The effects of age-based evaluations on older adults' gait variability

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Older adults are stereotyped as being slow, weak, and frail. In this study we examined how these stereotypes about age-related physical decline affect older adults’ walking performance. Healthy, community-dwelling older adults were asked to walk at their own comfortable pace along a 24’ temporospatial-measuring walkway 10 times. For some participants this was done with a normal-base of support (i.e., usual gait). However, for other participants this was done with a narrow-base of support (i.e., walking within a path of 15 cm outlined by tape). Walking tasks were done either in the presence or absence of a negative age-based evaluation. Results showed that the negative age-based evaluations were associated with greater stride-to-stride variability, particularly for participants who felt less confident in their abilities. Given that gait variability is a predictor of falling, this raises the possibility that negative age-based evaluations can produce concerns that are an intrinsic risk factor for falls.

Session 3385 (Symposium)

Cell non-autonomous mechanisms of aging

Chair: Scott Leiser, University of Michigan, Ann Arbor, Michigan, United States

It is now recognized that biological aging can be affected both positively and negatively by intercellular communication. This symposium will focus on recent discoveries related to cell non-autonomous mechanisms of aging.

Cell non-autonomous serotonin signaling mediates stress resistance and longevity

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The ability of organisms to perceive and respond to their environment is crucial to their long-term survival. Recent studies in model organisms identify signaling pathways that perceive environmental stress and cell non-autonomously modify systemic physiology. These pathways often originate in the neurons, where key cells monitor the external environment for changes including food availability, air quality, and the presence of dangerous toxins. Our previous work identified a key role for serotonin signaling in the induction of flavin-containing monoxygenase-2 (fmo-2) downstream of hypoxic signaling. fmo-2 expression is necessary and sufficient to promote stress resistance and longevity downstream of multiple genetic pathways, making it a useful tool for identifying key components of these pathways. Our current data defines environments, pathways, and signaling molecules that induce fmo-2 and subsequently increase lifespan. Our resulting data define key roles for serotonin signaling and fmo-2 that rely upon the perception of oxygen and food.

Neuronal FGF-21 signaling: a sensor of dietary protein

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Our data demonstrates that dietary protein restriction increases energy expenditure and improves glucose homeostasis, and that this effect is largely mediated by the metabolic hormone fibroblast growth factor 21 (FGF21). Considering that the central nervous system (CNS) is acknowledged as a major regulator of both energy and glucose homeostasis, we have extended our studies to identify the tissue site mediating these FGF21-dependent effects via dietary protein restriction. In this study, mice with dysfunctional FGF21-signaling in either the CNS or adipose tissue were fed a control or low protein (LP)-diet to assess changes in body weight and metabolic endpoints. Our data show that LP diet increased energy expenditure and reduced body weight in control littermates, but these effects were lost in mice bearing CNS-specific deletion of Klb. These data highlight a liver to brain FGF21-signal as the first known neuroendocrine mechanism to explain the coordinated metabolic changes induced by dietary protein restriction.

Increase in HSP25 extends lifespan and improves response to tau toxicity through a cell, non-autonomous mechanism

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The accrual of aggregation-prone cytotoxic proteins underlies neural pathologies seen in aging, Alzheimer’s disease and other dementias. Recent evidence indicates that heat shock protein 25kDa (HSP25) interacts with tau. To demonstrate a causal role for HSP25 in these pathologies, we overexpressed HSP25 protein in worms. This manipulation led to an increase in life span. Moreover, the longevity-effect was associated with increased expression of genes downstream of the SKN-1/Nrf2 stress-response transcription factor. HSP25 over-expression also reduces aggregate pathology and extends lifespan in a C. elegans neuronal-specific, aggregate-prone tau model. We propose that over-expression of HSP25 could provide protection from protein aggregation induced neurodegeneration. However, it is not yet clear whether this HSP25 effect could be efficaciously provided exogenously by other cell types. Thus, we will test whether increased peripheral HSP25 will reduce protein aggregation and stimulate a global Skn-1 stress-response pathway, reduce toxicity in neurons, and improve health outcomes.

