PNAS Plus Significance Statements

Climate network percolation reveals the expansion and weakening of the tropical component under global warming

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Climate change could threaten our society through impacts on social, cultural, and natural resources. Here, we develop an approach based on percolation theory and climate network frameworks to detect and quantify the impacts of past and future climate change. Our method of analysis provides a perspective on the evolution of climate systems in response to global warming and can potentially be used for predicting the consequences of future climate changes. Furthermore, our study may also enrich and facilitate the understanding of discontinuous phase transitions. (See pp. E12128–E12134.)

Robust forecast aggregation

Itai Arieli, Yakov Babichenko, and Rann Smorodinsky

The problem of conflicting advice from multiple experts is common to policy makers, corporate governors, patients facing medical prognosis, individuals requiring financial advice, and more. We ask, How should an ignorant advisee (one that observes experts' forecasts only) aggregate information when this is provided in probabilistic terms (such as forecasts over events)? We propose a robustness criterion based on the classical notions of scoring rule and regret. Under reasonable assumptions on the underlying information structure of the experts, we provide formulas that allow an ignorant aggregator to perform almost as well as an omniscient expert (one that aggregates perfectly all of the information) whenever there are two experts. We also show that this is hopeless when facing many experts. (See pp. E12135–E12143.)

Right temporal alpha oscillations as a neural mechanism for inhibiting obvious associations

Caroline Di Bernardi Luft, Ioanna Zioga, Nicholas M. Thompson, Michael J. Banissy, and Joydeep Bhattacharya

"Taking a less-traveled path" is often considered an effective approach to creativity (i.e., creative thinking calls for a break from habitual thinking and associations), yet little is known about its underlying neural mechanism. In a series of four independent experiments involving electrophysiological and brain stimulation methods we provide evidence that this process is mediated by the right temporal alpha oscillations. Alpha oscillations are known to represent a process of active inhibition to suppress irrelevant information, such as inhibiting distractions during visual search. Through monitoring the brain's electrical activity during different creativity tasks and by stimulating the right temporal brain region at the alpha frequency we show that a similar process of active inhibition is also key to creative thinking. (See pp. E12144–E12152.)

High-capacity preconscious processing in concurrent groupings of colored dots

Peng Sun, Charles Chubb, Charles E. Wright, and George Sperling

A critical visual process is segmenting a scene into objects to be processed (foreground) and the remainder (background). Humans are extraordinarily good at segmentation, but how they accomplish this still is not well understood. An important component process in segmentation is grouping by similarity, for example, by color, shape, size, etc., thereby organizing visual information into coherent chunks for subsequent stages in object recognition. That our subjects can also group dissimilar items shows that the grouping process itself is much more complex than previously believed. Furthermore, we present a fully quantitative account of the inclusiveness/exclusiveness of the grouping process and of its extraordinary perceptual capacity. The amount of information preconsciously utilized to form a group is many times greater than is consciously available. (See pp. E12153–E12162.)

Dominance rank-associated gene expression is widespread, sex-specific, and a precursor to high social status in wild male baboons

Amanda J. Lea, Mercy Y. Akinyi, Ruth Nyakundi, Peter Mareri, Fred Nyundo, Thomas Kariuki, Susan C. Alberts, Elizabeth A. Archie, and Jenny Tung

Social status can predict health, reproduction, and survival in social animals. To understand why, we investigated social status and immune gene expression in wild baboons, where kinship determines status in females but fighting ability determines status in males. We identified a much stronger relationship between status and gene expression in males than

females. Further, inflammation-related genes were more active in high-status than low-status males; the opposite effect has been reported in status hierarchies that are not determined by fighting ability. Our results suggest that males who compete successfully for high status are already immunologically distinct. They therefore emphasize that how social hierarchies are formed shapes their relationship to immune function and health. (See pp. E12163–E12171.)

