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Targeting metabolic function to improve aging and healthspan. Abstracts presented at the 2024 Masoro-Barshop conference on aging. October 10-13, 2024

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 2024 topic focused on "Targeting Metabolic Function to Improve Aging and Healthspan". 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 is held each year to assemble leaders in a thematic area of geroscience in an informal setting to maximize discussion on their recent research discoveries. This format also provides opportunities for investigators and trainees 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. This year's (held Oct 10-13, 2024) topic focused on "Targeting Metabolic Function to Improve Aging and Healthspan".

Metabolism and aging are intricately linked; the rate and efficiency of metabolic processes tend to change as we age and likely drive many of the pathological conditions and diseases associated with aging. Changes in metabolic function, across molecular, cellular and organismal functions, several age-related conditions, including muscle loss, increased fat accumulation, and decreased cardiovascular health. Functionally, aging is associated with multiple contributing metabolic factors including, decreased physical activity, hormonal changes, changes in dietary intake or needs, and chronic inflammation, which can severely limit function with aging. Moreover, aging is marked by impairments in metabolic hallmarks of aging, including mitochondrial function, oxidative stress and others. Thus, understanding how metabolism shifts over time can provide valuable insights into aging mechanisms and potential strategies for promoting longevity and healthy aging.

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Delineating potential metabolic targets that drive aging and metabolic disorders

Understanding how metabolism changes with age or disease has long been central to defining potential molecular markers, and therapeutic targets, of these outcomes. Dr. Rima Kaddurak-Daouk (Duke University) presented her precision medicine approach on understanding the biology of brain metabolic health and disease and outlined the potential role of bacterial metabolites in this process. Dr. Irina Conboy (University of California) outlined her approaches to define the variation and fluctuation of circulating proteins with age and highlighted the potential for plasma dilution to reduced aging signaling ligands as an approach to improve aging health. Dr. Blake Rasmussen (UT Health San Antonio) outlined the relationships between exercise and aging and highlighted the role that each have on modulating muscle transcriptomic and metabolomic outcomes that drive functional decline. Dr. Alan Saghatelian (Salk Institute) used lipidomic approaches to show how specific lipid classes in the brain are remodeled constantly to preserve brain health and could identify potential drivers of brain aging. In two talks from selected

submitted abstracts, Dr. Sijia He (UT Health San Antonio), a speaker selected from submitted abstracts, presented her work on using single nuclei RNA sequencing to define the role of myelin sulfatide in Alzheimer's disease and Hanna Kalenta (UT Health San Antonio) showed her thesis work characterizing the muscle lipidomic effect of acute and chronic activation of mTORC1. Similarly, Dr. Chan-Hyan Na (Johns Hopkins University) outlined the proteomic landscape of neurodegenerative diseases and how this affects the brain on a cell-type specific basis. Dr. Daniel Adekunbi (UT Health San Antonio), also selected to speak from submitted abstracts, presented data using cellular approaches to identify mitochondrial bioenergetics as a key factor in tying changes in the brain of baboons with a functional decline in walking speed with age. Similarly, Dr. Suarhav Saha (University of Kansas) outlined the age-related changes in physical resilience in mice and their tie to changes in mitochondrial function in his talk selected from submitted abstracts.

Metabolic timing and sensing

Biological rhythms play significant roles in the regulation of physiological function. Metabolism has long been known to be heavily influenced by external influences, including timing and environmental conditions. There is growing understanding that loss of the homeostatic regulation of appropriate rhythmic timing can be central to loss of function and increased risk of disease and may drive the aging process itself. Dr. Jake Chen (UT Health Houston) presented work on how circadian regulation in the muscle is essential for the maintenance of muscle function with age, and that dampening of this process can have profound negative effects on physiological function. Dr. Joseph Bass (Northwestern University) highlighted how macronutrients can alter clock oscillation and how this function may drive significant changes in metabolic function, including thermogenesis. Dr. Maria Chondronikola (University of Cambridge) brought the group up to date on the effects of meal timing on metabolic health and aging and offered perspectives on approaches targeting brown fat and thermogenesis in older subjects. Similarly, Dr. Qiang (Annabelle) Wang (City of Hope) showed approaches targeting the age-associated remodeling of adipose tissue and decline of thermogenic activity by using glucocorticoid receptor signaling to prevent metabolic decline. The aging adipose secretome was a main focus of the talk from Dr. Ian Lanza (Mayo Clinic), and with potential targets on TLR4 signaling, mitochondrial function and inflammation and senescence, even in the absence of dramatic changes in physiological function. Dr. Lisa Kilpela (UT Health San Antonio) addressed the potential of changing patterns in binge eating, particularly in older women, which has until recently been under-reported and not well understood, with her studies clarifying the potential aging health implications of targeting this behavior. Dr. Mengwei Zang (UT Health San Antonio) also showed the potential implications for metabolic changes in nutrient signaling and their role in the aging liver and hepatic metabolic disease from a molecular perspective.

