PNAS Plus Significance Statements

Chemical and cytokine features of innate immunity characterize serum and tissue profiles in inflammatory bowel disease

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Our study investigates chemical damage associated with chronic inflammation and relates these macromolecular damage products to inflammatory bowel disease activity. Using mice as a model system, we show (pp. E2332–E2341) that chronic inflammatory responses that are common to mice and humans produce similar types and quantities of damage products in both species. Additional analysis of signaling molecules in the serum and tissue of diseased samples highlights the role of the innate immune response in the overall pathology of inflammatory bowel disease.

Quantifying the topography of the intrinsic energy landscape of flexible biomolecular recognition

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Biomolecular binding, which controls the realization of biomolecular function, is ubiquitous and fundamental to many cellular processes. We quantified the intrinsic energy landscapes of flexible biomolecular recognition—i.e., the binding–folding. Our findings reveal that the energy landscape topography determines the thermodynamics, kinetics, and the association mechanism of the binding–folding dynamics. These three aspects are closely related to feasibility, efficiency, and the ways of realizing biomolecular function, respectively. Our results (pp. E2342–E2351) provide a unique way to address the long-standing debate of the "structure–dynamics–function" relationship using landscape topography and establish the connections between recognition landscape theory and experimental measurements.

Orientation-specific responses to sustained uniaxial stretching in focal adhesion growth and turnover

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Cells are mechanosensitive: a cell's adaptive responses to mechanical inputs will determine its morphology, gene expression, and post-translational protein modification. Focal adhesions (FAs), the integrin-containing complexes positioned between the extracellular matrix and the cell, are key in transmitting the mechanosignal to initiate these downstream adaptive responses. In this study (pp. E2352–E2361) we made the unique observation that FA and cellular morphology changes in response to sustained uniaxial stretch are orientation specific. Our results also suggest orientation-specific responses at the molecular level in individual FAs propagate up to regulate cell morphology, which may in turn mediate adaptive responses that promote tissue growth.

Conserved microRNA pathway regulates developmental timing of retinal neurogenesis

Anna La Torre, Sean Georgi, and Thomas A. Reh

The sequential generation of different types of neurons and glia is a fundamental property of neurogenesis, but little is known about the mechanisms controlling this phenomenon. Conditional deletion of Dicer prevents progenitors from progressing in their competence to generate late cell types, indefinitely generating early cell types. We now elucidate the molecular mechanism for this phenomenon. Three microRNAs, let-7, microRNA-125, and microRNA-9, serve as key regulators of the early to late developmental transition in retinal progenitors. These results show (pp. E2362–E2370) how progenitor temporal identity is controlled, a finding that will impact efforts to generate specific neural types from pluripotent stem cells.

Genetic circuitry of *Survival motor neuron*, the gene underlying spinal muscular atrophy

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Spinal muscular atrophy (SMA), the leading genetic cause of infant mortality, is a devastating neurodegenerative disease caused by reduced levels of Survival Motor Neuron (SMN) gene activity. Despite well-characterized aspects of the involvement of SMN in small nuclear ribonucleoprotein biogenesis, the gene circuitry affecting SMN activity remains obscure. Here (pp. E2371–E2380), we use *Drosophila* as a model system to integrate results from large-scale genetic and proteomic studies and bioinformatic analyses to define a unique SMN interactome to provide a basis for a better understanding of SMA. Such efforts not only help dissect *Smn* biology but also may point to potential clinically relevant targets.

Polyester synthesis genes associated with stress resistance are involved in an insect–bacterium symbiosis

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This study reports a previously unrecognized involvement of polyhydroxyalkanoate (PHA), known as a bacterial endocellular storage polymer, in an insect–bacterium symbiosis. Many bacteria in the

environment accumulate PHA granules within their cells, which provide resistance to nutritional depletion and other environmental stresses. Here (pp. E2381–E2389) we demonstrate that synthesis and accumulation of PHA in the symbiont cells are required for normal symbiotic association with, and, consequently, positive fitness effects for the host insect. The requirement of PHA for symbiosis suggests that, contrary to the general expectation, the within-host environment may be, at least in some aspects, stressful for the symbiotic bacteria.

