.