PNAS Plus Significance Statements

Nanomagnetic properties of the meteorite cloudy zone

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The cloudy zone is naturally occurring nanocomposite found in Fe–Ni metal-bearing meteorites. It not only is a potent carrier of paleomagnetic information from the early solar system but also shows promise as a sustainable alternative to rare earth-based permanent magnets. Here we explain how the remarkable magnetic properties of the cloudy zone are linked to its 3D chemical, crystallographic, and magnetic architecture, using a state-of-the-art combination of nanometer to subnanometer resolution tomography and micromagnetic simulations. We discover the mechanism by which paleomagnetic information becomes encoded into the cloudy zone and, inspired by our findings, point toward potential pathways to optimize synthetic analogues of the cloudy zone for industrial applications. (See pp. E11436–E11445.)

Contrasting temporal difference and opportunity cost reinforcement learning in an empirical money-emergence paradigm

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In the present study, we applied reinforcement learning models that are not classically used in experimental economics to a multistep exchange task of the emergence of money derived from a classic search-theoretic paradigm for the emergence of money. This method allowed us to highlight the importance of counterfactual feedback processing of opportunity costs in the learning process of speculative use of money and the predictive power of reinforcement learning models for multistep economic tasks. Those results constitute a step toward understanding the learning processes at work in multistep economic decision-making and the cognitive microfoundations of the use of money. (See pp. E11446–E11454.)

Design and in vitro realization of carbon-conserving photorespiration

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Photorespiration limits plant carbon fixation by releasing CO_2 and using cellular resources to recycle the product of ribulose-1,5-bisphosphate carboxylase/oxygenase (Rubisco) oxygenation, 2-phosphoglycolate. We systematically designed synthetic photorespiration bypasses that combine existing and new-to-nature enzymatic activities and that do not release CO_2. Our computational model shows that these bypasses could enhance carbon fixation rate under a range of physiological conditions. To realize the designed bypasses, a glycolate reduction module, which does not exist in nature, is needed to be engineered. By reshaping the substrate and cofactor specificity of two natural enzymes, we established glycolate reduction to glycolaldehyde. With the addition of three natural enzymes, we observed recycling of glycolate to the key Calvin Cycle intermediate ribulose 1,5-bisphosphate with no carbon loss. (See pp. E11455–E11464.)

Single nucleotide polymorphisms alter kinase anchoring and the subcellular targeting of A-kinase anchoring proteins

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Dissemination of chemical information throughout the cell is a fundamental biological process with clinical relevance. Pathological changes in local signaling enzyme activity are linked to diseases, including schizophrenia, Alzheimer's disease, cardiac arrhythmias, and seizures. Mining of patient datasets has uncovered genetic variation in A-kinase anchoring proteins (AKAPs) that promotes mislocalization of protein kinase A (PKA). We investigate 42 SNPs in AKAPs that interrupt association with PKA to impact local cAMP signaling. The most detrimental variants are situated within the hydrophobic face of a conserved helical region on the AKAP that is essential for kinase anchoring. An unexpected outcome is the discovery of an alternative targeting mechanism for AKAPs that utilizes the intact PKA holoenzymes as cytoplasmic "anchors." (See pp. E11465–E11474.)

Molecular dynamics simulations of nucleotide release from the circadian clock protein KaiC reveal atomic-resolution functional insights

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Circadian rhythms enable organisms to adapt to the 24-h day/night cycle. The importance of these rhythms is evident from their prevalence across the kingdoms of life and their dysregulation in many

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diseases. The core clock of the cyanobacterium *Synechococcus elongatus* serves as a paradigm for molecular studies of circadian rhythms because its oscillations can be reconstituted in vitro. There is evidence that the action of KaiC, the central component of the oscillator, depends critically on whether its active sites bind ADP or ATP, metabolites that function as the energy currency in cells. Here, we use molecular dynamics simulations to develop an atomic-resolution picture of ADP release and, in turn, hypotheses for the regulation of ADP/ATP exchange. (See pp. E11475–E11484.)

Ubiquilin 2 modulates ALS/FTD-linked FUS–RNA complex dynamics and stress granule formation

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Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are two devastating neurodegenerative diseases for which there are few treatments. ALS/FTD has been genetically and pathologically linked to both protein quality control (PQC) factors and RNA homeostasis, but the molecular players that bridge these pathways are not well characterized. Here, we identify a role for the ALS/FTD-linked PQC protein ubiquilin 2 (UBQLN2) in maintaining the solubility of RNA binding protein FUS in response to stress. UBQLN2 increases the dynamics of FUS–RNA complex formation, resulting in the negative regulation of stress granule (SG) formation. Because SGs potentially seed toxic inclusions of patients with ALS/FTD, these findings have implications for understanding ALS/FTD pathogenesis and designing new treatments for these diseases. (See pp. E11485–E11494.)

Species interactions limit the occurrence of urban-adapted birds in cities

Paul R. Martin and Frances Bonier

Urban environments are expanding worldwide, impacting the populations of many organisms. Understanding how and why species are affected by urbanization is thus an important goal. We examined the role of direct competitive interactions among species on the response of bird species to urbanization. We found evidence that urban-adapted, subordinate species were less widespread in cities than closely related dominant species, but only when dominant and subordinate species live together, which suggests that direct competitive interactions reduce the ability of subordinate species to persist in cities. This result depended on the level of economic development of the country, suggesting that economic development may heighten the effects of competition on subordinate species, thereby reducing species diversity in cities. (See pp. E11495–E11504.)

