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Dietary approaches to geroscience intervention: 2025 Masoro-Barshop Conference on aging

Editor: Adam B. Salmon

Abstract

The Masoro-Barshop Conference on Aging is held each year in Bandera, TX, to assemble leaders in a thematic area of geroscience in an informal setting to maximize discussion on their recent research discoveries. Supported by the aging research programs associated with the Barshop Institute for Longevity and Aging Research, the 2025 topic focused on "Dietary Approaches to Geroscience Intervention". This report briefly outlines and summarizes the research presented at this meeting with accompanying submitted abstracts from attendees.

Introduction

The Masoro-Barshop Conference on Aging focuses each year on a thematic area of geroscience and invites leaders in this area to an informal setting to maximize discussion on their recent research discoveries. Investigators and trainees come together each year to learn about this cutting-edge research and interact with leaders in the field. Held annually at the Mayan Dude Ranch in Bandera TX, this conference highlights rotating thematic areas of geroscience, since the process of aging is a complex biological phenomenon encompassing and affecting numerous changes at the cellular and physiological level. Previous topics have included have focused on topics such as resilience in aging, cellular senescence, healthspan and hallmarks of aging, and immune function in aging [1]. This year's meeting (held Oct 9-12, 2025) topic focused on "Dietary Approaches to Geroscience Intervention". Moreover, this meeting served as a moment to reflect on the impact that a namesake of this annual conference, Dr. Edward Masoro, had on the field of aging in general and dietary interventions in particular and built the foundations of aging research at UT San Antonio more than 50 years ago.

Dietary interventions have been one of the most important tools in identifying, targeting and applying the biology of aging to improve health. Studies in both animal models and humans suggest that approaches such as calorie restriction, intermittent fasting, and diets emphasizing nutrient-dense foods can influence pathways that regulate metabolism, inflammation, and cellular repair. These effects are thought to slow the biological processes of aging and reduce the risk of age-related diseases, including cardiovascular disease, diabetes, and neurodegenerative disorders. Rather than extending lifespan alone, dietary strategies appear to promote "healthspan", the period of life spent in good health and functional independence. Calorie restriction, known to alter aging trajectories for nearly a century in scientific literature, is still the gold standard intervention for targeting aging.

Modifying interventions have formed the backbone of understanding how diet, or diet timing, can influence aging at the molecular and physiological levels. Studies on calorie restriction and intermittent fasting have shown that these strategies can improve metabolic flexibility, reduce chronic inflammation, and enhance stress resistance. More recently, dietary patterns such as the Mediterranean diet, plant-forward diets, and time-restricted feeding, have been discovered to confer similar physiological and molecular benefits as calorie restricted diets while potentially being more practical for long-term use. Advances in metabolomics and microbiome science are also revealing how diet interacts with gut bacteria and circulating metabolites to shape aging trajectories.

Pathways to improved health

Understanding the biological pathways affected by diet, including molecular signals, regulation of cellular and subcellular functions, and epigenetic and inflammatory

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regulation, offers a foundation for developing more targeted and sustainable strategies to promote healthy aging. By identifying how specific foods and dietary patterns influence these pathways, researchers aim to design interventions that not only prevent age-related diseases but also extend healthspan. Ultimately, this knowledge may guide application of personalized nutritional approaches, allowing individuals to maintain physical function, cognitive health, and resilience as they age, thereby leveraging geroscience to improve healthy aging.

In this vein, research in geroscience focused on dietary interventions is bi-directional. Delineating how interventions like calorie restriction work can identify new approaches, including pharmacological, to translate the benefits of this approach. Conversely, understanding the functional and molecular targets of aging can guide development of better, or novel, dietary approaches that can be translated with relative ease. The overarching goal of this meeting was to highlight these novel outcomes from basic science to translational application and share the state-of-the-art scientific approaches and tools to address these functional aging outcomes and perhaps the process of aging itself. The discussion covered a broad range of interrelated topical areas within the field with a general focus on bringing basic findings to clinical impact. Outlined below are titles of the talks presented by invited speakers at this year's conference in order of presentation.

Invited speakers

James Nelson, PhD (The University of Texas Health Science Center At San Antonio): "A brief history of caloric restriction research and Edward Masoro's legacy".

Dudley Lamming, PhD (University of Wisconsin-Madison): "The regulation of healthy aging by dietary branched-chain amino acids".

Douglas Mashek, PhD (University of Minnesota Twin Cities): "Lipid droplets as mediators of aging".

Cristal Hill, PhD (University of Southern California): "Cellular and molecular adaptation during dietary protein restriction improves healthspan".

Sebastian Brandhorst, PhD (University of Southern California): "Fasting mimicking diets improve aging and disease".

Benjamin Miller, PhD (Oklahoma Medical Research Foundation): "An alternative perspective on protein supplementation for aging muscle".

