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HAL Id: hal-01724146
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Submitted on 6 Mar 2018

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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

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Accepted author version posted online: 26 Sep 2017.
Published online: 10 Nov 2017.

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Legionella pneumonia-induced cell death: Two hosts, two responses

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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, parapoptosis 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 sidf) and two involved in apoptosis (vipD and sidf) of macrophages. The genes flA 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 castellanii. Expression of flaA increased, while sdhA expression decreased. Expression of apoptosis-related genes vipD and sidf also differed during infections 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 caspasess 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 caspasess in amoebae, although caspase activities have been reported. Instead, caspase-like proteins (metacaspase or paracaspase) have been discovered. Despite similarities between caspasess 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


