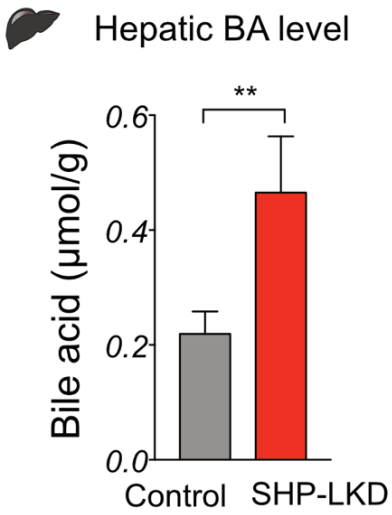
# Supplemental Information

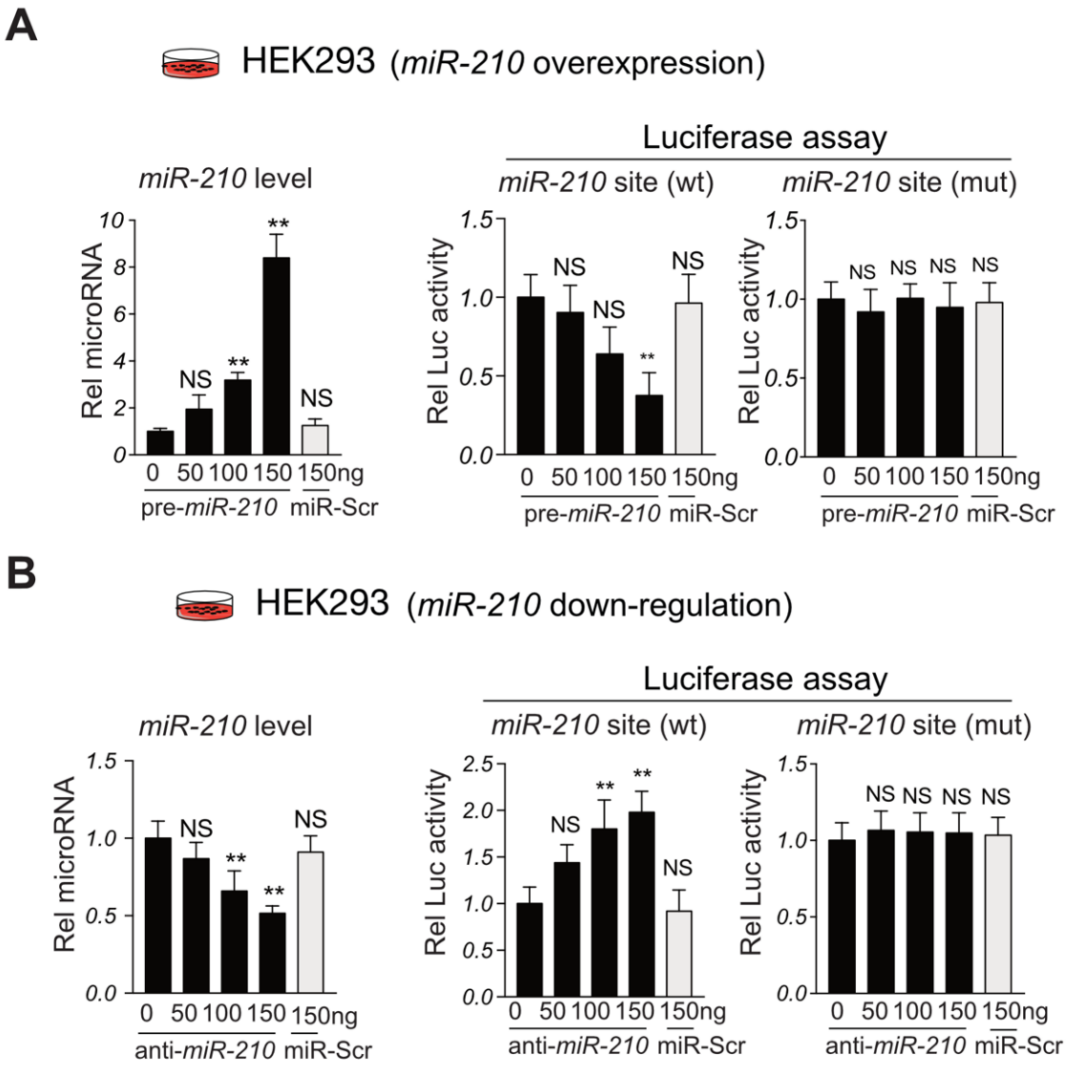
**Materials and reagents.**

Antibodies for MLL4 (ABE167) and MLL3 (ABE1851) were purchased from Millipore; for KLF4 (AF3158) from R&D system; for SHP (ab186874) from Abcam; for F4/80 (NB600-404SS) from Novus Biologicals; for LAMIN A (sc-20680) and $\beta$-TUBULIN (sc-9104) from Santa Cruz Biotechnology, and for $\beta$-ACTIN (CST-4970) from Cell Signaling Technology. Small interfering RNAs (ON-TARGETplus SMART pool) for *Klf4* (M-066785-00-0005), *Ahr* (M-044066-01-0005) and *Lrh1* (M-047044-00-0005) were purchased from Dharmacon. The target vector for lentivirus construction for the precursor of miR-210 (MmiR3303-MR03) was purchased from