SUPPLEMENTARY FIGURES

Supplementary Figure 1: Analysis of Mboat7 deficient livers

Panel A: The schema depicts the Mboat7 deletion cassette. The primers (5' CAS-F1 and 3' LOXP-R1) flank the loxP sites that flank exon 5. Therefore, the resulting product size is 172 bp in the Mboat7$^{\Delta hep}$ samples and 991 bp in Mboat7^{WT} samples.

Panel B: RNA sequencing from livers of Mboat7^{WT} and Mboat7$^{\Delta hep}$ mice shows deleted *Mboat7* exon 5.

Panel C: Genomic DNA was isolated from primary hepatocytes of Mboat7^{WT} and Mboat7$^{\Delta hep}$ mice and PCR was performed (using primers from panel A) to demonstrate cre-loxP-mediated recombination. The product size is 172 bp in the Mboat7$^{\Delta hep}$ samples and 991 bp in Mboat7^{WT} samples.

Supplementary Figure 2: Deletion of Mboat7 in mice results in spontaneous steatosis and altered lipidome in hepatocytes

Panel A: Liver weight of Mboat7^{WT} and Mboat7$^{\Delta hep}$ mice fed a normal diet. Data are presented as mean ± s.e.m. n=6-7 mice.

Panel B: Oil red O staining was performed in untreated primary hepatocytes isolated from Mboat7^{WT} and Mboat7$^{\Delta hep}$ mice fed a normal diet. Scale bars, 100 μm. The insert shows a zoomed-in region of the image.

Panel C: Lipidomic analysis of untreated primary hepatocytes isolated from Mboat7^{WT} and Mboat7$^{\Delta hep}$ mice fed a normal diet. Triglyceride (TAG) and cholesterol ester (CE) concentrations (pmol/μg of total protein). Data are presented as mean ± s.e.m. (Mann Whitney U test). *p < 0.05. n = 4 mice.

Panel D: Lipidomic analysis of livers from Mboat7^{WT} and Mboat7$^{\Delta hep}$ mice fed a normal diet. Hepatic concentrations of CE species are (pmol/μg of total protein). Data are presented as mean ± s.e.m. (Mann Whitney U test). *P < 0.05, **P < 0.01. n = 5 mice.

Panels E-G: Flow cytometry analysis was performed in non-parenchymal cells (NPCs) isolated from livers of Mboat7^{WT} and Mboat7$^{\Delta hep}$ mice fed a normal diet.

Panel E: Percentage of monocytes in livers of Mboat7^{WT} and Mboat7$^{\Delta hep}$ mice fed a normal diet. Data are presented as mean ± s.e.m. (Mann Whitney U test). n = 6-7 mice. ns, not significant.

Panel F: Percentage of macrophages in livers of Mboat7^{WT} and Mboat7$^{\Delta hep}$ mice fed a normal. Data are presented as mean ± s.e.m. (Mann Whitney U test). n = 6-7 mice. ns, not significant.

Panel G: Percentage of neutrophils in livers of Mboat7^{WT} and Mboat7$^{\Delta hep}$ mice fed a normal diet. Data are presented as mean ± s.e.m. (Mann Whitney U test). n = 6-7 mice. ns, not significant.

Panel H: mRNA expression of *Tnf*, *Il6*, *Il1b,* and *Ifng* was determined by qRT PCR in livers obtained from Mboat7^{WT} and Mboat7$^{\Delta hep}$ mice which were fed a normal diet. Expression levels were normalized to those of *B2m* and are presented as relative to the respective Mboat7^{WT} mice, set as 1. *Tnf*, tumor necrosis factor; *Il6*, interleukin 6; Il*1b*, interleukin 1 beta; *Ifng*, interferon gamma. Data are presented as mean ± s.e.m. ns, not significant. (Mann Whitney U test). n=6-7.

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Panel I: Multi-spot immunoassay for inflammatory molecules was performed in liver homogenates derived from Mboat7^{WT} and Mboat7$^{\Delta hep}$ mice fed a normal diet. Concentration of each protein was normalized to the total protein concentration. N=5. Data are presented as mean ± s.e.m. Mann Whitney U test.

