HCC

#P08 - Endothelial autophagy deficiency promotes liver carcinogenesis-related to MASLD

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Background & Aims

Hepatocellular carcinoma (HCC) development is a multistep process of cancerogenesis involving various cell types including liver endothelial cells (LSECs). Autophagy is a self-eating catabolic process involved in cell homeostasis and preventing liver injury in MASLD. While a dual role of hepatocytic autophagy has been demonstrated, the role of LSECs autophagy in HCC remains unknown. We evaluated the role of LSECs autophagy in MASLD/HCC.

Methods

LSECs autophagy during human MASLD/HCC was assessed on human primary LSECs by RNA-sequencing, qPCR and ELISA in non-tumoral LSECs (NT-LSECs) of patients without (n=10) or with MASLD (n=15), in NT-LSECs of patients with MASLD who developed (n=10) or not (n=5) HCC, and in NT-LSECs and tumoral LSECs (T-LSECs) from MASLD patients.
The effect of endothelial autophagy deficiency on liver carcinogenesis was assessed in endothelial autophagy deficient (Atg5lox/lox;VE-cadh-Cre+, n=10) and control (Atg5lox/lox, n= 5) mice receiving diethylnitrosamine, and monitored by MRI. Transcriptomic and proteomic profiles of the non-tumoral liver were studied.

Results

Gene analyses showed that autophagy was significantly downregulated in NT-LSECs of patients with MASLD compared to patients without MASLD and further reduced in MASLD-NT-LSECs of patients who developed HCC compared to MASLD-NT-LSECs from patients whitout HCC. Autophagy was upregulated in T-LSECs comparatively to NT-LSECs. These changes were confirmed by ELISA.
Liver tumors were detected earlier and were larger in Atg5lox/lox;VE-cadh-Cre+ than in Atg5lox/lox mice (23mm3 vs 2mm3, p=0.03). Comparative analyses of the NT liver showed that Atg5lox/lox;VE-cadh-Cre+ mice had altered total liver autophagy, apoptosis, DNA damages, and oxidative stress.

Conclusions

Defective endothelial autophagy promotes HCC development in MASLD.
Endothelial autophagy deficiency promotes HCC

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