GeroScience (2021) 43:1585–1589
https://doi.org/10.1007/s11357-021-00346-w

ORIGINAL ARTICLE

Proceedings from the annual University of Washington Geroscience Symposium, October 23, 2020

Mitchell B. Lee · Alessandro Bitto · Matt Kaeberlein

Received: 18 February 2021 / Accepted: 22 February 2021 / Published online: 31 March 2021

Abstract The University of Washington Nathan Shock Center of Excellence in the Biology of Aging in conjunction with the Healthy Aging and Longevity Research Institute held its annual geroscience symposium virtually on October 23, 2020. The symposium was divided into three sessions: (I) organ aging and growth signaling, (II) neurodegeneration and metabolism, and (III) innovative approaches in geroscience and aging research. Nine speakers affiliated with the University of Washington and three invited guest speakers, predominantly trainee, and junior faculty presented their research. Here, we summarize research presented during the symposium. A geroscience special issue, of which this is a part, collects submissions from symposium presenters as well as trainees supported by the Biological Mechanisms of Healthy Aging training program.

Keywords University of Washington · Nathan Shock Center · Geroscience · Symposium proceedings

Introduction

The University of Washington (UW) Geroscience Symposium was held virtually on October 23rd 2020. The symposium was divided into three sessions: (I) organ aging and growth signaling, (II) neurodegeneration and metabolism, and (III) innovative approaches in geroscience and aging research. The symposium was jointly hosted by the UW Nathan Shock Center of Excellence in the Basic Biology of Aging and the UW Healthy Aging and Longevity (HALO) Research Institute. Nine trainees (graduate student and post-doctoral fellows) and faculty members affiliated with HALO presented geroscience and biology of aging research. In addition, three outstanding trainee speakers were selected nationally to participate in the symposium. In light of the COVID-19 pandemic, the symposium was live-streamed online. Three-hundred thirty-nine registrants from 13 countries attended the virtual symposium. During the symposium, we utilized a separate business communication platform as an informal meeting space for attendees and speakers to interact. This platform was active before, during, and after the symposium to facilitate communication between registrants and presenters. For individuals who could not attend, the symposium recordings are available on the HALO Institute YouTube channel: https://www.youtube.com/channel/UCjMYW8INt5bVPxgCXqeFr_g

In this special issue, commentaries, research reviews, and primary research from presenters of the UW geroscience symposium are collected. To encourage trainee participation and growth, submissions from trainees in the NIH-supported University of Washington Biological Mechanisms of Healthy Aging (BMHA) training program are also included. Below, we provide brief summaries of each presenters' research and a short description of the BMHA training program.

M. B. Lee · A. Bitto · M. Kaeberlein (✉)
Department of Laboratory Medicine and Pathology, University of Washington, Box 357470, Seattle, WA 98195-7470, USA
e-mail: kaeber@uw.edu

Session one: organ aging and growth signaling

Dr. Ana Valencia began our symposium by discussing unexpected effects of diet on aging heart and muscle. Nutritional stress, in the form of high sugar and fat diets, synergizes with aging to drive tissue dysfunction. Old mice on a short-term high sugar diet show cardiac hypertrophy which is attenuated by elamipretide (otherwise known as SS-31, a small peptide that modifies mitochondrial function) treatment [4, 32]. Surprisingly, a high fat diet is protective against age-associated skeletal muscle sarcopenia and promotes fatigue resistance.

Dr. Claudia Moreno described mechanisms of age-related dysfunction in the cardiac pacemaker. Pacemaker rate declines with age and drives decreased heart rate that in some cases leads to the requirement of an artificial pacemaker [27]. Electrophysiology and super-resolution imaging reveal that age-associated changes in calcium channel function, organization, and modulation are the key in understanding declining pacemaker function [5, 25, 29]. At the tissue level, changes in pacemaker innervation and cytoarchitecture also contribute to age-associated slowdown of the heart.

Dr. Mariya Sweetwyne reported new data on the role of mitochondrial maintenance in healthy kidney aging. The glomerulus is the functional unit of the kidney and a major site of age-related kidney dysfunction. Podocyte loss leads to glomerular dysfunction and drives chronic kidney disease, a condition that impacts 45% of Americans over 70 [28]. Kidney samples from aged mice reveal that elamipretide treatment decreases senescence, podocyte damage, and other pathology associated with glomerular dysfunction [30]. Aged mice on a long-term high fat/high sugar diet show declines in kidney function which are reversed with elamipretide treatment. Interestingly, podocyte progenitor cells from aged mice treated with elamipretide had rejuvenated replicative ability and improved mitochondrial health.

