INTRACELLULAR PATHOGENS I

Chlamydiales
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EDITED BY

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Cover image: 3D model of *Chlamydia*-infected cell. EM reconstruction of a HeLa cell infected with *C. trachomatis* serovar L2 (L2/434/Bu), based on 3View serial block face SEM with 390 sections (each 60 nm thick, for a total thickness of ~23 µm). A representative EM section is shown below the 3D model. The inclusion membrane is shown in green, the nucleus is light blue, and the plasma membrane of the infected cell is pink. Elementary bodies are blue, and reticulate bodies are yellow. Courtesy of Jennifer Lee, Christine Suetterlin, and Ming Tan (University of California, Irvine, CA) and Masako Terada, Eric Bushong, Andrea Thor, Mark Ellisman, and Daniela Boassa (National Center for Microscopy and Imaging Research, Center for Research in Biological Systems, University of California San Diego, La Jolla, CA).

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We dedicate this book to our families, who had to share us with the book in the summer of 2011.

To Ru-ching, Julien, and Lei-Lei

To Christine, Toby, and Lucas
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More cases of *Chlamydia* infection are reported to the CDC each year than all other infectious diseases combined. This dubious distinction is due to a steady increase in the number of chlamydial infections while other major infectious diseases have become less common because of successful diagnosis, treatment, and prevention. Reported chlamydial infections almost doubled over 10 years to 1.2 million cases for 2009, which is the latest year for which statistics are available (CDC, 2011). In contrast, rates of gonorrhea have declined about fourfold since the mid-1970s. As a result of these opposite trends, *Neisseria gonorrhoeae* is no longer the most common bacterial cause of sexually transmitted infection and has ceded that “honor” to *Chlamydia trachomatis* since the mid-1990s (CDC, 2010).

The burden of chlamydial infections is even higher because the CDC numbers are almost exclusively for genital infections caused by *Chlamydia trachomatis* and do not include other infections caused by *Chlamydia* spp. Tens of millions in underdeveloped parts of the world suffer from trachoma, which is an infectious form of blindness that is also caused by *C. trachomatis*. In addition, the majority of individuals will have a *Chlamydia pneumoniae* respiratory infection at some point in their lifetime even though it may not be formally diagnosed. *Chlamydia* spp. are also a significant cause of disease in animals, and new evidence suggests that human chlamydial isolates have been acquired in our evolutionary past from animal hosts. To set the stage for this book, Byron Batteiger discusses the range of chlamydial infections in chapter 1 (“*Chlamydia* infection and epidemiology”), with an emphasis on relating clinical knowledge to the fundamental biology of *Chlamydia*.

A fascinating aspect of chlamydial biology is how these organisms have evolved to become such successful intracellular parasites while having one of the smallest bacterial genomes. In chapter 2 (“Deep and wide: comparative genomics of *Chlamydia*”), Garry Myers offers a glimpse of the enormous impact genomic analysis has had and continues to have on our understanding
of chlamydial biology and evolution. At last count, 33 chlamydial genome sequences were publicly available. Most of the sequenced genomes have come from reference strains, but many more clinical isolates will be sequenced in the coming years. The high level of sequence coverage with modern whole-genome sequencing methods (“deep sequencing”) suggests that individual chlamydial isolates are not homogenous but rather consist of a “metapopulation” of genomic variants. Comparative genome sequencing of different chlamydial species and isolates (“wide sequencing”) has demonstrated strain-specific differences within the overall context of genus-wide conservation and has provided a powerful means to learn about chlamydial biology in the absence of an experimental genetic system.

In chapter 3 (“Lessons from environmental chlamydiae”), Alexander Siegl and Matthias Horn discuss Chlamydia-like organisms within the order Chlamydiales. This is an expanding group of intracellular bacteria, such as the Parachlamydiaceae, with several new families identified in just the last few years. As descendants of an ancestral bacterium that learned to survive and replicate in eukaryotic cells, Chlamydia and the environmental chlamydiae are cousins, and much can be learned by comparing the biology of these two groups. For example, the genomes of environmental chlamydiae are two to three times larger than those of Chlamydia; many metabolic pathways that are truncated in Chlamydia are more completely represented in the environmental chlamydiae, supporting the notion that Chlamydia spp. have undergone reductive evolution of their genomes.

