SYMPOSIUM

Exploring the Diversity of the Microbial World

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Yale’s Microbial Diversity Institute (MDI†) comprises scientists who seek to understand the largely unknown microbial world. In the first MDI symposium at Yale’s West Campus in October 2010, four speakers discussed their research in diverse fields within the microbial sciences. The highlights of the symposium are presented here along with an outlook on the future of the MDI.

INTRODUCTION

The recently formed Microbial Diversity Institute (MDI) at Yale University gathers scientists with a common goal of understanding the diverse microbial world. Their research areas range from bacterial molecular biology to the role of microbes in the environment and human health. This effort should be applauded considering the omnipresent yet poorly characterized nature of our prokaryotic ancestors. In short, the MDI will likely play an integral role in discovering, describing, and disseminating information about the microbial world.

In October 2010, the MDI sponsored its first symposium on Yale’s West Campus. Dr. Howard Ochman, Chair of the Institute, began by expressing his excitement about the day’s events and the future of the MDI. The symposium was part of a larger effort to recruit microbiologists with diverse interests to share their research with the Yale community and foster new ideas and collaborations. The symposium provided a platform for four distinguished microbiologists to present their research, with topics ranging from bacterial cell biology to developing novel antibiotics.

SPATIAL ORGANIZATION OF TRANSCRIPTION IN PROKARYOTES

Paula Montero Llopis, a current Yale graduate student, presented recently published work that is changing our understand-
standing of prokaryotic cellular organization. She and her colleagues discovered that bacteria spatially localize mRNA to the site of its genetic locus [1]. Prior to their finding, the prevailing dogma was that after transcription, mRNA was free to diffuse. This was supported by studies showing that the diffusion coefficient of mRNA is sufficient for mRNA to move throughout the cell before being degraded [2,3]. However, using quantitative fluorescence in situ hybridization, Montero Llopis et al. demonstrated that mRNAs in both Caulobacter crescentus and Escherichia coli displayed limited mRNA dispersion. This work may result in a paradigm shift in how we view bacterial cell biology: prokaryotes may be able to localize important physiological reactions much as eukaryotes do, but without the need for defined intracellular organelles. The study also provides a basis for predictive models that may help to uncover novel protein-protein interactions by virtue of being encoded in proximate loci. By being encoded proximally in the genome, the proteins are translated within a defined spatial region that increases their propensity to interact. While this hypothesis awaits experimental elucidation, the prokaryotic cell now must be considered as an organized spatiotemporal system.

MARINE MICROBIAL DIVERSITY

Dr. Ed DeLong, Morton and Claire Goulder Professor in the Department of Civil and Environmental Engineering and Biological Engineering at MIT, explained his work uncovering the transcriptomes of marine microbes. To better understand the population dynamics of these microbes, he sequenced transcripts common to different bacterial populations in the world’s oceans. DeLong pointed out that the number of proposed phyla of bacteria has increased from 11 in 1987 to 100 in 2006, directly corresponding to the development of cultivation-independent techniques such as metagenomics. While population sequencing is a powerful tool, it has limitations. This method assesses bacteria at a given point in time, even though bacteria are among the most dynamic organisms on earth. Thus, DeLong argued that uncovering mRNA sequence dynamics is integral to understanding the functional impact of marine microbes. One method he stressed involved collecting RNA from a microbial community, amplifying and then converting the sequences to a cDNA library before pyrosequencing [4]. Repeating this procedure in the same community over time can elucidate the dynamics of gene expression. DeLong’s future research is poised to uncover novel processes and species of bacteria as well as provide important insights into how bacteria drive and respond to environmental changes.

SOURCE-SINK MODEL FOR VIRAL TRANSMISSION

Dr. Eddie Holmes, Professor in Biology and Eberly College of Science Distinguished Senior Scholar at Pennsylvania State University, discussed his research on the evolution and transmission of RNA viruses. He argued that despite a dramatic decrease in typhoid and whooping cough-related deaths over the last century, the relatively high morbidity rate caused by influenza warrants further research into RNA viruses. Uncovering the rules of viral evolution may help predict and prevent new outbreaks [5,6]. Holmes also described how comparative genomics assesses host switching in viruses that eventually infect humans. He used the evolution of influenza as an example [7]. Additionally, Holmes discussed how the global transmission of influenza might follow a source-sink model. In this scenario, viral transmission is highly seasonal in temperate regions, where influenza is strongly associated with the winter season. Therefore, these geographical regions act as sinks, with local viral extinction in the summer. Conversely, influenza has a more annual pattern of transmission in tropical regions, including Southeast Asia, which might act as a global source of virus. His more recent work has been aimed at understanding the emergence and spread of the swine flu from New York City to upstate
New York based on modeling from epidemiological data.

