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INVESTIGATIONS AND AUTHOR SUMMARIES

1475–1495 **Iron Deprivation in *Synechocystis*: Inference of Pathways, Non-coding RNAs, and Regulatory Elements from Comprehensive Expression Profiling**
Miguel A. Hernández-Prieto, Verena Schön, Jens Georg, Luísa Barreira, João Varela, Wolfgang R. Hess, and Matthias E. Futschik

Iron presents a double-edged sword for cyanobacteria. It is a necessary component of photosynthesis yet it can lead to the production of highly toxic molecules. Thus, cyanobacteria are likely to have evolved dedicated mechanisms to regulate iron homeostasis. To elucidate these control mechanisms, the authors simultaneously monitored the expression of protein-coding and non-coding transcripts in the model cyanobacterium *Synechocystis* under iron deprivation and discovered a wide range of transcriptional changes. The results of their analyses indicate an extensive transcriptional response affecting various processes and a complex regulatory network including both proteins and regulatory RNAs.

1497–1503 **Invariance (?) of Mutational Parameters for Relative Fitness Over 400 Generations of Mutation Accumulation in *Caenorhabditis elegans***
Chikako Matsuba, Suzanna Lewis, Dejerianne G. Ostrow, Matthew P. Salomon, Laurence Sylvestre, Brandon Tabman, Judit Ungvari-Martin, and Charles F. Baer

Mutation rate is typically considered a constant property of a group, but evidence is mounting that physiological condition may increase the mutation rate and/or the deleterious effects of mutations. In this study, the authors used replicate populations of *Caenorhabditis elegans* that had high and low fitness due to recently accumulated deleterious mutations. They allowed these populations to accumulate mutations for another 150 generations. The mutational properties of the "second-order" mutation accumulation lines were very similar to those of the initial experiment, although the hint of fitness-dependent mutation remained. These results suggest that mutational properties depend idiosyncratically rather than strongly on underlying fitness.

1505–1519 **Evidence for Population-Specific Positive Selection on Immune Genes of *Anopheles gambiae***
Jacob E. Crawford, Emmanuel Bischoff, Thierry Garnier, Awa Gneme, Karin Eiglmeier, Inge Holm, Michelle M. Riehle, Wamdaogo M. Guelbeogo, N'Fale Sagnon, Brian P. Lazzaro, and Kenneth D. Vernick

Anopheles gambiae s.s. is a primary vector of the human malaria parasite *Plasmodium falciparum* in sub-Saharan Africa. The vectorial capacity is genetically controlled and can vary among subpopulations. These authors analyzed the patterns of genetic variation in 28 immunity-related genes in four sympatric population strata of *Anopheles gambiae*. Their results suggest that differences in mosquito behavior and/or ecological niches are the likely explanation for the striking differences in molecular variation observed among subgroups, which may in turn have impact on malaria transmission.

1521–1528 **Differentiation-Driven Nucleolar Association of the Mouse Imprinted *Kcnq1* Locus**
Andrew M. Fedoriw, J. Mauro Calabrese, Weipeng Mu, Della Yee, and Terry Magnuson

The spatial organization of the mammalian genome within the nucleus is now thought to play a role in developmental and differentiation-dependent gene regulation. However, the nature of this relationship remains unclear. Using an *in vitro* model of extraembryonic differentiation, the authors

explored the requirement for the nucleolar periphery in the imprinted regulation of the paternal *Kcnq1* allele. Their results detail a differentiation-dependent process, linked regulation by the noncoding RNA *Kcnq1ot1*. Surprisingly, in cells lacking the polycomb group protein EED where many of the normally silent alleles within the *Kcnq1* domain are active, association with the nucleolus remains readily observable. These results suggest that compartmentalization to the nucleolar periphery is not sufficient for gene silencing and may have additional roles in the regulation of this locus in extraembryonic lineages.

