tainly turn out more complex than had been hoped. Nevertheless, the interaction of large-T with p53 is now known not only to play a crucial role in SV40-mediated oncogenesis, but also to provide a model for oncogenesis at large. As Watson points out, Hanahan's transgenic mice (made at Cold Spring Harbor) expressing large-T off the insulin promoter demonstrate how much more there is to carcinogenesis: the mice develop benign growths in the pancreas that seldom turn into true tumors.

Directors are notoriously unable to evaluate their own Institute objectively, in public at least. We can hardly complain if the account here of cancer research centers on Cold Spring Harbor. For a more balanced account, read the last chapter of *The Molecular Biology of the Cell*.

In the final sections of this book, we see Watson as both sage and gadfly applying himself to the public issues raised by DNA. On the war against cancer: more resources should be put into academic centers so as to attract bright students, on the MIT pattern. On apprehensions voiced at the famous Asilomar Conference concerning the hazards of recombinant DNA: they were maybe right about large-scale handling of oncogenes, but went too far. On unquantifiable risks: these should not be allowed to hold up science. On the human genome project: it should receive full support, and it is high time the Germans joined in. On genetically modified food: this is not a valid category, considering what orthodox plant-breeders get up to. These are sensible views with which most of us would now agree, and it has surely helped to have them put so forcibly by a scientist of such prestige. The problem is that Watson's impatience with the slow-witted works well in science, but can be counterproductive in the outside world of politicians, the media, and eco-publicists. Yet in spite of all, science surely need its Watson.

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Pathogen–Host Cell Molecular Interactions: Knowledge and Challenge

Cellular Microbiology
Edited by Pascale Cossart, Patrice Boquet, Staffan Normark, and Rino Rappuoli
Washington, DC: ASM Press (2000). 362 pp. $75.95

Bacterial Protein Toxins
Edited by Klaus Aktories and Ingo Just
Berlin Heidelberg: Springer-Verlag (2000). 700 pp. $449.00

Despite advances in science and technology, infectious diseases still constitute a threat to animal and human life. The scientific community has missed the opportunity to eradicate or even control the most dangerous of these infectious diseases. As Leonardo da Vinci said: "Iron rusts from disuse, stagnant water loses its purity and in cold weather becomes frozen; even so does inaction sap the vigors of the mind." Before the rust sets in, it is time to use the tools we designed to circumvent chronic diseases, such as atherosclerosis and cancer, to better understand the molecular interactions between pathogenic bacteria and host cells. Why such a hurry? Infectious diseases have been considered part of human history, and in industrialized countries we believed that tuberculosis, typhoid fever, typhus, smallpox, and many other epidemic diseases were under control. However, after a flurry of discoveries that included antibiotics and antivirals, very few new bug killers have been discovered during the last 25 years. Perhaps as a consequence, the last quarter century has been characterized by the emergence of new diseases and fear of ancient infectious diseases has returned. Although antimicrobial drugs have saved many lives, the appearance of bacterial strains resistant to antibiotics is now considered a serious public health concern. Penicillin-resistant *Staphilococcus aureus*, resistant strains of gonorrhoea, shigellae, salmonellae, and pneumococci are spreading rapidly. The most spectacular come-backs are malaria, tuberculosis, and cholera. Different factors such as abuse of antimicrobials, poverty, mass migration, and environmental modifications contribute to their expansion or appearance. Indeed, exposing pathogens to antibiotics causes them to pass their resistance genes to neighboring related bacteria by genetic transfer through conjugation, thus spreading antibiotic resistance.

