



**Supplementary Figure S1.** Generation and verification of the BTC knockout mouse. (A) Partial DNA sequence of *Btc* exon 2. The sgRNA binding site is indicated in blue, the protospacer adjacent motif (PAM) in red. Insertions (orange) of 1 bp lead a shift of reading frame. Partial amino acid sequences encoded by the WT and mutant *Btc* alleles. WT BTC aa sequence in black (aa coded by adjacent non-symmetrical exons in blue), missense aa sequence in red, and the premature termination codon as asterisk. WT=wildtype. KO=knockout. (B) Verification of the frame shift by reverse-transcriptase PCR of Li (liver), Ki (kidney), He (heart), Ut (uterus), SG (salivary gland), Br (brain) after the restriction of the 500 bp amplicon with *PfIM* into fragments of 290 and 210 bp, respectively. The successful cleavage by *PfIM* indicates wildtype *Btc* (*Btc*<sup>+/+</sup>), while the lack of cleavage indicates the successful frame shift introduced by CRISPR/Cas9 and hence the BTC knockout (*Btc*<sup>-/-</sup>). H<sub>2</sub>O served as negative control, *Gapdh* as control PCR. (C) The crossing of BTC<sup>-/-</sup> mice into the KC background showed no change of body or pancreatic weights at the ages of 2 or 12 months (m), respectively. (D) Immunohistochemistry targeting BTC in the pancreas of wildtype mice (BTC<sup>+/+</sup>) marking the islets of Langerhans and the cell membrane of acinar cells, BTC knockout mice (BTC<sup>-/-</sup>) presenting no signal for BTC staining. KC mice express BTC in premalignant lesions and BTC<sup>-/-</sup>;KC mice are immuno-negative for BTC. Scale bars: 100  $\mu$ m.