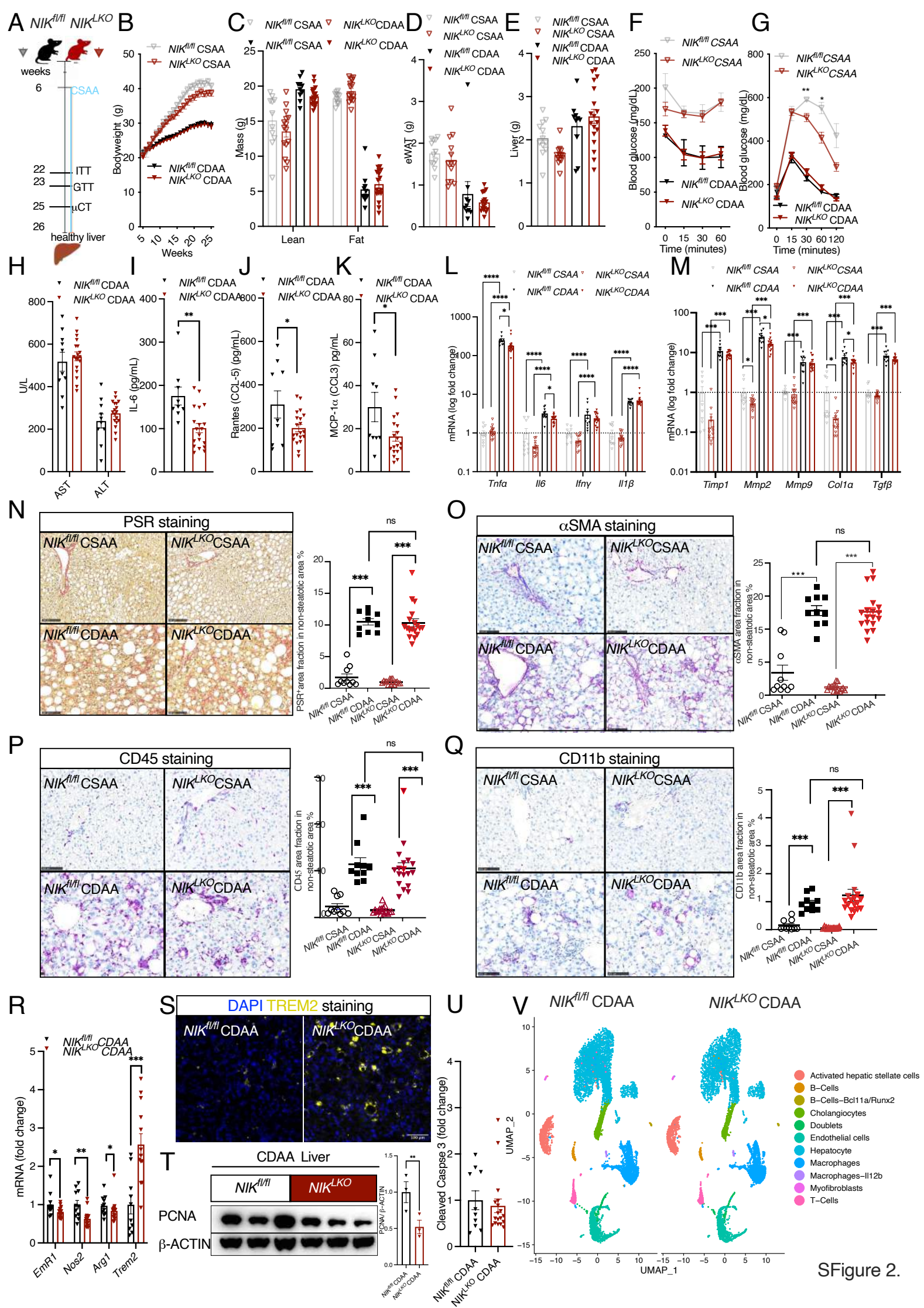
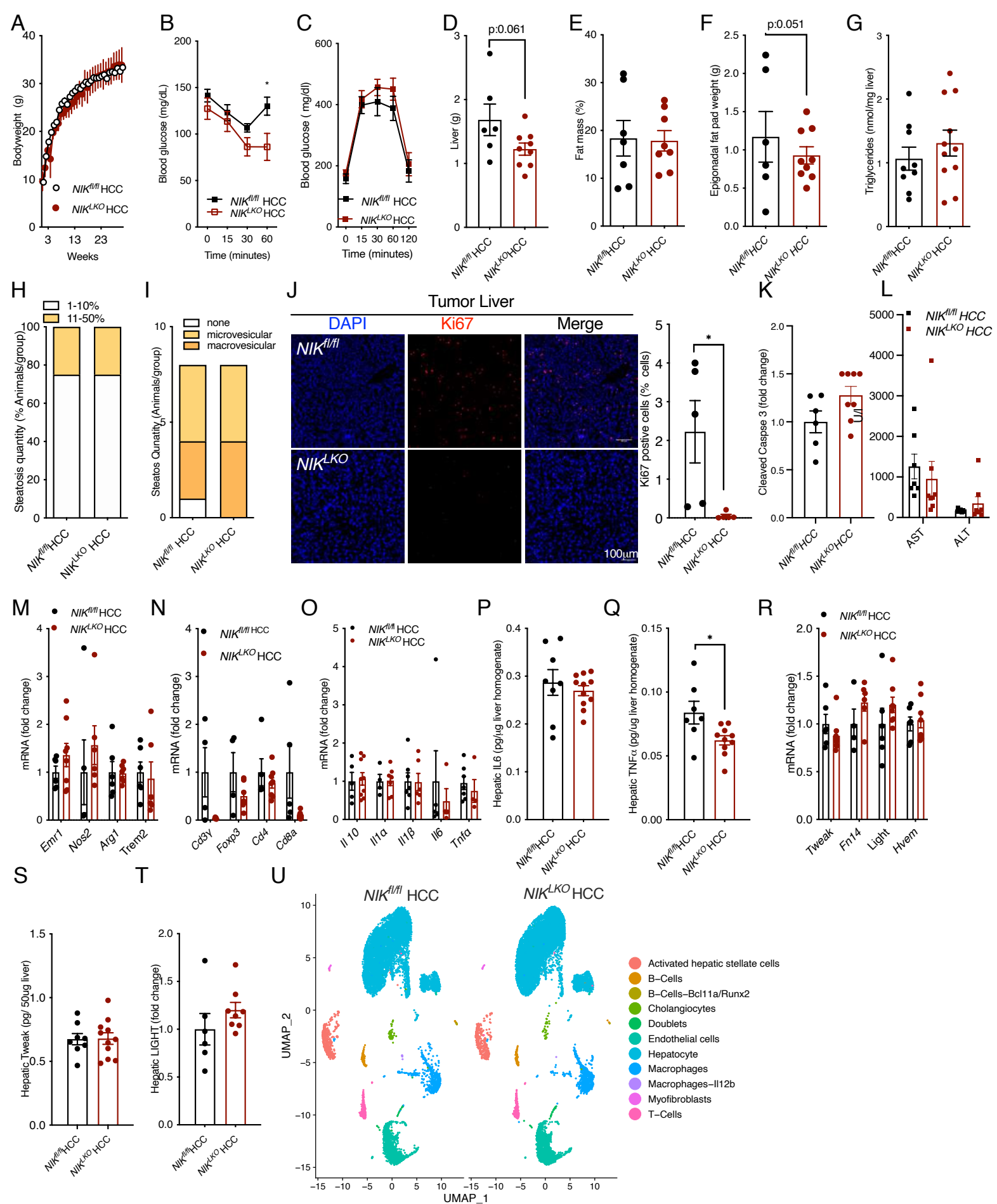


