GENETICS, Vol. 206, August 2017, Copyright © 2017

Evolving mistranslating tRNAs through a phenotypically ambivalent intermediate in *Saccharomyces cerevisiae*, pp. 1865–1879

Matthew D. Berg, Kyle S. Hoffman, Julie Genereaux, Safee Mian, Ryan S. Trussler, David B. Haniford, Patrick O'Donoghue, and Christopher J. Brandl

It is increasingly apparent that the genetic code is not static and that organisms use variations in the genetic code for selective advantage. Berg *et al*. investigate the mechanisms by which mistranslating tRNAs occur and how the genetic code evolves by examining the selection of serine tRNAs that incorrectly add serine at proline codons in *Saccharomyces cerevisiae*. They show that a serine tRNA with a proline anticodon is toxic; however, mistranslating tRNAs can evolve through intermediate tRNA variants that decrease function. tRNAs with these "ambivalent" mutations are maintained in cells, with no obvious consequence. If the ambivalent intermediates undergo an anticodon mutation, mistranslation results at low, non-toxic levels.

Towards universal forward genetics: using a draft genome sequence of the nematode *Oscheius tipulae* to identify mutations affecting vulva development, pp. 1747–1761

Fabrice Besnard, Georgios Koutsovoulos, Sana Dieudonné, Mark Blaxter, and Marie-Anne Félix

Understanding evolution requires the comparison of more than a few model species, and exploration of the genotype/phenotype relationship is limited for species without fully sequenced genomes. Besnard and Koutsovoulos *et al.* propose a rapid, cost-effective procedure that iteratively uses a draft genome assembly and genetic mapping-by-sequencing to perform forward genetics. Using the nematode *Oscheius tipulae,* they identified the phenotyping-causing mutations in vulva mutants of the *cov*-3 gene, revealing unexpected orthology with *C. elegans mig-13*. Their method provides a roadmap for forward genetics in non-model species.

Canalization by selection of *de Novo* induced mutations, pp. 1995–2006

Laura Fanti, Lucia Piacentini, Ugo Cappucci, Assunta M. Casale, and Sergio Pimpinelli

Waddington elaborated the concepts of "canalization and assimilation" to explain how an apparently somatic, stress-induced variant could become heritable through the germline in *Drosophila*. He resolved this seemingly Lamarckian phenomenon by positing the existence of cryptic mutations that can be expressed and selected under stress. To investigate the relevance of such mechanisms, Fanti and Piacentini *et al*. performed experiments similar to Waddington's before isolating and fixing phenotypic variants. Their analysis of these variants revealed they were generated *de novo* by transposon insertions or DNA deletions, thus highlighting a novel mechanism for the apparent assimilation process of an acquired character.

Networks underpinning symbiosis revealed through cross-species eQTL mapping, pp. 2175–2184

Yuelong Guo, Sylwia Fudali, Jacinta Gimeno, Peter DiGennaro, Stella Chang, Valerie M. Williamson, David McK. Bird, and Dahlia M. Nielsen

Interactions between species are pervasive among plants, animals, and microbes, and identifying the molecular signals involved is an active area of research. Since existing analysis tools often focus on only one of the species involved in an interaction, Guo *et al*. developed an approach that identifies genes concurrently in both interacting partners. By applying this methodology to plants infected with a parasitic nematode, they constructed cross-species gene networks. In these, genetic variants producing molecular signals were connected to both the plant and parasite genes reacting to those signals.

