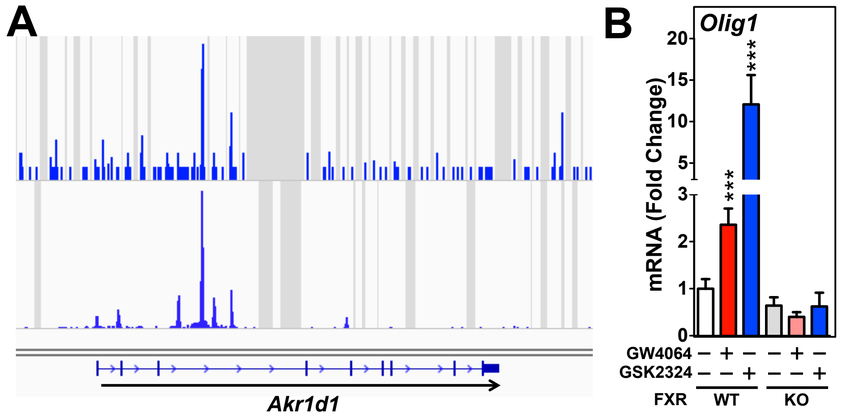
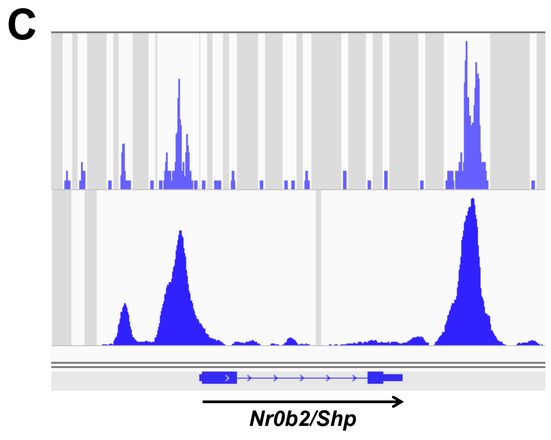
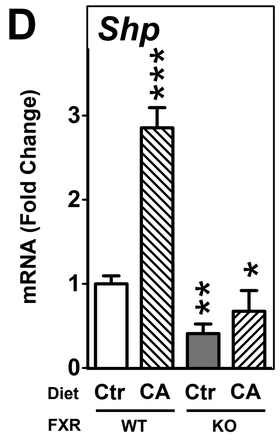
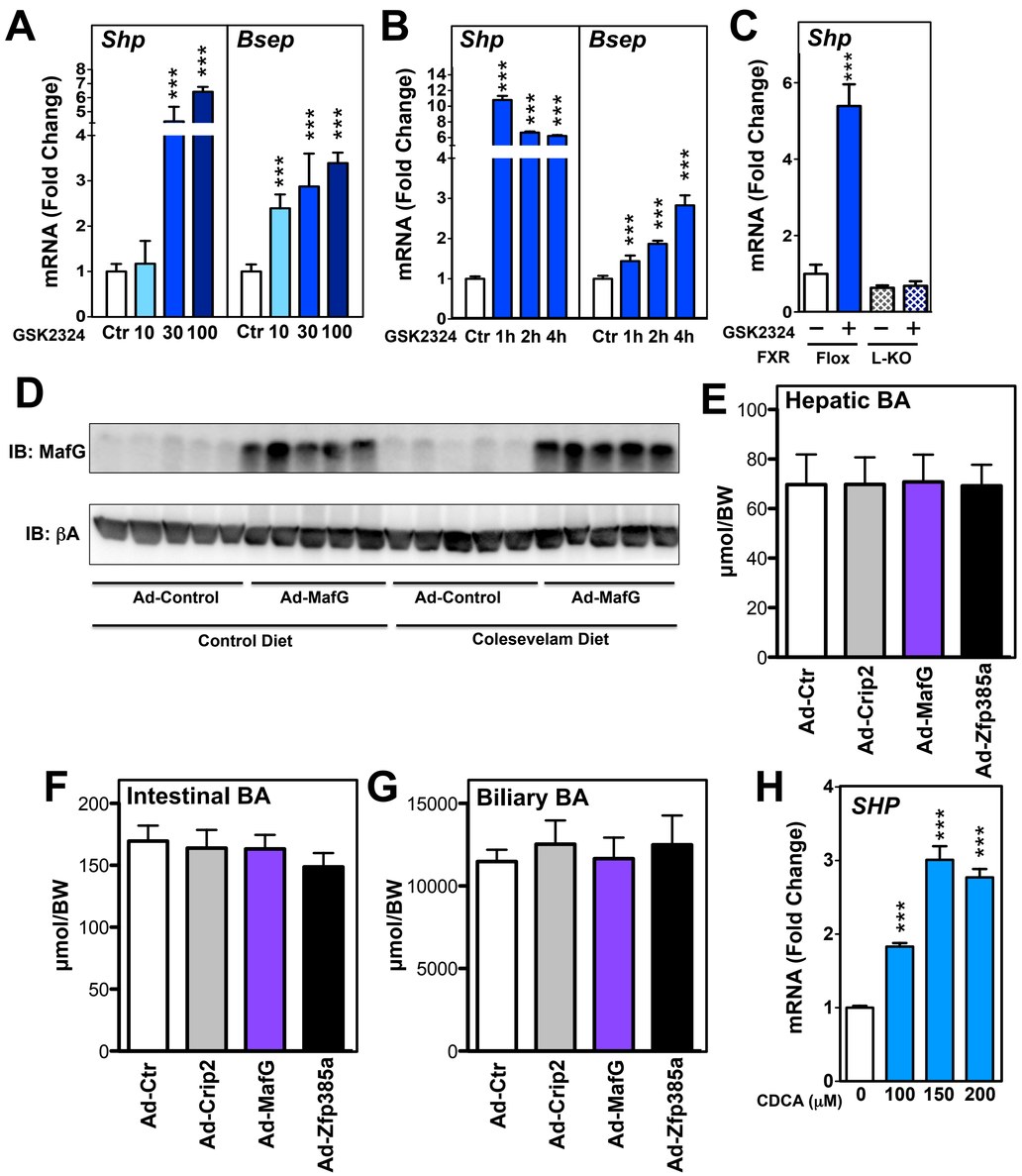






Supplementary Figure 1



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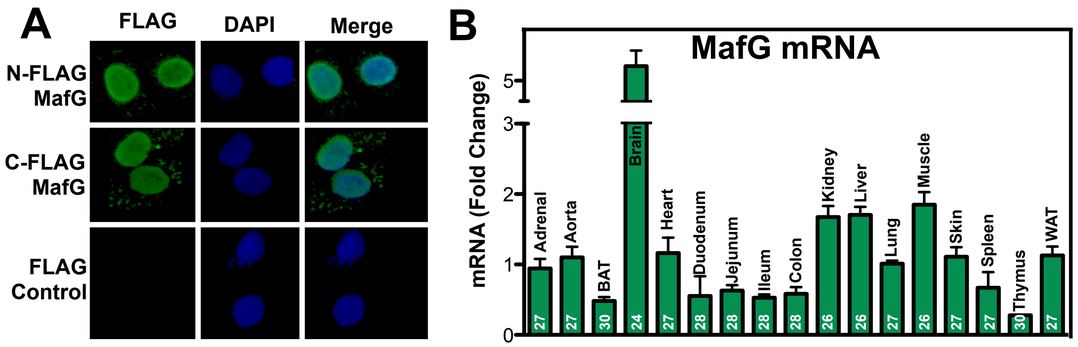

