**Supplementary information**

Number of supplementary figures = 9, number of supplementary tables = 11.

**Supplementary Figures**

**Figure S1.** Establishment of acquired sorafenib resistant HCC cells by continuous induction with sorafenib. (A) Schematic models of induction of acquired sorafenib resistant (SR) HCC cells. (B) IC₅₀ for sorafenib of CN- and SR- MHCC97H or Hep3B cells were evaluated by CCK-8 assay after different concentrations (1, 2, 4, 8, 16, 32, 64 μM) of sorafenib treatment for 72 h. (C) MRP1, MRP2, MRP3, MRP4, MRP6 and MDR1 mRNA expression in CN and SR- MHCC97H and Hep3B cells were determined by RT-qPCR. (D) Protein levels of MRP1 or MRP2 and MPR3 in CN- and SR- MHCC97H and Hep3B cells were determined by RT-qPCR. Data are expressed as means ± SEM (n = 3). *p < 0.05, **p < 0.01, ***p < 0.001.
Figure S2. Principal component analysis (PCA) of UHPLC-MS/MS composition in CN- and SR- MHCC97H or Hep3B cells (n=3).
Figure S3. Enzymes involved in TAG synthesis expressions in SR HCC cells. (A-B) mRNA levels of Enzymes involved in TAG synthesis in CN- and SR- MHCC97(A) and Hep3B(B) cells were examined by qPCR. (C) Analysis of GPAT3 expression in parental and oxaliplatin resistant MHCC97L cells (GSE129071), lenvatinib resistant Huh7 cells (GSE211850). Data are expressed as means ± SEM (n = 3). *p < 0.05, **p < 0.01, ***p < 0.001, ns represents no significant difference.
Figure S4. Linear correlation analysis between expression of GPAT3 and ABCC2, ABCC6 and ABCC11 expression in tumor tissues of HCC patients, data were obtained from TCGA database.
Figure S5. The effects of knockdown of GPAT3 on the proliferation of CN- and SR- HCC cells in vitro and in vivo. (A) PCA of TAG composition determined by UHPLC-MS/MS in WT- and sgGPAT3- MHCC97H SR or Hep3B SR cells (n=3). (B) LPA levels in CN-, SR-WT and SR-sgGPAT3 in MHCC97H or Hep3B cells were examined by ELISA (n=3). (C) GPAT3 levels in NC- and shGPAT3- Hep3B cells were examined by qPCR. (n=3). (D) The IC_{50} values for sorafenib in NC- and shGPAT3- Hep3B cells were determined using a CCK-8 assay following treatment with various concentrations (1, 2, 4, 8, 16, 32...
μM) of sorafenib for 72 hours. (E) Cell proliferation of NC- and shGPAT3 Hep3B cells were evaluated by CCK-8 assay. (F) Cell proliferation of CN, SR-WT and SR-sgGPAT3 in MHCC97H or Hep3B cells were evaluated by CCK-8 assay. (G-I) Curves of tumor growth (H), tumor entity view (G) and weight change curve (I) in group of CN, SR-WT and SR-sgGPAT3 in MHCC97H cells without any treatment. Data are expressed as means ± SEM (n = 3). *p < 0.05, **p < 0.01, ns represents no significant difference.
Figure S6. Knocking down DGATs or other GPATs does not affect TAG content and its sensitivity to sorafenib in SR cells. (A) mRNA levels of GPATs in NC- and siGPAT1- in MHCC97 and Hep3B SR cells were examined
by RT-qPCR. (B) NC- and siGPAT1- in MHCC97 and Hep3B SR cells were stained by Bodipy 558/568 C12, then were determined by flow cytometry. (C) The IC₅₀ values for sorafenib in MHCC97 and Hep3B SR cells were determined using CCK-8 assay after treatment with various concentrations (1, 2, 4, 8, 16, 32, 64 μM) of sorafenib for 72 hours, with and without siGPAT1. (D) mRNA levels of GPATs in NC- and siGPAT4- in MHCC97 and Hep3B SR cells were examined by RT-qPCR. (E) NC- and siGPAT4- in MHCC97 and Hep3B SR cells were stained by Bodipy 558/568 C12, then determined by and FCs. (F) The IC₅₀ values for sorafenib in MHCC97 and Hep3B SR cells were determined using a CCK-8 assay after treatment with varying concentrations (1, 2, 4, 8, 16, 32, 64 μM) of sorafenib for 72 hours, with and without siGPAT4. (G) MHCC97 and Hep3B SR cells treated with different concentrations A922500 or PF06424439 were stained by Bodipy 558/568 C12, then determined by FCs. (H) The IC₅₀ values for sorafenib in MHCC97 and Hep3B SR cells treated with 20 μM A922500 or PF06424439 were determined using a CCK-8 assay. The cells were exposed to various concentrations (1, 2, 4, 8, 16, 32, 64 μM) of sorafenib for 72 hours. Data are expressed as means ± SEM (n = 3). *p < 0.05, **p < 0.01, ***p < 0.001, ns represents no significant difference.
Figure S7. PCA of TAG composition determined by UHPLC-MS/MS in NC- and GPAT3 OE- MHCC97H and Hep3B cells (n=3).
Figure S8. The effect of knockdown or overexpression of GPAT3 to apoptosis. (A, B) After treatment with sorafenib (MHCC97H: 10 μM; Hep3B: 6μM) for 72h, cell apoptosis ratios (A) and lipid peroxidation levels (B) of NC- and GPAT3 OE- MHCC97H or Hep3B cells were determined by FCs. (C) After treatment with/without sorafenib (MHCC97H: 10 μM; Hep3B: 6μM) for 72h, protein levels of cle-caspase3, GSDMD, P62 and LC3 in NC- and GPAT3 OE-MHCC97H or Hep3B cells were detected by WB. (D) After treatment with sorafenib (MHCC97H: 10 μM; Hep3B: 6μM) for 72h, cell apoptosis ratios of WT- and sgGPAT3- MHCC97H SR or Hep3B SR cells were determined by FCs. Data are expressed as means ± SEM (n = 3). *p < 0.05, ns represents no significant difference.
Figure S9. The effects of GPATs inhibitors on mice weight and liver LPA 

_in vivo_. (A, B) Sensitivity of MHCC97H SR cell-transplanted tumors to sorafenib (2 mg/kg, once every 3 days), NEM (1 mg/kg, once every 2 days) and FSG67 (1 mg/kg, once every 2 days) were evaluated _in vivo_. Mice weight (A), and ELISA analysis for plasma LPA levels (B) and liver LPA levels (C). Data are expressed as means ± SEM (n = 5). **p < 0.01, ***p < 0.001, ns represents no significant difference.