The first step in the intracellular chlamydial infection is adherence of elementary bodies (EBs) to epithelial cells at specific mucosal surfaces in the body.
Binding between ligands on the chlamydial envelope and receptors on the surface of epithelial cells facilitates the internalization of chlamydiae. Chapter 4 (“The chlamydial cell envelope”) by David Nelson and chapter 5 (“Chlamydial adhesion and adhesins”) by Johannes Hegemann and Katja Moelleken give the most up-to-date reviews of the chlamydial envelope and describe how specific envelope components mediate these surface interactions between chlamydiae and susceptible cells. The proposed two-step binding process represents the culmination of 4 decades of painstaking research by many researchers. This model is elegant in its simplicity and has clarified what was once a confusing aspect of chlamydial pathogenesis.

Once inside a eukaryotic cell, Chlamydia grows and replicates within the safe confines of a membrane-bound vacuole called the chlamydial inclusion (Fig. 1). How chlamydiae initiate these events by manipulating the host cytoskeleton, establishing the inclusion, and converting from an EB into a reticulate body (RB) is comprehensively described by Ted Hackstadt in chapter 6 (“Initial interactions of chlamydiae with the host cell”). Further details about how chlamydiae interact with the host cell and subvert a range of cellular processes are discussed in chapter 8 (“Cell biology of the chlamydial inclusion”) by Raphael Valdivia and Marcela Kokes and in chapter 9 (“Protein secretion and Chlamydia pathogenesis”) by Ken Fields. These host-pathogen interactions provide the environment within the inclusion so that RBs can replicate and eventually convert into EBs that can infect a new host cell.

This serial conversion between two specialized forms is a unique feature of chlamydial biology, and two models have emerged to account for the progression of the chlamydial developmental cycle. In chapter 7 (“Temporal gene regulation during the chlamydial developmental cycle”), Ming Tan proposes a gene regulation model in which the sequential expression of chlamydial genes in developmental classes is controlled by the temporal expression of key regulators through a domino effect. For example, soon after an EB enters a cell, there is expression of early gene products including DNA gyrase, which is an enzyme that increases DNA supercoiling. Higher global supercoiling levels, which have been shown to peak in mid-cycle, are then proposed to upregulate mid genes through their supercoiling-responsive promoters. Among the mid gene products that are expressed is σ28, which subsequently directs the transcription of a subset of late genes to mediate RB-to-EB conversion. In chapter 16 (“Biomathematical modeling of Chlamydia infection and disease”), David Wilson describes the Type III secretion (T3S), contact-dependent model, which he has proposed together with Patrik Bavoil and colleagues. This model hypothesizes that contact between an RB and the inclusion membrane via T3S injectisomes is necessary for the RB stage and that loss of contact and associated disruption of T3S translocating activity induce RB-to-EB conversion. These two models are not mutually exclusive, however, and it is likely that gene regulation is coupled to external stimuli such as contact between an RB and the inclusion membrane and the activity state of the T3S apparatus.

As we learn more about how members of the Chlamydiaceae successfully infect and interact with eukaryotic cells, it is helpful and instructive to examine what aspects of this unusual biology are conserved features. Comparative genomic analysis makes clear that Chlamydia spp. are closely related and share a
core set of 668 conserved proteins, which amounts to about two-thirds of the genome (see chapter 2). However, a number of chlamydial proteins that are proposed to have important roles in the biology and pathogenesis of Chlamydia are not encoded in the genomes of environmental chlamydiae that have been sequenced (see chapter 3). For example, environmental chlamydiae do not have Tarp (translocated actin recruiting phosphoprotein), an actin-nucleating chlamydial protein that is proposed to promote EB entry into a host cell. Intriguingly, they also lack both the late temporal regulator σ28 and its target gene hctB, which encodes the histone-like protein Hc2 that plays a role in the condensation of DNA in EBs. Almost all environmental chlamydiae do not have MOMP, which is the major outer membrane protein and immunodominant antigen of Chlamydia, or IncA, which is involved in the homotypic fusion of chlamydial inclusions. Thus, these Chlamydia-specific factors are not strictly necessary for the intracellular lifestyle of Chlamydiales, and they may represent specializations that contribute to the ability of Chlamydia spp. to infect vertebrate host cells and cause disease.

The host immune response is important for protection against an infection, but chlamydial diseases exemplify the role that the immune system can play in pathogenesis. In chapter 10 (“Immune recognition and host cell response during Chlamydia infection”), Uma Nagarajan describes a number of mechanisms by which chlamydiae are recognized by the host immune system. In chapter 11 (“Chlamydia immunopathogenesis”), Toni Darville and Catherine O’Connell review how chlamydiae induce and modulate host immune responses and describe how these innate and adaptive responses to chlamydiae contribute to pathology. Distinguishing between protective and pathologic immune responses is of course critical in the ongoing efforts to develop a vaccine.

