Recessive autism genes

While the search for common variants that increase risk for autism has not been very fruitful, the identification of rare, often *de novo*, changes that lead to autism has met with more success. Now, Christopher Walsh and colleagues report the results of their effort to identify recessive genes for autism risk (*Science* 321, 218–223; 2008). The authors used a collection of 88 autism families with parental consanguinity. Homozygosity mapping in these families revealed several potentially linked loci that were mostly family-specific. Interestingly, some of the linked loci contained large inherited deletions. One deletion in a child with autism and seizures removed an uncharacterized gene the authors named *DIA1* (deleted in autism1) and was near the 5′ end of the *NHE9* gene, which encodes a $(Na^+,K^+)/H^+$ exchanger. The authors identified a heterozygous nonsense mutation in *NHE9* in a non-consanguineous autism family with epilepsy or seizures, and they found an excess of rare, nonconservative coding changes in *NHE9* in autism cases with epilepsy compared to controls. *NHE9* and *DIA1* were both identified in screens for genes regulated by neuronal activity in rat hippocampal neurons. This study identifies good candidates for future studies, and it also implicates neuronal activity–dependent regulation of gene expression as a potential pathogenic mechanism underlying the autism phenotype. *EN*

Repairing damaged muscle

Amy Wagers and colleagues (*Cell* **134**, 37–47; 2008) report detailed characterization of a population of skeletal muscle precursors (SMPs) that shows considerable potential for treating muscle degenerative diseases. The same group previously reported (*Cell* **119**, 543–554; 2004) purification and initial characterization of this SMP population from mouse adult skeletal muscle, which they isolated by fluorescence-activated cell sorting using a defined set of cell surface markers. Here, they tested the ability of SMPs to engraft and repair dystrophic muscle in mice with mutations in *Dmd* (*mdx*), a model of Duchenne's muscular dystrophy. They found that transplanted SMPs efficiently populated the muscle tissue of recipient mice and led to significant improvement in muscle force production, up to 5.5-fold greater than mock-transplanted muscles. They also found that the transplanted cells were able to populate the muscle satellite cell niche and could be recruited for subsequent rounds of repair after muscle injury by intramuscular injection of cardiotoxin. The regenerative capacity of these transplanted cells, and their potential to reseed the satellite cell niche, offer hope that similarly purified cell populations might be an effective approach for treating degenerative muscle disorders in humans. *KV*

Specifying the germline

A few of the key events of germline specification have been identified, beginning with the role of Bmp signaling in generating a small number of alkaline phosphatase–positive cells in the developing epiblast. A central regulator downstream of this inductive event is the transcription factor Blimp1, and Kazuki Kurimoto and colleagues now present a comprehensive, single-cell-based transcriptional profiling study of presumptive primordial germ cells (PGCs) in the presence or absence of Blimp1 (*Genes Dev.* **22**, 1617–1635; 2008). The authors prepared single-cell cDNAs from wild-type and *Blimp1*$^{-/-}$ proximal epiblast cells of prestreak (embryonic day 6.25) mouse embryos, as well as early-to-mid and late streak stages. Microarray analysis showed that all lineage-restricted PGC precursors express *Hoxb1* initially, but subsequently repress *Hoxb1* in a Blimp1-dependent manner. Subsequent genome-wide expression analysis further showed that Blimp1 is involved in repressing a 'somatic program' and activating a large suite of 'specification genes'. The repressed somatic genes include cell cycle regulators and factors involved in epigenetic modifications, consistent with previous evidence that PGCs lengthen their cell cycle time and undergo genome-wide epigenetic reprogramming. The Blimp1-dependent specification genes represent about half of the complete gene expression program involved in PGC specification, suggesting a role for Blimp1-independent reprogramming (see Yamaji *et al.* on page 1016 of this issue). *AP*

Written by Emily Niemitz, Alan Packer & Kyle Vogan

DNA methylation and reprogramming

Epigenomic reprogramming occurs in mammals in germ cells and the embryo, and it has thus been associated with the acquisition of a pluripotent state. Now Wolf Reik and colleagues report the first genome-wide comparison in the mouse of promoter DNA methylation among germ cells, pluripotent cells and differentiated cells (*PLoS Genet.* **4**, e1000116; 2008). The authors used methylated DNA immunoprecipitation and genome-wide promoter tiling array detection to profile promoter methylation in embryonic germ (EG), embryonic stem (ES) and trophoblast stem (TS) cells, and in sperm cells and primary embryonic fibroblasts (pMEFs). Clustering analysis showed that sperm, EG and ES promoter methylation patterns correlate well, suggesting that sperm promoters have largely been reprogrammed. Further analysis revealed a few promoters that are hypermethylated in sperm and hypomethylated in ES and EG cells; this group includes key pluripotency regulators such as *Nanog*. A comparison of ES cells and pMEFs revealed a set of 69 gene promoters that are hypomethylated in ES cells and hypermethylated in pMEFs; no promoters showed the reverse pattern. This gene list includes some known pluripotency regulators, and the remaining genes are strong candidates for regulators of the pluripotent state. *EN*

CALHM1 and Alzheimer's disease

Despite successful mapping of several genes, including *APP*, underlying rare, autosomal dominant, early-onset forms of Alzheimer's disease, there has been limited progress in identifying variants contributing to late-onset forms of the disease. Philippe Marambaud and colleagues (*Cell* 133, 1149–1161; 2008) now report an impressive series of studies implicating a previously uncharacterized gene, *CALHM1*, as a modulator of APP processing and Alzheimer's disease risk. The authors selected *CALHM1* as a candidate after an *in silico* screen for genes expressed in the hippocampus. Initial functional studies identified CALHM1 as an ion channel influencing cytosolic Ca^{2+} concentration. Consistent with previous work implicating cytosolic Ca^{2+} in APP processing, knockdown of CALHM1 in differentiated neuronal cells resulted in elevated amounts of amyloid-β. The authors then tested a common CALHM1 coding variant, P86L, for association with late-onset Alzheimer's disease in five independent case-control samples of European ancestry and found that the variant was significantly associated with disease risk (meta-analysis $P = 2 \times 10^{-10}$). Compared to the wild-type protein, the P86L variant showed reduced Ca^{2+} permeability and caused a marked increase in secreted amyloid-β in transfected cells, suggesting a mechanism to explain the elevated disease risk. *KV*