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
## CONTENTS

*Contributors* ix  
*Preface* xiii  

1. *Chlamydia Infection and Epidemiology*  
   Byron E. Batteiger  
   1  

2. *Deep and Wide: Comparative Genomics of Chlamydia*  
   Garry S. A. Myers, Jonathan Crabtree, and Heather Huot Creasy  
   27  

3. *Lessons from Environmental Chlamydiae*  
   Alexander Siegl and Matthias Horn  
   51  

4. *The Chlamydial Cell Envelope*  
   David E. Nelson  
   74  

5. *Chlamydial Adhesion and Adhesins*  
   Johannes H. Hegemann and Katja Moelleken  
   97  

6. *Initial Interactions of Chlamydiae with the Host Cell*  
   Ted Hackstadt  
   126  

7. *Temporal Gene Regulation during the Chlamydial Developmental Cycle*  
   Ming Tan  
   149  

8. *Cell Biology of the Chlamydial Inclusion*  
   Marcela Kokes and Raphael H. Valdivia  
   170  

9. *Protein Secretion and Chlamydia Pathogenesis*  
   Kenneth A. Fields  
   192
10. Immune Recognition and Host Cell Response during *Chlamydia* Infection
   Uma M. Nagarajan 217

11. *Chlamydia* Immunopathogenesis
    Toni Darville and Catherine M. O’Connell 240

12. Chlamydial Persistence Redux
    Gerald I. Byrne and Wandy L. Beatty 265

13. In Vivo Chlamydial Infection
    Roger G. Rank 285

14. *Chlamydia* Vaccine: Progress and Challenges
    Ashlesh K. Murthy, Bernard P. Arulanandam, and Guangming Zhong 311

15. Chlamydial Genetics: Decades of Effort, Very Recent Successes
    Brendan M. Jeffrey, Anthony T. Maurelli, and Daniel D. Rockey 334

16. Biomathematical Modeling of *Chlamydia* Infection and Disease
    Andrew P. Craig, Patrik M. Bavoil, Roger G. Rank, and David P. Wilson 352

Index 381
CONTRIBUTORS

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M ore 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 chlamydiae 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 σ²⁸⁸, 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 model, 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 $\sigma^{28}$ 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 chlamydio-logist 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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MING TAN
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INDEX

A
“Aberrant bodies,” 58
Abi1 protein, 131
Acanthamoeba, 52–54, 57, 59
Acanthamoeba polyphaga, 61–62
Actin
in inclusion integrity, 183
nucleation, 127–131
Adaptive immune response, 249–252, 364–365
Adhesion and adhesins, 97–125
attachment components, 102–103
glycosaminoglycans, 101–102
list of, 97–100
model for, 118
polymorphic membrane proteins, 77–78, 99,
109–117
receptors for, 117–118
AHNAK cellular actin binding protein, 130–131, 203
Animal models, 286–310
developmental cycle, 289–296
host impact, 303–304
mathematical models for, 304–305
pathogenicity, 300–303
persistence, 297–300
types, 286–289
vaccines, 313, 320
Animal pathogens, see also specific pathogens
environmental chlamydiaceae, 63–64
genomics, 37–43
models for, see Animal models
persistence, 274, 278–279
Antibiotic(s), based on secretion systems, 209
Antibiotic resistance, 265
Chlamydia trachomatis, 14
in genetic transformation, 336–338
Antibodies, function, 313–314
Antigen(s), for vaccines, 316–324
Antigenic variation, polymorphic outer membrane
proteins, 115–117
Anti-sigma factors, in developmental cycle, 156–157
Apolipoproteins, 118
Apoptosis, prevention, 183–184
Arp proteins, 131
ASC protein, in immune recognition, 223, 225
Asthma, 20–21
Atherosclerosis, 19–20
Autonomous immunity, 184
Autophagy, 184
Azithromycin
for genital infections, 14
for trachoma, 8

