

Supplementary Table S1. List of Human Islets Donor Information. Related to Figures 1C, 1D, 5H, 5I, 6A, and S1A.

	Donor (RRID)	Age (years)	Sex	BMI	Disease
1	SAMN25519947	32	Male	24.3	Non-diabetic
2	SAMN26646319	20	Male	20.5	Non-diabetic
3	SAMN27361473	34	Male	31.8	Non-diabetic
4	SAMN29771427	44	Male	27.9	Non-diabetic
5	SAMN32641506	16	Male	29.5	Non-diabetic
6	SAMN38518088	57	Female	30.1	Non-diabetic
7	SAMN38334492	51	Male	24.6	Non-diabetic
8	SAMN38226661	37	Female	30	Non-diabetic
9	SAMN37973608	55	Female	31.7	Non-diabetic
10	SAMN37871873	59	Male	41.7	Non-diabetic
11	SAMN36823227	41	Female	38.4	Non-diabetic
12	SAMN35301006	52	Male	31.6	Non-diabetic
13	SAMN34411471	45	Male	33.1	Non-diabetic
14	SAMN34033793	39	Male	33.4	Non-diabetic
15	SAMN33103085	49	Female	27.5	Non-diabetic
16	SAMN34033793	39	Male	33.4	Non-diabetic
17	UNOSIDAKE4447	27	Male	29.79	Type 1 Diabetic (10 years)
18	SAMN37680485	63	male	33.9	Type 2 Diabetic (>10 years)
19	SAMN36020139	46	Female	27.5	Type 2 Diabetic (0-5 years)
20	SAMN33293779	49	Male	68.5	Type 2 Diabetic (Duration unknown)
21	SAMN25980818	55	Male	31	Type 2 diabetic (0-5 years)
22	SAMN39639181	58	Male	38.3	Type 2 diabetic (6-10 years)
23	SAMN32273466	45	Female	33.5	Type 2 diabetic (Duration unknown)
24	SAMN40122446	63	Male	36	Type 2 diabetic (>10 years)
25	SAMN39243818	68	Male	25.2	Type 2 diabetic (>10 years)
26	SAMN40593976	43	Male	29.8	Type 2 diabetic

Supplementary Table S2. Antibody information. Related to Figures 2J, 3H, 3N, 4A, 4E and 5D.

Target	Primary Antibody (Dilution)	Secondary Antibody (1:1000 dilution)
Nidogen-2	Rat Monoclonal Antibody (1:50)	Anti-Rat Alexa fluor 633
GLUT4	Polyclonal Rabbit GLUT4 Antibody (1:100)	Anti-Rabbit Alexa fluor 488
α -sarcoglycan	Monoclonal mouse α -sarcoglycan Antibody (F-7) (1:100)	Anti-mouse Alexa fluor 594
UCP1	monoclonal rabbit UCP1 antibody (1:50)	Anti-Rabbit Alexa fluor 488
Insulin	Monoclonal Mouse Insulin Antibody (1:100)	Anti-mouse Alexa fluor 568
Somatostatin	Monoclonal Rat Somatostatin Antibody (1:50)	Anti-Rat Alexa fluor 633
Glucagon	Rabbit GluN F7 (1:100)	Anti-Rabbit Alexa fluor 488

Supplementary Table S3. Primers for qPCR amplification. Related to Figures 3G, 3I, 3M, 3O, 4D, and S2L.

