Supplemental Data

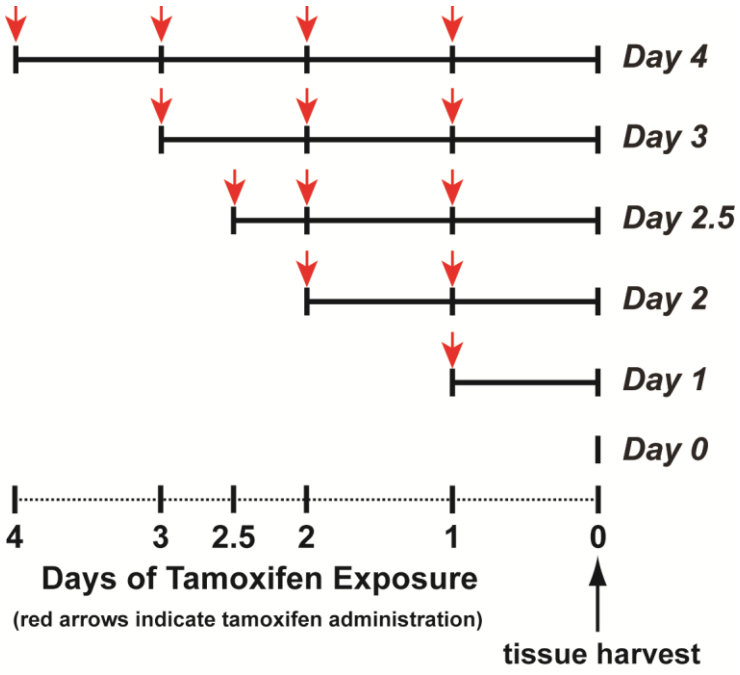

FIGURE S1. **Tamoxifen administration to *Vil-Scap*$^{-}$ mice.** In the experiments shown in Fig. 1 to Fig. 5, tamoxifen (2 mg per dose) was dissolved in corn oil and administered by orogastric gavage in staggered time-course fashion (indicated by red arrows) so that tissues were harvested from all mice in a given experiment at the same time. *Day 0* mice received corn oil vehicle by gavage *in lieu* of tamoxifen. *Day 1, day 2, day 2.5, day 3,* and *day 4* mice were exposed to tamoxifen for 1, 2, 2.5, 3, or 4 days, respectively.

