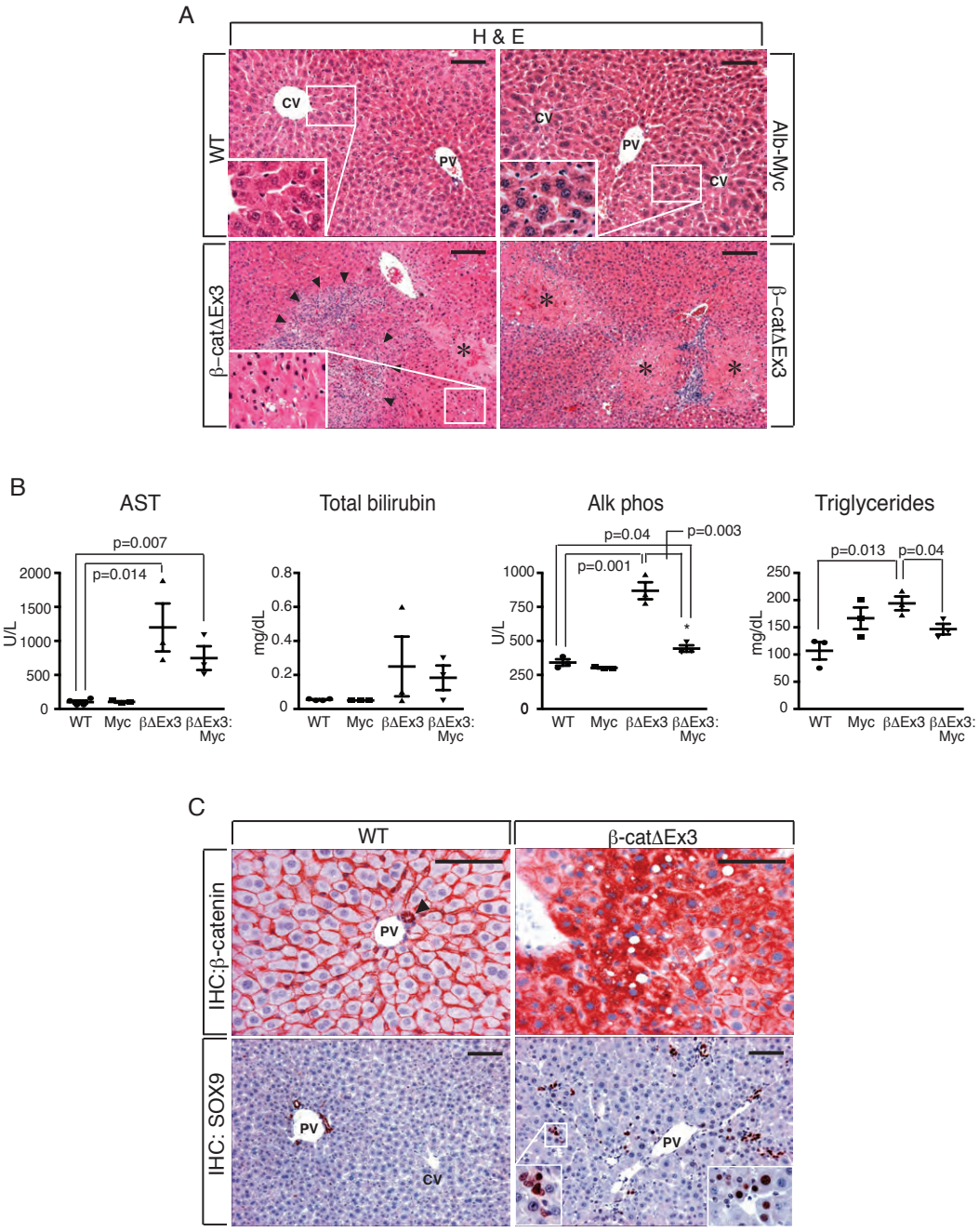
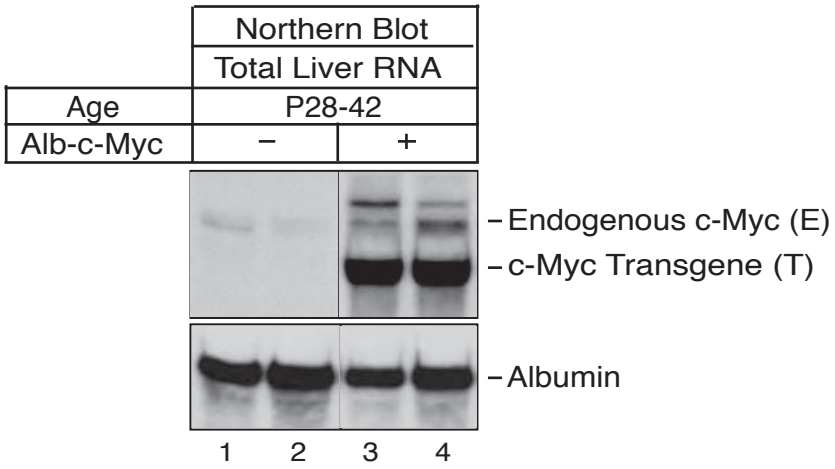
Supplemental Figure 1



Supplemental Figure 1. Pan-hepatic expression of mutant β-catenin induces severe liver damage and dysfunction. (A) Photomicrographs of H&E stained liver sections from 28 day old WT (top left), Alb-c-Myc (top right) and β-catΔEx3 (bottom left and right) mice. Note that while expression of the Alb-Myc transgene induces mild hepatocyte cell and nuclear enlargement and hyperchromatic nuclei (inset, top right), liver architecture is otherwise normal. Note atrophic hepatocytes indicative of possible impending necrosis (inset, bottom left), areas of overt focal necrosis (∗) and inflammatory infiltrates (arrowheads) in livers expressing mutant β-catenin. PV, portal vein; CV, central vein. (B) Graphs depicting biochemical analysis of liver function in WT, Alb-c-Myc, β-catΔEx3 and β-catΔEx3:Myc mice showing that mutant β-catenin results in significant liver dysfunction characterized by elevations in aspartate aminotransferase (AST), alkaline phosphatase (Alk phos) and triglycerides. Note that while liver function is unaffected by expression of the Alb-c-Myc transgene at 28 days, co-

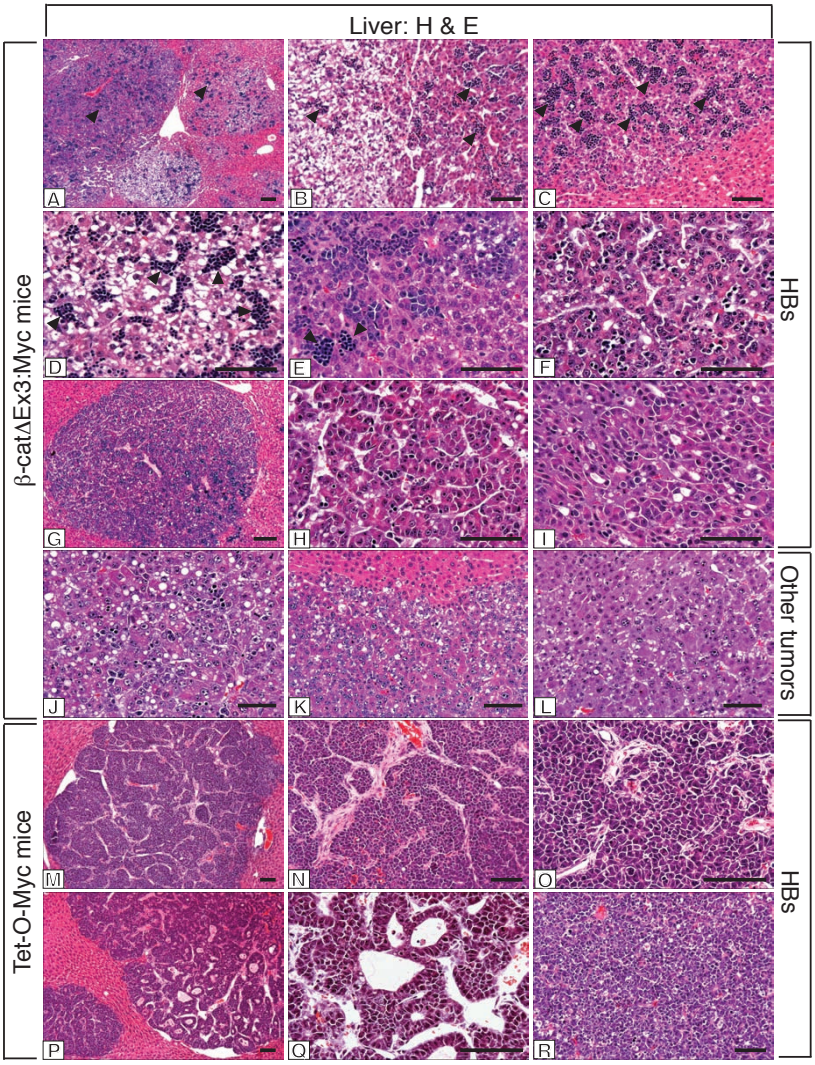
expression of the Alb-c-Myc transgene with mutant β-catenin partially ameliorates β-catenin-induced liver injury in β-catΔEx3:Myc mice as evidenced by lower alkaline phosphatase and triglyceride levels relative to β-catΔEx3 mice. n=3 mice/group except for AST and bilirubin where n=4 for the WT group. *P* values generated by a two-tailed unpaired t-test. Bars represent mean +/- SEM. (C) Photomicrographs of IHC for CTNNB1 (β-catenin) (top panels) and SOX9 (bottom panels) in WT (left top and bottom panels) and β-catΔEx3 (right top and bottom panels) livers. β-catenin is localized to the outer membranes of hepatocytes and biliary cells (black arrowhead) in WT liver (top left panel), but is overexpressed and mislocalized to the cytoplasm of hepatocytes in β-catΔEx3 mice (upper right panel) (β-catenin, red (AEC chromagen); hematoxylin counterstain, blue). In WT livers, SOX9, is exclusively expressed in the nuclei of biliary cells immediately adjacent to the portal vein (PV), but not in hepatocytes (bottom left panel). In β-catΔEx3 livers, SOX9-expressing cells are no longer restricted to the peri-portal area, but are visible throughout the lobule and a subset of hepatocytes now express SOX9 (insets) (bottom right panel), indicating possible induction of a regenerative response in an attempt to counteract hepatocyte loss and improve function. A higher magnification of the SOX9-stained bile ducts around the portal vein (PV) in the same WT liver (bottom left panel in C) is also shown in Figure 4B'. (AEC chromagen, red/brown; hematoxylin counterstain, blue). Scale bars represent 50μm.