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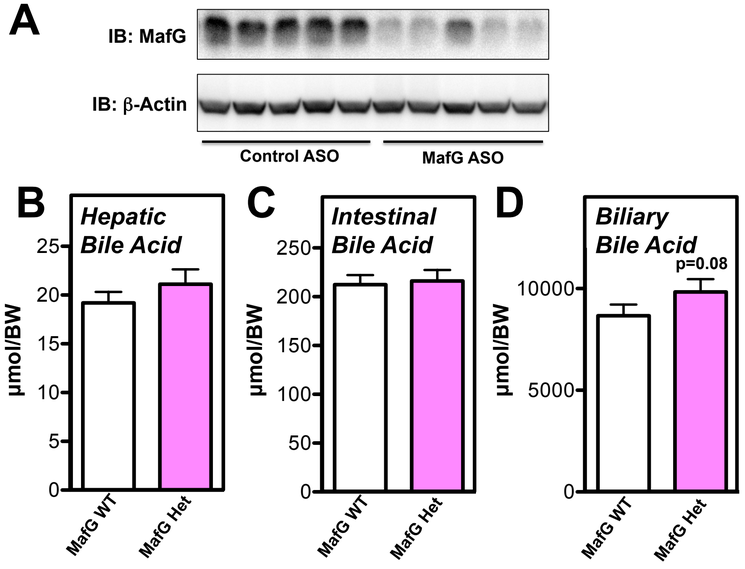
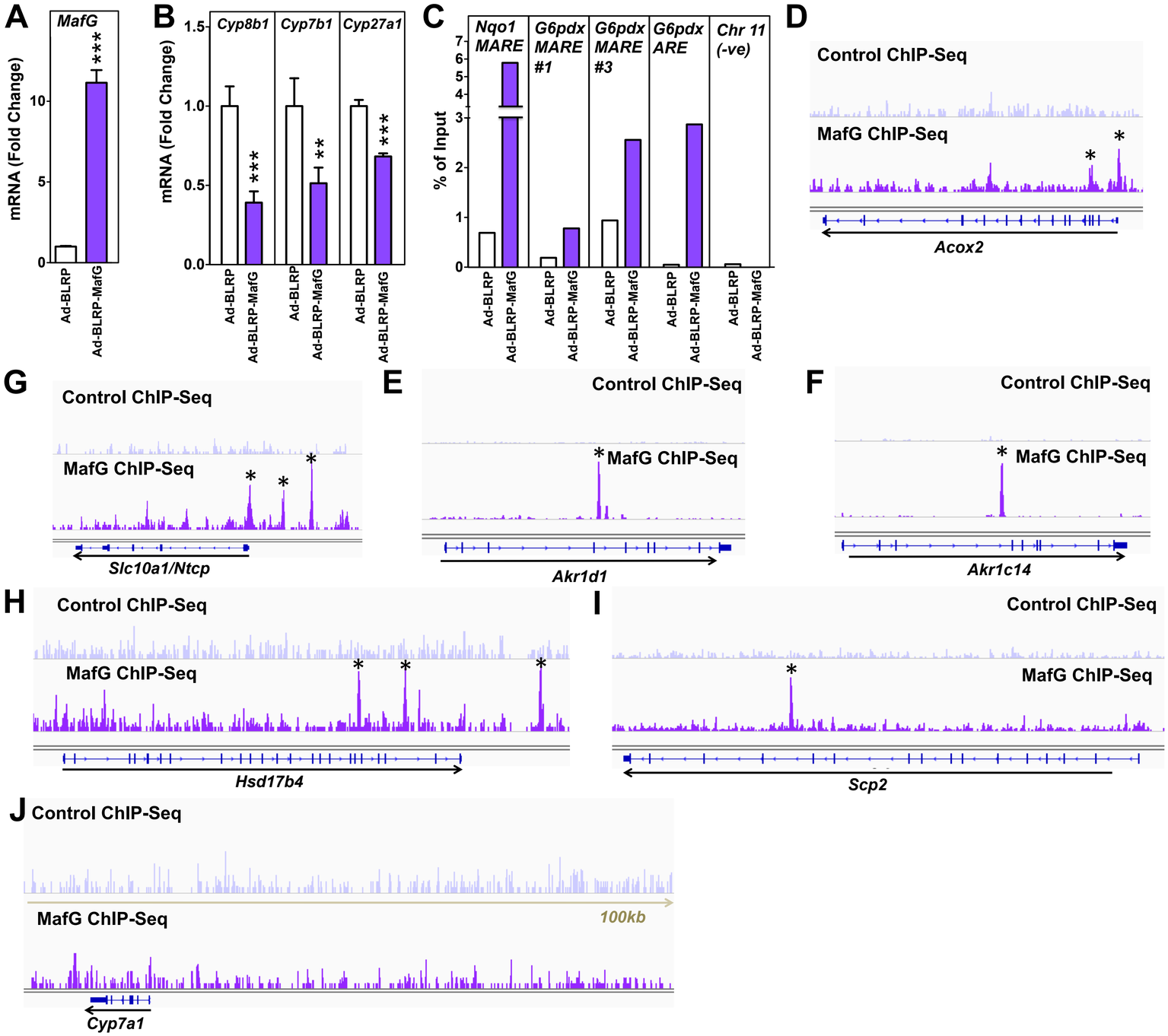
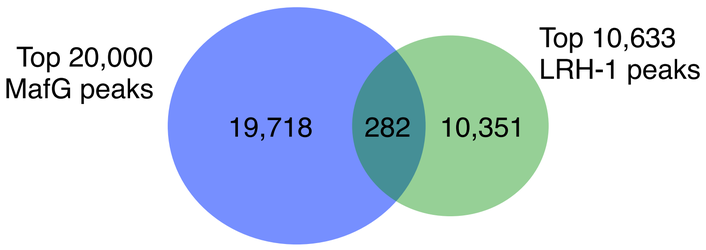


Supplementary Figure 4



Supplementary Figure 5

A



B

Term ID	Term Name	Enrichment p-value	Genes in Term	Target Genes in Term	Total Target Genes in Total	Fraction of Targets in Term
GO:0009892	negative regulation of metabolic process	3.67E-11	1715	53	243	22%

Supplementary Figure 6

Supplemental Figure Legends

Supplemental Figure 1 (related to Figure 2)– Identification of Transcriptional Repressors as Direct FXR Target Genes. (A) ChIP-Seq analysis of hepatic FXR from (Chong et al., 2010) (top) and (Thomas et al., 2010) (bottom) at *Akr1d1* genomic locus. (B) Hepatic expression of *Olig1* in C57BL/6 wild-type and $Fxr^{-/-}$ mice treated with vehicle, GW4064 or GSK2324 for 3 days (n=7-9 mice/group). (C) ChIP-Seq analysis of hepatic FXR from (Chong et al., 2010) (top) and (Thomas et al., 2010) (bottom) at *Shp* (gene symbol Nr0b2) genomic locus. (D) Hepatic expression of *Shp* in C57BL/6 wild-type and $Fxr^{-/-}$ mice fed either a control or 0.25% cholic acid (CA) diet for 7 days. All data shown as mean ± SEM. Asterisks indicate statistically significant differences comparing WT or KO vehicle treated against agonist treated mice (*p<0.05; **p<0.01; *** p<0.001).

