PNAS Plus Significance Statements

Design principles governing the motility of myosin V

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Myosin V, a two-headed motor protein, ferries cellular cargo by walking hand-over-hand on actin filaments. Interplay between ATP-driven conformational changes in the heads and stress due to load produces a variety of stepping dynamics: The motor can step forward or backward, or "stomp," where one head detaches and rebinds to the same site. We created an analytically solvable theory capturing all these behaviors, quantitatively matching a wide array of single-molecule experiments. We describe (pp. E4059–E4068) the structural and chemical design principles underlying the motor's robust function, providing a guide for how bioengineering might alter its dynamics.

Aryl hydrocarbon receptor deficiency causes dysregulated cellular matrix metabolism and age-related macular degeneration-like pathology

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Age-related Macular Degeneration (AMD) is the leading cause of vision loss. In its early stage, extracellular deposits accumulate below the retinal pigment epithelial layer (RPE), nurse cells to the retina. Identification of therapeutic treatments targeting deposit removal, which when left untreated exacerbate RPE and retinal damage, necessitates the discovery of pathways regulating deposit formation. We show (pp. E4069–E4078) that the activity of a nuclear receptor, essential to xenobiotic/toxin metabolism and cellular debris clearance, is critical to maintaining RPE cell health and that its deficiency in mice causes AMD pathology. This model provides a better understanding of AMD pathogenic mechanisms and a platform for testing novel therapeutics.

Intrinsic-mediated caspase activation is essential for cardiomyocyte hypertrophy

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Cardiac hypertrophy is a pathologic enlargement of the heart, an alteration that leads to contractile dysfunction and eventual organ failure. The hypertrophy phenotype originates from concentric growth of heart muscle cells and shares many biochemical features with programmed cell death, implying a common molecular origin. Here (pp. E4079–E4087), we show cell-autonomous activation of a mitochondrial cell death pathway during initial stages of muscle cell hypertrophy, a signal that is essential and sufficient to promote hypertrophy. Targeting individual cell death proteins may offer an effective means to limit the initial stage of cardiac disease, and forgo the transition to heart failure.

De novo identification of VRC01 class HIV-1–neutralizing antibodies by next-generation sequencing of B-cell transcripts

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An extraordinary influx of sequencing information is revolutionizing biological inquiry. While sequences of entire antibody repertoires are straightforward to obtain, understanding antibody function on the basis of sequence alone has remained elusive. Can bioinformatics identify function-specific antibodies within the ocean of B cell transcripts representing unrelated specificities? We undertook the challenge of identifying antibodies of the VRC01 class (pp. E4088–E4097). These antibodies individually neutralize up to 90% of HIV-1; although they share less than 50% sequence identity they do have characteristic sequence motifs and evolutionary relatedness. Our bioinformatics methods identified heavy and light chains from a new donor that could form functional antibodies and neutralize HIV-1 effectively. Identification of HIV-1 neutralizing antibodies of the VRC01 class can thus occur solely on the basis of bioinformatics analysis of a sequenced antibody repertoire.

Phagocytosis executes delayed neuronal death after focal brain ischemia

Jonas J. Neher, Julius V. Emmrich, Michael Fricker, Palwinder K. Mander, Clotilde Théry, and Guy C. Brown

Brain ischemia is a major cause of death and disability worldwide, but the cellular mechanisms of delayed neuronal loss and brain atrophy after cerebral ischemia are poorly understood and thus currently untreatable. Surprisingly, we find (pp. E4098–E4107) that after cerebral ischemia, brain macrophages phagocytose viable and functional neurons, causing brain atrophy and motor dysfunction. Our data show that delayed neuronal death and functional impairment after cerebral ischemia can be prevented by blocking specific phagocytic pathways, and therefore highlight new therapeutic targets for stroke and dementia.

Network model of top-down influences on local gain and contextual interactions in visual cortex

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Perceptual grouping links line segments that define object contours and distinguishes them from background contours. This process is reflected in the responses to contours of neurons in primary visual cortex (V1), and depends on long-range horizontal cortical connections. We present a network model (pp. E4108–E4117), based on an interaction between recurrent inputs to V1 and intrinsic connections within V1, which accounts for task-dependent changes in the properties of V1 neurons. The model simulates top-down modulation of effective connectivity of intrinsic cortical connections among biophysically realistic neurons. It quantitatively reproduces the magnitude and time course of the facilitation of V1 neuronal responses to contours.