Breaking barriers

Mice that lack Notch signaling in the skin die at early postnatal stages, although the precise reasons have been unclear. Shadmehr Demehri and colleagues now show that loss of signaling downstream of Notch results in defective barrier formation, which in turn promotes a systemic, cytokine-induced B-lymphoproliferative disorder (B-LPD) (*PLoS Biol.* 6, e123; 2008). The authors show that lethally irradiated mutant mice transplanted with bone marrow derived from wild-type littermates live longer than untransplanted mice, suggesting that the extremely high white blood counts in the mutant mice were at least in part responsible for the early postnatal lethality. Microarray analysis of postnatal skin samples revealed upregulation of thymic stromal lymphopoietin (TSLP), a cytokine produced by keratinocytes. Injection of recombinant TSLP into wild-type mice was sufficient to cause B-LPD during the first weeks of life. Additional evidence supports a model in which loss of Notch signaling in keratinocytes results in aberrant differentiation and a subsequent skin barrier defect characterized by incomplete formation of upper spinous and granular layers. The barrier defect then triggers release of TSLP into systemic circulation. Demehri *et al.* suggest that local skin perturbations may influence the course of a range of inflammatory disease in humans. ***AP***

Space for resistance

One recently identified bacterial mechanism for viral resistance involves genetic spacers within clustered regularly interspaced short palindromic repeats (CRISPR). These CRISPR spacers show sequence identity to viral genomes and have been shown to confer sequence-specific viral resistance. Jillian Banfield and colleagues now take a metagenomics approach to explore the connection between CRISPR loci and viral resistance within a natural microbial community (*Science* **320**, 1047–1049; 2008). The authors drew samples from two biofilms from mines in Redding, California, recovering about 100 Mb of genomic sequence from each. They identified 37 different CRISPR repeat sequences, a subset of which mapped to loci in Leptospirillum groups II and III, as well as I-plasma, E-plasma, G-plasma and A-plasma. They then showed that spacer-containing non-CRISPR (SNC) reads were enriched in BLAST matches to viral proteins or genes encoding proteins with viral functions, again suggesting their viral origin. The SNC contigs were assembled to larger fragments representing partial or complete viral genomes. They found that most microbial cells contained different sets of CRISPR spacers, with only a few shared globally, although most cells contained loci targeting several of these viral populations. Some of the constructed viral genomes showed high diversity and recombination rates, which may assist in escaping CRISPR-mediated resistance. *OB*

SMN and tissue-specific splicing

Mutations in the gene encoding the survival of motor neurons protein (SMN) cause spinal muscular atrophy, a motor neuron degenerative disease. SMN is part of a complex of proteins that assemble small nuclear ribonucleoprotein particles, which, along with small nuclear RNAs (snRNAs), are part of the spliceosome. Now, Gideon Dreyfuss and colleagues report that SMN deficiency in mice results in cell type–specific alterations in levels of snRNAs and widespread defects in mRNA splicing (*Cell* **133**, 585–600; 2008). The authors identified tissue-specific alterations in specific snRNAs in both affected and unaffected tissues, with detection of both decreased and increased levels of particular snRNAs. They also used exon arrays to profile transcriptome splicing in SMN-deficient mice, which revealed widespread splicing changes affecting hundreds of mRNAs in both affected and unaffected tissues. Like the changes in snRNAs, different splicing changes occurred in different tissues. Many of the splicing changes detected were predicted to create aberrantly spliced isoforms, such as isoforms that contain a premature termination codon. Although the mechanistic basis of these tissue-specific alterations is unknown, this study reveals a role for SMN in regulation of splicing and suggests new possibilities for the pathogenesis of motor neuron degeneration. *EN*

Written by Orli Bahcall, Emily Niemitz, Alan Packer & Kyle Vogan

Translational inhibition by plant miRNAs

Translational inhibition is a common mode of miRNA action in animals; however, it has been widely assumed that most plant miRNAs mediate repression by promoting degradation (slicing) of their target mRNAs rather than by blocking their translation. Now, a new study by Olivier Voinnet and colleagues (*Science* **320**, 1185–1190; 2008) challenges this notion by showing that translational inhibition, in addition to slicing, is necessary for effective miRNA- and siRNA-directed silencing in plants. As a starting point, the authors carried out a genetic screen in *Arabidopsis* to identify mutants defective in miRNA-mediated silencing. In addition to finding several mutants defective in miRNA biogenesis or miRNA-directed slicing, they identified two mutants in which neither process was altered, but where silencing of protein expression was impaired for a number of miRNA–mRNA target pairs. From this work, they conclude that translational repression is a widespread mode of miRNA action in plants which acts in parallel with miRNA-directed slicing to promote silencing. One of the mutants, *mad5*, carries a mutation in a subunit of the microtubule-severing enzyme katanin, suggesting a key role for microtubule dynamics in miRNA-mediated translational inhibition. *KV*

Small RNAs and X inactivation

In female mammals, dosage compensation is achieved by inactivation of one X chromosome (XCI), which is characterized by the expression of *Xist* RNA from the inactive X (Xi) and antisense *Tsix* RNA from the active X (Xa). Now Jeannie Lee and colleagues report that *Xist*-*Tsix* duplexes and small RNAs processed from these duplexes have a role in XCI (*Science* 320, 1336–1341; 2008). The authors identified small RNAs, named xiRNAs, which originate from within the *Xist*–*Tsix* gene. These RNAs were detected during the process of XCI in differentiating mouse ES cells. The authors used Dicer-deficient ES cells to investigate the role of RNA interference in XCI. These experiments showed that Dicer regulates xiRNA levels and represses *Xist* expression. Further, *Xist* did not properly coat the Xi and formation of H3K27me3 domains on the Xi was compromised in the absence of Dicer, indicating a global role for RNA interference in XCI. In addition to identifying an intersection between the X inactivation and RNA interference pathways, the authors propose an interesting hypothesis that *Xist*-*Tsix* duplexes on Xa give rise to xiRNAs, which repress *Xist* in *cis*. But in the end, the mechanisms of the contributions of RNA interference to XCI await further investigation. ***EN***