

PNAS Plus Significance Statements

Meteorite-catalyzed syntheses of nucleosides and of other prebiotic compounds from formamide under proton irradiation

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Modern research on the origin of life started with Urey–Miller’s 1953 report on the spontaneous formation of amino acids upon application of electric discharge on a model of the pristine Earth atmosphere. Formamide provides a chemically sound starting material for the syntheses of prebiotic compounds; its role in prebiotics is becoming recognized. Kiloparsecs-wide clouds of formamide were observed in the interstellar space. The energy sources for the syntheses explored so far were largely thermal, and the catalysts used were mostly terrestrial. In the presence of meteorites and with high-energy protons, we observe the production of unprecedented panels of nucleobases, sugars, and, most notably, nucleosides. Carboxylic acids and amino acids complete the recipe. These findings (pp. E2746–E2755) extend prebiotic plausible scenarios well beyond our planet.

Imaging metabolite dynamics in living cells using a Spinach-based riboswitch

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Developing sensors to image cellular metabolites and signaling molecules in living cells is challenging. Here (pp. E2756–E2765) we describe Spinach riboswitches, a novel class of genetically encoded metabolite sensor based on riboswitches, a group of naturally occurring ligand-binding RNAs. Spinach riboswitches use Spinach, an RNA aptamer that binds and activates the fluorescence of an otherwise nonfluorescent small-molecule fluorophore. Drawing upon structural insights into the mechanism of structural switching in riboswitches, we show that Spinach can be swapped into various riboswitches, allowing metabolite binding to induce Spinach fluorescence directly. Expression of Spinach riboswitches in cells allows metabolite levels to be imaged in real time in live bacterial cells. Spinach riboswitches thus provide a novel approach to image cellular metabolites in living cells.

Implausibility of the vibrational theory of olfaction

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The vibrational theory of olfaction posits detection of odorants through their vibrational frequencies rather than solely through “hand-in-glove” substrate/enzyme-like odorant–odorant receptor (OR) interactions. To test the theory, we compare responses of different human

and mouse ORs toward deuterated and undeuterated isotopomers (isotopic atom isomers) of receptor-responsive odorants because isotopomers should differ in their molecular vibrational frequencies. However, no differences in receptor response are seen with any tested labeled/unlabeled odorant/receptor pairs. Because published behavioral studies have shown that humans can distinguish isotopomers, perireceptor events or impurities, rather than receptor-level vibrational effects, are suggested. Because theoretical aspects of the vibration theory are also found wanting, the vibration theory is deemed implausible in the absence of compelling receptor-level experimental evidence to the contrary (pp. E2766–E2774).

A hypothesis to reconcile the physical and chemical unfolding of proteins

Guilherme A. P. de Oliveira and Jerson L. Silva

A comprehensive view of protein folding is crucial for understanding how misfolding can cause neurodegenerative diseases and cancer. When using physical or chemical perturbations, NMR spectroscopy is a powerful tool to reveal a shift in the native conformation toward local intermediates that act as seeds for misfolding. Using NMR, we show (pp. E2775–E2784) that the ensemble of dry and wet molten-globule intermediates populated by high pressure is different from that found when urea is used. The dissimilar actions of urea and pressure can be summarized by their “pull” and “push” effects, respectively. By combining NMR and small-angle X-ray scattering (SAXS), we demonstrate the action of urea at the initial stages of unfolding and the dominance of a direct interaction mechanism for urea-induced protein denaturation.

Let-7 family of microRNA is required for maturation and adult-like metabolism in stem cell-derived cardiomyocytes

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The adult human heart is incapable of significant regeneration after injury. Human embryonic stem cells (hESCs) have the capacity to generate an unlimited number of cardiomyocytes (CMs). However, hESC-derived CMs (hESC-CMs) are at a fetal state with respect to their functional and physiological characteristics, diminishing their utility for modeling adult-related heart disease and therapeutic screening. Thus, the potential for hESC-CMs may improve immensely in cardiac-related therapeutic applications if factors that drive their maturation are uncovered. In this study (pp. E2785–E2794), we show that members of let-7 miRNA family control CM metabolism, cell size, and force contractility, making them one of the best factors identified to date in promoting maturity of stem cell derivatives.

