

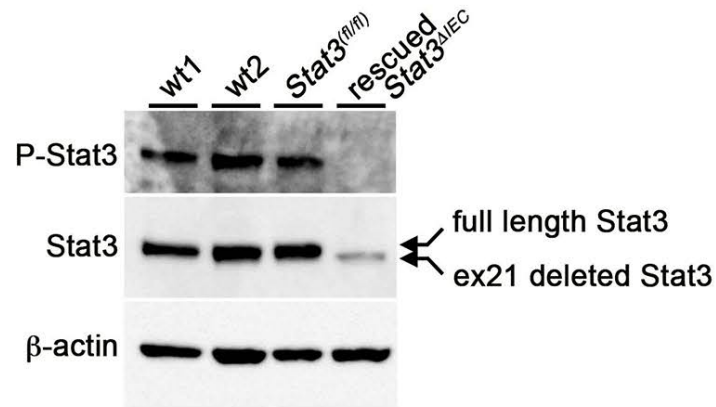
Stat3 is indispensable for damage-induced crypt regeneration but not for Wnt-driven intestinal tumorigenesis.

著者	Oshima Hiroko, Kok Sau-Yee, Nakayama Mizuho, Murakami Kazuhiro, Voon Dominic Chih-Cheng, Kimura Takashi, Oshima Masanobu
著者別表示	大島 浩子, 中山 瑞穂, 村上 和弘, 大島 正伸
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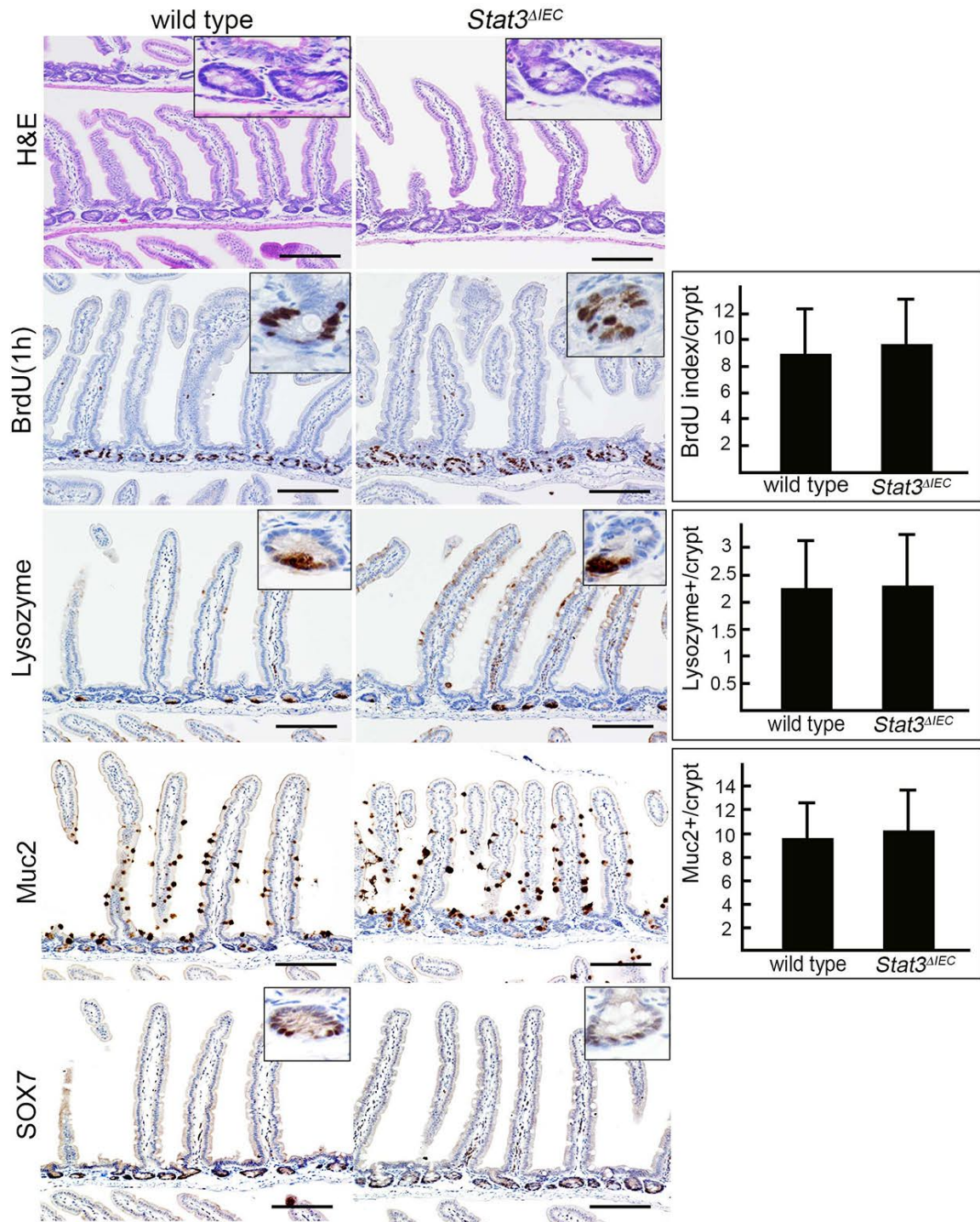


