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MEETING REVIEW

Recent Advances in the Expression, Evolution, and Dynamics of Prokaryotic Genomes[▽]

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Work on the molecular and cellular biology of prokaryotic microorganisms and their phage continues to be at the cutting edge in many areas of fundamental research in the life sciences. An important stimulus has been the large number of complete bacterial and archaeal genome sequences that have appeared over the past decade and that now are being produced at a rate of several hundred per year. This information is the foundation for all of the "-omics" leading to a global evaluation of the state of the cell under various conditions of growth or stress. An overview of the sequenced prokaryotic genomes has also greatly influenced our thinking about the evolution of life on earth. The EMBO Conference on Molecular Microbiology was the third in a series of meetings aimed at bolstering interest and support for fundamental research on prokaryotes (EMBL, Heidelberg, Germany, 19 to 23 October 2006). More than 140 participants from around the world contributed to an intensive 4-day series of talks and poster sessions. The topics included noncoding regulatory RNA in bacteria, introduced for the first time at this meeting, as well as pathogenicity, evolution, signal transduction, and chromosome dynamics. With about 60 talks and 70 poster presentations, nearly of all of the participants contributed to the scientific discussion, generating many lively exchanges. The only significant complaint about the organization of the meeting was that some participants felt that there was not enough time to visit the historic old city of Heidelberg. One interesting comment from several participants was that they very much enjoyed attending a relatively broad-based meeting allowing them to learn about recent developments in areas with potential connections to their own research, an opportunity lacking in more highly specialized meetings. In this review, we highlight the talks, mention some of the discussion that they generated, and cite a selection of recent research articles and reviews by the speakers.

NONCODING REGULATORY RNA

S. Gottesman (Bethesda, MD), who has greatly contributed to developing the study of noncoding regulatory RNA in *Escherichia coli*, opened the meeting with the keynote address, giving an overview of this exciting new field. She outlined strategies for identifying and characterizing small RNA (sRNA) and described several sRNAs that act in bacterial stress responses (44, 48, 66). For example, the DsrA and RprA sRNAs positively regulate the general stress sigma factor, RpoS, and the Fur-dependent sRNA, RyhB, responds to iron starvation by downregulating a large number of genes that encode nonessential iron storage proteins. These regulatory RNAs act posttranscriptionally, permitting a rapid response to changes in the environment. G. Wagner (Uppsala, Sweden) talked about the SOS-induced IstR sRNA of *Escherichia coli*, which functions to repress the synthesis of a toxic peptide, TisB, upon DNA damage. IstR can repress the translation of the *tisAB* mRNA by binding ~100 nucleotides (nt) upstream of the *tisB* ribosome-binding site. Wagner proposed a radically new concept of small RNA-mediated translation repression in which the sRNA does not mask the ribosome-binding site but instead prevents ribosome loading at an upstream "ribosome standby site" (30). H. Aiba (Nagoya, Japan) talked about the phosphosugar-stress induced sRNA, SgrS, of *E. coli* that represses the translation of *ptsG* mRNA (71, 72). He presented data on complexes of SgrS with RNase E and Hfq and also

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demonstrated that SgrS primarily acts to prevent PtsG protein synthesis upon phosphosugar stress; *ptsG* mRNA degradation is believed to be a consequence of the repression of translation. Aiba then presented work on in vitro RNA silencing of the *ptsG* mRNA in a reconstituted system using purified components. P. Bouloc (Orsay, France) talked about the identification of a new sRNA, RseX, a suppressor of extracytoplasmic stress mediated by the alternative sigma factor, RpoE (34). RseX represses the expression of two abundant *E. coli* outer membrane proteins (OMPs), OmpA and OmpC, and is a new member of a rapidly growing list of sRNAs that target mRNAs encoding OMPs.