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Supplementary Figure 3. Molecular analysis of Mboat7 deficient livers on normal diet

Panel A: RNA sequencing was performed in livers of Mboat7^{WT} and Mboat7$^{\Delta hep}$ mice fed a normal diet. Gene set enrichment analysis (GSEA) shows a negative correlation between fatty acid metabolism related genes and Mboat7 deficiency. For GSEA analysis, differential gene expression data (containing all expressed genes) were ranked using the -log10 transform of the p-value and then signed as positive or negative based on the direction of fold change. Then, the GSEA software (Broad Institute) was used to perform the GSEA pre-ranked analysis. NES, normalized enrichment score.

Panel B: Fatty acid metabolism related genes that were significantly (P< 0.05) upregulated or downregulated in Mboat7$^{\Delta hep}$ livers were plotted in a heat map using the online tool Morpheus. n = 6-7 mice.

Panels C-E: Data are presented as mean ± s.e.m. Mann Whitney U test. *p<0.05, **p<0.01. ns, not significant.

Panel C: From the pathway analysis (GO_Biological Process) performed using the RNA sequencing data set of normal diet fed livers, confirmation qRT-PCRs were performed for selected genes that belong to the fatty acid metabolic process and cholesterol metabolic process categories. Expression levels were normalized against *18s* rRNA and are presented as relative to the respective Mboat7^{WT} mice set as 1. N=6-7. *Scd1*, stearoyl-Coenzyme A desaturase 1; *Elovl3*, elongation of very long chain fatty acids; *Elovl5*, ELOVL family member 5, elongation of long chain fatty acids; *Acsf3*, acyl-CoA synthetase family member 3; *Decr2*, 2-4-dienoyl-Coenzyme A reductase 2, peroxisomal; *Cpt1a*, carnitine palmitoyltransferase 1a, liver; *Acaa1a*, acetyl-Coenzyme A acyltransferase 1A; *Acox1*, acyl-Coenzyme A oxidase 1, palmitoyl; *Ehhadh*, enoyl-

Coenzyme A, hydratase/3-hydroxyacyl Coenzyme A dehydrogenase; *Fabp2*, fatty acid binding protein 2, intestinal; *Cyb5r3*, cytochrome b5 reductase 3.

Panel D: mRNA expression of *Angptl3* was determined by qRT-PCR in livers obtained from Mboat7^{WT} and Mboat7$^{\Delta hep}$ mice which were fed normal diet. Expression levels were normalized against *18s* rRNA and are presented as relative to the respective Mboat7^{WT} mice set as 1. N=6-7. *Angptl3*, angiopoietin-like 3.

Panel E: Angptl3 protein was measured in serum of Mboat7^{WT} and Mboat7$^{\Delta hep}$ mice which were fed normal diet, by ELISA. N=6.

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Supplementary Figure 4. Analysis of Mboat7 deficient livers on HFCDD feeding

Panels A-D: Data derived from Mboat7^{WT} and Mboat7$^{\Delta hep}$ which were fed a HFCDD for 6 weeks. Data are presented as mean ± s.e.m. **P<0.01, *P<0.05. (Mann Whitney U test)

Panel A: Lipidomic analysis of livers from Mboat7^{WT} and Mboat7$^{\Delta hep}$ mice fed an HFCDD for 6 weeks. Hepatic concentrations of CE species are presented as pmol/µg of total protein. n = 7-8 mice.

Panel B-C: AST enzyme activity (B) and ALT enzyme activity (C) was measured in serum. (n=7-8).

Panels D: Western blot for TIMP1 was performed in livers obtained from Mboat7^{WT} and Mboat7$^{\Delta hep}$ mice which were fed a HFCDD for 6 weeks. Vinculin was used as loading control. N=4-5. Statistical test performed was Unpaired t test. Data are presented as mean ± s.e.m.

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Supplementary Figure 5. Analysis of Mboat7 deficient livers on HFCDD feeding

Panel A: Significantly upregulated genes from RNA sequencing (FDR < 0.05) in Mboat7$^{\Delta hep}$ livers as compared to Mboat7^{WT} livers (mice fed an HFCDD for 6weeks) were used to perform pathway analysis in Gene Trail. The top 20 significantly (P < 0.05) upregulated pathways (in the GO term Biological processes) are shown.

