Males in overdrive

Although evolutionary biologists explain the evolution of reproductive isolation as a side effect of adaptation to the ecological environment, Nitin Phadnis and H. Allen Orr now report findings to support the idea that genetic conflict, a form of adaptation to the internal genomic environment, may be an important force in the evolution of postzygotic isolation (*Science* advance online publication 11 December 2008; doi:10.1126/science.1163934). The authors examined two allopatric subspecies of fruit flies to determine whether genes responsible for segregation distortion may cause hybrid sterility. Crosses between subspecies produce hybrid males that are nearly completely sterile, and when these hybrid males age, they become weakly fertile and produce progeny that are almost all female. Genetic dissection of the X-chromosome region identified as having an essential role in both hybrid male sterility and hybrid segregation distortion revealed five predicted genes. One gene, *Overdrive*, which seems to have evolved rapidly, encodes a polypeptide that harbors a DNA-binding motif, is expressed in both pure subspecies and hybrid sterile male testes, and harbors eight nonsynonymous mutations, of which seven are fixed. Transgenic experiments showed that *Overdrive* is a newly identified distorter gene and as a result of single-nucleotide substitutions, affects hybrid sterility in evolutionary young taxa. *LK*

Regulatory micromanagers

The wide range of shapes and sizes of cartilage and bone, both within a species and between species, has led to the hypothesis that there must be specific genomic mechanisms directing variation in growth patterns. Catherine Guenther, Luiz Pantalena-Filho and David Kingsley now report a detailed analysis of *Bmp5* enhancers in transgenic mouse reporter assays, showing a notable degree of specificity and modularity in the regulatory elements that drive *Bmp5* expression in cartilage and bone (*PLoS Genet.* **4**, e1000308; 2008). Guenther *et al.* show that different *Bmp5* enhancers control expression both in individual bones and in restricted subdomains along the surface of individual skeletal structures, such as ribs and nasal cartilages. These regulatory elements are located in both the 5′ and 3′ flanking sequences, as well as in the coding region. Targeted mutations in some of the anatomy-specific sequences result in changes in skeletal morphology and disrupt normal growth rates on separate bone surfaces. The authors suggest that gain and loss of these discrete *cis*-acting sequences during evolution could provide a simple mechanism for changes in skeletal structures, and would preserve organismal fitness despite the known pleiotropic effects of *Bmp*-null mutations. *AP*

Pac Bio sequencing

Pacific Biosciences unveiled its real-time single-molecule DNA sequencing technology one year ago, to much excitement, and now report a proof-of-principle demonstration (*Science* **323**, 133–138; 2009). Testing on a linear 150-base template, and starting with only 15 molecules, they report sequencing at 15× coverage with median accuracy of 99.3%. They also report sequencing of a circular, single-stranded 72-base template (with a 2-base signature sequence pattern), and show the technology's capability for continuous sequencing of over 4,000 bases. The technology is distinctly different from other sequencers, as it involves the harnessing of individual Φ29 DNA polymerase enzymes and uses these to incorporate labeled nucleotides, which are detected by a zero-mode waveguide able to sense single fluorophores. One key benefit of this technology is an expected read length beyond that of sequencers currently on the market, which will reduce downstream assembly time and costs. The approach also allows observation of DNA polymerization in real time, allowing studies on kinetics of this reaction. Although the accuracy of sequencing was high, the most common type of error was found in deletions. The authors consider the accuracy of the current model appropriate for resequencing, but less so for *de novo* assembly or highly repetitive DNA sequences. *OB*

Congenital neutropenia syndrome

Severe congenital neutropenia describes a heterogeneous group of diseases marked by low neutrophil counts and susceptibility to life-threatening bacterial infections. Christoph Klein and colleagues (*N. Engl. J. Med.* **360**, 32–43; 2009) now report the clinical and molecular characterization of a severe congenital neutropenia syndrome caused by biallelic mutations in *G6PC3*, which encodes a catalytic subunit of the glycolytic enzyme glucose-6-phosphatase. By carrying out genome-wide linkage analysis on two consanguineous Aramean families from Turkey, the authors mapped a locus for severe congenital neutropenia to 17q21. Sequencing of candidate genes in the interval revealed a homozygous missense mutation in *G6PC3* in all affected family members. In functional assays, the altered protein was devoid of phosphatase activity. To extend these findings, they sequenced *G6PC3* in 104 additional individuals with genetically uncharacterized severe congenital neutropenia and identified seven with biallelic *G6PC3* mutations, including four with nonsense or frameshift mutations. Clinical features in individuals with G6PC3 deficiency included high incidences of cardiac and urogenital malformations and venous anomalies. Neutrophils and skin fibroblasts from these individuals were also found to be more susceptible to apoptosis, providing a possible cellular explanation for the severe neutropenia and associated phenotypes. *KV*

Tying telomerase

Sequence-specific telomeric DNA-binding proteins form a dynamic structure essential for telomere silencing, protection and length regulation. However, how cells coordinate cell-cycle progression and the recruitment of the telomerase complex to telomeres has been an open question. Shang Li and colleagues now show in yeast that upon specific phosphorylation by Cdk1, the major regulator of telomere access, Cdc13, can coordinate the binding of two opposing regulatory complexes critical to telomere elongation during late S and G2 phases of the cell cycle (*Cell* 136, 50–61; 2009). The authors identified the key residue of Cdc13 as substrate for Cdk1 and showed that inactivation of this residue resulted in less telomerase recruitment and compromised telomere elongation. They further showed that the negative regulatory complex of telomere elongation specifically competes for available Cdc13 to inhibit telomerase and shorten telomeres. Conversely, during cell-cycle progression into late S phase, when telomere elongation is necessary, they found that Cdc13 is phosphorylated by Cdk1 and that the positive regulatory complex binds preferentially, facilitating telomerase recruitment and lengthening telomeres. This work identifies the first Cdk1 substrate critical to regulate telomere elongation. However, whether similar regulatory mechanisms modulate telomerase action in human cells awaits further investigation. *LK*

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