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Manipulating cell motility by *Legionella*: Speeding up or slowing down?

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Legionella pneumophila is a Gram-negative intracellular parasite whose host in nature is some aquatic unicellular protists. When humans come into contact with infected water, opportunistic infections can occur, resulting in a severe type of pneumonia called Legionella pneumonia.[1,2] After entering the host cells, *L. pneumophila* transports about 330 effector proteins through the type IV secretion system (T4SS), targeting important intracellular life processes to evade the host immune response, which is essential for bacterial survival and proliferation in cells.[3,4] However, the functions of most of the effectors are unknown. It is expected to provide new therapeutic targets for the treatment of infectious diseases if the biological activities of these effectors are discovered.

As an important cell component, the cytoskeleton plays a key role in *L. pneumophila* infection and replication.[5] A previous study reported that the *Legionella* effector LegG1 promotes microtubule polymerization by acting as a guanine nucleotide exchange factor (GEF) for the Ran GTPase, thereby enhancing the migratory capacity of host cells.[6,7] It seems that *L. pneumophila* may speed up the host cell to facilitate its intracellular replication. Paradoxically, *L. pneumophila* inhibits the motility of infected cells dependent on the Dot/Icm system, suggesting the existence of other effector proteins that can regulate cell motility.[7] However, the mechanism remains unclear. Recently, Song *et al.*[8] reported that the *Legionella* effector protein Lem8 (Lpg1290) is a cysteine protease containing a Cys-His-Asp domain. Further research found that Lem8 showed protease activity only when it is bound to the host protein 14-3-3ζ, and self-cleaved at the carbon end to form a smaller molecular weight cleavage body. Similar to the full-length protein, the cleavage product activates its protease activity after binding to 14-3-3ζ, cleaves and degrades the host cell protein Phldb2 involved in cell motility, thereby inhibiting the migration of the host cell (Figure 1). They also revealed that Lem8 binds to 14-3-3ζ in a non-phosphorylated form through its own coiled coil domain. Migration to sites of disease (*e.g.*, infection and inflammation) is an important mechanism by which immune cells perform functions, and their results suggest that *L. pneumophila* may slow down the ability of macrophages in clearing pathogens or other damaged cells.

The results of this study revealed the interaction and functional correlation between effector proteins and host chaperone proteins (Lem8 and 14-3-3ζ), suggesting that bacteria use this mechanism to construct fine-tuned regulatory network to facilitate its successful infection. In addition, the researchers also reported a novel 14-3-3ζ-binding non-phosphorylated protein (Lem8), and revealed for the first time the mechanism by which the non-phosphorylated protein binds to the 14-3-3ζ protein family. In summary, this work has important implications for the study of bacterial gene evolution and co-evolution with host genes.

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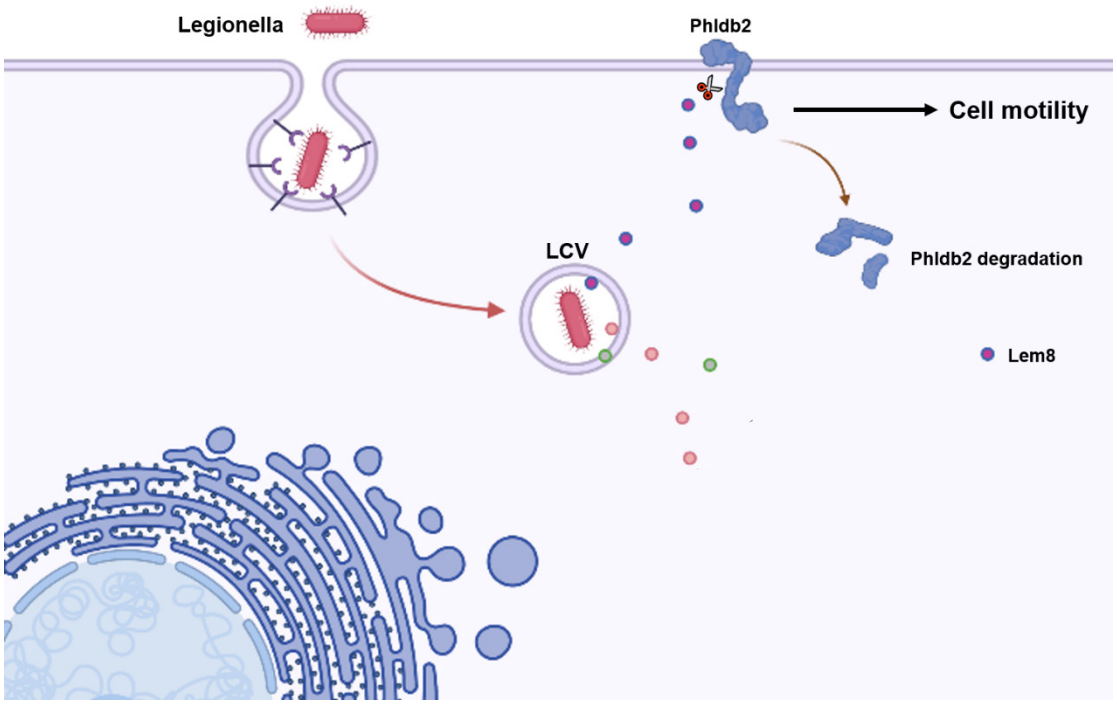

Figure 1: Mechanism underlying the inhibition of host cell motility by *Legionella*. LCV: legionella containing vacuole.

Conflict of Interest

The authors declare no conflicts of interest.

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