Figure S1

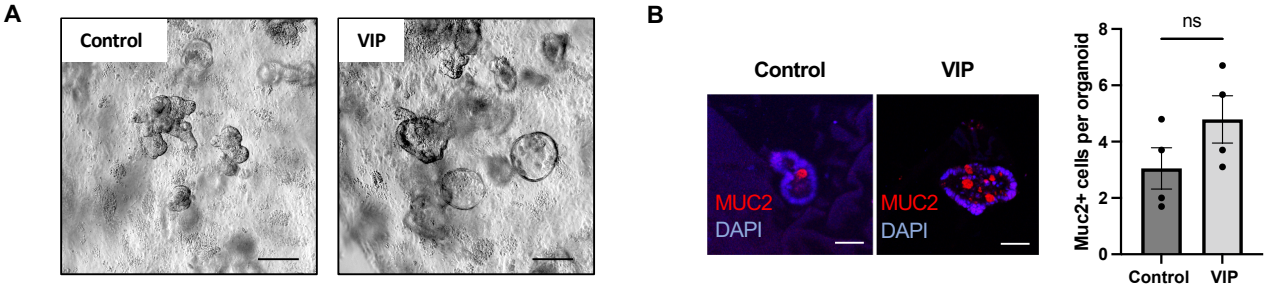

Figure S1. VIP mediates organoid growth and secretory differentiation. A, Representative images of control and VIP-treated organoids on day 5 post-plating (Scale bars=100 µm). **B**, Immunofluorescent analysis of MUC2 staining in control and VIP-treated organoids (Scale bars=50 µm). n=4 (Control), n=4 (VIP). Data are shown as means ± SEM, n = number of biological replicates. Statistical analysis was performed by paired Student's t-test in.