J. Vogel (Berlin, Germany) described the first systematic study of sRNA regulation in *Salmonella*, a model pathogen. His talk reinforced the idea that there is an important link between regulation by sRNAs and the expression of OMPs. In particular, the RpoE-controlled sRNA, RybB, plays a central in this process since it can repress all major *omp* mRNAs of *Salmonella* (75). Vogel also presented the identification and characterization of more than 25 *Salmonella* sRNAs and their targets. This work, using pulse expression of the sRNA and DNA microarray analysis of mRNA levels, suggests that several hundred *Salmonella* mRNAs are regulated by sRNA. F. Narberhaus (Bochum, Germany) talked about *cis*-regulatory elements in mRNA, which are located primarily in the 5′ untranslated regions of heat shock protein genes, which repress translation at normal growth temperature (ROSE elements). He presented a recently solved nuclear magnetic resonance structure of a ROSE element showing an unexpected network of noncanonical base pairs ensuring that the ribosome-binding site is inaccessible at normal growth temperature (20). P. Romby (Strasbourg, France) described the function of the *Staphylococcus aureus* RNAIII. Approximately 500 nt in length, this molecule is one of the longest bacterial regulatory RNAs known to date. RNAIII is a bifunctional molecule: it acts as an antisense regulator of *Staphylococcus* virulence genes and functions as an mRNA encoding a virulence protein (51). Romby presented new results showing that RNAIII also regulates the *rot* mRNA, which encodes a master regulator of virulence gene expression, placing RNAIII at the top of a cascade that orchestrates virulence gene expression in this important human pathogen.

R. Schroeder (Vienna, Austria) presented work in which proteins that bind *E. coli* sRNA were purified by affinity chromatography. Hfq, ribosomal protein S1, and the RNA polymerase beta subunit were the most abundant proteins detected in this analysis. Genomic SELEX, i.e., genomic systematic evolution of ligands by exponential enrichment, was performed to identify RNAs that tightly bind Hfq or RNA polymerase (64). A large number of antisense RNAs, novel intergenic transcripts, and mRNAs were identified. Genomic SELEX appears to be a useful tool for identifying low-abundance transcripts that are difficult to detect in total RNA preparations. In the archaea and the eukarya, noncoding RNAs are part of ribonucleoprotein complexes (RNPs) that modify rRNA at specific sites. The box C/D RNAs, a name that refers to their conserved C and D sequence motifs, are part of RNPs that methylate rRNA. Specificity is due to an antisense "guide" sequence in the box C/D RNA that base pairs with the target rRNA sequence. E. S. Maxwell (Raleigh, NC) presented recent work on the assembly and function of the *Methanococcus jannaschii* sR8 box C/D RNA into an RNP. The spacing between box C/D RNA sequence elements is highly conserved and critical for methylation. Different sRNPs assemble following different RNA folding pathways. The formation of an RNA duplex between the sRNP and the rRNA target, and the interaction of the rRNA with the nearby sRNP core proteins is required for efficient methylation (43, 90, 101).

RNases AND GENE EXPRESSION

U. Bläsi (Vienna, Austria) presented work on the mechanism of the DsrA and RyhB action in *E. coli* (2, 94) and asked whether the double-strand specific endonuclease RNase III affects the posttranscriptional control mediated by these sRNAs. This question generated a lively discussion regarding the relative importance of RNase III versus RNase E, which is a single-strand specific endonuclease. The consensus was that RNase E appears to be the major player in the degradation of the sRNAs, as well as their mRNA targets. Interesting new biochemical and structural work on bacterial and archaeal RNases was presented. C. M. Arraiano (Lisbon, Portugal) presented an analysis of *E. coli* RNase II, the founding member of a superfamily of exonucleases present in all three domains of life (4, 5, 42). Atomic structures of RNase II alone or complexed with RNA were presented. Together with biochemical data, this work gives new insight into the mechanisms of catalysis, translocation and processivity of this important RNA processing and degrading enzyme. The archaeal and eukaryotic exosomes, the bacterial RNase PH, and the bacterial PNPase form a superfamily of structurally conserved phosphate-dependent RNA-degrading enzymes. E. Lorentzen (Heidelberg, Germany) presented new structural data on the archaeal exosome complexed with an RNA substrate (61–63). Six RNase PH-like subunits form a hexamer organized around a central channel. One face of this hexamer is capped by a trimeric ring of S1 and KH RNA-binding domains, forming a continuous channel. The RNA-binding cleft of the active site recognizes 3′ ends mainly by interactions with phosphate groups, thus explaining at least in part the lack of nucleotide specificity in the degradation of RNA.