The first invited speaker, Dr. Cristal Hill (Pennington Biomedical Research Center) ended our first session by sharing how dietary protein restriction affects metabolism through FGF21 signaling. FGF21 signaling represents a major low nutrient stress signal [17]. Under protein restriction, FGF21 is secreted from the liver and contributes to multi-systemic metabolic improvements. Identified using a transgenic approach, weight loss associated with a low protein diet depends on neuronal FGF21 signaling [10]. Similarly, neuronal FGF21 also regulates food preference in response to low nutrient stress [11].

Session two: neurodegeneration and metabolism

Dr. Caitlin Latimer began the second session on neurodegeneration and metabolism by describing synergistic TDP-43 and tau proteotoxicity in Alzheimer's disease. TDP-43, like amyloid beta and tau, is an aggregate forming protein that is associated with cognitive dysfunction and neurodegeneration [18, 26]. Using *Caenorhabditis elegans* models that co-express pathogenic tau and TDP-43, synergistic interactions and genetic modifiers between these two proteins were analyzed. Combined expression of tau and TDP-43 drive movement defects and motor neuron loss which can be partially reversed by SUppressor of Tau pathology 2 (SUT-2) loss of function [9].

Dr. Nicole Liachko continued on the theme of neuronal proteotoxicity by discussing kinases and phosphatases that control TDP-43 neurotoxicity in nematode models of amyotrophic lateral sclerosis (ALS). Phosphorylation at two key sites on TDP-43 mediates its aggregation and toxicity [19]. To identify regulators of TDP-43 phosphorylation, a targeted RNAi screen focused on kinases was performed and led to the identification of *cdc-7*. CDC-7 phosphorylates TDP-43 and can be pharmacologically inhibited in cell culture and worms. Importantly, the same pharmacological inhibitor suppressed neuronal loss in worms [20]. A second screen for TDP-43 phosphatases identified further known and novel putative regulators of TDP-43 phosphorylation [21].

Invited speaker Dr. Melanie McReynolds (Princeton University) described studies of NAD^+ flux and how it changes during aging in mice. NAD^+ homeostasis is a critical regulator of mitochondrial function and energy metabolism [24]. Multi-tissue NAD^+ metabolomic analyses show tissue-specific, age-associated changes in NAD^+ pools [22, 23]. NAD metabolic flux reveals that increased breakdown (as opposed to decreased synthesis) of NAD^+ drives age-associated changes in NAD^+ homeostasis.

Invited guest speaker, Dr. Kenneth A. Wilson (Buck Institute), discussed how the fruit fly ortholog of human OXidation Resistance 1 (OXR1) mediates lifespan extension and neuroprotection under dietary restriction by enhancing retromer function. By measuring lifespan in a set of 200 genetically diverse *Drosophila melanogaster* strains on control and protein-restricted diets and performing GWAS, several novel genetic regulators that influence DR lifespan were identified [33]. One of these

regulators, OXR1, is conserved in humans and has disease variants associated with neurodegenerative disease [31]. Elevated OXR1 expression is associated with DR-mediated lifespan extension in different fly genetic backgrounds and diminished expression creates a neuropathological condition in fly photoreceptors.

Session three: innovative approaches in geroscience and aging research

Dr. Alessandro Bitto began our final session by detailing geroscience approaches to obesity. Geroscience posits that targeting mechanisms that drive aging will also result in delayed onset of numerous age-associated diseases [15]. Interestingly, targeting mechanisms of aging using geroscience strategies may also delay seemingly age-independent diseases, like juvenile mitochondrial disease and obesity [14]. Rapamycin treatment protected against diet-induced obesity in mice fed a high fat diet. The transcription factor CEBPβ increases fat metabolism and is upregulated by rapamycin, suggesting a mechanism for rapamycin obesity protection [35]. Another pharmacological CEBPβ activator is similarly protective against diet-induced obesity [34].

Dr. Jonathan An described applying geroscience to investigate oral health. Age-associated changes in the oral cavity drive oral decline and diseases like cavities and periodontitis. As an innovative new approach using a geroscience framework, instead of repairing oral damage downstream of age-associated dysfunction, targeting age-associated changes directly should broadly delay the onset of age-associated oral decline [2]. Age-associated periodontal bone loss in mice is suppressed in multiple different experimental cohorts when treated with rapamycin [1, 3]. Rapamycin treatment, even during treatment intervals as short as eight weeks, is associated with decreased inflammation as well as reversal of age-related periodontal bone loss and microbiome change.

Dr. Dan Eisenberg discussed paternal effects on offspring telomere length. Telomere length is associated with differences in survival, with shorter telomeres associated with shorter-lived individuals. Sperm production during aging requires active telomerase to maintain telomere length. Surprisingly, telomere length is longer in older males and the offspring of older males have longer telomere lengths [6, 8]. In human populations, both father and grandfather reproductive age effect offspring telomere length. This transgenerational effect is more pronounced in chimpanzee populations, suggesting a connection with sperm production rates [7].

