2025 Aging Research Day: Poster Abstracts

1. Intermittent Hypoxia Induces HIF-1-Dependent Adult Lifespan Extension in C. elegans

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Aging impairs cellular function and increases the risk of various human pathologies. Mitochondria, essential for energy production, accumulate damage with age, leading to reduced bioenergetics, altered oxygen consumption, and higher reactive oxygen species. The hypoxia-inducible factor (HIF-1) signaling pathway supports hypoxia-induced longevity in C. elegans. While developmental mitochondrial dysfunction can extend lifespan, often at the expense of healthspan, we found that restoring mitochondrial bioenergetics in adulthood enhances longevity. These results suggest that bioenergetic and metabolic contexts shape distinct longevity outcomes, though the underlying mechanisms remain unclear. We investigated whether hypoxia signaling influences lifespan beyond development by applying intermittent hypoxia treatment (IHT) at various life stages. Our findings showed that IHT initiated at the end of development, mid-life, or late-life significantly increased median lifespan, indicating that longevity pathways remain active in aging organisms. This lifespan extension depended on HIF-1, though its absence did not reduce lifespan. Additionally, IHT during young or mid-life stages temporarily improved swimming speed, reflecting enhanced vitality, but this effect was transient and unrelated to healthspan or sustained longevity. These results underscore the intricate relationship between hypoxia signaling, mitochondrial function, and aging, that the timing of interventions is critical for optimizing specific outcomes. By understanding how hypoxia signaling and mitochondrial function influence aging, we can advance treatments for age-related diseases and develop innovative strategies to enhance longevity through improved mitochondrial performance.

2. Integrative Genomic Analysis Reveals Function of GWAS Variants Within Transposable Elements in Human Diseases

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Over 90% of disease-associated variants identified in Genome-Wide Association Studies (GWAS) are located in non-coding regions of the genome, which complicates efforts to interpret their functional significance. Transposable elements (TEs), comprising ~50% of the human genome, play essential roles in development and aging. However, knowledge of how variants within TEs affect human diseases remains largely unknown. To this end, we analyzed data from over 5,000 GWAS traits with at least 10 significant variants ($p< 5\times10^{-8}$). Firstly, we investigate whether these variants are enriched in a specific TE family by intersecting them with annotated TEs from RepeatMasker using bedtools. Enrichment was assessed using Fisher's exact test across major TE classes (LINEs, SINEs, LTRs). We observed widespread enrichment of GWAS variants in LINEs and SINEs, especially in metabolic, musculoskeletal, and cardiovascular traits. To explore the functional implications, we further analyzed chromatin interaction data. We identified 10,000+ TE variants located in chromatin interaction regions, suggesting that 3D genome architecture disrupted by TE variants may modulate disease risk. Together, these findings support a model in which transposons and dynamic regulatory elements contribute to the noncoding architecture of complex traits. Future work will extend to enhancer

regions and integrate machine learning to predict the functional impact of these TE variants on TE activation and regulatory landscapes.

3. Best Practice Standards for Geriatric Trauma Activation Fail to Identify Older Adults with Significant Injury after a Ground-Level Fall

