

Identification of *Escherichia coli* host genes that influence the bacteriophage lambda (λ) T4rII exclusion (Rex) phenotype, pp. 1087–1102

Hibah Alattas, Shirley Wong, and Roderick A. Slavcev

Despite its historic role in evolving our understanding of modern molecular genetics, the mechanism governing the bacteriophage T4rII exclusion (Rex) phenotype has remained a mystery for over six decades. The Rex system is thought to be a form of defense by bacteriophage lambda to protect its host bacterium against other invading bacteriophage. While its mechanism remains undiscovered, Alattas, Wong, and Slavcev have revealed the involvement of key host genes and their products in Rex. For the first time, they have linked the manifestation of Rex to host stress responses. Understanding Rex can ultimately provide important clues toward eukaryotic exclusion systems and control mechanisms.

Humanized *Drosophila* model of the Meier-Gorlin syndrome reveals conserved and divergent features of the Orc6 protein, pp. 995–1007

Maxim Balasov, Katarina Akhmetova, and Igor Chesnokov

Orc6 is a component of the Origin Recognition Complex important for the initiation of DNA replication. In order to study the functions of Orc6 in vivo, Balasov, Akhmetova, and Chesnokov used fly, human and hybrid human-*Drosophila* genes to rescue the orc6 deletion in *Drosophila* and created the “humanized” *Drosophila* model of the Meier-Gorlin syndrome (MGS). Authors analyzed two Orc6 mutations causing MGS and discovered that, despite having different underlying molecular mechanisms, both MGS mutations resulted in similar phenotypes, deficient pre-replicative complex formation, and reduced DNA replication. Their studies also revealed the importance of evolutionary conserved and variable domains of Orc6 and allowed the studies of human protein functions in live animal heterologous system.

Inferring the allelic series at QTL in multiparental populations, pp. 957–983

Wesley L. Crouse, Samir N. P. Kelada, and William Valdar

Multiparent populations are experimental populations generated by breeding together a genetically diverse set of inbred founder strains to produce individuals whose genomes are random mosaics of the founder haplotypes. In such populations, quantitative trait loci are typically detected by associating traits with variation in local haplotype state. This technique is powerful for QTL discovery but at present falls short of determining the allelic series, the assignment of haplotypes to underlying functional alleles. Crouse, Kelada, and Valdar describe a statistical method to infer the allelic series, demonstrating its performance by simulation and its use on several real data examples in mice and *Drosophila*.

A model of indel evolution by finite-state, continuous-time machines, pp. 1187–1204

Ian Holmes

How do instantaneous rate models of insertion-deletion processes relate to distributions over pairwise sequence alignments? The only exactly-solved model is the 1991 Thorne Kishino Felsenstein (TKF) model, which is solved by a Pair Hidden Markov Model (HMM). Several attempts have been made to solve more realistic evolutionary models with long indels. Here, Holmes shows that by multiplying an alignment-generating Pair HMM with an infinitesimal alignment-perturbing evolutionary model, then renormalizing, Holmes obtains differential equations that closely approximate the true distribution and from which the TKF model emerges as a special case.

The broad transcription factor links hormonal signaling, gene expression, and cellular morphogenesis events during *Drosophila* imaginal disc development, pp. 1137–1152

Clinton Rice, Stuart J. Macdonald, Xiaochen Wang, and Robert E. Ward

Imaginal disc morphogenesis during metamorphosis in *Drosophila* provides an ideal system for studying the hormonal control of morphogenesis. During metamorphosis, ecdysone signaling initiates a gene regulatory network that drives the elongation and eversion of adult

legs. A key intermediate in this network is the transcription factor Broad. Here, Rice *et al.* show that Broad is necessary for remodeling the extracellular matrix, promoting cell shape changes and rearrangements, and for maintaining expression of metabolic genes during early metamorphosis. Additionally, *broad* expression shuts down at the onset of metamorphosis; expression beyond this time disrupts leg development during the late prepupal and pupal stages.

Survival following traumatic brain injury in *Drosophila* is increased by heterozygosity for a mutation of the NF- κ B innate immune response transcription factor relish, pp. 1117–1136

Laura C. Swanson, Edna A. Trujillo, Gene H. Thiede, Rebecca J. Katzenberger, Evgenia Shishkova, Joshua J. Coon, Barry Ganetzky, and David A. Wassarman

Using a *Drosophila melanogaster* model of traumatic brain injury (TBI), Swanson *et al.* found that the NF- κ B transcription factor Relish (Rel) is a dose-dependent modifier of TBI outcomes. Proteomics analysis revealed that the relative abundance of Rel protein increased in fly heads shortly after a primary injury. Genetic analysis revealed that heterozygosity, but not homozygosity, for a null mutation of *Rel* (*Rel^{del}*) reduced detrimental consequences of TBI. Finally, gene expression analysis differentiated transcriptional targets of the Toll and Imd innate immune response pathways following TBI and identified gene expression changes that may underlie the beneficial effects of heterozygosity for *Rel^{del}*.

A conserved NRDE-2/MTR-4 complex mediates nuclear RNAi in *Caenorhabditis elegans*, pp. 1071–1085

Gang Wan, Jenny Yan, Yuhua Fei, Daniel J. Pagano, and Scott Kennedy

Small regulatory RNAs such as siRNAs regulate splicing, transcription, and genome integrity in many eukaryotes. In *Caenorhabditis elegans*, siRNAs bind nuclear Argonautes, which interact with homologous pre-mRNAs to recruit downstream silencing effectors such as NRDE-2 to direct co-transcriptional gene silencing (cTGS or nuclear RNAi). Wan *et al.* identified a ubiquitously expressed nuclear protein MTR-4 as a new component of the *C. elegans* nuclear RNAi machinery. MTR-4 forms a conserved complex with NRDE-2 and is recruited to pre-mRNA by nuclear RNAi machinery to promote cTGS. Their work identifies a conserved complex that engages small regulatory RNAs to control fundamentally important biological processes in the nucleus.

This Month's Perspectives

John W. (Jan) Drake: a biochemical view of a geneticist *par excellence*

Linda J. Reha-Krantz and Myron F. Goodman

John W. Drake died February 2, 2020, a mathematical palindrome, which he would have enjoyed, given his love of “word play and logic,” as stated in his obituary, and echoed by his family, friends, students, and colleagues. Jan had a major influence on how scientists think about the molecular mechanisms of mutation. Beyond his scientific contributions, Jan, with the devoted assistance of his wife Pam, shepherded the Genetics Society of America's flagship journal *GENETICS* for 15 impactful years, from 1982 - 1996. Just before assuming the Editor-in-Chief role, Jan started from scratch the Laboratory of Molecular Genetics on the newly established Research Triangle Park campus of the National Institute of Environmental Health Science and led a renowned group of scientists for 30 years. Reha-Krantz and Goodman reflect on Jan's “creative and persistent interest in mutation,” as expressed in a Perspective article by Maurice Fox in the 1998 Mutation and Repair Issue of *GENETICS*, a special issue assembled in honor of Jan. Indeed, Jan exerted a profound influence on three generations (and counting) of scientists interested in replication fidelity, mutation rates, and the molecular basis of mutation. In the authors' view, the field of DNA polymerase fidelity was seeded by Jan's 1969 benchmark discovery of antitumorigenic T4 DNA polymerases, and by his willingness to share strains and insight with biochemists, including those of the authors. Reha-Krantz and Goodman hope that this review will provide insight into what meaning of Jan's phrase “think like a geneticist,” a vocation that Jan was proud to champion.