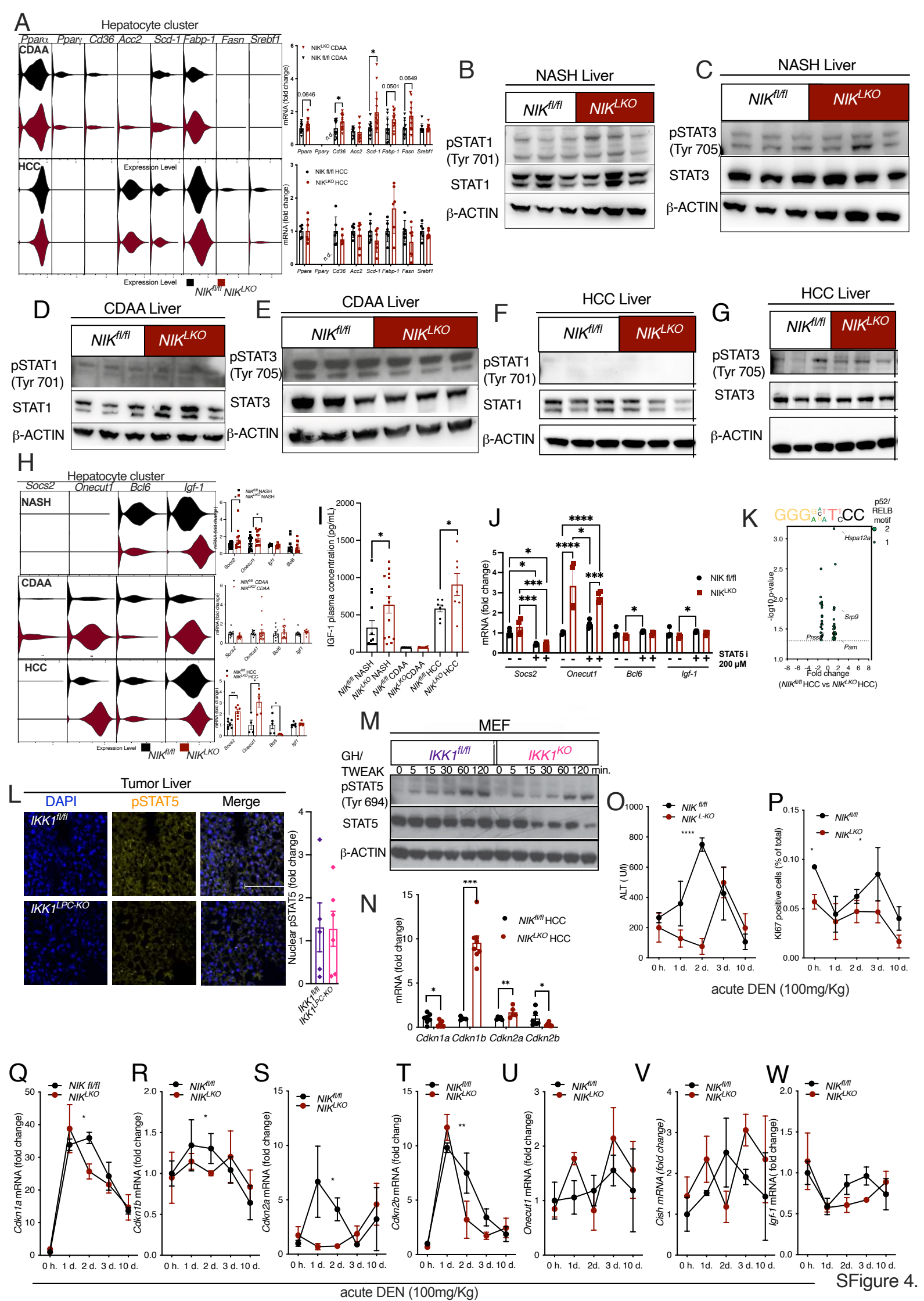
SFigure 1.