Debora Melo van Lent (The University of Texas Health Science Center At San Antonio): "Clinical trials to inform the effect of nutrition on dementia risk".

Catherine Kaczorowski, PhD (The University of Michigan): "Genetic determinants of brain response to caloric restriction and intermittent fasting in mice and man".

Tracy Anthony, PhD (Rutgers University): "Amino acid insufficiency and the integrated stress response".

Shangang Zhao, PhD (The University of Texas Health Science Center At San Antonio): "Repeated withdrawal of a GLPR agonist induces hyperleptinemia and deteriorates metabolic health in obese aging UM-HET3 mice".

Elena Volpi, MD, PhD, FGSA (University of Texas Health Science Center At San Antonio): "Identifying therapeutic targets of sarcopenia".

Satchidananda Panda, PhD (Salk Institute for Biological Studies): "Circadian rhythm theory for healthy lifespan".

Courtney Peterson, PhD, MSc, MS, MA (University of Alabama Birmingham): "Can intermittent fasting slow primary and secondary aging in humans?".

David Gius, MD, PhD (University of Texas Health Science Center At San Antonio): "Ketogenic diet promotes the accumulation of cells expressing senescence markers".

Pankaj Kapahi, PhD (Buck Institute for Research on Aging): "How dietary restriction influences brain aging and neurodegeneration".

Corinna Ross, PhD (Texas Biomedical Research Institute): "Fecal microbiome transplant, nutrition and aging in a nonhuman primate model".

Yan Du, PhD (University of Texas Health Science Center At San Antonio): "Dietary interventions to promote healthy aging: from evidence to community implementation".

Rozalyn Anderson, PhD (University of Wisconsin): "Caloric restriction in nonhuman primates".

Speakers selected from submitted abstracts

Jeremy Whitson, PhD (High Point University): "Assessment of anti-cataract and pro-longevity properties of flavonoids from edible plants".

Jennifer Stern, PhD (University of Arizona): "Glucagon receptor signaling is indispensable for the healthspan effects of caloric restriction in aging male mice".

Kristi Dietert, PhD (University of Texas Health Science Center At San Antonio): "Circadian reprogramming in cellular senescence".

Amy Vandiver, MD, PhD (University of California at Los Angeles): "Utilizing chimeric mitochondrial transcripts to understand the breadth of mitochondrial genome deletions in aging human tissue".

Thadeus Carlyon, BS (University of Arizona): "The role of glucagon receptor signaling in hepatocellular carcinoma in aging mice".

Erik Marchant, BS (University of Texas Health Science Center At San Antonio): "Elevated mTORC1 signaling skeletal muscle exacerbates diet-induced hyperglycemia and mitochondrial H_2O_2 production".

Conclusions

As discussed in the meeting, currently there are multiple dietary interventions known to impact healthy aging across functional domains up to and including longevity. In addition, there are known potential detriments, or challenges, to each approach translationally and the implications of such as they pertain to implementation to affect

personal health are still unclear. By defining the mechanisms that drive benefits to functional and physiological changes with age, there is opportunity to further refine approaches that use diet, or diet surrogates, to improve health and address the potential detriments or challenges in current approaches. Further, there may be synergistic effects developed using multi-pronged approaches involving diet, lifestyle interventions (*i.e.*, exercise, *etc.*) and pharmacological approaches for which we need a greater understanding. As with most research, there are still multiple opportunities both short- and long-term to refine approaches and interventions, assess their long-term safety, and establish their efficacy in humans.

Included with this overview of the meeting are submitted abstracts from attendees that were presented as part of a poster session, or selected for oral presentation as described above, during the conference. The poster session also recognized 3 participants for outstanding presentations: Guannan Li, PhD, Eduardo Gutiererrez Kuri, and Grant Goodman.

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Poster abstracts

Glucagon receptor agonism ameliorates obesity-induced hypercholesterolemia in aging mice

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Background: Obesity and aging are key risk factors for the development of hypercholesterolemia, leading to cardiovascular disease. Glucagon containing di- and tri-agonists are entering the market for the treatment of diabetes and obesity. Our data demonstrate that glucagon agonism alone may serve as a new line of treatment for hypercholesterolemia.
Methods: To examine the potential to lower cholesterol by enhancing glucagon receptor signaling in aging mice, we utilized a long-acting glucagon analogue (GCGA, Novo Nordisk) to enhance glucagon signaling in diet-induced obese wildtype C57BL/6J young (6 month), middle aged (10 month), and aged (18 month) mice.
Results: Ten days of twice daily GCGA (1.5 nmol/kg BW, subcutaneous) lowered serum cholesterol in young (6 month) and aged (18 month) obese mice ($P \leq 0.05$). A 3-month course of three times weekly injections (3 nmol/kg BW) lowered serum cholesterol ($P \leq 0.05$) without affecting body weight or food intake in middle aged and aged obese mice. A decrease in Serum Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) activity increases hepatic LDL clearance, lowering circulating cholesterol. Glucagon receptor signaling encourages PCSK9 protein degradation, mimicking the action of costly PCSK9 inhibitors that lower LDL cholesterol. In line with this mechanism, GCGA treatment lowered circulating PCSK9 at both 10 ($P \leq 0.01$) and18 ($P < 0.05$) months of age while increasing LDL receptor protein expression at the liver in both male and female obese mice ($P \leq 0.05$).
Conclusion: The development of glucagon containing agonists provides the potential for rapid translation of our findings to address hypercholesterolemia in aging, offering a cost-effective and accessible alternative to other pharmacological interventions.