The natural history as well as the hallmark of untreated chlamydial infection is a chronic infection that can lead to tissue damage and sequelae such as tubal infertility. In chapter 12 (“Chlamydial persistence redux”), Gerry Byrne and Wandy Beatty take a fresh approach to the oft-described but incompletely understood phenomenon of persistent chlamydial infection by noting the similarities and differences between persistent infections caused by Chlamydia and those caused by other human pathogens. In chapter 13 (“In vivo chlamydial infection”), Roger Rank discusses how animal models of chlamydial infection have been used to study chlamydial persistence and pathogenesis. These animal studies have been invaluable for learning how Chlamydia causes disease in humans and have a continuing role to play in the development of a vaccine and new antichlamydial agents.

A safe, effective chlamydial vaccine has been elusive. In chapter 14 (“Chlamydia vaccine: progress and challenges”), Ashlesh Murthy, Bernard Arulanandam, and Guangming Zhong review the considerable progress that has been made both in the selection of candidate vaccine antigens and in our understanding of the types of immune response that a vaccine must elicit. It might be sufficient if a chlamydial vaccine prevents disease rather than infection as a strategy for reducing long-term complications such as infertility in women. It might even be possible to develop a therapeutic vaccine or some other immunomodulatory approach to prevent long-term complications after the initial infection.
We appear to be at the dawn of a new age in *Chlamydia* research with the first published report of stable transformation of chlamydiae. In chapter 15, “Chlamydial genetics: decades of effort, very recent successes,” Brendan Jeffrey, Tony Maurelli, and Dan Rockey describe the groundbreaking work by Yibing Wang, Simona Kahane, Ian Clarke, and colleagues, wherein EBs have been transformed with a hybrid shuttle vector constructed from the chlamydial plasmid and an *Escherichia coli* plasmid containing a penicillin resistance gene. The researchers successfully selected for penicillin-resistant *C. trachomatis* and demonstrated that they could produce green fluorescent inclusions from chlamydiae expressing green fluorescent protein. This much-awaited breakthrough was published just as this book was about to go to press and followed on the heels of three other methodologic advances in developing an experimental genetic system. In the first approach, isogenic strains have been generated by chemical mutagenesis followed by identification of strains with specific sequence mutations. In a second approach, recombinant progeny with a specific phenotype, such as tetracycline resistance, have been produced by coinfecting a host cell with two parental chlamydial strains. In the third approach, transformation of chlamydiae and allelic exchange have been accomplished by electroporating EBs with plasmid DNA. These experimental tools will have a transformative effect on *Chlamydia* research because it is hoped that they will soon allow researchers to test the function of individual chlamydial genes with genetic approaches.

The book concludes with chapter 16 (“Biomathematical modeling of *Chlamydia* infection and disease”) by David Wilson, Andrew Craig, and colleagues. This is the first review of biomathematical modeling in a *Chlamydia* book. Mathematical modeling tools have been used to study and predict the behavior of viral infections, and the chapter describes how this approach is being applied to chlamydial infections with good success. Refinements of these models that take into account more parameters of the chlamydial infection and the host response will surely follow in the coming years and hold the promise of providing new insights into chlamydial biology and pathogenesis.

Of the major changes and developments in *Chlamydia* research that are described in this book, one more to mention is the new taxonomy, which amounts to a “family reunion.” Within the *Chlamydia* field, the *Chlamydiaceae* are now considered to consist of only the single genus *Chlamydia*; the genus name *Chlamydophila* is no longer in use, although the species names, such as *muridarum*, *caviae*, and all other veterinary species that were introduced in 1999, have not changed (Kuo et al., 2010).

This book showcases a wide range of *Chlamydia* basic research that is being done by hundreds of individuals around the world. We have selected authors who are playing a leading role in scientific discovery and who can summarize and synthesize the latest in *Chlamydia* research. We also wish to acknowledge the many other chlamydiologists who have contributed to the book through their superb work—your continued efforts are critical, and each individual has an important part to play if we are to reduce the number of chlamydial infections and their impact on public health.

This book is intended for those who are interested in the latest in *Chlamydia* research, which includes scientists, physicians, medical students, public health professionals, epidemiologists, biocomputational scientists, and government
policy makers. Because of the interdisciplinary nature of modern science, this audience also includes scientists studying other causes of sexually transmitted disease and other obligate intracellular pathogens. The esteemed chlamydologist Dr. Gerry Byrne, in his introduction to the previous Chlamydia book published in 2006 (Bavoil and Wyrick, 2006), laid down a challenge to future editors: we have accepted the challenge and hope that we have faithfully represented the exciting developments in Chlamydia research.

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