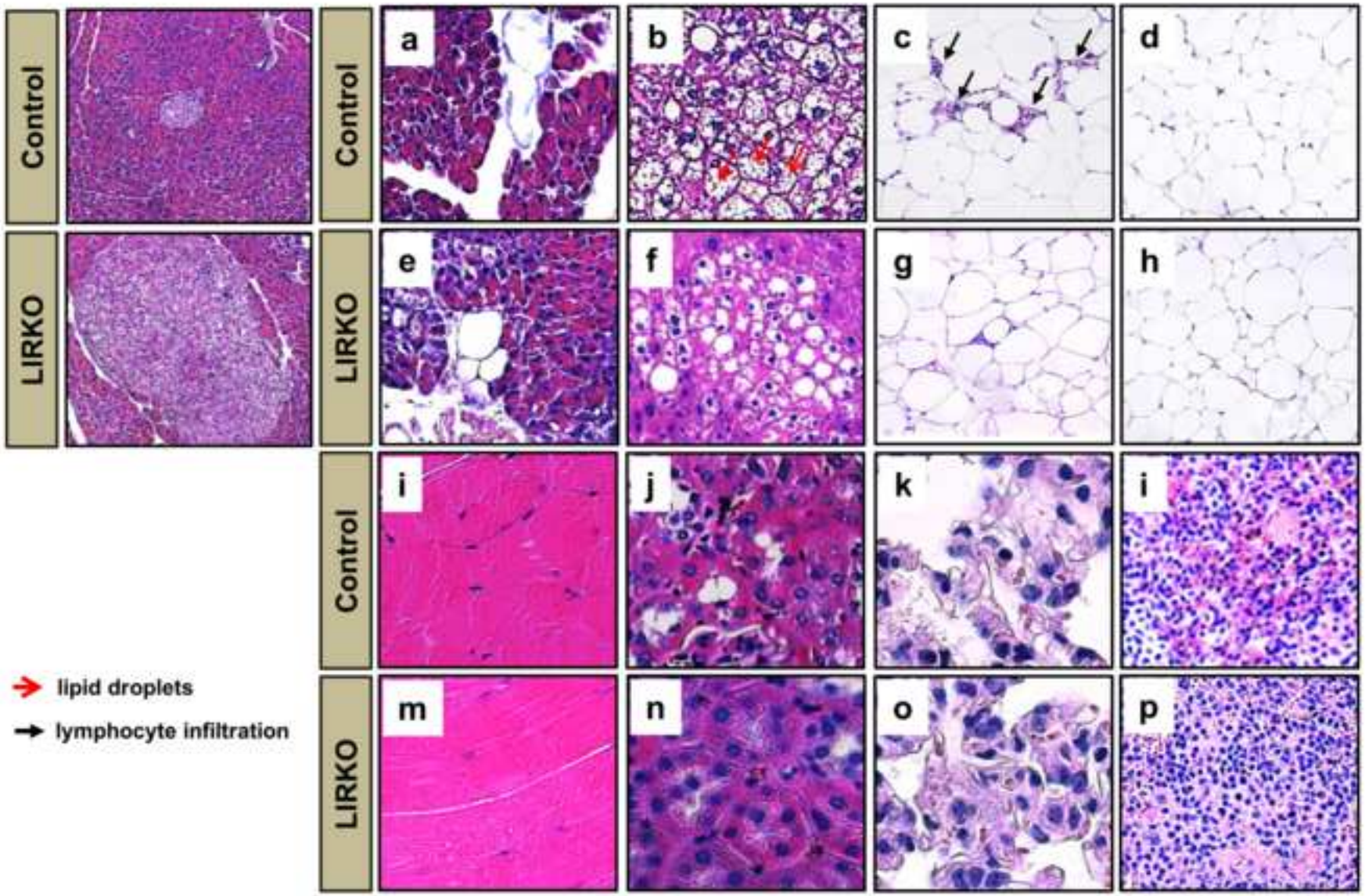
Figure S1

Figure S1: Hematoxylin and eosin staining of tissue sections from 12-month-old control and LIRKO mice



pancreas: a, e. liver: b,f. visceral adipose: c, g. subcutaneous adipose: d, h skeletal muscle: i, m. kidney: j, n. lung: k, o. spleen: i, p .

