EPIGENOME WIDE ASSOCIATIONS OF SMOKING BEHAVIOR IN THE HEALTH AND RETIREMENT STUDY

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DNA methylation (DNAm) is an increasingly popular biomarker of health and aging outcomes. Smoking behaviors have a significant and well documented correlation with methylation signatures within the epigenome and are important confounding variables to account for in epigenome-wide association studies (EWAS). However, the common classification of individuals as 'current', 'former', and 'never' smokers may miss crucial DNAm patterns associated with other smoking behaviors such as duration, intensity, and frequency of cigarette smoking, resulting in an underestimation of the contribution of smoking behaviors to DNAm and potentially biasing EWAS results. We investigated associations between multiple smoking behavioral phenotypes (smoking pack years, smoking duration, smoking start age, and smoking end age) and single site DNAm using linear regressions adjusting for age, sex, race/ethnicity, education, and cell-type proportions in a subsample of individuals who participated in the HRS 2016 Venous Blood Study (N=1,775). DNAm was measured using the Infinium Methylation EPIC BeadChip. All 4 phenotypes had significant associations (FDR < 0.05) with many methylation sites (packyears=6859, smoking duration=6572, start age=11374, quit age=773). There was not much overlap in DNAm sites between the full set of models with only 6 overlapping between all 4. However, the phenotypes packyears and smoking duration showed large overlap (N=3782). Results suggest additional smoking phenotypes beyond current/former/never smoker classification should be included in EWAS analyses to appropriately account for the influence of smoking behaviors on DNAm.

GENOMIC ANALYSIS OF NAD+ SYNTHESIS PATHWAYS INVOLVED IN AGING AND CANCER

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Cancer cells have elevated energy demands to sustain continuous growth and other malignant processes and undergo extensive metabolic reprogramming to meet these demands. One element of this reprogramming in many cancer subtypes is elevated synthesis of nicotinamide adenine dinucleotide (NAD+), a critical co-enzyme that supports energy production through both glycolysis and the TCA cycle. The kynurenine metabolic pathway is the evolutionarily conserved means by which cells produce NAD+ de novo from tryptophan. NAD+ levels drop with age, a contributing factor to many forms of age-related disease. While interventions that increase NAD+ have been shown to extend lifespan, previous work from our lab demonstrates that knockdown of several kynurenine pathway enzymes, thus decreasing de novo NAD+ production, results in increased longevity of Caenorhabditis elegans by 20-30%. To address this apparent contradiction, we propose that kynurenine pathway inhibition may produce metabolic feedback that results in upregulation of NAD+ recycling. Eukaryotic cells recycle NAD+ from nicotinamide (NAM) through one of two pathways: the Salvage pathway in mammalian cells and the Preiss-Handler pathway in C. elegans and related invertebrates species. We are using tools in C. elegans and human cell culture to examine the interaction between kynurenine/de novo NAD+ synthesis and NAD+ recycling through Salvage and Preiss-Handler. In particular, we are interested in how combining interventions between these pathways will influence activity throughout the NAD+ metabolic networks (measured via mass spectrometry), physiological phenotypes, and transcriptomic changes (via RNA sequence data) involved in aging and age-associated disease.

INSERTION OF THE PROTECTIVE APP A673T MUTATION BY CRISPR/CAS9 BASE EDITING OR PRIME EDITING.

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There is currently no treatment for Alzheimer disease (AD). However, the Icelandic mutation in the APP gene (A673T) has been shown to confer a protection against the onset and development of AD (Jonsson et al. Nature 2012). This single nucleotide mutation in APP exon 16 reduces the cleavage of the APP protein by the beta-secretase by 40% thus preventing the development of AD even in persons more than 95 years old. Our research group has initially shown that the presence of the A673T mutation in an APP gene reduced the secretion of beta-amyloid peptides even if there is also a FAD mutation in the gene. This is the case for 14 different FAD mutations. We have used CRISPR/Cas9 base editing and PRIME editing technologies to insert the A673T mutation in the APP gene. We have compared several different cytidine base editor complexes to achieve the most effective and accurate genome modification possible in HEK293T cells and in SH-SY5Y neuroblastomas. The insertion of the A673T mutation in cells containing the London mutation reduced the secretion of beta-amyloid peptides. We are currently using lentiviral vectors to infect neurons from a mouse model and human neurons induced from fibroblasts of a patient with the London mutation. The insertion of the protective Icelandic mutation in the APP gene using these editing technologies opens a new potential therapeutic avenue not only for Familial Alzheimer's diseases but also for sporadic Alzheimer's disease.

LINKS OF SLEEP DURATION WITH BIOMARKERS OF ACCELERATED AGING: THE BALTIMORE LONGITUDINAL STUDY OF AGING

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