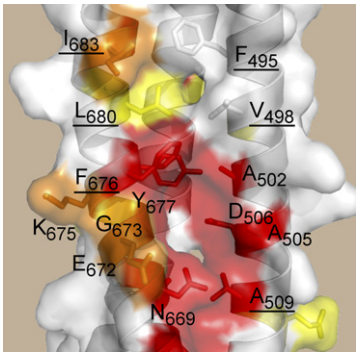
In This Issue

Cell

How an ALIXer Promotes Virus Budding



PAGE 841

The ALIX/AIP1 protein participates in protein sorting in cellular membranes. ALIX also binds to "late domain" motifs in retroviral Gag proteins including HIV-1, which facilitates virus budding. Using crystallography and biochemistry, Fisher et al. now find that the human ALIX protein has a banana-shaped N-terminal Bro1 domain and an unusual V-shaped central domain. HIV-1 Gag "late domains" bind close to the base of the V, whereas the cellular CHMP4/ESCRT-III proteins bind to a conserved patch on the Bro1 domain. Importantly, both interactions are required for virus budding. ALIX therefore connects retroviral Gag proteins to other cellular budding machinery.

Tanning with p53

PAGE 853

Skin pigmentation is a potent protector against sun burn and skin cancer. UV radiation stimulates expression and secretion of the melanocyte-stimulating hormone (MSH) in epidermal keratinocytes, thereby inducing pigmentation in adjacent melanocytes. Cui et al. report that UV induction of MSH expression occurs via the tumor suppressor p53, an important player in the DNA-damage response. Thus, p53 may act as a UV sensor, linking the control of pigmentation to DNA damage. This activity of p53 may also explain hyperpigmentation of the skin in response to DNA-damaging drugs and to inflammation or oncogenic transformation of keratinocytes.

Primase Halts in the Name of Hunger

PAGE 865

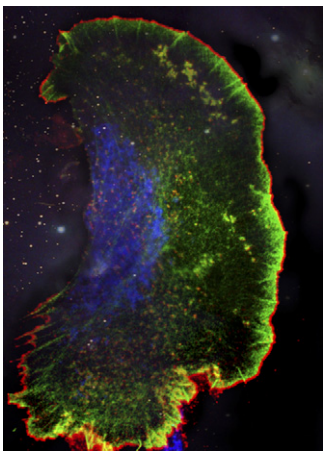
Accurate DNA replication is essential for the faithful propagation of genetic information. Hence, most organisms tightly regulate the decision to initiate DNA replication. In the bacterium *B. subtilis,* the progression of the replication fork (replication elongation) can also be arrested in response to unfavorable conditions such as transient nutrient starvation. Wang et al. report a new mechanism of replication elongation arrest via the second messengers guanosine tetraphosphate (ppGpp) and guanosine pentaphosphate (pppGpp). These molecules are produced upon starvation and halt replication elongation by targeting the essential replication component primase. This pathway probably helps to maintain genomic stability.

Histone H3K4 Trimethyl Wipeout

PAGE 877 and PAGE 889

Trimethylation of histone H3 lysine 4 (H3K4) correlates with increased transcriptional activity. Two papers in this issue identify the JARID family of JmjC-domain containing proteins as specific trimethyl H3K4 demethylases. Lee et al. reveal that a complex of JARID1d and a polycomb-like protein Ring6a/MBLR is recruited to the *Engrailed 2* promoter. Through its H3K4 demethylase activity, this complex promotes transcriptional silencing by regulating recruitment of the chromatin-remodeling complex, NURF, and basal transcription machinery. Klose et al. report that another family member, RBP2—previously implicated in differentiation control by Rb—erases trimethylation marks on H3K4 at the promoter of the cytokine *SDF1* gene. *RBP2* null mice display hematopoietic abnormalities reminiscent of *SDF1* null mice. These are the first reports of a family of H3K4 tridemethylases and their physiological function.

N-WASP Bridges the Actin and Membrane Divide



PAGE 901

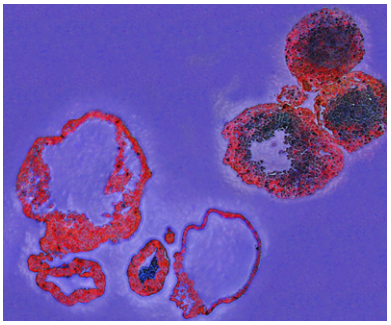
Actin filament networks drive membrane deformation events including cell migration. To dissect how membranes stay attached to growing actin networks, Co et al. show that N-WASP, a membrane-associated actin nucleation promoting factor, uses its WH2 domains to capture the fast-growing ("barbed") ends of new actin filaments. This interaction allows the actin network to maintain a connection to the membrane during filament growth. In a reconstituted motility system, WH2 mutations cause the actin network to detach from the membrane. WH2/barbed end interactions appear to create a high density of N-WASP on the membrane, which may locally amplify actin nucleation signals.