Figure S2

Figure S2: Weekly monitoring of body weight and blood glucose in parabionts

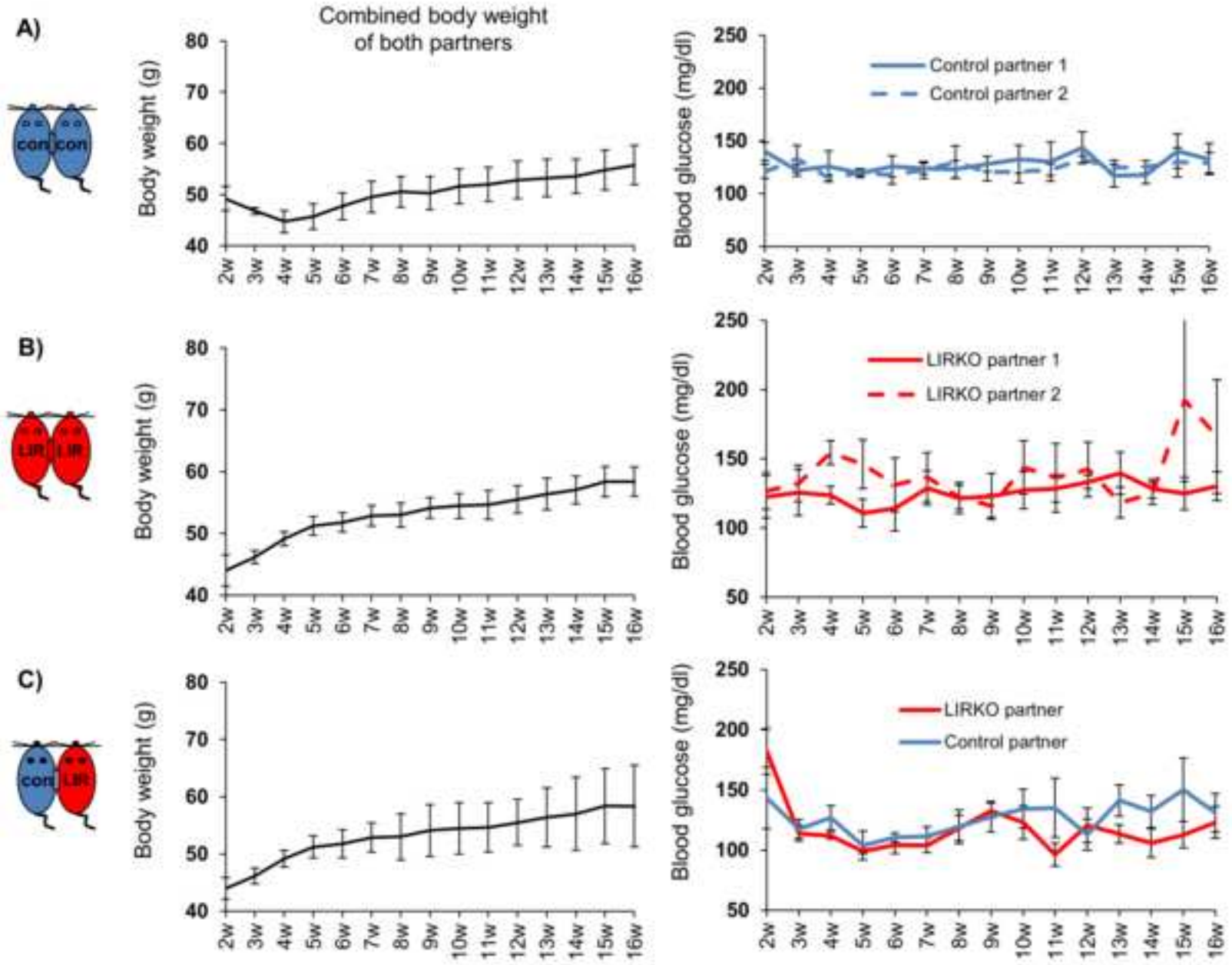


Figure S3

Figure S3: Blood glucose and insulin assays in parabiont pairs pre- and post-surgery

