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Turning pathogens into Cell Biology Tools

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ABSTRACT

Study of intracellular bacterial pathogens and the interactions with their host have revealed many interesting aspects of host-pathogen arms race. The gram-negative bacterium Legionella pneumophila (L.p.) causes a severe form of pneumonia known as Legionnaires disease and is particularly interesting as it manipulates several host traffic processes to establish its replicative niche in an endoplasmic reticulum (ER)-like vacuole. Thus, L.p. has emerged as an excellent model pathogen that can be used as a tool to detect fundamental principles of cell-biology. L.p. avoids fusion with the lysosome by injecting effector proteins via its type IV secretion system. Understanding how L.p. sabotages host vesicular transport processes and manipulates them to its own advantage has already provided invaluable insights into its disease and mammalian cell biology.

The unfolded protein response (UPR) is an important cytoprotective pathway in the ER that is manipulated by various pathogens. Given that L.p. actively engages the ER, we hypothesized that L.p. may manipulate specific arms of the UPR. Interestingly, while previous work demonstrated that most pathogens induce the UPR, we have discovered that L.p. both activates and inhibits it. We have shown that two L.p. effectors belonging to the glucosyltransferase family, Lgt1 and Lgt2 (Lgt1/2), block the IRE1-mediated XBP1u mRNA splicing. Furthermore, we have shown that L.p. infection alone leads to the processing/activation of ATF6 and down regulation of BiP/CHOP translation. Our current unpublished data suggests that L.p. uses a non-canonical method of ATF6 activation that does not require its translocation to the Golgi apparatus. Furthermore, we have discovered a L.p. kinase that plays an important role in blocking downstream UPR targets at the level of translation. Molecular dissection of Legionella's interaction with specific UPR arms will unravel novel mechanisms of bacterial pathogenesis and provide tools for probing and manipulating the UPR, which is implicated in numerous human diseases.