Cardiomyocytes reprogrammed

Defects in cardiomyocyte development and loss of cardiomyocytes are common causes of congenital heart defects and heart failure, respectively. Now, Deepak Srivastava and colleagues show that three transcription factors, Gata4, Mef2c and Tbx5, are sufficient to reprogram postnatal cardiac or dermal fibroblasts into functional beating cardiomyocytes (*Cell* 142, 375–386, 2010). The authors identified genes with higher expression levels in embryonic mouse cardiomyocytes compared to cardiac fibroblasts. Fourteen factors were then serially screened to identify a combination of factors sufficient to induce expression of a mature cardiomyocyte marker in cardiac fibroblasts. To rule out whether rare cardiac progenitors were differentiating into induced cardiomyocytes (iCMs), the authors tested if mouse dermal fibroblasts could be reprogrammed. These tail-tip fibroblasts also expressed the cardiomyocyte-specific marker α-actinin and formed well-defined sarcomeric structures. iCMs displayed spontaneous contraction after 4–5 weeks in culture and exhibited action potentials similar to those of adult mouse cardiomyocytes. The authors injected cardiac fibroblasts into mouse hearts 1 d after viral transduction with the reprogramming factors and found that these fibroblasts could reprogram into cardiomyocytes *in vivo*. Reprogramming of fibroblasts into iCMs may lead to an important source of cardiomyocytes in the clinic for use in regenerative therapies for damaged hearts. ***PC***

Scanning exomes

Joshua Akey and colleagues report a screen for positive selection in ten human exomes (*Genome Res.* published online, doi:10.1101/gr.106161.110, 6 August 2010). Their dataset includes the exome sequences of six individuals of European ancestry and four individuals of African ancestry. They used coalescent simulations to consider how various possible modes of positive selection would impact the population-wide genetic patterns detectable in the sequence dataset. They compared to the results of four genome-wide scans for selection based on large-scale SNP datasets, each of which used one of four different commonly used methods for detecting selection. They filtered a combined list of 1,043 candidate selected regions down to 281 candidate regions and identified those showing evidence of continent-specific selection. They further characterized population-specific differences for one candidate selected gene, the keratinization gene *IVL*, by sequencing an 800-bp region in 74 individuals from 7 populations. This study shows the promise of analyses of whole-exome sequences, even if only on a few individuals, in detecting signatures of selection. The work demonstrates how such analyses may benefit from the combined use of genome-wide SNP, exome and fine-scale sequencing datasets. *OB*

APOL1 and kidney disease

Previous admixture mapping studies identified a locus on chromosome 22 near *MYH9* associated with increased risk of focal segmental glomerular sclerosis and end-stage renal disease in African Americans. Now, Martin Pollak and colleagues (*Science* **329**, 841–845, 2010) have localized two candidate causal variants at this locus to an adjacent gene, *APOL1*. The authors performed a fine-mapping study using common variants identified in African individuals through the 1000 Genomes Project and identified two independent coding variants in *APOL1* that could account for the signal at this locus. The risk alleles are common in the African population but are absent from European and Asian HapMap samples, and they appear to have risen to high frequency in Africa through positive selection. Because previous work has shown that APOL1 confers resistance to trypanosome infections, the authors tested whether the positively selected *APOL1* coding variants might confer enhanced resistance to particular trypanosome subspecies. In support of this hypothesis, they found that serum samples from individuals carrying at least one of the two positively selected *APOL1* variants were able to preferentially lyse the *Trypansoma brucei rhodesiense* subspecies, providing a plausible basis for the elevated frequency of these alleles in Africa. *KV*

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

Genomic imprinting in the brain

About 100 imprinted genes—genes with preferential expression of either the maternal or the paternal allele—have been identified to date, but the extent of parent-of-origin effects on the transcriptome is not known. Now, Catherine Dulac and colleagues report a broad analysis of parent-of-origin effects on expression in the mouse brain (*Science* **329**, 643–648, 2010). The authors used RNA sequencing to determine parent-of-origin effects in the transcriptome of embryonic and adult brain tissues from reciprocal crosses between inbred mouse strains. Expressed SNPs were used to determine allelic expression from maternal and paternal alleles in generation F_1 hybrids. This analysis led to the identification of 1,308 candidate imprinted loci; this list includes many of the known imprinted transcripts and noncoding RNAs. Many candidate imprinted loci showed parent-of-origin bias in only one of the profiled tissues, suggesting tissue and temporal specificity. Detailed analysis revealed many loci with possible isoform-specific parent-of-origin expression. The authors validated observed expression biases for a handful of loci in an independent cohort of animals with a different platform, but broader validation efforts, analysis of different tissues and detailed investigation of specific loci will be necessary to gauge the impact of these parental expression biases on the brain transcriptome. *EN*

Different dogs

Domesticated dogs show tremendous phenotypic diversity and therefore represent a model system for studying the genetic basis of morphological variation. Elaine Ostrander, Carlos Bustamante and colleagues (*PLoS Biol.* 8, e1000451, 2010) have generated a high-density map of common genetic variation at 60,988 SNPs in 915 dogs, including dogs from 80 domestic breeds, wild canids and outbred African shelter dogs. The authors analyzed patterns of linkage disequilibrium (LD) and found that within each breed, LD extends over 1 Mb but decays rapidly across breeds. The authors then used the high-density map to perform genome-wide association scans across breeds for 57 traits, including body size, ear type, skull shape, snout length and coat color. For many traits, most of the genetic variance across breeds could be explained by three or less quantitative trait loci. Many genomic regions that are associated with canine morphology also display signatures of recent selection. The results suggest that the high levels of phenotypic diversity observed in dogs are largely governed by a small number of genetic variants of large effect. ***PC***

© 2010 Nature America, Inc. All rights reserved.