In This Issue

Getting to the Heart of Hypoxia through the Skin
PAGE 223
Mammalian skin responds to a wide range of environmental challenges, including temperature and hydration. The skin is also an active site of oxygen diffusion and respiration in many invertebrates and amphibians. Boutin et al. now show that skin acts as an oxygen sensor and effector of hypoxic response in mammals, as well. The authors find that loss of the transcription factor HIF-1α in keratinocytes inhibits systemic release of erythropoietin (EPO), and constitutive overexpression of HIF in epidermis induces high levels of EPO and polycythemia. Sensing of oxygen levels by the skin is independent of respiration and triggers nitric oxide-induced shifts in vascular flow. This study presents an unexpected role for the skin in adaptation to hypoxia.

Stress Takes a Toll on Lungs
PAGE 235
Multiple pathogens and chemical agents trigger acute lung injury (ALI) and result in high lethality. Imai et al. now provide insight into the disease pathways involved by identifying oxidative stress and innate immunity as a common susceptibility pathway that controls the severity of ALI. They show that lung injury induced by infectious or chemical agents in a mouse model is dependent on expression of the Toll-like receptor TLR4. These insults trigger the production of an oxidized phospholipid, which induces cytokine production by lung macrophages via TLR4. This common pathway may explain how diverse infectious agents cause severe and often lethal lung failure.

Inducing Pluripotency in Mature B Cells
PAGE 250
Induced pluripotent stem (iPS) cells can be derived from human and mouse fibroblasts by overexpression of the transcription factors Oct4, Sox2, c-Myc, and Klf4. However, it has remained an unresolved question whether somatic cells that have been reprogrammed so far have represented a pool of cells that were somewhat less differentiated and only therefore amenable to direct reprogramming. By generating a mouse model in which every cell can be reversibly induced to express the four factors, Hanna et al. now show that premature B cells can be reprogrammed with those four factors. The authors show that terminally differentiated B cells can become ES cell like as well; however, reprogramming requires an additional step—the inhibition of the transcription factor Pax5. The results show that also terminally differentiated cells can be manipulated to become pluripotent.

Providing a Gene Structure for VDJ Rearrangement
PAGE 265
The genomic sequences of a wide variety of organisms have been determined; however, how genomic loci are organized within the nucleus is largely unknown. In this issue, Jhunjhunwala et al. have used 3D fluorescence in situ hybridization, computer simulations, and geometry to determine the structure of the IgH locus at different stages during B cell development. The data provide support for a structural alteration, coincident with IgH rearrangement, which moves distal V gene segments into close proximity of D-J. The analysis provides insight into how an enormous diversity in antibodies is generated from a single genetic locus in white blood cells.

Cyclins Take Shifts in Meiosis
PAGE 280
In budding yeast, key events in meiotic progression are controlled by Clb cyclin-dependent kinases (Clb-CDKs). Using a novel method to synchronize meiotic cells, Carlile and Amon observe a surprising diversity in the regulation of Clb-CDKs during meiosis. Clb1-CDK activity is confined to meiosis I; Clb3-CDKs are only active during meiosis II. Confining Clb3-CDKs to meiosis II is accomplished through translational control of the CLB3 transcript and is essential for establishing the meiotic chromosome segregation pattern.

Longer Life Lost in Translation
PAGE 292
Dietary restriction increases life span in nearly all organisms studied. However, the mechanisms that regulate life-span extension by dietary restriction are not well understood. Steffen et al. show that specific reduction of 60S ribosomal subunit levels slows aging in yeast by a mechanism similar to dietary restriction. Full life-span extension by reduction of 60S subunits required Gcn4, a nutrient-responsive transcription factor conserved from yeast to man. Furthermore, Gcn4 is required to achieve the maximum lifespan benefit from dietary restriction or in genetic mimics of dietary restriction, tor1Δ, and sch9Δ. These results suggest that Gcn4 orthologs could regulate aging in higher eukaryotes.
Pioneering Efforts of the EJC in Translation

