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Legionella: from protozoa to humans

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Pathogens that are able to enter and multiply within human cells are responsible for multiple diseases and millions of deaths worldwide. Thus, the challenge is to elucidate these pathogen-specific and cell biological mechanisms involved in intracellular growth and spread. Bacteria from the genus *Legionella* belong to this group of pathogens. They are environmental bacteria and ubiquitous in nature, where they parasitize protozoa. Strikingly, the capacity to grow intracellularly in protozoa like *Acanthamoeba castellanii*, *Hartmannella* sp., or *Naegleria* sp., has generated a pool of virulence traits during evolution, which allow *Legionella* to infect also human cells. Thus important human pathogens are present within the genus *Legionella*, the most prominent are *L. pneumophila* (Fraser et al., 1977; Mcdade et al., 1977) and *L. longbeachae* (Mckinney et al., 1981). These bacteria are the causative agents of Legionnaires' disease, a severe pneumonia diagnosed mainly in people whose immune defenses are weakened. *Legionella* is transmitted through breathing infected aerosols present in many artificial water systems like air conditioning systems, cooling towers, showers, and other aerosolizing devices. When reaching the alveolar parts of the lungs *Legionella* is engulfed by macrophages where it is able to multiply resulting in a severe, often fatal pneumonia. Intracellular infection is a consequence of the bacterium's capacity to manipulate host cellular processes using bacterial proteins that are delivered into the host cell by specialized secretion systems (Isberg et al., 2009; Hubber and Roy, 2010). In this Research Topic, we present a collection of Review, Opinion, Perspective, and Primary research articles that present both the well-established and the newly discovered strategies used by *Legionella* to achieve this intracellular lifestyle while escaping from the host immune response.

Recent advance in genome sequencing has had a tremendous impact on our understanding of the pathogenesis, evolution and diversity of *L. pneumophila* and *L. long-*

beachae and the knowledge of the genome sequence has guided and facilitated the research on *Legionella* in many laboratories. Starting this issue, Gomez Valero et al. (2011) present a comprehensive review on what we have learned from the sequencing and analyses of six *L. pneumophila* and five *L. longbeachae* genomes published since 2004. In particular, genome sequence analysis revealed the presence of proteins with high similarity to eukaryotic proteins or proteins with domains preferentially or only present in eukaryotic genomes that are mimicking host functions helping the pathogen to replicate intracellularly (Cazalet et al., 2004, 2010). Further insight in the genetic basis of host differences and the evolution of the eukaryotic like proteins in these two pathogens are given.

The bacterial cell wall is at the forefront of the interaction with the host and is essential for cellular integrity and the resistance to external stress and aggressions. Shevchuk et al. (2011) provide an update on the structure, molecular composition, and virulence properties of the *L. pneumophila* cell envelope. In their review they show convincingly that lipopolysaccharide and several outer membrane proteins like Mip, a peptidyl-prolyl-*cis/trans* isomerase, a phospholipase A are essential virulence factors. It becomes clear that promising new fields of research will be the analyses of proteins, carbohydrates, and lipids of the cell envelope as they serve for both, structural and signaling roles. In the following review article Garduno et al. (2011) present us the current knowledge on the many functions that one of these outer membrane proteins, Hsp60 or HtpB plays in the *L. pneumophila* biology. This chaperonin is an unusual multifunctional protein which was discovered already as early as 1986 as an antigen that prominently reacted with patients diagnosed with Legionnaires' disease. Over 20 years later it has been shown to have protein folding as well as protein folding independent roles and that it is associated with virulence and survival of *L. pneumophila*.

Central to the pathogenesis of *L. pneumophila* and *L. longbeachae* is its Type IV secretion system (T4SS) called Dot/Icm. It is predicted to translocate over 270 effector proteins into the host cell which allow this bacterium to manipulate host cell functions to its advantage and to assure intracellular survival and replication. Nagai and Kubori (2011) recapitulate our present understanding of the T4SS apparatus and its components by taking advantage of genomic and structural information. Finally, using comparative genomics information of several bacteria and plasmids carrying similar systems a comparative analysis of T4SS components is presented. The following five reviews, research, and opinion articles discuss some of the secreted effectors of this T4SS and their diverse roles in pathogenesis of *L. pneumophila*. Hilbi et al. (2011) present evidence that *L. pneumophila* subverts phosphoinositide (PI) lipids by anchoring specific effectors through distinct PIs to the cytosolic face of the *Legionella* containing vacuole (LCV) to promote the interaction with host vesicles and organelles, catalyze guanine nucleotide exchange of small GTPases, or bind to PI-metabolizing enzymes. Interestingly, *L. pneumophila* secretes also three glycosyltransferases through its T4SS. Belyi et al. (2011) report on this novel family of effector proteins that are structurally similar to clostridial glycosylating toxins. However, in *L. pneumophila* they do not produce toxic effects but modify the eukaryotic elongation factor EF1A to inhibit protein synthesis and subsequently to induce cell death. Another exciting strategy employed by *L. pneumophila* by secreting proteins encoding a eukaryotic F-box domain is the exploitation of the host's polyubiquitination and farnesylation machineries. In an original research article Al-Quadani and Kwaik (2011) discuss in detail how one of the *L. pneumophila* encoded F-box proteins uses these conserved eukaryotic signaling pathways to proliferate in *Dictyostelium discoideum*, a model ameba used as infection