Supplemental Figure 2



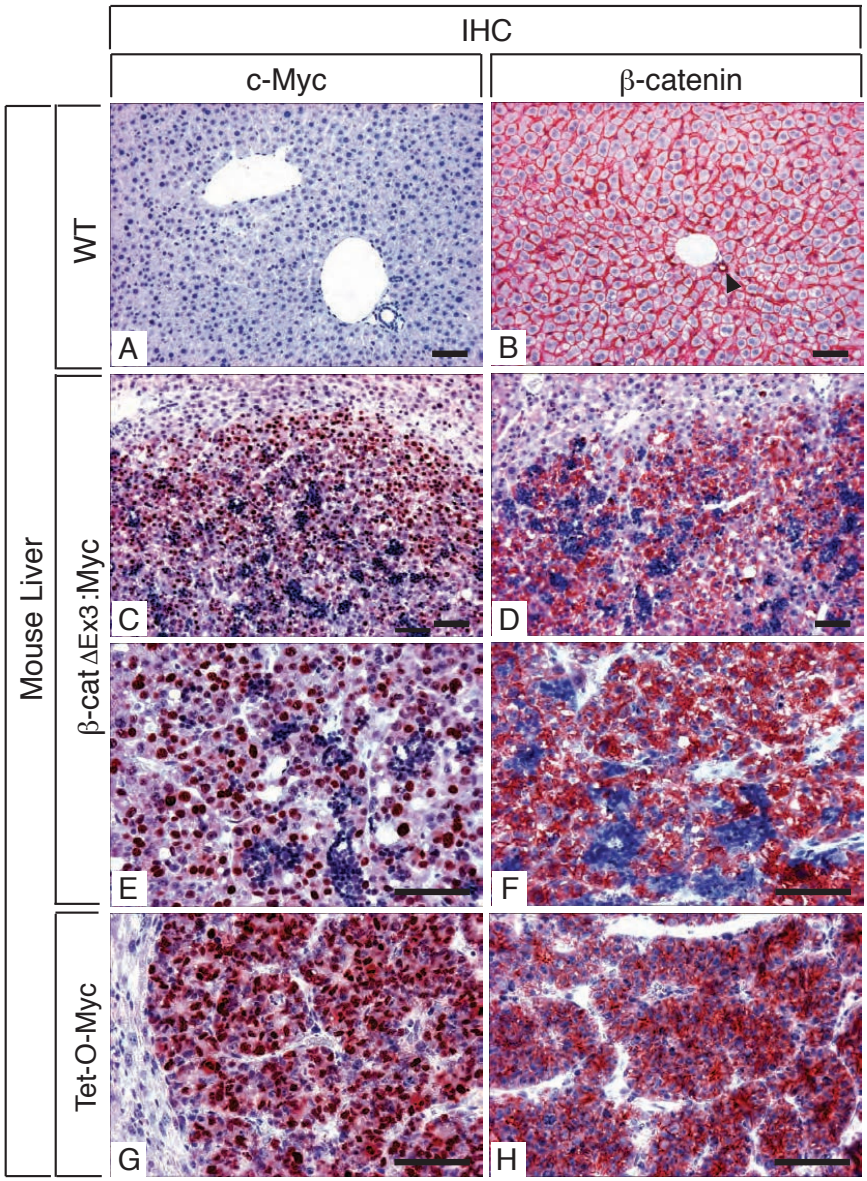
Supplemental Figure 2. Hepatic c-Myc mRNA expression driven by the Albumin-c-Myc transgene in adult liver. Northern blot showing levels of endogenous c-Myc (E) expressed in the livers of WT and Albumin-c-Myc transgenic mice (lanes 1, 2, 3 and 4) and expression of the Albumin-c-Myc transgene (T) in the livers of adult transgenic mice (lanes 3 and 4). Although transgene-derived c-Myc mRNA first becomes detectable by Northern blot during the first week after birth (Figure 2), maximal expression is not achieved until the liver has fully matured at ~ 3-4 weeks of age. Despite this high level of c-Myc, Alb-c-Myc mice do not develop liver tumors (hepatocellular carcinomas) until they reach ~10-12 months of age. Lanes 1-4 represent RNA samples that were run on the same gel, but were non-contiguous between lanes 2 and 3 (see separating black line).

Supplemental Figure 3



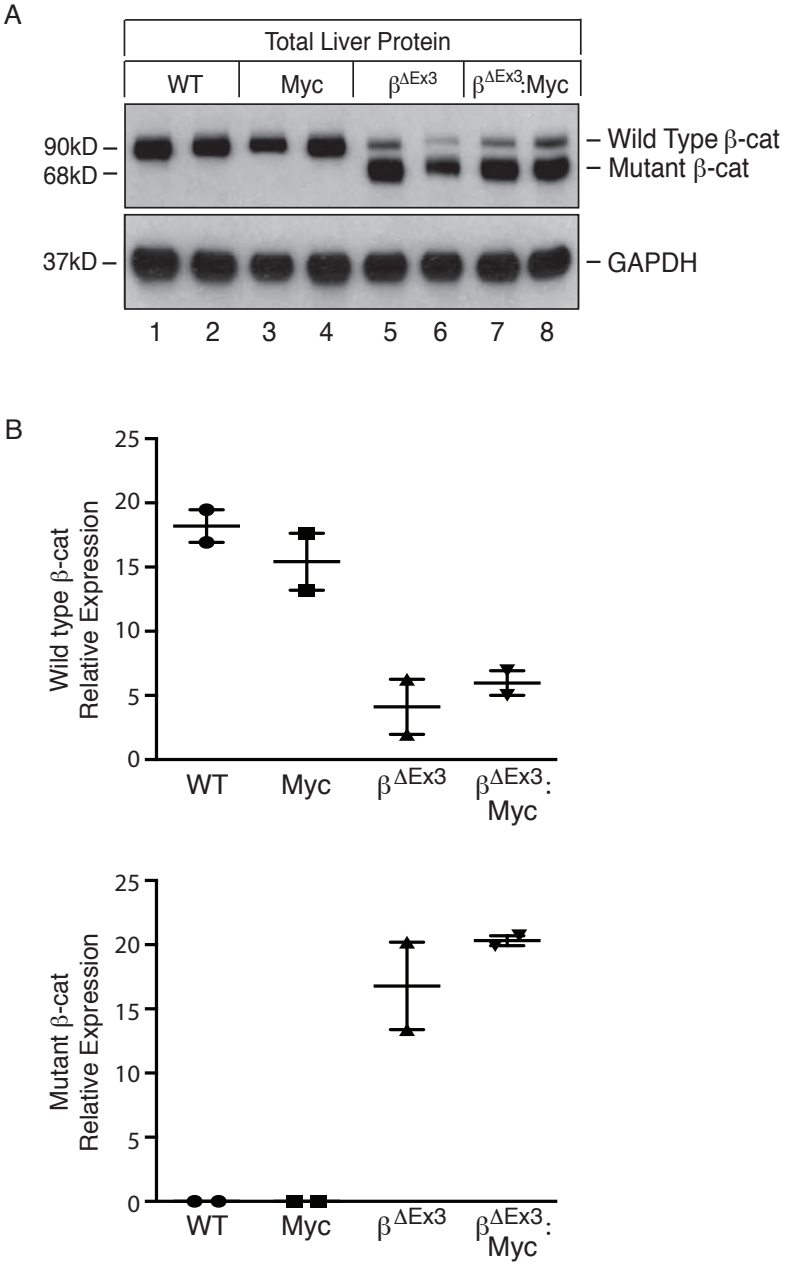
Supplemental Figure 3. Histopathology of HBs and other liver tumors that develop in β-catΔEx3 and Tet-O-Myc mice. Photomicrographs of H&E stained sections showing spectrum of HBs (A-I) and other liver tumors (J-L) in 3-6 week old β-catΔEx3 mice and 12-16 week old Tet-O-Myc mice (M-R). (A) Low-power image of fetal HBs showing adjacent tumors with characteristic clear and dark cell morphologies. (B) Higher power image of a fetal HB with clear cell morphology (left) juxtaposed to one with dark cell morphology (right). (C) Leading edge of a fetal HB depicting border with normal liver. (D) High power image of fetal HB with clear cell morphology. Extramedullary hematopoiesis (EMH) is prominent in many HBs (arrowheads), particularly those in A-D. (E) Mixed fetal-embryonal HB. (F) Mixed fetal-embryonal HB with a microtrabecular growth pattern. (G) Low power image of solitary fetal-embryonal HB. Contrast the well-demarcated border of the tumor in (G) with the less defined border of the fetal HB in C. (H and I) Embyonal HBs with macrotabecular (H) or solid (I) growth patterns. Cells have a high nuclear/cytoplasmic ratio, angulated nuclei and demonstrate reduced cohesion between cells. EMH is also largely absent. (J) Hepatocellular malignant neoplasm; not otherwise specified (HMN NOS). (K) Anaplastic HCC. (L) Trabecular HCC. (M-R) Tet-O-Myc-mice develop poorly differentiated HBs with primitive features. HBs contain small angulated cells that display reduced cohesion with one another (M, N, O) with tumors developing within the context of non-injured, relatively normal liver (M, P). Tet-O-Myc-derived HBs also contain tubulo-glandular structures (P, Q), and display trabecular (O) or solid (R) growth patterns, have clearly demarcated boundaries and generally lack EMH. Most β-catΔEx3:Myc-derived HBs resemble cells present during the latter stages of embryonic liver development (E15 onwards), while Tet-O-Myc-derived HBs are more similar to embryonic liver cells present at E12-14. Scale bars represent 50μm except for panels A and G where they represent 100μm.

