Characterization of epithelial membrane protein 1 in non-alcoholic steatohepatitis

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Background

✓**What is NASH?**

Non-alcoholic steatohepatitis (NASH), a severe form of **Non-alcoholic fatty liver disease (NAFLD)**, refers to **accumulation of fat in the liver** which isn't caused by alcohol intake abuse, leading to dysfunction of lipid homeostasis, inflammation and fibrosis which becomes a major cause of chronic liver disease that can progress to cirrhosis. However, until now the molecular pathology of NAFLD/NASH is not fully understood. Moreover, a lot of studies reported about increasing of NASH-related hepatocellular carcinoma (HCC) cases.

- 5th 6th 7th Most common cancer
- 3rd leading cause of cancer death 2020
- NAFLD/NASH is a fast-growing cause since 2019
- Fibrosis increase risk of discovering HCC

Complexity of the NAFLD/NASH

- Nonspecific/silent symptoms
- Absence of treatment
- Easily to be developed
- HCC progression risk

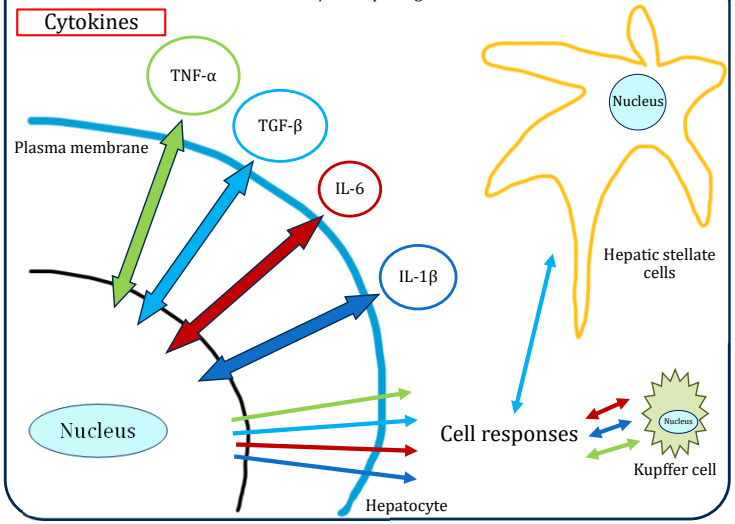
High risk of liver failure disease

✓**NAFLD/NASH and HCC statistics**

~0.6% NAFLD per year (global)
~0.3% NAFLD per year (Japan)
~0.71% NAFLD-related cirrhosis
~1.36% NASH-related HCC (2019-2021)

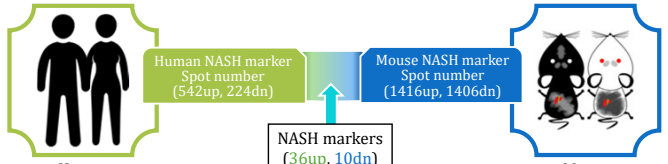
Purpose

Analysis interactions between cytokines and liver cells and uncover mechanism of NAFLD/NASH pathogenesis