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Objective: Age-based disparities in the identification and management of traumatic injury are well-documented in the literature. This study aims to assess potential disparities in current best practice standards for geriatric trauma activation (GTA) among a sample of older adults who experienced a ground-level fall. Methods: We conducted a retrospective cohort study of older adults (65+ years) who presented to the emergency department (ED) via ambulance after sustaining a fall. Demographic, prehospital, radiological, and clinical data were collected using the from the electronic medical records. We quantified the frequency of traumatic intracranial hemorrhage, ICU admission and in-hospital mortality among patients who did and did not meet the GTA best practice criteria. Results: A total of 1,064 patients who experienced a ground-level fall were included. The mean age was 81.9 ± 8.9 years and 39.3% were male. Of the 1,064 ground-level falls, 60 patients suffered an ICH (5.6%), 14 were admitted to the ICU (1.3%), and 38 died during their hospitalization (3.6%). Additionally, half (52.1%) of these patients met the GTA Criteria and 47.9% did not meet the criteria. Patients who met criteria were more likely to die during their hospitalization (4.9% vs. 2.2%, $p<0.05$). However, incidence of traumatic ICH and ICU admission did not differ significantly between patients who met the GTA Criteria and those who did not: 30 patients (5.4%) vs. 30 patients (5.8%) sustained a traumatic ICH, 10 patients (1.8%) vs. 4 patients (0.8%) were admitted to the ICU. Conclusion: Ground-level falls in older adults remain a challenging clinical presentation with significant risk of morbidity and mortality. Despite over half the sample meeting the best practice standards for geriatric trauma activation, these criteria still failed to identify all patients with significant injury. Additional work is needed to improve the risk stratification process for this particularly vulnerable patient population.

4. Effect of Oxidative Stress on Astrocytic Tau Uptake

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Alzheimer's Disease (AD) is a progressive neurodegenerative disease that results in progressive cognitive decline and dementia. AD is characterized by the accumulation of tau and amyloid beta aggregates, reactive astrocytes, activated microglia, and oxidative stress, with tau aggregation considered a primary driver of the disease. Astrocytes are known to uptake tau, but whether this is beneficial or detrimental is still debated. Mitochondrial reactive oxygen species (ROS) production is one regulator of astrocyte function, and astrocyte mitochondria are more prone to ROS generation than neurons. This mitochondrial ROS production is utilized for signaling that regulates many astrocytic functions. Despite oxidative stress being extensively studied in AD, the specific relationship between astrocytic ROS and tau pathology is unknown. Interestingly, exposure to pathological tau species induces mitochondrial dysfunction in astrocytes. To investigate this relationship, we examined

the effect of paraquat on the uptake of tau in primary mouse cortical astrocytes. Treatment with paraquat for 6 hours to induce oxidative stress in primary mouse astrocytes has a biphasic effect on astrocytic tau uptake, with 10uM paraquat reducing the uptake of tau and 100uM paraquat slightly increasing tau uptake. To further explore the specific impact of mitochondrial ROS production, we propose to use in vitro approaches that allow for spatially and temporally controlled ROS production within primary mouse astrocytes utilizing mitochondrial targeted d-amino acid oxidase. Treatment with d-alanine following transfection with mitochondrial targeted d-amino acid oxidase results in an increase in hydrogen peroxide within the mitochondria that is measurable with a mitochondrial targeted hyper7, a hydrogen peroxide biosensor. Further work will explore the impact of mitochondrial specific ROS generation on the trafficking and degradation of the endocytosed tau.

5. Aging enhances the pro-inflammatory responses of monocyte-derived macrophages to thoracic irradiation and influenza A virus infection resulting in increased lung injury.

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Aging alters a multitude of cellular and physiological processes that affect the efficacy and fidelity of the immune system and contributes to increased susceptibility of the elderly to age-related disorders, including cancer. Aging can heighten the toxic effects of radiotherapy on normal tissues in older patients. Radiation injury is also thought to accelerate aging since they share common biological processes. The lung is particularly sensitive to radiation injury. Factors such as age and respiratory infection are known to increase the risk of developing severe lung complications from radiation treatment. However, this remains poorly understood. Macrophages are innate immune cells that orchestrate immune responses to injury and infection. Age-related changes in the responses of macrophages are known to underlie the enhanced severity of respiratory pathogens in older patients. However, few studies have reported how aging alters macrophage responses to radiation toxicity. We developed an animal model to clearly define this risk. We exposed young (8 weeks) or old (60 weeks) female C57BL/6 mice to 5-12.5 Gy whole thorax RT followed 1 wk later by infection with 0.01 HAU of influenza A H1N1 PR8 (flu). Image analysis of lung pathology using density heatmaps, revealed that 5 Gy alone did not cause overt injury. However, when 5Gy was combined with flu major lung pathology resulted, including immune cell congestion and collagen deposition, reflecting pneumonitis and fibrosis. Furthermore, this was enhanced with advanced age. We also assessed the responses of monocyte-derived macrophages (MDMs) inflammatory effector cells that play a role in regulating inflammation and are known to promote inflammation and fibrosis in multiple lung injury models. We found that flu infection occurring after radiation exposure enhanced the accumulation and pro-inflammatory activation of MDMs, and increased markers associated with inflammatory and pro-fibrotic processes in isolated lung macrophages, and this was also further increased in aged mice. Respiratory infection is an underappreciated risk factor for lung radiation side effects, particularly in the aged population. By identifying the specific ways macrophage responses become altered with age, we seek to provide new strategies for developing more effective therapeutics.