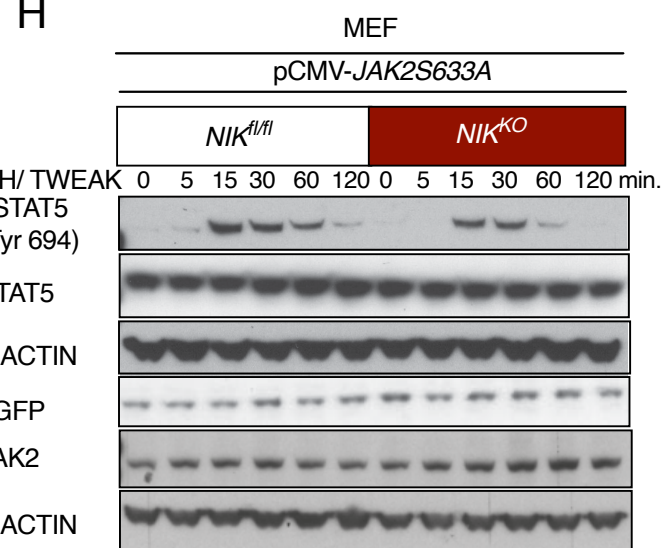
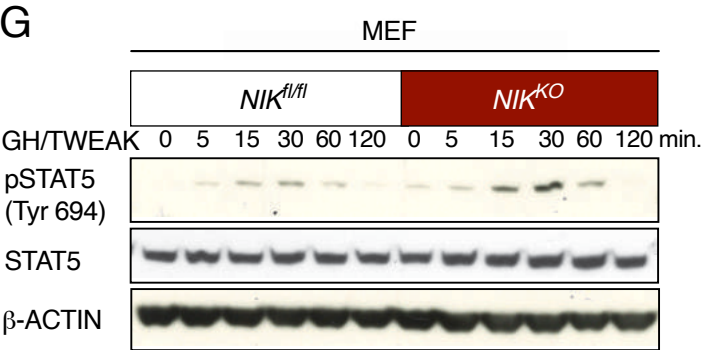
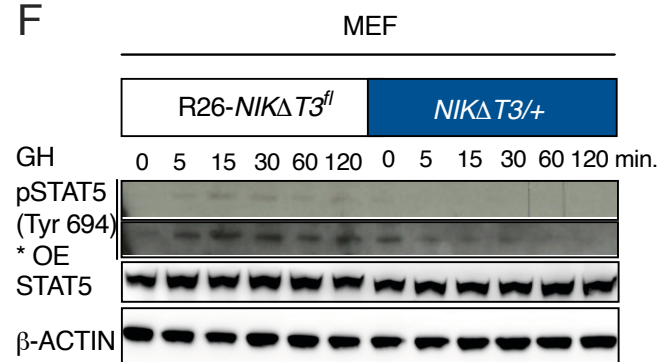
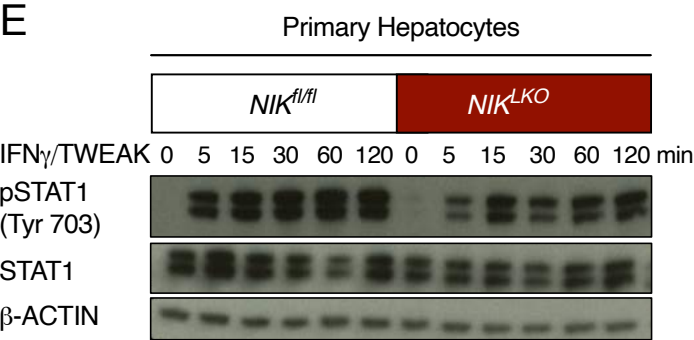
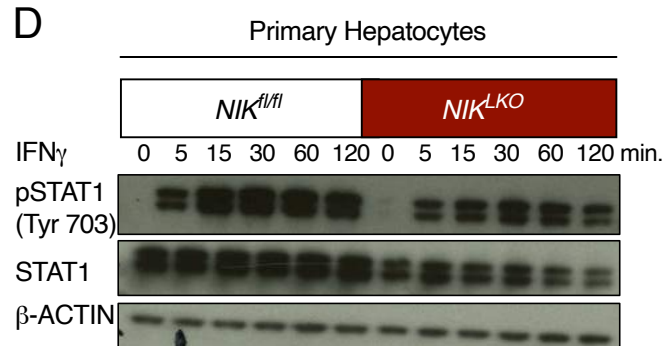
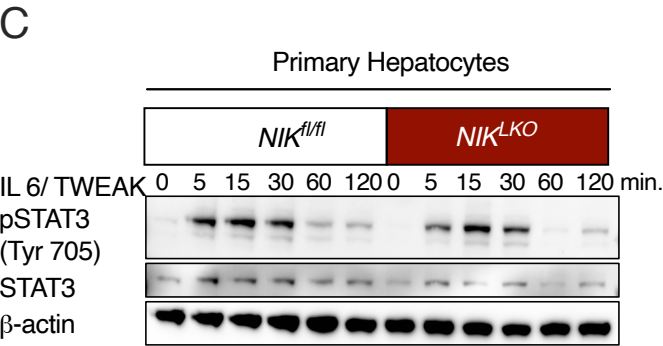
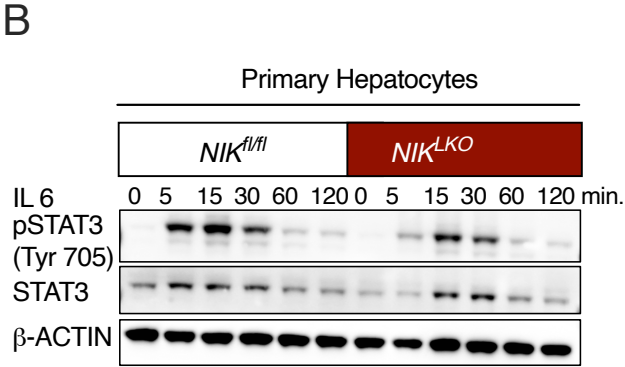
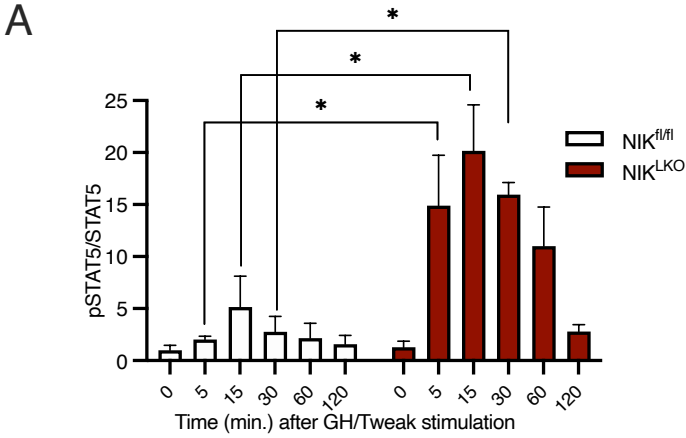