GeneCopoeia and for anti-miR-210 (mm30343) from Applied Biological Materials Inc. The lentiviral packaging vectors, psPAX2 (12260) and pMD2.G (12259) were obtained from Addgene. The miR-210 miRNA precursor (mmu-miR-210-3p, AM17100) and anti-miR-210 (mmu-miR-210-3p, AM17000) were purchased from Thermo Fisher. Lentiviruses expressing shRNA for *Mll4* and expression vectors for KLF4 were purchased from VectorBuilder.

# Supplemental Figures

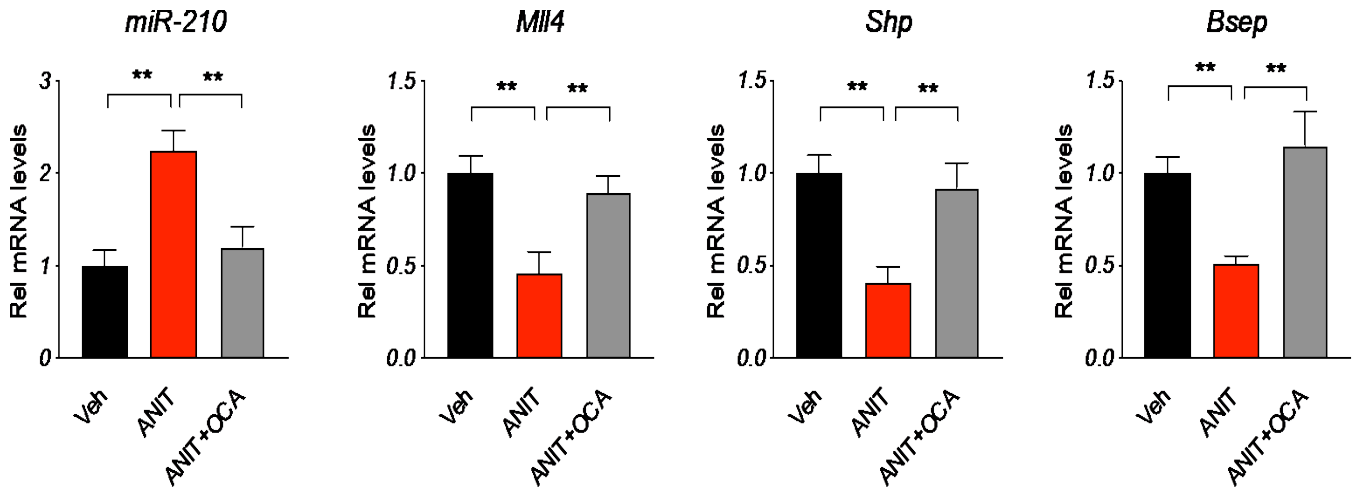



**Supplemental Figure S1. Increased hepatic BA levels in SHP-LKD mice compared to control mice.** SHP was downregulated as described in the Fig.1 legend and hepatic BA levels were measured. Statistical significance was determined by the Student's t-test, SD (n=5), ** $p < 0.01$.

