

SUPPLEMENTARY DATA

Supplementary Table S1. Liver and plasma parameters of cohorts 1 and 2. The percentage of liver fat (fat (g) per liver mass (g)), liver weight (g), and plasma ALT (U/L), AST (U/L), TG (mg/dL), and cholesterol (mg/dL) are shown for both cohort 1 and cohort 2. * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$, **** $p \leq 0.0001$ vs (V).

Cohort 1	V	R	D	RD	
Liver Fat (%)	6.6 ± 0.4	27.8 ± 1.91****	10.8 ± 1.2	31.3 ± 1.5****	
Liver Weight (g)	1.8 ± 0.1	4.5 ± 0.1****	2.9 ± 0.1****	4.3 ± 0.2****	
ALT (U/L)	115.5 ± 36.0	503.3 ± 75.4**	188.8 ± 57.9	432.1 ± 66.4**	
AST (U/L)	115.4 ± 16.5	366.5 ± 55.5*	163.0 ± 8.5	348.0 ± 63.9*	
TG (mg/dL)	259.7 ± 81.6	96.0 ± 13.0*	267.5 ± 35.6	90.14 ± 7.9*	
Chol (mg/dL)	118.0 ± 4.5	159.6 ± 10.8**	134.8 ± 11.1	147.9 ± 5.6	
Cohort 2	V	L	D	DL	Lean
Liver Fat (%)	8.2 ± 1.5	11.4 ± 0.8	10.1 ± 1.1	9.3 ± 0.4	4.7 ± 0.6
Liver Weight (g)	2.2 ± 0.2	2.1 ± 0.1	3.2 ± 0.1****	2.0 ± 0.1	0.9 ± 0.1
ALT (U/L)	59.0 ± 6.7	163.3 ± 30.0	127.5 ± 38.7	106.5 ± 20.2	46.7 ± 5.9
AST (U/L)	84.6 ± 8.8	130.1 ± 38.9	207.7 ± 60.9	99.9 ± 10.7	65.2 ± 8.3
TG (mg/dL)	256.8 ± 53.5	347.7 ± 27.1	199.5 ± 52.4	311.8 ± 17.9	128.5 ± 10.9
Chol (mg/dL)	111.8 ± 5.4	149.6 ± 3.4****	117.8 ± 3.4	146.7 ± 3.2****	107.1 ± 1.9

Supplementary Table S2. Quantitation of the percentage of Ki67 positive/insulin positive cells per islet. The percentage of Ki67 positive β -cells was quantitated from 25 islets per group (N ≥ 3).

Group	INS+/Ki67+ (%)
V	1.35 ± 1.08
R	1.47 ± 0.66
D	1.45 ± 0.74
L	1.42 ± 1.06
RD	1.66 ± 0.88
DL	1.33 ± 0.90
Lean	1.62 ± 0.74