Figure S2

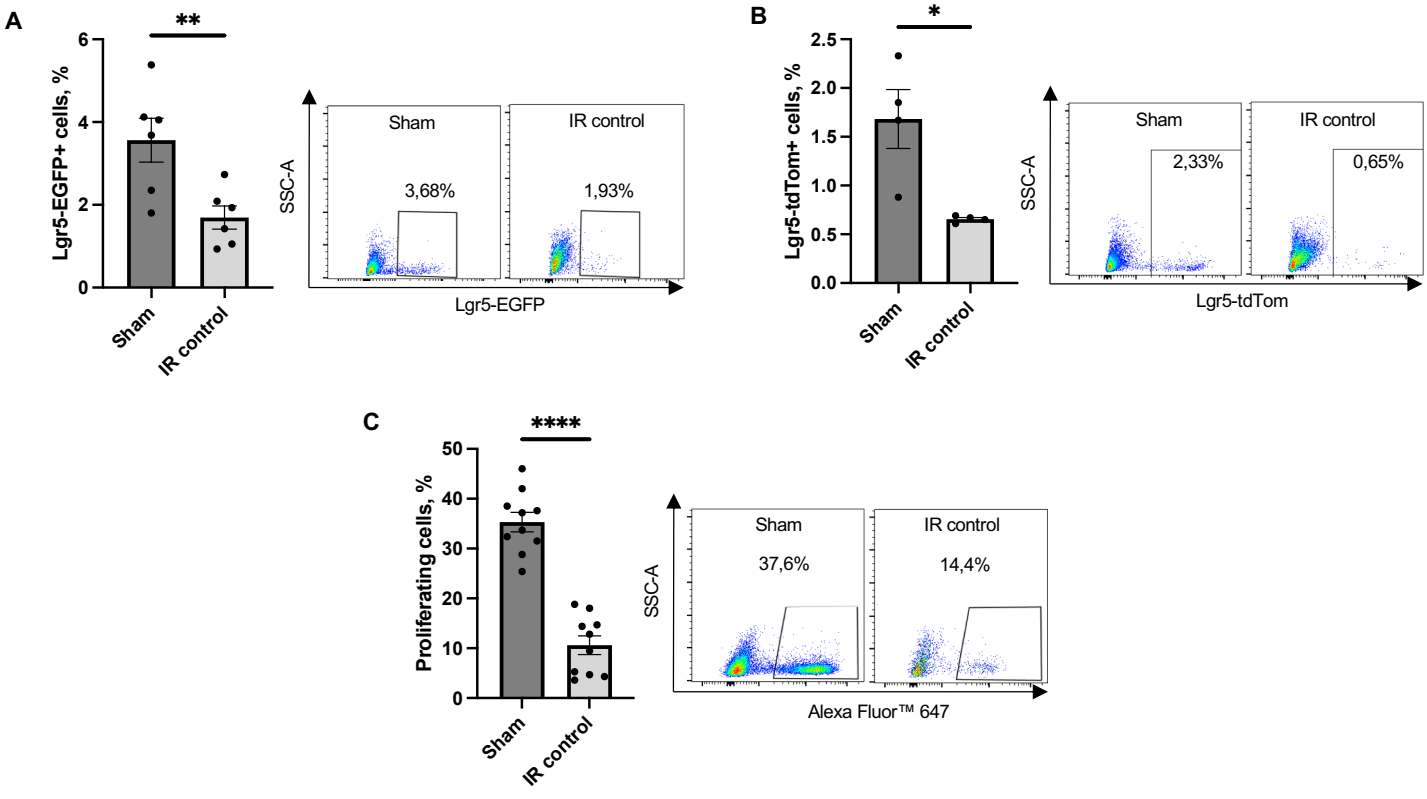

Figure S2. Irradiation disturbs Lgr5-EGFP+ cell proliferation in intestinal organoids. A, Flow cytometry analysis of Lgr5-EGFP+ cell number in sham-irradiated and irradiated organoids. n=6 per group. **B**, Flow cytometry analysis of Lgr5-EGFP+ cell progeny in sham-irradiated and irradiated organoids. n=4 per group. **C**, Analysis of cell proliferation in sham-irradiated and irradiated organoids determined by EdU assay. n=10 per group. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$. Data are shown as means ± SEM, n = number of biological replicates. Statistical analysis was performed by paired Student's t-test.

Figure S3

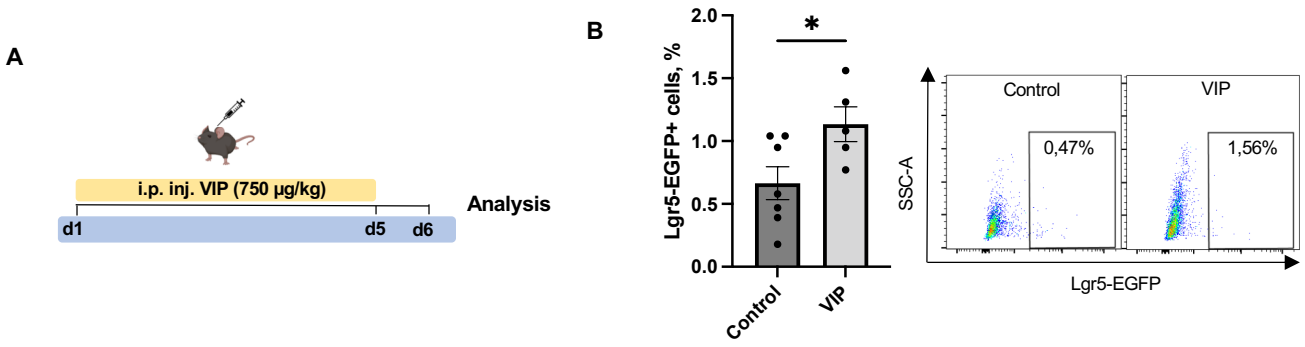

Figure S3. VIP mediated expansion on Lgr5-EGFP+ progenitor cells *in vivo*. ***A*,** Experimental outline and treatment scheme for administration of VIP in mice. **B**, Flow cytometry analysis of LGR5-EGFP+ progenitor cell number in jejunal crypts of mice treated with VIP. n=7 (Control), n=5 (VIP). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$. Data are shown as means ± SEM, n = number of biological replicates. Statistical analysis was performed by paired Student's t-test.

