Supporting Information

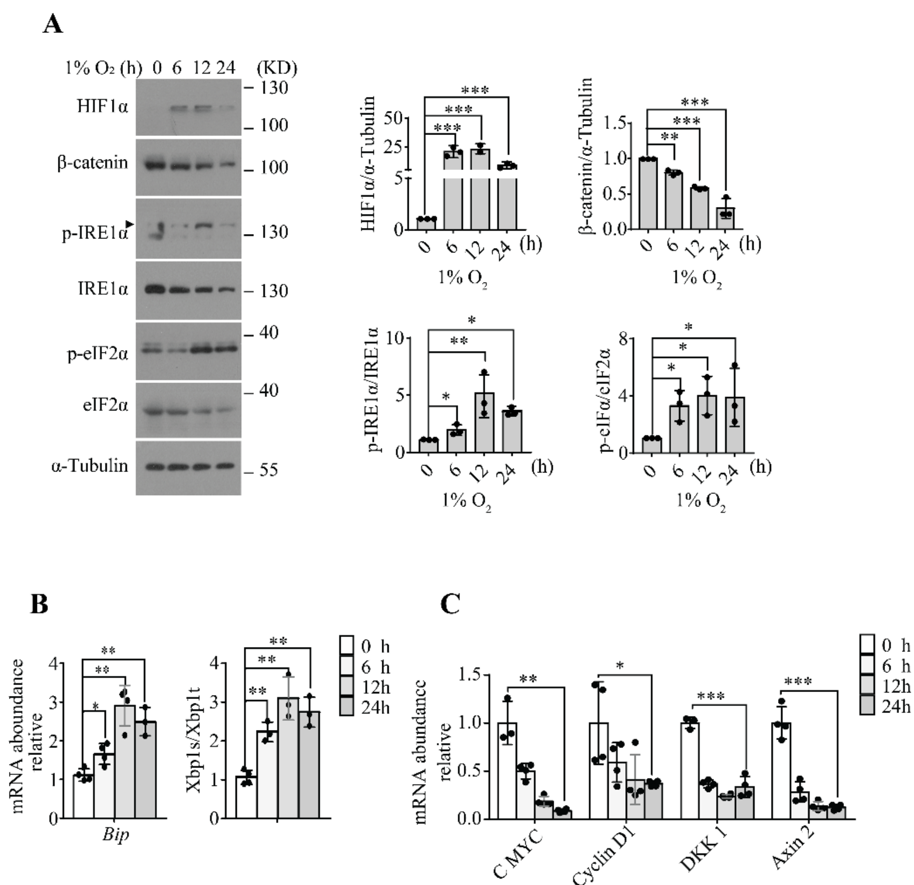

Fig. S1. Hypoxia results in activation of the UPR pathways along with downregulation of β-catenin signaling in HEK293 cells. (A) HEK293 cells were cultured under moderate hypoxia condition (1% O_2) for the indicated time intervals. Protein expression levels of HIF1α and β-catenin, as well as phosphorylation of IRE1α (p-IRE1α) and eIF2α (p-eIF2α), were analyzed by immunoblotting. Quantification of HIF1α and β-catenin levels (relative to α-tubulin), and p-IRE1α/IRE1α, p-elF2α/elF2α ratios, is shown after normalization to the value at 0 hours. (B) Quantitative RT-PCR analysis of the expression of the spliced form of *Xbp1* (*Xbp1s*) mRNA relative to the total amount of *Xbp1* (*Xbp1t*) mRNA, and the mRNA levels of *Bip* (relative to *Actin*). Values were normalized to normoxic levels. (C) Quantitative RT-PCR analysis of the mRNA levels of β-catenin target genes (*c-MYC, CyclinD1, DKK1, Axin2*). All data are shown as the mean ± SD from three independent experiments. *p<0.05, **p<0.01 and ***p<0.001 by Students *t*-test.

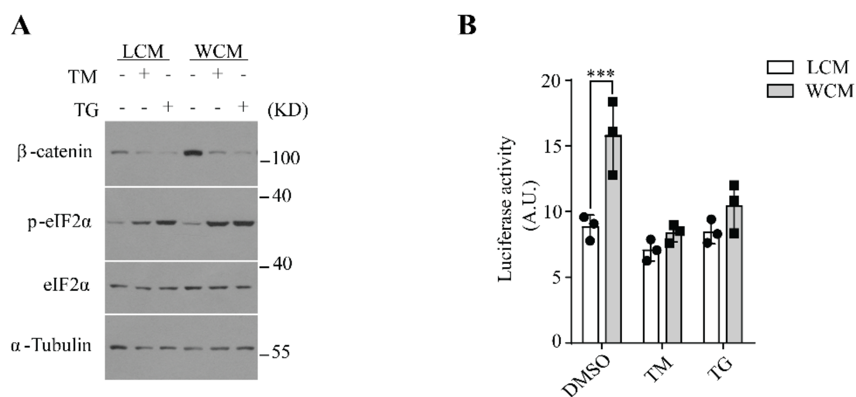

Fig. S2. Chemical-induced ER stress results in decreased stability of β-catenin. (A) HEK293 cells cultured in LCM or WCM were treated with DMSO, 10 μg/ml TM or 1 μM TG for 8 hours. Protein expression level of β-catenin and phosphorylation of eIF2α (p-eIF2α) were analyzed by immunoblotting. (B) HEK293 cells were transfected with TOPFlash luciferase reporter plasmid, and then cultured in LCM or WCM and treated with DMSO, 10 μg/ml TM or 1 μM TG for 8 hours. TopFlash luciferase activity was determined and is shown as the mean ± SD from three independent experiments. *p<0.05, **p<0.01 and ***p<0.001 by Students *t*-test.

