Legionella pneumophila -induced cell death: Two hosts, two responses
Ascel Samba-Louaka

To cite this version:
Ascel Samba-Louaka. Legionella pneumophila -induced cell death: Two hosts, two responses. Virulence, Landes Bioscience, 2018, 9 (1), pp.17-19. 10.1080/21505594.2017.1384527. hal-01724146
Legionella pneumophila-induced cell death: Two hosts, two responses

Ascel Samba-Louaka

To cite this article: Ascel Samba-Louaka (2018) Legionella pneumophila-induced cell death: Two hosts, two responses, Virulence, 9:1, 17-19, DOI: 10.1080/21505594.2017.1384527

To link to this article: https://doi.org/10.1080/21505594.2017.1384527
**Legionella pneumophila**-induced cell death: Two hosts, two responses

Ascel Samba-Louaka

Laboratoire Ecologie et Biologie des Interactions, Microbiologie de l’Eau, Université de Poitiers, UMR CNRS 7267, Poitiers, France

**ARTICLE HISTORY** Received 20 September 2017; Accepted 20 September 2017

**KEYWORDS** Acanthamoeba castellanii; apoptosis; Legionella pneumophila; macrophages; pyroptosis

**Legionella pneumophila** is a Gram-negative bacterium responsible of Legionnaire’s disease, a severe form of pneumonia. *L. pneumophila* resides within natural and man-made aquatic systems. It shares these habitats with protozoa such as free-living amoebae that feed on bacteria. After uptake by amoeba, *L. pneumophila* is able to resist intracellular digestion and to multiply within this environmental host. Amoebae are considered as training ground for pathogenic bacteria such as *L. pneumophila*. Importantly, entry and intracellular replication of *L. pneumophila* within amoebae and mammalian macrophages display several similarities. Once engulfed, *L. pneumophila* avoids fusion of the phagosome with lysosomes and creates a favorable environment for replication, the replicative vacuole, which is surrounded by the endoplasmic reticulum and mitochondria. The ability of *L. pneumophila* to manipulate host cell functions is conferred by hundreds of effectors that are secreted or injected into the cytosol and the vacuole through type II (T2SS) and type IV (T4SS) secretion systems. Intracellular growth of *L. pneumophila* increases its resistance to antimicrobials facilitating dispersion of the bacterium.

Although a number of mechanisms to infect amoebae and macrophages present common features and a shared evolutionary origin, some specificities were reported. For example, certain genetic loci allow *L. pneumophila* to infect macrophages, but not *Acanthamoeba*. In contrast, *L. pneumophila* mutants that are defective in inhibiting host translation have lowered growth in the amoeba *Dictyostelium* but show no replication defect in macrophages. Highlighting specific interactions between *L. pneumophila* and its different hosts is essential to understand the adaptation of *Legionella* to its multiple and evolutionarily distant hosts.

Another important issue is bacteria-induced cell death, which is relatively straightforward to observe, but difficult to characterize in detail. Difficulties come from the number of cell death pathways described to date. Bacteria could indeed induce cell death by activating apoptosis, pyroptosis, oncosis, necroptosis, NETosis, paraptosis or autophagic cell death. In amoebae, the absence of certain families of proteins such as caspases, renders the classification of the bacterial-induced host cell death arduous. In addition, bacteria can possess an arsenal of different effectors that either activate or repress the host cell death.

In this issue of Virulence, Mou and Leung address the expression of *L. pneumophila* genes that are involved in human monocyte and *Acanthamoeba* cell death. They also investigate the correlation of specific *L. pneumophila* gene expression patterns with the type of host cell death induced by the bacterium. The authors selected four set of genes, two which are involved in pyroptosis (*flaA* and *sdhA*) and two involved in apoptosis (*vipD* and *sidF*) of macrophages. The genes *flaA* and *vipD* encode respectively *L. pneumophila* flagellin and a phospholipase, and have been described to trigger host cell death. In contrast, *sdhA* and *sidF* are T4SS-translocated effectors that inhibit cell death.

