Lives in the balance

Interbreeding depends on genetic compatibility, with selection expected to weed out any incompatibilities from such populations. Hannah Seidel and colleagues report an unusual example of widespread incompatibility in *Caenorhabditis elegans* that seems to be maintained by balancing selection (*Science*, advance online publication 10 January 2008; doi:10.1126/science.1151107). The authors generated recombinant inbred lines from an intercross of the standard laboratory strain from Bristol, England (N2), and a strain from Hawaii. Among the F_2 progeny produced by self-fertilizing F_1 hermaphrodites, approximately 25% arrested as embryos. The incompatibility was found to be the consequence of a paternal effect-by-zygotic interaction, where embryos homozygous for the Hawaii allele of the zygotically acting locus fail to hatch when the sperm parent is a Hawaii × Bristol heterozygote. The tightly linked alleles underlying the incompatibility were found in many different populations. Seidel *et al.* determined that the gene responsible for the zygotically acting locus encodes a probable subunit of the CUL-2-based E3 ubiquitin ligase complex. Finally, the authors found dramatically elevated sequence divergence between the Bristol and Hawaii haplotypes and an excess of intermediate frequency alleles, consistent with maintenance by balancing selection. They propose that the genetic incompatibility is an incidental side effect of this balancing selection, whose cause is unknown. ***AP***

Secrets of the exosome

The exosome functions in RNA degradation and processing in both the nucleus and the cytoplasm; for example, it has roles in nonsense-mediated mRNA decay and degradation of mRNA fragments cleaved by RISC. Now Joseph Ecker and Dmitry Belostotsky report high-resolution genome-wide mapping of exosome substrates in *Arabidopsis* (*Cell* **131**, 1340–1353; 2007). The authors implemented an estradiol-inducible RNAi strategy: growth of transgenic plants on estradiol-containing medium allowed for conditional knockdown of RRP4 and RRP41, core subunits of the exosome. Whole-genome tiling array analysis of polyadenylated RNA from estradiol-treated plants and controls revealed upregulation of many classes of RNAs, including previously uncharacterized noncoding RNAs and previously undetected transcripts that map to 5′ ends of known mRNAs. The newly identified noncoding RNAs originate preferentially from centromeric and pericentromeric regions, suggesting that the exosome may have a role in regulating heterochromatin-associated RNAs. The authors named the class of newly identified transcripts that map to 5′ ends of known mRNAs "upstream noncoding transcripts" (UNTs) and suggested that they may be similar to human promoter-associated short noncoding RNAs (PASRs) detected by Kapranov *et al.* (*Science* **316**, 484–488; 2007). These analyses have revealed previously invisible transcripts that may yet be shown to have regulatory functions. *EN*

Targeting the HIV host

Although much of current HIV treatment efforts involve targeting viral enzymes, typically in combination, the alternative approach of targeting human host cell proteins required for the viral lifecycle has also been considered. Stephen Elledge and colleagues now report a genome-wide siRNA screen targeting human proteins required for HIV-1 infection, facilitating the identification of host factors that may be possible targets (*Science*, advance online publication 10 January 2008; doi: 10.1126/science.1152725). Previously, Deborah Nguyen and colleagues took a similar, although smaller-scale approach (*J. Virology* **80**, 130–137; 2006); they used a siRNA library targeting 5,000 genes and identified Pak3 as a host factor associated with HIV-1 infection. Elledge now reports a siRNA screen with a library of 21,121 siRNA pools transfected into HeLa cells, identifying 273 genes required for early or late stages of HIV-1 infection. These HIV dependency factors (HDFs), 36 of which were previously associated with HIV pathogenesis, show a wide distribution of Gene Ontology classifications. The authors found enriched expression of about one-third of the identified HDFs in immune cells. Additionally, they followed up on several HDFs with specific siRNA targeting in HeLa and Jurkat cell lines, and showed that two Golgi trafficking proteins, Rab6 and Vps53, have a role in viral fusion. *OB*

Riboswitches in *Arabidopsis*

Metabolite-sensing riboswitches are elements controlling gene expression typically found in the noncoding portions of mRNAs. Most known riboswitches are found in the 5′ UTRs of bacterial mRNAs or in introns of 5′ UTRs or coding regions of fungi. Andreas Wachter and colleagues now report the identification of thiamin pyrophosphate (TPP) riboswitches in the 3′ untranslated region of the thiamin biosynthetic gene (*THIC*) in a variety of plant species (*Plant Cell* **19**, 3437–3450; 2007). The authors show that the *THIC* TPP riboswitch in *Arabidopsis thaliana* controls the formation of transcripts with alternative 3′-UTR lengths. In turn, these variable 3′ UTRs affect transcript accumulation and protein production. For example, *A. thaliana* seedlings supplemented with thiamin show reduced transcription of *THIC*. Their data suggest a model whereby low levels of TPP allow for riboswitch interaction with the 5′ splice site in *THIC*, preventing splicing. The retained intron permits transcript cleavage and polyadenylation, resulting in transcripts with short 3′ UTRs and high expression of *THIC*. Overall, the study highlights the diversity of mechanisms through which riboswitches regulate gene expression, and suggests that riboswitches may be found in 3′ UTRs in other eukaryotes. *AP*

Genetics of itchy skin

Pruritus, or itchy skin, is a common dermatological condition which often manifests in the context of other clinical disorders. In rare instances, a pruritic condition known as primary localized cutaneous amyloidosis (PLCA) segregates in families as a dominant trait. John McGrath and colleagues (*Am. J. Hum. Genet.* 82, 73–80; 2008) now report mutations in the gene encoding the oncostatin M-specific receptor β (*OSMR*) in three families with PLCA. Following up on earlier work reporting linkage of PLCA to 5p13.1–q11.2 in a Taiwanese family, the authors confirmed linkage to this same region in a large Brazilian family. They then selected four genes encoding members of the IL-6 family of cytokine receptors as the most likely candidates in the region on the basis of prior work in mice implicating this pathway in skin inflammation. Sequencing of *OSMR* in the Brazilian family and two families from the United Kingdom and South Africa revealed missense mutations segregating with the disease phenotype in the three families. Consistent with the genetic findings, cultured keratinocytes from affected individuals showed defective responses following stimulation with oncostatin M or IL-31. These findings implicate OSMRβ as an important regulator of itching. ***KV***

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