**Supplemental Table title and legend**

**Table S1. Demographics of the non-IBD patients, related to Figure 1.**

| **BMI** | <25 | ≥25 | *P* value |
|---|---|---|---|
| **Total n** | 34 | 57 | |
| **Age (years old) (mean, range)** | 62.3 (19-65) | 61.2 (32-60) | 0.0962 |
| **Sex (M/F)** | 14/20 | 21/36 | 0.8240 |
| **Race (Caucasian vs. non-Caucasian)** | 24/10 | 48/9 | 0.1816 |
| **Smoking history (never vs. active/ex smoker)** | 17/17 | 30/27 | 0.8315 |

Statistical analysis was performed by Mann-Whitney test for continuous variables, and Fisher's exact test for categorical variables.

**Figure S1**

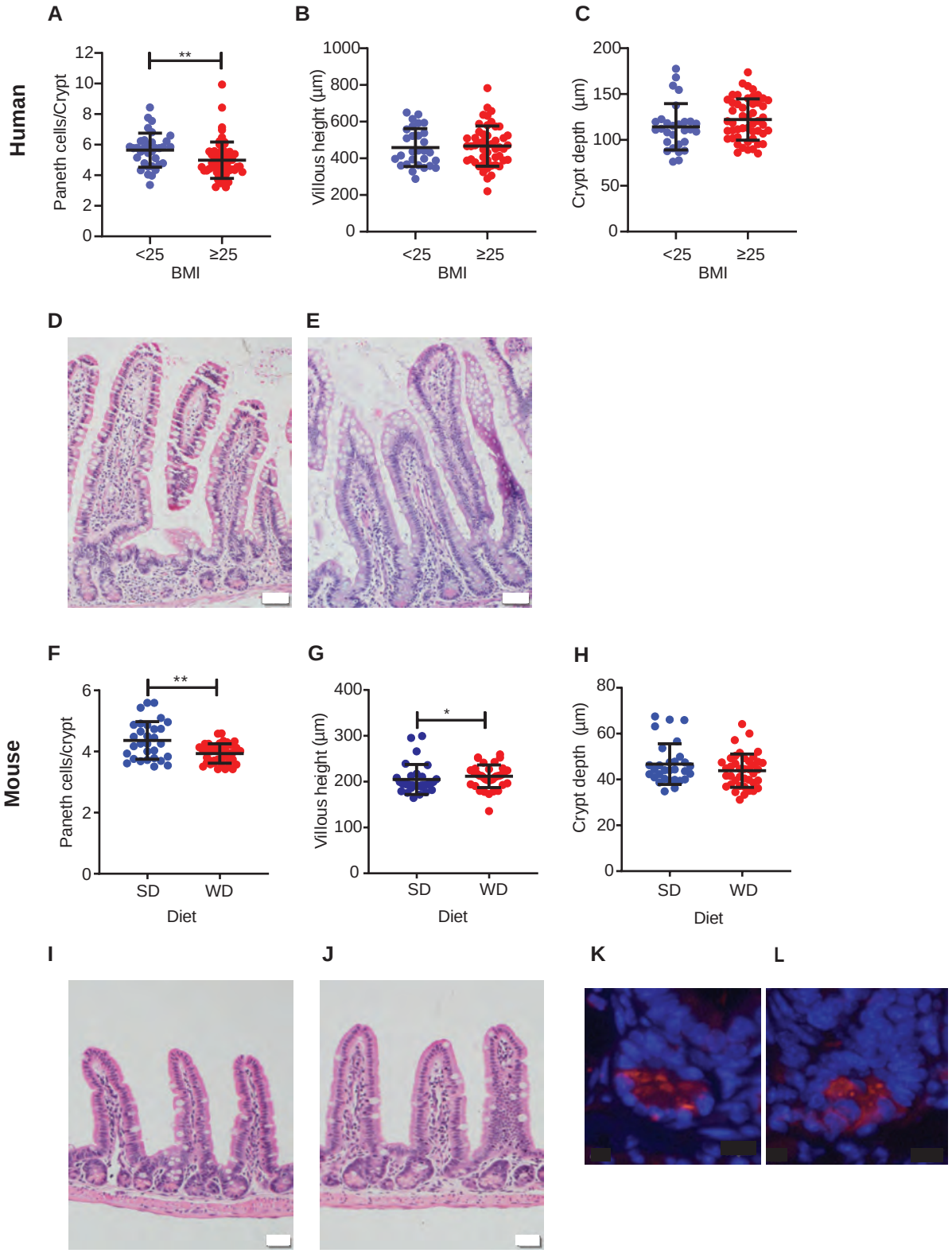


**Figure S1. Additional histology readout in overweight/obese non-IBD patients and mice fed with WD, related to Figure 1**. In non-IBD patients, those with BMI ≥25 (n=57) showed (A) reduced Paneth cells/crypt (*P*=0.002), but no changes in (B) villous height (*P*=0.7197), or (C) crypt depth (*P*=0.1220) compared to those with BMI<25 (n=34). Representative photomicrographs from patients with (D) BMI<25 and (E) BMI ≥25 are shown. (D, E) scale bar: 50 µm. WT mice fed with WD (n=41) for 8 weeks resulted in (F) reduced Paneth cells/crypt (*P*=0.0032), (G) an increase in villous height (*P*=0.0196), without significant changes in (H) crypt depth (*P*=0.3492) compared with those fed with SD (n=30). Representative photomicrographs from mice fed with (I) SD and (J) WD are shown. (I, J): scale bar: 20 µm. Representative photomicrographs of lysozyme immunofluorescence from mice fed with (K) SD and (L) WD are shown. Statistical analysis was performed by Mann-Whitney test. *: $P < 0.05$; **: $P<0.01$. Error bars represent standard deviations.