1529–1540 **Population Dynamics of *Phytophthora infestans* in the Netherlands Reveals Expansion and Spread of Dominant Clonal Lineages and Virulence in Sexual Offspring**
Y. Li, T. A. J. van der Lee, A. Evenhuis, G. B. M. van den Bosch, P. J. van Bekkum, M. G. Förch, M. P. E van Gent-Pelzer, H. M. G. van Raaij, E. Jacobsen, S. W. Huang, F. Govers, V. G. A. A. Vleeshouwers, and G. J. T. Kessel

A comprehensive survey of the structure and dynamics of the Dutch *Phytophthora infestans* population during a ten year period (2000 – 2009) has been performed. One single clonal lineage, "Blue_13," and several distinct clonal lineages were identified. This survey witnesses the most notable change of the emergence and spread of A2 mating type strain "Blue_13." The results also emphasize the importance of the sexual cycle in generating genetic diversity and the importance of the asexual cycle as the propagation and dispersal mechanism for successful genotypes. This study is the first to report *Rpi-blb1* breakers in the Netherlands, only occurring in sexual progeny.

1541–1554 **Multiple Mechanisms Contribute to Lateral Transfer of an Organophosphate Degradation (*opd*) Island in *Sphingobium fuliginis* ATCC 27551**
Emmanuel Vijay Paul Pandeeti, Toshisangba Longkumer, Deviprasanna Chakka, Venkateswar Reddy Muthyala, Sunil Parthasarathy, Anil Kumar Madugundu, Sujana Ghanta, Srikanth Reddy Medipally, Surat Chameli Pantula, Harshita Yekkala, and Dayananda Siddavattam

Due to extensive and indiscriminate use of insecticides, neurotoxic organophosphates (OP) residues are widespread in the environment. Certain soil bacteria have been shown to utilize OPs as a source of carbon due to their novel metabolic capacities. These authors report the existence of the organophosphate degradation (*opd*) island in a soil bacterium and provide evidence for its genetic exchange among soil bacteria. The plasmid pPDL2 borne *opd* island could function both as an integrative mobilizable element (IME) and a catabolic transposon. If the island is found to be functional upon artificial transfer to different soil microbial communities, the results of this study could have significant implications in the selection of optimally adapted microorganisms for bioremediation.

1555–1562 **The Enigmatic Conservation of a Rap1 Binding Site in the *Saccharomyces cerevisiae HMR-E* Silencer**
Leonid Teytelman, Erin A. Osborne Nishimura, Bilge Özaydin, Michael B. Eisen, and Jasper Rine

Repressor-Activator Protein (Rap1) of *Saccharomyces cerevisiae* activates many genes while repressing others by facilitating heterochromatic silencing. These authors discovered a surprising conservation of an unusual Rap1 binding motif at genes repressed by Rap1 and asked whether the DNA sequence recognized by Rap1 helps to differentiate between its roles. Contrary to the proposed models, the transcription-activating sequence can be substituted for the repressing one, without interfering with Rap1's ability to silence. The authors also ask whether there is spurious silencing in euchromatin and whether it restricts the distribution of Rap1 binding sites in the genome.

1563–1575 **A Targeted *In Vivo* RNAi Screen Reveals Deubiquitinases as New Regulators of Notch Signaling**
Junzheng Zhang, Min Liu, Ying Su, Juan Du, and Alan Jian Zhu

Protein ubiquitination regulates Notch signaling, a signaling pathway important for cell fate specification in development. Although the ubiquitination process has been extensively studied, the role of deubiquitination in Notch signaling is largely unknown. In this study, the authors annotated the deubiquitinases encoded in the *Drosophila melanogaster* genome and performed targeted *in vivo* RNAi screens for DUBs that regulate Notch signaling. They identified four novel deubiquitinases that differentially regulate Notch signaling in the developing wing and notum. Their results also provide genetic evidence demonstrating that these deubiquitinases are necessary to positively modulate Notch signaling.

1577–1584 **Mapping Six New Susceptibility to Colon Cancer (*Scc*) Loci Using a Mouse Interspecific Backcross**
Chevonne D. Eversley, Xie Yuying, R. Scott Pearsall, and David W. Threadgill

In this study, the authors exploited genetic differences segregating in an interspecific backcross to confirm previously mapping colon cancer modifiers. They were also able to genetically map six new

modifiers, including loci that control tumor penetrance, size, and, for the first time, location along the proximal-distal axis of the colon. Their results support a developing theory that cancer susceptibility is due to many small effect alleles, some which have no main effect.

1585–1593 **Genetic Interactions Between Brassinosteroid-Inactivating P450s and Photomorphogenic Photoreceptors in *Arabidopsis thaliana***
Kulbir Singh Sandhu, Katherine Hagely, and Michael M. Neff

Complex traits such as flowering time are highly quantitative. Cues that regulate flowering time include both environmental (external) and developmental (internal) factors. One of the fundamental questions in plant biology relates to how plants integrate external (*e.g.,* light) and internal (*e.g.,* hormones) signals to optimize growth and development in constantly changing environmental conditions. In this article, the authors describe the complex genetic interactions between photoreceptors that use light as a source of information and enzymes that inactivate growth-promoting brassinosteroid hormones for control of seed germination and flowering time.