model. Excitingly, this same effector also has another eukaryotic motif, which is used by the host's prenylation machinery for anchoring it in the outer leaflet of the LCV (Ivanov et al., 2010; Price et al., 2010). In another primary research article Price et al. (2010) show, that *L. pneumophila* contain several other proteins with this motif, that are also used by the host prenylation machinery to anchor proteins into cellular membranes contributing in this way to the evasion of lysosomal fusion by the LCV.

A further strategy of *L. pneumophila* to establish an environment beneficial to replication is to specifically targets and exploit the host phosphorylation system through T4SS effectors that act directly on phosphorylation cascades. Haenssler and Isberg (2011) present a comprehensive and exciting review on the different host kinases and phosphatases that are targeted during *L. pneumophila* infection and show how *L. pneumophila* modulates host cell signal transduction by phosphorylation at multiple levels. The part discussing the different strategies of *L. pneumophila* to modulate host functions through T4SS effectors of *L. pneumophila* finishes with an opinion article by Luo (2011b) that discusses a recent, stimulating finding. *L. pneumophila* has evolved an effector protein, which specifically target another bacterial effector protein for degradation to shutdown its action within the host cells at later stages of infection. This demonstrates a sophisticated level of coevolution between eukaryotic cells and *L. pneumophila* involving an effector that functions as a key regulator to temporally coordinate the function of a cognate effector protein and opens now the way for additional research into possible interaction of bacterial effectors among them and not only with host proteins.

To timely secret this large repertoire of different effectors and to adapt the metabolism and the physiology of *L. pneumophila* to the changing host environment, a tight regulation of the expression of the different genes coding these proteins is necessary. Thus *L. pneumophila* has evolved a complex regulatory system and many different regulatory elements governing its life cycle. One of the master regulators is CsrA that is regulated by binding to two small regulatory RNAs (Rasis and Segal, 2009; Sahr et al., 2009). Faucher and Shuman (2011)

give an overview of what is known about small regulatory RNAs in *L. pneumophila* and present in a second article the first transcriptome analysis of *L. pneumophila* infecting human macrophages (Faucher et al., 2011). A model of the regulatory networks involving small RNA mediated control of virulence gene regulation in *L. pneumophila* is presented.

In the following part of this Research Topic Joshi and Swanson stress important aspects of *Legionella*–host interactions, by providing a critical view on the *Legionella* response to autophagy, a host defense against invading microbes (Joshi and Swanson, 2011). They propose that *L. pneumophila* is able to halt the autophagosome maturation by secreting different effector proteins. Once *L. pneumophila* adapted to an acidic environment another effector, LepB releases this blockage and the now acid resistant *L. pneumophila* are able to continue replicating in these autophagolysosomes. In the following article, Luo discusses recent progress in understanding the mechanisms *L. pneumophila* employs to interfere with apoptosis and how this modulation also contributes to the intracellular life cycle of this bacterium (Luo, 2011a).

Finally, infection by a pathogen and its outcome is always an interplay between the pathogen and the host. Thus, the host response to infection with *L. pneumophila* is a very important research question. This topic is the focus of a review by Massis and Zamboni (2011) that summarizes the current knowledge of the innate immune response to *L. pneumophila* infection. The implication of the different families of pattern recognition receptors (PRR) like TLRs, NLRs, and RLRs are discussed and a comprehensive analyses of the events triggered by the recognition of intracellular *L. pneumophila* by these PRRs is presented. Schuelein et al. (2011) close this research topic by providing a thoughtful opinion article about the immune control of *Legionella* infection. The authors stress that macrophages play a pivotal role in initiating the host response to *L. pneumophila* infection, however, given the fact that the resolution of *L. pneumophila* infection needs multiple cell types and abundant cross talk between immune cells they propose that the role of other cell types such as dendritic cells and the mechanism of action of protective cytokines should be examined in the future.

The field of microbiology and the study of host pathogen interactions is moving fast ahead and, in conjunction with the avalanche of data provided by the application of new, powerful “omics” methods, the tremendous advances in imaging techniques allowing *in vivo*, and single cell analyses and improvements in analytical methods, will lead to many exciting new discoveries in the future.

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