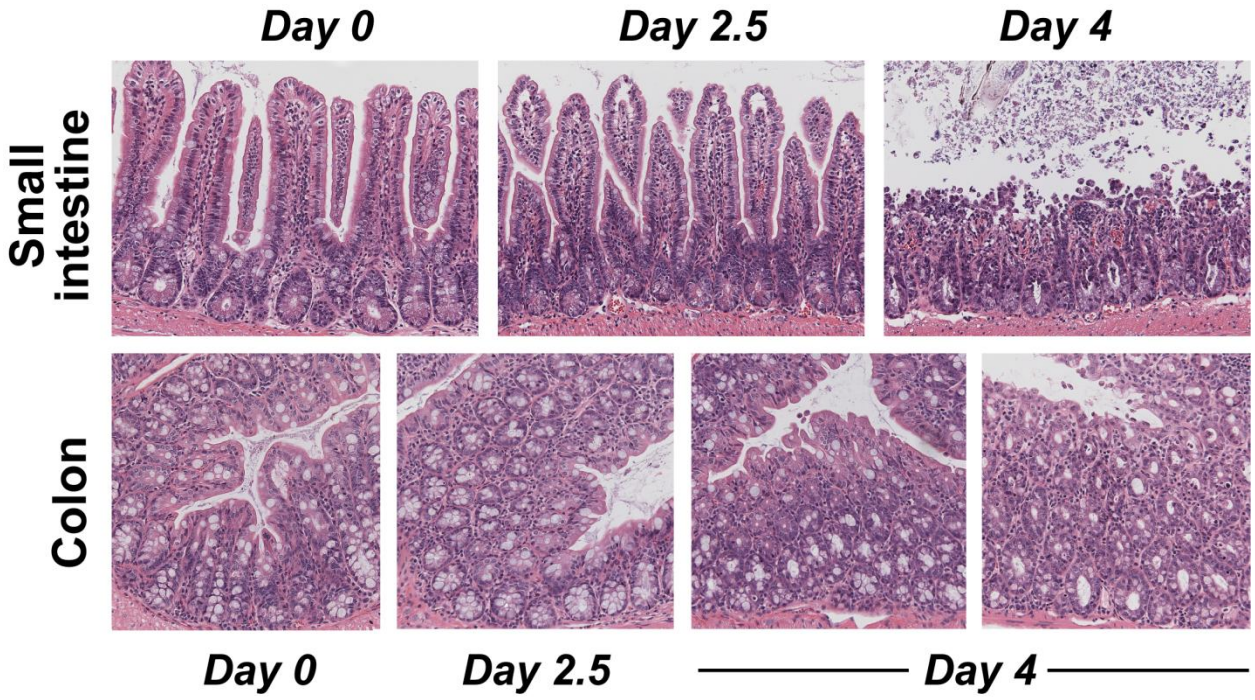

FIGURE S2. **Normal small intestine in *Vil-Scap*$^-$ mice at *day 2.5* post-tamoxifen.** Representative H&E-stained histologic sections from distal small intestine and colon from 13-week-old female *Vil-Scap*$^-$ mice that were administered tamoxifen as described in Fig. S1. Tissues were harvested on *day 0* (prior to tamoxifen administration) or on *day 2.5* or *day 4* after the initial dose of tamoxifen. Small intestine and colon at *day 2.5* in *Vil-Scap*$^-$ mice were indistinguishable from *day 0* controls. At *day 4*, severe necrotic injury was seen in small intestine, whereas areas of colon ranged from normal (*Day 4*, colon, left panel) to mild injury with loss of surface epithelial cells (*Day 4*, colon, right panel). Magnification 20x.

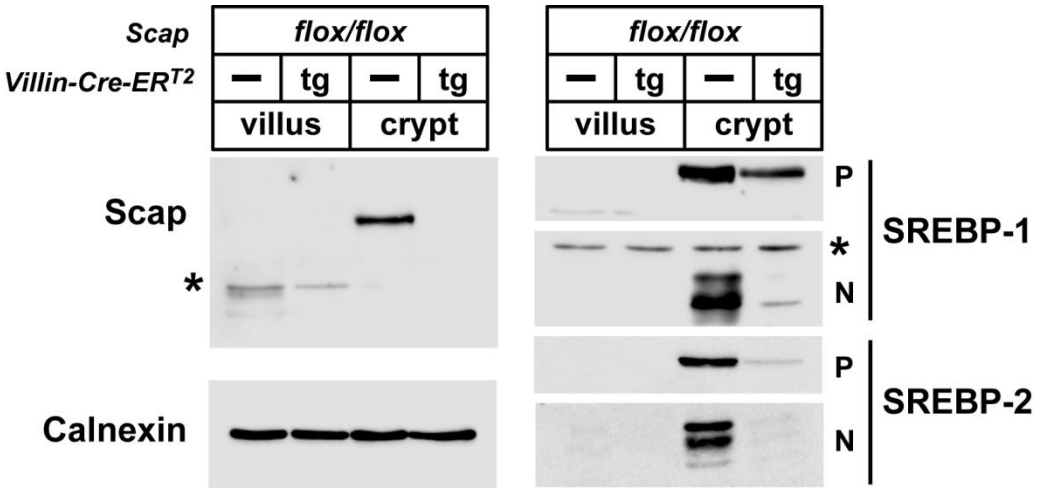

FIGURE S3. **Crypt-selective disruption of Scap and SREBP proteolysis in *Vil-Scap*$^{-}$ mice.** *Scap*^{flox} and *Vil-Scap*$^{-}$ mice (male, 14 weeks of age, 4 mice per group) were administered tamoxifen as described in Fig. S1, and then tissues were collected at *day 2.5* after the initial dose. Intestines were scraped with a glass slide to yield upper villi (villus) and then semi-purified crypts were prepared from the scraped mucosa (crypts). Villus and crypt samples were fractionated and aliquots of pooled membrane fraction and nuclear extract (30 μg) were subjected to SDS-PAGE and immunoblot analysis. The precursor and nuclear forms of SREBPs are denoted as P and N, respectively. Asterisks denote nonspecific bands. Scap, SREBP-1, and SREBP-2 are enriched in the crypts relative to villi in control mice and are greatly reduced in the crypts of *Vil-Scap*$^{-}$ mice. Transgenic, tg.