Target	Gene Name	Forward primer	Reverse Primer
<i>Ucp1</i>	Uncoupling protein 1	GATGGTGAACCCGACAAC TT	AGCACACAAACATGATGAC GT
<i>18S</i>	Small subunit 18 rRNA	GTAACCCGTTGAACCCCA TT	CCATCCAATCGGTAGTAGC G
<i>Cidea</i>	Cell Death Inducing DFFA- Like Effector A	TGCTCTTCTGTATCGCCCA GT	GCCGTGTTAAGGAATCTGC TG
<i>Zic1</i>	Zic Family Member 1	AACCTCAAGATCCACAAA AGGA	CCTCGAACTCGCACTTGAA
<i>Prdm16</i>	PR/SET Domain 16	CAGCACGGTGAAGCCATT C	GCGTGCATCCGCTTGTG
<i>Rbp4</i>	Retinol binding protein 4	TGTAGCCTCCTTTCTCCAG CG	ACAGGTGCCATCCAGATTC TG
<i>Cxcl14</i>	Chemokine(C-X-C motif) ligand 14	TACCCACACTGCGAGGAG AAG	CGCTTCTCGTTCCAGGCATT G
<i>Trarg1</i>	Trafficking regulator of GLUT4-1	TGGCACGGCTACTCAGCA TCA	TGCCTCTGCTAGAAACAGC TCC
<i>Glut4</i>	Glucose transporter type 4	GGTGTGGTCAATACGGTC TTCAC	AGCAGAGCCACGGTCATCA AGA

Supplementary Table S4. RNAseq Top 15 DEGs from DESeq2 of CB-100 treated versus sham-treated NOD Mouse's ingWAT. Related to Figure 3D.

Gene Symbol	BaseMean	log2 FoldChange	lfcSE	Stat	pvalue	padj	Note
Prr32	98.984989	9.89392454	1.56387026	6.32656353	2.5068E-10	6.4319E-09	upregulated
Sprr2a3	84.7456472	9.67043129	1.87952704	5.14514082	2.6732E-07	3.1905E-06	upregulated
Sprr2f	71.8354655	9.43189703	1.87675419	5.02564324	5.0175E-07	5.5401E-06	upregulated
Sprr1a	237.263237	7.96854276	1.12842095	7.06167566	1.6451E-12	7.0183E-11	upregulated
Lep	6639.40122	7.78243891	0.80491122	9.66869225	4.0958E-22	8.8054E-20	upregulated
<i>Slc2a5</i>	353.175461	6.60632428	1.35415758	4.87854911	1.0687E-06	1.0717E-05	upregulated
<i>Fpr1</i>	323.351452	6.56658049	1.42605491	4.60471784	4.1303E-06	3.4666E-05	upregulated
<i>Alb</i>	450.504986	6.43586345	0.54351805	11.8411217	2.3923E-32	2.3144E-29	upregulated
<i>Sncg</i>	15023.3037	6.23226359	0.34513761	18.0573299	6.9084E-73	1.1362E-68	upregulated
<i>Pnpla3</i>	5753.84419	6.20018137	0.73360627	8.45164721	2.8722E-17	2.9803E-15	upregulated