Electrostatics, proton sensor, and networks governing the gating transition in GLIC, a proton-gated pentameric ion channel

Haidai Hu, Kenichi Ataka, Anaïs Menny, Zaineb Fourati, Ludovic Sauguet, Pierre-Jean Corringer, Patrice Koehl, Joachim Heberle, and Marc Delarue

Several classes of membrane ion channels are sensitive to the intracellular or extracellular proton concentration. However, the detailed mechanism of channel gating induced by protonation proves in general difficult to address. Here we use a combined computational and experimental approach to identify the proton sensor in the pentameric proton-gated ion channel GLIC. Further electrophysiology and crystallography data help delineate the mechanism of the gating transition initiated by protonating this sensor, revealing that those positions that trap the receptor in a nonfunctional closed-pore conformation build up a continuous network. Our results provide an approach to search for and identify proton sensors as well as networks of residues important for the gating transition in the pentameric ligand-gated channels family. (See pp. E12172–E12181.)

Effective design principles for leakless strand displacement systems

Boya Wang, Chris Thachuk, Andrew D. Ellington, Erik Winfree, and David Soloveichik

The modern information age was enabled by encoding, transmitting, and manipulating information in a way that is robust to error. However, synthetic biology and molecular programming, fields that aim to recapitulate the successes of electronics within biochemistry, still struggle with error tolerance. The ability to create "smart" molecular systems capable of robust information processing and decision making would enable important applications in biomaterial production, biosensing, and therapeutics. Based on DNA strand displacement building blocks, we demonstrate de novo engineered molecular cascades robust to spurious interactions using an error correction scheme based on redundancy. In principle, arbitrary levels of error reduction could be attained. The information propagation cascades form a foundation for more complex, resilient, and faster programmable reaction networks. (See pp. E12182–E12191.)

Exploiting correlated molecular-dynamics networks to counteract enzyme activity–stability trade-off

Haoran Yu and Paul A. Dalby

Rigidifying flexible sites is a powerful method to improve enzyme stability. However, if the highly flexible regions form the active site, modifying them risks losing activity due to the activity–stability trade-off. We hypothesized here that regions outside the active site whose dynamics were highly correlated to flexible active sites, would provide good targets for stabilizing mutations. To test this hypothesis, six variants were constructed in the 3M variant of *Escherichia coli* transketolase. The best variant had a 10.8-fold improved half-life at 55 °C, and increased the T_m and T_{agg} by 3 °C and 4.3 °C, respectively. The variants even increased the activity, by up to threefold. This study highlights how protein engineering strategies could be potentially improved by considering long-range dynamics. (See pp. E12192–E12200.)

Eigenvector centrality for characterization of protein allosteric pathways

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Allosteric processes are ubiquitous in macromolecules and regulate biochemical information transfer between spatially distant sites. Despite decades of study, allosteric processes remain generally poorly understood at the molecular level. Here, we introduce the eigenvector centrality measure of mutual information to disentangle the complex interplay of amino acid interactions giving rise to allosteric signaling. The analysis of eigenvector centrality is tested in imidazole glycerol phosphate synthase (IGPS), a prototypical V-type allosteric enzyme. The resulting insights allow us to pinpoint key amino acids in terms of their relevance in the allosteric process, suggesting protein-engineering strategies for control of enzymatic activity. (See pp. E12201–E12208.)

Molecular basis for the acid-initiated uncoating of human enterovirus D68

Yue Liu, Ju Sheng, Arno L. W. van Vliet, Geeta Buda, Frank J. M. van Kuppeveld, and Michael G. Rossmann

Enterovirus D68 (EV-D68) is an emerging pathogen that primarily causes childhood respiratory infections and is linked to neurological diseases. It was unclear how the virus uncoats and delivers its genome into a host cell to establish viral replication. Using high-resolution cryoelectron microscopy, we showed that acid induces structural rearrangements of EV-D68 to initiate genome release from the virus. Structural analyses delineated a viral uncoating pathway that involves multiple distinct conformational states. Particularly, the structure of a previously unknown uncoating intermediate enabled the identification of potential molecular determinants that facilitate EV-D68 uncoating. These results advance the knowledge of cell entry of EV-D68 and open up possibilities for developing antiviral therapeutics that impede structural rearrangements of the virus. (See pp. E12209–E12217.)

