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Alternative polyadenylation directs tissue-specific miRNA targeting in *Caenorhabditis elegans* somatic tissues, pp. 757–774

Stephen M. Blazie, Heather C. Geissel, Henry Wilky, Rajan Joshi, Jason Newbern, and Marco Mangone

Alternative polyadenylation (APA) is observed in virtually all metazoans and results in mRNA isoforms with different 3'ends. It is routinely detected and can be altered in disease, but its biological role is still a mystery. Blazie *et al.* performed an in-depth analysis of the transcriptome and APAome of eight somatic tissues in worms and show mechanistic evidence that tissue-specific APA is used to evade miRNA regulation. This work also provides the first comprehensive tissue-specific worm transcriptome and APAome resource.

Increased power to dissect adaptive traits in global sorghum diversity using a Nested Association Mapping population, pp. 573–585

Sophie Bouchet, Marcus O. Olatoye, Sandeep R. Marla, Ramasamy Perumal, Tesfaye Tesso, Jianming Yu, Mitch Tuinstra, and Geoffrey P. Morris

In crop species, adaptation to different agroclimatic regions creates useful variation but also leads to unwanted genetic correlations. Bouchet *et al.* addressed this challenge in the cereal crop sorghum by developing a Nested Association Mapping (NAM) population, which reshuffles global genetic diversity for trait mapping. The NAM population consists of 2214 recombinant inbred lines genotyped at 90,000 markers, and was validated by mapping flowering time and plant height. Simulated traits demonstrated the NAM is a powerful tool for dissecting traits under strong selection.

Genotypic complexity of Fisher's geometric model, pp. 1049–1079

Sungmin Hwang, Su-Chan Park, and Joachim Krug

In his celebrated model of adaptation, Fisher assumed a smooth phenotype-fitness map with one optimum. This assumption is at odds with the rugged genotypic fitness landscapes with multiple peaks revealed by empirical studies. Hwang *et al.* performed a systematic analysis of the genotype-fitness map produced by Fisher's model and show that these fitness landscapes actually can be remarkably complex. They provide a precise quantitative characterization of ruggedness as a function of phenotypic dimensionality and distance from the optimal phenotype.

The hippo pathway maintains the equatorial division plane in the ciliate *Tetrahymena*, pp. 873–888

Yu-Yang Jiang, Wolfgang Maier, Ralf Baumeister, Gregory Minevich, Ewa Joachimiak, Zheng Ruan, Natarajan Kannan, Diamond Clarke, Joseph Frankel, and Jacek Gaertig

The mechanisms governing organelle pattern formation in ciliates are still poorly understood. Jiang *et al.* investigate how the cell duplicates its cortical pattern during cell division in the ciliate *Tetrahymena thermophila*. They used whole genome sequencing to identify a mutation that causes asymmetric cell division. The identified protein is a Hippo/Mst kinase that marks the cortex of the emerging anterior daughter cell, and is required to keep the division plane at the cell's equator.

Adipocyte Metabolic Pathways Regulated by Diet Control the Female Germline Stem Cell Lineage in *Drosophila melanogaster*, pp. 953–971

Shinya Matsuoka, Alissa R. Armstrong, Leesa L. Sampson, Kaitlin M. Laws, and Daniela Drummond-Barbosa

AND

Proteomics analysis identifies orthologs of human chitinase-like proteins as inducers of tube morphogenesis defects in *Drosophila melanogaster*, pp. 973–984

Sandra G. Zimmerman, Gennifer E. Merrihew, Michael J. MacCoss, and Celeste A. Berg

Two papers in this issue demonstrate novel proteomic approaches that enhance genetic analysis. Matsuoka *et al.* investigated how diet-regulated metabolic pathways influence *Drosophila* germline stem cells. They used proteomic analysis to find regulatory enzymes that respond rapidly to diet. Genetic manipulation of their expression uncovered new metabolic controls of germline stem cells. Zimmerman *et al.* investigated Chitinase-like proteins (CLPs), which contribute to antipathogenic responses and wound healing but are elevated in numerous diseases. *Drosophila* orthologs of human CLPs were identified by proteomics analysis as regulators of tube morphogenesis; genetic alteration of their expression disrupted epithelial tube formation.

