in blood samples of 452 MZ twins (56-80 years of age). Unsupervised IEA were conducted by the KeyPathwayMiner algorithm, while supervised IEA were performed by the KEGG and Reactome databases. No individual CpG site or probe passed correction for multiple testing. Investigating the overlap in genes with p-values<0.01, 0.005 or 0.001 in the EWAS and TWAS, revealed 67, 21 and 2 unique genes, respectively. The latter 2 were TESK2 and VWA1. By the supervised approach, the 67-gene overlap identified three pathways related to "antigen processing and presentation", driven by HLA-A, HLA-B, TAP2 and PSME2. With the unsupervised approach the 21-gene and 67-gene overlaps revealed networks containing 7 and 19 genes, respectively. Exception nodes (added by the algorithm for structure) were CREBBP and CSNK2A2 for the former, and APP and HSP90AB1 for the latter. The remaining IEA revealed no gene sets or networks. Several of these genes have previously been linked to HS relevant traits, e.g. arthritis (HLA-A, HLA-B and TAP2), smooth muscle and cardiovascular function (TESK2, HLA-B and APP) and sarcopenia (HSP90AB1). Hence, this study reports genes and pathways previously reported for physical functioning, yet also novel candidates for further verification.

A PANEL OF DNA METHYLATION AND PROTEOMIC BIOMARKERS FOR SPECIFIC AGING PATHWAYS

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Most aging biomarkers such as DNA methylation and proteomic clocks have focused on measuring overall "biological age," a single number that predicts age-related morbidity and mortality better than absolute chronological age. While intuitive and interpretable, this single biological age number does not account for the possibility that different individuals may preferentially experience aging in different molecular and cellular pathways, and therefore does not suggest personalized aging interventions. We reasoned that a panel of biomarkers each capturing specific aging pathways, such as mitochondrial dysfunction or cellular senescence, may capture the heterogeneity of aging better than existing composite measures. To address this, we employed weighted gene co-expression network analysis to cluster tissue-specific transcriptomes and the serum proteome into specific modules with distinct biological functions and characterized how these modules change with age. We trained DNA methylation proxies of these functional modules that we then applied to independent validation data to identify associations with age-related morbidity and mortality. Clustering analysis using the DNA methylation biomarkers showed that different individuals show distinct patterns of aging. These pathway-specific biomarkers will elucidate how different aging mechanisms interact with each other to produce the larger phenomenon of aging, and for evaluating novel therapeutics targeting specific hallmarks of aging.

AGE-DEPENDENT CHANGES IN NUCLEAR MECHANOTRANSDUCTION AS A DRIVER OF SARCOPENIA

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Informed by evidence that dysregulated nuclear dynamics and nuclear transport may contribute to atrophy in diseased skeletal muscle, the purpose of this study was to assess nuclear deformability, permeability, transport, and mechano-signaling outputs (YAP/TAZ, a marker of mechano-responsiveness, and their downstream genes) in aging skeletal muscle. We hypothesized that aging muscle would show changes in: proteins within LINC (linker of the nucleus to the cytoskeleton) complex, lamina and nuclear pore complex (NPC), and mechano-signaling outputs, with consequent decreased nuclear deformability and increased permeability. We further expected an increase in nuclear strain would increase nuclear YAP/TAZ and downstream indicators of YAP activity (Ankrd1, Cyr61). We used young, adult and aged C57BL6 mice (~4, 14, and 26 months, respectively). Nuclei were less deformable to passive mechanical stretch ex-vivo in adult muscle fibers compared to young muscle fibers. LINC protein gene expression, YAP/TAZ protein, and expression of their downstream genes were significantly increased in adult muscles compared to young muscles. YAP/TAZ protein and their downstream genes were further increased in aged muscles, indicating hyperactivation of YAP/TAZ in aging muscle. Changes with aging in the lamina and NPC included a loss of lamin β1, Nup107 and POM 121, which could underlie the increased nuclear permeability we found in nuclei of aged muscle. In summary, these data highlight a possible role for LINC, lamina and NPC in changes of aging-related nuclear dynamics and mechano-sensing, and may represent therapeutic targets for sarcopenia. Future studies will examine how altering these components affects muscle function during aging.

AGE-RELATED INCREASED ONSET AND PROGRESSION OF PROSTATE CANCER IS REVEALED IN NOVEL PTEN-NULL MOUSE MODELS

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Prostate cancer (PCa) is associated with advanced age. To better understand how age impacts PCa, it is critical to use PCa animal models generated at different ages (aged vs. non-aged). The PB-Cre4 driven phosphatase and tensin homolog (Pten) conditional knockout mouse model, which closely imitates human PCa initiation and progression. However, the Pten deletion is triggered in a 2-week-old prostate, when comparing the extent of PCa between aged and non-aged mice, it is difficult to distinguish the extent to which the onset and progression of PCa are due to the acceleration of the normal aging process or due to the manifestation of PCa pathologies over time. We present here a protocol to inject Cre-expressing adenovirus with luciferin tag intraductally