Yale Center for Molecular and Systems Metabolism (YMSM) Retreat

Thursday, May 21st, 2026

New Haven Lawn Club

193 Whitney Avenue, New Haven CT 06510

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8:00 – 9:00 a.m. Continental Breakfast

9:00 – 9:05 a.m. Welcoming Remarks – **Anton Bennett,** YMSM Director

9:05 – 9:55 a.m. KEYNOTE SPEAKER – **Andrew Goodman, Ph.D.,** C.N.H. Long Professor of Microbial Pathogenesis and Director of Microbial Sciences Institute, Yale University School of Medicine **– "*Drug-microbiome interaction*"**

10:00 – 10:40 a.m. Session 1 – (Session Chair – David Alagpulinsa)

9:55 – 10:10 a.m. **Hector Haddock-Martinez** – *Shaping Stress Circuitry: The Role of the Locus Coeruleus in Isolation Responses During Early Life*

10:10 – 10:25 a.m. **Lei Zhang** – *OGT-RBM33 controls HMGB1 mobility in cholangiocytes to drive cholestatic liver fibrosis*

10:25 – 10:40 a.m. **Boby Matthews** – *Shaping Stress Circuitry: The Role of the Locus Coeruleus in Isolation Responses During Early Life*

10:40 – 11:00 a.m. **Coffee Break**

11:00 – 12:00 p.m. Session 2 – (Session Chair – Xiaoai Zhao)

11:00 – 11:15 a.m. **Sourav Roy** – *Holocene selection at the INS locus trades metabolic efficiency for autoimmune diabetes risk*

11:15 – 11:30 a.m. **Amanda Rodriguez Diaz** – *How Obesity Disrupts Glymphatic Function and Compromises Brain Homeostasis*

11:30 – 11:45 a.m. **Susana Nakandakari** – *Exercise and High-Protein Diet as Preventive Strategies Against Sepsis Mortality*

11:45 – 12:00 p.m. **Bin Qiu** – *DUSP1 reprograms macrophages to drive adipose inflammation in obesity*

12:00 – 1:00 p.m. **Lunch**

1:00 – 2:15 p.m. Session 3 – Flash Talk's from Trainees (Session Chair – Yajaira Suarez, YMSM co-Director)

1:00 – 1:15 p.m.	**Bernardo Stutz/Anton Bennett** – YMSM Metabolic Core Facility
1:15 – 2:00 p.m.	*2-minute trainee flash talks from posters*
2:00 – 2:15 p.m.	**Hanming Zhang** – *Cell-Autonomous LXR Signaling in Vascular Smooth Muscle Cells Regulates Arterial Lipid Homeostasis and Vascular Stiffness During Atherogenesis*.
2:15 – 2:30 p.m.	**Coffee Break**

2:30 – 3:45 p.m. Session 4 – (Session Chair – Marc Schneeberger Pane)

2:30 – 2:45 p.m.	**Brent Wang** – *TET3-driven cellular senescence governs ovarian aging*
2:45 – 3:00 p.m.	**Diego Saenz de Urturi Indart** – Desmosterol modulation as anti-atherogenic therapy.
3:00 – 3:15 p.m.	**Hee-Hoon Kim** – *Decoding Healthy Longevity: Targeting Drivers of Immunometabolic Resilience in Muridae*.
3:15 – 3:30 p.m.	**Andrew Erikson** – *RISOP: A Reference-Assisted Approach for Enhanced Detection of Oxidized Phospholipids*.
3:30 – 3:45 p.m.	**Mateus D'Ávila dos Santos Silva** – *Feeding the Weight-Loss Circuit: AgRP Neurons in Semaglutide Action*.

4:00 – 6:00 p.m. Session 5 – **Poster Session and Happy Hour**

Pyruvate kinase restricts OXPHOS and induces mitochondrial membrane hyperpolarization

Davidson EA [1], Ruz-Maldonado I[1], Cardone RL[1], Kibbey RG[1,2]

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A bioenergetically informed model of glucose stimulated insulin secretion places control over cytosolic ATP/ADP ratio on pyruvate kinase (PK). Here, the PK substrate, phosphoenolpyruvate (PEP), limits OxPhos by mitochondrial ADP privation. Since the ADP privation model predicts hyperpolarization of mitochondrial membrane potential (MMP) to limit ATP synthesis by OxPhos, we quantitated the effect of PEP-driven PK activity on respiration and MMP. With respiration, MMP was monitored with 2μM TMRM (Oroboros NexGen O2K) in permeabilized INS-1 (β) and C2C12 (M) cells for State 3 (S3) respiration (2μM rotenone, 5mM succinate, and 250μM (β)/500 (M) ADP), State 4 (S4Om) respiration (5nM oligomycin (oligo)), and ADP privation with *in situ* PK (625μM PEP). Results are relative to S3 and MMP differences calculated by the Nernst equation. PEP lowered S3 respiration in β (-34±3.5%; $p<0.0001$) and M (-41±4 %; $p<0.001$) while PEP hyperpolarized MMP in β (-5.5±2.7 mV; $p<0.0001$) and M (-7.4±2.2 mV; $p<0.001$). PEP induced an S4Om-like state, a decreased magnitude of respiratory suppression (β, control -23±3% vs. PEP -4±1.5%;M, control -42±3% vs. PEP -13±6%) and MMP (β, control -8±3% vs. PEP +2.4±0.8%; M, control -14.8±2.8%vs. PEP -1.6±2.5%) by oligo. Oligo depolarized PEP-treated MMP consistent with PEP-driven reverse complex V activity (rCV) via ATP hydrolysis. Blocking electron transport (2.5μM antimycin a) after PEP identified CV's contribution to MMP (β, -4.1±0.1mV) and subsequent oligo identified the contribution of rCV to PEP-induced hyperpolarization (β, -3.11mV). PK hyperpolarizes the MMP by restricting ADP and driving rCV, supporting a model where PEP hydrolysis raises ATP/ADP not OxPhos.