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Glucagon receptor agonism regulates nutrient signaling pathways critical to aging and healthspan

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Background: While the aging field has primarily focused on the role of insulin signaling in aging and healthspan, recent findings from the Stern Laboratory have highlighted the critical role of glucagon signaling in mediating the healthspan extension achieved with caloric restriction. To build on these novel findings, we investigated the metabolic impact of pharmacologically enhancing glucagon signaling in young adult (9-month-old) and aged (18-month-old) wildtype C57BL/6JN male mice.
Methods: Mice were treated with a long-acting glucagon analogue (GCGA; 3 nmol/kg body weight, 3-times weekly subcutaneous injections; Novo Nordisk) over a 3-month course.
Results: GCGA treatment decreased hepatic mTOR activation in young ($P = 0.002$) and aged ($P = 0.008$) mice. Circulating levels of Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) rise with age, increasing the susceptibility to cardiovascular disease. GCGA treatment decreased serum PCSK9 in aged mice ($P = 0.0003$), restoring levels to those observed in young adult mice. Im-

portantly, GCGA treatment had no effect on body weight, glucose clearance, insulin sensitivity, basal insulin, or oral glucose-stimulated insulin secretion ($P > 0.05$ for all), demonstrating that the potential benefits of glucagon agonism in aging are independent of glucose homeostasis and body mass.

Conclusion: Our findings propose that pharmacological activation of the glucagon receptor holds potential as a treatment to slow aging and minimize age-related metabolic disease.

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The role of glucagon receptor signaling in hepatocellular carcinoma in aging mice

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Background: Hepatocellular Carcinoma (HCC) is third leading cause of cancer-related deaths worldwide. Key risk factors include aging and obesity, which is linked to non-alcoholic fatty liver disease (NAFLD). Glucagon signaling at the liver is a key regulator of both glucose and lipid metabolism. Yet, studies investigating the role of glucagon receptor signaling in HCC are limited and conflicting.

Methods: We used a mouse model of chemically induced HCC, dietary manipulation, and pharmacologic glucagon receptor activation in both young (6-month-old) and aged (18-month-old) C57BL/6J mice to understand the potential role of glucagon signaling in HCC progression.

Results: Glucagon receptor (Gcgr) mRNA expression is decreased in liver tumor tissue compared to non-tumor tissue in both chow-fed lean ($P = 0.041$) and high-fat diet induced obese ($P = 0.049$) mice. In line with this finding, the expression of gluconeogenic genes regulated by glucagon signaling at the liver are decreased in tumor relative to non-tumor tissue in both lean ($P < 0.05$), and obese ($P < 0.05$) mice. Using a long-acting glucagon analogue (GCGA, 3 nmol/kg BW, Novo Nordisk), we studied the effects of glucagon receptor agonism in young and aged obese mice for three months. GCGA treatment decreased the expression of key genes involved in the progression of HCC, including glucose transporter 1 (Slc2a1: $P = 0.016$), glucose transporter 2 (Slc2a2: $P = 0.008$), lactate dehydrogenase A (Ldha: $P = 0.014$) and monocarboxylate transporter 2 (Slc16a7: $P = 0.005$).

Conclusion: Pharmacologic glucagon receptor agonism may offer protection against the metabolic remodeling associated with aging and obesity that is permissive to tumor growth and development at the liver.

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The geriatric marmoset microbiome: a longitudinal study of intact and manipulated bacterial communities

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The common marmoset (*Callithrix jacchus*) is an emerging model for human health and aging, reflecting age-related chronic conditions such as cardiovascular changes, inflammation, and cognitive decline. Considered old at 8 years, with a lifespan of up to 21 years, marmosets may better model human gastrointestinal anatomy and microbiome, compared to mouse models. The gut microbiome plays a crucial role in regulating various pathologies, including age-related diseases, by contributing to immune function, nutrient metabolism, pathogen prevention, and intestinal barrier maintenance. In this longitudinal study, fecal microbiome samples from 68 marmosets were analyzed to examine age-related compositional differences. ANOVAS and Wald tests tested taxonomic differences between age and treatment groups, while linear models evaluated age-related associations. In the first 10 months, 46 species were significantly enriched in geriatric individuals, while 40 species were enriched in young individuals ($P < 0.05$). Notably, geriatrics were characterized by enriched Blautia, while the young were enriched by probiotic Bifidobacterium and Lactococcus ($P < 0.05$). Later, 23 geriatric marmosets received fecal microbiota transplants (FMT) from a healthy young donor pooled sample, while 17 marmosets received a control saline treatment. Within one week, FMT significantly increased alpha diversity (a measure of well-distributed and rich microbial community diversity) by 8% ($P = 0.0456$). Further analysis of beta diversity and differential enrichment will explore whether this type of FMT engrafts long-term, changes community dynamics, and promotes health-related commensal organisms. This study lays the groundwork for personalized FMT treatments aimed at improving the healthspan of the aging human population.