Figure S4

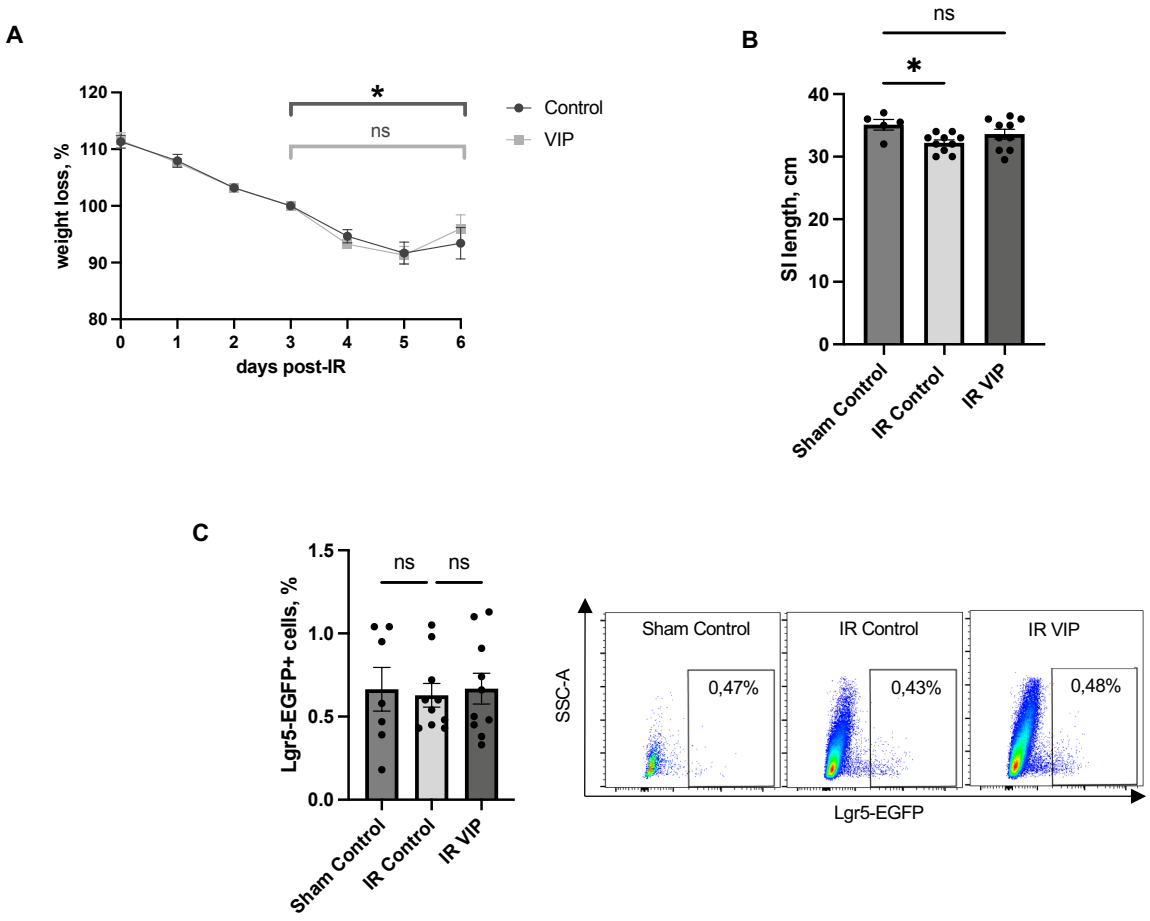

Figure S4. VIP-mediated effects on irradiation-induced injury in mice. A, Weight development of mice after abdominal irradiation. Data are normalized to the timepoint corresponding to the onset of the VIP treatment. n=6 per group. **B,** Total length of the small intestine in mice after abdominal irradiation. n=5 (Sham Control), n=10 (IR Control; IR VIP). **C**, Flow cytometry analysis of LGR5-EGFP+ progenitor cell number in jejunal crypts of irradiated mice treated with VIP. n=7 (Control, see Figure S3B), n=10 (IR Control and IR VIP). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$. Data are shown as means ± SEM, n = number of biological replicates. Statistical analysis was performed by unpaired Student's t-test in (**A**) and one-way ANOVA with Tukey's multiple comparisons test in (**B-C**).