SFigure 2.



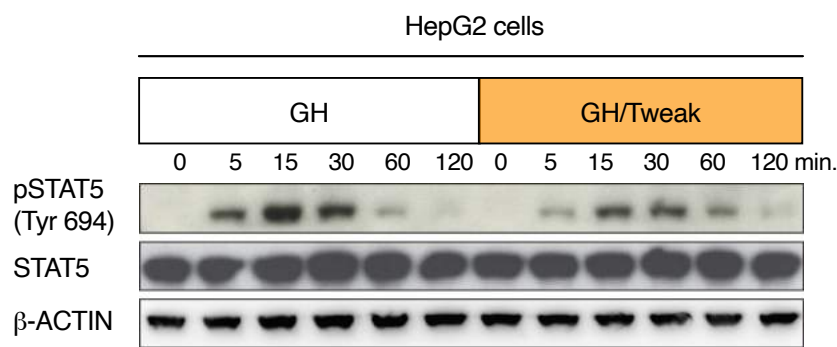
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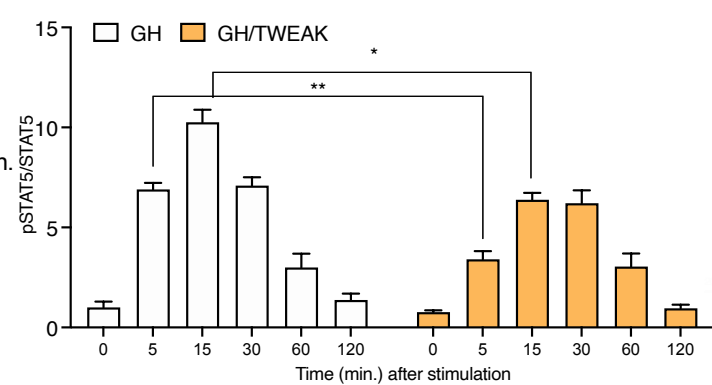


SFigure 5.