B
B cells, immune function, 252, 313–314
BAD protein, 183
Basic reproduction number, in biomathematical
modeling, 365–366
Betaproteobacteria, 55
Biomathematical modeling, 352–379
adaptive immune response variations, 364–365
for animal models, 304–305
basic reproduction number in, 365–366
competing strains, 366–369
epidemiological, 353, 355
future, 376–377
infectivity variations, 361–363
innate immune response variations, 363–364
microbiology and, 377–378

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Biomathematical modeling (continued)
overview, 353–355
parameter choices, 359
predator-prey framework, 355–365
Type III secretion system-mediated, 369–376
viral dynamics equations in, 355–369

Blindness, in trachoma, 5–8, 272–273
Blue Score Ratio, 33

Cancer, cervical, 15
Candidatus family, 55–56, 64, 67
CARD (caspase recruitment domain, NLRC), 222–223, 225–226
Caspase, effectors for, 225–226
Caspase recruitment domain (CARD), 222–223, 225–226
Cds proteins, secretion systems, 197–201, 208
Cell envelope, 74–96
composition, 74–85
developmental cycle and, 84–88
Cellular adaptive response, 249–252
Cellular hypothesis, 317
Cellular paradigm, of pathogenesis, 242–246
Centrosomes, inclusion migration to, 174
Cervical cancer, 15
Chaperones, 200–201
Chemical mutagenesis, 342–344
Chemokines, 243–244
Chimera, 281
Chlamydia abortus
adhesins, 109
antigens, 322
cell envelope, 77
genetic modification, 342
genomics, 27–28, 32–36
host cell interactions with, 139
persistence, 273, 281
Chlamydia caviae
adhesins, 97–99, 102, 105, 117
in animal model, 286, 288, 290, 299, 303–305
antibodies, 315
cell envelope, 82
genomics, 27–28, 33, 34
host cell interactions with, 127, 131, 135, 139–140
immune recognition, 231
inclusions, 178–179, 181, 185
secretion systems, 202–203
Chlamydia felis
genomics, 27–28, 33–34, 41
host cell interactions with, 139
Chlamydia muridarum
in animal models, 286–288, 290, 292, 295, 297–304, 313
antigens, 321–324
cell envelope, 81
genetic modification, 344
genomics, 27–28, 33–36
host cell interactions with, 127–128, 131, 139–140
inclusions, 184
persistence, 279
secretion systems, 202–203, 205
Chlamydia muridarum infections
immune recognition, 218–222, 225, 227–228, 231
immunopathogenesis, 248, 249–252, 254
Chlamydia pecorum
cell envelope, 75, 80
genomics, 27–28, 32–36, 41, 43, 46
persistence, 274
Chlamydia pneumoniae, see also Chlamydia pneumoniae infections
in animal models, 286, 299
antigens, 321–324
cell envelope, 76–78, 80–82
developmental cycle, 151, 159
elementary bodies, 57
genomics, 28–30, 32–42, 45–46
host cell interactions with, 126–128, 130–131, 140, 142
inclusions, 175–176, 181
persistence, 2, 19, 274, 278–279, 281
secretion systems, 198, 202, 204–205, 207, 209
Chlamydia pneumoniae infections, 16–21
asthma and, 20–21
atherosclerosis and, 19–20
clinical features, 18
diagnostic tests, 17–18
epidemiology, 18–19
immune recognition, 218–219, 222, 225, 227, 230
Chlamydia psittaci
adhesins, 98–100, 103, 106, 118
in animal models, 286, 288, 301
cell envelope, 78, 80–81, 85
developmental cycle, 158
genetic modification, 345–347
genomics, 27–28, 32–46
host cell interactions with, 139
inclusions, 181
persistence, 268–269, 273, 276
secretion systems, 205, 207
Chlamydia suis
adhesins, 117
Chlamydia trachomatis, see also Chlamydia trachomatis infections