Panels B: qRT-PCR for *Acta2* (actin, alpha 2, smooth muscle, aorta) was performed in livers of Mboat7^{WT} and Mboat7$^{\Delta hep}$ mice which were fed a HFCDD for 6 weeks. N=4-5. *p<0.05. Statistical test performed was Mann Whitney U test. Data are presented as mean ± s.e.m.

Panel C: Significantly downregulated genes from RNA sequencing (FDR < 0.05) in Mboat7$^{\Delta hep}$ livers as compared to Mboat7^{WT} livers (mice fed an HFCDD for 6 weeks) were used to perform pathway analysis in Gene Trail. The top 20 significantly (P < 0.05) downregulated pathways (in the GO term Biological processes) are shown.

Panels D: Flow cytometry analysis was performed in NPCs isolated from livers of Mboat7^{WT} and Mboat7$^{\Delta hep}$ mice fed a HFCDD for 6 weeks. Percentage of monocytes, macrophages, neutrophils, CD4 T cells and CD8 T cells (% of single cells) are shown.Data are presented as mean ± s.e.m. (Mann Whitney U test). n = 4-5 mice. ns, not significant.

Panels E: mRNA expression of *Tnf*, *Il6*, *Il1b,* and *Ifng* was determined by qRT-PCR in livers obtained from Mboat7^{WT} and Mboat7$^{\Delta hep}$ mice which were fed an HFCDD for 6 weeks. Expression levels were normalized to those of *B2m* and are presented as relative to the respective Mboat7^{WT} mice, set as 1. *Tnf*, tumor necrosis factor; *Il6*, interleukin 6; *Il1b*, interleukin 1 beta; *Ifng*, interferon gamma. Data are presented as mean ± s.e.m. ns, not significant. (Mann Whitney U test). n=4-5 mice.

Panels F: Multi-spot immunoassay for inflammatory mediators was performed in liver homogenates derived from Mboat7^{WT} and Mboat7$^{\Delta hep}$ mice fed a HFCDD. Concentration of each protein was normalized to the total protein concentration. N=7. Data are presented as mean ± s.e.m. Mann Whitney U test.

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Supplementary Figure 6. ER stress analysis in Mboat7 deficient mouse liver

Panels A-K: Data are presented as mean ± s.e.m. (Mann Whitney U test). *p < 0.05. ns, not significant.

Panel A-E: mRNA expression of (A) total *Xbp1*, (B) spliced *Xbp1*, (C) *Atf4*, (D) *Hspa5* and (E) *Ddit3* was determined by qRT-PCR in livers obtained from Mboat7^{WT} and Mboat7$^{\Delta hep}$ mice which were fed normal diet. Expression levels were normalized against *B2M* mRNA and are presented as relative to the respective Mboat7^{WT} mice set as 1. N=6-7. *Xbp1*, X-box binding protein 1; *Atf4*,; activating transcription factor 4 *Hspa5*, heat shock protein 5; *Ddit3*, DNA-damage inducible transcript 3.

Panel F: Western blot of ATF4, GADD153/CHOP, eIF2α and peIF2α(p-Ser51) was performed in livers obtained from Mboat7^{WT} and Mboat7$^{\Delta hep}$ mice which were fed normal diet. Vinculin was used as loading control.

Panels G-K: Densitometry of ATF4, GADD/CHOP, eIF2α and peIF2 α from the immunoblot in panel F. N=5-7.

Supplementary Figure 7. Remodelling pathway of phosphatidylinositol (PI) and generation of lysophosphatidylinositol (LPI)

The panel depicts the phosphatidylinositol (PI) remodeling pathway and the role of Mboat7 in it according to. PI undergoes deacylation process by phospholipase A1 (PLA1) and phospholipase A2 (PLA2) to produce 2-acyl LPI and 1-acyl LPI, respectively. Acyl-CoA:lysocardiolipin acyltransferase (AGPAT8) and MBOAT7 reacylate these products with stearic acid and arachidonic acid respectively. This product, in turn, gets deacylated by PLA2 and PLA1 and further gets reacylated by MBOAT7 and AGPAT8 producing the PI 38:4 and subsequently 1-stearoyl LPI and 2-arachidonoyl LPI.