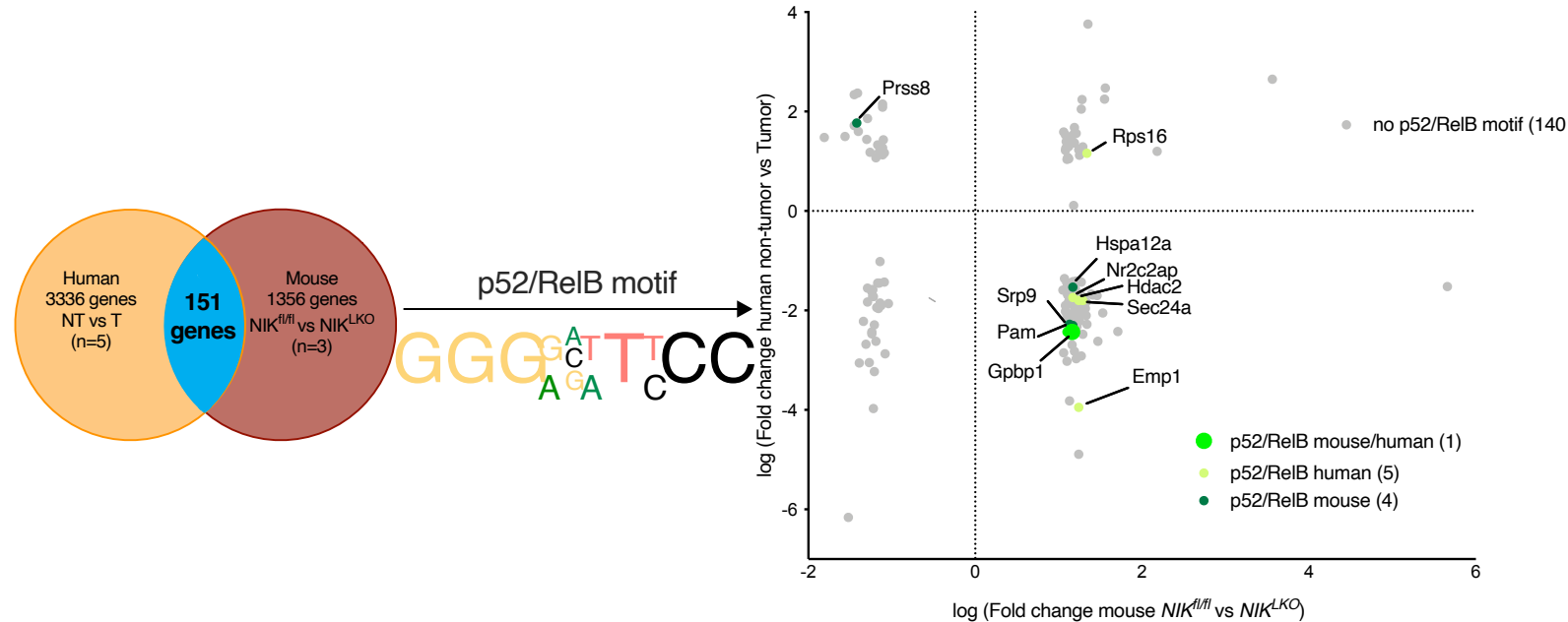
A



B



C



Supplementary Figure 1. related to Figure 1.

A) qPCR analysis of *Map3k14* (*NIK*) expression in livers and epigonadal fat pad weigh in NASH-fed *NIK*^{fl/fl} and *NIK*^{LK} (n=16/13). B) Western blot analysis of p100/p52 processing in primary hepatocytes isolated from DEN-injected *NIK*^{fl/fl} and *NIK*^{LKO} mice treated with 90 ng/mL TWEAK for the indicated timepoints. C) Bodyweight curve of *NIK*^{fl/fl} and *NIK*^{LKO} mice fed the NASH diet for 20 weeks (n=18/15). D) and E) Body composition analysis of *NIK*^{fl/fl} and *NIK*^{LKO} mice fed the NASH diet for 20 weeks (n=18/15). F) Liver and epigonadal fat pad weight of *NIK*^{fl/fl} and *NIK*^{LKO} mice fed the NASH diet for 20 weeks (n=17/15). G) qPCR expression of proinflammatory cytokines *Il6*, *Tnfα*, *Ifnγ* and macrophage marker *Emr1*, *Nos2*, *Arg1* and *Trem2* in livers of *NIK*^{fl/fl} and *NIK*^{LKO} mice fed the NASH diet for 20 weeks (n=16/14). H) Representative images of CD45⁺ of livers of 26 weeks old *NIK*^{fl/fl} and *NIK*^{LKO} mice fed the NASH diet for 20 weeks (n=16/14), scalebar 100 μm, and corresponding quantification. I) Representative images of CD11⁺ of livers of 26 weeks old *NIK*^{fl/fl} and *NIK*^{LKO} mice fed the NASH diet for 20 weeks (n=16/14), scalebar 100 μm, and corresponding quantification. J) qPCR analysis of proinflammatory cytokines *Tnfα*, *Il6*, Macrophage marker *Emr1* and the B-cell marker *Cd3δ* in the white adipose tissue of 26 weeks old *NIK*^{fl/fl} and *NIK*^{LKO} mice fed the NASH diet for 20 weeks (n=16/14). K) Mac2 staining on white adipose tissue of 26 weeks old *NIK*^{fl/fl} and *NIK*^{LKO} mice fed the NASH diet for 20 weeks (n=16/14). L) Representative images of Picro Sirius Red staining of livers of 26 weeks old *NIK*^{fl/fl} and *NIK*^{LKO} mice fed the NASH diet for 20 weeks (n=16/14) and corresponding quantification, scalebar 100 μm. M) Representative images of α-SMA staining of livers of 26 weeks old *NIK*^{fl/fl} and *NIK*^{LKO} mice fed the NASH diet for 20

