PNAS Plus Significance Statements

Metal-mediated diradical tuning for DNA replication arrest via template strand scission

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Pharmaceuticals often act within a lock-and-key model whereby molecules bind their targets nearly irreversibly, either stalling or initiating biological processes. Here, the agent itself performs no chemical transformation on its target but rather triggers an event or cascade. However, unwanted side effects become more likely as the reactivity of these molecules increases. In contrast, molecular compounds may irreversibly damage biological targets using metal-mediated radical chemistry, but controlling the onset and extent of reaction is challenging. Even so, multiple examples of metal-containing or metal-radical paradigms have been used clinically for imaging and chemotherapy. Within this framework we report a class of metal-mediated radical generators that attack DNA, outcompete DNA polymerase, and are cytotoxic in short times and modest concentrations. (See pp. E7405–E7414.)

On transient climate change at the Cretaceous–Paleogene boundary due to atmospheric soot injections

Charles G. Bardeen, Rolando R. Garcia, Owen B. Toon, and Andrew J. Conley

A mass extinction occurred at the Cretaceous–Paleogene boundary coincident with the impact of a 10-km asteroid in the Yucatán peninsula. A worldwide layer of soot found at the boundary is consistent with global fires. Using a modern climate model, we explore the effects of this soot and find that it causes near-total darkness that shuts down photosynthesis, produces severe cooling at the surface and in the oceans, and leads to moistening and warming of the stratosphere that drives extreme ozone destruction. These conditions last for several years, would have caused a collapse of the global food chain, and would have contributed to the extinction of species that survived the immediate effects of the asteroid impact. (See pp. E7415–E7424.)

Social network fragmentation and community health

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Fragmentation of social networks is needed in large-scale treatment campaigns. Direct vaccination of key individuals or the strategic provision of health education can prevent, respectively, the spread of viruses or misinformation. We present an easily implementable and generalizable network-based strategy for targeting households to induce fragmentation in social networks of low-income countries. Complete friendship and health advice networks were collected from 17 rural villages in Uganda. We discovered that acquaintance algorithms outperformed conventional field-based approaches for inducing social network fragmentation. Acquaintance algorithms targeted the neighbors of randomly selected nodes, whereas the latter method concerns targeting well-established community roles such as lay health workers, village government leaders, and schoolteachers. This algorithm also was effective in offsetting potential noncompliance to deworming treatments. (See pp. E7425–E7431.)

Prospect theory and the decision to move or stay

William A. V. Clark and William Lisowski

We use prospect theory and the endowment effect to provide a theoretical basis for an integrated approach to residential moving and residential staying. We link measures of risk aversion and the endowment effect to explain the tradeoff between moving and staying. We test Kahneman and Tervsky's observation that endowment effects are especially likely in goods that are not regularly traded, e.g., houses. Their use value creates the endowment effect, which works in favor of the locational status quo, increasing the probability of staying. We analyze survey data to confirm that a general self-assessed risk aversion is important in decisions to migrate or stay, and the endowment effect, measured as tenure and duration, is a substantial factor in residential decision-making. (See pp. E7432–E7440.)

Targeted PET imaging strategy to differentiate malignant from inflamed lymph nodes in diffuse large B-cell lymphoma

Jun Tang, Darin Salloum, Brandon Carney, Christian Brand, Susanne Kossatz, Ahmad Sadique, Jason S. Lewis, Wolfgang A. Weber, Hans-Guido Wendel, and Thomas Reiner

Diffuse large B-cell lymphoma (DLBCL) is the most common adult lymphoma, accounting for 37% of all non-Hodgkin lymphoma cases in the United States. Despite an approximate 50% cure rate, refractory or relapsed cases have a poor prognosis and require timely medical interventions. Therefore, accurate diagnostic methods play a pivotal role in managing DLBCL.

^{18}F- fluorodeoxyglucose positron emission tomography ([^{18}F]FDG-PET) imaging, the current standard imaging modality for diagnosing DLBCL, often fails to differentiate inflamed from malignant lymph nodes in patients with DLBCL. To address this urgent medical need, we have developed a targeted PET imaging method that accurately distinguishes malignancy from inflammation in the lymph nodes. Our targeted PET imaging approach could play an essential role in the clinical development of therapies that induce significant inflammation in DLBCL. (See pp. E7441–E7449.)