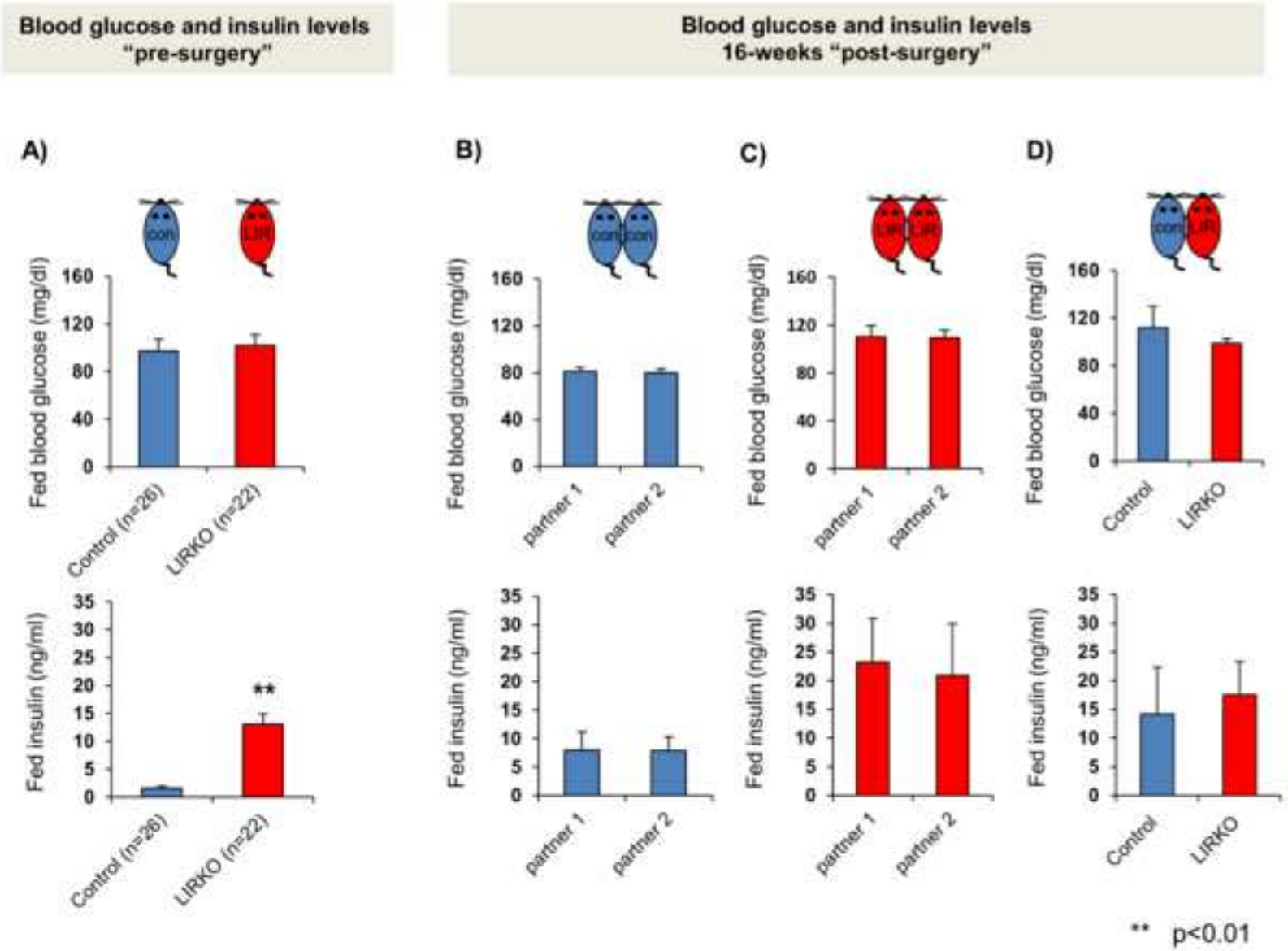


Figure S4

Figure S4: Quantification of pHH3+ insulin+ cells in parabiosis experiments. Single and parabiont animals were sacrificed and pancreases were dissected and immunostained with insulin, pHH3 and DAPI. ** p<0.01 n=5-6

