In This Issue

Cell

Neutralizing PlGF Stops Tumor Angiogenesis in Its Tracks

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New strategies are needed to maximize efficacy and minimize resistance in cancer therapies that target tumor angiogenesis. Fischer et al. report the therapeutic potential of an antibody against placental growth factor (αPlGF). Previous studies have shown that PlGF, a homolog of vascular endothelial growth factor (VEGF), regulates pathological angiogenesis but is redundant for vascular development and maintenance. The authors show that αPlGF inhibits tumor growth and metastasis and enhances the efficacy of chemotherapy and inhibitors of VEGF receptors (VEGFRIs). Also, αPlGF treatment does not switch on an angiogenic rescue program that is responsible for resistance to VEGFRIs, nor does it cause or enhance VEGFRI-related side effects. The efficacy and safety of αPlGF suggest that αPlGF may provide a new approach for cancer treatment.

Surface Proteins Go with the Flow

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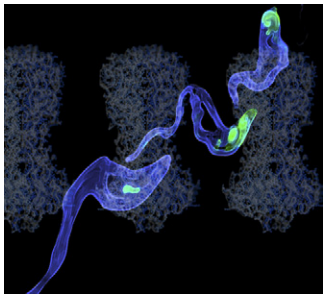


While in the circulatory system of its host, African trypanosomes are under constant attack from the immune system. To protect themselves from complement-mediated lysis, trypanosomes sort antibodies bound to cell-surface glycoproteins to the posterior cell pole, where they are internalized by endocytosis. Pfohl et al. provide evidence that the directional movement of immune complexes to the posterior pole is caused by the hydrodynamic flow force produced by the forward swimming of the cell. Thus, hydrodynamic drag forces can influence the distribution of cell-surface proteins. The authors propose that this type of protein redistribution may occur on other cell surfaces, such as the epithelial cells lining blood vessels.

The Skinny on Mitochondrial Dysfunction

PAGE 476

Recent studies have placed altered mitochondrial oxidative phosphorylation in muscle and liver as an underlying feature of insulin resistance. However, it is unknown whether these changes in mitochondrial function are a cause of insulin resistance or are compensatory. Pospisilik et al. generated several mouse models of primary mitochondrial dysfunction through the tissue-specific deletions of the mitochondrial protein AIF. These efforts revealed that a primary defect in oxidative phosphorylation alone does not cause insulin resistance and diabetes but instead results in increased insulin sensitivity and resistance to diabetes and obesity even when mice are fed a high-fat diet. These findings provide genetic evidence that reductions in oxidative phosphorylation can induce a state of insulin sensitivity and resistance to metabolic disease.

Immune Evasion, Malaria Style

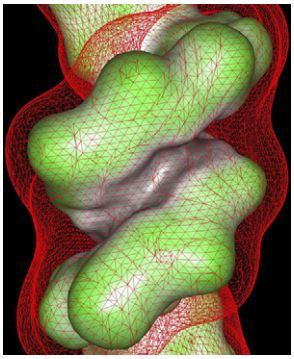
PAGE 492

It has been a longstanding question why liver cells infected by the malaria parasite Plasmodium are not attacked by infiltrating immune cells whereas neighboring noninfected cells are subject to attack. Singh et al. now report that the circumsporozoite (CS) protein, which Plasmodium introduces into the cytoplasm and nucleus of infected hepatocytes, helps the parasite to establish a favorable niche. The CS protein inhibits NF-κB nuclear translocation and causes altered expression of over one thousand host cell genes to alter cell metabolism and dampen the host inflammatory response. These findings provide insight into the mechanism of immune evasion by Plasmodium and have implications for future drug and vaccine development.

A Viral Coat Check at the ER

PAGE 516

The entry of Simian Virus 40 (SV40) into cells involves endocytosis and vesicular transport to the endoplasmic reticulum (ER), followed by escape to the cytosol and nuclear import. Schelhaas et al. show that the ER exposes the virus to a thiol oxidoreductase that initiates uncoating by eliminating disulfide bonds between capsid coat proteins. The virus also exploits the ER-associated degradation machinery, including Derlin-1 and Sel1L, presumably for escape from the ER lumen. These results indicate that SV40 has chosen the ER route of entry so that it can take advantage of the ER protein folding and quality control machinery for initial uncoating and membrane translocation.