6. SIRT6 Promotes Epigenome Stability and Increases healthspan in male mice

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With aging, there are significant epigenetic changes at all levels of chromatin and DNA organization. The aging process is accelerated by epigenetic alterations, such as reduced global heterochromatin, nucleosome remodeling and loss, and changes in histone marks. Sirtuin 6 (SIRT6) plays important roles in multiple regulatory functions including DNA repair, heterochromatin regulation, and telomere maintenance. Overexpression (OE) of SIRT6 extends lifespan in model organisms and SIRT6 activity correlates with maximum lifespan in mammalian species. The overarching role of this project is to understand the mechanisms by which SIRT6 rejuvenates the epigenome. Our preliminary methylation clock data showed that overexpression of SIRT6 in cells from elderly subjects rejuvenated the epigenetic clock. RNAseq data indicate that SIRT6 OE upregulated genes involved in heterochromatin assembly, organization, and DNA packaging. SIRT6 reduced the expression of transposable elements. ATACseq was analyzed to explore changes in genome-wide chromatin compaction in SIRT6 overexpressing cells, showing that chromatins in SIRT6 overexpressing cells are more compacted genome-wide compared to control cells. SIRT6 overexpression increased H3K9me3, which is associated with heterochromatin. DNA methylation, which is a major silencing mechanism of TEs (transposable elements), significantly increased in SIRT6 OE cells. Based on these results, we hypothesize that SIRT6 regulates global chromatin structure and facilitates heterochromatin compaction, in turn repressing transposable elements. To test whether the effects of SIRT6 observed in vitro can be replicated in aging mice, we generated adeno-associated viral vectors of serotype 8 (AAV8) carrying wild-type human SIRT6 (hSIRT6) and centenarian SIRT6 (centSIRT6). Our results demonstrate that SIRT6 gene transfer significantly decreased the frailty index score and DNA methylation clock while improving locomotor strength in male mice, suggesting a potential delay in aging-associated phenotypes and enhanced physiological resilience. Extensive molecular analyses have been conducted to corroborate these findings. Therefore, AAV-mediated SIRT6 gene transfer may represent a promising gene therapy strategy to delay aging and promote healthy longevity.

7. Ribosylome Profiling Reveals SIRT6's Novel Roles in Oxidative Stress

Yuan Liang, Gregory Tombline, Zhicheng Jin, Eric Hillpot, Jinn Guo, Seyed Ali Biashad, Andrei Seluanov and Vera Gorbunova, University of Rochester

SIRT6, a mammalian homolog of yeast SIR2, exhibits anti-aging effects by enhancing DNA-repair efficiency, repressing LINE1 activities and improving glucose metabolic processes. Even though it is well-known as a class III histone deacetylase, its MARylation (mono-ADP ribosylation) activity remains elusive in oxidative stress conditions. Here, we demonstrate SIRT6's novel roles in regulating cellular responses to oxidative damage by profiling a SIRT6-dependent ribosylome.