Structural–functional interactions of NS1-BP protein with the splicing and mRNA export machineries for viral and host gene expression

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A subset of cellular and viral RNAs relies on specific proteins to mediate splicing and nuclear export for proper gene expression. During influenza virus infection, the virulence factor NS1 protein binds the cellular protein NS1-BP to promote splicing and nuclear

export of a subset of viral mRNAs that encode critical proteins for viral trafficking and budding. Here we present structures of NS1-BP domains and their functional interactions with components of the splicing and mRNA nuclear export machineries to promote viral gene expression. Additionally, NS1-BP is important for proper expression of a subset of mRNAs involved in metastasis and immunity. These findings reveal basic features of NS1-BP that can be exploited in antiviral therapy and to investigate NS1-BP function in tumorigenesis. (See pp. E12218–E12227.)

SREBP-1a–stimulated lipid synthesis is required for macrophage phagocytosis downstream of TLR4-directed mTORC1

Jae-Ho Lee, Peter Phelan, Minsang Shin, Byung-Chul Oh, Xianlin Han, Seung-Soon Im, and Timothy F. Osborne

There is a growing appreciation for a fundamental connection between lipid metabolism and the innate immune response. Phagocytosis is a key macrophage innate immune response to pathogen exposure, and cytoplasmic membrane expansion is required to surround and capture the target pathogen prior to internalization. Sterol regulatory element binding proteins (SREBPs) are gene regulatory factors that sense the intracellular lipid environment and modulate key genes that drive fatty acid and cholesterol synthesis to maintain lipid homeostasis. In this study, we show that, in mutant cells that lack a key SREBP isoform, phagocytosis is impaired, and we track the defect to altered lipid composition of membrane phospholipids that results in decreased interaction between membrane lipid rafts and the actin cytoskeletal network. (See pp. E12228–E12234.)

Mitotic antipairing of homologous and sex chromosomes via spatial restriction of two haploid sets

Lisa L. Hua and Takashi Mikawa

Mitotic recombination must be prevented to maintain genetic stability across daughter cells, but the underlying mechanism remains elusive. We report that mammalian cells impede homologous chromosome pairing during mitosis by keeping the two haploid chromosome sets apart, positioning them to either side of a meridional plane defined by the centrosomes. Chromosome oscillation analysis revealed collective genome behavior of noninteracting chromosome sets. Male translocation mice with a maternal-derived supernumerary chromosome display the tracer chromosome exclusively to the haploid set containing the X chromosome. This haploid set-based antipairing motif is shared by multiple cell types, is doubled in tetraploid cells, and is lost in carcinoma cells. The data provide a model of nuclear polarity through the antipairing of homologous chromosomes during mitosis. (See pp. E12235–E12244.)

Profiling proliferative cells and their progeny in damaged murine hearts

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The adult mammalian heart does not functionally repair itself after injury. Therefore, identification of cardiac stem cell (CSC) populations is of great interest for regenerative intervention. However, the significance of such CSC populations remains heavily debated. Using single-cell mRNA sequencing and genetic lineage tracing, we interrogate the existence of CSCs with unbiased mouse models of proliferation. Cycling cardiomyocytes were only robustly observed in the early postnatal growth phase, while cycling cells in homoeostatic and damaged adult myocardium consisted mainly of various noncardiomyocyte cell types. Injury-activated cardiac fibroblasts that acquire a gene expression profile similar to that of neonatal cardiac fibroblasts signal—in an autocrine fashion—to prevent cardiac rupture. We find no evidence for the existence of a quiescent CSC population. (See pp. E12245–E12254.)

