This Month in Genetics

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An *NQO1* Variant Affects Breast Cancer Prognosis and Treatment Response

After radiation and surgery, women with early-stage breast cancer are often given adjuvant therapy containing an anthracycline. Because these chemotherapeutic agents can have serious side effects—including heart damage and an increased risk of leukemia—and don't have beneficial effects in a significant proportion of women, researchers have been searching for factors that could predict the utility of anthracycline adjuvant therapy in individual women. Fagerholm et al. report that a common missense mutation in *NQO1* is predictive of reduced survival in women with breast cancer and is strongly associated with a defective response to anthracyclines. *NQO1* encodes the NAD(P)H:quinone oxidoreductase 1, which is involved in protection against oxidative stress and has a role in p53 stabilization. The missense change in this gene is associated with a complete deficiency for NQO1 activity, and especially among women who have breast cancer and are treated with anthracycline adjuvant therapy, those homozygous for the *NQO1* mutation have reduced rates of survival of breast cancer. Experiments in cell culture support the idea that NQO1 activity influences the responsiveness of cancer cells to anthracyclines and that these effects are mediated by p53. The *NQO1* genotype is also prognostic in the setting of metastasis; in women with metastatic breast cancer, none of the women homozygous for the *NQO1* mutation survived more than 26.7 months after the detection of a metastasis, whereas 51% of women without this genotype survived to this point. The potential importance of this genetic variation in the setting of breast cancer prognosis and treatment decisions is evidenced by the fact that 4% of people of European descent and 20% of those of Asian descent are homozygous for this missense change.

Fagerholm et al. (2008). Nature Genetics. Published online May 30, 2008. 10.1038/ng.155.

Transgenic Nonhuman Primate Model of Huntington Disease

Researchers have gotten very adept at generating animal models of human genetic disease, and these models have substantially increased our understanding of many diseases. The question remains as to how well a mouse or a fly model truly reflects the human disease process. Nonhuman primate models of these diseases might circumvent some of these issues because of their relatedness to humans, so the report by Yang et al. of a transgenic nonhuman primate model of Huntington disease (HD) is an exciting advance. Their rhesus macaque model was generated through insertion of exon 1 of the human *HTT* gene; this is the portion of the gene containing the disease-associated CAG repeat. To date, there have been five live-born macaques expressing the transgene. Three of them had multiple copies of the transgene and died within a month of birth, although not before developing evidence of movement dysfunction. Histopathological evidence of Htt aggregation and the formation of inclusions in the brain and other tissues were also evident. Of the remaining two macaques, who are now more than six months old, each expresses a single copy of the transgene, albeit with different CAG repeat lengths. The first has a normal CAG repeat length of 29 and shows no signs of movement dysfunction, whereas the second has a pathogenic CAG repeat length of 83 and showed evidence of dystonia and chorea within a week of his birth. Although these studies are in their infancy, Yang et al. have pushed the door open to new and more closely linked models of human disease.

Yang et al. (2008). Nature. Published online May 18, 2008.10.1038/nature06975.

A Role for *ARMS2* in AMD

Age-related macular degeneration (AMD) has been one of the great success stories for genetic-association studies of complex traits. Two chromosomal loci, 1q31 and 10q26, are major genetic contributors to the development of this disorder, which in developed countries is the leading cause of visual impairment in the elderly. Surrounding the chromosome 10q26 locus is a large block of linkage disequilibrium that includes two plausible candidate genes, *HTRA1* and *ARMS2*. Which of these genes actually contributes to AMD has been a matter of debate. Fritsche et al. argue that *ARMS2* might be the relevant gene for AMD. They discovered that a deletion-insertion polymorphism in the 3′ untranslated region of *ARMS2* removes a polyadenylation signal and inserts an AU-rich element. These changes destabilize transcripts expressed from this allele and lead to

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DOI 10.1016/j.ajhg.2008.06.017.

reductions in the amount of ARMS2 protein that is expressed. In fact, homozygosity for the risk allele obviates detectable ARMS2 protein expression in placental tissue. The instability of ARMS2 transcripts encoded by the deletion-insertion allele implicates the loss of ARMS2 function as a potential key to the development of AMD in some people, but although ARMS2 colocalizes with mitochondria in the rods and cones of the photoreceptor, its exact function remains unclear. Because the *ARMS2* risk allele is found at a frequency of 19% in a control population, a functional role for ARMS2 in the development of AMD would mean this allele could have a substantial contribution to AMD in a general population.

Fritsche et al. (2008). Nature Genetics. Published online May 30, 2008. 10.1038/ng.170.

miR-10a Enhances Ribosomal Protein Translation

MicroRNAs (miRNAs) are small RNAs that posttranscriptionally regulate gene expression. Most microRNAs (miRNAs) that have been studied bind to the 3′ untranslated region (UTR) of their target mRNAs and repress their translation. On both counts, miR-10a seems to be an exception to this rule; it binds to the 5′ UTR of its targets and enhances their expression. Many of miR-10a's targets are mRNAs for ribosomal proteins. These RNAs contain a TOP motif that provides the RNAs with a level of translational regulation that is environmentally sensitive. Under starvation conditions, the TOP motif usually induces translational repression of the mRNAs. However, miR-10a binds just downstream of the TOP motif and counteracts this effect, so the repression is relieved. At least under certain conditions, miR-10a thus increases expression of the ribosomal proteins and stimulates ribosomal biogenesis. As a result, global protein synthesis increases, and this increased synthesis in turn seems to promote cells to undergo transformation in vitro. This work opens the door to studies of a new system of regulation by miRNAs; this system isn't unique to miR-10a but is shared by other members of the miR-10 family and so may be relevant in many cell and tissue types in the body.

Orom et al. (2008). Molecular Cell 30, 460–471. 10.1016/j.molcel.2008.05.001.

Is ASK the Answer to ALS?

Mutations in *SOD1* are the most common known cause of familial amyotrophic lateral sclerosis (ALS), a disease characterized by the selective loss of motor neurons. Although we know that *SOD1* encodes the Cu/Zn-superoxide dismutase and that these mutations cause the death of motor neurons, it doesn't appear that these effects are due to a loss of *SOD1* enzymatic activity. It is also not clear how mutations in this widely expressed enzyme cause a disease with such cell specificity. In trying to tease apart the mechanism of neuronal cell death, Nishitoh et al. discovered that *SOD1* mutations inhibit endoplasmic-reticulum-associated degradation (ERAD) and trigger ER stress. These effects occur as a result of a Derlin-1—a component of the ERAD machinery—interaction that is specific to mutant forms of SOD1. The interaction with Derlin-1 triggers the ASK1-dependent apoptosis pathway and thereby induces cell death. In mice, the SOD1-Derlin-1 interaction is only observed in liver and neuronal tissues, perhaps providing a clue to the specificity of the pathogenic effects of SOD1 mutations. In support of a role for this pathway in SOD1-mediated ALS, *ASK1*-deficient neurons are more resistant to cell death induced by *SOD1* mutations. However, mice that lack *ASK1* are not protected from ALS, although their mean time of survival is extended by 10%. Clearly, this pathway is not the full story behind ALS, but it does provide hints to a mechanistic link between *SOD1* mutations and motor-neuron cell death.

Nishitoh et al. (2008). Genes and Development 22, 1451–1464.