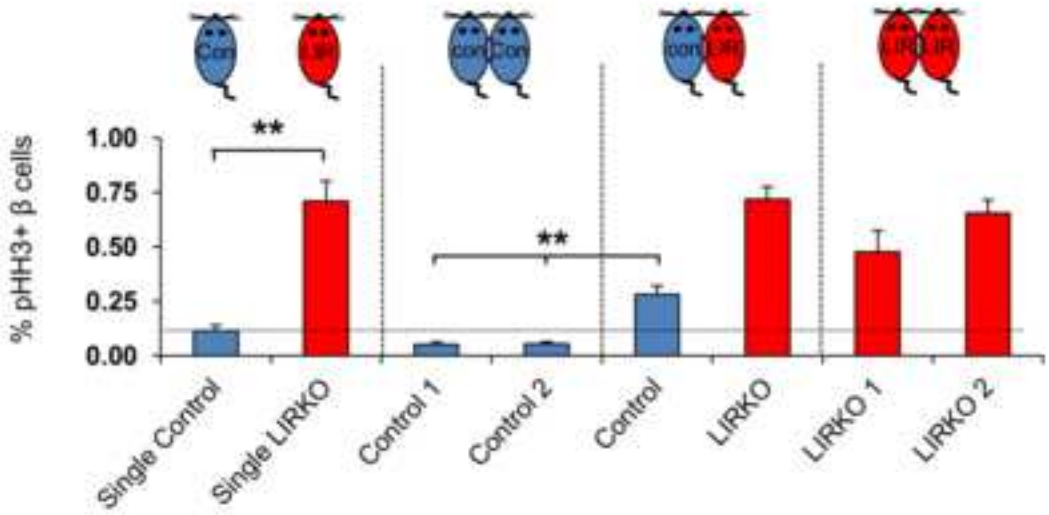


Figure S5

Figure S5: Quantification of Ki67+ insulin+ cells in serum-stimulated mouse islets. Islets were incubated for 24 or 48h with serum (diluted 1:10) from 3-month-old control or LIRKO animals. * $p<0.05$ n=4-5