Supplemental Figure 2 (related to Figure 3) – Regulation of *Crip2*, *MafG* and *Zfp385a* by FXR and Effect of MafG Overexpression on Total Bile Acid Levels.

(A) Hepatic expression of *Shp* and *Bsep* in C57BL/6 wild-type mice treated daily with vehicle, or 10, 30 or 100mpk of GSK2324 for 3 days (n=4-8 mice/group). (B) Hepatic expression of *Shp* and *Bsep* in C57BL/6 wild-type treated with 30 mpk of GSK2324 for 1, 2 or 4h before sacrifice (n=6 mice/group). (C) Hepatic expression of *Shp* in littermate C57BL/6 wild-type (Flox) or liver-specific $Fxr^{-/-}$ mice (L-KO) treated with GSK2324 (n=7-9 mice/group). (D) Western blotting analysis of MafG and beta actin for Ad-control or Ad-MafG-treated livers (n=5 mice/group) fed

either control or colesevelam (Colesev) diet. Quantification of Western blots are shown in Fig 3C. (E-G) Total bile acid levels measured following extraction from liver (E), intestine (F) or directly from biliary fluid (G), normalized to body weight (n=7/8 mice/group). (H) Expression levels of *SHP* in human HepG2 cells treated with 100,150 or 200μM chenodeoxycholic acid (CDCA) for 4 hours (n=4 wells/condition). All data shown as mean ± SEM. Asterisks indicate statistically significant differences comparing WT or KO vehicle treated against agonist treated mice, or in H, comparing vehicle with CDCA treatments (*** $p<0.001$).

Supplemental Figure 3 (related to Results section: MAFG Overexpression in Mouse Liver Represses Numerous Genes Involved in Bile Acid Metabolism) – Nuclear Localization and Tissue Expression of *MafG*. (A) Nuclear localization of MAFG protein following transfection of Hep3B cells with pcDNA3.1 expressing MAFG containing a FLAG peptide at either the N- or C-termini (identified with anti-FLAG antibody). (B) Expression of *MafG* mRNA in various tissues isolated from 8-week old C57BL/6 male mice (n=3 mice per tissue). Cp values, indicative of mRNA abundance, are listed for each tissue in white. All data are shown as mean ± SEM.

Supplemental Figure 4 (related to Figure 5)– Loss of MafG Does not Affect Total Bile Acid Levels. (A) Western blotting analysis of MAFG and β-ACTIN in livers of mice treated with control ASO or MafG ASO (100mpk) for 3 days. Quantification of the Western blots is shown in Fig. 5F. (B-D) Total bile acid levels measured following extraction from liver (B), intestine (C) or directly from biliary fluid (D), normalized to body weight (n=8-9 mice/group).

Supplemental Figure 5 (related to Figure 6) – Identification of MAFG-Response Elements (MAREs) in Known and Newly Identified MAFG Target Genes. (A) Hepatic levels of *MafG* mRNA or (B) *Cyp8b1* mRNA levels in C57BL/6 mice treated with either control (Ad-BLRP) or BLRP-tagged *MafG* adenovirus (Ad-BLRP MafG) (n=6-7 mice/group). All data shown as mean ± SEM. Asterisks indicate statistically significant differences comparing BLRP-Control versus BLRP MafG (** $p<0.01$; *** $p<0.001$). (C) Chromatin immunoprecipitation (ChIP) analysis of hepatic BLRP-*MafG* occupancy at the *Nqo1* and *G6pdx* loci determined by RT-qPCR using primers described in Hirotsu *et al*. (Hirotsu et al., 2012). (D-I) ChIP-Seq analysis of MAREs in chromatin isolated from livers of mice treated with Ad-BLRP (control; top) or Ad-BLRP MafG (bottom) at loci for (D) *Acox2* (E) *Akr1d1*, (F) *Akr1c14*, (G) *Ntcp*, (H) *Hsd17b4*, (I) *Scp2* and (J) *Cyp7a1*. Significant peaks are highlighted with *.

Supplemental Figure 6 (related to Results section: Identification of MAFG Binding Sites at Multiple Genes Involved in Bile Acid Synthesis and Metabolism) – Co-occupancy of Genes by MafG and LRH1. (A) Venn diagram for ChIP-Seq analysis from liver LRH1 and MafG binding sites, showing 282 genes are co-bound by MafG and LRH1. (B) Gene ontology analysis of 282 genes identifies negative metabolic processes as a significantly enriched category.

Supplemental Table 1 - RT-qPCR Primer Sequences

Gene	Forward	Reverse	Ref
Mouse *Crip2*	TGCTGAGCATGATGGGAAG	CGGTCTGAGGCTTCTCGTAG	
Mouse *MafG*	GACCCCCAATAAAGGAAACAA	TCAACTCTCGCACCGACAT	

Mouse *Zfp385a*	GTCTGTCAGATCCGCTTCAAT	GGCGATTACCCTTGTAGTGC	
Mouse *Bsep (Abcb11)*	AAGCTACATCTGCCTTAGACACAGAA	CAATACAGGTCCGACCCTCTCT	(Schmidt et al., 2010)
Mouse *Shp (Nr0b2)*	CGATCCTCTTCAACCCAGATG	AGGGCTCCAAGACTTCACACA	(Schmidt et al., 2010)
Mouse *Cyp7a1*	AGCAACTAAACAACCTGCCAGTACTA	GTCCGGATATTCAAGGATGCA	(Schmidt et al., 2010)
Mouse *Cyp8b1*	GCCTTCAAGTATGATCGGTTCCT	GATCTTCTTGCCCGACTTGTAGA	(Schmidt et al., 2010)
Mouse *Cyp7b1*	TAGCCCTCTTTCCTCCACTCATA	GAACCGATCGAACCTAAATTCCT	(Schmidt et al., 2010)
Mouse *Cyp27a1*	GCCTCACCTATGGGATCTTCA	TCAAAGCCTGACGCAGATG	(Schmidt et al., 2010)
Mouse *Cyp39a1*	ACCTATGATGAGGGCTTTGAGTA	CCATCTTTTGGATTTTGACCA	
Mouse *Acox2*	AGATTGGGCCTATAGGGAAGA	CACCGGGAGGTACCAAGAA	
Mouse *Akr1d1*	GAAAAGATAGCAGAAGGGAAGGT	GGGACATGCTCTGTATTCCATAA	
Mouse *Akr1c14*	TTATTCATTTCCCAATGGCTTT	TTTTCCATGTTCGTCTCGTG	
Mouse *Amacr*	GGCAGGTCATCGATTCAAG	GCTGGGTTTTCCACAGGA	
Mouse *Hsd17b4*	GGGAGCAGTACTTGGAGCTG	TCAGCAATAACTGCTTCACATTTT	
Mouse *Hsd3b7*	CGCTTTGGAGGTCGTCTATT	CAGTATGTGCATCCAAGCAAC	
Mouse *Ntcp* (*Slc10a1*)	GAAGTCCAAAAGGCCACACTATGT	ACAGCCACAGAGAGGGAGAAAG	(Schmidt et al., 2010)
Mouse *Scp2*	GATTGCTTCTCTGTCAATGAACTC	ACCAGGGTTCCACCTTGTC	
Mouse *Slc25a7*	AGGGTTTTTGCATTCCTGTG	TTGGTTCTTTCGAACCTTGG	
Mouse *36B4 (Rplp0)*	CACTGGTCTAGGACCCGAGAAG	GGTGCCTCTGGAGATTTTCG	
Mouse *Tbp*	CTCAGTTACAGGTGGCAGCA	ACCAACAATCACCAACAGCA	
Human *MAFG*	GTGGACAGGAAGCAGCTCA	TATTGGGGGTCGTCATAACC	
Human *CYP8B1*	CTGGGCAACATGCTTCAGT	ACTTGTCCTGCATAGCTGAGG	
Human *36B4* (*RPLP0)*	GGTGCCTCTGGAGATTTTAG	CACTGGTCTCGGGCCCGAGAA	