Supplemental Figure 4



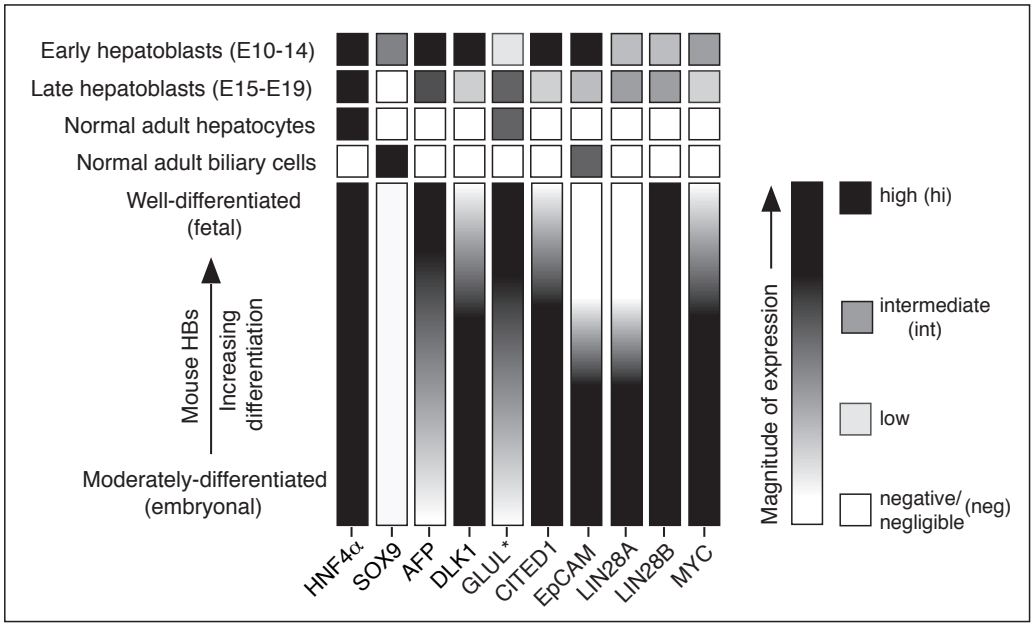
Supplemental Figure 4. Activated wnt/β-catenin and c-Myc cooperate to drive tumorigenesis in β-catΔEx3:Myc and Tet-O-Myc mice. Photomicrographs if immunohistochemistry with c-Myc- and β-catenin-specific antibodies showing expression and localization of c-Myc (A, C, E and G) and β-catenin (B, D, F and H) in livers of WT (A, B) β-catΔEx3:Myc (C-F) and Tet-O-Myc (G, H) mice. c-Myc is undetectable in WT liver (A), but is highly expressed in the nuclei of tumor cells in β-catΔEx3:Myc (C, E) and Tet-O-Myc (G) mice. β-catenin is localized to the outer membranes of hepatocytes and bile ducts (arrowhead) in WT livers (B), but is predominantly cytoplasmic in HBs from β-catΔEx3:Myc (D, F) and Tet-O-Myc (H) mice, although some membranous staining is also evident in (H). In each case β-catenin and c-Myc are more abundant in tumors relative to surrounding liver. Note the marked absence or reduction in membranous β-catenin in non-tumorous liver of β-catΔEx3:Myc mice in (D). c-Myc and β-catenin (AEC chromagen, red/brown), hematoxylin counterstain (blue). Scale bars represent 50μm.

Supplemental Figure 5



Supplemental Figure 5. Hepatic expression of mutant β-catenin results in reduced expression of endogenous β-catenin. (A) Western blotting of liver extracts prepared from 2 individual WT, Alb-c-Myc (Myc), β-catΔEx3 ($\beta^{\Delta Ex3}$) and β-catΔEx3:Myc ($\beta^{\Delta Ex3}$:Myc) mice using β-catenin- and GAPDH-specific antibodies. Note that while 90kD wild-type (endogenous) β-catenin is abundantly expressed in WT and Alb-c-Myc livers, there is a 65-80% reduction in wild-type β-catenin in livers of β-catΔEx3 (lanes 5 & 6) and β-catΔEx3:Myc (lanes 7 & 8) mice expressing mutant β-catenin. (B) Graphs showing relative hepatic expression of wild-type (upper graph) and mutant (lower graph) β-catenin. Graphs were generated by importing scanned images of each gel into Image J software and quantifying signal intensity. Bars represent the mean +/- SEM.

Supplemental Figure 6



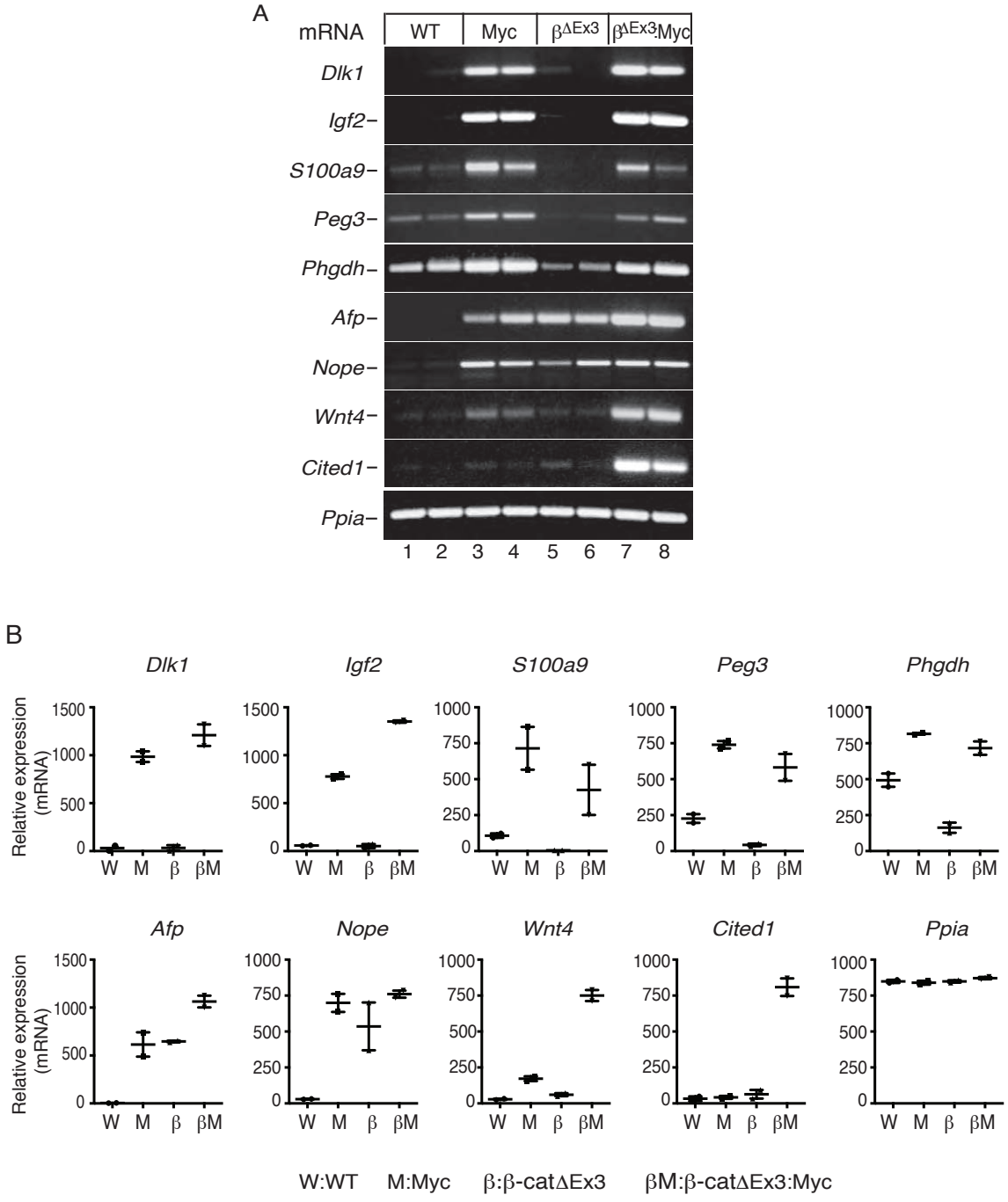
Well-differentiated HBs	Moderately differentiated HBs
HNF4α(hi)	HNF4α(hi)
AFP(hi)	AFP(low-int)
DLK1(low)	DLK1(hi)
GLUL(hi)	GLUL(low)
CITED1(hi)	CITED1(hi)
EpCAM(neg)	EpCAM(low-int)
LIN28A(neg)	LIN28A(low-int)
LIN28B(hi)	LIN28B(hi)
MYC(int)	MYC(hi)
cyto-β-cat(hi)	cyto-β-cat(hi)
SOX9(neg)	SOX9(neg)

* Perivenous hepatocytes only

cyto-β-cat; cytoplasmic localized β-catenin

Supplemental Figure 6. Scheme summarizing the expression of oncofetal genes and lineage markers as a function of tumor cell differentiation in HBs from β-catΔEx3:Myc and Tet-O-Myc mice. The magnitude of expression of lineage-restricted and developmentally regulated genes is represented as a function of tumor cell differentiation in tumors (long vertical bars) from both strains of mice. Small squares depict the magnitude of expression of each gene in normal hepatoblasts present during the early and latter stages of embryonic liver development, adult hepatocytes and biliary cells. Both types of HB express abundant HNF4α, a marker of hepatocytic commitment, but little to no SOX9, a marker of biliary cell commitment. IHC shows that well-differentiated fetal HBs can be discriminated from embryonal HBs on the basis of high AFP and GLUL expression and low or absent expression of DLK1, EpCAM and LIN28A. Fetal HBs completely lack expresssion of LIN28A and EpCAM suggesting that these may be the most useful markers for discriminating between well and poorly-differentiated HBs. LIN28B was highly expressed in both HB subtypes and provided no discrimination. Embryonal HBs also generally expressed higher levels of c-Myc than fetal HBs. Black, gray and white color indicates high, intermediate and low/negligible expression, respectively.

Supplemental Figure 7

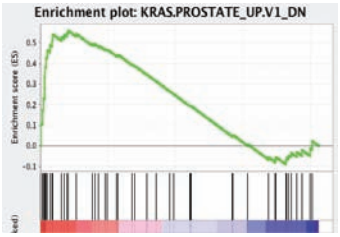


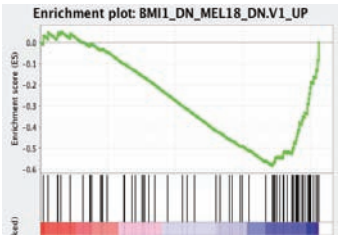
Supplemental Figure 7. Post-array verification of tumor-enriched and c-Myc-associated DEGs.
(A) Ethidium bromide stained gels of RT-PCR-amplified products for selected tumor-enriched DEGs in Table S1 as identified by array. Total RNA isolated from livers of 2 individual WT, Alb-c-Myc (Myc), β-catΔEx3 (βΔEx3) and β-catΔEx3:Myc (βΔEx3:Myc) mice was converted to cDNA and amplified using gene-specific primers listed in Supplemental Table 11. (B) Graphs showing quantitation of gels in (A) depicting relative hepatic mRNA expression of each gene. Graphs were generated by importing scanned images of each gel into Image J software and quantifying signal intensity relative to *Ppia* (cyclophilin A). W, WT; M, Myc; β, βΔEx3 and βM, βΔEx3:Myc mice. Horizontal bars for each genotype represents the mean of two individual samples. Error bars represent +/- SEM.