Interventional approaches to target aging and metabolic health

With the growth of Geroscience, there is growing evidence that many of the diseases of aging, including metabolic disease, can be targeted through approaches developed from the biology of aging. Caloric restriction (CR) without malnutrition is the standard for this type of approach and has been widespread in study prior to our understanding of the molecular regulators of aging. Dr. Na Zhao (Mayo Clinic) presented data showing the interrelatedness of molecular regulators of metabolism and CR with data showing differences in lifespan effects of this intervention that are depending on APOE-Genotypes. Dr. Bettina Mittendorfer (University of Missouri) highlighted the role of protein intake and preservation of muscle function with age; interestingly, her results show that while insufficient protein promotes sarcopenia, there is little benefit of additional protein beyond sufficient requirements. Dr. Chris Adams (Mayo Clinic) used approaches to identify the molecular mechanisms of sarcopenia to develop a novel approach using ursolic acid as a potential intervention to prevent age-related muscle decline. Additional talks on potential gerotherapeutics included those from Dr. Adam Konopka (University of Wisconsin) who highlighted ongoing and upcoming trials testing the potential functional effectiveness of rapamycin, and other rapalogs, in translational studies; Dr. Tiffany Cortes (UT Health San Antonio) showing results from her studies testing semaglutide in older patients and potential beneficial effects on body composition and physical function; Dr. Andrey Parkhitko (University of Pittsburgh) outlining the molecular effects of methionine restriction in animal models and development of novel genetic and pharmacological approaches to affect methionine metabolism to improve aging health; and Dr. Holly Brown Borg (University of North Dakota) who brought the attendees on a trip from basic discoveries in long-lived Ames dwarf mice, to identifying potential therapeutic targets in glutathione and methionine metabolism as potential approaches to treat age- and metabolism-related diseases. Dr. Masahiro Morita (UT Health San Antonio) outlined his strategy targeting mRNA decay through mTOR-related process as a means to control changes in energy regulation throughout aging. Eduardo Gutierrez Kuri (UT Health San Antonio) shared his thesis work regarding neuroinflammatory transcriptome profiling in brain health and the role of PLCG2 in this process. Overall, then the emphasis of this group of talks highlighted the functional role of geroscience, and targeting specific hallmarks of aging, in the development of novel interventions to aging and metabolic dysfunction associated with age.

Conclusions

As discussed in the meeting, currently there is no single approach for improving metabolism and preventing age-related diseases. However, by defining the functional changes with age and the molecular mechanisms driving these processes supports continued development of interventional targets and interventions through geroscience. There is growing evidence that lifestyle modifications (*e.g.*, exercise, caloric restriction, and diet) and pharmacological agents (*e.g.*, rapamycin, diabetogenic and obesogenic drugs, *etc.*) have the potential to provide synergistic effects in promoting healthy aging and reducing the burden of age-related diseases. However, further research and clinical trials are needed to refine these interventions, assess their 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 during the conference.

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Poster abstracts

Acetyl-CoA synthetase short chain family member-1 (ACSS1) acetylation status regulates thermogenesis

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Brown adipose tissue (BAT) is a crucial regulator of metabolism specialized in dissipating energy in the form of heat. Cold stimulus induces BAT to burn glucose and free fatty acids for thermogenesis, with positive impacts adiposity, glucose homeostasis, and insulin sensitivity. The different White adipose tissue depots (WAT) in the body also get stimulated by cold by transforming into beige adipose tissue getting a more metabolically active phenotype. For these reasons cold mimicking drugs and conditions and the mechanisms behind them are currently a hot subject of study in order to develop therapies to address obesity and other metabolic diseases that are more prevalent with age. Sirtuin 3 (SIRT3), an NAD^+-dependent deacetylase found within the mitochondria, is a key regulator of thermogenesis. Loss of SIRT3 in mice leads to impairment of BAT lipid metabolism, thermoregulation, and mitochondrial respiration. Acetyl-CoA Synthetase Short Chain Family Member-1 (ACSS1) is an established SIRT3 deacetylation target that synthetizes acetyl-CoA using acetate that is central for fatty acid oxidation (FAO) and mitochondrial metabolism. We generated a ubiquitous acetylation mimic knock-in mouse by mutating lysine 635 to glutamine (K635Q), previously shown to alter ACSS1 enzymatic activity, which represents a constitutive ACSS1-K635-Ac rendering a protein with altered functionality. Our studies showed that these mice were intolerant to stimulation with 3 adrenergic receptor agonist (cold mimicking) CL316243 and died within 24 hours. These mice were not able to maintain body temperature and glucose homeostasis and also displayed dysregulated levels of the major lipid synthesis and oxidation pathways in both BAT and inguinal subcutaneous WAT (iWAT). ACSS1-K635Q beige adipocytes showed impaired use of the lipid droplets when stimulated with Forskolin. BAT mitochondria of ACSS1-K635Q displayed lower respiration than WT mice. Histological analysis pointed to more unorganized BAT and iWAT tissues with higher expression levels of UCP1 protein in ACSS1-K635Q mice. These data suggest ACSS1 inability to be deacetylated in the ACSS1-K635Q tissues is the cause of the observed phenotypes and is an important regulator of adipose cells/tissue thermogenic function. Therefore, manipulating ACSS1 acetylation status is a potential therapeutic target for metabolic diseases. These results open a new roadmap to improve metabolic health through post-translational control of ACSS1.

