CAN WE SIMPLIFY AGING?

Svetlana Ukraintseva, and Anatoliy Yashin, *Duke University, Durham, North Carolina, United States*

Aging is indeed a complex process, but can it be simplified, so we could efficiently prioritize candidate anti-aging interventions and select those with largest impacts on key negative consequence of the aging, i.e., on increases in mortality risk and comorbidities with age? Here we argue that human aging and its negative consequences for health and lifespan are essentially driven by the interplay among three processes: (i) depletion of limited body reserves (e.g., of stem, immune, neural, muscle cells); (ii) inherent deficiency of cell/tissue repair mechanisms, which leads to accumulation of damage, allostatic load, and systems dysregulation; and (iii) general slowdown of physiological processes in the body (such as metabolism, proliferation and information processing) with age that results in slower responses to stressors and delayed recovery after damage (i.e., decline in resilience), which in turn contributes to increase in vulnerability to death with age. We show that the interplay among these processes can have ambivalent effects on health and longevity that should be taken into account to develop optimal anti-aging and pro-longevity strategies. In order to be efficient on the long-term, the anti-aging interventions may need to target the different causes of aging (reserve depletion, damage accumulation, and slowdown) simultaneously, to avoid undesirable trade-offs.

DEMONSTRATION OF AGE-RELATED INCREASE IN BLOOD-BRAIN BARRIER PERMEABILITY BY LONGITUDINAL INTRAVITAL MICROSCOPY

Adam Nyul Toth,[1] Stefano Tarantini,[1] Jordan DelFavero,[1] Feng Yan,[2] Priya Balasubramanian,[1] Qinggong Tang,[2] Anna Csiszar,[1] and Zoltan Ungvari,[1] *1. University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, United States, 2. University of Oklahoma, Norman, Oklahoma, United States*

Age-related blood-brain barrier disruption and cerebromicrovascular rarefaction contribute importantly to the pathogenesis of both vascular cognitive impairment and dementia (VCID) and Alzheimer's disease (AD). Recent advances in geroscience research enable development of novel interventions to reverse age-related alterations of the cerebral microcirculation for prevention of VCID and AD. To facilitate this research there is an urgent need for sensitive and easy-to-adapt imaging methods, which enable longitudinal assessment of changes in BBB permeability and brain capillarization in aged mice, that could be used in vivo to evaluate treatment efficiency. To enable longitudinal assessment of changes in BBB permeability in aged mice equipped with a chronic cranial window, we adapted and optimized two different intravital two-photon imaging approaches. By assessing relative fluorescence changes over the baseline within a volume of brain tissue, after qualitative image subtraction of the brain microvasculature, we confirmed that in 24 month old C57BL/6J mice cumulative permeability of the microvessels to fluorescent tracers of different molecular weights (0.3 kDa to 40 kDa) is significantly increased as compared to that of 5 month old mice. Real-time recording of vessel cross-sections showed that apparent solute permeability of single microvessels is significantly increased in aged mice vs. young mice. Cortical capillary density, assessed both by intravital two-photon microscopy and optical coherence tomography (OCT) was also decreased in aged mice vs. young mice. The presented methods have been optimized for longitudinal (over the period of 36 weeks) in vivo assessment of cerebromicrovascular health in preclinical geroscience research.

DIFFERENTIALLY METHYLATED GENES IN MUSCLE ASSOCIATED WITH GAIT SPEED IN A NON-HUMAN PRIMATE MODEL OF AGING

Ellen Quillen, Brett Frye, Bethany Wildeman, Maggie Stainback, Thomas Register, and Carol Shively, *Wake Forest School of Medicine, Winston Salem, North Carolina, United States*

Age-related changes in DNA methylation are potent regulators of gene expression and may in part explain the onset of disease and disability. Vervet monkeys are a well-described model of neurocognitive and physical aging. Like humans, gait speed declines with age in vervets, and variability in gait speed in older animals is associated with age-related musculoskeletal and cognitive decline. To identify methylation patterns linked to aging-related physical decline, we investigated differentially methylated loci in vastus lateralis biopsies of 29 female vervets aged 8-28 years (~25-90 years in humans). We evaluated 107,490 loci on the Illumina Infinium Methylation EPIC Human Array that aligned with high fidelity to the vervet genome using the R package minfi and fit generalized linear mixed models to account for underlying genetic relatedness. We found 13 CpG methylation sites associated with 12 genes (CALCR, EBF4, GDNF, GMCL1, HAND1, HOXC10, IRX2, LBX2, MPPED2, SHISA6, SOX2, and WNT2) significantly differentially methylated with gait speed. Increased methylation was negatively associated with gait speed for all loci except GMCL1, reflecting the pattern of global hypermethylation of skeletal muscle tissue with age. Several of the associated genes are involved in development and differentiation including HOXC10 and LBX2, which regulates myoblast migration. CACNG8 regulates voltage-dependent calcium gated channels, and GDNF promotes motor neuron innervation of skeletal muscle. Most associations with muscle phenotypes are novel, but several have been linked to age-related bone diseases. We are currently evaluating the relationships of these differentially methylated loci with muscle mRNA expression and protein abundance.

EFFECT OF COMBINED STRESSORS ON C. ELEGANS LIFESPAN

Bradford Hull,[1] and George Sutphin,[2] *1. University of Arizona, Arizona, United States, 2. The University of Arizona, Tucson, Arizona, United States*

Cellular stress is a fundamental component of age-associated disease. Cells experience many forms of stress (oxidative, heavy metal, etc.), and as we age the burden of stress and resulting damage increases while our cells' ability to deal with the consequences becomes diminished due to dysregulation of cellular stress response pathways. By understanding how cells respond to stress we aim to slow age-associated deterioration and develop treatment targets for age-associated disease. The majority of past work has focused on understanding responses to individual stressors. In contrast, how pathology and stress responses differ in the