adhesins, 97–118
in animal models, 286–289, 297–304
antigens, 316, 320–325
cell envelope, 76–82, 85–87
clinical features, 10, 16
developmental cycle, 149–151, 155–157, 159, 162
diagnostic tests, 9–10
discovery, 56
elementary bodies, 58
genetic modification, 342, 344, 346–347
genomics, 27, 29–30, 32–36, 38, 41, 43–46, 196
historical view, 266
host cell interactions with, 126–131, 134–142
lateral gene transfer, 339
persistence, 2, 266–267, 269–270, 274, 278–279, 280
secretion systems, 193, 196, 198–199, 201, 203–206
serovars, 5, 16
tissue tropism, 16

Chlamydia trachomatis infections
antibiotic resistance, 14
asymptomatic, 3–4, 10–11, 242
biomathematical modeling, 353
conjunctivitis, 5–7, 240–264, 286–289
genital, 9–15
repeated, 3, 14
sexually transmitted, 9–15
trachoma, see Trachoma

Chlamydial outer membrane complex, 75–79, 84–85, 87–88, 102–103
Chlamydial protease/proteasome-like factor (CPAF) in cytosol, 323
in immune recognition, 226
in secretion systems, 192, 204
Chlamydiaceae, families in, 53–54
Chlamydia-like bacteria, see Environmental chlamydiae

Cholesterol
in host cell interaction, 136–138
in inclusions, 176–177
Chromatin decondensation, 160–161
ChxR, transcription factor, in developmental cycle, 154–155
Coding sequences, 31–32
COMC (chlamydial outer membrane complex), 75–79, 84–85, 87–88, 102–103

Conjunctivitis, 5–7
animal models for, 286–297
immunopathogenesis, 240–246
Contraceptives, animal studies using, 303–304
Cop proteins, in secretion, 200–202, 208
Crescent bodies, 58

Criblamydia sequanensis, 52, 56
Criblamydiaceae, 52
“Cryptic” Chlamydia psittaci, 268–269
CT Inc proteins, 174–175, 198, 200–203
CTIG270, developmental cycle, 162–163

Cyclophilin, 102–103

Cystic fibrosis transmembrane conductance receptor, 102, 117–118
Cytokines, in immune recognition, 217–239, 243–244
Cytosol, antigens in, 323–324
Cytosolic lipid transfer protein, 178
Cytotoxin, chlamydial, 34, 36, 42–43, 131

D
Developmental cycle
animal models for, 289–297
cell envelope, 84–88
environmental chlamydiae, 56–59
gene expression during, 134
gene regulation in, 149–169
inclusions in, see Inclusion(s)
overview, 149–152
Type III secretion system and, 207–208

Waddlia chondrophila, 58

Differentiation, 133–134

Disease, See also specific diseases, eg, Conjunctivitis; Trachoma
causes, 4
epidemiology, see Epidemiology versus infections, 4
symptoms, 4
syndromes caused by, 2

DNA gyrase, in developmental cycle, 154
DNA sensors, in immune recognition, 228–229
DNA supercoiling, in developmental cycle, 152–154, 161