AgRP neurons are required for the weight-lowering effects of GLP-1R agonists.

Mateus d'Ávila[a,b], João Cavalcanti-de-Albuquerque[c], Roberto Collado-Pérez[b], ZhongWu Liu[b], Jenna Hunter[c], Anne White[c], Joseph Schlessinger[d], Giuseppe D'Agostino[c], Tamas L. Horvath[a,b,e]

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Semaglutide, a GLP-1 receptor agonist, induces durable weight loss, yet the neural circuits mediating this effect remain unclear. We tested whether hypothalamic agouti-related peptide (AgRP) neurons are required for semaglutide-induced weight loss and whether this requirement depends on diet composition. Mice received daily semaglutide (0.16 mg/kg, i.p.) for 2 or 15 days. Short-term treatment increased excitatory and inhibitory synaptic input onto AgRP neurons, reduced *Npy* expression, and failed to increase AgRP c-Fos, suggesting an early inhibitory state. In contrast, chronic treatment reduced inhibitory drive, increased *Agrp* and *Npy* expression, and elevated AgRP c-Fos, consistent with sustained AgRP activation.

To test necessity, we used AgRP-Sirt1 knockout mice. Although both WT and KO females initially lost ~10% body weight, KO animals rapidly regained weight despite continued treatment, demonstrating that AgRP neurons are required for sustained semaglutide efficacy. EchoMRI confirmed recovery of fat mass, and semaglutide-induced improvements in glycemia and insulin were absent in KO females. Surprisingly, diet composition strongly modulated this requirement: under chronic or acute high-fat diet (HFD), KO mice remained sensitive to semaglutide, whereas switching HFD-fed mice back to standard diet restored AgRP dependence.

To address whether developmental compensation explained these findings, we ablated AgRP neurons in adult diet-induced obese mice using AAV-DIO-taCaspase. Unlike developmental models, adult-ablated mice were resistant to GLP-1RA-induced weight loss under HFD, revealing that developmental plasticity masks AgRP dependence in obesity. Finally, deletion of glucocorticoid receptors in AgRP neurons impaired GLP-1RA-induced weight loss, identifying a GLP1RA–glucocorticoid–AgRP axis required for sustained pharmacological weight loss.

Blood-Brain Barrier Disruption Impairs Sleep via Downregulation of Orexin Signaling

Jessica Furtado, Amanda Rodriguez Diaz, Anne Eichmann, Marc Schneeberger

The Blood Brain Barrier (BBB) plays a critical role in maintaining brain homeostasis by tightly regulating the exchange of ions, nutrients, and immune cells between the circulation and the central nervous system. While sleep and the circadian rhythms are known to influence BBB function, the reverse relationship, how BBB integrity impacts sleep regulation, remains poorly understood. This question has broad clinical relevance, as disruption of the BBB is a hallmark of numerous neurological disorders, often accompanied by sleep disturbances.

To explore this link, we utilized a genetic mouse model with endothelial-specific deletion of *Unc5b*, which induces a size-selective BBB leak without gross vascular malformations. Spatial transcriptomic profiling revealed a marked downregulation of *Hcrt* (hypocretin/orexin) in the lateral hypothalamus, a region critical for sleep-wake regulation and metabolic homeostasis. Correspondingly, in vivo behavioral assays using PhenoTyper (Noldus) systems uncovered fragmented sleep-wave cycles and disrupted sleep architecture in the Unc5b mutant mice. These alterations were accompanied by anxiety-like behaviors and reduced exploratory activity across multiple tests. Metabolic phenotyping further demonstrated abnormalities in locomotor activity, feeding behavior, and energy balance..

Our findings reveal that BBB dysfunction can directly impair hypothalamic orexigenic signaling, disrupting sleep architecture and metabolic regulation. This work identifies the BBB as an active modulator of neurobehavioral states and implicates vascular dysfunction as a contributing factor in sleep-related and neuropsychiatric disorders.

Allosteric Regulation of MKP-1 in Liver Metabolism

Lubna Ghanem, Anton M. Bennett

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Mitogen-activated protein kinase phosphatase-1 (MKP-1) is a nuclear localized dual specificity phosphatase that preferentially dephosphorylates the nuclear pool of JNK1/2 and p38 MAPK and is found to play significant regulatory roles in metabolism. MKP-1 is upregulated in obese patients. Given the significant increase in liver disease as a result of obesity, understanding the mechanisms of aberrant MKP-1 signaling on liver metabolism is important. This is supported by liver-specific deletion of MKP-1 (MKP-1 LKO), which protects against hepatic steatosis. These observations raise the exciting possibility that MKP-1 can be targeted for the treatment of metabolic associated steatotic dysfunction liver disease (MASLD). Although MKP-1 represents an attractive target for pharmacological inhibition it has been considered largely 'undruggable' partly due to the high similarity between PTP active sites and the propensity for active site compound selection, which often leads to charged compounds hits with poor bioavailability. Our lab has recently developed specific allosteric inhibitors for MKP-5. These inhibitors bind to a previously undescribed allosteric site within the catalytic domain. Mutation of the allosteric site dramatically inhibits MKP-5 catalysis and serves as a docking site for MAPK. This site is highly conserved amongst all active MKPs, including MKP-1, suggesting that it has an essential conserved role for catalysis. Therefore, I hypothesize that the MKP-1 allosteric site is critical for the regulation of its catalytic activity and binding to MAPKs, and that this site represents a target for the development of allosteric small molecule inhibitors for the treatment of MASLD.

Taurine restrains inflammaging by deactivating the NLRP3 inflammasome in macrophages

Chenyang Guan[1,2,3], Seungjin Ryu[2,3], Yitao Zhu[1,2,3], Yun-Hee Youm[1,2,3,4], Hee-Hoon Kim[1,2,3], Tamara Dlugos[1,2,3], Vishwa Deep Dixit[1,2,3,4].