PAGE 303

Two studies in this issue of Cell address the poorly understood connections between splicing, translation, and nonsense-mediated mRNA decay (NMD). The exon junction complex (EJC) forms on newly spliced mRNA to ensure the accuracy and efficiency of gene expression. In mammalian cells, NMD generally requires that translation terminates sufficiently upstream of an EJC during the first, or pioneer, round of translation, and the study by Isken et al. now elucidates the mechanism by which this translational repression occurs. Binding of the NMD factor Upf1 to the EJC was found to trigger Upf1 phosphorylation, leading to impairment of the translation initiation factor eIF3 function and conversion of a competent pioneer translation initiation complex to a translationally compromised mRNP. In a related study, Ma et al. show that the EJC serves an important function in the assembly of the pioneer initiation complex when cell conditions are supportive of protein synthesis. The authors demonstrate that the S6K1 interactor, SKAR, is a component of the EJC, and that the EJC couples the mTOR/S6K1 signaling network to productive pioneer translation initiation.

Pseudokinase Sheds Its Prefix

PAGE 328

Mg\(^{2+}\) serves as an essential cofactor for all known kinases. The CaM-kinase domain of the CASK protein is presumed inactive—referred to as a pseudokinase—because of alterations in the canonical Mg\(^{2+}\)-binding motif. Now Mukherjee et al. demonstrate that the CASK CaM-kinase domain is an active kinase even in the absence of Mg\(^{2+}\) binding. CASK is recruited to neurexin-1 via its PDZ domain and phosphorylates neurexin-1 in a neuronal activity-regulated manner. This links CASK to synaptic cell adhesion, and possibly to autism in view of the involvement of neurexins in autism spectrum disorders. These results suggest that other pseudokinases, which comprise about 10% of the kinome, could also be catalytically active.

Illuminating Fly Courtship Circuitry

PAGE 354

The fruitless gene is a key determinant of sexual behavior in Drosophila, but how it regulates neural circuits in a sex-specific manner is not well understood. Clyne and Miesenböck use light-activated ion channels to stimulate the male and female versions of a sex-specific circuit, the pattern generator of the male courtship song, and search for functional differences. The artificial activation of the circuit reveals sex-specific neural control at multiple levels. Females possess a song-like motor program that remains latent under physiological conditions, presumably because the commands required to activate it are missing. And although female songs can be evoked, the pattern generator is too far off key to produce effective mating signals.

Feeding JNK to the Wnt Pathway

PAGE 340

Canonical Wnt signaling regulates cell fate and proliferation in development and disease. The Wnt signal activates the transcription factor β-catenin and caused its nuclear localization. Wu et al. now show that the nuclear localization of β-catenin is a regulated step in Wnt signaling and requires activation of the GTPase Rac1 and subsequent phosphorylation of β-catenin by JNK. Deletion of Rac1 in the mouse limb bud disrupted Wnt signaling and caused severe truncation of the limb, phenocopying β-catenin deletion. The authors propose a signaling cascade in which wnt activated Rac1 activates JNK, which phosphorylates β-catenin and induces its nuclear import. These essential steps in Wnt signaling might provide additional target sites for therapeutic interventions of this important pathway.

Three-Dimensional Atlas of Fly Embryonic Gene Expression

PAGE 364

Developing animals comprise complex, dynamic arrangements of cells that each express unique combinations of thousands of genes. It is currently a significant challenge to evaluate gene expression patterns from cell to cell within organisms, as it demands accurate quantitative measurements of both changing morphology and changing levels of proteins and mRNAs. Tackling Drosophila embryogenesis, Fowlkes et al. describe computational methods for combining image data from hundreds of embryos at different stages in development to construct a three-dimensional gene expression atlas. The resulting model embryo led to predictions of regulators for 95 genes whose expression is spatially patterned. This mapping approach has broad potential for examining regulated gene-expression patterns in a variety of organisms.