Building a chordate

The ascidian *Ciona intestinalis* is an emerging system in which to study chordate development and the underlying gene regulatory networks. Kaoru Imai and colleagues have now reported the outline of a network in the pre-gastrula *C. intestinalis* embryo (*Science* 312, 1183–1187; 2006). The authors selected 53 genes encoding transcription factors and 23 genes encoding components of signaling pathways that are zygotically expressed from the 16-cell to the early gastrula stage. With precise knowledge of the fates of these blastomeres in hand, they examined the effect of morpholino-dependent knockdown of these genes on gene expression and developmental phenotype. They found an early 'regulatory code', in which each of the blastomeres in the 16-cell embryo has a unique identity that can be assigned on the basis of a specific combination of transcription factors. Autoregulatory loops were identified, but surprisingly, most of them were negative. The network also suggests that the lineage of blastomere b6.5 serves as an organizer in patterning the nerve chord and inducing mesodermal derivatives. Targeted mutagenesis of relevant *cis*-regulatory regions will be required to distinguish direct from indirect targets, but this version of the network already provides a glimpse of how chordate tissues are constructed. ***AP***

Pituitary adenoma predisposition

Pituitary adenomas are benign tumors commonly characterized by oversecretion of growth hormone, leading to acromegaly or gigantism. Lauri Aaltonen and colleagues (*Science* **312**, 1228–1230; 2006) now report a new pituitary adenoma predisposition (PAP) phenotype associated with germline loss-of-function mutations in *AIP*, encoding the aryl hydrocardon receptor interacting protein. Starting with a cluster of familial pituitary adenoma cases from Northern Finland, the authors performed genome-wide linkage analysis using high-stringency criteria and identified a haplotype on chromosome 11 segregating with acromegaly in two linked pedigrees. Expression profiling of genes in the interval prioritized *AIP* for mutation screening, and sequence analysis revealed a nonsense mutation in *AIP* segregating perfectly with the PAP phenotype in the two pedigrees. Further screening of 45 adenoma samples from a population-based cohort from Northern Finland identified six individuals with the same nonsense mutation and seventh with a splice-site mutation in *AIP*. A different *AIP* nonsense mutation was found in two Italian siblings with growth-hormone secreting pituitary adenoma. Loss-of-heterozygosity studies in eight tumors from mutation-positive cases showed loss of the wild-type allele in all cases, suggesting that *AIP* acts as a tumor suppressor gene. *KV*

Syndromic mental retardation

A mental retardation syndrome with features of hypotonia, craniofacial malformations and heart defects has been associated with chromosome 9q subtelomeric deletions. The identification of an individual with syndromic features typical of 9q subtelomeric deletion and a balanced translocation in the euchromatic histone-lysine N-methyltransferase 1 (EHMT1) gene provided a good candidate for a causative haploinsufficient gene in the interval. Now, Tjitske Kleefstra and colleagues have taken the story one step further and identified individuals with mutations in the EHMT1 gene (*Am. J. Hum. Genet.*, in the press). Starting with a group of 23 patients with 9q deletion features, the authors identified three patients with 9q subtelomeric deletions and then went on to sequence EHMT1 in the remaining 20 patients. This approach led to the identification of two individuals with *de novo* mutations—a nonsense mutation and a 13-bp deletion that causes a frameshift and premature stop—that are likely to be loss-of-function. The phenotypic features of the individuals with the mutations were not different from individuals with deletions, suggesting that the syndrome is caused by haploinsufficiency for a single gene rather than continguous gene deletion. *EN*

Research Highlights written by Myles Axton, Orli Bahcall, Emily Niemitz, Alan Packer and Kyle Vogan.

p38 kinase in mammalian gastrulation

Soon after gastrulation begins on the embryonic day 6.25 of mouse development, the three basic germ layers of the embryonic body plan become established. The mesodermal cells receive their fate from a fibroblast growth factor (Fgf) signal as they pass through the primitive streak, acquiring differential adhesion properties and motility as they change from an epithelial to a mesenchymal cell type. This signal results in downregulation of the cell adhesion molecule E-cadherin under the control of the Snail transcription factor. Lee Niswander and colleagues (*Cell* **125**, 957–969; 2006) have now demonstrated that there is another input into this process in the form of the p38 protein kinase. Their evidence is that the product of the *droopy eye* gene, a protein called p38IP that binds to p38, is essential *in vivo* for activation of its protein kinase activity. *droopy eye* mutations produce a spectrum of eye, neural tube and gastrulation defects. The gastrulation defects result because p38 activation is essential for downregulation of E-cadherin independently from the Fgf signal and from Snail. It will be interesting to see whether this Snail-independent regulation of the epithelium-to-mesenchyme transition is also involved in cancer metastasis. *MA*

Relaxed phylogenetics

Traditional phylogenetic inference methods are based on the assumption of a molecular clock, in which the rate of mutation is assumed to be constant across all branches in a tree. As this assumption has been questioned and has been shown to bias inference, more recently, unrooted phylogenetic models that assume independence of rates between branches have gained favor. However, these aptly named unrooted models do not allow for the direct estimation of time of divergence from the most common recent ancestor. Andrew Rambaut and colleagues (*PLoS Biology* 4(5) e88; 2006) now present an alternative relaxed molecular clock model that simultaneously estimates both phylogeny and divergence time with a Markov Chain Monte Carlo–based method incorporated into the phylogenetic analysis program BEAST. Of note, the model does not require prior assumptions regarding tree topology, or correlation in mutation rates between adjacent branches. The authors tested five models for phylogeny inference, ranging from the strict molecular clock to a model with no correlation between rates at adjacent branches, and found that their model was the most robust. Testing their program on data sets of viruses, marsupials, plants, bacteria and yeast, the authors found that their relaxed phylogenetic model provided both more accurate and more precise estimates of phylogenetic relationships than currently popular unrooted methods. ***OB***