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Supplementary Figure 8. Lipidomic analysis of Mboat7 deficient mouse hepatocytes

Panel A: Lipidomic analysis of primary hepatocytes isolated from Mboat7^{WT} and Mboat7$^{\Delta hep}$ mice fed a normal diet. Concentrations of lipid classes (pmol / µg of total protein). *p < 0.05. n = 4 mice. Data are presented as mean ± s.e.m., (Mann Whitney U test)

Supplementary Figure 9: Lipidomic analysis of human liver biopsies stratified by MBOAT7 rs641738 genotype and disease condition

Panel A: Lipidomic analysis of human livers obtained from people with the CC or TT genotype (grouped for a disease condition, Table 1). Alterations in hepatic PI 38:4 levels presented as mol%, in normal (CC=10, CT=14, TT=6), healthy obese (CC=13, CT=17, TT=6), NAFL (CC=41, CT=71, TT=23), early NASH (CC=22, CT=17, TT=10) and NASH (CC=8, CT=17, TT=5) samples.

Panels B-G: Lipidomic analysis of human livers obtained from people with either the CC, CT or TT genotype (grouped for NAFLD with or without fibrosis, Table 1). Data are presented as mean ± s.e.m., (Mann Whitney U test). **P< .01.

Panel B: Alterations in hepatic TAG levels in NAFLD samples with fibrosis. CC, n=31; CT, n=42; TT, n=17.

Panel C: Alterations in hepatic lipid classes in NAFLD samples with fibrosis. CC, n=31; CT, n=42; TT, n=17.

Panel D: Alterations in hepatic lipid classes in NAFLD samples with fibrosis. Cer (CC, n=31; CT, n=42; TT, n=17); CL* (CC, n=20; CT, n=29; TT, n=8); LPA* (CC, n=13; CT, n=13; TT, n=4); LPC (CC, n=31; CT, n=42; TT, n=17); LPE (CC, n=31; CT, n=42; TT, n=17); LPG* (CC, n=30; CT, n=34; TT, n=17); LPI* (CC, n=25; CT, n=36; TT, n=17); LPS* (CC, n=29; CT, n=40; TT, n=16). *patient samples in which a specific lipid class was not detected were excluded from analysis.

Panel E: Alterations in hepatic TAG levels in NAFLD samples without fibrosis. CC, n=40; CT, n=63; TT, n=21.

Panel F: Alterations in hepatic lipid classes in NAFLD samples without fibrosis. CC, n=40; CT, n=63; TT, n=21.

Panel G: Alterations in hepatic lipid classes in NAFLD samples without fibrosis. Cer, ceramide (CC, n=40; CT, n=63; TT, n=21); CL* (CC, n=24; CT, n=41; TT, n=11); LPA (CC, n=22; CT, n=30; TT, n=4); LPC (CC, n=40; CT, n=63; TT, n=21); LPE (CC, n=40; CT, n=63; TT, n=21); LPG* (CC, n=36; CT, n=60; TT, n=20); LPI* (CC, n=39; CT, n=56; TT, n=20); LPS* (CC, n=40; CT, n=61; TT, n=21). *patient samples in which a specific lipid class was not detected were excluded from analysis.

Supplementary Figure 10: Lipidomic analysis of human liver biopsies stratified by MBOAT7 rs641738 genotype and disease condition

Panels A-O: Lipidomic analysis of human livers obtained from people with the CC, CT or TT genotype (grouped for a disease condition, Table 1). Data are presented as mean ± s.e.m., (Mann Whitney U). *P < 0.05, **P<0.01.

Panels A-C: (A) Alterations in hepatic TAG levels and (B-C) lipid classes (pmol/μg of protein), in normal control samples. Figure A-B; CC, n=10; CT, n=14; TT, n=6. Figure C; LPA* (CC, n=6; CT, n=5; TT, n=1), LPC (CC, n=10; CT, n=14; TT, n=6), LPE (CC, n=10; CT, n=14; TT, n=6), LPG* (CC, n=9; CT, n=13; TT, n=5), LPI* (CC, n=10; CT, n=14; TT, n=5), LPS* (CC, n=10; CT, n=14; TT, n=5), Cer (CC, n=10; CT, n=14; TT, n=6), CL* (CC, n=4; CT, n=5; TT, n=2).