**Figure S2**

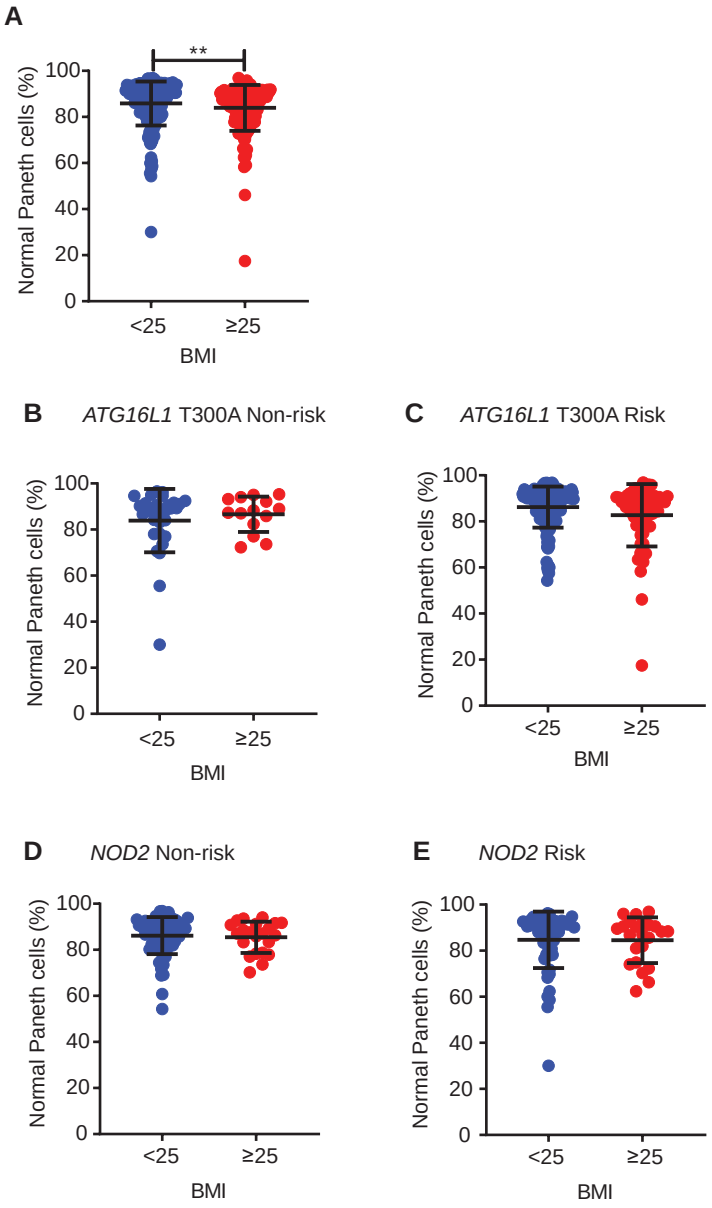


**Figure S2. BMI≥25 is associated with Paneth cell defects in CD patients irrespective of *ATG16L1* and *NOD2* genotypes, related to Figure 1**. (A) BMI≥25 was associated with reduced percentages of normal Paneth cells in CD patients (*P*=0.0172). Total n: BMI<25: n=190, BMI≥25: n=157. A subset of CD patients was also genotyped for the 2 genes commonly associated with Paneth cell defects in North America: (B, C) *ATG16L1* T300A and (D, E) *NOD2* (including R702W, G908R, L1007fs). There was no significant difference in percent normal Paneth cells when stratified by either genotype. (B) *ATG16L1* non-risk patients. Total n: BMI<25: n=30, BMI≥25: n=14. *P*=0.8325. (C) *ATG16L1* T300A patients. Total n: BMI<25: n=138, BMI≥25: n=60. *P*=0.0578. (D) *NOD2* non-risk