Session 4510 (Symposium)

BS GSA and AAA Joint Symposium

RIBOSOMAL PROTEIN 6 PHOSPHORYLATION REGULATES TRANSLATIONAL RESPONSES TO DIETARY RESTRICTION

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Forms of dietary restriction like intermittent fasting (IF) and caloric restriction (CR) promote health and longevity through changes in gene expression. While the transcriptional changes that occur in response to DR have been well described across several species, the role of translational regulation has lagged. Using polysome profiling and mRNA-seq, we quantified changes in actively translated mRNAs that occur in C. elegans under CR compared to well-fed conditions. The analysis revealed hundreds of transcripts regulated on the translational level that would have been missed using convential transcriptomics. Among the translationally down-regulated genes that where pro-longevity when knocked down were regulators of the cell-cycle: fbxb-24, sdz-33, kbp-1, and cdk-2. In search of the mechanisms regulating selective translation under CR we investigated a role for ribosomal protein 6 (RPS-6) as its phosphorylation status is thought to regulate cell cycle and selective translation of mRNA transcripts. Using RPS-6 phospho-null and phospho-mimetic mutants, we show that phosphorylation and de-phosphorylation of RPS-6 is necessary for the pro-longevity effects of CR and IF. Furthermore, we show that IF is more beneficial for retaining locomotion with age than CR and that endogenously tagged RPS-6 ::mCherry accumulates in body wall muscle under fasting. However, the benefit of IF on locomotion is lost in RPS-6 phospho-mimetic mutants. Together, results suggest that protein translation is enhanced in the muscle under IF to prevent sarcopenia in a way dependent on RPS-6. Translatome analysis of the phospho-mutant suggested a role for RPS-6 in selective translation of p38 mitogen-activated protein kinases.

AGE-RELATED NEUROPROTECTION BY DIETARY RESTRICTION REQUIRES OXR1-MEDIATED RETROMER FUNCTION

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Dietary restriction (DR) is the most robust method to delay aging and the onset of neurogenerative disorders across multiple species, though the mechanisms behind this phenomenon remain unknown. To elucidate how DR mediates lifespan extension, we analyzed natural genetic variants that associate with increased longevity under DR conditions in the Drosophila Genetic Reference Panel. We found that neuronal expression of the fly homolog of human Oxidation

Resistance 1 (OXR1) is necessary for DR-mediated lifespan extension. Neuronal knockdown of OXR1 also accelerated visual decline but not physical decline, arguing for a specific role of OXR1 in neuronal signaling. Further, we find that overexpression of the TLDc domain from human OXR1 is sufficient for lifespan extension in a diet-dependent manner. Studies from the Accelerating Medicines Partnership - Alzheimer's Disease network show that patients with reduced OXR1 protein levels are more prone to Alzheimer's disease diagnosis, and we find that overexpression of human OXR1 is protective in animal and cell Alzheimer's models. In seeking the mechanism by which OXR1 protects against age-related neuronal decline, we discovered that it provides a necessary function in regulating the neuronal retromer complex, which is essential for the recycling of transmembrane receptors and for maintenance of autophagy. We further discovered that OXR1 deficiency can be rescued by genetic or pharmacological enhancement of retromer function, and that this enhancement extends lifespan and healthspan. Understanding how OXR1 operates could help uncover novel mechanisms to slow neurodegeneration including Alzheimer's disease.

AGING PREDISPOSES B CELLS TO MALIGNANCY BY ACTIVATING C-MYC AND PERTURBING THE GENOME AND EPIGENOME

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Age is the single major risk factor for human cancer, but naturally occurring cancers are rarely studied in aging models. Like humans, mice spontaneously develop cancer with age, and standard laboratory strains are predisposed for B-cell lymphoma. Here, we uncover how B-cell lymphoma develops as a consequence of the aging immune system. We found that aged B cells acquire somatic mutations in tumor suppressors and oncogenes (e.g. Trp53, Pim1, and Myh11) and undergo monoclonal expansions, with some clones representing 86% of splenic B cells. Clonal B cells had hypermethylated promoters and globally silenced expression, suggesting a role of DNA methylation in clonal selection of premalignant B cells. B-cell size, spleen weight, and a novel population of B cells, which we named Myc+ cells, emerged as convenient markers of malignancy. High-throughput analyses of clonal B cells and the use of genetic mouse models revealed that c-Myc drives B-cell size increase and clonal expansion with age. Phoshoproteome and co-culture experiments revealed that c-Myc is activated by signals from the aging microenvironment. Moreover, single-cell RNA-seq suggested that clonal B cells originate from age-associated B cells, further underlying the importance of aging environment in cancer transformation. Longitudinal analyses demonstrated a negative impact of premalignant B

cells on mouse lifespan and linked it to age-related myeloid bias. Together, our study revealed cell-autonomous changes that cooperate with the aging microenvironment to give rise to preneoplastic B cells. This stidy established a novel model to study how aging predisposes cells to cancer transformation.

