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

Oshima Hiroko, Kok Sau-Yee, Nakayama Mizuho, Murakami Kazuhiro, Voon Dominic Chih-Cheng, Kimura Takashi, Oshima Masanobu

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| 著者 | 西島武 | 田中瑞穗 | 村上和弘 | 大島正伸 |
|---|---|---|---|---|
| 著者別表示 | 大島 浩子 中山 瑞穂 村上 和弘 大島 正伸 |
| 事務局 | 田中瑞穂 |
| 事務局 | 大島正伸 |
| 事務局 | 村上和弘 |
| 事務局 | 大島浩子 |
| 事務局 | 西島武 |

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**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$^{+/+}$ mouse-derived organoid, and Stat3$^{aIEC}$ 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$^{aIEC}$, and that mutant Stat3 (with the deletion of exon21) was detected in the rescued organoids.
Supplementary Figure 2. The morphology, proliferation and differentiation of the intestinal mucosa of wild-type (left) and Stat3^MEC 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. The submucosal invasion of intestinal tumors in Apc\(^{\Delta716}\) Stat3\(^{\DeltaEC}\) 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\(^{\Delta716}\) mice (left) and Apc\(^{\Delta716}\) Stat3\(^{\DeltaEC}\) 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\(^{\Delta716}\) Stat3\(^{+/+}\) and Apc\(^{\Delta716}\) Stat3\(^{\DeltaEC}\) mice. Asterisks, p < 0.05.
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.