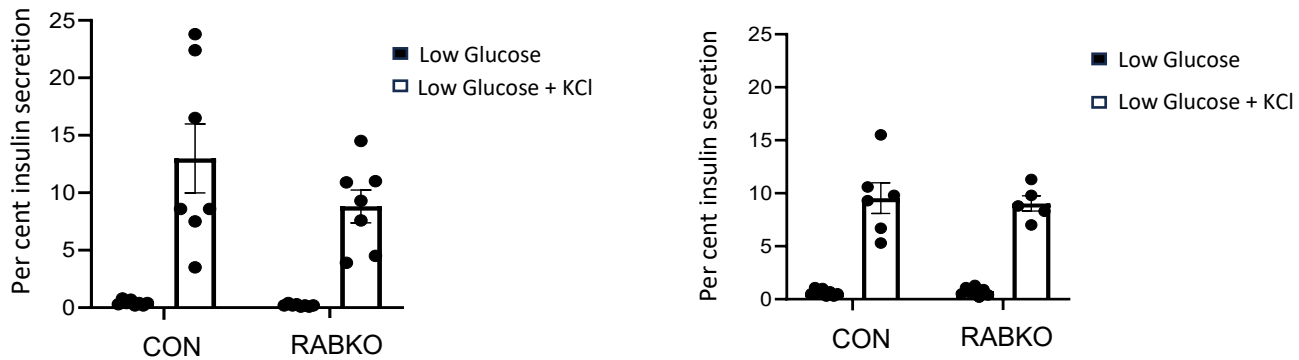


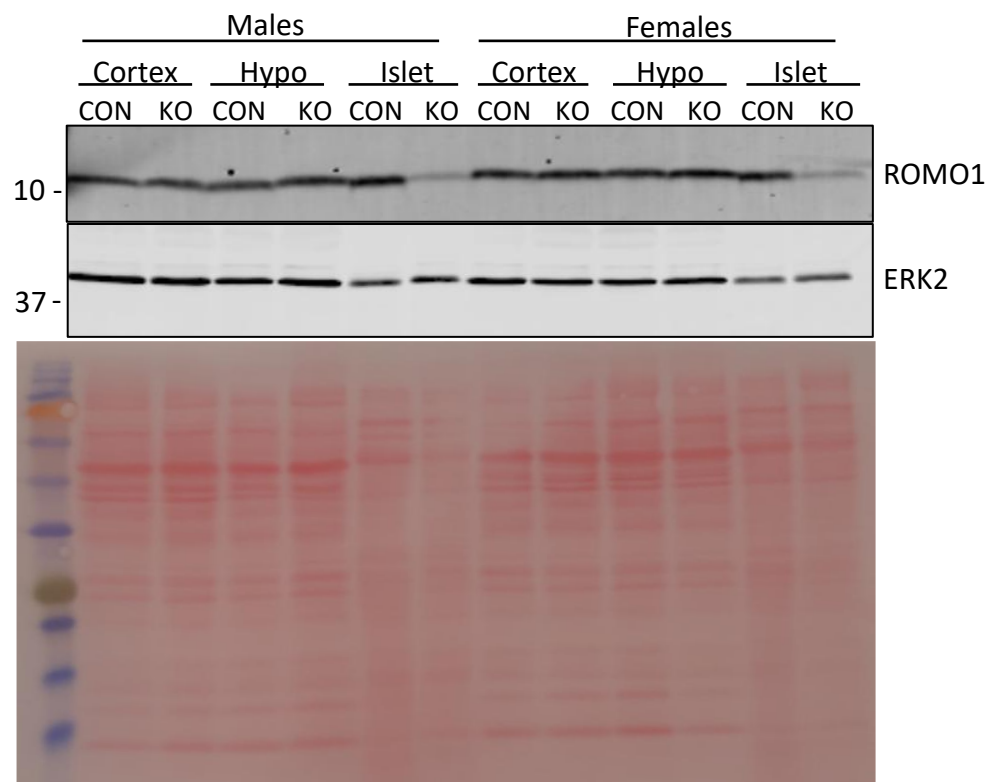
ESM Fig. 1



ESM Fig. 1 Legend

In vitro KCl-induced insulin secretion assay using islets from control (CON) or RABKO male (left) and female (right) mice. Islets cultured in 2.8 mmol glucose (low glucose) were stimulated with 45 mmol KCl. p-values for KCl + low glucose vs. low glucose are all n.s.