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Whether decline of taurine drives aging is debated, and despite high millimolar intracellular concentrations, its function as potential guardian of cytosolic homeostasis is unclear. Here, we show that aging increased circulating taurine concentrations in humans and mice. Further elevating taurine in aged mice enhanced healthspan, engaging anti-inflammatory pathways previously linked to youthfulness, and reduced mortality from sepsis and inflammasome-mediated inflammation suggesting an enantiostatic response. Mechanistically, diverse NLRP3-specific 'danger signals' induced taurine efflux from macrophages as a proximal step to activate inflammasome and resultant pyroptosis. Taurine restoration in macrophages prevented NLRP3-induced *trans*-Golgi network disassembly, thereby suppressing NLRP3 inflammasome activation. Conversely, lowering taurine biosynthesis combined with reduced bioavailability in macrophages exacerbated inflammasome activation. In humans, sustained caloric restriction elevated adipose tissue taurine and was accompanied by decreased inflammation. Together, we identify taurine as an immunometabolic rheostat that links danger sensing to NLRP3 inflammasome activation, suggesting taurine-based strategies to alleviate inflammaging and inflammasomopathies.

Mapping Noradrenergic Locus Coeruleus Activity During Maternal Isolation in Infant Mice

Héctor Haddock-Martínez[1,2,3], Marcelo Zimmer[1], Marcelo O. Dietrich[1]

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In infant mammals, caregiver presence, typically the mother, regulates stress responses and shapes early learning, yet the neural mechanisms remain poorly understood. Here, we investigated the infant brain's response to maternal isolation. Postnatal day 10 mice, an age in which pups are completely dependent on their mother for nutrition and survival, were isolated from the mother and littermates for 90 minutes, followed by whole-brain activity mapping. We identified the locus coeruleus (LC) as the brain region most responsive to isolation, with mean Fos-positive cell counts increasing from 2.5 in undisturbed controls to 475 after isolation. Using immunohistochemistry and in situ hybridization, we confirmed that activated LC neurons express dopamine beta-hydroxylase (DBH), identifying them as LC noradrenergic neurons (LC-NE). Next, we tested whether LC-NE activation is sensitive to maternal-like sensory cues by isolating pups with access to warmth or a source of tactile stimulation. Both warmth and the tactile stimulus blunted LC-NE activation. To determine LC-NE activity dynamics in vivo, we used fiber photometry in awake pups. We standardized neonatal LC targeting in P1 DBH-Cre mice and optic fiber implantation at P14, with postmortem analyses confirming viral expression and fiber placement. Preliminary recordings in P16 mice suggest that LC-NE neurons display phasic-like activity in the home nest, but increased activity and tonic-like dynamics during isolation. Warmth reduced LC-NE activity and partially restored phasic-like patterns. Together, these findings identify LC-NE neurons as a key population activated by maternal isolation and establish foundational approaches for studying their role in early-life stress and learning.

Establishing an In Vivo Platform to Study Infant Locus Coeruleus Dynamics During Isolation and Sensory Buffering

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Caregiver presence regulates infant stress responses and shapes early-life learning, yet the neural dynamics underlying these processes remain poorly understood. To address this gap, we investigated infant brain responses to maternal isolation and caregiver-like sensory cues. First, postnatal day 10 mice were separated from the mother and littermates for 90 minutes or 4 hours, followed by whole-brain activity mapping. We identified the locus coeruleus (LC), a noradrenergic brainstem nucleus involved in arousal and stress regulation, as a key isolation-responsive region. We also confirmed that dopamine beta-hydroxylase (DBH)-expressing neurons constitute the principal activated LC population.

Next, we tested whether LC Fos expression responds to buffering-like cues by isolating infants for 90 minutes with tactile stimulation or thermal support, which model caregiver-derived input. These analyses showed that LC Fos activation is sensitive to these stimuli, with warmth significantly reducing LC activation.

To characterize LC dynamics in vivo, we recorded LC activity in awake infant mice using fiber photometry. Because neonatal LC coordinates are not well established, we standardized GCaMP delivery in DBH-Cre mice at postnatal day 1 and optic fiber implantation at postnatal day 14. Postmortem analyses confirmed viral expression and fiber placement. Using this platform, preliminary postnatal day 16 recordings suggest that undisturbed nest conditions are associated with patterned phasic activity, whereas isolation increases LC activity and shifts responses toward a more tonic state. Thermal support reduced LC activity and partially restored patterned fluctuations, establishing a foundation for studying LC dynamics during early-life isolation and sensory buffering in vivo.

Sex-divergent cognitive aging linked to phospholipid remodeling enzyme *Mboat2*

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Lipids are among the most abundant biomolecules in the brain, and altered lipid composition has been associated with brain aging and neurodegenerative diseases. However, whether membrane lipids functionally contribute to brain aging remains unclear. Using adult mouse neural stem cells (NSCs) as a model, previous study demonstrated that deficiency of phospholipid remodeling enzyme membrane-bound O-acyltransferase 2 (*Mboat2*) exacerbates NSC aging while *Mboat2* overexpression boosts NSC proliferation in old mice. Given that a decreased transcriptional level of *Mboat2* has been observed in different brain regions and cell types, in this study, we investigate the role of *Mboat2* in regulating cognitive aging. We used lentiviral-mediated approach to overexpress *Mboat2* in the hippocampus of young (3–5-month-old) and old (20–22-month-old) male and female mice. Synaptic plasticity was assessed by electrophysiology, while cognitive effects were evaluated using assays of recognition memory, spatial learning, contextual fear memory, and anxiety-like behavior. We observed that *Mboat2* overexpression is associated with sex-specific effects on memory and cognition. Specifically, while anxiety, recognition memory, and spatial memory was improved in old males, anxiety, recognition memory, and spatial memory was worsened in old females with MBOAT2 overexpression compared to old control animals. Contextual fear recall was improved in both old males and females with MBOAT2 overexpression. These findings suggest a functional role for membrane lipid remodeling in cognition. Uncovering the role of membrane lipid remodeling in regulating cognitive aging may identify potential therapeutic targets for age-associated cognitive decline.

