Structural Biology of Bacterial Pathogenesis. Gabriel Waksman, Michael Caparon and Scot Hultgren (eds). American Society for Microbiology, ASM Press, Washington DC. 2005. 273 pp. Price: US$ 115.95.

Structural biology has allowed us to understand host–pathogen interactions in a way it was never possible with conventional molecular microbiology. The volume under review is the very first compilation on this subject. The structural biology of conventional proteins of the pathogens such as toxins has been scrupulously excluded, as publications are already available on this subject. The structural biology of host–pathogen interactions is undoubtedly turning out to be extremely intricate, but rewards in terms of the possibility of designing highly specific structure-based antimicrobials and vaccines based on the information that may accrue from such studies, may be equally satisfying. There is a great and growing interest in this area because of the attractive possibility of designing antimicrobials that may not easily run into rough weather of drug resistance.

It is well known that gene regulation in bacteria is controlled at the transcription initiation level. Sigma factors (σ) play a crucial role and are required for promoter-specific interaction of DNA-dependent RNA polymerase (RNAP). A pool of sigma factors is present within the bacterial cell because the bacterium faces changing environments and is required to adapt quickly to these. Under normal conditions, these alternative sigma factors are held in an inactive state by the regulatory proteins called anti-σ factors. Structural studies of the sigma factors and their cognate anti-sigma factors involved in *Bacillus* sporulation (σ^F/SpoIIAB factor), periplasmic stress responses (σ^E/RseA factor) and flagellar synthesis (FliA/FlaM) reveal that all undergo remarkable rearrangements of their discrete structural domains during binding. Interestingly, the anti-sigma factors are highly diverse but nevertheless target the conserved ó domains (chapter 1).

The two-component signal transduction systems couple environmental stimuli to cellular responses and are used by most bacteria for quick adaptability to the changing environment. The pathogenic bacteria use these to acclimatize and to initiate an infection when these re-enter a host after their sojourn outside the host. The biochemistry and the molecular biology of these systems have been the subject of intense research and kinases are the key enzymes involved. The structural features of the histidine kinases and their response regulators involved in bacterial chemotaxis, a very well-characterized two-component system, have been discussed (chapter 2). The diversity of histidine kinases is created by a combination of their sensing, catalytic and auxiliary domains all of which are modular in structure. The response regulators are basically transcription factors with N-terminal regulatory and C-terminal DNA-binding domains respectively. The three-dimensional structure of regulatory domains showed that many share the same fold. Being universally present in Gram-positive and Gram-negative bacteria, absent in animals and their role in bacterial virulence and possibly drug resistance too, make two-component signal transduction systems attractive for antimicrobial intervention. Structural data of both histidine kinases and the response regulators of a number of two-component systems would help in designing proper inhibitors for antimicrobial chemotherapy. With multidrug resistance among pathogenic microorganisms spiralling into a major global concern, it is imperative that novel strategies are designed and tested.

Colonization of host surfaces through interaction of bacterial adhesins with host receptors (frequently sugar residues) is a prerequisite for most bacterial pathogens to initiate an infectious process. Structural studies of such molecules were started very early for viral pathogens especially the influenza viruses. For bacterial pathogens, the appendages (pili/fimbriae) involved in such interactions are extremely complex. The available structural information about type 1 pili (*E. coli*), p pili (*E. coli* associated with pyelonephritis), and G and F17 fimbriae (enterotoxigenic *E. coli* or ETEC), and the lectin adhesins namely FimH, papG and GafD has been discussed. The type IV pili (examples *Neisseria meningitidis* and *N. gonorrhoeae*) are long hair-like filamentous appendages, which help bind pathogens not only to host surfaces but also amongst themselves forming microcolonies. Being one-dimensional assemblies, these are not amenable to crystallization. So these have been studied only in co-crystallized form in association with a binding protein (chapter 6). Structurally, pili are very complex and their biogenesis may involve the participation of more than a hundred proteins. All this is orchestrated by a chaperone usher-pathway, which consists of a periplasmic chaperone and an outer membrane usher (chapter 5). Besides pili and other filamentous appendages, bacterial surface proteins too promote adhesion to host. These proteins are anchored to the bacterial surface by sortase pathway. The three-dimensional structure of truncated sort A (*Staphylococcus aureus*) revealed that it possesses a novel eight strand β-barrel fold. Limited mutagenesis of regions around this fold showed its role in pathogenesis. Sortases are widely distributed almost exclusively in Gram-positive bacteria but seem to be absent in mycobacteria and mycoplasmas. These are also present in archeal methanobacteria (chapter 7). Cryoelectron microscopy, X-ray crystallography, NMR spectroscopy and the more recent atomic force microscopy have provided detailed structural information about the proteins involved in all these mechanisms. It is envisaged that structural analogues that may be wedged between pathogen adhesin and host receptor may serve as antimicrobials that have the potential to abort an infection even before it is initiated. However, this can be made possible only if high-resolution crystal structures of adhesins, receptors and proteins involved in chaperone-usher and sortase pathways are made available.

