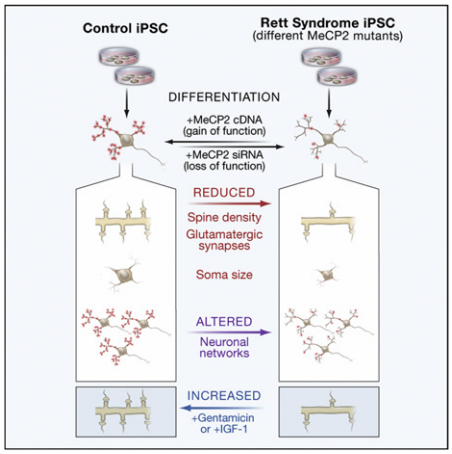
In This Issue

Cell



Making Neurons from Rett Patient Stem Cells

PAGE 527

Using Rett syndrome (RTT) as a prototype autism spectrum disorder (ASD), Marchetto et al. generated induced pluripotent stem cells (iPSCs). Neurons derived from RTT-iPSCs had fewer synapses and altered connectivity when compared to control neurons. Strikingly, synaptic defects in RTT neurons could be rescued pharmacologically, suggesting that there is a developmental window in an autism syndrome when potential therapies could be effective. These RTT patient-derived neurons also provide a promising cellular tool for drug screening, biomarker identification, and personalized treatment.

Translation Gets Pol II's Stamp of Approval

PAGE 552

Rpb4/7, a heterodimer of RNA polymerase II (Pol II) subunits, regulates pre-mRNA synthesis. It stays bound to the mRNA and accompanies it to the cytoplasm where, Harel-Sharvit et al. now report, the dimer interacts directly with eIF3 to regulate translation. Efficient translation depends on Rpb4/7's prior association with RNA Pol II in the nucleus. Thus, Rpb4/7 integrates the various stages of gene expression into one functional system.

Strippers for Protein Polyglutamylation

PAGE 564

Proteins can be polyglutamylated, but the enzymes that remove these groups are unknown. Rogowski et al. now identify several protein deglutamylases as members of the cytosolic carboxypeptidase (CCP) family and describe the enzymatic mechanism of protein deglutamylation. Mice lacking CCP1 are subject to hyperglutamlyation of tubulin, and subsequent neurodegeneration, suggesting regulatory roles for control of polyglutamylation.

Hrd-ing Misfolded Proteins out of the ER

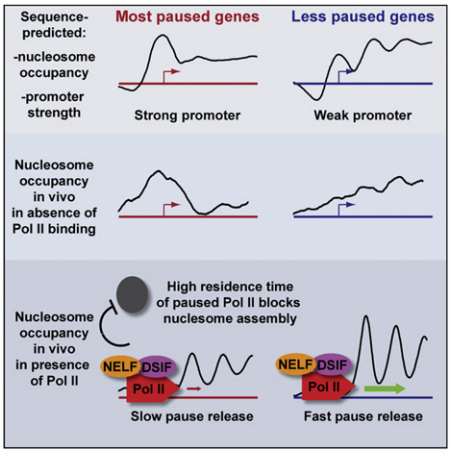
PAGE 579

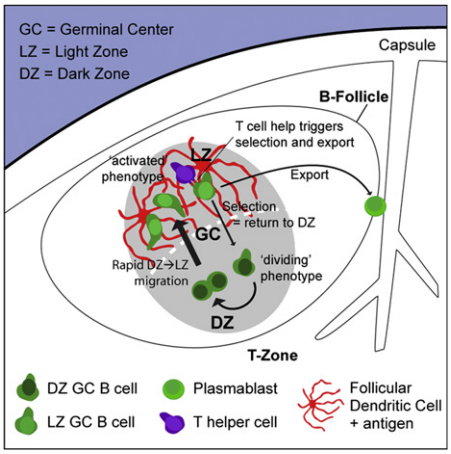
Misfolded proteins in the endoplasmic reticulum (ER) need to be transported back into the cytosol for polyubiquitination and degradation. In this issue, Carvalho et al. show that the ubiquitin ligase Hrd1p is the crucial membrane component in this retrotranslocation. The authors propose that Hrd1p cooperates with the cytosolic Cdc48p ATPase complex to move misfolded proteins through the ER membrane.

