Connectivity Map

Todd Golub and colleagues present an initial Connectivity Map capturing the effects of small-molecule 'perturbagens' on gene expression signatures (*Science* 313, 1929–1935; 2006). This ongoing project includes a public reference database of expression signatures for a wide range of drugs and genes, as well as pattern-matching tools used for analyses. In the current paper, Justin Lamb *et al.* tested 164 small molecules, mostly in MCF7 breast cancer cell lines. Cells were profiled 6 hours after treatment to assay early effects of the compounds. For analyses, the authors selected a nonparametric rank-based method in which genes were ranked according to their expression relative to control. Genes were also assigned a connectivity score, reflecting correlation to the query signature. In initial applications, the authors show how querying a signature derived from a class of small molecules (here, HDAC inhibitors) can uncover other molecules with similar mechanisms of action. Similarly, querying with signatures for particular disease states can reveal new connections and candidate genes. As an example, querying with either of two different Alzheimer disease signatures uncovered strong negative connectivity to 4,5-dianilinophthalimide (DAPH), which has been considered a target of interest in this disease. ***OB***

Proximal muscle weakness and DOK7

DOK7 is a key, muscle-intrinsic regulator of neuromuscular synapse formation that binds to the muscle-specific receptor kinase MuSK and promotes clustering of acetylcholine receptors on the postsynaptic side of the neuromuscular junction. David Beeson and colleagues (*Science* **313**, 1975–1978; 2006) now show that biallelic mutations in *DOK7* underlie an early-onset, congenital myasthenic syndrome characterized by proximal muscle weakness of the upper and lower extremities, frequently associated with weakness of muscles in the trunk, neck and face. All 21 affected individuals with *DOK7* mutations were found to carry at least one allele harboring a frameshift mutation in exon 7, with a single founder mutation present among individuals of diverse European ancestry accounting for over half of the mutant alleles identified in the study. Biopsies from affected individuals showed that neuromuscular junctions were reduced in size and showed reduced postsynaptic folding. This phenotype is less severe than the phenotype previously reported for *Dok7*-null mice, which die postnatally with marked disruption of neuromuscular synaptogenesis. These findings suggest that the truncated DOK7 proteins produced from the mutated alleles retain partial activity and that these mutations interfere with normal synaptic maturation or maintenance. *KV*

Scanning for epistasis in GWA studies

Recent studies have suggested that epistasis (gene-gene interaction) has a role in complex diseases and that its prevalence may contribute to difficulties in replicating reported genetic association studies. Searching for epistasis in genome-wide association (GWA) studies has also been an area of interest, despite limitations imposed by weighty statistical issues such as multiple testing. In a previous study, Lon Cardon and colleagues showed the computational feasibility of such searches at realistic sample sizes, assuming one of several underlying disease models (*Nat. Genet.* **37**, 413–417; 2005). Now, Cardon and colleagues have expanded this work by considering other genetic models and comparing the performance of single- and two-locus genome screens and two alternative two-stage designs (*PLoS Genet.* **2**, 1424–1432; 2006). Given the statistical and computational costs of testing all possible pairwise combinations in a genome-wide screen, they tested only subsets passing a threshold for single-locus association in a first-stage screen. The second stage then consisted of testing two-locus combinations of each of these loci with either all markers or only those passing the first-stage threshold. Their simulations suggest that in the presence of epistatic relationships, testing all markers for two-locus interaction provided greater power to detect epistasis than either of these two-stage approaches. *OB*

Research Highlights written by Orli Bahcall, Emily Niemitz and Kyle Vogan.

Sumoylation and cleft palate

Through efforts to identify genetic pathways involved in the etiology of cleft lip and palate, Richard Maas and colleagues have implicated sumoylation in palatogenesis (*Science* **313**, 1751; 2006). In an individual with cleft lip and palate and a balanced translocation between chromosomes 2 and 8, the authors determined that *SUMO1*, encoding a small ubiquitin-like modifier, was disrupted at the breakpoint on chromosome 2. In mice, *Sumo1* shows strong expression in the developing lip and palate. The authors proceeded to generate *Sumo1* knockdown mice from an existing gene-trap embryonic stem cell line. Heterozygous mice showed variable reduction in *Sumo1* expression, and 9% of heterozygous mice showed cleft palate defects. A genetic cross to a mouse line with a mutation in *Eya1*, known to be involved in clefting, resulted in an increase in the incidence of palatal defects. Of particular interest is the potential for sumoylation to be modified by environmental influences, which are known to be important for development of cleft lip and palate. Although it remains to be determined what fraction of sporadic cleft lip and palate cases are due to defects in sumoylation, this work opens to the door to investigations in a potentially important pathway in palatogenesis. *EN*

Helping bat wings take flight

Retention of interdigital webbing in forelimbs is a morphological innovation critical for the evolution of powered flight in bats. In ducks, development of webbed feet is achieved via localized expression of the BMP antagonist Gremlin in hindlimb interdigital mesenchyme, which blocks apoptosis normally induced by BMPs in species with free-toed feet such as mice and chickens. Lee Niswander and colleagues (*Proc. Natl. Acad. Sci. USA* 103, 15103–15107; 2006) now show that localized expression of Gremlin also contributes to, but is not sufficient for, retention of interdigital webbing in bats. Gremlin expression in bat forelimbs occurs prominently in the two most anterior interdigits and later expands to include much of the forelimb interdigital region. *Fgf8*, a member of the FGF family, is also highly expressed in the bat forelimb interdigital region, most notably in the two most posterior interdigits, in contrast to most vertebrates, in which *Fgf8* is restricted to the distal tips of the growing limbs. The authors then showed that coapplication of BMPs with an FGF antagonist induced significant apoptosis in cultured bat forelimbs, but neither treatment did so on its own, suggesting that Gremlin and Fgf8 synergize to promote the characteristic webbed morphology of the bat wing. ***KV***