PNAS Plus Significance Statements

Clouds at Barbados are representative of clouds across the trade wind regions in observations and climate models

Brian Medeiros and Louise Nuijens

This paper shows that clouds near Barbados exhibit similar properties to those over much of the tropical oceans. This finding allows observations taken at Barbados to be generalized to the broader tropics. The same approach is applied to climate models to show that errors in simulated clouds near Barbados are similar to errors across the tropical oceans. The errors are related to the representation of the vertical structure of clouds and the boundary layer and the underlying turbulent and convective mixing that create the clouds. Because trade wind clouds are a key contribution to the spread in climate model estimates of climate sensitivity, improvements in these clouds could reduce uncertainty in climate projections. (See pp. E3062–E3070.)

Empirical redefinition of comprehensive health and well-being in the older adults of the United States

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Health has long been conceived as not just the absence of disease but also the presence of physical, psychological, and social well-being. Nonetheless, the traditional medical model focuses on specific organ system diseases. This representative study of US older adults living in their homes amassed not only comprehensive medical information but also psychological and social data and measured sensory function and mobility, all key factors for independent living and a gratifying life. This comprehensive model revealed six unique health classes, predicting mortality/incapacity. The healthiest people were obese and robust; two new classes, with twice the mortality/incapacity, were people with healed broken bones or poor mental health. This approach provides an empirical method for broadly reconceptualizing health, which may inform health policy. (See pp. E3071–E3080.)

A binding site outside the canonical PDZ domain determines the specific interaction between Shank and SAPAP and their function

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Synaptic scaffold proteins, such as Shank and SAPAP, play critical roles in organizing protein complexes essential for neuronal development and signaling. Approximately 50% of protein concentration changes resulting from genetic mutations can cause various forms of psychiatric disorders; however, the molecular mechanism underlying such dosage-sensitive functional changes for the two scaffold proteins are not clear. Here we discover that a previously unrecognized PDZ domain-mediated binding mode renders an exquisitely specific interaction between Shank and SAPAP. Mutations of either of these proteins lead to quantitative reductions of the Shank/SAPAP complex in synapses. We also demonstrate that a Shank/SAPAP complex inhibitory peptide can modulate excitatory synaptic activities, providing a proof of concept of modulating synaptic activities by targeting the Shank PDZ domain. (See pp. E3081–E3090.)

Variants within the SP110 nuclear body protein modify risk of canine degenerative myelopathy

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Degenerative myelopathy (DM) is a canine disease very similar to amyotrophic lateral sclerosis (ALS) in humans. We previously showed that DM is a promising model for ALS, because genome-wide association identified a mutation in superoxide dismutase 1 gene (*SOD1*), a known ALS gene. This mutation found in many dog breeds increases the risk of DM, and the pathological findings and clinical progression of the two diseases are similar. In this study, we identify a modifier gene, SP110 nuclear body protein (*SP110*), which strongly affects overall disease risk and age of onset in Pembroke Welsh Corgis at risk for DM. Dissecting the complex genetics of this disease in a model organism may lead to new insights about risk and progression in both canine and human patients. (See pp. E3091–E3100.)

Natural mutations in a *Staphylococcus aureus* virulence regulator attenuate cytotoxicity but permit bacteremia and abscess formation

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Staphylococcus aureus is a major cause of life-threatening bacterial infection. A significant risk factor for infection

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is nasal carriage. Previously, we reported spontaneous mutations during carriage associated with infection, including loss-of-function of the gene *repressor of surface proteins* (*rsp*). Here we use genomic screens, experimental assays, and molecular examination of *rsp* mutants from patients to understand how *rsp* is involved in infection; we find it has far-reaching effects on gene regulation. Paradoxically, *rsp* mutants exhibited attenuated toxicity and reduced disease severity early in experimental infection, without sacrificing the ability to cause abscesses and bloodstream infection. This work reveals a complex relationship between correlates of disease in the laboratory and in patients, demonstrating that life-threatening disease can be associated with reduced severity early in infection. (See pp. E3101–E3110.)

Coronavirus receptor switch explained from the stereochemistry of protein–carbohydrate interactions and a single mutation

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A wide variety of vertebrate viruses, representative of at least 11 families, use sialic acid (Sia) for host cell attachment. In betacoronaviruses, the hemagglutinin-esterase envelope protein (HE) mediates dynamic attachment to *O*-acetylated Sias. HE function relies on the concerted action of carbohydrate-binding lectin and receptor-destroying esterase domains. Although most betacoronaviruses target 9-*O*-acetylated Sias, some switched to using 4-*O*-acetylated Sias instead. The crystal structure of a "type II" HE now reveals how this was achieved. Common principles pertaining to the stereochemistry of protein–carbohydrate interactions facilitated the ligand/substrate switch such that only modest architectural changes were required in lectin and esterase domains. Our findings provide fundamental insights into how proteins "see" sugars and how this affects protein and virus evolution. (See pp. E3111–E3119.)

