

Preface

Tuberculosis has been with mankind ever since the dawn of civilization, with evidence of human infection as early as 9,000 years ago. Although the causative agent, *Mycobacterium tuberculosis*, has been identified more than a century ago, tuberculosis remains one of the most prevalent diseases on the globe, with currently one third of the population being latently infected with *M. tuberculosis*. Despite concerted efforts from scientists with diverse backgrounds, including medical doctors, microbiologists, cell biologists and immunologists, global control of tuberculosis continues to be highly challenging. However, research over the past few years has highlighted several issues that may contribute to overcoming some of the difficulties of eradicating *M. tuberculosis*. In this volume, a number of experts discuss various topics related to the virulence of *M. tuberculosis*.

Mycobacterium tuberculosis is an obligate intracellular pathogen that has gained the capacity to survive within those cells of the immune system that are in fact designed to eradicate microbial pathogens, the macrophages. As a result, pathogenic mycobacteria are able to cope with a plethora of antimicrobial activities, against which these bacilli have evolved numerous mechanisms of resistance. In addition, one emerging problem is the appearance of strains of *M. tuberculosis* that show various degrees of drug resistance. This problem has become of increasing concern also because of the recent discovery of extremely drug-resistant (XDR) as well as totally drug resistant (TDR) strains of *M. tuberculosis*. The emergence of these highly problematic strains may be a result of the slow generation time of *Mycobacterium spp.*, their exposure to a battery of drugs for prolonged time periods, the sometimes poor compliance of patients with anti-tuberculosis therapy or most likely a combination of these factors. One realization however has been that there is a need for a better understanding of the genetic diversity in different strains of *M. tuberculosis*, as outlined by Gagneux (Chap. 1). Also, recent work suggests that *M. tuberculosis*, unlike many other bacterial pathogens, relies heavily on chromosomal mutagenesis to drive its evolution within the human host. The intricate balance between maintenance of chromosome integrity and evolutionary progress is discussed in detail by Warner and colleagues in Chap. 2.

The emerging problem of multi-drug resistance requires a far better understanding of the mechanisms involved in drug resistance, and Smith and colleagues (Chap. 3) review the current understanding of the molecular basis of the

development of resistance mechanisms. Furthermore, despite the fact that *M. tuberculosis* is extensively exposed to diverse antimycobacterial drugs as well as host antimicrobials, the bacilli can survive exposure to many of these compounds through the upregulation of antimicrobial efflux pumps. In Chap. 4, Szumowski and colleagues propose that drug tolerance has mainly evolved as a result of the need of intracellularly residing mycobacteria to employ efflux pumps to protect against environmental toxins.

To successfully survive under challenging conditions, *M. tuberculosis* not only needs to be able to fight off attacks from toxic components through efflux pumps and other drug resistance mechanisms, but it also requires a diverse array of secretion systems in order to communicate with and modulate its environment, the macrophage. Van der Woude and colleagues (Chap. 5) review the different secretion systems that are employed by *M. tuberculosis*, which have recently attracted much interest as determining factors for intracellular survival.

Mycobacterium tuberculosis is notoriously able to survive in a so-called “dormant” or non-growing state within host macrophages. The capacity to survive without growth also creates challenges in terms of finding anti-mycobacterial drugs that are able to interfere with survival of non-proliferating bacteria rather than controlling growth per se. Manina and McKinney (Chap. 6) highlight the importance of analyzing bacteria that are non-growing but metabolically active, knowledge that might be important for designing better strategies to eliminate non-replicating mycobacteria. Metabolism becomes also important when considering the natural niche of *M. tuberculosis*, the macrophage phagosome. In Chap. 7, Ehrt and Rhee discuss the importance of the metabolic network of intracellularly residing *M. tuberculosis* for survival within its host.

Once within macrophage phagosomes, *M. tuberculosis* can rely on several distinct mechanisms to subvert the antimicrobial activities of the macrophages. Many of these mechanisms allow *M. tuberculosis* to prevent intraphagosomal destruction, and in Chap. 8 Jayachandran and colleagues discuss work that has deciphered several of these mechanisms. Besides intraphagosomal survival, *M. tuberculosis* can also extensively interact with other host components, and Stanley and Cox (Chap. 9) review recent work that has added several layers of complexity to the interaction of *M. tuberculosis* with its host.

Together, these Chapters provide a topical overview on the current understanding of diverse mechanisms that are involved in the virulence of *M. tuberculosis*, ranging from their genetic, metabolic and molecular makeup as well as the exquisite strategies these bacteria utilize to circumvent host innate immune responses. The work described in this volume may therefore provide a stimulus for further exploration of the intricate biology of *M. tuberculosis* and its interaction with their hosts.

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Pathogenesis of Mycobacterium tuberculosis and its
Interaction with the Host Organism

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2013, VIII, 245 p. 22 illus., 11 illus. in color., Hardcover

ISBN: 978-3-642-40231-9