patients. Total n: BMI<25: n=108, BMI≥25: n=45. *P*=0.0520. (E) *NOD2* patients with R702W, G908R, or L1007fs variants. Total n: BMI<25: n=59, BMI≥25: n=23. *P*=0.5745. Statistical analysis was performed by Mann-Whitney test. Error bars represent standard deviations.

**Figure S3**

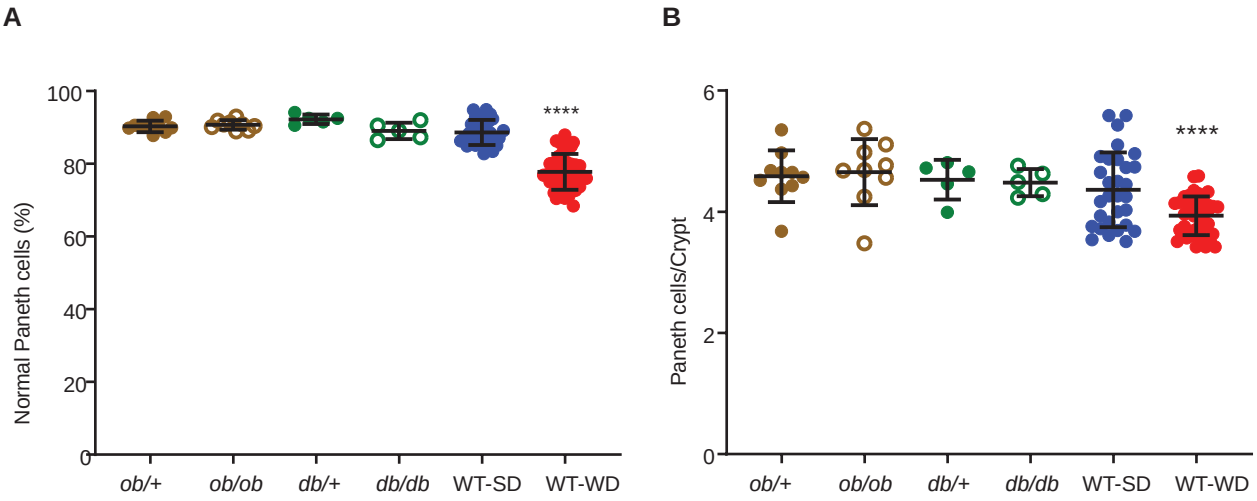


**Figure S3. Genetically obese mice do not develop Paneth cell defects**, **related to Figure 1**. *ob/+*, *ob/ob*, *db/+*, and *db/db* mice were analyzed for (A) percent normal Paneth cells and (B) Paneth cells/crypt and the results were compared to wild type (WT) mice fed with SD or WD. ****: $P < 0.0001$. Statistical analysis was performed by Kruskal-Willis tests. Total n: *ob/+*: n=10, *ob/ob*: n=9, *db/+*: n=5, *db/db*: n=5, WT-SD: 30, WT-WD: 41. Error bars represent standard deviations.

