and function, neuronal cells were transfected with SIRT1 isoforms v1, v2 or v3 plasmids, respectively. Gene expression was measured by quantitative reverse transcription PCR (RT-qPCR). Our data showed SIRT1 isoforms v1, v2 and v3 differentially regulated PCG-1alpha and PCG-1beta, which are the upstream regulators of mitochondrial structure and function. SIRT1v1 upregulated mitofusin-1 (MFN1), the mitochondrial dynamin-like GTPase (OPA1) gene, and the transcription factor A mitochondrial (TFAM) gene. In contrast, the SIRT1-v2 isoform repressed the MFN1, MFN2, and TFAM genes, while the SIRT1-v3 isoform repressed the MFN1 gene. In addition, the three SIRT1 isoforms differentially affected the mitochondrial respiratory complex I genes, including NDUFAB1, NDUFS1, NDUFV1, NDUFV2. The data indicates that SIRT1 regulates mitochondrial biogenesis and function through a signaling pathway involving PGC-1alpha, PCG-1beta, mitofusin 1 and 2, OPA1, and TFAM genes. Taken together, alternative splicing generated three SIRT1 isoform proteins with diverse functions. Age-related changes in the alternative splicing events are likely to impact sirtuin-regulated cellular functions and signaling pathways in aging and senescence.

THE INTERPLAY BETWEEN STRESS RELATED GENES AND ITS ROLE IN HUMAN LONGEVITY: INSIGHTS FOR TRANSLATIONAL STUDIES

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Human lifespan is a multifactorial trait resulted from complicated interplay among many genetic and environmental factors. Despite substantial progress in clarifying many aspects of lifespan' variability the mechanism of its multifactorial regulation remains unclear. In this paper we investigate the role of genes from integrated stress response (ISR) pathway in such regulation. Experimental studies showed that persistent cellular stress may result in cellular senescence (for proliferating cells), or in apoptosis (for post-mitotic cells) which may affect health and lifespan in laboratory animals. These studies also showed which ISR genes are likely to interplay to produce joint effects on these traits. Note that in humans, the interplay between these genes does not necessarily influence these traits. This is because biological mechanisms regulating these traits in laboratory animals and humans may differ. This means that, when possible, the experimentally detected connections promising for human applications, should be verified using available human data before their testing in expensive clinical trials. In this paper we used HRS data to test connection between SNPs from the EIF2AK4 gene that senses cellular stress signals and the DDIT3 gene from the apoptosis regulation part of the ISR. We found genome wide significant associations between interacting SNPs from these genes and longevity. This result shows that available human data may be successfully used for making important steps in translation of experimental research findings towards their application in humans. Following this strategy may increase efficiency of clinical trials aiming to find appropriate medications to promote human health and longevity.

USING THRESHOLD REGRESSION AS AN APPROACH TO INCORPORATE INFORMATIVE MISSINGNESS IN LONG LIFE FAMILY STUDY DATA

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Genetics of aging is important since aging is a major risk factor in most diseases. Variables describing physiological state and cognitive functioning that influence morbidity and mortality risks can serve as biomarkers of aging. They change with increasing age and the ways in which these variables change can also influence these risks. Missing data due to dropout or death create problems in longitudinal studies producing biased results especially if the gap between exams is relatively long, as is the case in the Long Life Family Study (LLFS). We applied the threshold regression model to LLFS data to investigate the vitality and its rate, which are conceptualized as latent variables characterizing health and longevity, and to cope with such a problem. We performed genome-wide association study by sex and age groups to discover genetic signals on these phenotypes. We found 11 variants from the DACT2 gene, p-values < 1E-6 and variants rs12151399 (p-value = 8.43E-8, intron variant, gene AGAP1, in females), rs27958 (p-value = 8.39E-8, intron variant, gene ARHGAP26, in males) showing associations with the vitality. Olfactory receptors showed significant enrichment among the group of males over 80 years for the rate of aging phenotype. Results showed that vitality and its rate differ among sex and age groups. This work is an important step toward understanding the processes of aging linking the vitality with individual genetics using data from deceased and living individuals.

Session 9090 (Poster)

Biology of Aging and Biobehavioral Health

A NOVEL PROBIOTICS THERAPY FOR AGING-RELATED LEAKY GUT AND INFLAMMATION

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Inflammaging characterized with increased low grade inflammation in older adults is common determinant of unhealthy aging; and is a major risk factor of morbidity and mortality in older adults. The precise origin of inflammation in older adults is not known, however, emerging evidence indicate that increased intestinal epithelial permeability (leaky gut) and abnormal (dysbiotic) gut microbiota could be one of the key source. However, no preventive and treatment therapies are available to reverse the leaky gut and microbiome dysbiosis in older adults. Here, we presented the evidence that a human-origin probiotics cocktail containing 5 Lactobacillus

