PNAS Plus Significance Statements

Uracil DNA glycosylase initiates degradation of HIV-1 cDNA containing misincorporated dUTP and prevents viral integration

Amy F. Weil, Devlina Ghosh, Yan Zhou, Lauren Seiple, Moira A. McMahon, Adam M. Spivak, Robert F. Siliciano, and James T. Stivers

Misincorporation of dUTP into DNA is detrimental to eukaryotes, prokaryotes, and viruses. This study (pp. E448–E457) reveals the fate of uracilated HIV-1 DNA in human cells. Early stages of the viral life cycle are unaffected, but integration of uracilated viral DNA into the host genome is prevented. This effect is wholly dependent on the presence of UNG2, a nuclear enzyme that excises uracil from DNA. This study stablishes that UNG2 is a restriction factor for uracilated HIV-1 DNA and explains why this pathway is not fully engaged in CD4+ T cells and macrophages.

Mechanistic basis of infertility of mouse intersubspecific hybrids

Tanmoy Bhattacharyya, Sona Gregorova, Ondrej Mihola, Martin Anger, Jaroslava Sebestova, Paul Denny, Petr Simecek, and Jiri Forejt

Hybrid sterility contributes to speciation by restricting gene flow between related taxa. Although four hybrid sterility genes have been identified in *Drosophila* and mouse so far, the underlying molecular mechanisms are largely unknown. We describe extensive asynapsis of chromosomes in male and female meiosis of F1 hybrids between two closely related mouse subspecies. Using the intersubspecific chromosome-substitution strains (pp. E468–E477), we demonstrate that the heterospecific pairing of homologous chromosomes is a preexisting condition of asynapsis and may represent a universal mechanism of pachytene arrest in interspecific hybrids. Sex-specific manifestation of asynapsis can explain the mechanism of Haldane's rule.

Pattern and synchrony of gene expression among sympatric marine microbial populations

Elizabeth A. Ottesen, Curtis R. Young, John M. Eppley, John P. Ryan, Francisco P. Chavez, Christopher A. Scholin, and Edward F. DeLong

Microbial communities regulate the cycling of energy and matter in the environment, yet how they respond to environmental change is not well-known. We describe here a day in the life of wild planktonic microbial species using robotic sampling coupled with genome-wide gene expression analysis. Our results (pp. E488–E497) showed that closely related populations, as well as very different bacterial and archaeal species, displayed remarkably similar time-variable synchronous patterns of gene expression over 2 d. Our results suggest that specific environmental cues may elicit cross-species coordination of gene expression among diverse microbial groups, potentially enabling multispecies coupling of metabolic activity.

HSV carrying WT REST establishes latency but reactivates only if the synthesis of REST is suppressed

Guoying Zhou, Te Du, and Bernard Roizman

HSV expresses numerous functions to suppress the host and replicate at body orifices and yet establishes silent, latent infections in sensory neurons. One hypothesis that addresses the apparent contradiction is that peripheral ganglia serve as barriers to the spread of viruses via neurons in the CNS and that HSV usurps these functions to establish a latent state. This report (pp. E498–E506) examines the role of the corepressor element-1 silencing transcription factor (CoREST)/REST repressor complex in establishment of latency and reactivation. Mirroring earlier studies showing that expression of dominant-negative REST suppresses latency and increases virulence, aWT REST inserted into the viral genome enables latency but blocks reactivation.

Human retinal gene therapy for Leber congenital amaurosis shows advancing retinal degeneration despite enduring visual improvement

Artur V. Cideciyan, Samuel G. Jacobson, William A. Beltran, Alexander Sumaroka, Malgorzata Swider, Simone Iwabe, Alejandro J. Roman, Melani B. Olivares, Sharon B. Schwartz, András M. Komáromy, William W. Hauswirth, and Gustavo D. Aguirre

The first retinal gene therapy in human blindness from *RPE65* mutations has focused on safety and efficacy, as defined by improved vision. The disease component not studied, however, has been the fate of photoreceptors in this progressive retinal degeneration. We show (pp. E517–E525) that gene therapy improves vision for at least 3 y, but photoreceptor degeneration progresses unabated in humans. In the canine model, the same result occurs when treatment is at the disease stage equivalent to humans. The study shows the need for combinatorial therapy to improve vision in the short term but also slow retinal degeneration in the long term.

Compromised fidelity of endocytic synaptic vesicle protein sorting in the absence of stonin 2

Natalia L. Kononenko, M. Kasim Diril, Dmytro Puchkov, Michael Kintscher, Seong Joo Koo, Gerit Pfuhl, York Winter, Martin Wienisch, Jürgen Klingauf, Jörg Breustedt, Dietmar Schmitz, Tanja Maritzen, and Volker Haucke

Brain function depends on neurotransmission, and alterations in this process are linked to neuropsychiatric disorders. Neurotransmitter release requires the rapid recycling of synaptic vesicles (SVs) by endocytosis. How synapses can rapidly regenerate SVs, yet preserve their molecular composition, is poorly understood. We demonstrate (pp. E526–E535) that mice lacking the endocytic protein stonin 2 (Stn2) show changes in exploratory behavior and defects in SV composition, whereas the speed at which SVs are regenerated is increased. As Stn2 is implicated in schizophrenia and autism in humans, our findings bear implications for neuropsychiatric disorders.

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Distinct features of neurotransmitter systems in the human brain with focus on the galanin system in locus coeruleus and dorsal raphe

Erwan Le Maître, Swapnali Shantaram Barde, Miklos Palkovits, Rochellys Diaz-Heijtz, and Tomas G. M. Hökfelt

For decades rodents have been used to explore normal brain functions and mechanisms underlying brain diseases. Such data often have been the basis in the search for new drugs. In this study (pp. E536–E545) we selected chemical markers associated with central noradrenaline and serotonin neurons, key systems in research on and current treatment of depression, and studied their expression with in situ hybridization in postmortem human brains. The results show some distinct species differences between human and rodent noradrenergic and serotonergic neurons which may better inform the development of novel anxiolytic/antidepressant drugs.

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