upregulations in the group of genes involved in neurotransmission. In particular, genes encoding the transporters and receptor components of glutaminergic transmission were significantly upregulated in exercised muscles, as exemplified by Gria 1, Gria 2 and Grin2c encoding glutamate receptor 1, 2 and 2C respectively, Grin1 and Grin2b encoding N-methyl-D-aspartate receptors (NMDARs), Nptx1 responsible for glutaminergic receptor clustering, and Slc1a2 and Slc17a7 regulating synaptic uptake of glutamate. These changes were accompanied by an increase in post-synaptic NMDARs and acetylcholine receptors (AChRs), as well as their innervation at neuromuscular junctions (NMJs). These results suggest that neural responses predominate aged skeletal muscle following exercise, and indicate a possibility that glutaminergic transmission at NMJs may be responsible for synaptic protection and neural remodeling accompanying the exercise-induced functional enhancement in aged skeletal muscle.

GENES CONTRIBUTING TO RESILIENCE AND SENSITIVITY TO LISINOPRIL AT OLD AGE: CLINICAL TRANSLATION OF GWA IN DROSOPHILA

Mariann M. Gabrawy,[1] Nick Khosravian,[2] George S. Morcos,[3] Meagan Jezek,[2] Jeremy Walston,[1] Peter M. Abadir,[1] and Jeff Leips,[2] *1. Johns Hopkins University School of Medicine, Baltimore, Maryland, United States, 2. University of Maryland Baltimore County, Baltimore, Maryland, United States, 3. University of Maryland School of Medicine, Baltimore, Maryland, United States*

Despite impressive results in restoring physical performance in rodent models, treatment with Renin-Angiotensin System (RAS) inhibitors such as Lisinopril have highly mixed results in humans, likely, in part, due to genetic variation in human populations. To date, the genetic determinants of responses to drugs such as RAS inhibitors remain unknown. Given the complexity of the relationship between physical traits and genetic background, genomic studies which predict genotype- and age-specific responses to drug treatments in humans or vertebrate animals are difficult. Here, using 126 genetically distinct lines of Drosophila, we tested the effects of Lisinopril on climbing speed and endurance at young and old age (N=14,310). Our data show that functional response and sensitivity to Lisinopril ranges from significant protection against physical decline (8–100% faster, $P< 0.0001$) to increased weakness ($P< 0.0001$) depending on both genotype and age ($P< 0.0001$). Genome-wide analyses revealed little to no overlap in candidate polymorphisms influencing sensitivity between ages nor between treatments within each age. Furthermore, network analyses led to identification of evolutionarily conserved genes in the WNT signaling pathway as being significantly associated with variations in sensitivity to Lisinopril. Genetic knockdown of Axin, frizzled, nemo, and wingless, genes with human orthologs AXIN1, FZD1, NLK, and WNT1, respectively, abolished the effects of Lisinopril treatment. Our results implicate these genes as contributors to the genotype- and age-specific effects of Lisinopril treatment and as potential therapeutic targets for improvement of resiliency. Our approach should be widely applicable for identifying genomic variants that predict age-dependent responses to pharmaceutical treatments.

IMMATURE PEAR EXTRACT CONSTITUENTS EXERT MULTIFACETED ANTI-AGING EFFECTS

Akira Ogita,[1] Wakae Murata,[2] Ken Yamauchi,[3] Akiko Sakai,[1] Yoshihiro Yamaguchi,[1] Toshio Tanaka,[1] and Ken-ichi Fujita,[1] *1. Osaka City University, Osaka, Osaka, Japan, 2. Yonago National College of Technology, yonago, Tottori, Japan, 3. Keio University, Yokohama, Kanagawa, Japan*

Cellular senescence causes a gradual loss of physiological functions and induces chronic diseases, which negatively affect the quality of human life. Intervention in the cellular senescence process may reduce the incidence of these diseases while delaying the progression of age-related diseases, thereby prolonging human lifespan. In our previous study, we found that extending the chronological lifespan of budding yeast cells, a suitable cellular model for research on mammalian cells, could be achieved by adding immature pear extract (iPE). Moreover, at the 2020 GSA meeting, using a colony-counting method, we reported that both hydrophilic (WiPE) and hydrophobic (OiPE) iPE components exhibited a chronological lifespan prolongation on yeast cells. In this study, the expression of sirtuin-related genes, which regulate cellular senescence, was verified by quantitative real-time reverse-transcription polymerase chain reaction. Interestingly, sirtuin-related gene expression was significantly increased in the WiPE-treated cells only, and OiPE could extend the chronological lifespan of yeast cells through the mechanisms not involved in sirtuin-related gene expression. In general, hydrophobic and hydrophilic components exhibit different degradation and metabolism in cells. Since each component has a different strategy of absorption and excretion in the body, we hypothesize that iPE with multiple active components will have multifaceted effects on anti-aging. Our research on elucidating the mechanism of lifespan extension by OiPE and its application to mammalian cells is ongoing.

KYNURENINE METABOLISM LIFESPAN EXTENSION MEDIATED BY OXIDATIVE STRESS RESPONSE AND HYPOXIC RESPONSE IN C. ELEGANS

Raul Castro-Portuguez,[1] Jeremy Meyers,[2] Sam Freitas,[1] Hope Dang,[2] Emily Turner,[2] Destiny DeNicola,[1] Luis Espejo,[3] and George Sutphin,[1] *1. The University of Arizona, Tucson, Arizona, United States, 2. University of Arizona, Tucson, Arizona, United States, 3. UNIVERSITY OF ARIZONA, TUCSON, Arizona, United States*

Aging is characterized by a progressive decline in the normal physiological functions of an organism, ultimately leading to mortality. Metabolic changes throughout the aging process disrupt the balance and homeostasis of the cell. The kynurenine metabolic pathway is the sole de novo biosynthetic pathway for producing NAD+ from ingested tryptophan. Altered kynurenine pathway activity is associated with both aging and a variety of age-associated diseases, and kynurenine-based interventions can extend lifespan in Caenorhabditis elegans. Our laboratory recently demonstrated knockdown of the kynurenine pathway enzymes kynureninase (KYNU) or 3-hydroxyanthranilic acid dioxygenase (HAAO) increases lifespan by 20-30% in C elegans. However, the mechanism of how these interventions may modulate response against different stressors during the aging process has yet to be explored. Fluorescent reporter