G. de La Cueva-Mendez (Cambridge, United Kingdom) showed that the Kid toxin encoded by plasmid R1 is an endonuclease that cleaves mRNA. Kid RNase activity is repressed by the Kis antitoxin. A model was proposed in which Kid/Kis is part of a presegregational copy number control system (32, 77). H. Putzer (Paris, France) described the recent identification and characterization of two novel RNases from *Bacillus subtilis*, RNase J1 and J2, which are paralogues (36). These enzymes, which belong to the metallolactamase family of enzymes, are functional analogues of the RNase E of *E. coli* but not homologues. That is, there is no conservation of protein sequence or structure. However, like RNase E, RNase J1/J2 is an endonuclease whose activity is sensitive to the phosphorylation state of the 5′ end of an RNA substrate. Since the genomes of *B. subtilis* and related gram-positive bacteria do not encode authentic RNase E homologues, RNase J might substitute for RNase E in RNA processing and degradation. C. Condon (Paris, France) presented new results on the maturation of the 5′ end of the *B. subtilis* 16S rRNA, which was shown

to be a two-step process, with the mature 5′ end being generated by RNase J1. Mutation of the predicted catalytic site of RNase J1 abolished both 16S rRNA processing and cell viability. In vitro results suggest that RNase J1 processes the precursor 16S rRNA after it is assembled into 70S ribosomes (12). (See also more recent work from this speaker on RNase J, which was not covered in the meeting [68].)

M. Ehrenberg (Uppsala, Sweden) presented results clarifying the role and the interplay of IF1, IF2, and IF3 in the initiation of translation in bacteria. He demonstrated that IF3 has an important role in the selection of mRNA with an AUG initiation codon. IF1, ribosomal recycling factor RRF and elongation factor EF-G contribute to the step preceding the initiation of protein synthesis (6). W. McAllister (Stratford, NJ) described a novel mechanism of nucleotide misincorporation during transcription by T7 RNA polymerase (52, 79). Misincorporation occurs when the same base in the DNA template is used during two consecutive cycles of nucleotide addition. McAllister suggested that this type of misincorporation may be universal for all RNA polymerases and that, in contrast to DNA replication, halted transcription complexes may be more deleterious to the cell than the occasional misincorporation of a nucleotide.

GENOMICS, EVOLUTION, AND BACTERIOPHAGE

There was an interesting encounter of three different philosophies in talks on bacterial genomics. T. Dagan (Düsseldorf, Germany) from W. Martin's group presented an analysis of the phylogenetic tree of the prokaryotes with special attention to its early branching, demonstrating a closer relationship between bacterial and human proteins than between bacterial and archaeal proteins (27, 28). This diagnosis contrasts with the highly resolved tree of life presented by P. Bork (Heidelberg, Germany), who sees eukaryotes closer to the archaea using 30 informational genes (what T. Dagan called "the tree of 1%"). The principal interest of P. Bork is bioinformatics, and hence his talk focused on a new tool, called STRING, which combines experimental, in silico, and semantic information to find interacting genes and proteins (98). Another aspect of Bork's talk was how to make sense of metagenomics, illustrated with data from different environmental niches (97). Although such data are typically very incomplete, they are at the same time information-rich, documenting the metabolic capacity of an entire microbial community. Finally, J. Parkhill (Cambridge, United Kingdom) represented a third genomics philosophy. As one of the most experienced practitioners of complete genome sequencing, he was somewhat wary of metagenomics and stressed the value of sequencing different clones from the same species or even bacteria from the same clone grown from individual colonies. He illustrated this concept with data from *Bacteroides*, revealing extensive reshuffling in genes encoding surface components and DNA restriction systems (17). These variations were attributed to mechanisms involved in avoiding phage infection in the gut where this bacterium lives commensally. Interestingly, the reshuffling in genes encoding surface components could be an evolutionary precursor to the antigenic variability of animal pathogens trying to avoid the immune system.