Loss of protein synthesis quality control in host-restricted organisms

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This case study reveals that parasitic and symbiotic lifestyles affect the structure of essential molecular machineries of a living cell. We provide evidence that intracellular parasitism and endosymbiosis cause degeneration of the editing domains in aminoacyl-tRNA synthetases, a defect that is known to cause inaccurate translation of the genetic code. This finding suggests that most intracellular pathogens, including causative agents of human disease, have an unanticipated proteome diversity caused by inaccurate translation of the genetic code. Our finding may change current approaches to the study of proteomes of intracellular parasites, parasite–host interactions, and parasites' sensitivity to drugs, which cause errors in transcription, translation, and protein folding. (See pp. E11505–E11512.)

The $CD4^{-}CD8^{-}$ MAIT cell subpopulation is a functionally distinct subset developmentally related to the main $CD8^{+}$ MAIT cell pool

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Mucosa-associated invariant T (MAIT) cells are unconventional innate-like T cells recognizing microbial riboflavin metabolites presented by the monomorphic MR1 molecule. Here, we show that the $CD8^{+}CD4^{-}$ and $CD8^{-}CD4^{-}$ subpopulations of human MAIT cells represent transcriptionally and phenotypically discrete subsets with distinct functional profiles. Furthermore, T cell receptor repertoire analysis, as well as MAIT cell data based on human fetal tissues, umbilical cord blood, and culture systems indicate that the $CD8^{-}CD4^{-}$ subset may derive from the main $CD8^{+}CD4^{-}$ MAIT cell pool. Thus, MAIT cells, a major antimicrobial effector T cell population in humans, segregate into two functionally distinct but developmentally related subsets separated by the expression of CD8. This functional difference may have significant implications in infectious and inflammatory diseases. (See pp. E11513–E11522.)

Excessive endosomal TLR signaling causes inflammatory disease in mice with defective SMCR8-WDR41-C9ORF72 complex function

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Activation of Toll-like receptors by microbes or host-derived molecules triggers signaling that promotes inflammation and may contribute to the development of autoimmunity. Here we show that excessive signaling by the innate immune Toll-like receptors (TLRs) TLR3, TLR7, and TLR9 is causative for inflammatory disease in mice with mutations of *Smcr8*. The cellular mechanism for their hyperactivation is likely prolonged ligand–receptor contact in lysosomes and phagosomes, the trafficking of which is regulated by the SMCR8-WDR41-C9ORF72 complex in immune cells. We also show that *Smcr8* and *Wdr41* mutations sensitize mice to chemically induced colitis. Our findings reveal an important negative regulatory mechanism that limits endosomal TLR signaling and shed light on the mechanism by which deficiencies of C9ORF72 or SMCR8 cause inflammation. (See pp. E11523–E11531.)

Genetic deletion of vesicular glutamate transporter in dopamine neurons increases vulnerability to MPTP-induced neurotoxicity in mice

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Parkinson's disease (PD) is a chronic dopamine (DA) neuron degenerative disorder. Little is known about factors that impact

vulnerability of DA neurons to pathological insults. In this study, we found that vesicular glutamate transporter 2 (VgluT2) expression may play an important role in protecting DA neurons. Selective deletion of VgluT2 in DA neurons led to a significant reduction in expression of brain-derived neurotrophic factor and its receptor tyrosine receptor kinase B and a significant increase in DA neuron death caused by the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Restoration of VgluT2 expression in DA neurons reversed these alterations. These findings suggest that reduced VgluT2 expression in DA neurons may constitute a risk factor in the development of PD and suggest potential therapeutic strategies for boosting resilience of DA neurons. (See pp. E11532–E11541.)

Interlinked regulatory loops of ABA catabolism and biosynthesis coordinate fruit growth and ripening in woodland strawberry

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Using strawberry fruit as a model system, we uncover the mechanistic interactions between auxin, gibberellic acid (GA), and abscisic acid (ABA) that regulate the entire process of fruit development. Interlinked regulatory loops control ABA levels during fruit development. During the early stages, auxin/GA turns on a feedback loop to activate the removal of ABA via *FveCYP707A4a*-dependent catabolism needed for fruit growth. Down-regulation of auxin/GA results in the suppression of the feedback loop and the activation of the ABA biosynthesis-dependent feedforward loop, leading to a steep ABA accumulation for fruit ripening. The interlinked regulatory loops provide a conceptual framework that underlies the connection between the regulation of fruit growth and that of ripening as well as a molecular basis for manipulation of fruit sizes and ripening times. (See pp. E11542–E11550.)

Resistance protein Pit interacts with the GEF OsSPK1 to activate OsRac1 and trigger rice immunity

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The plant genome encodes *resistance* (*R*) genes that are one of the major genomic resources to enhance disease resistance in various crops. *R* gene products, R proteins, serve as intracellular receptors for pathogen effectors, leading to activation of effector-triggered immunity. Due to the importance of R proteins, elucidation of their signaling pathways is an important research goal. We revealed that OsSPK1, a GDP/GTP exchange factor for the small GTPase OsRac1, is a direct binding protein of the rice R protein Pit, which is a resistance protein to rice blast fungus. OsSPK1 is a key signaling molecule in Pit signaling. Our results provide a critical new insight into molecular mechanisms underlying R protein activation and new knowledge for crop improvement. (See pp. E11551–E11560.)