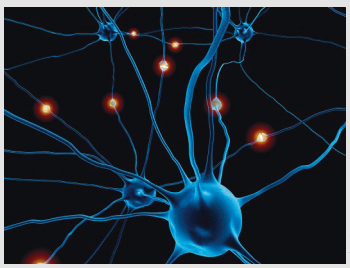
NEWS

Ubiquitination reduces pathogenicity of huntingtin aggregates



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Huntington disease (HD) is a progressive and fatal neurological disorder in which genomic expansion of the cytosine-adenine-guanine (CAG) repeat in exon 1 of the huntingtin gene, *HTT*, results in cytotoxic aggregates. These pathogenic aggregates are often found in tight association with components of the proteasomal degradation system, particularly ubiquitin. In a recent article published in the *Proceedings of the National Academy of Sciences* (www.pnas.org/cgi/doi/10.1073/pnas.2007667117), Hakim-Eshed and colleagues report that ubiquitination of pathogenic *HTT* may mitigate its harmful effects on cells. The researchers analyzed the ubiquitination profile of proteins extracted from striatal and cortical brain sections of bacterial artificial chromosome HD (BACHD) rats. BACHD rats, which express full-length human *HTT* with 97 CAG repeats under its own promoter and regulatory elements, display robust and early onset of HD-like deficits, including the accumulation of neuronal aggregates. The researchers determined that lysine residues 6 and 9 of pathogenic *HTT* were highly and specifically ubiquitinated. In contrast, these residues were not modified in age-matched wild-type animals. Next, the researchers modified a pathogenic version of *HTT* to harbor arginine residues in place of the affected lysine residues. When they observed rat cortical neurons expressing this construct or one with lysine residues, they found that the lysine expressing cells displayed larger aggregates than the arginine expressing cells. The finding suggests that the nucleation rate of large aggregates is faster in cells that harbor the lysine residues. Follow-up experiments revealed that the arginine-containing version of *HTT* produced consistently higher numbers of aggregates than the lysine-containing version. Lysine ubiquitination also only appeared in the insoluble fraction, suggesting that ubiquitination is unique to insoluble aggregates. Additionally, cells expressing the arginine construct were associated with reduced cell viability and more cell death compared with cells expressing the lysine construct. Finally, the researchers conducted proteomic analyses on the soluble fractions of cells expressing the two constructs. They found that many proteins were more abundant in cells expressing the lysine construct than the arginine construct, including those involved in RNA metabolism, intracellular transport, mitochondrial-related metabolism, and gene regulation. The results imply that cells expressing the lysineless protein mount a weaker response to pathogenic *HTT* and are less able to cope with proteotoxic stress. The authors conclude that, taken together, the data indicate a novel and beneficial role for ubiquitination of pathogenic *HTT*. —*V. L. Dengler, News Editor*

Toward the genetic origins of allergy risk

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Although genetic predisposition and early-life exposure to microbes and allergens can lead to complex disease later in life, little is known about regulation of gene expression in infancy and its impact on predisposing someone to disease in adulthood. In a recent article published in *Nature Communications* (https://www.nature.com/articles/s41467-020-17477-x), Huang and colleagues show the potential role for regulation of gene expression during the neonatal period in the pathogenesis of allergies and autoimmunity. The researchers collected cord blood samples from 152 neonates and conducted expression quantitative trait loci (eQTL) analysis on cells derived from cultures of resting and stimulated myeloid cells and T cells. They found that the majority of eQTL signals were specific to one cell type or condition, with stimulated cells bearing a larger number of *cis*-eQTLs and associated genes (eGenes) than resting cells. To examine the effect of external stimuli, the researchers identified response eQTLs (reQTLs) and response eGenes (reGenes) via interaction tests on the top eSNPs of each eGene. Similarly, they found that reQTL and reGene numbers were higher under stimulated versus resting conditions. The researchers then conducted GARFIELD enrichment analysis to assess the genetic overlap between neonatal gene expression and disease. The investigation revealed enrichment in *cis*-eQTLs for genetic variants associated with inflammatory bowel disease and allergic conditions such as asthma, hay fever, and eczema. A follow-up analysis identified 68 variants that shared eQTL and disease-associated genome-wide association study signals. For example, at the *BACH2* locus, the A allele at the top eSNP (rs72928038) was associated with reduced *BACH2* expression and increased risk for autoimmune thyroid disease, celiac disease, multiple sclerosis, and rheumatoid arthritis. Finally, the researchers performed two-sample Mendelian randomization analysis to identify causal effects of neonatal gene expression on autoimmune and allergic disease risk. They found several cause-and-effect relationships. For example, increased expression of *BTN3A2* in resting T cells was associated with decreased risk of childhood- and adult-onset asthma, allergic rhinitis, and systemic lupus erythematosus, but increased risk for inflammatory bowel disease, including Crohn disease. Neonatal HLA-C expression in T cells was associated with autoimmune diseases such as psoriasis and primary biliary cirrhosis. The authors conclude that the results suggest an important role for the genetic basis of gene expression during the neonatal period in understanding the origins of autoimmune and allergy risk. —*V. L. Dengler, News Editor*

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