Figure S1. The AAV8-TBG-Cre vector is hepatocyte-specific and does not result in significant genetic recombination of extra-hepatic tissues. **(a)** Representative IHC photos of liver (left), kidney (middle) and brain (right) sections of control and ΔMdm2Hep stained for RFP and p53; mice were culled 4 days post AAV injection. **(b), (c), (d)** Automated quantification of p53+ cells and RFP+ area on liver, renal cortex and brain tissue respectively, n=4 and 5 control and ΔMdm2Hep mice, respectively, in all graphs. For panel **(b)**, unpaired t-test (RFP) and Mann-Whitney test (p53) were used. For panels **(c)** and **(d)**, Welch’s t-test (RFP) and Mann-Whitney test (p53). Bars are mean ± S.E.M. and the numbers on the graphs are p values. Scale bars are 50μm.

Figure S2. Liver senescence is associated with renal senescence. **(a)** Representative photos of control and ΔMdm2Hep liver sections stained for SA β-Gal. n=8 mice per group. **(b)** Targeted GSEA on the whole liver RNA-seq dataset. **(c)** RT-qPCR for Cdkn1a, Cdkn2a, Cdkn2b, Bcl-2, Tgfβ1, Tgfβ2, Tgfβ3 and Lif on whole liver lysates. n=5 mice per group. **(d)** Representative photos of control and ΔMdm2Hep kidney sections stained for SA β-Gal. n=8 mice per group. **(e)** Targeted GSEA on the whole kidney RNA-seq dataset. **(f)** Cytokine arrays on whole kidney lysates for a range of SASP factors. n=4 control mice and n=5 ΔMdm2Hep mice. Unpaired t-test (IL-17, LIF, GM-CSF, CXCL-1 and CCL3) or Mann-Whitney test (CCL-2, CXCL-5). For all graphs, mice were culled 4 days post AAV injection. Bars are mean ± S.E.M. and the numbers on the graphs are p values. Scale bars are 50μm.

Figure S3. ΔMdm2Hep mice show liver damage and dysfunction in contrast to KrasG12D mice. **(a)** Alanine aminotransferase (ALT) and alkaline phosphatase (ALP) in the plasma of ΔMdm2Hep and control mice, n=7 and 14 control and ΔMdm2Hep mice, respectively, for both graphs; Mann-Whitney test (ALT) or Welch’s t-test (ALP). **(b)** Representative photos of cleaved caspase 3 (CC3) IHC on liver sections of ΔMdm2Hep and control mice. Arrowheads highlight CC3+ cells. **(c)** Automated quantification of CC3 IHC on liver sections: data are presented as CC3+ area as a percentage of total liver area, n=6 and 7 control and ΔMdm2Hep mice respectively; Welch’s t-test. **(d)** Plasma bilirubin in ΔMdm2Hep and control mice, n=9 and 11 control and ΔMdm2Hep mice respectively; Mann-Whitney test. **(e)** Schematic of AAV-mediated induction of the KrasG12D mice. 8-12 weeks old mice were injected with either AAV-Null or AAV-Cre and were culled 7 days post induction. **(f)** ALT and ALP levels in the plasma of KrasWT and KrasG12D mice. n=7 and 6 KrasWT and n=6 KrasG12D mice, respectively, for both ALT and ALP. Mann-Whitney test (ALT) or unpaired t-test (ALP). **(g)** Plasma bilirubin in KrasWT and KrasG12D mice, n=7 and 6 KrasWT and n=6 KrasG12D mice respectively; Mann-Whitney test. Bars are mean ± S.E.M. and the numbers on the graphs are p values. Scale bars are 50μm.

Figure S4. Renal and brain dysfunction in response to liver senescence. **(a)** Urine levels of Glutamine, Serine and Valine identified by liquid chromatography-mass spectrometry (LC-MS) in ΔMdm2Hep mice pre- and post- AAV-Cre injection: dots represent the average peak area of n=3 mice at days -2 and 0, n=4 mice at day 4 and n=5 mice at days -1 and 3; 2-way ANOVA comparing each time point to induction day (day 0). **(b)** Proportion of time spent by control and ΔMdm2Hep mice in the novel arm of the Y-maze 4 days before and 4 days after AAV injection: dots represent the average percentage of time spent in the novel arm for n=7 and 9 control and ΔMdm2Hep mice respectively; 2-way ANOVA showed no statistically significant difference for the control group. **(c), (d)** Area under the curve (area power) and frequency (Hz) of the brain slice oscillations after stimulation with carbachol. n=12-14 brain slices from 4 control mice and n=14 brain slices from 4 ΔMdm2Hep mice for every time point. Unpaired t-tests for each time point did not show any statistically significant difference for **(c)**. Bars are mean ± S.E.M. and the numbers on the graphs are p values.

