Shank3 mouse model of autism

Heterozygous mutations in SHANK3 that disrupt binding to HOMER have been previously reported in autism spectrum disorder (*Nature Genetics* 39, 25–27, 2006). Now, Paul Worley and colleagues have generated mice with heterozygous mutations in Shank3 that delete the C terminus and remove the Homer binding site (*Cell* 145, 758–772, 2011). *Shank3* (+/ΔC) mice have a 90% decrease of Shank3 protein in synapses despite equivalent mRNA levels compared to wild-type littermates. They observed a twofold increase in polyubiquitinated Shank3 in *Shank3* (+/ΔC) mice as well as increased co-localization with Rpt6, a proteosomal marker. These data suggest that increased polyubiquitination leads to increased proteosomal degradation of Shank3. Behavioral tests of long-term spatial memory and fear memory showed that *Shank3* (+/ΔC) mice retain learning and memory functions. However, *Shank3* (+/ΔC) mice showed lower levels of social investigation compared to wild-type mice in an assay of reciprocal social interaction. *Shank3* (+/ΔC) mice also showed significant increases in approach latency when presented with sexually receptive females, although no differences were seen with male stimulus mice. Nevertheless, the data suggest *Shank3* (+/ΔC) mice have altered social interaction and social approach behaviors, which parallel social deficits seen in autism spectrum disorder in humans. ***PC***

Industrial melanism in peppered moths

The emergence of a darkly pigmented form of the peppered moth in nineteenth century Britain in response to industrialization is a classic example of evolutionary adaptation in response to environmental change. Ilik Saccheri and colleagues (*Science* **332**, 958–960, 2011) have now used genetic mapping to trace the origins of this adaptive change. The authors constructed linkage and physical maps for the peppered moth *Biston betularia* and localized the gene responsible for the *carbonaria* (darkly pigmented) morph to a 200-kb region. Next, they examined SNP markers across this region in peppered moth samples collected throughout the UK between 1925 and 2009. They found that all 97 *carbonaria* morphs shared a common allele for one marker in this region, suggesting that all were derived from a single ancestral haplotype that spread rapidly in the population under strong selective pressure. The authors have not determined which gene or variant in the region mediates the pigmentary effects that distinguish the *carbonaria* morph from the wild-type form. However, the region is coincident with the position of pigmentation loci that have been mapped in other lepidopteran species, suggesting that the underlying pigmentary system might be ancestrally derived. *KV*

Evolution of CpG islands

CpG islands are genomic regions with high CpG content; most CpG islands are unmethylated. Unmethylated CpGs escape deamination-mediated hypermutability of methylated cytosines, explaining their evolutionary maintainence, but it isn't clear how methylated CpG islands are evolutionarily maintained. Now Amos Tanay and colleagues report models that identify the evolutionary processes that maintain CpG islands (*Cell* **145**, 773–786, 2011). The authors use substitution dynamics from alignments of five primate genomes to model the evolutionary dynamics of CpG-rich regions of the human genome. Their analyses reveal classes of CpG islands that have been maintained by different evolutionary forces. They confirm the category of classical unmethylated CpG islands with low deamination rates and discern a second class of CpG-rich regions, located far from transcription start sites, which have high methylation levels and rapid deamination rates. The authors find that the evolutionary stability of these methylated regions is because of a balance between high rates of CpG deamination and high rates of CpG-gaining substitution, which they attribute to GC-biased gene conversion. The authors also find that CpG content at imprinting control regions is conserved by purifying selection, whereas CpG content at tissue-specific differentially methylated regions is conserved by neutral processes similar to those acting at hypomethylated CpG islands. *EN*

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

Adaptive epistasis

Two new studies examine the role of epistasis in adaptive evolution. They report experimental measurements of epistasis among beneficial mutations in two different bacteria adapting in lab settings. Tim Cooper and colleagues examined *Escherichia coli* from a long-term evolution experiment and sequenced the genome of a strain evolved for 20,000 generations (*Science* **332**, 1193–1196, 2011). They examined the first five mutations fixed in this population and constructed all combinations of these on the ancestral background. They measured the fitness of each and used this information to build a local fitness landscape. In a complementary approach, Christopher Marx and colleagues examined an engineered strain of *Methylobacterium extorquens* and sequenced the genome of the evolved isolate with the highest fitness after 600 generations (*Science* **332**, 1190–1192, 2011). They also constructed strains with all combinations of four selected mutations, measured fitness values and constructed the fitness landscape. Both studies show that the fitness landscape had a single peak, and that each mutation was beneficial to the background on which it arose. Interestingly, they both report prevalent antagonistic epistasis and observed diminishing returns of beneficial mutations on higher fitness backgrounds. They suggest that antagonistic epistasis contributed to a reduced rate of adaptation over time. *OB*

Antibiotic sensitivity switch

Antibiotics can rapidly kill bacteria *in vitro*, but treatment of chronic bacterial infections such as tuberculosis typically requires at least six months. The reasons for this are not well understood, but it has been hypothesized that the reduced growth and metabolism shown by *Mycobacterium tuberculosis* in chronically infected organisms is responsible, as almost all antibiotics are more effective on rapidly replicating bacteria. Christopher Sassetti and colleagues have screened a library of transposon mutants grown at a low-oxygen environment and looked for mutants showing a growth or survival advantage (*PLoS Biol.* 9, e1001065, 2011). They found that genes involved in DosR-triggered triacylglycerol (TAG) accumulation were important for growth in hypoxic conditions. The Δ*tgs1* mutant did not accumulate TAG in hypoxic conditions and grew to a tenfold higher density than wild type. The Δ*tgs1* mutant also remained sensitive to an array of antibiotics under several stressful conditions. The results suggest that synthesis of TAG is a stress response that leads to tolerance of antibiotics by decreasing growth and metabolism. The authors hypothesize that manipulating these metabolic pathways could be a strategy used to improve the effectiveness of antibiotics. ***PC***