Figure S4

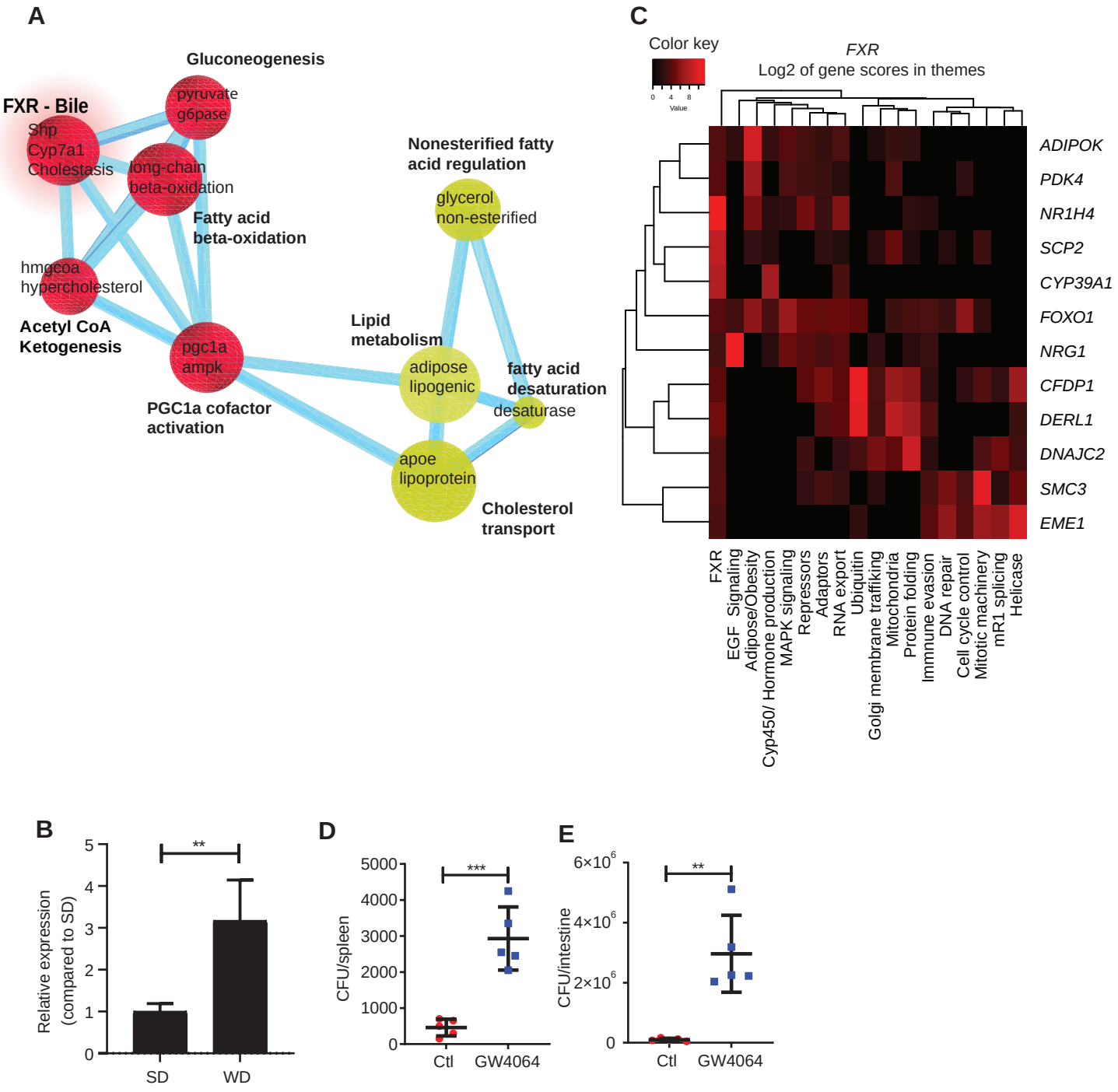


**Figure S4. FXR activation is seen in ileum in WD-fed mice and overweight and obese non-IBD patients, related to Figures 2 and 3.** (A) Transcriptomic analysis by Compbio highlighted upregulated *Fxr* as a major theme involved in the ileum of WD-fed mice. Each sphere represents a transcriptomic theme (bolded) composed of several transcriptomic concepts (key concepts within each theme are highlighted). (B) Enhanced expression of *Fgf15* was seen in the crypt base compartment (enriched with Paneth cells) of WD-fed mice. N=4/group. Statistical analysis was performed by Mann-Whitney test. Error bars represent standard deviations. (C) Full-thickness transcriptomics from ileum samples from non-IBD patients also showed upregulation of *FXR*-associated genes in overweight/obese subjects that contributed specifically to the *FXR* theme. WT mice pretreated with GW4064 followed by *Salmonella* infection were analyzed for bacteria recovery on day 4 in (D) spleen ($P$=0.0003) and (E) intestine ($P$=0.0011). CFU: colony-forming units. n=5/group. Statistical analysis was performed by Mann-Whitney test.

