PNAS Plus Significance Statements

Structural ensemble and microscopic elasticity of freely diffusing DNA by direct measurement of fluctuations

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Deformation of the double helix is a ubiquitous feature of the protein–DNA interactions that regulate, replicate, repair, and pack DNA in cells. Understanding the energetics of DNA deformation is therefore of central importance. DNA is generally modeled as a linear elastic rod, but it has not been possible to test this directly by observing the nanometer-scale bending and twisting of the helix. Using an X-ray interferometry technique, we measured the structural fluctuations of a short B-form duplex. The results (pp. E1444–E1451) expose a potential nonlinearity of DNA elasticity and illustrate how to measure the structural ensemble of a freely diffusing macromolecule.

Shaping organs by a wingless-int/Notch/nonmuscle myosin module which orients feather bud elongation

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How are specific organs shaped? To convert organ primordia from small domes to polarized, thin, conical structures, the orientation and duration of the elongation process must be carefully regulated. Using a feather bud elongation model, we identify a molecular module that directs precisely oriented elongation by converting a chemical gradient into a sharp boundary zone, which mediates mechanical processes. The module (pp. E1452–E1461) involves wingless-int (Wnt)7a, β-catenin, and nonmuscle myosin IIB and is modulated by Notch activity. Our mathematical simulations confirm the module's effect on reducing variations and fluctuations in the system via gradient-threshold conversion.

Using a preclinical mouse model of high-grade astrocytoma to optimize p53 restoration therapy

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Glioblastoma is the most common and aggressive form of brain cancer. GBM patients typically respond poorly to conventional therapies. The tumor-suppressor protein 53 pathway is disrupted in a majority of GBM cases. Using a mouse model that mimics the progression of human GBM, we evaluate and optimize the therapeutic efficacy of functional p53 restoration in gliomas. We show (pp. E1480–E1489) that the efficacy of p53 restoration therapy in the animal model as well as in human GBM cells is improved markedly by an episodic dosing regimen that circumvents the selective pressure for adaptive resistance when p53 function is chronically restored.

Genome-wide reprogramming of the chromatin landscape underlies endocrine therapy resistance in breast cancer

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Resistance to treatment with endocrine therapy occurs in ~50% of all breast cancer patients. The pathway(s) leading to drug resistance is ill-defined. We show (pp. E1490–E1499) that accessibility to the genome is altered in drug-resistant compared with responsive breast cancer cells. This coincides with the overactivation of the NOTCH pathway in drug-resistant compared with responsive cancer cells. The transcription factor PBX1, a known NOTCH target gene, is required for the growth of endocrine therapy-resistant breast cancer cells. Accordingly, a gene expression signature based on NOTCH-PBX1 activity can discriminate a priori breast cancer patients that are responsive or not to endocrine therapy.

Autoantigen can promote progression to a more aggressive TCL1 leukemia by selecting variants with enhanced B-cell receptor signaling

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These studies (pp. E1500–E1507) indicate that autoantigen-reactivity plays a role in the progression of a murine leukemia that models human chronic lymphocytic leukemia. This indication is consistent with the notion that chronic lymphocytic leukemia evolves by selection of normal B cells that bind autoantigen via the B-cell antigen receptor.

Flagella stator homologs function as motors for myxobacterial gliding motility by moving in helical trajectories

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Gliding is a form of enigmatic bacterial surface motility that does not use visible external structures such as flagella or pili. This study (pp. E1508–E1513) characterizes the single-molecule dynamics of the *Myxococcus xanthus* gliding motor protein AglR, a homolog of the *Escherichia coli* flagella stator protein MotA. However, the *Myxococcus* motors, unlike flagella stators, lack peptidoglycan-binding domains. With photoactivatable localization microscopy (PALM), we found that these motor proteins move actively within the cell membrane and generate torque by accumulating in clusters that exert force on the gliding surface. Our model unifies gliding and swimming with conserved power-generating modules.

Increased axonal bouton dynamics in the aging mouse cortex

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Synaptic plasticity is considered an essential process for the formation and maintenance of memory. It had been assumed for decades that cognitive deficits within the aging brain result from reduced synaptic density and plasticity. By imaging axonal arbors and boutons in the aged brain, we surprisingly find (pp. E1514–E1523) the opposite, i.e., dramatically increased rates of synapse formation, elimination, and destabilization in specific cortical circuits. This observation suggests that learning and memory deficits in the aged brain may arise not through an inability to form new synapses but rather through decreased synaptic tenacity.

Neural progenitors organize in small-world networks to promote cell proliferation

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Synchronized activity among groups of interconnected cells is essential for diverse functions in the brain. Most studies on neuronal networks have been performed in the mature brain when chemical synapses have been established. However, less is known about networking during embryonic development. We have studied neural progenitors and found that they form gap junction-mediated small-world networks, which, via electrical depolarization, drive spontaneous calcium activity to stimulate cell proliferation. Our data (pp. E1524–E1532) underscore the critical role of intricate cell signaling during embryonic development and show that complex networks of immature cells exist in the brain before birth.

Phosphodiesterase-8A binds to and regulates Raf-1 kinase

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The ERK pathway is a ubiquitous mechanism for transducing a variety of extracellular signals into intracellular events. It also is misregulated in a number of different disease states including several cancers. The ERK pathway crosstalks with other signaling cascades, including the cAMP system. In this paper (pp. E1533–E1542), we show that a key component of the ERK pathway, Raf-1 kinase, can associate with a specific cyclic nucleotide phosphodiesterase, phosphodiesterase 8A (PDE8A), to modulate the activity of the kinase. We report that the interaction between Raf-1 and PDE8A underpins functional consequences of ERK signaling in several different model systems.