PNAS Plus Significance Statements

Continental crust beneath southeast Iceland

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The Iceland hotspot is widely thought to be the surface expression of a deep mantle plume from the core–mantle boundary that can be traced back in time at least 62 My. However, some lavas contain continental material, which has previously been proposed to have been recycled through the plume. Here (pp. E1818–E1827), we argue that the plume split off a sliver of continent from Greenland in the Early Eocene. This sliver is now located beneath southeast Iceland where it locally contaminates some of the plume-derived magmas.

Eluding catastrophic shifts

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Catastrophic shifts such as desertification processes, massive extinctions, or stock market collapses are ubiquitous threats in nature and society. In these events, there is a shift from one steady state to a radically different one, from which recovery is exceedingly difficult. Thus, there is a huge interest in predicting and eventually preventing catastrophic shifts. Here (pp. E1828–E1836) we explore the influence of key mechanisms such as demographic fluctuations, heterogeneity, and diffusion, which appear generically in real circumstances. The mechanisms we study could ideally be exploited to smooth abrupt shifts and to make transitions progressive and easier to revert. Thus, our findings could be of potential importance for ecosystem management and biodiversity conservation.

Chiral structures from achiral liquid crystals in cylindrical capillaries

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Nematic liquid crystals (LCs) are arguably the simplest examples of partially ordered condensed matter, and they are core materials in many commercial products. Our experiments (pp. E1837–E1844) explore fundamental questions about how chiral configurations of LCs can arise from achiral building blocks. Left- and right-handed chiral structures are produced by a delicate balance of LC bulk elasticity and surface conditions in confinement. The key experimental ingredients are biocompatible aqueous lyotropic chromonic LCs that twist easily. Combined with the new constraints, this class of achiral LC exhibits chiral structures and a rich assortment of defects, which hint at applications in sensing and optics.

Reconstitution of a prokaryotic minus end-tracking system using TubRC centromeric complexes and tubulin-like protein TubZ filaments

Gero Fink and Jan Löwe

Bacteria carry large extrachromosomal circular DNA molecules, called plasmids, that contain specific genes causing virulence and drug resistance. An active molecular machine based on actin- or tubulin-like filaments ensures proper inheritance of these low-copy-number plasmids. Tubulin-like filaments are involved in the maintenance of virulence plasmids in pathogens such as *Bacillus thuringiensis*, *Bacillus anthraxis*, and *Bacillus cereus*. We discovered (pp. E1845–E1850) that filaments of tubulin-like TubZ protein and TubRC centromeric complexes, containing TubR protein and *tubC* DNA, encoded on plasmid pBtoxis, self-assemble into a prokaryotic minus end-tracking system. Filament depolymerization and processive TubRC binding to shrinking minus ends cause directed DNA motility, most likely through pulling forces.

Cis and trans interactions between atlastin molecules during membrane fusion

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The membrane-anchored GTPase atlastin (ATL) mediates the fusion of endoplasmic reticulum membranes into a network of tubules and sheets, but the mechanism of ATL function is still poorly understood. Here (pp. E1851–E1860) we show that vesicle fusion is preceded by GTP hydrolysis-dependent tethering, caused by the interaction of ATL molecules in opposing membranes. GTP hydrolysis also dissociates ATL dimers sitting in the same membrane (cis dimers), generating a pool of ATL monomers that can dimerize with molecules on a different (trans) membrane. Multiple rounds of GTP hydrolysis and the cooperation of several ATL molecules in each membrane are required for a successful fusion event. These results lead to a model of ATL-mediated fusion that also may have implications for SNARE-mediated fusion.

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Islet 1 specifies the identity of hypothalamic melanocortin neurons and is critical for normal food intake and adiposity in adulthood

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Food intake and body weight regulation depend on a group of hypothalamic neurons that release satiety-induced neuropeptides known as melanocortins. Central melanocortins are encoded by the proopiomelanocortin gene (*Pomc*), and mice and humans carrying deleterious mutations in the *Pomc* gene display hyperphagia and severe obesity. Although the importance of these neurons is well understood, the genetic program that establishes hypothalamic melanocortin neurons and maintains normal *Pomc* expression levels remains unknown. Here (pp. E1861–E1870), we combined molecular neuroanatomical and biochemical analyses with functional genetic studies in transgenic mice and zebrafish and discovered that the transcription factor Islet 1 determines the identity of central melanocortin neurons during early brain development and is critical for melanocortin-induced satiety and normal adiposity throughout the entire lifetime.

