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Special topic on *Francisella tularensis* and tularemia

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Francisella tularensis was first identified exactly a century ago in California as part of a plague surveillance program and the resulting disease, tularemia, is still referred to as "rabbit plague" in many languages. In nature, rodents and rabbits appear to be the species most frequently affected by tularemia but *F. tularensis* is a highly versatile pathogen and the disease has been identified in some 190 mammalian species. Moreover, the disease is commonly vector-borne and the bacterium has the capability to survive within arthropods and, in fact, one of its natural reservoirs appears to be protozoa. Thus, it is an extremely adaptive pathogen with an astounding wide range of potential vectors and target species. There has been a resurgent research interest in the pathogen during the last decade. This has resulted in numerous intriguing discoveries and this special topic summarizes our current knowledge about the bacterium and tularemia. Reviews written by experts in various aspects of tularemia research have provided comprehensive up-to-date summaries of the rapid progress recently achieved as well as providing perspectives on important conceptual questions that need to be addressed in the next years.

One timely review by Lederballe-Meibom and Charbit (2011) summarizes the relationship between *F. tularensis* virulence and metabolic and nutritional genes. They emphasize that there is close association between nutritional starvation and virulence gene expression via the stringent response and therefore conclude that expression of its virulence is intimately dependent on its ability to capture nutrients from the host and to regulate its metabolism in response to the nutrients available.

Chong and Celli (2011) recapitulate our present understanding of the complex intracellular lifecycle of *F. tularensis* in a variety of mammalian cell types. The authors discuss the data regarding the intracellular survival strategy of the pathogen and outline the consensus view of the intracellular lifecycle. Moreover, they also attempt to settle discrepancies that exist in our views of the *Francisella*–phagocyte interaction. Intimately related to many or most stages of the bacterium's intracellular life cycle is the *Francisella* pathogenicity island (FPI), which contains almost 20 genes. Many of these appear be essential for the intricate intracellular lifecycle and although our current understanding of the genes' functions are far from complete, this is one of the most active areas of *Francisella* research and the basis for a review by Bröms et al. (2010). The review emphasizes the fact that the suggested role of the FPI as a type VI secretion system (T6SS) is still far from clear since it is evolutionary distinct and shares few if any functions compared to all other described secretion systems. It is concluded that the FPI constitutes a system essential for the intracellular lifecycle and the virulence of the bacterium and that it shares some similarities to components of T6SS and T4SS.

The review by Dai et al. (2011) that summarizes the current knowledge of environmental adaptation by the *F. tularensis*, its transcriptional regulators and their relationship to animal virulence. On one hand, the authors point out that there are surprisingly few sensory and regulatory factors described for the pathogen, particularly in view of its proven ability to survive in a multitude of environmental niches. However, it is also noted that there has been rapid progress in elucidating the gene regulation and identifying novel regulatory factors. One reason for recent, rapid progress in understanding the genetics of *F. tularensis* has been the development of suitable tools for genetic manipulation of the organism. Recently developed genetic techniques, such as transposon mutagenesis and targeted gene disruption, described in the review by Zogaj and Klose (2011) have significantly improved our understanding of *F. tularensis* virulence.

Host responses during the intracellular lifecycle of *F. tularensis* are the focus of three reviews by Jones et al., Cremer et al., and Asare and Kwaik, *F. tularensis*, in particular *F. novicida*, has become one of the most studied model organisms for elucidating the function of the inflammasome and the review by Jones et al. (2011) describes mechanisms of its activation by the bacterium and the consequences *in vitro* and *in vivo*. Moreover, it also discusses the coordination between the inflammasome and other cytosolic host responses and how these are affected by *Francisella* virulence factors. The review by Cremer et al. (2011) addresses how signaling pathways of phagocytic cells are targeted by *Francisella*, with a focus on the phosphatidylinositol 3-kinase/Akt pathway but also the role of microRNAs, specifically miR-155, as a key regulator of host signaling and defense. The third review by Asare and Kwaik (2011) describes the mechanisms used for uptake and internalization of the pathogen and the various host signaling pathways that are engaged during infection. A review by Bosio (2011) describes the subversion of specific immune mechanisms, both innate and adaptive ones, by *F. tularensis*. It describes recent advances based on findings in the mouse model and *in vitro* studies with human cells that have identified specific bacterial and host compounds that mediate generalized suppression of the host immune response.

One of the most studied *F. tularensis* virulence factors has been the type IV pilus system (Tfp) described in the review by Salomonsson et al. (2011). The Tfp and assembly of PilA have been shown to be required for full virulence of strains, however, there is much genetic variation in the encoding genes and therefore the authors hypothesize that the variations reflect adaptation to different environmental niches of the subspecies and play a role in transmission of tularemia. Another virulence system, the *cap* system, is described in an original article by Su et al. (2011). They demonstrate that a *capBCA* mutant of Schu S4 demonstrated significant attenuation *in vivo* and even more so the corresponding mutant of *F. tularensis* LVS.

An original article by Soni et al. (2010) is based on a comprehensive analysis of the enigmatic, so called gray variant of *F. tularensis* LVS. It showed defective replication in human, rat, but not mouse macrophages and conferred no protection to a virulent strain in the mouse model. It displayed structural differences in both the

core and lipid A regions. The latter were identified as decreased galactosamine modifications and correlated to reduced transcription of the *flmF2* and *flmK* genes.

The review by Cowley and Elkins (2011) describes immune mechanisms operative to control tularemia, mainly in the widely used mouse model. Many controlling mechanisms are analogous to those operational against other intracellular pathogens, but there are also recently identified mediators such as IL-17A, Toll-like receptor 2, and the inflammasome. In addition, the authors elaborate on the important roles of CD4 and CD8 T cells for control of tularemia but also emphasize that the roles of new T cell subpopulations are beginning to be unraveled. They conclude that also B cells contribute in important ways to protection but this varies depending on the virulence of the *F. tularensis* strain. A number of studies of the targets of anti-*Francisella* antibodies have been published and the results are summarized in the review by Kilmury and Twine (2011). The authors state that the detailed information generated from the immunoproteomics studies have the potential to be exploited in the identification of new diagnostic or protective antigens and in the development of vaccines.

There has been much interest to develop alternative models for *F. tularensis* and one organism that has attracted special attention is *Drosophila melanogaster* as a model for arthropod vectors. The review by Akimana and Kwaik (2011) concludes that it is a useful vector amenable for the identification of *F. tularensis* virulence mechanisms, also for those operative in evolutionarily distant mammalian hosts. Another model for tularemia is described in the original article by Santic et al. (2011). They demonstrate that *F. novicida* survives and replicates within the ameba *Hartmannella vermiformis* but with a lifestyle that is distinct to the one within mammalian cells (Santic et al., 2011).

The review by Telford and Goethert (2011) summarizes the rather extensive but also to some extent conflicting knowledge regarding the ecology of *F. tularensis*. The authors argue that the epidemiological information regarding tularemia to some extent has been used incorrectly to postulate ecological models for the bacterium. They identify the need to develop quantitative models for the reproduction of *F. tularensis* and suggest that the models may be distinct for subspecies *holarctica* and *tularensis* since they exhibit fundamental differences in their ecology.

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