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Biology of *Chlamydia*

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Preface

Chlamydiae are obligate intracellular bacteria. They live in an intracellular vacuole (the inclusion) that they customise to permit delivery of nutrients and to provide protection against host cell defences. *Chlamydiae* have two developmental forms: one is infectious (the elementary body) but has little metabolism and the other one divides very actively but is not infectious (the reticulate body). Once a cell is infected, EBs differentiate to RBs; after a cycle of about two days, re-differentiated EBs are released, either by lysis of the host cell or by the active release of intact inclusions.

What seems rather complicated is a very successful strategy. The phylum *Chlamydiae* has been around for about two billion years, with the extant *Chlamydiae* in their extremely wide spectrum of bacterial species and vastly differing hosts having split into separate lines around 700 million years ago. Many species of unicellular and multicellular hosts have their specialised *Chlamydia* but infection across these borders also occurs. The two species commonly found in humans are *Chlamydia pneumonia* (which is very common but causes only mild disease in most cases) and *C. trachomatis*, with a lower but still very substantial prevalence and great clinical importance, especially in causing infertility in female patients and scarring damage to the eyes.

We can categorise *chlamydia*l infection biology and research into *Chlamydia* into two areas, both under intensive research. The first considers the interaction of the bacteria with the individual host cell: how does *Chlamydia* manage to set up its inclusion, which is accepted by the host cell basically like another organelle? The inclusion is embedded by the cytoskeleton, it is supplied with all the necessary nutrients, and it is able to set up an equilibrium with the host cell's innate defences; how does that work?

The second issue is about the infection of multicellular hosts like humans: what are the mechanisms on either side that determine immune recognition, immunopathology and potentially anti-infective protection? The biggest clinical problem of *C. trachomatis* infection is damage to tissue, either in the female genital tract (worldwide) or to the eye (blinding trachoma, especially in Africa). Human chlamydial infection may be very prolonged affairs; it is much under investigation

whether *Chlamydia* can be persistent in vivo, lying low within one host cell, or whether chronic infections reflect slowly propagating bacteria in vivo (or even re-infection).

Progress in all of these areas is rapid, and this book is the endeavour to present important developments and current thinking. The first four articles address questions of *chlamydia*l microbiology and the bacterial interaction with the (human) host cell: the unusual cell wall of *Chlamydia*, where peptidoglycan was discovered only three years ago, is the focus of one article.

The next two chapters address questions of the early establishment of the bacteria in a host cell. The elementary body, the infectious form of *Chlamydia*, long considered an inactive particle, has in recent years been found to be a highly specialised form of *Chlamydia*, and its characteristics and abilities are discussed. The second of the two chapters will illustrate the ways how *Chlamydia* interacts with the host cytoskeleton; these interactions have been found to be crucial for uptake and establishment of the inclusion as well as for its maintenance and ultimately the release of the bacteria.

The enigma how *Chlamydia* manages to escape the host cell's defence mechanisms is the focus of the following article. Even epithelial cells—the regular host cell of *Chlamydia*—have numerous systems, such as apoptosis, autophagy, inflammasome and interferon signalling that can serve in the defence against microbial invaders. *Chlamydia* has to deal with these machineries, and that chapter discusses current views on this issue.

The genomic structure of *Chlamydia trachomatis* is at the centre of the next article. It focusses on the question how recent technological advances, in particular through whole-genome sequencing, have changed our perception of the genomic structure of the bacteria. Apart from the population structure, the appreciation of what is a successful strain and a new understanding of the relationship between strains causing distinct forms of disease has only become clear through these studies. One important underlying mechanism was found to be the unexpectedly large extent of recombination between chlamydial strains.

This surprising capacity for recombination has been one of the areas of discovery that have also informed the recent endeavours to manipulate the genome of *Chlamydia trachomatis*. For a long time, many papers on *Chlamydia* included the wistful statement that *Chlamydia* is not genetically tractable. This is no longer the case. Progress has been made, and some genetically modified bacteria have been characterised. The newly developed techniques will help us understand chlamydial virulence. However, we are still a long way off routine manipulation. The article on genetic dissection of *chlamydial* virulence provides an honest appraisal of exciting yet small advances and sketches out the way ahead.

Turning to the infection of the complex (especially human) host, three articles cover a number of questions that are highly relevant to human infection. One of the striking features of human genital infection with *Chlamydia trachomatis* is the chronic infection: unless the infection is cleared right away, as it is in some patients, the infection may be persistent with spontaneous rates of clearance of as low as

50% per year. One article in the book investigates the reasons and likely mechanisms of persistence and of the individually differential response to the infection.

As already mentioned, the clinically biggest problem of human infection with *Chlamydia trachomatis* is the damage to the infected tissue, which frequently is associated with female infertility but also with eye scarring. It is clear that this is at least in part immunopathology: both innate and adaptive immunity contribute to the damage. Current state of knowledge in this field, in particular from animal models, is summarised in the article on the immunopathogenesis of chlamydial infection.

The last chapter covers the prospect for a vaccine. With few exceptions, vaccines tend to be less than completely successful against bacteria, and past endeavours do not suggest that *Chlamydia* will be much different. Nevertheless, there has been progress: understanding correlates of protection and the development of subunit vaccines has been moving forward, and the opportunities and problems will be discussed in this chapter.

Like many other areas of science, research into *Chlamydia* has benefitted from new methods and has been fertilised by the interaction of specialists with different backgrounds. I do believe that this collection of articles, prepared by experts in the relevant fields, will be a great repository of up-to-date information in a fast developing area.

Freiburg, Germany Georg Häcker
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Contents