**Figure S5**

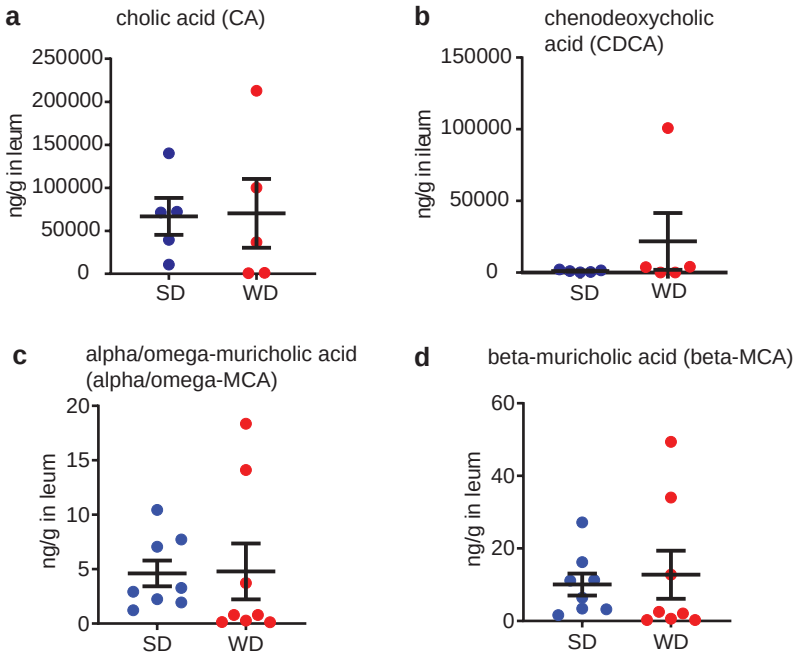


**Figure S5. WD consumption did not induce increase in primary bile acids in ileum, related to Figure 3.** WD did not induce significant increase in (a) cholic acid (CA; *P*=0.6905), (b) chenodeoxycholic acid (CDCA; *P*=0.6905), (c) α/Ω-muricholic acid (α/Ω-MCA; *P*=0.2786), and (d) β-MCA (*P*=0.4418) in the distal ileum. n=5-10/group. Statistical analysis was performed by Mann-Whitney test. Error bars represent standard deviations.