MLKL forms disulfide bond-dependent amyloid-like polymers to induce necroptosis

Shuzhen Liu, Hua Liu, Andrea Johnston, Sarah Hanna-Addams, Eduardo Reynoso, Yougui Xiang, and Zhigao Wang

Necroptosis is a programmed form of necrotic cell death which is implicated in a wide range of human pathological conditions. It is controlled by receptor-interacting protein kinase 3 (RIPK3) and its substrate mixed-lineage kinase domain-like protein (MLKL). Phosphorylated MLKL forms tetramers and translocates to membrane fractions to induce cell death. Here we report that MLKL tetramers further polymerize to form disulfide bond-dependent amyloid-like fibers, which are required for necroptosis. Furthermore, induced polymerization of the MLKL N-terminal domain is sufficient to activate necroptosis without RIPK3. This work reveals a mechanism for MLKL activation and generates exciting directions for necroptosis regulation. (See pp. E7450–E7459.)

Foldamer hypothesis for the growth and sequence differentiation of prebiotic polymers

Elizaveta Guseva, Ronald N. Zuckermann, and Ken A. Dill

Today's lifeforms are based on informational polymers, namely proteins and nucleic acids. It is thought that simple chemical processes on the early earth could have polymerized monomer units into short random sequences. It is not clear, however, what physical process could have led to the next level—to longer chains having particular sequences that could increase their own concentrations. We study polymers of hydrophobic and polar monomers, such as today's proteins. We find that even some random sequence short chains can collapse into compact structures in water, with hydrophobic surfaces that can act as primitive catalysts, and that these could elongate other chains. This mechanism explains how random chemical polymerizations could have given rise to longer sequence-dependent protein-like catalytic polymers. (See pp. E7460–E7468.)

Reversal of hyperactive Wnt signaling-dependent adipocyte defects by peptide boronic acids

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Deregulated Wnt signaling is often observed in diverse human diseases, including cancers, and is a potential therapeutic target. Here we report that hyperactivated Wnt/Wg signaling disrupts fat metabolism in *Drosophila* larvae, and that peptide boronic acids, a unique class of proteasome inhibitors, can potently rescue the fat defects by inhibiting Wg signaling through stabilization of α-catenin. We show that Axn^{127} mutant is an attractive system for screening for and optimizing small molecules that target Wnt signaling and proteasome in vivo. This work suggests that pharmacologic strategies for stabilizing α-catenin may represent an attractive approach to attenuate Wnt signaling, rather than directly targeting components of the Wnt signaling pathway. (See pp. E7469–E7478.)

Involvement of posttranscriptional regulation of *Clock* in the emergence of circadian clock oscillation during mouse development

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Circadian clocks reside in each cell level throughout the body in mammals. Intrinsic cellular circadian clocks develop cell autonomously during the cellular differentiation process. However, mechanisms controlling the emergence of cellular circadian clock oscillation in vivo are not fully understood. Here, we show that Dicer/Dgcr8-mediated posttranscriptional mechanisms control the CLOCK protein expression in both mouse fetal hearts and in vitro differentiating ES cells, which contributes to the emergence of circadian clock in mammalian cells. This event occurs after cell lineage determination into hearts or loss of pluripotent stem cell markers in differentiating ES cells, suggesting the cellular differentiation-coupled clock development may be conducted by a two-step program consisting of cellular differentiation and subsequent establishment of circadian transcriptional/translational feedback loops. (See pp. E7479–E7488.)

Host-derived viral transporter protein for nitrogen uptake in infected marine phytoplankton

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Viruses often carry genes acquired from their host. In the present work, we show that a virus of a marine alga carries a gene encoding a transporter protein that mediates nutrient uptake. We confirm that the viral transporter protein is expressed during infection and show that the protein functions to take up sources of nitrogen. This is important because acquisition of nutrients often determines the ecological success of phytoplankton populations. This work demonstrates how a virus can amend host–viral dynamics by modulating acquisition of nutrients from the environment. (See pp. E7489–E7498.)

