cuprizone (0.2%w/w) for four weeks to induce demyelination. One group was allowed four additional weeks for recovery and remyelination. We performed voiding spot assay (VSA), urethane-anesthetized cystometry, and CNS-histology to assess demyelination-induced differences in urinary performance. We observed that cortical demyelination causes significant aberrance in voiding behavior (conscious cortical control) characterized by increased micturition frequency and reduced volume per micturition. Interestingly, remyelination restored healthy bladder function. However, there were no significant changes in the cystometric parameters (brainstem reflex) between the treatment groups. While MS is not classically considered a disease of aging, extending the longevity of these patients has not been reciprocated with improved treatments for their most-bothersome conditions, notably urinary symptoms that persist throughout life. Our data represent a novel compelling connection and strong correlation between CNS-myelination and cortical control of bladder function, which has potential implications in MS, aging, and aging-associated neurological disorders.

SENOLYTICS IN A MODEL OF ALZHEIMER'S DISEASE

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The therapeutic effects of senescent cell killing with senolytics in neurodegeneration mouse models poise this strategy as an intervention candidate for Alzheimer's Disease (AD). However, it is unclear whether senolytic therapies for AD are translatable to human cells. To determine whether senolytics could be a viable therapeutic for AD, we have treated long-term mixed human neuron/astrocyte primary cultures with amyloid beta oligomers (ABO), which we have shown to induce a phenotype consistent with senescence in neurons. Fifteen days after ABO treatment, we administered Navitoclax (Nav) and the natural killer cell-line NK92, which are known to selectively kill senescent cells in the periphery. Following treatment, we assessed senescence markers in our cultures as well as senescent cell killing selectivity through cleaved Caspase 3 quantification. Our preliminary data show that Nav (8, 4, and 0.5uM) kills both control and ABO treated cells. NK92 cells (10 to 1 effector to target ratio) also kill some control cells, suggesting there is not a clear cut mechanism by which NK92 cells can distinguish senescent from non-senescent neurons or astrocytes. Although analysis of selective killing is ongoing, off-target killing indicates that we need more refined senolytic strategies to implement their safe human use.

SHORT-TERM DIESEL EXHAUST EXPOSURE RESULTS IN NEUROINFLAMMATION AND WHITE MATTER INJURY

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Ambient air pollution (AAP) exposure is associated with white matter injury and cognitive decline in older adults(Chen et al. 2020,Erickson et al. 2020). Neuroinflammation and oxidative stress may contribute to this white matter injury. Diesel exhaust particulate matter (DEP) is a neurotoxic component of AAP.This study characterizes the time course by which neuroinflammation/oxidative stress occurs and results in white matter injury following DE exposure in a murine model. DEP (Sigma) was re-aerosolized for exposure. Mice were exposed to 100 µg/m3 DEP or filtered air (FA) for 5 hours (n=8/group), 100 hours (n=6/group), or 200 hours (n=6/group). Immunohistochemical analysis of degraded myelin basic protein (dMBP), a marker of myelin damage, was performed. Neuroinflammation and oxidative stress were assessed by histological analysis of complement C5a, an anaphylatoxin, and 4-Hydroxynonenal (4-HNE), a marker of lipid peroxidation.dMBP integrated density was increased in the corpus callosum of DEP mice at 5 ($p<0.01$), 100 ($p<0.01$), and 200 hours ($p<0.001$) compared to FA mice.C5a integrated density was increased in the corpus callosum of DEP mice at 5 ($p<0.01$), 100 ($p<0.01$), and 200 hours ($p<0.01$) compared to FA mice. 4-HNE integrated density was increased in the corpus callosum of DEP mice at 5 ($p<0.001$), 100 ($p=0.001$), and 200 hours ($p<0.001$) compared to FA mice. Neuroinflammation and oxidative stress are upregulated with associated white matter injury in the corpus callosum after 5 hours of DEP exposure.Short-term DEP exposure activates inflammatory/oxidative stress pathways, which may contribute to the pathogenesis of white matter injury.Erickson et al. 2020,PMID:32182984; Chen et al. 2020,PMID:32669395.

SIGNIFICANT ASSOCIATIONS OF THE INTERPLAY BETWEEN STRESS RELATED GENES WITH ALZHEIMER'S DISEASE

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The lack of efficient medication against Alzheimer's disease (AD) is the most important problem for this health disorder today. One possible reason for this -- the implementing medical interventions "too late in the disease stage" – has been recently addressed in the initiative that defined the preclinical AD stage by measuring changes in preclinical AD biomarkers. According to this definition, beta amyloid (Aβ) is one of the key preclinical AD biomarkers. Experimental studies showed that Aβ results from proteolytic cleavage of APP by β- and γ-secretases. Production of β-secretase involves BACE1 gene, activated by cellular stress response. This suggest that AD might be initiated by cellular stressors and that multifactorial regulation of AD is likely to be driven by genes involved in cellular stress response. In this paper we investigate whether interplay between SNPs from the EIF2AK4 gene involved in sensing cellular stress signals and the APP gene dealing with Aβ production may be associated with AD in human data. For this, we evaluated association of the interactions of the pairs of SNPs from these genes with AD in the analysis of HRS data. We found that interactions between several SNPs have statistically significant associations with AD. The results of this analysis confirm that the interplay between gene served as a sensor of cellular stress and gene involved in production of preclinical AD biomarker in response to

stress may influence human AD. This analysis illustrates an important step towards translation of the results of experimental AD studies to human applications.

