Title:	Elucidating the role of LC3-interacting regions in listeriolysin O and its interaction with host autophagy machinery
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Abstract:	Listeria monocytogenes is a foodborne, facultative intracellular bacterial pathogen that causes listeriosis [17]. After getting phagocytosed, Listeria exploits its virulence factor, listeriolysin O (LLO), which exhibits pH sensitivity, to escape the phagosomal compartment before its maturation to lysosomes [22]. Once in the cytosol, Listeria manipulates host cellular processes, including evading recognition by the autophagy machinery through the formation of actin clouds around itself, facilitating cell-to-cell spread and avoiding degradation [25]. Short-linear motifs (SLiMs) are 3-10 amino acid residues length sequences that play important roles in protein-protein interactions and biological signalling cascades in eukaryotes. Pathogens have evolved to exploit eukaryotic SLiMs to interact with diverse host proteins and disrupt various host cellular processes due to their functional and structural adaptability. For instance, the M2 protein of influenza A virus exploits LC3-interacting motifs, thereby regulating the cytosolic distribution of LC3 and influencing host cellular pathways. To identify SLiMs in Listeria genome, an in silico motif analysis was performed to identify the regions involved in autophagy. As a result, LC3-interacting regions (LIR motifs) were found to be present in a few of its virulent proteins, including LLO [52]. LLO, a cholesterol- dependent cytolysin, known to interact with cholesterol in membrane and form pores, facilitating bacterial escape into the cytosol. Previous studies have indicated that during the early stages of infection in human macrophages, Listeria monocytogenes recruits LC3, a key protein associated with autophagy [30]. However, as the infection progresses, the bacterium evades recognition by the host's autophagic machinery. While the actin-assembly inducing protein (actA) of Listeria has traditionally been implicated in this evasion mechanism, recent reports have demonstrated that even in Listeria mutants lacking actA, the bacterium can still effectively evade recognition by the host's autophagy system. This highlights the existence of additional mechanisms employed by Listeria to evade autophagic recognition [32]. Listeriolysin O (LLO), as a secretory factor, consistently resides within the cytosol. This study aims to delineate the significance of LC3-interacting region (LIR) motifs within LLO and their implications for host-pathogen interactions. Specifically, we aim to elucidate whether these interactions are exploited by Listeria monocytogenes or contribute to bacterial clearance by the host cell. Through a comprehensive approach encompassing in silico, in vitro, and in vivo methodologies, we endeavor to elucidate the functional relevance of the LLO-LC3 interaction. This investigation aims to deepen our understanding of the intricate dynamics governing host-pathogen interactions, thereby offering insights into potential therapeutic strategies against Listeria infection.
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