TANGO1 and SEC12 are copackaged with procollagen I to facilitate the generation of large COPII carriers

Lin Yuan, Samuel J. Kenny, Juliet Hemmati, Ke Xu, and Randy Schekman

Collagen is a major component of the extracellular matrix, and its secretion requires cytoplasmic proteins that assemble on the surface of the endoplasmic reticulum to bud ∼100-nm-diameter cargo transport vesicles (COPII). Bulky collagens, such as the 300-nm procollagen I (PC1), are too big to fit into normal COPII vesicles. Recently, large COPII-coated vesicles were found to act as PC1 carriers, but how these large COPII carriers are generated remains unclear. Here, we show copackaging of PC1 along with its cargo receptor TANGO1, a coreceptor protein, cTAGE5, and the COPII initiating factor SEC12. Because SEC12 is excluded from small COPII vesicles, we propose that TANGO1 targets SEC12 to PC1-containing endoplasmic reticulum and drives the formation of large COPII-coated vesicles. (See pp. E12255–E12264.)

Steroidogenic differentiation and PKA signaling are programmed by histone methyltransferase EZH2 in the adrenal cortex

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The adrenal cortex plays a central role in regulating body homeostasis through production of glucocorticoids and mineralocorticoids that control metabolism, inflammation, and blood pressure. The production of these hormones, known as steroidogenesis, is achieved by differentiated steroidogenic cells that arise from undifferentiated progenitors and are constantly renewed throughout life. Until now, the mechanisms that ensured that progenitors differentiated as steroidogenic cells and maintained this differentiated state were unknown. Our data show that the histone methyltransferase EZH2, a key epigenetic factor, is the central regulator of this process. Consequently, adrenal-specific EZH2 knockout mice fail to normally differentiate steroidogenic cells, which results in a life-threatening condition known as primary glucocorticoid insufficiency in patients. (See pp. E12265–E12274.)

Different iron storage strategies among bloom-forming diatoms

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The availability of the micronutrient iron has profound influences on primary productivity and biogeochemical cycling in the ocean.

Here we describe iron storage mechanisms in diatoms, a predominant group of phytoplankton. We substantiate evidence with environmental data that diatoms have evolved to cope with iron limitation by storing iron in different ways. One iron storage mechanism, the protein ferritin, may be well suited for less frequent and pulsed iron inputs. As a result, the diatom community composition may shift to ferritin-using diatoms in potential scenarios where iron availability is reduced. (See pp. E12275–E12284.)

Apurinic endonuclease-1 preserves neural genome integrity to maintain homeostasis and thermoregulation and prevent brain tumors

Lavinia C. Dumitrache, Mikio Shimada, Susanna M. Downing, Young Don Kwak, Yang Li, Jennifer L. Illuzzi, Helen R. Russell, David M. Wilson III, and Peter J. McKinnon

The nervous system consumes a large quotient of oxygen and as such is at risk for high levels of oxidative DNA damage. A key DNA-repair factor, apurinic/apyrimidinic endonuclease 1 (APE1), is essential for repair of oxidative DNA lesions, although the specific role(s) for this enzyme in the nervous system is unknown. Surprisingly, mice lacking APE1 throughout neurogenesis were viable and showed little discernible phenotype at birth. However, after birth, when tissue oxygenation shifts from the placenta to respiration, loss of APE1 led to rapid and pronounced genome instability, resulting in widespread apoptosis, demyelination, thermoregulation defects, and brain tumors. Our findings reveal unrestrained oxidative DNA damage in the nervous system can result in specific pathology implicated in many human diseases. (See pp. E12285–E12294.)

RNA-mediated gene fusion in mammalian cells

Sachin Kumar Gupta, Liming Luo, and Laising Yen

This report provides striking evidence that expression of a chimeric RNA mimicking a fusion RNA can drive the formation of gene fusions in mammalian cells. However, it is the antisense rather than sense chimeric RNAs that effectively drive gene fusion. The discovery that the cellular *AZI1* RNA, not *AZI1* protein, can act as an "initiator" RNA to induce *TMPRSS2–ERG* gene fusion indicates that this mechanism may have important biological relevance to oncogenesis. RNA-mediated gene fusion, a mechanism that relies on sequence-specific interactions, can account for the "specificity" of genes that were selected to undergo gene fusion. The results could also have fundamental implications in mammalian genome stability, as well as gene-editing technology via mechanisms native to mammalian cells. (See pp. E12295–E12304.)