Human *TBP*	CGGCTGTTTAACTTCGCTTC	CACACGCCAAGAAACAGTGA	

Supplemental Table 2 – BLRP-*MafG* ChIP qPCR Primer Sequences

Primer Pair	Forward	Reverse	Ref
Cyp8b1 -2652bp	AACTGCAAGCAGCATTTCTTC	GAAGCCAGGGCAGGAATC	
Cyp8b1 -2299bp	GAGTTCTCCCCAGCAAGGA	GCCCCAGAGATGGGATAGTC	
Cyp8b1 -1874bp	CTAATGGCAACTAAGGAGACACC	TCTCCATCAGACATCTGCTAGTTT	
Cyp8b1 -1211bp	GCCAGACACTGTCCTAAGAGC	GAGTACACCCATGTCAGTGATTTT	
Cyp8b1 -890bp	CAGGGAGAGATCCTGACTCAA	GGGTTCTCTGGAAAAGCAGA	
Cyp8b1 -382bp	TCATTGGCTAGCTCATTCACTAA	ACAGACACGCACTTTAAAAACAAT	
Cyp8b1 -83bp	TCCCTGTGCCAGCTAACTAGA	GTTCCTGCCCTTGGACTTT	
Cyp8b1 +39bp	GAGCTGACAAGTGGAGCTCAG	GCAGGGCTCCTAGCACTGTA	
Cyp8b1 +485bp	AACTCAACCAGGCCATGC	GCACCCAGACTCGAACCTT	
G6pdx ARE	GTGGCAGGGGACTGGTCTGC	TGTCAGTTGCAGGCTGAGCCAA	(Hirotsu et al., 2012)
G6pdx MARE #1	GGCCTTGCAGGAGTGAGGCA	AGCCGACCCTCAGTCGCAGT	(Hirotsu et al., 2012)
G6pdx MARE #3	GGGAGCCTGAGCCCAATGGC	AAGCCCAGCTGGCAGCAAGT	(Hirotsu et al., 2012)
Nqo1	GCACGAATTCATTTCACACGAGG	GGAAGTCACCTTTGCACGCTAG	(Hirotsu et al., 2012)
Negative	CTAGGCCACAGAATTGAAAGATCT	GTAGGTGGAAATTCTAGCATCATCC	

Extended Experimental Procedures

Animals. All animals were bred and housed in a pathogen-free animal facility and unless otherwise stated, were maintained on a C57BL/6 background (Jackson Laboratories). The generation of liver- and intestine-specific $Fxr^{-/-}$ mice and their respective (littermate) wild-type (flox) controls, and whole body $Fxr^{-/-}$ mice was previously described (de Aguiar Vallim et al., 2013). Littermate wild-

type and *MafG*$^{+/-}$ mice on a mixed background, were generated after re-derivation at UCLA from *MafG*$^{+/-}$ mating pairs.

Primary Hepatocyte Isolation: Primary hepatocytes were isolated as described previously from wild-type C57BL/6 mice (de Aguiar Vallim et al., 2013).

Bile Acid Analysis. Gall bladders were removed from all experimental mice after a 4-6 hour fast and bile removed and stored at -80ºC. Bile acid species were measured by the HPLC System. Conjugated bile acids were analyzed by high-pressure liquid chromatography using a Kinetex 5m C-18 100A 250 x 4.6 mm column (Phenomenex, Torrance, CA) with isocratic elution at 0.75 ml/min. The eluting solution was composed of a mixture of methanol and 0.01M KH_2PO_4 (67.4% v/v), adjusted to an apparent pH of 5.25 with H_2PO_4. Bile acids were quantified by measuring their absorbance at 205 nm and were identified by matching their relative retention times with those of known standards.

Total bile acids were extracted from liver and intestine by homogenizing a piece (approx. 250mg) of liver or the entire small intestine with contents in 96% ethanol. Samples were incubated at 55˚C overnight, and centrifuged at 2000xg the following day, where bile acids in the supernatant were collected. Pellets were re-suspended in the same volumes described above of 96% ethanol and incubated at 55˚C for a second overnight period. Samples were centrifuged as above, and supernatants combined, with the pellet being resuspended in half volume of chloroform:methanol (2:1 ratio) at incubated at room temperature for a final overnight period. Total bile acids were quantified with a calorimetric assay (Diazyme) calculated using a standard curve from different concentrations of Na-

tauro-cholic acid. For biliary bile acids, samples were diluted 1:1000 and assayed, for intestine, extracted samples were diluted 1:10 and for liver, undiluted extracted samples were used for the assay. Bile acid levels were then corrected for total body weight.

RNA Isolation, RT-qPCR Quantification. Liver samples (approximately 100mg) were removed from mice and immediately flash-frozen in liquid nitrogen and stored at -80ºC. Frozen tissue was then homogenized in Qiazol (Qiagen) and extracted according to the manufacturer's instructions. RNA was then DNAse-treated (rDNAseI, Ambion/Life Technologies) for 1 hour at 37ºC RNA was re-extracted by phenol:chloroform:isoamyl alcohol (25:24:1, pH 6.6, Life Technologies). Complementary DNA (cDNA) was synthesized from 500ng of RNA using the High Capacity cDNA Reverse Transcriptase kit (Applied Biosciences/Life Technologies) according to manufacturers' instructions. RT-qPCR analysis and microarray analysis are described in Supplemental Materials.

ChIP, ChIP-Seq and RNA-Seq Analysis. The biotin-ligase recognition peptide (BLRP) (Heinz et al., 2010) was cloned at the N-terminus of *MafG*, and used to generate at BLRP-tagged *MafG* adenovirus. C57BL/6 mice were infused with adenovirus particles as described above. Liver chromatin was isolated as described in detail in Supplemental Materials. FXR ChIP-Seq data have been previously described (Chong et al., 2010; Thomas et al., 2010). BED files were converted to BigWig files and visualized using the IGV browser or UCSC genome browser. Publically available RNA-Seq data (Menet et al., 2012) BedGraph files were downloaded from GEO datasets and visualized using IGV browser. For

MAFG ChIP-Seq analysis, libraries from IP chromatin isolated as described above were prepared using the Kapa Library Prep kit (Kapa Bioscience), sequences using the Illumina HiSeq sequencer (Illumina) by the UNGC at UCLA. Data analysis was carried out using Galaxy suite and visualized as described above. Peak and motif analysis was carried out using HOMER as previously described (Heinz et al., 2010). LRH1 ChIP-Seq peaks (identified using MACS2) (Chong et al., 2012) were converted to coordinates in mm10 and compared with MafG peaks identified as described above.