SYSTEMIC BIOENERGETIC CAPACITY CHANGES WITH COGNITIVE STATUS AND INSULIN SENSITIVITY IN OLDER ADULTS

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Systemic mitochondrial dysfunction is reported with AD progression, suggesting that peripheral blood cells may be used to investigate systemic mitochondrial alterations related to cognitive decline. We aimed to identify bioenergetic signatures associated with AD-related dementia and differences in insulin sensitivity associated with AD risk. We analyzed mitochondrial bioenergetics in peripheral blood cells collected from 365 older adults with varying cognitive status (normal, mild cognitive impairment, and AD) and insulin sensitivity. Normoglycemic individuals exhibited lower maximal bioenergetic capacity with AD (PBMCs: 239.6 pmol·min–1, p = 0.02; Platelets: 151.7 pmol·min–1, p = 0.06) compared to normal cognition (PBMCs: 271.5 pmol·min–1; Platelets: 171.7 pmol·min–1). Individuals with impaired insulin sensitivity exhibited lower maximal bioenergetic capacity in platelets with AD (171.6 pmol·min–1, p = 0.008) compared to normal cognition (210.6 pmol.min–1). Participants with impaired insulin sensitivity also exhibited unique bioenergetic profiles exemplified by overall higher levels of mitochondrial respiration, indicating that comorbidities such as diabetes can significantly influence bioenergetic capacity. We observed strong positive associations between maximal respiration in normoglycemic individuals with cognitive function, as measured by Modified Preclinical Alzheimer's Cognitive Composite (mPACC5) (p = 0.06), and fatty acid oxidation in individuals with impaired insulin sensitivity with cortical thickness (p = 0.05). This study demonstrates that circulating cells may provide a cost-effective and minimally invasive way to monitor systemic bioenergetic changes associated with AD risk, progression, and insulin sensitivity. These findings also suggest that blood-based bioenergetics are related to key features of AD development and progression and should be further developed as a potential biomarker.

THE HUMAN GENES THAT LINK MIDDLE-AGE COMORBIDITIES AND ALZHEIMER'S DISEASE

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Advancements in biomedical research have identified the genes influencing life spans, stress resistance and age-related diseases, including Alzheimer's disease. Stress resistance includes resistance to multiple forms of stress, pathogens and toxic beta-amyloid which is tightly associated with Alzheimer's disease. We have investigated 431 human genes that are associated with co-morbidities (Vahdati Nia et al, 2017; Le et al., 2020). Those genes are involved in lipid metabolism, hemostasis, hemostasis, neuroendocrine and immune functions. The genes are relevant to middle-life health. We explore a wide variety of co-morbidities that could happen in middle to late life. I will give a brief review of increased stress resistance, and genetic markers associated with co-morbidities. I will discuss how the studies may benefit to fight against COVID-19. References: 1. Vahdati Nia B, Kang C, Tran MG, Lee D, Murakami, S. (2017) Front. Genet. 8:55. doi: 10.3389/fgene.2017.00055 2. Le D, Crouch N, Villanueva A, Phong Ta, Dmitriyev R, Tunzi M, and Murakami S. (2020) Journal of Neurology and Experimental Neuroscience. 6;S1.

USING DROSOPHILA TO IDENTIFY NATURALLY-OCCURRING MODIFIERS OF ALZHEIMER'S DISEASE

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Despite significant progress in identifying risk factors for late-onset Alzheimer's Disease (LOAD), much of the variance in disease pathogenesis remains unexplained, likely due to the contribution of many genes of small effect size. Model organisms such as Drosophila Melanogaster exhibit conservation in both disease-causing genes and cellular processes implicated in Alzheimer's Disease (AD), offering a genetically tractable model that can be statistically leveraged to identify causal variants. Here, we combine a Drosophila model of AD with the Drosophila Genetic Reference Panel (DGRP), a model of natural variation consisting of over 200 fully sequenced, isogenic lines derived from a wild-caught population. Expression of two proteins closely associated with AD pathogenesis, A□42 and Tau, in the Drosophila eye results in a "rough eye" phenotype, an easily quantifiable phenotype caused by degeneration of the ommatidial array. By quantifying the degree of A□42- and Tau-mediated degeneration across 164 lines of the DGRP and using a gene-based approach to map associations, we have identified and validated a subset of naturally occurring modifiers of degeneration in Drosophila. Enrichment analysis reveals that the set of genes identified in our screen show significant enrichment for genes identified as significant or suggestive (4x10-6>p>2x10-11) in human GWAS studies. The results presented here provide proof-of-principal for an approach that combines the strengths of forward genetic screens in model organisms with the power of human GWAS studies to identify and validate potential risk factors that have been difficult to detect in human studies alone.

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Alzheimer's Disease and Other Dementias II

COLLECTION OF DATA ON PERSONS LIVING WITH DEMENTIA WHO GO MISSING: FIRST RESPONDER PERSPECTIVES

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