8. Sirt6 activator fucoidan extends healthspan and lifespan in aged wild-type mice

Seyed Ali Biashad, Eric Hillpot, Francesco Morandini, Cheyenne Rechsteiner, Victoria Paige, Gregory Tombline, Minseon Lee, Zhizhong Zheng, Yuan Liang, John Martinez, Natasha Sieczkiewicz, Annette

Sebrell, Miraz Sadi, Zhihui Zhang, Valentin Volobaev, Denis Firsanov, Matthew Simon, Lei Zhang, Paul Robbins, Andrei Seluanov, Vera Gorbunova, University of Rochester

Sirtuins are NAD+-dependent deacetylases/deacylases and ADP-ribosyltransferases. Mice overexpressing SIRT6 experience extended lifespan and reduced frailty. As such, SIRT6 pharmacological activation is a promising therapeutic target. Here we report that fucoidan strongly stimulated SIRT6's mono-ADP-ribosylation activity. Dietary supplementation of fucoidan extends lifespan of male mice and promotes health in both sexes.

9. Transposable element methylation state predicts age and disease

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Transposable elements (TEs) are DNA sequences that expand selfishly in the genome, possibly causing severe cellular damage. While normally silenced, TEs have been shown to activate during aging. DNA 5-methylcytosine (5mC) is one of the main epigenetic modifications by which TEs are silenced and has been used to train highly accurate age predictors. Yet, one common criticism of such predictors is that they lack interpretability. In this study, we investigate the changes in TE 5mC methylation that occur during aging in human blood using published methylation array data. We find that evolutionarily young long interspersed nuclear elements 1 (L1s), the only known TEs capable of autonomous transposition in humans, undergo the fastest loss of 5mC methylation, suggesting an active mechanism of de-repression. The same young L1s also showed preferential gain in chromatin accessibility but not expression. The long terminal repeat retrotransposons THE1A and THE1C also showed very rapid 5mC loss. We then show that accurate age predictors can be trained on both 5mC methylation of individual TE copies and average methylation of TE families genome wide. Lastly, we show that while old L1s gradually lose 5mC during the entire lifespan, demethylation of young L1s only happens late in life and is associated with cancer.

10. Translational Resistance to the Incorporation of Oxidative Damage Within Nascent Proteins

Philip, Bellomio PhD candidate

Increased oxidation of cellular proteins and a reduced ability to repair this oxidative damage is a key molecular mechanism of aging. Among the amino acids which make up proteins, methionine (Met) with its sulfur-containing sidechain is especially vulnerable to oxidation by reactive oxygen species (ROS). Hydrophobic Met is oxidized to hydrophilic methionine sulfoxide (MetO), often with negative implications for protein folding and function. Alternatively, Met in both its free and protein bound forms may act as a redox buffer by helping to soak up the deleterious effects of ROS production. This mechanism relies on efficient repair of MetO by methionine sulfoxide reductases (Msr), an evolutionarily conserved family of proteins with diminishing activity throughout the course of one's life. Met oxidation has been extensively investigated in the context of mature proteins. However, the formation of tRNA-bound MetO, and its potential incorporation into nascent polypeptides during translation have not been well studied. For example, it is not known if translation factors for either protein initiation or elongation can also serve a quality control function in preventing MetO-tRNA from reaching the ribosome. Here, I have utilized recombinant proteins from E. coli, an in vitro

reconstituted transcription + translation system (IVTT), and HPLC-MS/MS to reveal the effects of MetO on specific steps leading up to translation, as well as to determine the actual degree of MetO incorporation within reaction products. I have demonstrated that MetO can be charged to tRNA with reduced efficiency by methionyl-tRNA synthetase (MetRS), and that even with the addition of excess MetRS alone, both the rate of translation and the frequency of MetO incorporation remained low in a mixed Met-MetO system. The addition of excess elongation factor-thermal unstable (EF-Tu) in conjunction with MetRS however, largely alleviated the negative effects of MetO and confirmed the existence of a second level of quality control during translation elongation. Together, these experiments provide insight into a previously undescribed mechanism to prevent the damage-inducing incorporation of a common oxidized amino acid within proteins. Inherent to the translational apparatus, this mechanism does not require Msr function and may offer a critical line of protection against increased oxidative stress in old age.

