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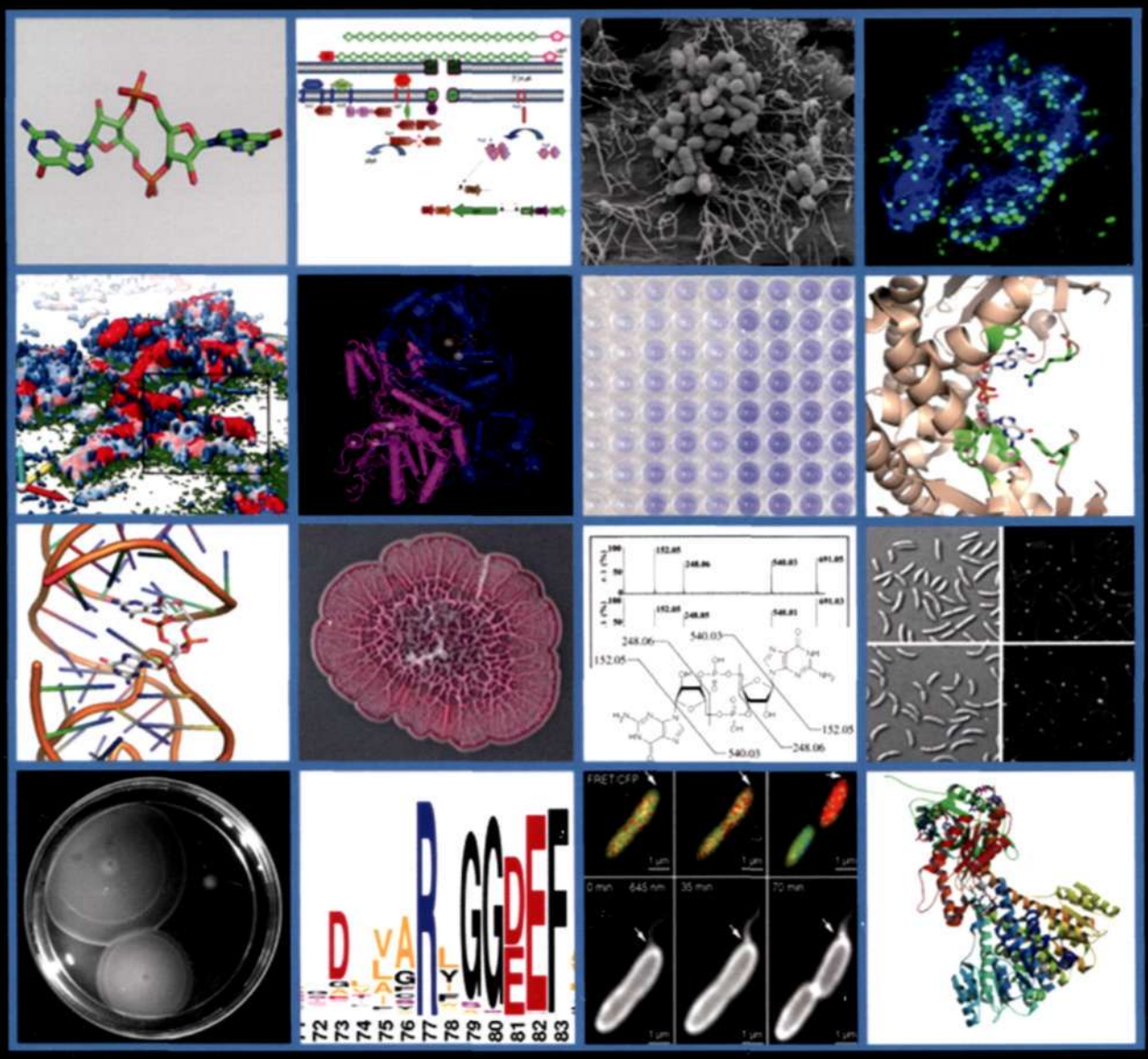

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REVIEWS

Cyclic di-GMP: the First 25 Years of a Universal Bacterial Second Messenger 1–52
Ute Römling, Michael Y. Galperin, Mark Gomelsky

