This Month in Genetics

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Long-Term Epigenetic Consequences to Famine

In the late stages of World War II, Germany imposed a food embargo on The Netherlands, giving rise to a famine known as the Dutch Hunger Winter. Although this was a very unfortunate circumstance, the health-care and birth registries that were maintained during that time provide a valuable resource for examining the effects of famine on human development. These registries allowed the discovery that prenatal exposure to famine increases the risk of certain complex traits, including coronary artery disease and schizophrenia. Heijmans et al. provide a piece of data that hints at the involvement of epigenetics in these associations. They identified individuals who were born around the time of the Dutch Hunger Winter and used blood samples from these people—who are now in their sixties—to look for long-term methylation differences as a consequence of the famine. Comparing methylation levels at the *IGF2* imprinted locus in same-sex siblings—one conceived during the famine and one who was born before or conceived after the famine—they found a small but significant reduction in methylation at the *IGF2* differentially methylated region. These differences were observed only when the mothers went hungry early in fetal development; children conceived before the famine who had a late gestational exposure had *IGF2* methylation levels similar to those of their control siblings. This supports the idea that epigenetic marks are sensitive to environmental forces very early in development and that these exposures could have long-lived consequences that can be observed molecularly. Whether this explains any of the famine-associated risks of complex disease remains to be seen.

Heijmans et al. Proc. Natl. Acad. Sci. 105, 17046–17049. 10.1073/pnas.0806560105.

Genome Shuffle in Cultured ES Cells

When you make a new knockout mouse line, you have to assume that the knockouts differ from the parental strain only at the gene of interest; otherwise, you could be chasing down a red herring. Because you start with embryonic stem cells from an inbred line, this seems like a pretty safe assumption. New data from Liang et al. suggest that we may need to be somewhat wary of copy number variation (CNV) that arises during culturing of mouse embryonic stem (ES) cells. They used comparative genomic hybridization to compare 24 different germline-competent ES cell clones with their parental lines and found that there were 1–2 Mb deletions or duplications in seven of them. Even with relatively few cell divisions in culture, appreciable CNV gains or losses arose during these mitotic divisions, and these CNVs could be transmitted to the germline along with the targeted mutation. Some recurrent CNVs were identified in the study because they arose in subclones from different parental ES cell lines. Sequence analysis at the breakpoints suggests that these events are mediated by related sequences surrounding the CNVs. Not only are the mitotically derived CNVs that were observed in this study something to watch out for in mouse work, they open the question as to what might happen in human embryonic stem cells when they are in culture. They also hint at the idea that mitotically arising CNVs might yield more somatic variation in the genome than we might have thought.

Liang et al. Proc. Natl. Acad. Sci. 105, 17453–17456. 10.1073/pnas.0805638105.

Arabidopsis Uses Transcription to Prevent Transcription

The portion of the eukaryotic genome that encodes proteins is quite small, but we've recently recognized that a major portion of the genome is actually transcribed. The role of this widespread transcription is as yet unknown. In *Arabidopsis*, at least, Wierzbicki et al. found that some of these transcripts silence overlapping and nearby genes. The transcripts they studied are produced by the plant-specific RNA polymerase Pol V, and at the silenced sites, they mediate repressive chromatin modifications that impede transcription by the RNA polymerases II and III. Pol V seems to work in a promoter-independent fashion, so the selection of its targets is not understood. Once the transcripts are produced, however, they are necessary but not sufficient for the observed gene silencing; siRNA production is also required. Because we don't have Pol V in our cells, it remains to be seen whether any of the transcribed noncoding regions in our DNA have a similar role in gene regulation. These results do help explain the contradictory observation—which is not limited to plants—that you need

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transcription to maintain transcriptional silencing in heterochromatic regions.

Wierzbicki et al. Cell 135, 635–648. 10.1016/j.cell.2008.09.035.

Chromosome 11p15 Abnormalities in Nonsyndromic Wilms Tumor

Scott et al. report chromosome 11p15 defects in a significant proportion of people with nonsyndromic Wilms tumor, and the finding has important implications for these patients and their families. The imprinted chromosome 11p15 region is well known for its association with growth disturbance, particularly Beckwith-Wiedemann syndrome (BWS). Individuals with BWS are at increased risk of the childhood renal tumor Wilms tumor, but the association of constitutional abnormalities of this region with nonsyndromic Wilms tumor was not appreciated previously. In 3% of the sporadic cases and one familial case of nonsyndromic Wilms tumor in the study, an abnormality was identified. In most cases, the defect was either paternal uniparental disomy or hypermethylation of the H19 differentially methylated region (DMR). However, an atypical H19 DMR microdeletion and the first example of an H19 DMR microinsertion were also identified. Hypermethylation associated with the H19 DMR defects was found on only a proportion of the mutated alleles, at least in the blood, but this mosaicism does not appear to explain why the phenotype in these individuals was limited to Wilms tumor. Bilateral tumors were much more common in the individuals with an 11p15 defect, leading the authors to propose that an evaluation of this chromosomal region be performed for all individuals with Wilms tumor to allow their risk of a contralateral tumor to be assessed and also to provide better risk assessment for their relatives.

Scott et al. Nature Genetics 40, 1329–1334. 10.1038/ng.243.

AML Genome Sequence

The Philadelphia chromosome in chronic myelogenous leukemia, gene amplification of *HER2* in breast cancer, mismatch repair mutations in Lynch syndrome—we know several cytogenetic and molecular defects that are key to the initiation or progression of particular types of cancer. But some types of cancer, such as acute myeloid leukemia (AML), have been reticent in revealing their underlying genetic causes. Even genome-wide approaches to studying AML, including comparative genomic hybridization and single nucleotide polymorphism arrays, have yielded very little information on AML pathogenesis. Ley et al. thus decided to use a method of brute force, made possible by recent developments in sequencing technology, to identify some of these changes. Through sequence comparisons of a cytogenetically normal tumor genome with that of the patient's constitutional genome, they identified somatic mutations that arose in the tumor of a patient with AML. Many of the more than 63,000 single-nucleotide differences that resulted from this comparison were either in nongenic regions or were found in a sequence database, but eight of the single-nucleotide variants that were predicted to alter gene function were validated as somatic mutations. Four of these changes occurred in genes that belong to gene families known to be involved in cancer pathogenesis, but the other four have not previously been implicated in cancer. In all cases, these mutations were present at a frequency of ~50% in the tumor genome, so it is believed they are found in virtually all tumor cells in a heterozygous state. They are thus believed to have arisen very early in carcinogenesis and to be "drivers" of this pathologic process, making them some of the first candidate genes for involvement in AML initiation.

Ley et al. Nature 456, 66–72. 10.1038/nature07485.