Though the dreadful coevolution between bugs and hosts continues, improvement of scientific knowledge has been successful in pointing out the specific role of certain pathogens in chronic diseases. For instance, *Helicobacter pylori* has been shown to be involved in gastric ulcers and *Chlamydia pneumoniae* in coronary atherosclerosis. A clear challenge for scientists of the new millenium is to unravel the molecular mechanisms underlying infections, in order to gain knowledge that will certainly be the basis for new vaccine designs. Cellular microbiology, first termed such in 1996 (Cossart et al., Science *271*, 315–317, 1996), is a discipline cross-linking cell biology and microbiology that has emerged to meet this challenge. A new text book, "Cellular Microbiology", is evidence for the success of the combined approach. The book describes the fundamental cellular mechanisms that can fall prey to bacteria or bacterial products such as signal transduction, membrane trafficking and organelle biogenesis, cytoskeletal dynamics, cell adhesion, and the regulation of cell survival versus cell death.

The book starts with a discussion of the first aspect of infection, contact between the pathogen and the host cell. The extracellular matrix and the host cell surface are potential sites for interactions with pathogens. For instance, fibronectin, the mannose-receptor and complement-receptors (CR) play an important role in the attachment and uptake of *Mycobacterium* by professional phagocytes, and are also involved in the uptake of either heat-killed or live *Legionella pneumophila*. Most pathogens express adhesins, proteins that mediate, by

a synergistic mechanism, adherence to the extracellular matrix. Not all adhesins are essential virulence factors and the complex cross-talk between adhesins and invasins, proteins directly involved in invasion, is still a nightmare for the cellular microbiologist. For instance, InvA is an invasin that can mediate adherence, a prerequisite for invasion of nonprofessional phagocytes. *lpf*-encoded fimbriae are involved in the adherence of *Salmonella* to Peyer's patches in mouse intestine. *Salmonella* strains containing both *lpfC* and *invA* mutations display a much stronger attenuated phenotype than that of the single mutants; they are incapable of intestinal colonization. However, delivered intraperitoneally, these double mutants are fully virulent, indicating that in some tissues, invasins and adhesins are directly involved in host cell recognition specificity and tissue colonization.

Pathogen–host cell matrix interaction triggers signal transduction, inducing a cascade of events that often promotes parasite internalization. The binding of bacterial pathogen to host cell surfaces promotes the interaction between integrins and the extracellular matrix that induces the formation of focal adhesions. The focal adhesion tyrosine kinase and tensin associate with the cytoplasmic domain of the β-integrin and become tyrosyl phosphorylated. This primary event is followed by a massive recruitment of vinculin, talin, and α-actinin and then by cortactin and p120, substrates of the Src tyrosine kinase. This clustering recruitment is controlled by the Rho GTPases. This subversion of the cytoskeleton by pathogens precedes their eventual entry. *L. pneumophila* enters cells by coiling phagocytosis, a process characterized by the formation of pseudopods that coil around the bacterium. In contrast, *Listeria* or *Yersinia* internalization occurs by a zipper-type mechanism in which bacterial surface proteins bind to host cell surface receptors, and that requires an active actin cytoskeleton and at least one tyrosine kinase. *Salmonella* and *Shigella* use a trigger mechanism. In these bacteria, type III secretion systems, needle-like structures that resemble the flagellum-specific secretion apparatus spanning inner and outer bacterial membranes (Kubori et al., Science *280*, 602–605, 1998), deliver virulence factors directly into the host cytoplasm. The interaction of *Salmonella* virulence factors SipA and SopE with Rac and Cdc42 in the host cytoplasm triggers cytoskeletal rearrangements, membrane ruffling and bacterial uptake. In *Shigella*, Ipa proteins are similar to *Salmonella* Sip proteins. Other bacteria like *Yersinia* and enteropathogenic *Escherichia coli* also use a type III secretion system, but to translocate different effectors. The antiphagocytic activity of *Yersinia* requires YopH, a tyrosine phosphatase involved in the disassembly of focal adhesion structures, and YopE, an effector that could be a target for small GTPases.