Nuclear receptor HNF4A transrepresses CLOCK:BMAL1 and modulates tissue-specific circadian networks

Meng Qu, Tomas Duffy, Tsuyoshi Hirota, and Steve A. Kay

Interlocked feedback loops promote robustness and stability in a system and are a feature of circadian clocks in both animal and plants. The mammalian circadian clock is known to consist of two transcriptional feedback loops, relying on the transcriptional activity of the master complex CLOCK:BMAL1 and the feedback regulation by its target genes. Our research extends this knowledge by proposing a feedback loop in peripheral circadian oscillators and highlights the underlying mechanisms mediated by the unappreciated CLOCK:BMAL1 transrepression activity of the circadian nuclear receptor HNF4A. Further, our data suggest that the hepatic roles of HNF4A are circadian. (See pp. E12305–E12312.)

Protein kinase p38α signaling in dendritic cells regulates colon inflammation and tumorigenesis

Tingting Zheng, Baohua Zhang, Ce Chen, Jingyu Ma, Deyun Meng, Jian Huang, Ran Hu, Xinguang Liu, Kinya Otsu, Andrew C. Liu, Huabin Li, Zhinan Yin, and Gonghua Huang

Dendritic cells (DCs) are known to mediate immune regulatory networks in response to intestinal epithelial barrier disruption, but underlying signaling pathways and molecular mechanisms are not well understood. Here, we show that genetic disruption of p38α in DCs leads to higher levels of differentiated type 1 regulatory T cells and group 3 innate lymphoid cells. Specifically, p38α signaling in intestinal cDC1s, but not cDC2s or T cells, mediates colitis pathogenesis. Together, our results suggest that p38α MAPK represents a major signaling network in DCs that regulates inflammation and contributes to epithelial barrier function in colitis and associated colorectal cancer. Furthermore, our finding suggests that p38α signaling in DCs may represent a target for the treatment of inflammatory intestinal diseases. (See pp. E12313–E12322.)

Autoimmunity to hypocretin and molecular mimicry to flu in type 1 narcolepsy

Guo Luo, Aditya Ambati, Ling Lin, Mélodie Bonvalet, Markku Partinen, Xuhuai Ji, Holden Terry Maecker, and Emmanuel Jean-Marie Mignot

This work shows that the amidated terminal ends of the secreted hypocretin (HCRT) peptides ($HCRT_{NH2}$) are autoantigens in type 1 narcolepsy, an autoimmune disorder targeting HCRT neurons. The autoimmune process is usually initiated by influenza A flu infections, and a particular piece of the hemagglutinin (HA) flu protein of the pandemic 2009 H1N1 strain was identified as a likely trigger. This HA epitope has homology with $HCRT_{NH2}$ and T cells cross-reactive to both epitopes are involved in the autoimmune process by molecular mimicry. Genes associated with narcolepsy mark the particular HLA heterodimer (DQ0602) involved in presentation of these antigens and modulate expression of the specific T cell receptor segments (TRAJ24 and TRBV4-2) involved in T cell receptor recognition of these antigens, suggesting causality. (See pp. E12323–E12332.)

Nanotechnology-mediated crossing of two impermeable membranes to modulate the stars of the neurovascular unit for neuroprotection

Bapurao Surnar, Uttara Basu, Bhabatosh Banik, Anis Ahmad, Brian Marples, Nagesh Kolishetti, and Shanta Dhar

Neurodegenerative disorders touch many lives in the form of various diseases. Therapeutic interventions of such disorders are limited due to the difficulty in reaching the neurons by crossing

the impermeable blood–brain barrier. Scientists have created nanoscopic particles to take therapeutics to the brain; however, the results have not been very encouraging due to the inefficient ability of the nanoplatforms in crossing the blood–brain barrier and to accumulate in the target neuron cells effectively as uptake of nanomaterials by neurons is difficult to achieve. We provide a biodegradable nanoparticle platform with efficient brain astrocyte accumulation properties to provide an alternative approach to tackle neurodegenerative processes by improving and enhancing astrocyte's natural protection ability toward neurons for neuromedicine. (See pp. E12333–E12342.)