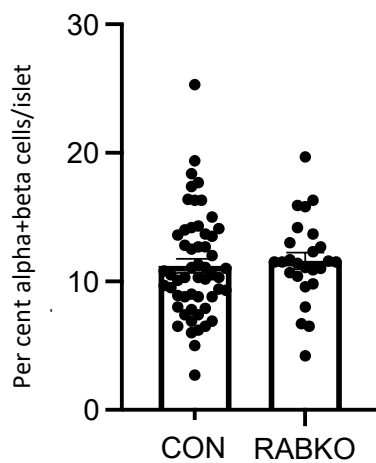
ESM Fig. 2



ESM Fig. 2 Legend

Western blot of ROMO1 in cortex, hypothalamus (Hypo), and islets of male and female CON and RABKO mice showing loss of ROMO1 protein only in the islet samples. ERK2 loading control blot is shown. Ponceau S staining to show protein loading is shown.

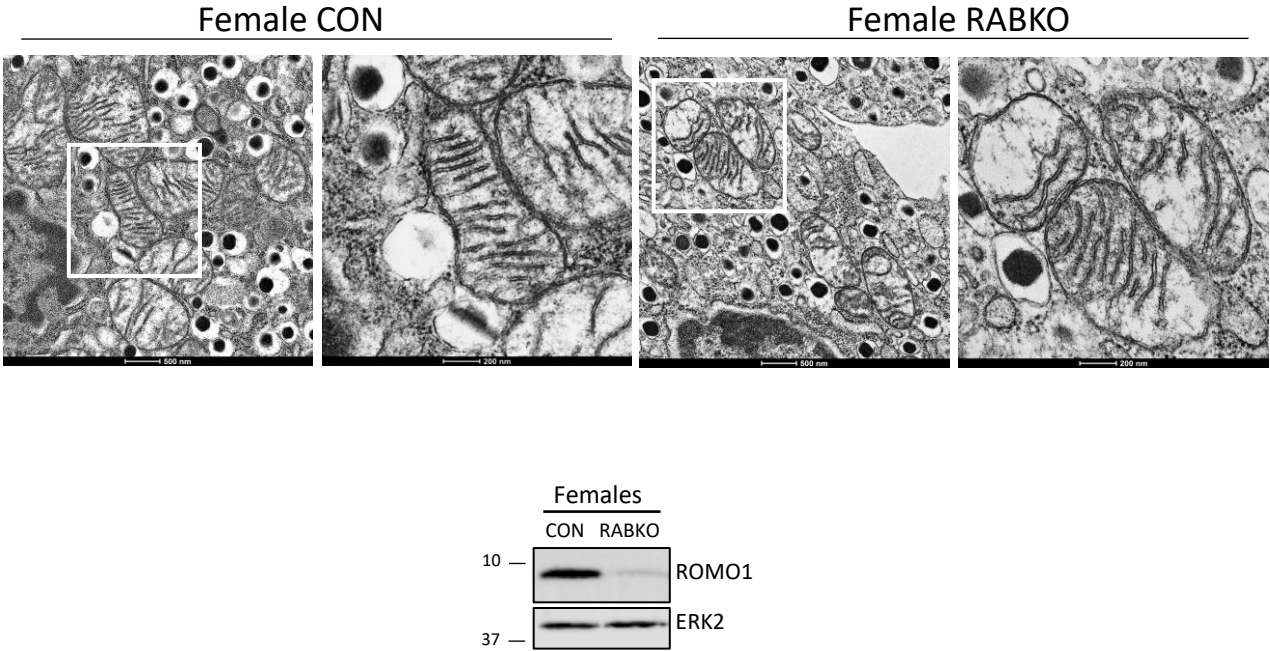
ESM Fig. 3



ESM Fig. 3 Legend

Barplot showing % of alpha+beta cells per islet in young male control (CON, n = 50 islets) and RABKO (n = 26 islets) mice.

