PNAS Plus Significance Statements

Robust excitons inhabit soft supramolecular nanotubes

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The scientific community has been broadly inspired by tiny deep-sea bacteria, the green sulfur bacteria, that are able to harvest minute amounts of incoming sunlight with exquisite efficiency. Nature's masterpiece consists of soft, cylindrical-shaped, supramolecular structures that are densely packed in superstructures. Only little is known about the fundamental processes that govern nature's efficiency. Here (pp. E3367–E3375) we unravel, for the first time to our knowledge, the impact of structural complexity through the use of a model system akin to that found in nature, focusing on the properties that are prerequisite for nature's efficient light harvesting. Our work suggests that the cylindrical geometry presents a rational design that may be key for protecting the system's quantum properties upon dense packing.

Spliceostatin hemiketal biosynthesis in *Burkholderia* spp. is catalyzed by an iron/α-ketoglutarate–dependent dioxygenase

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Spliceostatins are bacterial natural products that show promising anticancer activity. Understanding how the bacterium makes spliceostatins will aid efforts toward a sustainable route for their production. Moreover, altering the chemical structure of a natural product is usually necessary to improve its pharmaceutical properties. For example, the parent spliceostatin molecule contains an unstable hemiketal chemical group. Contrary to previous hypotheses, we report on the identification of a dioxygenase enzyme responsible for hemiketal biosynthesis. Deletion of the corresponding dioxygenase gene led to a strain that produces exclusively spliceostatin congeners that are more stable than, and as active as, the parent compound, when derivatized to increase cell permeability. The strain generated in this study (pp. E3376–E3385) will be the basis for future development.

Free-energy inference from partial work measurements in small systems

Marco Ribezzi-Crivellari and Felix Ritort

Fluctuation relations (FRs) provide general results about work (or total entropy production) distributions in nonequilibrium systems. However, in many cases the full work is not measurable and only partial work measurements are possible. The latter do not fulfill a FR and cannot be used to extract free-energy differences from irreversible work measurements. We show how FRs can be used to infer the full work distribution from partial work measurements. We illustrate the inference process, using dual-trap optical tweezers where two forces (one per trap) are measured, and we can access both the full and the partial work distributions (pp. E3386–E3394). We derive a set of results of direct interest to single-molecule scientists and, more generally, to physicists and biophysicists.

Protective hinge in insulin opens to enable its receptor engagement

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Insulin provides a model for analysis of protein structure and evolution. Here we describe in detail a conformational switch that enables otherwise hidden nonpolar surfaces in the hormone to engage its receptor. Whereas the classical closed conformation of insulin enables its stable storage in pancreatic β cells, its active conformation is open and susceptible to nonnative aggregation. Our findings (pp. E3395–E3404) illuminate biophysical constraints underlying the evolution of an essential signaling system and provide a structural foundation for design of therapeutic insulin analogs.

Cyclin D3 promotes pancreatic β-cell fitness and viability in a cell cycle-independent manner and is targeted in autoimmune diabetes

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Autoimmune diabetes is caused by the lymphocyte-mediated destruction of the pancreatic insulin-producing β cells. The inflammatory niche surrounding β cells prior to diabetes onset provokes death-inducing molecular changes in these cells. Unknown molecular pathways related to β-cell viability that are altered by inflammation in vivo, and therefore potential therapeutic targets, remain to be identified, because most of the previous studies took in vitro approaches. Here (pp. E3405–E3414), we report that cyclin D3, classically related to cell proliferation, is targeted in autoimmune diabetes and exerts a protective role on β cells by promoting their survival and fitness without affecting proliferation. These findings unveil a dual, cell cycle-independent role of cyclin D3 with high potential in the areas of autoimmunity and metabolism.

