human cell culture. We have preliminary evidence for activation of broad-spectrum cellular stress response, enhanced immune function, and reduced inflammation. Among other roles, the kynurenine pathway is the sole metabolic route for de novo synthesis of nicotinamide adenine dinucleotide (NAD+) from tryptophan in Eukaryotic cells. We are examining the regulatory interaction between kynurenine metabolism and the two NAD+ recycling pathways, Salvage and Preiss-Handler, both as potential mechanistic mediators and as possible parallel targets for combined interventions with synergistic benefits in aging. We are further evaluating the impact of these interventions in several models of specific age-associated diseases, including sepsis, chronic inflammation, stroke, Alzheimer’s disease, and cancer. Finally, we are developing pharmaceutical strategies to replicate key genetic and metabolic interventions within the kynurenine pathway that can be readily translated into clinical applications.

THE INTERACTION OF OSMOTIC AND HEAVY METAL STRESS IN C. ELEGANS

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Cellular stress is an ever-present aspect of aging and a primary driver of many common age-associated diseases such as cancer, diabetes, or neurodegenerative diseases. As we age, stress-induced damage accumulates over time, along with reduced efficacy of stress response pathways at combatting such damage. Molecular stress response pathways are well studied in the context of individual stressors, but there is a lack of understanding of how these responses change when multiple stressors are encountered at the same time. The goal of this work is to explore the impact of multiple simultaneous stressors on health and survival, and to investigate the underlying molecular pathways involved. To accomplish this, we utilize the nematode Caenorhabditis elegans to monitor lifespan changes in response to various stressors. We simultaneously exposed C. elegans to high concentrations of sodium chloride and cadmium chloride, known to induce osmotic and heavy metal stress, respectively. We found that lifespan is drastically decreased by the combined stress, significantly more so than the reduction in lifespan caused by either individual stress. Our results show that glycerol levels, which are normally increased in response to osmotic stress, are significantly lowered when the two stresses are combined compared to levels detected for osmotic stress alone. This suggests that the presence of cadmium may sensitize worms to sodium and other osmotic stressors by blunting cells’ ability to mount an appropriate molecular response. In ongoing work, we will continue to dissect the mechanisms through which cadmium influences glycerol production and other aspects of osmotic stress response.

THE PROTECTIVE EFFECTS OF APIGENIN ON COGNITIVE FUNCTION AND THE BRAIN TRANSCRIPTOME IN OLD MICE

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Age-related declines in cognitive function increase the risk of developing mild cognitive impairment and dementia, but select nutraceuticals (bioactive plant compounds) may hold promise for protecting the brain and improving cognitive function with age. Apigenin is a flavonoid nutraceutical found in chamomile and reported to inhibit multiple hallmarks of aging; however, it has not been studied in the context of brain aging specifically. We treated young (6 mo) and old (27 mo) C57BL/6N mice with apigenin (0.5 mg/mL in 0.2% carboxymethylcellulose) or control (0.2% carboxymethylcellulose) drinking water for 6 weeks. Then, we assessed cognitive function and performed RNA-seq to characterize global transcriptomic changes and potential mechanisms of action in the brain. We observed impaired novel object recognition (NOR) test performance (an index of learning/memory) in old vs. young control mice (P<0.0001), but old apigenin mice had ~3-fold higher NOR performance relative to old control mice (P=0.02). Transcriptomic analyses also showed age-associated gene expression changes related to immune function and inflammation, consistent with the established role of inflammation in brain aging. However, some of these key changes were reversed by apigenin. In fact, >300 genes were differentially expressed in old apigenin-treated mice vs. old controls, and the biological processes linked with these differences were related to innate and adaptive immune function, and cytokine and chemokine regulation. We are performing protein/signaling pathway analyses to elucidate downstream cellular changes associated with apigenin treatment, but our current results suggest apigenin may be a promising nutraceutical candidate for preventing brain aging.

THE RELATIONSHIP BETWEEN PHYSICAL ACTIVITY INTENSITY AND VOLUME ON PROSPECTIVE FALLS IN OLDER ADULTS

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The benefits of Physical Activity (PA) for older adults have been well documented relative to several physiological and neuromuscular factors, but the direct relationship of PA to fall incidence is unclear. In particular, the influence of the intensity and volume of habitual activities of daily living is poorly understood. The purpose of this study was to evaluate the influence of general PA intensity and overall volume on prospective falls in older adults. The PA of 134 participants was recorded using accelerometers (ActiGraph-GT3X+) over 7 consecutive days. Intensity was classified as light, moderate and vigorous by step frequency. The activity of all participants was graded as sedentary to low intensity, no participant exhibited activity in the vigorous category. During the following 12-months, participants maintained a daily falls diary and completed monthly phone calls to monitor fall incidence. Responses were used to categorize participants as fallers or non-fallers. Eighteen participants experienced one or more falls during the 12-month period. There was no
statistical difference between fallers and non-fallers in either total step count or the percentage of time spent in sedentary or light PA. While previous reports suggest that many falls occur during light PA, our results do not suggest that greater volumes of low intensity activities alone result in greater fall incidence. However, we suggest this result may be influenced by physical stimuli participants received within the larger overall study design including a session of repeated exposure to forward loss of balance.