DeltaNp63-dependent super enhancers define molecular identity in pancreatic cancer by an interconnected transcription factor network

Feda H. Hamdan and Steven A. Johnsen

Distinct molecular subtypes of pancreatic cancer have recently been identified with the squamous subtype exhibiting a particularly poor prognosis. Precision-medicine approaches are needed in pancreatic cancer due to its dismal prognosis. Accordingly, novel and specific dependencies in these aggressive subtypes need to be identified. This study uncovers a group of transcription factors which form an interdependent network driving the squamous subtype via subtype-specific super enhancers. These factors include deltaNp63 which we show specifically cooperates with BHLHE40, HIF1A, and RXRA to control transcription in the squamous subgroup. Importantly, an epigenetic signature identified in this study is capable of accurately identifying squamous subtype samples in pancreatic cancer patient-derived xenograft tumors. (See pp. E12343–E12352.)

Integrating host response and unbiased microbe detection for lower respiratory tract infection diagnosis in critically ill adults

Charles Langelier, Katrina L. Kalantar, Farzad Moazed, Michael R. Wilson, Emily D. Crawford, Thomas Deiss, Annika Belzer, Samaneh Bolourchi, Saharai Caldera, Monica Fung, Alejandra Jauregui, Katherine Malcolm, Amy Lyden, Lillian Khan, Kathryn Vessel, Jenai Quan, Matt Zinter, Charles Y. Chiu, Eric D. Chow, Jenny Wilson, Steve Miller, Michael A. Matthay, Katherine S. Pollard, Stephanie Christenson, Carolyn S. Calfee, and Joseph L. DeRisi

Lower respiratory tract infections (LRTIs) are the leading cause of infectious disease-related deaths worldwide yet remain challenging to diagnose because of limitations in existing microbiologic tests. In critically ill patients, noninfectious respiratory syndromes that resemble LRTIs further complicate diagnosis and confound targeted treatment. To address this, we developed a metagenomic sequencing-based approach that simultaneously interrogates three core elements of acute airway infections: the pathogen, airway microbiome, and host response. We studied this approach in a prospective cohort of critically ill patients with acute respiratory failure and found that combining pathogen, microbiome, and host gene expression metrics achieved accurate LRTI diagnosis and identified etiologic pathogens in patients with clinically identified infections but otherwise negative testing. (See pp. E12353–E12362.)

Virus-inclusive single-cell RNA sequencing reveals the molecular signature of progression to severe dengue

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A fraction of the 400 million people infected with dengue annually progresses to severe dengue (SD). Yet, there are currently no biomarkers to predict disease progression. We profiled the landscape of host transcripts and viral RNA in thousands of single blood cells from dengue patients prior to progressing to SD. We discovered cell type-specific immune activation and candidate predictive biomarkers. We also determined preferential virus association with specific cell populations, particularly naive B cells and monocytes. We explored immune activation of bystander cells, clonality and somatic evolution of adaptive immune repertoires, as well as viral genomics. This multifaceted approach could advance understanding of pathogenesis of any viral infection, map an atlas of infected cells, and promote the development of prognostics. (See pp. E12363–E12369.)

Human cytomegalovirus US21 protein is a viroporin that modulates calcium homeostasis and protects cells against apoptosis

Anna Luganini, Giovanna Di Nardo, Luca Munaron, Gianfranco Gilardi, Alessandra Fiorio Pla, and Giorgio Gribaudo

During coevolution with its host, human cytomegalovirus (HCMV) has invested a large part of its protein coding potential to ensure the dysregulation of the majority of cellular homeostatic circuits. Defining the role of these HCMV proteins is important to understand viral pathogenesis and to design new antiviral strategies able to exploit their functions. Here, we report on the functional characterization of the protein encoded by the US21 gene, the founding member of the HCMV US12 gene family. The pUS21 acts as a calcium-permeable multitransmembrane channel able to reduce the calcium content of intracellular stores; pUS21-mediated tampering with intracellular calcium homeostasis, in turn, decreases the cells' susceptibility to apoptosis, thus contributing to the overall HCMV protein toolbox evolved to blunt apoptosis in infected cells. (See pp. E12370–E12377.)