Shrinking daughters: Rlm1-dependent G_1/S checkpoint maintains *Saccharomyces cerevisiae* daughter cell size and viability, pp. 1923–1938

Sarah Piccirillo, Deepshikha Neog, David Spade, J. David Van Horn, LeAnn M. Tiede-Lewis, Sarah L. Dallas, Tamas Kapros, and Saul M. Honigberg

How do cells ensure everything is set for cell division *before* they start the process? Piccirillo *et al*. demonstrate that a checkpoint in budding yeast can delay the birth of new buds in response to cell-wall stress. In an *rlm1D* mutant, this checkpoint was bypassed, resulting in precocious bud emergence. These precocious buds grew into daughter cells, but after cytokinesis the daughter cells suddenly shrank and died. In contrast, mother cells continued to divide, resulting in a characteristic "satellite group" morphology. By restoring the G1 delay to the mutant, Piccirillo *et al*. restored normal daughters and so conclude that the checkpoint monitors an event in G1 that is needed after cytokinesis.

A lysine desert protects a novel domain in the Slx5-Slx8 SUMO targeted Ub ligase To maintain sumoylation levels in *Saccharomyces cerevisiae*, pp. 1807–1821

Pragati Sharma, Janet R. Mullen, Minxing Li, Mikel Zaratiegui, Samuel F. Bunting, and Steven J. Brill

Sumoylation is required to repair protein-linked DNA damage, but its presence can limit the use of alternative repair pathways. Through a suppressor screen of mutants sensitive to protein-linked DNA damage, Sharma *et al*. isolated a variety of SUMO regulators, including two alleles of the ubiquitin ligase subunit *slx5-K*. These alleles created new lysine resides, highlighting the presence of a 400 amino acid lysine desert normally found within the Slx5 ligase. The new lysines resulted in auto-ubiquitination, partial Slx5 degradation, and increased global polysumoylation. The lysine desert is one solution to the problem that ubiquitin ligases face when evolving new domains.

Rapid evolution of ovarian-biased genes in the yellow fever mosquito (*Aedes aegypti*), pp. 2119–2137

Carrie A. Whittle and Cassandra G. Extavour

Males and females exhibit marked differences in phenotypes and gene expression, particularly in the gonads. Genes with male- or testis-biased expression typically have been shown to evolve rapidly in metazoans. Here, Whittle and Extavour provide an uncommon example that shows rapid evolution of protein sequences and shifts in codon usage of ovary-biased genes in the mosquito *Aedes aegypti*. They propose that this fast evolution may be explained by sexual selection during male swarming, ovary-sperm chemotaxis, and/or reduced male-male sperm competition.

Powerful genetic association analysis for common or rare variants with high-dimensional structured traits, pp. 1779–1790

Xiang Zhan, Ni Zhao, Anna Plantinga, Timothy A. Thornton, Karen N. Conneely, Michael P. Epstein, and Michael C. Wu

Genetic association studies often collect a wide range of complex traits, including high-dimensional and structured omics measurements. The complex nature of these data poses a challenge for traditional statistical and computational methods. Zhan *et al*. propose a novel method for testing the association between these high-dimensional structured traits and a set of common or rare genetic variants. By incorporating the high-dimensionality and structure in traits, their approach provides a new method that is methodologically flexible, biologically meaningful, statistically powerful, and computationally efficient.

This Month in the American Journal of Human Genetics

CRISPR/Cas9 mediated scanning for regulatory elements required for HPRT1 expression via thousands of large, programmed genomic deletions Am. J. Hum. Genet. 101(2)

Molly Gasperini, Gregory M. Findlay, Aaron McKenna, Jennifer H. Milbank, Choli Lee, Melissa D. Zhang, Darren A. Cusanovich, and Jay Shendure

The majority of known mutations that underlie Mendelian disorders lie in the coding region; the contribution of noncoding regions remains unclear. Now, Gasperini *et al*. devise a CRISPR/Cas9-based screening system, which they term ScanDel, to address the contribution of noncoding sites to phenotypes relevant to human disease. In a ScanDel screen, thousands of programmed deletions are used to scan a region of interest in a cell-based assay. Proof-of-concept work at the *HPRT1* locus suggests that variation in distal regions most likely does not contribute substantially to Lesch-Nyhan syndrome mutational burden. Further application of ScanDel will enable high-throughput interrogation of the contribution of noncoding genome to human disease.