**TOTAL TRANSCRIPTOME RESPONSES TO LOW AND HIGHER INTENSITY AEROBIC EXERCISE INTERVENTIONS IN OLDER ADULTS**

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Aerobic exercise is a universally recommended strategy for increasing healthspan, and recent advances in next-generation sequencing and bioinformatics (e.g., RNA-seq/ transcriptomics) have made it possible to broadly profile the molecular transducers of exercise. However, most transcriptome studies of exercise have focused on coding genes only, and the transcriptomic response to different exercise interventions has not been characterized by RNA-seq in older adults. Therefore, we performed total RNA-seq (to capture both coding and non-coding gene expression) on peripheral blood mononuclear cells collected from healthy, previously sedentary older adults (males and females, aged 70 ± 1 years). Samples were collected before and after 16 weeks of either low-intensity continuous training (LICT, 50% maximum heart rate, 3 x 30 min/week) or moderate-intensity continuous training plus interval training (MICT+IT, 60-80% maximum heart rate, progressively increased to include IT, 3 x 30 min/week). We found that both interventions modified biological processes (transcriptome modules) related to oxygen transport and reduced inflammatory signaling/immune activation processes (more pronounced with LICIT). Interestingly, transcriptome changes unique to LICIT subjects included increased expression of genes linked to vascularization and endothelial cell migration, whereas MICT+IT was uniquely associated with a robust increase in antioxidant response gene expression. We also observed numerous changes in long non-coding RNAs and microRNAs that could be linked with these exercise-associated gene expression changes with both interventions. These data provide a first comprehensive look into transcriptomic changes associated with moderate vs. low intensity aerobic exercise in older adults, and they suggest distinct benefits of each exercise strategy.

**TREADMILL TRAINING IMPROVES AEROBIC CAPACITY IN AGED MALE MICE COMPARED TO VOLUNTARY WHEEL RUNNING**

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Preclinical exercise studies typically use two forms of exercise training protocols: 1) voluntary wheel running and 2) forced treadmill running. Previous work from our group clearly demonstrates that older (18-month-old) male mice do not voluntarily engage in wheel running, especially compared to younger males or female mice. Therefore, we implemented a forced exercise treadmill training protocol to determine if treadmill training was superior to wheel running in improving aerobic capacity in older male mice.

**Purpose:** To determine if a 3-week treadmill training protocol improved time to exhaustion (TTE) in older male mice.

**Methods:** 18-month-old male mice (n=5) were provided a running wheel in their individual cage for 2 weeks or underwent daily treadmill training (n=6) for 3 weeks with increasing speed/incline. At the end of the training period we assessed TTE.

**Results:** Older male mice that trained on the treadmill demonstrated higher TTE compared to wheel (1382 ± 32 seconds versus 500 ± 99 seconds, respectively). In addition, older male mice that trained on the treadmill improved on average ~8% in their TTE test.

**Conclusion:** A 3-week treadmill training protocol improves aerobic capacity in older male mice to a greater extent than voluntary wheel running. Ongoing experiments will utilize this training protocol to understand age-related declines in cardiorespiratory fitness, circadian rhythm, and to test exercise as an intervention in the aging population.

**VALSARTAN AND SACUBITRIL COMBINATION TREATMENT ENHANCES COLLAGEN PRODUCTION IN OLDER ADULT HUMAN SKIN CELLS**

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Collagen is a major component of the skin’s support system, allowing for firmness, elasticity, and mechanical strength. In older adults, skin collagen production decreases significantly, and is associated with increased sagging, wrinkling, and thinning. The Renin Angiotensin System (RAS) is a key hormonal system that changes with age and affects multiple organ systems. While primary health benefits of Angiotensin (Ang) receptor type1 (AT1 R) blockers (ARBs) are believed to arise from systemic effects on blood pressure. There exists a skin-specific Renin Angiotensin System (RAS), but the impact of ARBs on older skin is unknown. Human skin fibroblasts from individuals aged 2 (young individual) and 57 (older individual) were treated with drugs that alter RAS: Valsartan (an ARB) and neprilysin inhibitor Sacubitril. Fibroblast proliferation and collagen production was quantified in response to the drug treatment using fluorescence microscopy. Fibroblasts from 57-year-old individuals were slower to proliferate and had less collagen content as compared to fibroblasts from young individual. Valsartan alone treatment had no effect on collagen production from young or old fibroblasts. In contrast, Sacubitril treatment increased collagen production by approximately three-fold in young (2.87 ± 0.27 RFU, P<.0001), and older (2.93 ± 0.53 RFU, P<.0001) fibroblasts. Concomitant treatment with Valsartan and Sacubitril increased collagen production by five-fold increase (5.36 ± 1.08 RFU, P<.0001) in young