



**Supplementary Figure 4.** (A) IRTKS is tyrosine-phosphorylated in the liver cancer cell line Huh-7 in response to insulin stimulation. (B and C) The phosphorylation level of IR at tyrosine residues Tyr1162/1163 and Akt at serine 473 in adipose tissue (B) and muscle (C) from WT and IRTKS KO mice. (D) Ubiquitination of insulin receptor-β in liver from WT and IRTKS KO mice. (E) The phosphorylation levels of IR at tyrosine residues Tyr1162/1163 and Akt at serine 473 in Huh-7 cells upon IRTKS knockdown. (F) The phosphorylation level of IR at tyrosine residues Tyr1162/1163 and ERK at Thr202/Tyr204 in YY8103 cells upon IRTKS overexpression. Data are presented as the mean ±s.d. \*P < 0.05, \*\*P < 0.01 versus control.