Annual Review of Microbiology, 2007. L. Nicholas Ornston, Susan Gottesman and Caroline S. Harwood (eds). Annual Review, 4139 El Camino Way, P.O. Box 10139, Palo Alto, California 94303-0139, USA. Vol. 61. 634 pp. Price not mentioned.

The *Annual Review of Microbiology, 2007*, typically contains diverse subject matter under the umbrella of microbial biology. Purely for the sake of conciseness, information on some of its contents is provided in slight detail. As a norm, every issue of the *Annual Review* is preceded by an autobiographical account of an influential scientist and in this volume, Margarita Salas presents a historical account of her work on the biology of bacteriophage ∅29 (phi 29), entitled '40 years with bacteriophage ∅29'. As an aside, Salas mentions that the actual amount of time spent by her on phage ∅29 researches is 46 years! It is always instructive to read such accounts because it is in articles of such kind that one gets to know the inner workings of a top-level researcher. Salas describes her early education in organic chemistry and a chance meeting with the Nobel Laureate Severo Ochoa, which led to a career switch into biochemistry. Furthermore, she describes her discovery of translation initiation factors (a significant finding) with S. Ochoa and her early work with phage ∅29. One striking feature of this research is her elucidation of the mechanism of initiation of phage ∅29 DNA replication, wherein DNA synthesis is primed by a protein, in stark contrast to the conventional DNA primer-based initiation. Although the protein priming mechanism has been intensively studied for ∅29, it is not anecdotal in the sense that ∅29 is not its only example; replication of some prokaryotic viruses, linear plasmids and adenoviral replication also occurs in this way. Perhaps more striking are the properties of the ∅29 DNA polymerase, the enzyme mediating ∅29 DNA replication, another subject of her research. The ∅29 DNA polymerase possibly has the highest processivity amongst DNA polymerases, capable of synthesizing accurately large stretches of DNA and possesses a strong strand-displacement activity, making it the enzyme of choice for whole genome and rolling circle amplification, two techniques much in use these days. Along the way Salas describes the evolution of her laboratory from its very modest beginnings to a leading centre of phage biology.

Moving to the subject matter of the review, Vilchèze and Jacobs (p. 35) describe the current state of knowledge on the mechanism by which isoniazid (INH), a much employed antitubercular drug, mediates its antitubercular activity. They trace the history of antitubercular chemotherapies up to the discovery of INH and its mechanism of action, namely that of inhibition of mycolic acid biosynthesis. Mycolic acids are essential components of the mycobacterial cell wall. INH is a prodrug requiring intracellular activation mediated by the enzyme KatG, converting INH into a highly reactive isonicotinoyl radical. Vilchèze and Jacobs rightly point out that the high reactivity of this radical has confounded meaningful interpretations on the mechanism of INH action; almost any intracellular metabolite or macromolecule can react with this radical. Genetics, however, has played a large role in solving this conundrum and the studies reported by Vilchèze and Jacobs that lead to the discovery of InhA, an essential enzyme involved in mycolic acid biosynthesis, as the target of INH, are instructive. One telling remark the authors make in this regard is that 'the primary target of a cidal drug can be identified as a factor whose physiological function is disrupted by the drug and whose genetic disruption leads to cell death' – a statement that can almost be viewed as a maxim. It is pleasing to note the recognition on the authors' part of a significant contribution made by the Indian researchers Saroja and Gopinathan, towards elucidation of the mechanism of INH action.

A biological structure, namely, the bacterial cell envelope comprising the periplasm sandwiched between the outer (OM), and inner cytoplasmic (IM) membranes, encloses the cytoplasm in Gram-negative bacteria. The envelope is a hotbed of biological activity with an array of protein-folding catalysts that mediate quality control during protein and lipid export. Bos *et al.* (p. 191) review the biogenesis of the Gram-negative OM, an asymmetric lipid bilayer with lipopolysaccharides (LPS) and phospholipids predominating in its outer and inner leaflets respectively. The OM while constituting a permeability barrier is sufficiently porous to allow the influx of nutrients through channels formed by OMPs (outer membrane proteins) a major class of OM proteins. Bos *et al.* review the pathway of OMP biogenesis, wherein OMPs synthesized as cytoplasmic precursors are translocated across the IM and subjected to the action of periplasmic chaperones, with their eventual sequestration and insertion into the OM by Omp85 and its associated protein partners. Structural studies of the periplasmic chaperones and Omp85 are discussed to yield information on how OMPs during translocation into the OM are recognized and ferried into the OM. Mechanisms of sorting of lipoproteins and LPS into the OM mediated by the Lol proteins and ImpA respectively, are discussed. It is worth mentioning (and discussed by Bos *et al.*) that integrated within the OM biogenesis processes, in *Escherichia coli* and other Gram-negative bacteria is the periplasmic stress response, an adaptive response that enables cells to cope with environmental conditions that induce protein misfolding in the cell envelope.