11. Deletion of PYHIN cytoplasmic DNA sensors slows inflammaging, and decreases age-related frailty in mice

Joseph Cutting, Ines Drissi Qeytoni, Zhizhong Zheng, Victoria Park, Domenico D. Fraia, Andrei Seluanov, Vera Gorbunova, University of Rochester

Chronic inflammation is a major contributor to aging and is recognized as a major hallmark of age-related decline. Persistent immune activation is implicated in many conditions of aging, such as arthritis, neurodegenerative disorders, and overall frailty. While the drivers of inflammation remain unclear, strong evidence ties chronic inflammation to accumulation of cytoplasmic DNA. Sources such as micronuclei or cDNA from transposable elements have been shown to accumulate with age, creating persistent immune activation that leads to cell death or senescence. The PYHIN (Pyrin and HIN domain-containing) protein family is central to the detection and response to cytoplasmic DNA, binding DNA in a sequence-independent manner to activate interferon signaling and inflammasome pathways. Interestingly, PYHIN proteins are absent in bats-a clade enriched in long-lived species whose unique immune system is linked to their extended healthspan and lifespan. To investigate the role of PYHIN proteins in age-related inflammation and mortality, we conducted a lifespan study on mice lacking all 13 mouse PYHIN proteins. PYHIN-deficient mice show reduced cytokine expression then age-matched wildtype mice, and showed decreased frailty. Furthermore, Pyhin-deficient females performed better at physical exercise at older ages. Taken together, these results suggest decreasing Pyhin-driven cytoplasmic DNA sensing can improve healthspan of older mice.

12. Structural proteomics of the human ubiquitinome

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The concept of "age" is typically discussed at the level of whole organisms, yet it also extends to macromolecules such as proteins. Like organisms, proteins undergo a life cycle of synthesis and degradation. However, how a protein's molecular age influences its fate and function remains largely unexplored. To address this gap, we employ stable isotopic labeling to partition the proteome based on molecular age. We then use quantitative proteomics and AlphaFold-based structural analyses to

examine the degradation patterns in these proteins. Our results indicate that the vast majority of ubiquitinated proteins in a cell are newly synthesized, and that these nascent proteins constitute the bulk of the degradative flux through the proteasome. We show that, unlike mature ubiquitinated proteins, nascent ubiquitinated proteins are modified at lysine residues that are expected to be buried within the native structure of correctly folded proteins. Our data suggest that a large fraction of cellular proteins are either prematurely terminated during translation or misfold soon after synthesis. These damaged nascent proteins are polyubiquitinated at lysine residues that would otherwise be buried within correctly folded proteins and are subsequently targeted for degradation by the proteasome. Together, our analyses provides further insights into the age selectivity of ubiquitination and the quality control mechanisms that ensure the fidelity of the nascent proteome.