Summary: Twenty-five years have passed since the discovery of cyclic dimeric (3′→5′) GMP (cyclic di-GMP or c-di-GMP). From the relative obscurity of an allosteric activator of a bacterial cellulose synthase, c-di-GMP has emerged as one of the most common and important bacterial second messengers. Cyclic di-GMP has been shown to regulate biofilm formation, motility, virulence, the cell cycle, differentiation, and other processes. Most c-di-GMP-dependent signaling pathways control the ability of bacteria to interact with abiotic surfaces or with other bacterial and eukaryotic cells. Cyclic di-GMP plays key roles in lifestyle changes of many bacteria, including transition from the motile to the sessile state, which aids in the establishment of multicellular biofilm communities, and from the virulent state in acute infections to the less virulent but more resilient state characteristic of chronic infectious diseases. From a practical standpoint, modulating c-di-GMP signaling pathways in bacteria could represent a new way of controlling formation and dispersal of biofilms in medical and industrial settings. Cyclic di-GMP participates in interkingdom signaling. It is recognized by mammalian immune systems as a uniquely bacterial molecule and therefore is considered a promising vaccine adjuvant. The purpose of this review is not to overview the whole body of data in the burgeoning field of c-di-GMP-dependent signaling. Instead, we provide a historic perspective on the development of the field, emphasize common trends, and illustrate them with the best available examples. We also identify unresolved questions and highlight new directions in c-di-GMP research that will give us a deeper understanding of this truly universal bacterial second messenger.

Diverse Functions of Restriction-Modification Systems in Addition to Cellular Defense 53–72
Kommireddy Vasu, Valakunja Nagaraja

Summary: Restriction-modification (R-M) systems are ubiquitous and are often considered primitive immune systems in bacteria. Their diversity and prevalence across the prokaryotic kingdom are an indication of their success as a defense mechanism against invading genomes. However, their cellular defense function does not adequately explain the basis for their immaculate specificity in sequence recognition and nonuniform distribution, ranging from none to too many, in diverse species. The present review deals with new developments which provide insights into the roles of these enzymes in other aspects of cellular function. In this review, emphasis is placed on novel hypotheses and various findings that have not yet been dealt with in a critical review. Emerging studies indicate their role in various cellular processes other than host defense, virulence, and even controlling the rate of evolution of the organism. We also discuss how R-M systems could have successfully evolved and be involved in additional cellular portfolios, thereby increasing the relative fitness of their hosts in the population.

Exploiting Quorum Sensing To Confuse Bacterial Pathogens 73–111
Breah LaSarre, Michael J. Federle

Summary: Cell-cell communication, or quorum sensing, is a widespread phenomenon in bacteria that is used to coordinate gene expression among local populations. Its use by bacterial pathogens to regulate genes that promote invasion, defense, and spread has been particularly well documented. With the ongoing emergence of antibiotic-resistant pathogens, there is a current need for development of alternative therapeutic strategies. An antivirulence approach by which quorum sensing is impeded has caught on as a viable means to manipulate bacterial processes, especially pathogenic traits that are harmful to human and animal health and agricultural productivity. The identification and development of chemical compounds and enzymes that facilitate quorum-sensing inhibition (QSI) by targeting signaling molecules, signal biogenesis, or signal detection are reviewed here. Overall, the evidence suggests that QSI therapy may be efficacious against some, but not necessarily all, bacterial pathogens, and several failures and ongoing concerns that may steer future studies in productive directions are discussed. Nevertheless, various QSI successes have rightfully perpetuated excitement surrounding new potential therapies, and this review highlights promising QSI leads in disrupting pathogenesis in both plants and animals.

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Molecular Regulation of Antibiotic Biosynthesis in *Streptomyces* 112–143
Gang Liu, Keith F. Chater, Govind Chandra, Guoqing Niu, Huarong Tan

Summary: Streptomycetes are the most abundant source of antibiotics. Typically, each species produces several antibiotics, with the profile being species specific. *Streptomyces coelicolor*, the model species, produces at least five different antibiotics. We review the regulation of antibiotic biosynthesis in *S. coelicolor* and other, nonmodel streptomycetes in the light of recent studies. The biosynthesis of each antibiotic is specified by a large gene cluster, usually including regulatory genes (cluster-situated regulators). These are the main point of connection with a plethora of generally conserved regulatory systems that monitor the organism's physiology, developmental state, population density, and environment to determine the onset and level of production of each antibiotic. Some CSRs may also be sensitive to the levels of different kinds of ligands, including products of the pathway itself, products of other antibiotic pathways in the same organism, and specialized regulatory small molecules such as gamma-butyrolactones. These interactions can result in self-reinforcing feed-forward circuitry and complex cross talk between pathways. The physiological signals and regulatory mechanisms may be of practical importance for the activation of the many cryptic secondary metabolic gene cluster pathways revealed by recent sequencing of numerous *Streptomyces* genomes.

