Francisella tularensis: Host–parasite interaction

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"The bubo is usually about the size of a pea and the gland structure is generally replaced by a firm caseous mass." This, the first description of tularemia, is from 1911 and appeared in the publication 'A Plague-like Disease of Rodents' [1]. The author was George McCoy, a surgeon and pathologist working in California. Though Umeå of today, the location of the First International Meeting on Tularemia, has little in common with California of that time. McCoy and all the participants of this meeting certainly have many things in common. Many of us are preoccupied with the disease McCoy so accurately described and its etiological agent, the intracellular bacterium Francisella tularensis, and we try to continue building on the foundation McCoy laid 84 years ago. The most recent parts of the continuously ongoing work on Francisella are yet to be presented at the meeting and therefore we will here look at the progress of the last 8 decades.

Not long after McCoy’s initial report, there was published evidence of the same agent as the cause of human disease. The causative agent was at this time known as Bacterium tularense, named after one of the counties in California where the disease appeared to be endemic among rodents. Tulare County. A similar disease was reported under different names from various regions of the United States during the next years. For example, Edward Francis published a report in 1919 on 'Deer-fly fever—a disease of man of hitherto unknown etiology'. The same author wrote a comprehensive review 1921, in which he suggested that the disease was transmitted to man from rodents by bites of blood-sucking insects [2]. Moreover, he proposed the disease to be named tularemia. In the commemoration of the pioneering work of Francis, the bacterium eventually received its present name. Francisella tularensis. After these pioneering publications, reports on tularemia were quickly accumulating: by 1929 more than 800 cases had been reported in the United States, and by 1945 more than 14 000. By this time, it was obvious that the bacterium and its related disease were not only confined to North America, since reports on a similar disease had been published by Ohara in Japan in the 1920’s and in Russia a few years later [3,4]. Indeed, it became clear that by far the greatest epidemics occurred in Russia and this was particularly obvious during and immediately after the Second World War when hundreds of thousands were affected [5]. Eventually, it became clear that F. tularensis occurs in many countries in the Northern hemisphere, and not in the Southern hemisphere.

The numerous reports on tularemia until the
1950’s laid the basis for several classifications of tularemia. The classifications depend upon the clinical picture, epidemiology, or source of infection. Based on the clinical picture, the following forms are widely recognized: ulceroglandular or glandular, oropharyngeal, and respiratory tularemia. With regard to epidemiology, the most significant classification was suggested by Olsufiev and others [6]. They proposed in 1959 that two distinct types of \( F. \) tularensis exist, which differ in virulence, geographic distribution, and animal reservoirs. The names, \( F. \) tularensis subspecies tularensis for the organism prevalent in North America and \( F. \) tularensis subspecies palaearctica for the European and Asian form, also found in North America, were proposed. The latter form, nowadays also denoted type B, is responsible for the great epizootics in beaver, vole rat, and muskrat in North America and the former Soviet Union. It has a moderate or low virulence and human fatalities are rare. It can be isolated from water in epizootic areas. In contrast, \( F. \) tularensis subspecies tularensis, also denoted type A, is highly virulent for most mammals. Its principal animal reservoir appears to be the cottontail rabbit (\( SylviLAGUS \) spp.). It causes epizootics in sheep and is frequently transmitted by ticks. This species causes an estimated 70% of the human cases in the United States [7].

During these early years of Francisella research, the relatively high incidence of tularemia in particularly in the United States and Russia led to an intensive research for an efficient vaccine. The hopes of a working vaccine were based on the observation that previous tularemia infection results in efficient protection against reinfection. This protection is, however, not absolute and as a matter of curiosity it can be noted that Francis contracted to the disease at least 3 times. In contrast to most other researchers, he exposed himself deliberately to \( F. \) tularensis by performing autopsies of animals without wearing gloves.

The intensive hunt for a vaccine led to the development in the USSR during the 1930’s of live, attenuated strains that appeared to confer efficient protection and as many as 60 million individuals were immunised with live tularemia vaccines until 1960. In 1956, one of the live vaccine strains of \( F. \) tularensis was brought to the US. This strain was denoted \( F. \) tularensis LVS (live vaccine strain) by the American researchers and it has been extensively used in the United States and elsewhere since then [8,9]. The incidence of laboratory-acquired infections with \( F. \) tularensis before and after the introduction of the live vaccine strain has been reviewed by Burke [10]. He showed that after the introduction the incidence of respiratory tularemia dramatically decreased, whereas the incidence of ulceroglandular tularemia remained unchanged. \( F. \) tularensis LVS has also found a wide-spread use in experimental models, as it remains virulent for mice and causes a disease similar to human tularemia.

During the last decades it has been recognized that the genus Francisella is more complex than originally believed. Besides the division of \( F. \) tularensis strains into type A and type B strains, additional species have been recognized. Francisella novicida was originally isolated in nature and has been reported to cause disease in animals but only rarely in man. Francisella philomiragia has rarely been isolated from humans and appears to be an opportunistic pathogen. The identification of additional species within the genus has largely been based on phenotypical characteristics. However, it has recently been recognized that the hitherto recognized classification does not fully agree with results on the genetical relationship within the genus [11].

