Invited Contribution

The Second Annual Symposium of the Midwest Aging Consortium: The Future of Aging Research in the Midwestern United States

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Abstract

While the average human life span continues to increase, there is little evidence that this is leading to a contemporaneous increase in “healthy years” experienced by our aging population. Consequently, many scientists focus their research on understanding the process of aging and trialing interventions that can promote healthspan. The 2021 Midwest Aging Consortium consensus statement is to develop and further the understanding of aging and age-related disease using the wealth of expertise across universities in the Midwestern United States. This report summarizes the cutting-edge research covered in a virtual symposium held by a consortium of researchers in the Midwestern United States, spanning topics such as senescence biomarkers, serotonin-induced DNA protection, immune system development, multisystem impacts of aging, neural decline following severe infection, the unique transcriptional impact of calorie restriction of different fat depots, the pivotal role of fasting in calorie restriction, the impact of peroxisome dysfunction, and the influence of early life trauma on health. The symposium speakers presented data from studies conducted in a variety of common laboratory animals as well as less-common species, including Caenorhabditis elegans, Drosophila, mice, rhesus macaques, elephants, and humans. The consensus of the symposium speakers is that this consortium highlights the strength of aging research in the Midwestern United States as well as the benefits of a collaborative and diverse approach to geroscience.

Keywords: Aging, Animal models, Gerontology, Metabolism, Senescence

Age is the greatest risk factor for the majority of human diseases, and as our population ages and the burden of aging and aging-associated diseases mounts, it is increasingly important that research into healthy aging is prioritized (1). Due to the complexity of aging, it is essential that the field engages expertise in both basic biological and translational aging research to fully develop a comprehensive molecular and physiological picture of aging across organisms. As such, a broad range of subject matter and an ever-expanding range of techniques and model organisms are needed to continue to advance our understanding of the biology of aging.

The Midwest Aging Consortium (MAC) was organized in 2019 across 6 states in the Midwestern United States: Indiana, Illinois,
Iowa, Minnesota, North Dakota, and Wisconsin. The MAC includes the Mayo Clinic; the Universities of Wisconsin–Madison, Minnesota, Iowa, Northwestern, and North Dakota; Iowa State; Southern Illinois University; and Indiana University-Bloomington. The main goals of the MAC are to leverage the respective strengths of different programs, centers, and institutes of aging across the Midwestern region to accelerate basic and translational geroscience and to provide a strong training environment for postdoctoral fellows and graduate students.

Following a successful inaugural meeting at the University of Minnesota in 2019, plans made to host a follow-up meeting in 2020 were disrupted by the coronavirus disease 2019 (COVID-19) global pandemic. To continue to build this community, the MAC and Aging Science Talks (2) hosted a virtual meeting on February 18, 2021. This report provides a brief summary of the 10 talks that were part of the program, which was organized by D.E.C. of Indiana University. The program featured 9 short talks by early-career investigators as well as a keynote talk by D.W.L. of the University of Wisconsin–Madison. Over 140 scientists representing all career stages, from across the Midwestern United States and around the world, participated in real time, with many others engaging after the event through a viewing of the recorded talks. This report will briefly describe the research presented at the Second Annual Symposium of the MAC.

**The Power of Nutritional Intervention to Delay Aging**

Calorie restriction (CR) is one of the most well-studied and robust interventions to extend life span and improve healthspan across species (3). However, despite nearly a century of research (4), the fully realized mechanisms underpinning the benefits of CR and other nutritional interventions such as protein restriction remain elusive. During the last decade, there has been considerable research completed in the nutritional intervention field of aging, notably the impact of sex and strain (5), degree of restriction (6), age on onset (7), tissue type (8,9), and macronutrient composition (7) on health and longevity. Despite this, gaps in our knowledge and reliance on assumptions remain.

This was discussed by H.H.P., University of Wisconsin–Madison, in her exploration of the impact of fasting on the response to CR in mice, through the use of a series of feeding regimens. Once-per-day feeding, typical in CR regimens in the laboratory, imposes a prolonged fasting period on CR mice as the animals binge and consume their food in about 2 hours (10). H.H.P. examined how CR without fasting, through the ad libitum feeding of a low-energy-density cellulose-diluted diet, blocked the ability of CR to improve insulin sensitivity and increase fatty acid oxidation in multiple strains and sexes of mice. Furthermore, in line with another recent study (11), reduced calorie intake without imposing fasting did not reduce frailty or increase life span. Conversely, H.H.P. found that the imposition of a prolonged daily fast without reduced calorie intake, which was recently shown to extend life span (12,13), is sufficient to reproduce many of the metabolic and molecular effects of CR. This work suggests that if humans respond similarly to mice, increasing the maximum intermeal interval may help promote healthy aging without requiring reduced calorie intake, but more research is required.