J. Bamford (Jyväskyä, Finland) presented work on the *Tectiviridae*, bacteriophage containing a lipid membrane, identified in the infection of the gram-negative bacterium, *E. coli*, and the gram-positive bacterium, *Bacillus thuringiensis* (1, 80). The crystal structure of coliphage PRD1 shares structural elements with adenoviruses. Their common coat protein fold has also been found in viruses infecting insects, algae, mammals, and amoebae. The structural biology data thus point to a common ancestor for a large virus family with origins in the distant evolutionary past. Comparative genomics by H. Krisch (Toulouse, France) traced the evolution of T4-like phage that infect *Proteobacteria* and *Cyanobacteria* (25, 38, 39). The chromosomes of these phage contain highly conserved structural and DNA replication genes interspersed with a large number of novel genes. This work demonstrates a remarkable plasticity in genome content and explains much of the genome size variation in this phage family. N. Mann (Warwick, United Kingdom) demonstrated in a marine cyanobacterium a possible ecological role for novel T4-like phage genes that encode S-layer proteins and key components of the photosynthetic apparatus (22, 23, 70). Intriguingly, the nonsystematic distribution of photosynthetic capacities in bacteria might be explained by the horizontal transfer of photosynthesis genes through phages. In *Synechococcus* spp., the transcription of the phage-encoded genes ensures unabated photosynthetic capacity in the phage-infected cell. M. Smith (Aberdeen, United Kingdom) reported on a novel serine recombinase from the *Streptomyces* phage phiC31 (86, 87). Although DNA excision is normally believed to require helper proteins, gain-of-function mutants were isolated that can perform both integration and excision in their absence. The mutations were mapped to the C-terminal noncatalytic domain of the recombinase, which is believed to be involved in synapse formation. C. Lambert (Nottingham, United Kingdom) presented *Bdellovibrio bacteriovorus*, a bacterial predator with a phage-like life cycle, as a potential alternative to phage therapy (58, 59). The role of the multiple flagellum genes for motility and prey hunting, as well as numerous hydrolytic enzymes expressed during the intracellular phase of the life cycle *B. bacteriovorus*, was investigated by genetic analysis.

SIGNAL TRANSDUCTION, PROTEIN INTERACTIONS, AND NETWORKS

The regulation of complex bacterial promoters was the topic of an agile and comprehensive presentation by S. Busby (Birmingham, United Kingdom). He introduced the *pnir* promoter, in which two transcription factors (NarL and FNR) and three global DNA-binding proteins (Fis, IHF, and H-NS) intervene (13, 45). These five proteins form an intricate regulation system that controls transcriptional activity in response to environmental conditions. Busby furthermore presented a genomewide analysis of the distribution of transcription factors by chromatin immunoprecipitation and DNA microarray analysis (ChIP on Chip) (46, 47). The use of antibodies to FNR, H-NS, Fis, and IHF permitted the identification of many target sequences, with 60% of them falling into intergenic regions. Of these targets, 67 are shared by H-NS and Fis. RNA polymerase was often found to be associated, suggesting that H-NS and Fis might help to bind the RNA polymerase. The interplay of chromatin topology and transcription in *E. coli* was discussed

by G. Muskhelishvili (Bremen, Germany), who addressed the question how global transcription is coordinated in the genome. He showed that alterations in the chromatin architecture lead to changes in transcription patterns, suggesting a homeostatic mechanism in which chromosomal supercoiling coordinates growth phase-dependent transcription (11). K. Pflüger (Madrid, Spain) from V. de Lorenzo's group described a novel electrophoretic method to separate phosphorylated proteins directly from intact cells. The procedure was instrumental in monitoring the flow of high-energy phosphate through the abridged phosphoenolpyruvate-carbohydrate phosphotransferase system of *Pseudomonas putida* (76). This work suggests that the phosphoenolpyruvate-carbohydrate phosphotransferase system in this bacterium is not connected to sugar transport but rather serves as a sensor of the metabolic state of the cell.

J. Schumacher (London, United Kingdom) discussed transcriptional activation by AAA+ enhancer binding proteins in an informative presentation using PspF (named for phage shock protein F) of *E. coli* as an example. PspF drives the transition of the sigma^{54}-RNA polymerase-promoter complex from a closed conformation to a transcriptionally active open conformation in a reaction requiring ATP hydrolysis (82, 83). The AAA+ enhancer binding proteins are part of a larger family of AAA+ proteins involved in diverse cellular activities. K. Turgay (Berlin, Germany) talked about another AAA+ protein, ClpC, which is a component of the ClpCP protease in *B. subtilis*. In addition to removing misfolded proteins, ClpC is involved in the proteolysis of several regulatory proteins controlling steps in sporulation. The take-home message of the talk was that ClpC requires adaptor proteins that target the protease to specific substrates and regulate its activity (55, 56).

