Crop apomixis in the crosshairs

The ability to harness apomixis—asexual reproduction through seed to generate clonal progeny of maternal origin—in crops has long been sought by plant breeders as a way to fix hybrid vigor. However, these efforts have been thwarted by the need to simultaneously circumvent meiosis (apomeiosis), activate the egg without fertilization (parthenogenesis) and initiate endosperm formation without compromising agronomically important traits. Ravi *et al.* use an *Arabidopsis thaliana* mutant defective in *DYAD/SWITCH1*, a gene that regulates sister chromatid cohesion and centromere organization, to show that meiotic recombination and reduction can be bypassed by a single-gene manipulation. As *A. thaliana* mutations that mimic early parthenogenesis and initiate autonomous endosperm development have been reported previously, the demonstration that fertile female apomeiosis can be engineered in a sexually reproducing plant eliminates yet another obstacle to creating apomictic species. (*Nature* **451**, 1121–1124, 2008) *PH*

MS drug targets from proteomics

A proteomic analysis of the abundances of >2,500 proteins in three classes of multiple sclerosis (MS) lesions has identified proteins associated with disease progression. Perhaps the most striking observation of Han *et al.* is the strong association they found between five coagulation proteins and chronic active plaques. They used a mouse model of experimental autoimmune encephalomyelitis to demonstrate that two of these, tissue factor and protein C inhibitor, are indeed potential therapeutic targets. Inhibition of either protein at the peak of disease—using the approved drugs hirudin and recombinant activated protein C (aPC), respectively—ameliorated the severity of the symptoms, abated antigen-specific T-cell responses and reduced levels of inflammatory cytokines. Both the anticoagulant and signaling functions of aPC contributed to its therapeutic capacity. The study provides one of the most compelling examples to date of the potential of proteomics to reveal unanticipated mechanisms underlying complex pathologies. (*Nature* **451**, 1076–1081, 2008) *PH*

Dynamic nucleosomes

Higher order structures along chromosomes, such as histone modification patterns or nucleosome position, figure prominently in schemes for regulating gene expression. Whereas genome-wide profiles of histone modification have been created, nucleosome-positioning studies to date have involved restricted regions of genomes. Schones *et al.* now describe a method for analyzing on a large-scale nucleosome position by aligning along human chromosomes short sequence tags of micrococcal nuclease-digested chromatin. Using this method, they compared nucleosome positions around transcription start sites (TSS) in resting and activated $CD4^+$ T cells, and found more nucleosome boundaries in actively transcribed regions (eight nucleosomes phased relative to the TSS in active regions versus only one in an inactive region). In addition, they precisely mapped nucleosome repositioning that ensues when T cells are activated by T-cell receptor (TCR) signaling; in regions repressed by TCR signaling, more upstream nucleosome tags were detected, whereas in activated genes, nucleosomes disappeared from upstream positions and increased in downstream ones. This approach validates previous analyses of nucleosome redistribution and represents an improvement over other methods used, such as tiling microarrays, where resolution can be no greater than the probe density on the array. (*Cell* **132**, 887–898, 2008) *LD*

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Reprogrammed cells ID'd

Induced pluripotent stem (iPS) cells have so far been generated from mouse and human fibroblast cells by retroviral delivery of a handful of pluripotency-associated genes. But the identity of the cells that undergo reprogramming has not been conclusively established, and the low efficiency of the process has suggested that they may be rare stem cells rather than differentiated fibroblasts. Using their four original factors (Oct 3/4, Sox2, Klf4 and c-Myc), Yamanaka and colleagues have now generated iPS cells from adult mouse hepatocytes and gastric epithelial cells. These iPS cells differed from iPS cells derived from mouse embryonic fibroblasts (MEFs) in three ways: (i) they could be generated by selection for expression of *Fbx15*, (ii) chimeric mice derived from them had no tumors at 30 weeks, unlike chimeric mice derived from MEF-iPS cells, and (iii) they had fewer retroviral integration sites than MEF-iPS cells. A genetic lineage–tracing experiment showed that hepatocyte iPS cells arose from albumin-expressing cells, supporting the conclusion that the cells undergoing reprogramming were indeed differentiated cells. (*Sciencexpress*, published online 14 February 2008; doi: 10.1126/science.1154884) *KA*

Cyclophilin D and muscular dystrophy

Muscular dystrophies belong to a group of genetic diseases that cause muscle wasting and premature death. Many muscular dystrophy mutations affect proteins that repair the sarcolemma, the skeletal muscle cell membrane, or structural proteins that connect myofilament proteins to the sarcolemma, resulting in membrane microtears, an increased influx of calcium and cell death. Because no cures or good treatments exist, Millay *et al.* determine whether resistance to calcium-induced swelling can attenuate disease in distinct mouse models of muscular dystrophy. Deletion of the gene encoding cyclophilin D, a mitochondrial matrix prolyl *cis-trans* isomerase that directly regulates calcium-dependent mitochondrial permeability transition and necrotic cell death, reduced myofiber cell death and dystrophic disease in mice lacking δ-sarcoglycan ($Scgd^{-/-}$) or the α-2 chain of laminin-2. The authors also demonstrate that treatment of $Scgd^{-/-}$ or *mdx* mice—the latter being a Duchenne muscular dystrophy model—with Debio-025, a small molecule that inhibits most cyclophilin members equally, attenuated mitochondrial swelling and dystrophic disease. (*Nat. Med.* **14**, 442–447, 2008) *JWT*