Supplemental Figures and Information

Supplemental Figure Legends

Supplemental Figure 1-related to Figure 1

Bile duct ligation was performed on *WT* (*Shp2*$^{fl/fl}$) animals, and sacrificed 1 month later. Liver sections were stained with Manson's trichrome, reticulin and CK-19 antibody.

Supplemental Figure 2-related to Figure 3

(A) Feces were collected for 72 hrs from single-housed WT and Shp2$^{hep-/-}$ animals. Feces were air-dried for 72 hrs and dry feces weight was adjusted to daily excretion per gram body weight.
(B) BA compositions in BA pool, liver and feces were adjusted to body, liver and feces weight, respectively.

Supplemental Figure 3-related to Figure 5

(A) Cyp7a1 protein levels were determined by immunoblot analysis of whole liver lysates derived from *WT* and *Shp2*$^{hep-/-}$ mice with two other antibodies (Cyp7a1 #2 Abcam, Cyp7a1 #3 Cosmo Bio). The samples and loading amounts were the same as in Fig. 5b. Each lane represents an individual animal.
(B-D) Band intensity of Cyp7a1 was calculated to loading control. The graph in (B) was from Figure 5B, (C) from Figure 5C and (D) from Figure 5F.
(E) *WT* and *Shp2*$^{hep-/-}$ animals were fed either with vehicle or GW4064 dissolved in vehicle by oral gavage. The animals were fed at 6am and 6pm (US pacific time) for consecutive 10 days. After the last feeding (6 am), the animals were starved for 6 hours before sacrifice. RNAs from ileums and livers were isolated and assayed for qRT-PCR.

Supplemental Figure 4-related to Figure 6

(A) Shp2, Cyp7a1 and β-actin protein levels were determined by immunoblot analysis of whole liver and ileum lysates from *WT* and *Shp2*$^{hep-/-}$ mice. For direct comparison, the image from Fig. 5b was used here. Each lane represents an individual animal. Corresponding liver and ileum samples were collected from the same animals.

(B) Band intensity of Cyp7a1 in Figure 6C was calculated to loading control.

(C) Band intensity of indicated proteins in Figure 6D was calculated to loading control.

(D) Immunoblot analysis of liver lysates was performed with antibodies against pFRS2α(Y196), pErk, Erk1, p-p90RSK, p-PKC (pan) (βII Ser660), pJNK, JNK, p-p38, p38, β-Klotho and GAPDH. Two-month-old *WT* or *Shp2*$^{(H+K)-/-}$ mice were fasted for 5.5 hours before i.p. injection of PBS or hFGF19 (1 mg/kg body weight). The animals were sacrificed 30 min after injection.

(E) Band intensity of Cyp7a1 in Figure 6F was calculated to loading control.

Supplemental Figure 5-related to Figure 7

(A) Heat maps of the K-means cluster analysis for gene expression changes in *Shp2*$^{hep-/-}$, *FXR*$^{-/-}$ */SHP*$^{-/-}$ and FGF15/19-treated mice. The colors in heat maps represent log2 ratios of gene expression fold change, which were calculated as KO versus WT mice, and FGF15/19- versus PBS-treated mice, respectively. Yellow means up-regulation, black means no change, and blue means down-regulation of expression. The clusters are labeled with colored numbers.

(B) Bar chart representation of gene ontology of clustered genes. Each bar chart is labeled with colored numbers on the left that correspond to the clusters in heat maps. Bars represent -log10 of p values.

(C) Band intensities of FGFR4 in Figure 7G and 7H were calculated against loading control.

(D) Relative expression of *FGFR4* mRNA in *WT* or *Shp2*$^{hep-/-}$ livers (n = 4-5) as determined by qRT-PCR. Relative gene expression was normalized to *β-actin*. Fold change was calibrated to the *WT* group.

Supplemental Table 1 List of primers

Shp2-F	TCCATGGTCACTTGTCTG GA	(Zhu et al., 2011)
Shp2-R	GACGTGGGTCACTTTGGACT	(Zhu et al., 2011)
FXR-F	GCTTGATGTGCTACAAAAGCTG	PrimerBank 6677831a1
FXR-R	CGTGGTGATGGTTGAATGTCC	PrimerBank 6677831a1
SHP-F	CTCATGGCCTCTACCCTCAA	(He et al., 2011)
SHP-R	GGTCACCTCAGCAAAAGCA T	(He et al., 2011)
Cyp7a1-F	GGGATTGCTGTGGTAGTGAGC	PrimerBank 31542445a1
Cyp7a1-R	GGTATGGAATCAACCCGTTGTC	PrimerBank 31542445a1
Cyp7b1-F	GGAGCCACGACCCTAGATG	PrimerBank 6681127a1