P. Aldridge (Newcastle upon Tyne, United Kingdom) introduced his talk with an impressive animation explaining the steps of flagellum assembly in bacteria. In *Salmonella enterica*, one major checkpoint, dictated by the length of the intermediate hook-basal body structure, is the substrate specificity switch of the flagellar type III secretion apparatus (3). Flagellar gene expression is regulated by a cascade of type III secretion chaperones and their substrates. Chaperone antagonism was the topic of an informative talk by P. Genevaux (Geneva, Switzerland), who highlighted the role of SecB, trigger factor (TF), and DnaK/DnaJ in protein folding and secretion (91). A deletion of the *secB* gene results in a cold-sensitive phenotype that can be relieved by knocking out the gene encoding TF (*tig*). The antagonistic effect of TF is due to its activity as a chaperone and is independent of its peptidyl-prolyl *cis*/*trans* isomerase activity. Furthermore, he showed that in a *tig*-null mutant more SecA protein and ribosomes are associated to the inner membrane, suggesting that TF is involved directly or indirectly in targeting proteins cotranslationally to the *sec* translocon.

J. Greenblatt (Toronto, Canada) gave a comprehensive talk on the identification and analysis of protein complexes. His presentation was divided into two parts. In the first part he described the systematic identification of protein complexes in *E. coli* by affinity purification using SPA (sequential peptide affinity) tags inserted into the chromosome (15). The SPA tag permits efficient purification of protein complexes containing the tagged gene product using a relatively simple procedure. Chromosomal tagging avoids overproduction of the target protein, thus allowing the purification and identification of protein complexes from cells that are physiologically equivalent to their wild-type parent. In the second part, Greenblatt introduced the so-called synthetic genetic array technology that allows the generation of genetic-interaction maps (E-MAP [epistatic miniarray profile]) (24). This procedure permits the detection of functional interactions between gene products, thus providing complementary information to the physical interaction map of gene products. As examples, he presented the E-MAP of the yeast early secretory pathway and gave insights into genetic interactions in *E. coli*.

PATHOGENICITY, VIRULENCE, AND ENDOSYMBIOSIS

A central subject of the session on pathogenicity, virulence, and endosymbiosis was how bacteria send signals to target cells. Molecular syringes of different kinds were a popular topic. G. Cornelis (Basel, Switzerland) charmed the audience with beautiful pictures of the *Yersinia* injectisome. This type III secretion system is evolutionarily related to bacterial flagella and functionally related to bacteriophage tails (26, 88). In contrast to phage, which inject DNA into their host bacteria, bacterial pathogens inject proteins to manipulate their eukaryotic hosts. Despite the difference in cargo and target cell, there are surprising similarities between both injection devices; the tail and syringe employ an analogous length determination mechanism involving a "tape measure" protein. H. Shuman (New York, NY) analyzed the proteins transported by another molecular syringe, the type IV secretion system. The broad host range of *Legionella*, which replicates intracellularly in both amoebae and human phagocytes, was exploited to identify gene products that perturb organelle trafficking in yeast (84). These effectors from *Legionella* not only act on basic eukaryotic functions, they appear to be encoded by genes that were acquired from eukaryotes by horizontal transfer (31). B. Uhlin (Umea, Sweden) described another player in the bacterial secretion game, namely, a type I transport system from pathogenic gram-negative bacteria. It not only secretes virulence factors into the medium, it also packages them in outer membrane vesicles for delivery to the target tissue (8). Uropathogenic *E. coli* and *Vibrio cholerae* transport toxins using these membrane vesicles. V. Pelicic (London, United Kingdom) described a bacterial surface structure mediating adhesion to the host cell, the type IV pilus of *Neisseria*. Genetic analysis divided its morphogenesis into four stages: assembly of the fibers in the periplasm, functional maturation, a peculiar retraction–counter-retraction step, and emergence of the pili on the cell surface (16).

