Fig. S1. Deletion of \textit{Mdm2} in hepatocytes induces hepatocyte apoptosis and BEC proliferation. (A) Blood serum biochemistry for liver function at baseline (d0) and d3 and d7 following \textit{Mdm2} inactivation. (B) Immunohistochemistry showing positivity for cleaved Caspase-3 (red) following inactivation of \textit{Mdm2} in hepatocytes. DNA is shown in white. Yellow box denotes region of high magnification image, inset. White arrows denote Caspase-3 positive hepatocytes. (C) Immunohistochemical staining of BECs using the markers Keratin-19 (upper panels) and SOX9 (lower panels) following hepatocyte loss of \textit{Mdm2}. (D) mRNA expression following the recombination of \textit{Mdm2} in hepatocytes, for \textit{Notch2} and \textit{Dll1}, a Notch receptor ligand. mRNA expression is normalised to the housekeeping gene \textit{Gapdh}. Scale bar = 50µm. N=4-6 mice per group. Each point represents a biological replicate. For data with two groups, a Student’s t-test was performed where multiple groups are analysed an ANOVA and a Dunnett’s multiple comparison test were used.
**Fig. S2. In vitro inhibition of Notch signalling reduces BEC proliferation.** (A) MTT assay showing the response of the mouse BEC cell line, BMOL, in vitro when treated with a scaling dose of Notch-i, DAPT or vehicle alone. (B) The number of Edu+ (proliferating) BECs in vitro when treated with the Notch-i, DAPT or vehicle alone. (C) mRNA expression of Notch pathway target genes Hey1 and Hes1 following Notch pathway inhibition. (D) MTT assay of BECs following treatment with a control blocking antibody targeting the intermediate filament protein, Desmin or targeting either NOTCH1 or NOTCH2 specifically. Individual groups represent distinct antibody clones. (E) mRNA expression of Notch3 in BECs in vitro following treatment with two RNAi targeting Notch3 normalised to cells treated with a scrambled RNAi. (F) Number of Ki67+BECs in vitro following knock-down of Notch3 compared to untransfected and scrambled RNAi transfected cells. (G) Blood serum biochemistry for ALT following Mdm2 inactivation and early (days 2-4) treatment with the Notch-i, DAPT (H) Blood serum biochemistry for ALT following Mdm2 inactivation and late (days 7-9) treatment with the Notch-i, DAPT. (I) Blood serum biochemistry for ALT following Mdm2 inactivation and treatment with either Notch1, Notch2 or Desmin (an intermediate filament protein that acts as a control) blocking antibodies. (J) Blood serum biochemistry for ALT following Mdm2 inactivation in mice harboring wild-type Notch3 or null for Notch3 (Notch3\/-). (K) Blood serum biochemistry for Bilirubin following Mdm2 inactivation and treatment with either Notch1, Notch2 or Desmin (an intermediate filament protein that acts as a control) blocking antibodies. (L) Blood serum biochemistry for Bilirubin following Mdm2 inactivation in mice harboring wild-type Notch3 or null for Notch3 (Notch3\/-). N=4-6 mice per group. Each point represents a biological or experimental replicate. For data with two groups, a Student’s t-test was performed where multiple groups are analysed an ANOVA and a Dunnett’s multiple comparison test were used.
Fig. S3. Notch signaling regulates IGF1 sensitivity by regulating IGF1R activity. (A) Dot plots showing that the Notch-i, DAPT reduces proliferation of BECs in the Choline Deficient Ethionine-Supplemented (CDE), left graph, and Methionine-Choline Deficient, MCD diet, right graph. (B) mRNA expression of *Igf1* in pBECs following treatment with the Notch-i, DAPT. (C) mRNA expression of Igf1R and the Notch target gene, HeyL in whole liver tissue following induction of hepatic injury. (D). Protein expression of IGF1R in vehicle treated pHPCs, compared to pHPCs treated with Notch-i, DAPT. N≥5 mice per group. Each point represents a biological replicate. For data with two groups, a Student’s t-test was performed where multiple groups are analysed an ANOVA and a Dunnett’s multiple comparison test were used.
Fig. S4. mTOR signalling can control BEC proliferation following hepatic injury. (A) MTT assay of HPC growth with increasing concentrations of AG1024, an IGF1R-i or vehicle alone. (B) Immunohistochemistry of phosphorylated mTOR in HPCs undergoing hepatocyte regeneration. (C) Quantification of total Keratin-19+ BEC number, left graph, and Ki67+(proliferating) BECs, right graph, following induction of hepatocyte regeneration and subsequent treatment with the mTOR inhibitor, Rapamycin. (D) Immunohistochemistry of panCK+ BECs in livers where Mdm2 has been inactivated and animals have been treated with either vehicle or Rapamycin, images represent animals that were culled at 10 days following initiation of injury and which were treated with Rapamycin or vehicle from days 6-9. N≥3 mice per group. Each point represents a biological replicate or experimental replicate. Scale bar = 50μm. For data with two groups, a Student’s t-test was used.
Fig. S5. Single-channel images for immunofluorescence data. (A to C). Single fluorescence channels from Fig. 1. (D) Single fluorescence channels from Fig. 3.
Table S1. Antibodies used in this study.

| Antibodies used in this study | Antigen source | IHC/WB dilution | Catalog number |
|-------------------------------|----------------|-----------------|---------------|
| Caspase-3                    | Cell Signaling Technology | IHC 1/500 | 9662 |
| Keratin-19                   | Developmental studies hybridoma bank | IHC 1/200 | Troma-III |
| Hnf4α                         | R&D systems | IHC 1/200 | H1415 |
| IGF1                          | Abcam | IHC 1/200 | ab40657 |
| IGF1 receptor β              | Cell Signalling Technologies | IHC 1/200 | 9750 |
| Jagged-1                      | Abcam | IHC 1/100 | ab109536 |
| Ki67                          | Abcam | IHC 1/200 | ab16667 |
| mCherry                       | Siggen | IHC 1/100 | #AB0081 |
| Notch1-ICD                    | Abcam | IHC 1/50 | Ab8925 |
| Notch3                        | Abcam | IHC 1/200 | Ab23426 |
| panCK                         | DAKO | IHC 1/200 | Z0622 |
| PCNA                          | Abcam | IHC 1/2000 | ab29 |
| YFP                           | Abcam | IHC 1/200 | ab6673 |

Table S2. Primers used in this study.

| Primers used in this study | Antigen source | Catalog number |
|---------------------------|----------------|---------------|
| DLL1                      | Qiagen | QT00113239 |
| DLL3                      | Qiagen | QT00113477 |
| DLL4                      | Qiagen | QT01053598 |
| Gapdh                     | Qiagen | QT01658692 |
| Hes1                      | Qiagen | QT00313537 |
| Hey1                      | Qiagen | QT00115094 |
| Igf1                      | Qiagen | QT00154469 |
| Igf1r                     | Qiagen | QT00155351 |
| Jagged1                   | Qiagen | QT00115703 |
| Jagged2                   | Qiagen | QT01043819 |
| Notch1                    | Qiagen | QT00156982 |
| Notch2                    | Qiagen | QT00153496 |
| Notch3                    | Qiagen | QT01051729 |
| Notch4                    | Qiagen | QT00135653 |