

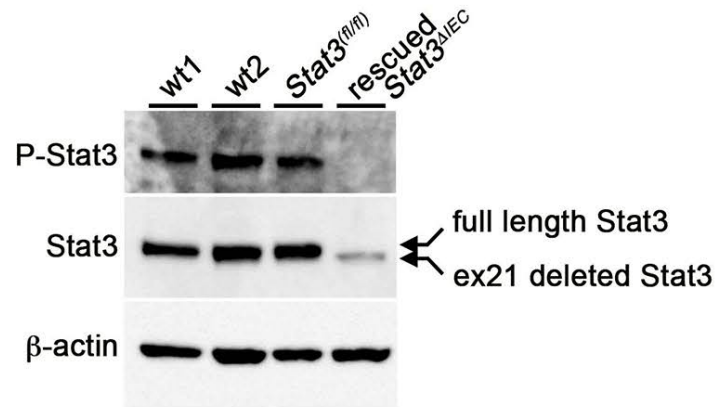
Stat3 is indispensable for damage-induced crypt regeneration but not for Wnt-driven intestinal tumorigenesis.

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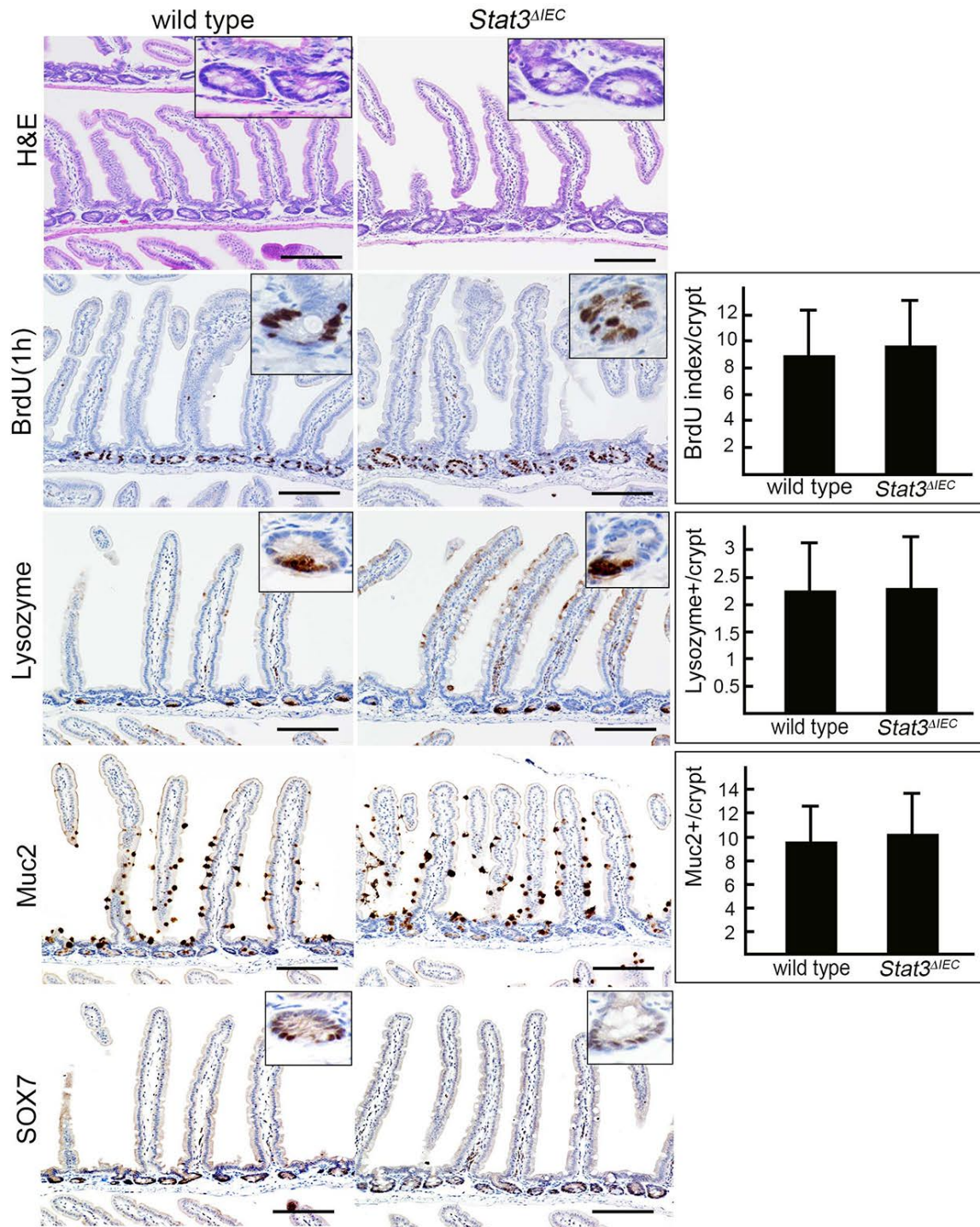