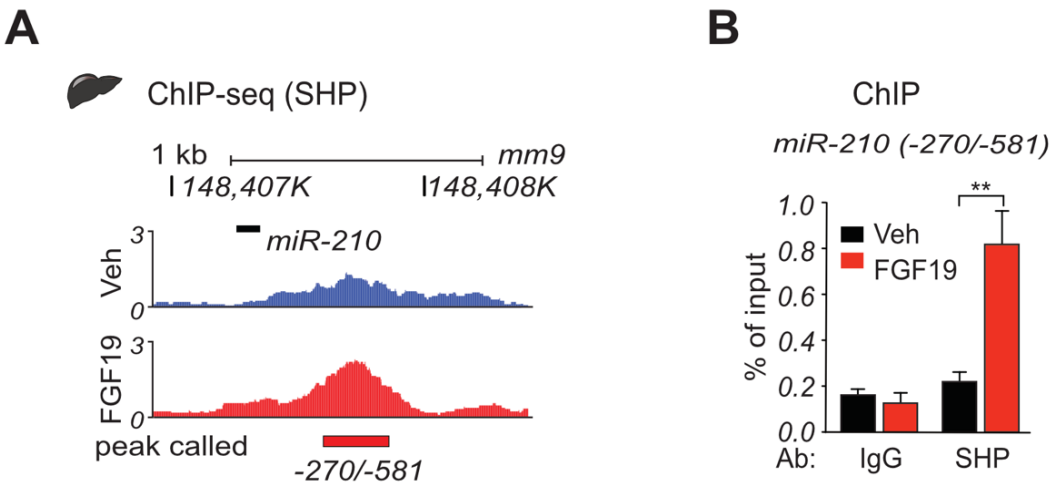



**Supplemental Figure S2. MiR-210 inhibits MLL4 expression in human HEK293 cells.**

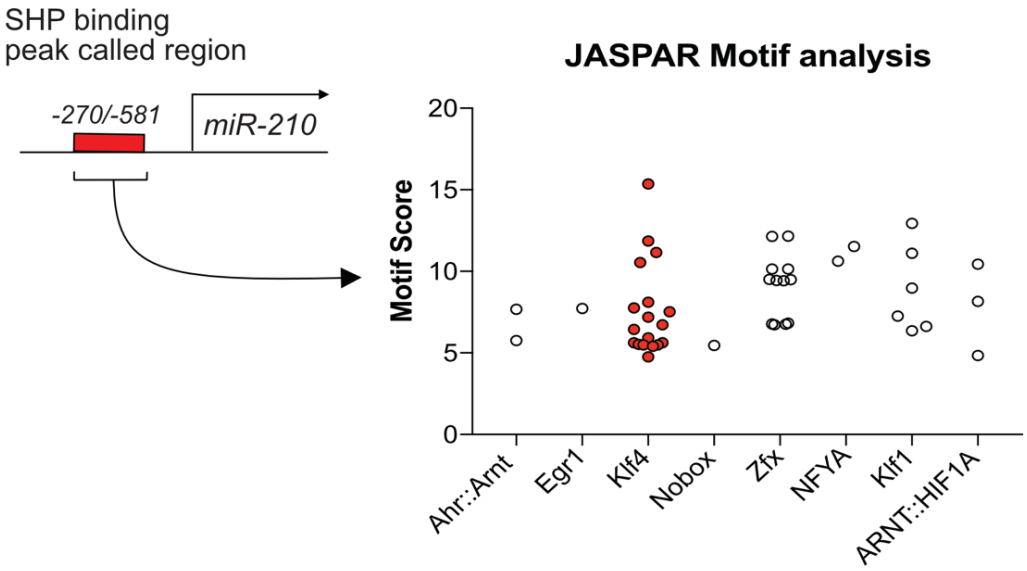
HEK293 cells were transfected with the indicated luciferase plasmids and with the indicated amounts of pre-miR-210 (A), anti-miR-210 (B), or scrambled RNA (miR-Scr) as a control, and 48 h later, luciferase activity was determined and normalized to $\beta$-galactosidase activity. Statistical significance was determined by one-way ANOVA, SD (n=3), ** $p < 0.01$, NS, not significant.