Mou and Leung point out differences in infection mechanisms depending on the host infected. Regarding genes related to pyroptosis, the authors observed a decrease of *flaA* expression and an increase of *sdhA* during infection of THP1 monocytes. Interestingly, the opposite result was obtained with the amoeba *Acanthamoeba* during infection of both THP1 cells and *A. castellanii*. Infection of
THP1 cells induced a decrease in mRNA levels of both vipD and sidF. In contrast, *A. castellanii* infection induced a very weak regulation of sidF and an earlier down-regulation of vipD, followed by a later up-regulation. Although the two genes involved in pyroptosis were differently expressed in *L. pneumophila* infecting THP1 and *A. castellanii* cells, they could promote a same phenomenon: repression of pyroptosis in monocytes or induction of cell death in amoebae. The biological relevance regarding the expression of apoptosis-related genes was less obvious, underlying the need to increase the panel of genes to study.

On the host side, the authors observed differences in uptake and replication of *L. pneumophila*. They found a higher replication of *L. pneumophila* in *A. castellanii* compared to THP1 cells. Moreover, the infection of monocytes with *L. pneumophila* was associated with a reduction of caspase-1 expression compared to uninfected cells. However, relationship between caspases expression and host cell death is not clear and need to be investigated. Overall, this study cumulated evidence suggesting that *L. pneumophila* could inhibit pyroptosis of THP1 cells.

The authors faced several limitations when they compared *L. pneumophila* infection of the two different hosts. For example, there is no evidence of the presence of caspases in amoebae, although caspase activities have been reported. Instead, caspase-like proteins (metacaspase or paracaspase) have been discovered. Despite similarities between caspases and caspase-like proteins, there are a few significant differences, such as the target cleavage site sequence. Another issue is that, in addition to the programmed cell death, metacaspases contribute to several cellular functions. Thus, the metacaspase-1 is involved in encystation of *A. castellanii*. Mou and Leung found that, over the incubation time, *L. pneumophila* induced an increasing metacaspase-1 expression, which was associated with the formation of cysts. This result has to be confronted with other studies showing that *A. castellanii* infected with *L. pneumophila* do not exhibit a cell wall containing cellulose as observed in mature cyst and present a low expression of metacaspase-1 at 48h post-infection.

In summary, Mou and Leung demonstrated that expression of *L. pneumophila* genes involved in host cell death is diametrically opposite depending on the infected host. This study contributes to a better understanding of *L. pneumophila* adaptation to its very large spectrum of hosts. The expression pattern of pyroptosis-related genes in the environmental amoebal host could suggest the need of host cell death to ensure dissemination of *L. pneumophila*. In contrast, the control of monocyte cell death could be essential to maintain infection, as Humans are accidental dead-end hosts.

**Disclosure of potential conflicts of interest**

No potential conflicts of interest were disclosed.

**References**

1. Escoll P, Rolando M, Gomez-Valero L, Buchrieser C. From Amoeba to Macrophages: Exploring the Molecular Mechanisms of Legionella pneumophila Infection in Both Hosts. Cur. Top. Microbiol. Immunol. 2013;376:1–34. PMID:23949285

2. Isberg RR, O’Connor TJ, Heidtman M. The Legionella pneumophila replication vacuole: making a cozy niche inside host cells. Nat Rev Microbiol. 2009;7:13–24. doi:10.1038/nrmicro1967. PMID:19011659

3. Hubber A, Roy CR. Modulation of host cell function by Legionella pneumophila type IV effectors. Annu Rev Cell Dev Biol. 2010;26:261–83. doi:10.1146/annurev-cellbio-100109-104034. PMID:20929312

4. Truchan HK, Christman HD, White RC, Rutledge NS, Cianciotto NP. Type II Secretion Substrates of Legionella pneumophila Translocate Out of the Pathogen-Occupied Vacuole via a Semipermeable Membrane. MBio. 2017;8. e00870–17. https://doi.org/10.1128/mBio.00870-17.