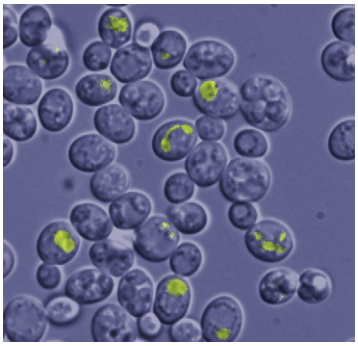
Exd Gets Hox into the Groove

PAGE 530

Homeodomain-containing proteins have low DNA-binding specificities, which contrast with the specific functions these proteins execute in vivo. For the Hox family of transcription factors, the cofactor Exd provides additional specificity, but the biophysical basis for this phenomenon has remained obscure. Joshi et al. now show that Exd allows the Hox protein Scr to make additional DNA contacts, but only with the correct DNA-binding site. In the heterodimer, two Scr residues can insert into a narrow region of the binding site's minor groove. Thus, in addition to base pair-specific contacts in the major groove, homeodomain proteins, and perhaps other families of DNA-binding proteins, use structural features of the DNA for the recognition of their specific binding sites.

Cell-to-Cell Variability in Meiosis? It's About Ime1!

PAGE 544



Cell-to-cell variability in the timing of fate decisions can be advantageous for a population of single-celled organisms growing in a fluctuating environment. How cell-to-cell variability is controlled and factors critical to cell-fate decisions in this context are open questions. Nachman et al. study the variability in the timing of meiosis in *Saccharomyces cerevisiae*, initiated upon nutritional starvation. Surprisingly, they find that cell-cycle variability and nutritional history have little effect on the timing of meiosis. Instead they link the variable timing of meiosis to variability in the rate of production of the meiotic master regulator Ime1 and its gradual increase over time. These results tie phenotypic variability with expression dynamics of a transcriptional regulator.

Unfolded OMPs Lets DegS RIP

PAGE 572

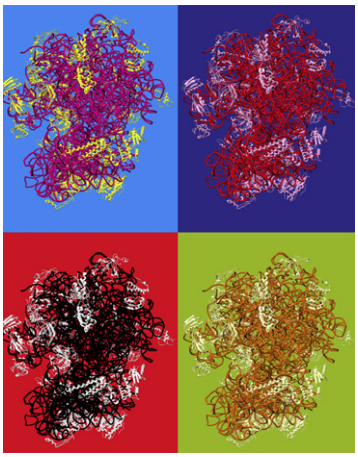
Regulated intramembrane proteolysis (RIP) is a method for transducing signals between cellular compartments. When protein folding is compromised in the *E. coli* periplasm, the C termini of unfolded outer-membrane proteins (OMPs) bind to the PDZ domains of the DegS protease and activate cleavage of RseA, a transmembrane transcriptional regulator. Here Sohn et al. determine the mechanism by which this RIP cascade is initiated and show that DegS is a classical allosteric enzyme. Crystallographic and biochemical experiments show that the unliganded PDZ domains are inhibitory and suggest that OMP binding is sufficient to stabilize the relaxed conformation and activate DegS.

HIF1α ubiquitination: SUMO on, SUMO off

PAGE 584

DeSUMOylation, the removal of SUMO peptides from target proteins, is mediated by a family of Sentrin/SUMO-specific proteases (SENPs). Now Cheng et al. report that deletion of the *SENP1* locus in mouse results in severe fetal anemia stemming from deficient erythropoietin production. The authors find that during hypoxia SUMOylation of hypoxia-inducible factor 1α (HIF1α) promotes its binding to the ubiquitin ligase VHL, leading to HIF1α ubiquitination and degradation. SENP1-mediated deSUMOylation of HIF1 is required for its stabilization. These findings shed new light on the hypoxia-response pathway and suggest that SUMO can serve as a direct signal for ubiquitin-dependent degradation.

The Right Ribosome for the Job



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Ribosomes are commonly thought to be functionally identical; however, Komili et al. now show that the cellular pool of ribosomes is not only heterogeneous, but that this heterogeneity has significant consequences. Through examination of a localized transcript in yeast, the authors find that ribosomal protein paralogs, long thought to be redundant, exhibit specialized activities in regulating translation. Furthermore, these paralogous ribosomal proteins have differential effects on other cellular processes and have unique processing requirements. These findings support the existence of a ribosomal "code" in which ribosomes composed of different combinations of duplicated ribosomal proteins play specialized cellular roles.

Shuttling Chaperone for Calcium Homeostasis

PAGE 596

Communication between the endoplasmic reticulum (ER) and mitochondria is important for bioenergetics and cell survival. The ER supplies calcium directly to the mitochondria via IP3 receptors at regions of close contacts between the two organelles called mitochondrion-associated ER membranes (MAMs). Hayashi and Su find that the sigma-1 receptor (Sig-1R) acts as a calcium-sensitive and ligand-operated chaperone at MAMs. By sensing ER calcium concentrations, Sig-1Rs "chaperone" IP3 receptors to MAMs to ensure proper mitochondrial calcium signaling. However, when ER calcium levels drop to chronic low levels, Sig-1Rs can translocate from MAMs throughout the ER to help attenuate the stress. Sig-1Rs thus regulate ER-mitochondrial interorganellar calcium signaling and cell survival.