Doxycycline, for genital infections, 14
Dynein, 174
### E
- Early genes, regulation, 160–161
- Effector proteins, 202–205
- Elementary bodies, 56–59, 74–75
  - adhesins, see Adhesion and adhesins
  - attachment, 84
  - chlamydial outer membrane complex and, 75–79, 84–85, 87–88
  - in developmental cycle, 84–88
- DNA introduction into, 335–336
- endosome fusion with, 171
- exit, 87–88
- function, 149–152
- glycoproteins, 81
- glycosaminoglycans, 81–82
- host cell entry, 84–85
- in host cell interactions, 126–135
- isolated versus intact, 75
- lipids, 79–80
- outer membrane modeling, 82–84
- polymorphic outer membrane proteins, 77–78
- porins, 78–79
- reticulate body transition to/from, 86–87, 134, 142, 208, 294, 296
- Endocytosis, 171–174
- Endosomes, 171–172, 180–181
- Envelope, see Cell envelope
- Environmental chlamydiae, 51–73
  - developmental cycle, 56–59
  - diversity, 51–54
  - genomics, 64–66
  - host cell interactions, 59–60
  - host range, 54–56
  - pathogenicity, 60–64
- Environmental factors, in pathogenesis, 256
- Epidemiology, 1, 2–3
  - biomathematical modeling and, 352, 353
  - Chlamydia pneumoniae, 18–19
  - Chlamydia trachomatis, 5–6, 9
- Epithelial cells
  - immune response, 243–244
  - polarized, 141–142
- Epitheliocystis, 55, 63–64
- Estrella, 52
- EUO protein, 2, 158
- Exoglycolipids, 81
- Exosomes, 179–180
- Extrusion, inclusions, 184–185

### F
- Fish, chlamydiae in, 55–56, 63–64, 67
- Flagellar proteins, 196, 198

### G
- Gammaproteobacteria, 55
- Gastrointestinal tract, Chlamydia in, 300–302
- Gel electrophoresis, for antigen detection, 318–319
- Gene regulation, in developmental cycle, see Temporal gene regulation
- Genetic predisposition, 8, 254–255, 301–303
- Genetic transformation technology, 334–351
  - challenges in, 335–338
  - chemical mutagenesis, 342–344
  - lateral gene transfer, 338–341
  - plasmids, 345–347
  - recombination, 344–345
- Genital infections
  - animal models for, 286–289
  - cervical cancer and, 15
  - Chlamydia trachomatis, 9–15
    - clinical features, 9–10
    - complications, 10–11
    - diagnostic tests, 9–10
    - immune recognition in, 217–232
    - immunopathogenesis, 240–264
    - lymphogranuloma venereum, 14–16
    - natural history, 12–13
    - repeated, 14
    - screening for, 11–12
    - serovars and, 16
    - vaccines for, 311–312
- Genomics, 27–50, 64–66, 265, see also specific Chlamydia spp.
  - animal models for, 300–303
  - animal pathogens, 37–43
  - for antigen detection, 319
  - future research, 45–47
  - lateral gene transfer and, 338–341
  - pangenome, 31–32
  - plasticity zone, 32–37
  - sequencing techniques for, 27–28, 31
  - Type III secretion system, 194–196
- Glucosylceramide, in host cell interaction, 141–142
- Glycerophospholipids, in inclusions, 176–177
- Glycoproteins, 81
- Glycosaminoglycans, 81–82, 101–102
- Golgi apparatus, interactions with, 136–138, 177–179
- Guinea pig models, 288

### H
- Hc proteins, 133–134, 159
- Heparan sulfate, 81–82, 101
- Heparin, 81–82, 101, 106
- Herpes simplex virus infections, 304
- Histone-like proteins, in developmental cycle, 133–134, 158–161
HIV infection, 254
Hormones, animal studies using, 304–305
Host(s)
  animal studies concerning, 303–304
  environmental chlamydiae, 54–56
  lysis, 184–185
Host cells
  actin nucleation machinery, 131–132
  chlamydia effects on, 46–47
  chlamydia recognition by, see Immune recognition
  chlamydiae interactions with, 126–148
  entry into, 84–85, 126–128
  gene expression modulation in, 204–205
  Golgi apparatus invasion of, 136–138
  inclusion interactions with, see Inclusion(s)
  microtubule-dependent trafficking in, 138–139
  polarized epithelial barrier in, 141–142
  proteolysis, 204
  toxin effects on, 131
  T3S effectors effects on, 130–131
  tyrosine phosphorylation and, 128–130
  vesicle trafficking in, 139–141
Human papillomavirus, in cervical cancer, 15

