

# Preface

Legionnaires' disease is a potentially fatal pneumonia primarily affecting elderly and immunocompromised persons. The disease is caused by the ubiquitous environmental bacterium *Legionella pneumophila*, which was first identified more than 35 years ago in the aftermath of a pneumonia epidemic that swept through a convent of the American Legion in Philadelphia, USA. The water-borne bacteria are inhaled via contaminated aerosols, resist degradation by alveolar macrophages, and trigger a fulminant pneumonia. Direct inhalation represents the sole route of infection with *L. pneumophila*; person-to-person transmission does not occur.

Macrophage resistance of *L. pneumophila* is a prerequisite for its virulence. This trait has likely been acquired through long-standing evolutionary cross-talk with free-living protozoa. Accordingly, the genome of *L. pneumophila* encodes a number of eukaryotic-like genes presumably acquired by horizontal transkingdom gene transfer. Thus, the adaptation of *L. pneumophila* to bactericidal protozoa did select for virulence traits required for growth in mammalian cells. Many aspects of pathogen–phagocyte interactions seem to be mechanistically conserved between protozoan natural hosts and mammalian “accidental” target cells. Given these similarities, protozoa such as *Dictyostelium*, *Acanthamoeba*, *Hartmanella*, or *Tetrahymena* spp. are powerful models to dissect cell-autonomous aspects of *L. pneumophila* infection.

The interactions of *L. pneumophila* with phagocytes are regulated by at least four different two-component systems (PmrAB, CpxRA, LetAS, and LqsRS). These networks involve and converge on small regulatory RNAs, as well as RNA-binding proteins. *L. pneumophila* survives intracellularly in macrophages and amoebae by forming a specific replication-permissive compartment, the *Legionella*-containing vacuole (LCV). LCVs communicate with the endocytic, secretory, and retrograde vesicle trafficking pathways, but do not fuse with lysosomes. To gain insights into the composition of LCVs, intact pathogen vacuoles have recently been purified and analyzed by proteomics.

*L. pneumophila* governs the formation of LCVs and other pathogen–host interactions through distinct protein secretion systems, such as the Lsp type II secretion system (T2SS) and the Icm/Dot type IV secretion system (T4SS).

Whereas the Lsp T2SS secretes at least 25 proteins, the Icm/Dot T4SS translocates the astonishing number of  $\sim 300$  different “effector” proteins into host cells. The function of most of these proteins is not understood, but they are thought to subvert host signal transduction and vesicle trafficking pathways.

Some Icm/Dot substrates are exceptionally intriguing, since they catalyze novel biochemical reactions. The eukaryotic small GTPase Rab1, which is implicated in secretory vesicle trafficking, is targeted by no fewer than six different *L. pneumophila* effectors. Whereas SidM (*alias* DrrA) activates Rab1 through its guanine nucleotide exchange factor (GEF) activity, LepB functions as a Rab1 GTPase activating protein (GAP). Furthermore, SidM and AnkX covalently modify Rab1 by attaching an AMP or a phosphocholine moiety, respectively. The reverse deadenylation or dephosphocholination reactions are catalyzed by the effector proteins SidD or Lem3. Finally, the Icm/Dot substrate LidA assists SidM by binding with high affinity to activated Rab1.

Another interesting aspect of *L. pneumophila* host cell subversion is how translocated effectors localize to the cytoplasmic face of LCVs. Whereas the Icm/Dot substrate LegG1 is lipidated by the host prenylation machinery, the Rab1 GEF SidM and the ER interactor SidC anchor to LCVs through the phosphoinositide (PI) lipid phosphatidylinositol-4-phosphate (PtdIns(4)P). In contrast, the Rab1 deadenylylase SidD as well as the Arf1 GEF RalF, bind to the LCV membrane via unknown receptors apparently without targeting lipids. The host cell lipid pattern is directly modified by approximately 20 *L. pneumophila* T2SS or T4SS substrates, which act as phospholipases or PI phosphatases, respectively, thereby destroying host membranes and/or modulating host signaling pathways.

An important class of *L. pneumophila* effectors interferes with host cell ubiquitination. Icm/Dot substrates such as LubX and AnkB are functional mimics of eukaryotic E3 ubiquitin ligases that mark bacterial and host proteins for proteasomal degradation or modification of activity. Moreover, cytotoxic *L. pneumophila* glucosyltransferases modify the ribosome, thereby inhibiting protein synthesis (Lgt1-3), or subvert endosomal vesicle trafficking (SetA). Finally, *L. pneumophila* and host cell kinases, as well as the protein phosphorylation pattern and corresponding signal transduction pathways define pathogen–host interactions.

Whereas many aspects of *L. pneumophila* virulence can be satisfactorily analyzed using uni-cellular (protozoan) models, the study of inflammation and immune responses relies on mouse models of Legionnaires’ disease, which faithfully mimic human pathology. To this end, the A/J strain of mice proved instrumental, as macrophages with this genetic background fail to restrict *L. pneumophila* replication. This is due to a Naip5 (*alias* Birc1e) protein that does not recognize flagellin, and consequently, does not trigger flagellin-dependent inflammasome activation.

In summary, this book contributes to an in-depth understanding of Legionnaires’ disease by comprising comprehensive reviews about different facets of *L. pneumophila* pathogenesis. Topics covered include comparative phagocyte infection, virulence gene regulation, biochemical functions of effector proteins,

cellular pathogen–host interactions, as well as host responses and immunity against *L. pneumophila*. Thus, this compilation provides a state-of-the-art overview of current insights into the molecular pathogenesis of an opportunistic but potentially fatal bacterial respiratory pathogen.

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Molecular Mechanisms in Legionella Pathogenesis

Hilbi, H. (Ed.)

2014, X, 295 p. 19 illus., 2 illus. in color., Hardcover

ISBN: 978-3-642-40590-7