DICER1 mutations in rare cancer syndrome

Pleuropulmonary blastoma is a rare childhood cancer of the lung that occasionally arises in individuals with a family history of other childhood cancers, including cystic nephroma and rhabdomyosarcoma. Ashley Hill and colleagues (*Science* published online; doi:10.1126/science.1174334; 25 June 2009) now show that inherited predisposition to pleuropulmonary blastoma can result from germline mutations in *DICER1*. The authors used linkage analysis to map a susceptibility locus for this rare pediatric tumor to a 7-Mb region on chromosome 14q. Among the 72 genes in the interval, *DICER1* stood out as an attractive candidate on the basis of earlier knockout studies in mice. Sequence analysis of *DICER1* in affected members of 11 families revealed 10 different truncating mutations and 1 missense mutation, all predicted to result in loss of function. Notably, DICER1 protein was frequently absent from the benign epithelial component but retained in the mesenchymal component of the tumor, suggesting that loss of DICER1 from the epithelium acted non-cell-autonomously to promote tumor formation in the adjacent mesenchyme. The spectrum of cancers associated with *DICER1* mutations reveals a small subset of tissues for which DICER1-dependent small RNA pathways are important for suppressing tumorigenesis. ***KV***

Polarity determinant in plants

Cell polarity is a fundamental characteristic of multicellular organisms. In animals, several well conserved polarity complexes have been identified, including the PAR/aPKC proteins. However, the absence of PAR/aPKC homologs in plants suggests that plants use alternative pathways to generate asymmetry in cells. Dominique Bergmann and colleagues now report the identification of BASL, a novel polarity determinant in *Arabidopsis* (*Cell* **137**, 1320–1330; 2009). Using the asymmetric cell divisions of the stomatal-lineage cells as a model system, the authors identified *basl-1* in a screen for stomatal patterning defects. The authors positionally mapped and cloned *BASL* and found that during asymmetric division in stomatal-lineage cells, BASL accumulates in a polarized manner at one edge of the cell's periphery. After asymmetric division, BASL remains polarized at the periphery in one of the daughter cells and localizes to the nucleus of the other daughter cell. BASL localization predicts what cell fate the daughters eventually assume. The authors also observed that BASL maintains its polarized localization when ectopically expressed in cells other than the stomatal lineage, suggesting that BASL has a wide role in cell polarity in plants. Future work to identify BASL-interacting proteins will help to unravel the polarity determinants that act in plants. *PC*

Wnt signaling and metastasis

Lung adenocarcinomas are able to rapidly metastasize. Joan Massagué and colleagues report that hyperactive WNT/TCF signaling mediates the metastatic capability of these tumors (*Cell* **138**, 51–62; 2009). The authors evaluated the expression signatures of several candidate signaling pathways in a clinical cohort of lung adenocarcinomas and determined that a TCF4 target gene activation signature was associated with a lower rate of metastasis-free survival. To further investigate the role of WNT/TCF signaling, the authors generated a cell model of lung adenocarcinoma metastasis by applying *in vivo* and *in vitro* selection procedures to human lung adenocarcinoma cell lines to derive lines with enhanced *in vivo* metastatic activity in mice. The derived lines had higher basal TCF transcriptional activity and enhanced responsiveness to Wnt ligand, and expression of dominant-negative TCFs reduced the metastatic activity of these lines. The authors further showed that knockdown of the WNT/TCF targets *LEF1* or *HOXB9* decreased the metastatic ability of the derived lines and that overexpression of *LEF1* and *HOXB9* increased the metastatic ability of the parental lines. No mutations in WNT/TCF pathway components were identified in the derived lines, and somatic mutations are not common in lung adenocarcinomas, suggesting that other alterations must promote WNT/TCF pathway hyperactivity. *EN*

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

A genetic system for regeneration

Scientists have long been intrigued by the ability of some animals to regenerate body parts. Historically, regeneration has been investigated in amphibians, but previous work has also shown that implantation of *Drosophila* larval imaginal discs into the abdomens of adult female flies leads to regenerative growth of wings and legs. Wide use of this model had been hampered by the technical difficulty of disc implantation. Iswar Hariharan and colleagues (*Dev. Cell* **16**, 797–809; 2009) report the development of a nonsurgical method for inducing tissue ablation and regenerative growth in *Drosophila* larvae. The authors developed a temperature-sensitive method for controlling expression of the proapoptotic gene *eiger* in larval wing discs. The authors expressed *eiger* during 40 hours of larval development to ablate most of the wing blade primordia. If *eiger* is expressed until eclosion, adult flies lack wings. However, if *eiger* expression is turned off after the ablation period, flies hatch with morphologically damaged, but recognizable, wings. This system allowed the authors to examine the regenerative capacity of wing discs. These studies showed that both Wingless and Myc are upregulated in regenerating discs, and that ectopic expression of Myc leads to an increase in adult wings that regenerate more completely. Future studies should help reveal pathways involved in regenerative growth. *PC*

Imputation scales up

Genome-wide association studies commonly use imputation to infer genotypes at SNPs not directly typed in study samples, thereby increasing power. With more reference panels becoming available, including the 1,000 Genomes Project, there is a need for imputation programs able to use larger and higher-resolution reference datasets. Jonathan Marchini and colleagues now report a new release of their imputation software, IMPUTE version 2 (*PLoS Genet.* 5, e1000529; 2009), designed for use with expanded reference data sets, which may include larger sample sizes as well as unphased and incomplete genotypes. Their method also allows the combination of SNP imputation across multiple reference panels, which is useful in meta-analysis. Their MCMC method separates the phasing and imputation phase, first modeling haplotypes at typed SNPs jointly across the study sample and then imputing untyped SNPs for each individual independently. IMPUTE v2 shows higher imputation accuracy than IMPUTE v1, with fewer false-positive heterozygous calls. The authors also compare performance of their method to other programs commonly used for imputation, including MACH, BEAGLE, fastPHASE and PLINK, and demonstrate that their method has better accuracy and lower computational requirements for large datasets, as well as for imputing at rare SNPs. ***OB***