Parallel origins of pelvic reduction

Isolated, polar freshwater populations of threespine stickleback fish commonly show reduction or loss of the pelvic girdle, in contrast to all saltwater and most freshwater populations, in which the pelvic region develops normally. Mapping studies have shown that this derived trait results from *cis*-regulatory changes in *Pitx1* and concomitant loss of *Pitx1* expression from the prospective pelvic region. David Kingsley and colleagues (*Proc. Natl. Acad. Sci. USA* 103, 13753–13758; 2006) now show that parallel evolutionary changes may underlie similar pelvic reduction phenotypes in other vertebrate lineages. Taking advantage of the fact that threespine and ninespine sticklebacks can produce viable hybrid offspring, the authors analyzed the pelvic phenotypes in the progeny of such crosses and found evidence of non-complementation, suggesting that the same genes are responsible for pelvic reduction in the two genera. Ninespine stickleback populations with pelvic reduction show selective loss of *Pitx1* expression from the pelvic region and characteristic left-right asymmetries commonly found in other models of *Pitx1* loss, including threespine sticklebacks and *Pitx1* knockout mice. The authors also report similar hindlimb asymmetries in a natural population of Florida manatees, suggesting parallel origins for pelvic reduction across distinct vertebrate classes. ***KV***

Sirtuins and insulin secretion

Sirtuins are homologs of the yeast Sir2 protein, which is known primarily for its histone deacetylase activity and regulation of lifespan. There are many sirtuins in mammals, and they have been implicated in diverse cellular processes in addition to histone deacetylation. Now Lenny Guarente and colleagues report a role for the mammalian SIRT4 enzyme in regulating insulin secretion in pancreatic β cells (*Cell* **126**, 941–954; 2006). They determined that SIRT4 acts as a mitochondrial ADP ribosyltransferase that inhibits glutamate dehydrogenase (GDH), a mitochondrial enzyme involved in controlling insulin secretion. Knockdown of *SIRT4* in cultured β cells leads to increased amino acid (AA)-stimulated insulin secretion that is GDH-dependent. After this biochemical characterization, the authors tested the *in vivo* function of SIRT4 by generating *SIRT4* knockout mice. These mice were hyperinsulinemic in response to AA stimulation, confirming that SIRT4 is a negative regulator of insulin secretion. To determine if SIRT4, like other sirtuins, has a role in physiological responses to caloric restriction, the authors showed that caloric restriction causes β cells to secrete insulin in response to AA stimulation. This is accompanied by increased GDH levels, similar to the phenotype of SIRT4 knockout β cells. Thus the authors hypothesize that SIRT4 activity is downregulated during calorie restriction. This work cements the important role of sirtuins in nutrient sensing. *EN*

Cancer mutation spectrum revealed

Bert Vogelstein, Kenneth Kinzler, Victor Velculescu and colleagues (*Science*, published online 7 September 2006; doi:10.1126/science.1133427) report the most comprehensive survey to date of somatic mutations in cancer. The authors sequenced the coding regions and consensus splice sites of more than 11,000 genes in 11 breast and 11 colorectal cancers and catalogued the spectrum of sequence alterations present in each sample. Starting with an initial list of more than 800,000 sequence changes, the authors applied a series of filters to eliminate synonymous base changes, germline polymorphisms and experimental artifacts, arriving at a curated list of 1,307 candidate somatic mutations in 1,149 genes. These 1,149 genes were further sequenced in an additional 24 breast or colorectal cancers, resulting in the identification of an additional 365 somatic mutations in 236 genes. The authors then applied statistical criteria to distinguish passenger mutations from those likely to have a causal role in tumorigenesis, yielding a final list of 191 candidate cancer-associated genes. This list includes a large subset of genes previously implicated in cancer as well as several genes not previously suspected of having roles in neoplasia, revealing the value of unbiased approaches to mutation screening in cancer. *KV*

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

Genetics and global warming

Detection of change in the genetic composition of species and observation of climate change both require data sampled over long periods of time. Now Joan Balanyá and colleagues have used historical data of chromosomal inversions in wild populations of *Drosophila subobscura* on three continents, along with historical climate data from the site of sample collection, to show that genetic changes in these animals over time correlate with climate warming (*Science*, published online 31 August 2006; doi10.1126/science.1131002). Because inversion frequencies in *Drosophila* were one of the first genetic markers measured in natural populations, the authors were able to compare new data with measurements taken 13 to 46 years ago in 26 different populations. It was known that frequencies of many inversions vary clinally with latitude; this is thought to reflect natural selection, since gene flow is very high. This argument is particularly strong for inversions that vary in the same direction with latitude in populations on different continents. The authors used principal component analyses of changes in inversion frequency and changes in temperature to show that genotypes associated with low latitudes increased in frequency between sampling times in 24 of the 26 populations. The force driving this genetic change is not identified, but this work provides insight into population dynamics in a changing environment. *EN*

SERPINH and premature birth

Premature birth affects African American women disproportionately. Hongyan Wang and colleagues report that a functional SNP in the promoter of *SERPINH1*, encoding the chaperone HSP47, is associated in African American women with preterm premature rupture of membranes (PPROM), the leading identifiable cause of preterm delivery (*Proc. Natl. Acad. Sci. USA* 103, 13463–13467; 2006). HSP47 stabilizes the collagen triple helix and is essential for collagen synthesis, a role that would make it important in the deposition of fibrillar collagen in the amnion, which strengthens fetal membranes. Wang and colleagues first confirmed the previously reported finding that the -656 T allele of *SERPINH* is approximately three times more common in women of African descent than in women of European descent. They then carried out two independent case-control association studies and found significant associations of the -656 T allele with PPROM (combined odds ratio 2.77). Although the individual study groups were small, and the authors concede that a gene in linkage disequilibrium with *SERPINH* could be involved, the -656 T SNP was found to have less promoter activity than the major C allele in amnion fibroblasts. If confirmed, *SERPINH* would be the first gene to be associated with ethnic disparity in risk of preterm birth. ***AP***