Figure S5

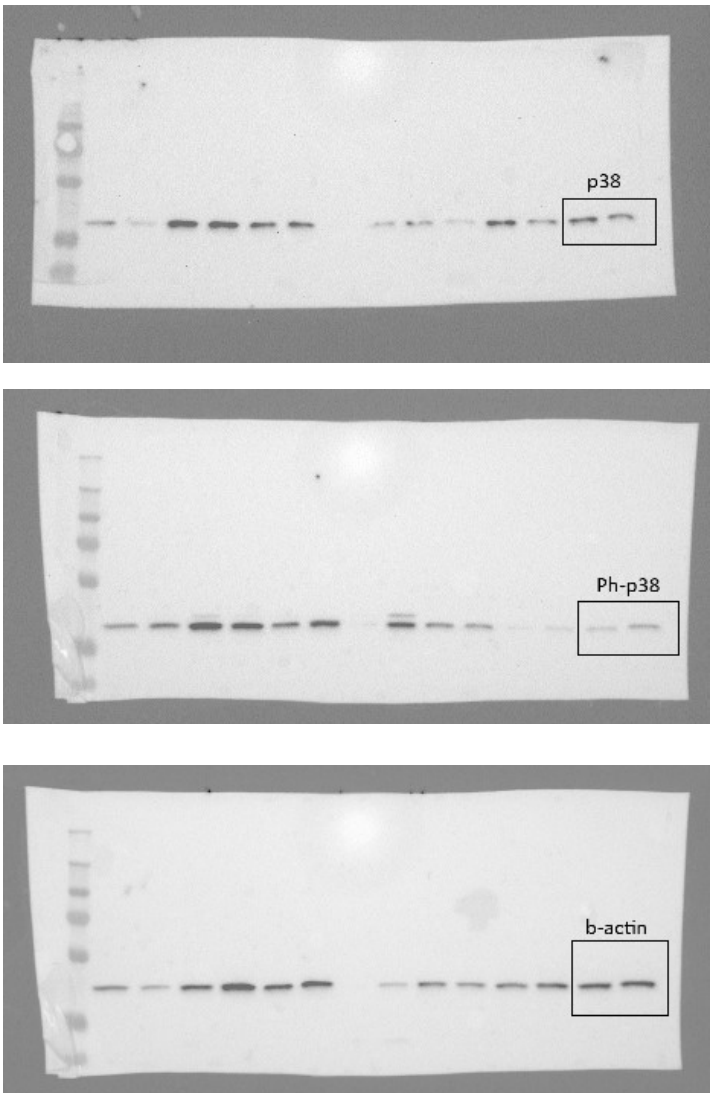

Figure S5. Full-length Western Blots according to cropped gels shown in Figure 2C. A, p38. **B,** Phospho-p38. **C,** Beta-Actin.

Table S1

Table S1. Primers used for RT-qPCR analysis.

Gene	Primer	Sequence
Hmbs	Forward	5'-TTGGAAACACCCTGGAAACC-3'
	Reverse	5'-TGAATTCCTGCAGCAGCTCATCC-3'
Lys1	Forward	5'-GGAATGGATGGCTACCGTGG-3'
	Reverse	5'-CATGCCACCCATGCTCGAAT-3'
Muc2	Forward	5'-AACATCTCAGGGCCGAAA-3'
	Reverse	5'-TGCGCTTGGAGTGATAGAAA-3'
Clca1	Forward	5'-GATCGCTCAGCACTCCAT-3'
	Reverse	5'-GAGCCATTCATCCATTGGTTA-3'
Dclk1	Forward	5'-AGTACATTCGGACCCTCTCTC -3'
	Reverse	5'-CGTACCAGTCAAGGTGTGCTT-3'
NeuroD	Forward	5'-ATGGCGATGAAAGCGGTGTG-3'
	Reverse	5'-TGCACTGGTACAGCCTTGTGT-3'
Lgr5	Forward	5'-GACGCTGGGTTATTTCAAGTTCA-3'
	Reverse	5'- CAGCCAGCTACCAAATAGGTGCT-3'

Table S2

Table S2: Inhibitors used *in vitro*

Drug	Concentration	Article number (Manufacturer)
SB202190	10 µM	1264 (Tocris)
PD98059	20 µM	1213 (Tocris)
JNK-inhibitor II	20 µM	420119 (Sigma-Aldrich)
BMS-345541	1 µM	B9935 (Sigma-Aldrich)
Stausporine	0.02 µM	S1421 (Selleckchem)