AN EVOLVING ROLE FOR THE LONG NON-CODING RNA H19 IN AGING AND SENESCENCE

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The long non-coding RNA (lncRNA) H19 is a maternally imprinted gene transcript that, in conjunction with the neighboring Igf2 gene, is critical in controlling embryonic growth. Loss of H19 results in fetal overgrowth associated with Beckwith Weidemann syndrome, while elevated H19 occurs in human cancers. In the adult, H19 functions in cancer cells where it promotes migration and is correlated with poor prognosis, and in adult stem cells where it is a key regulator of cell fate decisions during differentiation. While the function of H19 in primary somatic cells has not been defined, a reduction in the abundance of H19 has been reported during senescence in endothelial cells. Given the critical importance of H19 in cell fate decisions, it is likely that understanding the precise function of H19 in somatic cells in general and why reduced levels occur with cellular senescence will provide novel insights into both somatic cell maintenance and the senescence program. Towards this end, we examined the role of H19 in somatic cell growth using cardiac interstitial fibroblasts. Our results indicate that H19 is not only vital for somatic cell proliferation and survival, but that depletion of H19 leads to cell cycle arrest and the formation of abnormal nuclei resulting in senescent cells. We are defining both the upstream regulators of H19 and the downstream mediators of senescence following H19 depletion. Overall, these results indicate an essential role for H19 in cell cycle progression, chromatin structure, and possibly proper mitotic division.

Session 4515 (Symposium)

CHANGE, CORRELATES, AND STRUCTURE OF PERSONALITY ACROSS ADULTHOOD

Chair: Olivia Atherton
Co-Chair: Emorie Beck

Personality is both stable and changing across the lifespan. However, many questions remain about the factors that account for individual differences in change, the consequences of personality for life outcomes, and how best to assess personality at different points in the lifespan. First, Olivia Atherton will discuss research on the development of the Big Five personality traits from young adulthood to midlife with a sample of Mexican-origin individuals, as well as sociodemographic and cultural predictors of personality change in this population. Second, Bill Chopik uses data from 90 countries to examine the consistency of age differences in positive personality traits in the second half of life, from midlife to old age, as well as how cultural characteristics moderate the terminal decline in positive personality traits. Third, Emorie Beck will present research demonstrating that personality traits from the Big Five to beyond are robustly associated with a number of key life events across countries, decades, sociodemographic moderators, and even when controlling for selection bias. Finally, Josh Jackson uses network psychometric techniques to examine coherence and differentiation among indicators of the Big Five from 14 to 85 in a large multinational sample, tracking age differences with consequences for the assessment of personality traits in older adulthood. We will conclude with a panel discussion of emerging issues in personality change, prediction, and assessment across adulthood, with each speaker providing unique experience and insight into the study of each area.

BIG FIVE DEVELOPMENT FROM YOUNG ADULTHOOD TO MIDLIFE: FINDINGS FROM A LONGITUDINAL STUDY OF MEXICAN-ORIGIN ADULTS

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A large body of research has documented how personality develops across adulthood, yet very little longitudinal work has examined whether these findings generalize beyond predominantly middle-class, highly-educated White American or Western European individuals. This pre-registered study uses longitudinal data from 1,110 Mexican-origin adults who completed a well-validated personality measure, the Big Five Inventory, up to 6 times across 12 years (median age at Wave 1 = 37.7; range = 26 to 65). Individuals generally maintained their rank ordering on the Big Five over time (rs=.66-.80), and all of the Big Five traits showed small, mean-level decreases across adulthood. These trajectories had few associations with sociodemographic factors (sex, education level, IQ) and cultural factors (generational status, age at immigration, Spanish/English language preference, Mexican cultural values, American cultural values, ethnic discrimination). Divergences between the present findings and previous research highlight the need to study personality development across diverse aging samples.

CULTURAL CONSISTENCY IN LATE-LIFE DECLINES IN POSITIVE PERSONALITY TRAITS

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Personality has elements of both stability and change across the adult lifespan. There has also been evidence for terminal decline—late-life decreases in positive psychological characteristics. However, many of these studies have examined these patterns in primarily Western populations. The current study examined the consistency of age differences in positive personality traits (i.e., character strengths) across cultures. I examined 2,895,051 participants ranging in age from 13 to 100 (Mage = 34.31; 65.3% women) from 90 different countries. I reproduced patterns of terminal decline across cultures. In addition to mean differences between cultures (e.g., focusing on the present is associated with more positive traits [Mr = .45]), cultural characteristics often moderated the effects of age on positive personality traits. For example, terminal decline was more dramatic among people from collectivistic cultures and flatter among people from