This Month in Genetics

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New Directions for Stuck Cholesterol

Niemann-Pick disease type C is caused by a defect in the movement of unesterified cholesterol from the late endosomal/lysosomal compartment to the cytosol. Throughout the body, cholesterol accumulates in these cellular compartments and ultimately leads to liver dysfunction and progressive neurological disease. Liu et al. realized that if they could circumvent the block in cholesterol movement, perhaps they could alter the disease course. They did single injections of the cholesterol-binding agent 2-hydroxypropyl-β-cyclodextrin (CYCLO) into 7-day-old *npc1*$^{-/-}$ mice and found that this agent solubilizes the cholesterol trapped in the lysosomes and allows it to proceed to the metabolically active cholesterol pool. Although CYCLO treatment had no observed effects in wild-type mice, treatment of *npc1*$^{-/-}$ mice led to significant declines in liver sterol concentration and normalized rates of sterol synthesis. More strikingly, although CYCLO was rapidly cleared from the body and cholesterol began to again accumulate in the lysosomal system, the single injection of the compound at day 7 had observable effects when the same mice were 49 days old. Treated mice had lower cholesterol levels in the liver and other organs, better liver function, and twice as many surviving Purkinje cells in the cerebellum as did their untreated counterparts. Further, the single injection led to an approximately 25% increase in longevity of the *npc1*$^{-/-}$ mice. There is still a lot to learn about the effects of this sterol-binding agent on Niemann-Pick disease, but CYCLO could be a useful tool to studying cholesterol trafficking out of the lysosomal system and the pathogenesis of this devastating disease.

Liu et al. (2009). Proc. Natl. Acad. Sci. USA 106, 2377–2382. 10.1073/pnas.0810895106.

Plant Model of Triplet Repeat Expansions

Despite the fact that trinucleotide repeat expansions cause more than a dozen different human neurologic diseases, we have a very limited understanding of how these repeats undergo large expansions within a single generation. An experimental system to study this mutational mechanism has so far been elusive because a model in which these mutations are similarly dynamic had not been found. That is, until the work by Sureshkumar et al. in which they found a strain of *Arabidopsis thaliana* that has a growth defect resulting from an intronic triplet repeat expansion. The phenotype in this strain is due to reduced expression of the gene in which the expansion occurs; overexpression of the mature RNA in mutant plants rescues the phenotype, and all of the 17 spontaneous revertants had reductions in the trinucleotide repeat length. Modifying factors seem to have a role in this phenotype, as evidenced by the fact that a minority of EMS-induced phenotypic revertants had repeat length reductions. These strains presumably have second site mutations within genes that influence the phenotypic consequences of the repeat expansion.

Sureshkumar et al. (2009). Science 323, 1060–1063. 10.1126/science.1164014.

Rescuing Yeast from Parkinson Disease

Although yeast obviously can't get Parkinson disease, that does not mean they can't be a useful model in which to study the disease. Proving this, Gitler et al. use yeast to identify an interaction between two Parkinson genes as well as an environmental risk factor. Dosage changes and mutations in α-synuclein cause familial Parkinson disease. Although this lipid binding protein is clearly involved in vesicle trafficking, we have a limited understanding of the pathogenesis of the synucleinopathies, including the relationship of α-synuclein to other Parkinson genes. Although yeast lack a clear homolog of α-synuclein, expression of human α-synuclein causes dose-dependent toxicity in yeast. Gitler et al. use this simple system to screen for modifiers of this toxicity and here find the first genetic connection between α-synuclein and *PARK9*, another gene involved in familial Parkinson disease. The yeast homolog of *PARK9* suppressed α-synuclein toxicity in their screen and also rescued the defect in trafficking from the ER to Golgi in these cells. The relevance of this interaction is underscored by the suppression of α-synuclein toxicity that was also found with *PARK9* homologs in *C. elegans* and in rat neurons. Beyond the link between two parkinsonism genes, the authors also tie this network to an environmental risk factor for parkinsonism, manganese. Yeast lacking the *PARK9* homolog are hypersensitive to manganese, and Gitler et al. suggest that PARK9 functions as a manganese transporter that protects cells from exposure to this neurotoxin.

Gitler et al. (2009). Nat. Genet., in press. Published online February 1, 2009. 10.1038/ng.300.

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LIS1 Overexpression Affects Brain Development

Sometimes too much of a good thing can be almost as bad as too little. Bi et al. identify duplications around chromosome 17p13.3, which corresponds to a region that, when deleted, is associated with lissencephaly and Miller-Dieker syndrome. The genes relevant to the deletions are *PAFAH1B1*, which encodes LIS1, and *YWHAE*. The majority of the seven duplications are de novo, and each has unique breakpoints. Only one encompasses both *PAFAH1B1* and *YWHAE*. Phenotypic comparisons indicate that *YWHAE* duplications tend to be associated with macrosomia, mild developmental delay, and a shared facial appearance. Increased dosage of *PAFAH1B1,* on the other hand, is associated with failure to thrive, more severe developmental delay, and microcephaly. In support of the relevance of the duplications to the phenotype of these patients, mice that overexpress LIS1 in the developing brain have smaller brains, along with disorganization in the ventricular zone that is marked by reductions in cell polarity and defects in neuronal migration. This work adds to the number of genomic regions that exhibit phenotypes when there is either an increased or a decreased dosage.

Bi et al. (2009). Nat. Genet. 41, 168–177. 10.1038/ng.302.

Correction of Methylation Defects by RNAi

Small RNAs can silence genes in various ways, but we normally think of them as acting on messenger RNA translation or stability. But—particularly in plants—RNAi mechanisms can also be used to guide epigenetic modifications. Teixeira et al. studied transgenerational remethylation in *Arabidopsis*. Mutations in the ATPase chromatin-remodeler gene *DDM1* cause severe loss of DNA methylation overall, but crosses with wild-type plants can progressively restore remethylation of many of these sequences over generations. However, if you look at the demethylated sequences more specifically, it turns out that some can be remethylated in this system, but others cannot, and these differences are consistent over many plant lines. An abundance of 24 nt RNAs corresponds to the remethylatable sequences and are crucial to this process; blocking production of these siRNAs prevents remethylation. Preventing transgenerational epigenetic defects is thus another in the list of functions for RNAi in *Arabidopsis*. The importance of this function is illustrated by the fact that transposable elements associated with remethylated sequences become resilenced when methylation occurs, whereas those in nonremethylated regions remain active.

Teixeira et al. (2009). Science, in press. Published online January 29, 2009. 10.1126/science.1165313.