Psoriasis risk variants

Ann Begovich and colleagues (*Am. J. Hum. Genet.*, in the press) report results of a multi-tiered, gene-centric SNP scan for genetic variants associated with psoriasis. Starting with a 25,215-SNP marker panel and an initial discovery sample of 466 psoriasis cases and 500 controls and following up by additional testing in two independent replication samples from the same North American population, the authors identified two common variants in *IL12B* that were consistently associated with psoriasis risk across all three data sets. These two markers also defined a common risk haplotype and a less common protective haplotype that were each strongly and consistently associated with the disease. The authors then examined SNPs in other genes implicated in IL12 signaling and found that variation in *IL23R*, encoding a receptor for the related cytokine IL23, was also strongly and consistently associated with psoriasis. Recently, one of the psoriasis-associated risk variants in *IL23R* was independently associated with increased risk of inflammatory bowel disease (*Science* **314**, 1461–1463; 2006), suggesting that variants in this pathway might be common susceptibility factors for several distinct inflammatory diseases. *KV*

Nodule development without rhizobia

Leguminous plants can undergo a special developmental process to form root nodules that are inhabited by symbiotic nitrogen-fixing rhizobia. To initiate infection, rhizobia produce Nod factors that stimulate signaling events within the plant to trigger the formation of a nodule primordium and infection threads that deliver rhizobia to the nodule primordium. The pathways that trigger nodulation are not well understood, but now Jens Stougaard and colleagues show that cytokinin signaling is required for the initiation of nodule development (*Science*, published online 16 November 2006; doi:10.1126/science.1132397). The authors studied the dominant *snf2* mutant of *Lotus japonicus*, which develops root nodules in the absence of rhizobial infection. The authors genetically mapped the *snf2* mutant and identified a missense mutation in *LHK1*, which encodes a histidine kinase with cytokinin binding domains. In an assay of kinase function, wild-type LHK1 was active only when stimulated by cytokinin, but the *snf2* mutant exhibited cytokinin-independent activity, showing that the mutation causes a gain of function. Transformation of a *snf2* mutant construct into *Lotus* lines with mutations in Nod factor receptors demonstrated that *snf2* caused spontaneous nodule formation in these lines, indicating that cytokinin signaling acts downstream of Nod factor signaling. *EN*

Rhizobial infection without nodules

In a complementary approach to that of Jens Stougaard and colleagues (see above), Krzysztof Szczyglowski and colleagues show that loss-of-function mutations in *LHK1* impair nodule development (*Science*, published online 16 November 2006; doi:10.1126/science.1132514). In *Lotus japonicus*, the HAR1 receptor kinase negatively regulates nodulation; upon inoculation with rhizobia, *har1* mutants form an excessive number of nodules. In a previous effort to discover new members of nodulation signaling pathways, the authors screened for suppressors of a *har1* mutant. The screen turned up three allelic suppressor lines; the corresponding locus was named *HIT1*. The *har1 hit1* double mutant lines had a hyperinfected phenotype with excessive formation of infection threads but low numbers of nodules and failure to form nodule primordia. Because *HIT1* is located in the same genetic interval as the *snf2* mutant, the *LHK1* gene was a strong candidate. Indeed, the authors identified mutations predicted to cause premature stop codons in *LHK1* in all three *hit1* lines. Roots of *hit1* mutants were abnormally insensitive to exogenous application of cytokinin, supporting the hypothesis that the *hit1* mutants are loss-of-function alleles of *LHK1*. Taken together, these results show that cytokinin signaling is an essential event during the formation of nodule symbioses. *EN*

Research Highlights written by Emily Niemitz, Alan Packer and Kyle Vogan.

Neuronal asymmetry gets an early start

In *Caenorhabditis elegans*, the two postmitotic chemosensory neurons, ASE left and ASE right, demonstrate functional asymmetry despite similar patterns of gene expression. The small differences in chemoreceptor expression that establish functional asymmetry are controlled by a microRNA-dependent feedback loop. New work by Richard Poole and Oliver Hobert shows that this program is triggered by asymmetries that are already present in the early embryo (*Curr. Biol.* **16**, 2279–2292; 2006). Taking advantage of a *C. elegans* mutant in which visceral asymmetries in the adult are reversed by randomization of spindle rotation at the six-cell stage, Poole and Herbert observed that ASE asymmetry was also randomized. They went on to use a temperature-sensitive *glp-1* mutant to generate an ectopic left-sided lineage on the right side of the embryo, and vice versa. As the fate acquired by each ASE chemosensory neuron was lineage dependent rather than position dependent, the authors concluded that this decision is determined by early blastomere identity. Additional experiments indicate that ASE asymmetry is generated in part by asymmetries that exist as early as the one-cell stage, and the authors suggest that neural asymmetries in other animals are similarly established by very early symmetry-breaking events. *AP*

Intestinal folate transport

Folate is an essential nutrient that is absorbed in the small intestine through the activity of a specific transport protein whose identity, until now, remained elusive. David Goldman and colleagues (*Cell* **127**, 917–928; 2006) now show that this key transport activity in humans is mediated by SLC46A1, a protein previously described as an intestinal heme transporter (*Cell* **122**, 789–801; 2005). Like the endogenous intestinal folate transporter, SLC46A1 functions optimally at low pH and shows high specificity for folate and anti-folate compounds. Electrophysiological studies show that SLC46A1-mediated folate transport is proton coupled, suggesting that efficient folate uptake is partially driven by the pH gradient that exists across the intestinal brush border. The physiological role of SLC46A1 in mediating folate uptake in humans is further supported by genetic evidence showing that two affected siblings with hereditary folate malabsorption carried a homozygous mutation in a splice acceptor site of *SLC46A1*, yielding a nonfunctional protein with an in-frame deletion of 28 amino acids. In both cases, the disease symptoms were alleviated though high-dose folate supplementation, suggesting that SLC46A1 is not essential for normal iron homeostasis. *KV*