**Supplemental Figure Legends**

**Supplemental Figure S1. Up-regulation of HDAC8 in murine NAFLD-associated HCC models.** (A) Schematic diagram of two murine obesity-HCC models. The tissue samples used for expression profiling of chromatin modifiers are listed. (B) Representative images of H&E staining in livers of the dietary (LFD and HFD) and genetic (db/m and db/db) obesity-HCC models (Low power, magnification 200×; High power, magnification 400×). (C and D) Representative Western blot analysis of pAkt, pStat3 and H4ac levels in the tumor (T) and non-tumor (NT) tissues of the murine models. Total Akt, Stat3 and Gapdh were used as internal controls. (E and F) Quantitative RT-PCR analysis of pro-inflammatory (*Il6* and *Tnfα*) and lipogenic (*Acc1* and *Fas*) gene expression in the murine models. \* *p*<0.05, \*\* *p*<0.01, \*\*\* *p*<0.001.

**Supplemental Figure S2. HDAC8 is directly regulated by SREBP-1 in HCC cells.** (A) Double immunofluorescence staining and (B) Western blot analysis of HDAC8 and histone H4 acetylation (H4ac) in immortal hepatocyte LO2 and HCC cell lines. (C) Schematic diagram of *HDAC8* promoter region showing two putative Sterol Response Elements (SREs) at upstream (-651bp) and downstream (+779bp) of the transcription start site. Core and Matrix similarity scores of both SREs derived from the TRANSFAC database are also depicted. (D) Western blot of SREBP-1 expression in human NAFLD-associated tumor tissue and vector control or SREBP-1c over-expressing LO2 and HepG2 cells. (E) Ectopic expression (HepG2 cells) and (F) knockdown (BEL-7404 cells) experiments demonstrated that SREBP-1 directly up-regulates HDAC8 as shown by quantitative ChIP-PCR (left), RT-PCR (middle) and Western blot analysis (right). \*\* *p*<0.01, \*\*\* *p*<0.001.

**Supplemental Figure S3. HDAC8 promotes insulin resistance.** (A) Schematic diagram of the dietary obesity-NASH model. (B) Quantitative RT-PCR analysis of *Acc1* and *Fas* mRNA levels in livers of the LFD- and HFD-fed mice. (C) Representative Western blot analysis of Hdac1, Hdac2 and Hdac3 expressions and (D) H&E staining of livers of the LFD- and HFHC-fed mice following lentivirus administration (Low power, magnification 200×; High power, magnification 400×). (E) Schematic diagram of the cell model of insulin resistance. (F) Quantitative RT-PCR analysis of *FAS* and *LXRα* mRNA levels in PLC5 cells stably-transduced with lentivirus expressing shRNA (left), or treated with a HDAC8 inhibitor, PCI-34051 (25 µM; right). (G) Western blot of pAKT and AKT expressions in PLC5 cells transfected with vector expressing shCtrl or an independent shRNA against HDAC8 (shHDAC8 #2). (H) Histone deacetylase activity assay of immunoprecipitated Class I HDACs in BEL-7404 cell lysates upon PCI-34051 treatment. \* *p*<0.05, \*\* *p*<0.01.

**Supplemental Figure S4. Down-regulation of HDAC8 inhibits NAFLD-HCC tumorigenicity *in vivo*.** (A) Schematic diagram of the dietary obesity-HCC model. (B) Representative images and H&E staining of livers of the LFD- and HFHC-fed mice following lentivirus administration. (C and D) Representative images of Ki-67 and TUNEL staining in nodules formed by (C) vector control or HDAC8 over-expressing LO2 and HepG2 cells and (D) shCtrl- or shHDAC8-expressing BEL-7404 and PLC5 cells (magnification 400×).

**Supplemental Figure S5. HDAC8 promotes growth and inhibits apoptosis of HCC cells**. (A) Colony formation assay of vector control or HDAC8 over-expressing HepG2 cells (left) and PLC5 cells stably-transduced with lentivirus expressing shCtrl or shHDAC8 (right). Representative images of foci formation are shown. (B) Colony formation assay of BEL-7404 cells transfected with vector expressing shCtrl or an independent shRNA against HDAC8 (shHDAC8 #2). (C) Western blot of H4ac, p53, p21 and cleaved PARP expressions (top) and Annexin V staining of cell apoptosis (bottom) in vector control or HDAC8 over-expressing HepG2 cells (left) and PLC5 cells transfected with siRNAs against control sequence or *HDAC8* (right). (D) Flow cytometry of cell cycle distribution in vector control or HDAC8 over-expressing HepG2 cells (left) and PLC5 cells transfected with siRNAs against control sequence or *HDAC8* (right). (E) Western blot of HDAC8 expression in human NAFLD-associated tumor tissues and vector control or HDAC8 over-expressing LO2 cells. \* *p*<0.05, \*\* *p*<0.01.

**Supplemental Figure S6. HDAC8 activates β-catenin signaling to promote hepatocellular growth.** (A) An independent experiment of luciferase reporter array revealed signal deregulation by HDAC8 in over-expressing LO2 cells. (B) Knockdown of HDAC8 and (C) HDAC8 inhibitor, PCI-34051, suppressed Wnt/β-catenin signaling activity in BEL-7404 cells determined by Western blot (left) and quantitative RT-PCR (right) analysis. (D and E) Knockdown of β-catenin abolished HDAC8-promoted Wnt/β-catenin signaling activity in HepG2 cells determined by (D) Western blot (left), quantitative RT-PCR (right) analysis and (E) colony formation assay. \* *p*<0.05, \*\* *p*<0.01.

**Supplemental Figure S7. HDAC8 acts in concert with EZH2 to epigenetically repress Wnt antagonists.** (A and B) Quantitative RT-PCR analysis of Wnt antagonists in (A) HepG2 cells following ectopic HDAC8 expression and (B) PLC5 cells upon HDAC8 siRNAs. (C) Quantitative ChIP-PCR of HDAC8, EZH2 occupancy and histone modifications in *AXIN2*, *NKD1* and *PPP2R2B* promoters of PLC5 cells upon HDAC8 knockdown. (D) Co-immunoprecipitation of HDAC8 and EZH2 in PLC5 cells. IgG represents a control antibody used for IPs. Total lysates were used as input controls. (E) Semi-quantitation of Ezh2, H3K27me3, active β-catenin, β-catenin and Ccnd1 protein expressions in representative tumors (T) and paired non-tumors (NT) from dietary (left) and genetic (right) obesity-promoted HCC models. \* *p*<0.05, \*\* *p*<0.01.

**Supplemental Figure S8. HDAC8 expression positively correlates with its signaling components in primary human NAFLD-associated HCCs.** Quantitative RT-PCR analysis of *HDAC8*, *SREBP-1c* and *CCND1* in primary human NAFLD-associated HCCs.