Asymmetric cues in plants

The plant life cycle alternates between the diploid, spore-producing stage (sporophyte) and the haploid, gamete-producing stage (gametophyte). In contrast to other land plants, flowering plants (angiosperms) produce highly reduced gametophytes, with gametes capable of double fertilization. During double fertilization, angiosperms form seeds with a single diploid embryo and endosperm, a tissue with highly variable ploidy. Although gametophyte development is a fundamental process in the plant life cycle, the underlying molecular mechanisms are not well understood. Now, Pagnussat *et al.* (Science published online, doi:10.1126/science.1167324; 4 June 2009) report that asymmetric distribution of the phytohormone auxin is critical for establishing cell fate within the female gametophyte (embryo sac) in *Arabidopsis*. The authors followed expression of auxin using a GFP reporter under the control of DR5, an auxin responsive promoter, and saw polarized accumulation of GFP at the micropylar pole of the embryo sac. Perturbing the asymmetric distribution of auxin by ectopically expressing key enzymes in auxin biosynthesis led to abnormal patterning within embryo sacs. In addition, disrupting genes that mediate the auxin response induced switching between cell fates. The study suggests that cell fate specification in the *Arabidopsis* embryo sac may be regulated by a morphogenetic mechanism that relies on positional cues conferred by distance from the auxin source. ***PC***

miR-92a and angiogenesis

microRNAs in the miR-17-92 cluster were previously reported to play a role in tumor angiogenesis (*Nat. Genet.* **38**, 1060–1065; 2006). Now, Stefanie Dimmeler and colleagues report that one of these microRNAs, miR-92a, is expressed in endothelial cells (ECs) and has a role in the regulation of physiological angiogenesis (*Science* published online, doi: 10.1126/science.1174381; 21 May 2009). The authors report that overexpression of miR-92a in cultured ECs blocked angiogenesis-related cellular phenotypes such as sprout formation in a spheroid-based assay. Accordingly, inhibition of miR-92a with antagomirs increased sprout formation. Systemic treatment of mice with antagomirs reduced necrosis and enhanced recovery of blood flow in a mouse limb ischemia model and improved recovery of heart function in a mouse model of acute myocardial infarction. The authors further identified integrin subunit α5 (ITGA5) mRNA as a direct target of miR-92a and showed that overexpression of ITGA5 mRNA partially rescued sprout formation in ECs overexpressing miR-92a. This work shows that miR-92a has a regulatory role in angiogenesis and suggests that it may be a therapeutic target for treatment of ischemic injury. *EN*

Mice with humanized Foxp2

Heterozygous loss-of-function mutations in human *FOXP2* cause a developmental syndrome marked by speech and language deficits. Comparative sequence analyses have also led to the proposal that *FOXP2* has been subject to positive selection in the human lineage, resulting in the fixation of two amino acid substitutions in human FOXP2 compared to chimpanzee. To test whether these substitutions have functional effects *in vivo*, Svante Pääbo and colleagues (*Cell* **137**, 961–971; 2009) engineered mice expressing a humanized version of Foxp2 with these two specific amino acid changes. They then comprehensively assessed close to 300 phenotypic parameters and found that the mice showed a specific phenotype marked by reduced exploratory behavior. The mice also exhibited reduced dopamine levels in the brain, increased dendritic length of striatal neurons and increased long-term synaptic depression of corticostriatal synapses. The authors also examined vocalization patterns and found that the mice showed subtle alterations in the structure of their isolation calls. These observations are consistent with the hypothesis that the emergence of these two amino acid substitutions in the human lineage was driven by positive selection for traits related to brain functions mediated by cortico-basal ganglia circuits. *KV*

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OPHN1 and synapse function

Many genes have been linked to mental retardation, but the pathophysiological mechanisms that disrupt cognitive function are not well characterized. Several loss-of-function mutations in *OPHN1* (oligophrenin-1), encoding a Rho-GTPase-activation protein (Rho-GAP), have been reported in mental retardation, although the neuronal function of OPHN1 has been difficult to define. Linda Van Aelst and colleagues report (*Genes Dev.* **23**, 1289–1302; 2009) that OPHN1 regulates activity-dependent synaptic maturation and plasticity by controlling synaptic stability. Using OPHN1 RNAi in hippocampal slices, the authors demonstrated that OPHN1 is necessary for excitatory synaptic transmission and regulates glutamatergic synapse maturation. Disruption of OPHN1 signaling also led to destabilization of synaptic receptors and spine structure, resulting in eventual synaptic loss. By chemically blocking spontaneous neuronal activity, the authors further showed that OPHN1's effect on the functional maturation of synapses is activity dependent. These results reveal a positive feedback loop between OPHN1 signaling and synaptic activity, suggesting that decreased activity during critical stages of synaptic development may result in weakened synapses. These data offer a potential link between loss of OPHN1 function in mental retardation and impaired synaptic function and development in the brain. *PC*

Selective geography

In exploring the genetic basis of human adaptation, recent genome-wide screens have sought to pinpoint specific genes showing evidence for positive selection. Confirming selection, differentiating signals from extremes of the neutral distribution, and interpreting these reports in the context of human evolution have proven more challenging. Jonathan Pritchard and colleagues now examine the geographical distribution of proposed selected alleles in order to consider the strength of positive selection acting on the human genome in recent history (*PLoS Genet.* 5, e1000500; 2009) The authors draw on two genome-wide SNP datasets, HapMap Phase II and CEPH-HGDP. They find that few SNPs show extreme allele frequency differences between closely related populations (as measured by mean F_{st}), and that the allele frequency distribution can largely be predicted from patterns in neutral loci. This suggests that strong selection driving allele frequencies to high levels in close populations has been rare in recent history, and that neutral processes such as population history, migration and drift have exerted a strong force. Although they did not find support for strong selection at individual loci, weaker selection at multiple loci could also drive local adaptation. ***OB***