Supplementary Fig 1. Inefficient expression of *MMTV-Cre* in the mammary gland of $Pten^{-/-}$. (A) Pten immunohistochemical staining of a mammary gland tissue section from a $Pten^{-/-}$ mouse. Pten was expressed throughout the mammary epithelium of $Pten^{-/-}$ mice. (B) Mammary whole mounts showed normal ductal outgrowth in $Pten^{-/-}$ mice.

Supplementary Fig 2. Salivary gland tumor development in $Apc^{-/-}Pten^{-/-}$ and $Apc^{+/-}Pten^{-/-}$ mice. (A) Tumor volume was measured in a cohort of $Apc^{-/-}Pten^{-/-}$ and $Apc^{+/-}Pten^{-/-}$ mice at various times following the first measurement. (B) Immunohistochemical staining of indicated proteins on tumor tissues from $Apc^{+/-}Pten^{-/-}$ and $Apc^{-/-}Pten^{-/-}$ mice. Notice the similarity in β-catenin staining in tumor tissues from $Apc^{+/-}Pten^{-/-}$ and $Apc^{-/-}Pten^{-/-}$ mice. As expected, all tumor cells lacked Pten expression. Original magnification was 40x.

Supplementary Fig 3. Pten phenotype. (A) Shown are salivary glands from 1-year-old littermate $Pten^{+/+}$ and $Pten^{-/-}$ mice. The salivary glands of $Pten^{-/-}$ mice were larger than those of wild-type control mice. (B) Hematoxylin and eosin staining of the neoplastic lesion shown in Fig 3D. (C) Immunohistochemical staining of indicated proteins on salivary gland tissues from $Apc^{-/-}Pten^{-/-}$ $\beta\text{-}catenin^{-/-}$ mice. Positive staining for p-S6 was seen in both normal (#) and enlarged cells (*). Normal cells but not enlarged cells stained for β-catenin confirming that recombination of the floxed alleles had occurred in the enlarged cells.

Supplementary Fig 4. Rapamycin effectively blocks mTOR signaling in tumors from $Apc^{-/-}$ $Pten^{-/-}$ and $Apc^{+/-}Pten^{-/-}$ mice. (A) Immunohistochemical staining for p-S6 showed abundant amounts in tumor sections from untreated $Apc^{-/-}Pten^{-/-}$ mice. A loss of p-S6 was seen in tumor

sections of *Apc*$^{-/-}$*Pten*$^{-/-}$ mice 4 hours after a single dose of 1 mg/kg rapamycin. (B) Immunohistochemical staining for β-catenin showed continued nuclear accumulation of β-catenin in tumor cells following rapamycin therapy. The fibrotic tissue that developed during rapamycin therapy did not contain nuclear accumulation of β-catenin (blue staining).

Supplementary Fig 5. Immunohistochemical staining of human AcCC using antibodies against β-catenin and Pten. Shown in (A-B) are representative staining results (sample AcCC-6). (A) In 10/11 AcCC specimens, only membrane staining of β-catenin was observed in the tumor tissue. (B) Pten was expressed in the tumor tissue.