Sex specific changes in mitochondrial bioenergetics in the brain of aging baboon correlates with walking speed

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Mitochondria play a crucial role in brain aging due to their involvement in energy metabolism and brain steroid synthesis. Mitochondrial dysfunction is linked to age-related neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease. We investigated changes in the respiratory activities of the electron transport chain (ETC) complexes in normally aging baboon brains and

determined how these changes relate to donor sex, morning cortisol levels, and walking speed. Using a novel approach, we assessed mitochondrial bioenergetics from frozen prefrontal cortex (PFC) tissues from a large cohort (60 individuals) of well-characterized aging baboons (6.6–22.8 years, approximately equivalent to 26.4–91.2 human years). Aging caused a decline in respiration linked to each ETC complex in the PFC, while citrate synthase activity did not change with age, suggesting that the decline in respiration is independent of mitochondrial content loss. Moreover, when donor sex was used as a covariate, we found that mitochondrial respiration was preserved with age in females, whereas males showed significant loss of ETC activity with age. Males had higher activities of each individual ETC complex and greater lactate dehydrogenase activity relative to females. We also observed a positive predictive relationship between walking speed and respiration linked to complexes I, II, and IV in males but not in females. Circulating cortisol levels correlated only with complex II-linked respiration in males. This study highlights a potential molecular mechanism for sexual dimorphism in brain resilience and suggests that changes in PFC bioenergetics contribute to reduced motor function with age, at least in males.

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The role of sialylation in cerebral amyloid angiopathy

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Glycosylation is the most common post-translational modification in the brain. Aberrant glycosylation patterns have been observed in cerebrospinal fluid and homogenized brain tissue of Alzheimer's disease (AD) cases. Our work has identified significantly increased N-sialylation intensity of microglia within parenchymal Aβ plaque microenvironment compared to no plaque control regions in AD. Thus, we were curious if increased microglia sialylation patterns were similar in brains with Alzheimer's Disease and Cerebral Amyloid Angiopathy (CAA) pathologies. CAA is defined as the deposition of amyloid beta aggregates in the vascular walls of cerebral arteries and arterioles. The present study investigates sialylation patterns of microglia and endothelial cells of blood vessels in the frontal cortex across 30 post-mortem human brains with CAA+AD ($N = 11$), AD ($N = 10$), Control ($N = 9$). Utilizing serial histologically stained slides, the area coverage of amyloid, sialylation, and microglia were quantified in vascular and perivascular regions (75-micron diameter). We identified greater amyloid deposition in the perivascular region in CAA+AD cases compared to AD and Control cases. Additionally, we observed significant differences in vascular sialylation patterns across disease states. These included greater sialylation of leptomeningeal vessels compared to parenchyma in CAA+AD while greater parenchymal vessel sialylation was observed in AD. Lastly, we found a trending increase in microglia sialyation near parenchymal vessels in CAA+AD compared to Control cases. These findings suggest sialylation may be a marker of disease-associated phenotype and possibly indicate vessels in CAA+AD may be more vulnerable to pathological aggregation due to an increase with sialylation.

Lipopolysaccharide-induced neuroinflammatory transcriptome profiling in PLCG2 deficient mice

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Phospholipase C gamma 2 (PLCG2), known to play a crucial role in immune regulation, has recently emerged as a significant player in Alzheimer's disease, with genetic variants conferring both risk and protection. In the brain, PLCG2 is predominantly but not exclusively expressed in microglia, where it influences key cellular functions including phagocytosis, cytokine secretion, cell survival, and proliferation. We investigated PLCG2's role in neuroinflammation using heterozygous and homozygous constitutive knockout mice with lipopolysaccharide-induced acute inflammation.

PLCG2 gene KO was validated in an allele dose-dependent manner. As expected, LPS treatment induced 211 differentially expressed genes in the brain ($P < 0.05$) and significant alterations in pathways related to the innate and adaptive immune responses, inflammatory signaling, and microglial function. Notably, homozygous KO mice exhibited a distinct gene signature in response to LPS compared to the other genotypes, with 16 uniquely upregulated genes associated with interleukin signaling, prostaglandin response, and interferon pathways. Further analysis revealed that interferon-responsive microglial genes were upregulated in homozygote KO mice post-LPS treatment, a cellular phenotype that has been linked to white matter pathology and myelin loss. PCA analysis using all available myelin-enriched genes for all three LPS-treated genotypes revealed that homozygote KO samples clustered separately from those of the other two genotypes. Behaviorally, LPS-treated KO mice displayed more severe sickness behavior in open field tests (reduced distance moved, time spent moving and average velocity) that correlated with expression of genes known to regulate sickness behavior. These findings suggest that PLCG2 deficiency enhances interferon responses, potentially driving the observed behavioral changes and myelin pathologies.