Climatic dipoles drive two principal modes of North American boreal bird irruption

Courtenay Strong, Benjamin Zuckerberg, Julio L. Betancourt, and Walter D. Koenig

This study (pp. E2795–E2802) is the first, to our knowledge, to reveal how climate variability drives irruptions of North American boreal seed-eating birds. Patterns of Pine Siskin irruption and associated climate drivers manifest as two modes (North-South and West-East) in which dipoles of temperature and precipitation anomalies push and pull irruptive movements across the continent at biennial to decadal periodicities. Our study accentuates the value of sustained and synoptic biological observations, contributed by citizen scientists in this case, that match the spatial and temporal scales at which climatic phenomena are observed and understood. Such observations can help probe new questions, such as the role of climatic dipoles in other large-scale ecological processes.

Inositol phosphate pathway controls transcription of telomeric expression sites in trypanosomes

Igor Cestari and Ken Stuart

African trypanosomes cause human and animal diseases and evade the host immune systems by periodically switching which variant surface glycoprotein (VSG) they express. The mechanisms that result in expression of one of the numerous VSG genes at a time and the switching of expression between different VSG genes are poorly understood. We show (pp. E2803–E2812) that specific steps in the inositol phosphate (IP) pathway control both monoallelic VSG gene transcription and the switching of VSG gene expression. The data indicate that the cellular amounts, locations, and molecular interactions of specific IP pathway enzymes and their metabolites control both processes. The results offer new drug targets and insights into the epigenetic control of gene expression by this biologically ubiquitous pathway.

Deep-sea hydrothermal vent bacteria related to human pathogenic *Vibrio* species

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During *Alvin* and *Nautile* dives in 1999, samples were collected from water surrounding sulfide chimneys of a hydrothermal vent along the East Pacific Rise and four mesophilic bacteria were isolated, including a novel *Vibrio* species, *Vibrio antiquarius*. Genomic, functional, and phylogenetic analyses indicate an intriguing blend of genomic features related to adaptation and animal symbiotic association, and also revealed the presence of virulence genes commonly found in *Vibrio* species pathogenic for humans. The presence of these virulence genes in an ecologically distinct *Vibrio* species was surprising. It is concluded that pathogenicity genes serve a far more fundamental ecological role than solely causation of human disease (pp. E2813–E2819).

Superficial white matter fiber systems impede detection of long-range cortical connections in diffusion MR tractography

Colin Reveley, Anil K. Seth, Carlo Pierpaoli, Afonso C. Silva, David Yu, Richard C. Saunders, David A. Leopold, and Frank Q. Ye

It is widely recognized that studying the detailed anatomy of the human brain is of great importance for neuroscience and medicine. The principal means for achieving this goal is presently diffusion magnetic resonance imaging (dMRI) tractography, which uses the local diffusion of water throughout the brain to estimate the course of long-range anatomical projections. Such projections connect gray matter regions through axons that travel in the deep white matter. The present study (pp. E2820–E2828) combines dMRI tractography with histological analysis to investigate where in the brain this method succeeds and fails. We conclude that certain superficial white matter systems pose challenges for measuring cortical connections that must be overcome for accurate determination of detailed neuroanatomy in humans.

Pheromones mediating copulation and attraction in *Drosophila*

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Mating interactions in *Drosophila melanogaster* depend on a number of sensory cues targeting different modalities like hearing, taste, and olfaction. From an olfactory perspective, only negative fly-derived signals had been identified, whereas a positive signal mediating mating was missing. Here (pp. E2829–E2835) we demonstrate the presence of such a signal (methyl laurate) and dissect the neural mechanism underlying its detection. We also show that the same odorant together with two additional fly-derived odorants (methyl myristate and methyl palmitate) mediate attraction via a pathway separated from that involved in courtship. Interestingly, the odorants identified are attractive to several closely related species. Thus, we describe two highly important neural circuits involved in mating and attraction that seem to be conserved in *Drosophila*.

Light signaling controls nuclear architecture reorganization during seedling establishment

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Nuclear organization and genome expression are subject to massive reprogramming during most developmental transitions. The mechanisms triggering them in response to environmental stimuli are only poorly understood. Here (pp. E2836–E2844) we describe that dynamic changes in higher-order nuclear organization occurring in cotyledons (embryonic leaves) upon germination are impacted by light availability in the plant *Arabidopsis thaliana*. Upon light perception, master regulators of the light signaling pathway trigger rapid and massive nuclear expansion, condensation of large chromatin domains, and increased transcriptional activity of genes. These findings establish a foundation for deciphering the relationships between topological genome organization and transcriptional regulation associated with the establishment of photosynthesis.