## Supplementary Figure 1



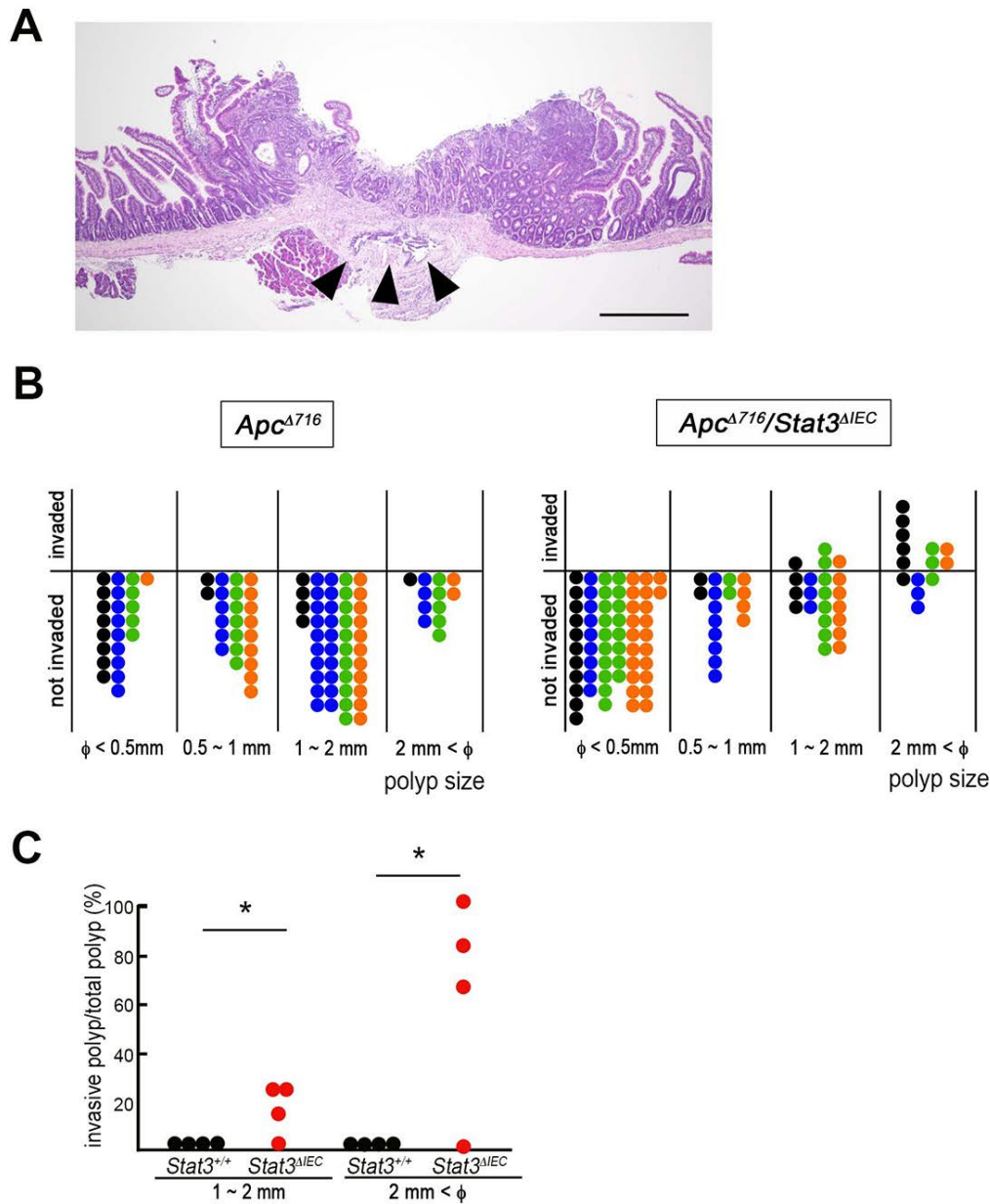
**Supplementary Figure 1.** The confirmation of *Stat3* gene disruption in the rescued organoids. Protein samples of two wild-type mouse-derived organoids (*wt1* and *wt2*), *Stat3<sup>fl/fl</sup>* mouse-derived organoid, and *Stat3<sup>ΔIEC</sup>* mouse-derived rescued organoids were analyzed for phosphorylated Stat3 (P-Stat3) and total Stat3. β-Actin was used as an internal control. Note that full-length Stat3 was lost in *Stat3<sup>ΔIEC</sup>*, and that mutant Stat3 (with the deletion of exon21) was detected in the rescued organoids.

