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DNA rereplication is susceptible to nucleotide-level mutagenesis, pp. 467–482

Duyen T. Bui and Joachim J. Li

The initiation of eukaryotic DNA replication at replication origins is tightly regulated to prevent re-initiation and re-replication within each cell cycle. This regulation is critical for genome stability as re-replication is an extremely potent inducer of chromosomal rearrangements, such as amplifications and aneuploidy. Bui and Li show in budding yeast that passage of a re-replication fork also facilitates frameshift mutations and base substitutions through the apparent attenuation of DNA mismatch repair during re-replication. This susceptibility to nucleotide level mutations broadens the potential role of re-replication in the genome instability of cancer cells, which often exhibit deregulated replication initiation proteins.

***beditor*: a computational workflow for designing libraries of guide RNAs for CRISPR-mediated base editing, pp. 377–385**

Rohan Dandage, Philippe C. Després, Nozomu Yachie, and Christian R. Landry

The biological relevance of the present method pertains to CRISPR-mediated base editing technology that has opened new avenues for scar-free genome-wide mutagenesis and thus to a wide range of applications in genome editing. In this manuscript, Dandage *et al*. present an easy-to-use computational workflow called *beditor* that facilitates the design of guide RNAs libraries for CRISPR-mediated base editing and demonstrate its potential to be used widely. The novelty of this method lies in the ability to explore the full potential of CRISPR-mediated base editing technology and therefore, to uncover novel biological insights that are not possible with other currently-available methods.

Proteostasis environment shapes higher-order epistasis operating on antibiotic resistance, pp. 587–597

Rafael F. Guerrero, Samuel V. Scarpino, João V. Rodrigues, Daniel L. Hartl, and C. Brandon Ogbunugafor

Epistasis is widely regarded as one of the most important phenomena in genetics. It proposes that the combined effects of mutations cannot be easily predicted from their individual effects. In the present study, Guerrero *et al*. examine how a key aspect of the cellular environment influences epistasis acting on an enzyme target of antibiotics: the protein quality control network. The authors measure how different protein quality control environments dictate epistasis acting on drug resistance. The findings fortify the role of the environment in how mutations interact, which may help us to predict how antibiotic resistance will evolve and understand how transgenic mutations affect a phenotype of interest.

Genetic variation for ontogenetic shifts in metabolism underlies physiological homeostasis in *Drosophila*, pp. 559–574

Omera B. Matoo, Cole R. Julick, and Kristi L. Montooth

Organismal physiology emerges from metabolic pathways and structures that can vary across development and among individuals. Matoo, Julick, and Montooth found significant variation, both genetic and ontogenetic, in mitochondrial physiology in wild-type and mitochondrial-nuclear genotypes of *Drosophila*. Despite significant variation in the timing of a vital metabolic shift from anaerobic to aerobic ATP production, the authors found remarkable physiological homeostasis for mitochondrial physiology and organismal metabolic rate. A genotype with a mitochondrial-nuclear incompatibility that compromises oxidative phosphorylation appeared to physiologically compensate by relying on multiple ways to generate ATP, but at the cost of generating more free radicals and having compromised mitochondrial membrane potential.

Instability of the pseudoautosomal boundary in house mice, pp. 491–509

Andrew P. Morgan, Timothy A. Bell, James J. Crowley, and Fernando Pardo-Manuel de Villena

Faithful segregation of mammalian X and Y chromosomes in male meiosis depends on pairing and recombination in a short interval of residual sequence homology known as the pseudoautosomal region (PAR). Yet despite this apparent functional constraint, the size and structure of the PAR varies widely within and between species. Here Morgan *et al*. characterize recombination and copy-number variation in PARs from different subspecies of house mice (*Mus musculus*). They identify several independent shifts of the PAR boundary in the Mus genus, at least one involving a complex rearrangement, and demonstrate pervasive copy-number variation at the PAR boundary in wild populations. Their findings suggest that the intensity of recombination activity in and near the PAR and weak constraints on its structure lead to unusual levels of allelic diversity, consistent with a growing body of evidence for distinct pathways regulating PAR and autosomal recombination.

The role of insulators in transgene transvection in *Drosophila*, pp. 511–530

Pawel Piwko, Ilektra Vitsaki, Ioannis Livadaras, and Christos Delidakis

Precise activity of a gene requires its promoter to be matched with an appropriate enhancer. Insulators are DNA elements which can limit inappropriate enhancer-promoter interactions. More recently, their ability to stimulate gene activity has been also recognized. Piwko *et al*. explore the role of insulators in mediating transvection, a case of interchromosomal enhancer-promoter interaction in *Drosophila*. The authors find that the activity of insulators underlies transvection and that the strength of this interaction is determined by the relative arrangement and identity of interacting insulators, enhancers and promoters. The present study highlights the role of insulators as powerful and versatile gene regulators.

Divergent allele advantage provides a quantitative model for maintaining alleles with a wide range of intrinsic merits, pp. 575–586

Thorsten Stefan, Louise Matthews, Joaquin M. Prada, Colette Mair, Richard Reeve, and Michael J. Stear

A striking feature of the antigen coding genes of the Major Histocompatibility Complex (MHC) is their genetic diversity. However, the exact mechanisms maintaining this diversity remain elusive. Modelling indicates that Divergent Allele Advantage (DAA) can maintain high levels of allelic diversity without requiring that all alleles confer unrealistically similar levels of fitness. Stefan *et al*. develop a model that can be applied to both livestock breeding and conservation, providing a better way of identifying superior heterozygotes and quantifying the advantages of genetic diversity at the MHC. The model also moves beyond additive genetic effects to provide a route to incorporate interactions between alleles in selective breeding programs.

This Month's Perspectives

Sex and the single fly: a perspective on the career of Bruce S. Baker

Michelle Arbeitman, Deborah Andrew, Elizabeth Chen, Devanand Manoli, and Lisa Ryner

Bruce Baker's laboratory made a huge impact on our understanding of *Drosophila* sex determination mechanisms. To celebrate these accomplishments, members of Bruce's laboratory describe the trailblazing science that led to mechanistic understanding of how sex differences in morphology and behavior arise, as well as how having only a single X chromosome is compensated for in males. Several decades of cutting-edge research from the Baker lab revealed both compelling and unexpected molecular mechanisms at work in the biology of sex differences.