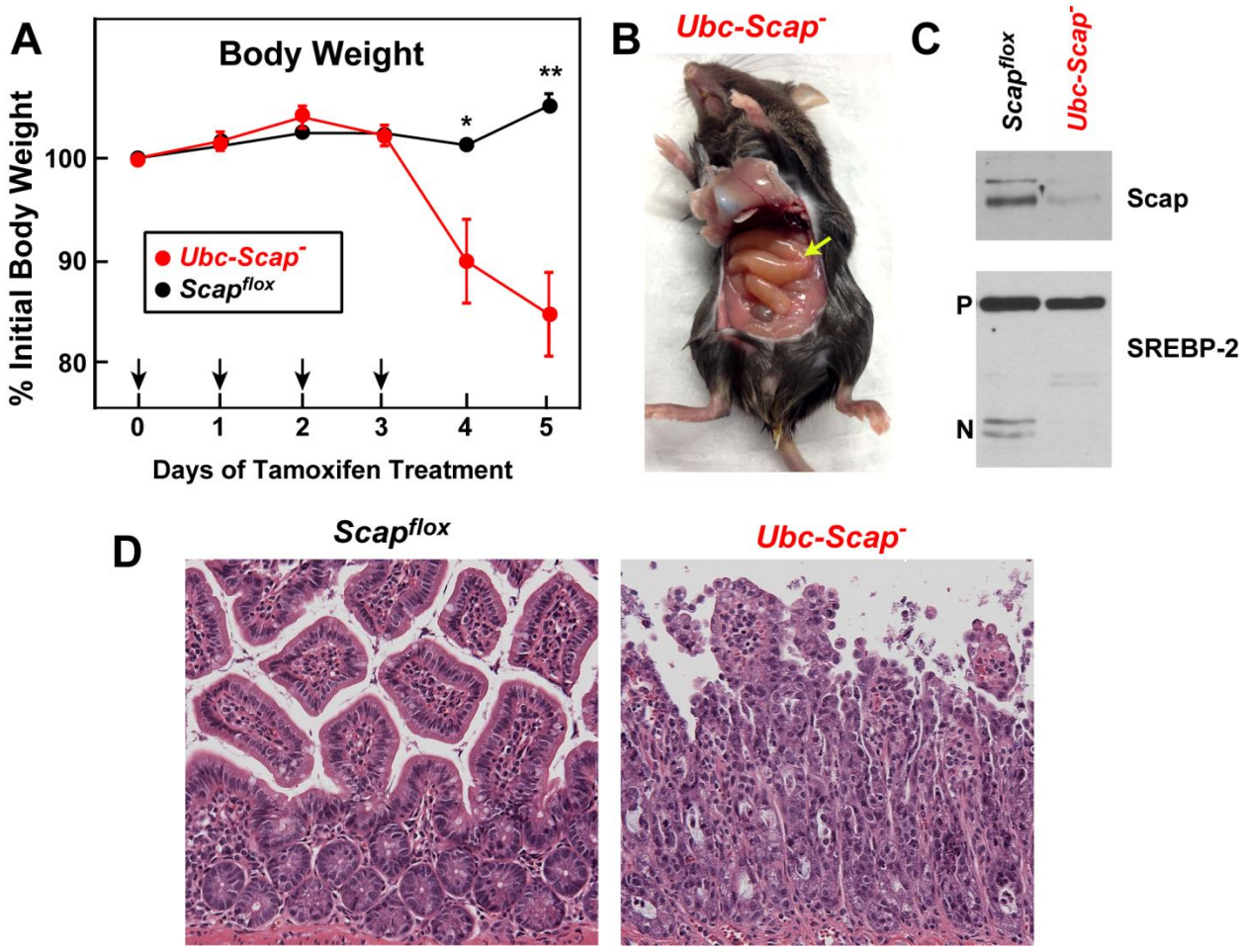

FIGURE S4. **Inducible whole-body Scap deletion parallels gut-selective deletion.** Ligand-induced ubiquitous Scap disruption was accomplished by intercrossing *Ubc-CreER*^{T2} transgenic mice with *Scap*^{flox} mice. *Ubc-Scap*$^{-}$ (*Scap*$^{flox/flox}$; *Ubc-CreER*^{T2} transgenic) developed weight loss, loose stools, and patchy destruction of gastrointestinal mucosa five days after tamoxifen administration. *(A)* Body weights of and *Scap*^{flox} *and Ubc-Scap*$^{-}$ mice (7-8 weeks of age, male, 8 mice per group) that were administered tamoxifen once daily for 4 days as indicated by black arrows. *(B)* Gross appearance of viscera of a *UBC-Scap*$^{-}$ mouse on the fifth day after the initial dose of tamoxifen. A yellow arrow denotes a distended, fluid-filled small intestine. *(C)* Scap and SREBP-2 immunoblots from whole cell extracts of small intestine (30 µg aliquots). The precursor and nuclear forms of SREBPs are denoted as P and N, respectively. *(D)* H&E-stained histologic sections of proximal small intestine of *Scap*^{flox} and *Ubc-Scap*$^{-}$ mice (female, 8-weeks of age) harvested on the fifth day after start of tamoxifen, magnification, 20x. * $p < 0.05$; ** $p < 0.01$ level (Student's *t* test).

Supplemental Table S1

Metabolic parameters of *Scap*^{flox} and *Vil-Scap*$^{-}$ mice at *day 2.5* post-tamoxifen

Parameter	*Vil-Scap*$^{-}$ Corn oil	*Scap*^{flox} Tamoxifen	*Vil-Scap*$^{-}$ Tamoxifen
Number of mice	6	6	6
