

Retirement Study (HRS) to determine if any of the DNAm subcomponents were driving observed associations. A representative subsample of individuals who participated in the HRS 2016 Venus Blood Study were included in this analysis (N=3430). DNAm was measured with the Infinium Methylation EPIC BeadChip. Deaths that occurred between 2016 and 2018 contributed to 2-year mortality estimates (N=159, 4.5% of the sample). Weighted logistic regression estimated the association first between GrimAge and 2-year mortality and second between the DNAm subcomponents and 2-year mortality. All models were adjusted for age, sex, race/ethnicity, education, current smoking status, smoking pack years and cell composition of the biological sample. The average GrimAge for participants with and without 2-year mortality was 77 years 68 years respectively. A one-year increase in GrimAge was associated with 17% higher odds of 2-year mortality (95% CI: 1.16, 1.17). Two of the seven DNAm blood protein subcomponents of GrimAge (TIMP metalloproteinase inhibitor 1, adrenomedullin) and DNAm smoking pack years were associated with 2-year mortality and DNAm smoking pack years appeared to drive the overall GrimAge association with 2-year mortality. GrimAge was a better predictor of 2-year mortality than the DNAm subcomponents individually.

GLOBAL PHOSPHOPROTEOMIC PROFILING OF SKELETAL MUSCLE IN OVARIAN HORMONE-DEFICIENT FEMALE MICE

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Dynapenia, the age-related loss of skeletal muscle strength without the loss of muscle mass, significantly impacts the activities and quality of life of the aging population. Studies have shown that dynapenia occurs earlier in females than males in both human and rodent studies. Moreover, in females, estrogen deficiency has been shown to contribute to the loss of skeletal muscle strength as well as blunted recovery of strength after injury. The maintenance of skeletal muscle contractile function is vital to the overall health of women, especially as women live 1/3 of their life in an estrogen deficient state. Reversible protein phosphorylation is an indispensable post-translational modification, playing a key role in signal transduction pathways. Phosphorylation of skeletal muscle proteins have been shown to regulate sarcomeric function, excitation-contraction coupling, energy metabolism, and fiber-type composition. To define the physiological changes in the skeletal muscle phosphoproteome associated with estrogen deficiency, we used an ovariectomy model coupled with mass spectrometry. We identified, in total, 5,424 unique phosphorylation sites and 1,177 phosphoproteins in the tibialis anterior muscle. Ingenuity Pathway Analysis show decreased phosphorylation of contractile proteins and significant predicted inhibition of the upstream kinase, CDK6 (z-score -2.0) in ovariectomized compared to control muscles. Our results suggest that estrogen deficiency remodels the skeletal muscle phosphoproteome which may alter phosphorylation signaling that might contribute to the loss of strength in females.

IN SILICO IDENTIFICATION OF ANTI-AGING PHARMACEUTICS FROM COMMUNITY KNOWLEDGE

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In this era of Big Data, the volume of biological data is growing exponentially. Systematic profiling and analysis of these data will provide a new insight into biology and human health. Among diverse types of biological data, gene expression data closely mirror both the static phenotypes and the dynamic changes in biological systems. Drug-to-drug or drug-to-disease comparison of gene expression signature allows repurposing/repositioning of existing pharmaceuticals to treat additional diseases that, in turn, provides a rapid and cost-effective approach for drug discovery. Thanks to technological advances, gene expression profiling by mRNA-seq became a routine tool to address all aspects of the problem in modern biological research. Here, we present how drug repositioning using published mRNA-seq data can provide unbiased and applicable pharmaco-chemical intervention strategies to human diseases and aging. In specifics, we profiled over a half-million gene expression profiling data generated from various contexts, and using this, we screened conditions that can suppress age-associated gene expression changes. As a result, our analysis identified various previously validated aging intervention strategies as positive hits. Furthermore, our analysis also predicted a novel group of chemicals that has not been studied from an aging context, and this indeed significantly extended the life span in model animals. Taken together, our data demonstrate that our community knowledge-guided in silico drug-discovery pipeline provides a useful and effective tool to identify the novel aging intervention strategy.

INTERPRETABLE MACHINE LEARNING OF HIGH-DIMENSIONAL AGING HEALTH TRAJECTORIES

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We have built a computational model of individual aging trajectories of health and survival, that contains physical, functional, and biological variables, and is conditioned on demographic, lifestyle, and medical background information. We combine techniques of modern machine learning with an interpretable network approach, where health variables are coupled by an explicit interaction network within a stochastic dynamical system. Our model is scalable to large longitudinal data sets, is predictive of individual high-dimensional health trajectories and survival from baseline health states, and infers an interpretable network of directed interactions between the health variables. The network identifies plausible physiological connections between health variables and clusters of strongly connected health variables. We use English Longitudinal Study of Aging (ELSA) data to train our model and show that it performs better than traditional linear models for health outcomes and survival. Our model can also be used to generate synthetic individuals that age realistically, to impute missing data, and to simulate future aging outcomes given an arbitrary initial health state.