

**Supplementary Table S1**

	<b>SD</b>	<b>WD</b>
DGL Activity (nmol/mg/mL)	$1.94 \pm 0.25$	$1.25 \pm 0.19$ $t(11) = 2.25$ ; * $p = 0.0461$
MGL Activity (nmol/mg/mL)	$24.09 \pm 1.048$	$23.65 \pm 1.789$ $t(12) = 0.19$ ; $p = 0.8510$
2-AG (nmol/g)	$24.078 \pm 2.031$	$17.999 \pm 1.582$ $t(13) = 2.39$ ; * $p = 0.0326$
2-DG (nmol/g)	$5.646 \pm 1.616$	$1.829 \pm 0.4679$ $t(11) = 2.77$ ; * $p = 0.0184$
2-LG (nmol/g)	$181.787 \pm 42.377$	$40.732 \pm 11.360$ $t(12) = 3.66$ ; ** $p = 0.0033$
2-OG (nmol/g)	$97.678 \pm 17.207$	$74.170 \pm 17.339$ $t(12) = 0.94$ ; $p = 0.3656$
AEA (pmol/g)	$10.04 \pm 1.892$	$10.14 \pm 1.879$ $t(9) = 0.03$ ; $p = 0.9710$
DHEA (pmol/g)	$34.76 \pm 3.677$	$35.65 \pm 2.800$ $t(12) = 0.20$ ; $p = 0.8481$
OEA (pmol/g)	$343.4 \pm 57.93$	$156.7 \pm 9.33$ $t(13) = 3.41$ ; ** $p = 0.0047$

**Supplementary Table S1** DGL activity, MGL activity, and lipid levels in the large intestinal epithelium of mice fed SD or WD. Statistical differences between SD and WD were determined via t-tests (two-tailed, unpaired); data displayed includes t-values, degrees of freedom, and p-values; \* =  $p < 0.05$ , \*\* =  $p < 0.01$ . SD = standard diet, WD = western diet.

**Supplementary Table S2**

Gene of interest	intCB <sub>1</sub> +/+	intCB <sub>1</sub> -/-
Tjp-1 mRNA (Relative Expression)	1.00 ± 0.30	0.89 ± 0.37 $t(10) = 0.19$ ; $p = 0.854$
Ocln mRNA (Relative Expression)	1.00 ± 0.25	0.76 ± 0.13 $t(10) = 0.93$ ; $p = 0.372$
Cldn-1 mRNA (Relative Expression)	1.00 ± 0.42	1.28 ± 0.26 $t(13) = 0.61$ ; $p = 0.551$
Cnr1 mRNA (Relative Expression)	1.00 ± 0.27	0.36 ± 0.03 $t(11) = 2.54$ ; * $p = 0.027$

**Supplementary Table S2:** Relative expression levels of mRNA relative to Hprt housekeeping gene in intCB<sub>1</sub>+/+ control mice and intCB<sub>1</sub>-/- mice. Details of the unpaired multiple t-tests analysis performed on RT-qPCR quantified genes in baseline intCB<sub>1</sub>+/+ and intCB<sub>1</sub>-/- mice. Data displayed includes t-ratios, degrees of freedom, and p-values; \* =  $p < 0.05$ .

