CRISPR screen for metastasis

The genome-editing technology derived from the bacterial CRISPR/Cas9 system is revolutionizing biomedical research. Using a CRISPR-based strategy, Feng Zhang, Phillip Sharp and colleagues performed a genome-wide loss-of-function genetic screen *in vivo*, uncovering new genes involved in tumor growth and metastasis (*Cell* doi:10.1016/j.cell.2015.02.038; 5 March 2015). They started by transducing a non-metastatic lung cancer cell line with a library of 67,405 single-guide RNAs (sgRNAs). When transplanted into immunocompromised mice, the mutated cell pool readily generated metastases in the lung. These tumors were then analyzed to look for gene-specific sgRNA enrichment. The list of top candidates includes known tumor-suppressor genes but also genes with no previously described role in tumor development. This work advances the understanding of cancer evolution and elegantly underscores the potential of CRISPR/Cas9-based screens to study biological phenomena *in vivo*. It will be interesting to conduct similar cancer studies in other organs, potentially using gain-of-function approaches to identity novel oncogenes. ***TF***

The two sides of *GIGANTEA*

The *Arabidopsis thaliana* late-flowering mutation *gigantea* (*GI*) alters the circadian period and abiotic stress resistance. Now, C. Robertson McClung and colleagues report the fine mapping and cloning of the causal polymorphism in the *Brassica rapa GI* locus using recombinant inbred lines and show that it is responsible for variation in cold and salt tolerance (*Proc. Natl. Acad. Sci. USA* **112**, 905–910, 2015). Null alleles for this gene were then identified among *B. rapa* TILLING mutants, and the authors show that these plants were arrhythmic or had abnormally long circadian periods in response to high temperature, as in *Arabidopsis*. The *B. rapa* alleles from the two parental strains could both rescue the photoperiodic flowering defect of the *Arabidopsis gi* null mutant. However, only one of the two *B. rapa* alleles was able to rescue the mutant phenotypes of increased freezing tolerance, decreased nitrogen accumulation and increased salt resistance. These results indicate that the effect of *GI* on flowering time is independent from its role in abiotic stress resistance and that these functions can be separated at the genetic level, which may have practical implications for targeted breeding programs in *Brassica* crops. *BL*

Epigenetic evolution of corticogenesis

Human brains have a uniquely large and functionally complex neocortex. To understand the features of cortical development that are unique to humans, James Noonan and colleagues mapped active promoters and enhancers during human, rhesus macaque and mouse corticogenesis (*Science* **347**, 1155–1159, 2015). The authors profiled H3K27ac and H3K4me2 histone marks in cortical tissues at multiple homologous stages of corticogenesis to map active promoters and enhancers. They identified 8,996 enhancers and 2,855 promoters that had an increase in H3K27ac or H3K4me2 levels in human tissues compared to rhesus macaque and mouse tissues. Using available corticogenesis expression data, they generated a network model of cortical development and identified 96 sets of genes with highly correlated expression (modules). They integrated the lists of enhancers and promoters with human increases in H3K27ac or H3K4me2 signals and identified 17 modules that were enriched for these signals. These modules include genes associated with cortical development, neuronal progenitor proliferation, the extracellular matrix, and TGF-β and FGF signaling. *EN*

ALS susceptibility genes

Tim Harris and colleagues (*Science* doi:10.1126/science.aaa3650; 19 February 2015) report the results of an exome sequencing study designed to identify new susceptibility genes for amyotrophic lateral sclerosis (ALS). The authors sequenced and analyzed the exomes of 2,874 ALS cases and 6,405 controls, with follow-up analyses of 51 selected genes in an additional 1,318 ALS cases and 2,371 controls. In gene-based burden tests comparing cases with controls, they observed a genome-wide significant excess of rare variants in *SOD1*, a known ALS susceptibility gene, and in *TBK1*, a gene not previously implicated in disease risk. They also found supportive evidence for several previously reported ALS susceptibility genes in their data set, including *TARDBP*, *OPTN*, *VCP* and *SPG11*. *TBK1* encodes a kinase that functions in the NF-κB pathway and that phosphorylates several proteins in the autophagy pathway, including OPTN. Additional studies will be needed to clarify the molecular mechanisms by which *TBK1* variants contribute to disease risk. The work also suggests that ongoing sequencing studies in larger collections of ALS cases and controls will yield additional insights into the genes and pathways influencing ALS pathogenesis. *KV*

Mouse modeling of Alzheimer's disease

Most cases of familial Alzheimer's disease are caused by mutations in *PSEN1* (encoding presenilin-1). However, whether these missense mutations function through a loss- or gain-of-function mechanism is unclear. Previously, a gain-of-function mechanism was proposed on the basis of increased Aβ42/Aβ40 ratios in patients with *PSEN1*-mutant familial Alzheimer's disease. Now, Raymond Kelleher III, Jie Shen and colleagues report that *Psen1* knock-in mice generated with either of two missense mutations from familial Alzheimer's disease show complete loss of presenilin-1 function due to loss of catalytic activity, confirming earlier *in vitro* results (*Neuron* 85, 967–981, 2015). The phenotypes of homozygous knock-in mice were indistinguishable from those of *Psen1*-null mice: perinatal lethality, developmental defects and impaired neurogenesis due to disruption of Notch signaling. Heterozygous mutants developed normally but had reduced Aβ production and increased Aβ42/Aβ40 ratios by 3 months of age and showed Alzheimer's disease–like age-dependent neurodegeneration and memory impairment. These results suggest that restoration of normal presenilin-1 function might be a promising therapeutic strategy for some patients with Alzheimer's disease. ***BL***

Written by Tiago Faial, Brooke LaFlamme, Emily Niemitz & Kyle Vogan