Hepatocellular senescence and mitochondrial dysfunction in the GAN diet-induced obese mouse model of NASH

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Background & Aim

The prevalence of obesity-associated non-alcoholic steatohepatitis (NASH) with development of advanced hepatic fibrosis and hepatocellular carcinoma (HCC) increases with age. This study aimed to characterize key markers of hepatocellular senescence and mitochondrial respiratory capacity in relation to disease progression in the GAN (Gubra-Amylin NASH) diet-induced obese (DIO) mouse model of NASH.

Study outline

Increased markers of hepatocellular senescence

Compromised hepatocellular mitochondrial respiratory capacity

Transcriptomic profile for hepatocellular senescence

Age and GAN diet-induced disease progression

CONCLUSION

- Aged DIO-NASH mice demonstrated clinical NAFLD Activity Score (≥4) after ≥28 weeks on GAN diet.
- Aged DIO-NASH mice progressed to bridging fibrosis (stage F3) after ≥48 weeks on GAN diet.
- Aged DIO-NASH mice developed tumors including HCC after ≥58 weeks on GAN diet.
- Aged DIO-NASH mice demonstrated increased histological markers of hepatocellular senescence.
- Aged DIO-NASH mice demonstrated compromised hepatocellular mitochondrial respiratory capacity.
- Aged DIO-NASH mice demonstrated hepatic senescence-associated gene expression signatures.
- The aged GAN DIO-NASH mice display features of accelerated hepatocellular senescence including impaired mitochondrial respiration, highlighting the utility of this model for profiling and targeting novel senescence-associated drug therapies.