Immunometabolic Resistors of Aging in Long-Lived Golden Spiny Mice

Hee-Hoon Kim[1,2,3], Tali Sagiv-Zangi[4], Yun-Hee Youm[1,2,3], Hagar Vardi-Naim[4], Tamara Dlugos[1,2,3], Francesco Strino[5], Monica Bodogai[6], Arya Biragyn[6], Yuval Kluger[1,5,7], Noga Kronfeld-Schor[4], Vishwa Deep Dixit[1,2,3,7]

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Sustained complement system activation in humans is associated with inflammaging, a chronic inflammatory state that contributes to age-related diseases. We recently found that pro-longevity intervention, caloric restriction, lowers complement activation in humans, suggesting that endogenous targets that reduce complement may promote healthspan. Studying long-lived wild animals that exhibit negligible immune-metabolic senescence may enable the identification of dormant pathways that maintain homeostasis during aging. To achieve this, we leveraged the resilience of exceptionally long-lived golden spiny mice (*Acomys russatus*, GSM). An analysis of aging cohorts spanning the lifespan of GSM, its sister species (*A. dimidiatus*), and laboratory mice (*Mus musculus*) revealed that GSM has a close clade relationship with the laboratory mice. However, interestingly, GSM live for more than 5 years in the wild (rocky desert area), resisting the age-related functional decline, thymic involution, and fibro-inflammation typically observed in other species. At the molecular level, bulk or single-cell RNA sequencing of liver and visceral adipose tissue showed that GSM withstands age-associated transcriptomic perturbations in immune-metabolic pathways. Notably, we found a specific elevation of clusterin, a secretory inhibitor of the terminal complement cascade, in the adipose tissue macrophages of aged GSM. Interestingly, we found that clusterin levels are associated with maximum lifespan across orders of animals, including humans. Furthermore, elevating clusterin in aged laboratory mice suppressed complement activation and recapitulated key resilience phenotypes of GSM, including lowered inflammaging and enhanced healthspan. Our findings establish clusterin as an evolutionarily conserved immunometabolic checkpoint of aging, offering a promising target for promoting healthspan.

Metabolic and inflammatory crosstalk underlying cancer-related fatigue (CRF) in a mouse model of breast cancer (BC)

Abigail Ama Koomson, Susana Castelo Branco Ramos Nakandakari, Andin Fosam, Rosalie M Grijalva, Rachel Jamison Perry

Cancer-related fatigue (CRF) is among the most prevalent and debilitating side effects of breast cancer and its treatment in women, severely reducing adherence to treatment and quality of life. However, standardized, preclinical metrics for CRF remain poorly defined, impeding the development of therapeutic interventions. We hypothesized that breast cancer-induced physical fatigue is due to metabolic dysregulation in skeletal muscle mitochondria. Using the syngeneic E0771 mouse model of breast cancer, we characterized physical fatigue, assessed cytokine profiles, and performed targeted metabolomic analyses of muscle. Tumor-bearing mice showed significantly reduced survival and fat mass although overall body weight and lean mass were stable. Physical performance declined after three weeks of tumor growth as shown by reduced grip strength, maximum speed and peak oxygen consumption. Metabolic cage activity of mice revealed reduced oxygen consumption, carbon dioxide production, respiratory exchange ratio, energy expenditure, and water intake, consistent with suppressed metabolic function. Metabolomic profiling of skeletal muscle revealed upregulation of pipecolate and pyridoxamine, metabolites linked to amino acid metabolism and oxidative stress signaling, while key mitochondrial and antioxidant metabolites including glutathione, riboflavin and isocitrate were suppressed. These alterations suggest mitochondrial dysfunction, redox imbalance, and impaired energy production as contributors to the physical fatigue phenotype. These changes were accompanied by reduced IL-2, IL-10, MIP-1α and increased IP-10 in the plasma implicating inflammation-driven metabolic reprogramming. Breast cancer induced coordinated inflammatory and metabolic changes in the skeletal muscle, disrupting mitochondrial pathways that contribute to physical fatigue. This study identifies distinct metabolic signatures associated with CRF and highlights mitochondrial pathways as promising targets for therapeutic intervention to improve the quality of life in breast cancer patients.

TMEM86a Regulates Keratinocyte Lipid Homeostasis and Differentiation Following UV Stress

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TMEM86A is a recently identified LXR-regulated lysoplasmalogenase involved in plasmalogen metabolism; however, its role in the skin remains unknown. Here, we investigated the role of TMEM86A in epidermal barrier regulation under inflammatory and ultraviolet (UV) stress conditions. Analysis of human psoriasis and atopic dermatitis datasets demonstrated dysregulated TMEM86A expression associated with epidermal differentiation programs, including LCE and SPRR gene families. In vivo, TMEM86A deficiency resulted in increased transepidermal water loss (TEWL), erythema, epidermal hyperplasia, and enhanced inflammatory responses following imiquimod (IMQ) treatment and UV exposure. Transcriptomic analyses revealed disrupted differentiation pathways and increased stress signaling in TMEM86A-deficient skin. Additionally, pharmacologic LXR activation partially rescued differentiation-associated gene expression, supporting functional crosstalk between TMEM86A and epidermal lipid regulatory pathways. Collectively, these findings identify TMEM86A as a novel regulator of keratinocyte homeostasis and epidermal barrier integrity under stress conditions.