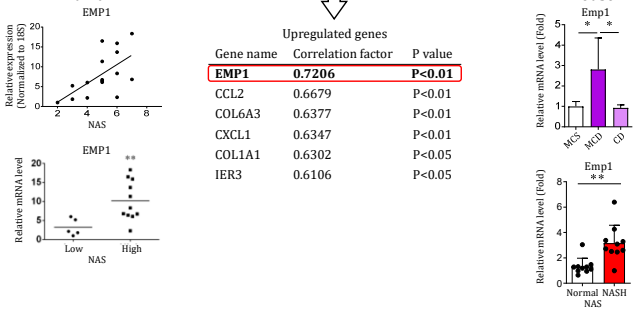
Result 1

Gene expression change analysis in human and mouse NASH models

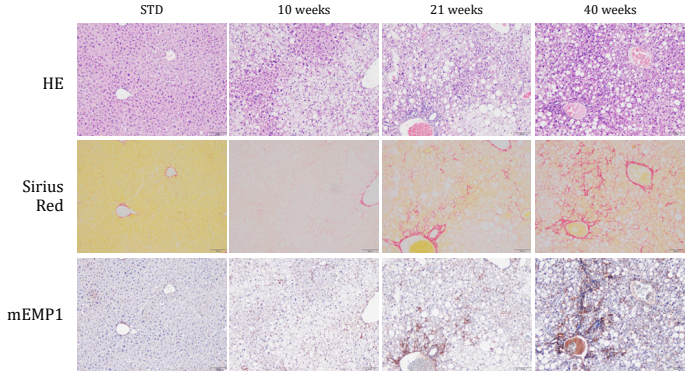


Upregulated genes

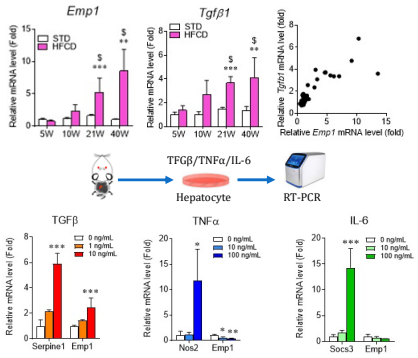
Gene name	Correlation factor	P value
EMP1	**0.7206**	**P<0.01**
CCL2	0.6679	P<0.01
COL6A3	0.6377	P<0.01
CXCL1	0.6347	P<0.01
COL1A1	0.6302	P<0.05
IER3	0.6106	P<0.05



EMP1 staining of high-fat cholesterol diet (HFCD)-fed mouse liver tissues

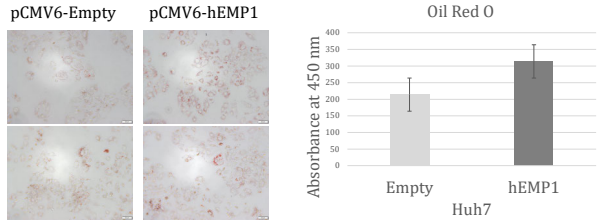


TGF-β expression regulates EMP1 expression level

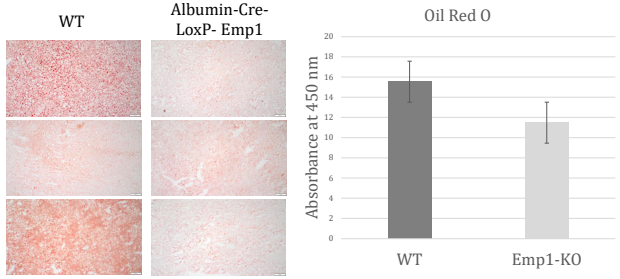


Result 2

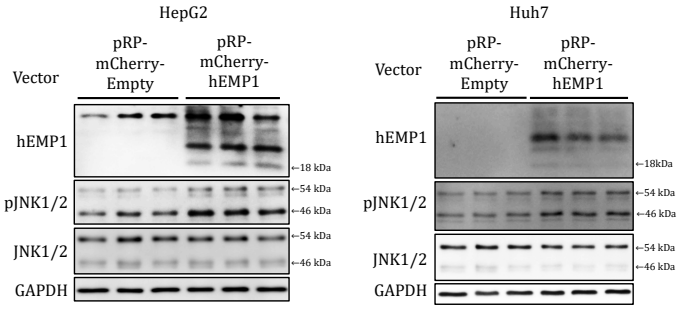
EMP1 enhances lipid droplet accumulation in HCC cells



Emp1-knockout reduces lipid droplet accumulation in mouse NASH models



EMP1 increases activation of JNK1/2 in HCC cells



Summary

- ✓ EMP1 gene is upregulated in human and mouse NASH models.
- ✓ Area of EMP1 expression at protein level was similar to fibrosis area.
- ✓ TGF-β regulated EMP1 expression in primary hepatocytes.
- ✓ EMP1 overexpression enhances lipid droplet accumulation in hepatocellular carcinoma cells *in vitro*.
- ✓ Hepatocyte-Emp1-knockout mice showed a reduction of lipid droplet deposition.
- ✓ EMP1 overexpression increased phosphorylation c-Jun N-terminal kinase in hepatocellular carcinoma cells.

Conclusion

➢ EMP1 is involved in the pivotal process(es) of human and mouse NASH progression, thus fully uncovering the role of EMP1 can provides a profound understanding of NASH pathology which is a potential target for NASH therapy development.