Another series of chapters clearly shows the interactions between vacuoles containing ingested microorganisms and intracellular organelles. A detailed description of the dynamic process of membrane trafficking and the endocytic route is a prerequisite for understanding the strategies evolved by pathogens to avoid phagolysosomes, thereby evading the killing mechanisms designed by host cells. Once internalized, *Shigella*, *Listeria,* and *Rickettsia* rapidly lyse the vacuole membrane, while *Mycobacterium*, *Salmonella,* and *Leishmania* block their vacuole maturation and trafficking at various levels of interactions with endosomal compartments. Some other pathogens exploit alternate routes in order to replicate in a specialized intracellular niche (*Legionella*, *Brucella, Chlamydia*) (Méresse et al., Nat. Cell Biol. *7*, 183–188, 1999).

The last chapter of this book is devoted to a description of how pathogens can avoid being killed, for instance by macrophages, and how they can circumvent both innate and adaptive immunity. This points out the key mechanisms that enable the host cell invaders to fight more efficiently against the immune response. The molecular interactions between caspases involved in apoptosis, and bacterial effectors such as *Shigella* IpaB are direct evidence of the different strategies used by pathogens to avoid being degraded by the host.

Another strategy used by pathogens to perturb host cell life involves toxins. Bacterial toxins were the first virulence factors to be identified, and their use as inhibitors of specific cellular processes has had a large impact on the study of cell biology. The book *Bacterial Protein Toxins*, edited by K. Aktories and I. Just, is dedicated to describing in detail the knowledge accumulated about toxins at the cell biological, microbiological, pharmacological, and structural levels. Among the best known toxins are the tetanus toxin from *Clostridium tetani* and the botulinum neurotoxins from *Clostridium botulinum* that block membrane docking/fusion at the level of the postsynaptic membrane by cleaving VAMP/synaptobrevin, SNAP-25 or syntaxin molecules, components of the SNARE complex. Cholera and pertussis toxins, that block at levels of signal transduction by ADP-ribosylating GTP binding proteins, can be used to study nucleotide binding proteins. *C. botulinum* C2 and *C. perfringens* toxins help elucidate the regulation of the actin cytoskeleton. *C. difficile*, CNF1 and 2 are specifically involved in the dysfunction of small GTPases, while botulinum toxins and streptolysin O interfere with exocytosis and membrane integrity, respectively. The crystal structure of many toxins, solved in recent years, has greatly contributed to rapid advances in this important field of research. The volume represents an up-to-date view of the various aspects of the most studied protein toxins, with a glance at the nonprotein endotoxins at the end of the book, a chapter which could be the subject of another entire book.

A striking result from these studies has had a direct impact on vaccine design. Among the bacterial toxins, ADP-ribosylating toxins are probably the best studied, and their molecular mechanisms the best understood. Computer modeling and site-directed mutagenesis followed by crystal structure analysis allowed generation of toxin mutants free of toxin activity. These mutants have been used as acellular vaccines against pertussis. The modified protein provokes an immune response efficient enough to induce protection against the disease. Another toxin, the VacA protein from *Helicobacter pylori*, correlates with a vacuolating activity that leads to the cell destruction. Although the mechanisms of this vacuolation are not yet understood, VacA was also a candidate for vaccination. Animals injected with a formylated form of the protein that does not display any vacuolating properties, were able to develop a protective response. Throughout this book, the interface be-

tween microbiology, biochemistry, and immunology is very well documented. Superantigens are molecules that efficiently stimulate T-lymphocytes by cross-linking the MHC class II molecules expressed at the surface of antigen presenting cells and the T cell receptor (TCR). The most common superantigen is the staphylococcal enterotoxin B. One chapter contains an interesting discussion on the intriguing pseudosuperantigens such as the M proteins of *S. pyrogenes* or the staphylococcal epidermolytic toxins and whether they act as unconventional superantigens, or are simply artifacts. More work is needed to prove that these proteins are involved in mitogenic activity.

The two books reviewed here represent pioneering work in the new discipline of cellular microbiology. They compile an enormous amount of information obtained from more fundamental disciplines such as cell biology, immunology, pharmacology, and microbiology, in a nice synthesis of the mechanisms of interactions of pathogens with host cells.