Supplemental Figure 8
(**A**) Putative tumor-enriched DEGs; genes differentially expressed between β-cat:Myc & β-cat livers. (corresponding to yellow box, Fig. 5)

I. Enriched Oncogenic Signature Gene Sets

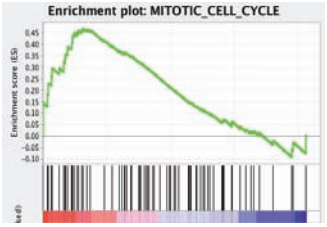
GS DETAILS	SIZE	ES	NES	NOM p-val	FDR q-val
KRAS.PROSTATE_UP.V1_DN	48	0.56	1.66	0.002	0.218
P53_DN.V2_UP	60	0.53	1.62	0.002	0.179
P53_DN.V2_DN	65	0.51	1.61	0.000	0.138
CYCLIN_D1_P.V1_DN	89	0.47	1.57	0.007	0.149
KRAS.AMP.LUNG_UP.V1_UP	47	0.51	1.54	0.017	0.159
BMI1_DN_MEL18_DN.V1_UP	70	-0.58	-1.85	0.000	0.008
CSR_LATE_UP.V1_DN	58	-0.60	-1.82	0.000	0.008
MEL18_DN.V1_UP	73	-0.56	-1.77	0.000	0.016
KRAS.DF.V1_DN	66	-0.56	-1.76	0.000	0.014
BMI1_DN.V1_UP	74	-0.55	-1.74	0.000	0.014

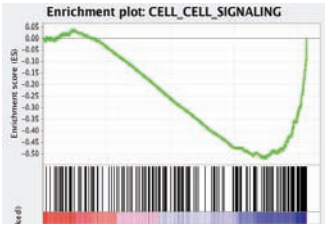




II. Enriched Gene Ontology Biologocal Processes Terms

GS DETAILS	SIZE	ES	NES	NOM p-val	FDR q-val
MITOTIC_CELL_CYCLE	77	0.47	1.51	0.009	1.000
CELL_CYCLE_PHASE	83	0.45	1.46	0.019	1.000
GLYCOPROTEIN_BIOSYNTHETIC_PROCESS	31	0.53	1.46	0.044	1.000
CELL_CYCLE_PROCESS	93	0.44	1.45	0.022	1.000
REGULATION_OF_CYCLIN_DEPENDENT_ PROTEIN_KINASE_ACTIVITY	19	0.57	1.40	0.060	1.000
CELL_CELL_SIGNALING	186	-0.52	-1.86	0.000	0.027
CELLULAR_MORPHOGENESIS_ DURING_DIFFERENTIATION	19	-0.73	-1.81	0.000	0.059
AXONOGENESIS	17	-0.74	-1.79	0.000	0.055
NEURITE_DEVELOPMENT	20	-0.72	-1.78	0.002	0.044
NEURON_DEVELOPMENT	23	-0.65	-1.69	0.013	0.128



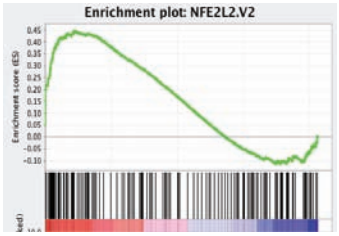


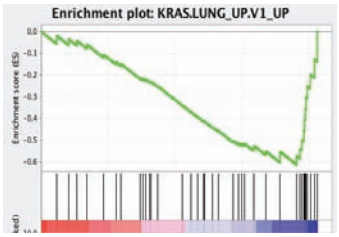
Supplemental Figure 8A. GSEA (Enriched oncogenic signature gene sets and gene ontology biological processes terms) of the putative tumor-enriched DEGs in Supplemental Table 1 (β-cat:Myc vs. β-cat comparison) (Fig. 5, yellow box).

Supplemental Figure 8
(**B**) DEGs co-regulated by β-cat & Myc; genes differentially expressed between β-cat:Myc and WT livers. (corresponding to green box, Fig. 5)

I. Enriched Oncogenic Signature Gene Sets

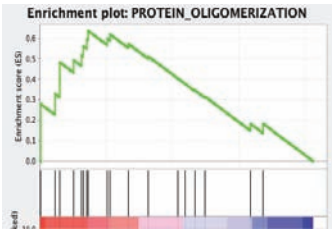
GS DETAILS	SIZE	ES	NES	NOM p-val	FDR q-val
➤ NFE2L2.V2	153	0.45	1.74	0.000	0.058
ESC_J1_UP_LATE.V1_UP	83	0.43	1.52	0.017	0.336
LEF1_UP.V1_DN	89	0.41	1.47	0.009	0.355
ATM_DN.V1_DN	57	0.42	1.41	0.035	0.420
ESC_V6.5_UP_LATE.V1_UP	73	0.38	1.33	0.044	0.631
KRAS.LUNG_UP.V1_UP	41	-0.61	-1.83	0.000	0.031
KRAS.DF.V1_UP	85	-0.54	-1.78	0.000	0.031
KRAS.BREAST_UP.V1_UP	50	-0.57	-1.76	0.000	0.029
KRAS.600.LUNG.BREAST_UP.V1_UP	95	-0.51	-1.74	0.000	0.031
RPS14.DN.V1_UP	85	-0.51	-1.69	0.003	0.047

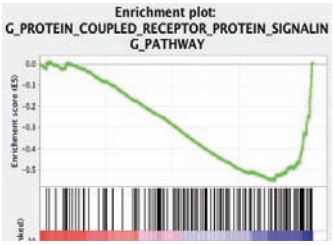




II. Enriched Gene Ontology Biological Processes Terms

GS DETAILS	SIZE	ES	NES	NOM p-val	FDR q-val
PROTEIN_OLIGOMERIZATION	19	0.64	1.65	0.009	0.864
CHROMATIN_MODIFICATION	22	0.53	1.41	0.065	1.000
MRNA_PROCESSING_GO_0006397	27	0.49	1.41	0.071	1.000
M_PHASE_OF_MITOTIC_CELL_CYCLE	45	0.44	1.41	0.061	1.000
MITOCHONDRION_ORGANIZATION _AND_BIOGENESIS	22	0.51	1.38	0.101	1.000
G_PROTEIN_COUPLED_RECEPTOR_ PROTEIN_SIGNALING_PATHWAY	157	-0.55	-2.00	0.000	0.004
LOCOMOTORY_BEHAVIOR	51	-0.65	-1.99	0.000	0.003
CELL_SURFACE_RECEPTOR_LINKED_ SIGNAL_TRANSDUCTION_GO_0007166	288	-0.50	-1.94	0.000	0.005
IMMUNE_RESPONSE	115	-0.56	-1.94	0.000	0.004
IMMUNE_SYSTEM_PROCESS	160	-0.52	-1.88	0.000	0.011



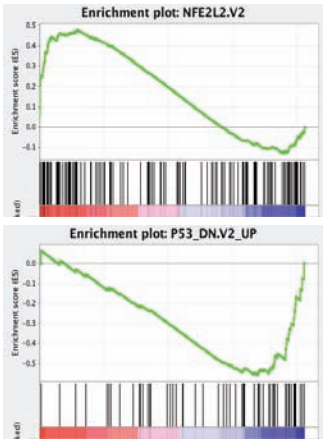


Supplemental Figure 8B. GSEA (Enriched oncogenic signature gene sets and gene ontology biological processes terms) of the DEGs co-regulated by β-catenin and Myc (β-cat:Myc vs. WT comparison) (Fig. 5, green box). (Related to Online GEO submission GSE 79084).

Supplemental Figure 8.
(**C**) β-catenin-regulated DEGs; genes differentially expressed between β-cat and WT livers. (corresponding to red box, Fig. 5)

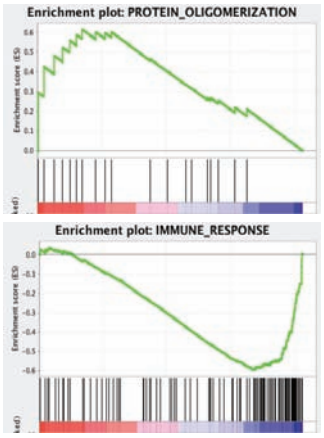
I. Enriched Oncogenic Signature Gene Sets

GS DETAILS	SIZE	ES	NES	NOM p-val	FDR q-val
NFE2L2.V2	153	0.48	1.84	0	0.026
LEF1_UP.V1_DN	89	0.43	1.54	0.007	0.396
MEK_UP.V1_UP	87	0.43	1.52	0.007	0.315
ESC_J1_UP_LATE.V1_UP	83	0.43	1.50	0.013	0.292
ESC_V6.5_UP_LATE.V1_DN	75	0.42	1.45	0.020	0.350
P53_DN.V2_UP	60	-0.56	-1.81	0.002	0.049
KRAS.600.LUNG.BREAST_UP.V1_UP	95	-0.52	-1.80	0.000	0.028
KRAS.BREAST_UP.V1_UP	50	-0.55	-1.72	0.000	0.055
JAK2_DN.V1_UP	62	-0.51	-1.68	0.006	0.068
KRAS.PROSTATE_UP.V1_UP	56	-0.52	-1.68	0.000	0.059