What if a host does not have receptors to bind a pathogen? In these circumstances, certain pathogens have mechanisms to target indigenously synthesized receptors onto the host and then use these to enter the host cells. This eliminates the need for host-derived receptors to initiate an infection. The translocated intimin receptor (Tir) of enteropathogenic *E. coli* is one such receptor. A detailed description of Tir and its cognate intimin-binding factor has been provided (chapter 4). A similar mechanism has recently been discovered in *Helicobacter pylori* too and

studies on its structural features have just begun.

Several pathogens secrete an array of proteins, some of which may be precisely targeted into the host cells using sophisticated machinery. Inclusion of four chapters on the subject in this volume shows its significance. Type V secretion system (example *Haemophilus influenzae*) is an autotransporter type of secretion pathway. Although a variety of these are known, the crystal structure of FHA (filamentous haemagglutinin of *Bordetella pertussis*) has been solved recently. Crystal structure studies have also provided important insights as to how type V secretion proteins are presented on the bacterial surface and then interact with host cells (chapter 8). Structural studies have revealed that the type III secretion systems (examples *Salmonella enterica* var. *typhimurium* and *Yersinia enterocolitica*), also called TTSS, are modelled into complex needle-like structures, which inject effector proteins into the host cells (chapter 9). The needle complex consists of three regions – the extracellular needle, the outer membrane rings and the base that spans the inner membrane and extends into periplasmic space. The needle complex is characterized by a radial symmetry throughout. This is a marvel of the supermolecular organelle-sized entity. Although tremendous strides have been made in understanding the TTSS, high-resolution structural studies are still lacking. Type IV secretion systems (T4SS) are involved in transport of specific substrates from bacterial donors to prokaryotic and eukaryotic target cells. Consequently these are implicated in human, animal and plant pathogens as also in bacterial conjugation. It is a multiprotein complex spanning the inner and the outer membrane of the Gram-negative donor bacteria, forming a transport channel. A variety of substrates are transported through this channel. Crystal structure of a family of widely distributed T4SS substrates, the conjugative relexes has recently been solved. T-DNA of *Agrobacterium tumefaciens* is transported by such relexes (chapter 10). The newly discovered 'injectosomes' in Gram-positive bacteria are functionally analogous to T3SS of Gram-negative bacteria but are structurally unrelated to it. In injectosomes, the Sec-dependent secretory pathway is coupled with the pore-forming activity (chapter 11).

The discovery of Toll-like receptors (TLRs) in the innate immune system of the vertebrates has been responsible for a paradigm shift in immunology from the much-accepted non-specificity of innate immune response to its exquisite specificity. The TLRs recognize various conserved molecular structures of pathogenic microorganisms called pathogen-associated molecular patterns (PAMPs). The lipopolysaccharide (LPS), commonly called endotoxin, present in cell wall of Gram-negative bacteria is a PAMP recognized by TLRs. Structural studies have revealed that TLRs share a conserved intracellular domain with interleukin-1 receptor (IL-1R) and is called Toll/IL-1 receptor (TIR) domain. The amino acid sequence of most TIR domains is characterized by (F/Y) DA and FW motifs near the N- and C-terminal ends respectively. It is expected that structural studies of TIR would help unravel the molecular mechanisms, which underlie the specificity in signalling processes.

Like most other books coming from ASM press, this too is a heady mix of state-of-the-art information on structural biology of host–pathogen interaction, with the bibliography as best as it can get. Every chapter has been illustrated with high quality colour pictures of the structures of important proteins under discussion. For those involved directly in the study of microbial pathogens and pathogenicity though not necessarily their structural biology, reading this book, I am sure, would be an exhilarating experience. Besides the structural biologists, this book would be extremely informative for medical microbiologists, molecular biologists, immunologists and those involved in designing antimicrobials for infectious agents.

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