weeks (n=16/14) and corresponding quantification, scalebar 100 μ m. L) qPCR analysis of extracellular matrix remodeling genes *Timp1*, *Mmp2*, *Mmp9*, *Col1 α* and *Tgf β* in livers of 26 weeks old *NIK^{fl/fl}* and *NIK^{LKO}* mice fed the NASH diet for 20 weeks (n=16/14). O) UMAP visualization of hepatocyte nuclei in *NIK^{fl/fl}* and *NIK^{LKO}* CDAA liver samples. P) Representative pictures of Ki67 IHC (red) in livers of CDAA-fed *NIK^{fl/fl}* and *NIK^{LKO}* mice, scalebar 100 μ m. Quantification of Ki67 positive cells in livers (n=14/11). Q) Fold change of activated caspase 3 activity in livers lysates isolated from NASH-fed *NIK^{fl/fl}* and *NIK^{LKO}* mice (n=14/16). R) ALT and AST activity in serum of 26 weeks old *NIK^{fl/fl}* and *NIK^{LKO}* mice fed the NASH diet for 20 weeks (n=16/14). S) Circulating plasma triglyceride, cholesterol and T) free fatty acid levels of 26 weeks old *NIK^{fl/fl}* and *NIK^{LKO}* mice fed the NASH diet for 20 weeks (n=16/14). U) Experimental outline for the CD to NASH diet experiment, which served as control. Male *NIK^{fl/fl}* and *NIK^{LKO}* mice were fed a NASH diet for 20 weeks. With 22 and 23 weeks of age ITT and GTT analysis was performed. Body composition was assessed by computed tomography (CT) at 25 weeks. V) Bodyweight curve of *NIK^{fl/fl}* and *NIK^{LKO}* mice fed the CD-NASH diet for 20 weeks (n=10/14). W) Insulin tolerance test in 22 weeks old CD-NASH-fed *NIK^{fl/fl}* and *NIK^{LKO}*, (n=10/14). X) Glucose tolerance test in 23 weeks old CD-NASH-fed *NIK^{fl/fl}* and *NIK^{LKO}* *NIK^{LKO}* (n=10/14). Y) Body composition analysis of *NIK^{fl/fl}* and *NIK^{LKO}* mice fed the CD-NASH diet for 20 weeks (n=10/14). Z) Liver weight and epigonadal weight of 26-week-old *NIK^{fl/fl}* and *NIK^{LKO}* mice fed the CD-NASH diet for 20 weeks (n=10/14). AA) Representative pictures of Ki67 IHC (red) in livers of CD_NASH-fed *NIK^{fl/fl}* and *NIK^{LKO}* mice, scalebar 100 μ m. AB) Quantification of Ki67 positive cells in livers (n=7/8).

AC) Fold change of activated caspase 3 activity in livers lysates isolated from CD-NASH-fed $NIK^{fl/fl}$ and NIK^{LKO} mice (n=6/8). Data are presented as mean \pm SEM; * $p \leq 0.05$, ** $p \leq 0.01$, versus control. Statistical analyses were performed using Student's *t*-test and two-way ANOVA plus Fisher's LSD test.

Supplementary Figure 2. related to Figure 2.

A) Schematic experimental protocol for mice receiving CSAA control HFD feeding. B) Bodyweight curve of $NIK^{fl/fl}$ and NIK^{LKO} mice fed the CDAA diet for 20 weeks (n=11/18). C) Body composition analysis of $NIK^{fl/fl}$ and NIK^{LKO} mice fed the CDAA diet for 20 weeks (n=10/18). D) Epigonadal fat pad weight of $NIK^{fl/fl}$ and NIK^{LKO} mice fed the CDAA diet for 20 weeks (n=10/18). E) Liver weight of $NIK^{fl/fl}$ and NIK^{LKO} mice fed the CDAA diet for 20 weeks (n=10/18). F) Insulin tolerance test in 22 weeks old $NIK^{fl/fl}$ and NIK^{LKO} mice fed the CDAA diet for 20 weeks (n=10/18). G) Glucose tolerance test in 25 weeks old $NIK^{fl/fl}$ and NIK^{LKO} mice fed the CDAA diet for 20 weeks (n=10/18). H) Systemic levels of IL-6 I) RANTES (CCL5), J) CCL3 in the plasma of 26 weeks old $NIK^{fl/fl}$ and NIK^{LKO} mice fed the CDAA diet for 20 weeks (n=10/18). K) qPCR analysis for proinflammatory cytokines *Tnf α* , *Il6*, *Inf γ* , *Cd19* and *Il1 β* in livers of 26 weeks old $NIK^{fl/fl}$ and NIK^{LKO} mice fed the CDAA diet for 20 weeks (n=10/18). M) qPCR analysis of extracellular matrix remodeling genes *Timp1*, *Mmp2*, *Mmp9*, *Col1 α* and *Tgf β* in livers of 26 weeks old $NIK^{fl/fl}$ and NIK^{LKO} mice fed the CDAA diet for 20 weeks (n=10/18). N) Representative images of Picro Sirius Red staining of livers of 26 weeks old $NIK^{fl/fl}$ and NIK^{LKO} mice fed the CDAA diet for 20 weeks (n=10/18) and corresponding

