Title:	Lysosome-Mediated Plasma Membrane Repair Is Dependent on the Small GTPase Arl8b and Determines Cell Death Type in Mycobacterium tuberculosis Infection
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Abstract:	Mycobacterium tuberculosis is an extremely successful pathogen, and its success is widely attributed to its ability to manipulate the intracellular environment of macrophages. A central phenomenon of tuberculosis pathology enabling immune evasion is the capacity of virulent M. tuberculosis (H37Rv) to induce macrophage necrosis, which facilitates the escape of the mycobacteria from the macrophage and spread of infection. In contrast, avirulent M. tuberculosis (H37Ra) induces macrophage apoptosis, which permits Ag presentation and activation of adaptive immunity. Previously, we found that H37Rv induces plasma membrane microdisruptions, leading to necrosis in the absence of plasma membrane repair. In contrast, H37Ra permits plasma membrane repair, which changes the host cell death modality to apoptosis, suggesting that membrane repair is critical for sequestering the pathogen in apoptotic vesicles. However, mechanisms of plasma membrane repair induced in response to M. tuberculosis infection remain unknown. Plasma membrane repair is known to induce a Ca2+-mediated signaling, which recruits lysosomes to the area of damaged plasma membrane sites for its resealing. In this study, we found that the small GTPase Arl8b is required for plasma membrane repair by controlling the exocytosis of lysosomes in cell lines and in human primary macrophages. Importantly, we found that the Arl8b secretion pathway is crucial to control the type of cell death of the M. tuberculosis–infected macrophages. Indeed, Arl8b-depleted macrophages infected with avirulent H37Ra undergo necrotic instead of apoptotic cell death. These findings suggest that membrane repair mediated by Arl8b may be an important mechanism distinguishing avirulent from virulent M. tuberculosis–induced necrotic cell death.
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