**Supplementary Figure 1. RBFOX3 was identified as an hTERT promoter binding protein in HCC cells. (A)** The hTERT promoter probe simulated structure. **(B)** QGY7703 cells were transfected with RBFOX3 or vector control plasmid. Binding of RBFOX3 on the 5’-biotin labeled hTERT promoter probe or a nonspecific probe (NSP) was detected by Western blot using anti-RBFOX3 antibody. **(C)** Hep3B cells were knockdown by shRBFOX3 or shNC control plasmid. Binding of RBFOX3 on the 5’-biotin labeled hTERT promoter probe or a nonspecific probe (NSP) was detected by Western blot using anti-RBFOX3 antibody. **(D)** The 5’-biotin labeled probes corresponding different fragment of hTERT promoter structures (-234/+41, -321/+41, -387/+41, -902/+41, -321/-157, -387/-157, -902/-157).

**Supplement****ary Figure 2. RBFOX3 regulated hTERT promoter activity and expression in HCC cells. (A)** Relative hTERT promoter activity in RBFOX3 over-expressing SNU449 cells and RBFOX3 knockdown HepG2 cells. **(B)** Relative hTERT mRNA level was determined by quantitative real-time PCR analyses in RBFOX3 overexpressing QGY7703 cells and RBFOX3 knockdown Hep3B cells. **(C)** hTERT protein expression was up-regulated in RBFOX3 overexpressing QGY7703 cells, and down-regulated in RBFOX3 knockdown Hep3B cells. **(D)** hTERT protein expression was detected with RBFOX3 knockdown in U373 cell lines. **(E)** Relative hTERT mRNA and protein levels were determined in RBFOX1 knockdown HepG2 cell lines by quantitative real-time PCR and Western blot, respectively. **(F)** Relative hTERT mRNA and protein levels were determined in RBFOX2 knockdown HepG2 cell lines by quantitative real-time PCR and Western blot, respectively**.** Results were shown as means ± SD, by two-tailed Student’s *t*-test. \**p*<0.05. All experiments were performed in at least 3 independent trials.

**Supplementary Figure 3. RBFOX3 regulated HCC growth via hTERT signaling pathway. (A)** RBFOX3 overexpression increased propagative cell viability(upper panel) and colony formation capacity(middle panel) in SNU-449 cells. Lower panel showed the quantifcation of colonies. **(B)** RBFOX3 knockdown decreased propagative cell viability and colony formation capacity in HepG2 cells. **(C)** Overexpression of hTERT reversed the inhibition of TERT expression, cell viability and colony formation mediated by RBFOX3 knockdown in QGY7703 cells. **(D)** hTERT expression was down-regulated in RBFOX3-depleted QGY7703 cells, and it was rescued by overexpression of RBFOX3. **(E)** Overexpression of RBFOX3 activated hTERT downstream PI3K/AKT signaling in SNU-449 cells. Western blot was used to detected the expression levels of p-PI3K, p-AKT, p-JNK, p-ERK, PI3K, AKT, JNK and ERK in RBFOX3 over-expressing SNU-449 cells.Lower panel showed the quantifcation of protein expression. **(F)** QGY7703 cells with RBFOX3 overexpression plasmid or vector control were subcutaneously implanted into nude mice. The tumor volumes were measured and recorded every 2 days, and tumor growth curves were created for each group (n=5) (left panel). The weight of excised tumor grafts were recorded (right panel). **(G)** Hep3B cells with sh-RBFOX3, sh-NC, sh-RBFOX3/hTERT or sh-RBFOX3/vector were subcutaneously implanted into nude mice. The tumor volumes were measured and recorded every 2 days, and tumor growth curves were created for each group (n=5) (left panel). The weight of harvested tumor grafts were recorded (right panel). Dots represent the mean, while bars indicate the SEM. (\**p*<0.05).

**Supplementary Figure 4. RBFOX3 regulated HCC cell migration and invasion *in vivo* and *in vitro* via hTERT signaling pathway**. **(A)** The relative cell migration and invasion ratio were increased in RBFOX3 overexpressed cells compared with vector overexpressed cells in SNU449 cells. **(B)** The relative cell migration and invasion ratio were effectively decreased in RBFOX3 knockdown HepG2 cells. **(C)** MMP9 and MMP2 protein level were detected and quantified in RBFOX3 or vector overexpressed SNU449 cells. **(D)** MMP9 and MMP2 protein level were detected and quantified in sh-RBFOX3 or sh-NC treated HepG2. **(E)** Overexpression of hTERT reversed the inhibition of cell migration and invasion by RBFOX3 knockdown in SNU449 cells. **(F)** Overexpression of hTERT reversed the inhibition of cell migration and invasion by RBFOX3 knockdown in HepG2 cells. \**p*<0.05 by two-tailed Student’s *t*-test. The experiments were performed with at least 3 independent trials.

**Supplementary Figure 5. RBFOX3 regulated HCC cell apoptosis and cell cycle progression via hTERT signaling pathway.** **(A)** The number of apoptotic cells was increased in RBFOX3 knockdown HepG2 cells. **(B)** The expression of pro-apoptotic protein cleaved-cas9 and cleaved-cas3, and anti-apoptotic protein PARP were detected and quantified in RBFOX3 knockdown HepG2 cells. **(C)**The number of G0/G1 phase cells was decreased in RBFOX3 overexpressed cells compared with vector overexpressed cells in SNU449 cells. **(D)** The number of G0/G1 phase cells was increased in RBFOX3 knockdown HepG2 cells. **(E)** Overexpression of hTERT reversed the inhibition of cell cycle progression by RBFOX3 knockdown in QGY7703 cells. **(F)** Expression of cell cycle related protein p27, Cyclin D1 and Cyclin A were detected and quantified in RBFOX3 overexpression SNU449 cells. **(G)** Expression of cell cycle related protein p27, Cyclin D1 and Cyclin A were detected and quantified in RBFOX3 knockdown HepG2 cells. G0/G1 cells were sorted and counted by fluorescence-activated cell sorting (FACS). Data were shown as means ± SD. \**p*<0.05, by two-tailed Student’s *t*-test. The experiments were performed in at least 3 independent trials.

**Supplementary Table 1.** The theoretical m/z values of the amino acid residues derived from band in Figure 1A(red arrow) which identified to be VNNATARVMTNK.

Supplemental-Figure 1-N

supplemental-Figure 2N-01

supplemental-Figure 3N-01

supplemental-figure 4D-01

supplemental-figure 5N-01

supplemental Table