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CHKA AND MBOAT7 AS POTENTIAL TARGETS FOR MASLD-HCC WITH EARLY STAGE OF FIBROSIS: REVEALED BY METABOLOMICS AND TRANSCRIPTOMIC ANALYSIS

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Background

Metabolic dysfunction Associated Steatotic Liver Disease (MASLD) is recognized as a major health burden in developed countries. It can eventually progress to HCC and up to 30-50% of MASLD-HCC arise in the absence of severe liver fibrosis, posing a challenge for early detection and treatment (De A et al., 2020, J clin Exp Hepatol). We previously reported the existence of 2 phenotypes of MASLD-HCC by metabolomics analysis according to fibrosis level (F0F1 vs. F3F4) (Buchard et al., 2021, Metabolites, Buchard et al., 2021, AASLD Hepatology). The aim of our current study is to explore lipid pathways and identify potential biomarkers related to MASLD-HCC according to fibrosis level.

Materials & Methods

Our cohort includes 56 pairs of human hepatic tissues, tumoral (TT) and non-tumoral (NTT) (F0F1 = 28, F3F4 = 28), as well as 5 healthy liver tissues (CRB Liver). An untargeted metabolomic analysis approach by liquid chromatography-mass spectrometry (LC-MS) was performed. In parallel, an analysis by qRT-PCR focusing on the expression of 14 genes involved in the main pathways of lipid metabolism was studied (Table 1). For each group, the HCC was compared to both: its own NTT and also to healthy liver tissues.

Results

The results of metabolomic analysis by LC-MS:

- In total, 30 metabolites were identified in the lipid liver tissue extracts (Fig.1).
- In MASLD-HCC-F0F1, the level of Ceramide Cer(d18:1/22:0), Sphingomyelin SM(41:1) and Phosphatidylethanolamine PE(O-16:1_20:4) were down-regulated compared with NTT-F0F1. In contrast, the content of SM(35:1), SM(40:2) and SM(42:3) were increased, as well as Phosphatidylcholine PC(16:0_14:0), PC(16:0/16:0), PC(18:0_18:1), PC(40:8) and Lysophosphatidylcholine LPC(18:1) and Lysophosphatidylethanolamine LPE(18:1) were up-regulated.
- In MASLD-HCC-F3F4, 50% of the metabolite content decreased in tumor tissue compared with NTT-F3F4. However, LC-MS analysis indicated that PC(18:0_18:1) and PC(18:0_20:3) were increased as well as, Phosphatidylinositol PI(16:0_18:1), which is known as an onco-metabolite.

The results of transcriptomic analysis by qRT-PCR:

- Among the 14 genes studied, the RNA expression of 6 genes, respectively coding for CHKA, DGAT1, MBOAT7, SPTLC2, SMPD1 and SGMS1, were exclusively up-regulated in MASLD-TT-F0F1 compared to NTT-F0F1. This observation was confirmed when comparing these tumors with healthy liver tissues, except for SPTLC2, DGAT1 and SGMS1 (Table 1, Fig. 2).
- In contrast, concerning MASLD-HCC-F3F4, the RNA expression of the same 14 genes remained unchanged compared with their own NTT (Fig.3b). All together, the data confirmed the existence of two phenotypes of MASLD-HCC according to the degree of fibrosis.
- Our transcriptomic results has revealed the increase of CHKA in MASLD-HCC-F0F1, which in accordance with our previous metabolomic data obtained by both ¹H-NMR and LC-MS. Our findings demonstrated a strong accumulation of PC levels, suggesting that choline could serve as a marker in imaging in MASLD-HCC in patients with minimal fibrosis from stage F0 to F1 (Buchard et al., 2021, Metabolites, Buchard et al., 2021, AASLD Hepatology). The synthesis of PC is mainly involved in phospholipid membrane turnover and in tumor cell differentiation.

