Cichlid fish coloration

Genetic conflicts arise when mutations lead to phenotypic changes that are beneficial to one sex and detrimental to the other. In rock-dwelling cichlids in Lake Malawi, the orange-blotch (OB) phenotype increases fitness in females only by camouflaging the animals against the mottled rock substrates. OB males are rare, likely because the OB phenotype disrupts their nuptial coloring, which is necessary for mating. Thomas Kocher and colleagues report (*Science*, published online 1 October 2009; doi:10.1126/science.1174705) that within 36 distinct lake-wide populations, there is a single, shared haplotype at the *OB* locus, suggesting a single origin of the OB phenotype in Lake Malawi cichlids. The peak of linkage disequilibrium at *OB* is located at a noncoding SNP within *Pax7*. OB animals have higher expression of *Pax7* in tailfin tissue, and allele-specific analysis shows that the *OB* allele of *Pax7* is upregulated, suggesting that *cis*-regulatory differences in *Pax7* lead to the OB pigmentation phenotype. The *OB* locus appears to be very tightly linked to the dominant female sex determination locus *W*. The authors suggest that this tight linkage resolves the genetic conflict caused by the sexually antagonistic selection on the OB phenotype. ***PC***

Active mitochondria in long-lived flies

Previous research suggests that mRNA translation may regulate aging and contribute to dietary restriction (DR)-induced lifespan extension. Pankaj Kapahi and colleagues conducted a genome-wide survey of mRNA translational changes in *Drosophila* undergoing DR and identify mRNAs that show increased ribosomal loading and enhanced overall activity (*Cell* **139**, 149–160, 2009). The 201 genes that were upregulated as a result of DR were enriched for mitochondrial components. RNAi knockdown of two genes encoding components of the mitochondrial electron transport chain showed that these genes are required for lifespan extension under DR. In addition, several mitochondrial genes had shorter and less structured 5′ UTRs than the average *Drosophila* gene, which contributed to their enhanced mRNA translation. The authors then tested whether the translation initiation factor 4E-BP is necessary for lifespan extension upon DR and found that *4E-BP* mutants did not show lifespan extension under DR. Interestingly, flies overexpressing an activated (but not a wild-type) form of *4E-BP* had extended lifespans, but only when fed a rich-food diet. The results suggest a causal link between increased mitochondrial capacity and the protective effects of dietary restriction. *PC*

Hepatitis and liver cancer

Chronic hepatitis is an established risk factor for hepatocellular carcinoma (HCC), although the molecular pathways that link the two conditions are not well understood. Mathias Heikenwalder and colleagues report (*Cancer Cell* **16**, 295–308, 2009) that sustained signaling by the proinflammatory cytokines lymphotoxin (LT)-α and LT-β can lead to liver inflammation and HCC. Among transgenic mice overexpressing high levels of *LT*α (*Lta*) and *LT*β (*Ltb*), 35% develop HCC, and often multifocal HCC. Analysis of multifocal tumors in individual animals suggests that there is a clonal relationship between tumors. To test the requirement of lymphocytes in the progression of HCC, the authors crossed the *LT*α and *LT*β transgenic mice to *Rag1*$^{-/-}$ mutants, which lack lymphocytes, and found that these mice did not develop hepatitis or HCC. *LT*α and *LT*β transgenic mice that lacked Ikkβ function also did not develop hepatitis or HCC, showing that Ikkβ signaling is required for LT-induced HCC. Because inhibition of LTβ receptor (LTβR) signaling with an antagonistic LTβR antibody also protects against LT-induced HCC, the authors propose that antibodies against LTβR may be beneficial in treating liver disease states caused by LT signaling. *PC*

Combined immunodeficiency syndrome

Helen Su and colleagues (*N. Engl. J. Med.*, published online 23 September 2009; doi:10.1056/NEJMoa0905506) describe a variant form of combined immunodeficiency caused by biallelic mutations in *DOCK8*. Hallmarks of this syndrome include recurrent cutaneous viral infections, upper- and lower-respiratory tract infections, severe allergies and cancer susceptibility. To define the molecular basis of this disorder, the authors performed array comparative genomic hybridization analysis of index cases from two consanguineous families and identified homozygous deletions in *DOCK8* in both cases. They then expanded their analyses and found homozygous or compound heterozygous *DOCK8* mutations in five additional families. The mutations, which include deletions spanning multiple exons, frameshifts and nonsense changes, are predicted to result in loss of DOCK8 function. DOCK8 belongs to a superfamily of guanine nucleotide exchange factors that interact with Rho GTPases and regulate cytoskeletal dynamics, suggesting a function for DOCK8 in cell migration, adhesion or similar processes. Previous studies have also found somatic *DOCK8* deletions in primary lung cancers and gliomas. Cancers in individuals with germline *DOCK8* mutations included squamous cell carcinoma, microcystic adenoma and T-cell lymphoma-leukemia, suggesting that DOCK8 has a broad tumor suppressor function in multiple tissues. *KV*

From association to function

Common variants at chromosome 17q12–17q21 have been associated with asthma and autoimmune diseases in multiple ethnic groups, but the mechanism of their contribution to disease risk is unknown. Tomi Pastinen and colleagues now report an investigation into allele-specific properties of this disease-associated region (*Am. J. Hum. Genet.* 85, 377–393, 2009). The authors used HapMap lymphoblastoid cell lines to analyze allele-specific expression (ASE) and identified a haplotype associated with expression levels of multiple genes in the region. To investigate potential functional properties of the ASE-associated SNPs, the authors screened them with the formaldehyde-assisted isolation of regulatory elements (FAIRE) assay, which detects potential regulatory regions devoid of nucleosomes. This analysis identified an SNP with allele-specific nucleosome depletion; this SNP was further shown to exhibit allele-specific binding to the CTCF protein and differential promoter activity in a reporter assay. Finally, the authors showed that this functional SNP and the haplotype on which it resides are associated with asthma in three family based asthma cohorts. Although the causal variant and mechanism remain unknown, this study illustrates the range of approaches that can be used to functionally dissect a risk-associated region, as well as the difficulty of these endeavors. ***EN***

Written by Pamela Colosimo, Emily Niemitz and Kyle Vogan