Western Blotting. Antibodies used for Western Blotting were MAFG (Genetex; GTX114541; 1:1000), β-ACTIN (Sigma, 1:5000), BLRP (Avi-tag; Genescript 1:1000), GAPDH (Genetex, 1:2000), LAMIN A/C (Santa Cruz, 1:1000) and for immuno-staining M2 FLAG (Sigma, 1:1000). For ASO-treated, or Ad-MafG treated livers (Colesevelam), Western blots were quantified using HRP detection with ECL prime reagent (GE Healthcare) according to manufacturer's instructions. HRP signal detection was determined electronically using GE Image Quant LAS 4000 system and parameters set strictly below the saturation point. Densitometric analysis was carried out using Quantity One software (BioRad) and relative protein levels expressed as fold change from control after normalization to β-actin protein levels, with vehicle, Ad-control or control ASO-treated mice set to 1.

Promoter Reporter Analysis and Cell Culture. Mouse *MafG* promoter (2kb) or *Cyp8b1* promoter luciferase reporter constructs (3kb, 1kb and 0.5kb) were generated by amplifying these regions from mouse genomic DNA using KAPA

HiFi polymerase (Kapa) and cloning them into pGL4.10[luc2] plasmid (Promega). Mutations were made with a nested PCR approach, and primers were designed with the Quick Change Site-Directed Mutagenesis website (Agilent). Luciferase reporter constructs were transfected using Fugene HD (Promega) according to manufacturer's instructions into human HepG2 cells (ATCC) or Hep3B cells (ATCC), plated onto 48-well dishes (n=6 wells/condition). After 24 hours, medium was replaced and cells were treated with either vehicle (DMSO or water) or GSK2324 (1μM in water) in medium containing 10% charcoal-stripped serum (Omega Scientific) for a further 24 hours. For siRNA transfections, HepG2 cells were seeded in 6 well plates transfected with 1μM siRNA (MafG siRNA; Cat #SI00036701, CCGGGTATTTATTGCTGTACA, or Allstars negative control (SI03650318) Qiagen) for 24 hours and then medium was replaced with 10% charcoal-stripped serum for further 24 hours before cells were harvested in Qiazol for RNA analysis or RIPA buffer for protein analysis.

Anti-sense oligonucleotides (ASO). A chimeric 16-mer phosphorothioate oligonucleotide targeted to mouse *MafG* (5'- GGCCAATACGCCGTCA -3') or control (5'- TAATGTCTGATAACTC -3') containing 2′-4' constrained ethyl groups at bases underlined was synthesized and purified as described in (Seth et al., 2010).

ChIP Analysis: One lobe of the liver was frozen in liquid nitrogen, and the remainder (~80%) of the liver was then macerated in PBS containing 1% formaldehyde and protease inhibitor cocktail 1 (PIC1, comprised of 1μg/ml leupeptin, 1.4μg/ml pepstatin, 0.2mg/ml PMSF (Sigma), 1mM EGTA, 1mM

EDTA) for 10 minutes with gentle rotation at room temperature. Crosslinking was then stopped by the addition of glycine (0.125M) and samples were further incubated for 5 minutes at room temperature. Fixed livers were then placed on ice and then centrifuged (2,000 x g for 10 minutes) and the pellet resuspended in 8ml of PBS containing protease inhibitor cocktail. Resuspended pellets were gently homogenized and again centrifuged as above. The resulting pellet was resuspended in 5ml lysis buffer (5mM PIPES, pH 8.0, 85mM KCl, 0.5% NP-40 alternate) supplemented with protease inhibitor complex 2 (PIC2, 10μg/ml leupeptin, 5μg/ml pepstatin, 0.2mg/ml PMSF, 50μg/ml ALLN, Sigma). Nuclei were released after 30 strokes using a Dounce homogenizer and collected after centrifugation as above. Pellets were resuspended in 6ml homogenization buffer (10mM HEPES, pH 7.6, 25mM KCl, 1mM EDTA, 1mM EGTA, 1M Sucrose, 10% glycerol, 0.15mM spermine, supplemented with PIC1) and layered onto 3ml of the same buffer. Nuclei were then pelleted at 26,000rpm for 1 hour (Beckman SW41 rotor) and stored at -80ºC. Nuclear pellets were re-suspended in 0.3ml nuclear lysis buffer (50mM Tris pH 7.6, 10mM EDTA and 1% SDS), and diluted with 0.6ml immunoprecipitation (IP) dilution buffer (0.01% SDS, 1.1% Triton x100, 167mM NaCl, 16.7mM Tris pH 7.6, 1.2mM EDTA). For sonication, 0.3ml (1/3) of nuclear lysate was sonicated for 25-30 cycles 30 seconds on 30 seconds off at 4ºC with BioRuptor twin sonicator (Diagenode). Sonicated chromatin was then further diluted to 1ml with IP dilution buffer, which is sufficient for three ChIP reactions. The BLRP antibody (Genescript) was conjugated to Protein G Dynabeads (Life Technologies) in PBS containing 0.5% BSA overnight at 4ºC

with gentle rotation. Sonicated DNA (0.33ml made up to 1ml in IP dilution buffer) was then incubated overnight with Protein G-BLRP beads at 4ºC with gentle rotation. For input samples, 10% was used. Samples were then washed twice with wash buffer I (20mM Tris, pH 7.4, 150mM NaCl, 0.1% SDS, 1% Triton X100, 2mM EDTA), three times with alternate wash buffer III (10mM Tris, pH 7.4, 250mM LiCl, 1% NP-40 alternate, 0.7% Deoxycholate, 1mM EDTA), two washes with 0.2% Triton X100 TE buffer and two final washes with 50mM NaCl containing TE buffer. Chromatin was recovered and DNA from IP and input was isolated after reverse crosslinking (incubating at 65ºC overnight in 0.3M NaCl and Proteinase K digestion) and DNA purified using gel/PCR extraction kit (Clontech). For qPCR analysis, samples were diluted 1:10 and run in triplicate as described above. A standard curve for PCR was generated from 4 log serial dilutions of input samples and data expressed as percentage of input. Primer sequences for ChIP analysis are provided in Table S2.

RT-qPCR Analysis: RT-qPCR standards were prepared from an aliquot from each cDNA reaction that was then pooled. Standards which were diluted over 3 log range (dilution range 1:5, 1:10, 1:50, 1:100, 1:500, 1:1000). Quantitative PCR was carried out with primers designed to cross exon-exon boundaries using the Roche UPL primer design website. RT-qPCR primer sequences are provided in Table S1. Quantitative PCR was carried out in triplicate for each sample in 384-well format using Kapa LC480 SYBR green mix (Kapa Biosciences). Quantitative PCR was carried out using a Lightcycler 480 (Roche) and concentrations were determined from the standard curve using the efficiency corrected method (2^{nd}

derivative max, Roche). Relative quantification was determined by normalizing the expression of each gene to a housekeeper. Two housekeepers were used to normalize gene expression data (*36B4* and *Tbp*).