Candidate phylum TM6 genome recovered from a hospital sink biofilm provides genomic insights into this uncultivated phylum

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This research highlights the discovery and genome reconstruction of a member of the globally distributed yet uncultivated candidate phylum TM6 (designated TM6SC1). In addition to the 16S rRNA gene, no other genomic information is available for this cosmopolitan phylum. This report (pp. E2390–E2399) also introduces a mini-metagenomic approach based on the use of high-throughput single-cell genomics techniques and assembly tools that address a widely recognized issue: how to effectively capture and sequence the currently uncultivated bacterial species that make up the "dark matter of life." Amplification and sequencing random pools of 100 events enabled an estimated 90% recovery of the TM6SC1 genome.

Multiple risk pathways for schizophrenia converge in serine racemase knockout mice, a mouse model of NMDA receptor hypofunction

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We sought to determine whether the diverse hippocampal neuropathology observed in schizophrenia could be recapitulated in an animal model of NMDA receptor (NMDAR) hypofunction. Serine racemase-deficient ($SR^{-/-}$) mice, which lack one of the NMDAR coagonists D-serine, display impaired hippocampal plasticity, as well as the morphological, neurochemical, and cognitive abnormalities consistent with what is observed in schizophrenia. Importantly, treatment in adulthood with D-serine reversed the electrophysiological, neurochemical, and cognitive deficits. These results (pp. E2400–E2409) demonstrate that NMDAR hypofunction can reproduce the hippocampal deficits associated with schizophrenia and point to potential interventions for the currently untreatable negative and cognitive symptoms of this disorder.

Tissue plasminogen activator regulates Purkinje neuron development and survival

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Cerebellar Purkinje neurons (PNs) strongly affect motor coordination and learning. PN study has contributed significantly to fundamental concepts of modern neuroscience. The present investigation defines distinctive molecular signaling pathways through which tissue plasminogen activator/plasmin-based proteolysis regulates postnatal PN dendrite development, synapse formation, mitochondrial morphology and function, and PN survival. These pathways involve differentially acting downstream constituents, including protein kinase Cγ, brain-derived neurotrophic factor, and a voltage-dependent anion channel. The metabolic mechanisms established here (pp. E2410–E2419) may apply to the development and degeneration of PNs and additional types of neurons in many animal and human brain diseases in which PNs are notably vulnerable.

Ca^{2+}/calmodulin-dependent protein kinase kinase β phosphorylation of Sirtuin 1 in endothelium is atheroprotective

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Different flow patterns in the arterial tree determine the severity and topographic distribution of atherosclerosis. Atheroprotective flow exerts anti-inflammatory and antioxidative effects on vascular endothelial cells, and the underlying mechanism involves the flow-induced upregulation of Sirtuin (SIRT)1. This study (pp. E2420–E2427) reveals that athero-protective flow activates Ca^{2+}/calmodulin-dependent protein kinase kinase (CaMKK)β, which, in turn, phosphorylates SIRT1 at Ser-27 and Ser-47 to increase the stability and activity of SIRT1. The mechanosensitive CaMKKβ-SIRT1 pathway alleviates inflammatory and redox status in the endothelium. Such a conclusion is evident from the drastically increased atherosclerosis in mice lacking CaMKKβ or endothelial SIRT1.

Single dose of L-dopa makes extinction memories context-independent and prevents the return of fear

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Traumatic events can engender persistent excessive fear responses to trauma reminders that may return even after successful treatment. In the psychotherapy of fear or anxiety disorders, patients make safety experiences that generate fear-inhibitory safety memories. Fear, however, frequently returns because safety memory retrieval fails. We find (pp. E2428–E2436) that safety memories can be strengthened and are more easily retrieved when adding a standard anti-Parkinson drug that augments brain levels of the neurotransmitter dopamine directly after a safety experience. In mice and humans, this treatment up-regulates an anti-fear area in the frontal cortex. Our findings open a unique avenue for improving psychotherapy.