Juvenile hormone-activated phospholipase C pathway enhances transcriptional activation by the methoprene-tolerant protein

Pengcheng Liu, Hong-Juan Peng, and Jinsong Zhu

Juvenile hormone (JH) controls many key processes during insect life cycles. Some of the effects of JH are mediated by a membrane-associated mechanism. In other circumstances, an intracellular JH receptor, methoprene-tolerant protein (MET), is activated upon binding of JH and directly regulates the expression of JH target genes. Here (pp. E1871–E1879) we use adult female mosquitoes as an example to demonstrate that both mechanisms are interconnected to coordinate hormonal responses. Our results indicate that the phospholipase C pathway is activated shortly after hormone exposure. Activation of this pathway induces phosphorylation of MET and profoundly increases the ability of MET to bind to JH target. This study establishes the link between the membrane-initiated JH signaling and the MET-mediated genomic action of JH.

Sae2 promotes DNA damage resistance by removing the Mre11–Rad50–Xrs2 complex from DNA and attenuating Rad53 signaling

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Chromosomal double-strand breaks (DSBs) are cytotoxic forms of DNA damage that must be accurately repaired to maintain genome integrity. The conserved Mre11–Rad50–Xrs2/NBS1 nuclease/ATPase complex plays an important role in repair by functioning as a damage sensor and by regulation of DNA end processing to ensure repair by the most appropriate mechanism. Yeast Sae2 is known to function with Mre11 to process DNA ends, but its precise role is poorly understood. Here (pp. E1880–E1887) we show that it is the failure to remove Mre11 from DNA ends, leading to persistent DNA damage signaling and cell cycle arrest, that causes sensitivity of Sae2-deficient cells to DNA damaging agents.

RNA-binding protein hnRNPLL regulates mRNA splicing and stability during B-cell to plasma-cell differentiation

Xing Chang, Bin Li, and Anjana Rao

Plasma cells produce immunoglobulin and provide long-lasting protective immunity. Differentiation of B cells to plasma cells is accompanied by major changes in gene expression, which are regulated at both transcriptional and posttranscriptional levels. We have used (pp. E1888–E1897) genome-wide methods to identify the binding sites and RNA targets of heterogeneous nuclear RNA-binding protein LL (hnRNPLL), whose expression is up-regulated during B-cell to plasma-cell differentiation. In addition to its recognized function in promoting exon splicing, hnRNPLL shapes the transcriptome of plasma cells by regulating exon inclusion and promoting mRNA stability. hnRNPLL binds to preferred sequences in RNA and is critical for complete plasma-cell differentiation, by mediating the down-regulation of B-cell–specific transcription factors and maximizing immunoglobulin production.

αIIbβ3 variants defined by next-generation sequencing: Predicting variants likely to cause Glanzmann thrombasthenia

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Next-generation sequencing is identifying millions of novel gene variants, presenting challenges to researchers and clinicians. Variations in the genes *ITGA2B* and *ITGB3* affect integrin αIIbβ3, leading to the bleeding disorder Glanzmann thrombasthenia. We analyzed (pp. E1898–E1907) novel missense variants on ∼32,000 alleles of *ITGA2B* and *ITGB3* and found missense variants affecting ∼10% of the amino acids in each protein in ∼1.3% of the population. Almost all variants are rare, indicating recent entry into the population. Two novel variants we predicted would be deleterious profoundly affected recombinant protein expression. At cut-off values that correctly predicted at least 69% of the known Glanzmann thrombasthenia mutations as deleterious, three variant prediction algorithms predicted that at least 27% of the novel variants are deleterious.

Structural basis for the geometry-driven localization of a small protein

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Despite extensive studies of protein trafficking across length scales of many microns, how proteins correctly localize within the smaller

length scales of bacterial cells is still poorly understood. Recently, we proposed that slight membrane curvature, defined by the surface geometry of a bacterium, can drive the localization of certain shape-sensing proteins. Here (pp. E1908–E1915), we developed an assay to quantify membrane curvature recognition by the small bacterial protein SpoVM and used NMR to determine the structural basis of curvature recognition. NMR and molecular dynamics simulations suggested a model wherein unusually deep membrane insertion allows the protein to sense subtle acyl chain packing differences between differently curved membranes, a distinct curvature-sensing mechanism from those used by proteins that sense high membrane curvature.

