In This Issue

Cell

XBP1 Bridges ER Stress and Intestinal Inflammation

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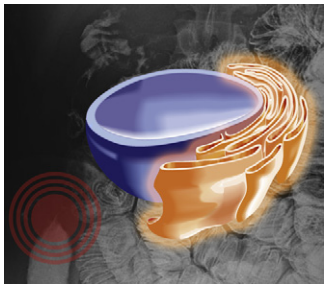

Several genetic risk factors for inflammatory bowel disease (IBD) have been identified. In this issue, Kaser et al. report a mouse model of spontaneous enteritis arising from alterations in a novel genetic risk factor for human IBD. Diminished activity of the endoplasmic reticulum stress response factor, XBP1, in the intestinal epithelium leads to spontaneous enteritis typical of IBD. Consistent with the animal data, genetic analyses of IBD patients revealed rare variants of XBP1 that are associated with the disease.

Breaking the Prion Species Barrier

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Prions are unconventional infectious agents composed exclusively of the misfolded prion protein (PrP^{Sc}), which transmits the disease by propagating its abnormal conformation onto the cellular prion protein (PrP^{C}). A key unexplained characteristic of prions is their "species barrier"—whereby prions from one species can only infect a limited number of other species. Castilla et al. now report the in vitro generation of infectious prions by mixing PrP^{Sc} and PrP^{C} from different species. Characterization of the disease produced in both species indicates that the in vitro-generated material corresponds to a new prion form that does not exist in nature. These results suggest that, like infectivity, species barrier and strain generation are determined by the propagation of PrP misfolding.

Combination Therapy Beats Proteins into Shape

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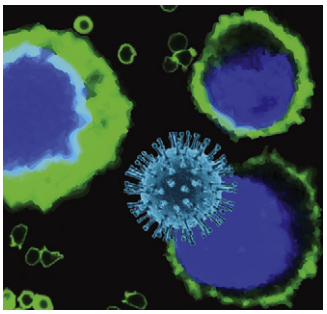
Diseases due to loss of protein function, like lysosomal storage disorders, are often caused by a mutation that compromises the normal balance between protein folding, trafficking, and degradation. Mu et al. now report a strategy to elevate the levels of correctly folded and trafficked proteins associated with these disorders.They show that small molecules can improve cellular protein folding capacity by activating the unfolded protein response and that combining one of these small molecules with a known pharmacologic chaperone causes a synergistic rescue of protein function. This approach holds promise for raising functional protein levels to therapeutically relevant thresholds.

HIV Breaches the Actin Barrier



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Binding of the HIV envelope to the chemokine coreceptors triggers membrane fusion, but whether signalling through these coreceptors is also critical for viral infection has remained elusive. Yoder et al. report that the cortical actin in resting T cells acts as a barrier for viral postentry migration. HIV utilizes viral envelope-CXCR4 signalling to activate a cellular actin depolymerization factor, cofilin, to overcome this restriction. HIV-triggered cofilin activation increases cortical actin dynamics and promotes viral intracellular migration towards the nucleus. Thus, HIV exploits CXCR4 signalling in resting T cells to overcome the infection barrier posed by the actin cytoskeleton.

SNARing a Ride Back to the Golgi

PAGE 817

SNAREs provide the specificity and energy for the fusion of vesicles with their target membrane and need to be recycled after fusion. Now Pryor et al. demonstrate that the clathrin-mediated endocytosis of the post-Golgi SNARE VAMP7 is directly mediated by Hrb, a clathrin adaptor and ArfGAP. Hrb wraps 20 residues of its unstructured C-terminal tail around the folded VAMP7 longin domain, demonstrating that unstructured regions of clathrin adaptors can select cargo. Furthermore, the authors demonstrate that VAMP7 can only be endocytosed when it is part of a SNARE complex. These results elucidate the mechanism of retrieval of a postfusion SNARE protein in clathrin-coated vesicles.

p97 Expands Its Hit List

PAGE 804

p97, an essential component of the ubiquitin-proteasome system (UPS), has been extensively studied for its role in extracting proteins from the endoplasmic reticulum for subsequent degradation by the proteasome. By using "network proteomics" to identify molecules linked to p97, Alexandru et al. identified a large number of ubiquitin ligases implicated in the turnover of soluble, cytosolic regulatory proteins. In particular, turnover of the oxygen sensor HIF1α was linked to p97. These data argue for a far more pervasive role of p97 in the UPS than previously envisioned.