Not all virulence is based on secreted factors. For example, lipids play an important role in mycobacterial pathogenicity, where they act as a protective barrier and as an immunomodulator. C. Guilhot (Toulouse, France) reported on polyketide synthases involved in the biosynthesis of mycobacterium-specific lipids (18). Two transferases are needed to activate these biosynthetic enzymes, making them attractive targets for drug treatment. Y. Av-Gay (Vancouver, Canada) presented results concerning the functions of 11 eukaryotic-like protein kinases (Pkn) found in *Mycobacterium tuberculosis*, which are also attractive potential drug targets. A systematic analysis similar to

the one described by C. Guilhot, combining the strengths of biochemistry, genetics, and proteomics, was used to characterize these kinases. Several examples were presented, including the PknH protein that was found to be important for the downregulation of intracellular growth, thus playing a role in the establishment of the well-known chronic infection by *M. tuberculosis* (74).

A relatively consistent observation with pathogenic bacteria is that virulence factors are frequently encoded on mobile DNA elements and that virulence genes are actively transcribed during infection but mostly silent during growth in laboratory cultures. M. Rhen (Stockholm, Sweden) presented a transcriptome analysis of *Salmonella* both during infection and in culture. Using mutational analysis, a phosphate-dependent RNA degrading enzyme, PNPase, was identified as a negative regulator of virulence gene expression in laboratory cultures (100). The virulence genes under the control of PNPase are clustered in two "islands of pathogenicity." J. Casadesus (Seville, Spain) talked about the regulation of virulence factors in *Salmonella* by DNA adenine methylation (Dam) (7, 99). The mechanisms of regulation are diverse. In the fimbrial operon, adenine methylation prevents transcriptional repression at the promoter by the nucleoid protein H-NS. On the other hand, methylation of a control sequence upstream of *traJ* prevents binding of the transcriptional activator Lrp. M. Van der Woude (York, United Kingdom) described the epigenetic regulation in *E. coli* of the reversible switching of gene expression, known as phase variation, which is dependent on Dam (89, 93). Switching of expression of the OMP, Ag43, involves interplay between the OxyR transcription repressor and methylation of its binding site. A mechanism for the inheritance of the methylation state was proposed.

CHROMOSOME DYNAMICS

The session on chromosome dynamic covered talks on the different steps in the bacterial cell cycle involving chromosome replication, chromosome partition, and cell division. B. Michel (Gif-sur-Yvette, France) reviewed multiple pathways characterized in *E. coli* permitting the reinitiation of DNA synthesis at a stalled replication fork. The rescue of stalled forks is a critical function since chromosome replication in bacteria involves the continuous synthesis of several million base pairs of DNA. Despite the high processivity of the DNA replication machinery, stalling probably occurs multiple times during a single round of replication. The failure to reinitiate a stalled fork can lead to chromosome instability and cell death. Michel then described recent work on the role of the DNA helicase UvrD in reinitiating DNA replication at stalled forks (10, 40, 41). UvrD works in concert with homologous recombination at the stalled replication fork in a pathway that is independent of the role of UvrD in mismatch and excision DNA repair. P. Polard (Jouy-en-Josas, France) talked about PriA, a DNA helicase involved in replication restart at stalled forks in *B. subtilis* (14, 96). Recent results show that PriA localizes with the *B. subtilis* DNA replication "factory" and that a protein-protein interaction between PriA and SSB, the major single-stranded DNA-binding protein, is necessary to recruit PriA to stalled forks.

F. Boccard (Gif-sur-Yvette, France) described recent work showing that the *E. coli* chromosome is organized into four macrodomains and two nonstructured regions (35, 92). Each macrodomain is localized to a specific region in the cell and follows a characteristic choreography during chromosome replication and cell division. R. Dame (Amsterdam, The Netherlands) reported single-molecule studies on the "bridging" of duplex DNA by H-NS, a nucleoid protein involved in the compaction of the bacterial chromosome (29). Chromosome "unzipping" involves the stepwise breaking of individual H-NS bridges and requires relatively little force. These results suggest an explanation for how H-NS can compact the chromosome without interfering with processes such as transcription and DNA replication.