Short sequences can efficiently recruit histone H3 lysine 27 trimethylation in the absence of enhancer activity and DNA methylation

Philip Jermann, Leslie Hoerner, Lukas Burger, and Dirk Schübeler

Polycomb repressive complex 2 functions in gene repression and acts by methylating histone H3 at lysine 27 (H3K27me3). Despite its relevance, it remains elusive how this complex is recruited to its target sites in the genome. Here, we used repeated genomic targeting in embryonic stem cells to identify DNA sequence determinants that autonomously confer H3K27me3 recruitment. We show (pp. E3415–E3421) that surprisingly small CG-rich DNA sequences are sufficient to recruit H3K27me3, but only if they are devoid of DNA methylation and transcriptional activity. This study provides new insights into the mechanisms recruiting H3K27me3 and the cross-talk between diverse chromatin modifications.

IL-17 drives psoriatic inflammation via distinct, target cell-specific mechanisms

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Psoriasis is an inflammatory disease affecting the skin, a barrier site. The disease is characterized by abnormal growth of keratinocytes and infiltration of inflammatory cells. Clinical trials targeting the IL-17 cytokine have shown remarkable efficacy, and IL-17 also has been strongly implicated in the imiquimod-induced mouse model of psoriasis. However why IL-17 cytokines should be so central is not known, because target cells and their functions have not been clearly delineated. Here (pp. E3422–E3431) we demonstrate that IL-17 signaling into nonkeratinocytes, specifically dermal fibroblasts, induces mediators that further increase IL-17 production by innate γδT cells and promote cellular infiltration, whereas IL-17 signaling into keratinocytes aids proliferation and blocks their differentiation. These findings reveal the circuitry underpinning critical disease-driving effects of IL-17.

Critical role of *all-trans* retinoic acid in stabilizing human natural regulatory T cells under inflammatory conditions

Ling Lu, Qin Lan, Zhiyuan Li, Xiaohui Zhou, Jian Gu, Qiang Li, Julie Wang, Maogen Chen, Ya Liu, Yi Shen, David D. Brand, Bernhard Ryffel, David A. Horwitz, Francisco P. Quismorio, Zhongmin Liu, Bin Li, Nancy J. Olsen, and Song Guo Zheng

Natural regulatory T cells (nTregs) play important roles in preventing autoimmune diseases, but they may be unstable in the presence of inflammation. Here we report that *all-trans* RA (atRA) but not rapamycin prevents human nTregs from converting to Th1/Th17 cells and sustains their suppressive function in inflammatory environments. Adoptive transfer of nTregs pretreated with atRA enhances their suppressive effects on xenograft-vs.-host diseases. Moreover, we show that atRA suppresses IL-1 receptor upregulation, accelerates IL-6 receptor downregulation, and affects the epigenetic modifications in *Foxp3* locus in nTregs following inflammatory stimulation. We suggest (pp. E3432–E3440) that nTregs primed with atRA may represent a novel treatment strategy to control established chronic immune-mediated diseases.

Cross-resistance mechanism of respiratory syncytial virus against structurally diverse entry inhibitors

Dan Yan, Sujin Lee, Vidhi D. Thakkar, Ming Luo, Martin L. Moore, and Richard Karl Plemper

Respiratory syncytial virus (RSV) causes major disease in pediatric and elderly patients, urging the development of efficacious therapeutics. This study (pp. E3441–E3449) establishes a recombinant RSV reporter strain for drug discovery and identifies an entry inhibitor class targeting the viral fusion (F) protein. Biochemical, structural, and functional characterization of the inhibitor spotlights two microdomains governing the conformational stability of prefusion F. Mutations in these domains cause broad cross-resistance against the compound and RSV entry inhibitors in preclinical and clinical development, without mandatory loss of in vivo pathogenicity, challenging the possible clinical benefit of current RSV entry inhibitor classes. Anti-RSV campaigns should better target postentry steps or proactively circumvent resistance to entry inhibition. The resistant RSV reporter strain developed here establishes a strategy toward this goal.