<i>Areg</i>	1544.70625	6.18068349	1.2612098	4.90059899	9.5545E-07	9.7209E-06	upregulated
Scd1	672756.834	6.14968158	0.68303094	9.00351835	2.186E-19	3.1957E-17	upregulated
<i>Upk3a</i>	107.441587	6.04186451	1.76080707	3.4313041	0.00060069	0.00262152	upregulated
<i>Mup10</i>	134.373557	6.02375742	1.1716738	5.1411557	2.7305E-07	3.2518E-06	upregulated
<i>Mup22</i>	133.025014	6.00902777	1.16948656	5.13817599	2.7742E-07	3.2966E-06	upregulated
<i>Hamp2</i>	65.2044088	-5.37225207	0.74256854	-7.23468845	4.666E-13	2.1832E-11	downregulated
<i>Ighv1-49</i>	66.5498465	-4.50562545	0.86899177	-5.18488852	2.1614E-07	2.6519E-06	downregulated
<i>Ighe</i>	1259.95447	-3.86656127	0.98426646	-3.9283684	8.5524E-05	0.00048245	downregulated
<i>Igkv11-125</i>	65.3703606	-2.95852355	0.7937741	-3.72716059	0.00019365	0.00097307	downregulated
<i>Apoc3</i>	59.3517823	-2.90471797	0.68151176	-4.26216855	2.0245E-05	0.00013736	downregulated
<i>A530030E21Rik</i>	145.876251	-2.8646756	0.23770678	-12.0512993	1.9092E-33	2.0257E-30	downregulated
<i>Gm18748</i>	63.5887462	-2.72271781	0.49317453	-5.52079975	3.3746E-08	5.0941E-07	downregulated
<i>Gm47782</i>	203.285799	-2.71880525	0.44753582	-6.07505621	1.2394E-09	2.7125E-08	downregulated
<i>Gm31804</i>	270.517933	-2.70462141	0.42806294	-6.3182797	2.6449E-10	6.7389E-09	downregulated
<i>Abca13</i>	55.4327726	-2.6672388	0.48798094	-5.46586673	4.6065E-08	6.7283E-07	downregulated
<i>Ptgds</i>	62.7145289	-2.65517546	0.49570735	-5.35633664	8.4926E-08	1.163E-06	downregulated
<i>Gm12490</i>	63.6375533	-2.62447864	0.42457837	-6.18137625	6.3545E-10	1.4814E-08	downregulated
<i>Gm47780</i>	241.250346	-2.62399536	0.46867817	-5.59871464	2.1595E-08	3.4431E-07	downregulated
<i>Olfr109</i>	217.333967	-2.49909268	0.37270234	-6.70533142	2.0095E-11	6.7724E-10	downregulated
<i>Mir142b</i>	76.7799563	-2.48147157	0.45053798	-5.50779663	3.6335E-08	5.4475E-07	downregulated