J. Errington (Oxford, United Kingdom) talked about the formation of the septum during cell division in *B. subtilis*, presenting recent results on the genes involved in this process, on the composition and structure of the septum, and on the dynamics of the closure of the septum (50, 78, 81). J. Lowe (Cambridge, England) presented structural and functional data on FtsK, a DNA translocase involved in the partition of the replicated chromosome into daughter cells. The translocase domain of FtsK forms a hexameric ring structure encircling double-stranded DNA and recognizes a specific signal, the KOPS sequence, involved in controlling the partition of the replicated chromosomes (67, 85). J. Alonso (Madrid, Spain) presented genetic and structural work on systems controlling segregation of the low-copy-number plasmid pSM19035, a broad-host-range plasmid in the gram-positive bacterium *Streptococcus pyogenes* (33, 60). A "random walk" model for segregation, driven by the binding of the segregation proteins to the plasmid, was proposed.

COMPETENCE, DNA UPTAKE, AND MULTICELLULAR BEHAVIOR

Competence is the physiological state in which a bacterium is capable of importing exogenous DNA. Transformation is the process in which the imported DNA is integrated into the genome. B. Maier (Münster, Germany) reported single-molecule experiments on DNA import using live *B. subtilis* (65). Exogenous DNA enters at the pole of the elongated bacillus. Force measurements indicate that a powerful molecular motor feeds DNA into the cell in a continuous process. D. Dubnau (Newark, NJ) presented his latest molecular model for the DNA uptake machinery in *B. subtilis* (19, 49, 57). This protein complex consists of a type IV-like pseudopilus that fixes exogenous double-stranded DNA to the cell wall and mediates contact with a DNA receptor protein associated with the membrane channel complex. Retraction of the pseudopilus is powered by the proton motive force across the membrane creating a movement that drags the DNA molecule through the channel. The DNA strands are separated upon internalization; an unidentified nuclease digests one strand of the DNA as the other strand translocates into the cytoplasm. In support of this model Dubnau presented work showing that a DNA helicase and an ssDNA-binding protein involved in transformation colocalize with the DNA as it enters the cytoplasm.

P. Graumann (Freiburg, Germany) presented work on the function and cellular localization of the DNA-binding proteins RecA, RecN, and Smf during transformation in *B. subtilis* (53,

54). J.-P. Claverys (Toulouse, France) reported on the interaction between two ssDNA binding proteins in the cytoplasm during the transformation of *Streptococcus pneumoniae* (9, 21, 73). DprA binds cooperatively and protects the ssDNA against nucleases as it enters the cytoplasm. The recombination protein RecA is then loaded by a protein-protein interaction with DprA forming a complex that mediates exchange of the ssDNA with the recipient chromosome. An alternative outcome of the internalization of the exogenous DNA is degradation. DNA uptake, thus, could have a second role: the supply of deoxyribonucleotides for chromosome replication.

A link between competence and nutrition was described by M. Blokesch working in G. Schoolnik's group (Stanford, CA). Environmental strains of *Vibrio cholerae* become competent upon exposure to chitin (69), which they meet when forming biofilms on the exoskeletons and molds of copepods, tiny crustaceans that are important elements of marine food webs. Chitin induces the expression of genes involved in the extracellular degradation and uptake of this polysaccharide, as well as the expression of genes encoding the pseudopilus that mediates the import of exogenous DNA. Transformation during chitin-induced competence could explain much of the mosaic structure of the *V. cholerae* genome.

G. Velicer (Tübingen, Germany) capped the last session of the meeting with a particularly fascinating story on the social life of bacteria. The main character is a common soil proteobacterium, *Myxococcus xanthus*, with uncommon characteristics. It has behavior that ranges from social motility to cooperative predation and the development of collective spore-bearing fruiting bodies as a reaction to starvation. Under conditions of ample food, an obligate cheater arose, which exploited the social instinct of its comrades. When starvation cycles resumed, the dominant cheater population crashed, but a social phoenix ascended from the ashes. The 9-Mb genome of the mutant was sequenced revealing a single point mutation, which distinguishes it from its cheater ancestor, in an uncharacterized acetyltransferase gene (37, 95).

CONCLUSION

The meeting bought together researchers working on a broad range of topics in the molecular and cellular microbiology of prokaryotic organisms. Certain talks, including those by J. Parkhill, N. Mann, and G. Velicer, demonstrated that current methodologies can be used to link a complex phenotype to a genotype. Informal discussions about the organization of future conferences led to the decision to introduce more ecologically oriented microbiology into the next meeting since the panoply of "-omics" developed over the past decade should begin to permit the analysis at the molecular and cellular level of complex behavior within microbial communities.

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