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Single-nucleus RNA sequencing reveals myelin sul-

fatide depletion-induced cellular and transcriptomic changes relevant to Alzheimer's disease

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The mammalian brain is highly enriched in lipids, among which sulfatide (ST), a class of glycosphingolipids largely distributed in myelin, dramatically declines in the early stages of Alzheimer's disease (AD) brains. Central nervous system (CNS) ST depletion in mice led to AD-like cognitive impairment and neuroinflammation, suggesting ST loss may function as a critical driving factor for AD progression. However, the exact mechanism by which ST decline leads to brain dysfunction remains elusive.
Here we present the analysis of single-nucleus RNA sequencing from 214316 nuclei sampled from the whole-cerebrum tissues of control and ST-deficient mice. Among major cell groups, we identified a significant induction of microglial population in ST-deficient mice, transcriptomic signature analysis suggested an enhanced transition of homeostatic microglia toward disease-associated microglial phenotype upon ST loss. Meanwhile, we detected an expansion and activation of oligodendrocytes, accompanied by enhanced proliferation of oligodendrocyte precursor cells (OPCs). Moreover, we surprisingly discovered a $Satb1^+$ interneuron population with sex and age-specific enrichment pattern. Specifically, ST deletion down-regulated the enrichment of $Satb1^+$ interneurons in females, indicating enhanced neuronal senescence, which resembles the effect of aging. Lastly, loss of ST significantly down-regulated cholinergic interneurons, reminiscent of the diminished cholinergic system in human AD.
Collectively, our findings demonstrated that deficiency of myelin ST promotes aging-associated and AD-like phenotypes at the cellular and transcriptomic levels, emphasizing the crucial roles of myelin lipid homeostasis in maintaining normal brain function.
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Muscle lipidomic profile following acute exercise in mice with constitutively active mTORC1

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An increase in mechanistic target of rapamycin complex I (mTORC1) kinase activity stimulates muscle protein synthesis in response to amino acids, growth factors, energy, and mechanical stimuli. We previously found muscle hypertrophy and increased mitochondrial respiration in resting mice with chronically active mTORC1 (*i.e.*, an inducible skeletal muscle specific DEPDC5 knockout (KO) model), but no improvement in muscle quality and function. The purpose of this study was to determine the lipidomic profile of skeletal muscle in DEPDC5 KO and wild-type (WT) male and female mice following 1-hour of treadmill exercise. A targeted lipidomics approach was performed on quadriceps muscle, with a total of 1088 lipids being analyzed. Our lipidomics analysis revealed large genotype-dependent differences in the lipidome of KO and WT mice, while exercise-induced changes were comparatively fewer. There was a total of 13 significantly downregulated and 22 significantly upregulated lipids in WT after the exercise bout ($P < 0.05$, FC = 1.5). KO mice had 14 significantly downregulated and 50 significantly upregulated lipids after exercise ($P < 0.05$, FC = 1.5). There was a significant upregulation of CER(16:0) – CER(24:1) in KO mice post-exercise, with CER 20:1 levels increasing 27-fold ($P < 0.05$). Additionally, KO mice had an increased turnover of TAGs post-exercise. We conclude that chronic activation of mTORC1 in skeletal muscle alters the lipid profile which may impact overall muscle function and development of sarcopenia.
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Lipidomic and metabolomic response of skeletal muscle to short term disuse atrophy

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We investigated how short-term muscle disuse altered the skeletal muscle metabolome and lipidome and how these changes are reversed by exercise rehabilitation in middle aged adults. We report that the energy metabolism pathways; nicotinic acid (NAD^+), Glycolysis and TCA cycle pathways, were reduced after 7 days of muscle disuse which is reversed by 5 days of exercise rehabilitation. Amino acid pathways including phenylalanine, tyrosine and tryptophan metabolism pathways showed the same response to muscle disuse and exercise rehabilitation. The skeletal muscle lipidome experienced a divergent response

where, Phosphatidylinositols (PI) were reduced but Phosphatidylglycerols (PG) and Diacylglycerols (DAG) were elevated after short term muscle disuse. The lipidome also experienced a divergent response to exercise rehabilitation where DAG and PG returned to pre-disuse levels after 1 and 5 days of exercise rehabilitation respectively, whereas PI did not recover after 5 days of exercise rehabilitation.

Ferroptosis signaling contributes to age-associated axonal fusion

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The reconnection between the regenerated axon extending from the amputated nerve's proximal and distal axon, known as axonal fusion, is an efficient way to recover function after nerve injury. However, axonal fusion does not always occur, and its underlying mechanisms are largely unknown. Using *C. elegans* as a model, we found that aged neurons often show a higher axonal fusion rate, despite the reduced axon regrowth capacity. Through a genetic screen, we identified that mutations of GPX genes, key inhibitors of ferroptosis, led to enhanced axonal fusion after nerve injury in young animals. Interestingly, we found that low doses of ferroptosis inducing drugs enhanced axonal fusion, while elevated concentrations led to the formation of debris-like structures, underscoring the importance of precise regulation of ferroptosis in determining the responses to nerve injury. Ferroptosis a type of regulated cell death characterized by iron-dependent oxidative damage to phospholipids within the cell membrane. During aging, there is often an increase in oxidative stress, iron accumulation, and impaired antioxidant defense mechanisms, which can contribute to enhanced ferroptosis. Age-related changes in lipid metabolism also increase the availability of polyunsaturated fatty acids (PUFAs) that are prone to peroxidation, further promoting ferroptotic processes. Consistent with the notion that ferroptosis signaling promotes axonal fusion, we found that aged neurons had a higher rate of axonal fusion after injury than young neurons. Aged neurons also displayed enhanced debris formation, which could be lowered by ferroptosis inhibiting agents or GPX overexpression. Mechanistically, we found that ferroptosis signaling elevated injury-induced externalization of phosphatidylserine (PS) that is recognized by its receptor PSR-1 to facilitate axonal reconnection. We found that PSR-1 formed phase-separated condensates which underwent phase transition into protein aggregate in an oxidative environment. Inhibition of phase separation by 1,6-hexanediol (1,6-HD) reduced ferroptosis-inducible axonal fusion. Notably, we found that overexpression of PSR-1 in aged neurons greatly enhanced axonal fusion, whereas it did not occur in young neurons. This suggests that the oxidative environment and the subsequent lipid peroxidation contributes to the enhanced axonal fusion in aged neurons by promoting PSR-1 phase transition. Therefore, our study uncovers a previously unknown connection between aging, lipid peroxidation, and axonal fusion.

