Fragile X protein stalls ribosomes

Fragile X syndrome is the most commonly inherited form of intellectual disability and is caused by mutations affecting fragile X mental retardation protein (FMRP, encoded by *FMR1*). FMRP binds RNA and is thought to regulate translation, which is of interest because protein synthesis is necessary for long-term synaptic plasticity, a process involved in forming and maintaining memory. Now, Robert and Jennifer Darnell and colleagues use high-throughput sequencing–cross-linking immunoprecipitation (HITS-CLIP) to identify 842 RNA targets of FMRP (*Cell* 146, 247–261, 2011). The authors observed significant overlap of the FMRP targets with pre- and postsynaptic proteins, suggesting a direct role for FMRP in regulating the synaptic proteome. Unexpectedly, they found that 66% of FMRP binding occurs within the coding regions of transcripts. The authors hypothesized that the number of ribosomes associated with FMRP targets would decrease when FMRP is not present. However, their results showed no differences in target mRNA-polyribosome binding between *FMR1* knockout and wild-type littermates. Because the number of ribosomes on a transcript is not an accurate measurement of active translation, the authors looked at the ratio of translocating to stalled ribosomes on target transcripts. They found that ribosomes are stalled on FMRP-bound targets, but not in mice lacking FMRP function. ***PF***

Oligodendroglioma exome sequencing

Kenneth Kinzler and colleagues have identified recurrent somatic mutations in *CIC* and *FUBP1* in oligodendroglioma, the second most common malignant brain tumor in adults (*Science*, published online 4 August 2011; doi:10.1126/science.1210557). The authors sequenced the exomes of seven anaplastic oligodendrogliomas and they identified recurrent mutations in *PIK3CA*, *NOTCH1* and *IDH1*, confirming prior work. They then focused their attention on genes located on 1p and 19q, as these chromosome arms show frequent losses in oligodendrogliomas. *FUBP1* and *NOTCH2*, on 1p, were each mutated in two of seven tumors, whereas *CIC*, on 19q, was mutated in six of seven tumors. Follow-up sequencing of these three genes in 27 additional tumors identified 3 further mutations in *FUBP1* and 12 mutations in *CIC*. In *Drosophila*, the product of the *CIC* homolog *capicua* acts downstream of receptor tyrosine kinases to repress transcriptional targets in the absence of pathway stimulation. The *FUBP1* gene product binds single-stranded DNA and has been shown to regulate *MYC* expression. The patterns of somatic mutations are consistent with tumor-suppressor roles for both genes in oligodendroglioma. *KV*

Proteus syndrome exomes

Leslie Biesecker and colleagues report exome sequencing identifying the genetic basis of Proteus syndrome (*N. Engl. J. Med.*, published online 27 July 2011; doi:10.1056/NEJMoa1104017). Proteus syndrome is a rare developmental disorder characterized by severe overgrowths of tissue and bones that is also widely known by the name 'Elephant Man syndrome'. The authors sequenced 12 exomes, including 6 individuals with Proteus syndrome, their parents and one unaffected identical twin. They included samples from both affected and unaffected tissue and followed this with validation sequencing in additional cases, identifying somatic mutations in *AKT1* in 26 of 29 of individuals with Proteus syndrome. The *AKT1* mutation was found only in affected tissues, providing further support for the genetic mosaicism hypothesis proposed for this disorder over 20 years ago. Using an assay for AKT activation in tissues from cases and controls, the authors found that this *AKT1* mutation causes constitutive activation of AKT in affected tissues. AKT1 is in the same regulatory pathways as PTEN, which has previously been associated with Proteus-like syndromes. This may explain some of the clinical overlap in these segmental overgrowth disorders. *OB*

Written by Orli Bahcall, Pamela Feliciano, Emily Niemitz & Kyle Vogan

Neurons from Alzheimer's fibroblasts

The conversion of mouse skin fibroblasts directly to neurons was recently demonstrated, and now Asa Abeliovich and colleagues report the conversion of human skin fibroblasts from individuals with Alzheimer's disease (AD) directly into functional neurons (*Cell* **146**, 359–371, 2011). Viral co-transduction of human skin fibroblasts with the three factors sufficient for neuronal reprogramming in mouse was ineffective. However, co-transduction with two additional transcriptional regulators in the presence of neural survival factors led to the generation of neuronal-like cells (human-induced neuronal cells, or hIN cells). Further experiments showed that *ASCL1*, *BRN2* (also called *POU3F2*) and *ZIC1* were sufficient to convert human fibroblasts to hIN cells. To test whether reprogramming was directed or requires passage through a progenitor state, the authors looked at expression of Sox2 and Pax6 and found no evidence of a neuronal progenitor state. hIN cells possessed physiological properties of typical neurons and could integrate into neuronal circuits *in vitro* and *in vivo*. hiN cells from individuals with familial AD showed an increased Aβ42/Aβ40 ratio, consistent with phenotypes seen in persons with AD. The authors note that these experiments validate the utility of patient-derived cell models of neurodegenerative diseases and suggest that future work should focus on testing whether hIN cells from AD patients integrate into neuronal circuits *in vivo*. *PF*

Patient-derived isogenic iPSCs

Derivation of patient-specific induced pluripotent stem cells (iPSCs), and zinc-finger nuclease (ZFN)-mediated genome editing of human embryonic stem cells (ESCs) and iPSCs, have both been previously described. Now, Rudolf Jaenisch and colleagues report the combination of these methods to generate isogenic cell lines that differ solely at specific disease-related nucleotide variants (*Cell* 146, 318–331, 2011). The authors used ZFN-mediated genome editing, in which ZFNs were engineered to introduce a precise double strand break in α-synuclein, the disease underlying familial Parkinson's disease. They employed an exogenous donor template containing the Parkinson's-causing mutation A53T to introduce this single-base-pair change into human ESCs by homologous recombination. The authors then genetically repaired the A53T mutation in iPSCs derived from an individual with Parkinson's disease using a donor template containing the wild-type sequence. They found no evidence of possible off-target effects of ZFN-mediated genome editing when they looked for nonhomologous end-joining–created insertions or deletions. They also comparatively profiled the cells pre- and post-targeting by performing genome-wide copy-number variation (CNV) analysis and found no evidence of increased levels of genomic alterations due to ZFN-mediated genome editing. The combined use of these methods will allow for *in vitro* disease modeling that controls for genetic background effects. ***EN***