Panels D-F: (D) Alterations in hepatic TAG levels and (E-F) lipid classes (pmol/μg of protein), in healthy obese samples. Figure D-E; CC, n=13; CT, n=17; TT, n=6. Figure F; LPA* (CC, n=4; CT, n=8; TT, n=2), LPC (CC, n=13; CT, n=17; TT, n=6), LPE (CC, n=13; CT, n=17; TT, n=6), LPG* (CC, n=12; CT, n=16; TT, n=6), LPI* (CC, n=11; CT, n=14; TT, n=6), LPS* (CC, n=12; CT, n=17; TT, n=6), Cer (CC, n=13; CT, n=17; TT, n=6), CL* (CC, n=7; CT, n=12; TT, n=3).

Panels G-I: (G) Alterations in hepatic TAG levels and (H-I) lipid classes (pmol/μg of protein), in NAFL samples. Figure G-H; CC, n=41; CT, n=71; TT, n=23. Figure I; LPA* (CC, n=20; CT, n=30; TT, n=4), LPC* (CC, n=41; CT, n=71; TT, n=23), LPE* (CC, n=41; CT, n=71; TT, n=23), LPG* (CC, n=37; CT, n=63; TT, n=22), LPI* (CC, n=39; CT, n=62; TT, n=22), LPS* (CC, n=41; CT, n=69; TT, n=22), Cer (CC, n=41; CT, n=71; TT, n=23), CL* (CC, n=26; CT, n=50; TT, n=10).

Panels J-L: (J) Alterations in hepatic TAG levels and (K-L) lipid classes (pmol/μg of protein), in early NASH samples. Figure J-K; CC, n=22; CT, n=17; TT, n=10. Figure I; LPA* (CC, n=13; CT, n=7; TT, n=2), LPC (CC, n=22; CT, n=17; TT, n=10), LPE (CC, n=22; CT, n=17; TT, n=10), LPG* (CC, n=22; CT, n=16; TT, n=10), LPI* (CC, n=20; CT, n=15; TT, n=10), LPS* (CC, n=20; CT, n=16; TT, n=10), Cer (CC, n=22; CT, n=17; TT, n=10), CL* (CC, n=13; CT, n=12; TT, n=7).

Panels M-O: (M) Alterations in hepatic TAG levels and (N-O) lipid classes (pmol/μg of protein), in samples with NASH. Figure M-N; CC, n=8; CT, n=17; TT, n=5. Figure O;

LPA* (CC, n=2; CT, n=6; TT, n=2), LPC (CC, n=8; CT, n=17; TT, n=5), LPE (CC, n=8; CT, n=17; TT, n=5), LPG* (CC, n=7; CT, n=15; TT, n=5), LPI* (CC, n=5; CT, n=15; TT, n=5), LPS* (CC, n=8; CT, n=16; TT, n=5), Cer (CC, n=8; CT, n=17; TT, n=5), CL* (CC, n=5; CT, n=8; TT, n=2).

*Patient samples in which a specific lipid class was not detected were excluded from the analysis.

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Supplementary figure 11: Lipidomic analysis of human liver biopsies stratified by MBOAT7 rs641738 genotype and patients without statin treatment

Panels A-C: Lipidomic analysis of human livers stratified by rs641738T genotype and excluding patient samples on statin medication. (A) Total PI; CC=93, CT=125, TT=48. (B) Alterations in PI species presented as mol% (% of total PI); CC, n=93; CT, n=125; TT, n=48. (C) Alterations in PI species presented as mol% (% of total PI); *PI 32:0 (CC, n=67; CT, n=96; TT, n=36) *PI 32:1 (CC, n=54; CT, n=55; TT, n=28) *PI 34:0 (CC, n=86; CT, n=107; TT, n=35); *PI 34:1 (CC, n=91; CT, n=117; TT, n=44); *PI 34:2 (CC, n=92; CT, n=119; TT, n=44); *PI 36:1 (CC, n=92; CT, n=125; TT, n=48); *PI 38:3 (CC, n=3; CT, n=3; TT, n=2); *PI 38:6 (CC, n=91; CT, n=118; TT, n=48); *PI 40:4 (CC, n=34; CT, n=34; TT, n=10); *PI 40:7 (CC, n=27; CT, n=30; TT, n=18). *patient samples in which a specific lipid species was not detected were excluded from the specific analysis. Data are presented as mean ± s.e.m., *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001.

