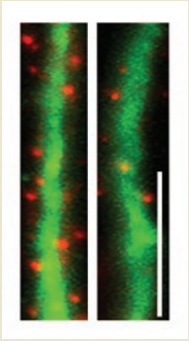
Rett's-like neurons from iPS cells



Induced pluripotent stem (iPS) cells offer the possibility of creating disease-specific cells that model pathology and can be used for screening therapies. Using skin biopsies from Rett syndrome patients, Marchetto *et al.* create iPS cells, from which they are able to create both neuronal progenitor cells and mature neurons. Whereas the progenitor cells appear normal, the Rett's-like neurons are both morphologically and functionally abnormal. This recapitulates the onset of disease, as symptoms don't appear until as long as 18 months after birth (when progenitors have differentiated). The authors show that knockdown of methyl-CpG–binding protein (MeCpG), which is mutated in Rett's patients, leads to cells with fewer synapses than neurons derived from iPS cells generated from normal individuals. Finally, the application of two drugs—insulin-like growth factor, which reverses the phenotype in a Rett's mouse model, and gentamicin, which reverses premature protein termination—partially rescues the Rett's-like neurons. By staining cell populations for proteins involved with X inactivation—of interest as MeCP2 is X linked—the authors could select iPS cells that had two active X chromosomes. Even so, during neuronal differentiation, re-inactivation of the X chromosomes was not random, suggesting the presence of some remnant of X inactivation after reprogramming. (*Cell* **143**, 527–539, 2010) *LD*

Personalizing epigenetic therapy

Unlike the genetic changes that contribute to the progression of liver cancer, the epigenetic modifications responsible for driving the development of the disease can be reversed by pharmacological intervention. Nonetheless, there is little understanding of the factors that influence whether the therapeutic effects of broad-spectrum chemical inhibitors of DNA methylation (e.g., reactivation of epigenetically silenced tumor suppressor genes) over-ride any detrimental consequences. Working with the cytidine analog zebularine, Anderson *et al.* use transcriptomic and epigenomic profiling to reveal a response signature that classifies liver cancer cell lines as being either sensitive or resistant to the drug. The ability of zebularine to promote apoptosis in sensitive cell lines correlates with reduced growth and metastasis of drug-sensitive tumors and prolonged survival of mice bearing xenografts of sensitive human tumors. In contrast, the drug increased tumor growth rates and decreased survival rates of mice bearing resistant xenografts—consistent with zebularine's ability to upregulate oncogenic pathways in cell lines predicted to be resistant to the drug. The ability of the signature to predict clinical outcome with 84–96% accuracy in a relatively small cohort of liver cancer patients suggests its value for identifying individuals most likely to benefit from methyltransferase inhibitors. (*Sci. Transl. Med.* **2**, 54ra77, 2010) *PH*

The 'omics of protein–small molecule interactions

Metabolites are important regulators of many proteins. Nonetheless, the systematic analysis of small molecule–protein interactions has lagged behind efforts to characterize, for example, the entirety of protein-protein or protein-DNA interactions. Now, Li *et al.* perform a large-scale analysis of hydrophobic metabolites that bind the enzymes of the ergosterol synthesis pathway and protein kinases in yeast. They affinity purify tagged versions of proteins of interest and identify protein-bound molecules by mass spectrometry after methanol extraction. In the ergosterol pathway, the authors uncover many previously unknown interactions between intermediate products and enzymes at other levels of the synthetic cascade. This suggests more integrated control of sterol synthesis than previously appreciated, although a detailed functional analysis of the significance of the interactions was not performed. Among the 103 kinases studied, 21 bind a total of ten different metabolites. The authors go on to demonstrate that the binding of ergosterol stabilizes Ssk22 and activates the highly conserved Ypk1 kinase. It seems likely that the approach could be adapted for hydrophilic molecules. (*Cell* **143**, 639–650, 2010) *ME*

Efficient discovery of rare genetic variants

With sequencing single genomes now commonplace, efforts are shifting to gather data from many individuals. The resulting increase in statistical power should identify rare genetic variants, which may underlie disease. Initial results toward this goal are reported in *Nature* by the 1000 Genomes Project Consortium, with analytic algorithms detailed in *Genome Research*. Three pilot sequencing efforts demonstrate efficient uses of sequencing to survey genetic variation. First, by reducing the average number of times any given region of the genome was sequenced, called 'low coverage' sequencing, the project analyzed 179 genomes. This identified most common single-nucleotide variants present in >5% of individuals and many less-common variants. Second, targeted sequencing of a subset of the genome allowed 8,140 exons to be analyzed across 697 individuals. Third, sequencing related individuals—in this case a mother, father and child from two families—enabled *de novo* germline mutations to be identified. In *Science*, Sudmant *et al.* used single, unique nucleotides found within repetitive regions of the genome to discover remarkable plasticity in copy number variation in duplicate genes, thereby making them amenable to genetic association studies. (*Nature* **467**, 1061–1073, 2010; *Genome Res.*, published online 27 October 2010, doi:10.1101/gr.1123267.110, doi:10.1101/gr.111120.110, doi:10.1101/gr.113084.110; *Science* **330**, 641–646, 2010) *CM*

lincRNAs in reprogramming

The reprogramming of somatic cells to induced pluripotent stem cells (iPSCs) is accompanied by widespread changes in gene expression and epigenetic marks. A recent study by Loewer *et al.* explores whether it also involves changes in the expression of long intervening noncoding RNAs (lincRNAs), a class of RNAs with diverse roles, including regulation of gene expression and of the epigenome. The authors began by comparing the expression of ~900 lincRNAs in human fibroblasts, in iPSCs derived from the fibroblasts and in human embryonic stem cells. This analysis identified 133 upregulated and 104 downregulated lincRNAs in the pluripotent cells compared with the fibroblasts. Twenty-eight of the upregulated lincRNAs were expressed more highly in iPSCs than in embryonic stem cells, suggesting a possible involvement in reprogramming. To identify a more generic association with reprogramming, the authors looked for lincRNAs upregulated in iPSCs derived both from fibroblasts and from $CD34^+$ cells. This approach yielded ten candidate lincRNAs, one of which was shown experimentally to influence reprogramming. (*Nat. Genet.* published online, 7 November 2010; doi:10.1038/ng.710) *KA*

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