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Circadian reprogramming in cellular senescence

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Aging and age-related diseases have become a public health crisis. Circadian rhythms become dysfunctional with age and disrupted rhythms elevate risk for diseases associated with aging. We aim to improve understanding of the reciprocal relationship between aging and circadian rhythms.
Cellular senescence is a major driver of age-related disease. Studies suggest circadian disruptions elevate senescence and senescent cells themselves display circadian dysfunction. The mechanisms governing this relationship are incompletely understood and require further investigation.
Our preliminary data suggest expression of prominent players in the senescence program are dependent on *Bmal1*, a core clock component. We identified that p21, a cell-cycle protein driving senescence, is highly upregulated at night but this rhythm is disrupted with circadian misalignment, implicating clock regulation. We also found that both senescence status, treatment with exogenous SASP factors and co-culture with senescent cells can robustly alter cellular rhythmicity. Finally, we observe increased markers of senescence and disrupted circadian behaviors coincide in aged mice.
Taken together, we hypothesize that the molecular clock regulates cellular senescence and that senescence drives circadian dysfunction with age. We aim to determine how the clock contributes to senescence, define the rhythm of senescent cells, and elucidate how they influence circadian function of neighboring non-senescent cells.
We are using *in vivo* and *in vitro* approaches to strategically manipulate the molecular clock and cellular senescence to disentangle their effects on each other. A better understanding of the biological processes that drive aging will provide insight toward therapeutic interventions capable of ameliorating diverse age-related diseases.
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Whole body knockout of alpha/beta-hydrolase domain containing 6 (ABHD6) reduces bace1 expression and attenuates amyloid beta pathology and neuroinflammation in 5xFAD mice

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Alzheimer's disease (AD) is characterized by amyloid beta (Aβ) accumulation and chronic neuroinflammation. The β-site amyloid precursor protein cleaving enzyme 1 (BACE1) is critical for Aβ production, making it a key target in AD pathogenesis. α/β-Hydrolase domain-containing 6 (ABHD6) is a lipid hydrolase with emerging roles in neuroinflammatory signaling, but its contribution to amyloid pathology is not well understood. This study investigates the impact of whole-body ABHD6 knockout on Aβ production, amyloid plaque burden, and neuroinflammatory responses in the 5xFAD transgenic mouse model of AD. ABHD6 deletion in 5xFAD mice significantly reduced Aβ40-42 levels and decreased amyloid plaque burden in the hippocampus. Notably, ABHD6 knockout was associated with a reduction in BACE1 protein expression, suggesting a mechanistic link to decreased Aβ production. Furthermore, neuroinflammatory markers were significantly reduced in ABHD6-deficient mice. Our findings reveal that ABHD6 contributes to AD pathology by promoting BACE1 expression, Aβ accumulation, and neuroinflammation. Whole-body knockout of ABHD6 mitigates these pathological features, identifying ABHD6 as a potential upstream regulator and therapeutic target in Alzheimer's disease.

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Disuse-induced muscle atrophy and inflammation in aging

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Background: Sarcopenia, the age-related loss of muscle mass and function, is accelerated by disuse events such as immobilization. Older individuals exhibit impaired regeneration, heightened atrophy, and dysregulated immune responses, but the mechanisms linking aging, disuse, inflammation, and functional decline are not fully understood.
Methods: To model disuse-induced atrophy, 24-month-old UM-HET3 mice underwent 14 days of unilateral hindlimb immobilization using custom 3D-printed casts. One week prior to casting, a subset of mice received the mTOR inhibitor rapamycin which was continued throughout the immobilization period. Contractile force of the tibialis anterior and the extensor digitorum longus (EDL) was assessed via *in vivo* and *ex vivo* electrophysiology (Aurora Scientific, Inc). Muscle and organ tissues were

collected for immunohistochemistry and western blot to evaluate immune infiltration into muscle, mTORC1 signaling, and systemic inflammation.
Results: Immobilization reduced force production in both immobilized and contralateral limbs compared to controls, indicating localized and systemic effects. EDL mass declined, body weight decreased, and mortality occurred only in immobilized animals, suggesting increased frailty under disuse stress. Preliminary immunohistochemistry data show altered macrophage infiltration and polarization in immobilized muscles, with evidence of systemic immune activation.
Conclusion: Disuse accelerates atrophy and functional decline in aged mice, accompanied by immune dysregulation and systemic vulnerability. Immobilization induced not only local atrophy but also contralateral weakness, frailty, and systemic inflammation. Ongoing work is evaluating the contribution of mTORC1 signaling to the effects of disuse, and the potential for gerotherapeutic rapamycin to mitigate these outcomes.
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PLCG2 deficiency alters the neuroinflammatory transcriptome and sickness behavior response to LPS