I
IhtA protein, in developmental cycle, 162–163
Immune recognition, 218–229
  NOD proteins in, 222–226
  nucleic acids and nucleotide sensors in, 227–229
  signaling after, 229–231
  Toll-like receptors in, 218–222, 229–231, 238–249, 253–254
Immune response, in trachoma, 8
Immunity, autonomous, 184
Immunity-related GTPases, 184
Immunoblotting, for antigen detection, 317–318
Immunoglobulins, function, 314–315
Immunopathogenesis, 240–264
  adaptive response in, 249–252
  clinical implications, 246
  in coinfections, 254–255
  environmental factors, 255
  genetic factors, 253–254
  innate immune mechanisms in, 242–246
  pathogen recognition receptor signaling in, 217–218, 223, 231, 246–249
  physiologic factors, 254
Immunoproteomics, for antigen detection, 319
In vivo studies, see Animal models
Inc proteins, 140–141, 172–174, 178
  secretion and, 203–204
  for vaccines, 321–324
Inclusion(s), 170–191
  animal models, 289–297
  in apoptosis prevention, 183–184
  autophagy and, 184
  biogenesis, 203–204
  cellular interactions with, 134–139
  developmental cycle and, 181–182
  endosome association with, 180–181
  extrusion, 184–185
  function, 132–133, 174–182
  Golgi body fragmentation and, 178–179
  host lipid acquisition, 176–180
  in innate immunity defense, 182–184
  integrity, 183
  migration, 174
  mitochondria association with, 181
  nascent, 171–174
  vesicle interactions with, 139–141
Indolamine 2,3-dioxygenase, 270
Infections, see also Genital infections;
  Trachoma; individual Chlamydia species
  asymptomatic, 3–4, 10–11, 242
  versus disease, 4
  epidemiology, see Epidemiology
  immune recognition in, 218–229
  natural history, 2–3
  pathogenesis, see Pathogenicity
  persistence, see Persistence, chlamydial
  repeated, 3
Inflammasomes, 224–225
Injectosomes, 195, 208
Innate immunity
  in biomathematical modeling, 363–364
  defenses against, 182–184
  Interferon(s), production, 315
  Interleukin-1, in immunopathogenesis, 245
  Invasion-associated effectors, 202–203

K
Koala, Chlamydia pneumoniae, 37–39

L
Late genes, regulation, 155–158
Lateral gene transfer, 338–341
Lipid(s)
  cell envelope, 80–81
  in host cell interactions, 136–138
  inclusion acquisition, 176–180
  Lipid droplets, 180
  Lipid rafts, 128
Lipopolysaccharides, 80–81, 102–103, 219
Lymphogranuloma venereum, 14–16
Lysophospholipids, in inclusions, 176–177

M
Major histocompatibility complex molecules, for antigen detection, 320
Major outer membrane protein (MOMP), 75–86, 99, 102, 150, 317–318, 321–322
Malaria, persistence, 266–269
Mannose receptor, 118
Matrix metalloproteinases, in immunopathogenesis, 245–246
MAVS protein, in immune recognition, 227
Membrane attack complex/perforin protein, 34, 180
Membrane contact sites, 177–178
Microarray studies, developmental cycle, 150–152
Microbe-associated molecular patterns (MAMPs), 217–221, 227
Microtubule(s), in host cell interactions, 138–139
Microtubule-organizing center, 174
Midcycle genes, regulation of, 152–155
Miscarriage, Waddlia chondrophila in, 61–62
Mitochondria, interactions with, 181
Models
· animal, 286–310
· mathematical, see Biomathematical modeling
Monkeys, as animal models, 289–290
Mouse models, 287–289
Mucosa, immune response, 243–244
Multiple cargo secretion chaperone, 201
Multivesicular bodies, 179–180
Mutagenesis, chemical, 343–345
Mycobacterium tuberculosis, persistence, 276–278, 281–282
MyD88, immune recognition, 220–221, 248–249