TET3-driven cellular senescence governs ovarian aging

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Abstract

Ovarian aging is a fundamental driver of female infertility and a catalyst for systemic health decline. Unique among organ systems, the ovary undergoes functional senescence approximately two decades before the rest of the body, beginning on average at age 35. While this decline triggers a spectrum of mid-life health issues, ranging from osteoporosis to cognitive impairment, the underlying cellular and molecular mechanisms of this process remain poorly defined. Through multimodal analysis incorporating scRNA-seq, multiplex immunofluorescence, and in vivo models, we identify a distinct population of senescence-like macrophages (SnMacs) in human and mouse ovaries. Characterized by high TET3 expression, these cells reshape the aging ovarian microenvironment. We demonstrate that SnMacs bypass immune clearance and maintain a pro-inflammatory secretome via a dual-action mechanism regulated by TET3. Beyond its established role in the epigenetic upregulation of the NLRP3 inflammasome and the PD-L1 immune checkpoint, TET3 unexpectedly functions as a molecular scaffold to stabilize the canonical senescence markers p16 and p21. Concurrently, TET3-mediated epigenetic activation of a self-sustaining NGF-TrkA autocrine loop provides the essential survival signals required to maintain SnMac viability. Pharmacological clearance of this population via a VHL-recruiting, TET3-specific molecular glue degrader effectively eliminated SnMacs, suppressed inflammation, and restored ovarian reserve and fertility in middle-aged mice. Our results establish TET3 as a master regulator of macrophage senescence, functioning as both an epigenetic rheostat and a molecular scaffold. By leveraging the endogenous co-upregulation of TET3 and VHL in SnMacs, we demonstrate a selective elimination strategy that provides a precise framework for ovarian rejuvenation therapy.

Hunger-sensing hypocretin/orexin neurons are responsible for detection of social deficiency in the lateral hypothalamus in animals

Da-Ming Li[1, *], Zhong-Wu Liu[1], Yuexuan Li [1], Sheng-Nan- Qiao[2], Bandy Chen[3], Fei He [1, 6], Marc Schneeberger Pané [3, 5], Marcelo Dietrich[1, 5], Tamas Horvath[1, 4, 5], Yong-Hui Jiang [4], and Xiao-Bing Gao [1, 4, 5]

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Sociability is a characteristic that determines social interactions in animals. Altered sociability or social interaction has been identified as a hallmark of many neurodevelopmental, mental/ psychiatric diseases (such as autism) in humans. Recent studies suggest that social interaction is homeostatically regulated in animals; however, the mechanisms underlying this regulation remain unclear. In this study, we hypothesize that the lateral hypothalamus (LH), a homeostatic center for many essential physiological functions, also serves as a hub for social interaction by "sensing" social deficiency. To test this hypothesis, we examined changes in the LH of mice under acute social isolation (SI). High-throughput activity mapping revealed that SI induced marked increases in c-fos expressions in the LH and other brain areas. Transcriptomic analysis of total RNA from the LH identified 895 genes significantly up-regulated and 402 genes down-regulated in SI animals. Up-regulated genes comprised those encoding proteins responsible for neurotransmission, signaling, neuropeptides (including the neuropeptide hypocretin/orexin, Hcrt), and neurotransmitter receptors. Real-time q-PCR confirmed that SI-induced increase in Hcrt expression was time- and age-dependent. Furthermore, we identified potentiation of glutamatergic synapses on Hcrt cells. Interestingly, SI-induced changes in the Hcrt system was absent in aging (>12 months) and autism mouse models. Blocking Hcrt signaling decreased SI-induced gene expressions in the LH and subsequent social behaviors after SI. In summary, our results suggest that the Hcrt system may "sense" social deficiency in animals, which is likely impaired in certain physiological (such as aging) and pathological (such as autism) processes.

The role of synapse organizer proteins in autonomic nerve regulation of the endocrine functions of pancreas

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The autonomic nervous system (ANS) coordinates communication between the brain and peripheral metabolic organs, including the pancreas. Neural regulation of islet secretion is essential for systemic glucose homeostasis. Although central-to-peripheral neural pathways have been extensively mapped, the molecular mechanisms mediating communication between autonomic nerves and target endocrine cells remain poorly understood. Specifically, autonomic neuroeffector junctions, specialized contact sites where peripheral neurons interact with non-neuronal cells within organs, remain poorly characterized at the molecular level. This project aims to define the molecular components of autonomic neuroeffector junctions formed between sympathetic or parasympathetic neurons and distinct pancreatic islet cell types, and to determine how these junctions regulate endocrine function, glucose metabolism, and insulin sensitivity. Confocal imaging revealed cell-type-specific expression of synapse organizer proteins classically studied in the brain, with neuroligin 2 (NLGN2) enriched in beta cells and CADM1 enriched in alpha cells. Using confocal microscopy and tissue clearing-based 3D imaging, we investigated how loss of these synapse organizers affects pancreatic autonomic innervation. Pilot analyses showed reduced sympathetic innervation, marked by tyrosine hydroxylase (TH), in CADM1 knockout pancreas compared with controls. Functional metabolic assays further revealed endocrine defects related to autonomic regulation. NLGN2 knockout mice showed improved glucose clearance in fed L-arginine tolerance tests and pyruvate tolerance tests, as well as increased insulin release during the cephalic phase, suggesting altered autonomic regulation of islet function when synapse organizer proteins are absent. To molecularly map these junctions, we are applying proximity labeling proteomics by expressing cell-surface HRP in alpha cells, beta cells, sympathetic neurons, and parasympathetic neurons, enabling promiscuous labeling and identification of proteins localized at pancreatic-autonomic neuroeffector junctions.