α/β-hydrolase domain-containing 6 negatively regulates insulin sensitivity in the liver

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Background: α/β-hydrolase domain-containing 6 (ABHD6) is a lipase that is capable of hydrolyzing monoacylglycerol. Previous studies have shown that inhibition of ABHD6 ameliorates high-fat-diet (HFD) induced diabetes by increasing glucose-induced insulin secretion in the islet and white adipose browning and energy expenditure in the adipose tissue via monoacylglycerol (MAG) signal. However, it is unknown whether ABHD6 can regulate insulin sensitivity. Moreover, the role of ABHD6 in the liver remains unclear.
Methods: In this study, we used liver specific ABHD6 knockout and overexpression mouse models, in vitro primary hepatocytes culture and lipidomics to study the role of ABHD6 in the liver.
Results: Our data showed that ABHD6 level was increased in the liver by HFD. In the liver-specific ABHD6 overexpression mouse, we found that ABHD6 exacerbated HFD induced diabetes by antagonizing insulin signal and thus increasing hepatic glucose production. In mouse primary hepatocytes, it is verified that ABHD6 negatively regulated insulin signal, especially reduced the inhibitory phosphorylation of FOXOs by AKT, the key gluconeogenic factors in the liver. Consequently, overexpression of ABHD6 in primary hepatocyte led to increased expression of gluconeogenic genes and glucose production. On the contrary, knockout of ABHD6 increased inhibitory phosphorylation of FOXOs and inhibited gluconeogenesis.
Conclusion: Together, our data suggests that ABHD6 is an important negative regulator of insulin sensitivity, largely due to its role in regulating AKT phosphorylation of FOXOs and gluconeogenesis.

A novel method of protein secretion from liver reveals time-dependent hepatokines

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The circadian clock is a cell-autonomous, molecular timekeeper that orchestrates diverse metabolic pathways, and disruption of metabolic rhythms is associated with metabolic disease. The liver is a highly circadian organ that acts as a metabolic hub for systemic energy homeostasis through releasing proteins and metabolites that mediate intercellular communication with peripheral organs. Here-

ABSTRACT

in, we describe a novel and simple method for obtaining proteins secreted from the liver. Utilizing this method, we performed proteomics analyses, identifying hundreds of proteins exclusively in the secreted fraction and revealing sex-dependent differences in protein secretion (Mup8/20), concordant with previous work. Additionally, differences in secretion of proteins involved in extracellular matrix and blood clotting were uncovered between the day and nighttime (*i.e.* Col18a1, Fgb). Further investigation identified circadian clock control of endostatin, a cleavage product of Col18a1, in the liver. Furthermore, validation of this hepatokine at multiple levels suggests systemic regulation of endostatin by the liver clock. As endostatin is anti-angiogenic protein known to regulate metabolic function, future work will investigate the time-dependent role of endostatin in metabolism. Interestingly, increased serum levels of endostatin have been found in aging mice, and are correlated with kidney fibrosis.

The effects of mTORC1 hyperactivation on the skeletal muscle transcriptome

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Mechanistic target of rapamycin complex 1 (mTORC1) is an important regulator of protein synthesis and is acutely activated in the presence of amino acids and exercise. While acute activation of mTORC1 is important for cellular homeostasis and growth, long-term hyperactivation of mTORC1 is suspected to play a role in aging. Therefore, we sought to determine the transcriptional changes that occur in skeletal muscle following chronic hyperactivation of mTORC1. To induce mTORC1 hyperactivation specifically in skeletal muscle, we used an inducible DEPDC5 (DEP domain containing 5) knockout mouse. DEPDC5 is a negative regulator of mTORC1 activation. This model has previously been shown to increase mTORC1 signaling and induce mild muscle hypertrophy, but in the absence of improved muscle function. Following 6 weeks of DEPDC5 knockout, we collected gastrocnemius muscles for subsequent RNA extraction and RNA sequencing (NovaSeq S4, 100PE). DEPDC5 knockout resulted in 374 downregulated ($p < 0.1$, $\log_2$[fold-change] < -0.4) and 722 upregulated genes ($p < 0.1$, $\log_2$[fold-change] > 0.4). GO enrichment analysis (biological processes) indicated that the top downregulated pathways were related to mitochondrial metabolism and muscle contraction, while top upregulated pathways included extracellular matrix reorganization and response to peptides. Given the large decrease in mitochondrial gene expression, we measured mitochondrial function in gastrocnemius muscle homogenates using high-resolution respirometry but observed no changes. Overall, these findings suggest that mTORC1 activity influences many biological processes within skeletal muscle, many of which may be related to the aging process.