Figure S6

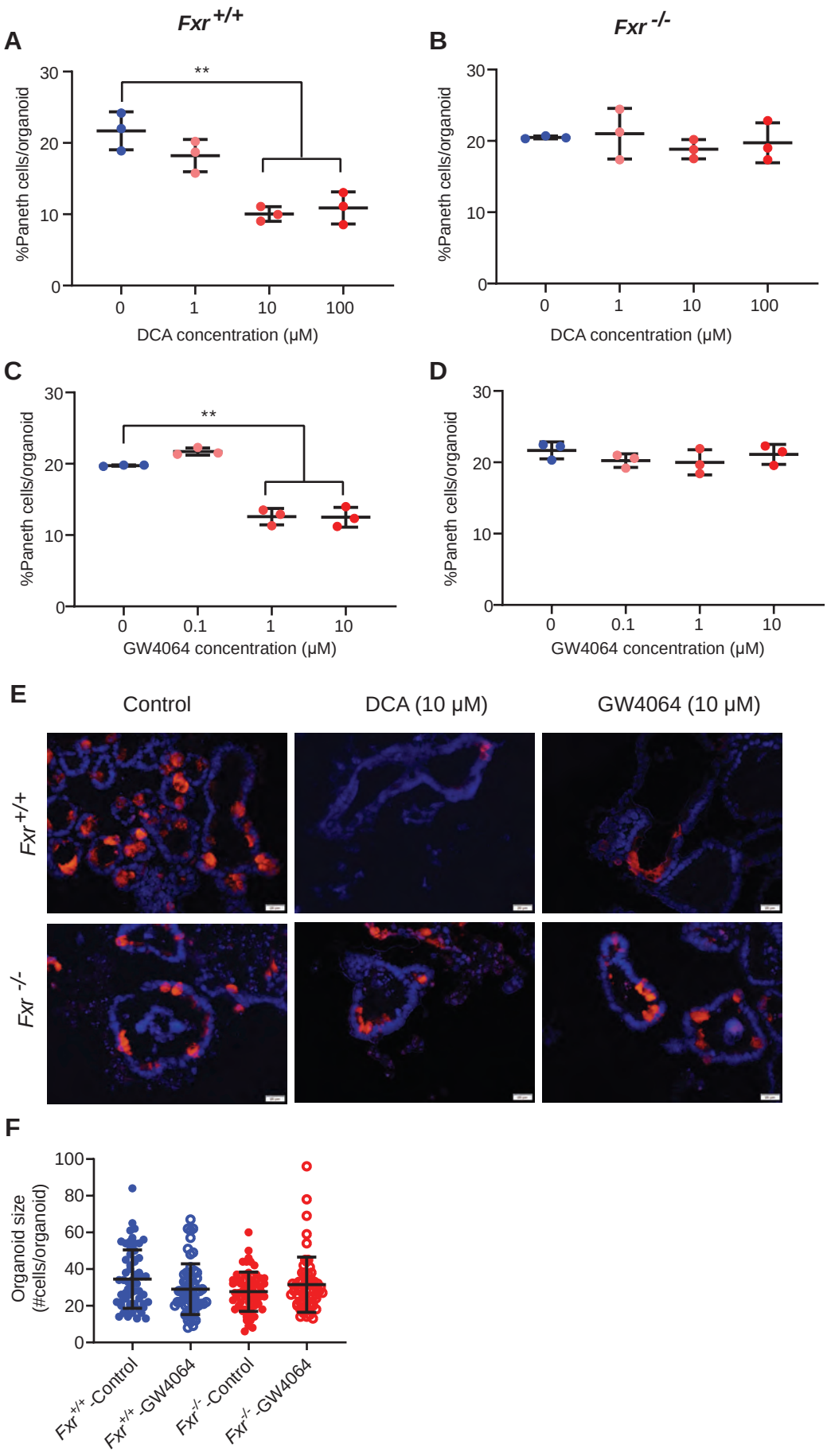


**Figure S6. Dose-responses for organoids derived from *Fxr*$^{-/-}$ and *Fxr*$^{+/+}$ mice, related to Figure 4**. (A, C) *Fxr*$^{+/+}$ organoids; (B, D) *Fxr*$^{-/-}$ organoids. (A, B) results from treatment with different concentrations of DCA. (C, D) results from treatment with different concentrations of GW4064. Paneth cell defects were induced in *Fxr*$^{+/+}$ organoids by higher doses of DCA ($P$=0.0032) and GW4064 ($P$=0.0019). Each data point represents an independent experiment, which includes 20 organoids/condition. **: $P$<0.01. (E) Represent photomicrographs of Paneth cells derived from *Fxr*$^{-/-}$ and *Fxr*$^{+/+}$ small intestinal organoids. Red: lysozyme; blue: Hoechst stain. Scale bar: 20 μm. (F) GW4064 treatment (10μM) did not significantly affect organoid sizes. All organoids analyzed in (A-D) were shown (n=60/group). (A-D, F): Statistical analysis was performed by Kruskal-Willis tests. Error bars represent standard deviations.