Exoproteome of calorie-restricted humans identifies complement deactivation as an immunometabolic checkpoint reducing inflammaging

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Abstract

While caloric restriction (CR) extends lifespan across diverse organisms, the effects of CR on human aging and on healthspan are only beginning to be uncovered. Here, we apply proteomics to plasma samples collected longitudinally from participants achieving on average 14% CR over 2 years as part of the CALERIE trial. We identified that inhibition of the complement pathway is linked to lower inflammaging. In humans, the C3a/C3 ratio was significantly lowered by CR, thus reducing inflammation emanating from three canonical complement pathways. Further, circulating C3a is elevated during aging in humans and in mice; we identify a non-senescent age-associated macrophage (AAM) subset that expands in visceral fat as the predominant source. In macrophages, C3a-C3AR1 autocrine signaling via ERK regulates age-related inflammation. Intra-adipose administration of a C3a-specific neutralizing antibody reduced inflammaging in mice. Furthermore, FGF21-overexpression and deficiency of phospholipase A2 group VII (PLA2G7/lp-PLA2), which enhance lifespan and healthspan in mice, lowered C3a in aging. Thus, complement C3a reduction is a metabolically-regulated inflammatory checkpoint that can be harnessed to attenuate inflammaging.

Can diet and exercise improve sepsis outcomes?

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Background: Sepsis represents 20% of deaths worldwide, and the survivors have a greater risk of death within 5 years. The reprogramming of metabolism by infection causes organ dysfunction and poor outcomes in patients; however, little is known about metabolism interventions to improve outcomes and decrease complications in survivors. High-protein diet combined with exercise may be a great intervention for prevention and recovery of sepsis.
Objectives: The hypothesis of this proposal is high-protein diet combined with voluntary exercise will protect mice from outcomes of sepsis due to increase in muscle mass. The specific aim is to define the impact of high-protein diet and physical activity pre-sepsis in survival, physiological and metabolically parameters.
Methods: To test the hypothesis, C57BL male mice, with 8 weeks old, were exposed to high-protein diet (HP) or chow diet (CT) with or without access to running wheels (SED or EXE) during 4 weeks before be submitted to the gold standard model of sepsis (cecal ligation and puncture).
Results: Our data showed that mice fed with HP diet for 4 weeks before sepsis had a better probability of survival (66.66%) compared to mice fed with chow (CT) diet (42.85%). In this same experiment, when added exercise, HP+EXE mice had even better survival (87.50%) compared to CT-EXE (50%).
Conclusions: High-protein diet combined with voluntary exercise for 4 weeks before sepsis increased lean mass and improved survival in mice.

Neurovascular Plasticity and Neurodegeneration in the Obese Brain

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Abstract

This study investigates how metabolic perturbations drive neurovascular plasticity and their consequences on cognition. Specifically, we investigate the metabolic perturbations incurred by a high fat diet induced obesity. While prior work in the obesity field has identified localized structural changes, such as altered vascular density and blood–brain barrier (BBB) permeability, within the feeding-related hypothalamus, the broader system-level implications of these adaptations remain poorly understood. Here, we asked whether obesity induced neurovascular remodeling extends beyond canonical energy homeostasis centers to impact distributed higher-order brain circuits.

We hypothesized that obesity induces widespread, brain-wide neurovascular remodeling and that these reduced vasculature in the higher-order brain regions are a primary driver of the cognitive deficits associated with metabolic disease. To test this, we combined advanced 3D imaging approaches to map changes in vascular architecture, myelination, and neuronal activity across the whole brain in obese models. In parallel, we employed ultrasound localization microscopy (ULM) to quantify microvascular blood flow dynamics with high spatial resolution. To establish causality, we used a conditional endothelial-specific deletion of *Flt1* in obese mice to induce angiogenesis and queried whether this rescued cognitive performance.

Our findings demonstrate that metabolic-driven neurovascular plasticity is not regionally restricted but instead represents a distributed, brain-wide phenomenon. By linking vascular remodeling to cognitive function, this work identifies the neurovasculature as a central and potentially actionable mediator of the neurological complications of obesity.

Disruption of MAPK Binding and Activity Prevents Development of Dystrophic Muscle Disease

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Mitogen-activated protein kinases (MAPKs) are critical enzymes that regulate cellular processes, and their dysregulation is implicated in numerous diseases. One key negative regulator of the stress-activated MAPKs, p38 and JNK, is the dual-specificity phosphatase DUSP10, also known as MKP5. Previous research has established MKP5 as a significant factor in pro-fibrotic diseases, where its complete genetic knockout in animal models of Duchenne's Muscular Dystrophy (DMD), pulmonary fibrosis, and cardiomyopathy proved to be protective. This highlighted MKP5 as a promising candidate for therapeutic inhibition. Moving beyond simple gene deletion, our study sought to model a more pharmacologically relevant approach to blocking MKP5's function in a whole-body system.

To achieve this, we developed a novel mouse model with a Y435A point mutation that renders the MKP5 enzyme catalytically inactive, effectively mimicking a "perfectly drugged" state without eliminating the protein itself. These mice were then crossed with the dystrophic *mdx* mouse model to investigate the impact of this targeted inhibition on DMD pathology. Our major findings reveal that MKP5 Y435A-mdx mice exhibit enhanced JNK signaling, a reduction in diaphragm mass, and improved myofiber survival in mature adulthood compared to littermate controls. These results demonstrate that specific, targeted inhibition of MKP5's enzymatic activity is sufficient to ameliorate key aspects of dystrophic pathology, reinforcing its potential as a powerful therapeutic target for the treatment of DMD.

SHP2 genetic variants in NSML-associated RASopathies disrupt the PZR–IRX transcription factor signaling axis

