presence of multiple stressors is relatively unknown; we investigate that here. We cultured worms on agar plates with different combinations of arsenic, copper, and DTT (which create oxidative/proteotoxic, heavy metal, and endoplasmic reticulum (ER) stress, respectively) at doses that result in 20% lifespan reduction individually and measured the effect on lifespan. We found that arsenic/copper and arsenic/DTT combinations created additive lifespan reductions while the copper/DTT combination created an antagonistic lifespan reduction when compared to controls ($p<0.05$). This antagonistic toxicity suggests an interaction either between the mechanisms of toxicity or the cellular response to copper and DTT. We are now evaluating the impact of copper and DTT individually and in combination on unfolded protein and heavy metal response pathways to understand the underlying mechanism of the interaction. Additionally, we are continuing to screen stressors to identify combinations that cause non-additive (synergistic or antagonistic) toxicity to build a comprehensive model of the genetic stress response network in C. elegans.

EFFECTS OF FOXO3 ON MARKERS OF AGING IN BLOOD : AN OKINAWAN LONGEVITY COHORT STUDY

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FOXO3 is among only a few genes that demonstrate a consistently reproducible genetic association with human longevity. We previously demonstrated, in a cross-sectional study of Okinawan Japanese, that the principal longevity variant of FOXO3 (rs 2802292 "G allele") protects against age-associated attrition of telomere length. We now expand upon this initial observation in a more detailed cross-sectional analysis of the effect of FOXO3 on telomerase activity, FOXO3 expression and inflammatory cytokine levels in both men and women. In agreement with our initial study, we found the FOXO3 longevity variant conferred significant protection against telomere shortening to roughly the same degree in elderly (ages 55 and older) men and women. Carriers of the G - allele also had slightly higher levels of blood telomerase activity in young (ages 20 – 54) and elderly participants ($P\leq0.1$). The expression (mRNA) of FOXO3 increased steadily with age in young and old G – allele carriers (borderline $P\leq0.08$), in contrast to a lack of association with age in non-carriers. The FOXO3 G - allele was also observed to significantly impact levels of both interleukin 6 (IL 6) and IL10, but in a sex dependent manner ($P<0.05$). These sex-specific effects may point to different mechanisms by which FOXO3 exerts its effect on longevity in men and women.

EPIGENETIC SIGNATURE OF CHILDHOOD ADVERSITY IN OLDER ADULTS

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Past research has shown that childhood adversity (CA) affects the health of older adults; however, the biological mechanisms underlying this association are unclear. Though past research has implicated DNA methylation (DNAm), studies utilizing representative data from older adults and reliable DNAm measures are needed to answer key questions about how stable DNAm changes associated with CA are in later life. Methylation risk scores (MRSs) are an emerging tool that can be used as biomarkers of exposure and as a dimension reduction approach for mediation analyses. This study clarifies the association between CA and later life health by generating MRSs for childhood adversity based on an epigenome wide association study conducted in an independent sample and validating that measure in a nationally representative sample of older adults living in the US from the Health and Retirement Study (HRS), including 2016 methylation data from the HRS Innovative Subsample of the Venous Blood Study. For these 4,018 respondents, DNAm was assessed in whole blood using the Illumina Infinium Human Methylation EPIC BeadChip microarray. Results indicate that retrospective report of childhood SES is significantly associated with an MRS for CA after controlling for demographic factors (viz., race and ethnicity, age, gender, smoking status, and BMI), suggesting that DNAm signal from CA persists across the life course into older adulthood. This study helps clarify the biological processes underlying the association between CA and adult health.

EPIGENETIC TRAJECTORIES OF AGING AND REPROGRAMMING

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The epigenetic landscape is remodeled with age, bringing about widespread consequences for cell function. With the revolutionary discoveries by Yamanaka and Takahashi, as well as those that built on this work, the transcription factors Oct4, Sox2, KLF4, and C-Myc (OSKM) can be expressed in a variety of cells, including fibroblasts, to make iPSCs. Once cells are reprogrammed, they show an erasure of epigenetic remodeling, suggesting an avenue to reverse aging. It has been recently shown that ectopic expression of three factors, OSK, can restore vision in mouse glaucoma model and reduces epigenetic age. It is not known the path epigenetic remodeling takes or whether all three factors, OSK, are required to remodel the epigenetic landscape. We hypothesize that during reprogramming, cells will reverse along a similar path they took during aging and eventually reverse along that path they took during differentiation. Alternatively, it may also be possible that cells take entirely new paths to reach a state of partial reprogramming or pluripotency. We used DNA methylation and RNA-seq as a multi-omics approach to map the trajectories cells make during aging, differentiation, and reprogramming. In human fibroblasts and hepatocytes, we tested the three-factor OSK mix, as well as pairwise factors OS, OK, and SK and individual Oct4, Sox2, and KLF4 for their effect on cell trajectories. This study provides a dynamic model for epigenetic changes in aging, differentiation, and reprogramming and highlights barriers and bottlenecks throughout the process.