Heterochronic control of aging in worms

In *Caenorhabditis elegans*, the microRNA (miRNA) *lin-4* and its regulatory target *lin-14* are heterochronic genes that regulate the timing of larval transitions during development. Michelle Boehm and Frank Slack (*Science* 310, 1954–1957; 2005) now show that the same two genes function in adult worms to regulate life span and aging. The authors found that worms with loss of *lin-4* or gain of *lin-14* function had shortened life spans, whereas worms overexpressing *lin-4* or lacking *lin-14* function had extended life spans. The mutants also showed reciprocal changes in sensitivity to heat shock and accumulation of intestinal autofluorescence, two well-studied markers of aging in worms. Notably, interfering with adult *lin-14* function recapitulated the extended life span phenotype and partially rescued the shortened life span of *lin-4* mutants. The authors further showed that *lin-4* and *lin-14* interacted genetically with components of the *daf-2/daf-16* insulin-like signaling pathway, which has a conserved role in regulating life span across multiple species. The results suggest that heterochronic genes such as *lin-4* and *lin-14* may influence organismal aging in a manner analogous to their roles in regulating the timing of key transitions during larval development. ***KV***

Viral beacon

Gang Bao and colleagues present a new method for real-time *in vivo* characterization of RNA viruses (*J. Virol.* **80**, 682–688; 2006). The method is based on molecular beacons, double-labeled oligonucleotide probes designed to fluoresce only upon hybridization that have previously been used for detection of genes and viruses *in vivo*. Here, the authors show that the course of bovine respiratory syncytial virus (bRSV) infection in living cells can be monitored effectively using this system, with high specificity and sensitivity. Molecular beacons were designed to target several repeat sequences within the bRSV genome. The progression of viral infection was followed in live cells over the course of 7 days post-infection, and the spread of infection was quantified. By counting the number of infected and uninfected cells as well as their growth rate, the authors were able to compare the observed *in vivo* viral dynamics to previous simulation models. They found that the model predicted dynamics well, up to 7 days post-infection. Such methods provide much-needed tools for rapid detection of viruses, examination of the dynamics of infection and possibly for monitoring the direct effect of drugs in live cells at a single-cell resolution. *OB*

Toward a catalog of human promoters

Sara Cooper and colleagues have reported a comprehensive analysis of promoters in 1% of the human genome, part of the ENCODE (Encyclopedia of DNA Elements) project's effort to carry out a deep annotation of all functional elements in a 30-Mb region (*Genome Res.* **16**, 1–10; 2006). Cooper *et al.* cloned 642 putative promoters, 60% of which had activity in at least 1 of 16 cell types and a number of which lie upstream of transcripts of unknown function. Positive promoter elements were typically found in the –350 to –40 bp region, whereas negative regulatory sequences were found further upstream. Interestingly, the authors found that 28% of the variation in steady-state mRNA levels could be attributed to differences in promoter activity, suggesting that the expression of at least some genes is regulated in large part not by upstream enhancers, but by promoter sequences themselves. Finally, the authors found a widespread use of alternative promoters, suggesting an important contribution of this mechanism to generating a diverse human transcriptome and proteome. This is the first quantitative estimate of promoter contribution to gene regulation and should be followed by targeted mutagenesis and other genetic approaches to mapping the determinants of gene expression. *AP*

Medical sequencing of a complex trait

Although many mendelian syndromes involve a cleft lip and/or cleft palate, nonsyndromic cleft lip is a complex trait, probably influenced by both genetic and environmental risk factors. Jeffrey Murray and colleagues have investigated the genetic contribution to nonsyndromic cleft lip with or without cleft palate by sequencing 20 candidate genes (*PLoS Genetics* **1**, e64; 2005). Sequencing over 77 kb in total in each of 184 cases selected for severity of phenotype or family history, they identified 16 rare missense mutations in nine genes. Although none of the variants were found in 186 matched controls, testing of a larger, diverse control set revealed that four of the variants could be identified in controls. Establishing causality for the remaining mutations proved difficult because of a lack of evidence for segregation. Testing common variants and haplotypes of the candidate genes for association in 500 family triads revealed only borderline associations. In the end, the authors concluded that rare mutations in six of their candidate genes, *FOXE1*, *GLI2*, *MSX2*, *SKI*, *SATB2* and *SPRY2*, could contribute to 5% of cases of nonsyndromic cleft lip. This study illustrates the difficulties in determining causality of rare mutations identified by the medical sequencing approach. *EN*

Innervating the gut

The migration of neural crest cells that populate and innervate the gut is of great interest for basic research and also has clear medical relevance, as failure of this migration results in aganglionosis and intestinal obstruction (as in Hirschsprung disease, for example). Jacy Pietsch and colleagues report the positional cloning of a gene that is newly implicated in the development of the enteric nervous system (*Development* 133, 395–406; 2006). After screening ENU-mutagenized zebrafish for recessive mutations that affect enteric neurons, they identified one mutant allele associated with a 66% reduction in the number of such neurons 96 hours post-fertilization. The lack of enteric neurons is accompanied by defects in development of the pharyngeal cartilages. Positional cloning identified a single-nucleotide change resulting in a premature stop codon in *trap100*. In mice, mutant Trap100 affects the placenta and results in embryonic lethality. In zebrafish, Pietsch *et al.* show that it is required in the endoderm for proliferation of enteric neuronal precursors. Trap100 is part of the mediator complex that coactivates transcription, and the authors suggest that its relevant function in zebrafish may be in promoting transcription downstream of the thyroid or vitamin D receptors. ***AP***

Research Highlights written by Orli Bahcall, Emily Niemitz, Alan Packer and Kyle Vogan.