In the next presentation, J.C., University of Wisconsin–Madison, presented data from his rhesus macaque studies in which aging is delayed through CR. He showed that differing adipose depots from CR animals have unique changes in their gene expression programs. Despite the difference in gene expression between the subcutaneous and visceral adipose, the 2 tissues differentially regulate similar gene pathways in order to elicit a conserved CR response. J.C. then showed that along with the well-established regulation of inflammatory and metabolic pathways in response to CR (14,15), the diet also induces many RNA-processing pathways as part of the CR gene expression program (16,17).

The keynote address was given by D.W.L., University of Wisconsin–Madison, who presented recent and ongoing work from his laboratory, focused on disentangling the role of protein and of particular amino acids on health and longevity. It has recently become clear that higher protein consumption is associated with diabetes, insulin resistance, and mortality in both mice and humans (11,18,19), and D.W.L. presented data demonstrating that protein restriction could promote metabolic health in humans (20). Blood levels of the 3 branched-chain amino acids (BCAAs; leucine, isoleucine, and valine) are reduced in protein-restricted humans, and D.W.L.'s group has found that BCAA restriction improves the metabolic health of lean mice and restores normal body composition and glycemic control to diet-induced obese mice (20,21). While they are most often grouped together, there is emerging evidence that that the BCAAs may have distinct physiological and molecular effects (22,23). D.W.L. reported that the beneficial effects of a protein-restricted or low BCAA diet are mediated by reduced consumption of isoleucine and valine and highlighted that restriction of isoleucine alone was both necessary for the beneficial effects of a low protein diet and sufficient to improve metabolic health (24). Intriguingly, dietary isoleucine levels are associated with higher body mass index in humans (24), and higher blood levels of isoleucine are associated with mortality (25), suggesting that dietary BCAA levels also play a role in human health.

D.W.L. also presented recent work investigating how dietary BCAAs influence not just longevity, but healthy aging in mice (26,27). BCAA supplementation promotes hyperphagia and shortens the life span (28). D.W.L.'s laboratory found that lifelong consumption of a low BCAA diet could promote health and longevity in progeroid mice (29). Next analyzing wild-type mice, his laboratory ascertained that lifelong feeding of a low BCAA diet selectively inhibits signaling through the protein kinase mechanistic target of rapamycin complex 1 (mTORC1) in male, but not female mice. In parallel with this, lifelong feeding of a low BCAA diet reduces frailty and extends life span in male mice, but not in females (29).

**The Role of Senescence in Aging**

As the aging human population grows, it is imperative that our research focuses on interventions that optimize health and prevent disability. Cellular senescence, which was first described in the 1960s (30), has become an eminent, potentially reversible, target for the amelioration of aging (31). Indeed, genetic and pharmacologic clearance of senescent cells restores tissue health and offsets the progression of numerous age-related conditions in mice (32). In response to the preclinical promise of targeting senescent cells as a translatable intervention for humans, much work has gone into identifying viable biomarkers of cellular senescence (33). D.A.E., Mayo Clinic, explored the responsiveness of candidate senescence biomarkers to an intervention known to promote health and function in older adults (structured exercise). While the direct effects of exercise on senescent cells are unclear, indirect evidence suggests exercise may influence senescent cell burden (34,35). D.A.E. found that the intervention improved multiple parameters of muscle strength and physical function and, impressively, decreased the expression of senescence-associated
genes in circulating immune cells and concentrations of senescence-related proteins in plasma. These senescence biomarkers were associated with longitudinal changes in physical function, highlighting their potential to predict clinical outcomes, and, potentially, serve as surrogate endpoints in clinical trials of senotherapeutic interventions.

The importance of senescent immune cells was further highlighted by M.J.Y., University of Minnesota, who showed that deletion of Ercc1 in hematopoietic cells of mice (Vav-iCre+;Ercc1−/− mice) can promote features of immunosenescence (36,37). Premature aging of the immune system resulted in secondary senescence of nonlymphoid organs and ultimately reduced life span of Vav-iCre+;Ercc1−/− mice. Consistent with other cell types (38), transplantation of senescent immune cells into young mice can promote systemic senescence in trans. Conversely, transplantation of young immune cells into Ercc1−/− progeroid mice alleviated senescent burden and reduced markers of tissue dysfunction. Like previous studies of rapamycin treatment in older humans (39,40), a brief course of rapamycin treatment in Vav-iCre+;Ercc1−/− mice partially rescued the immune deficits and reduced markers of senescence in immune cells. These findings demonstrate the impact of aged (37), senescent immune cells, and their importance as a therapeutic target to suppress age-related diseases.

