This Month in Genetics

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Potential Treatment of Polycystic Kidney Disease with TNF-α Inhibitor

Dominant mutations in either *PKD1* or *PKD2* cause autosomal-dominant polycystic kidney disease (ADPKD), but it has been proposed that a two-hit mechanism—in which the remaining functional copy of the gene is somatically inactivated—is required for cyst formation in this disease. Arguing against this mechanism are the high rate at which cyst formation occurs in mutation carriers and the fact that hypomorphic alleles of *Pkd1* are sufficient for cyst formation in mice. Li et al. announce TNF-α as a nongenetic factor that might contribute to ADPKD, a result that suggests a potential pharmacologic intervention for reducing cyst formation. In mice, the authors found that TNF-α promotes cyst formation, particularly when polycystin-2 levels are reduced. Mechanistically, treatment of inner medullary collecting duct cells with TNF-α altered the localization of polycystin-2 protein and disrupted its interaction with polycystin-1, effects that appeared to occur through the action of the TNF-α-induced protein FIP2. The relevance of these findings is supported by the fact that TNF-α, FIP2, and the TNF-α-converting enzyme TACE accumulate in cyst fluids of people with ADPKD. Being as it is that an FDA-approved inhibitor of TNF-α, etanercept, is available, Li et al. tested its effects on cyst formation in mice. Etanercept prevented cyst formation in $Pkd2^{+/-}$ mice, yielding the hope that this drug might be useful in preventing or slowing the progression of cyst formation in individuals who carry ADPKD-associated mutations.

Li et al. (2008). Nature Medicine. Published online June 15, 2008. 10.1038/nm1783.

Metal Homeostasis in Alzheimer Disease

Despite having a variety of direct effects, many of the drugs that are under development for the treatment of Alzheimer disease (AD) are aimed at reducing β amyloid (Aβ) levels. One of the approaches targets brain metal ions, particularly Cu and Zn, because some researchers believe that disruption of their homeostasis is intimately tied to AD pathogenesis. In support of this idea, Adlard et al. find that one such drug, the 8-hydroxy quinoline PBT2, improves cognitive performance in two mouse models of AD within days of administration. But how exactly does PBT2 work? The levels of several Aβ species decrease in response to PBT2 treatment, but the only one that is consistently significant between both AD models is soluble interstitial Aβ, which means it could be the key to PBT2's utility in AD, and—more generally—that it has a key role in the acute cognitive deficits that are ameliorated by treatment with PBT2. Comparisons of the effects of PBT2 with the closely related drug clioquinol, which has weaker effects on cognitive performance in the mouse models, imply that the improved effects of PBT2 are due to its increased abilities to promote uptake of Zn and Cu, to cross the blood-brain barrier, and to inhibit the effects of excess metal binding to Aβ. Beyond suggesting that targeting Cu and Zn is a plausible approach for AD treatment, this work also highlights the idea that some of the cognitive defects associated with AD in mouse models are reversible.

Adlard et al. (2008). Neuron 59, 43–55. 10.1016/j.neuron.2008.06.018.

Beyond BRCA

The availability of genetic testing for mutations in *BRCA1* and *BRCA2* has had major implications for many families at high risk of breast cancer, a fact that is appreciated by much of the general public. The subtlety that tends to be underappreciated is this: Many families, even if they are at high risk of breast cancer, don't have mutations in either of these two genes. So what is the relevance of genetic testing for them? Could the common risk alleles that have been discovered for breast cancer through genome-wide association studies over the past couple of years provide the basis for genetic testing that would be relevant in a general population? This is the question explored by Pharoah et al., who generated risk profiles based on these common susceptibility alleles. The profiles suggest that, other than distinguishing between women in the highest and lowest risk groups, genetic testing for these alleles would not sufficiently discriminate between individuals in terms of breast cancer risk. For example, the 20% of the population at highest risk of breast cancer on the basis of this testing would account for less than 30% of breast cancer cases in the population. As additional susceptibility alleles are discovered, however, the

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risk profiles predict that genetic testing will be able to discriminate meaningful differences in risk for individuals. Currently, the utility of this testing, as envisioned by Pharoah et al., would be in the context of population-based screening. Genetic testing could permit the implementation of more efficient breast cancer screening programs wherein women at higher risk have earlier or more intense screening and those at lower risk may delay or avoid further screening.

Pharoah et al. The New England Journal of Medicine 358, 2796–2803.

DNA Methylation Map

We know that regulation of gene expression through DNA methylation is an essential process, and it has been possible for some time to examine DNA methylation on a limited scale through the use of bifulphite sequencing. Now Meissner et al. introduce reduced representation bisulphate sequencing (RRBS), which allows them to examine DNA methylation patterns on a genomic scale, including sequences from an estimated 90% of all CpG islands. Through RRBS, they compare, for example, DNA methylation patterns for different types of cells and promoters. They observe extensive changes to DNA methylation patterns during cellular differentiation, and they find that DNA methylation patterns are more closely correlated to histone methylation than to the underlying DNA sequence content. Undoubtedly, using this technique for further comparisons of DNA methylation patterns will give us an even greater understanding of the process and the role of DNA methylation in gene regulation.

Meissner et al. (2008). Nature. Published online July 6, 2008. 10.1038/nature07107.

Aging and DNA Methylation

While we're on the subject of DNA methylation, work by Bjornssen et al. looks at changes to DNA methylation with age. It has been hypothesized that epigenetic changes associated with aging could alter gene expression and ultimately contribute to some of the common adult-onset genetic diseases, but few data are available to prove that these age-related changes occur. In fact, Eckhardt et al. (Nature Genetics [2006] *38*, 1378–1385) grouped individuals by age and did not find evidence that DNA methylation changes over time. Now Bjornsson et al. have been able to examine DNA methylation on an individual level. Using two data sets in which blood samples were collected from the same individuals several years apart, they find evidence that global increases or decreases in DNA methylation can occur over a period of several years. The magnitude and direction of the change in DNA methylation tends to be similar between members of the same family, indicating that maintenance of the methylation pattern is a heritable trait. Because global DNA methylation decreased in approximately the same number of people as it increased, averaging the results across different age groups would neutralize the effects observed on an individual level, thus providing a likely explanation for the negative result of the previous work.

Bjornsson et al. (2008). JAMA 299, 2877–2883.