**Supplementary Table S3**

	<b>+/- SD vs -/- SD</b>	<b>+/- SD vs +/+ WD</b>	<b>-/- SD vs -/- WD</b>	<b>+/+ WD vs -/- WD</b>
Week 0 FITC-Dextran ( $\mu\text{g/mL}$ )	$0.73 \pm 0.14$ vs. $0.58 \pm 0.11$ $t(28) = 0.81$ ; $F = 1.45$ n.s. $p = 0.425$	N/A	N/A	N/A
Week 2 FITC-Dextran ( $\mu\text{g/mL}$ )	$0.66 \pm 0.08$ vs. $0.49 \pm 0.04$ $t(25) = 0.897$ n.s. $p = 0.6124$	$0.66 \pm 0.08$ vs. $1.06 \pm 0.17$ $t(25) = 2.286$ n.s. $p = 0.1185$	$0.49 \pm 0.04$ vs. $0.98 \pm 0.13$ $t(25) = 2.692$ n.s. $p = 0.0609$	$1.06 \pm 0.17$ vs. $0.98 \pm 0.13$ $t(25) = 0.458$ n.s. $p = 0.6509$
Week 8 FITC-Dextran ( $\mu\text{g/mL}$ )	$0.56 \pm 0.05$ vs. $0.58 \pm 0.10$ $t(26) = 0.092$ n.s. $p = 0.9274$	$0.56 \pm 0.05$ vs. $1.28 \pm 0.21$ $t(26) = 2.65$ $*p = 0.0396$	$0.58 \pm 0.10$ vs. $2.45 \pm 0.28$ $t(26) = 7.35$ $***p < 0.0001$	$1.28 \pm 0.21$ vs. $2.45 \pm 0.28$ $t(26) = 4.45$ $***p = 0.0006$
Epididymal Fat (mg)	$0.62 \pm 0.09$ vs. $0.64 \pm 0.12$ $t(53) = 0.093$ n.s. $p = 0.9261$	$0.62 \pm 0.09$ vs. $2.04 \pm 0.21$ $t(53) = 6.73$ $***p < 0.0001$	$0.64 \pm 0.12$ vs. $2.44 \pm 0.14$ $t(53) = 8.41$ $***p < 0.0001$	$2.04 \pm 0.21$ vs. $2.44 \pm 0.14$ $t(53) = 1.92$ n.s. $p = 0.1165$
Large Intestine Length (cm)	$7.63 \pm 0.16$ vs. $7.32 \pm 0.16$ $t(53) = 1.56$ n.s. $p = 0.2357$	$7.63 \pm 0.16$ vs. $6.87 \pm 0.14$ $t(53) = 3.95$ $**p = 0.0012$	$7.32 \pm 0.16$ vs. $6.75 \pm 0.08$ $t(53) = 2.93$ $*p = 0.0199$	$6.87 \pm 0.14$ vs. $6.75 \pm 0.08$ $t(53) = 0.608$ n.s. $p = 0.5458$
Large Intestine Weight (mg)	$189 \pm 5.47$ vs. $168 \pm 10.86$ $t(42) = 1.65$ n.s. $p = 0.428$	$189 \pm 5.47$ vs. $166 \pm 9.96$ $t(42) = 1.88$ n.s. $p = 0.342$	$168 \pm 10.86$ vs. $173 \pm 7.60$ $t(42) = 0.35$ n.s. $p = 0.929$	$166 \pm 9.96$ vs. $173 \pm 7.60$ $t(42) = 0.55$ n.s. $p = 0.929$
Weight to Length Ratio (mg/cm)	$24.9 \pm 0.72$ vs. $23.2 \pm 1.88$ $t(42) = 0.87$ n.s. $p = 0.915$	$24.9 \pm 0.72$ vs. $24.6 \pm 1.57$ $t(42) = 0.19$ n.s. $p = 0.944$	$23.2 \pm 1.88$ vs. $25.5 \pm 1.19$ $t(42) = 1.15$ n.s. $p = 0.832$	$24.6 \pm 1.57$ vs. $25.5 \pm 1.19$ $t(42) = 0.50$ n.s. $p = 0.944$

**Supplementary Table S3:** Summary of data and t-tests performed on serum FITC-Dextran at baseline (Week 0) and the ordinary two-way ANOVA analysis of weeks two and eight serum FITC-Dextran, epididymal fat mass, large intestine length, weight, and weight to length ratio across diet or genotype. Holm-Sidak's multiple comparison test was performed as post-hoc analysis. Data displayed includes F-values, t-ratios, degrees of freedom, and p-values; \* =  $p < 0.05$ , \*\* =  $p < 0.01$ , \*\*\* =  $p < 0.001$ . SD = standard diet, WD = western diet, n.s. = not significant.

