STRUCTURAL BIOLOGY OF BACTERIAL PATHOGENESIS
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INTRODUCTION

Recent years have seen a rapid increase in structural information for proteins implicated in bacterial pathogenesis. From structures involved in adhesion and host recognition to those describing elements of bacterial secretion systems, this explosion in the field of structural microbiology has led to spectacular advances in our understanding of bacterial pathogenesis. To our knowledge, this book is the first attempt at compiling the structural biology work that has taken place in the field of bacterial pathogenesis in recent years. It is only an attempt because the repertoire of structural successes in this field is now so large that recruiting all the people responsible for it to write chapters turned out to be impossible. Moreover, it would have made for a rather unwieldy book. We have thus excluded the structural biology of toxins, as this area has already been covered in other books published by ASM Press. Instead, we have focused on a few areas that represent elements of the basic paradigm of bacterial pathogenesis. Bacteria enter the host and use sophisticated sensory pathways to upregulate expression of virulence factors. They recognize and bind to host receptors by using a diverse array of adhesins whose display on the bacterial cell surface often requires a dedicated assembly pathway. Once bound to the host cell, a bacterium begins to manipulate host cell behavior, using specialized secretion systems to deliver effector proteins to the host-pathogen interface. The actions of these effectors then provoke the host’s response.

Bacterial pathogens actively probe the environment in which they live. Successful virulence relies on bacterial sensing of environmental cues. This is achieved by molecular mechanisms, the most important of which are described in the first two chapters. In chapter 1, Campbell and Darst provide an overview of the molecular basis of regulation of bacterial transcription by anti-σ factors. For bacteria, gene regulation is controlled primarily at the level of transcription initiation, by controlling the ability of σ factors to recognize promoter sequences. Anti-σ factors are an example of proteins involved in linking various cellular processes and signal transduction pathways to the control of σ factor function leading to gene regulation. Some anti-σ factors, notably those that interact with the class of σ factors known as the extracellular function σ factors, have been implicated in bacterial pathogenesis. In chapter 2, Lubetsky and Stock describe another system used by bacteria to sense and respond to their environment, the ubiquitous two-component system. Coordination of expression of virulence factors and changes in housekeeping functions that occur when bacteria migrate from a free-living state to association with a host is essential, and two-component signaling systems are commonly involved in many of these processes. Two-component systems are also attractive targets for design of antibiotics, and this issue is discussed in great and fascinating detail in chapter 2.

Early events in infection must include bacterial attachment and host recognition. Chapter 3, by Smith et al., provides an overview of what is known about the structural biology of adhesion molecules, while chapter 4, by Yip et al., focuses on one particular interaction
which determines adhesion of enteropathogenic *Escherichia coli*, the interaction of intimin with the bacterially encoded Tir receptor. This is a remarkable system in which the bacterium uses a type III secretion system to deliver its own receptor to the targeted eukaryotic cells.

Recognition of receptors requires that adhesion molecules be exposed to the host cell membrane, often at a tip of a pilus structure. Thus, assembly of adhesins often requires specialized secretion machineries. Chapter 5, by Sauer et al., provides the structural details of our understanding of the chaperone-usher pathway. This system, which is geared for the production of adhesive pili, is probably the structurally best-documented system involved in bacterial pathogenesis. Moreover, because pilus biogenesis by chaperone-usher pathways is a polymerization process involving protein monomer subunits that are structurally truncated, its molecular basis could have been unraveled only by using structural biology approaches. Other important adhesive fibers are the type IV pili, which are assembled by a specialized transport machinery that is related to type II secretion systems. In chapter 6, Forest provides an overview of type IV pilus structure and assembly. Finally, the mechanisms leading to display of adhesion molecules at the surface of gram-positive bacteria are addressed by Connolly and Clubb in chapter 7, which focuses on the role and structure of sortases in that process.

The next four chapters are devoted to the structural biology of general secretion systems. There are six secretion systems in bacteria that have been well characterized to date: types I to V, which operate mostly in gram-negative bacteria, and the recently discovered injectosome in gram-positive bacteria. Recent structural progress has been made in type III, IV, and V secretion as well as the injectosome, and thus we are covering those systems most extensively. We start this section of the book with a chapter that could also have found a place in the previous group of chapters. Chapter 8, by Surana et al., describes the use of the type V secretion system (otherwise known as autotransporters) to display bacterial adhesions at the cell surface of *Haemophilus influenzae*. Autotransporters are fascinating molecules that possess within their primary structure the necessary sequence encoding their own machinery for export through the outer membrane of gram-negative bacteria. Recent structural advances have provided clues as to how this happens. In chapter 9, Stebbins provides an overview of the rapid progress made in defining the molecular basis of type III secretion assembly and effector function. The structural biology of type III effectors has provided insights into the various means that bacteria have developed to hijack host functions and subvert them to their advantage. A general theme has emerged: type III secretion effectors are molecular mimics of existing host proteins and thus utilize their ability to bind to host proteins to inhibit or trigger cellular functions that increase the pathogen’s chances of surviving the onslaught of host defenses to eventually proceed with successful infection.

Chapter 10, by Schröder et al., describes another secretion system of gram-negative bacteria, the type IV secretion system. The type IV secretion system distinguishes itself by being used for export of both proteins and DNAs. It is ancestrally related to bacterial conjugation systems and also exports virulence factors such as the protein CagA of *Helicobacter pylori*, the causative agent of gastric ulcers, and the pertussis toxin of *Bordetella pertussis*, which is responsible for whooping cough. This group of chapters concludes with a chapter (chapter 11, by Tweten and Caparon) on the newly discovered injectosome in gram-negative bacteria. The injectosome appears to be similar to type III secretion machinery in
that both systems appear to be geared for injection of virulence factors directly into the host cells.

Successful bacterial infections mobilize an arsenal of bacterial effectors which serves to overcome host defenses. What do those defenses consist of, and what is their molecular basis? These questions are the focus of the last chapter of the book (chapter 12, by Tong), which describes recent advances in the structural biology of Toll-like receptors. These receptors directly sense the presence of bacteria and thus trigger the first-line defenses against bacterial pathogens.

We hope that this book will provide a flavor of the enormously productive contribution that structural biology has made to our understanding of bacterial diseases. Many more chapters could have been written on the subject. Type I secretion, for example, has seen extraordinary advances in recent years. We would have loved to include a chapter on recent advances in type II secretion. Toxin structures could provide the subject of an entire book. The pace of discovery in these areas has been impressive, and we expect it to accelerate even further. Two factors contribute to this trend: a larger number of structural biology research groups interested in bacterial pathogenesis and the advent of fast methods for structure determination. However, as hinted in chapter 9, one discipline should make a resounding entry into the field in the next few years: high-resolution electron microscopy (cryo-electron microscopy). Most of the systems under study will be unraveled only when visualization of the protein complexes that they form is achieved. Thus, a combined effort in the areas of biochemistry, to purify such complexes, and crystallography and cryo-electron microscopy, to visualize them, holds the key to the future.

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