Coevolutionary arms race versus host defense chase in a tropical herbivore–plant system

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Although plants and their herbivores account for most of macroscopic, terrestrial biodiversity, we do not fully understand the evolutionary origins of this high diversity. Coevolutionary theory proposes that adaptations between plants and their herbivores are reciprocal and that their interactions might have driven diversification and community composition. Contrary to this scenario of defense and counterdefense, we find an apparent asymmetry in the interactions between plants and herbivores. Specifically, despite the evolutionary constraints of long lifetimes for trees, plant–antiherbivore defenses may be more evolutionarily labile than herbivore adaptations to their hosts, allowing long-lived plant species to persist in the arms race with their insect herbivores. In contrast, herbivores may be evolutionarily "chasing" plants, feeding on species for which they have preadaptations. (See pp. E7499–E7505.)

Indoles from commensal bacteria extend healthspan

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Increases in human life expectancy over the next century will be accompanied by increased frailty and massive and unsustainable health care costs. Developing means to extend the time that individuals remain healthy and free of age-related infirmities, called healthspan, has therefore become a critical goal of aging research. We show that small molecules produced by the microbiota and related to indole extend healthspan in geriatric worms, flies, and mice, without attendant effects on lifespan. Indoles act via the aryl hydrocarbon receptor and cause animals to retain a youthful gene expression profile. Indoles may represent a new class of therapeutics that improve the way we age as opposed to simply extending how long we live. (See pp. E7506–E7515.)

Vertebrate-like CRYPTOCHROME 2 from monarch regulates circadian transcription via independent repression of CLOCK and BMAL1 activity

Ying Zhang, Matthew J. Markert, Shayna C. Groves, Paul E. Hardin, and Christine Merlin

Daily rhythms in animal behavior, physiology, and metabolism are driven by cell-autonomous mechanisms that keep time and control overt rhythms via transcriptional feedback loops, making it fundamental to define the mechanisms driving rhythmic transcription. In mammals, PERIOD and CRYPTOCHROME (CRY) rhythmically repress CLOCK:BMAL1 transcriptional activity, but the mechanisms by which CRY represses CLOCK:BMAL1 activity are not fully understood. Using CRISPR/Cas9 for in vivo genetic manipulations in the monarch, we show that repression of circadian transcription by vertebrate-like CRY is mediated primarily by a BMAL1 transactivation domain (TAD)-independent mechanism involving the CLK-PAS B domain, while repression on the BMAL1 TAD is dispensable for the generation of rhythms but alters circadian phase during the first day of constant darkness by affecting activation levels. (See pp. E7516–E7525.)

DNA methylation of intragenic CpG islands depends on their transcriptional activity during differentiation and disease

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The human genome contains ∼30,000 CpG islands (CGIs), long stretches (0.5–2 kb) of DNA with unusually elevated levels of CpG dinucleotides. Many occur at genes' promoters, and their DNA nearly always remains unmethylated. Conversely, intragenic CGIs are often, but not always, methylated, and thus inactive as internal promoters. The mechanisms underlying these contrasting patterns of CGI methylation are poorly understood. We show that methylation of intragenic CGIs is associated with transcription running across the island. Whether or not a particular intragenic CGI becomes methylated during development depends on its transcriptional activity relative to that of the gene within which it lies. Our findings explain how intragenic CGIs are epigenetically programmed in normal development and in human diseases, including malignancy. (See pp. E7526–E7535.)

Foxp3-independent mechanism by which TGF-β controls peripheral T cell tolerance

Soyoung A. Oh, Ming Liu, Briana G. Nixon, Davina Kang, Ahmed Toure, Michael Bivona, and Ming O. Li

A functional immune system requires a highly diverse repertoire of T cells to optimize protection against foreign pathogens while maintaining tolerance against self-antigens. Two critical pathways in the control of T cell tolerance are the cytokine TGF-β and Foxp3-expressing Treg cells. However, since TGF-β promotes Treg cell development, and Treg cells also produce the cytokine, whether TGF-β and Treg cells are part of the same regulatory module to repress self-reactive T cells or function as distinct pathways remains incompletely understood. Using a mouse model of autoimmune diabetes, this study elucidates a dominant role for a Foxp3-independent mechanism of TGF-β signaling in the regulation of T cell tolerance. (See pp. E7536–E7544.)

Cytochrome P450 monooxygenase lipid metabolites are significant second messengers in the resolution of choroidal neovascularization

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Abnormal blood vessel growth occurs in many common diseases, from cancers and cardiovascular diseases to ocular conditions like age-related macular degeneration (AMD) and is thus a major target of many recent treatment approaches. Long-chain polyunsaturated fatty acids are of significant interest in this context, since bioactive lipid metabolites derived from this pathway have been shown to be potent regulators of inflammation and angiogenesis. Our study has identified key compounds of the cytochrome P450 metabolic pathway that are responsible for resolving abnormal vascular growth in AMD, which work in part by modulating the recruitment of inflammatory immune cells. We believe these findings have significant therapeutic implications not only for AMD but also for other inflammatory disorders. (See pp. E7545–E7553.)