**Supplementary Table S4**

Transcript of Interest	+/- SD vs -/- SD (Welch's t-test)	+/- SD vs +/WD (Welch's t-test)	-/- SD vs -/- WD (Welch's t-test)	+/- WD vs -/- WD (Welch's t-test)
CXCL13	1.00 ± 0.30 vs. 0.86 ± 0.10 t(2) = 0.428; F = 9.00 n.s. p = 0.352	1.00 ± 0.30 vs. 1.56 ± 0.14 t(3) = 1.69; F = 4.96 n.s. p = 0.098	1.00 ± 0.12 vs. 1.55 ± 0.11 t(5) = 3.49; F = 1.67 **p = 0.008	1.00 ± 0.09 vs. 0.86 ± 0.06 t(4) = 1.34; F = 1.08 n.s. p = 0.127
CXCR3	1.00 ± 0.21 vs. 0.68 ± 0.10 t(3) = 1.36; F = 4.90 n.s. p = 0.137	1.00 ± 0.21 vs. 0.83 ± 0.07 t(2) = 0.76; F = 10.3 n.s. p = 0.258	1.00 ± 0.14 vs. 2.08 ± 0.44 t(6) = 2.36; F = 19.1 *p = 0.029	1.00 ± 0.08 vs. 1.71 ± 0.36 t(5) = 1.93; F = 40.1 n.s. p = 0.053
IFNGR1	1.00 ± 0.14 vs. 0.93 ± 0.06 t(3) = 0.49; F = 5.11 n.s. p = 0.330	1.00 ± 0.14 vs., 0.92 ± 0.04 t(2) = 0.56; F = 10.0 n.s. p = 0.311	1.00 ± 0.07 vs. 0.72 ± 0.07 t(6) = 2.91; F = 2.14 *p = 0.014	1.00 ± 0.05 vs. 0.73 ± 0.07 t(7) = 3.23; F = 4.18 **p = 0.007
ICAM1	1.00 ± 0.10 vs. 1.13 ± 0.18 t(3) = 0.65; F = 3.14 n.s. p = 0.281	1.00 ± 0.10 vs. 1.20 ± 0.10 t(4) = 1.44; F = 1.02 n.s. p = 0.112	1.00 ± 0.16 vs. 1.97 ± 0.30 t(7) = 2.90; F = 7.23 *p = 0.012	1.00 ± 0.08 vs. 1.85 ± 0.28 t(6) = 2.95; F = 23.2 *p = 0.013
HLA-DRA	1.00 ± 0.26 vs. 1.11 ± 0.44 t(3) = 0.22; F = 2.97 n.s. p = 0.420	1.00 ± 0.26 vs. 0.99 ± 0.23 t(4) = 0.04; F = 1.25 n.s. p = 0.486	1.00 ± 0.40 vs. 3.11 ± 0.81 t(7) = 2.35; F = 8.33 *p = 0.026	1.00 ± 0.23 vs. 3.51 ± 0.91 t(6) = 2.67; F = 30.9 *p = 0.020
CD247	1.00 ± 0.23 vs. 0.98 ± 0.26 t(4) = 0.05; F = 1.19 n.s. p = 0.483	1.00 ± 0.23 vs. 1.27 ± 0.07 t(2) = 1.12; F = 12.5 n.s. p = 0.183	1.00 ± 0.26 vs. 3.20 ± 0.72 t(6) = 2.88; F = 15.4 *p = 0.014	1.00 ± 0.05 vs. 2.48 ± 0.56 t(5) = 2.64; F = 229 *p = 0.023
HLA-DQA1	1.00 ± 0.14 vs. 0.81 ± 0.03 t(2) = 1.32; F = 21.6 n.s. p = 0.154	1.00 ± 0.14 vs. 0.82 ± 0.03 t(2) = 1.23; F = 29.2 n.s. p = 0.169	1.00 ± 0.04 vs. 1.24 ± 0.09 t(7) = 2.57; F = 10.3 *p = 0.020	1.00 ± 0.03 vs. 1.22 ± 0.08 t(6) = 2.42; F = 13.9 *p = 0.025
CXCR6	1.00 ± 0.18 vs. 0.84 ± 0.19 t(4) = 0.64; F = 1.10 n.s. p = 0.278	1.00 ± 0.18 vs. 1.18 ± 0.03 t(2) = 0.97; F = 32.8 n.s. p = 0.214	1.00 ± 0.22 vs. 1.82 ± 0.14 t(4) = 3.14; F = 1.29 *p = 0.020	1.00 ± 0.03 vs. 1.30 ± 0.10 t(6) = 2.90; F = 28.0 *p = 0.015
CXCR5	1.00 ± 0.26 vs. 0.89 ± 0.09 t(2) = 0.40; F = 8.92 n.s. p = 0.360	1.00 ± 0.26 vs. 1.27 ± 0.24 t(4) = 0.87; F = 1.24 n.s. p = 0.243	1.00 ± 0.10 vs. 2.07 ± 0.29 t(6) = 3.52; F = 17.1 **p = 0.006	1.00 ± 0.19 vs. 1.45 ± 0.20 t(6) = 1.65; F = 2.38 n.s. p = 0.075
IL1A	1.00 ± 0.25 vs. 1.12 ± 0.16 t(3) = 0.41; F = 2.44 n.s. p = 0.352	1.00 ± 0.25 vs. 1.06 ± 0.01 t(2) = 0.22; F = 776 n.s. p = 0.422	1.00 ± 0.14 vs. 1.96 ± 0.38 t(6) = 2.39; F = 14.6 *p = 0.027	1.00 ± 0.01 vs. 2.09 ± 0.40 t(5) = 2.70; F = 4635 *p = 0.021