Ocular Tropism of Respiratory Viruses 144–156
Jessica A. Belser, Paul A. Rota, Terrence M. Tumpey

Summary: Respiratory viruses (including adenovirus, influenza virus, respiratory syncytial virus, coronavirus, and rhinovirus) cause a broad spectrum of disease in humans, ranging from mild influenza-like symptoms to acute respiratory failure. While species D adenoviruses and subtype H7 influenza viruses are known to possess an ocular tropism, documented human ocular disease has been reported following infection with all principal respiratory viruses. In this review, we describe the anatomical proximity and cellular receptor distribution between ocular and respiratory tissues. All major respiratory viruses and their association with human ocular disease are discussed. Research utilizing *in vitro* and *in vivo* models to study the ability of respiratory viruses to use the eye as a portal of entry as well as a primary site of virus replication is highlighted. Identification of shared receptor-binding preferences, host responses, and laboratory modeling protocols among these viruses provides a needed bridge between clinical and laboratory studies of virus tropism.

Cover photograph (Copyright 2013, American Society for Microbiology. All Rights Reserved.): (Top row, leftmost column) c-di-GMP in open conformation (from Protein Data Bank [PDB], accession number 3N3T [Tchigvintsev et al.]). (Top row, second column) Schematic presentation of the c-di-GMP signaling circuit that controls surface location of LapA in *Pseudomonas fluorescens* (Römling et al., Microbiol. Mol. Biol. Rev. **this issue,** 2013). (Top row, third column) Micrograph of biofilm-forming *Escherichia coli* TOB1 interacting with HT-29 epithelial cells (reprinted from Wang et al., "Impact of biofilm matrix components on interaction of commensal *Escherichia coli* with the gastrointestinal cell line HT-29," Cell. Mol. Life Sci. **63:**2352–2363, 2006 [Fig. 2e], with kind permission of Springer Science + Business Media). (Top row, rightmost column) *Salmonella enterica* serovar Typhimurium cells expressing the biofilm regulator CsgD (green) and cellulose (blue) (reprinted from Grantcharova et al., J. Bacteriol. **192:**456–466, 2010). (Second row, leftmost column) Three-dimensional architecture of a *Vibrio cholerae* biofilm with cells (in blue) and protein matrix components in grey, red, and green (reprinted from Berk et al., Science **337:**236–239, 2012, with permission of AAAS). (Second row, second column) Molecular structure of the c-di-GMP phosphodiesterase BlrP1, a photoreceptor (from the Molecular Modeling Database [MMDB], accession number 73882). (Second row, third column) *Listeria monocytogenes* biofilm levels measured using a crystal violet dye-binding assay. The EGD-e strain and mutants in c-di-GMP phosphodiesterases were grown for 6 days at 30°C in LB supplemented with 3% glycerol (L. H. Chen and M. Gomelsky, unpublished data). (Second row, rightmost column) Molecular structure of the eukaryotic c-di-GMP receptor STING in complex with c-di-GMP (from PDB, accession number 4EMT [Shu et al.]). (Third row, leftmost column) Molecular structure of the GEMM type 1 riboswitch bound to c-di-GMP (from PDB, accession number 3IRW). (Third row, second column) Red, dry, and rough (rdar) biofilm-forming *Escherichia coli* Nissle 1917 grown on Congo Red agar plate (YESCA [yeast extract-Casamino Acids] medium) at 28°C for 48 h (U. Römling, unpublished data). (Third row, third column) Ion fragmentation pattern of c-di-GMP obtained by mass spectrometry (reprinted from Simm et al., Mol. Microbiol. **53:**1123–1134, 2004). (Third row, rightmost column) Localization of the c-di-GMP receptor PopA to the cell pole in *Caulobacter crescentus* (Duerig et al., Genes Dev. **23:**93–104, 2009). (Bottom row, leftmost column) Swimming behavior of *E. coli* MG1655 wild type and YcgR c-di-GMP receptor mutants (reprinted from Fang and Gomelsky, Mol. Microbiol. **76:**1295–1305, 2010). (Bottom row, second column) Part of the sequence logo of the GGDEF diguanylate cyclase domain (Römling et al., Microbiol. Mol. Biol. Rev. **this issue,** 2013). (Bottom row, third column) Asymmetrical distribution of c-di-GMP upon cell division in *Pseudomonas aeruginosa* (reprinted from Christen et al., Science **328:**1295–1297, 2010, with permission of AAAS). (Bottom row, rightmost column) Molecular structure of the di-guanylate cyclase PleD of *C. crescentus* (from PDB, accession number 2WB4 [Wassmann et al.]).