attributed to non-telomeric Rap1. To test this, we generated a Rap1 mutant knock-in (KI) mouse model using CRISPR/Cas9 editing, in which Rap1 at telomeres is prevented, leaving only non-telomeric Rap1. Cell fractionation/western blotting of primary fibroblasts from Rap1 KI mice demonstrated decreased Rap1 expression and Rap1 re-localization off telomeres, with an altered cellular distribution. This same difference in Rap1 is also observed in human cells with telomere erosion, indicating that aberrant Rap1 in our model may recapitulate Rap1 in aging and human telomere biology disorders. Compared to wild-type control mice, Rap1 KI mice exhibited increased body weight, altered cytokine levels, behavioral deficits, and decreased lifespan. In conclusion, our results reveal a novel mechanism by which telomere shortening may contribute to age-related pathologies by disrupting Rap1 expression and cell localization.

APOLIPOPROTEIN E IMPAIRS AGED BONE FRACTURE HEALING

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Bone fracture healing and osteoblast differentiation are impaired with advanced age. Using a combination of parabiosis and proteomic models, we identified apolipoprotein E (ApoE) to be an aging factor in bone regeneration. Circulating levels of ApoE increased with age in patients and in mice. ApoE impaired bone fracture healing by decreasing bone deposition in the fracture callus which subsequently decreased the mechanical strength of healed tissue. Osteoblasts serve as the sole bone forming cells within the body. In tissue culture models, ApoE treatment decreased osteoblast differentiation and activity which led to decreased matrix formation and mineralization. This inhibition of osteoblast differentiation relied on down-regulation of the Wnt/β-catenin pathway. In mouse models, aged bone repair was rejuvenated when we lowered circulating ApoE levels using a hepatotropic AAV-siRNA model – serving as a proof of concept that ApoE can be targeted to improve bone repair in an older population. While promising, knockdown of circulating ApoE in such a fashion is likely not translatable to patient care. Thus, current work in our laboratory is focused on developing treatment strategies that temporally decrease circulating ApoE levels and consequently improve bone healing after acute injury and/or surgical orthopedic procedure in the geriatric population.

BDNF SNP C270T MODIFIES THE ASSOCIATION BETWEEN HISTORY OF HEAD INJURY AND COGNITIVE STATUS IN OLDER ADULTS

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Brain derived neurotrophic factor (BDNF), is a neurotrophin involved in neurogenesis and neuroplasticity. Several BDNF genes have been associated with cognitive function. Studies suggest head injury (HI) alters BDNF levels, and activities enhancing BDNF signaling promote better cognitive outcomes. We investigated the relationship between HI and BDNF single-nucleotide polymorphisms (SNPs) in predicting cognitive performance in a population-based sample of older adults. 4165 participants (56.7% female), dementia-free at baseline, were assessed triennially [follow-up years: mean (SD) = 5.85 (4.20), median = 7.33, maximum = 11.39]. Mean (SD) age was 75.36 (6.84). Cognition was assessed using the Modified Mini-Mental State Exam (3MS) and HI history from self-report. We examined interactions between BDNF SNPs [rs56164415 (BDNF C270T), rs6265 (Val66Met), rs2289656 (BDNF receptor trkB), and rs2072446 (NGF/BDNF receptor p75)] and history of HI (none, one, or multiple) in predicting cognitive decline. Covariates included age, education, sex, and apolipoprotein (APOE) E4 allele presence. Linear mixed-effect models indicated BDNF C270T significantly modified the association between HI and cognitive status ($p < .006$). Specifically, minor T allele carriers with single or multiple HI scored on average 2.08 and 3.21 points lower on the 3MS, respectively, than non-T carriers with no HI. Unexpectedly, there was a trend for APOE4*HI ($p = .078$) in that APOE E4 carriers with multiple HI scored higher than those lacking APOE E4 and HI. In this population-based sample, rs56164415 predicted cognitive outcomes that varied by history of HI. Factors influencing BDNF signaling may provide a potential avenue for intervention in recovery from HI.

BIOLOGICAL AGING, MORTALITY, AND ALZHEIMER'S DISEASE RELATED BIOMARKERS FROM MIDLIFE TO OLD AGE

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People age at different rates and in different biological systems that may differentially contribute to accelerated decline. Better understanding of biological aging may contribute to identification of better targets for intervention. In 1005 VETSA participants we created 3 indicators of biological age: physiological age (PA), frailty, and brain age. PA included hemoglobin, glucose, lipids, height, weight, waist, systolic and diastolic blood pressure, and age. PA was calculated using the Klemera and Doubal (2006) method. The frailty index summed 37 health deficits (Jiang et al. 2017). A machine learning algorithm was used to estimate brain age across cortical and subcortical regions (Liem et al, 2017); predicted brain age subtracted from chronological age comprised the predicted brain age difference score (PBAD). Frailty and PBAD were calculated at waves 1, 2 and 3 when participants were average age 56, 62, and 68, respectively. PA markers were only available at waves 2 and 3. Outcome measures included mortality by wave 3 and scores on AD-related plasma biomarkers—Neurofilament light (NFL), Tau, and AB40 and AB42 at wave 3. Frailty at wave 1 and 2 predicted mortality. Frailty at wave 1 was significantly associated with wave 3 NFL, AB42 and AB40. Wave 2 & 3 frailty was associated with all biomarkers. Neither PA nor PBAD predicted biomarkers or mortality. The results are striking given the relatively young age of the sample. Even as early as one's 50s, frailty in a community-dwelling sample predicted accelerated decline and mortality when the outcome age was only 66-73.