Coronin Choreographs Cell Migration

PAGE 915

Coronins are highly conserved F-actin-binding proteins that have been implicated in cell motility in model organisms, yet their function in mammalian cells is unknown. Here, Cai et al. report that Coronin 1B, a ubiquitous mammalian Coronin, interacts with two important regulators of actin dynamics at lamellipodia: the Arp2/3 complex, which nucleates actin filaments and Slingshot phosphatase, and a regulator of Cofilin, which drives filament turnover. Their results suggest that Coronin coordinates the activities of these two regulators at the leading edge of migrating cells.

Autophagy Calls in the Garbage Man



PAGE 931

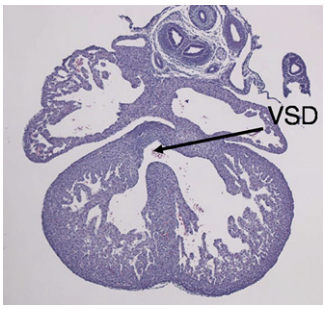
During development, autophagy actively participates in programmed cell death. Now, Qu et al. describe a new role for autophagy in development. The authors show that autophagy genes are required for the clearance of apoptotic cells during mouse embryonic morphogenesis. Autophagy causes an increase in ATP levels in dying cells, which causes the exposure of an engulfment signal on these cells to ensure their removal. These findings further our understanding of the role of autophagy in development and may have important implications in the prevention of diseases—such as inflammation and autoimmunity—that are associated with inefficient removal of dying cells.

Neurons Set Their Sights on Jelly Belly

PAGE 961

In order to assemble functional neuronal circuits during development, axons must accurately select their postsynaptic partner neurons. Using the visual system of the fruit fly as model, Bazigou et al. provide evidence that the ligand Jelly Belly (Jeb) expressed in photoreceptor axons activates the receptor tyrosine kinase Alk in optic lobe target neurons. Disruption of the signaling results in aberrant expression of downstream axon guidance molecules. These results suggest that Jeb and Alk act as an anterograde signaling system that mediates photoreceptor axon targeting.

Keeping Cardiac Progenitor Numbers in Check



PAGE 947

Congenital heart defects can be caused by mutations in the homeodomain transcription factor Nkx2-5. Prall et al. now describe a pathway in which Nkx2-5 controls cardiac progenitor cell numbers by repressing its immediate upstream inducer, *Bmp2*. In *Nkx2-5* mutant mice, the Bmp2-Smad1 pathway is overactive, leading initially to progenitor overspecification but then to a catastrophic decrease in progenitor proliferation and truncation of heart structures. Thus, this Nkx2-5/Bmp2/Smad1 negative feedback loop exerts an important temporal influence on cardiac progenitor numbers in mouse embryos. They also show that interfering with this negative feedback loop in a mouse model can cause congenital heart defects.

Do *BRCA1* Mice Lead a Normal XISTence?

PAGE 977 and PAGE 991

XIST RNA is a noncoding RNA that coats the inactive X chromosome and helps maintain its silenced state. The tumor suppressor gene *BRCA1* was previously reported by Livingston and colleagues in *Cell* to regulate XIST RNA localization. A hypothesis that has emerged from their data is that loss of XIST RNA and reactivation of X-linked genes in BRCA1-mutant female cells may contribute to tumorigenesis. Here, Xiao et al. provide data that female BRCA1-mutant cells exhibit normal XIST RNA localization. These findings indicate that reactivation of X-linked genes due to loss of XIST RNA is unlikely to contribute to development or progression of BRCA1 mutant tumors. In response to this Matters Arising, Livingston and colleagues (Silver et al.) provide new data to further support a role for BRCA1 in XIST localization.

Custom-Made Histone Methylations

PAGE 1003

Histone modifications, such as lysine mono-, di-, and trimethylation, can transmit epigenetic information. Understanding the biochemical functions of these and other histone modifications has been challenging partly because it is difficult to isolate large quantities of homogeneously methylated histones. Using protein chemistry, Simon et al. describe a way to efficiently confer site specificity as well as a specific degree of methylation to any position in a histone. The resulting methyl lysine analogs function similarly to their natural counterparts, thereby providing researchers with a powerful new resource to study these important epigenetic marks.