The circadian oscillator in *Synechococcus elongatus* controls metabolite partitioning during diurnal growth

Spencer Diamond, Darae Jun, Benjamin E. Rubin, and Susan S. Golden

Cyanobacteria are increasingly being considered for use in large-scale outdoor production of fuels and industrial chemicals. Cyanobacteria can anticipate daily changes in light availability using an internal circadian clock and rapidly alter their metabolic processes in response to changes light availability. Understanding how signals from the internal circadian clock and external light availability are integrated to control metabolic shifts will be important for engineering cyanobacteria for production in natural outdoor environments. This study (pp. E1916–E1925) has assessed how "knowing" the correct time of day, via the circadian clock, affects metabolic changes when a cyanobacterium goes through a dark-to-light transition. Our data show that the circadian clock plays an important role in inhibiting activation of the oxidative pentose phosphate pathway in the morning.

α-Synuclein, a chemoattractant, directs microglial migration via H_2O_2-dependent Lyn phosphorylation

Shijun Wang, Chun-Hsien Chu, Tessandra Stewart, Carmen Ginghina, Yifei Wang, Hui Nie, Mingri Guo, Belinda Wilson, Jau-Shyong Hong, and Jing Zhang

α-Synuclein (α-syn) aggregates released from neurons activate microglia, leading to chronic neuroinflammation that causes damage to neurons in brains with synucleinopathies, such as Parkinson's disease (PD). However, little is known about the mechanism by which α-syn affects microglial activity, especially motility, and why microglia migrate toward the injured neurons and preferentially accumulate along with α-syn aggregates in the affected areas, e.g., in the substantia nigra of PD brains. Here (pp. E1926–E1935) we show that neuron-derived α-syn aggregates are chemoattractants that direct microglial migration by acting on NADPH oxidase and several specific downstream proteins. Blocking the targets involved in α-syn–mediated microglial directional migration may represent a therapeutic strategy to protect against progressive neuronal loss in PD and related synucleinopathies.

SOX2 primes the epigenetic landscape in neural precursors enabling proper gene activation during hippocampal neurogenesis

Alejandro Amador-Arjona, Flavio Cimadamore, Chun-Teng Huang, Rebecca Wright, Susan Lewis, Fred H. Gage, and Alexey V. Terskikh

Sex-determining region Y-related HMG box 2 (SOX2) is a well-established marker of neural stem and progenitor cells, and its function was shown to be required for the self-renewal of these cells. However, the function of SOX2 in neuronal differentiation is poorly understood. Here (pp. E1936–E1945) we described a novel role of SOX2 in neuronal differentiation in which SOX2 binds to bivalently marked promoters of poised proneural genes in neural progenitor cells and limits the activity of polycomb repressive complex 2 and excessive levels of histone H3 Lys 27 trimethylation. We propose a novel function of SOX2 in maintaining a permissive epigenetic state thus enabling proper activation of the neuronal differentiation program under neurogenic cue.

Transcriptome analysis reveals transmembrane targets on transplantable midbrain dopamine progenitors

Chris R. Bye, Marie E. Jönsson, Anders Björklund, Clare L. Parish, and Lachlan H. Thompson

An important challenge for improving cell-based approaches for Parkinson's disease is the development of techniques that facilitate greater standardization of the donor material. This report (pp. E1946–E1955) describes the enrichment of transplantable progenitors for dopamine neurons from the ventral mesencephalon based on targeting of transmembrane proteins. It is an important step toward the development of clinically relevant techniques that allow for greater standardization of cell preparations used in transplantation and potentially, more predictable clinical outcomes. The findings are highly relevant for current efforts to develop stem cell-based therapies for Parkinson's disease, where current techniques yield mixed cell populations that may contain unwanted cell types and thus, would benefit from a cell selection step prior to grafting.

Tectal microcircuit generating visual selection commands on gaze-controlling neurons

Andreas A. Kardamakis, Kazuya Saitoh, and Sten Grillner

Neurons in the optic tectum are involved in stimulus selection and also control gaze reorientation. This study (pp. E1956–E1965) relies on an in vitro preparation that allows visual activation of the retina while providing accessibility for whole-cell recordings from specific cells that control gaze action. We show the tectal (collicular in mammals) GABAergic interneurons generate rivalry between visual areas and that tectal gaze-controlling cells integrate this inhibition along with local retinal excitation to form stimulus selection commands that will move the eyes and head, and may also contribute to edge detection. We propose that this subcortical visuomotor circuit is phylogenetically conserved throughout vertebrate evolution.