Cyp7b1-R	TGCCAAGATAAGGAAGCCAAC	PrimerBank 6681127a1
Cyp27a1-F	CCTCACCTATGGGATCTTCATC	This study
Cyp27a1-R	TTTAAGGCATCCGTGTAGAGC	This study
Cyp8b1-F	CCTCTGGACAAGGGTTTTGTG	PrimerBank 31981808a1
Cyp8b1-R	GCACCGTGAAGACATCCCC	PrimerBank 31981808a1
Cyp3a11-F	TGAATATGAAACTTGCTCTCACTAAAA	This study
Cyp3a11-R	CCTTGTCTGCTTAATTTCAGAGGT	This study
Cyp17a1-F	GCCCAAGTCAAAGACACCTAAT	PrimerBank 6681097a1
Cyp17a1-R	GTACCCAGGCGAAGAGAATAGA	PrimerBank 6681097a1
FGF15-F	ATGGCGAGAAAGTGGAACGG	PrimerBank 6679777a1
FGF15-R	CTGACACAGACTGGGATTGCT	PrimerBank 6679777a1
FGFR4-F	GGCTGTATTCCCCTCCATCG	PrimerBank 6671509a1
FGFR4-R	CCAGTTGGTAACAATGCCATGT	PrimerBank 6671509a1
HMGCR-F	GGCTGTATTCCCCTCCATCG	PrimerBank 6671509a1
HMGCR-R	CCAGTTGGTAACAATGCCATGT	PrimerBank 6671509a1
Acat2-F	GGCTGTATTCCCCTCCATCG	PrimerBank 6671509a1
Acat2-R	CCAGTTGGTAACAATGCCATGT	PrimerBank 6671509a1
β-actin-F	GGCTGTATTCCCCTCCATCG	PrimerBank 6671509a1
β-actin-R	CCAGTTGGTAACAATGCCATGT	PrimerBank 6671509a1

Supplemental Table 2 List of antibodies

Antibody name	Vendor	Cat#	Dilution
Mouse anti-Cyp7a1	Cosmo Bio	CAC-ABN-M01-CY	1:500
Goat anti-Cyp7a1	Santa Cruz	sc-14426	1:300
Rabbit anti-Cyp7a1	abcam	ab65596	1:500
pErk	Cell Signaling	4370	1:1000
pFRS2α(Y196)	Cell Signaling	3864	1:1000
Lamin B1	Cell Signaling	9087	1:1000
p38	Cell Signaling	9212	1:1000
p-p38	Cell Signaling	9216	1:1000

FGFR4(c16)	Santa Cruz	sc-124	1:1000 (mouse liver lysate WB)
FGFR4	Cell Signaling	8562	WB: 1:1000 IP: 1:200 Human cell lysate
GADPH	GeneTex	GTX627408	1:1000
β-actin	Sigma-Aldrich	A5316	1:5000
Rabbit anti-Shp2	Home-made	(Shi et al., 2000)	WB: 1:10,000 IP: 1:1000
Rabbit anti-Erk	Home-made	(Shi et al., 2000)	1:2000
Mouse anti-v5	Invitrogen	R960-25	1:5000
Rabbit anti-FRS	Kind gift from Dr. Zhengjun Chen	(Zhou et al., 2009)	WB: 1:5000 IP: 1:500
Phospho-PKC(pan)(βII Ser660)	Cell Signaling	9371	1:1000
Phospho-p90RSK (Thr359/Ser363)	Cell Signaling	9344	1:1000
Anti-Phosphotyrosine Antibody, clone 4G10®	Millipore	05-321	1:5000
Anti-Phosphotyrosine antibody [PY20]	Abcam	ab10321	1:5000
p-Tyr Antibody (PY99)	Santa Cruz	sc-7020	1:5000
Anti-Phosphoserine, clone 4A4	Millipore	05-1000	1:5000

Supplemental Table 3 Primer for Adenovirus generation and purification

VP16-ad-F	CACCATGGCCCCCC
VP16-ad-R	CCCACCGTACTCGTCATT
FXR-ad-R	CTGCACATCCCAGATCTCA
mSHP-ad-F	CACCATGAGCTCCGGCCAGTCA
mSHP-ad-R	CCTCAGCAAAAGCATGTCTTC

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