Lastly, Dr. Kelly Jin introduced us to the canine epigenetic clock. The domesticated dog provides an innovative new approach to test geroscience hypotheses in a natural population with genetic variation while growing our understanding of canine gerontology and age-associated disease. The epigenetic clock, which measures chromatin modification across different tissues, is a new method to assess biological aging [12, 13]. In a pilot project as part of the Dog Aging Project [16], the canine epigenome was constructed using two different experimental modalities (DNA methylation and ATACseq) from blood samples across multiple dog breeds. Both clocks independently and accurately predicted canine age in the sample cohort. Interestingly, gene set enrichment analysis revealed that features from the two separate clocks were enriched for different biological pathways, suggesting that these two epigenetic data types may reveal different, yet possibly complementary, aspects of mammalian aging.

The Biological Mechanisms of Healthy Aging training program

The BMHA training program is an NIH-supported training program for graduate students and postdoctoral fellows studying biological mechanisms of aging. There are currently 12 trainees and 34 program faculty. Trainees participate in didactic coursework focused on foundational topics in aging research and critical evaluation of the geroscience literature. BMHA trainees also select external speakers for the annual HALO and UW Nathan Shock Center seminar series and present their work at regular research meetings and annual symposia. All of the current BMHA trainees are Trainee Members of the American Aging Association.

Acknowledgements We thank Shelby Knowles for technical and logistical support in organizing the symposium. MK directs the HALO Research Institute, UW Nathan Shock Center of Excellence in the Basic Biology of Aging (P30AG013280), and the Biological Mechanisms of Healthy Aging training program (T32AG066574).

Funding A.B. is supported by the UW Nathan Shock Center of Excellence in the Basic Biology of Aging (P30AG013280). M.B.L is supported by the National Institutes of Health (NIH) Alzheimer's Disease training program (T32AG052354).