Microarray Analysis: Hepatic RNA was isolated from 3 mice treated with Ad-Control or Ad-MafG and global gene expression measured by the UCLA Neuroscience Genomics Core (UNGC) using Illumina microarrays (Illumina). Microarray analysis was carried out using Genome Suite (Illumina) and differential gene expression determined from probes that that had expression of $p>0.05$, (approximately 10,000 genes left over after filtering). Of those, genes that were altered 1.5 fold were considered differentially expressed. Gene enrichment analysis was carried out using DAVID and pathway analysis using KEGG (Huang da et al., 2009).

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Supplemental Figure Legends

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Supplemental Figure 2 (related to Figure 3) – Regulation of *Crip2*, *MafG* and *Zfp385a* by FXR and Effect of MafG Overexpression on Total Bile Acid Levels.

(A) Hepatic expression of *Shp* and *Bsep* in C57BL/6 wild-type mice treated daily with vehicle, or 10, 30 or 100mpk of GSK2324 for 3 days (n=4-8 mice/group). (B) Hepatic expression of *Shp* and *Bsep* in C57BL/6 wild-type treated with 30 mpk of GSK2324 for 1, 2 or 4h before sacrifice (n=6 mice/group). (C) Hepatic expression of *Shp* in littermate C57BL/6 wild-type (Flox) or liver-specific $Fxr^{-/-}$ mice (L-KO) treated with GSK2324 (n=7-9 mice/group). (D) Western blotting analysis of MafG and beta actin for Ad-control or Ad-MafG-treated livers (n=5 mice/group) fed

either control or colesevelam (Colesev) diet. Quantification of Western blots are shown in Fig 3C. (E-G) Total bile acid levels measured following extraction from liver (E), intestine (F) or directly from biliary fluid (G), normalized to body weight (n=7/8 mice/group). (H) Expression levels of *SHP* in human HepG2 cells treated with 100,150 or 200μM chenodeoxycholic acid (CDCA) for 4 hours (n=4 wells/condition). All data shown as mean ± SEM. Asterisks indicate statistically significant differences comparing WT or KO vehicle treated against agonist treated mice, or in H, comparing vehicle with CDCA treatments (*** $p<0.001$).

Supplemental Figure 3 (related to Results section: MAFG Overexpression in Mouse Liver Represses Numerous Genes Involved in Bile Acid Metabolism) – Nuclear Localization and Tissue Expression of *MafG*. (A) Nuclear localization of MAFG protein following transfection of Hep3B cells with pcDNA3.1 expressing MAFG containing a FLAG peptide at either the N- or C-termini (identified with anti-FLAG antibody). (B) Expression of *MafG* mRNA in various tissues isolated from 8-week old C57BL/6 male mice (n=3 mice per tissue). Cp values, indicative of mRNA abundance, are listed for each tissue in white. All data are shown as mean ± SEM.

Supplemental Figure 4 (related to Figure 5)– Loss of MafG Does not Affect Total Bile Acid Levels. (A) Western blotting analysis of MAFG and β-ACTIN in livers of mice treated with control ASO or MafG ASO (100mpk) for 3 days. Quantification of the Western blots is shown in Fig. 5F. (B-D) Total bile acid levels measured following extraction from liver (B), intestine (C) or directly from biliary fluid (D), normalized to body weight (n=8-9 mice/group).

Supplemental Figure 5 (related to Figure 6) – Identification of MAFG-Response Elements (MAREs) in Known and Newly Identified MAFG Target Genes. (A) Hepatic levels of *MafG* mRNA or (B) *Cyp8b1* mRNA levels in C57BL/6 mice treated with either control (Ad-BLRP) or BLRP-tagged *MafG* adenovirus (Ad-BLRP MafG) (n=6-7 mice/group). All data shown as mean ± SEM. Asterisks indicate statistically significant differences comparing BLRP-Control versus BLRP MafG (** $p<0.01$; *** $p<0.001$). (C) Chromatin immunoprecipitation (ChIP) analysis of hepatic BLRP-*MafG* occupancy at the *Nqo1* and *G6pdx* loci determined by RT-qPCR using primers described in Hirotsu *et al*. (Hirotsu et al., 2012). (D-I) ChIP-Seq analysis of MAREs in chromatin isolated from livers of mice treated with Ad-BLRP (control; top) or Ad-BLRP MafG (bottom) at loci for (D) *Acox2* (E) *Akr1d1*, (F) *Akr1c14*, (G) *Ntcp*, (H) *Hsd17b4*, (I) *Scp2* and (J) *Cyp7a1*. Significant peaks are highlighted with *.

Supplemental Figure 6 (related to Results section: Identification of MAFG Binding Sites at Multiple Genes Involved in Bile Acid Synthesis and Metabolism) – Co-occupancy of Genes by MafG and LRH1. (A) Venn diagram for ChIP-Seq analysis from liver LRH1 and MafG binding sites, showing 282 genes are co-bound by MafG and LRH1. (B) Gene ontology analysis of 282 genes identifies negative metabolic processes as a significantly enriched category.

Supplemental Table 1 - RT-qPCR Primer Sequences

Gene	Forward	Reverse	Ref
Mouse *Crip2*	TGCTGAGCATGATGGGAAG	CGGTCTGAGGCTTCTCGTAG	
Mouse *MafG*	GACCCCCAATAAAGGAAACAA	TCAACTCTCGCACCGACAT	

Mouse *Zfp385a*	GTCTGTCAGATCCGCTTCAAT	GGCGATTACCCTTGTAGTGC	
Mouse *Bsep (Abcb11)*	AAGCTACATCTGCCTTAGACACAGAA	CAATACAGGTCCGACCCTCTCT	(Schmidt et al., 2010)
Mouse *Shp (Nr0b2)*	CGATCCTCTTCAACCCAGATG	AGGGCTCCAAGACTTCACACA	(Schmidt et al., 2010)
Mouse *Cyp7a1*	AGCAACTAAACAACCTGCCAGTACTA	GTCCGGATATTCAAGGATGCA	(Schmidt et al., 2010)
Mouse *Cyp8b1*	GCCTTCAAGTATGATCGGTTCCT	GATCTTCTTGCCCGACTTGTAGA	(Schmidt et al., 2010)
Mouse *Cyp7b1*	TAGCCCTCTTTCCTCCACTCATA	GAACCGATCGAACCTAAATTCCT	(Schmidt et al., 2010)
Mouse *Cyp27a1*	GCCTCACCTATGGGATCTTCA	TCAAAGCCTGACGCAGATG	(Schmidt et al., 2010)
Mouse *Cyp39a1*	ACCTATGATGAGGGCTTTGAGTA	CCATCTTTTGGATTTTGACCA	
Mouse *Acox2*	AGATTGGGCCTATAGGGAAGA	CACCGGGAGGTACCAAGAA	
Mouse *Akr1d1*	GAAAAGATAGCAGAAGGGAAGGT	GGGACATGCTCTGTATTCCATAA	
Mouse *Akr1c14*	TTATTCATTTCCCAATGGCTTT	TTTTCCATGTTCGTCTCGTG	
Mouse *Amacr*	GGCAGGTCATCGATTCAAG	GCTGGGTTTTCCACAGGA	
Mouse *Hsd17b4*	GGGAGCAGTACTTGGAGCTG	TCAGCAATAACTGCTTCACATTTT	
Mouse *Hsd3b7*	CGCTTTGGAGGTCGTCTATT	CAGTATGTGCATCCAAGCAAC	
Mouse *Ntcp* (*Slc10a1*)	GAAGTCCAAAAGGCCACACTATGT	ACAGCCACAGAGAGGGAGAAAG	(Schmidt et al., 2010)
Mouse *Scp2*	GATTGCTTCTCTGTCAATGAACTC	ACCAGGGTTCCACCTTGTC	
Mouse *Slc25a7*	AGGGTTTTTGCATTCCTGTG	TTGGTTCTTTCGAACCTTGG	
Mouse *36B4 (Rplp0)*	CACTGGTCTAGGACCCGAGAAG	GGTGCCTCTGGAGATTTTCG	
Mouse *Tbp*	CTCAGTTACAGGTGGCAGCA	ACCAACAATCACCAACAGCA	
Human *MAFG*	GTGGACAGGAAGCAGCTCA	TATTGGGGGTCGTCATAACC	
Human *CYP8B1*	CTGGGCAACATGCTTCAGT	ACTTGTCCTGCATAGCTGAGG	
Human *36B4* (*RPLP0)*	GGTGCCTCTGGAGATTTTAG	CACTGGTCTCGGGCCCGAGAA	