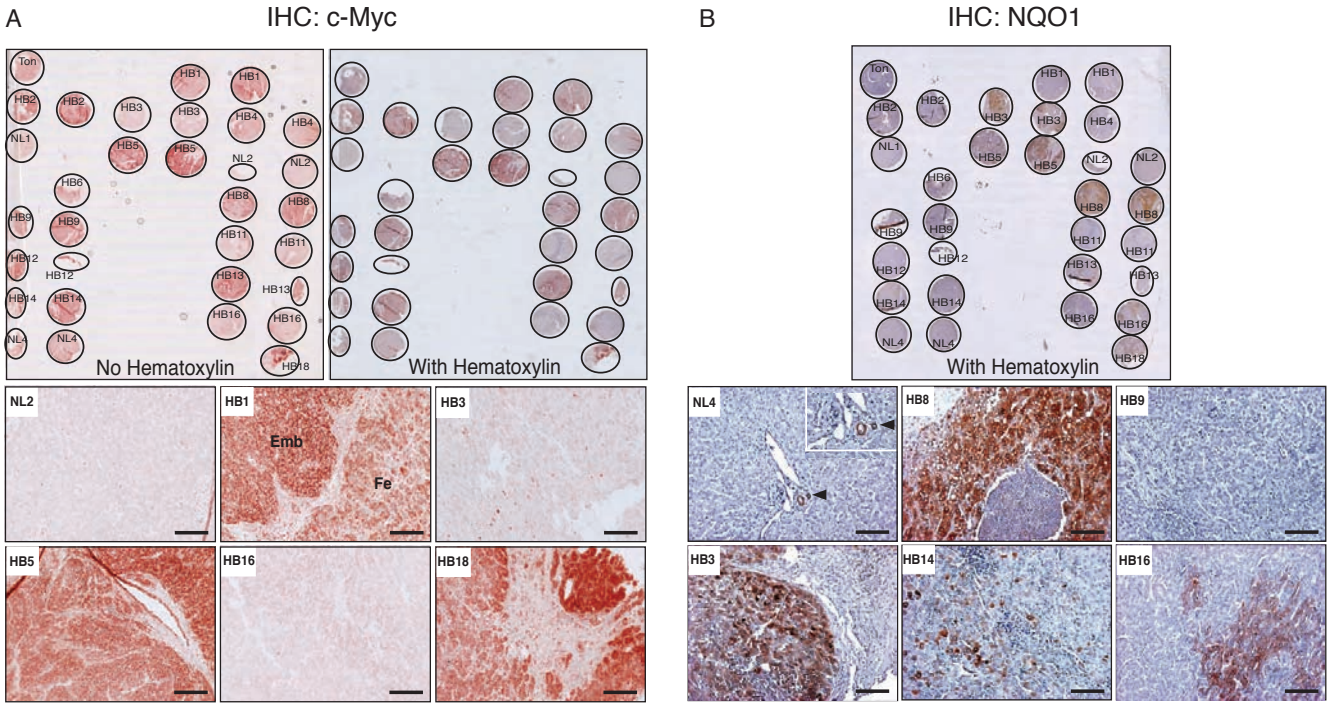
II. Enriched Gene Ontology Biological Processes Terms

GS DETAILS	SIZE	ES	NES	NOM p-val	FDR q-val
PPROTEIN_OLIGOMERIZATION	19	0.62	1.63	0.020	1.000
REPRODUCTIVE_PROCESS	70	0.42	1.42	0.033	1.000
AMINE_TRANSPORT	21	0.54	1.40	0.088	1.000
NUCLEOTIDE_METABOLIC_PROCESS	21	0.51	1.39	0.068	1.000
RESPONSE_TO_ABIOTIC_STIMULUS	38	0.44	1.35	0.083	1.000
IMMUNE_RESPONSE	115	-0.60	-2.14	0.000	0.000
IMMUNE_SYSTEM_PROCESS	160	-0.56	-2.10	0.000	0.001
LOCOMOTORY_BEHAVIOR	51	-0.64	-1.99	0.000	0.007
DEFENSE_RESPONSE	113	-0.56	-1.97	0.000	0.006
CELLULAR_DEFENSE_RESPONSE	28	-0.71	-1.95	0.000	0.006
INFLAMMATORY_RESPONSE	61	-0.59	-1.90	0.000	0.013
G_PROTEIN_COUPLED_RECEPTOR_ PROTEIN_SIGNALING_PATHWAY	157	-0.50	-1.87	0.000	0.017
CELL_SURFACE_RECEPTOR_LINKED_ SIGNAL_TRANSDUCTION_GO_0007166	288	-0.46	-1.82	0.000	0.029
BEHAVIOR	73	-0.55	-1.80	0.000	0.033
RESPONSE_TO_EXTERNAL_STIMULUS	155	-0.48	-1.78	0.000	0.039



Supplemental Figure 8C. GSEA (Enriched oncogenic signature gene sets and enriched gene ontology biological processes terms) of the DEGs regulated by β-catenin alone (β-cat vs. WT) (Fig. 5, red box). (Related to Figure 6 and Online GEO submission GSE 79084).

Supplemental Figure 9



Supplemental Figure 9. Expression of c-Myc and the canonical Nrf2 target, NQO1, in a panel of human HBs. (Tissue microarray (TMA) format). IHC analysis was available for 14 cases after discounting loss of cores due to sectioning and IHC processing. Higher magnification images of a representative example of staining in normal liver (NL) and the range of staining in 5 of the HBs on the TMA is shown below. (A) 7/14 (50%) HBs expressed high levels of c-Myc in a significant proportion of cells. In c-Myc-positive HBs, c-Myc appears more intense in the embryonal (Emb) component than in the fetal (Fe) component (see HB1). (B) 8/14 (57%) HBs expressed NQO1 in a moderate-high number of cells. NQO1 is localized to the cytoplasm of tumor cells and is heterogeneous within tumors (see HB14 and HB16). In normal liver (NL4), NQO1 is undetectable in hepatocytes, yet readily detectable in normal biliary cells (inset, arrowheads). Scoring of c-Myc and NQO1 expression for each sample is shown in Supplemental Table 7. Slides were scanned on a NanoZoomer slide scanner (Hamamatsu Photonics, Hamamatsu, Japan). Low and high power images were captured using NDP View Software (Hamamatsu Photonics, Japan). AEC chromagen, red; hematoxylin, blue. HB, hepatoblastoma; NL, normal (non-cancerous) liver; Ton, tonsil. Scale bars represent 50μm.

Supplemental Table 2: IPA Summary of Putative Tumor Enriched DEGs (β-catΔEx3:Myc vs β-cat Comparison).

Molecular and Cellular Functions		
Name	p-value	No. of Molecules
Cell-To-Cell Signaling and Interaction	2.07E-12 - 1.32E-03	86
Cell Growth and Proliferation	2.66E-10 - 1.43E-03	132
Cellular Movement	3.73E-10 - 1.45E-03	91
Cellular Development	7.42E-10 - 1.43E-03	103
Cell Death and Survival	1.67E-07 - 1.43E-03	108
Top Canonical Pathways		
Name	p-value	Ratio
Wnt/β-catenin Signaling	3.31E-04	10/169(0.059)
Agranulocyte Adhesion and Diapedesis	2.95E-03	9/189 (0.048)
Colorectal Cancer and Metastasis	4.07E-03	10/236(0.042)
Granulocyte Adhesion and Diapedesis	6.73E-03	8/177 (0.045)
VDR/RXR Activation	7.46E-03	5/78 (0.064)
Top Tox Lists		
Name	p-value	Ratio
Hepatic Fibrosis	1.29E-04	8/96 (0.083)
Increased Renal Proliferation	9.54E-04	8/129 (0.062)
Hepatic Stellate Cell Activation	2.08E-03	4/35(0.114)
Renal Glomerulus Panel (Human)	2.17E-03	3/17 (0.176)
LPS/IL1-Mediated Inhibition of RXR Function	6.23E-03	10/51 (0.04)
Hepatotoxicty		
Name	p-value	No. of Molecules
Liver Fibrosis	8.02E-04 - 1.72E-01	8
Liver Inflammation/Hepatitis	9.41E-04 - 5.00E-01	13
Liver Damage	4.65E-03 - 1.40E-01	10
Liver Hyperplasia/Hyperproliferation	1.13E-02 - 6.29E-01	32
Liver Steatosis	1.44E-02 - 3.25E-01	10

Supplemental Table 3: IPA Summary of DEGs co-regulated by β-catenin and Myc (β-catΔEX3:Myc Livers vs WT Comparison).

Molecular and Cellular Functions		
Name	p-value	No. of Molecules
Cellular Movement	4.61E-22 - 3.57E-05	233
Cellular Function and Maintenance	6.08E-20 - 3.11E-05	292
Cell-To-Cell Signaling and Interaction	8.02E-19 - 3.53E-05	217
Cellular Development	1.94E-18 - 3.31E-05	339
Protein Synthesis	1.23E-15 - 1.65E-05	127
Top Canonical Pathways		
Name	p-value	Ratio
Complement System	2.73E-09	13/33(0.394)
B-Cell Development	4.00E-08	12/34 (0.353)
LPS/IL-1-Mediated Inhibition of RXR Function	5.98E-07	30/219(0.137)
iCOS-iCOSL Signaling in T-Helper Cells	1.68E-06	19/108 (0.176)
T-Helper Cell Differentiation	1.94E-06	15/71 (0.211)
Top Tox Lists		
Name	p-value	Ratio
LPS/IL-1-Mediated Inhibition of RXR Function	3.42E-13	44/251 (0.175)
NRF2-Mediated Oxidative Stress Response	8.25E-08	33/234 (0.141)
Xenobiotic Metabolism Signaling	1.05E-06	39/336 (0.116)
Persistent Renal Ischemia-Reperfusion Injury (Mouse)	1.09E-05	9/30 (0.3)
Cytochrome P450 Panel-Substrate is a Xenobiotic (Mouse)	2.00E-05	8/25 (0.32)
Hepatotoxicty		
Name	p-value	No. of Molecules
Liver Steatosis	1.01E-06 - 1.49E-01	35
Liver Inflammation/Hepatitis	1.34E-06 - 4.89E-01	36
Hepatocellular Carcinoma	4.41E-06 - 1.06E-01	49
Liver Hyperplasia/Hyperproliferation	4.41E-06 - 4.62E-01	90
Liver Cirrhosis	2.22E-05 - 5.03E-02	23

Supplemental Table 4: IPA Summary of β-cat regulated DEGs (β-cat vs WT Comparison)