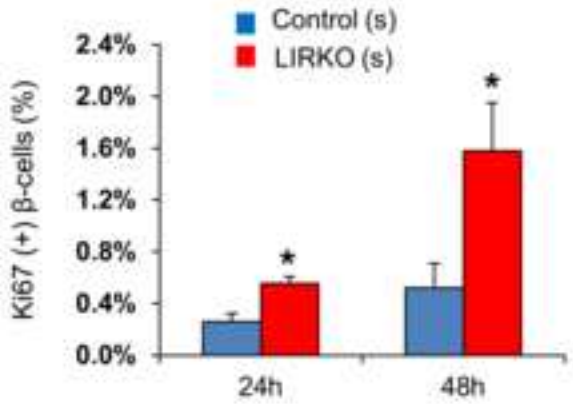


Figure S6

Figure S6: Glucose and insulin assays in culture media

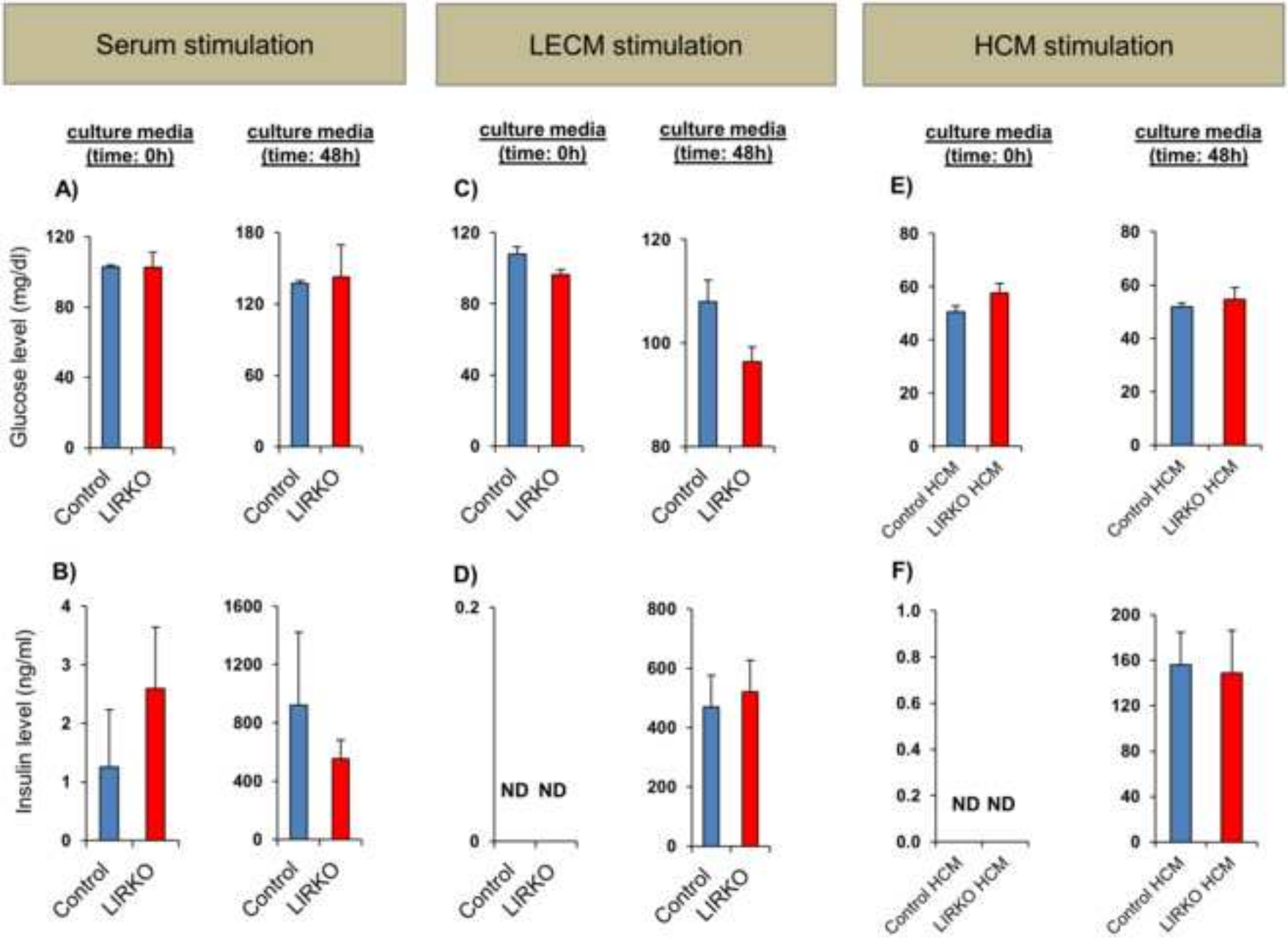


Table S1

Table S1: Assays of circulating growth factors, hormones, cytokines and chemokines in young vs. old Control and LIRKO mice.