The Gram-negative cell envelope is the hub of protein secretory pathways, with its origin in the inner cytoplasmic membrane. Protein secretion assumes importance as it provides bacteria with a means of nutrient acquisition, adaptation to fluctuating environments and manifestation of virulence. To date at least seven distinct pathways of protein secretion have been recognized, and Dautin and Bernstein (p. 89) describe the workings of the autotransporter pathway of protein export, whose occurrence is widespread. The autotransporter is unique in the sense that it is nearly a self-contained protein exporter relying upon the cellular secretion machinery only at the initial step of its translocation, which is across the IM. The authors give detailed accounts of the autotransporter domain structure, comprising a signal sequence, an N-terminal passenger domain and a C-terminal translocator or β-domain. They describe studies on prototype autotransporters which suggest that the β-domain after signal sequence-mediated IM translocation, inserts in the OM following which the passenger domain is moved out into the external milieu, after it is freed from the main body of the autotransporter mainly through proteolytic events. The passenger domain usually bears activities of an adhesin, a degradative enzyme or can function as a cytotoxin. Despite considerable information on the various types of autotransporter systems, the mechanism by

which the passenger domain is exported via the β-domain remains unclear, and Dautin and Bernstein discuss possible modes of passenger domain export.

The initial discovery of many a biological process has occurred in prokaryotes and in a departure from this trend, Pitcher *et al.* (p. 259) describe the workings of the prokaryotic non homologous end joining (NHEJ), a low-fidelity DNA repair process that was first discovered in eukaryotes. NHEJ like the classical (but high fidelity) process of DNA double-strand break (DSB) repair, is a protective cellular measure against lethal effects of DNA DSBs. Studies from yeast have shown that the activities of the Ku70/Ku80 heterodimeric complex and the ligase IV complex lie at the heart of NHEJ. Pitcher *et al.* describe the initial identification of prokaryotic Ku homologues from sequences of microbial genomes with the (then) striking finding that prokaryotic Ku genes were usually found close to genes capable of encoding ATP-dependent DNA ligase, LigD. Furthermore, unlike in eukaryotes, prokaryotic Ku in general functions as a homodimer and LigD in many bacterial species is a multidomain protein bearing nuclease, ligase and DNA polymerase domains, endowing it with DNA end-processing activities. The possible evolution of prokaryotic Ku activity is provided with an interesting bit of information; certain bacteriophages encode proteins that perform a rudimentary Ku like function. As an example Pitcher *et al.* cite the case of the Mu phage Gam protein, which is thought to protect the Mu DNA from nucleolytic degradation, by binding to the Mu DNA ends. As a prototype of prokaryotic NHEJ, the workings of *Mt*-Ku and *Mt*-LigD, a two-component NHEJ system from *Mycobacterium tuberculosis*, are described. Pitcher *et al.* speculate on the need for NHEJ and suggest that it may play a protective role during periods of bacterial dormancy.

The ensemble of mRNA turnover in *E. coli*, that is, the RNA degradosome is reviewed by Carpousis (p. 71). The central role of the only essential component of the degradosome RNase E, including several aspects of its function and structure are described. However, the basis for RNase E essentiality is not well understood at present. Carpousis also describes biochemical, structural and genetic studies on other components of the degradesome, namely RhlB, an RNA helicase; PNP, a polynucleotide phosphorylase and enolase, a glycolytic enzyme of unknown function within the degradosome. Based upon heterogeneity in the size of the degradosome complex it is speculated that the degradosome may be dynamic and possible ways in which the degradosome may assemble are presented. Recent studies have shown that many proteins tend to copurify with the degradosome and instinctively there is a tendency to draw meaningful interpretations of such association. The reader is served well here by the restraint shown by Carpousis in doing likewise for, in most cases, the functional significance of these interactions is not clear. The variability in the composition of RNase E multiprotein complexes and its widespread occurrence are discussed.