Molecular and Cellular Functions		
Name	p-value	No. of Molecules
Cellular Function and Movement	1.66E-15 - 1.47E-03	232
Cell Morphology	1.81E-13 - 1.37E-03	161
Protein Synthesis	6.78E-12 - 1.32E-03	97
Cell-To-Cell Signaling and Interaction	1.23E-11 - 1.51E-03	148
Cell Death and Survival	9.30E-09 - 1.30E-03	274
Top Canonical Pathways		
Name	p-value	Ratio
LPS/IL-1-Mediated Inhibition of RXR Function	1.18E-10	33/219 (0.151)
B-Cell Development	6.70E-08	11/34 (0.324)
Nicotine Degradation	5.13E-06	12/60 (0.2)
Xenobiotic Metabolism Signaling	8.33E-06	28/271 (0.103)
Glutathione-Mediated Detoxification	1.22E-05	8/28 (0.286)
Top Tox Lists		
Name	p-value	Ratio
LPS/IL-1-Mediated Inhibition of RXR Function	3.26E-16	44/251 (0.175)
NRF2-Mediated Oxidative Stress Response	3.97E-11	35/234 (0.15)
Xenobiotic Metabolism Signaling	5.62E-10	41/336 (0.122)
Cytochrome P450 Panel-Substrate is a Xenobiotic (Mouse)	2.55E-10	10/25 (0.4)
Oxidative Stress	5.56E-08	14/57 (0.246)
Hepatotoxicty		
Name	p-value	No. of Molecules
Liver Cholestasis	1.14E-05 - 2.87E-01	16
Glutathione Depletion	1.15E-04 - 1.12E-01	8
Liver Inflammation/Hepatitis	3.35E-04 - 4.96E-01	26
Liver Damage	8.46E-04 - 6.05E-01	22
Liver Necrosis/Cell Death	9.15E-04 - 1.69E-01	23

Supplemental Table 5: Stress and toxicity-associated gene expression in livers of β-cat:Myc, β-cat and Alb-c-Myc mice

Gene Symbol	Gene Name	Stress Pathway	Fold change vs. WT Liver		
			β-catΔEx3	β-catΔEx3:c-Myc	c-Myc
Nqo1	NAD(P)H dehydrogenase, quinone 1	Ox	32.93	26.72	1.40
Slc2a1	Solute carrier family 2 (facilitated glucose transporter), member 1	Hyp	17.85	13.21	5.29
Gsr	Glutathione reductase	Ox	6.01	4.79	0.83
Hmox1	Heme oxygenase (decycling) 1	Ox	5.22	4.34	1.41
Gclc	Glutamate-cysteine ligase, catalytic subunit	Ox	4.66	5.05	0.89
Gstp1	Glutathione S-transferase Pi 1	Ox	4.16	5.04	0.45
Edn1	Endothelin 1	Os	3.84	4.44	5.74
Serpine1	Serpin peptidase inhibitor, clade E (plasminogen activator inhibitor type 1), member 1	Hyp	3.81	1.46	2.80
Txnrd1	Thioredoxin reductase 1	Ox	3.51	2.92	0.91
Tnfrsf10b	Tumor necrosis factor receptor superfamily, member 10b	CD/Nec	3.50	2.31	3.55
Atg7	Autophagy related 7	CD/Aut	3.24	2.15	0.92
Fth1	Ferritin, heavy polypeptide 1	Ox	3.22	4.44	1.06
Atr	Ataxia telangiectasia and Rad3 related	DDR	2.98	2.10	1.60
Txn1	Thioredoxin	Ox	2.21	3.36	2.05
Sqstm1	Sequestosome 1	Ox	2.18	2.47	0.45
Bid	BH3 Interacting domain death agonist	HSP/UPR/CD/Apop	2.14	1.76	1.45
Mre11a	MRE11 Meiotic recombination 11 homolog A (S. Cerevisiae)	DDR	2.07	1.66	2.76
Pvr	Poliovirus receptor	CD/Nec	1.94	1.58	1.52
Prdx1	Peroxiredoxin 1	Ox	1.93	1.73	1.23
Gapdh	Glyceraldehyde-3-phosphate dehydrogenase		1.92	1.63	1.03
Chek1	Checkpoint kinase 1	DDR	1.90	1.19	4.38
Atg12	Autophagy related 12	CD/Aut	1.86	1.88	1.13
Cftr	Cystic fibrosis transmembrane conductance regulator	Os	1.85	0.61	1.06
Gclm	Glutamate-cysteine ligase, modifier subunit	Ox	1.82	1.98	0.78
Cdkn1a	Cyclin-dependent kinase inhibitor 1a	DDR	1.81	1.70	4.06
Adm	Adrenomedullin	Hyp	1.78	1.67	2.10
Rad51	RAD51 recombinase	DDR	1.64	1.66	4.42
Chek2	Checkpoint kinase 2	DDR	1.51	0.65	2.46
Parp1	Poly (ADP-Ribose) polymerase 1	CD/Nec	1.45	0.59	1.29
Arnt	Aryl hydrocarbon receptor nuclear translocator	Hyp	1.44	0.98	1.58
Ddb2	Damage-specific DNA binding protein 2	DDR	1.43	0.91	1.19
Bnip3l	BCL2/Adenovirus E1B 19kDa interacting protein 3-like	Hyp	1.32	1.44	1.22
Atf6	Activating transcription factor 6	HSP/UPR	1.29	1.10	1.70

Supplemental Table 5: Stress and toxicity-associated gene expression in livers of β-cat:Myc, β-cat and Alb-c-Myc mice

Gene Symbol	Gene Name	Stress Pathway	Fold change vs. WT Liver		
			β-catΔEx3	β-catΔEx3:c-Myc	c-Myc
Xpc	Xeroderma pigmentosum, complementation group C	DDR	1.26	0.88	1.00
Atf6b	Activating transcription factor 6b	HSP/UPR	1.24	0.97	0.87
Tnfrsf1a	Tumor necrosis factor receptor superfamily, member 1A	CD/Nec	1.23	1.12	1.13
Ccl12	Chemokine (C-C motif) ligand 12	IR	1.18	0.58	4.43
Hus1	HUS1 checkpoint homolog (S. Pombe)	DDR	1.18	1.18	2.70
Hsp90ab1	Heat shock protein 90 alpha (cytosolic), class B member 1		1.14	1.20	0.84
Becn1	Beclin 1	CD/Aut	1.12	1.14	1.17
Txnl4b	Thioredoxin-like 4B	CD/Nec	1.12	0.45	1.15
Grb2	Growth factor receptor-bound protein 2	CD/Nec	1.09	0.89	1.07
Actb	Actin, beta		1.08	1.02	1.01
Hspa4	Heat shock 70kDa protein 4	HSP/UPR	1.07	1.22	0.92
Ripk1	Receptor (TNFRSF)-interacting serine-threonine kinase 1	CD/Nec	1.07	0.64	1.06
Rad9	RAD9 homolog A (S. Pombe)	DDR	1.06	0.73	1.45
Rad17	RAD17 homolog (S. Pombe)	DDR	1.01	0.84	1.14
Trp53	Tumor protein P53	DDR	1.00	0.94	0.88
Hsp90aa1	Heat shock protein 90kDa alpha (cytosolic), class A member 1	HSP/UPR	0.99	0.61	0.94
Atg5	Autophagy related 5	CD/Aut	0.98	0.71	0.96
Nbn	Nibrin	DDR	0.98	0.77	1.31
Atm	Ataxia telangiectasia mutated	DDR	0.93	0.60	1.01
Akr1b3	Aldo-keto reductase family 1, member B1 (aldose reductase)	Os	0.92	0.83	1.23
Atf4	Activating transcription factor 4	HSP/UPR	0.84	1.10	0.94
Mcl1	Myeloid cell leukemia sequence 1 (BCL2-Related)	CD/Apop	0.82	0.86	1.13
Hspa4l	Heat shock 70kDa protein 4-Like	HSP/UPR	0.80	0.81	0.90
Vegfa	Vascular endothelial growth factor A	Hyp	0.70	0.52	0.80
B2m	Beta-2 microglobulin		0.70	0.89	0.99
Nfat5	Nuclear factor of activated T-cells 5, tonicity-responsive	Os	0.69	0.53	1.35
Ddit3	DNA-damage-inducible transcript 3	DDR	0.67	1.07	0.85
Dnajc3	DnaJ (Hsp40) homolog, subfamily C, member 3	HSP/UPR	0.66	0.62	1.06
Hspa5	Heat shock 70kDa protein 5 (glucose-regulated protein, 78kDa)	HSP/UPR	0.64	0.55	1.03
Calr	Calreticulin	HSP/UPR	0.62	0.51	0.86
Hsp90b1	Heat shock protein 90kDa beta (Grp94), member 1	HSP/UPR	0.62	0.52	0.92
Gusb	Glucuronidase, beta		0.61	0.57	1.16
Epo	Erthyropoietin	Hyp	0.60	0.90	0.83

Supplemental Table 5: Stress and toxicity-associated gene expression in livers of β-cat:Myc, β-cat and Alb-c-Myc mice

Gene Symbol	Gene Name	Stress Pathway	Fold change vs. WT Liver		
			β-catΔEx3	β-catΔEx3:c-Myc	c-Myc
Gadd45a	Growth arrest and DNA-Damage-inducible, alpha	DDR	0.57	0.69	0.84
Il1a	Interleukin 1, alpha	IR	0.54	0.20	1.78
Gadd45g	Growth arrest and DNA-damage-inducible, gamma	DDR	0.53	0.49	0.57
Xbp1	X-Box binding protein 1	HSP/UPR	0.47	0.39	0.85
Car9	Carbonic anhydrase IX	Hyp	0.46	0.26	1.21
Ldha	Lactate dehydrogenase A	Hyp	0.45	0.30	1.25
Aqp2	Aquaporin 2	Os	0.43	0.90	0.52
Crp	C-reactive protein	IR	0.42	0.31	0.90
Fas	Fas cell surface death receptor/CD95	CD/Apop	0.41	0.35	1.44
Tnf	Tumor necrosis factor	IR	0.38	0.70	2.45
Tlr4	Toll-like receptor 4	IR	0.37	0.16	3.39
Il6	Interleukin 6 (interferon, beta 2)	IR	0.35	0.63	10.67
Ripk3	Receptor-interacting serine-threonine kinase 3	CD/Nec	0.34	0.46	4.19
Aqp4	Aquaporin 4	Os	0.32	0.12	2.73
Aqp1	Aquaporin 1	Os	0.31	0.19	0.96
Slc5a3	Solute carrier family 5 (sodium/myo-inositol cotransporter), member 3	Os	0.31	0.25	1.01
Il1b	Interleukin 1, beta	IR	0.29	0.15	0.92
Ulk1	Unc-51 like autophagy activating kinase 1	CD/Aut	0.27	0.25	0.69
Casp1	Caspase 1	CD/Apop	0.26	0.25	2.72
Mmp9	Matrix metallopeptidase 9 (gelatinase B, 92kDa type IV collagenase)	Hyp	0.24	0.64	2.53
Slc9a3	Solute carrier family 9, subfamily A, member 3	Os	0.22	0.75	0.43
Cd40lg	CD40 ligand	IR	0.20	0.36	0.58
Ifng	Interferon, gamma	IR	0.15	0.34	1.55
Housekeeping genes					

