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## *Legionella pneumophila* pathogenesis: Mechanisms of iron aquisition, pilus production, and toxin secretion

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Our laboratory studies the molecular pathogenesis of *Legionella pneumophila*, the bcterial agent of Legionnaires' disease. Strains of this bacterium are widespread within aquatic environments and can infect humans following the inhalation of aerosols generated by air-conditioners, showers, and other devices. In the lower respiratory tract, *L. pneumophila* invades and proliferates within alveolar macrophages and can, if unchecked, result in fatal pneumonia. The more serious forms of legionellosis are restricted to immunocompromised individuals, including transplant patients, smokers, and alcoholics. The *Legionella* organism is a significant cause of community-acquired and hospital-acquired pneumonia, accounting for 1-30% of cases. In a broad sense, legionellosis is the consequence of a bacterium's capacity to flourish in both man-made water systems and the human lung. On the one hand, the aquatic distribution of *L. pneumophila* is a result of the bacterium's ability to replicate extracellularly in biofilms as well as intracellularly within amoebae. On the other hand, both the infection of alveolar macrophages and the elaboration of toxins facilitate intrapulmonary spread of the legionellae. Incidentally, it is widely believed that the ability of *L. pneumophila* to parasitize macrophages is derived from its prior adaptation to intracellular growth within protozoans. Bacterial persistence in the aquatic and mammalian environments is a complex, multifactorial process. However, one bacterial trait that is uniformly critical to survival is the capacity to adhere to surfaces. Work in our laboratory has identified two adherence systems. The first involves hairlike-projections known as type IV pili or fimbriae, and the second a large, afimbrial outer membrane protein. Current research is focused on the regulation of pilus formation as well as its impact on attachment to macrophages, alveolar epithelia, and amoebae. A second, bacterial trait that is required for pathogenesis is the secretion of proteins that damage host tissue, subvert host defenses, or promote nutrient assimilation. We have discovered a secretion apparatus (known as type II secretion) that is critical for intracellular infection and virulence, and ongoing efforts are defining the regulation of this system, its secreted products, and its precise intracellular function. Recent studies indicate that the type II

system promotes the secretion of a protease, lipase, and phospholipase C. The latter two degradative enzymes may trigger bacterial release from the infected macrophages. A third pathogenic characteristic of *L. pneumophila* is the capacity to scavenge iron from its host. We have isolated mutants that are defective for both iron uptake and macrophage infection, and current analysis of these strains is uncovering effectors of intracellular iron acquisition, which may include an exclusively intracellular siderophore (i.e., an excreted, non-proteinaeous, iron chelator) as well as a novel transporter of iron-loaded peptides. In addition, we have identified the iron-responsive Fur protein as a transcriptional regulator of *Legionella* infectivity genes. The characterization of the Fur regulon represents an alternate approach to elucidating iron-scavenging activities. Biochemical characterization of *Legionella* supernatants has uncovered an additional siderophore that appears to be unusual in structure; i.e., it is not a typical hydroxymate or phenolate. Interestingly, this siderophore, which we have deemed legiobactin, is subject to a relatively complex form of regulation that may include quorum sensing, explaining, at least in part, why it was overlooked in earlier studies. A final bacterial trait that can contribute to the prevalence of an infectious disease is antibiotic resistance. We have discovered several antibiotic resistance genes in *L. pneumophila*, including one that encodes a new type of spectinomycin-inactivating enzyme. In addition to bacterial attributes, host factors play a major role in determining the outcome of an infection. As one approach to understanding host susceptibility, our laboratory is determining how alcohol consumption facilitates infection by *L. pneumophila* and other intracellular parasites such as *Listeria monocytogenes*. In sum, our lab uses a multifaceted approach to understand the pathogenesis and natural history of Legionnaires' disease, with the hope that basic insights can lead to new methods of disease prevention, diagnosis, or treatment.


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