13. Mix23 contributes to movement deficits through binding to Prohibitin/AFG3L2 complex
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MIX23, also known as CCDC58, is a small protein residing in the mitochondrial intermembrane space (IMS). As an "orphan protein" of the mitochondria IMS, there is limited information regarding MIX23's function. Interestingly, a recent study revealed that humans with a Mix23 variant display chorea-athetosis and intellectual disability, suggesting a neurological impact. To investigate the role of MIX23 in these symptoms, we analyzed a mouse line with an exon 4 deletion in the Mix23 gene (Mix23-E4). Motor and cognitive assessments were conducted at 4, 8, 12, and 13-15 months of age. Mix23-E4 female mice begin to display signs of disturbed mobility at 4 months of age. By 12-15 months, both male and female Mix23-E4 mice show significant motor impairments in rotarod, beam walk assays, and via gait analysis. Additionally, Mix23-E4 mice show reduced freezing in contextual fear conditioning, indicating deficits in associative learning. After tissue collection, cerebellum lysates from Mix23-E4 mice displayed increased S-OPA1, indicating mitochondrial stress and fragmentation. A Mix23 knockout HeLa cell line was utilized to elucidate the protein's functional impact in the mitochondria. Co-immunoprecipitation and mass spectrometry analysis revealed MIX23 and its strongest binding partner, SMIM12, associate with the Prohibitins/AFG3L2 complex in Mix23 WT cells. However, loss of MIX23 prevents SMIM12's binding with the PHB/AFG3L2 complex but increases its binding to Complex IV assembly factors. This suggests MIX23 and SMIM12 bind to the PHB/AFG3L2 protease complex to regulate respiratory chain assembly. Finally, Seahorse MitoStress assays revealed Mix23 knockout cells display mitochondrial respiration deficits compared to wild-type cells. In conclusion, MIX23 and SMIM12 associate with the Prohibitin/AFG3L2 complex to regulate protein quality control pathways of the mitochondria. Loss of this MIX23 function triggers motor and cognitive impairments in mice.

14. The Intersection of Ableism and Ageism: The Impact on Older Adults with IDD
Laura M. Robinson, MPH, PhD Student, Warner School of Education, University of Rochester; Division of Geriatrics, University of Rochester Medical Center

Age is not a simple construct nor a single process, it's multidimensional. Disability is part of the human condition. Most people will be temporarily or permanently impaired at some point in life, and

those who survive to old age will experience increasing difficulties in functioning. People who are older and people with disabilities experience significant discrimination in the US and around the world. This poster will describe ageism, ableism, and the intersectionality of these two types of discrimination resulting in harm to adults who identify as both older and disabled.

15. Long-term outcome of chromatin derepression under Sirt6 loss

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Transposable-element (TE) activity can provoke type-I interferon (IFN-I) signaling, yet how organisms adapt to chronic TE pressure in vivo remains unclear. SIRT6, a chromatin-coupled NAD^+ deacylase/mono-ADP-ribosyltransferase, restrains LINE-1 (L1) via KAP1-dependent heterochromatin; whole-body Sirt6 loss unleashes TE activity and shortens lifespan. Here we show that a banana-based hydrocolloid diet markedly prolongs survival of Sirt6-knockout (KO) mice (to ~2 years) but does not restore wild-type (WT) longevity. To delineate tissue programs compatible with survival under persistent TE stress, we profiled rRNA-depleted RNA-seq from brain, heart, kidney, lung, and liver in KO and WT animals at 1 and 12 months. TE-aware quantification revealed pan-tissue derepression at 1 month in KO. By 12 months, trajectories bifurcated: brain, heart, and kidney re-established TE repression ("containment"), whereas lung and liver remained TE-high ("tolerance"). In WT, the 1→12 month transition (young adult→adult) was associated with a shift toward higher TE signals in several tissues, without implying advanced age. Across containment tissues, transcriptomes converged on an IFN-I/ISG-high, cell-cycle-low state with reinforced mitochondrial and peroxisomal metabolism, unfolded-protein response, and DNA-repair signatures-consistent with enhanced restriction/clearance of TE nucleic acids and reduced permissiveness for transcriptional bursts. Tolerance tissues maintained TE- and IFN-high profiles with energetic rewiring (OXPHOS and lipid metabolism) but less pervasive proteostatic reinforcement. These data position Sirt6 KO as a sensitized in-vivo model that separates durable containment from damage tolerance under chronic TE load and show that nutritional support can unmask tissue-specific adaptive solutions without normalizing organismal risk. Therapeutically, they motivate TE-targeted, metabolism-aware interventions (e.g., reverse-transcriptase inhibition, cGAS-STING tuning, SIRT6 activation) to shift TE-stressed tissues from tolerance toward lasting containment.