Bacterial β-Kdo glycosyltransferases represent a new glycosyltransferase family (GT99)

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Glycosyltransferase enzymes synthesize complex sugar-containing macromolecules that play pivotal roles in the biology of all cells. Bacteria produce a remarkable range of these glycoconjugate structures, often containing unusual sugars. For example, Gram-negative bacteria exploit an unusual eight-carbon sugar (Kdo) as a linkage point between diverse glycan structures and conserved lipid termini in LPS and (some) capsules. Here, we describe the distribution and phylogenetic relationships of a new family of β-Kdo glycosyltransferases. Although these enzymes resemble some other glycosyltransferases, including those forming α-Kdo linkages, they are not readily identified as glycosyltransferases by bioinformatics approaches. The structure of a prototypical enzyme reveals extensive insertions, deletions, and rearrangements in the normally highly conserved GT-B–fold, highlighting the unusual structure of this glycosyltransferase family. (See pp. E3120–E3129.)

Immunization with a heat-killed preparation of the environmental bacterium *Mycobacterium vaccae* promotes stress resilience in mice

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The hygiene, or "old friends," hypothesis proposes that lack of exposure to immunoregulatory microorganisms in modern urban societies is resulting in an epidemic of inflammatory disease, as well as psychiatric disorders in which chronic, low-level inflammation is a risk factor. An important determinant of immunoregulation is the microbial community occupying the host organism, collectively referred to as the microbiota. Here we show that stress disrupts the homeostatic relationship between the microbiota and the host, resulting in exaggerated inflammation. Treatment of mice with a heat-killed preparation of an immunoregulatory environmental microorganism, *Mycobacterium vaccae*, prevents stress-induced pathology. These data support a strategy of "reintroducing" humans to their old friends to promote optimal health and wellness. (See pp. E3130–E3139.)

Selectivity and tolerance for visual texture in macaque V2

Corey M. Ziemba, Jeremy Freeman, J. Anthony Movshon, and Eero P. Simoncelli

The brain generates increasingly complex representations of the visual world to recognize objects, to form new memories, and to organize visual behavior. Relatively simple signals in the retina are transformed through a cascade of neural computations into highly complex responses in visual cortical areas deep in the temporal lobe. The representations of visual signals in areas that lie in the middle of this cascade remain poorly understood, yet they are critical to understanding how the cascade operates. Here, we demonstrate changes in the representation of visual information from area V1 to V2, and show how these changes extract and represent information about the local statistical features of visual images. (See pp. E3140–E3149.)

Tissue-specific dynamin-1 deletion at the calyx of Held decreases short-term depression through a mechanism distinct from vesicle resupply

Satyajit Mahapatra, Fan Fan, and Xuelin Lou

Endocytosis is crucial for sustained synaptic transmission. During high-frequency neurotransmission, endocytosis recycles vesicular components rapidly and may promote the clearance of used SNAREs and other membrane proteins from release sites. We report that tissue-specific dynamin-1 deletion significantly reduces synaptic depression during bursts of the high-frequency stimulation at the mature calyx of Held in mice. This effect is contrary to the expected consequence of reduced recycling and cannot be explained by the commonly known mechanisms underlying short-term depression. Rather, the data imply that endocytosis may have a rapid, retrograde effect on transmitter release (e.g., through alterations of release site clearance) during high rates of synaptic vesicle fusion. Our finding indicates a role of dynamin-1 in high-frequency synaptic transmission and short-term plasticity. (See pp. E3150–E3158.)

Striatal cholinergic interneurons generate beta and gamma oscillations in the corticostriatal circuit and produce motor deficits

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Exaggerated beta oscillations within the cortico-basal ganglia-thalamic (CBT) network are putative electrophysiological signatures of bradykinesia and rigidity in Parkinson's disease (PD). However, it is unclear how exaggerated beta oscillations emerge and how such oscillation patterns are related to PD motor deficits. In this study, we demonstrate that a single cell type, the striatal cholinergic interneuron, mediates the emergence of exaggerated beta oscillations within CBT circuits of normal mice and induces parkinsonian-like motor deficits. Because the striatal cholinergic system is uninhibited by loss of dopamine, these results provide mechanistic insights into the therapeutic effects of anticholinergic drugs in the treatment of PD and highlight the potential for developing beta oscillation-based biomakers for PD. (See pp. E3159–E3168.)

Phasic dopamine release in the medial prefrontal cortex enhances stimulus discrimination

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Much of our knowledge about the role of dopamine (DA) during learning comes from studying the ventral tegmental area (VTA)-to-striatum pathway, and considerably less is known about the function of phasic DA release in other regions, such as the medial prefrontal cortex (mPFC). By pairing auditory conditioned stimuli (CSs) with optogenetically activated VTA-to-mPFC projections, we show that mice learn faster a subsequent task that involves discrimination of the same CSs against unpaired stimuli. During and after CS-DA pairing, mPFC neurons specifically increase firing in response to the paired CSs, and blocking DA receptors in mPFC during learning impairs stimulus discrimination. Thus, phasic DA acts in mPFC to enhance discrimination of behaviorally relevant stimuli during learning. (See pp. E3169–E3176.)

Open chromatin reveals the functional maize genome

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The maize genome, similar to those of most plant genomes, is 98% noncoding. Much of the remainder is a vast desert of repeats that remain repressed throughout the cell cycle. The plant cell orchestrates its complex activities by restricting access to functional regions with an open chromatin configuration. Here, we identify the small portion (<1%) of the maize genome residing in open chromatin. We demonstrate that open chromatin predicts molecular phenotypes such as gene expression and recombination. Furthermore, we show that genetic variation within open chromatin regions accounts for ~40% of phenotypic variation in agronomic traits. By greatly narrowing the scope of the functional maize genome, this study can help to accelerate the pace of crop improvement through highly focused genomic selection and genome editing. (See pp. E3177–E3184.)