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PLCG2, a critical immune regulator, has emerged as a key factor in Alzheimer's disease, with genetic variants conferring both risk and protection. In the brain, PLCG2 is mainly expressed in microglia, influencing cellular functions including calcium signaling. We investigated PLCG2's role in neuroinflammation using constitutive and inducible knockout mouse models with LPS-induced acute inflammation.
In the constitutive KO, LPS treatment induced >200 diLerentially expressed genes in the brain, altering pathways related to innate and adaptive immune responses, inflammatory signaling, and microglial function. KO mice exhibited a distinct gene signature in response to LPS, with upregulated genes associated with interleukin signaling, prostaglandin response, and interferon pathways. Interferon-responsive genes were upregulated in homozygote KO mice post-LPS treatment, a phenotype that has been linked to white matter pathology. Consistently, principal component analysis of myelin-enriched genes revealed LPS-treated homozygote KO samples clustering separately from other genotypes. Behaviorally, LPS-treated KO mice displayed reduced locomotion in open field tests, correlating with expression of sickness behavior-related genes. These findings suggest PLCG2 deficiency enhances interferon responses, potentially driving behavioral changes and myelin pathology phenotypes. Inducible KO mice showed distinct behavior, with ongoing eLorts focused on assessing their brain transcriptomes.

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Senolytic treatment to modulate the progression of aging in geriatric marmosets

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Drugs targeting senescent cells (senolytics) are promising candidates to slow progression of aging. Clinical trials are testing the effects of senolytics on diverse diseases, including Alzheimer's, cancer, and chronic kidney disease. In this pilot study, part of a mentored career development program supported by the San Antonio Pepper Center, we tested the effectiveness of the senolytics dasatinib and quercetin (D+Q) in removing senescent cells in aged marmosets to assess translational potential of this approach to enhance healthspan. Geriatric common marmosets (n = 4, 10-13 years old) received oral doses of D (5 mg/kg) + Q (50 mg/kg) on 2 consecutive days every two weeks for 10 weeks. Before and after treatment, we collected blood, biopsies of skeletal muscle and skin, and behavioral data from the detoured reach task (DRT). Each animal served as its own control. There were no adverse events. Each marmoset showed borderline improved DRT performance in retrieving treats from the test box after treatment (P > 0.05). From pre- to post-treatment, we observed changes to circulating triglycerides (197.5 ± 137.4 SD *vs*. 295.8 ± 211.3; P = 0.06), sodium (149.8 ± 2.9 *vs*. 144.5 ± 3.1; P = 0.002), mean corpuscular hemoglobin (21.5 ± 0.6 *vs*. 20.7 ± 0.6; P = 0.003), and platelets (647.3 ± 72.2 *vs*. 592.3 ± 87.7; P = 0.006). Future studies include testing the molecular effects of this treatment (*i.e*., effect on senescent cells). The outcomes of this study will broaden knowledge of feasibility, safety, and efficacy of D+Q to slow the progress of aging in healthy individuals, while simultaneously preparing an early career investigator to make vital

contributions to the field of geroscience.

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COL18A1/Endostatin, a clock-dependent hepatokine; investigating its dysregulation with aging

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Liver secreted proteins (hepatokines) are critical to systemic functions and are of broad interest as biomarkers and novel therapeutics. A key gap hindering progress is that the current hepatokine literature is based on narrow snapshots that do not capture the dynamic nature of the underlying biology. Based on previous studies showing rhythmic and clock-dependent abundance of secreted proteins within the liver, we hypothesized that hepatokine secretion is under circadian control. Employing a novel *ex vivo* liver secretion assay and DIA LC-MS/MS proteomic analyses, we identified 60 time-dependent secreted proteins in male and/or female C57BL/6 mice. Further interrogation of hepatocyte-specific *Bmal1* knockout mice revealed 33 *Bmal1*-dependent secreted proteins, many of which were time-dependent in WT mice. COL18A1, a heparan sulfate proteoglycan, and its cleavage product, endostatin, were released from the liver more during the day in a *Bmal1*-dependent manner. Molecular studies identified a repressive, transcriptional mechanism whereby CRY1 reduces *Col18a1* expression *in vitro*. Interestingly, injection of endostatin during the day had a sex-dependent effect on adipocyte metabolism *in vivo* and blunted mitochondrial respiration *in vitro*. With aging, we show that endostatin levels are increased in the liver, particularly during the active phase. Moreover, we observe an age-dependent increase in COL18A1 in a previously published database, without any corresponding changes in RNA expression, suggesting post-transcriptional regulation with age. Future studies will investigate circadian mechanisms governing endostatin release from the liver with aging to inform its chronotherapeutic potential.