Phototaxis in a wild isolate of the cyanobacterium *Synechococcus elongatus*

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The cyanobacterium *Synechococcus elongatus* PCC 7942 is widely used in basic and applied research. However, this model organism appears to have lost, through laboratory domestication, behaviors that are important in a natural environment, such as biofilm formation and phototaxis. We characterized a wild isolate of *S. elongatus*, UTEX 3055, that forms biofilms and is phototactic and investigated the mechanisms that regulate phototaxis. Our findings suggest a simpler design for phototactic motility in UTEX 3055 than that previously described for the cyanobacterium *Synechocystis*, because a single 5-GAF–domain photoreceptor

senses the direction of illumination by wavelengths that induce both positive and negative responses. This study expands our knowledge of the mechanisms responsible for phototaxis in cyanobacteria and establishes a phototactic model organism. (See pp. E12378–E12387.)

Translational switching of Cry1 protein expression confers reversible control of circadian behavior in arrhythmic Cry-deficient mice

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Circadian rhythms dominate our lives through our daily cycle of sleep and wakefulness. They are controlled by a brain master clock: the suprachiasmatic nucleus (SCN). SCN timekeeping pivots around a molecular loop incorporating Cryptochrome (Cry) proteins; global loss of these proteins disables the clock. We developed a biologically appropriate translational switch based on genetic code expansion to achieve reversible control of Cry1 expression. Cry1 translation in neurons of arrhythmic Cry-null SCN slices immediately, reversibly, and dose-dependently initiated circadian molecular rhythms. Cry1 translation in SCN neurons was sufficient to initiate circadian behavior rapidly and reversibly in arrhythmic Cry-null mice. This demonstrates control of mammalian behavior using translational switching, a method of broad applicability. (See pp. E12388–E12397.)

Ventral striatum's role in learning from gains and losses

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A broad set of neural circuits, including the amygdala and frontal-striatal systems, has been implicated in mediating learning from gains and losses. The ventral striatum (VS) has been implicated in several aspects of this process. Here, we examined the specific contribution of the VS to learning from gains vs. losses. We found that the VS plays a role in learning to choose between two options that vary in gains but plays no role in learning to choose between two options when one or both is associated with a loss. Computational modeling supported this by showing that animals with VS lesions specifically learned slowly when choosing between gains but not losses. (See pp. E12398–E12406.)

MTSS1/Src family kinase dysregulation underlies multiple inherited ataxias

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The Src family of nonreceptor tyrosine kinases (SFK) is essential for nervous system function and may contribute to neurodegeneration. Spinocerebellar ataxias (SCAs) are neurodegenerative diseases in which Purkinje neurons fire irregularly and degenerate leading to motor problems. We show that the SFK suppressor Missing-in-metastasis (MTSS1) is an ataxia gene that links multiple SCAs. MTSS1 loss results in increased SFK activity, degenerating Purkinje neurons with low firing rates, and cell death. Surprisingly, mouse models for three different SCAs show elevated SFK activity, with SCA1 and SCA2 models displaying dramatically reduced MTSS1 protein levels. Treatment of each SCA model with an SFK inhibitor corrects Purkinje basal firing and delays ataxia progression in MTSS1 mutants. Our results identify a common link among disparate neurodegenerative diseases. (See pp. E12407–E12416.)

