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

Jonah Fisher,[1] Colter Mitchell,[2] Helen Meier,[1] Eileen Crimmins,[3] Bharat Thyagarajan,[4] and Jessica Faul,[2] *1. University of Michigan, Ann Arbor, Michigan, United States, 2. University of Michigan, University of Michigan, Michigan, United States, 3. University of Southern California, Los Angeles, California, United States, 4. University of Minnesota, Minneapolis, Minnesota, United States*

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

Jeremy Meyers,[1] Raul Castro-Portuguez,[2] Luis Espejo,[3] and George Sutphin,[2] *1. University of Arizona, Tucson, Arizona, United States, 2. The University of Arizona, Tucson, Arizona, United States, 3. UNIVERSITY OF ARIZONA, TUCSON, Arizona, United States*

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.

Jacques Tremblay,[1] Antoine Guyon,[2] Joël Rousseau,[1] Guillaume Tremblay,[1] Francis-Gabriel Begin,[1] and Gabriel Lamothe,[1] *1. Laval university, Québec, Quebec, Canada, 2. Laval university, Quebec, Quebec, Canada*

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

Emily Smail,[1] Brion Maher,[2] Ann Moore,[3] Pei-Lun Kuo,[4] Mark Wu,[5] Dominique Low,[6] Katie Stone,[7] and Adam Spira,[2] *1. University of Florida, Baltimore, Maryland, United States, 2. Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States,*

3. National Institute on Aging, Baltimore, Maryland, United States, 4. National Institute on Aging, National Institute on Aging, Maryland, United States, 5. Johns Hopkins University School of Medicine, Baltimore, Maryland, United States, 6. Stanford University School of Medicine, Stanford, California, United States, 7. University of California, Berkley, San Francisco, California, United States

Sleep disorders and sleep deprivation have been linked to markers of biological aging, including methylation change and increases in white blood cell and neutrophil counts. However, little is known regarding the association of sleep duration with biological markers of aging. We investigated links of self-reported sleep duration with biological aging markers in 615 participants in the Baltimore Longitudinal Study of Aging (BLSA) aged ≥50 years (mean = 71.0 ± 11.2, 49.6% women, 68.8% white) with data on self-reported sleep duration in hours (i.e., ≤6 (n=131), >6 to 7 (n=234), >7 (n=250)), demographics, and genetic and methylation data (mDNA). Our aging biomarker outcomes were four epigenetic clocks (Horvath, Hannum, PhenoAge, and GrimAge), mDNA-estimated PAI1, and estimated granulocyte count. After adjustment for age, sex, and race, compared to those sleeping ≤6 hours, those reporting >7 hours of sleep had faster biological aging according to Hannum age-acceleration, PhenoAge, GrimAge, mDNA-estimated PAI1, and granulocyte count. In addition, sleep duration interacted with age, such that compared to individuals reporting ≤6 hours of sleep, individuals reporting >6 to 7 hours showed lower GrimAge with increasing age, and with sex, such that males with longer sleep duration (>6 to 7 and >7 hours) showed a lower granulocyte count compared to females. Findings suggest that both short and long sleep duration are associated with and may contribute to accelerated aging. Prospective studies in larger samples are needed to examine whether changes in sleep duration precede changes in aging biomarkers.

LONGITUDINAL COURSE OF GDF15 LEVELS BEFORE ACUTE HOSPITALIZATION AND DEATH IN THE GENERAL POPULATION

Juliette Tavenier,[1] Ove Andersen,[1] Jan O. Nehlin,[1] and Janne Petersen,[2] *1. Copenhagen University Hospital Hvidovre, Hvidovre, Hovedstaden, Denmark, 2. Copenhagen University Hospital Frederiksberg, Frederiksberg, Hovedstaden, Denmark*

Growth differentiation 15 (GDF15) is a potential novel biomarker of biological aging. To separate the effects of chronological age and birth cohort from biological age, longitudinal studies investigating associations of GDF15 levels with adverse health outcomes are needed. We investigated changes in GDF15 levels over 10 years in an age-stratified sample of the general population and their relation to the risk of acute hospitalization and death. Serum levels of GDF15 were measured three times in 5-year intervals in 2176 participants aged 30, 40, 50, or 60 years from the Danish population-based DAN-MONICA cohort. We assessed the association of single and repeated GDF15 measurements with the risk of non-traumatic acute hospitalizations. We tested whether changes in GDF15 levels over 10 years differed according to the frequency of hospitalizations within 2 years, or survival within 20 years, after the last GDF15 measurement. The change in GDF15 levels over time was dependent on age and sex. Higher GDF15 levels and a greater increase in GDF15 levels were associated with an increased risk of acute hospitalization in adjusted Cox regression analyses. Participants with more frequent admissions within 2 years, and those who died within 20 years, after the last GDF15 measurement already had elevated GDF15 levels at baseline and experienced greater increases in GDF15 levels during the study. The change in GDF15 levels was associated with changes in C-reactive protein and biomarkers of kidney, liver, and cardiac function. Monitoring of GDF15 starting in middle-age could be valuable for the prediction of adverse health outcomes.

METABOLIC SYNDROME AND NEUROCOGNITIVE FUNCTION AMONG OLDER HISPANICS/LATINOS WITH HIV

Maria Marquine,[1] Lily Kamalyan,[2] David Yassai-Gonzalez,[1] Mariana Cherner,[3] Ronald Ellis,[4] Anya Umlauf,[4] Dilip Jeste,[1] and Robert Heaton,[4] *1. University of California San Diego, La Jolla, California, United States, 2. San Diego State University/University of California San Diego Joint Doctoral Program in Clinical Psychology, San Diego, California, United States, 3. University of California San Diego, SAN DIEGO, California, United States, 4. University of California San Diego, San Diego, California, United States*

Neurocognitive impairment is prevalent among persons with HIV (PWH), particularly among Hispanics/Latinos/as/x (henceforth Hispanics). We examined disparities in HIV-associated neurocognitive function between older Hispanic and non-Hispanic White PWH, and the potential role of metabolic syndrome (MetS) in explaining these disparities. Participants included 116 community-dwelling PWH ages 50-75, who were enrolled in a cohort study in southern California (58 Hispanic [53% Spanish-speaking] and 58 age-comparable non-Hispanic White; Overall group: Age: M=57.9, SD=5.7; Education: M=13, SD=3.4; 83% male, 58% AIDS, 94% on antiretroviral therapy [ART], 4% detectable plasma RNA). A global neurocognition score was derived from T-Scores on a comprehensive neurocognitive battery, with separate demographic adjustments for English and Spanish-speakers. MetS was ascertained via standard criteria that considered central obesity, elevated triglycerides, low high-density lipoprotein cholesterol, and elevated fasting glucose, as well as current medical treatment for these conditions. Covariates examined included sociodemographic, psychiatric, substance use and HIV-disease characteristics. Hispanics had higher rates of MetS (56%) than non-Hispanic Whites (37%; $p<.05$). A stepwise regression model on global neurocognition including ethnicity and covariates that differed between ethnic groups, selected only Hispanic ethnicity as a significant predictor (B=-3.82, SE=1.27, $p<.01$). A comparable model also including MetS showed that both Hispanic ethnicity (B=-3.39, SE=1.31, p=.01) and MetS (B=-2.73, SE=1.31, p=.04), were significantly associated with worse global neurocognition. Findings indicate that MetS does not fully explain disparities in neurocognitive function between Hispanic and non-Hispanic White older PWH, but rather is an independent predictor of neurocognitive function along with Hispanic ethnicity.