N
Naegleria, chlamydia associated with, 52
Nascent inclusions, 171–174
National Institutes of Health, psittacosis and, 41
Natural history
· infections, 2–3
· trachoma, 7
Neochlamydia hartmannellae, 52
Neochlamydia vermiformis, 52
Neutrophils, in immunopathogenesis, 246
NLRC proteins, 222–223, 225–226
NLRPs (Pyrin domain, PYD), 222–226
NOD proteins, 222–226
Nuclear factor-kB, 142, 204–206, 230–231
Nucleic acids, in immune recognition, 227–229
Nucleotide oligomerization domain (NOD) proteins, 222–226
Nucleotide sensors, in immune recognition, 227–229
Nutrient acquisition, 174–182

O
Omp proteins, 75–76, 79, 83
Opr proteins, 79
Outer membrane, structure, 82–83, 86
Outer membrane complex, 75–79, 84–85, 87–88
Outer membrane proteins, 75–86
Outer membrane vesicles, 194

P
Pangenome, Chlamydiaceae, 31–32
Parachlamydia
· in animals, 63
· secretion systems, 195
Parachlamydia acanthamoebae, 52, 59
Parachlamydiaceae, 55
· chlamydia associated with, 53
· discovery, 52
· diseases due to, 63
· genomics, 66
Partner switching, in developmental cycle, 156–157
Pathogen recognition receptors (PPRs), 217–218, 223, 231, 246–249
Pathogenicity
· animal models for, 300–303
· environmental chlamydiae, 60–64
· immune recognition in, 218–229
· protein secretion in, 192–216
· Pelvic inflammatory disease, 10–14, 242
· Persistence, chlamydial, 2–3, 265–284
· animal models for, 297–300
· versus persistence in other pathogens, 266–278
Phagocytosis, 59–60
Plants, chlamydiae associated with, 54–55
Plasmid(s), chlamydial, 65–66, 345–347
Plasmid glycoprotein, 323
Plasmodium vivax, persistence, 266–269
Plasticity zone, 32–37
Pneumonia, 16–21, 63
Polarized host cells, 141–142
Polymorphic outer membrane (Pmp) proteins, 77–78, 99, 109–117
Polymorphonuclear leukocytes, animal models, 290, 292–297, 300
Porins, 78–79, 322
Predator-prey framework, for biomathematical modeling, 355–365
Primate models, 288–289
Proctocolitis, 15
Protective antigens, 319
Protein(s), secretion, see Secretion systems; Type III secretion system
Protein disulfide isomerase (PDI), 97, 118–119, 127
Proteoglycans, 101–102
Proteolysis, host proteins, 204
Proteomics, for antigen detection, 319
Protochlamydia, 58–60, 155
Protochlamydia amoebophila, 52, 58–60, 63–65
Protochlamydia naegleriophila, 52, 63
Psittacosis, 27–28, 32–46

R
Rab family of GTPases, 140–141, 171–172, 174–176, 179
Rac protein, 131
Radioimmunoprecipitation, 318
Reactivation, Chlamydia trachomatis, 270
Reactive arthritis, 11, 281
Recombination, 339, 344–345
Repeat motifs, polymorphic outer membrane proteins, 114–115
Respiratory infections, animal models for, 286
Reticulate bodies, 56, 58, 74–75, 207
animal models, 289–297
DNA introduction into, 336
elementary body transition to/from, 86–87, 134, 142, 208, 294, 296
function, 149–152, 199
growth, 86–87
lipids, 79–80
Rhabdochlamydiaceae, 56
Rig-like receptors (RLRs), 227–229
RNA polymerases, in developmental cycle, 152, 155–156, 159–160
RNAs, small, in developmental cycle, 161–163
RsbW, in developmental cycle, 156–157

