PNAS Plus Significance Statements

Probing biological nanotopology via diffusion of weakly constrained plasmonic nanorods with optical coherence tomography

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Many diseases are characterized by nanostructural changes in connective fibers and soluble proteins, which can indicate or drive disease progression. Noninvasive methods sensitive to nanotopological changes in 3D tissue models can elucidate biophysical changes associated with disease progression. Nanoparticles probe their environment via their diffusion, which is impacted by the size and connectivity of pores into which they freely diffuse. Here (pp. E4289–E4297), we show that optical coherence tomography provides depth-resolved imaging of gold nanorods (GNRs) to infer local biological nanotopology. We demonstrate the broad potential of this method by sensing changes in diffusion of GNRs in 3D models of mammary ECM and pulmonary mucus.

Mantle updrafts and mechanisms of oceanic volcanism

Don L. Anderson and James H. Natland

Lord Kelvin's name is associated with the laws of thermodynamics and the cooling Earth hypothesis. The widely accepted mantle plume conjecture has been justified by experiments and calculations that violate the laws of thermodynamics for an isolated cooling planet. Hotspots such as Hawaii, Samoa, Iceland, and Yellowstone are due to a thermal bump in the shallow mantle, a consequence of the cooling of the Earth (pp. E4298–E4304). They are not due to ∼100- to 200-km-wide tubes extending upward from fixed points near the Earth's core. Seismic imaging shows that features associated with hotspots are thousands of kilometers across, and inferred ascent rates are low. Plate tectonic-induced updrafts and a cooling planet explain hotspots and the volcanoes at oceanic ridges.

Structural basis of cellular dNTP regulation by SAMHD1

Xiaoyun Ji, Chenxiang Tang, Qi Zhao, Wei Wang, and Yong Xiong

SAMHD1 is a dNTPase that depletes the cellular dNTP pool to inhibit the replication of retroviruses, including HIV-1. The dNTPase activity of SAMHD1 also enables the enzyme to be a major regulator of cellular dNTP levels in mammalian cells, in addition to be implicated in the pathogenesis of chronic lymphocytic leukemia (CLL) and Aicardi Goutières syndrome (AGS). Here (pp. E4305–E4314) we present extensive structural and enzymatic data to reveal how SAMHD1 is activated and regulated via the combined actions of GTP and all cellular dNTPs. Our work establishes a complete spectrum of nucleotide binding and the exquisite regulatory mechanism of SAMHD1 in cellular dNTP metabolism, retrovirus restriction, and the pathogenesis of CLL and AGS.

Upregulation of eIF5B controls cell-cycle arrest and specific developmental stages

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This study uncovers a critical role for a general translation factor in specific developmental stages, including immature oocytes and ES cells, and during growth-factor deprivation of mammalian cells, which induces the transition to cell-cycle arrest. These conditions alter and decrease general translation yet maintain ongoing translation. We reveal (pp. E4315–E4322) upregulation of the eukaryotic translation factor 5B (eIF5B), which becomes essential for general translation, specifically in these conditions. Importantly, our data demonstrate that eIF5B controls these cell-cycle transition and developmental stages, promoting oocyte maturation and inhibiting cell-cycle arrest. These findings underscore the importance of translational regulation in cell-cycle transitions and development.

Caenorhabditis elegans RSD-2 and RSD-6 promote germ cell immortality by maintaining small interfering RNA populations

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Here (pp. E4323–E4331), we establish a role for small RNAs in promoting transgenerational fertility via an endogenous temperature-sensitive silencing process that is promoted by the RNAi spreading defective (RSD)-2 and RSD-6 proteins, which have been implicated in RNA interference in response to exogenous double-stranded RNA triggers. This process could be broadly relevant to transgenerational maintenance of heterochromatin and is plausibly relevant to regulation of aging of somatic cells as they proliferate.

Retroviral envelope *syncytin* capture in an ancestrally diverged mammalian clade for placentation in the primitive Afrotherian tenrecs

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Syncytins are genes of retroviral origin that have been captured by their host as symbionts for a function in placentation. They can mediate cell–cell fusion, consistent with their ancestral retroviral envelope gene status, and are involved in fusion of mononucleate trophoblast cells to form the syncytial layer—the syncytiotrophoblast—of the feto–maternal interface. We proposed that such genes have been pivotal for the emergence of placental mammals from egg-laying animals and should be present all along the Placentalia radiation. We searched (pp. E4332–E4341) for *syncytins* in a superorder of eutherian mammals that emerged ancestrally during the

Cretaceous terrestrial revolution and identified *syncytin-Ten1*, conserved over millions years of evolution of the Afrotherian tenrecs, regarded as among the most primitive of living mammals.