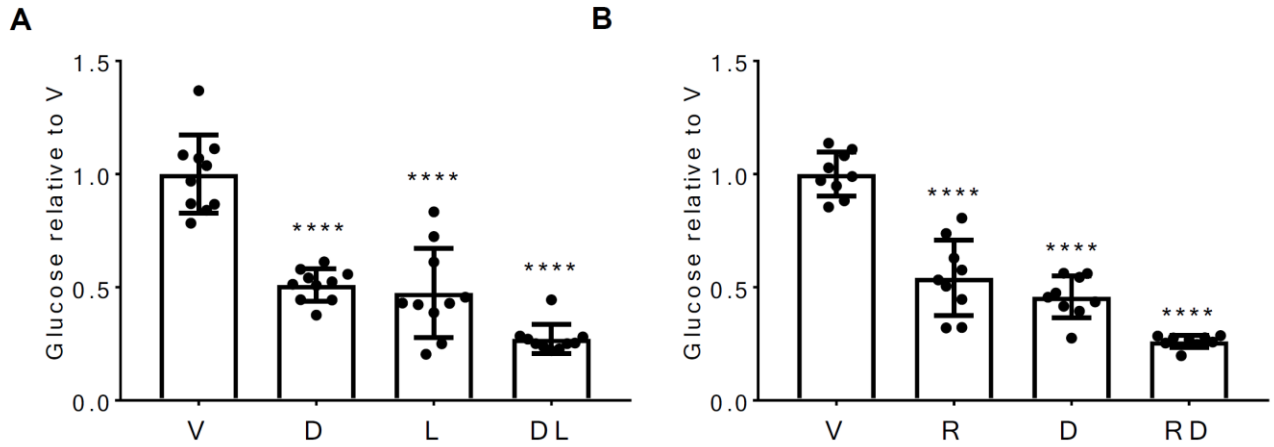
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Supplementary Table S3. Quantitation of percent MafA intensity in insulin positive cells per islet. Quantitation of MafA intensity was performed by identifying the percentage of insulin positive cells that were MafA negative (INS+/MafA-), MafA positive (INS+/MafA+), and MafA very positive (INS+/MafA++) from 10 islets per group (N ≥ 3). *** $p \leq 0.001$, **** $p \leq 0.0001$ vs (V) for each MafA intensity.

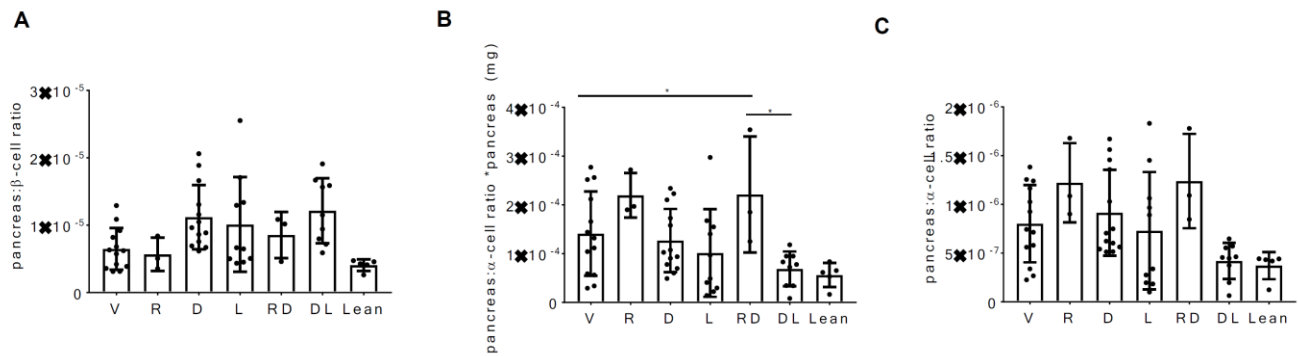
Group	INS+/MafA- (%)	INS+/MafA+ (%)	INS+/MafA++ (%)
V	20.32 ± 13.35	74.64 ± 13.07	5.04 ± 2.34
R	14.54 ± 8.21	79.40 ± 7.63	6.06 ± 3.14
D	15.32 ± 8.35	78.92 ± 8.66	5.73 ± 2.72
L	14.97 ± 7.48	75.95 ± 7.54	8.08 ± 4.13
RD	4.51 ± 2.30****	76.18 ± 8.21	19.31 ± 9.02***
DL	4.09 ± 1.46****	76.87 ± 5.44	19.04 ± 6.33***
Lean	10.22 ± 7.49	76.81 ± 7.20	12.98 ± 4.95

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Supplementary Figure S1. Six hour fasting glucose relative to vehicle in (A) Cohort 1 and (B) Cohort 2. (N ≥ 6). **** $p \leq 0.0001$ vs (V)