S
SAFE strategy, 8–9
Salmonella enterica serovar Typhi, persistence, 277–278
Sanger sequencing, 28
Scarring, 3, 5–7, 240–241, 272
Scc4 transcription regulator, 159–160
SCH1 protein, 130
Secretion systems, see also Type III secretion system definition, 192
effectector proteins in, 202–207
therapeutic uses, 208–209
types, 192–194
Serovars, Chlamydia trachomatis, 5, 16
Sexually transmitted infections, Chlamydia trachomatis, 9–15
Sigma factors, in developmental cycle, 155–158
Simkania, 57
Simkania negevensis, 52, 65–66
SNARE (soluble NSF attachment protein receptor) proteins, 139–140, 172–173, 177
Sphingolipids, in inclusions, 176–177
Sphingomyelin, in host cell interaction, 136–138, 141–142
Sphingomyelin synthases, 178
Spindle assembly checkpoint, 182
Sponges, chlamydiae associated with, 52
Syphilis, persistence, 271–275, 279–281

T
T cells
for antigen detection, 319
immune function, 250–252, 314–315
Targeted induced local lesions in genomes (TILLING), 342–344
Tarp (translocated actin recruiting phosphoprotein), 127–131, 199, 202–203, 205
Temporal gene regulation, in developmental cycle, 149–169
early genes, 160–161
in elementary bodies, 158–160
late genes, 155–158
midcycle genes, 152–155
model for, 163–165
overview, 149–152
small RNAs in, 161–163
Tetracycline, for trachoma, 8
TILLING (targeted induced local lesions in genomes), 342–344
Tim-Tom mitochondrial protein import complex, 181
Tissue tropism, Chlamydia trachomatis, 16
Toll-like receptors, 218–222, 229–231, 246–249, 253–254
Toxoplasmases, in developmental cycle, 154
Toxoplasmosis, persistence, 269–271, 279–280
Trachoma, 5–9
  animal models for, 289
  clinical features, 5–7
  control efforts, 8–9
  distribution, 5–6
  epidemiology, 5–6
  genetic predisposition, 8
  grading, 6–7
  immune mechanisms in, 8
  immunopathogenesis, 240–264
  natural history, 7
  pathogenesis, 315–316
  persistence, 273
  serovars and, 16
  transmission, 5–6
  vaccines for, 311–312, 315–316
Transcriptional profiles, developmental cycle, 150–152
Transcriptional repressor, in developmental cycle, 157–158
Transferrin, 180–181
Transformation, see Genetic transformation technology
Translocated actin recruiting phosphoprotein (Tarp), 127–131, 199, 202–203, 205
Translocation
definition, 192
effector, 201–207
mechanisms, 193–194
Transposons, 339–341
Treponema pallidum, persistence, 271–275, 279–282
Trichiasis, 7, 240–241
TRIF, in immunopathogenesis, 247–248
Tryptophan, deficiency, 276–277
Tryptophan operon, 34
Tsp protein
  in immunopathogenesis, 249
  in secretion system, 205
Tuberculosis, persistence, 275–276, 280–281
Tumor necrosis factor alpha, in immunopathogenesis, 244–245
Type II secretion system, 193–194, 206
Type III secretion system, 127, 171, 194–202
chaperones in, 200–201
components, 196–198
in contact-dependent hypothesis model, 369–376
developmental cycle and, 207–208
effector translocation in, 201–207
genomics, 194–196
mechanisms, 192–193
regulation, 199–200
W
Waddlia chondrophila
  in animals, 63
  chlamydiae associated with, 55
developmental cycle, 58
discovery, 52
  genomics, 64–65
  host cell interactions with, 60
  miscarriage due to, 61–62
WAVE2 protein, 131
Whiteflies, chlamydiae associated with, 55–56
Whole-genome shotgun sequencing, 27–31
Wiskott-Aldrich syndrome protein homology domain, 128
World Health Organization, trachoma grading system, 6–7
X
Xenoturbella, chlamydiae associated with, 55, 57
Y
Yersinia, secretion systems, 197, 199–201
Z
Zoonotic pathogens, see Animal pathogens