Table. 1 Different Gene Expressions According to Liver Fibrosis Level

Genes	Abbreviation	F0F1 TT vs. NTT	F3F4 TT vs. NTT
Acetyl-CoA Acetyltransferase 2	ACAT2	-	-
Acyl-CoA Oxidase 1	ACOX1	-	-
Arylacetamide deacetylase-like 1	AADACL1	-	-
Choline Kinase Alpha	CHKA	↑	-
Diacylglycerol acyltransferase-1	DGAT1	↑	-
Diacylglycerol acyltransferase-2	DGAT2	-	-
Glutamate-ammonia ligase	GLUL	-	-
Membrane bound O-acyltransferase domain containing 7	MBOAT7	↑	-
Serine palmitoyltransferase long chain base subunit 1	SPTLC1	-	-
Serine palmitoyltransferase long chain base subunit 2	SPTLC2	↑	-
Sphingomyelin phosphodiesterase 1	SMPD1	↑	-
Sphingomyelin phosphodiesterase 3	SMPD3	-	-
Sphingomyelin Synthase 1	SGMS1	↑	-
Sphingomyelin Synthase 2	SGMS2	-	-

Fig. 2

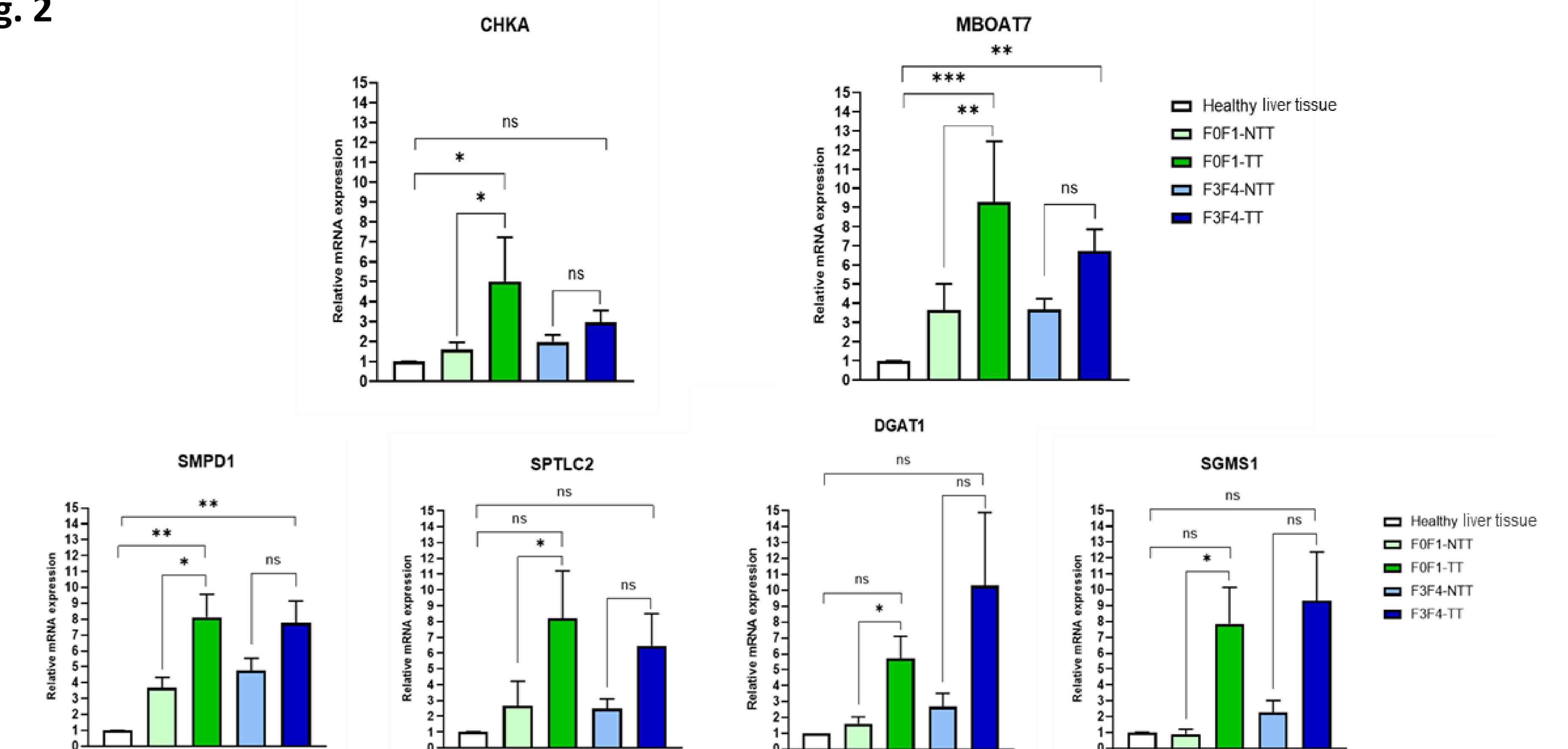


Fig. 1

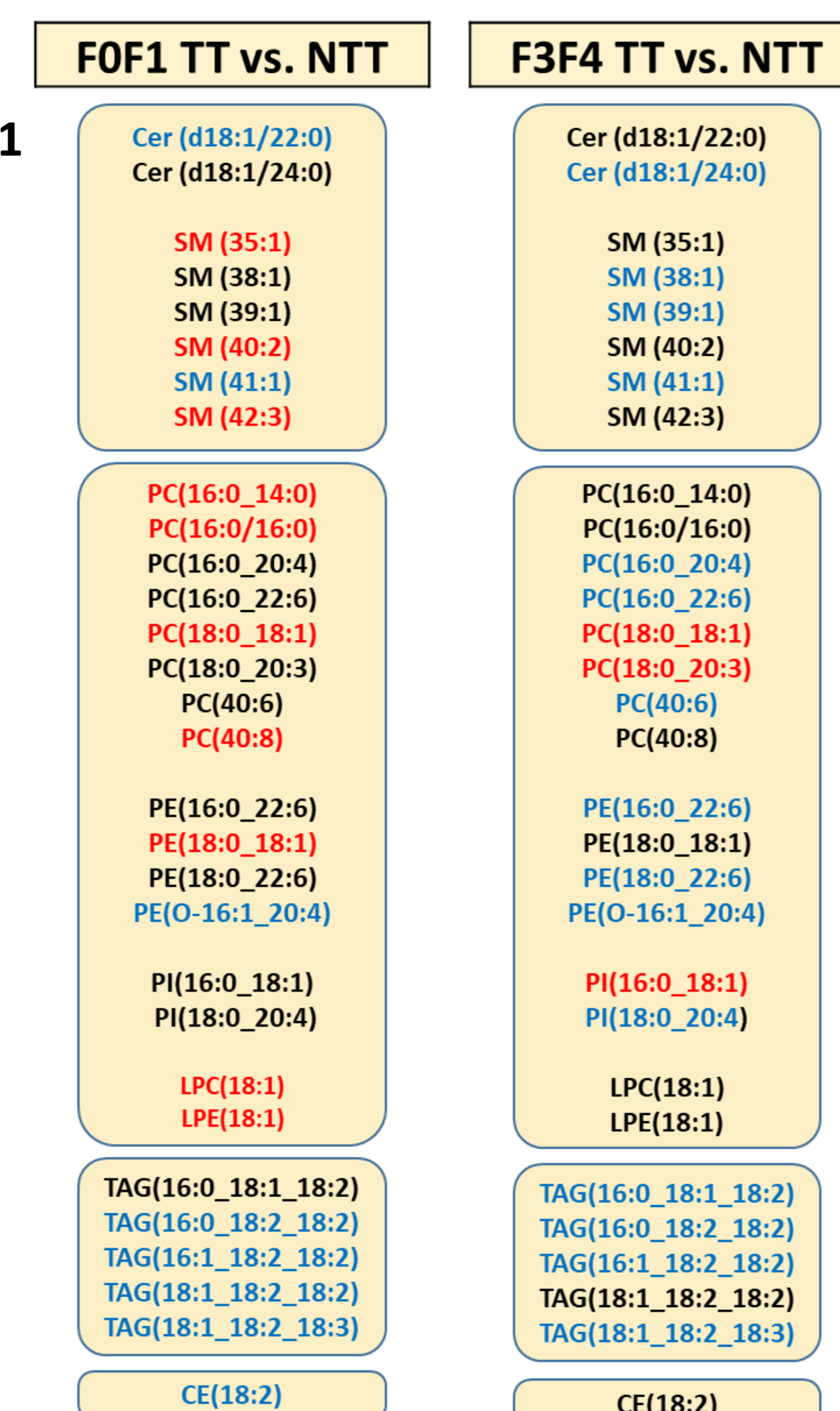


Fig. 3 a

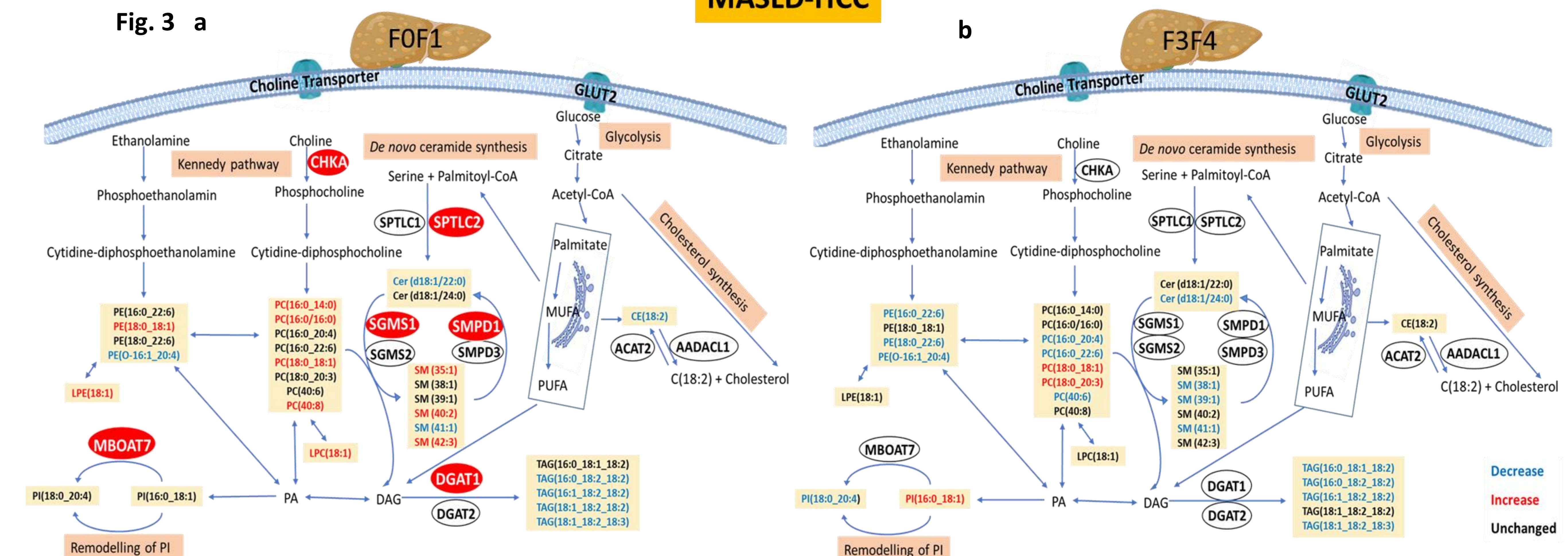


Fig. 1 Metabolomic analysis by LC-MS. Cer, Ceramide; CE, Cholesterol Ester; LPC, Lysophosphatidylcholine; LPE, Lysophosphatidylethanolamine; PC, Phosphatidylcholine; PE, Phosphatidylethanolamine; PI, Phosphatidylinositol; SM, Sphingomyelin; TAG, Triacylglycerol

Fig. 2 Transcriptomic analysis by qRT-PCR. *, $P < 0.05$; **, $P < 0.005$; ***, $P < 0.0005$; ns, Non-Significance

Fig. 3 Graphical representation showing the difference in MASLD-F0F1 and F3F4 regarding lipid metabolic pathways. In each group, tumor tissues were compared with non-tumor tissues, and healthy liver tissues were used as control. a) MASLD-HCC-F0F1; b) MASLD-HCC-F3F4

Conclusions

Metabolomics and transcriptomic analysis allow us to:

- Discriminate MASLD-HCC based on the severity of fibrosis.
- Propose biomarkers for MASLD-HCC with or without minimal fibrosis: "CHKA and MBOAT7". These observations could lead to a clinical application, suggesting that choline could be used as a tracer in imaging for patients suffering from MASLD-HCC at an early stage of fibrosis, consistent with the increase in the levels of PC and the RNA expression coding for choline kinase (CHKA).