events, including whole chromosome events, were detected in 180 out of the 338 individuals. A total of 165 duplications, 97 deletions, and 9 copy-number neutral loss of heterozygosity were detected. Additionally, there were 42 events whose copy number state could not be determined with high confidence. 236 events out of the 313 were detected in individuals aged 100 and older. Our analysis of chromosomal alteration frequency by age indicates that, within centenarians, the proportion of individuals with mCAs significantly decreases with increased age ($p < 0.05$, correlation -0.73).

INCREASED BETA2-ADRENERGIC RECEPTOR SIGNALING ENHANCES PROGRESSION OF HEPATOCELLULAR CARCINOMA

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We investigated whether increased signaling by beta2-adrenergic receptors (β2-ARs), which mediate the action of catecholamines, enhances the progression of hepatocellular carcinoma (HCC). Mean age of patients with HCC, the most prolific form of liver cancer, has progressively increased over the last decade. Beta2-AR-mediated signaling in liver increases with age. We also observed increased β2-AR levels in liver tissues of patients with HCC compared to control subjects. We, therefore, hypothesized that increased β2-AR signaling enhances HCC progression while inhibition of β2-AR signaling by treatment with beta blockers suppresses its progression. To test this hypothesis, we used N-nitrosodiethylamine (DEN) to induce HCC in liver-specific β2-AR knockout (LKO) and control mice in the absence or presence of beta blocker propranolol. At the end of 25 weeks, we observed increased numbers of visible tumors, disarray of liver architecture, and mortality in DEN-induced control mice which was reduced by propranolol treatment. We also observed that DEN-treated LKO mice demonstrated reduced mortality, disarray of architecture, and phosphorylation of oncogene Src compared to DEN-treated control mice. Taken together, these results indicate that decreased β2-AR signaling because of a lack of receptors in the liver or inhibition of receptor action with propranolol reduces HCC progression. Studies are in progress to determine the β2-AR-mediated mechanisms involved in HCC progression. Our studies suggest that beta blocker propranolol, used to treat cardiovascular diseases, may be repurposed as a potential therapeutic option for treatment of HCC.

LEFT VENTRICULAR REMODELING PROCEEDS FROM YOUNG ADULTHOOD INTO MIDLIFE IN INTRAUTERINE GROWTH RESTRICTION BABOONS

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Previous cross-sectional studies have shown young adult baboons (~5-6 y.o.), subjected to intrauterine growth restriction (IUGR) by maternal calorie restriction during pregnancy and lactation, exhibit ventricular remodeling with mildly impaired heart function relative to age/sex-matched controls (CTL). METHODS: In this longitudinal study cardiac MRI was performed on male IUGR baboons (n=7). A 3 Tesla, Siemens TIM Trio MRI system was used with phase-array coils with parallel imaging acquisition and breath-holding during the scan. Studies of IUGR animals occurred at 4.7 + 0.1 yr. intervals; the first scan (scan1) at 5.8 + 1.2 y (human equivalent - HE ~24 years) and the second (scan2) at 10.4 + 1.2 yr (HE~40 y). Scans on the CTL animals (N=4) occurred at 5.3 + 1.4 years and 10 + 1.4 years. RESULTS: Change in body weight over 4.7 years was less in the IUGR group (Δwt=6.3 + 6.1 kg) than in the control group (Δwt =11.5 + 8.2 kg). Left ventricular (LV) ejection fraction (EF) was significantly greater in IUGR animals for scan2 (+10.7%, p=0.03) but not in normal controls (+1.8%, p=0.75). Stroke volume and end-diastolic LV volume were normalized to body surface area (BSA). SV/BSA (17.6 + 4.9, 31.5 + 12.3 mL/sq.m; p=0.016) and EDV/BSA (47.3 + 13.6, 64.5 + 18.8 mL/sq.m; p=0.045) were also significantly increased in IUGR animals but not controls. In IUGR subjects, Δweight was significantly and positively correlated with ΔEF (r=0.86, p=0.01). CONCLUSIONS: In IUGR, but not in CTL baboons, cardiac function adaptations continue into midlife and are related to increases in body weight with aging. We conclude that IUGR programs cardiovascular function and that programmed changes continue into midlife.

AGING INDUCES NLRP3 INFLAMMASOME DEPENDENT ADIPOSE B CELL EXPANSION TO IMPAIR METABOLIC HOMEOSTASIS

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Visceral adiposity in elderly is associated with alterations in adipose tissue immune cells leading to inflammation and metabolic dysfunction. The Nlrp3 inflammasome is a critical regulator of macrophage activation, inflammation, and immunometabolism in visceral adipose tissue during aging; however, the potential contribution of adipose tissue B cells is unexplored. Here, we show that aging expands adipose-resident B cells and fat-associated lymphoid clusters (FALCs) in visceral white adipose tissue of female mice. Adipose tissue B cells exhibit a memory-like B cell profile similar to the phenotype of aged B cells that are increased in spleen of old mice. Mechanistically, the age-induced FALC formation and adipose B cell expansion, but not B cell transcriptional program, is dependent on the Nlrp3 inflammasome. Furthermore, B cell depletion in aged mice improves insulin sensitivity and metabolic capacity of adipose tissue. These data reveal that inhibiting Nlrp3-dependent B cell accumulation can be targeted to reverse metabolic impairment in aging adipose tissue.

METABOLIC CONSEQUENCES OF METHIONINE REDOX IN METHIONINE RESTRICTION

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