## Supplementary Figure 2



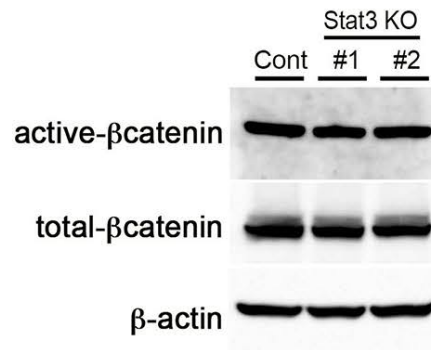
**Supplementary Figure 2.** The morphology, proliferation and differentiation of the intestinal mucosa of wild-type (*left*) and *Stat3<sup>ΔIEC</sup>* mice (*right*). Representative photographs of H&E staining, and immunohistochemical staining for BrdU, Lysozyme, Muc2 and SOX7. Insets show enlarged views. Bars, 100 μm. The bar graphs on the right show the labeling index values for immunostaining-positive cells (mean ± s.d.).

## Supplementary Figure 3



**Supplementary Figure 3.** The submucosal invasion of intestinal tumors in  $Apc^{\Delta 716} Stat3^{\Delta IEC}$  compound mutant mice. **(A)** Representative photographs of submucosal invasion (H&E). Bar, 500  $\mu$ m. Arrowheads indicate invading tumor cells. **(B)** The size classification of the invading and non-invading intestinal tumors of  $Apc^{\Delta 716}$  mice (left) and  $Apc^{\Delta 716} Stat3^{\Delta IEC}$  mice (right) were scored using “Swiss roll” histological sections. Each dot indicates an individual polyp. Different colors indicate independent mice ( $n=4$  for each genotype). **(C)** The invasion ratio of size-classified polyps (1-2 mm and  $>2$  mm in diameter) in  $Apc^{\Delta 716} Stat3^{+/+}$  and  $Apc^{\Delta 716} Stat3^{\Delta IEC}$  mice. Asterisks,  $p < 0.05$ .

## Supplementary Figure 4



**Supplementary Figure 4.** Western blotting results for active and total  $\beta$ -catenin in control AKTP cells (Cont), and *Stat3*-disrupted KO#1 (#1) and KO#2 (#2) cells.  $\beta$ -actin was used for internal control.