This Month in Genetics

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Epigenetic Changes Increase Gene Conversion

One of the most common situations in which we see gene conversion is in cancer, for which loss of heterozygosity is an important consideration. The mechanisms regulating gene conversion and the selection of proper donor sequences are not well understood, so Cummings et al. attack this using a cell culture system and find a role for epigenetic modification in the regulation of gene conversion. DT40 cells are a chicken B cell line that continues to diversify immunoglobulin (Ig) chains through gene conversion. Through use of a lac system, the authors tether modifiers of chromatin activation—either VP16 or HIRA—to donor sequences and find that either protein increases the rate of gene conversion by 10-fold. This stimulation works through epigenetic mechanisms, although the two proteins use distinct epigenetic marks. Whereas VP16 increases the level of acetylated histones H3 and H4 in the donor sequences, HIRA alters the distribution of nucleosomes and increases histone H3.3. Thus, although epigenetic modifications influence gene conversion, it appears that this can occur through multiple, distinct marks.

Cummings et al. (2008). PLOS One 3, e4075. 10.1371/journal.pone.0004075.

DNA Demethylation Resembles DNA Repair

An important way in which cells modulate gene expression is through cytosine methylation at CpG dinucleotides in gene promoters. Multiple DNA methyltransferases have been characterized, but the process of demethylation is more of a mystery. Two recent papers suggest that demethylation occurs in a DNA repair-like fashion, rather than through the simple removal of a methyl group. Both papers implicate Gadd45 proteins as having a role in active DNA demethylation. First, in zebrafish embryos, Rai et al. find active demethylation of a microinjected in vitro-methylated DNA fragment. The process they observe appears to occur in two steps: methylcytosine deamination mediated by AID, followed by thymine base excision from a G:T intermediate, performed by the thymine glycosylase Mbd4. This process is promoted by Gadd45 family members, albeit through a mechanism that is unclear. In addition to being involved in demethylation in an artificial system, Ma et al. observed a role for a Gadd45 protein in vivo. In mice, synchronous neuronal activation by electroconvulsive treatment induced DNA demethylation and subsequent increases in expression of genes involved in adult neurogenesis, including BDNF and FGF. This process required Gadd45b, and it is a novel mechanistic link between transient neural activation and adult neurogenesis. Both papers put Gadd45 proteins at the scene of active DNA demethylation, but more work is required to fully unravel their role in this process.

Ma et al. (2009). Science, in press. Published online January 1, 2009. 10.1126/science.1166859.

Rai et al. (2008). Cell 135, 1201–1212.

Melatonin Receptor Associated with Plasma Glucose Levels

Four papers in the January issue of *Nature Genetics* link a key player in regulation of circadian rhythms with fasting plasma glucose levels and with risk of type 2 diabetes (T2D). SNPs in *MTNR1B*, which encodes the melatonin receptor 2, were associated with fasting plasma glucose even in samples of healthy, nondiabetic individuals, and they also predicted risk of T2D in multiple prospective samples. Melatonin is believed to inhibit insulin secretion, and there is an inverse relationship between the levels of melatonin and insulin over the course of the circadian cycle. In support of this relationship, Lyssenko et al. and Bouatia-Naji et al. both show that *MTNR1B* is expressed in pancreatic islets. Further, Lyssenko et al. demonstrate that beta cells incubated with melatonin secrete less insulin. Together, these papers provide strong support that *MTNR1B* is involved in glucose homeostasis, and they suggest a novel therapeutic avenue for the prevention or treatment of T2D.

Sabatti et al. (2009). Nat. Genet. 41, 35–46.

Prokopenko et al. (2009). Nat. Genet. 41, 77–81.

Lyssenko et al. (2009). Nat. Genet. 41, 82–88.

Bouatia-Naji et al. (2009). Nat. Genet. 41, 89–94.

Expanding the 15q13.3 Microdeletion Phenotype

Over the last year, microdeletions at chromosome 15q13.3 have been reported in people with schizophrenia, autism spectrum disorder, and a syndrome of mental retardation, epilepsy, and dysmorphic features. Helbig et al. report that the same microdeletions at 15q13.3 are even more commonly associated with idiopathic generalized epilepsy. The majority of their 12 probands had no intellectual

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disability or dysmorphic features, so they do not appear to have the previously described mental retardation and epilepsy syndrome. Penetrance appears to be an important consideration for these microdeletions; analysis of five sets of parental samples revealed three apparently unaffected carriers of the same deletion. A fourth parent also carried the deletion but had panic disorder, a phenotype that has already been associated with this microdeletion. This is the most common genetic risk factor identified for the generalized epilepsies to date. The obvious candidate gene in the deleted region is *CHRNA7*, which encodes a subunit of the nicotinergic acetylcholine receptor.

Helbig et al. (2009). Nat. Genet. Published online January 11, 2009. 10.1038/ng.292.

Treatment of Hemophilia A in Mice with Induced Pluripotent Cells

Through demonstrated survival of a normally fatal bleeding assay by mice with hemophilia A, Xu et al. have been the second group successful in their attempt to use induced pluripotent (iPS) cells to correct a monogenic disorder in mice. The wild-type iPS cells used in their study were derived from tail tip fibroblasts of a C57BL/6 mouse, a close relative of the hemophilia A mouse model. They were used to generate endothelial cells that were directly injected into the livers of affected mice. This treatment resulted in increased factor VIII expression in multiple organs with plasma factor VIII levels up to 12% of that in controls. This work follows on the heels of Hanna et al. (Science *318*, 1920–1923), who successfully treated sickle cell disease in a mouse using autologous iPS cells derived from tail tip fibroblasts. The genetic defect in the iPS cells was corrected in a targeted fashion, and they were used to make bone marrow cells for transplant. Concerns still exist regarding the use of viral vectors to express the factors needed to generate iPS cells, but these studies show that working out these issues could lead to valuable treatments for some Mendelian disorders.

Xu et al. (2009). Proc. Natl. Acad. Sci. U. S. A. 106, 808–813.