quantification, scalebar 100 μ m. O) Representative images of α -SMA staining, P) Representative images of CD11b⁺, O) Representative images of CD45⁺ of livers of 26 weeks old *NIK^{fl/fl}* and *NIK^{LKO}* mice fed the CDAA diet for 20 weeks (n=10/18), scalebar 100 μ m, and corresponding quantification. R) qPCR for indicated macrophage markers of CDAA fed mice with the indicated genotypes (n=10/18). S) Representative IHC for TREM2 of CDAA diet fed animals with indicated genotypes T) Western blot with quantification for PCNA of livers from CDAA-fed *NIK^{fl/fl}* and *NIK^{LKO}* mice, (n=3/3). U) Fold change of activated caspase 3 activity in livers lysates isolated from CDAA-fed *NIK^{fl/fl}* and *NIK^{LKO}* mice (n=10/18). V) UMAP visualization of annotated nuclei in *NIK^{fl/fl}* and *NIK^{LKO}* NASH isolated from CDAA liver samples. Data are presented as mean \pm SEM; *p \leq 0.05, **p \leq 0.01, versus control. Statistical analyses were performed using Student's *t*-test and two-way ANOVA plus Fisher's LSD test.

Supplementary Figure 3. related to Figure 2.

A) Bodyweight curve of *NIK^{fl/fl}* and *NIK^{LKO}* mice injected with DEN (25mg/kg) at p15 for 30 weeks (n=5/5). B) Insulin tolerance test in 11 weeks old DEN-injected and CD-fed *NIK^{fl/fl}* and *NIK^{LKO}*, (n=8/10). C) Glucose tolerance test in 12 weeks old DEN-injected *NIK^{fl/fl}* and *NIK^{LKO}*, (n=6/6). D) Liver weight of DEN-injected and CD-fed *NIK^{fl/fl}* and *NIK^{LKO}* mice at 32 weeks of age (n=8/6). E) Overall fat mass analysis of DEN-injected *NIK^{fl/fl}* and *NIK^{LKO}* mice performed by NMR at 32 weeks of age (n=8/6). F) Epigonadal fat pad weight of DEN-injected *NIK^{fl/fl}* and *NIK^{LKO}* mice at 32 weeks of age (n=8/6). G) Triglyceride Elisa performed on livers from DEN-injected *NIK^{fl/fl}* and *NIK^{LKO}* mice (n=8/7). H) Steatosis score determined by

Pathologist of livers from DEN-injected $NIK^{fl/fl}$ and NIK^{LKO} mice (n=8/7). I) Steatosis quantification determined by Pathologist of livers from DEN-injected $NIK^{fl/fl}$ and NIK^{LKO} mice (n=8/7). J) Representative pictures of Ki67 IHC (red) in livers of DEN injected CD-fed mice $NIK^{fl/fl}$ and NIK^{LKO} mice, scalebar 100 μ m. Quantification of Ki67 positive cells in livers (NIK^{LKO} 2.22 \pm 0,80 vs. control 0.60 \pm 0.04 $p \leq 0.0272$) (n=5/5). K) Fold change of activated caspase 3 activity in livers lysates isolated from DEN-injected $NIK^{fl/fl}$ and NIK^{LKO} mice (n=8/7). L) ALT and AST activities in plasma of DEN-injected and CD-fed $NIK^{fl/fl}$ and NIK^{LKO} mice (n=6/6). M) qPCR analysis for macrophage marker *Emr*, *Nos2*, *Arg1* and *Trem2* in livers of DEN-injected and CD-fed $NIK^{fl/fl}$ and NIK^{LKO} mice (n=6/8). N) qPCR analysis for T-cell markers *Cd3 γ* , *Foxp3*, *Cd4* and *Cd8a* in liver tissue of DEN-injected $NIK^{fl/fl}$ and NIK^{LKO} mice (n=5/8). O) qPCR analysis for proinflammatory cytokines *Il10*, *Il1a*, *Il1 β* , *Il-6*, *Tnf α* in liver tissue of DEN-injected $NIK^{fl/fl}$ and NIK^{LKO} mice (n=7/7). P) Hepatic IL-6 levels from DEN- injected $NIK^{fl/fl}$ and NIK^{LKO} mice assessed by IL6 ELISA (n=7/8). Q) Hepatic TNF α levels in DEN-injected and CD-fed $NIK^{fl/fl}$ and NIK^{LKO} mice assessed by ELISA (n=7/8). R) mRNA expression of *Tweak* (n=6/8), *Fn14* (n=4/6), *Light* (n=6/8) and *Hvem* (n=6/8) in livers of DEN-injected $NIK^{fl/fl}$ and NIK^{LKO} mice. S) Hepatic TWEAK levels from DEN-injected $NIK^{fl/fl}$ and NIK^{LKO} mice assessed by ELISA (n=8/8). T) Hepatic LIGHT levels from DEN-injected $NIK^{fl/fl}$ and NIK^{LKO} mice assessed by ELISA (n=6/8). U) UMAP visualization of annotated nuclei liver samples from NASH-fed animals. Data are presented as mean \pm SEM; * $p \leq 0.05$, ** $p \leq 0.01$, versus

control. Statistical analyses were performed using Student's *t*-test and two-way ANOVA plus Fisher's LSD test.

Supplementary Figure 4. related to Figure 3.