Human DNA tumor viruses generate alternative reading frame proteins through repeat sequence recoding

Hyun Jin Kwun, Tuna Toptan, Suzane Ramos da Silva, John F. Atkins, Patrick S. Moore, and Yuan Chang

Kaposi's sarcoma-associated herpesvirus and Epstein–Barr virus latent antigens, latency-associated nuclear antigen 1 (LANA1) and Epstein–Barr nuclear antigen 1 (EBNA1), are multifunctional proteins involved in the maintenance of episome, latency, regulation of transcription, cell cycle, and immune surveillance. These latent antigens generate +1/−2 frameshifted alternative reading frame (ARF) isoforms by programmed ribosomal frameshifting. EBNA1 recoding generates a LANA1-like glutamine- and glutamic acid-rich $EBNA1_{ARF}$, implicating a crucial role for these sequences in both viruses, whereas high recoding ability of LANA1 generates a serine/arginine-rich repeat sequence protein similar to those found in neurodegenerative disorders. Here (pp. E4342–E4349) we show that repeat recoding in oncogenic human herpesviruses increases the genetic coding capacity of their latent viral proteins. Repetitive elements may be an unexpected source for human and virus protein expression diversity.

Transmembrane domain of surface-exposed outer membrane lipoprotein RcsF is threaded through the lumen of β-barrel proteins

Anna Konovalova, David H. Perlman, Charles E. Cowles, and Thomas J. Silhavy

In *Escherichia coli*, most outer membrane (OM) lipoproteins are thought to be soluble proteins that are simply tethered to the inner leaflet of this membrane by lipid moieties attached to the N terminus. Here (pp. E4350–E4358) we show that lipoprotein RcsF (regulator of capsule synthesis) adopts a transmembrane orientation with the lipidated N terminus on the cell surface and the folded C-terminal domain in the periplasm. The short, unstructured, polar linker domain spans the hydrophobic membrane by passing through the lumen of several different OM β-barrel proteins. This remarkable, interlocked structure is formed by the Bam complex, which folds and inserts all β-barrel proteins in the OM, suggesting that this assembly machine translocates the lipid moieties and then folds the β barrel around the RcsF linker.

Vitamin D prevents cognitive decline and enhances hippocampal synaptic function in aging rats

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Higher blood levels of vitamin D are associated with better health outcomes. Vitamin D deficiency, however, is common among the elderly. Despite targets in the brain, little is known about how vitamin D affects cognitive function. In aging rodents, we modeled human serum vitamin D levels ranging from deficient to sufficient and tested whether increasing dietary vitamin D could maintain or improve cognitive function. Treatment was initiated at middle age, when markers of aging emerge, and maintained for ∼6 mo. Compared with low- or normal-dietary vitamin D groups, only aging rats on higher vitamin D could perform a complex memory task and had blood levels considered in the optimal range. These results (pp. E4359–E4366) suggest that vitamin D may improve the likelihood of healthy cognitive aging.

Resting-state networks link invasive and noninvasive brain stimulation across diverse psychiatric and neurological diseases

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Brain stimulation is a powerful treatment for an increasing number of psychiatric and neurological diseases, but it is unclear why certain stimulation sites work or where in the brain is the best place to stimulate to treat a given patient or disease. We found that although different types of brain stimulation are applied in different locations, targets used to treat the same disease most often are nodes in the same brain network. These results (pp. E4367–E4375) suggest that brain networks might be used to understand why brain stimulation works and to improve therapy by identifying the best places to stimulate the brain.

Proteopathic tau seeding predicts tauopathy in vivo

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Prion-like propagation of proteopathic seeds may underlie the progression of neurodegenerative diseases, including the tauopathies and synucleinopathies. We aimed to construct a versatile and simple cell assay to sensitively and specifically detect proteopathic seeding activity. Using a combination of FRET flow cytometry and a tau monoclonal FRET biosensor cell line, we report (pp. E4376–E4385) seed detection in the femtomolar range. This assay is easily applied to human brain homogenates and selectively responds to Alzheimer's disease but not Huntington's disease brains. By comparing seeding activity in a mouse model of human tauopathy, we demonstrate detection of proteopathic seeding far in advance of standard histopathological markers. Proteopathic seeding is thus an early marker of tauopathy, consistent with a causal role for tau seeds in neurodegeneration.

Basal p21 controls population heterogeneity in cycling and quiescent cell cycle states

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Population heterogeneity can make the treatment of tumors more challenging. Whereas a therapeutic agent may be effective against one fraction of a population, it may be less effective against another fraction. Although heterogeneity can be genetic and attributed to mutations, there can also be nongenetic heterogeneity, where a clonal population can harbor distinct subpopulations. Here (pp. E4386–E4393), we identified a single gene, p21, that was responsible for population heterogeneity in cell cycle activity and explain that this heterogeneity can arise from regulatory relationships of p21 with Cyclin-dependent kinase 2 (CDK2) and E3 ubiquitin ligases. We suggest that, instead of using CDK inhibitors (CKIs) in cancer therapy, CKIs themselves should be targeted. Given concurrently with chemotherapy agents, CKI inhibitors would reduce tumor heterogeneity and thus increase chemotherapy efficacy.