References

1. An JY, Quarles EK, Mekvanich S, Kang A, Liu A, Santos D, et al. Rapamycin treatment attenuates age-associated periodontitis in mice. Geroscience. 2017;39:457–63.
2. An JY, Darveau R, Kaeberlein M. Oral health in geroscience: animal models and the aging oral cavity. Geroscience. 2018;40:1–10.
3. An JY, Kerns KA, Ouellette A, Robinson L, Morris HD, Kaczorowski C, et al. Rapamycin rejuvenates oral health in aging mice. Elife. 2020;9:e54318.
4. Campbell MD, Duan J, Samuelson AT, Gaffrey MJ, Merrihew GE, Egertson JD, et al. Improving mitochondrial function with SS-31 reverses age-related redox stress and improves exercise tolerance in aged mice. Free Radic Biol Med. 2019;134:268–81.
5. De La Mata A, Tajada S, O'Dwyer S, Matsumoto C, Dixon RE, et al. BIN1 induces the formation of T-tubules and adult-like Ca(2+) release units in developing cardiomyocytes. Stem Cells. 2019;37:54–64.
6. Eisenberg DTA, Kuzawa CW. The paternal age at conception effect on offspring telomere length: mechanistic, comparative and adaptive perspectives. Philos Trans R Soc Lond Ser B Biol Sci. 2018;373:20160442.
7. Eisenberg DT, Tackney J, Cawthon RM, Cloutier CT, Hawkes K. Paternal and grandpaternal ages at conception and descendant telomere lengths in chimpanzees and humans. Am J Phys Anthropol. 2017;162:201–7.
8. Eisenberg DTA, Lee NR, Rej PH, Hayes MG, Kuzawa CW. Older paternal ages and grandpaternal ages at conception predict longer telomeres in human descendants. Proc R Soc B Biol Sci. 2019;286:20190800.
9. Guthrie CR, Schellenberg GD, Kraemer BC. SUT-2 potentiates tau-induced neurotoxicity in Caenorhabditis elegans. Hum Mol Genet. 2009;18:1825–38.
10. Hill CM, Laeger T, Dehner M, Albarado DC, Clarke B, et al. FGF21 Signals protein status to the brain and adaptively regulates food choice and metabolism. Cell Rep. 2019;27:2934–2947.e2933.
11. Hill CM, Qualls-Creekmore E, Berthoud H-R, Soto P, Yu S, McDougal DH, et al. FGF21 and the physiological regulation of macronutrient preference. Endocrinology. 2020;161:bqaa019.
12. Horvath S. DNA methylation age of human tissues and cell types. Genome Biol. 2013;14:3156.
13. Horvath S, Raj K. DNA methylation-based biomarkers and the epigenetic clock theory of ageing. Nat Rev Genet. 2018;19:371–84.
14. Johnson SC, Yanos ME, Kayser EB, Quintana A, Sangesland M, Castanza A, et al. mTOR inhibition alleviates mitochondrial disease in a mouse model of Leigh syndrome. Science. 2013;342:1524–8.
15. Kaeberlein M. Translational geroscience: a new paradigm for 21st century medicine. Transl Med Aging. 2017;1:1–4.
16. Kaeberlein M, Creevy KE, Promislow DE. The dog aging project: translational geroscience in companion animals. Mamm Genome. 2016;27:279–88.
17. Laeger T, Henagan TM, Albarado DC, Redman LM, Bray GA, Noland RC, et al. FGF21 is an endocrine signal of protein restriction. J Clin Invest. 2014;124:3913–22.
18. Latimer CS, Burke BT, Liachko NF, Currey HN, Kilgore MD, Gibbons LE, et al. Resistance and resilience to Alzheimer's disease pathology are associated with reduced cortical pTau and absence of limbic-predominant age-related TDP-43 encephalopathy in a community-based cohort. Acta Neuropathol Commun. 2019;7:91.
19. Liachko NF, Guthrie CR, Kraemer BC. Phosphorylation promotes neurotoxicity in a Caenorhabditis elegans model of TDP-43 proteinopathy. J Neurosci. 2010;30:16208–19.
20. Liachko NF, McMillan PJ, Guthrie CR, Bird TD, Leverenz JB, Kraemer BC. CDC7 inhibition blocks pathological TDP-43 phosphorylation and neurodegeneration. Ann Neurol. 2013;74:39–52.
21. Liachko NF, Saxton AD, McMillan PJ, Strovas TJ, Currey HN, Taylor LM, et al. The phosphatase calcineurin regulates pathological TDP-43 phosphorylation. Acta Neuropathol. 2016;132:545–61.
22. Liu L, Su X, Quinn WJ 3rd, Hui S, Krukenberg K, et al. Quantitative analysis of NAD synthesis-breakdown fluxes. Cell Metab. 2018;27:1067–1080.e1065.
23. Lu W, Wang L, Chen L, Hui S, Rabinowitz JD. Extraction and quantitation of nicotinamide adenine dinucleotide redox cofactors. Antioxid Redox Signal. 2018;28:167–79.
24. McReynolds MR, Chellappa K, Baur JA. Age-related NAD+ decline. Exp Gerontol. 2020;134:110888.
25. Moreno CM, Dixon RE, Tajada S, Yuan C, Opitz-Araya X, et al. Ca2+ entry into neurons is facilitated by cooperative gating of clustered CaV1.3 channels. eLife. 2016;5:e15744.
26. Nelson PT, Dickson DW, Trojanowski JQ, Jack CR, Boyle PA, Arfanakis K, et al. Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report. Brain. 2019;142:1503–27.
27. Peters CH, Sharpe EJ, Proenza C. Cardiac pacemaker activity and aging. Annu Rev Physiol. 2020;82:21–43.
28. Puelles VG, Cullen-McEwen LA, Taylor GE, Li J, Hughson MD, Kerr PG, et al. Human podocyte depletion in association with older age and hypertension. Am J Physiol-Ren Physiol. 2016;310:F656–68.
29. Rosendo-Pineda MJ, Moreno CM, Vaca L. Role of ion channels during cell division. Cell Calcium. 2020;91:102258.
30. Sweetwyne MT, Pippin JW, Eng DG, Hudkins KL, Chiao YA, Campbell MD, et al. The mitochondrial-targeted peptide, SS-31, improves glomerular architecture in mice of advanced age. Kidney Int. 2017;91:1126–45.
31. Wang J, Rousseau J, Kim E, Ehresmann S, Cheng YT, Duraine L, et al. Loss of oxidation resistance 1, OXR1, Is Associated with an autosomal-recessive neurological disease with cerebellar atrophy and lysosomal dysfunction. Am J Hum Genet. 2019;105:1237–53.
32. Whitson JA, Bitto A, Zhang H, Sweetwyne MT, Coig R, et al. SS-31 and NMN: two paths to improve metabolism and function in aged hearts. Aging Cell. 2020;19:e13213.
33. Wilson KA, Beck JN, Nelson CS, Hilsabeck TA, Promislow D, et al. GWAS for lifespan and decline in climbing ability in flies upon dietary restriction reveal decima as a mediator of insulin-like peptide production. Curr Biol. 2020;30:2749–2760.e2743.

34. Zaini MA, Müller C, Ackermann T, Reinshagen J, Kortman G, Pless O, et al. A screening strategy for the discovery of drugs that reduce C/EBPβ-LIP translation with potential calorie restriction mimetic properties. Sci Rep. 2017;7:42603.
35. Zidek LM, Ackermann T, Hartleben G, Eichwald S, Kortman G, Kiehntopf M, et al. Deficiency in mTORC1-controlled C/EBPβ-mRNA translation improves metabolic health in mice. EMBO Rep. 2015;16:1022–36.