PNAS Plus Significance Statements

Nanospherical arabinogalactan proteins are a key component of the high-strength adhesive secreted by English ivy

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Despite the significant progress that has been made in exploring the molecular basis for multiple adhesive events in the animal kingdom, the exceptional adhesion behaviors of climbing plants, such as English ivy, are still poorly understood. In this study, the spheroidal nanoparticles observed in the mucilage exuded by the English ivy were identified to be predominantly composed of arabinogalactan proteins (AGPs). The roles of these AGP-rich nanoparticles in favoring the generation of strong adhesion strength are elucidated. The Ca^{2+}-driven electrostatic interactions among uronic acids within AGPs and pectin upon curing could be exploited as guidelines in the design and fabrication of novel synthetic adhesives, and the ivy-derived adhesive composite is capable of serving as a template for inspiring the development of diverse adhesive biomaterials. (See pp. E3193–E3202.)

Search for supersolidity in solid ^{4}He using multiple-mode torsional oscillators

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The concept of a supersolid state in solid ^{4}He was first suggested in 1968, yet it was only in 2004 that experimental evidence for the existence of this new state of matter was presented. The possible discovery of the long-sought supersolid state created much excitement and was followed, however, by experimental and theoretical work that suggested that the original interpretation was not satisfactory. It is now clear that many of the originally observed signals can be explained by changes in the shear modulus of the solid in the experimental cells. In the experiments reported here, we have used an experimental technique that enables the distinction between the effects of the shear modulus and those of a possible supersolid state. (See pp. E3203–E3212.)

O-linked *N*-acetylglucosamine transferase (OGT) interacts with the histone chaperone HIRA complex and regulates nucleosome assembly and cellular senescence

Jong-Sun Lee and Zhiguo Zhang

Nucleosome assembly is regulated at multiple levels to impact distinct cellular processes. Mutations in factors involved in nucleosome assembly, such as histone chaperones and histone variants, result in genome instability and gene expression defects that, in turn, promote the development of human disease including cancer and aging. Therefore, it is important to determine how nucleosome assembly of H3.3 is regulated. Our findings demonstrate a role for O-linked *N*-acetylglucosamine (GlcNAc) transferase in regulating H3.3 deposition/exchange and establish the O-GlcNAc modification of HIRA as a previously unidentified mechanism regulating nucleosome assembly of H3.3 and cellular senescence. (See pp. E3213–E3220.)

Multiensemble Markov models of molecular thermodynamics and kinetics

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Molecular dynamics simulations can provide mechanistic understanding of biomolecular processes. However, direct simulation of slow transitions such as protein conformational transitions or protein–ligand dissociation are unfeasible with commonly available computational resources. Two typical strategies are (*i*) conducting large ensembles of short simulations and estimating the long-term kinetics with a Markov state model, and (*ii*) speeding up rare events by bias potentials or higher temperatures and estimating the unbiased thermodynamics with reweighting estimators. In this work, we introduce the transition-based reweighting analysis method (TRAM), a statistically optimal approach that combines the best of both worlds and estimates a multiensemble Markov model (MEMM) with full thermodynamic and kinetic information at all simulated ensembles. (See pp. E3221–E3230.)

β1-subunit–induced structural rearrangements of the Ca^{2+}- and voltage-activated K^+ (BK) channel

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Large-conductance Ca^{2+}- and voltage-activated K^+ (BK) channels play many physiological roles, ranging from the maintenance of smooth muscle tone to the modulation of alcohol tolerance. In most cases, this physiological versatility of the BK channel is due to the association of the pore-forming α-subunit with β-subunits. Therefore, it is of importance to know what the structural consequences of this association are. Here, using lanthanide-based resonance energy transfer, we were able to determine the extracellular position of transmembrane segments S0–S2 with and without the β1-subunit and the position of the two transmembrane segments of the β1 subunit in the α/β1-subunit complex. We concluded that β1 produces rearrangements of the BK voltage sensor domain. (See pp. E3231–E3239.)

CYP450-derived oxylipins mediate inflammatory resolution

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A number of lipid mediators are known to contribute to inflammatory resolution. Fatty acid metabolites of cytochrome P450 (CYP) enzymes are found in abundance; however, their roles in inflammatory resolution are not known. Targeted lipidomics revealed that CYP450-epoxy-oxylipins were present during acute inflammation and inflammatory resolution. Using mice lacking soluble epoxide hydrolase, the major metabolizing pathway for CYP450-derived fatty acid mediators, and CYP450 epoxygenase inhibition specifically during resolution, we show that CYP450-derived lipids dramatically limit the accumulation of inflammatory monocytes during resolution. Moreover, all cells of the monocyte lineage examined showed a dramatic alteration in their proresolution phenotype following epoxygenase inhibition. These findings demonstrate that the CYP450-epoxy-oxylipins pathway has a critical role in monocyte lineage recruitment and resolution activity during inflammatory resolution. (See pp. E3240–E3249.)

Growth hormone is permissive for neoplastic colon growth

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Growth hormone (GH) excess in acromegaly is associated with increased colon polyps and cancer, whereas short-stature humans harboring a GH receptor mutation do not develop cancer. Administration of a GH receptor blocker in acromegaly patients induced colon p53. In contrast, p53 is suppressed by GH in colon cells, in vivo in colon tissue, and in induced pluripotent stem cell-derived intestinal organoids. GH excess leads to cell survival with downregulated adenomatous polyposis coli, nuclear β-catenin accumulation, and increased epithelial–mesenchymal transition factors. Because locally expressed GH is abundant in conditions predisposing to colon cancer, GH appears to be a molecular component of the milieu permissive for neoplastic colon growth. These results explain the protective effects of GH deficiency against development of neoplasms. (See pp. E3250–E3259.)

