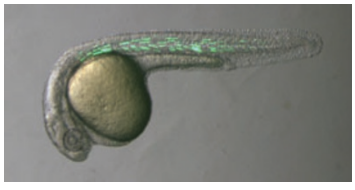
A CLICK OF THE RSK

Because of the functional redundancy built into the MEK-ERK signal transduction pathway, it has been difficult to develop specific inhibitors for individual kinases in this cascade. Cohen *et al.* have now done just that for the p90 ribosomal S6 kinases RSK1 and RSK2. These kinases are activated by ERK through phosphorylation of the RSK C-terminal kinase domain (CTD), which then phosphorylates and activates the N-terminal kinase domain (NTD). Their specific inhibitor, fmk-pa, works through covalent modification of the RSK CTD, which also allows it to be visualized using a bioorthogonal fluorescent reporter attached by "click" chemistry. Using this potent and irreversible inhibitor, the authors found that p90 RSKs and p70 S6 kinases both contribute to ribosomal protein S6 phosphorylation in cells. In addition, they found evidence for an unidentified kinase that bypasses RSK CTD activity. [**Letters, p. 156; News & Views, p. 138**] *MB*

Small activating RNAs

Genetically encoded RNA molecules, such as small interfering RNA (siRNA) and microRNA (miRNA), are known to regulate gene expression by binding to complementary RNA sequences in target mRNAs. In addition, synthetic RNA and other oligonucleotide analogs are now widely used to induce silencing of target genes within cells. Until recently, small RNAs were thought to mediate only downregulation of gene expression. Now Janowski *et al.* report that certain synthetic duplex RNAs targeted to the promoter region of the progesterone receptor gene activate, rather than suppress, gene expression in human cells. The reported 'RNA activation' is associated with changes in chromatin remodeling and suggests that small RNAs may adopt a greater diversity of regulatory roles than previously imagined. [**Articles, p. 166; News & Views, p. 136**] *TLS*

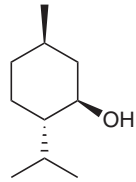
Small-molecule zebrafish switch



Zebrafish has become an increasingly popular model organism because it is easily manipulated genetically and its optical transparency permits *in vivo* imaging. However, the zebrafish model has lacked a robust system for temporal control of gene expression. Esengil *et al.* have now developed a small molecule–inducible system for conditional regulation of zebrafish gene expression. When a modified version of the insect-specific ecdysone receptor was fused to a gene of interest, ecdysone receptor agonists rapidly induced gene expression. By combining this system with tissue-specific promoters, the localization of gene expression could also be controlled. The ability to temporally and spatially regulate gene expression will further increase the usefulness of zebrafish in biomedical research. [**Brief Communications, p. 154; News & Views, p. 135**] *JK*

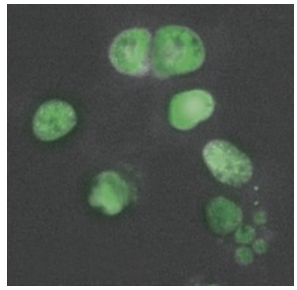
In This Issue written by Mirella Bucci, Catherine Goodman, Joanne Kotz and Terry L. Sheppard

Cold and menthol add up



Voltage-gated potassium channels sense voltage through the movement of a cluster of positively charged residues relative to the transmembrane electrical field, which results in opening or closing of the pore. For voltage-gated transient receptor potential (TRP) channels, which are regulated by both temperature and chemical ligands, it is not clear how thermal and chemical stimuli are integrated or how voltage is sensed. Through mutagenesis of the cold- and menthol-sensing TRPM8 channel, Voets *et al.* identified specific positively charged residues that form part of the voltage sensor. Mutations in these voltage-sensing residues also altered the channel's sensitivity to temperature and its affinity for menthol, which suggests spatial and functional coupling of the three inputs. Based on these data, the authors present a quantitative model describing the combined effects of temperature, ligand and voltage on TRPM8 gating. [**Articles, p. 174**] *JK*

Vitamin B6 gets a gRIP



Pyridoxal 5′-phosphate (PLP), which is metabolically derived from vitamin B6, is an important enzymatic cofactor and also interacts with receptors and transcription factors via an unknown mechanism. Now Huq *et al.* provide insight into this mechanism by demonstrating the covalent attachment of PLP to RIP140, a nuclear corepressor. RIP140 operates by recruiting histone deacetylases (HDACs) to transcription complexes. In support of a biological role for PLP modification, this attachment significantly enhanced the interaction of RIP140 with HDAC3. This study further provides a mechanistic basis for the observed effect of vitamin B6 in facilitating fat accumulation, as RIP140 knockdowns had decreased triglyceride accumulation in 3T3 cells. Surprisingly, PLP attachment occurs at only one of 88 residues on RIP140, which suggests that the modification may be controlled by external factors. [Letters, p. 161] *CG*

A sensitive hydroxylation

Post-translational modifications, which modulate the structure and function of proteins, are installed by modifying enzymes specific for each chemical transformation and substrate class. Though phosphorylation and glycosylation may be the most familiar classes of post-translational modification, protein hydroxylation is now recognized as an important element in cellular sensors and regulatory pathways. In a Review article, Ozer and Bruick discuss our current knowledge of iron(II)- and 2-oxoglutarate–dependent dioxygenases, a class of enzymes that hydroxylate diverse amino acid side chains. In addition to examining the structures and mechanisms of these proteins, the authors highlight their important cellular roles, which include sensing cellular oxygen levels and reversing histone methylation. [**Review, p. 144**] *TLS*