Legionella: from protozoa to humans
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To cite this version:

HAL Id: pasteur-01422821
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Submitted on 27 Dec 2016

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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 cellular 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; Mccade 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 (T4SS) called Dot/Icm. It 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 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 clodistial glycylating 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-Quadan 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 contains 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 function 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 targets another bacterial effector protein for degradation during infection and show 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) likeTLRs, 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 tre- mendous 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.

REFERENCES

Frontiers in Microbiology | Cellular and Infection Microbiology
This article was submitted to Frontiers in Cellular and Infection Microbiology, a specialty of Frontiers in Microbiology.

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