16. The role of STING S357 in cytosolic DNA response

Jing Guo, PhD candidate

Bats are exceptional long-lived species relative to other animals in their weight class. One potential reason for this is their attenuated immune responses, as chronic inflammation is one of the strongest hallmarks of aging. Interestingly, this characteristic may be linked to key differences in the innate immune system of bats, particularly within the cGAS-STING pathway. The cGAS-STING pathway plays a critical role in the innate immune system by detecting cytosolic DNA and triggering an interferon response. In most mammals, STING serves as a mediator in this cytosolic DNA sensing pathway, initiating downstream interferon production. This pathway is crucial for immune defense against

pathogens like DNA viruses. However, bats exhibit a unique modulation of this pathway, which may contribute to their longevity. Recent studies have identified that bats possess hypervariability at a highly conserved serine residue (S358 of human STING, equivalent to S357 in mice) of the STING protein. Phosphorylation of this serine is key to STING activation upon detection of cytosolic DNA. However, the precise mechanisms by which this phosphorylation influences STING activity, and its broader physiological significance, remain unclear. In this study, we utilize mouse models with CRISPR knock-in mutations to investigate the role of STING S357 in immune response modulation and its potential impact on longevity.

17. DNA Repair and Epigenetic Regulation in Mice Overexpressing SIRT6 Variants from Long- and Short-lived Species

Mila Kaplan, Joseph Cutting, Seyed Ali Biashad, Andrei Seluanov, Vera Gorbunova

The large increase in the aging population in the US and around the world, along with aging-associated diseases highlights the need for a better understanding of the mechanisms of these pathologies. Sirtuin 6 (SIRT6), a NAD-dependent enzyme, regulates several of the hallmarks of aging including genomic stability, epigenetic modifications, inflammation, and cellular senescence. DNA damage repair plays a major role in genomic stability and SIRT6 has been shown to enhance DNA double-strand break (DSB) repair efficiency. SIRT6 overexpression in mice also significantly increases longevity and SIRT6 variants in longer-lived species were found to have increased activity. To explore this phenomenon we isolated mouse, beaver, human and bowhead whale SIRT6 variants and overexpressed these variants in mice to understand how overexpression of the SIRT6 variants from short and long-lived species impacts aging. To study how these variants impact DNA DSB repair activity, lung fibroblasts were isolated from these mice, and the percentage of live and apoptotic cells was measured after oxidative stress induced by H2O2 treatment. There was a significant increase in live cells in cells overexpressing human and bowhead whale SIRT6 compared to controls with 600 µM H2O2 treatment after 48hr, suggesting that the SIRT6 from humans and bowhead whales may reduce apoptosis due to oxidative stress. Additionally, we assessed the cognitive and locomotive differences in the mice to determine the effect of human and bowhead whale SIRT6 overexpression on the mice's physical and mental ages via an open field maze. Younger mice demonstrated significantly increased in-center frequency (a measure of decreased anxiety) compared to older mice. Furthermore, old human SIRT6 overexpressing male mice showed a trend in increased in-center frequency compared to the older mice, which demonstrates that human SIRT6 may be ameliorating the age- related anxiety of the mice. Lastly, to understand why there are differences in DNA DSB repair activity, we investigated post-translational modifications between SIRT6 from long- lived and short-lived species. Phosphorylation of mouse, beaver, and bowhead whale SIRT6 was compared by a western blot of samples with and without phosphatase treatment. SIRT6 from bowhead whale left a higher band on the western blot than the SIRT6 from the mouse and beaver SIRT6, and left a lower band after phosphatase treatment. Therefore, increased phosphorylation of bowhead whale SIRT6 may be responsible for its enhanced DNA DSB repair activity.