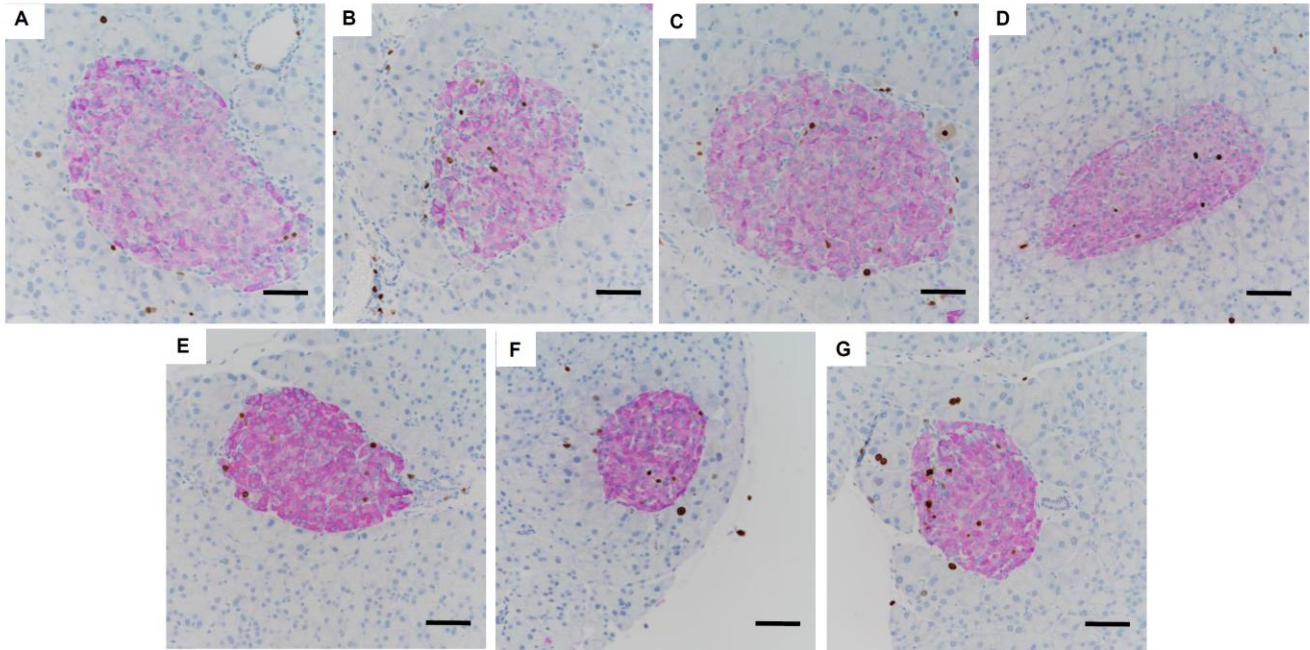


Supplementary Figure S2. β and α -cell mass analysis (A) Ratio of total pancreatic area to insulin positive area, (B) α -cell mass and (C) ratio of total pancreatic area to α -cell area (N ≥ 3). * $p \leq 0.05$ vs (DL).



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Supplementary Figure S3. Representative immunohistochemical staining of fixed pancreata for insulin and Ki67. Immunohistochemical staining of insulin (purple) and Ki67 (brown) of pancreata from KS *db/db* mice treated with (A) vehicle, (B) rosiglitazone, (C) dapagliflozin, (D) liraglutide, (E) rosiglitazone/dapagliflozin, (F) dapagliflozin/liraglutide, and (G) untreated lean control KS *db/+* mice (N ≥ 4). Scale bar = 1 mm.



Supplementary Figure S4. *In vitro* glucose-stimulated insulin secretion (GSIS) of cultured islets incubated with dapagliflozin and/or rosiglitazone. (A) GSIS assay of human islets or (B) overnight cultured C57/BL6 mouse islets pre-incubated for 4 hours with 0.2% DMSO (V), 10 μM rosiglitazone (R), 10 μM dapagliflozin (D), or their combination (RD) in KRBH containing basal (2.8 mM) or stimulatory (16.7 mM) glucose containing the same pre-incubation compounds (N ≥ 4).