Stress Pathway
Ox: Oxidative Stress
Os: Osmotic Stress
Hyp: Hypoxia
IR: Inflammatory Response
CD: Cell Death: Apop:Apoptosis, Aut:Autophagy, Nec: Necrosis
HSP/UPR: Heat Shock Proteins/Unfolded Protein Response

Supplemental Table 6: Oxidative stress-associated gene expression in livers of β-cat:Myc, β-cat and Alb-c-Myc mice

Gene Symbol	Gene Name	Fold-change vs. WT Liver			nrf2 target
		β-catΔEx3	β-catΔEx3:c-Myc	c-Myc	
Gpx2	Glutathione peroxidase 2	956.09	682.81	5.72	Yes
Srxn1	Sulfiredoxin 1 homolog (S. cerevisiae)	45.03	46.06	0.92	Yes
Nqo1	NAD(P)H dehydrogenase, quinone 1	32.36	29.56	0.77	Yes
Gpx3	Glutathione peroxidase 3	26.99	24.29	2.89	Yes
Gsr	Glutathione reductase	8.50	7.39	0.88	Yes
Aox1	Aldehyde oxidase 1	8.23	8.51	0.58	Yes
Gclc	Glutamate-cysteine ligase, catalytic subunit	7.94	6.34	0.93	Yes
Gstp1	Glutathione S-transferase, pi 1	7.53	9.40	0.70	Yes
Hmox1	Heme oxygenase (decycling) 1	7.25	5.63	1.01	Yes
Fmo2	Flavin containing monooxygenase 2	6.62	4.92	0.78	Yes
Nox1	NADPH oxidase 1	5.77	6.93	2.05	Yes
Gpx6	Glutathione peroxidase 6	4.78	3.58	2.14	Yes
Prdx3	Peroxiredoxin 3	4.03	3.64	0.86	Yes
Txnrd1	Thioredoxin reductase 1	3.92	3.49	0.88	Yes
Noxo1	NADPH oxidase organizer 1	3.53	2.61	2.18	Yes
Atr	Ataxia telangiectasia and rad3 related	3.20	2.63	1.42	
Sqstm1	Sequestosome 1	3.14	3.98	0.71	Yes
Fth1	Ferritin heavy chain 1	3.13	2.69	0.88	Yes
Gpx4	Glutathione peroxidase 4	3.08	2.97	0.54	Yes
Prdx6	Peroxiredoxin 6	2.74	2.45	0.80	Yes
Prdx5	Peroxiredoxin 5	2.66	2.20	0.96	Yes
Gss	Glutathione synthetase	2.50	2.45	0.85	Yes
Gapdh	Glyceraldehyde-3-phosphate dehydrogenase	2.38	1.83	1.16	
Prdx2	Peroxiredoxin 2	2.36	3.14	1.35	Yes
Park7	Parkinson disease (autosomal recessive, early onset) 7	2.29	1.80	1.13	
Psmb5	Proteasome (prosome, macropain) subunit, beta type 5	2.21	1.74	0.52	
Recql4	RecQ protein-like 4	1.95	1.63	1.25	
Sod2	Superoxide dismutase 2, mitochondrial	1.86	2.00	1.17	
Gclm	Glutamate-cysteine ligase, modifier subunit	1.71	1.97	0.75	Yes
Ift172	Intraflagellar transport 172 homolog (Chlamydomonas)	1.64	1.51	1.01	
Txn1	Thioredoxin 1	1.58	2.76	1.23	Yes
Duox1	Dual oxidase 1	1.57	3.31	1.62	
Gpx7	Glutathione peroxidase 7	1.55	1.81	0.94	

Supplemental Table 6: Oxidative stress-associated gene expression in livers of β-cat:Myc, β-cat and Alb-c-Myc mice

Gene Symbol	Gene Name	Fold-change vs. WT Liver			nrf2 target
		β-catΔEx3	β-catΔEx3:c-Myc	c-Myc	
Prdx1	Peroxiredoxin 1	1.45	1.34	0.61	
Hsp90ab1	Heat shock protein 90 alpha (cytosolic), class B member 1	1.37	1.48	0.98	
Xpa	Xeroderma pigmentosum, complementation group A	1.23	1.20	0.88	
Epx	Eosinophil peroxidase	1.20	1.32	1.78	
Gstk1	Glutathione S-transferase kappa 1	1.20	1.01	0.97	
Actb	Actin, beta	1.09	0.97	0.99	
Ccs	Copper chaperone for superoxide dismutase	1.04	1.03	1.00	
Dnm2	Dynamin 2	1.01	1.10	0.79	
Prnp	Prion protein	0.99	1.09	1.14	
Il19	Interleukin 19	0.95	2.05	1.41	
Il22	Interleukin 22	0.95	0.96	1.41	
Lpo	Lactoperoxidase	0.95	1.23	1.41	
Mb	Myoglobin	0.95	0.96	461.76	
Sod1	Superoxide dismutase 1, soluble	0.94	0.90	0.72	
Ercc6	Excision repair cross-complementing rodent repair deficiency, complementation group 6	0.93	1.03	0.78	
Cygb	Cytoglobin	0.92	0.79	1.04	
Ptgs2	Prostaglandin-endoperoxide synthase 2	0.90	0.73	1.62	
Apc	Adenomatosis polyposis coli	0.81	0.61	0.97	
Cat	Catalase	0.81	0.83	0.47	
Gpx1	Glutathione peroxidase 1	0.79	0.78	0.89	
Apoe	Apolipoprotein E	0.75	0.61	1.07	
Ercc2	Excision repair cross-complementing rodent repair deficiency, complementation group 2	0.75	0.83	0.69	
Rag2	Recombination activating gene 2	0.71	0.72	1.06	
Vim	Vimentin	0.68	0.51	1.96	
Ctsb	Cathepsin B	0.68	0.74	0.86	
Txnrd3	Thioredoxin reductase 3	0.68	0.93	0.80	
Txnip	Thioredoxin interacting protein	0.64	0.32	2.00	
Gusb	Glucuronidase, beta	0.63	0.72	0.93	
Serpinb1b	Serine (or cysteine) peptidase inhibitor, clade B, member 1b	0.59	0.56	2.63	
Nos2	Nitric oxide synthase 2, inducible	0.53	0.60	0.75	
Ucp3	Uncoupling protein 3 (mitochondrial, proton carrier)	0.52	0.76	13.22	
Fancc	Fanconi anemia, complementation group C	0.51	0.76	0.79	
Txnrd2	Thioredoxin reductase 2	0.46	0.58	0.93	

Supplemental Table 6: Oxidative stress-associated gene expression in livers of β-cat:Myc, β-cat and Alb-c-Myc mice

Gene Symbol	Gene Name	Fold-change vs. WT Liver			nrf2 target
		β-catΔEx3	β-catΔEx3:c-Myc	c-Myc	
Gpx5	Glutathione peroxidase 5	0.46	0.82	0.99	
B2m	Beta-2 microglobulin	0.45	0.53	0.95	
Ehd2	EH-domain containing 2	0.44	0.41	1.61	
Idh1	Isocitrate dehydrogenase 1 (NADP+), soluble	0.41	0.46	0.61	
Ccl5	Chemokine (C-C motif) ligand 5	0.40	0.39	1.14	
Krt1	Keratin 1	0.36	0.36	12.15	
Als2	Amyotrophic lateral sclerosis 2 (juvenile) homolog (human)	0.34	0.34	0.45	
Cyba	Cytochrome b-245, alpha polypeptide	0.33	0.43	1.85	
Ucp2	Uncoupling protein 2 (mitochondrial, proton carrier)	0.33	0.77	1.33	
Noxa1	NADPH oxidase activator 1	0.29	0.46	2.23	
Alb	Albumin	0.28	0.23	0.82	
Ncf2	Neutrophil cytosolic factor 2	0.25	0.38	1.47	
Ncf1	Neutrophil cytosolic factor 1	0.23	0.25	1.38	
Ngb	Neuroglobin	0.21	0.35	1.01	
Ptgs1	Prostaglandin-endoperoxide synthase 1	0.21	0.17	0.20	
Slc38a1	Solute carrier family 38, member 1	0.20	0.42	1.84	
Sod3	Superoxide dismutase 3, extracellular	0.17	0.12	1.31	
Nox4	NADPH oxidase 4	0.16	0.02	1.42	
Prdx4	Peroxiredoxin 4	0.16	0.18	0.62	
Mpo	Myeloperoxidase	0.14	11.12	4.92	
Hspa1a	Heat shock protein 1A	0.07	0.19	0.30	
Tpo	Thyroid peroxidase	0.07	0.07	0.43	
Scd1	Stearoyl-Coenzyme A desaturase 1	0.00	0.01	0.04	
Housekeeping genes					

Supplemental Table 7.
Scoring of c-Myc and NQO1 Protein Expression in Human HBs

c-Myc					NQO1				
Tissue[a] Sample	Intensity Score[b]			c-Myc[c] Status	Tissue[d] Sample	Intensity Score[b]			NQO1[e] Status
	Core 1	Core 2	Avg			Core 1	Core 2	Avg	
Tonsil	3.0	NA	3.0	+	Tonsil	0	NA	0	-
NL1	0.5	NA	0.5	-	NL1	0	NA	0	-
NL2	0	0	0	-	NL2	0	0	0	-
NL4	0	0	0	-	NL4*	0	0	0	-
HB1	3.5	4.5	4.0	+	HB1	0	0.5	0.3	-
HB2	3.5	4.5	4.0	+	HB2	1.5	1.5	1.5	+
HB3	0.5	1.0	0.8	-	HB3	4.0	3.0	3.5	+
HB4	0.5	0	0.3	-	HB4	0	NA	0	-
HB5	3.5	4.5	4.0	+	HB5	3.0	4.5	3.8	+
HB6	0.5	NA	0.5	-	HB6	0.5	NA	0.5	-
HB8*	0.5	0.5	0.5	-	HB8	4.5	4.5	4.5	+
HB9*	0.5	1.0	0.8	-	HB9	0	0	0	-
HB11	1.0	0.5	0.8	-	HB11	0	0	0	-
HB12	3.5	NA	3.5	+	HB12	0	NA	0	-
HB13	4.5	3.5	4.0	+	HB13	2.0	1.5	1.8	+
HB14	3.0	4.0	3.5	+	HB14	2.0	2.0	2.0	+
HB16	0	0.5	0.3	-	HB16	0.5	2.5	1.5	+
HB18	4.5	NA	4.5	+	HB18	3.5	NA	3.5	+

[a] NL- normal human liver, HB- hepatoblastoma.