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Loss of the myelin lipid sulfatide modulates amyloid-β deposition and distribution in amyloidosis mice

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Amyloid-β (Aβ) accumulation is a central feature of Alzheimer's disease (AD), but the influence of myelin-derived lipids on plaque development is not fully understood. Sulfatide (ST), a class of sulfogalactosphingolipids enriched in myelin and synthesized by cerebroside sulfotransferase (CST), shows profound depletion in AD brains. To evaluate whether sulfatide deficiency alters amyloid pathology in vivo, we generated CST-depleted 5xFAD mice. At three months of age, these animals displayed a striking reduction in parenchymal plagues. The observation clearly reflects a direct impact of sulfatide loss on Aβ deposition, since APP C-terminal fragment analysis indicated enhanced amyloidogenic processing in the brain. At two months, biochemical fractionation revealed elevated TBS-soluble Aβ40 and Aβ42, indicating the altered distribution between soluble and deposited pools. To investigate underlying molecular mechanism(s), we purified microglia and astrocytes by magnetic sorting. Microglia from CST knockout brains contained substantially less intracellular Aβ. Complementary BV2 cell assays showed that adding exogenous sulfatide increased uptake of fluorescent Aβ42, supporting a role of sulfatide in regulating phagocytosis. Together, these findings indicate that sulfatide depletion reduces microglial uptake and compaction of Aβ, leading to fewer plaques but a larger soluble pool. By influencing microglia-mediated Aβ clearance, our data help explain the paradox of reduced deposition despite elevated soluble Aβ, and link sulfatide loss to synaptic vulnerability. These results identify sulfatide as a key lipid determinant of Aβ deposition and clearance, and a potential therapeutic target for AD treatment.

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Timing of castration modulates its life-extending effect in genetically heterogeneous mice: castration at midlife is more effective than at earlier ages

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Sex differences in aging are well-established in human populations. Males typically have shorter lifespans and face significantly higher mortality risks during early to middle adulthood compared to females. However, the underlying mechanisms remain unclear, partly due to the lack of experimental animal models. Our lab previously demonstrated that genetically diverse UM-HET3 mice, like humans, exhibit consistent sex differences in survival

and mortality, validating their use as a model for studying these differences. More recently, we found that prepubertal castration at 20 days eliminates this longevity gap by selectively reducing male mortality during early-to-middle adulthood. Here we delineate the duration and ages when testicular hormones exert their detrimental effects on mortality by castrating mice at 20, 60, and 240 days of age. The finding that castration as late as 8 months was as effective in reducing mortality as castration at 20 days, indicates that neither the pubertal surge in gonadal hormones nor their actions during a substantial period of adult life play any role in limiting male longevity. In fact, later-life castration at 240 days was associated with a significantly longer lifespan and healthspan compared to castration at earlier ages. Together these results suggest that exposure to testicular hormones up to 8 months provides long-term benefits, whereas exposure after 8 months is causal to the reduced longevity observed in males.

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Modulation of microglia by L-type calcium channels Cav1.2 and Cav1.3

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Aging disrupts calcium homeostasis throughout the body which results in dysregulation of various processes, including inflammation and autophagy. The L-type calcium channels (LTCCs) form an important source of dysregulated intracellular calcium in the brain and their expression increases with aging. Work from our group suggests that certain LTCC antagonists reduce microglia pro-inflammatory cytokine production, and can also reduce dystrophic neurite pathology in the 5xFAD mouse model of Alzheimer's disease. However, studies elucidating the functional role of LTCC in microglia are limited. We hypothesize that microglial phenotype is regulated by LTCCs, particularly the subunits Cav1.2 and Cav1.3. To study this, we utilized both *in vivo* and *in vitro* microglia-specific conditional knockout (CKO) models of Cav1.2 and Cav1.3. *In vivo*, we found that microglial CKO of Cav1.2 and Cav1.3 in adult mice did not significantly alter behaviour in the open field, novel object recognition, and Barnes maze tasks in the absence of immune stimulation. Future studies will examine how stimulation with lipopolysaccharide (LPS) alters sickness behaviour in Cav1.2 and Cav1.3 CKO mice. *In vitro*, we found that CKO of Cav1.2 and Cav1.3 in neonatal microglia altered some responses to LPS. Quantitative PCR revealed that expression of the lysosomal cysteine protease, cathepsin B (*Ctsb*) was suppressed by LPS, and a 3-way ANOVA revealed an interaction between LPS and Cre treatment. Additionally, LPS increased expression of the pro-inflammatory cytokine gene, *Il1b*. Overall, the current results suggest that microglial Cav1.2 and Cav1.3 have a limited role in regulating microglia phenotype, although additional work is required to understand how LTCC antagonists modulate microglia phenotype and function.

