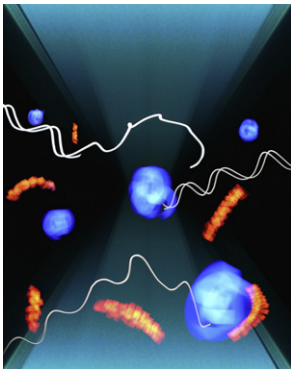
In This Issue

Cell

Schizophrenia, Disrupted

PAGE 1017

The *Disrupted In Schizophrenia 1* (*DISC1*) gene is mutated in a familial form of schizophrenia and depression and has been shown to play a role in brain development. Mao et al. now find that DISC1 directly interacts with and inhibits the kinase GSK3β, impacting β-catenin/TCF signaling and impairing neural progenitor cell proliferation. Strikingly, inhibition of the GSK3β/β-catenin pathway fully rescues the defect in progenitor proliferation caused by DISC1 deficiency. In the adult mouse brain, loss of DISC1 specifically in the dentate gyrus elicits depression-like behavior and hyperlocomotion, which is reversed by a GSK3β inhibitor. Thus, this pathway may prove to be a promising therapeutic target for treating psychiatric disorders.



BRCA2 Focuses RAD51 for Repair

PAGE 1032

The breast cancer susceptibility protein, BRCA2, plays a key role in recombinational repair of DNA breaks by recruiting RAD51 to breaks through its BRC repeats. Processed breaks comprise both single-stranded and double-stranded DNA (ssDNA and dsDNA), and RAD51 association with ssDNA is required for repair. Using biochemical and single-molecule techniques, Carreira et al. show that the BRC repeats target RAD51 to ssDNA and simultaneously prevent its nucleation onto dsDNA. The BRC repeats then stabilize the complex with ssDNA by inhibiting RAD51-mediated ATP hydrolysis. As a consequence, BRCA2 modulates RAD51's association with DNA, assuring formation of the functional RAD51-ssDNA complex.

Some Reassembly Required

PAGE 1044

The bacterium *Deinococcus radiodurans* is extremely resistant to DNA damage, capable of reassembling a genome shattered by ionizing radiation. The repair of the broken fragments is a two-step process comprising interdependent recombination and replication events. By exploring these processes in vivo, Slade et al. define the key enzymes and the sequence of the reactions for which they are required. Recombination proteins RecA and RadA promote DNA repair synthesis, which is initiated by DNA polymerase III and elongated by DNA polymerases III and I. These findings dissect the mechanism of the most efficient and precise process of DNA fragment reassembly known to date.

Without DNA Repair Factor, Insulin Says Not So FAS

PAGE 1056

After consumption of a carbohydrate-rich meal, excess calories are converted to fatty acids (lipogenesis). During this process, transcription of fatty acid synthase (FAS), a central enzyme in lipogenesis, increases drastically. Wong et al. now show that the transcription factor USF-1 acts as a molecular switch by recruiting various interacting proteins to the FAS promoter. During feeding, USF-1 is phosphorylated by DNA-PK, a kinase involved in DNA damage repair, which allows recruitment of and acetylation by P/CAF, leading to activation of FAS transcription. In SCID mice, which are deficient in DNA-PK, USF-1 phosphorylation and acetylation is attenuated, and lipogenesis impaired. This work demonstrates that DNA-PK mediates insulin-dependent activation of lipogenesis.

Scaffolds Get In On the Catalytic Act

PAGE 1085

Scaffold proteins are thought to control the flow of signaling information by tethering kinases and substrates in close proximity. However Good et al. uncover a different function for the scaffold protein Ste5 in the yeast mating pathway. They show that although the MAP kinase Fus3 is an intrinsically poor substrate for its upstream enzyme, the MAPKK Ste7, a previously uncharacterized domain in Ste5 interacts with Fus3 to selectively increase the catalytic constant (k_{cat}) of Ste7-mediated phosphorylation. The dual requirement for Ste7 and the Ste5 scaffold in Fus3 phosphorylation explains why Fus3 is selectively activated by the mating pathway, and not by other pathways that also utilize Ste7.

HATs Off to a Nu Acetylation Substrate

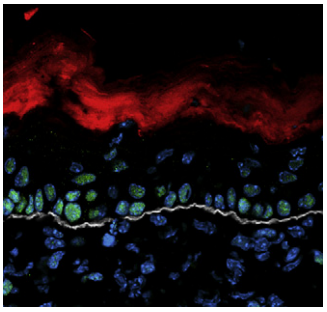
PAGE 1073

Although histone acetyltransferases and deacetylases conduct many critical functions via nonhistone targets in metazoans, the only nonhistone substrates known in *Saccharomyces cerevisiae* are chromatin associated. Using yeast proteome microarrays, Lin et al. identify non-chromatin substrates of the nucleosome acetyltransferase of H4 (NuA4) complex. They show that acetylation of the metabolic enzyme phosphoenolpyruvate carboxykinase (Pck1p) at lysine 514 is crucial for its enzymatic activity and the ability of yeast cells to grow on nonfermentable carbon sources. Interestingly, the sirtuin Sir2p deacetylates Pck1p both in vitro and in vivo. Loss of Pck1p activity blocks the extension of yeast chronological life span caused by starvation. These results demonstrate a regulatory function for the NuA4 complex in glucose metabolism and life span via acetylation of a key metabolic enzyme.