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Survival Strategies

Bacterial Stress Responses
Edited by Gisela Storz and Regine Hengge-Aronis
Washington, DC: American Society for Microbiology (2000). 502 pp. $109.95

Bacteria are the ultimate survivors: rapid responses to various insults quickly induce protective and repair functions, allowing adaptation to new and noxious growth conditions. When conditions are bad enough that growth is not an option, they may pull up the covers and hibernate until the situation improves, forming heat- and insult-resistant spores or entering other quiescent states. To achieve all this, the cells need sensitive and rapid sensing and response mechanisms, as well as ways to return to equilibrium when the threat is past. Not too surprisingly, then, the regulatory circuits that have evolved in bacteria for dealing with stress reveal an impressive array of overlapping mechanisms for assessing the environment and for integrating multiple signals. This is rich hunting ground for anyone interested in the ways signals are transduced from the environment to modulate gene expression. The second source of treasures in the study of bacterial stress responses lies in the functions that actually deal with the stresses—DNA and protein repair processes and systems responsible for resisting or repairing damage from oxidation or heavy metals or pH fluctuations. While the regulatory mechanisms may vary significantly from one organism to another, many of the response proteins themselves are well conserved, and function in similar stress pathways in eukaryotes as well as prokaryotes. Putting it all together requires an understanding of both the molecular biology of the regulatory mechanisms and an understanding of the physiology of the cell.

Consider one of the most universal of stresses, high temperature. The products of the response are remarkably similar in prokaryotes and eukaryotes. Highly conserved chaperones and proteases that play important roles under normal growth conditions are rapidly induced, becoming major components of the cells. Because these proteins help the cell rid itself of misfolded or unfolded proteins, either by refolding (chaperones) or degradation (proteases), it seems likely that the primary or most serious damage caused by heat shock is protein misfolding. Nonetheless, it is still not entirely clear how temperature is sensed, and the specific regulatory mechanisms differ from organism to organism. In *E. coli*, one level of sensing is via changes in the secondary structure of the messenger RNA for the heat shock sigma factor; the proposal is that temperature leads directly to melting of a structure that inhibits translation (reviewed in the chapter by Yura et al.). A second level of control, regulation of heat shock sigma factor degradation, depends on the titration of a specific chaperone system, the DnaK-J-GrpE (Hsp70) by misfolded protein. Titration leads to sigma factor stabilization, and therefore induction of the genes dependent on the sigma factor for transcription, including the chaperones themselves. As the level of these chaperones increases, titration is overcome and sigma factor is once again rapidly degraded, providing an efficient return to equilibrium. This type of mechanism is attractive, since it provides a direct link to the expected heat-induced protein damage. However, although much is understood about this response in *E. coli*, in vitro reconstitution of the effects on degradation have not yet been possible. In *B. subtilis*, the heat shock proteins, similar to those in *E. coli*, are regulated by at least three separate regulators, each sensing temperature in different ways. Why *E. coli* uses a single regulatory circuit for heat shock induction, while *B. subtilis* uses multiple ones is not fully understood.

Thus, even though the genetic and biochemical aspects of bacterial responses to stress have been studied extensively, this is still a very active field. There are relatively few instances in which we can describe, at the molecular level, an entire pathway—how the stress is sensed, the functions of all the activities induced in response to stress and the hierarchy of induction, and how the cell reestablishes normal growth. In addition to the sensing of cytoplasmic heat shock, discussed above, cells also contain a regulatory system for sensing protein misfolding stress in the periplasm, leading to induction of periplasmic proteases and chaperones. While many of the genetic components of the downstream parts of this pathway have been identified (reviewed in the chapter by Raivio and Silhavy), how stress is actually sensed and how that signal is transmitted to the regulators are only beginning to be understood. A large number of stress responses are controlled by the so-called "two-component regulatory systems," in which a sensor histidine kinase transduces the signal to a response regulator via phosphorylation of an aspartate residue. The structure and biochemistry of these proteins is well understood (see *Two-Component Signal Transduction*, ed. by J. A. Hoch and T. J. Silhavy, ASM