PNAS Plus Significance Statements

Timing the impact of literacy on visual processing

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How does learning to read affect visual processing? We addressed this issue (pp. E5233–E5242) by scanning adults who could not attend school during childhood and either remained illiterate or acquired partial literacy during adulthood (ex-illiterates). By recording event-related brain responses, we obtained a high-temporal resolution description of how illiterate and literate adults differ in terms of early visual responses. The results show that learning to read dramatically enhances the magnitude, precision, and invariance of early visual coding, within 200 ms of stimulus onset, and also enhances later neural activity. Literacy effects were found not only for the expected category of expertise (letter strings), but also extended to other visual stimuli, confirming the benefits of literacy on early visual processing.

A model for the generation and interconversion of ER morphologies

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The endoplasmic reticulum (ER) is an important membrane-bound organelle in all eukaryotic cells. Depending on cell type and functional state, the ER membrane can adopt different morphologies, including a network of interconnected tubules, and sheets that can contain fenestrations or be stacked on top of each other. How these different morphologies are generated is unclear. Here (pp. E5243–E5251), we present a comprehensive theoretical model that explains the formation and interconversion of virtually all known ER morphologies. The model is based on two types of membrane-shaping proteins, exemplified by the reticulons and lunapark, which both stabilize the high membrane curvature in cross-sections of tubules and sheet edges, but favor straight or concave sheet edges, respectively. The predictions of the model are experimentally verified.

Actin stress in cell reprogramming

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Mechanical signaling plays many roles in cell physiology, including stem cell differentiation and reprogramming. To better understand the roles of mechanical forces in stem cells, we created (pp. E5252–E5261) genetically coded probes for actin that enables the direct measurement of forces in actin in living cells. This is the first force probe created for oligomeric proteins. We reprogrammed HEK-293 and Madin-Darby canine kidney cells into stem-like cells by culturing them on a soft substrate without using transcription factors. The mechanical properties of the microenvironment, and thus the local forces, promote cell reprogramming. Surprisingly, the cells showed close association of stemness to high tension in actin. Given the universal presence of actin in animal cells, the actin force probes have broad applications in biology.

Wnts produced by Osterix-expressing osteolineage cells regulate their proliferation and differentiation

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Despite the importance of Wnt signaling in bone biology, there is a knowledge gap in the identity of the cells that produce the Wnt ligands and the functions of Wnts produced by specific cell types. In our study (pp. E5262–E5271), we comprehensively characterized the expression patterns of all 19 Wnts in the developing mouse bone by in situ hybridization, and further showed that Osterix-expressing cells can produce Wnts and respond to Wnt signaling. Additionally, we found that Wnts produced by these Osterix-expressing cells regulate their differentiation and proliferation. Through providing a better understanding of how Wnt signaling contributes to bone biology, our findings also have clinical implications for the mechanism of the osteoporotic drug that targets Sclerostin, a Wnt signaling antagonist.

Measuring missing heritability: Inferring the contribution of common variants

David Golan, Eric S. Lander, and Saharon Rosset

Studies have identified thousands of common genetic variants associated with hundreds of diseases. Yet, these common variants typically account for a minority of the heritability, a problem known as "missing heritability." Geneticists recently proposed indirect methods for estimating the total heritability attributable to common variants, including those whose effects are too small to allow identification in current studies. Here (pp. E5272–E5281), we show that these methods seriously underestimate the true heritability when applied to case–control studies of disease. We describe a method that provides unbiased estimates. Applying it to six diseases, we estimate that common variants explain an average of 60% of the heritability for these diseases. The framework also may be applied to case–control studies, extreme-phenotype studies, and other settings.

Disruption of FAT10–MAD2 binding inhibits tumor progression

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FAT10, a ubiquitin-like modifier, is an oncogene that interacts with mitotic arrest-deficient 2 (MAD2) and confers cellular malignancy.

www.pnas.org/cgi/doi/10.1073/pnas.ss11149

Here (pp. E5282–E5291) we identified the MAD2-binding residues of FAT10 and determined the first solution structure, to our knowledge, of the first FAT10 ubiquitin-like domain. Importantly, we demonstrated the proof-of-mechanism for a novel and specific drug-targeting strategy that entails the specific inhibition of the pathological activity of a therapeutic target but not its reported physiological function, thus minimizing undesirable side effects: Abrogation of the FAT10–MAD2 interaction curtailed tumor progression without affecting FAT10's interaction with its other known physiological binding partners. This study presents a paradigm for drug targeting and paves the way for the development of a novel small-molecule anticancer inhibitor targeting the MAD2-binding interface of FAT10.

A calcium-dependent protease as a potential therapeutic target for Wolfram syndrome

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Wolfram syndrome is an autosomal recessive disorder characterized by juvenile diabetes and neurodegeneration, and is considered a prototype of human endoplasmic reticulum (ER) disease. Wolfram syndrome is caused by loss of function mutations of Wolfram syndrome 1 or Wolfram syndrome 2 genes, which encode transmembrane proteins localized to the ER. Despite its rarity, Wolfram syndrome represents the best human disease model currently available to identify drugs and biomarkers associated with ER health. Furthermore, this syndrome is ideal for studying the mechanisms of ER stress-mediated death of neurons and β cells. Here (pp. E5292–E5301) we report that the pathway leading to calpain activation offers potential drug targets for Wolfram syndrome and substrates for calpain might serve as biomarkers for this syndrome.

Plasma DNA aberrations in systemic lupus erythematosus revealed by genomic and methylomic sequencing

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Through the use of massively parallel sequencing, we have demonstrated (pp. E5302–E5311) a spectrum of plasma DNA abnormalities in patients with systemic lupus erythematosus. These abnormalities include aberrant measured genomic representations, hypomethylation, and DNA fragment size shortening. The binding of anti-double–stranded DNA antibody to plasma DNA appears to be an important factor associated with these abnormalities. These findings provide valuable insights into the biology of plasma DNA in an autoimmune disease and have potential implications for the development of new molecular markers for systemic lupus erythematosus.

The cholesterol-dependent cytolysins pneumolysin and streptolysin O require binding to red blood cell glycans for hemolytic activity

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The pneumococcus accounts for 25% of deaths in children under 5 y of age in developing countries. One of the most important virulence factors expressed by this pathogen is the pore-forming toxin, pneumolysin (Ply), an example of a Gram-positive cholesterol-dependent cytolysin (CDC). We show (pp. E5312–E5320) that Ply interacts with the Lewis histo-blood group antigen sialyl LewisX and that blocking this interaction can protect RBCs from lysis. We also identify glycan receptors on RBCs for the CDC streptolysin O from group A streptococcus. Our study supports the emerging paradigm shift that CDCs have cellular receptors other than cholesterol that define target cell tropism.

Network dynamics of the brain and influence of the epileptic seizure onset zone

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In epilepsy, seizures elicit changes in the functional connectivity of the brain that shed insight into the seizures' nature and onset zone. We investigated (pp. E5321–E5330) the brain connectivity of patients with partial epileptic seizures from continuous multiday recordings and found that (*i*) the connectivity defines a finite set of brain states, (*ii*) seizures are characterized by a consistent progression of states, and (*iii*) the seizure onset zone is isolated from the surrounding regions at seizure onset but becomes most connected toward seizure termination. Our results suggest that a finite-dimensional state space model may characterize the dynamics of the epileptic brain and ultimately help localize the seizure onset zone, which is currently done by clinicians through visual inspection of electrocorticographic recordings.