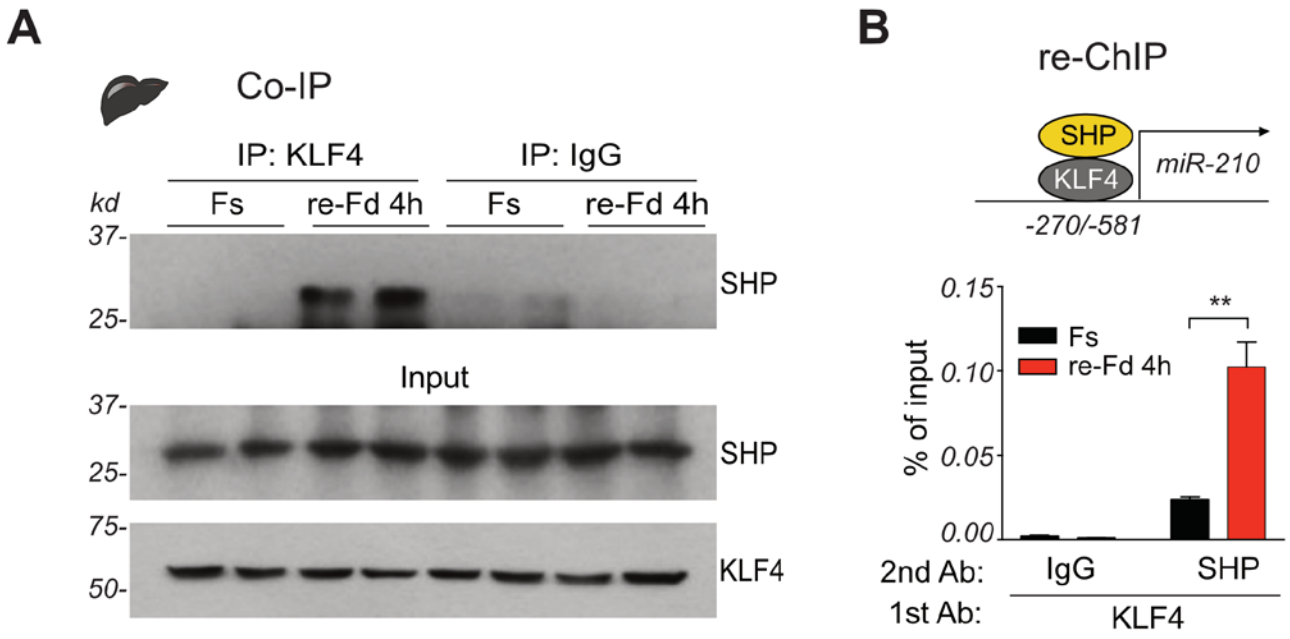

**Supplemental Figure S3. Activation of FXR in cholestatic mice can reverse the increase in miR-210 levels.** To examine the effects of OCA on ANIT-induced cholestasis, mice were treated with vehicle or 10 mg/kg of OCA, i.p., and after five days, treated with 35 mg/kg ANIT by gavage daily for 2 days. Hepatic mRNA levels of indicated genes were determined by RT-qPCR analysis. Statistical significance was determined by one-way ANOVA, SD (n=5), ** $p < 0.01$.




**Supplemental Figure S4. SHP occupancy is increased at the hepatic miR-210 promoter in response to FGF19 treatment.** (A) SHP binding peak at the hepatic miR-210 promoter from published ChIP-seq data (11). (B) Mice were fasted overnight and treated with vehicle or FGF19 for 2 h and standard liver ChIP assays were done to confirm SHP occupancy at the *miR-210* gene promoter. Statistical significance was determined by two-way ANOVA, SD (n=5), ** $p < 0.01$.