NEW ANTIBIOTICS TARGET QUORUM SENSING

The last speaker, Dr. Bonnie Bassler, Professor of Molecular Biology at Princeton University, illustrated how basic research can translate into practical applications. Bassler’s work focuses on quorum sensing, bacterial communication via chemical messages. This allows individuals to distinguish members of their own species and other species within their environment. The chemical messages eventually lead to changes in gene expression, eliciting a range of bacterial cellular responses, including antibiotic production, sporulation, symbiosis, virulence, conjugation, competence, motility, and biofilm formation [8,9]. Bassler focused on how to hijack this communication system to dampen bacterial virulence.

Quorum sensing is not a new concept. Hastings and colleagues provided initial evidence for quorum sensing in 1970. In newly inoculated Photobacterium fischeri cultures, luminescence did not increase until a sufficient cell density was reached [10]. Luminescence is an adaptive property that serves this bacterium well in its symbiotic relationship with marine squid. Shortly thereafter, Silverman uncovered the signaling cascade underlying quorum sensing [11]. However, quorum sensing did not become a prominent research topic until the last decade, when Bassler discovered while working in Silverman’s laboratory as a postdoctoral candidate how luminescence in Vibrio harveyi was linked to quorum sensing [12].

Now, in her own laboratory, Bassler uses information on V. harveyi quorum sensing to develop novel antibiotics. Bassler explained how Gram-negative bacteria typically use acyl-homoserine lactone molecules as autoinducers to communicate with one another. This bacterial lexicon may elicit group behavioral changes. A chemical message may bind to a receptor on a neighbor’s membrane and transmit information via a phosphorylation cascade [8]. Alternatively, the chemical may pass through the membrane and bind to a transcription factor in the cytoplasm.

One of the outputs of quorum sensing is virulence. Disrupting quorum sensing in pathogenic bacteria may lead to new antibiotics. Bassler’s group screened for molecules that disrupted the function of LuxR- and LuxN-type proteins, which are respectively the cytoplasmic and membrane-bound receptors for the autoinducer. To identify potential antibiotics, researchers used Chromobacterium violaceum, a pathogenic bacteria, to screen for analogs that inhibited quorum sensing. The screen determined several molecules that antagonize CviR, a LuxR-type protein in C. violaceum. The molecules disrupted quorum sensing by either preventing CviR binding to DNA or by reducing its ability to activate transcription [13]. After demonstrating its ability to impede quorum sensing in an isolated bacterial population, the strongest antagonist, chlorolactone, was used to test if C. violaceum’s quorum sensing, and thus pathogenicity, could be disrupted in a live model organism. Using Caenorhabditis elegans, Bassler et al. showed that chlorolactone was effective in halting C. violaceum’s pathogenesis. Twenty micromoles of chlorolactone returned the lifespan of C. elegans fed with C. violaceum to near control level. In the near future, Bassler plans to perform similar experiments in mice with the hope that this type of work will lead to antibiotic development for clinical use.

At the end of her talk, Bassler put quorum sensing into a broader context. From an evolutionary perspective, she claimed that prokaryotic communication may have been the precursor of some aspects of eukaryotic life. For example, bacteria are able to distinguish self from non-self, which is reminiscent of the immune system. Bacteria provide a model system for studying basic cell-to-cell communication. Additionally, quorum sensing may be hijacked to promote the prevalence of “good” bacteria. Finally, Bassler believes that it is worth trying to uncover yet-unknown natural quorum sensing strategies, noting that “it is absurd to think that our few years of studying the phenomenon is any match for 4 billion years of evolution.”
CONCLUSION

The first Yale MDI Symposium invited four leading scientists to share their research. Each speaker not only discussed what has been discovered, but also gave a sense of what awaits exploration. Perhaps E. O. Wilson put it most aptly when describing the microbial world in his 2007 Technology, Engineering, Design (TED) Prize talk: “Nowadays in addressing microbial biodiversity, scientists are like explorers in a rowboat launched onto the Pacific Ocean. But that is changing rapidly with the aid of new technologies” [14]. That is precisely the nature of research at the MDI, the future of which could not be brighter.

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