and siRNA knockdown of XPO1 in HUH7 cells reduced activation of IKK2DS2. Vaccination of KIR-transgenic mice with a KIR2DS2-targeting DNA vaccine increased activation of NK cells in both spleens and livers as determined by KLRG1 expression (p < 0.01), and this was most marked on mature CD11b+CD27−KIR2DS2+ NK cells (p < 0.01). NK cells from vaccinated mice had peptide-specific NK cell responses in vitro, which were not observed in peptide control vaccinated mice. Adoptive transfer of NK cells from vaccinated mice led to impaired growth of HUH7 cells in NOD/SCID/γc KO mice, as compared to NK cells from mice vaccinated with a control vaccine. Conclusion: We describe the first known HLA class I restricted tumour associated antigen to be targeted specifically by NK cells. We also demonstrate proof-of-concept for an NK cell targeting peptide vaccination strategy for HCC.

FRI511
Myeloid IRE1α deletion alters hepatic macrophage phenotype and attenuates experimental non-alcoholic steatohepatitis-related hepatocellular carcinoma
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Background and Aims: Obesity, diabetes and associated non-alcoholic steatohepatitis (NASH) are characterized by adipose tissue and hepatic fat accumulation and inflammation and are rising causes of hepatocellular carcinoma (HCC). Macrophages are important immune cells involved in inflammation and tumour development. Inositol-requiring enzyme 1 alpha (IRE1α) has shown to be involved in macrophage cytokine production and myeloid-specific IRE1α knock-out (mKO) mice showed reduced weight gain during high fat diet feeding. However, the effect of myeloid-specific IRE1α deletion on NASH and subsequent HCC development has not been examined.

Method: Mice with non-functional myeloid IRE1α were created by crossing IRE1α floxed mice with LysM-Cre mice. Two-day old mKO and wild type (WT) mice were subcutaneously injected with streptozotocin (STZ) or PBS as control and male mice were fed a high-fat, -sucrose, -cholesterol diet (Western diet, WD) or control diet from the age of 4 weeks until 21 weeks. Mice were evaluated for obesity, diabetes, NASH and HCC. The macrophage population was evaluated by flow cytometry and RNA sequencing on FACS isolated cells.

Results: STZ+WD feeding resulted in impaired glucose tolerance, advanced NASH with fibrosis and HCC development. mKO STZ mice showed lower fasting glucose levels at the start of WD feeding, and an improved glucose tolerance and attenuated HCC development after 17 weeks of WD feeding despite a similar degree of liver steatosis and inflammation compared to WT mice. Transcriptomic analysis of liver Kupffer cells (KCs), macrophages and monocytes revealed phenotypic changes in NASH-HCC. Myeloid IRE1α deletion in healthy mice resulted in an altered transcriptomic profile with downregulation of pathways involved in immune system activation in KCS and macrophages, downregulation of metabolic pathways in KCS, whereas pathways involved in cell division and metabolism were upregulated in monocytes. Macrophages showed both up- and downregulated metabolic pathways. NASH-HCC attenuated the differential gene expression profile of mKO and WT liver isolated macrophages.

Conclusion: Our results show that myeloid-specific IRE1α deletion results in an altered transcriptional profile of hepatic macrophages and attenuates diabetes induction and NASH-related HCC development.

FRI512
TAK1 is a novel therapeutic target for hepatocellular carcinoma and contributes to sorafenib resistance
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Background and Aims: TAK1 has a dual role in cancer development and is associated with drug resistance in HCC. The upregulation and activation of TAK1 in intermediate and advanced HCC remains unclear. Mechanistically, little is known about K48-linked ubiquitination and proteasomal degradation of TAK1. This article aims to uncover the mechanism of TAK1 overexpression and its contribution to sorafenib resistance in HCC, and to verify whether targeting TAK1 pharmacologically could be a promising combinational therapy with sorafenib.