Paused Polymerase Takes On DNA-Encoded Nucleosome Formation

PAGE 540

Pausing of RNA polymerase II during early elongation was initially thought to be a rare mechanism for attenuating transcription; however, it's now known to be widespread, raising questions about the role of paused polymerase. Here, Gilchrist et al. report that pausing stimulates transcription potential by preventing formation of repressive promoter chromatin. Their findings suggest that competition between paused polymerase and nucleosomes for promoter occupancy has evolved as a prevalent gene regulatory strategy.





T Cells Help B Cells Help Themselves

PAGE 592

Selection for B cells with high-affinity B cell receptors occurs in the germinal centers (GCs). This process was thought to involve competition of B cells for antigen in the GC. Using a novel live-microscopy approach, Victora and colleagues visualize the dynamics of GC selection. Their findings suggest that access to help from GC-resident T cells, and not competition for antigen, is the limiting factor in GC selection.

UPBEAT in the Zone

PAGE 606

In *Arabidopsis*, stem cell progeny at the root tip rapidly proliferate in an amplifying zone and then increase in size and differentiate in an adjacent elongation zone. In this issue, Tsukagoshi et al. identify a transcription factor, UPBEAT1 (UPB1), that regulates the balance between proliferation and differentiation at the interface of these two zones. UPB1 regulates levels of reactive oxygen species (ROS) in the transition zone by controlling the expression of a set of peroxidases. Comparison to ROS-regulated growth control in animals suggests that a similar mechanism is used in plants and animals.

A Gemisch of EpiSCs

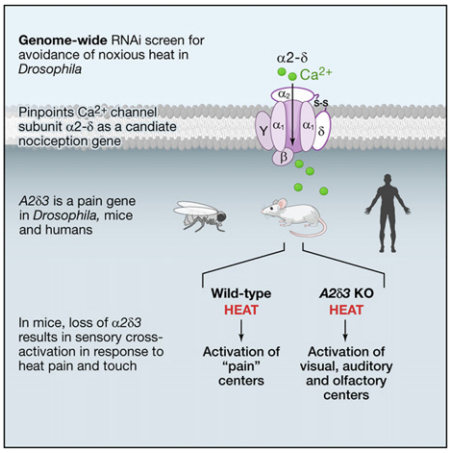
PAGE 617

Pluripotent stem cells contribute to teratomas when injected into an organism or to chimeras when injected into an early embryo. However, stem cells derived from mouse epiblast tissue (EpiSCs) show restricted pluripotency and rarely form chimeras. Han et al. now show that EpiSCs actually comprise two different subpopulations of cells in culture. The major subpopulation shares features with late mouse epiblast cells and cannot form chimeras, whereas cells in the minor population resemble early mouse epiblast cells and can readily form chimeras, thus explaining the restricted potency of EpiSCs.

Sounds Painful

PAGE 628

Acute and chronic pain affects millions of people worldwide. In this issue, Neely et al. use genome-wide RNAi screening in *Drosophila* to identify genes involved in heat nociception. Mice mutant for one of these genes, $\alpha 2\delta 3$ (*straightjacket* in flies), have impaired heat pain sensitivity, and in humans, $\alpha 2\delta 3$ SNP variants associate with reduced sensitivity to acute noxious heat and chronic back pain. Surprisingly, functional brain imaging of $\alpha 2\delta 3$ mutant mice indicated that thermal pain and tactile stimulation trigger strong sensory cross-activation of brain regions involved in vision, olfaction, and hearing.



Metabolites Move up the Regulatory Chain

PAGE 639

Small metabolites represent the vast majority of molecules in a cell. Li et al. now provide insight into protein-metabolite interactions, suggesting that they have an extensive role in the regulation of protein activity. Among the many prospective interactions identified, the authors specifically characterize those involving ergosterol, the yeast analog of cholesterol, which they show binds to many proteins including kinases, thereby affecting their functions and levels.