How Stress Affects the Way We Age

Mild or short-term exposure to stress during development is thought to contribute to a greater protective phenotype by galvanizing the cellular stress response and is thought of as a viable candidate to improve healthy aging and increase longevity (41). However, in many cases, stress and related phenotypes, such as inflammation and metabolic dysregulation, can promote aging and aging-associated diseases. Stressors are numerous, can occur anytime during the life cycle, and can include food limitation, reactive oxygen species, thermal stress, radiation, and trauma. At a cellular level, the heat shock response is cell-autonomous, whereas, at an organismal level, the heat shock response is regulated in a noncell autonomous manner. S.D., University of Iowa, described how sensory perception of heat by neurons causes the release of serotonin, which in turn activates the conserved stress-responsive transcription factor, heat shock factor 1 (HSF1). The intracellular signal transduction pathway by which the release of serotonin activates HSF1 is conserved in Caenorhabditis elegans and mammalian neurons and, in both cases, acts through activation of Protein Kinase A, posttranslational modification of HSF1, and recruitment of the histone chaperone facilitates chromatin transcription. S.D. showed that in C. elegans this mechanism of noncell autonomous control through serotonin release enables the maternal perception of stress to initiate a protective transcriptional program in the germ cells to ensure their survival and alter long-term physiology (42,43).

However, some stressors, especially those that occur early in the life of animals that form complex, hierarchical social groups, such as the elephant, have negative health consequences. D.E.C., Indiana University-Bloomington, highlighted the potential impact of early-life adversity on chronic disease and early death in her work tracking endocrine, immune, glycemic, and body condition parameters in elephants that have experienced trauma. With growing evidence of the prevalence and long-term deleterious effects of adverse childhood experiences, it is critical to better understand how early-life trauma influences an individual’s biological and social trajectory once in a stable environment. Wild elephant populations may provide invaluable translational information; elephants share many traits with humans while having unique characteristics, in addition to many human-associated confounders being irrelevant (e.g., socioeconomic status, education, smoking, ethnicity, and exercise). Elephants have a long life span (70 years or greater (44)) and similar developmental stages (45) to humans. In addition, while humans only have one copy of tumor protein 53 (TP53), elephants have on average 20 copies (46,47). The gene TP53 encodes for the protein p53, which is a primary regulator of the cellular response to stress, and plays an important role in aging (48). The extra copies of TP53 may be responsible for why elephants appear to have an enhanced apoptotic response to DNA damage and may protect against accelerated aging. Elephants have high levels of intelligence, a remarkable memory (thus making them capable of developing posttraumatic stress disorder), and live in close-knit, matrilineal family units with cooperative breeders. Calves are highly dependent on their mother and other family members to learn social norms, behaviors, and life skills. With a severe uptick in human–elephant conflict and poaching, many calves are orphaned after witnessing their mother being killed. This natural experiment, where some elephants randomly become orphans, while other elephants do not, will allow for the investigation of casual inference between early-life trauma, health, and aging.

The consequences of stress resulting from the disease were discussed by R.A.G., Northwestern University, who demonstrated the negative impact of influenza infection in aging mice. This results in persistent activation of the integrated stress response (ISR) in microglia and activates transcriptional pathways involved in neuroinflammation. R.A.G. showed data linking severe pneumonia with cognitive dysfunction in aged mice. Older survivors of pneumonia or other severe infection are at increased risk of cognitive impairment for up to 10 years after hospitalization (49,50), presenting a substantial public health threat to aging populations (51,52). This is of particular concern during the severe acute respiratory syndrome coronavirus 2 pandemic, which has overwhelmingly affected older adults, and has been linked to many neurological complications including delirium (53,54), a strong predictor of cognitive impairment after infection (55). While the mechanisms underlying this increased risk are still being elucidated, evidence suggests that proinflammatory populations of microglia accumulate in the aged brain (56,57). These cells are then “primed” for a hyperinflammatory response to systemic inflammation, potentially through activation by endocrine cytokine signaling (58,59). Through transcriptomics data from bulk brain tissue and flow-sorted microglia, R.A.G. showed that microglia from old animals have reduced expression of essential molecular chaperone genes and adopt a proinflammatory phenotype in the steady state. This is exacerbated by persistent activation of the ISR after pneumonia, in addition to aberrant increases in antigen presentation.