Noteworthy genes are highlighted in red.

BaseMean = the average of the normalized counts taken over all samples / lfcSE = standard error of the log2FoldChange estimate/stat = Wald statistic / pvalue = Wald test p-value / padj = Benjamini-Hochberg adjusted p-value¹.

Supplementary Table S5. RNAseq Top 15 DEGs from DESeq2 of CB-100 treated versus sham-treated NOD Mouse's BAT. Related to Figure 3J.

Gene Symbol	BaseMean	log2 FoldChange	lfcSE	stat	pvalue	padj	Note
<i>Fosb</i>	377.940493	5.423568265	1.630662935	3.325989785	0.000881052	0.014228774	upregulated
<i>Scd1</i>	43378.4807	4.404576517	0.502375191	8.767504048	1.8267E-18	4.4462E-15	upregulated
<i>Egr3</i>	193.339786	4.170345034	1.138303094	3.663650792	0.000248646	0.005892108	upregulated
<i>Gm44502</i>	147.105008	3.430936505	0.600836449	5.710266926	1.12799E-08	2.66927E-06	upregulated
<i>Dio2</i>	1536.95743	3.073423038	1.144592535	2.685167816	0.00724934	0.060724803	upregulated
<i>Gm38357</i>	480.556497	3.009943113	0.745179096	4.039221079	5.3629E-05	0.001887874	upregulated
<i>Fos</i>	424.388827	2.951669149	1.39495136	2.115965642	0.03434773	0.16517545	upregulated
<i>Slco4a1</i>	133.237886	2.825701883	0.963917187	2.931477849	0.003373534	0.036218196	upregulated
<i>Fndc5</i>	65.938467	2.644053492	0.656213661	4.029257007	5.59534E-05	0.001957565	upregulated
<i>Akap5</i>	142.150916	2.628803173	0.313919397	8.374134244	5.56313E-17	1.05316E-13	upregulated
<i>Gk</i>	1773.065	2.573316009	0.462775949	5.560608789	2.68835E-08	5.45287E-06	upregulated
<i>A830018L16Rik</i>	183.331672	2.515879267	0.52175858	4.82192218	1.42181E-06	0.000114015	upregulated
<i>S100b</i>	336.242184	2.490030416	0.423136754	5.884694227	3.98791E-09	1.23538E-06	upregulated
<i>Gm43605</i>	122.466743	2.467060482	0.561606957	4.392859542	1.11869E-05	0.000552473	upregulated
<i>Gm42613</i>	51.4196396	2.441051139	0.56734788	4.302565015	1.68832E-05	0.000775286	upregulated
<i>Gm45061</i>	548.29461	-3.843311266	0.486025033	-7.90764057	2.62313E-15	4.06299E-12	downregulated
<i>Otof</i>	145.001663	-3.829071067	1.257713583	-3.044469837	0.002330908	0.027768239	downregulated
<i>Cyp2b10</i>	809.7713	-3.778733581	0.762610567	-4.954997669	7.23312E-07	6.52052E-05	downregulated
<i>Chrn4</i>	52.0726661	-3.728396563	1.523326905	-2.447535424	0.014383699	0.094914584	downregulated
<i>Itih4</i>	137.694373	-3.51309137	0.902616415	-3.892119967	9.93721E-05	0.002982145	downregulated
<i>Zim1</i>	682.570621	-3.441861698	0.478980903	-7.185801513	6.68141E-13	7.11486E-10	downregulated
<i>Gm45060</i>	132.597611	-3.383178152	0.358909528	-9.426270106	4.24931E-21	2.41333E-17	downregulated
<i>Gm16143</i>	60.2954912	-3.222388937	0.462843773	-6.962152515	3.35112E-12	2.48245E-09	downregulated
<i>BB365896</i>	1183.13087	-3.047122329	0.774020225	-3.936747687	8.25934E-05	0.002586812	downregulated
<i>Mycl</i>	297.128494	-2.999406415	0.550259653	-5.450892858	5.01176E-08	8.63586E-06	downregulated
<i>D630039A03Rik</i>	68.4987102	-2.973999314	1.189594744	-2.500010469	0.012418964	0.086271408	downregulated
<i>Cpne9</i>	182.564779	-2.824471637	0.495642026	-5.698612077	1.20787E-08	2.78103E-06	downregulated
<i>Tmem132b</i>	125.969361	-2.797054301	0.90575213	-3.088101266	0.002014398	0.025219015	downregulated
<i>Hmgcs2</i>	154.102529	-2.716866552	0.602274369	-4.51101141	6.45192E-06	0.000382662	downregulated
<i>Aldoc</i>	90.026831	-2.696693801	0.290174448	-9.293353778	1.49502E-20	5.09442E-17	downregulated

Noteworthy genes are highlighted in red.

BaseMean = the average of the normalized counts taken over all samples / lfcSE = standard error of the log2FoldChange estimate/stat = Wald statistic / pvalue = Wald test p-value / padj = Benjamini-Hochberg adjusted p-value¹.

Supplementary Table S6. Detailed information for key resources

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Antibodies		
Akt (pan) (40D4) Mouse mAb	Cell Signaling	Cat# 2920 RRID: AB_1147620
Anti-phospho-IRS1 (Tyr608) mouse/ (Tyr612) human Antibody	Sigma-Aldrich	Cat# 09-432 RRID: AB_1163457
a-sarcoglycan Antibody (F-7)	Santa Cruz	Cat# sc-390647
CD68 antibody	Abcam	Cat# ab125212 RRID: AB_10975465
GAPDH antibody	ProteinTech	Cat# 10494-1-AP RRID: AB_2263076
Glucagon Antibody	AvantGen	Cat# GLUN F7
GLUT4 Polyclonal Antibody	Invitrogen	Cat# PA5-23052 RRID: AB_11153908
Goat Anti-Mouse IgG (H L)-HRP Conjugate	Bio-Rad	Cat # 172-1011 RRID: AB_11125936