A) Violin blots of hepatocytes from snRNAseq data and verification by qPCR in livers of mice exposed to the different paradigms. Western blot analysis of B) pSTAT1, STAT1 and β -ACTIN levels and C) of pSTAT3, STAT3 and β -ACTIN levels in liver tissue from NASH-fed *NIK^{fl/fl}* and *NIK^{LKO}* mice (n=3/3). D) pSTAT1, STAT1 and β -ACTIN levels and E) of pSTAT3, STAT3 and β -ACTIN levels in non tumor liver tissue from CDAA-fed *NIK^{fl/fl}* and *NIK^{LKO}* mice (n=3/3); F) pSTAT1, STAT1 and β -ACTIN levels and G) of pSTAT3, STAT3 and β -ACTIN levels in liver tissue from non tumor DEN-HCC *NIK^{fl/fl}* and *NIK^{LKO}* mice (n=3/3). H) Violin blots of hepatocytes from snRNAseq data and verification by qPCR in livers of mice exposed to the different paradigms. I) Plasma IGF1 ELISA of mice exposed to the different paradigms J) STAT5 target gene expression of primary hepatocytes isolated from indicated mice non treated or treated with 200 μ M STAT5i (n=4/4) K) Motif search for 52/RELB target genes on data sets from Affimetrix microarray analysis of liver tissue from DEN injected *NIK^{fl/fl}* and *NIK^{LKO}* mice (n=3/3). L) Representative images of pSTAT5 staining (yellow) and DAPI (blue) in HCC liver tissue from *IKK1^{fl/fl}* and *IKK1^{LPC-KO}* mice with 40x magnification, scale bar 100 μ M and respective quantification of pSTAT5 staining (n=5/6). M) Western blot analysis of pSTAT5, STAT5 and β -ACTIN levels in *IKK1^{fl/fl}* and *IKK1^{KO}* MEFs after *ex vivo* stimulation with GH (500 ng/mL) and TWEAK (90 ng/mL) for the indicated timepoints. N) mRNA expression of *Cdkn1a* (n=7/8), *Cdkn1b* (n=5/8), *Cdkn2a* (n=5/5) and *Cdkn2b* (n=5/8), in liver tissue of DEN-injected CD-fed

NIK^{fl/fl} and *NIK^{LKO}* mice assessed by qPCR analysis. 8 weeks old mice with respective genotype were injected with 100 mg/kg DEN for indicated timepoints and examined for O) plasma ALT activity P) proliferation Ki67 positive cells per section and gene expression for Q) *Cdkn1a* R) *Cdkn1b* S) *Cdkn2a* T) *Cdkn2b* U) *Onecut1* V) *Cish* W) *Igf1*. Data are presented as mean \pm SEM; * $p \leq 0.05$, ** $p \leq 0.01$, versus control. Statistical analyses were performed using Student's *t*-test and two-way ANOVA plus Fisher's LSD test.

Supplementary Figure 5. related to Figure 4.

A) Quantification of pSTAT5 levels relative to Stat5 from the Western Blot in Figure 4A (n=3/3). B) Western blot analysis of pSTAT3, STAT3 and β -ACTIN levels in primary hepatocytes isolated from *NIK^{fl/fl}* and *NIK^{LKO}* mice after *ex vivo* stimulation with IL6 (50 ng/mL). C) Western blot analysis of pSTAT3, STAT3 and β -ACTIN levels in primary hepatocytes isolated from *NIK^{fl/fl}* and *NIK^{LKO}* mice after *ex vivo* double stimulation with TEAK (90 ng/mL) and IL-6 (50 ng/mL). D) Western blot analysis of pSTAT1, STAT1 and β -ACTIN levels in hepatocytes isolated from *NIK^{fl/fl}* and *NIK^{LKO}* mice after *ex vivo* stimulation with IFN γ (100 ng/mL). E) Western blot analysis of pSTAT1, STAT1 and β -ACTIN levels in hepatocytes isolated from *NIK^{fl/fl}* and *NIK^{LKO}* mice after *ex vivo* double stimulation with IFN γ (100 ng/mL) and TWEAK (90 ng/mL). F) Western blot analysis of pSTAT5, STAT5 and β -ACTIN levels in R26-*NIK Δ T3^{fl}* and *NIK Δ T3* MEFs after *ex vivo* stimulation with GH for the indicated time points (n=3). G) Western blot analysis of pSTAT5, STAT5 and β -ACTIN levels in R26-*NIK Δ T3^{fl}* and *NIK Δ T3* MEFs after *ex vivo* stimulation with GH for the indicated time points (n=3). H) Western blot analysis of pSTAT5, STAT5 and β -ACTIN levels in *NIK^{fl/fl}* and *NIK^{KO}* MEFs transfected with pCMV-*JAK2S633A* and treated with GH for the indicated timepoints (n=3). Data are presented

as mean \pm SEM; * $p \leq 0.05$, ** $p \leq 0.01$, versus control. Statistical analyses were performed using Student's *t*-test and two-way ANOVA plus Fisher's LSD test.

Supplementary Figure 6. related to Figure 5.

A) Western blot analysis of NIK and β -ACTIN levels in HepG2 cells after *ex vivo* stimulation with GH (500 ng/mL) or GH and TWEAK (90 ng/mL) for the indicated timepoints (n=1/1) B) Overlap of human and mouse gene signature. Scatterplot of fold change *NIK*^{fl/fl} vs *NIK*^{LKO} (n=3/3) against human non-tumor vs tumor (n=5/5). All genes plotted are significant both in human and mouse data set. Genes that have a p52/RELB motif in both the human and mouse data set are annotated by gene name. GPBP1 is the only gene regulated in both datasets, that shows a RELB/p52 binding motif in both human and mouse data sets.