CEP290 and childhood blindness

Two groups recently showed that mutations in *CEP290*, which encodes a protein localized to centrosomes and cilia, underlie a pleiotropic recessive disorder characterized by cerebellar, retinal and renal disease symptoms. Now, Anneke den Hollander and colleagues (*Am. J. Hum. Genet.*, in the press) report that mutations in *CEP290* are also a common cause of retinal disease without cerebellar or renal involvement. By performing a linkage scan in a consanguineous French Canadian kindred, the authors mapped a locus for Leber congenital amaurosis (LCA) to the region of chromosome 12 containing *CEP290*. Affected siblings were found to be homozygous for a mutation in intron 26, resulting in an aberrantly spliced transcript with a premature stop codon. The authors screened 76 additional unrelated individuals with LCA and found four who were homozygous for the same splicing mutation and 12 who were compound heterozygous for the splicing mutation and a second mutation in *CEP290*. The *CEP290* splicing mutation was found in individuals from Germany, The Netherlands, Italy and Canada, identifying this as a frequent cause of LCA in populations of European ancestry. Low levels of wild-type transcript produced from the mutant allele may explain the absence of cerebellar and renal involvement in individuals carrying this mutation. ***KV***

New small RNAs

Argonaute proteins are components of the RNA silencing effector complex. The Piwi subfamily of Argonaute proteins is known to be required for spermatogenesis in the mouse, but their function and targets are unknown. Now, three groups have independently identified a new class of small RNAs that interact with Piwi proteins in mammals (*Science*, published online 15 June 2006 (doi 10.1126/science.1130164); *Nature* advance online publication 4 June 2006 (doi 10.1038/nature04916) and *Nature* advance online publication 4 June 2006 (doi 10.1038/nature04917)). By cDNA sequencing of Piwi-associated RNAs in the testis and by searching for small RNA populations in the testis, the groups identified a new class of small RNAs that they term Piwi-interacting RNAs (piRNAs). The authors show that piRNAs are 29–30 nucleotides long, have a strong bias for U at the first nucleotide position and are encoded by distinct genomic regions that occur in clusters. Interestingly, piRNAs are produced from similarly located clusters in mouse, rat and human, although the sequence conservation of piRNAs is low. Gregory Hannon and colleagues and Thomas Tuschl and colleagues both report that piRNAs are first expressed in spermatocytes in the pachytene stage of meiosis but that production ceases before the production of mature sperm. Robert Kingston and colleagues report detection of a weak cleavage activity directed against a complementary RNA substrate. The function of this new class of small RNAs is open to investigation. *EN*

CDK and meiotic recombination

DNA replication, recombination and chiasma formation must be temporally coordinated prior to and during meiotic prophase. Although some evidence suggests that the cyclin-dependent kinase Cdc28 is required in budding yeast for both pre-meiotic DNA replication and subsequent exit from the pachytene stage, it has not been clear if it also regulates recombination. Kiersten Henderson and colleagues now report experiments showing that Cdc28 does have such a role in yeast (*Cell* **125**, 1321–1332; 2006). They began by demonstrating that Mer2, originally identified as a protein required for meiotic recombination, is associated with chromatin during the stages when recombination takes place. Subsequently, Henderson *et al.* showed that Mer2 is a phosphoprotein that is phosphorylated *in vitro* on two different serine residues by Cdc28. *In vivo*, Mer2 phosphorylation is reduced by an inhibitor of Cdc28. Moreover, in cells containing Mer2 mutants with substitutions at these serines, double-strand break formation and recombination were not detectable above background levels. Finally, these Mer2 mutants have a reduced capacity to interact with several other proteins that are involved in double-strand break formation. Together, these results show that there is a direct connection between a key regulator of the cell cycle and the machinery of meiotic recombination. *AP*

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

Generating follicle patterns in mice

Denis Headon and colleagues (*Proc. Natl. Acad. Sci. USA* **103**, 9075–9080; 2006) propose a model to explain the generation of the primary hair follicle pattern in mice. The authors noted that the ectodysplasin receptor (Edar), required for primary hair follicle formation, is expressed uniformly in naïve epidermis but becomes upregulated in nascent follicles and downregulated in surrounding cells as the primary follicle pattern emerges. To explain this pattern, they hypothesized that Edar activates its own expression locally but induces a diffusible inhibitor that represses *Edar* expression in surrounding cells. Indeed, they found that members of the bone morphogenetic protein (BMP) family, which are known to inhibit follicle formation, are expressed in the dermis underlying nascent follicles and can repress *Edar* expression in explants. They also found that connective tissue growth factor (CTGF), an inhibitor of BMP signaling, is expressed in follicle placodes and upregulated by Edar signaling, providing a mechanism to antagonize the inhibitory effects of BMPs locally. The data are consistent with a model in which interactions between Edar and BMP signaling act as an activation-inhibition system to determine the ordered pattern of primary hair follicles in developing skin. *KV*

Fitness cost of resistance

Mycobacterium tuberculosis resistance to the antibiotic rifampicin is commonly conferred by mutations in *rpoB*, which encodes the β subunit of RNA polymerase, and individual *rpoB* mutations have been associated with a fitness cost within laboratory settings. Now, Sebastien Gagneux and colleagues have examined the fitness of a range of acquired *rpoB* mutations conferring rifampicin resistance within *in vitro* competition assays. (*Science* 312, 1944–1946; 2006) They studied two common pan-susceptible *M. tuberculosis* strains, CDC1551 (a clinical strain associated with Europe and the Americas) and the T85 Beijing strain (associated with East Asia). The *rpoB* mutants isolated from either strain all showed reduced fitness compared with their susceptible ancestor strain. Moreover, some of the same *rpoB* mutations showed different fitness costs between the two strains, suggesting a combined influence of mutation and genetic background on strain fitness. To consider the relevance of these laboratory competition studies on resistance emerging in patients, they examined the prevalence of the individual *rpoB* mutations in ten patients with acquired rifampicin resistance. Within this limited sample, they found that the *rpoB* mutation with the lowest fitness cost *in vitro* (*rpoB* S531L) was present in five out of ten of these clinical samples and showed either equal or slightly greater fitness than the susceptible ancestor strain, while the other mutations all showed reduced fitness. ***OB***