PNAS Plus Significance Statements

Accurate secondary structure prediction and fold recognition for circular dichroism spectroscopy

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Circular dichroism (CD) spectroscopy is widely used for protein secondary structure analysis. However, quantitative estimation for β-sheet–containing proteins is problematic due to the huge morphological and spectral diversity of β-structures. We show (pp. E3095–E3103) that parallel/antiparallel orientation and twisting of β-sheets account for the observed spectral diversity. Taking into account the twist of β-structures, our method accurately estimates the secondary structure for a broad range of protein folds, particularly for β-sheet–rich proteins and amyloid fibrils. Moreover, the method can predict the protein fold down to the topology level following the CATH classification. We provide a general tool for a quick and reliable structure analysis using conventional or synchrotron radiation CD spectroscopy, which is especially useful when X-ray or NMR techniques fail.

Ionic imbalance, in addition to molecular crowding, abates cytoskeletal dynamics and vesicle motility during hypertonic stress

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Maintenance of cell volume and ionic homeostasis are fundamental to cell function. Cells shrink when extracellular osmolality is increased, and although mechanisms controlling cell volume recovery are well documented, the mechanisms underlying changes in membrane trafficking that occur during adaptation to high osmolality are not well understood. Molecular crowding arising from cell shrinkage can alter protein structure and has been proposed to provoke changes in trafficking events. However, cell volume recovery involves a rapid influx of ions, and the effects of ionic imbalance on trafficking dynamics in living cells remain largely unexplored. We found (pp. E3104–E3113) that high levels of chloride and loss of ATP, in addition to molecular crowding, contribute to altered cytoskeletal and vesicular dynamics during hypertonic stress.

Extrachromosomal circular DNA is common in yeast

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We performed a screen for extrachromosomal circular DNAs containing segments of genomic yeast DNA (pp. E3114–E3122). We found 1,756 such extrachromosomal circular DNAs containing about 23% of the total yeast genomic information. The abundance of these circular forms of genomic DNA suggests that eccDNA formation might be a common mutation that can arise in any part of the genome, and not in only a few special loci. We propose that eccDNAs may be precursors to the copy number variation in eukaryotic genomes characteristic of both the evolutionary process and cancer progression.

Oxytocin modulates fMRI responses to facial expression in macaques

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Oxytocin (OT), a mammalian hormone, may serve as a treatment for psychiatric disorders because of its beneficial effect on social behavior. Here, we found that in monkeys, OT selectively altered brain activity within multiple neural systems (visual perception, emotion, attention, and higher cognition function) and functional coupling between the amygdala and areas in the ventral visual pathway evoked by negative emotional expressions. Our findings (pp. E3123–E3130) provide key information for understanding the behavioral consequences of OT administration and indicate homologies between monkeys and humans in the neural circuits mediating the effects of OT. Thus, the monkey may be an ideal animal model to explore the development of OT-based pharmacologic strategies for treating patients with dysfunctional social behavior.

Progressive maturation of silent synapses governs the duration of a critical period

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During critical periods, cortical neural circuits are refined to optimize their functional properties. The prevailing notion is that the balance between excitation and inhibition determines the onset and closure of critical periods. Here (pp. E3131–E3140), we show that postsynaptic density protein-95 (PSD-95)–dependent maturation of silent glutamatergic synapses onto principal neurons was sufficient to govern the duration of the critical period for ocular dominance plasticity (ODP) in the visual cortex of mice. Loss of PSD-95 before the onset of CPs resulted in lifelong ODP, loss after CP closure reinstated silent synapses, and ODP. Thus, PSD-95–dependent silent synapse maturation terminates the critical period of ODP, and in general, once silent synapses are consolidated in any neural circuit, critical periods may end.

Rab3-interacting molecules 2α and 2β promote the abundance of voltage-gated $Ca_V1.3$ Ca^{2+} channels at hair cell active zones

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Sound encoding relies on Ca^{2+}-regulated transmitter release from inner hair cells (IHCs). Here (pp. E3141–E3149) we demonstrate a role of Ras-related in brain 3 (Rab3)–interacting molecule 2 (RIM2) in Ca^{2+} channel-clustering and vesicle-tethering at the active zones of IHCs. Active zones of RIM2α-deficient IHCs cluster fewer synaptic voltage-gated $Ca_V1.3$ Ca^{2+} channels, resulting in reduced synaptic Ca^{2+} influx. Exocytosis was diminished in RIM2α-deficient IHCs, likely contributing to the mild hearing impairment of RIM2α knockout mice. Hair cell-specific disruption of all RIM2 isoforms caused a stronger decrease of Ca^{2+} current and exocytosis in IHCs and impaired the encoding of sound onset in spiral ganglion neurons. We conclude that RIM2α and RIM2β promote synaptic clustering of Ca^{2+} channels at IHC active zones and are required for normal hearing.