Dementia in a dish

Lawrence Goldstein and colleagues report the generation of induced pluripotent stem cell (iPSC) lines and their derived neurons from patients with sporadic late-onset Alzheimer's disease (LOAD), the most common form of the disease (*Cell Stem Cell* 16, 373–385, 2015). Although hundreds of genetic variants have been reported to associate with sporadic LOAD, the genetic heterogeneity of the disease and low penetrance of risk variants make it extremely difficult to determine how risk variants contribute to pathogenicity. Goldstein and colleagues focused on a single candidate risk gene, *SORL1*, which encodes an endocytic trafficking protein involved in regulation of APP processing. They observed no difference in *SORL1* expression levels between iPSC-derived neurons from patients with probable sporadic LOAD and those from patients without apparent dementia. However, only neurons carrying a known protective haplotype of *SORL1* were sensitive to a brain-derived neurotrophic factor (BDNF)-induced increase in SORL1 expression. Analysis of available case-control data supported the finding that the protective haplotype is dominant. The authors found that BDNF-induced SORL1 expression was correlated with a decrease in production of Aβ peptides and that this decrease required *SORL1*. These results point to a potential mechanism underlying the association between *SORL1* variants and LOAD. ***BL***

BRAF pseudogene induces cancer

The *in vivo* role of many pseudogenes remains largely unexplored, especially in cancer. Pier Paolo Pandolfi and colleagues show that overexpression of the *Braf* pseudogene *Braf-rs1* in mice causes the development of an aggressive malignancy similar to human diffuse large B cell lymphoma (*Cell* doi:10.1016/j.cell.2015.02.043; 2 April 2015). Their data suggest that the oncogenic potential of both *Braf-rs1* and its human ortholog, *BRAFP1*, is based on the function of their transcripts as competitive endogenous RNAs (ceRNAs). Indeed, *BRAFP1* seems to function as a sponge, sequestering microRNAs that target *BRAF*. As a consequence of elevated *BRAFP1* levels, BRAF is also upregulated, leading to the activation of MAPK signaling and increased cell proliferation. Importantly, *BRAFP1* is often altered in several human cancer types on a genomic or transcriptional level. This work provides an interesting example of a pseudogene involved in disease progression and proposes a ceRNA-mediated mechanism that underpins cancer development. *TF*

MicroRNAs dampen noisy expression

MicroRNAs repress gene expression by triggering mRNA degradation and inhibiting translation, but they generally have very modest effects on individual target genes. Now, Alexander van Oudenaarden and colleagues explore a possible function for microRNAs in the repression of expression noise (*Science* **348**, 128–132, 2015). The authors used mouse embryonic stem cells to quantify the effect of endogenous microRNAs on the levels of fluorescent reporter proteins in single cells and used this system to measure noise in protein expression when they varied the numbers and strengths of microRNA-binding sites in the reporter genes. They observed that microRNAs caused a reduction in noise at low levels of reporter protein expression and an increase in noise at high levels of reporter expression. They used the data to construct a mathematical model of microRNA-regulated gene expression noise. The model and the experiments suggest that reduction of intrinsic transcriptional noise is a general property of microRNAs. The authors also show that combinatorial microRNA regulation, in which mRNAs contain many binding sites for different microRNAs, enhances noise reduction. The authors conclude that the function of microRNAs in noise reduction may explain both combinatorial microRNA targeting and preferential targeting of weakly expressed genes by microRNAs. *EN*

Fine-tuning of transcription factor binding

Many transcription factors bind to regulatory genomic regions through the recognition of specific DNA sequences. Eran Segal and colleagues developed a new high-throughput method, termed BunDLE-seq (Binding to Designed Library, Extracting and Sequencing), that quantitatively measures transcription factor binding to thousands of 200-bp sequences in a single experimental assay (*Genome Res.* doi:10.1101/gr.185033.114; 11 March 2015). As proof of principle, they studied the binding dynamics of two yeast transcription factors, Gal4 and Gcn4. Interestingly, their data indicate that sequence variation flanking the core transcription factor binding site has a significant impact on binding. They also investigated the role of transcription factor concentration and the number and position of binding sites in events involving single or multiple transcription factors. This method, combined with cell type–specific epigenetic information, could have the potential to elucidate transcriptional mechanisms that contribute to the differential regulation of transcription factor target loci. It will be interesting to perform detailed comparisons of BunDLE-seq and ChIP-seq profiles and to test combinations of different transcription factors and other chromatin-binding proteins. *TF*

Bladder exstrophy risk variants

Bladder exstrophy is a congenital anomaly in which the bladder protrudes through the abdominal wall. To identify genetic risk factors for this disorder, Heiko Reutter and colleagues performed a genome-wide association study and meta-analysis comprising 208 bladder exstrophy cases and 1,703 unaffected controls (*PLoS Genet.* 11, e1005024, 2015). In their combined analysis, they identified a cluster of common variants at 5q11.1 that were associated with a twofold higher risk of developing classic bladder exstrophy. The top candidate gene in this region, *ISL1*, encodes a transcription factor expressed in a wide range of developing tissues, including a broad domain of expression in the cloacal region during urogenital development. Notably, conditional knockout studies in mice have shown that *Isl1* is required for normal kidney and ureteric development, supporting the suggestion that altered expression of *ISL1* could contribute to the etiology of human congenital anomalies of the kidney and urinary tract and could underlie the newly discovered association between variants in the 5q11.1 region and genetic predisposition to bladder exstrophy. ***KV***

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