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Ketogenic diet reverses age-related kidney failure: small molecule mimetic of dietary restriction which inhibits proteotoxicity, inflammation, and glycolysis

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As with aging and dietary restriction (DR), it is generally assumed that diabetic complications cannot be reversed even by complete correction of blood glucose, referred to as "metabolic memory", though can be delayed. We hypothesize that metabolic memory is driven by a cumulative effect of glycolysis causing epigenetic metabolic reprogramming, that age-related impairments are driven by a similar but slower process, and that protective effects of DR are conversely mediated by reduced glycolysis and epigenetic reprogramming. However, we have previously reported that a ketogenic diet does reverse diabetic nephropathy, which we attribute to its robust inhibition of glycolysis and reversal of related epigenetic reprogramming. We now report that in AJ mice a ketogenic diet also both prevents nephropathy, when initiated at 9 months of age before nephropathy, and completely reverses nephropathy when initiated at 17 months, after nephropathy has developed, associated with reversal in age-related gene expression (*e.g.*, markers of kidney integrity such as podocin were induced and markers of oxidative stress such as glutathione peroxidase were inhibited), when assessed at 20 months of age. We have now undertaken a high-throughput screen to discover small molecules which mimic these protective effects, leading to the synthesis of the novel small molecule GM-310. GM-310 mimics metabolic reprogramming produced by dietary restriction and the ketogenic diet, including reduced glycolysis, delays impairments in *C. elegans* models of Alzheimer's and Huntington's Diseases and increase lifespan. GM-310 is highly concentrated in brain after oral delivery and completely blocks impairments in a mouse model of hemorrhagic stroke.

Effects of environmental circadian disruption on metabolic and brain health in a humanized tau gene-replacement mouse model

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Epidemiological evidence links disturbed circadian rhythms resulting from shift work, sleep disorders, or ag-

ing to increased risks of metabolic syndrome and AD. In AD, circadian disruption manifests as fragmented/shifted sleep patterns and "sundowning". Although impaired circadian rhythms have long been assumed to be a consequence rather than a cause of AD, several lines of recent evidence suggest that circadian disruption may be a significant contributor to the development and progression of AD. Here we leveraged a next-generation clinically relevant animal model expressing physiological levels of human tau in the absence of mouse tau that spontaneously develops tauopathy at old age to assess the effects of chronic environmental circadian disruption on whole-body metabolism, dementia-like behaviors, and healthspan. A cohort of 32 mice were placed at mature adulthood under either a normal light cycle (NLC, 12h light/12h dark) or a chronic jet lag (CJL) paradigm that shifts the light cycle 8 hours ahead twice per week with continuous locomotor activity monitoring. Behavioral testing revealed sex-dependent disruption of spatial memory at mature adulthood, and consistent increases in aggressive- and repetitive-like behaviors induced by CJL. Metabolic health was assessed using metabolic cages, quantitative MRI, and blood glucose/ketone measurements. CJL led to significant losses in body and fat weight that worsened over time. Metabolic flexibility to fasting was impaired. Frailty index scoring showed CJL negatively impacted healthspan, especially at middle age. The study demonstrates chronic environmental circadian disruption accelerates aging biology, negatively affecting metabolic and brain health. Ongoing research hypothesizes this will accelerate AD-like tauopathy.

Sulfatide deficiency induces myelin lipidome imbalance via disruption of phosphatidic acid metabolism

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Introduction: Alzheimer's disease (AD) is the main cause of dementia and one of the most costly and burdensome diseases of this century. We have previously reported that sulfatide (ST), a myelin-enriched lipid mainly produced in oligodendrocytes, was significantly lost in post-mortem human AD brains and spinal cords, leading to an overall lipidome dysregulation in the central nervous system (CNS). Among lipids that were altered by ST deficiency, phosphatidic acid (PA) functions as a precursor for other phospholipids, potentially driving the alteration of the lipidome. However, the molecular mechanisms of ST loss-induced PA dysregulation and thereafter alteration in AD remains elusive.
Methods: A multidimensional mass spectrometry-based shotgun lipidomics approach was used to analyze lipid molecular species from post-mortem human AD brain tissues and mice tissues. Whole-body (KO) and oligodendrocyte-specific cerebroside sulfotransferase (CST) knockout (CKO) mouse models were used to mimic the loss of ST in AD. Brain nuclei were extracted for single nuclei sequencing analysis.
Results: ST levels were decreased in the white matter of human AD brain compared to controls. Additionally, levels of PA showed strong positive correlations with ST in both brain white matter (Spearman $r = 0.733$, $p = 0.031$) ($n = 11$, 77.25 ± 8.41 (yr)) and grey matter ($r = 0.680$, $p =$ 8.17e-009) ($n = 56$, 77.22 ± 9.59 (yr)). In CST KO mice, loss of ST led to marked PA reduction from young age. Positive correlations of PA and ST were detected in multiple brain regions, including cortex, cerebrum, cerebellum, and spinal cord. Additionally, ST deficiency resulted in interrupted myelin lipidome including decreased phospholipids and cholesterol, increased lyso-phospholipids and cerebroside. Mechanistically, amelioration of neuroinflammation by microglial elimination did not prevent alterations of ST and PA in CST KO mouse model, suggesting that microglia is not responsible for ST loss-induced PA dysregulation. Interestingly, single nuclei sequencing analysis detected down-regulation of PA synthesis genes *Pld1* and *Agpat4*, and up-regulation of PA catabolic gene *Pla2g4e* specifically in the OPC and oligodendrocytes populations of CKO mice, suggesting oligodendrocytes are the main modulator of ST loss-related PA dysregulation.
Summary: The present study identified that ST loss resulted in PA metabolic disorder. Oligodendrocytes might be one of the mainly cell clusters affected. The present study provides a molecular mechanistic understanding on the disrupted lipidome in AD pathology and neurodegenerative conditions.
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Visualizing tau protein dynamics in native environments using 4DAFM: towards therapeutic targets for Alzheimer's disease

