CORRELATION BETWEEN FRAILTY AND DNA DAMAGE IN HEMATOPOIETIC STEM CELLS: A PILOT STUDY

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Frailty is an age-related syndrome characterized by a progressive impairment of multiple physiological systems and leading to poor clinical and functional outcomes. Our aim was to explore the DNA damage, as an effect of increased oxidative stress related to frailty, on peripheral blood mononuclear cells (PBMC) and circulating hematopoietic stem cells (cHSC). According to Fried's operating definition of frailty, we enrolled three groups of subjects: frail seniors (age >65 years, n=19), fit seniors (>65 years, n= 16) and young controls (age 25-35 years, n=19). We carried out a comprehensive assessment and obtained 3 vials of whole blood for cells and plasma separation. We separated PBMC by Ficoll-Paque and stained with specific conjugated antibodies leucocyte lineage and HSC. We evaluated DNA damage by FACS detection of γ-H2AX in the total PBMC and cHSC subpopulation. We observed an increased percentage of cells, although not significant, with DNA damage in PBMC from frail seniors (0.70%) compared to fit seniors (0.37%) and young controls (0.13%). The percentage of cells with DNA damage in cHSC of frail seniors (2.97%) was higher compared to fit seniors (1.66%, not significant) and young controls (0.46%, statistically significant). Moreover, cHSC present the statistically higher amount of DNA damage, measured as fluorescence intensity, compared to fit seniors and young controls. cHSC from frail seniors show the highest total DNA damage, compared to fit seniors and young controls. This is probably linked to an increase of oxidative stress related to frailty, which we are going to analyze in the near future.

SUPPRESSION OF GHRELIN SIGNALING EXACERBATES ULCERATIVE COLITIS IN OLDER MICE

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The aging process is characterized by increased chronic low-grade inflammation, aka inflamm-aging, which offend is accompanied by 'leaky gut' syndrome. Inflamm-aging is a highly significant risk factor for both morbidity and mortality in the older adult population (>65 years of age). In addition, there is a growing prevalence of inflammatory bowel disease (IBD), a chronic inflammatory condition of the gastrointestinal tract in the older adult population. The pathogenesis of late-onset IBD is suggested to be more complex compared with younger IBD patients; the causes determining the age of IBD onset remain unexplained. Ghrelin is a 28-amino-acid peptide hormone mainly produced by X/A-like cells of the stomach, with well-characterized functions in growth hormone secretion, food intake, adiposity and insulin resistance. Ghrelin's biological relevant receptor is Growth Hormone Secretagogue Receptor (GHS-R). Ghrelin and ghrelin mimetics have been considered viable candidates for treating cachexia, sarcopenia, and gastrointestinal disorders. As expected, we observed that the expression of tight junction proteins in colon mucosal layer decreases with age. When challenged with dextran sulfate sodium (DSS) to induce experimental ulcerative colitis, 18-months old male C57BL/6 mice exhibited exacerbated disease activity scores compared to young male mice (5-months), showing worsened pathology such as rectal bleeding and difficulty in defecation. DSS-induced colitis was exacerbated in both ghrelin-deficient (Ghrl-/-) and ghrelin receptor-deficient (Ghsr-/-) mice. Together, these data suggest endogenous ghrelin signaling contributes to susceptibility to colitis, and ghrelin signaling pathway may present a novel target for prevention and treatment of leaky gut syndrome in aging.

GENOME-WIDE META-ANALYSIS SUPPORTS HETEROGENEITY IN POLYGENIC ARCHITECTURE OF DISABILITY

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Disability and frailty increase steeply with age after midlife. They comprise broad, non-specific aging-related health/well-being declines. Understanding the molecular mechanisms of these declines could help in combating processes related to intrinsic aging. We performed genome-wide meta-analysis of disability using data on N=12,550 disabled individuals of Caucasian ancestry from five independent studies with N=24,068 genotyped participants. Disability was measured using the Activities of Daily Living (ADL) scale. A subject was considered disabled if he/she had at least one ADL impairment. All subjects in our study were aged 50+ years. The analysis followed a discovery-replication strategy using two studies as discovery samples and three others as replication samples. At the discovery stage, we selected SNPs at nominal significance ($p<0.05$) and evaluated their associations with disability in the replication samples. Meta-analysis across all studies identified 30 SNPs (24 loci) at $p<10e-4$. SNPs from four loci (chromosomes 2, 8, and 12) attained suggestive significances at $p<10-5$. We constructed two polygenic risk scores (PGRS) using these 30 SNPs whose minor alleles were positively (19 SNPs) and negatively (11 SNPs) associated with disability, PGRS_p and PGRS_n, respectively. Meta-analysis across all studies identified strong effects for PGRS_p (beta=0.436, $p=1.18\times10e-32$) and PGRS_n (beta=-0.426, $p=8.74\times10e-19$). The associations for the PGRSs observed in two discovery studies were replicated in three independent studies. The lack of genome-wide significant effects of individual SNPs combined with the highly significant effects of the PGRSs shows that, in line with the heterogeneous origin of disability, its genetic architecture is of highly heterogeneous polygenic origin.

WHOLE-BODY MRI TO ASSESS SUBCLINICAL CARDIOVASCULAR DISEASE AND FRAILTY DEVELOPMENT

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