1595–1605 **Comparison Between Linear and Non-parametric Regression Models for Genome-Enabled Prediction in Wheat**
Paulino Pérez-Rodríguez, Daniel Gianola, Juan Manuel González-Camacho, José Crossa, Yann Manès, and Susanne Dreisigacker

Parametric, semi-parametric, and non-parametric regression models have been used in genome-enabled prediction. In this study, the authors assessed the predictive ability of linear and non-linear models using molecular markers. The linear models included the Bayesian LASSO, Bayesian ridge regression, Bayes A, and Bayes B. The non-linear models were reproducing kernel Hilbert space regression (RKHS), Bayesian regularized neural networks (BRNN), and neural network with radial basis functions (RBFNN). The authors compared these statistical models using 306 elite wheat lines from CIMMYT genotyped with 1717 diversity array technology. They measured days to heading and grain yield in each of 11 environments. Their results show that the three non-linear models had better overall prediction accuracy than the linear regression specification.

1607–1612 **Natural Variation in the Yeast Glucose-Signaling Network Reveals a New Role for the Mig3p Transcription Factor**
Jeffrey A. Lewis and Audrey P. Gasch

Glucose signaling plays a central role in cellular physiology. In budding yeast, the glucose repressors Mig1p and Mig2p play well-characterized roles in glucose signaling, while little function has been assigned to the related Mig3p. These authors studied a wild yeast isolate and uncovered a critical role for Mig3p that has been largely lost in laboratory strains. Their results suggest that Mig3p plays a complex role under both standard and stress conditions, but only in wild yeast strains. By expanding their attention to multiple genetic backgrounds, they uncovered an important missing link in the glucose signaling network.

1613–1623 **Interactions of NADP-Reducing Enzymes Across Varying Environmental Conditions: A Model of Biological Complexity**
Teresa Z. Rzezniczak and Thomas J. S. Merritt

In this study, the authors examined the consistency of genetic interactions across multiple environmental conditions using a metabolic network in *Drosophila melanogaster*. By using a targeted approach, they were able to directly quantify the magnitude and directionality of genetic interactions across multiple genetic backgrounds. They found that environment and genetic background strongly impact interactions, both in directionality and magnitude, with stress conditions resulting in an amplification of the responses. These results emphasize the dynamic nature of genetic interactions and stress the importance of using genetic backgrounds in these types of studies.

1625–1641 **Genetic Control of Vulval Development in *Caenorhabditis briggsae***
Devika Sharanya, Bavithra Thillainathan, Sujatha Marri, Nagagireesh Bojanala, Jon Taylor, Stephane Flibotte, Donald G. Moerman, Robert H. Waterston, and Bhagwati P. Gupta

Vulval development in the nematode *Caenorhabditis elegans* is an established model to study the molecular genetic basis of organ formation. With the objective of understanding the conservation and divergence in developmental mechanisms of vulva formation, the authors isolated mutants in another leading nematode species, *Caenorhabditis briggsae*, which is morphologically similar to *C. elegans*. They report characterization of 13 genes including 3 that are *C. elegans* orthologs. Despite an overall conservation in phenotypic classes, the authors found novel differences in the spectrum of mutations

and some of the phenotypes when compared to *C. elegans*. Their work serves as a foundation for the comparative analysis of vulva formation in the two species.

1643–1649 **Assessing the Genome-Wide Effect of Promoter Region Tandem Repeat Natural Variation on Gene Expression**
Martha H. Elmore, John G. Gibbons, and Antonis Rokas

Although it is widely recognized that copy number polymorphisms of nucleotide tandem repeat (TR) regions can directly modulate phenotype, the generality and genome-wide impact of TR variation on phenotype remains largely untested. These authors measured and quantified relationships between TR polymorphism and gene expression levels in 16 isolates of the filamentous fungi *Aspergillus oryzae* and *Aspergillus flavus*. Their results suggest that, in contrast to previous hypotheses, the vast majority of TR polymorphisms do not function as "evolutionary tuning knobs." They also indicate that the molecular phenotypic differences between the two species of fungi are largely explained by molecular variation unrelated to TRs.