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Background: Tau protein stabilizes neuronal microtubules; however, modifications like electrostatic imbalances and hyperphosphorylation lead to tau aggregation, a hallmark of tauopathies such as Alzheimer's. While scanning electron microscopy and scanning tunneling microscopy provide structural insights, they cannot simultaneously capture spatiotemporal and nanomechanical data at atomic resolution. The 4D Atomic Force Microscopy (4DAFM) technique offers unique advantages by directly measuring interactions between the nano-probe and bio-

molecules, allowing real-time observation of structural dynamics in their natural milieu.
Methods: 30 µL of tau 40-41 isoform protein samples (1 ng/mL) were deposited on mica and left for 3 minutes to stabilize. PinPoint mode-4DAFM was used in PBS to preserve the near-physiological environment, allowing accurate tau protein dynamic growth observations.
Results: AFM imaging revealed distinct stages of tau aggregation, such as small amorphous clusters, granular-shaped oligomers, annular-shaped structures, and dense ordered neurofibrillary tangles (NFTs). These findings illustrate a progression from tau monomers to NFTs, highlighting different morphological pathways during aggregation. These findings may usher in developing targeted therapeutic strategies to disrupt specific stages of tau aggregation, particularly focusing on NFTs in Alzheimer's.
Conclusion: AFM proves to be an exceptional tool for visualizing the dynamic growth of tau proteins in near physiological environments. By elucidating the mechanisms underlying tau aggregation, this study may provide critical insights for identifying therapeutic targets to prevent tauopathies, specifically Alzheimer's. Future research will refine imaging techniques and investigate the effects of potential therapeutic interventions on disrupting tau fibril formation, ultimately contributing to a comprehensive visual map of therapeutic impacts on tauopathies.

CNOT6: a master metabolic regulator in early age?

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Attaining growth milestones is an integral part of early development. Metabolic factors are essential for attaining adequate body size and growth. FGF21 is a major regulator of basal metabolic rate and responses to fasting and feeding conditions. Evidence links FGF21 to feeding activity and energy metabolism—a hepato-neural axis of behavioral and energy homeostatic change. FGF21 is being widely studied in adult models, but the metabolic regulation in early postnatal growth remains to be understood. Here, we show that the deadenylase CNOT6 has the capability to regulate FGF21 levels in young mice and create a distinct metabolic state. Decreasing CNOT6 prevents FGF21 degradation, leading to increased overall expression of FGF21. CNOT6 knockout (KO) mice begin to show a depressed growth curve and significantly smaller bodies than control mice. Moreover, this decrease in growth is apparent specifically in the liver and fatty tissue. As FGF21 levels are increased, we begin to see a suppression of the IGF1 pathway and other metabolic processes. Additionally, the transcriptomic profile of CNOT6 KO mice shows a ketogenic shift, decreased feeding, and increased lipid metabolism pathway scores. We believe that CNOT6 plays an essential role in early postnatal growth via FGF21 regulation. The CNOT6 KO model can be tested for understanding how metabolic regulation in young age leads to adequate growth and adaptation to metabolic stressors. Furthermore, CNOT6 can be a therapeutic target for childhood obesity and diabetes.

Age-related changes in physical resilience and mitochondria in C57BL6/J mice

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Resilience, the capacity to recover from stress or adverse events, is critical for maintaining health and longevity during aging. Although resilience typically diminishes with age, the underlying metabolic and molecular mechanisms driving this decline remain inadequately characterized. This study investigates the impact of aging on resilience in male C57BL/6 mice, focusing on the interplay between physical resilience and mitochondrial complex activity. We assessed resilience in young (6 months) and old (24 months) mice through various stress tests, including downhill treadmill running, capsaicin exposure (0.005%), anesthesia (4% isoflurane), and thermoregulatory challenges in hot (50°C) and cold (5°C) conditions. Gastrocnemius muscle tissue was analyzed post-experiment for mitochondrial complexes I-V, PGC-1α, and SIRT3 using western blotting. Mitochondrial DNA copy number and biomass were also quantified using qPCR. Older mice exhibited diminished resilience across multiple measures, including prolonged recovery times post-anesthesia, increased sensitivity to high temperatures, and greater susceptibility to capsaicin. Although recovery after downhill running was not statistically significantly different, older mice exhibited greater variability. Resilience to cold temperatures did not differ with age. Additionally, older mice showed reduced expression of mitochondrial complexes I and V and decreased expression of PGC1α and SIRT3. Our findings suggest that aging significantly impairs physical resilience in mice, especially with temperature stress and anesthesia, associated with reduced mitochondrial and metabolic components. These results highlight the potential for therapeutic strategies targeting mitochondrial function to mitigate the adverse impacts of aging on resilience.