Figure S7

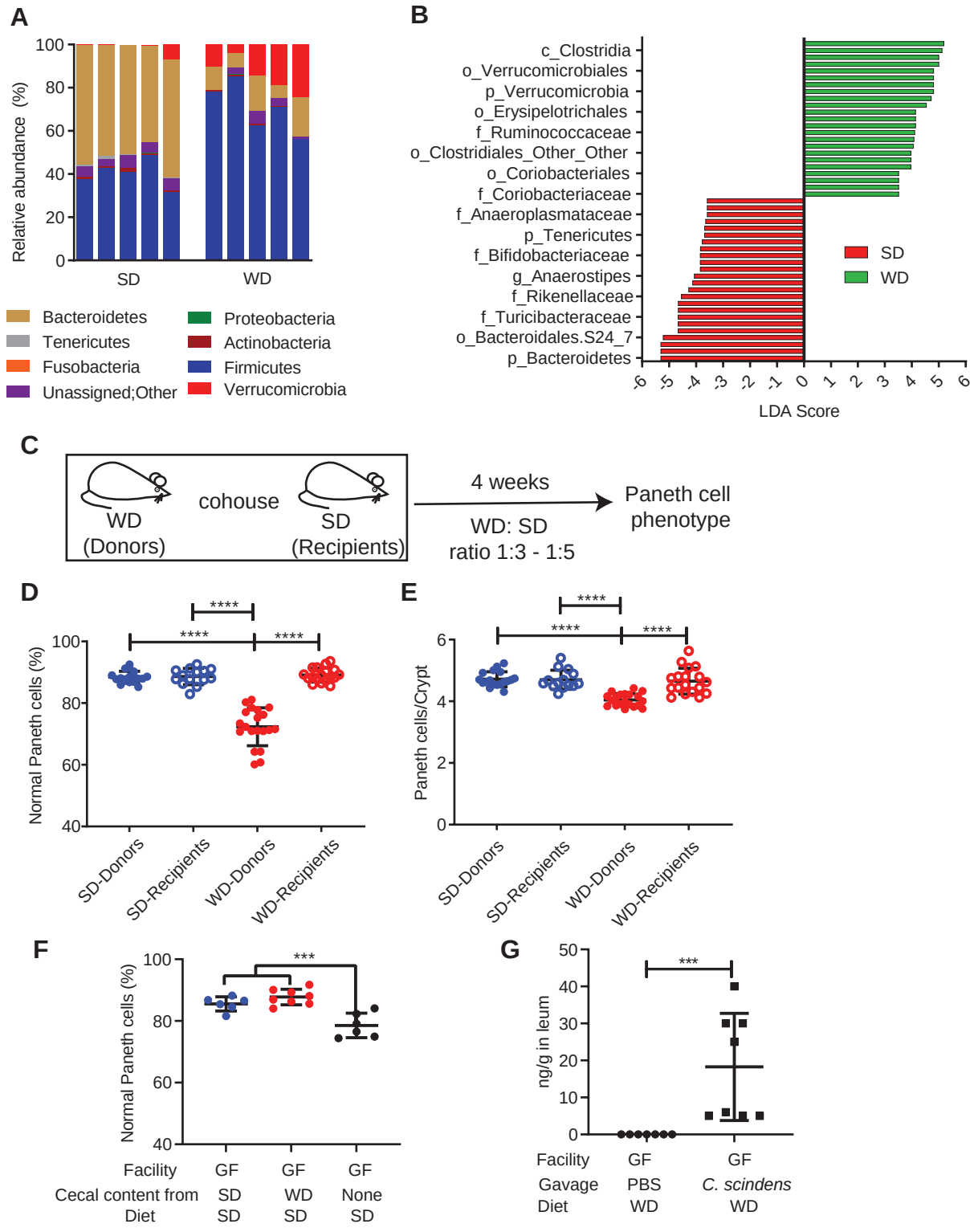


**Figure S7. Microbiota alone do not trigger Paneth cell defects, related to Figure 5.** (A) Bar plot and (B) LDA score demonstrating changes in *Bacteroidetes*: *Firmicutes* ratio in the fecal microbiota in WD- and SD-fed mice (n=5/group). (C) Experimental design for cohousing experiment. Fecal microbiota transfer from WD-fed microbial donors did not induce (D) Paneth cell defects or (E) reduced Paneth cells/crypt in microbial recipients. (C-E) Total n: SD-Donors: 15, SD-Recipients: 14, WD-Donors: 20, WD-Recipients: 18. Statistical analysis was performed by Kruskal-Willis tests followed by Dunn's multiple comparison tests. (F) Gnotobiotic mice maintained on SD and gavaged with cecal contents from SD- or WD-fed mice housed in SPF showed higher percentages of normal Paneth cells compared to those gavaged with PBS and maintained on SD ($P$=0.0007). Total n: SD-Con: 6, WD-Con: 8, PBS: 6. (G) Germ-free mice colonized with *C. scindens* and exposed to WD showed increased DCA in the ileum. Total n: PBS: 7, *C. scindens*: 8. Statistical analysis was performed by Kruskal-Wallis test. ***: $P$<0.001; ****: $P$<0.0001. (D-G): Error bars represent standard deviations.