1651–1660 ***In Vivo* Regulation of E2F1 by Polycomb Group Genes in *Drosophila***
Jun-Yuan Ji, Wayne O. Miles, Michael Korenjak, Yani Zheng, and Nicholas J. Dyson

The E2F transcription factors are important regulators of the cell cycle and commonly misregulated in cancer. In this study, the authors performed a dominant modifier genetic screen to look for factors that regulate E2F1 activity *in vivo*. They identified mutant alleles of *Su(z)2* (*Suppressor of zeste 2*) and multiple Polycomb group (PcG) genes as strong suppressors of the E2F1-RNAi phenotypes. Their analyses suggest that PcG may affect cell proliferation by repressing the transcription of dE2f1 and certain dE2F1 target genes. This mechanism may play an important role in coordinating cellular differentiation and proliferation during *Drosophila* development.

1661–1664 **Nuclear Gene Variation in Wild Brown Rats**
Rob W. Ness, Yao-Hua Zhang, Lin Cong, Yu Wang, Jian-Xu Zhang, and Peter D. Keightley

This study provides the first estimate of nucleotide diversity in wild brown rats. Diversity is very low, only twice as high as observed in humans. The authors estimate that the recent effective population size in brown rats is about 130,000.

1665–1685 **A Discovery Resource of Rare Copy Number Variations in Individuals with Autism Spectrum Disorder**
Aparna Prasad, Daniele Merico, Bhooma Thiruvahindrapuram, John Wei, Anath C. Lionel, Daisuke Sato, Jessica Rickaby, Chao Lu, Peter Szatmari, Wendy Roberts, Bridget A. Fernandez, Christian R. Marshall, Eli Hatchwell, Peggy S. Eis, and Stephen W. Scherer

De novo and rare inherited copy number variations (CNVs) have been shown to be etiologic in approximately 10% of individuals having a diagnosis of autism spectrum disorder (ASD). In this study, the authors analyzed an extensively phenotyped Canadian ASD cohort of 696 individuals using comparative genomic hybridization (CGH) microarray with one million probe features. From this high-resolution and high-quality dataset, they uncovered several novel CNVs that reveal new ASD risk loci and validate findings from other studies. Their data also reveal a previously unknown pathway of nucleotide metabolism involved in ASD.

1687–1701 **Suppressors of *ipl1-2* in Components of a Glc7 Phosphatase Complex, Cdc48 AAA ATPase, TORC1, and the Kinetochore**
Lucy C. Robinson, Joshua Phillips, Lina Brou, Evan P. Boswell, and Kelly Tatchell

The protein kinase Aurora B plays a pivotal role in ensuring that replicated chromosomes are partitioned properly to daughter cells at mitosis. The phosphoprotein phosphatase PP1 opposes Aurora B for this activity. Here the authors describe a traditional genetic screen in the yeast *Saccharomyces cerevisiae* designed to identify gene products that act with or regulate Aurora B or PP1. Suppressors of a conditional Aurora B mutant include three intragenic, second site revertants in Aurora B (*IPL1*), and 22 extragenic suppressors. The extragenic suppressors alter the TORC1 complex, known regulators of the PP1 phosphatase, and two kinetochore proteins, Ndc80 and Duo1.

1703–1718 **Genetic Analysis of Mps3 SUN Domain Mutants in *Saccharomyces cerevisiae* Reveals an Interaction with the SUN-Like Protein Slp1**
Jennifer M. Friederichs, Jennifer M. Gardner, Christine J. Smoyer, Christine R. Whetstine, Madelaine Gogol, Brian D. Slaughter, and Sue L. Jaspersen

The conserved inner nuclear membrane SUN protein Mps3 is essential for vegetative growth and sporulation in three commonly used budding yeast strains. These authors performed a genome-wide

screen for yeast deletion mutants that exhibited synthetic fitness defects in combination with mutants in the Mps3 SUN domain. The screen yielded hits in components of the spindle apparatus, in chromatin and DNA recombination/repair, and in lipid metabolism. These results suggest that Mps3 is required in these processes. Two uncharacterized ER-membrane associated proteins, Slp1 and Emp65/Yer140w, were also required for growth of *mps3* SUN domain mutants due to their role in localization of Mps3 to the nuclear envelope.

1719–1720 **REVIEWER INDEX**