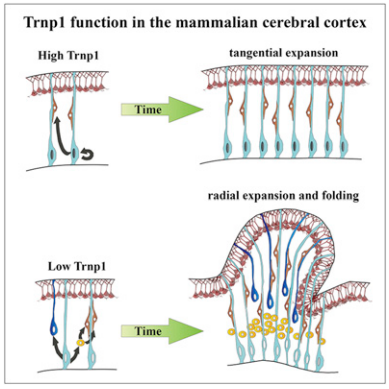
In This Issue

Cell



Brain Origami Master

PAGE 535

During evolution, the mammalian brain has undergone enormous expansion, with corresponding changes in gyrification (folding). Stahl et al. show that levels of a DNA-associated protein, Trnp1, determine whether the cortex expands tangentially or radially and also regulate its gyrification. Trnp1 levels in the developing human brain correlate with regional levels of folding.

TNF Excess: TB or Not TB

PAGE 521

Tumor necrosis factor has been shown to be protective in tuberculosis. Roca and Ramakrishnan find that excess TNF levels, however, induce mitochondrial ROS and lead to macrophage necroptosis. This results in the lysis of infected macrophages and release of mycobacteria into the extracellular milieu, where they are able to grow unfettered. Pharmacological modulation of necroptosis may help to preserve macrophage microbicidal activity and confer tuberculosis resistance to individuals with excess TNF.

Cell Sorting Nixes Noise in Development

PAGE 550

Patterning and morphogenesis often occur concurrently in development. Using in toto imaging in the zebrafish neural tube, Xiong et al. show that cell movements during morphogenesis create "noise" in the positional information encoded by the Sonic hedgehog morphogen gradient. As a result, cells of different fates are specified in mixed and overlapping patterns. Fate-specific cell movements then create sharp boundaries between cell-type domains. Thus, morphogenetic cell movements can both limit and correct positional information.

RNA Editor Meets RNA Silencer

PAGE 575

ADAR1 is a homodimeric RNA-editing enzyme that converts adenosine to inosine in dsRNA. Ota et al. now show that ADAR1 also plays a completely different role as an RNAi regulator. When an ADAR1 monomer forms a complex with Dicer, it acts as an RNA silencer by promoting miRNA processing, RISC loading, and RNAi efficacy. miRNA expression is globally suppressed in mouse embryos lacking ADAR1, altering expression of miRNA targets and contributing to embryonic lethality.

Vitamins Smack Down SMAD in Liver Injury

PAGE 601

Ding et al. show that vitamin D receptor (VDR) signaling inhibits liver fibrosis (scarring) by antagonizing the action of SMAD transcriptional regulators in hepatic stellate cells. SMADs are activated by liver injury and, in the absence of VDR ligands, activate profibrotic genes. However, they also enable their own repression by making the chromatin around their target sites more accessible to VDR that will bind and inhibit SMAD activity in the presence of VDR ligands.

Tanking the Proteasome

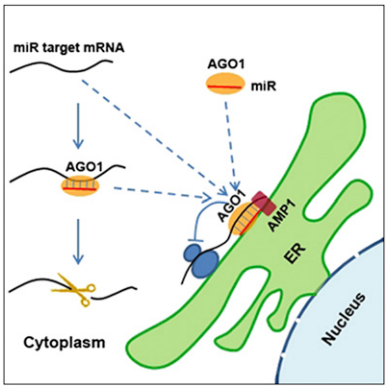
PAGE 614

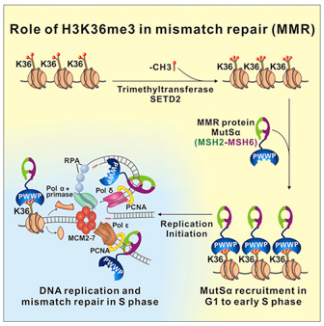
Selective protein degradation by the ubiquitin-proteasome system plays a vital role in cellular homeostasis. Defects in this process are associated with various human diseases, and the proteasome is a validated drug target in cancer therapy. Cho-Park and Steller show that Tankyrase-mediated ADP-ribosylation of PI31 activates proteasomes by promoting 26S proteasome assembly and that this process can be blocked with Tankyrase-inhibitors. These results reveal a mechanism of proteasome regulation that can be targeted with existing small-molecule inhibitors.

miRNA Inhibition at the ER

PAGE 562

Translational repression is a conserved mode of action of plant and animal microRNAs, but where it takes place subcellularly is unknown. Li et al. show that the integral ER membrane protein AMP1 is required for translational repression of microRNA target transcripts and inhibits their loading onto membrane-bound polysomes, indicating that the ER is an important locus of translational repression.