ESM Fig. 4

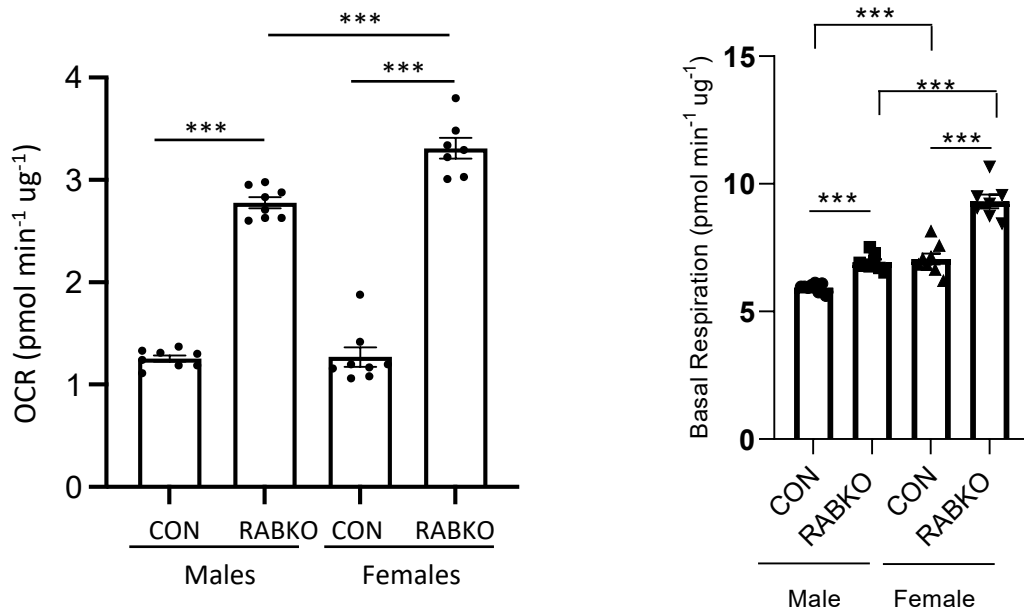


ESM Fig. 4 Legend

Top: Electron micrographs of beta cells from female *Romo1*^{+/+};*Pdx1-CreERTam* (CON) and *Romo1*^{fl/fl};*Pdx1-CreERTam* knockout (RABKO) mice at 12 week of age (4 weeks post-tamoxifen injection) showing normal cristae morphology in CON and RABKO female mice. Scale bar = 500 nm for low magnification, 200 nm for higher magnification.

Bottom: Western blot showing loss of Romo1 protein in islets from female RABKO mice.

