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Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see Authors & Referees and the Editorial Policy Checklist.

Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. figure legend, table legend, main text, or Methods section).

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ An indication of whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistics including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated
☐	☒ Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	STAR Aligner v2.5.1. Image J for western blot quantification. Adobe Illustrator CC 2018.
Data analysis	RNA-seq was analyzed by Cufflinks v2.2.1 (including Cuffdiff). Statistics were analyzed using GraphPad Prism (version 7) and Microsoft Office Excel 2017. Primer express software (based on Primer 3 program) was used to design all the qPCR primers and probes. Primer3, Blast program, Alggen Promo 8.3, and Eukaryotic Promoter Database were used to design DNA cloing primers, ChIP primers and mutagenesis oligos. Bar graphs with the corresponding dot plots were created using GraphPad Prism (version 7).

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

The data that support the findings of this study are available on request from the corresponding authors (SH, MJ) due to the patent application

Field-specific reporting

Please select the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/authors/policies/ReportingSummary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	No statistical methods were used to predetermine sample size (n). Number of sample was determined based on experimental approach, availability, feasibility required to obtain definitive results.
Data exclusions	No data excluded from analysis
Replication	All of experiments have been successfully repeated at least three times and/or with sufficient cells/animals/human tissues per group to demonstrate statistical significance. All experiments were statistically analyzed.
Randomization	The samples or age-matched male mice were allocated into experimental groups randomly.
Blinding	The investigators were blinded to group allocation during data collection and/or analysis.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☐	☒ Unique biological materials
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology
☐	☒ Animals and other organisms
☒	☐ Human research participants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Unique biological materials

Policy information about availability of materials

Obtaining unique materials	Human liver samples were obtained from the Liver Tissue Cell Distribution System (LTCDS) at University of Minnesota. Healthy liver tissues (HH909, 58 y.o. female; HH911, 61 y.o. female; HH916, 48 y.o. male; HH917, 29 y.o. male; HH921, 6 y.o. female), as well as primary biliary cirrhosis (PBS; UMN932, 40 y.o. female; UMN950, 53 y.o. female; UMN987, 55 y.o. male; UMN989, 53 y.o. female; UMN1003, 62 y.o., male) and fulminant liver failure (FLF; UMN1023, 60 y.o. female; UMN1027, 15 y.o. male; UMN1034, 35 y.o. female; UMN1193, 48 y.o. female; UMN1297, 34 y.o. male) patient liver tissues were obtained from donors or autopsies (n=5 each condition). All specimens were obtained by protocols approved by the Human Investigation Review Committee of University of Minnesota. Fresh human hepatocytes isolated from human donors (HUM4266, 8 y.o. female; HUM4269, 30 y.o. female; HUM4271, 36 y.o. male; HUM4272, 68 y.o. female; HUM17292A, 18 y.o. male; HUM17292B, 53 y.o. male) were

obtained through the Triangle Research Labs, Lonza Walkersvile Inc. (Walkersville, MD, USA), and seeded in 6-well plate with overlay.

Antibodies

Antibodies used

Rabbit Polyclonal KLF15 (LS-C169702, LifeSpan BioSciences, Inc) Validated by LifeSpan BioSciences, Inc.
Goat Plyclonal KLF15 (ab2647, Abcam) PMID: 26040986.
Rabbit polyclonal PXR (sc-25381, Santa Cruz Biotechnology) PMID: 20693526.
Rabbit polyclonal FXR (sc-13063, Santa Cruz Biotechnology) PMID: 21081494.
Rabbit polyclonal CYP3A (sc-25845, Santa Cruz Biotechnology) Validated by Santa Cruz Biotechnology.
Rabbit polyclonal OSTa/SLC51A (sc-100078, Santa Cruz Biotechnology) PMID: 18292224.
Mouse monoclonal BSEP/ABCB11 (sc-74500, Santa Cruz Biotechnology) PMID: 28027573.
Mouse monoclonal b-actin (sc47778, Santa Cruz Biotechnology) PMID: 30692621
Rabbit polyclonal CAR (ab186869, Abcam) PMID: 30048740.
Rabbit polyclonal UGT1A9 (ab180707, Abcam) PMID: 29054804.
Rabbit polyclonal SULT1A1 (ab38411, Abcam) PMID: 27342868.
Rabbit polyclonal SULT2A1 (ab38416, Abcam) PMID: 29743239.
Rabbit polyclonal MRP2/ABCC2 (ab110740, Abcam) PMID: 25488932.
Rabbit polyclonal b-actin (ab8227, Abcam) PMID: 30253198.
Rabbit polyclonal CYP2B10 (AB9916, EMD MilliporeSigma Corporation) PMID: 23055538.
Rabbit polyclonal CYP2E1 (AB1252, EMD MilliporeSigma Corporation) PMID: 28530644.
Mouse monoclonal ABCB1/MDR1 (C219, Thermo Fisher Scientific) PMID: 26801902.
Rabbit polyclonal CYP2B6/CYP2B9 (ABIN2432914, Antibodies-online Inc) Validated by Antibodies-online Inc.
Rabbit polyclonal NRF2 (16396-1-AP, Proteintech) PMID: 29481323.

Validation

All of antibodies were validated by vendors or other researchers. We based specificity on their provided data sheets.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)

Hepa1-6 cell line was obtained from ATCC.

Authentication

Hepa 1-6 cell lines obtained from ATCC are already authenticated using STR profiling.

Mycoplasma contamination

Hepa 1-6 cell line was maintained under the recommended culture conditions and media requirements. Mycoplasma detection was performed in accordance with department protocols (and tested negative).

Commonly misidentified lines
(See ICLAC register)

None

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals

1. Heterozygous Albumin-Cre (Alb-Cre+/-) mice were generated by crossing male Alb-Cre+/- mice and female C57BL/6J mice. To maintain the C57BL/6J background, Alb-Cre+/- mice were backcrossed to the standard C57BL/6J strain for at least 10 generations prior to these experiments. All transgenic mice were genotyped to differentiate heterozygotes and wild type.
2. Homozygous Klf15 loxp+/+ mice were generated by crossing male Klf15 loxp+/+ mice and female Klf15 loxp+/+ mice. To maintain the C57BL/6J background, Klf15 loxp+/+ mice were backcrossed to the standard C57BL/6J strain for at least 10 generations prior to these experiments.
3. Male Alb-Cre+/- mice and female Klf15 loxp+/+ mice were crossed to produce Alb-Cre+/-, Klf15 loxp+/- homozygous mice which were followed with the crossing with Klf15 loxp+/+ mice to generate liver specific Klf15 knockout mice [Li-KO (Alb-Cre+/-, Klf15 loxp+/+)]. Male Alb-Cre+/-,Klf15 loxp+/+ mice were backcrossed with female Klf15 loxp+/+ mice for 10 generations prior to these experiments. All transgenic mice were genotyped to differentiate heterozygotes and wild type.
Age-matched (8 to 16-week-old) Alb-Cre+/- and liver-specific Klf15-knockout (Li-KO) male mice on C57BL/6J background were used for all the animal studies.

Wild animals

All the studies did not involve wild animals.

Field-collected samples

All the studies did not involve samples collected from the field.