Restoration of hypoxia signaling improves aging-associated loss of skeletal muscle regenerative potential

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Skeletal muscle retains the ability to regenerate throughout life, but this decreases significantly with aging.
The present study investigates whether aging-associated loss of muscle hypoxia signaling limits regenerative potential. Utilizing young (3 months) and old (22-24 months) mice, skeletal muscle from old mice exhibited a 40% decline in the cross-sectional area (CSA) of newly regenerating fibers following cryoinjury at day 10 (p < 0.01) post-injury as compared to young. Focused PCR array demonstrated a greater than 3-fold decline in expression of the majority of hypoxia signaling genes. In particular, aryl hydrocarbon receptor nuclear translocator (ARNT), which is required for downstream hypoxia signaling and the transcription of hypoxia response genes, is 5-fold lower for both gene expression (p < 0.01) and protein levels (p < 0.01) in old versus young mice. To determine the effects of ARNT on muscle regeneration, we utilized a genetically modified mouse which results in an 80% decrease in ARNT gene expression following activation, specifically in skeletal muscle. Compared to littermate controls, mice with a muscle specific knockdown of ARNT (mKO ARNT) exhibited a 30% decline in regenerating fiber sizes at day 10 (p < 0.01) following cryoinjury, without any loss of regenerative potential in FACS isolated satellite cells ex vivo. Administration of a pharmacologic hypoxia activator, MI228, induced a 30% increase in regenerating fiber CSA in both old mice and mKO ARNT mice (p < 0.01) as compared to treatment with vehicle control. These data suggest hypoxia signaling declines with aging in skeletal muscle and activation of hypoxia signaling may promote regeneration.

**SESSION 3390 (PAPER)**

**DEMENTIA IN THE LONG-TERM CARE SETTING**

**MEDICATION DISCREPANCIES AND COMMUNICATION ERRORS DURING NURSING HOME INTAKE: A MIXED-METHODS ANALYSIS**

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Older adults experience high medication discrepancy rates during transitions from inpatient to nursing home settings. Dosage changes and multiple prescribers increases the risk of inaccurate handoffs and creates challenges for medication reconciliation at nursing home intake. Our objectives were to 1) Characterize medication discrepancies occurring at nursing home intake and 2) Identify resident and medication related factors associated with medication discrepancies. Demographics, comorbidities, medications, discrepancy types and location were prospectively collected over 9-months. Chi-square tests were used to determine factors associated with discrepancies. A focus group of nurse practitioners, pharmacists, and administrators from four long-term care facilities was convened to discuss medication reconciliation challenges at resident intake. Thematic analysis was used to determine key themes. 22%, 12%, and 3% of residents experienced one, 2 to 5, or six or more discrepancies, respectively. The most prevalent discrepancies were omission (34%), frequency (20%), and therapeutic duplication (13%) occurring in analgesics, respiratory and genitourinary medications. 44% of discrepancies occurred between nursing homes and hospitals and 39% involved the community pharmacy. The most significant risk factors for discrepancies included age over 70, Charlson comorbidity indices over 7, readmission to nursing homes, or the prescribing of at least 17 medications. Staff faced challenges of delayed and/or inaccurate data, incompatible documentation forms and inefficient workflows for resolving discrepancies. Residents at greatest risk for medication discrepancies require additional attention during admission medication reconciliation to prevent errors. Nursing home intake and medication reconciliation workflow needs to be improved with data sharing technology to increase accuracy and efficiency.

**OUTCOMES OF DISCONTINUING CHOLINESTERASE INHIBITORS IN NURSING HOME RESIDENTS WITH SEVERE DEMENTIA**

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Some clinical guidelines advocate for the withdrawal of cholinesterase inhibitors (ChEIs) in patients with severe dementia. However, there have been no studies of the outcomes of deprescribing ChEIs specifically in patients with severe dementia, and concerns about subsequent worsening of behavioral symptoms may serve as a barrier to ChEI discontinuation. Our objective was to evaluate the impact of deprescribing ChEIs on aggressive behaviors and depression severity in older nursing home (NH) residents with severe dementia. We conducted a retrospective cohort study using Medicare claims, Part D prescriptions, Minimum Data Set (MDS) v3.0, Area Health Resource File, and Nursing Home Compare, for non-skilled NH residents aged 65+ with severe dementia receiving AChEIs with ≥2 MDS assessments in 2016 (n=30,788). The Aggressive Behavior Scale (ABS) and the Patient Health Questionnaire (PHQ-9) evaluated aggression and depression, respectively. Marginal structural models with inverse probability of treatment weights evaluated the association of deprescribing with outcomes, accounting for time-dependent confounding. The sample was primarily white (78.7%), female (76.6%), ≥80 years old (77.6%), and 22.8% were deprescribed ChEIs. In adjusted models, deprescribing was not associated with aggression (0.002 point increase in ABS, p=0.90) or depression (0.04 point increase in PHQ-9, p=0.50). Deprescribing ChEIs in NH residents with severe dementia did not lead to an increase in aggressive behaviors or depression severity. Our findings provide insight into the potential risks and benefits associated with deprescribing ChEIs and help inform decision-making in patients with severe dementia.

**THE IMPACT OF MUSIC AND MEMORIES ON RESIDENT MOOD, BEHAVIORS, AND USE OF MEDICATIONS IN NURSING HOMES**

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