Cyclic diguanylate (c-di-GMP) is a recent entrant to the fold of second messengers, small molecules that typically relay signals at the cell surface to intracellular targets. Names like cyclic AMP or guanosine tetraphosphate spring to mind as examples of molecules with similar roles. Tamayo *et al.* (p. 131) describe the physiology of c-di-GMP action within the bacterial cell. Not surprisingly, it emerges that the c-di-GMP effects within cells appear to result from a balance between its biosynthesis and degradation. In general, c-di-GMP in many bacterial species regulates (promotes) the formation of biofilms on the one hand, while on the other hand, it inhibits bacterial motility, thus regulating interconversions between sedentary and motile lifestyles, a switch which may prove advantageous during bacterial pathogenesis. As an example, Tamayo *et al.* describe the working model for *Vibrio cholerae*, wherein studies on various *V. cholerae* mutants have revealed an association between their virulence phenotypes and c-di-GMP levels. This model postulates that during the sedentary aquatic lifestyle of *V. cholerae*, c-di-GMP levels are high. Subsequently in the human host, c-di-GMP levels are actively lowered to the gain of motility and colonization. It is thought that c-di-GMP levels would be subsequently elevated to resume the biofilm lifestyle. Somewhat ill-understood is the means by which c-di-GMP is sensed, and Tamayo *et al.* discuss recent studies on how sensing may occur.

The biosynthesis of lantibiotics, which are small ribosome-synthesized peptides produced by Gram-positive bacteria with antibacterial activity, is reviewed by Willey and van der Donk (p. 477). Lantibiotics are complex polycyclic peptides with broad functional and structural diversity. Following their synthesis on the ribosome, lantibiotic peptides undergo modification via introduction of lanthionine and methyllanthionine bridges; hence the name lantibiotics. Willey and van der Donk review the current understanding on lantibiotic biosynthesis and propose a scheme for their classification depending upon the mechanism by which they acquire posttranslational modification and their activities. Lantibiotics are exported out of the cell and they exert their antibacterial effects mostly on Gram-positive bacteria by target cell-membrane damage. Not surprisingly, lantibiotic-producing bacteria have evolved protective mechanisms. Willey and van der Donk note that unusually so far, there has been little evidence of occurrence of a resistance mechanism against treatment with the lantibiotic nisin, commonly used in food preservation. Lantibiotics thus seem to be attractive candidates for use as antibacterial agents to combat infection. The authors also note some striking properties of lantibiotic biosynthetic enzymes to suggest that they may serve as avenues for rational bioengineering of lantibiotics for the generation of peptides with novel biological activities.

A microbial ecosystem that is ubiquitous and found associated within the pore spaces of rocks is the endolithic ecosystem. Walker and Pace (p. 331) review current studies in understanding the workings of such an ecosystem, and there are at least three points of note here. First, based on recent developments in culture-independent studies of microbial ensembles, endolithic ecosystems appear to possess low diversity making them simple in nature, an attribute that is thought to be suitable for ecological studies. Second, genesis of an endolithic community seems to occur by seeding of the endolithic niche by a uniquely adapted microbial subpopulation derived from a much larger and diverse population, with airborne dispersal as a means of spread. Third, endolithic communities can be preserved in geological records or in the authors' words form distinct 'biosignatures', which may be useful in the study of past life on earth.

Apart from the above-mentioned material, this volume of *Annual Review of Microbiology* contains other articles of

interest, among which a few are mentioned below. Leigh and Dodsworth (p. 349) review the central role of the PII proteins in sensing (indirectly) nitrogen limitation. Liande *et al.* (p. 423) describe the important roles of heterotrimeric G proteins in the growth and virulence of filamentous fungi. Mackenzie *et al.* (p. 283), based on the availability of genome sequence of and proteomic studies on *Rhodobacter sphaeroides*, present a case as to how such studies may shape future *R. sphaeroides* research. Drake and Horn (p. 169) describe the interactions of soil microorganisms with the earthworm gut and their impact on terrestrial nitrogen cycle. Overall, the editors have collated a diverse and a rich assortment of reviews, a must read for microbiologists. The exceptional organization of reference sections of the various reviews is another noteworthy feature.