Coxiella burnetii effector CvpB modulates phosphoinositide metabolism for optimal vacuole development

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The biogenesis of a replicative vacuole is an essential step of *Coxiella burnetii* infections and involves the hijack of several host membrane trafficking pathways. Here we describe *Coxiella* vacuolar protein B (CvpB) as a *Coxiella* effector that interacts with phosphoinositides on host cell membranes and manipulates phosphatidylinositol 3-phosphate [PI(3)P] metabolism for optimal *Coxiella*-containing vacuole (CCV) development. This is achieved by perturbing the activity of the phosphatidylinositol 5-kinase PIKfyve, leading to an enrichment of PI(3)P on CCV membranes, which is required for the autophagy machinery to mediate CCV homotypic fusion. The importance of this process is highlighted by a homotypic fusion defect between CCVs in cells infected with CvpB *Coxiella* mutants, which translates into an attenuated virulence in the insect model *Galleria mellonella*. (See pp. E3260–E3269.)

Severe adult malaria is associated with specific PfEMP1 adhesion types and high parasite biomass

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The clinical presentation of severe malaria differs between children and adults, but the factors leading to these differences remain poorly understood. Here, we investigated parasite virulence factors in adult patients in India and show that specific endothelial protein C receptor (EPCR)-binding parasites are associated with severe adult malaria and act together with parasite biomass in patient hospitalization and disease severity. We found substantial differences in EPCR binding activity from severe malaria isolates. However, even parasite domains that partially obstructed the interaction between EPCR and its ligand activated protein C were sufficient to interfere with activated protein C-barrier protective activities in human brain endothelial cells. Thus, restoration of EPCR functions may be a key target for adjunctive malaria drug treatments. (See pp. E3270–E3279.)

Active dendrites regulate the impact of gliotransmission on rat hippocampal pyramidal neurons

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Glial cells in the brain actively communicate with neurons through release of transmitter molecules that result in neuronal voltage deflections, thereby playing vital roles in neuronal information processing. Although a significant proportion of information processing in neurons is performed in their dendritic arborization, the impact of gliotransmission on neuronal dendrites has not been mapped. Here, we show that gliotransmission, acting through differentially localized slow receptors, results in strikingly large voltage deflections in neuronal dendrites, with the strength and spread of these deflections critically regulated by dendritic ion channels. Our results add a significantly complex dimension to neuron–glia interactions by demonstrating that neuronal dendrites and their voltage-gated channels play active roles in regulating the impact of such interactions. (See pp. E3280–E3289.)

Osmoregulatory inositol transporter SMIT1 modulates electrical activity by adjusting $PI(4,5)P_2$ levels

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Cells living in variable environments evolve ways to adapt to altered extracellular conditions. During hypertonic stress, the expression of several human osmolyte transporters increases, thereby accumulating more osmolytes and elevating intracellular osmolarity. We focused on one of these osmolytes, myo-inositol, which is also the precursor of membrane phosphoinositide lipids. We found that intracellular accumulation of myo-inositol via its transporter SMIT1 is able to increase phosphoinositide levels and thereby modulate the activities of phosphoinositide-dependent ion channels. We provide evidence for a previously unidentified connection between the extracellular osmotic changes and the electrical properties of excitable cells. Our findings may help elucidate mechanisms underlying several diseases characterized by either perturbed myo-inositol levels or increased extracellular tonicity. (See pp. E3290–E3299.)

Combinatorial effects of odorants on mouse behavior

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Odor detection in the mouse nose is mediated by ~1,000 different odorant receptors (ORs) and 14 trace amine-associated receptors (TAARs). Different OR combinations generate different odor perceptions. However, a few TAARs are associated with innate odor attraction or aversion, suggesting they signal through hard-wired neural circuits resistant to combinatorial receptor inputs. Contrary to this prediction, we find that different ligands for a given TAAR can be attractive or aversive, or instead neutral. In addition, some attractive and aversive odorants block one another's behavioral effects. Odor blocking can occur without receptor antagonism in the nose and can require sensory input from one receptor. Thus, innate odor-induced behaviors can be context-dependent and modulated by interactions in the brain among signals derived from different receptors. (See pp. E3300–E3306.)

Neuronal energy-sensing pathway promotes energy balance by modulating disease tolerance

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The *Drosophila* coactivator cAMP-regulated transcription coactivator (Crtc) functions in neurons to promote energy balance. We found that Crtc and its binding partner cAMP response element binding protein (CREB) maintain metabolic homeostasis by stimulating the expression of the neuropeptide-Y–like neuropeptide short neuropeptide F (sNPF). Loss of sNPF disrupted gut epithelial integrity and increased immune response gene expression, leading to decreases in triglyceride and glycogen stores. Conversely, overexpression of Crtc or sNPF in neurons of wild-type flies attenuated the immune response and enhanced starvation resistance. By enhancing gut barrier integrity, the CREB/CRTC pathway maintains energy homeostasis in response to stress. (See pp. E3307–E3314.)