Rapamycin's role in reversing age-related lipid dysregulation in the marmoset liver and heart

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The common marmoset (*Callithrix jacchus*), a small, short-lived non-human primate with human-like physiology, serves as an ideal model for investigating aging

mechanisms and potential therapeutics. This study aimed to: 1) identify age-related effects on lipid metabolism in marmoset liver and heart, and 2) assess whether rapamycin, known to slow aging in rodents, could reverse these changes. We employed multidimensional mass spectrometry-based shotgun lipidomics in liver and heart tissue from young, old, and old rapamycin-treated (1 mg/kg/day, > 3 years) marmosets. Unsupervised statistical analysis revealed lipidome alterations between groups in both organs, with more pronounced changes in the liver. Ceramide, linked to age-related pathologies, nearly doubled in old marmoset livers compared to young controls. Levels of total ceramides strongly correlated with chronological age. Notably, rapamycin prevented this accumulation, restoring hepatic ceramide levels to those of young animals. Phosphatidylserine (PS), associated with apoptosis, increased with age in the liver, albeit modestly. Hepatic levels of total and specific PS species strongly correlated with chronological age. Again, rapamycin restored PS to young-like levels. Moreover, the relative abundance of palmitate-containing TAG species was significantly reduced with age in both organs, while rapamycin partially prevented this depletion. Conversely, lysophosphatidylcholine, associated with inflammation, increased with age and was further elevated by rapamycin, accumulating in both organs of old rapamycin-treated marmosets relative to young controls. Our findings bridge the gap between rodent studies and human aging, offering insights into age-related metabolic changes and rapamycin's rejuvenating effects, as well as potential side effects, in a clinically relevant primate model.

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Methionine restriction effects on molecular aging mechanisms in a tissue- and sex-dependent manner with potential roles of methionine sulfoxide reductase A (MsrA)

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Methionine restriction (MR) has been shown to impact many different molecular mechanisms of aging including decreasing reactive oxygen species generation, improving mitochondrial function, and increasing hydrogen sulfide production capacity via the transsulfuration pathway (TSP). Methionine can be oxidized to methionine sulfoxide which can be repaired by methionine sulfoxide reductase A (MsrA). It is currently unclear how MsrA and its role in methionine quality control may impact the beneficial effects of MR. Utilizing a MsrA knock-out mouse model we investigated these aspects in the liver and kidney since both tissues highly express MsrA and the TSP. While TSP enzymes and 3-mercaptopyruvate sulfurtransferase (3MST) expression was changed in a tissue-dependent manner by MR, there was largely no effect of MsrA. Hydrogen sulfide production was increased only in the liver regardless of MsrA status. Utilizing isolated mitochondria, we found that hydrogen peroxide production was increased in the kidney by MR regardless of sex or MsrA status, while in the liver hydrogen peroxide production was increased by MR only in females with loss of MsrA resulting in slightly increased levels regardless of sex. Isolated mitochondria oxygen consumption tended to be changed more by MR in females than in males, with the effects of MsrA being context dependent. Surprisingly, mitochondrial complex expression was largely unchanged, regardless of tissue. Expression of methionine sulfoxide reductases was impacted by MR in a tissue- and sex-dependent manner. Our results indicate a complex interaction between sex, diet, tissue, and MsrA status.

Lipidomic insights into the pathogenesis of amyotrophic lateral sclerosis

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Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder that primarily affects motor neurons in central nervous system. Understanding its metabolic dysregulation is crucial to understand the disease and mitigate its progression.

In this study, we specifically focused on lipid metabolism in ALS. The lumbar spinal cord specimens from neurologically normal and TDP-43 positive sporadic ALS patients (10 cases/group) were proceeded. The mean ages and standard deviations were 72 ± 9 and 71 ± 9 years for control and ALS patients, respectively, without statistical difference. Total 12 lipid classes with over 200 species were tested in the current study using multi-dimensional mass spectrometry-based shotgun lipidomics (MDMS-SL). Based on the lipidomics results, several lipid classes/species, which majorly involve in oxidative stress, apoptosis, and myelin integrity, showed overt changes. Specifically, plasmalogen was significantly decreased in ALS spinal cords, indicating increased oxidative stress or reduced buffering ability in response to oxidative stress with ALS. Secondly, there was a reduction in phosphatidylserine in ALS group, might indicate increased cellular apoptosis with disease condition. Lastly, the reduction of myelin-specific lipids, *i.e.*, cerebroside and sulfatide species, implied that myelin disruption occurs in ALS spinal cord compared to control.

In summary, our study raises evidence from lipidomics perspective to support the current understanding of the ALS disease mechanisms, which involves oxidative stress and apoptosis. In addition, this study is the first ever to reveal that myelin disruption might be involved in ALS pathogenesis.

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