Farsighted to the extreme

Nanophthalmos is a rare genetic disorder in which the distance from the lens to the retina is unusually short due to inadequate postnatal growth along the visual axis, resulting in extreme hyperopia (farsightedness). Olof Sundin and colleagues (*Proc. Natl. Acad. Sci. USA* 102, 9553–9558; 2005) now show that a recessive form of this disorder results from mutations in *MFRP*, encoding a putative extracellular antagonist of Wnt signaling. Sundin and colleagues used linkage analysis and haplotype mapping in a large Amish kindred to localize a candidate locus for recessive nanophthalmos to a 2.1-Mb interval on 11q23. By sequencing candidate genes in the interval, they identified a frameshift mutation in *MFRP* that was homozygous in four affected individuals and heterozygous in a fifth affected member of the kindred. They then screened 26 independent kindreds and found two other families with homozygous or compound heterozygous *MFRP* mutations. Because mouse *Mfrp* is expressed predominantly in the retinal pigmented epithelium, Sundin and colleagues speculate that MFRP participates in a feedback mechanism to control growth of ocular tissues and maintain an optimal focal length during postnatal development. ***KV***

Transcriptional compensation

A range of mechanisms may contribute to the phenomenon, known as robustness, by which a cell compensates for the disruption of a gene. Recent studies explored transcriptional compensation, in which loss of a gene is followed by upregulation of a paralog or synthetic lethal (SSL) partner (*Nat Genet.* **37**, 295–299; 2005 and *Genetics* **167**, 35–49; 2004). Fritz Roth and colleagues, using a large collection of SSL interactions in *S. cerevisiae* (*Science* **303**, 808–813; 2004), have now quantified the extent of transcriptional compensation (*Genetics*, published online 5 July 2005; doi:10.1534/genetics.105.046060). They examined the transcriptional profiles of SSL pairs in strains in which one member of the gene pair was disrupted. In a screen that included 872 SSL pairs and a control set of more than 100,000 noninteracting pairs, they found a similar distribution for the log ratio of the expression of genes in mutant and control strains. This suggests that altered expression of the synthetic lethal pair after gene loss may not be a common occurrence on a global level. But the authors identified 13 examples of transcriptional upregulation, including 7 not previously described. Remaining questions include whether transcriptional upregulation, in the examples where it has been observed, is required for compensation. *OB*

Screens get a *REST*

Identifying genes that suppress tumorigenesis is a challenging but important endeavor. In a recent paper, Stephen Elledge and colleagues report their efforts to identify tumor suppressors using a loss-of-function screen for genes that prevent anchorage-independent proliferation of human mammary epithelial cells (*Cell* **121**, 837–848; 2005). They screened 28,000 'barcoded' shRNAs that target 9,000 genes; anchorage-independent colonies were pooled and microarray hybridization was used to identify the barcodes. Ninety percent of the identified growth-promoting shRNAs target eight genes, including putative or known tumor suppressors such as *PTEN*. But the screen also turned up shRNAs directed against *REST*, a transcriptional repressor that recruits Sin3A and histone deacetylase to promote silenced chromatin. In addition, array comparative genomic hybridization independently identified *REST* as a frequent target of deletion in colon cancer, and a truncating mutation of *REST* was identified in a colon cancer cell line. Signaling studies showed that PI(3)K-dependent signaling is required for transformation conferred by loss of *REST*. This work indicates that *REST*, previously known to repress neuronal gene transcription in non-neuronal cells, may additionally function to control PI(3)K signaling and act as a tumor suppressor. *EN*

The life and death of hot spots

The molecular features of meiotic recombination hot spots are still largely unknown. Alec Jeffreys and Rita Neumann have now reported an analysis by sperm typing of the *NID1* hot spot, located in intron 4 of the gene encoding nidogen (*Hum. Mol. Genet.*, published online 29 June 2005; doi:10.1093/hmg/ddi232). The *NID1* hot spot contains a highly palindromic minisatellite. Unlike the previously described hot spot associated with a minisatellite on chromosome 1, recombination exchange points in the *NID1* hot spot avoid the minisatellite, effectively establishing a 'cold spot' that splits the regions of high recombinational activity in two. Like the *DNA2* hot spot, the *NID1* hot spot contains a SNP near its center (M-57.8C→T) that shows crossover asymmetry and transmission distortion, with the recombination-suppressing T allele being incorporated into crossovers almost 75% of the time. At the population level, this distortion increases the likelihood of fixation of the T allele to >95%, providing more evidence for a general bias toward the fixation of recombination-suppressing alleles. The origin of the replacements for these dying hot spots remains an open and urgent question. *AP*

Individuality of twins

Different environmental exposures have been blamed for phenotypic discordance between monozygotic twins. Manel Esteller and colleagues have now shown a potential molecular basis for monozygotic twin discordance: the genomes of monozygotic twins accumulate epigenetic differences as they age (*Proc. Natl. Acad. Sci. USA* 102, 10604–10609; 2005). The authors measured genomic 5-methylcytosine and acetylated histone H3 and H4 content in 40 monozygotic twin pairs and showed that 35% of twin pairs had significantly different levels of all three epigenetic marks. Notably, there was a positive correlation between the age of the twins and the magnitude of the epigenetic divergence. A screen for loci with methylation differences identified both repetitive sequences and single-copy genes, and profiling of methylation at CpG islands showed that older twin pairs had 2.5 times as many methylation differences as younger twin pairs. Finally, microarray profiles showed greater differences in gene expression between the oldest twins compared with the youngest twins. It is not yet known whether these epigenetic changes occur because of environmental exposures or accumulate naturally, and so we can not yet identify the ultimate cause of phenotypic discordance. But given the importance of epigenetics in the control of cellular individuality, a role for epigenetics in the determination of organismal individuality seems plausible. ***EN***

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