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Evolution rapidly optimizes stability and aggregation in lattice proteins despite pervasive landscape valleys and mazes, pp. 1047–1057

Jason Bertram and Joanna Masel

The fitness landscapes of genetic sequences are high-dimensional and "rugged" due to sign epistasis. Empirical limitations and the abstractness of many landscape models limit our understanding of how ruggedness shapes the mode and tempo of sequence evolution. Bertram and Masel develop a biophysical model of protein evolution that captures the fundamental molecular tradeoff between stability and aggregation risk. In spite of abundant local peaks, adaptive paths are able to successfully complete the ascent from low to high fitness along "maze-like" paths. This represents a delicate balance of "hard but possible" adaptation that could apply more broadly wherever tradeoffs are present.

Gene–diet interactions: dietary rescue of metabolic defects in *spen*-depleted *Drosophila melanogaster*, pp. 961–975

Claire M. Gillette, Kelsey E. Hazegh, Travis Nemkov, Davide Stefanoni, Angelo D'Alessandro, J. Matthew Taliaferro, and Tânia Reis

Obesity results from a complex interplay of diet, behavior, and genetic background. Our genes are out of our control, but it may be possible to customize our diet to match changes in metabolism resulting from our genetic background. Here, Gillette *et al*. test this possibility using *Drosophila* predisposed to obesity by depletion of an RNA-binding protein called Split ends. Having carefully studied metabolism in these animals, they attempt to use customized diets to ameliorate their obesity and other metabolic phenotypes. Their results provide valuable information to support future endeavors to treat obesity through a deeper understanding of gene-diet interactions.

A cell fate switch in the *Caenorhabditis elegans* seam cell lineage occurs through modulation of the Wnt asymmetry pathway in response to temperature increase, pp. 927–939

Mark Hintze, Sneha L. Koneru, Sophie P. R. Gilbert, Dimitris Katsanos, Julien Lambert, and Michalis Barkoulas

Developmental phenotypes are often consistent across individuals within a population in the face of environmental and genetic challenges. However, these challenges can exceed the level of system robustness and change developmental outcomes. Hintze *et al*. use a set of epidermal stem cells in *Caenorhabditis elegans* to investigate cell fate patterning in response to changes in temperature and the genetic background. They find that asymmetric cell divisions shift to symmetric upon temperature increase through changes in the Wnt asymmetry pathway activation. Furthermore, different genetic backgrounds show varying degrees of sensitivity to cell fate errors upon temperature increase.

Imipridone anticancer compounds ectopically activate the ClpP protease and represent a new scaffold for antibiotic development, pp. 1103–1120

Samuel Jacques, Almer M. van der Sloot, Caroline C. Huard, Jasmin Coulombe-Huntington, Sarah Tsao, Sylvain Tollis, Thierry Bertomeu, Elizabeth J. Culp, Daniel Pallant, Michael A. Cook, Eric Bonneil, Pierre Thibault, Gerard D. Wright, and Mike Tyers

The imipridones ONC201 and ONC212 selectively kill cancer cells and have been ascribed multiple mechanisms-of-action. Genome-wide CRISPR knockout screens revealed that loss of the mitochondrial proteases CLPP and MIPEP confer strong resistance to both compounds. The impridones ectopically activate CLPP to cause uncontrolled lethal proteolysis, whereas MIPEP is required for CLPP processing to the active form. The imipridones similarly activate ClpP from Gram-positive and Gram-negative species to cause lethal proteolysis, and exhibit antibiotic activity against several clinically important human pathogens, including antibiotic-tolerant persister cells in *Staphylococcus aureus* biofilms. These mechanistic insights poise the impridone scaffold for anticancer and antibiotic development.

Decoupling of apoptosis from activation of the ER stress response by the *Drosophila* Metallopeptidase *superdeath*, pp. 913–925

Rebecca A. S. Palu, Hans M. Dalton, and Clement Y. Chow

Genetic diseases display a great deal of variability in patient outcomes, much of which is caused by differences in genetic background. The endoplasmic reticulum (ER) stress response commonly modifies degenerative disease. Understanding the genetic sources of variation in the ER stress response could improve individual diagnosis and treatment. In this study, Palu, Dalton, and Chow characterized one such modifier in *Drosophila melanogaster*, the membrane-bound metallopeptidase *CG14516* (*superdeath*). Loss of this enzyme suppresses ER stress-induced degeneration by reducing cell death without altering the beneficial activation of the unfolded protein response. Our findings make *superdeath* and its orthologues attractive therapeutic targets in degenerative disease.

