PNAS Plus Significance Statements

Evidence for deposition of 10 million tonnes of impact spherules across four continents 12,800 y ago

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We present (pp. E2088–E2097) detailed geochemical and morphological analyses of nearly 700 spherules from 18 sites in support of a major cosmic impact at the onset of the Younger Dryas episode (12.8 ka). The impact distributed ∼10 million tonnes of melted spherules over 50 million square kilometers on four continents. Origins of the spherules by volcanism, anthropogenesis, authigenesis, lightning, and meteoritic ablation are rejected on geochemical and morphological grounds. The spherules closely resemble known impact materials derived from surficial sediments melted at temperatures >2,200 °C. The spherules correlate with abundances of associated melt-glass, nanodiamonds, carbon spherules, aciniform carbon, charcoal, and iridium.

Experimentally calibrated population of models predicts and explains intersubject variability in cardiac cellular electrophysiology

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Causes of intersubject variability in electrophysiological activity are unknown. We describe (pp. E2098–E2105) a methodology to unravel the ionic determinants of variability exhibited in experimental cardiac action potential recordings, based on the construction and calibration of populations of models. We show that 213 of 10,000 candidate models are consistent with the control experimental dataset. Ionic properties across the model population cover a wide range of values, and particular combinations of ionic properties determine shape, amplitude, and rate dependence of specific action potentials. Finally, we demonstrate that the calibrated model population quantitatively predicts effects caused by four concentrations of a potassium channel blocker.

Local circadian clock gates cell cycle progression of transient amplifying cells during regenerative hair cycling

Maksim V. Plikus, Christopher Vollmers, Damon de la Cruz, Amandine Chaix, Raul Ramos, Satchidananda Panda, and Cheng-Ming Chuong

Here (pp. E2106–E2115), we show that cell autonomous circadian clock optimizes physiological regeneration of hair follicles by synchronizing mitotic progression in transient amplifying hair-matrix cells. The daily mitotic rhythm makes hairs grow faster in the morning than in the evening. Also, because of high sensitivity of mitotic cells to radiation, significantly greater hair loss occurs in the morning than in the evening following exposure to the same dose of γ-radiation. These results provide a roadmap for developing new radiation therapy protocols, when radiation cytotoxicity can be either minimized or maximized by timing its delivery throughout the course of the day.

Construction of self-recognizing regulatory T cells from conventional T cells by controlling CTLA-4 and IL-2 expression

Tomoyuki Yamaguchi, Ayumi Kishi, Motonao Osaki, Hiromasa Morikawa, Paz Prieto-Martin, Kajsa Wing, Takashi Saito, and Shimon Sakaguchi

Naturally occurring regulatory T (Treg) cells suppress aberrant or excessive immune responses, thereby maintaining immune self-tolerance and homeostasis. This study (pp. E2116–E2125) shows that a combination of IL-2 repression, CTLA-4 expression, and antigenic stimulation is able to convert conventional T cells to potently immunosuppressive Treg-like cells, which are able to deprive IL-2 and CD28 signal from other T cells. Like natural Treg cells, they acquire a self-skewed T-cell receptor repertoire in the course of their thymic development, enabling them to control autoimmune responses effectively. This Treg construction by targeting IL-2 and CTLA-4 in conventional T cells is a novel way of immune suppression.

Dietary choice affects Shiga toxin-producing *Escherichia coli* (STEC) O157:H7 colonization and disease

Steven D. Zumbrun, Angela R. Melton-Celsa, Mark A. Smith, Jeremy J. Gilbreath, D. Scott Merrell, and Alison D. O'Brien

We demonstrated (pp. E2126–E2133) that dietary fiber content affects susceptibility to Shiga toxin (Stx)-producing *Escherichia coli* (STEC) infection in mice. We showed that high fiber diet (HFD)-fed mice had elevated levels of butyrate, a beneficial gut metabolite that paradoxically enhances the cell-killing capacity of Stx. We also found that the amount of gut bacteria in HFD-fed mice increased whereas the percent of commensal *Escherichia* species (spp) decreased compared with animals fed a low fiber diet (LFD). These changes led to higher *E. coli* O157:H7 colonization levels, more weight loss, and greater rates of death in HFD-fed than in LFD-fed STEC-infected animals.

Functional diversity among sensory receptors in a *Drosophila* olfactory circuit

Dennis Mathew, Carlotta Martelli, Elizabeth Kelley-Swift, Christopher Brusalis, Marc Gershow, Aravinthan D. T. Samuel, Thierry Emonet, and John R. Carlson

The coding of olfactory information is based on the activity of odor receptors. The larval olfactory system of *Drosophila* contains 21 olfactory receptor neurons and a comparable number of odor receptors. Through a screen of >10,000 receptor–odorant combinations, we identify (pp. E2134–E2143) for each of 19 receptors an odorant that excites it strongly. These odorants elicited little cross-activation of other receptors under test conditions. Systematic analysis reveals dramatic diversity in the sensitivity and temporal dynamics of responses to cognate odorants. The odorants elicited diverse behavioral responses. The analysis provides a foundation for elucidating the circuitry that translates receptor responses into behavior.