SH2 Links Kinase to Substrate

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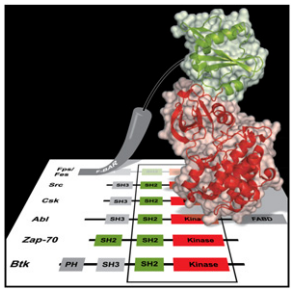


The SH2 domain was originally identified in the Fps/Fes tyrosine kinase and is commonly found in tyrosine kinases, where it enhances activity, substrate recognition, and oncogenicity of the linked catalytic domain. Yet, the exact molecular mechanism by which the SH2 domain can stimulate kinase function is poorly understood. Filippakopoulos et al. now show that the active conformation of Fes requires cooperative interactions between the SH2 and kinase domains and the substrate, so that kinase activation is coupled to substrate recognition. Related findings with Abl kinase indicate an integrated SH2-kinase mechanism essential for effective signaling by these tyrosine kinases.

Actin Branches Dethroned by Coronin

PAGE 828

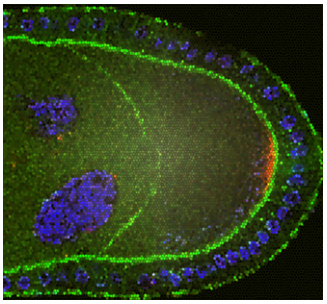
Leading edge protrusion, endocytosis, and intracellular junction formation all require the formation of branched actin networks that are generated by the Arp2/3 complex. Cai et al. present evidence that Coronin 1B can trigger disassembly of Arp2/3 branches in a manner that is antagonistic with Cortactin. Coronin 1B can also replace the Arp2/3 complex at branch junctions and generate a new branched actin network with altered structural properties. While the formation of these networks has been extensively studied, the results now elucidate the remodeling and ultimate recycling of the Arp2/3 branched actin network.

Secreted Scaffold Supports Embryonic Patterning

PAGE 854

The formation of dorsal structures in vertebrate embryos, such as the brain, is surprisingly resistant to perturbations in patterning signals during early development. For instance, embryos can develop almost normally even after partial ablation or deletion of the patterning organizer tissue. Inomata et al. now identify in the Xenopus embryo a dorsally expressed, secreted protein, ONT1, which helps to buffer changes in the organizer activity during dorsal axial formation. ONT1 fine-tunes the organizer activity by acting as a secreted scaffold that enhances protease-mediated degradation of Chordin, another important component of the signalling cascade. These results reveal an unexpected function for a secreted scaffold protein in embryonic patterning.

Subtle Performance by Kinesis Is *oskar* Worthy



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Drosophila anterior-posterior axis formation depends on the localization of *oskar* mRNA to the oocyte posterior, but the mechanism of this localization is controversial. By imaging *oskar* mRNA in living oocytes, Zimyanin et al. show that the mRNA forms particles that move in all directions with a slight excess of posterior movements. Since almost all of these movements are mediated by the plus end-directed microtubule motor, kinesin, they propose that the mRNA localizes by taking a biased random walk along a weakly polarized cytoskeleton. Thus, kinesin-dependent transport can amplify a weak microtubule asymmetry into a robust directional transport.

Complex Cleavage Kills

PAGE 866

The human genome encodes nearly 600 proteases that regulate many complex biological processes, including cell death. Here, Mahrus et al. describe a method for characterizing proteolytic products that allows the N-terminal peptides to be selectively biotinylated. Applying this technology to study apoptosis, the authors identified 292 proteins that are cleaved by caspases, usually at one or two sites. Strikingly, a large number of caspase substrates physically interact, suggesting that caspases target protein complexes and networks to elicit cell death.

Getting Ten Gr*iPS* on Human Diseases

PAGE 877

Immortal tissue culture cell lines from diseased patients are an invaluable resource for medical research but are largely limited to tumor cell lines or transformed derivatives of their native tissues. Park et al. now use the somatic reprogramming technique to generate self-renewing induced pluripotent stem (iPS) cells from patients with ten different serious genetic disorders. This collection of cells provides the scientific community with a powerful resource to recapitulate normal and pathologic human tissue formation in vitro and for potential drug development.