**Supplemental Figure S5. Potential transcription factor binding sites within the SHP binding peak region (312 bp) at the miR-210 promoter.** Potential binding sites for transcription factors detected by ChIP-seq were determined using the JASPAR online program (2018; http://jaspar.genereg.net/). The JASPAR motif scores for the individual potential binding motifs for the indicated factors are plotted.




**Supplemental Figure S6. Functional interaction between SHP and KLF4 is increased in the late fed-state.** C57BL/6J mice were refed for 4 h after fasting overnight. **(A) CoIP:** SHP protein levels in anti-KLF4 or IgG immunoprecipitates and SHP and KLF4 protein levels in the input samples. **(B) Re-ChIP:** Chromatin was immunoprecipitated with KLF4 antibody and then, eluted and re-precipitated with SHP antibody. Enrichment of the *miR-210* promoter sequence determined by qPCR. Statistical significance was determined by two-way ANOVA, SD (n=5), ** $p < 0.01$.

## Supplemental Table S1

### Mouse RT-qPCR primers

| | Forward (5'-3') | Reverse (5'-3') |
|---|---|---|
| *Cxcl2* | TCCAGAGCTTGAGTGTGACG | TTCAGGGTCAAGGCAAACTT |
| *Tnfα* | AGCCCCCAGTCTGTATCCTT | GGTCACTGTCCCAGCATCTT |
| *Shp* | CAAGAAGATTCTGCTGGAGG | GGATGTCAACATCTCCAATG |
| *Klf4* | CTGAACAGCAGGGACTGTCA | GTGTGGGTGGCTGTTCTTTT |
| *Cyp7a1* | AACGGGTTGATTCCATACCTGG | GTGGACATATTTCCCCATCAGTT |
| *Cyp8b1* | GAATCTAACCAGGCCATGCT | AGGAGCTGGCACCTAGACT |
| *Fgf15* | GTTTCACCGCTCCTTCTTTG | CATCCTCCACCATCCTGAAC |
| *36b4* | CGACATCACAGAGCAGGC | CACCGAGGCAACAGTTGG |
| *Bsep* | CAATGTTCAGTTCCTCCGTTCA | TTTGGTGTTGTCCCCSTSCTTG |
| *Mrp2* | TATCCCCGGGAAATCTGTTC | TAACCAACATTCTCCGCGC |
| *Oatp1* | GTCTTACGAGTGTGCTCCAGAT | GGAATACTGCCTCTGAAGTGGATT |
| *Ntcp* | TACCTCCTCCCTGATGCCTTTC | TGCGTCTGCAGCTTGGATTTA |
| *Mll3* | GCAACCTCTTACCGGTTGAA | GTTCTCTCGGGAACCCTTGT |
| *Mll4* | GCACCGAGTGGAGAGACAAT | TAAATACCCGCGGTTCTGCTC |
| *Ahr* | TCCACAACTGGCTTTGTTTG | CCAGAATAAGCTGCCCTTTG |
| *Lrh-1* | TCATGCTGCCCAAAGTGGAGA | TGGTTTTGGACAGTTCGCTT |
| *Cck* | AAGTGACCGGGACTACATGG | CCCACTACGATGGGTATTCG |
| *Mdr1* | CTGGTGTGCTCATAGTTG | CCTAATCTTGTGTATCTGTCTT |

### Mouse ChIP primers

| | Forward (5'-3') | Reverse (5'-3') |
|---|---|---|
| *Shp* | CAGTGAGAACCCTGGTCTT | CTGGCCAAACAACCTTGAC |
| *Bsep* | CGACCTTTCCTCTCATGTCA | CATTGAACAGAAATCAGGCTTTT |

### Human RT-qPCR primers

| | Forward (5'-3') | Reverse (5'-3') |
|---|---|---|
| *KLF4* | ACCCTGGGTCTTGAGGAAGT | ACGATCGTCTTCCCCTCTTT |
| *36B4* | TGCTGAACATGCTCAAC | GTCGAACACCTGCTGGATGAC |
| *SHP* | CAGAGATCAGGTGGGCAGAG | TGTGGCTGAGTGAAGAGCTG |
| *MLL4* | GCACAATGCTGTCAGGAGAA | GTGCAGCAGAAGATGGTGAA |