Recurrent *cis*-regulatory evolution

The pelvic apparatus of threespine stickleback fish has been lost in several independent populations as a result of previously unidentified mutations at the *Pitx1* locus. Now, David Kingsley and colleagues report that deletions of a *cis*-regulatory enhancer (*Pel*) upstream of *Pitx1* are consistently observed in pelvic-reduced stickleback populations worldwide (*Science* advance online publication 10 December 2009, doi:10.1126/science.1182213). High-resolution genetic mapping and linkage disequilibrium analysis in dimorphic populations suggested that the causal variant at the *Pitx1* locus was located in a 23-kb region upstream of *Pitx1*. In order to identify pelvic-specific enhancer elements, the authors tested different subfragments of the 23-kb region in transgenic reporter assays and identified a 501-bp fragment that is sufficient to drive pelvic expression. To test whether *cis*-regulatory changes are responsible for pelvic reduction, the authors used a 2.5-kb fragment containing *Pel* to drive *Pitx1* expression and showed that the transgene led to the development of pelvic structures in fish from a pelvic-reduced population. Sequencing and genotyping of the *Pitx1* locus showed that in 9 out of 13 pelvic-reduced populations, there were consistent deletions within and around the *Pel* enhancer. These studies offer a striking example of how regulatory elements can lead to major morphological changes in natural populations. ***PC***

Tumor self-seeding

Cancer is typically divided into primary tumors and secondary metastases. Joan Massague and colleagues now report (*Cell* **139**, 1315–1326, 2009) that cancer tumor cells can infiltrate their tumors of origin in mouse models of cancer. The authors first transduced cells from a metastatic cancer cell line with a green fluorescent protein–luciferase vector and then injected labeled and unlabeled cells into contralateral mouse mammary glands. The majority (85%) of tumors that formed at the site of injection of the unlabeled cells showed seeding by labeled cells. In experiments with other cancer cell lines, the seeding phenomenon was widely observed. Comparing self-seeding between metastatic derivative cell lines and parental cancer cell lines showed that metastatic cancer cells were more successful at self-seeding than the parental cells. The authors found that adding IL-6 or IL-8 to conditioned media from non-tumorigenic cells was sufficient to increase cancer cell migration *in vitro*, and removing IL-6 receptor expression with RNA interference led to a significant decrease in self-seeding ability *in vivo*. The authors suggest that self-seeding may be an additional mechanism that could explain the well-known association between large primary tumor size and poor prognosis in many types of cancer. *PC*

Asthma susceptibility locus

Hakon Hakonarson and colleagues (*N. Engl. J. Med.* **362**, 36–44, 2010) report the discovery of a locus on chromosome 1q31 that is associated with asthma susceptibility in children. The authors performed a genome-wide association study of children of European ancestry with asthma and identified multiple SNPs on 1q31 showing genome-wide significant association with the disease. The association to this locus was replicated in an independent case-control sample, with the most strongly associated variant having $P < 1 \times 10^{-10}$ in the combined analysis. The authors also tested these SNPs for association with asthma in children of African-American ancestry; they identified several SNPs showing strong association with asthma, but the directions of the effects were opposite to those seen among individuals of European ancestry, suggesting that there are population differences in the allelic architecture at this locus. One of the genes in the associated haplotype block, *DENND1B*, is a plausible candidate for mediating the effects of this locus on disease susceptibility because it encodes a protein expressed in natural killer cells and dendritic cells and is implicated in tumor necrosis factor-α signaling. *KV*

Written by Orli Bahcall, Pamela Colosimo, Emily Niemitz and Kyle Vogan

Leprosy GWAS

Jian-Jun Liu and colleagues report a genome-wide association study (GWAS) for susceptibility to leprosy, resulting in one of the most fruitful GWAS for an infectious disease to date (*N. Engl. J. Med.* **361**, 2609–2618, 2009). In an initial GWAS dataset of 706 Han Chinese affected cases and 1,225 unaffected controls from eastern China, the authors found 93 SNPs that passed a significance threshold to take forward for replication in 3 cohorts, totaling 3,254 cases and 5,955 controls. In the combined analysis, they found SNPs at six loci that met genome-wide significance levels, including *HLA-DR-DQ*, *NOD2*, *CCDC122*, *C13orf31*, *TNFSF15* and *RIPK2*. They tested for association stratified by clinical subtype and found that the variants at four of these loci showed stronger association to the localized multibacillary form of the disease than to the disseminated paucibacillary form, demonstrating the importance of testing for subtype-specific associations. These findings highlight both plausible candidate genes and their connections with related diseases. *NOD2* has been implicated in tuberculosis, through signaling pathways mediated by *RIPK2*. Nod2-deficient mice show susceptibility to tuberculosis infection, and Nod2- or Ripk2-deficient mice show susceptibility to *Chlamydophila pneumoniae*. The newly associated genes implicated in this study may be involved in NOD2-mediated pathways and the early innate immune and inflammation responses to disease. In humans, *NOD2* and *TNFSF15* have also been associated to Crohn's disease, which shares features with mycobacterial diseases, such as Th1-cell response. *OB*

miR-206 and regeneration

Amyotrophic lateral sclerosis (ALS) is an adult-onset disease characterized by motor neuron degeneration. Investigation of pathways regulating interactions between motor neurons and muscle fibers may lead to insights into ALS pathogenesis. Now, Eric Olson and colleagues report the identification of a regulatory role for microRNA (miR)-206 in regeneration of neuromuscular junctions (*Science* 326, 1549–1554, 2009). The authors identified miR-206 by profiling skeletal muscle tissue of a transgenic mouse model of ALS, which expresses a mutated form of superoxide dismutase (S1OD1). They found that miR-206 is upregulated upon disease onset in these mice and also after denervation in wild-type mice. The authors generated a miR-206–targeted deletion allele and showed that loss of miR-206 impairs the formation of new neuromuscular junctions after nerve injury. When these mice are crossed with SOD1 mutant mice, the miR-206 knockout causes accelerated disease progression, suggesting that miR-206 has a role in reinnervation during the asymptomatic phase of ALS. The authors further implicated histone deacetylase 4 (HDAC4), a target of miR-206, and fibroblast growth factor binding protein 1, a target of HDAC4, in miR-206–mediated reinnervation at the neuromuscular junction. ***EN***