Multiple loci control eyespot number variation on the hindwings of *Bicyclus anynana* butterflies, pp. 1059–1078

Angel G. Rivera-Colón, Erica L. Westerman, Steven M. Van Belleghem, Antónia Monteiro, and Riccardo Papa

Body plans often evolve through changes in the number of repeated parts or serial homologs. Using the butterfly *Bicyclus anynana*, Rivera-Colón *et al*. studied the genetics underlying heritability and regulation of serial homologs by examining the genetic architecture of the dorsal hindwing eyespot number in this species. By making crosses of butterfly families they determined a moderately high heritability for this phenotype. Next, using genome-wide markers, they identified a series of genomic loci that contribute to eyespot number variation. These findings suggest that serial homolog number variation is likely determined by regulatory changes at multiple loci and not by single master regulators.

Chromosome-level assembly of the *Caenorhabditis remanei* genome reveals conserved patterns of nematode genome organization, pp. 769–780

Anastasia A. Teterina, John H. Willis, and Patrick C. Phillips

Caenorhabditis is a group of nematodes that contains the important model organism *C. elegans*. Several chromosome-level genome assemblies exist for species within this group, but it has been a challenge to fully assemble the genome of members of the group with extensive within-population genetic variation. Here, Teterina, Willis, and Phillips present a chromosome-level assembly for highly polymorphic, outcrossing species *C. remanei*, which has emerged as an important model system for evolutionary genetics that complements the powerful functional genetics possible within the self-reproducing *C. elegans*. They also provide a comparison between the genomes of these two species.

Insights into the involvement of spliceosomal mutations in myelodysplastic disorders from analysis of SACY-1/DDX41 in *Caenorhabditis elegans*, pp. 869–893

Tatsuya Tsukamoto, Micah D. Gearhart, Seongseop Kim, Gemechu Mekonnen, Caroline A. Spike, and David Greenstein

Mutations affecting spliceosomal proteins are frequently found in hematological malignancies. DDX41/Abstrakt is a metazoan-specific spliceosomal DEAD-box RNA helicase found to be recurrently mutated in relapsing cases of acute myeloid leukemia, as well as in inherited myelodysplastic syndromes. Here, Tsukamoto *et al*. conduct a comprehensive molecular genetic analysis of the *Caenorhabditis elegans* DDX41 ortholog, SACY-1, to gain insights into its conserved functions. Their results reveal general essential functions for SACY-1 in both the germline and the soma, as well as specific functions affecting germline sex determination and cell cycle control. SACY-1 depletion affects the transcriptome through splicing-dependent and splicing-independent mechanisms.

This Month's Perspectives

A reflection on 50 years of John Maynard Smith's "protein space", pp. 749–754

C. Brandon Ogbunugafor

In this Perspectives article, Ogbunugafor revisits a famous and influential analogy introduced by renowned evolutionary biologist John Maynard Smith in a 1970 manuscript entitled "Natural selection and the concept of protein space (Smith 1970)." This Perspectives will commemorate the 50th anniversary of this seminal work by discussing its unique legacy across sub-disciplines of evolutionary genetics, and by describing its intriguing historical context.

In CBE — Life Sciences Education (LSE)

Infusing active learning into the large-enrollment biology class: seven strategies, from the simple to complex, CBE—Life Sci. Edu. Cell Biol. Edu. Vol. 4, No. 4. https://doi.org/10.1187/cbe.05-08-0113

Deborah Allen and Kimberly Tanner

The benefits of active learning have been well established, yet it may be difficult to start implementing techniques that support such learning. This is particularly true for those who teach large-enrollment, introductory courses, even though this is perhaps where they are needed most. How can we convert the methods of engaging students in active learning, which likely were developed in small classes, to large-enrollment environments? In answer to this question, Allen and Tanner have provided an excellent resource that identifies seven different approaches utilized in large-classroom environments. These approaches range from simple to more complex, allowing the instructor to choose the model that works best. In each case, the authors provide background and resources to help with implementation.