Methyl Mark for Mismatch Repair

PAGE 590

DNA mismatch repair (MMR) maintains genome stability by correcting replication-generated errors. Li et al. now show that a histone mark, H3K36me3, regulates MMR by directly interacting with mismatch recognition protein MutSα and localizing it onto chromatin in G1 to early S phase, before DNA replication. Cells lacking the H3K36 trimethyltransferase SETD2 display a mutator phenotype similar to that caused by MutSα deficiency. This work explains the longstanding puzzle of MMR-deficient cancer cells that lack detectable mutations in MMR genes.

Domino Effect in Protease Ring

PAGE 628

The homohexameric AAA+ ATPase ClpX unfolds and translocates substrates into the ClpP peptidase for degradation, but how ATP interacts with ClpX subunits is not known. Stinson et al. develop an assay to test the conformations and ATP-binding properties of individual subunits. They find that ClpX subunits convert between ATP-loadable and unloadable during the functional cycle of ClpX and that ATP binding initiates stepwise allosteric changes in the ClpX ring. The approach should be applicable to the study of other multisubunit protein machines.

CLASH of the miRNAs

PAGE 654

miRNAs play many important regulatory roles, but their targets have been difficult to identify systematically. Helwak and colleagues present an experimental approach termed CLASH, which allows identification of more than 18,000 interactions between miRNA and mRNA molecules in human cells. The transcriptome-wide data set and accompanying functional studies show many noncanonical interactions involving bulged or mismatched nucleotides, as well as interactions outside of the proposed 5' "seed" region of miRNAs, revealing a diversity of miRNA interaction modes and targets.

Weaving Together Cancer Genomes

PAGE 666

Genomic rearrangements drive cancer growth by creating oncogenic gene fusions and disrupting tumor suppressor genes. Baca et al. sequence 57 prostate cancer genomes and model the genesis of chromosomal alterations based on thousands of detected somatic rearrangements. Their model reveals interdependent rearrangements that shuffle DNA from five or more chromosomes in a process that they term "chromoplexy" (from the Greek *pleko*, "to weave"), suggesting that a few punctuated rounds of chromoplexy may suffice to induce the substantial derangement characteristic of cancer genomes.

Setting Sights on Cytosine Demethylation

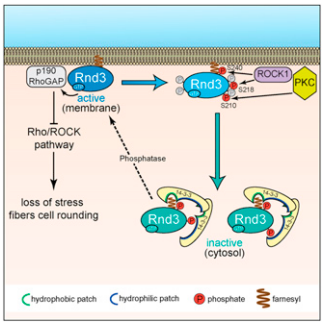
PAGE 678 and PAGE 692

DNA demethylation involves oxidation of 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5fC), and 5-carboxylcytosine (5caC) and subsequent excision of 5fC and 5caC by the DNA glycosylase TDG. Two papers now present methods for mapping the genome-wide locations of 5hmC, 5fC, and 5caC in mouse ESCs. Song et al. use selective chemical labeling and base resolution to look at 5fC distribution, whereas Shen et al. employ modification-specific antibodies to detect all three forms. Together, the two studies show that active cytosine demethylation occurs at multiple sites throughout the genome and is particularly prevalent at poised enhancers, where 5fC accumulation correlates with increased binding of the transcriptional coactivator p300. The results suggest a role for cytosine demethylation in the epigenetic tuning of regulatory elements.

Integrative Approach to AD Network

PAGE 707

Zhang et al. integrate transcriptional profiling of postmortem brains from late onset Alzheimer's disease (AD) patients and controls, with a rank-ordering and Bayesian inference approach to identify remodeled networks in the diseased brains and key nodes within them. The results point toward a module for immune functions and microglial phagocytosis as an important mechanism in AD pathology. The data provide a resource for probing the molecular underpinnings of disease and may aid drug discovery efforts.



Off Switch for a Perpetually On Protein

PAGE 640

Signaling through G proteins normally involves conformational switching between GTP- and GDP-bound states. Rnd proteins are atypical constitutively GTP-bound Rho proteins, whose regulation remains elusive. Now, Riou et al. show that Rnd G proteins demonstrate an alternative regulation mechanism by binding to 14-3-3 proteins through a C-terminal hybrid motif that includes adjacent phosphorylated serine and prenylated cysteine groups. 14-3-3 inhibits Rnd proteins by extracting them from their site of action on membranes, which is regulated by Rnd phosphorylation.