Goat Anti-Rabbit IgG (H+L)-HRP Conjugate	Bio-Rad	Cat# 1721019 RRID: AB_11125143
Human/Mouse Somatostatin Antibody	Biotechne R&D Systems	Cat# MAB2358 RRID: AB_2722572
Insulin Antibody (2D11-H5)	Santa Cruz	Cat# sc-8033 RRID: AB_627285
IRDye® 680RD Goat anti-Rabbit IgG Secondary Antibody	LI-COR	Cat# 926-68071 RRID: AB_10956166
IRS-1 (59G8) Rabbit mAb	Cell Signaling	Cat# 2390 RRID: AB_10692516
Nidogen-2 Antibody	ProteinTech	Cat# 13530-1-AP RRID: AB_10598468
Phospho-Akt (Ser473) (D9E) XP® Rabbit mAb	Cell Signaling	Cat # 4060 RRID: AB_2315049
UCP1	Abcam	Cat# ab234430 RRID: AB_2905638
Biological samples		
Human Islets (non-diabetic, Type 2 diabetic). See Table S1	Integrated Islet Distribution Program (IIDP)	N/A
Human islets (type 1 diabetic). See Table S1	Laboratory of Al Powers in Vanderbilt University Medical Center	N/A
Chemicals, peptides, and recombinant proteins		
3,3', 5-Triiodo-L-thyronine sodium salt hydrate (T3)	Sigma-Aldrich	Cat# T6397
3-Isobutyl-1-methylxanthine (IBMX)	Sigma-Aldrich	Cat# I7018
6x Laemmli SDS sample buffer	Bioland Scientific	Cat# SAB0301
Accutase	Innovative Cell Technologies	Cat# 07920
Adomeglivant	MedChemExpress	Cat# HY-19904/CS-5729
Antibiotic-Antimycotic (100X)	Thermo Fisher	Cat # 15240062
Collagenase P	Roche	Cat# 11 213 873 001
CYN 154806	TOCRIS	Cat# 1843
Dexamethasone (water soluble)	Sigma-Aldrich	Cat# D2915
Diva Decloaker	Biocare Medical	Cat# DV2004
DMEM Medium	Gibco	Cat# 11885-084
DMEM/F-12 medium	Gibco	Cat# 10565-018
Exendin-3	APExBIO	Cat# B6943
HBSS	Gibco	Cat# 14025-076
Histopaque 1077	Sigma-Aldrich	Cat# 10771
Histopaque 1119	Sigma-Aldrich	Cat# 11191
Humulin R	Lilly	Cat# HI-213
Indomethacin	Sigma-Aldrich	Cat# I7378

Insulin	Sigma-Aldrich	Cat# I19278
KYL	TOCRIS	Cat# 5290
Lipofectamine RNAiMAX		Cat# 13778075
Nidogen2	Biotechne R&D Systems	Cat# 6760-ND
Prime Western Blotting Detection Reagent	Cytiva Amersham™ ECL™	Cat # 45-002-401
ProLong Glass Antifade Mountant	Invitrogen	Cat# P36982
Protein standard mix 15-600kDa for testing of SEC/GFC columns	Sigma-Aldrich	Cat# 69385
Rh-Laminin 521	Gibco	Cat# A29249
RPMI 1640 medium	Gibco	Cat# 11879-020
S961	Phoenix Pharmaceuticals inc	Cat# 051-86
TRIzol Reagent	Invitrogen	Cat# 15596026
Western Blotting Detection Reagents	Cytiva Amersham™ ECL™	Cat # 45-000-875
Critical commercial assays		
Glucagon ELISA Kit	Crystal Chem	Cat# 81518
Glucagon Immunoassay	Promega	Cat# W8020
Glucose assay kit (fluorometric, high sensitivity)	Abcam	Cat# AB169559
Insulin Immunoassay	Promega	Cat# CS3037A01
TriFECTa RNAi Kit	Integrated DNA Technology	N/A
Ultra-sensitive Mouse Insulin ELISA Kit	Crystal Chem	Cat# 90080
Deposited data		
proteomic Raw Data Files	This publication	PXD051972
Brown adipose tissue CB-100 treated vs. sham RNA-seq Raw Data Files	This publication	GSE265915
inguinal white adipose tissue CB-100 treated vs. sham RNA-seq Raw Data Files	This publication	GSE265914
Experimental models: Cell lines		
3T3-L1	ATCC	Cat# CL-173 RRID: CVCL_0123
Alpha TC1 clone 6	ATCC	Cat# CRL-2934 RRID: CVCL_B036
AML12	ATCC	Cat# CRL-2254 RRID: CVCL_0140
C2C12	ATCC	Cat# CRL-1772 RRID: CVCL_0188
imBAT	Rosell et al ²	N/A
L6-GLUT4myc Rat Myoblast Cell Line	Kerafast	Cat # ESK202-FP RRID: CVCL_0P25