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'*The Annual Review of Physiology* strives to bring molecular and mechanistic insights to problems concerning the physiology of the whole organism' – a goal that is currently known by somewhat trendier terms. The 2008 *Annual Reviews* exemplifies this approach in several reviews, notably those on obesity. Obesity with its implications for heart attacks, stroke, and diabetes is a problem that is growing as rapidly as the weight of the population. Understanding energy balance, feeding behaviour and weight reduction requires understanding mechanisms in both the central nervous system and peripheral mechanisms of monitoring and control. Sandoval *et al.* suggest that the remarkably precise balance maintained between caloric intake and expenditure may be mediated by signals for both glucose homeostasis and energy homeostasis converging onto the same region of the hypothalamus. Both sets of signals modulate the same subset of pathways, leading to the precise balance.

Some of these pathways involve the use of Ca^{++} as a 'second messenger'. The central place of calcium in physiology can be discerned by the number of reviews devoted to processes involving calcium signalling. Donald Bers reviews signalling in cardiac myocytes, and points to the importance of considering integrative influences at the tissue and cellular levels of numerous individual molecular regulatory mechanisms – many involving calcium. Calcium currents underlie the upstroke of the action potential in pacemaker cells while the ion, either directly or through calmodulin or calmodulin-regulated kinases, modulates a range of other cardiac currents, including K^+ and Na^+ currents. And that is besides its role in excitation–contraction coupling. The authors highlight the complexity of the kinetics of exchange of Ca^{++} for Na^+, which is regulated by the thermodynamics of the rapidly changing ion gradients in the course of cardiac pumping. The exchanger (NCX) mediates both inward and outward fluxes during the same action potential, and also has roles to play in pacemaker function and in some arrhythmias, making it a transporter of some importance. Watch this space for a review of this antiporter in the not too distant future.

Ca^{++} signalling is critical in life-and-death decisions for cells. Rong and Distelhorst review Ca^{++} signalling regulating Bcl2 family members and hence survival vs programmed cell death in T-cells of the immune system. While developing in the thymus these cells are exposed to a range of molecules made by the host organism. Strong activation of the developing T-cells causes sustained elevation of Ca^{++} levels in the cytosol and leads to death; weak activation results in oscillation of Ca^{++} concentration in the cytosol and leads to survival. This process serves to eliminate cells that would otherwise have gone on to mount an immune response against host molecules – as in auto-immune diseases. And selects for cells that are capable of mounting a response against foreign invaders. The mechanisms by which these responses are generated are discussed and shown to operate in other systems as well, including a form of cell death in the nervous system that is responsible for some types of neurodegenerative disease.

Yet another review emphasizing precise control of Ca^{++} transients is that by Kaupp and co-workers on sperm chemotaxis. Sperm can respond to almost homeopathically low (femtomolar) concentrations of the chemoattractant resact and its response has a dynamic range spanning six orders of magnitude. Here again the authors suggest calcium waves underlying the response, and trace a pathway for generating such waves. Essentially the system responds to changes in concentration rather than the concentration itself, i.e. a temporal as opposed to spatial sampling. The parallels with bacterial chemotaxis are striking. The authors, one of whom first cloned genes for the cyclic nucleotide gated channels involved in vertebrate vision, compare sensory transduction in the olfactory and visual systems to sperm chemotaxis. They suggest that sperm also responds to single molecules of attractants much as a photoreceptor can respond to a single photon of absorbed light.

Signalling is critical in physiology and this volume introduces a relatively new receptor for estrogen. Prossnitz and co-workers inform us that estrogen operates through the classical nuclear receptor for steroid hormones, but also signals through a receptor based in the plasma or cell membrane. The existence of the latter had been speculated in the 1990s. The membrane receptor was first identified in 2000 and falls into a well-known class of receptors – those that pass on the extracellular signal to a G-protein, which amplifies and passes on the signal to initiate a cascade of phosphorylation steps in the cell. Traditionally, incoming signals were presumed to either use this cascade approach or to actually enter the cell and proceed to the nucleus where they affected the expression of specific genes. Apparently estrogen does both (possibly through both sets of receptors) and this may have implications to the formation and possible targetting of hormonally regulated cancers.

A place where one does not normally associate such fine-tuned signalling is in the mucous layer of airways – a place traditionally associated with gas exchange but contaminated with inhaled microorganisms, particulates and a range of oxidative pollutants that one would like to keep clear of. Keeping the airways clear is the job of the mucins – a family of large, heavily glycosylated proteins. Both secreted and tethered versions