5. Barker J, Scaife H, Brown MR. Intraphagocytic growth induces an antibiotic-resistant phenotype of Legionella pneumophila. Antimicrob Agents Chemother. 1995;39:2684–8. doi:10.1128/AAC.39.12.2684. PMID:8593002

6. Gao LY, Harb OS, Kwaik YA. Identification of macrophage-specific infectivity loci (mil) of Legionella pneumophila that are not required for infectivity of protozoa. Infect and Immun. 1998;66:883–92. PMID:9488371

7. Fontana MF, Banga S, Barry KC, Shen X, Tan Y, Luo ZQ, Vance RE. Secreted bacterial effectors that inhibit host protein synthesis are critical for induction of the innate immune response to virulent Legionella pneumophila. PLoS Pathogen. 2011;7:e1001289. doi:10.1371/journal.ppat.1001289. PMID:21390206

8. Jorgensen I, Rayamajhi M, Miao EA. Programmed cell death as a defence against infection. Nat Rev Immunol. 2017;17:151–64. doi:10.1038/nri.2016.147. PMID:28138137

9. Labbe K, Saleh M. Cell death in the host response to infection. Cell Death Differ. 2008;15:1339–49. doi:10.1038/cdd.2008.91. PMID:18566602

10. Mossine VV, Waters JK, Chance DL, Mawhinney TP. Transient Proteotoxicity of Bacterial Virulence Factor Pyocyanin in Renal Tubular Epithelial Cells Induces ER-Related Vacuolation and Can Be Efficiently Modulated by Iron Chelators. Toxico Sci: An of & Applied Toxicology. 2008;100:109–104034. PMID:20929312

11. Mou Q, Leung PHM. Differential expression of virulence genes in Legionella pneumophila growing in Acanthamoeba and human monocytes. Virulence. 2017;8:512–24. doi:10.1080/21505594.2017.1373925

12. Silveira TN, Zamboni DS. Pore formation triggered by Legionella spp. is an NlrC4 inflammassome-dependent host cell response that precedes pyroptosis. Infect and Immun. 2010;78:1403–13.

13. Zhu W, Hammad LA, Hsu F, Mao Y, Luo ZQ. Induction of caspase 3 activation by multiple Legionella pneumophila Dot/Icm substrates. Cellul Microbiol. 2013;15:1783–95. PMID:23773455
14. Banga S, Gao P, Shen X, Fiscus V, Zong WX, Chen L, Luo ZQ. Legionella pneumophila inhibits macrophage apoptosis by targeting pro-death members of the Bcl2 protein family. Proc Natl Acad Sci U S A. 2007;104:5121–6. doi:10.1073/pnas.0611030104. PMID:17360363

15. Ge J, Gong YN, Xu Y, Shao F. Preventing bacterial DNA release and absent in melanoma 2 inflammasome activation by a Legionella effector functioning in membrane trafficking. Proc Natl Acad Sci U S A. 2012;109:6193–8. doi:10.1073/pnas.1117490109. PMID:22474394

16. Wu D, Qiao K, Feng M, Fu Y, Cai J, Deng Y, Tachibana H, Cheng X. Apoptosis of Acanthamoeba castellanii Trophozoites Induced by Oleic Acid. J Eukaryot Microbiol. 2017. doi:10.1111/jeu.12454. [Epub ahead of print]

17. Saheb E, Trzyna W, Bush J. Caspase-like proteins: Acanthamoeba castellanii metacaspase and Dictyostelium discoideum paracaspase, what are their functions? J Biosci. 2014;39:909–16. doi:10.1007/s12038-014-9486-0. PMID:25431419

18. Trzyna WC, Legras XD, Cordingley JS. A type-1 metacaspase from Acanthamoeba castellanii. Microbiol Res. 2008;163:414–23. doi:10.1016/j.micres.2006.06.017. PMID:16891103

19. Mengue L, Regnacq M, Aucher W, Portier E, Hechard Y, Samba-Louaka A. Legionella pneumophila prevents proliferation of its natural host Acanthamoeba castellanii. Sci Rep. 2016;6:36448. doi:10.1038/srep36448. PMID:27805070

20. Ohno A, Kato N, Sakamoto R, Kimura S, Yamaguchi K. Temperature-dependent parasitic relationship between Legionella pneumophila and a free-living amoeba (Acanthamoeba castellanii). Appl Environ Microbiol. 2008;74:4585–8. doi:10.1128/AEM.00083-08. PMID:18502936