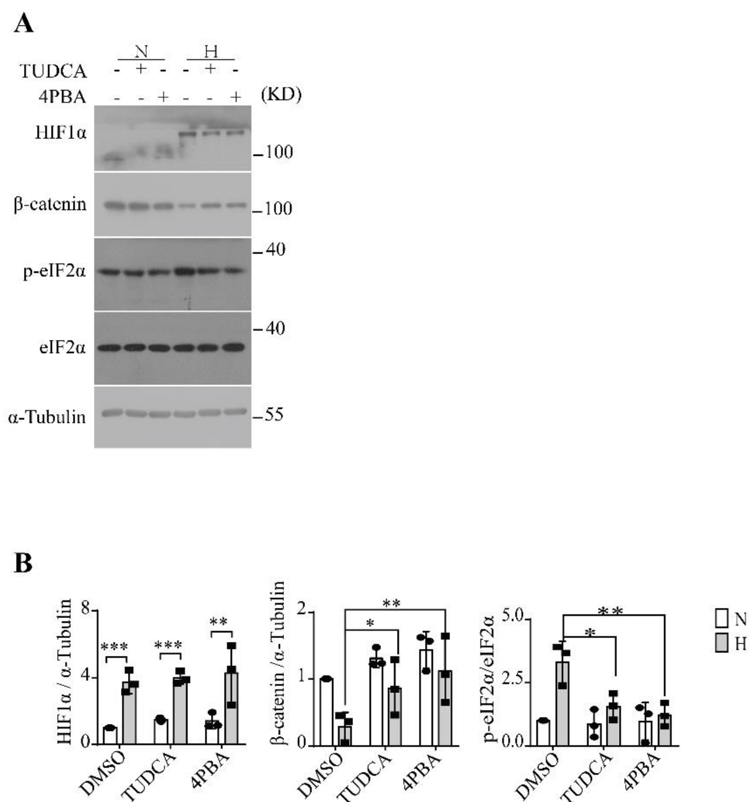

Fig. S3. Chemical alleviation of ER stress partially reverses hypoxia-induced reduction of β-catenin in RKO cells. (A) RKO cells were pre-treated with DMSO, 2 mM 4PBA or 2 mM TUDCA for 2 hours and then subjected to normoxia (N) or hypoxia (H) for 12 hours. Phosphorylation of eIF2α (p-eIF2α) and protein expression levels of HIF1α and β-catenin were analyzed by immunoblotting. (B) Quantification of p-elF2α/elF2α ratio and HIF1α and β-catenin levels (relative to α-tubulin) is shown after normalization to the value of DMSO control cells. Results are shown as the mean ± SD from three independent experiments. *p<0.05, **p<0.01 and ***p<0.001 by Students *t*-test.

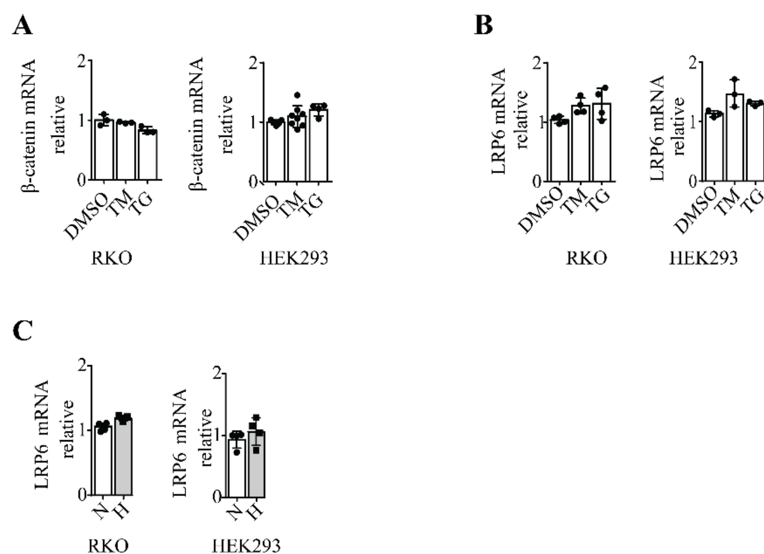

Fig. S4. Effects of chemical-induced ER stress or hypoxia on the mRNA abundance for β-catenin or LRP6. RKO or HEK293 cells were (A-B) treated with DMSO, 10 μg/ml TM or 1 μM TG for 8 hours, or (C) subjected to normoxia (N) or 1% O_2 hypoxia (H) for 12 hours. Quantitative RT-PCR analysis of the abundance of mRNA encoding (A) β-catenin or (B-C) LRP6. Data are shown as the mean ± SD from three independent experiments.