ISSUE HIGHLIGHTS

Intratumor heterogeneity in evolutionary models of tumor progression, pp. 461–477

Rick Durrett, Jasmine Foo, Kevin Leder, John Mayberry and Franziska Michor

At the time of diagnosis most tumors show a striking amount of heterogeneity in measurable phenotypes, despite their monoclonal origin. Such heterogeneity has implications for diagnosis, treatment efficacy, and the identification of drug targets. These investigators obtain analytical estimates for the extent of intratumor heterogeneity, and they quantify the effects of system parameters on a tumor trait. This work contributes to a mathematical understanding of intratumor heterogeneity and is also applicable to organisms like bacteria, agricultural pests, and other microbes.

Germline fitness-based scoring of cancer mutations, pp. 383–393

Andrej Fischer, Chris Greenman and Ville Mustonen

Cancer develops by Darwinian evolution of a cell population: malignant cells have a fitness advantage over normal cells. Because these dynamics are complex, finding the key alterations among a large background of passenger variation is difficult. Would knowing the germline fitness effects of these variants help? Meaningful estimates for germline fitness effects of mutations can be extracted from protein domain alignments by application of population genetic theory. The authors show that for cancer mutations in protein kinases, germline fitness indeed helps explain the variation seen in tumor suppressor genes.

The Hog1 mitogen-activated protein kinase mediates a hypoxic response in *Saccharomyces cerevisiae*, pp. 325–338

Mark J. Hickman, Dan Spatt and Fred Winston

Most types of cells respond to changes in oxygen levels by altering gene expression. This article describes a previously unknown pathway that yeast cells use to respond to low oxygen (hypoxia) that involves the Hog1 mitogen-activated protein kinase (MAPK), a protein kinase conserved from yeasts to humans that is well known for its role in the osmotic stress response. The authors show that Hog1 receives distinct signals—hypoxia and osmotic stress—and activates distinct downstream events.

Wheat hybridization and polyploidization results in deregulation of small RNAs, pp. 263–272

Michal Kenan-Eichler, Dena Leshkowitz, Lior Tal, Elad Noor, Cathy Melamed-Bessudo, Moshe Feldman and Avraham A. Levy

Interspecies hybridization and polyploidization play an important role in plant speciation. This article describes epigenetic events that occur early during speciation via allopolyploidization. The abundance of small RNAs corresponding to transposable elements decreased greatly in the allopolyploid, and this correlated with hypomethylation of transposable elements, a hallmark of active elements. This deregulation of small RNAs involved in maintaining genome integrity may be one of the barriers that controls gene flow between related species.

Circumventing heterozygosity: Sequencing the amplified genome of a single haploid *Drosophila melanogaster* embryo, pp. 239–246

Charles H. Langley, Marc Crepeau, Charis Cardeno, Russell Corbett-Detig and Kristian Stevens

Heterozygosity hampers genome assembly and hinders a full accounting of genomic polymorphism and divergence. The authors solve these problems for Drosophila by sequencing the genome of a single haploid *Drosophila melanogaster* embryo after its *in vitro* amplification. This facilitates extensive population genomic analysis of the natural variation of this model organism and demonstrates the feasibility of routine genome sequencing from very small amounts of tissue.

Detecting major genetic loci controlling phenotypic variability in experimental crosses, pp. 435–447

Lars Rönnegård and William Valdar

Traditional methods for detecting genes that affect complex traits ask whether differences in genotype produce differences in the mean phenotype. Largely ignored are differences in variability about that mean, despite the fact that the relative constancy of an individual's character is often of great interest practically (*e.g.*, blood pressure). This article describes a flexible statistical procedure for detecting genes that affect variability in commonly used experimental populations.

Differential contributions of histone H3 and H4 residues to heterochromatin structure, pp. 291–308

Qun Yu, Lars Olsen, Xinmin Zhang, Jef D. Boeke and Xin Bi

Transcriptional silencing is mediated by heterochromatin and affected by specific histone residues. How do specific histone residues contribute to heterochromatin structure? These authors describe an extensive set of histone mutations that affect silencing by altering the structure, stability, and/or conformational heterogeneity of heterochromatin. Surprisingly, some histone mutations that have no apparent effect on heterochromatin structure affect silencing, suggesting that a conventionally defined heterochromatin structure is necessary but not sufficient for silencing.