	Control (3Mo)	LIRKO (3Mo)	p	Control (12Mo)	LIRKO (12Mo)	p
Growth factors						
IGF1 (ng/mL)	211.9 ±18.9	68.9 ±16.6	**0.0002**	525.1 ±35.6	194.4 ±18.6	**2.91E-06**
HGF (ng/mL)	5.3 ±0.41	4 ±0.69	0.145	2.1 ±0.3	4.3 ±0.8	**0.03**
EGF (ng/mL)	54.75 ±17.33	79.8 ±23.73	0.4	11.7 ±3.1	14.5 ±6.1	0.7
PDGFAA (ng/mL)	0.142 ±0.05	0.163 ±0.05	0.88	3.4 ±0.4	3.6 ±0.4	0.7
PDGFBB (ng/mL)	0.073 ±0.02	0.17 ±0.07	0.22	9 ±1.5	9.8 ±1.2	0.6
VEGF (pg/mL)	2.1 ±0.2	1.3 ±0.1	**0.006**	1.8 ±0.3	2.1 ±0.4	0.5
FGF21 (pg/mL)	58.6 ±12.6	43.6 ±11.1	0.4	1203 ±224.6	143.2 ±29.3	**0.001**
Hormones						
Insulin (ng/mL)	2.3 ±0.7	11.6 ±2.4	**0.01**	8.2 ±1	17.8 ±4.4	**0.06**
Amylin (pg/mL)	103.6 ±40.9	206.8 ±51.1	0.1	358.4 ±38	900.8 ±309.6	0.1
Glucagon (pM)	25.8 ±3.4	20.9 ±4.8	0.4	13.1 ±3.9	11.5 ±3.8	0.8
Ghrelin (pg/mL)	3.5 ±0.5	2.5 ± 0.4	0.1	1.7 ±0	4.5 ±1.9	0.2
PP (pg/mL)	11.8 ±2.9	19.7 ±4	0.1	18 ±4.8	42.2 ±17.4	0.2
PYY (pg/mL)	63.1 ±12	74.8 ±13	0.5	145.9 ±38.3	86.7 ±7.6	0.2
GIP (pg/mL)	108.5 ±11.4	152.9 ±18.7	0.06	284.5 ±25	95.2 ±13.9	**2.1E-05**
Total GLP-1 (pg/mL)	32.1 ±5	43.6 ±11.6	0.4	59.4 ±11.4	65.9 ±17.9	0.7
Active GLP-1 (pg/mL)	23.6 ±7.4	22.5 ±6.3	0.9	25.5 ±7.6	27.7 ±9.8	0.8
Leptin (ng/mL)	12.3 ±4	8.9 ±1.7	0.4	42.9 ±6.2	27.7 ±1.7	**0.04**
Resistin (ng/mL)	2.4 ±0.2	2.7 ±0.2	0.3	1.3 ±0.1	1.5 ±0.1	0.2
Adiponectin (µg/mL)	10.9 ±1.4	17.5 ±2.6	**0.04**	21.2 ±2.3	18.8 ±1.3	0.4
Osteopontin (ng/mL)	146.2 ±8.1	157.1 ±24.6	0.7	161.3 ±16.9	232.1 ±20.5	**0.01**
Osteocalcin (ng/mL)	12.6 ±1.2	12.6 ±2.9	1	11.8 ±2.2	12.9 ±2.7	0.8
Gastrin (pg/mL)	39.4 ±2.3	43.1 ±4.6	0.5	45.7 ±6.2	40.9 ±5.9	0.6
Cytokines & Chemokines						
IL-1a (pg/mL)	12.4 ±2.7	14.3 ±6.4	0.8	9.4 ±3.6	21.2 ±8.4	0.2
IL-1b (pg/mL)	6.6 ±2.9	3.2 ±0.6	0.3	3.3 ±0.4	5.8 ±2.5	0.3
IL-2 (pg/mL)	1.4 ±0.1	1.2 ±0.05	0.1	1.3 ±0.3	1.5 ±0.2	0.6
IL-3 (pg/mL)	1.4 ±0.07	1.3 ±0.1	0.6	1.4 ±0	2.36 ±1	0.3
IL-4 (pg/mL)	0.7 ±0.04	0.9 ±0.2	0.4	0.8 ±0.35	0.5 ±0.04	0.4
IL-5 (pg/mL)	7.3 ±1.8	8.3 ±2.1	0.7	2.7 ±1.2	1.9 ±0.9	0.6
IL-6 (pg/mL)	3.4 ±1.4	2.8 ±1.6	0.7	27.8 ±3.4	19.4 ±2.3	0.06
IL-7 (pg/mL)	1.4 ±0.2	3.5 ±1.8	0.2	17.5 ±9.1	15 ±9.8	0.8
IL-9 (pg/mL)	13.8 ±4.2	9.1 ±2.9	0.4	3.5 ±1	7.9 ±4.3	0.3
IL-10 (pg/mL)	11.8 ±1.4	9.7 ±1.6	0.3	11.2 ±2.5	12.8 ±3.5	0.7
IL-12(P40) (pg/mL)	16.7 ±2.5	10.2 ±2.5	0.08	6.3 ±2.2	4.3 ±1	0.4
IL-12 (p70) (pg/mL)	10.5 ±2.6	9.3 ±2.9	0.7	10.2 ±7.3	6.3 ±2.1	0.6
IL-13 (pg/mL)	103.4 ±12.7	84.6 ±14.6	0.3	83.8 ±12.7	134.1 ±33.2	0.2
IL-15 (pg/mL)	7.7 ±2.2	12.5. ±7	0.5	35.7 ±18	48 ±29.4	0.7
IL-17 (pg/mL)	1.3 ±0.2	0.9 ±0.3	0.2	2.5 ±1	1.4 ±0.3	0.3
IFN-g (pg/mL)	2.9 ±0.6	2 ±0.2	0.2	3 ±2.1	1.1 ±0.2	0.4
TNF-a (pg/mL)	2.4 ±0.5	2 ±0.5	0.5	2.9 ±0.08	4.7 ±1.6	0.3
PAI-1 (ng/mL)	1.4 ±0.2	1.3 ±0.1	0.5	1.6 ±0.3	1.3 ±0.3	0.3
G-CSF (pg/mL)	217.6 ±40.7	120.6 ±25	0.06	243.8 ±51.9	169.1 ±41.5	0.3
GM-CSF (pg/mL)	12.7 ±3.4	11.2 ±4.3	0.8	ND	ND	ND
M-CSF (pg/mL)	10.3 ±3.4	4.4 ±1.2	0.1	5.2 ±3	5.3 ±2.5	1
KC (pg/mL)	84.1 ±24.7	91.8 ±11.8	0.8	47.2 ±10.3	37.4 ±8.7	0.5
IP-10 (pg/mL)	92.8 ±10.6	68.9 ±9.5	0.1	178.8 ±20.5	167.3 ±15	0.6
Eotaxin (pg/mL)	344.6 ±23.4	342.4 ±39.4	1	295.8 ±19.1	337.1 ±42	0.4
MCP-1 (pg/mL)	9.9 ±1.8	5.4 ±0.8	**0.04**	3.9 ±0.4	5.8 ±2.4	0.5
MIP-1a (pg/mL)	16.3 ±4	11 ±3.9	0.3	11.6 ±2.8	7.9 ±3.6	0.4
MIP-1b (pg/mL)	24.8 ±4.7	13.6 ±4	0.08	17.6 ±5.2	14.3 ± 5.1	0.6
MIP-2 (pg/mL)	6.07 ±1.5	6.07 ±1.5	0.9	ND	ND	ND
MIG (pg/mL)	131.3 ±18.6	129 ±18.7	0.9	156.3 ±28.3	108.5 ±17.1	0.2
RANTES (pg/mL)	13.9 ±1.7	10.3 ±3	0.3	5.5 ±1.4	11.9 ±2.1	**0.03**
LIX (ng/mL)	0.9 ±0.3	0.7 ±0.2	0.7	0.3 ±0.1	0.4 ±0.1	0.7

