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

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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.
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 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 dis-
 ease [31]. Elevated OXR1 expression is associated with
DR-mediated lifespan extension in different fly genetic
backgrounds and diminished expression creates a neu-
ropathological 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 dis-
 eases [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, suggest-
ing 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 dam-
age downstream of age-associated dysfunction,
targeting age-associated changes directly should broad-
ly delay the onset of age-associated oral decline [2].
Age-associated periodontal bone loss in mice is sup-
pressed 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 off-
spring telomere length. Telomere length is associated
with differences in survival, with shorter telomeres as-
associated with shorter-lived individuals. Sperm pro-
duction 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

The Biological Mechanisms of Healthy Aging
training program

The BMHA training program is an NIH-supported train-
ing program for graduate students and postdoctoral fel-
lows 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 evalu-
ation 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.

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