TJP2	1.00 ± 0.21 vs. 1.04 ± 0.15 t(4) = 0.17; F = 2.06 n.s. p = 0.438	1.00 ± 0.21 vs. 1.07 ± 0.07 t(2) = 0.30; F = 8.28 n.s. p = 0.395	1.00 ± 0.14 vs. 0.76 ± 0.05 t(3) = 1.57; F = 3.47 n.s. p = 0.115	1.00 ± 0.07 vs. 0.75 ± 0.05 t(4) = 2.92; F = 1.16 *p = 0.019
TJP3	1.00 ± 0.10 vs. 1.15 ± 0.26 t(3) = 0.56; F = 7.32 n.s. p = 0.311	1.00 ± 0.10 vs. 1.08 ± 0.07 t(4) = 0.65; F = 1.64 n.s. p = 0.278	1.00 ± 0.22 vs. 0.73 ± 0.06 t(2) = 1.16; F = 3.84 n.s. p = 0.176	1.00 ± 0.07 vs. 0.78 ± 0.06 t(5) = 2.31; F = 1.75 *p = 0.033
CLDN-7	1.00 ± 0.11 vs. 1.20 t(4) = 1.18; F = 1.56 n.s. p = 0.154	1.00 ± 0.11 vs. 1.15 ± 0.02 t(2) = 1.45; F = 30.8 n.s. p = 0.138	1.00 ± 0.11 vs. 0.75 ± 0.08 t(4) = 1.86; F = 1.01 n.s. p = 0.068	1.00 ± 0.02 vs. 0.78 ± 0.08 t(5) = 2.70; F = 47.8 *p = 0.020
CLDN-8	1.00 ± 0.18 vs. 0.75 ± 0.13 t(4) = 1.12; F = 1.99 n.s. p = 0.166	1.00 ± 0.18 vs. 0.50 ± 0.04 t(2) = 2.69; F = 23.7 p = 0.053	1.00 ± 0.17 vs. 0.80 ± 0.10 t(3) = 1.01; F = 1.50 n.s. p = 0.191	1.00 ± 0.07 vs. 1.20 ± 0.15 t(7) = 1.19; F = 7.95 n.s. p = 0.137
CLDN-12	1.00 ± 0.08 vs. 0.73 ± 0.21 t(3) = 1.26; F = 7.40 n.s. p = 0.156	1.00 ± 0.08 vs. 0.53 ± 0.05 t(3) = 5.25; F = 2.30 **p = 0.005	1.00 ± 0.28 vs. 0.71 ± 0.13 t(3) = 0.91; F = 2.24 n.s. p = 0.215	1.00 ± 0.10 vs. 0.99 ± 0.19 t(7) = 0.06; F = 7.59 n.s. p = 0.475
CLDN-19	1.00 ± 0.01 vs. 0.83 ± 0.03 t(3) = 5.31; F = 4.93 **p = 0.008	1.00 ± 0.01 vs. 0.91 ± 0.02 t(4) = 4.02; F = 1.83 **p = 0.009	1.00 ± 0.04 vs. 1.80 ± 0.42 t(5) = 1.91; F = 277 n.s. p = 0.057	1.00 ± 0.02 vs. 1.64 ± 0.38 t(5) = 1.68; F = 739 n.s. p = 0.077
MAGL	1.00 ± 0.16 vs. 1.14 ± 0.16 t(4) = 0.63; F = 1.04 n.s. p = 0.282	1.00 ± 0.16 vs. 0.85 ± 0.02 t(2) = 0.92; F = 45.1 n.s. p = 0.226	1.00 ± 0.14 vs. 0.91 ± 0.06 t(3) = 0.62; F = 3.27 n.s. p = 0.292	1.00 ± 0.03 vs. 1.22 ± 0.08 t(6) = 2.68; F = 14.4 *p = 0.018

DAGLBETA	1.00 ± 0.22 vs. 0.99 ± 0.16 t(2) = 0.03; F = 131 n.s. p = 0.490	1.00 ± 0.22 vs. 0.79 ± 0.04 t(2) = 0.93; F = 31.1 n.s. p = 0.222	1.00 ± 0.02 vs. 0.76 ± 0.06 t(6) = 3.91; F = 18.6 **p = 0.004	1.00 ± 0.05 vs. 0.95 ± 0.08 t(7) = 0.55; F = 4.14 n.s. p = 0.299
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**Supplementary Table S4:** Summary of the relative expression of the differentially expressed genes (DEGs) and the statistical analysis performed to identify these DEGs from the NanoString analysis. Unpaired one-tailed t-test with Welch's correction was performed to identify significant differences across conditions. Data presented includes t-ratios, degrees of freedom, F-values, and p-values; \* =  $p < 0.05$ , \*\* =  $p < 0.01$ . SD = standard diet, WD = western diet, n.s. = not significant.