Supplementary figure 12: **Graphical abstract**

Loss of *Mboat7* in mouse hepatocytes results in spontaneous steatosis under steady state condition. Upon feeding *Mboat7* deficient mice (Mboat7$^{\Delta hep}$) with a high fat methionine low, choline deficient diet (HFCDD) results in an inflammation independent increase in fibrosis compared to the controls (Mboat7^{WT}), due to increased LPI, altered PI sidechain remodeling and deregulated phospholipids in hepatocytes.

Supplementary figures 13-19

In supplementary figures 13-19, all the mouse data are shown again as dot plots.

Supplementary figures 13

Panels A-F: Data derived from Mboat7^{WT} and Mboat7$^{\Delta hep}$ which were fed a normal diet. Data are presented as mean ± s.e.m. (Mann Whitney U test).

Panel A: mRNA expression of Mboat7 was determined by qRT-PCR in Mboat7^{WT} (n=6) and Mboat7$^{\Delta hep}$ (n=7) mice.

Panel B: Hepatic-concentrations of triglyceride (TAG) and cholesterol ester (CE) (n=5 mice).

Panel C-F: Flow cytometry analysis was performed in NPCs isolated from the liver of normal diet fed mice. (C) Total number of NPCs (n=6-7 mice), (D) number of monocytes (CD45^{+}/Ly6G^{-}/CD11b^{+}/F4/80^{-}), (E) macrophages (CD45^{+}/Ly6G^{-}/CD11b^{+}/F4/80^{+}) and (F) neutrophils (CD45^{+}/Ly6G^{+}/CD11b^{+}) are shown (n=6-7 mice).

Panels G-O: Data derived from Mboat7^{WT} and Mboat7$^{\Delta hep}$ which were fed a HFCDD for 6 weeks. Data are presented as mean ± s.e.m. (Mann Whitney U test).

Panel G: Liver weight of Mboat7^{WT} and Mboat7$^{\Delta hep}$ mice (n=7-8 mice).

Panel H: Hepatic-concentrations of TAG and CE (n=7-8 mice).

Panel I: Quantification of picrosirius red positive area in livers. (n=7-8 mice).

Panel J: Quantification of hepatic-hydroxyproline (n=4-5 mice).

Panel K: qRT PCR results (n=4-5 mice).

Panel L-M: Flow cytometry analysis was performed in NPCs isolated from the liver of HFCDD fed mice. (L) Total number of NPCs, (M) monocytes, macrophages, neutrophils, CD4 T cells and CD8 T cells (n=4-5 mice).

Panel N-O: (N) AST activity and (O) ALT activity was measured in serum. (n=7-8).

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Supplementary figures 14

Panels A-B: Hepatic free fatty acid levels on normal diet (A) and HFCDD diet (B). (n=6-8 mice). Data are presented as mean ± s.e.m. (Mann Whitney U test).

Supplementary figures 15

Panels A-F: Data are presented as mean ± s.e.m. (Mann Whitney U test). *P<0.05, **P< 0.01, ***P< 0.001. ND, not detected. Lipidomic analysis of livers on a normal diet (A-C, n=5 mice) and HFCDD diet (D-F, n=7-8 mice).

Supplementary figures 16

Panels A-H: Data are presented as mean ± s.e.m. (Mann Whitney U test). *P<0.05, **P< 0.01. ns, not significant.

Panels A, C-H: Data derived from Mboat7^{WT} and Mboat7$^{\Delta hep}$ which were fed a normal diet.

Panel A: Liver weight of mice. n=6-7 mice.

Panel B: Lipidomic analysis of untreated primary hepatocytes isolated from Mboat7^{WT} and Mboat7$^{\Delta hep}$ mice fed a normal diet. Triglyceride (TAG) and cholesterol ester (CE) concentrations (pmol/µg of total protein). n = 4 mice.