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Inhibiting the GABA shunt increases circulating GABA and improves metabolic and physical function in aged male mice

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Background: Aging is associated with progressive declines in metabolic and physical function reducing both lifespan and health span. γ-Aminobutyric acid (GABA) has been identified as a dietary supplement with protective effects against aging. We hypothesized that we could increase circulating GABA by pharmacologically limiting hepatic GABA clearance, elevating systemic GABA concentrations to improve physical and metabolic function in aged mice.
Methods: To test this, we provided 17-mo old C57BL/6JN male mice (source: NIA aged rodent colony) with either normal drinking water or drinking water with the GABA transaminase inhibitor, ethanolamine-O-sulfate (EOS; 3 g/L), for 1 month. After 1-month, mice underwent tests of metabolic (4 h fasted insulin and glucose, oral glucose tolerance and insulin tolerance tests) and physical function (grip strength and rotarod). At the conclusion of these studies, we collected, and snap froze tissues for wet lab analyses.
Results: EOS nearly doubled liver GABA concentration ($P = 0.0345$) and lowered serum insulin ($P = 0.0113$) and HOMA-IR ($P = 0.0183$) without affecting serum glucose concentrations ($P = 0.25$). Although there was no effect on insulin tolerance or oral glucose tolerance, oral glucose stimulated serum insulin was decreased in EOS treated mice ($P = 0.0173$), indicating improved insulin sensitivity. EOS also increased forelimb ($P = 0.0042$) and all limb (P

ABSTRACT

< 0.0001) grip strength and extended the time to fall on rotarod ($P = 0.0127$).
Conclusion: Pharmacological inhibition of hepatic GABA clearance increases systemic GABA levels and improves metabolic and physical function in aged mice. These findings suggest that targeting hepatic GABA metabolism may represent a novel therapeutic strategy to mitigate age- and obesity-related metabolic dysfunction.

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Glucagon receptor signaling is indispensable for the healthspan effects of caloric restriction in aging male mice

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Background: Most research aimed at understanding the mechanism by which caloric restriction (CR) slows aging has focused on insulin signaling. However, this focus on insulin has largely limited investigation into other hormones that are similarly altered by calorie restriction. Glucagon sensitivity, like insulin sensitivity, increases with chronic CR.
Methods: Using dietary manipulation, global (GKO) and liver specific (LKO) glucagon receptor knockout, and pharmacologic glucagon receptor activation in aging mice, we aimed to understand how glucagon, which counter-regulates insulin, affects CR-induced improvements in aging and healthspan.
Results: Globally eliminating glucagon receptor signaling decreased median lifespan by 35%. Extending these findings to metabolic health, chronic, lifelong CR (15% since 4 months of age), decreases liver fat ($P < 0.01$), serum triglyceride ($P < 0.05$), and serum cholesterol ($P < 0.01$) in wildtype littermates (WT), yet these metabolic benefits are absent in GKO mice. In line with these observations, critical nutrient sensing pathways known to improve aging are dysregulated in aging mice lacking glucagon receptor signaling at the liver. Liver-specific deletion of the glucagon receptor decreases hepatic AMP Kinase activation ($P = 0.0005$), regardless of diet. CR decreases hepatic mTOR activity in WT, but not LKO mice ($P < 0.05$). In contrast, pharmacologic glucagon receptor agonism decreases mTOR signaling at the liver in young ($P = 0.005$) and aged ($P = 0.04$) mice.
Conclusion: These findings propose that glucagon signaling plays a critical role in the healthspan extension driven by caloric restriction. Commercially available glucagon receptor agonists and those in late phase clinical trials highlight the potential for translating this research to improve healthspan in our aging population.

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Acetyl-CoA synthetase short chain family member-1 acetylation turnover is needed for thermogenesis

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Obesity, characterized by excess adipose tissue, is a leading risk factor for type 2 diabetes. Activation of brown adipose tissue (BAT), beige adipocytes, and the browning of white adipose tissue (WAT) offer promising therapeutic avenues. These processes require fatty acid oxidation (FAO) and induction of uncoupling protein 1 (UCP1). The mitochondrial enzyme ACSS1 (Acyl-CoA Synthetase Short Chain Family Member 1), a SIRT3 deacetylation target, catalyzes the conversion of acetate and CoA to acetyl-CoA, supporting mitochondrial bioenergetics. However, the role of ACSS1 acetylation in adipose thermogenesis remains unclear. To investigate this, we generated a knock-in mouse model harboring a lysine-to-glutamine substitution at position 635 (K635Q), mimicking constitutive ACSS1 acetylation (ACSS1-K635-Ac). Acss1$^{K635Q/K635Q}$ mice exhibited reduced body size and weight. Following 48-hour fasting, these mice developed hypothermia and showed decreased ATP and lactate levels. Despite the upregulated *Ucp1* expression in BAT and WAT, brown adipocytes from mutant mice displayed reduced oxygen consumption and impaired mitochondrial respiration. Beige adipocytes failed to respond to β-adrenergic stimulation, indicating functional uncoupling of UCP1 expression and activity. Administration of the β3-adrenergic agonist CL-316243 further revealed impaired thermogenic signaling *in vivo*. These findings suggest that ACSS1-K635 acetylation disrupts FAO and mitochondrial function, impairing adaptive thermogenesis despite increased UCP1 expression. ACSS1 acetylation may thus serve as a novel regulator of adipose tissue thermogenic capacity and represent a potential therapeutic target for metabolic diseases.