Experimental models: Organisms/strains		
C57BL/6	Jackson Laboratory	Cat# 000664 RRID: IMSR_JAX:000664
GCGCre-RFP	Marchand and Piston ³	N/A
NOD/ShiLtJ	Jackson Laboratory	Cat# 001976 RRID: IMSR_JAX:001976
Oligonucleotides		
Primer for <i>18S</i> , <i>Cidea</i> , <i>Cxcl14</i> , <i>Glut4</i> , <i>Nid2</i> , <i>Prdm16</i> , <i>Rbp4</i> , <i>Tbx1</i> , <i>Tmem26</i> , <i>Trarg1</i> , <i>Ucp1</i> , <i>Zic1</i> - See Table S3	This paper	N/A
DsiRNA_Nid2 13.1 & 13.2 (for nidogen-2 knockdown)	Integrated DNA Technologies	Cat# mm.Ri.Nid2.13.1 & Cat# mm.Ri.Nid2.13.2
Software and algorithms		
DIA-NN	Kistner, Grossmann, Sinn and Demichev ⁴	1.8.2 beta 27
Image Studio	LI-COR	Ver5.2
ImageJ	NIH	Java 1.8.0_172
MATLAB	MathWorks	R2021b
Orbitrap Eclipse	Thermo Fisher Scientific	N/A
Prism	GraphPad	10.1.2
QuantUMS	Kistner, Grossmann, Sinn and Demichev ⁴	N/A
R Studio	Posit	R version 4.2.1
Scaffold4 Viewer	Scaffold	Ver 4.11.1
SwissProt proteome	Expasy	N/A
Zen	Zeiss	Zen 3.5
Other		
μPAC™ Trapping column	PharmaFluidics	N/A
50 cm μPAC™ column	PharmaFluidics	N/A
Amicon Stirred Cells system	Milipore Sigma	Cat#UFSC40001
C18 ZipTips	Milipore Sigma	N/A
Capto Q resin	Cytiva	Cat#17531602
HiScale 26/20	Cytiva	Cat#28964514
LSM 880 confocal microscope	Zeiss	LSM 880
NTA ZetaView	Analytik	N/A
Optima LE-80K	Beckman Coulter	8043-30-1192
RSLCnano Ultimate 3000	Thermo Fisher Scientific	N/A
Superdex 200 Increase 10/300 GL	Cytiva	Cat#28990944
μPAC™ Trapping column	PharmaFluidics	N/A
50 cm μPAC™ column	PharmaFluidics	N/A
Amicon Stirred Cells system	Milipore Sigma	Cat#UFSC40001
C18 ZipTips	Milipore Sigma	N/A
Capto Q resin	Cytiva	Cat#17531602

HiScale 26/20	Cytiva	Cat#28964514
Airyscan Two-photon confocal microscope	Zeiss	LSM880
NTA ZetaView	Analytik	N/A
Optima LE-80K	Beckman Coulter	8043-30-1192
RSLCnano Ultimate 3000	Thermo Fisher Scientific	N/A
Superdex 200 Increase 10/300 GL	Cytiva	Cat#28990944

References

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