Figure S5. Sub-clustering and cell type assignment in the scRNA-seq data. **(a)** UMAP of 24,215 single-cell transcriptomes from 6 mouse kidneys (3 kidneys from ΔMdm2Hep mice and 3 from control mice). **(b),** **(c), (d)** UMAP plots after subclustering of proximal tubular cells (PTC), distal tubular cells (DTC) and mesenchymal cells subclusters of the control cells (left) and integration of the ΔMdm2Hep cells on the identified control subclusters according to their transcriptome (right). **(e)** UMAP of the single-cell transcriptomes obtained from clustering the 3 control kidneys (left). UMAP showing the integration of the single-cell transcriptomes obtained from the 3 ΔMdm2Hep kidneys to the clusters identified by clustering the control cells, according to their transcriptome (right). **(f)** Table with violin plots showing the expression levels of marker genes across the 22 clusters and subclusters. **(g)** The original UMAP (resulting from clustering of all the cells together) coloured according to the new clusters and subclusters. **(h)** Table with the number of cluster identified by the clustering of the control cells, together with the broad cell types and sub-types of these cells. EC: Endothelial cells; PTC: Proximal tubular cells; LOH: Loop of Henle; DTC: Distal tubular cells; Collecting ducts-PC: Collecting ducts-Principal cells; Collecting ducts-IC: Collecting ducts-Intercalated cells; APC: Antigen-presenting cells; MΦ: Macrophages.

Figure S6. Liver senescence results in transcriptional changes in the renal proximal tubular cell compartment. **(a)** Dot plots of pathways resulting from unsupervised GSEA of differentially expressed genes between ΔMdm2Hep and control PTCs. Differential expression analysis was performed between ΔMdm2Hep and control PTCs and the ranked gene set was used to perform unsupervised GSEA against Gene Ontology (GO) and KEGG pathways. The size of the dots represents the number of upregulated (activated, left) or downregulated (suppressed, right) genes in the ΔMdm2Hep PTCs for each pathway (count). **(b)** Heatmap of relative expression of Slc transporter genes in the PTC compartment grouped by p21 signature score.

Figure S7. Liver senescence-induced renal senescence is associated with a repair and reprogramming phenotype in the kidney. **(a)** UMAPs showing the distribution of the cells that have a positive score for the proliferation gene signature in the control (left) and the ΔMdm2Hep (right) cells. **(b)** Pie charts showing the share of PTCs with a positive proliferation signature score in the control and ΔMdm2Hep samples; contingency was tested with the chi-square test. **(c)** Representative photos of BrdU IHC on kidney sections of ΔMdm2Hep and control mice. **(d)** Manual quantification of BrdU+ renal tubular cells on kidney sections of control and ΔMdm2Hep mice: data are presented as BrdU+ tubular cells/FOV, n=6 and 11 control and ΔMdm2Hep mice respectively; Welch’s t-test. **(e)** Representative photo of duplex (p21/BrdU) IF stain on ΔMdm2Hep kidney sections. **(f)** Automated quantification of the p21/BrdU-stained kidney sections, n=5 ΔMdm2Hep mice. **(g)** UMAPs showing the distribution of the cells that express at least one read of *Sox9* (*Sox9+* cells) in the control (left) and the ΔMdm2Hep (right) samples. **(h)** Pie charts showing the share of *Sox9+* PTCs in the control and ΔMdm2Hep samples; contingency was tested with the chi-square test. **(i)** Representative photos of SOX9 IHC on kidney sections of ΔMdm2Hep and control mice. **(j)** Automated quantification of SOX9+ renal cortical cells on kidney sections of control and ΔMdm2Hep mice: data are presented as percentage of total renal cortical cells, n=6 and 8 control and ΔMdm2Hep mice respectively; Welch’s t-test. **(k)** Representative photo of duplex (SOX9/BrdU) IF stain on ΔMdm2Hep kidney sections. **(l)** Automated quantification of the Sox9/BrdU-stained kidney sections, n=6 ΔMdm2Hep mice. Bars are mean ± S.E.M. and the numbers on the graphs are p values. Scale bars are 50μm.