The main focus of the research on \( F. \) tularensis has been on the presumed intracellular nature of the pathogen and the host-parasite interaction during tularemia. The bacterium was suggested to be an intracellular parasite already in the 1920’s. Francis demonstrated that it had the ability to proliferate inside cells. Much later, in the 1960’s, results suggested that the bacterium not only survived, but also multiplied intracellularly in mononuclear phagocytes, although the findings were not conclusive. Moreover, the critical finding was made that resistance to tularemia in mammals was conferred by living lymphoid cells, but not by antiserum [12]. The latter results are similar to those obtained on other intracellular organisms. Much more recently, the intracellular replication of \( F. \) tularensis LVS in mononuclear cells from various mammals has been observed by electron microscopy [13]. The histopathology of tularemia originated with McCoy and has ever since been the focus of numerous studies. Similar to other
in intracellular pathogens, *F. tularensis* causes granulomas. This was also established in studies on higher mammals, such as monkeys. In man, both type A and type B strains of *F. tularensis* cause granulomatous lesions similar to those seen in tuberculosis. Collectively, these results strongly suggest that *F. tularensis* is an intracellular pathogen.

This intracellular nature of *F. tularensis* has attracted an interest of the organism as a model of intracellular parasitism. Work in the 1970's on tularemia in the rat pointed to the macrophage as the cell type through which resistance is ultimately expressed. Recent work on the mouse has further strengthened this view. Generally, host defence against intracellular parasites is dependent on the ability of specific T cells to enhance the microbicidal capacity of macrophages. Accordingly, it has been demonstrated that murine peritoneal macrophages can kill ingested *F. tularensis* LVS, but only after exposure to gamma interferon (IFN-γ), a T-cell-derived lymphokine. Moreover, mice treated with a monoclonal antibody (mAb) directed against IFN-γ quickly succumbed to an otherwise sublethal inoculum of *F. tularensis* LVS [14]. Recent work suggests that neutrophils also play a critical role in resistance to murine tularemia [15]. Results of vaccination studies in man suggested that protection against virulent strains of *Francisella* was only slightly, or not at all, dependent on humoral immunity. In contrast, in the experimental model of murine tularemia, antibodies appear to substantially affect the infection, although they cannot fully substitute for cell-mediated protection.

Little is known about the intracellular survival of *Francisella*. Some rather recent pieces of work have provided some clues. It has been suggested that *F. tularensis* not only multiplies within macrophages, but also that the pathogen survives within phagosomal vesicles that are not fused with lysosomes [13]. A recent publication investigated the underlying mechanisms of the intracellular habit of *Francisella*. It was demonstrated that sequestration of iron was a very efficient means of restricting its intracellular replication [16].

The studies on the human immune response to *Francisella* have mainly focused on characteristics of the cell-mediated immune response to antigens of the bacterium. To this end, most information is based on assaying the lymphocyte reactivity of previously vaccinated or tularemia-infected individuals (reviewed in [17]). Similar to results on other intracellular pathogens, a variety of antigens appear to be efficiently T-cell-stimulatory, but the patterns of response vary widely from one individual to another. The capacity to respond to specific *Francisella* antigens seemed to reside in both CD4+ and CD8+ T cells [18].

Unlike most other human pathogens, no information exists that might elucidate the genetic basis of the virulence of *F. tularensis*. One major drawback is the lack of genetic systems that efficiently can be employed for manipulation of the pathogen. There are recent reports on plasmids that can be used in standard procedures for genetic manipulation [19,20]. However, they have not been utilised to delineate virulence determinants. It should be noted that there are recent reports on the related organism *F. novicida* with regard to the genetic basis of its intracellular survival.

More than eight decades of research on *F. tularensis* has resulted in tremendous insights into the extraordinary tale of an intracellular pathogen. Some information has been in agreement with that of other intracellular parasites, whereas other pieces have shown that *Francisella* also has many unique features. Thus, the work on *F. tularensis* not only adds to a common basis for future work on the bacterium, but it also adds to the general knowledge on intracellular bacteria in general. There are particularly a number of features that makes *F. tularensis* an attractive model organism for studies on intracellular parasitism. *F. tularensis* LVS is one of few examples of a vaccine against intracellular bacteria that affords good, although not complete protection. The understanding of the basics of the immune response against *F. tularensis* LVS may provide important clues to what constitutes effective protection against intracellular bacteria. Compared to many other intracellular parasites, it is relatively rapidly growing in vivo and in vitro. Thus, experiments on the growth of *Francisella* in different experimental systems are relatively easily performed. The model organism in murine tularemia, *F. tularensis* LVS, is relatively virulent in the system and thereby presumably a relevant experimental organism. The cell-mediated immune response to *F. tularensis* appears to be
highly immunospecific and thereby relevant to studies of the specificity of protective immunity.

References