[b] NA- duplicate sample: not available or insufficient tissue

[c] The sample was designated c-Myc-positive if the average intensity score of 2 cores was > 1. Using this criterium, 50% of HBs were c-Myc-positive and 50% were c-Myc-negative. HBs 1, 2, 5, 12, 13, 14 and 18 were strongly positive for c-Myc. * HB8 & HB9 demonstrated high background staining.

[d] NL- normal human liver, HB- hepatoblastoma. * NL4 had no staining in hepatocyes but had robust staining in bile ducts.

[b] NA- duplicate sample: not available or insufficient tissue

[e] The sample was designated NQO1-positive if the average intensity score of 2 cores was equal to or greater than 1.5. Using this criterium, 57% of HBs were NQO1-positive and 43% were NQO1-negative. HBs 3, 5, 8 & 18 were strongly positive for NQO1.

Supplemental Table 8

Cell Line	Organ Derivation-Tumor Type	*NFE2L2* (reads/million)	*NFE2L2* (compared to median)
UHR	Universal	1521.9	0.92
Daoy	Brain	1418.3	0.85
Hep293TT	Liver-HB	3337.9	2.01
Hep3b	Liver-Pediatric HCC	2124.2	1.28
HepG2	Liver-Pediatric HCC	2494.1	1.50
MOLT4	ALL (Relapse)	700.0	0.42
RDES	Bone-Ewings	934.2	0.56
SKES1	Ewings	1090.6	0.66
SKNBE2	Adrenal-NB	3310.5	1.99
SuPB15	ALL/Ph+	796.2	0.48
WERI-RB-1	Eye-Retinoblastoma	1144.8	0.69
Y79	Eye-Retinoblastoma	1129.9	0.68
WiT49	Kidney-Wilms Tumor	1593.0	0.96

Supplemental Table 8. Table of RNA-seq data showing relative abundance of *NFE2L2* in Hep293TT cells relative to other human pediatric tumor-derived cell lines. Hep293TT cells were derived from an aggressive human HB and express *NFE2L2* at a level that is 2-fold above the median. UHR; Universal Human Reference comprising 10 different human cell lines, HB; hepatoblastoma, HCC; hepatocellular carcinoma, ALL; Acute lymphoblastic leukemia, PH+; Philadelphia Chromosome-positive.

Supplemental Table 9: Primer sequences and PCR conditions for genotyping of mice and analysis of recombination of the β-cateninΔEx3 allele

Genotyping			
Allele	**Forward Primer (5'-3')**	**Reverse Primer (5'-3')**	**Amplicon Size(s) (bp)**
Albumin-c-Myc	ATC AGC AAC AAC CGC AAG TGC	CTC CAT ACC ACC CCC CTC	~300
WT & β-cat$^{lox(Ex3)}$	AGG GTA CCT GAA GCT CAG CG	CAG TGG CTG ACA GCA GCT TT	412 (wt β-cat); 645 (β-cat$^{lox(Ex3)}$)
Alb-Cre	GCT GCC ACG ACC AAG TGA CAG CAA TG	GTA GTT ATT CGG ATC ATC AGC CAC AC	402

Allele	**PCR Conditions**
Albumin-c-Myc	95°C 3 min: 54°C 10 min (1 cycle): 95°C 1min, 54°C 2 min, 72°C 3 min (25 cycles): 95°C 1 min, 54°C 2 min, 72°C 10 min (1 cycle): 4°C hold
WT & β-cat$^{lox(Ex3)}$	95°C 3 min: 56°C 10 min (1 cycle): 95°C 1min, 56°C 2 min, 72°C 3 min (35 cycles): 95°C 1 min, 56°C 2 min, 72°C 10 min (1 cycle): 4°C hold
Alb-Cre	95°C 2 min: 58°C 2 min, 72°C 3 min (1 cycle): 95°C 1 min, 58°C 30 sec, 72°C 2 min (25 cycles): 72°C 10 min (1 cycle): 4°C hold

Recombination			
Allele	**Forward Primer (5'-3')**	**Reverse Primer (5'-3')**	**Amplicon Size(s) (bp)**
β-catΔEx3	GGT AGG TGA AGC TCA GCG CAG AGC	GGC CAG TAC TAG TGA ACC TCT TCG	343
PCR Conditions	95°C 10 min (1 cycle): 95°C 30 secs, 60°C 1 min, 72°C 1 min (35 cycles): 72°C 10 min (1 cycle): 4°C hold		

Supplemental Table 10: Antibodies and IHC Reagents/Conditions

IHC						
Primary Antibody	**Species**	**Supplier**	**Cat. No.**	**Dilution/Conc**	**Antigen Retrieval**	
					Buffer	**Time (mins)**
Afp	Rabbit	DAKO	A0008	1 in 200	Not Required	
β-catenin	Mouse	BD Biosciences	610153	1 in 50	Tris/EDTA/Tween pH 8	50
Cited1	Rabbit	Sigma	AV 32705	1 in 300	Citrate pH 6	12
Dlk1	Rabbit	Santa Cruz	sc-25437	1 in 100	Citrate pH 6	15
Epcam	Rabbit	Sino Biological	50591-RP02	1 μg/ml	Citrate pH6	15
Glul	Mouse	BD Biosciences	610517	1 in 1000	Citrate pH 6	20
Lin28a	Rabbit	Cell Signaling	8641	1 in 50	Citrate pH 6	12
Lin28b	Rabbit	Proteintech	16178-1-AP	1 in 50	Not Required	
Myc	Rabbit	Santa Cruz	sc-764	1 in 150	Citrate pH 6	50
Nqo1	Rabbit	Sigma	HPA007308	1 in 50	Citrate pH6	30
PCNA	Mouse	Novocastra	NCL-L-PCNA	1 in 75	Citrate pH 6	10
Sox9	Rabbit	Millipore	AB5535	1 in 1000	Citrate pH 6	12
Secondary Antibody	**Species**	**Supplier**	**Cat. No.**	**Dilution**		
Biotinylated anti-rabbit	Goat	Jackson Immunoresearch	111-065-045	1 in 500		
Biotinylated anti-mouse	Rabbit	Jackson Immunoresearch	315-065-003	1 in 1750		
Other Reagents		**Supplier**	**Cat. No.**	**Dilution**		
Streptavidin-HRP		Invitrogen	43-4323	1 in 750		
Hematoxylin QS		Vector Labs	H-3404	As supplied		
AquaPolymount		Polysciences Inc.	18606	As supplied		
AEC Chromagen		Invitrogen	00-2007	As supplied		

Western Blotting				
Primary Antibody	**Species**	**Supplier**	**Cat. No.**	**Dilution**
β-catenin	Mouse	BD Biosciences	610153	1 in 2000
GAPDH	Rabbit	Cell Signaling	2118	1 in 2000
Nqo1	Mouse	Santa Cruz	SC-376023	1 in 1000
p62/Sqstm1	Rabbit	Cell Signaling	5114	1 in 1000

Supplemental Table 11: Primers for Semi-quantitative (Sq) RT-PCR Analysis of Gene Expression (Mice)

mRNA	Forward Primer (5' - 3')	Reverse Primer (5' - 3')	Amplicon Size (bp)	Source
Afp	CTT CCC TCA TCC TCC TGC TAC	ACA AAC TGG GTA AAG GTG ATG G	145	Primer Bank
Bex1	AGT GAG TCC AAA GAT CAA GGC G	CTG GCT CCC TTC TGA TGG TA	106	Primer Bank
Cbr3	GTA ACT GGG GCT AAC AAA GGC	TTG ACC AGC ACG TTA AGT CCC	239	Primer Bank
Cited1	AAC CTT GGA GTG AAG GAT CGC	GTA GGA GAG CCT ATT GGA GAT GT	128	Primer Bank
Cyclophilin A *(Ppia)*	GAG CTG TTT GCA GAC AAA GTT C	CCC TGG CAC ATG AAT CCT GG	125	Primer Bank
Dlk1	AGT GCG AAA CCT GGG TGT C	GCC TCC TTG TTG AAA GTG GTC A	148	Primer Bank
Ggt1	TTT GTC ATC ATC GGC CTC TGT	CCC GTC CAA TCT CTG AGC AG	115	Primer Bank
Gpr49	AAT CGC GGT AGT GGA CAT TC	GAT TCG GAA GCA AAA ATG GA	155	Giera et al. (2010)
Gpx2	GCC TCA AGT ATG TCC GAC CTG	GGA GAA CGG GTC ATC ATA AGG G	143	Primer Bank
Gsta1	AAG CCC GTG CTT CAC TAC TTC	GGG CAC TTG GTC AAA CAT CAA A	159	Primer Bank
Gsta4	TGA TTG CCG TGG CTC CAT TTA	CAA CGA GAA AAG CCT CTC CGT	135	Primer Bank
Gstm2	TGG AAC CCA AAG TAG GAT TAC AAA	TGA GGA CCA AGG CAG CAC AC	313	Giera et al. (2010)
Igf2	GTG CTG CAT CGC TGC TTA C	ACG TCC CTC TCG GAC TTG G	222	Primer Bank
Nope	CTC TGC AAG AGA CAT TCT CAG AC	GTG GGA GCT TTG TCG TAG GC	125	Primer Bank
Nqo1	TAT CCT TCC GAG TCA TCT CTA GCA	TCT GCA GCT TCC AGC TCC TTG	85	Qu et al. (2014)
Peg3	GAG ACC ATC ATG CCT AGC CC	GTT CAC GCT CAT TAT CTC TGT CA	172	Primer Bank
Phgdh	ATG GCC TTC GCA AAT CTG C	AGT TCA GCT ATC AGC TCC TCC	134	Primer Bank
Rasl10b	GAC AGC TTT GAG TAC GTC AAG A	TAG CCG CAC TTC CAG GTC T	173	Primer Bank
S100a9	ATA CTC TAG GAA GGA AGG ACA CC	TCC ATG ATG TCA TTT ATG AGG GC	129	Primer Bank
Wisp2	CGC TGT GAT GAC GGT GGT TT	CCT GGC ACC TGT ATT CTC CTG	101	Primer Bank
Wnt4	AGA CGT GCG AGA AAC TCA AAG	GGA ACT GGT ATT GGC ACT CCT	126	Primer Bank

References: Geira et al. (2010) Toxicol. Sciences. **115**:22-33. Qu et al. (2014) Toxicology. **324**:35-42