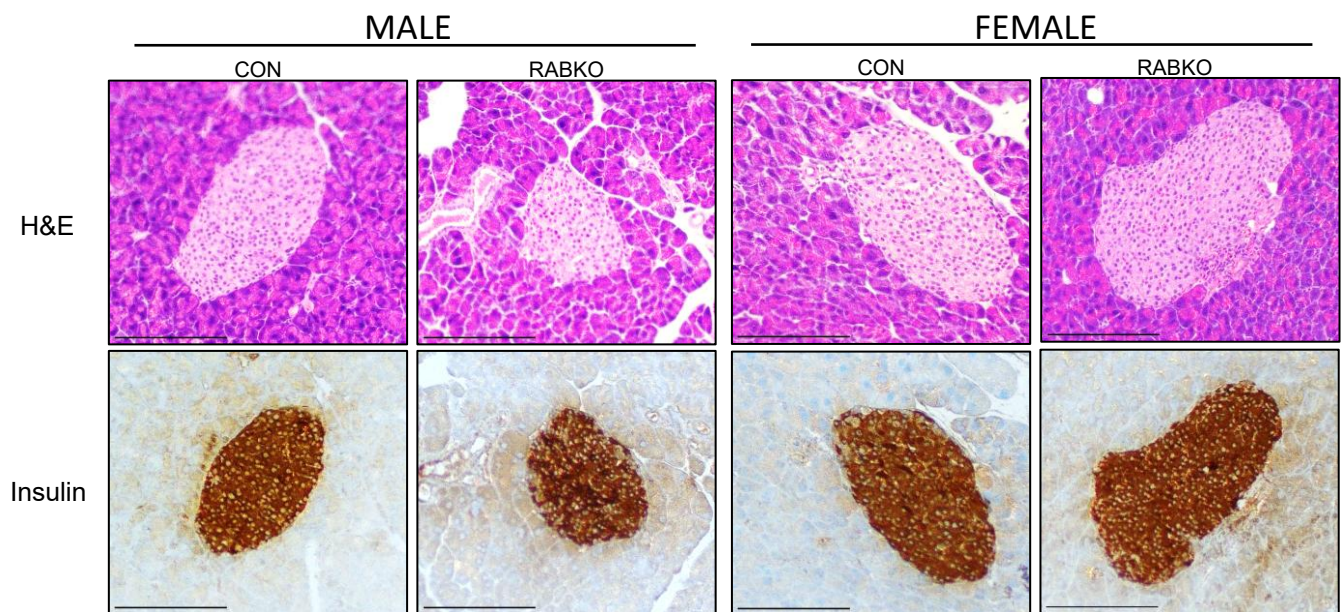
ESM Fig. 5



ESM Fig. 5 Legend

Left: Oxygen consumption rate attributed to proton leak in islets isolated from female and male CON and RABKO mice. Two-tailed t-tests were performed. ***p<0.001 Right: Basal respiration in islets isolated from female and male CON and RABKO mice. Two-tailed t-tests were performed.***p<0.001.

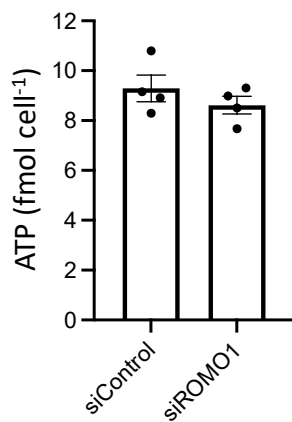
ESM Fig. 6



ESM Fig. 6 Legend

Hematoxylin and eosin micrographs (top) and insulin staining (bottom) in 1 year old male and female control and RABKO mice. Scale bars = 100 μ m.

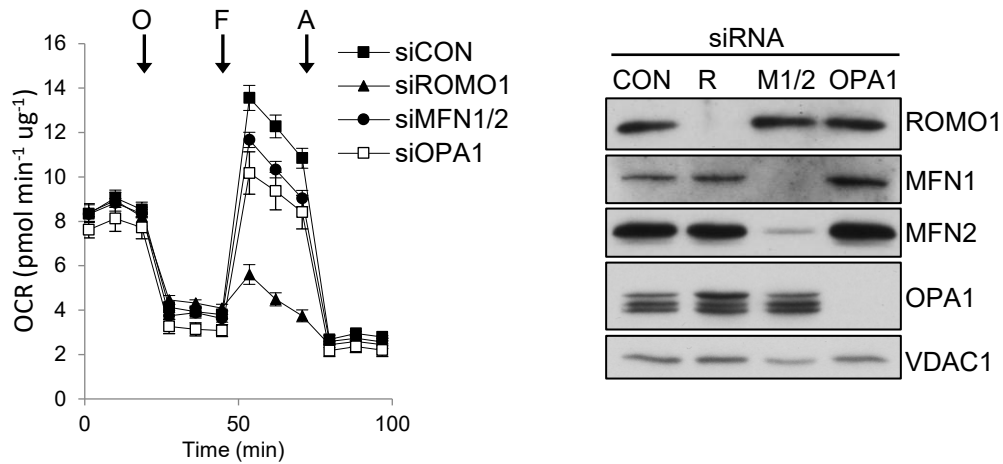
ESM Fig. 7



ESM Fig. 7 Legend

ATP levels in U2OS cells transfected with control non-targeting (CON) or ROMO1 RNAi duplexes were determined by mass spectrometry.

