# This Month in Genetics

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## Another Potential Benefit of Antioxidants

Several groups have reported a high frequency of mitochondrial DNA (mtDNA) mutations in tumors, but the significance of these mutations to cancer development and progression is not fully understood. Ishikawa et al. report evidence that these mutations are important, not for tumor development, but for the development of metastatic potential. They compared mouse lung carcinoma cell lines, one of which had high metastatic potential (A11) and one of which had low metastatic potential (P29). The highly metastatic A11 cells exhibited reduced activity of the mitochondrial respiratory complex I, and complete replacement of the P29 mitochondria with A11 mitochondria transferred both the increased metastatic potential and decreased complex I activity to P29 cells. Similar results were obtained for another set of mouse cancer cell lines and a set of human cancer cell lines. Perhaps key to the metastasis-promoting character of A11 mtDNA is its association with increased production of reactive oxygen species (ROS) and subsequent changes in gene expression. These effects, including the increased potential for metastasis in a mouse model, could all be reversed if cells were treated with the ROS scavenger N-acetylcysteine. Of note, the antiapoptotic gene *MCL-1* was upregulated when A11 mtDNA was present, but the metastatic potential of these cells was suppressed if siRNA was used to downregulate expression of this gene. Not only do these results give us a greater understanding of the role of mtDNA in cancer, but they also suggest that ROS scavengers are of interest in therapies for controlling tumor metastasis.

*Ishikawa et al. (2008). Science Express March 3. 10.1126/science.1156906.*

## New Avenues for Cystic Fibrosis Research

How is cystic fibrosis like a lysosomal storage disorder? It appears that, similar to lysosomal storage disorders, cystic fibrosis is associated with an enzymatic deficiency that leads to build-up of a substrate that is normally degraded in lysosomes. Teichgraber et al. argue that reductions in the activity of certain lysosomal enzymes, namely acid sphingomyelinase (Asm) and—to a greater extent—acid ceramidase, are central to the pathogenic process in cystic fibrosis. Whereas Asm results in production of ceramide by cleavage of sphingomyelin, acid ceramidase degrades it to sphingosine. In mice deficient for CFTR, alkalinization of lysosomes alters the relative activity of these enzymes, resulting in higher levels of ceramide in the respiratory epithelium. Similar increases in ceramide were found in the nasal respiratory epithelium, the respiratory epithelium of the lung, and in submucosal glands of people with cystic fibrosis. The role of increased ceramide in the lung destruction that devastates people with cystic fibrosis is probably at least two-fold: The ceramide leads to increased inflammation in the absence of infection, and it also promotes cell death in the respiratory epithelium. When the respiratory epithelial cells die, their DNA is deposited on the mucosal surface, which promotes adherence of *Pseudomonas aeruginosa*, the major pathogen that infects people with cystic fibrosis. Perhaps most exciting from a medical perspective, all of these observations can be reversed by genetic or pharmacologic reductions in Asm activity, suggesting that ceramide plays a large role in the pathogenesis of cystic fibrosis. The drug used in these studies, amytriptyline, is an inhibitor of Asm activity and is already approved for use in humans as an antidepressant. Provided these results are validated, ceramide might become a key target for management of cystic fibrosis.

*Teichgraber et al. (2008). Nature Medicine 14, 382–391. 10.1038/nm1748.*

## If I Were a Geneticist …

If you've ever discussed your job with people at a cocktail party, I'm sure you're aware that the general public has some misconceptions about genetics research. Perhaps it's not surprising when cover stories such as "Fat Gene" and "Know Your Genetic Risks and How to Fight Them" appear on popular news magazines. As part of the GenEdNet project of ASHG, Shaw et al. decided to quantify genetic misconceptions among high-school students in the United States through use of essays submitted to the GenEdNet website as part of a contest. Of the 500 essays that were systematically reviewed in their study, over half (55.6%) contained at least one obvious misconception about genetics. When Shaw et al. grouped the misconceptions into related topics, they found that the most frequent category included statements in which the capabilities of genetic technology were overestimated. Such

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overestimates included the thought that perfect, designer babies will be possible in the near future. Perhaps more surprisingly, of the essays that had a misconception about patterns of inheritance, 80% inaccurately described a basic Mendelian principle, and terms such as DNA, gene, and chromosome were often used imprecisely. This work suggests that improvements need to be made in teaching genetics, even the basics, to our young people. Because these students are going to be the future consumers of genetic information, we might all begin to think about our role in the education of the public, both at school age and beyond.

*Shaw et al. (2008). Genetics 178, 1157–1168. 10.1534/genetics.107.084194.*

## When to Have HAART

Although it has huge benefit in the HIV-positive population, highly active antiretroviral therapy (HAART) is also expensive and has the potential for long-term toxicity. Thus, to reduce its negative effects, current guidelines for the prescription of HAART suggest that it not be given until the $CD4^+$ T cell count drops below a level of 350 $CD4^+$ T cells/$mm^3$. However, there is variability in the recovery of T cell counts in response to therapy, so a one-size-fits-all recommendation on the timing of HAART might not be the best way to go. Ahuja et al. report genetic underpinnings for some of the variability in response to HAART. They found that variation in the genes for CCR5, the major HIV coreceptor, and its ligand CCL3L1 influence the reconstitution of $CD4^+$ T cell counts in people on HAART. Specifically, there are *CCL3L1-CCR5* genetic risk groups that predicted impaired $CD4^+$ T cell recovery with HAART when it was initiated at $<350$ $CD4^+$ T cellsmm$^3$. They suggest that perhaps individuals with a genetically determined poor response to HAART might benefit if they are identified and given HAART early so that they can minimize the time they spend with risky $CD4^+$ T cell counts.

*Ahuja et al. (2008). Nature Medicine 14, 413–420. 10.1038/nm1741.*

## Rare Variants under Pressure

It is becoming evident that common genetic variants will be able to explain some of the phenotypic variation in complex traits, as proposed in the common disease-common variant hypothesis. But genome-wide association studies for some common traits, such as hypertension, haven't produced the same level of exciting results. Ji et al. wondered whether rare genetic variants might be the key to traits such as hypertension. They figured that carriers of rare mutations that cause severe recessive blood-pressure disorders might have different blood pressures than noncarriers. Indeed, in the Framingham Heart Study offspring cohort, they identified proven or inferred loss-of-function mutations in three genes—*SLC12A3*, *SLC12A1*, and *KCNJ1*—that produced clinically significant reductions in blood pressure. By age 60, mutation carriers have a striking 59% reduction in risk of hypertension when they are compared with noncarriers, an effect that is similar in size to that of current antihypertensive agents. Although these variants don't explain the majority of hypertension in a general population, they do suggest that perhaps multiple rare variants will together play a big role in the variability of certain complex traits.

*Ji et al. (2008). Nature Genetics, published online April 6, 2008, in press. 10/1038.ng.118.*