PNAS Plus Significance Statements

Hydrodynamic collective effects of active protein machines in solution and lipid bilayers

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Biological cells contain large numbers of active proteins that repeatedly change their conformations and need a supply of ATP or other substrates to maintain their cyclic operation. Whereas these protein machines have a variety of specific functions, acting as motors, ion pumps, or enzymes, they also induce fluctuating hydrodynamic flows in the cytoplasm. Because such fluctuating flows are nonthermal, energy can be extracted from them and work can be performed. We show that these flows can substantially enhance diffusive motions of passive particles. Furthermore, when gradients in concentrations of active proteins or substrate (ATP) are present, a chemotaxis-like drift should take place. Such nonequilibrium effects are universal: They hold for all passive particles and also for the protein machines themselves. (See pp. E3639–E3644.)

Nanoscale β-nuclear magnetic resonance depth imaging of topological insulators

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The surface states of topological insulators (TIs) and magnetically doped TIs exhibit considerable inhomogeneities at the nanoscale. Methods are needed to probe the degree of heterogeneity as a function of depth in nanoscale layers. We present a method that can directly visualize TIs in a depth-resolved manner and report on their electronic and magnetic properties. For example, in epitaxial thin films we demonstrate an increase in the density of states, a weakening of the ferromagnetic order when approaching the TI edges, as detected by measurements of the electron–nuclear hyperfine interaction, the effective *s–d* exchange integral, and local moment density. Depth profiling is expected to help uncover exotic physics of pure and ferromagnetic TIs and TI heterostructures. (See pp. E3645–E3650.)

Tenebrionid secretions and a fungal benzoquinone oxidoreductase form competing components of an arms race between a host and pathogen

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Although entomopathogenic fungi and their invertebrate hosts share a >300 million year co-evolutionary history, little is known concerning the biochemical and genetic basis of insect defensive tactics and the countermeasures evolved and evolving by the pathogen to thwart these defenses. Our results provide a molecular mechanism to help explain why some insects are more resistant to broad host-range entomopathogenic fungi. We identify beetle cuticular secretions and a fungal detoxifying enzyme as components of an arms race between insects and the fungal pathogen, suggesting an evolving role for the quinone reductase enzyme as a specific virulence factor for host quinone detoxification. As races have winners and losers, this paper captures a snapshot where the host is leading the race. (See pp. E3651–E3660.)

Magnetic levitation of single cells

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Cells consist of micro- and nanoscale components and materials that contribute to their fundamental magnetic and density signatures. Previous studies have claimed that magnetic levitation can only be used to measure density signatures of nonliving materials. Here, we demonstrate that both eukaryotic and prokaryotic cells can be levitated and that each cell has a unique levitation profile. Furthermore, our levitation platform uniquely enables ultrasensitive density measurements, imaging, and profiling of cells in real-time at single-cell resolution. This method has broad applications, such as the label-free identification and monitoring of heterogeneous biological changes under various physiological conditions, including drug screening in personalized medicine. (See pp. E3661–E3668.)

Structural insights into the assembly of the histone deacetylase-associated Sin3L/Rpd3L corepressor complex

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Gene transcription in eukaryotes is regulated by enzymes that post-translationally add or remove acetyl groups from histones and render the underlying DNA more or less accessible to the transcription machinery. How histone deacetylases (HDACs), the enzymes responsible for deacetylation that are commonly found in multiprotein complexes, are assembled and targeted to their sites of action to affect transcription repression is largely unknown. We show biochemically and structurally how two key subunits of a conserved HDAC complex recruit multiple copies of HDACs into the complex in a manner that allows the enzymes to explore a large conformational space when the complex is targeted to specific genomic loci. This complex seems to be tailored for efficient deacetylation of nucleosomes that are situated far apart. (See pp. E3669–E3678.)

Small GTP-binding protein Ran is regulated by posttranslational lysine acetylation

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The small GTPase Ran plays fundamental roles in cellular processes such as nucleo-cytoplasmic transport, mitotic spindle formation, and nuclear envelope assembly. Recently, Ran was found to be lysine acetylated, among others, in functionally important regions such as switch I and switch II. Using the genetic code expansion concept we show that lysine acetylation affects many important aspects of Ran function such as RCC1-catalyzed

nucleotide exchange, intrinsic nucleotide hydrolysis, import/export complex formation, and Ran subcellular localization. Finally, we present evidence for a regulation of Ran acetylation by sirtuin deacetylases and lysine acetyltransferases. (See pp. E3679–E3688.)