Supplementary Figure 1



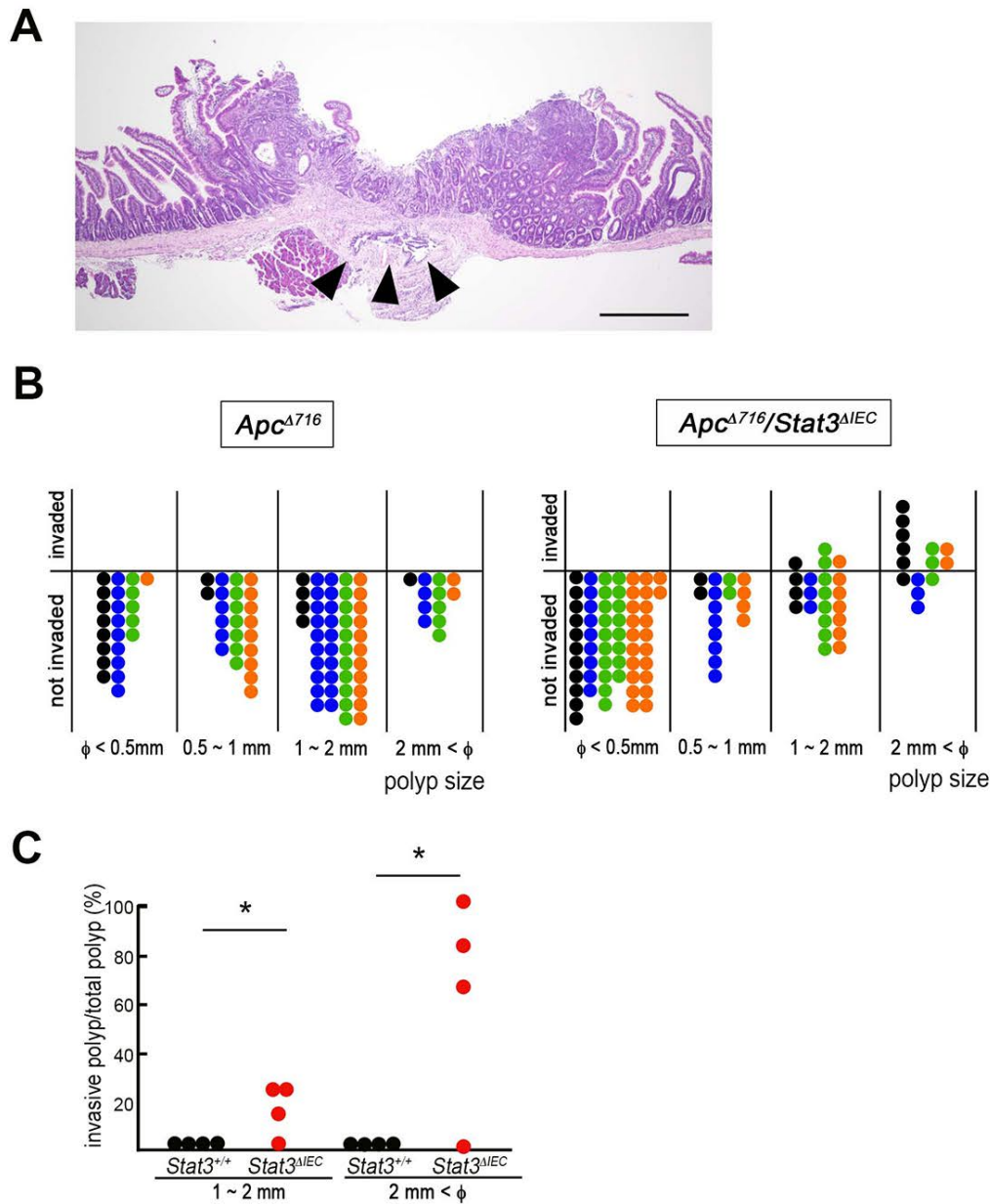
Supplementary Figure 1. The confirmation of *Stat3* gene disruption in the rescued organoids. Protein samples of two wild-type mouse-derived organoids (*wt1* and *wt2*), *Stat3^{fl/fl}* mouse-derived organoid, and *Stat3^{ΔIEC}* mouse-derived rescued organoids were analyzed for phosphorylated Stat3 (P-Stat3)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

Supplementary Figure 2



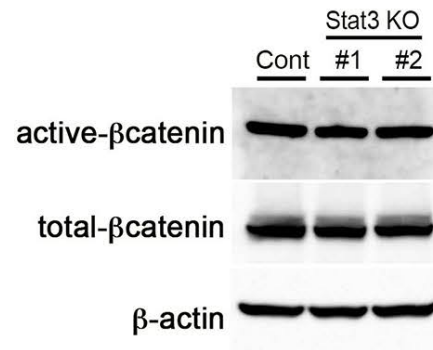
Supplementary Figure 2. The morphology, proliferation and differentiation of the intestinal mucosa of wild-type (*left*) and *Stat3^{ΔIEC}* mice (*right*). Representative photographs of H&E staining, and immunohistochemical staining for BrdU, Lysozyme, Muc2 and SOX7. Insets show enlarged views. Bars, 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 μ 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 β-catenin in control AKTP cells (Cont), and *Stat3*-disrupted KO#1 (#1) and KO#2 (#2) cells. β-actin was used for internal control.