Human *TBP*	CGGCTGTTTAACTTCGCTTC	CACACGCCAAGAAACAGTGA	

Supplemental Table 2 – BLRP-*MafG* ChIP qPCR Primer Sequences

Primer Pair	Forward	Reverse	Ref
Cyp8b1 -2652bp	AACTGCAAGCAGCATTTCTTC	GAAGCCAGGGCAGGAATC	
Cyp8b1 -2299bp	GAGTTCTCCCCAGCAAGGA	GCCCCAGAGATGGGATAGTC	
Cyp8b1 -1874bp	CTAATGGCAACTAAGGAGACACC	TCTCCATCAGACATCTGCTAGTTT	
Cyp8b1 -1211bp	GCCAGACACTGTCCTAAGAGC	GAGTACACCCATGTCAGTGATTTT	
Cyp8b1 -890bp	CAGGGAGAGATCCTGACTCAA	GGGTTCTCTGGAAAAGCAGA	
Cyp8b1 -382bp	TCATTGGCTAGCTCATTCACTAA	ACAGACACGCACTTTAAAAACAAT	
Cyp8b1 -83bp	TCCCTGTGCCAGCTAACTAGA	GTTCCTGCCCTTGGACTTT	
Cyp8b1 +39bp	GAGCTGACAAGTGGAGCTCAG	GCAGGGCTCCTAGCACTGTA	
Cyp8b1 +485bp	AACTCAACCAGGCCATGC	GCACCCAGACTCGAACCTT	
G6pdx ARE	GTGGCAGGGGACTGGTCTGC	TGTCAGTTGCAGGCTGAGCCAA	(Hirotsu et al., 2012)
G6pdx MARE #1	GGCCTTGCAGGAGTGAGGCA	AGCCGACCCTCAGTCGCAGT	(Hirotsu et al., 2012)
G6pdx MARE #3	GGGAGCCTGAGCCCAATGGC	AAGCCCAGCTGGCAGCAAGT	(Hirotsu et al., 2012)
Nqo1	GCACGAATTCATTTCACACGAGG	GGAAGTCACCTTTGCACGCTAG	(Hirotsu et al., 2012)
Negative	CTAGGCCACAGAATTGAAAGATCT	GTAGGTGGAAATTCTAGCATCATCC	

Extended Experimental Procedures

Animals. All animals were bred and housed in a pathogen-free animal facility and unless otherwise stated, were maintained on a C57BL/6 background (Jackson Laboratories). The generation of liver- and intestine-specific $Fxr^{-/-}$ mice and their respective (littermate) wild-type (flox) controls, and whole body $Fxr^{-/-}$ mice was previously described (de Aguiar Vallim et al., 2013). Littermate wild-

type and *MafG*$^{+/-}$ mice on a mixed background, were generated after re-derivation at UCLA from *MafG*$^{+/-}$ mating pairs.

Primary Hepatocyte Isolation: Primary hepatocytes were isolated as described previously from wild-type C57BL/6 mice (de Aguiar Vallim et al., 2013).

Bile Acid Analysis. Gall bladders were removed from all experimental mice after a 4-6 hour fast and bile removed and stored at -80ºC. Bile acid species were measured by the HPLC System. Conjugated bile acids were analyzed by high-pressure liquid chromatography using a Kinetex 5m C-18 100A 250 x 4.6 mm column (Phenomenex, Torrance, CA) with isocratic elution at 0.75 ml/min. The eluting solution was composed of a mixture of methanol and 0.01M KH_2PO_4 (67.4% v/v), adjusted to an apparent pH of 5.25 with H_2PO_4. Bile acids were quantified by measuring their absorbance at 205 nm and were identified by matching their relative retention times with those of known standards.

Total bile acids were extracted from liver and intestine by homogenizing a piece (approx. 250mg) of liver or the entire small intestine with contents in 96% ethanol. Samples were incubated at 55˚C overnight, and centrifuged at 2000xg the following day, where bile acids in the supernatant were collected. Pellets were re-suspended in the same volumes described above of 96% ethanol and incubated at 55˚C for a second overnight period. Samples were centrifuged as above, and supernatants combined, with the pellet being resuspended in half volume of chloroform:methanol (2:1 ratio) at incubated at room temperature for a final overnight period. Total bile acids were quantified with a calorimetric assay (Diazyme) calculated using a standard curve from different concentrations of Na-

tauro-cholic acid. For biliary bile acids, samples were diluted 1:1000 and assayed, for intestine, extracted samples were diluted 1:10 and for liver, undiluted extracted samples were used for the assay. Bile acid levels were then corrected for total body weight.

RNA Isolation, RT-qPCR Quantification. Liver samples (approximately 100mg) were removed from mice and immediately flash-frozen in liquid nitrogen and stored at -80ºC. Frozen tissue was then homogenized in Qiazol (Qiagen) and extracted according to the manufacturer's instructions. RNA was then DNAse-treated (rDNAseI, Ambion/Life Technologies) for 1 hour at 37ºC RNA was re-extracted by phenol:chloroform:isoamyl alcohol (25:24:1, pH 6.6, Life Technologies). Complementary DNA (cDNA) was synthesized from 500ng of RNA using the High Capacity cDNA Reverse Transcriptase kit (Applied Biosciences/Life Technologies) according to manufacturers' instructions. RT-qPCR analysis and microarray analysis are described in Supplemental Materials.

ChIP, ChIP-Seq and RNA-Seq Analysis. The biotin-ligase recognition peptide (BLRP) (Heinz et al., 2010) was cloned at the N-terminus of *MafG*, and used to generate at BLRP-tagged *MafG* adenovirus. C57BL/6 mice were infused with adenovirus particles as described above. Liver chromatin was isolated as described in detail in Supplemental Materials. FXR ChIP-Seq data have been previously described (Chong et al., 2010; Thomas et al., 2010). BED files were converted to BigWig files and visualized using the IGV browser or UCSC genome browser. Publically available RNA-Seq data (Menet et al., 2012) BedGraph files were downloaded from GEO datasets and visualized using IGV browser. For

MAFG ChIP-Seq analysis, libraries from IP chromatin isolated as described above were prepared using the Kapa Library Prep kit (Kapa Bioscience), sequences using the Illumina HiSeq sequencer (Illumina) by the UNGC at UCLA. Data analysis was carried out using Galaxy suite and visualized as described above. Peak and motif analysis was carried out using HOMER as previously described (Heinz et al., 2010). LRH1 ChIP-Seq peaks (identified using MACS2) (Chong et al., 2012) were converted to coordinates in mm10 and compared with MafG peaks identified as described above.

