Organization of the brain transcriptome

In order to generate a framework that can accurately describe complex patterns of gene expression in the human brain, Michael Oldham, Dan Geschwind and colleagues performed a network analysis of gene coexpression (*Nat. Neurosci.* advance online publication 12 October 2008; doi: 10.1038/nn.2207). The authors analyzed gene expression datasets generated from microarray analysis of human brain samples taken from cortical areas, the caudate nucleus and the cerebellar hemisphere. This analysis identified coexpression modules enriched for markers of major cell classes (oligodendrocytes, astrocytes and neurons) and of specialized cell types such as Purkinje neurons and meningeal cells. The authors showed that module membership can be used to annotate gene function. For example, their data predict that *C11orf9*, a gene of unknown function, is involved in oligodendroglial function and that *PREPL* and *TPD52* are associated with neuronal function. The authors also showed that comparisons based on differences in module membership can be used to identify gene expression patterns that can distinguish between subpopulations of cells. For example, the authors identified a set of genes, including *ALDH1L1*, whose expression can distinguish between subventricular zone astrocytes and protoplasmic astrocytes. This analysis reveals principles of transcriptome organization in the human brain and provides a useful resource for a variety of neurogenetic investigations. ***EN***

Unraveling Mre11 nuclease activity

The recognition, binding and repair of DNA double-strand breaks (DSBs) is a complex process that draws upon a multitude of proteins, including the Mre11-Rad50-Nbs1 (MRN) complex and ATM (ataxia-telangiectasia mutated). Besides tethering loose DSBs before repair and activating ATM, Mre11 possesses highly conserved DNA nuclease activities that have unknown roles in mammals. Now, Jeffrey Buis and colleagues (*Cell* **135**, 85–96, 2008) have engineered targeted mouse Mre11 alleles that either abrogate nuclease activity or inactivate the entire MRN complex. Nuclease-deficient embryos failed to develop normally, indicating that Mre11 nuclease activities are essential in the MRN complex. Cell lines derived from embryos generated from crosses harboring conditionally inactive wild-type and nuclease-deficient alleles showed that nuclease-deficient Mre11 is stable and maintains interactions within MRN. The spectrum of anomalies associated with nuclease-deficient Mre11 revealed a frequency and pattern of genomic instability with marked similarity to Mre11 null cells. They show definitively that the nuclease component is not required to activate ATM but is indispensable for repair of DSB lesions via homologous recombination. This work, in combination with an accompanying manuscript (*Cell* **135**, 97–109, 2008), now provides a mechanistic understanding of early events at DSBs, highlighting essential mitotic functions of MRN unrelated to ATM control. *LK*

Endodermal lineages reconsidered

During early mammalian development, the embryo proper arises from the epiblast, which produces the three principal germ layers—ectoderm, mesoderm and definitive endoderm. The visceral endoderm, which overlies the epiblast, is displaced by definitive endoderm during gastrulation and is thought to contribute exclusively to extraembryonic tissues. Now, a study by Anna-Katerina Hadjantonakis (*Dev. Cell* **15**, 509–520, 2008) shows, unexpectedly, that some visceral endoderm cells remain intermingled with the definitive endoderm as it emerges from the primitive streak and are eventually incorporated into the developing gut tube. To obtain a dynamic picture of the cell movements underlying early endoderm formation in mice, the authors marked visceral endoderm cells with live tracers and followed the fates of these cells during gastrulation. Rather than observing a mass displacement of visceral endoderm cells to extraembryonic regions, they instead found that definitive endoderm cells became intercalated with visceral endoderm cells to form an intermingled sheet. Although the authors were unable to follow the fate of the marked cells through late development, lineage-tracing in 12- to 18-somite stage embryos revealed persistence of labeled cells in the early gut tube, suggesting that the visceral endoderm contributes to both embryonic and extraembryonic lineages. *KV*

Nontelomeric role for TRF2

Telomere repeat factor 2 (TRF2) has a key role in protecting chromosome ends and maintaining telomere integrity. Now, Mark Mattson and colleagues report a nontelomeric role for TRF2 in the regulation of neuronal gene expression and control of neuronal cell fate (*Curr. Biol.* **18**, 1489–1494, 2008). The authors showed that expression of a dominant-negative form of TRF2 in neuroblastoma or embryonal carcinoma stem cells demonstrates that TRF2 is required for the maintenance of neural progenitors and stem cells in an undifferentiated state. Accordingly, they found that TRF2 interacts with REST, a master repressive regulator of neuronal genes. Expression of the dominant-negative form of TRF2 caused dissociation from and degradation of REST, indicating that TRF2 is involved in maintaining the stability of REST. The authors also determined that the dominant-negative form of TRF2 reduced REST binding at bona fide REST target genes and resulted in derepression of REST targets. Notably, the authors showed that these roles for TRF2 occur independently of telomere damage responses. This study reveals a new telomere-independent role for TRF2, and implicates TRF2 in processes controlling cell fate. *EN*

Duplication-rich regions getting richer

Up to 28% of larger interindividual copy number variants (CNVs) may result from meiotic rearrangement of existing segmental duplications (SD)—larger than 1 kb and with >90% sequence identity—that are fixed in the human population. SD are distributed according to a power law, according to a study of over 600 breakpoint sequences by Kim *et al.* published online in *Genome Research* (doi:10.1101/gr.081422.108). This means that the small number of duplication-containing regions are subject to processes in which the rich regions get richer. Segmental duplications co-localize with Alu repetitive elements. However, the correlation falls off with increasing similarity between repeats, suggesting that some of the segmental duplications were generated in a burst of Alu transposition some 40 Myr ago, a finding supported by similar divergence times for the SDs and the Alus. More recently, SDs themselves, microsatellites and LINE repetitive elements continue to be associated with CNVs. However, less than 10% of the sequenced CNV breakpoints had extensive stretches of homology that could attribute their genesis to regions of SD; rather, most had very short regions of homology, suggesting that nonhomologous end joining is the main current process of CNV genesis, as it is in subtelomeric regions. ***MA***

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