Lin-28 blocks miRNA processing

Primary miRNA transcripts are processed to mature miRNAs through the activity of the Microprocessor complex; for some miRNAs, this critical processing step seems to be developmentally regulated. Richard Gregory and colleagues (*Science*, published online 21 February 2008; doi:10.1126/science.1154040) now show that Lin-28, an RNA binding protein first identified as a regulator of developmental timing in *C. elegans*, functions in ES cells and other undifferentiated cell types to block processing of the *let-7* family of miRNAs. After noting that primary *let-7* transcripts selectively accumulate in undifferentiated ES cells, the authors used affinity purification and mass spectroscopic sequencing to identify Lin-28 as one of several proteins co-purifying with pre–*let-7g*. They then showed, through numerous assays, that Lin-28 was necessary and sufficient to block processing of *let-7* family members to their mature miRNA forms. Notably, Lin-28 did not affect processing of other miRNAs tested, suggesting that Lin-28 selectively regulates a subset of primary miRNA transcripts. The authors propose that this post-transcriptional regulatory mechanism could serve as a means to coordinate the activity of multiple related miRNAs or to uncouple the activity of intronic miRNAs from the expression of their host transcripts. ***KV***

Differential allelic expression

Different expression of the two alleles of a gene can indicate a regulatory polymorphism or the presence of epigenetic regulation. David Serre and Thomas Hudson and colleagues report the use of an array-based high-throughput method to measure differential allelic expression (*PLoS Genet.* **4**, e1000006; 2008). The method compares the ratio of each allele in RNA to the ratio in DNA and detects deviations of allelic expression ratio larger than 60:40. The authors used the method to measure allelic expression for 2,968 SNPs (in 1,380 genes) in lymphoblastoid cell lines of over 80 individuals selected from Utah residents in the CEPH collection. Their analysis revealed differential allelic expression in 22% of genes. Many of these genes are located on the X chromosome, likely indicating clonality in the analyzed cell lines, or are imprinted, confirming the ability of the method to detect epigenetic mechanisms of regulation. The authors also tested for association between differential allelic expression and close-by SNPs, which were genotyped in these cell lines by the HapMap project. This analysis showed statistically strong evidence for regulatory haplotypes for 23 genes. This work demonstrates the feasibility and potential utility of high-throughput studies of differential allelic expression. *EN*

Genetics and personalized nutrition

Cecile Janssens and colleagues report a critical assessment of genetic associations that form the basis for genomic profiles used by companies in offering advice on personalized nutrition (*Am. J. Hum. Genet.* **82**, 593–599; 2008). The authors identified seven companies that offer predictive genetic testing using multiple markers and searched for meta-analyses that evaluated claims of association for the genes and polymorphisms used by each company to generate its profile. All told, the 7 companies tested at least 69 different polymorphisms in 56 genes, and Janssens *et al.* found 260 meta-analyses that evaluated the strength of the evidence associating these polymorphisms with disease. Of the 160 unique polymorphism-disease associations examined by meta-analysis, only 60 were statistically significant, and, when significant, the associations generally had modest odds ratios. Additional significantly associated polymorphisms often were found for diseases other than those associated with the genomic profile offered by the company. The authors conclude that "these results raise concern about the validity of combining tests for many different genetic variants into profiles, especially when the companies offering them do not describe how they created a composite profile from the results of tests for single genetic markers." *AP*

Written by Emily Niemitz, Alan Packer and Kyle Vogan

Breast cancer risk locus at 6q22

Following on recent efforts to identify common variants influencing breast cancer risk, Kenneth Offit and colleagues (*Proc. Natl. Acad. Sci. USA* **105**, 4340–4345; 2008) report results of a genome-wide association study for breast cancer in the Ashkenazi Jewish population. In their primary scan, the authors analyzed 150,080 SNPs in 299 cancer-free controls and 249 probands with a family history of breast cancer but lacking mutations in the known high-penetrance breast cancer risk genes *BRCA1* and *BRCA2*. The authors then selected 343 SNPs from 123 regions for genotyping in a replication cohort comprising 950 cases and 979 controls and collected data from 243 additional sporadic cases and 187 controls genotyped on the Affymetrix 500K SNP platform. In a joint analysis of all three phases, the authors found strong evidence of association to a cluster of SNPs on 6q22.33, with an estimated odds ratio of 1.4–1.5. The associated region contains two known genes, *RNF146* and *ECHDC1*; the adjacent linkage disequilibrium block includes *RSPO3*, encoding a ligand for the Wnt pathway. Given the well-established role for Wnt signaling in cancer, it seems possible that the variants confer risk through effects on *RSPO3* expression. *KV*

miR-17-92 and B-cell development

The miR-17-92 cluster of microRNAs has been implicated in tumorigenesis because it is frequently overexpressed in different tumor types, including B-cell lymphomas. Tyler Jacks and colleagues have created a targeted deletion of the miR-17-92 cluster in mice (*Cell* 132, 875–886; 2008), and they report that mice lacking miR-17-92 die shortly after birth and have hypoplastic lungs, ventricular septal defects, and defective B-cell development at the pro-B to pre-B transition. Conditional deletion of miR-17-92 in hematopoietic cells resulted in reduction of pre-B cells as a result of enhanced cell death. The authors determined that *Bcl2l11* (Bim), which is known to have a role in controlling lymphocyte apoptosis, is a direct target of miR-17-92 and BIM is upregulated in miR-17-92 null pro-B cells. In a separate publication, Klaus Rajewsky and colleagues also report the identification of *Bcl2l11* as a potential target of miR-17-92, (*Cell* 132, 860–874; 2008). These authors conditionally deleted Dicer, which has a key role in generation of mature microRNAs, in the B-cell lineage and found a block in B-cell development and overexpression of *Bcl2l11*. The authors crossed the conditional Dicer knockout onto a Bim null background, which generated a partial rescue of B-cell development. These papers bring insight into the function of miR-17-92 in embryonic and B-cell development. ***EN***