Figure S8. Liver senescence-induced renal senescence is associated with low level renal damage with no cell death. **(a)** Representative photos of Lipocalin-2 IHC on kidney sections of ΔMdm2Hep and control mice. **(b)** Automated quantification of Lipocalin-2+ renal cortical area on kidney sections of control and ΔMdm2Hep mice: data are presented as percentage of total renal cortical area, n=4 and 7 control and ΔMdm2Hep mice respectively; Welch’s t-test. **(c)** Representative photos of Haematoxylin and eosin stain on kidney sections of ΔMdm2Hep and control mice. **(d)** Representative photos of cleaved caspase 3 (CC3) IHC on kidney sections of ΔMdm2Hep and control mice. **(e)** Automated quantification of CC3+ renal cortical area on kidney sections of control and ΔMdm2Hep mice: data are presented as percentage of total renal cortical area, n=6 and 8 control and ΔMdm2Hep mice respectively; unpaired t-test. Bars are mean ± S.E.M. and the numbers on the graphs are p values. Scale bars are 50μm.

Figure S9. The plasma of ΔMdm2Hep mice contains increased concentrations of SASP factors that affect the TGFΒ and LIF/JAK-STAT signalling pathways. **(a)** GSEA plot for a SASP gene set on the significant differentially expressed genes from the bulk liver RNA-seq. **(b)** Table with the full results of the cytokine arrays on plasma samples of control and ΔMdm2Hep mice. Factors whose plasma concentration increases in the ΔMdm2Hep mice are coloured red and those whose concentration decreases are coloured blue. **(c)** GSEA plot for a TGFβ signalling pathway gene set on the significant differentially expressed genes from the bulk liver RNA-seq. **(d)** Western blotting for pSMAD2 and pSMAD3 and their respective total protein on whole kidney lysates from ΔMdm2Hep and control mice. n=5 mice in each group. 1 gel was run for pSMAD2/SMAD2 and another one for pSMAD3/SMAD3. β-actin was used as a loading control on both gels. **(e)** Representative photos of ISH (RNAScope) for *TgfβR1* on kidney sections of ΔMdm2Hep and control mice. Dashed lines highlight renal tubules. **(g)** Representative photos of ISH (RNAScope) for *Tgfβ1* and *Tgfβ2* on liver sections of ΔMdm2Hep and control mice. **(h)** GSEA plot for a LIF signalling pathway gene set on the significant differentially expressed genes from the bulk liver RNA-seq.

Figure S10. Systemic inhibition of the TGFβ signalling pathway does not affect liver senescence and partly inhibits the repair and reprogramming phenotype in the kidney. **(a)** Western blotting for pSMAD2, pSMAD3 and their unphosphorylated forms on whole kidney lysates from vehicle- and TGFβR1i-treated ΔMdm2Hep mice. n=5 mice in each group. 1 gel was run for pSMAD2/SMAD2 and another one for pSMAD3/SMAD3. β-actin was used as a loading control on both gels. **(b)** Representative photos of p21 IHC on liver sections of vehicle- and TGFβR1i-treated ΔMdm2Hep mice. **(c)** Automated quantification of p21+ liver cells on liver sections of vehicle- and TGFβR1i-treated ΔMdm2Hep mice: data are presented as percentage of total liver cells, n=6 mice for each group; unpaired t-test. **(d)** Representative photos of p21 IHC on kidney sections of vehicle- and TGFβR1i-treated KrasG12D mice. **(e)** Manual quantification of p21+ renal tubular cells in vehicle- and TGFβR1i-treated KrasG12D mice: data are presented as p21+ tubular cells per field of view (FOV), n=6 and 7 vehicle- and TGFβR1i-treated KrasG12D mice respectively; Welch’s t-test. **(f)** Representative photos of Lipocalin-2, BrdU and Sox9 IHC on kidney sections of vehicle- and TGFβR1i-treated ΔMdm2Hep mice. **(g)** Automated quantification of Lipocalin-2+ renal cortical area on kidney sections of vehicle- and TGFβR1i-treated ΔMdm2Hep mice: data are presented as percentage of total renal cortical area. n=8 mice for each group; unpaired t-test. **(h)** Manual quantification of BrdU+ renal tubular cells: data are presented as BrdU+ tubular cells per field of view (FOV), n=7 and 8 vehicle- and TGFβR1i-treated mice respectively; Welch’s t-test. **(i)** Automated quantification of Sox9+ renal cortical cells. Data are presented as percentage of total renal cortical cells: data are presented as percentage of Sox9+ cortical cells, n=8 mice for each group; unpaired t-test. **(j)** Urine levels of Serine in ΔMdm2Hep mice before and after AAV-Cre injection. n=4 and 5 Vehicle- and TGFβR1i-treated mice, respectively, per time point; Welch’s t-test comparing Vehicle- to TGFβR1i-treated mice at day 4. In all bar graphs, bars are mean ± S.E.M. and the numbers on the graphs are p values. Scale bars are 50μm.