PNAS Plus Significance Statements

Fast structural responses of gap junction membrane domains to AB5 toxins

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We used 3D Bessel beam plane illumination and spinning disk microscopy to reveal fast structural changes in the architecture of gap junctions (GJs). Previously, GJ plaques were considered relatively stable structures. We demonstrate (pp. E4125–E4133) extremely rapid remodeling of proteins and lipids within GJ plaques in response to bacterial toxin exposure. Connexin channels within GJ plaques undergo dramatic rearrangements that lead to increased connexin packing and lipid reorganization. These changes likely reflect lipid-phase separation events in the biological membrane. Toxin-induced connexin reorganization depends on lipids and is little modified by membrane–cytoskeletal interactions. We suggest that fast GJ changes upon toxin exposure reveal an early-response system of cells and that GJ plaques are much more dynamic structures than previously recognized.

Chromosome missegregation rate predicts whether aneuploidy will promote or suppress tumors

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Aneuploidy, an abnormal chromosome content that commonly occurs because of errors in chromosome segregation, can promote or suppress tumor formation. What determines how aneuploidy influences tumorigenesis has remained unclear. Here (pp. E4134–E4141) we show that the rate of chromosome missegregation, rather than the level of accumulated aneuploidy, determines the effect on tumors. Increasing the rate of chromosome missegregation beyond a certain threshold suppresses tumors by causing cell death. Increasing errors of chromosome segregation did not affect tumor formation caused by genetic mutations that do not themselves alter chromosome inheritance. These results suggest that accelerating chromosome missegregation in chromosomally unstable tumors may be a useful strategy therapeutically.

Nitric oxide mediates local activity-dependent excitatory synapse development

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The development of brain networks is regulated through plasticity and activity-dependent mechanisms that control the continuous formation and pruning of spine synapses. However, the molecular events that contribute to these aspects of structural plasticity remain unclear. By assessing synapse development and spine dynamics in the rodent hippocampus, we find that activity-dependent spine formation is mediated by a postsynaptic signaling cascade implicating NO, cGMP, and vasodilator-stimulated phosphoprotein phosphorylation. Loss of this NO signaling mechanism interferes with the development of excitatory synapses and prevents structural adaptation of hippocampal excitatory synapses to environmental enrichment. These results (pp. E4142–E4151) provide a new understanding of the role played by NO in cognitive deficits and diseases, such as schizophrenia.

A *Drosophila* model of closed head traumatic brain injury

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Traumatic brain injury (TBI) occurs when a strong jolt to the head causes damage to brain cells, resulting in immediate and long-term consequences including physical, behavioral, and cognitive problems. Despite the importance of TBI as a major health issue, our understanding of the underlying cellular and molecular mechanisms is limited. To unravel these mechanisms, we have developed a model of TBI in the fruit fly, *Drosophila melanogaster*, where we can apply many powerful experimental tools. The main features of human TBI also occur in flies, suggesting that the underlying mechanisms are conserved. Our studies (pp. E4152–E4159) demonstrate the value of a fly model for understanding the consequences of TBI and may ultimately enable development of therapies for their prevention and treatment.

Drug resistance confounding prion therapeutics

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As people live longer, the prevalence and economic impact of neurodegenerative diseases rise. No cures or effective treatments exist for any of these fatal disorders, so identifying potential therapeutics that extend survival in animal models is vital. Many neurodegenerative illnesses have been shown to be caused by the accumulation of self-propagating misfolded proteins—the hallmark of prion diseases. We report (pp. E4160–E4169) the efficacy of 2-aminothiazoles, which were identified in cell-based screens as antiprion compounds, in extending the lives of prion-infected animals. Efficacy was limited by the development of drug-resistant prions, which is likely to have important implications for creating therapeutics in many different neurodegenerative diseases.

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