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Abstract

Noonan Syndrome (NS) and Noonan Syndrome with Multiple Lentigines (NSML) are rare autosomal dominant disorders that presents with cardio-craniofacial cutaneous abnormalities. NSML patients develop hypertrophic cardiomyopathy (HCM). RNA-Sequencing in the hearts of NSML mice identifies the Iroquois (Irx) homeodomain transcription factors 3 and 5 as novel PZR/Shp2 targets. The Iroquois homeodomain homeobox transcription factors IRX3 and IRX5 have been linked to the regulation of genes involved in cardiac growth, morphogenesis, and vascular defects. We have identified that IRX3 and 5 mRNA and protein expression levels are upregulated in NSML and rescued by the introduction of PZR^{Y242F} in NSML mice. The complete molecular mechanism(s) of how IRX3 and 5 are regulated by PZR/Shp2 is unknown. We have observed that both IRX3 and IRX5 upregulation in the heart of NSML mice was inhibited by low-dose Dasatinib. To establish whether PZR tyrosyl phosphorylation regulates Irx3 and Irx5 expression, we treated WT and PZR^{Y242F} derived fibroblasts with ConA to stimulate PZR and examined Irx3 and Irx5 protein expression. We have found that Irx3 and Irx5 protein expression increased in WT derived fibroblasts. In contrast, in PZR^{Y242F} fibroblasts, Irx3 was undetectable and Irx5 was markedly suppressed. These results indicate that PZR/Shp2 signaling positively regulates Irx3 and Irx5 expression. Furthermore, we have observed that IRX3 and 5 mRNA and protein expression is elevated by both NS and NSML Shp2 mutants. We have also measured the established IRX3 and IRX5 target genes (BMP10) that regulates heart growth. A crystal structure of the tandem SH2 domains of SHP2 bound to tyrosyl phosphorylated PZR reveals that recruitment constrains the open SHP2 conformation to facilitate cellular-Src (c-Src) binding. Remarkably, we found that BMP10 mRNA and protein expression is decreased in NSML and rescued upon introduction of PZR^{Y242F} in NSML mice. These results implicate that PZR/Shp2/IRX3/IRX5/BMP10 pathway plays a crucial role in the development of cardiovascular defects and likely hypertrophic cardiomyopathy in NSML mouse model.

The role of synapse organizer proteins in autonomic nerve regulation of the endocrine functions of pancreas

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The autonomic nervous system (ANS) coordinates communication between the brain and peripheral metabolic organs, including the pancreas. Central-to-peripheral neural pathways have been extensively mapped, but the molecular mechanisms that mediate communication between autonomic nerves and their target endocrine cells are not well-understood. Autonomic neuroeffector junctions, specialized contact sites where peripheral neurons interact with non-neuronal cells within organs, remain poorly characterized at the molecular level. This project aims to define the molecular components of autonomic neuroeffector junctions formed between sympathetic or parasympathetic neurons and distinct pancreatic islet cell types, and to determine how these junctions regulate endocrine function, glucose metabolism, and insulin sensitivity. Confocal imaging revealed cell-type-specific expression of synapse organizer proteins classically studied in the brain, with neuroligin 2 (NLGN2) enriched in beta cells and CADM1 enriched in alpha cells. Using confocal microscopy and tissue clearing-based 3D imaging, we investigated how loss of these synapse organizers affects pancreatic autonomic innervation. Pilot analyses showed reduced sympathetic innervation, marked by tyrosine hydroxylase (TH), in CADM1 knockout pancreas compared with controls. Functional metabolic assays revealed autonomic nerve-dependent endocrine defects. NLGN2 knockout mice showed improved glucose clearance in fed L-arginine tolerance tests and pyruvate tolerance tests, as well as increased insulin release during the cephalic phase, suggesting altered autonomic regulation of islet function in the absence of synapse organizer proteins. We apply proximity labeling proteomics by expressing cell-surface HRP in alpha cells, beta cells, sympathetic neurons, and parasympathetic neurons, enabling promiscuous labeling and identification of proteins localized at autonomic neuroeffector junctions in the pancreas.

DUSP1 reprograms macrophages to drive adipose inflammation in obesity

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Abstract Adipose tissue macrophage (ATM) driven chronic inflammation is a cornerstone of obesity-associated insulin resistance and cardiovascular disease, yet the molecular regulators controlling this process remain elusive. Here, we identify *DUSP1* (encoding MKP1) as the predominant *DUSP* family member upregulated in human obese ATMs. Utilizing a macrophage-specific knockout model (MKP1-MacKO), we demonstrate that MKP1 deficiency confers robust protection against diet-induced obesity, hepatic steatosis, and systemic glucose intolerance. Beyond reducing overall adiposity, the loss of macrophage MKP1 promotes a "lean-like" adipose microenvironment characterized by constrained adipocyte hypertrophy and an activated lipolytic program. Advanced volumetric 3-dimensional imaging and single-cell manifold analysis
(PHATE/MELD) further reveal that MKP1 deletion triggers a global remodeling of the ATM landscape. Mechanistically, MKP1 deficiency effectively constrains the expansion and transcriptional maturation of pathogenic niches, specifically lipid-associated macrophages
(LAMs) and pro-inflammatory subsets, while fostering the reciprocal expansion of metabolically adaptive, lipid-handling, and pro-resolving macrophage niches. Trajectory inference establishes MKP1 as a critical kinetic regulator that drives the persistence of the pathological ATM lineage. Collectively, our findings position MKP1 as a pivotal molecular switch in ATM polarization in obesity and suggest that targeting MKP1-dependent macrophage reprogramming represents a potent therapeutic strategy for metabolic diseases.

How Obesity Disrupts Glymphatic Clearance and Compromises Brain Homeostasis

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The brain relies on tightly coordinated clearance and immune surveillance systems to maintain homeostasis while adapting to systemic metabolic demands. The discovery of the glymphatic system and meningeal lymphatic vasculature has redefined the central nervous system as a metabolically integrated organ capable of fluid exchange, solute clearance, and neuroimmune communication. Disruption of this brain-wide clearance axis is increasingly recognized as a key driver of neurotoxic metabolite accumulation and neurodegenerative disease progression.

Obesity is a chronic metabolic overload marked by nutrient excess, dysregulated lipid and glucose homeostasis, low-grade systemic inflammation, and altered hormonal signaling, all of which can impair brain function. However, the mechanisms by which peripheral metabolic dysfunction compromises brain clearance remain poorly understood. We hypothesize that chronic metabolic stress disrupts region-specific glymphatic-lymphatic pathways, resulting in impaired waste removal, altered neuroimmune homeostasis, and increased vulnerability to neurodegeneration.