Molecularly targeted drug combinations demonstrate selective effectiveness for myeloid- and lymphoid-derived hematologic malignancies

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Mononuclear cells obtained from freshly isolated patient samples with various hematologic malignancies were evaluated for sensitivities to combinations of drugs that target specific cell-signaling pathways. The diagnostic, genetic/cytogenetic, and cellular features of the patient samples were correlated with effective drug combinations. For myeloid-derived tumors, such as acute myeloid leukemia, several combinations of targeted agents that include a kinase inhibitor and venetoclax, a selective inhibitor of BCL2, are effective. (See pp. E7554–E7563.)

Structures of phlebovirus glycoprotein Gn and identification of a neutralizing antibody epitope

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Bunyaviruses are emerging zoonotic pathogens of public-health concern. Lack of structures for proteins on the viral membrane ("envelope") surface limits understanding of entry. We describe atomic-level structures for the globular "head" of the envelope protein, glycoprotein N (Gn), from two members, severe fever with thrombocytopenia syndrome virus (SFTSV) and Rift Valley fever virus (RVFV), of *Phleboviruses* genus in the bunyavirus family, and a structure of the SFTSV Gn bound with a neutralizing antibody Fab. The results show the folded Gn structure and define virus-specific neutralizing-antibody binding sites. Biochemical assays suggest that dimerization, mediated by conserved cysteines in the region ("stem") connecting the Gn head with the transmembrane domain, is a general feature of bunyavirus envelope proteins and that the dimer is probably the olimeric form on the viral surface. (See pp. E7564–E7573.)

Coupling between D-3-phosphoglycerate dehydrogenase and D-2-hydroxyglutarate dehydrogenase drives bacterial L-serine synthesis

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D-3-Phosphoglycerate dehydrogenase (SerA) is a key enzyme in L-serine biosynthesis. It couples the dehydrogenation of D-3-phosphoglycerate to 3-phosphohydroxypyruvate and the reduction of 2-ketoglutarate to D-2-hydroxyglutarate (D-2-HG). This provides an example of how nonenergetically favorable and energetically favorable reactions are linked together to allow metabolic processes to proceed. D-2-HG is often considered as an abnormal metabolite produced by several enzymes with "promiscuous" activities. Our findings offer insights into how an enzymatic reaction that was considered promiscuous or accidental plays a key role in metabolism. We have identified a bacterial D-2-hydroxyglutarate dehydrogenase (D2HGDH), which converts D-2-HG produced during L-serine biosynthesis back to 2-ketoglutarate. D-2-HG is a normal metabolite that is simultaneously produced and catabolized without accumulation in bacterial metabolism. (See pp. E7574–E7582.)

Paradoxical enhancement of chemoreceptor detection sensitivity by a sensory adaptation enzyme

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Escherichia coli cells track chemical gradients with high sensitivity over a wide dynamic range, using a feedback-controlled sensory adaptation system. CheR, a receptor methyltransferase, is a key component of the adaptation system. We discovered that CheR can enhance the response sensitivity of chemoreceptor molecules, a role that opposes the known signaling consequences of its catalytic activity. This enhancement effect requires CheR-receptor binding interactions, but is quantitatively inconsistent with a simple equilibrium binding mechanism. Rather, CheR binding appears to promote a long-lasting conformational or covalent change that enhances the affinity of chemoreceptor molecules for their attractant ligands. The CheR response enhancement effect opens a new window on the functional architecture of chemoreceptor molecules and their interactions with sensory adaptation enzymes. (See pp. E7583–E7591.)

Genomic diversification of giant enteric symbionts reflects host dietary lifestyles

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Gastrointestinal symbionts of organisms are important in the breakdown of food for the host, particularly for herbivores requiring exogenous enzymes to digest complex polysaccharides in their diet. However, their role in the digestion of algae in marine piscine herbivores remains unresolved. Here, we show that the diversity of food sources available to herbivorous surgeonfishes is directly linked with the genetic makeup of their enteric microbiota. Importantly, the genomic blueprint of dominant enteric symbionts belonging to diverse *Epulopiscium* clades differs according to the host diet. Thus, the acquisition of a unique enteric microbiota specialized to their diets likely shapes the nutritional ecology of piscine herbivores, in turn facilitating the coexistence of a high diversity of marine species within coral reefs. (See pp. E7592–E7601.)