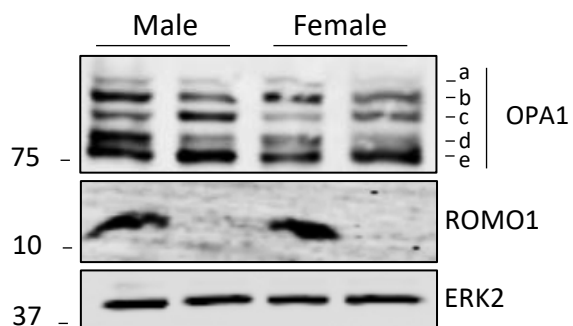
ESM Fig. 8



ESM Fig. 8 Legend

Left: Seahorse Assay showing OCR in U2OS cells after silencing ROMO1, outer membrane fusion GTPases MFN1 and MFN2, or inner membrane fusion GTPase OPA1. O = oligomycin, F = FCCP, A = antimycin A. Right: Western blotting to showing loss of protein targets in Seahorse samples shown on left. siRNA targeting ROMO1 (R), MFN1+MFN2 (M1/2), or OPA1 alongside control siRNA (CON) is shown.

ESM Fig. 9



ESM Fig. 9 Legend

Western blot assay of OPA1 on isolated islets from young (3 months) control and RABKO male and female mice. OPA1 isoforms (a-e) are indicated. Loading controls for ROMO1 and ERK2 shown.

Checklist for reporting human islet preparations used in research

Adapted from Hart NJ, Powers AC (2018) Progress, challenges, and suggestions for using human islets to understand islet biology and human diabetes. Diabetologia <https://doi.org/10.1007/s00125-018-4772-2>

Islet preparation	1	2	3	4	5	6	7	8 ^a
MANDATORY INFORMATION								
Unique identifier	ADJQ078	R199	H2388	H2389	20923891	20926064	22818629	H2397
Donor age (years)	45	56	39	46	45	62	45	54
Donor sex (M/F)	M	M	M	F	M	F	F	M
Donor BMI (kg/m ²)	24.6	18.3	35.1	36.6	50.60	26.8	21.70	28.7
Donor HbA _{1c} or other measure of blood glucose control	Average blood glucose-218.40mg/dl	5.3%			Average blood glucose 150.20mg/dl	Average blood glucose 177.40mg/dl	Average blood glucose 173.20mg/dl	
Origin/source of islets ^b	IIDP	ADI Islet Core	Clinical Islet Laboratory	Clinical Islet Laboratory	IIDP	IIDP	IIDP	Clinical Islet Laboratory
Islet isolation centre	University of Miami	University of Alberta	University of Alberta	University of Alberta	Loyola	SC-ICRC	University of Pennsylvania	University of Alberta
Donor history of diabetes? Please select yes/no from drop down list	No	No	No	No	No	No	No	No
If Yes, complete the next two lines if this information is available								
Diabetes duration (years)								
Glucose-lowering therapy at time of death ^c								
RECOMMENDED INFORMATION								
Donor cause of death	Head Trauma	Neurological			Head Trauma	Cerebrovascular /stroke	Anoxia	

Warm ischaemia time (h)								
Cold ischaemia time (h)	16h 33min	21h			10h 12min	10h 59min	17h 43min	
Estimated purity (%)	90	95%	38.8	25	95	90	90	40
Estimated viability (%)	90		84	82	98	96	94	90
Total culture time (h) ^d	4d	46h	2d	1d	60h	66h	68h	2d
Glucose-stimulated insulin secretion or other functional measurement ^e		4.42 (mean 16.7mM to 2.8mM stimulation index	Seahorse Assay	Seahorse Assay	Seahorse Assay	Seahorse Assay	Seahorse Assay	Seahorse Assay
Handpicked to purity? Please select yes/no from drop down list	No	No	Yes	Yes	No	No	No	Yes
Additional notes								

^aIf you have used more than eight islet preparations, please complete additional forms as necessary

^bFor example, IIDP, ECIT, Alberta IsletCore

^cPlease specify the therapy/therapies

^dTime of islet culture at the isolation centre, during shipment and at the receiving laboratory

^ePlease specify the test and the results