To address this, we investigated how chronic high-fat diet (HFD)-induced obesity remodels brain clearance systems. Using intracisternal tracer delivery combined with whole-brain imaging, we quantified glymphatic influx and clearance across brain regions. In parallel, we assessed meningeal lymphatic vessel architecture, cerebrospinal fluid (CSF) drainage to deep cervical lymph nodes, and astrocytic aquaporin-4 (AQP4) polarization. These analyses were integrated with sleep phenotyping, given the coupling among metabolic state, circadian regulation, and glymphatic function. To probe reversibility, we tested VEGF-C-mediated lymphangiogenesis and melatonin treatment. Our preliminary data indicate that both approaches improve structural and functional features of the glymphatic-lymphatic system under obesogenic conditions.

Holocene selection at the *INS* locus trades metabolic efficiency for autoimmune diabetes risk

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Abstract

Major shifts in dietary plant carbohydrate intake during the late Pleistocene and Holocene required physiological adaptation in carbohydrate metabolism, yet the endocrine loci that enabled such adaptation remain incompletely defined. Here we show that regulatory variation at the insulin gene (INS) locus encodes an evolutionary trade-off between metabolic efficiency and autoimmune diabetes susceptibility. The INS rs689/rs3842753 haplotype, strongly associated with autoimmune diabetes risk, is also associated with reduced type 2 diabetes risk and favorable glycemic and endocrine profiles, including lower HbA1c, glucose, and IGF-1, whereas the alternate haplotype tagged by rs3842752 shows reciprocal effects. The rs689/rs3842753 haplotype further defines β-cell transcriptional states consistent with increased insulin production burden and elevated endoplasmic reticulum stress. Selection inference analyses indicate positive selection of the high insulin-output haplotype during Holocene subsistence transitions, corroborated by ancient genome analyses showing sustained increases in its frequency, while archaic genomes lack the derived haplotype, consistent with recent evolutionary emergence. Present-day global allele frequency differences further mirror the timing of agricultural adoption, with higher frequencies of the high-output haplotype among Asian, admixed American, and European populations and lower frequencies among African populations. Together, these findings support the INS locus as a target of recent human adaptation shaped by subsistence change and suggest that selection favoring enhanced glycemic efficiency incurred autoimmune cost through antagonistic pleiotropy. Our findings challenge the long-standing view that INS-associated autoimmune diabetes risk is principally mediated through altered thymic central tolerance and instead support enhanced β-cell insulin output and proteostatic stress as central components of disease susceptibility.

Integrated genomics reveals neurovascular and neuroimmune architecture of coronary artery disease

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Coronary artery disease (CAD) is consistently associated with neurocognitive comorbidity and accelerated cognitive decline, yet the genetic and biological bases underlying these relationships remain poorly understood. Here, we show through cross-trait genetic correlation analyses that CAD exhibits inverse genome-wide correlations with multiple cognitive traits. Polygenic overlap analyses further reveal extensive sharing of genetic variants between CAD and both cognitive and neuroanatomical phenotypes. Integration of genome-wide association data with single-cell chromatin accessibility profiles reveals enrichment of CAD heritability in brain vascular cells from prenatal development into adulthood, as well as microglia during adulthood. We additionally identify significant enrichment of CAD heritability in hematopoietic stem and progenitor cells (HSPCs) and mature immune cells across multiple lineages, suggesting direct involvement of hematopoietic regulatory mechanisms in CAD biology. As a comparator, type 1 diabetes heritability showed enrichment in microglia across development but not in brain vascular cells, and in peripheral T cells rather than HSPCs, indicating disease-specific neuroimmune architectures. Shared CAD–neurocognitive loci were predominantly enriched in regulatory regions active in hematopoietic cells. Mendelian randomization analyses did not support a causal effect of genetic liability to CAD on cognitive traits, including educational attainment, intelligence, and executive function. In contrast, genetic liability to higher cognitive function, particularly executive function and educational attainment, was associated with reduced CAD risk. Together, these findings identify a coordinated neurovascular and neuroimmune architecture underlying CAD and support a model in which brain vascular, microglial, and hematopoietic regulatory programs contribute to cardiometabolic and neurocognitive comorbidity.

Molecular mechanisms linking regulatory variation in *RPS26* to pancreatic beta-cell autoimmunity and neural function

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Type 1 diabetes (T1D) is a chronic autoimmune disease characterized by T cell–mediated destruction of insulin-producing beta cells in the pancreas. In addition to the resulting metabolic dysfunction, individuals with T1D frequently exhibit neurocognitive deficits, such as impaired executive function, slower processing speed, and reduced learning performance, as well as psychiatric disorders. However, the molecular mechanisms that connect beta-cell autoimmunity and neurocognitive phenotypes remain poorly understood. Our preliminary analyses utilized statistical genetics analysis tools, including summary-data-based Mendelian randomization and heterogeneity in dependent instruments (SMR/HEIDI) and colocalization (COLOC) to integrate GWAS for T1D and neurocognitive-trait GWAS with brain, immune, and beta-cell expression quantitative loci (eQTLs). These analyses identified *RPS26*, a gene that codes for a component of the 40S small ribosomal subunit. *RPS26* recognizes and binds the mRNA Kozak sequence, a key regulator of translation-initiation. These preliminary analyses reveal that increased *RPS26* expression, mediated by SNP rs1131017 at 12q13.2 locus, is associated with higher T1D risk but also with enhanced cognitive performance, suggesting a pleiotropic trade-off between immune tolerance and neurocognitive function. We propose that genetic modulation of *RPS26* expression shapes cellular translational control in fidelity and efficiency, influencing pathways that enhance cognitive capacity while increasing susceptibility to autoimmune attack of beta cells. By integrating human genetics with mechanistic cellular models, we can better understand how *RPS26* genetic variation affects translational fidelity across tissues and to elucidate the mechanisms through which it contributes to both autoimmune beta-cell destruction and neurocognitive resilience.