Evidence for cue-independent spatial representation in the human auditory cortex during active listening

Nathan C. Higgins, Susan A. McLaughlin, Teemu Rinne, and G. Christopher Stecker

Individuals determine horizontal sound location based on precise calculations of sound level and sound timing differences at the two ears. Although these cues are processed independently at lower levels of the auditory system, their cortical processing remains poorly understood. This study seeks to address two key questions. (*i*) Are these cues integrated to form a cue-independent representation of space? (*ii*) How does active listening to sound location alter cortical response to these cues? We use functional brain imaging to address these questions, demonstrating that cue responses overlap in the cortex, that voxel patterns from one cue can predict the other cue and vice versa, and that active spatial listening enhances cortical responses independently of specific features of the sound. (See pp. E7602–E7611.)

Cell-type–specific inhibition of the dendritic plateau potential in striatal spiny projection neurons

Kai Du, Yu-Wei Wu, Robert Lindroos, Yu Liu, Balázs Rózsa, Gergely Katona, Jun B. Ding, and Jeanette Hellgren Kotaleski

Dendritic plateau potentials generated by the activation of clustered excitatory inputs play a crucial role in neuronal computation and are involved in sensory perception, learning, and memory. Current studies largely focus on the genesis of plateau potentials. However, little is known about how somatic and local dendritic inhibitions control dendritic plateau potentials. The conventional view of the effectiveness of local dendritic inhibition relies on shunting inhibition. Moreover, massive excitatory conductance could overweigh the shunting inhibition. Here we describe a form of cell-type–specific dendritic inhibition in the striatal spiny projection neurons, in which the inhibition provides precise control over the amplitude, kinetics, and duration of plateau potentials, and thus the spiking output of spiny projection neurons. (See pp. E7612–E7621.)

CD146 coordinates brain endothelial cell–pericyte communication for blood–brain barrier development

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Development of the blood–brain barrier (BBB) requires spatiotemporal coordination of cerebrovascular endothelial cells (ECs) and pericytes. Until now, the molecular mechanism(s) coordinating the pericyte–EC behaviors during this process have been incompletely understood. In this study, combining the analysis of EC-/pericyte-specific *Cd146*-KO mice and in vitro BBB models, we report CD146 as a dynamic coordinator regulating the communication between ECs and pericytes within the neurovascular unit during BBB development. Our study demonstrates that a single cell-adhesion receptor, CD146, acts as an essential regulator to coordinate pericyte–EC communication and BBB formation during embryogenesis. Furthermore, it identifies CD146 as a potential key therapeutic target for neurological diseases related to cerebrovascular disorders. (See pp. E7622–E7631.)

Predicting gene regulatory networks by combining spatial and temporal gene expression data in *Arabidopsis* root stem cells

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We developed a computational pipeline that uses gene expression datasets for inferring relationships among genes and predicting their importance. We showed that the capacity of our pipeline to integrate spatial and temporal transcriptional datasets improves the performance of inference algorithms. The combination of this pipeline with *Arabidopsis* stem cell-specific data resulted in networks that capture the regulations of stem cell-enriched genes in the stem cells and throughout root development. Our combined approach of molecular biology, computational biology, and mathematical biology, led to successful findings of factors that could play important roles in stem cell regulation and, in particular, quiescent center function. (See pp. E7632–E7640.)

Auxin minimum triggers the developmental switch from cell division to cell differentiation in the *Arabidopsis* root

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The maintenance of boundaries between neighboring groups of distinct cell types is vital during development of multicellular organisms, as groups of cells with distinct functions must be kept physically separated to guarantee correct control of organ and body growth and function. In the *Arabidopsis* root, the transition zone is a developmental boundary in the meristem that separates dividing from differentiating cells. Here, we infer that a well-defined and tightly controlled minimum of the hormone auxin acts as a signal to establish the position of the transition zone by controlling the developmental switch from cell division to cell differentiation. We provide the mechanistic and genetic basis of how another hormone, cytokinin, controls and positions this auxin minimum, thus regulating root size. (See pp. E7641–E7649.)