Body Weight (g)	25.9 ± 0.7	26.5 ± 0.7	27.3 ± 0.8
Intestine weight (g)	1.12 ± 0.05	1.09 ± 0.04	1.13 ± 0.04
Intestine length (cm)	38.2 ± 0.6	38.4 ± 0.5	38.9 ± 0.5
Liver weight (g)	1.26 ± 0.02	1.37 ± 0.04*	1.35 ± 0.05
Total plasma cholesterol (mg/dl)	130 ± 10	110 ± 7	117 ± 4
Total plasma triglyceride (mg/dl)	110 ± 21	90 ± 6	83 ±- 3
Plasma insulin (ng/ml)	1.44 ± 0.37	0.75 ± 0.09	0.74 ± 0.15
Plasma NEFA (mM)	0.28 ± 0.04	0.26 ± 0.05	0.23 ± 0.04

Mice shown here are the same as those used in Figure 4. Each value represents the mean ± SEM of six values. * $p < 0.05$ level (Student's *t* test) versus *Vil-Scap* $^{-}$mice dosed with corn oil.

Supplemental Table S2

Tissue lipids contents in *Scap*^{flox} and *Vil-Scap*$^{-}$ mice at *day 2.5* post-tamoxifen

Parameter	*Scap*^{flox}	*Vil-Scap*$^{-}$
Number of mice	6	5
Body Weight (g)	21.6 ± 0.7	21.4 ± 0.7
Intestine weight (g)	0.89 ± 0.06	0.94 ± 0.05
IEC total cholesterol (mg/g protein)	25.9 ± 1.5	24.2 ± 1.5
IEC triglyceride (mg/g protein)	87 ± 14	86 ± 17
Liver weight (g)	1.11 ± 0.04	1.09 ± 0.06
Liver total cholesterol (mg/g tissue)	2.01 ± 0.06	2.41 ± 0.09*
Liver triglyceride (mg/g tissue)	10.5 ± 0.8	11.7 ± 1.8

Scap^{flox} and *Vil-Scap*$^{-}$ mice (female, 14-16 weeks of age) were administered tamoxifen as described in Fig. S1, and then tissues were collected 2.5 days after the initial dose and isolated small intestinal epithelial cell (IEC) and liver lipid contents were measured. Each value represents the mean ± SEM of five or six values. * $p < 0.01$ level (Student's *t* test).