Epigenetic regulator UHRF1 inactivates REST and growth suppressor gene expression via DNA methylation to promote axon regeneration

Young Mi Oh, Marcus Mahar, Eric E. Ewan, Kathleen M. Leahy, Guoyan Zhao, and Valeria Cavalli

Functional impairment and poor recovery following central nervous system injury is due to the failure of injured axons to regenerate and rebuild functional connections. In contrast, axon regeneration occurs in injured peripheral nerves. Expression of regeneration-associated genes is essential to activate the axon regeneration program. Less is known about the contribution of gene inactivation. We reveal an epigenetic mechanism that silences gene expression by ubiquitin-like containing PHD ring finger 1 (UHRF1)-dependent DNA methylation to promote axon regeneration. We suggest that the transient increase in the transcriptional regulator REST, controlled by miR-9 and UHRF1, allows neurons to enter a less mature state that favors a regenerative state. These results provide a better understanding of the transient gene regulatory networks employed by peripheral neurons to promote axon regeneration. (See pp. E12417–E12426.)

Spatiotemporal activation of the C/EBPβ/δ-secretase axis regulates the pathogenesis of Alzheimer's disease

Hualong Wang, Xia Liu, Shengdi Chen, and Keqiang Ye

Our most recent reports demonstrate that δ-secretase (AEP) cleaves both APP and Tau, promoting Ab and neurofibrillary tangle formation. Depletion of δ-secretase diminishes Alzheimer's disease (AD) pathologies and restores cognitive functions in AD mouse models. Moreover, we found that C/EBPβ, an inflammatory cytokine or Ab-activated transcription factor, dictates δ-secretase expression during aging. Overexpression of C/EBPβ facilitates AD pathologies via upregulating δ-secretase, whereas depletion of C/EBPβ reduces AD pathologies. In the current study, we examined the pathological roles of the C/EBPβ/δ-secretase axis in different AD mouse models, at different time points, and in different brain regions and found that this pathway plays a critical role in mediating AD pathologies and cognitive function. Hence, C/EBPβ/δ-secretase spatiotemporally mediates AD pathogenesis. (See pp. E12427–E12434.)

Transgenerational hypocortisolism and behavioral disruption are induced by the antidepressant fluoxetine in male zebrafish *Danio rerio*

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Due to the high incidence of depression during childbearing, antidepressants such as fluoxetine (FLX) are highly prescribed during pregnancy, yet the risks to offspring are unknown. We report that a 6-day FLX exposure during early zebrafish development induces hypocortisolism for at least three generations. Gene expression analysis indicates that pathways controlling cortisol synthesis are altered in the descendants in the third generation. This FLX-induced low-cortisol phenotype is more prominent in males and is associated with significantly reduced exploratory behaviors for two generations. This is an important demonstration that, in an animal model, even a brief ancestral exposure to a common antidepressant modifies the stress response and critical coping behaviors for several generations. (See pp. E12435–E12442.)

Fluctuating selection on migrant adaptive sodium transporter alleles in coastal *Arabidopsis thaliana*

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The natural landscape contains a highly heterogeneous array of environments that drive the adaptive differentiation of populations, including adaptation to elevated salinity. Our research emphasizes an integrated genetic, physiological, and ecological approach to understand the role of naturally evolved high-affinity K^+ transporter (*HKT1;1*) allelic variants in the adaptation of *Arabidopsis thaliana* populations to fluctuating salinity dynamics in nature. This information not only provides a case study fruitfully taking identification of natural variants through population demographic dynamics to molecular function but also is valuable for improving the sustainability of crop yields as the stress from salinity escalates due to increasing population pressures and global climate change. (See pp. E12443–E12452.)

SOG1 activator and MYB3R repressors regulate a complex DNA damage network in *Arabidopsis*

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DNA damage triggers a highly conserved response that coordinates processes necessary to maintain genome integrity, including cell cycle arrest, DNA repair, and cell death. Despite the identification of primary transcription factors (TFs) that control these processes, knowledge regarding the downstream genes and regulatory networks controlled by these TFs remains poorly understood. Using *Arabidopsis*, we generated the first model of the DNA damage response transcriptional network, revealing 11 coexpressed gene groups with distinct biological functions and *cis*-regulatory features. Our characterization of this model demonstrates that SOG1 and three MYB3R TFs are, respectively, the major activator and repressors within this network, coordinating the rapid induction of DNA repair genes and TF cascades as well as the subsequent repression of cell cycle genes. (See pp. E12453–E12462.)