Coarse-grained simulations of bacterial cell wall growth reveal that local coordination alone can be sufficient to maintain rod shape

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The rod shape of walled bacteria is determined by the peptidoglycan (PG) sacculus, but how rod shape is maintained as cells grow remains a fundamental question in bacterial cell biology. We have developed a coarse-grained modeling method to study rod shape maintenance. Individual PG remodeling enzymes, including transglycosylases, transpeptidases, and endopeptidases, are for the first time, to our knowledge, explicitly modeled to explore how they can coordinate to remodel a sacculus several orders of magnitude larger than the enzymes themselves. Rather than requiring top-down regulation of new PG insertion sites, our work shows that local coordination of the PG remodeling enzymes within discrete complexes can be sufficient to maintain the integrity and rod shape of the sacculus. (See pp. E3689–E3698.)

Massive accumulation of luminal protease-deficient axonal lysosomes at Alzheimer's disease amyloid plaques

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Amyloid plaques, a key feature of Alzheimer's disease brain pathology, comprise an extracellular β-amyloid core surrounded by tissue enriched in lysosome-like organelles. As a foundation for understanding the mechanisms that drive amyloid plaque formation, we have elucidated the cellular origins and molecular composition of such organelles. The majority of the lysosomes at amyloid plaques reside within swollen neuronal axons. Interestingly, these organelles contain low levels of multiple luminal lysosomal proteases and closely resemble a lysosome subpopulation that naturally occurs in distal neuronal processes. These results suggest that extracellular β-amyloid deposits cause a local impairment in retrograde axonal transport, leading to the accumulation of lysosome precursors and a blockade in their further maturation that has implications for both β-amyloid production and clearance. (See pp. E3699–E3708.)

Structural asymmetry in a conserved signaling system that regulates division, replication, and virulence of an intracellular pathogen

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Brucella abortus is an intracellular bacterial pathogen that inflicts a significant health burden on both humans and their livestock on a global scale. We demonstrate that an essential regulatory system controls the growth and morphology of *B. abortus*, and that this system is required for survival inside mammalian host cells. Using experimental and computational tools of structural biology, we further define how the protein components of this regulatory pathway interact at the atomic scale. Our results provide evidence for multiple, asymmetric modes of binding between essential pathway proteins that control transcription. The multimodal molecular interactions we observe provide evidence for new layers of allosteric control of this conserved gene regulatory system. (See pp. E3709–E3718.)

Triangulation of the neurocomputational architecture underpinning reading aloud

Paul Hoffman, Matthew A. Lambon Ralph, and Anna M. Woollams

Reading is a critical linguistic skill, but understanding of its cognitive and neural bases is incomplete. Using functional MRI, we found reading-related activation in two areas of anterior temporal cortex, an area not previously associated with reading. Activation profiles of these sites were consistent with the predictions of computational reading models that ascribe a key role to semantic knowledge in reading words with irregular spellings. We also found individual differences in the reading neural network that were predicted by an independent measure of semantic reliance in reading. Such individual differences have been hypothesized on theoretical grounds to explain variation in reading abilities among neurodegenerative patients. Here we provide the first direct evidence, to our knowledge, for their existence in the healthy brain. (See pp. E3719–E3728.)

Noradrenergic blockade stabilizes prefrontal activity and enables fear extinction under stress

Paul J. Fitzgerald, Thomas F. Giustino, Jocelyn R. Seemann, and Stephen Maren

Posttraumatic stress disorder is characterized by a resistance to extinction learning and dysregulated signaling of the neurotransmitter norepinephrine. Previous research suggested the prelimbic and infralimbic subdivisions of the medial prefrontal cortex (mPFC) regulate fear expression and suppression, respectively. However, noradrenergic signaling in response to psychological stress may disrupt mPFC function, contributing to extinction deficits. Here we show, for the first time to our knowledge, that footshock stress dysregulates mPFC spike firing; this can be stabilized by propranolol, a β-noradrenergic receptor blocking drug, which in turn facilitates extinction when it normally fails. These findings suggest that propranolol may be a particularly effective adjunct to behavioral therapy soon after trauma, when stress is high, at least in part by normalizing prefrontal cortical function. (See pp. E3729–E3737.)

Maternal intestinal HIF-2α is necessary for sensing iron demands of lactation in mice

Sadeesh K. Ramakrishnan, Erik R. Anderson, Angelical Martin, Brook Centofanti, and Yatrik M. Shah

The benefits of breast milk in neonatal development are well characterized. However, very little is known about the essential nutrient components in breast milk that are critical for neonatal development and how these nutrients are maintained at adequate levels in breast milk. The present work demonstrates that the intestine is an essential sensor of systemic iron demand during lactation. During high iron demand from lactation, hypoxia-inducible factor-2α–mediated increase in maternal intestinal iron absorption is essential to maintain milk iron levels. This work demonstrates the significant role of maternal intestinal iron absorption in postnatal iron homeostasis of newborns and provides a therapeutic target to maintain iron homeostasis during pregnancy and lactation in anemic patients who are refractory to iron supplementation. (See pp. E3738–E3747.)