Structural variation shapes the landscape of recombination in mouse, pp. 603–619

Andrew P. Morgan, Daniel M. Gatti, Maya L. Najarian, Thomas M. Keane, Raymond J. Galante, Allan I. Pack, Richard Mott, Gary A. Churchill, and Fernando Pardo-Manuel de Villena

Meiotic recombination ensures the faithful segregation of chromosomes and influences patterns of genetic diversity. Morgan *et al.* used genotype data from 6,886 Diversity Outbred mice to study local variation in recombination rates and the impact of genetic diversity on crossover distribution. They found almost one fourth of crossovers occur outside of putative recombination hotspots identified by previous CHIP-seq experiments. Crossovers were also suppressed in genomic regions with copy number variation (CNV), perhaps because CNVs alter chromatin structure, preventing chromosomes carrying different structural alleles from pairing normally.

Genetic dissection of nutrition-induced plasticity in insulin/insulin-like growth factor signaling and median lifespan in a *Drosophila* multiparent population, pp. 587–602

Patrick D. Stanley, Enoch Ng'oma, Siri O'Day, and Elizabeth G. King

The insulin/insulin-like growth factor signaling (IIS) and target of rapamycin (TOR) pathways have long been thought to be involved in how organisms respond to their nutritional environment. However, little is known about the genetic basis of naturally occurring variation in these pathways. In this study, Stanley *et al.* used a multiparent population to genetically dissect diet-dependent IIS/TOR expression and connect it to diet-dependent changes in lifespan.

Epistatic networks jointly influence phenotypes related to metabolic disease and gene expression in Diversity Outbred mice, pp. 621–639

Anna L. Tyler, Bo Ji, Daniel M. Gatti, Steven C. Munger, Gary A. Churchill, Karen L. Svenson, and Gregory W. Carter

In this study, Tyler *et al.* analyzed the complex genetic architecture of metabolic disease-related traits using the Diversity Outbred mouse population. By jointly analyzing epistasis across multiple phenotypes, they inferred a multi-scale network of quantitative trait loci (QTL) involving QTL-QTL, QTL-sex, and QTL-diet interactions that jointly influence body composition, serum markers, and transcriptome expression. They found that genetic contributions from different founder ancestries often combine to drive more extreme phenotypes, leading to the broad phenotypic diversity observed in this population.

This Month's Perspectives

A physicist's quest in biology: Max Delbrück and "complementarity", pp. 641–650

Bernard S. Strauss

Max Delbrück was trained as a physicist but made his major contribution in biology and ultimately shared a Nobel Prize in Physiology/Medicine. He was the acknowledged leader of the founders of molecular biology yet he failed to achieve his key scientific goals. His ultimate scientific aim was to find evidence for physical laws unique to biology: so-called "complementarity." He never did. The specific problem he initially wanted to solve was the nature of biological replication but the discovery of the mechanism of replication was made by others, in large part because of his disdain for the details of biochemistry. His later career was spent investigating the effect of light on the fungus Phycomyces, a topic that turned out to be of limited general interest. He was known both for his informality but also for his legendary displays of devastating criticism. His life and that of some of his closest colleagues was acted out against a background of a world in conflict. This essay describes the man and his career and searches for an explanation of his profound influence.

This Month in the American Journal of Human Genetics

MARRVEL: Integration of human and model organism genetic resources to facilitate functional annotation of the human genome, Am. J. Hum. Gent. 97(6)

Julia Wang, Rami Al-Ouran, Yanhui Hu, Seon-Young Kim, Ying-Wooi Wan, Michael Wangler, Shinya Yamamoto, Hsiao-Tuan Chao, Aram Comjean, Stephanie E. Mohr, Members of UDN, Norbert Perrimon, Zhandong Liu, Hugo J. Bellen

Model systems have been used to generate a wealth of information about genes whose homologs are implicated in human disease. However, accessing all the relevant information can be time-intensive and cumbersome. Now, Wang *et al.* introduce MARRVEL (Model organism Aggregated Resources for Rare Variant ExpLoration; http://marrvel.org), a curated database that provides users with experimental and computational information about human genes and their homologs. How might MARRVEL be used? In an example provided by the authors, investigators could turn to MARRVEL when evaluating and prioritizing variants identified in the exomes of humans with rare disorders. By bringing together pertinent information form more than a dozen existing databases, MARRVEL might just become a site for one-stop 'shopping' in the study and evaluation of human mutations.