Panel C: Lipidomic analysis of livers. Hepatic concentrations of CE species are shown (pmol/µg of total protein). n = 5 mice.

Panels D-F: Percentage of (D) monocytes, (E) macrophages and (F) neutrophils are shown (% of single cells).n = 6-7 mice.

Panel G: mRNA expression of *Tnf*, *Il6*, *Il1b,* and *Ifng* was determined by qRT PCR. Expression levels were normalized to those of *B2m* and are presented as relative to the respective Mboat7^{WT} mice, set as 1. n=6-7.

Panel H: Multi-spot immunoassay for inflammatory molecules was performed in liver homogenates. Concentration of each protein was normalized to the total protein concentration. N=5.

Supplementary figures 17

Panels A-C: Data are presented as mean ± s.e.m. (Mann Whitney U test). *P<0.05, **P< 0.01. ns, not significant.

Panel A: mRNA expression of *Angptl3* was determined by qRT-PCR in livers obtained from Mboat7^{WT} and Mboat7$^{\Delta hep}$ mice which were fed normal diet. Expression levels were normalized against *18s* rRNA and are presented as relative to the respective Mboat7^{WT} mice set as 1. N=6-7.

Panel B: Angptl3 protein was measured in serum of Mboat7^{WT} and Mboat7$^{\Delta hep}$ mice which were fed normal diet, by ELISA. N=6.

Panel C: From the pathway analysis (GO_Biological Process) performed using the RNA sequencing data set of normal diet fed livers, confirmation qRT-PCRs were performed for selected genes that belong to the fatty acid metabolic process and cholesterol metabolic process categories. Expression levels were normalized against *18s* rRNA and are presented as relative to the respective Mboat7^{WT} mice set as 1. N=6-7.

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Supplementary figures 18

Panels A-M: Data derived from Mboat7^{WT} and Mboat7$^{\Delta hep}$ mice fed a HFCDD for 6 weeks. Data are presented as mean ± s.e.m. (Mann Whitney U test). *P < 0.05, **P < 0.01, ***P < 0.001. n.s, not significant.

Panel A: Lipidomic analysis of livers. Hepatic concentrations of CE species are presented as pmol/µg of total protein. n = 7-8 mice.

Panels B-F: Flow cytometry analysis was performed in NPCs isolated from livers. Percentage of (B) monocytes, (C) macrophages, (D) neutrophils, (E) CD4 T cells and (F) CD8 T cells (% of single cells) are shown. n = 4-5 mice.

Panels G-J: mRNA expression of (G) *Tnf*, (H) *Il6*, (I) *Il1b,* and (J) *Ifng* was determined by qRT-PCR in livers. Expression levels were normalized to those of *B2m* and are presented as relative to the respective Mboat7^{WT} mice, set as 1. n=4-5 mice.

Panel K: Multi-spot immunoassay for inflammatory molecules was performed in liver homogenates. Concentration of each protein was normalized to the total protein concentration. N=7.

Panel L: Western blot for TIMP1 was performed in livers. Vinculin was used for normalization. N=4-5.

Panels M: qRT-PCR for *Acta2* (actin, alpha 2, smooth muscle, aorta) was performed in livers N=4-5.

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Supplementary figures 19

Panels A-K: Data are presented as mean ± s.e.m. (Mann Whitney U test). *p < 0.05. ns, not significant.

Panel A: Lipidomic analysis of primary hepatocytes isolated from Mboat7^{WT} and Mboat7$^{\Delta hep}$ mice fed a normal diet. Concentrations of lipid classes (pmol / µg of total protein). n = 4 mice.

Panels B-F: mRNA expression of (B) total *Xbp1*, (C) spliced *Xbp1*, (D) *Atf4*, (E) *Hspa5* and (F) *Ddit3* was determined by qRT-PCR in livers obtained from Mboat7^{WT} and Mboat7$^{\Delta hep}$ mice which were fed normal diet. Expression levels were normalized against *B2M* mRNA and are presented as relative to the respective Mboat7^{WT} mice set as 1. N=6-7.

Panels G-K: Densitometry of (G) ATF4, (H) GADD/CHOP, (I) eIF2α and (J) peIF2 α from immunoblot in Supplementary Figure-4G. Vinculin was used for normalization. N=5-7.