NEMO Found with Linear Ubiquitin

PAGE 1098

NF-κB, a key mediator of transcription in development and immunity, is activated via a kinase complex consisting of IKKα, IKKβ, and NEMO. Activation of NF-κB requires binding of NEMO to ubiquitinated substrates, but the precise mechanism of ubiquitin recognition by NEMO has remained elusive. Rahighi et al. report the crystal structure of a ubiquitin-binding domain in NEMO complexed with diubiquitin, revealing that NEMO selectively recognizes linear (head-to-tail) ubiquitin chains, and that this specific recognition is important for NF-κB activation by multiple inflammatory agonists. Their study provides insight into the detrimental effect of NEMO mutations in patients suffering from X-linked ectodermal dysplasia and immunodeficiency.



When PRC Clocks Out, AP1 Takes Over

PAGE 1122

Polycomb repressor complexes (PRCs) have been identified as key regulators of differentiation in pluripotent embryonic stem cells. Here, Ezhkova et al. used skin as a model to test whether Polycomb-mediated mechanisms control fates of multipotent progenitors in developing tissues. They find that an essential PRC component, Ezh2, is expressed in epidermal progenitors but diminishes concomitant with embryonic differentiation and with postnatal decline in proliferative activity. Ezh2 appears to prevent the recruitment of the transcriptional activator AP1, which is required to selectively activate epidermal terminal differentiation. In so doing, Ezh2-mediated chromatin repression maintains proliferative potential and global silencing of differentiation lineages in embryonic epidermal progenitors.

A PIPstop on the Road to Endosomal Maturity

PAGE 1110

Internalization of cell surface receptors is followed by their transport to endosomes. A subpopulation of endosomes defined by the presence of the protein APPL has a specialized role in propagating signaling of internalized receptors. Zoncu et al. show that APPL endosomes are intermediate stations for signaling cargo, which subsequently convert into classical early endosomes. This progression is controlled by the generation of PI3P at their surface, which acts as a molecular switch triggering endosomal maturation. Upon impairment of this switch, endosome maturation is reverted and signaling is altered. Thus, signaling activity of cargo is intimately connected to trafficking and maturation of APPL endosomes.

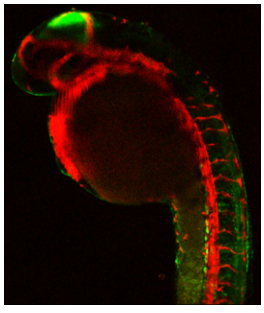
Ankyrin Bouncer Restricts Admission to the Axon Club

PAGE 1148

In polarized neurons, distinct cellular components are partitioned between the somatodendritic and axonal compartments, but mechanisms underlying the development and maintenance of this segregation remain unclear. In this study, Song et al. identify an ankyrinG- and F-actin-dependent structure that emerges at the junction between the axon and cell body within 2 days after axon/dendrite differentiation. This structure imposed a selective filter for the diffusion of macromolecules and the transport of vesicular carriers into the axon. Axonal entry is allowed for KIF5-driven carriers of synaptic vesicle protein VAMP2, but not for KIF17-driven carriers of NMDA receptor subunit NR2B. Further studies using chimeric motors suggest that axonal entry depends on the transport efficacy of the KIF-cargo complexes.

Wnt Pathway Gets a PG Rating

PAGE 1136



Hematopoietic stem cells (HSCs) have been used therapeutically to treat cancer and other blood diseases. Here, Goessling et al. demonstrate in zebrafish that two well-known signaling pathways, Wnt and prostaglandin (PG), interact to control the formation of HSCs during embryonic development. PGE2 augments the Wnt pathway at the level of β-catenin stability via cAMP/PKA-mediated phosphorylation. Furthermore, the PGE2 and Wnt interaction regulated murine stem and progenitor populations both in vitro and in vivo and was also conserved during regeneration of other organ systems. These results provide evidence that Wnt activation in stem cells requires PGE2 and suggests the importance of the PGE2/Wnt interaction as a conserved regulator of vertebrate regeneration.

For Neurotrypsin Function, Timing Is Everything

PAGE 1161

Mutation of the protease neurotrypsin in humans causes severe mental retardation. After its release from presynaptic terminals in a manner dependent on neuronal activity, neurotrypsin is activated and then cleaves the proteoglycan agrin in the extracellular space of the synapse. Matsumoto-Miyai and colleagues now show that the activation of neurotrypsin and cleavage of agrin relies on processes mediated by postsynaptic NMDA receptors. Formation of filopodia on dendritic spines, a possible precursor to synapse formation, is defective in neurons lacking neurotrypsin, but filopodia formation is restored upon treatment with the cleaved form of agrin. The results suggest a role for the neurotrypsin-agrin system in activity-controlled coordination of pre- and postsynaptic activation and thus a possible role in synaptic circuit organization and remodeling important for plasticity.