and 5 Enterococcus strains isolated from healthy human infant gut can ameliorate aging-related metabolic, physical and cognitive dysfunctions in older mice. We show that the Feeding this probiotic cocktail prevented high-fat diet–induced (HFD-induced) abnormalities in glycose metabolism and physical functions in older mice and reduced microbiota dysbiosis, leaky gut, inflammation. Probiotic-modulated gut microbiota reduced leaky gut by increasing tight junctions on intestinal epithelia, which in turn reduced inflammation. Mechanistically, probiotics increased bile salt hydrolase activity in older microbiota, which in turn increased taurine deconjugation from bile acids to increase free taurine abundance in the gut. We further show that taurine stimulated tight junctions and suppressed gut leakiness. Further, taurine increased life span, reduced adiposity and leaky gut, and enhanced physical function in Caenorhabditis elegans. Whether this novel human origin probiotic therapy could prevent or treat aging-related leaky gut and inflammation in the elderly by reversing microbiome dysbiosis requires evaluation.

A PHASE 2B CLINICAL TRIAL ASSESSING LOMECEL-B INFUSION IN INDIVIDUALS WITH AGING FRAILTY: STUDY DESIGN AND RATIONALE

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Frailty is a common and important geriatric syndrome characterized by age-associated declines in physiology and function across multiple organ systems, which lead to increased vulnerability to adverse health outcomes. A biological mechanism that underlies the decline in physical function associated with aging frailty is chronic inflammation. The MSCs in Lomecel-B have immuno-modulatory capacity and control inflammation and the cytokine production of lymphocytes. An individual's endogenous stem cell production decreases with age, this decrease likely contributes to reduced ability to regenerate and repair organs and tissues. Aging Frailty represents an exciting potential indication for cellular based therapies like Lomecel-B. This study is intended to evaluate the effects of Lomecel-B infusion compared to placebo on mobility and exercise tolerance, patient-reported physical function assessments and biomarkers for inflammation in individuals with Aging Frailty. This is a randomized, double-blind placebo-controlled, parallel multi-arm multicenter study enrolling adults aged 70-85 years identified as mildly or moderately frail per the CSHA Clinical Frailty Scale (CFS), with reduced six minute walk test (6MWT) and elevated Tumor Necrosis Factor-α (TNF-α), at screening. 150 subjects (30 per group) were randomized to receive a single peripheral intravenous infusion of 25, 50, 100, or 200 million doses, or placebo. Safety and efficacy assessments were conducted at 30, 90, 180, and 270 days after infusion. A follow up telephone call to subjects was placed at 365 days. We describe the design and rationale in detail of this 2b study assessing the effects of Lomecel-B on older adults with Aging Frailty.

CLAIMS-BASED NETWORK ANALYSIS OF DISEASE PROGRESSIONS IN COMPLEX AND NON-COMPLEX OLDER ADULTS

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Older adults are the fastest growing subset of complex patients with high medical, behavioral, and social needs. Understanding differences in disease progression patterns between complex and non-complex older adults is critical for understanding disease risk and tailoring patient-centered interventions. We identified complex patients as those having frequent medical encounters and multiple chronic conditions within the first year of the study period and non-complex patients as the converse. This study compares the disease progression patterns of (a) complex and (b) non-complex older adults by creating disease progression networks (DPN) from claims data of 762,362 patients (mean age = 73) from 2016 to 2020. We characterized the network size and density between the complex patient DPN (C-DPN) and non-complex patient DPN (NC-DPN), and compared disease progression incidence, time-to-progression, and age- and gender-related risk. Results show that the C-DPN was denser and had a wider range of values for risk of progression compared to the NC-DPN. This implies more varied disease progression patterns occurring in the complex adults. We were also able to compare (median) time-to-progressions of diseases relative to each subpopulation and found variation in disease progression time. Furthermore, k-means clustering on the network allowed us to identify highly connected diseases involved in many disease pathways that are prevalent among older adults. (e.g., lipoprotein disorders, hypertension, major depressive disorder). Our results suggest that DPNs can be used to identify important conditions and time-points for tailoring care to the complex and non-complex older adults.

EFFECTS OF SMOKING CESSATION ON EPIGENETIC AGING

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"Epigenetic clocks" have become widely used to assess individual rates of biological aging. However, experimental data are limited in humans to identify potential confounding factors that may influence one's rate of epigenetic aging and multiple health outcomes. We examined multiple epigenetic aging measures among regular smokers who quit smoking for two weeks. DNA methylation markers were assessed in both whole blood and saliva at multiple time points using a customized DNA methylation microarray. Generally, no changes in epigenetic aging rates were detected in the two week observation period with the exception of pronounced decreases over time in rate of Hannum's clock and Extrinsic Epigenetic Age Acceleration in blood DNA. In saliva DNA, decreases over time were detected in the rates of the GrimAge and DNAmPhenoAge clocks, but we saw an increase in the