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Utilizing chimeric mitochondrial transcripts to understand the breadth of mitochondrial genome deletions in aging human tissue

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Large deletions within the mitochondrial genome have been repeatedly reported in aging tissue and are implicated as a driver of age-related pathology in mouse models. These events have clear functional relevance to the aging process and thus the potential to serve as both a metric of biological age and a target for anti-aging interventions. Despite this potential, the challenges of sequencing the mitochondrial genome make mitochondrial genome deletions hard to quantify without specialized assays. Further, the limits of mitochondrial reverse genetics prevent understanding the direct consequences of these mutations. We recently reported a novel class of transcripts, chimeric mitochondrial RNAs, which are detectable within RNA sequencing data. Here, we extend these findings to illustrate the potential of utilizing chimeric mitochondrial transcripts to understand the scope and consequences of mitochondrial deletions in human tissue. Using publicly available data profiling multiple tissues from matched donors from the GTEx project, we demonstrate the tissue type specificity of chimeric mitochondrial transcript frequency and location. Using paired RNA and long read DNA sequencing of human skin, we demonstrate a close correspondence between the frequency and locations of chimeric mitochondrial transcripts and mitochondrial genome deletions. We compare deletions detected in long read sequencing to chimeric mitochondrial transcripts identified within single cell and spatial RNA sequencing data of human skin. Together, these data highlight the potential and caveats of using chimeric mitochondrial transcripts to understand mitochondrial genome deletions in aging human tissue samples.

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Modulation of astrocyte reactivity by LRP1 in neuroinflammation

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Chronic neuroinflammation significantly increases the risks of neurodegenerative diseases, particularly in aging and in pathological conditions such as brain injury and infection. A hallmark of chronic neuroinflammation is the shift of astrocytes into reactive states, including subtypes that disrupt neuronal function and actively cause neural cell death. Markers associated with these neurotoxic reactive astrocytes are substantially elevated in brain tissue from individuals with major neurodegenerative diseases such as Alzheimer's and Parkinson's, implicating them in disease pathogenesis. Targeting mechanisms that modulate astrocyte reactivity may therefore help preserve neuronal integrity in these conditions. This project investigates the role of astrocytic low-density lipoprotein receptor-related protein 1 (LRP1) in regulating inflammatory responses. We hypothesize that astrocyte-LRP1 dampens astrocyte reactivity to pro-inflammatory signals. To test this, we are assessing how astrocyte-specific LRP1 knockout (KO) alters astrocyte responses to cytokine exposure. Our current findings indicate that astrocyte-specific LRP1KO enhances cytokine-induced reactivity *in vitro*, promoting astrocytic transition into reactive states with elevated expression of genes associated with neurotoxic astrocyte phenotypes. Ongoing experiments are evaluating the functional impact of astrocyte-LRP1KO on neurons in co-culture, characterizing the effects of astrocyte-specific LRP1KO *in vivo*, testing whether an LRP1 agonist can reduce astrocyte reactivity after inflammatory stimulation, and profiling whole-brain transcriptomic changes in response to astrocyte-LRP1KO via single-cell RNA sequencing.

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Assessment of anti-cataract and pro-longevity properties of flavonoids from edible plants

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The efficacy of four flavonoid compounds found in edible plants (quercetin, apigenin, daidzein, and flavone) in preventing photooxidation-induced protein aggregation of lens proteins was tested by incubating rhesus macaque lens homogenates with 1% (v/v) H_2O_2 solution within a UV crosslinker for 4 hours. Daidzein and apigenin significantly ($P < 0.05$) reduced the photooxidation-induced aggregation of lens proteins when present at a concentration of 500 μM, while the other tested compounds did not have a significant effect. The longevity promoting effects of these compounds were also assessed by sponsoring their testing in Ora Biomedical's Million Molecule Challenge. All four compounds were administered to *C. elegans* cultures to generate survival curves. Daidzein and quercetin

both significantly ($P < 0.05$) increased median lifespan by 6.2% while the other flavonoids did not have an effect. Based on these results, further longevity testing of worms incubated with daidzein or quercetin was initiated to determine dose responsiveness and effects of stress conditions (starvation, heat, and UV).

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