The Interplay Between Cell Signaling Dysregulation and Subcellular Organelles

Mitochondrial decline and dysfunction have long been associated with aging and age-related disease and are thought to contribute to cellular stress (60,61). The interplay between cell signaling and the immune system was highlighted by M.M.H., Northwestern University. M.M.H. discussed how mitochondrial transcription factor A (TFAM) is essential for the differentiation of alveolar macrophages, which are essential for the maintenance of lung homeostasis. They are the most abundant immune cells in the lungs and play a role in the phagocytosis of pathogens and
inhaled particles, as well as in the orchestration of immune responses. Moreover, alveolar macrophages are involved in the uptake and clearance of pulmonary surfactants. TFAM plays an essential role in the maintenance and organization of the mitochondrial genome and is involved in the regulation of genes from the oxidative phosphorylation system. Absence of Tfam in cells from the immune system, such as regulatory T cells, CD4, and CD8 T cells, results in the development of systemic inflammation and age-related phenotypes, indicating the essential role of Tfam and mitochondrial genes in supporting cell functions and homeostasis. Using a mouse strain in which Tfam is selectively deleted in CD11c-expressing cells (CD11c-Cre/Tfam<sup>lox/lox</sup> mice), M.M.H. showed that alveolar macrophages isolated from wild-type and genetically modified mice to elephants to the MAC include a diverse spectrum of animal models of aging from states and suggests that the region is well-equipped to perform the strength and diversity of aging research in the Midwestern United States and that the idea that the genetic, molecular, and cellular mechanisms of aging impactful discoveries in aging research. The concept of geroscience—Organelles can also affect each other through complex mechanisms, which was explored by P.L., Iowa State University, who focused on how dysregulating biogenesis of another organelle, the peroxisome, alters mitochondrial dynamics through mechanistic target of rapamycin complex 2 (mTORC2) pathway. The peroxisome is well known for its role in cellular redox homeostasis, oxidation of very long-chain fatty acids, and biosynthesis of phospholipids. The interplay between peroxisomes and mitochondria is important for maintaining cellular and metabolic homeostasis. It has been shown that the hepatocytes of peroxisomal adaptor Pex5 knockout mice exhibit enlarged mitochondria and loss of mitochondrial function. However, the mechanism underlying Pex5-regulated mitochondrial dynamics is largely unknown. By using <i>Drosophila</i> as a genetic model, P.L. found that Pex5 knockdown induces the phosphorylation of AKT, suggesting an activation of mTORC2 signaling upon peroxisomal dysfunction. In addition, P.L. showed that overexpression of the mTORC2 subunit <i>Rictor</i> attenuates Pex5 KD-induced mitochondrial enlargement. These findings suggest that activation of mTORC2 might act as an adaptive response to protect mitochondria from cellular damage associated with peroxisome dysfunction.

Conclusions

With recent advances in technology, high-throughput computational approaches, and aging biology, the time is ripe to make major and impactful discoveries in aging research. The concept of geroscience—the idea that the genetic, molecular, and cellular mechanisms of aging make aging the major risk factor and driver of common chronic conditions and diseases—is driving excitement in the field and making aging research attractive to early-career scientists. The work presented by the early career researchers highlighted in this Second Annual Symposium of the MAC demonstrates the strength and diversity of aging research in the Midwestern United States and suggests that the region is well-equipped to perform the kind of basic and translational research needed to discover, develop, and translate geroprotective interventions to the clinic. Strengths of the MAC include a diverse spectrum of animal models of aging from worms to wild-type and genetically modified mice to elephants to nonhuman primates, the Translational Geroscience Network for facilitating clinical trials, and access to cutting-edge “omics” methodologies. The MAC provides exceptional resources to early career researchers, as exemplified by this meeting, in addition to access to world-renowned aging experts. We hope to see these early career researchers and many others next year at the next in-person meeting of the MAC, following the conclusion of the COVID-19 pandemic.

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Conflict of Interest

D.W.L. has received funding from, and is a scientific advisory board member of, Aevion Pharmaceuticals, which seeks to develop novel, selective mTOR inhibitors for the treatment of various diseases. The University of Wisconsin–Madison has applied for a patent based in part on the findings reported here, for which D.W.L. is an inventor.

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References