Table S2: Histological characteristics of Control and LIRKO mice

	Control	LIRKO
Pancreas	mild pancreatitis	very mild pancreatitis
Liver	severe steatosis	no steatosis + focal dysplasia+ hyperplastic nodules
Skeletal muscle	normal	normal
Visceral adipose	severe lymphocyte infiltration	mild lymphocyte infiltration
Subcutaneous adipose	normal	normal
Spleen	normal	normal
Kidney	normal	normal
Lung	normal	normal

Table S3

Table S3: Islet-donor characteristics

UNOS ID	Donor	Gender	Ethnicity/Race	Age (years)	BMI	Diabetic donor status	Experiment
XHU114	**1**	Male	White	55	20.1	No	stimulation with serum
XHV125	**2**	Male	White	23	25.6	No	stimulation with serum
XHW271	**3**	Female	White	18	26.4	No	stimulation with serum
XJW381	**4**	Male	Hispanic/Latino	25	29.3	No	stimulation with serum
XFK479	**5**	Male	Hispanic/Latino	50	26.5	No	stimulation with serum
XKJ390	**6**	Unkown	Unkown	64	30	No	stimulation with serum
XLT243	**7**	Female	African american	41	42	No	stimulation with serum
YD3485	**8**	Male	White	54	19.5	No	stimulation with serum
YEC248	**9**	Male	African american	20	31.3	No	stimulation with serum
XLK052	**10**	Male	Unknown	53	31	T2D	stimulation with serum
XHK168A	**11**	Female	White	38	37.8	T2D on metformin	stimulation with serum
YAL054	**12**	Unknown	Unknown	65	31	No	stimulation with LECM
YAJ498A	**13**	Unknown	Unknown	54	34	T2D	stimulation with LECM
YBG327	**14**	Male	White	52	50	T2D	stimulation with HCM