Western Blotting. Antibodies used for Western Blotting were MAFG (Genetex; GTX114541; 1:1000), β-ACTIN (Sigma, 1:5000), BLRP (Avi-tag; Genescript 1:1000), GAPDH (Genetex, 1:2000), LAMIN A/C (Santa Cruz, 1:1000) and for immuno-staining M2 FLAG (Sigma, 1:1000). For ASO-treated, or Ad-MafG treated livers (Colesevelam), Western blots were quantified using HRP detection with ECL prime reagent (GE Healthcare) according to manufacturer's instructions. HRP signal detection was determined electronically using GE Image Quant LAS 4000 system and parameters set strictly below the saturation point. Densitometric analysis was carried out using Quantity One software (BioRad) and relative protein levels expressed as fold change from control after normalization to β-actin protein levels, with vehicle, Ad-control or control ASO-treated mice set to 1.

Cell Culture. For GSK2324 treatments, cells were transfected for 24 hours and then treated with either vehicle (DMSO or water) or GSK2324 (1μM in water) in medium containing 10% charcoal-stripped serum (Omega Scientific) for a further

24 hours. For siRNA transfections, HepG2 cells were seeded in 6 well plates transfected with 1μM siRNA (MafG siRNA; Cat #SI00036701, CCGGGTATTTATTGCTGTACA, or Allstars negative control (SI03650318) Qiagen) for 24 hours and then medium was replaced with 10% charcoal-stripped serum for further 24 hours before cells were harvested in Qiazol for RNA analysis or RIPA buffer for protein analysis.

Anti-sense oligonucleotides (ASO). A chimeric 16-mer phosphorothioate oligonucleotide targeted to mouse *MafG* (5'- GGCCAATACGCCGTCA -3') or control (5'- TAATGTCTGATAACTC -3') containing 2′-4' constrained ethyl groups at bases underlined was synthesized and purified as described in (Seth et al., 2010).

ChIP Analysis: One lobe of the liver was frozen in liquid nitrogen, and the remainder (~80%) of the liver was then macerated in PBS containing 1% formaldehyde and protease inhibitor cocktail 1 (PIC1, comprised of 1μg/ml leupeptin, 1.4μg/ml pepstatin, 0.2mg/ml PMSF (Sigma), 1mM EGTA, 1mM EDTA) for 10 minutes with gentle rotation at room temperature. Crosslinking was then stopped by the addition of glycine (0.125M) and samples were further incubated for 5 minutes at room temperature. Fixed livers were then placed on ice and then centrifuged (2,000 x g for 10 minutes) and the pellet resuspended in 8ml of PBS containing protease inhibitor cocktail. Resuspended pellets were gently homogenized and again centrifuged as above. The resulting pellet was resuspended in 5ml lysis buffer (5mM PIPES, pH 8.0, 85mM KCl, 0.5% NP-40 alternate) supplemented with protease inhibitor complex 2 (PIC2, 10μg/ml

leupeptin, 5μg/ml pepstatin, 0.2mg/ml PMSF, 50μg/ml ALLN, Sigma). Nuclei were released after 30 strokes using a Dounce homogenizer and collected after centrifugation as above. Pellets were resuspended in 6ml homogenization buffer (10mM HEPES, pH 7.6, 25mM KCl, 1mM EDTA, 1mM EGTA, 1M Sucrose, 10% glycerol, 0.15mM spermine, supplemented with PIC1) and layered onto 3ml of the same buffer. Nuclei were then pelleted at 26,000rpm for 1 hour (Beckman SW41 rotor) and stored at -80ºC. Nuclear pellets were re-suspended in 0.3ml nuclear lysis buffer (50mM Tris pH 7.6, 10mM EDTA and 1% SDS), and diluted with 0.6ml immunoprecipitation (IP) dilution buffer (0.01% SDS, 1.1% Triton x100, 167mM NaCl, 16.7mM Tris pH 7.6, 1.2mM EDTA). For sonication, 0.3ml (1/3) of nuclear lysate was sonicated for 25-30 cycles 30 seconds on 30 seconds off at 4ºC with BioRuptor twin sonicator (Diagenode). Sonicated chromatin was then further diluted to 1ml with IP dilution buffer, which is sufficient for three ChIP reactions. The BLRP antibody (Genescript) was conjugated to Protein G Dynabeads (Life Technologies) in PBS containing 0.5% BSA overnight at 4ºC with gentle rotation. Sonicated DNA (0.33ml made up to 1ml in IP dilution buffer) was then incubated overnight with Protein G-BLRP beads at 4ºC with gentle rotation. For input samples, 10% was used. Samples were then washed twice with wash buffer I (20mM Tris, pH 7.4, 150mM NaCl, 0.1% SDS, 1% Triton X100, 2mM EDTA), three times with alternate wash buffer III (10mM Tris, pH 7.4, 250mM LiCl, 1% NP-40 alternate, 0.7% Deoxycholate, 1mM EDTA), two washes with 0.2% Triton X100 TE buffer and two final washes with 50mM NaCl containing TE buffer. Chromatin was recovered and DNA from IP and input was

isolated after reverse crosslinking (incubating at 65ºC overnight in 0.3M NaCl and Proteinase K digestion) and DNA purified using gel/PCR extraction kit (Clontech). For qPCR analysis, samples were diluted 1:10 and run in triplicate as described above. A standard curve for PCR was generated from 4 log serial dilutions of input samples and data expressed as percentage of input. Primer sequences for ChIP analysis are provided in Table S2.

RT-qPCR Analysis: RT-qPCR standards were prepared from an aliquot from each cDNA reaction that was then pooled. Standards which were diluted over 3 log range (dilution range 1:5, 1:10, 1:50, 1:100, 1:500, 1:1000). Quantitative PCR was carried out with primers designed to cross exon-exon boundaries using the Roche UPL primer design website. RT-qPCR primer sequences are provided in Table S1. Quantitative PCR was carried out in triplicate for each sample in 384-well format using Kapa LC480 SYBR green mix (Kapa Biosciences). Quantitative PCR was carried out using a Lightcycler 480 (Roche) and concentrations were determined from the standard curve using the efficiency corrected method (2^{nd} derivative max, Roche). Relative quantification was determined by normalizing the expression of each gene to a housekeeper. Two housekeepers were used to normalize gene expression data (*36B4* and *Tbp*).

Microarray Analysis: Hepatic RNA was isolated from 3 mice treated with Ad-Control or Ad-MafG and global gene expression measured by the UCLA Neuroscience Genomics Core (UNGC) using Illumina microarrays (Illumina). Microarray analysis was carried out using Genome Suite (Illumina) and differential gene expression determined from probes that that had expression of

p>0.05, (approximately 10,000 genes left over after filtering). Of those, genes that were altered 1.5 fold were considered differentially expressed. Gene enrichment analysis was carried out using DAVID and pathway analysis using KEGG (Huang da et al., 2009).

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