Synthesis and scavenging role of furan fatty acids

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Fatty acids comprise a large class of compounds that serve broad roles in cells and society. These hydrophobic compounds provide integrity for biological membranes, make them impermeable to solutes and toxins, and modulate the cellular response to signals or stresses. Fatty acids, or the products derived from them, are also important as dietary supplements, lubricants, specialty chemicals, and fuels. Their potential utility in biology or industry could be increased by producing novel classes of fatty acids. This paper (pp. E3450–E3457) reports on the occurrence and synthesis of a newly discovered class of furan-containing fatty acid. It also provides evidence that furan-containing fatty acids scavenge toxic reactive oxygen species, suggesting a previously unnoticed role for this class of compounds in bacteria and other cells.

T-cell TGF-β signaling abrogation restricts medulloblastoma progression

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Medulloblastoma (MB) is a tumor of the cerebellum that primarily forms in pediatric patients during brain development. The immune system ultimately fails to eradicate MB because it is "blind" to tumor cells as a result of poor brain immune surveillance caused by the existence of the blood–brain barrier and the brain's immune privileged status. Another mechanism of tumor escape is immune suppressors that act as a "smokescreen," blocking effective antitumor immunity. We show that blockade of the TGF-β signaling pathway promotes memory T cell development, conferring antitumor immunity to the *smoothened A1* mouse model of MB. Our data (pp. E3458–E3466) lay the cellular immune mechanistic framework for blocking T cell TGF-β signaling in pediatric brain cancer.

Curvature-processing network in macaque visual cortex

Xiaomin Yue, Irene S. Pourladian, Roger B. H. Tootell, and Leslie G. Ungerleider

The brain processes visual stimuli along different feature dimensions, including edge orientation, visual motion, and color. To expedite visual processing, cells that process a common visual dimension are often anatomically grouped in cortical columns, patches, and/or areas. Here (pp. E3467–E3475), we tested the hypothesis that (*i*) image curvature is one of these fundamental visual dimensions and, as such, (*ii*) curvature-selective cells are grouped together in discrete cortical areas. Using neuroimaging techniques, we confirmed this hypothesis and localized the curvature-processing sites in extrastriate visual cortex. These sites lay along a common cortical strip, spanning lower- to higher-level processing stages. Furthermore, the curvature-processing sites are adjacent to the well-known face-processing cortical areas, suggesting a possible functional link between them.

Robust efficiency and actuator saturation explain healthy heart rate control and variability

Na Li, Jerry Cruz, Chenghao Simon Chien, Somayeh Sojoudi, Benjamin Recht, David Stone, Marie Csete, Daniel Bahmiller, and John C. Doyle

Reduction in human heart rate variability (HRV) is recognized in both clinical and athletic domains as a marker for stress or disease, but previous mathematical and clinical analyses have not fully explained the physiological mechanisms of the variability. Our analysis of HRV using the tools of control mathematics reveals that the occurrence and magnitude of observed HRV is an inevitable outcome of a controlled system with known physiological constraints (pp. E3476–E3485). In addition to a deeper understanding of physiology, control analysis may lead to the development of timelier monitors that detect control system dysfunction, and more informative monitors that can associate HRV with specific underlying physiological causes.

Structural basis for the recognition–evasion arms race between *Tomato mosaic virus* and the resistance gene *Tm-1*

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The Red Queen hypothesis proposes that host defense genes evolve to counter the adverse effects of rapidly evolving invasive viruses. Although 3D structures of host–viral protein complexes have provided great insights into the molecular conflicts between them, a single structure represents only an evolutionary snapshot. Here (pp. E3486–E3495) we present the atomic details of the step-by-step arms race between tomato mosaic virus replication protein and the host inhibitor protein Tm-1, in which host recognition of a viral molecule, viral adaptive evasion of the recognition, host counter-adaptation, and viral counter-counteradaptation are depicted by determination of the complex structures of Tm-1 variants and the viral protein and by biochemical analyses and molecular dynamics simulations of the interactions between these proteins.