SUPPLEMENTARY DATA

Protein expression by SILAC mouse

We used a previously described a SILAC method (Lanza IR, Zabielski P, Klaus KA, Morse DM, Heppelmann CJ, Bergen HR 3rd, Dasari S, Walrand S, Short KR, Johnson ML, Robinson MM, Schimke JM, Jakaitis DR, Asmann YW, Sun Z, Nair KS. Chronic caloric restriction preserves mitochondrial function in senescence without increasing mitochondrial biogenesis. Cell Metab.2012 Dec 5;16(6):777-88) for comparing the relative expression of quadriceps muscle tissue proteins between ND, STZ-I and STZ+I mice (n=6 per group). The reference labeled mice were generated by feeding female DBA2H strain mice (F0 parental generation) an in-house designed diet containing [$^{13}C_6$]-lysine stable isotope labeled amino acid (Cambridge Isotope Laboratories, Cambridge, MA) as the only source of biologically available lysine. When the plasma free lysine enrichment approached the value of that of the chow enrichment (by GC-MS/MS), all animals were bred to obtain fully labeled pups (F1 generation). Mice from F1 generation were put on [$^{13}C_6$]-lysine diet until sacrificed at 14 weeks. We observed >98% labeling of lysine in muscle tissue, measured at peptide level.

Quadriceps muscle samples from ND, STZ-I and STZ+I mice and fully labeled reference mice were pulverized into fine powder in liquid nitrogen. Muscle powder was suspended in RIPA buffer containing 5mM TCEP and protease and phosphatase inhibitors (Complete Mini protease inhibitors and PhosphoSTOP phosphatase inhibitors, ROCHE Applied Science, Indianapolis, IN) and sonicated on ice (Model 100 Sonic Dismembrator, Fisher Scientific, Waltham, MA). After incubation at 4°C for 30 minutes, samples were centrifuged at 15000g to remove cell debris. Protein content in the resulting supernatant was measured using Pierce 660nM Protein Assay Kit.

Samples were prepared for SDS-PAGE in NuPAGE LDS Sample Buffer with 5mM TCEP at a final protein concentration of 1μg/μl. After heating at 70°C for 10 minutes, samples from experimental animals were mixed in 1:1 (protein/protein) ratio with a reference sample obtained from a labeled animal. 15μg of each combined protein sample was resolved on NuPAGE Novex Bis-Tris Midi precast gels. ANOVA analysis of Vinculin reference protein expression data obtained by LC-MS/MS revealed no significant difference between the amounts of samples loaded in the lanes (Table S1). Gel lanes were cut into 8 sections and the excised gel fractions were incubated in 200 mM Tris for 30 minutes prior to destaining with 50 mM Tris/50% acetronitrile (ACN) for 2 hours. Fractions were then dehydrated with 100% ACN until gel pieces appeared opaque. Proteins were reduced with 20 mM DTT in 50 mM Tris for 60mins at 60°C, followed by dehydration with 100% ACN and alkylation with 40 mM iodoacetamide in 50 mM Tris for 60mins at room temperature. Proteins in the samples were digested overnight at 37°C using 0.2 ug of trysin (Promega, Madison, WI) in 20 mM Tris and 0.0002% zwittergent 3-16. Peptides were extracted using 2% trifluoroacetic acid (TFA) for 30 minutes followed by two ACN extractions, each for another 30 minutes. The peptide-containing fractions were dried to completeness under vacuum and stored at -20°C until further analysis.

LC-MS/MS

Samples were brought up in 0.15% formic acid (FA)/0.05% TFA/ 0.002% zwittergent 3-16. Peptides were loaded onto an OptiPak 0.25 uL cartridge (Optimize Technologies, Oregon City, OR), custom-packed with Michrom Magic C8 (5 um, 200 A), using a 15μL/min flow of 0.15% FA and 0.05 % TFA. After loading and washing, the column was placed in line with a 180mmX0.075mm spray tip packed with Magic C18 (5u, 200A, Michrom BioResources, Auburn, CA). After an initial hold for 5 minutes at 5% B, a gradient to 40%B in 60 minutes was performed, followed by a second gradient to 90% B before re-equilibrating at initial conditions. Mobile phase A was water/ACN/FA (98/2/0.1 by volume). Mobile phase B was ACN/isopropanol/water/FA (80/10/10/0.1 by volume). Survey scans were acquired in the Orbitrap (Thermo Scientific Velos) at 60,000 resolving power using a target ion population of 1e6 charges. Data-dependent MS/MS was conducted on the top 5 doubly- or triply-charged precursors using an isolation width setting of 2.0, normalized collision energy of 35%, and a linear ion trap target ion population of 1e4 charges. Precursor masses selected for tandem MS experiments were placed on an exclusion list for 45 seconds.

Elucidator analysis

Data files were imported into the Rosetta Elucidator software (Seattle, WA) and the multidimensional labeled-pair pipeline was used for analysis. Peptide peaks were detected from MS1 data and detected peaks were aligned across the sample runs of the same gel section. Peptide peaks with peak time score > 0.8, peak m/z score > 0.9, peak confidence score > 0.6, and charge state < 5 and > 1 were selected for identification. MS/MS spectra present in these peptide peaks were identified using Mascot database search engine (Matrix Science, London, UK) configured to use mouse SwissProt database appended with common contaminants and a reverse decoy database. Mascot was configured to use a peptide precursor tolerance of 10 ppm, fragment tolerance of 0.6 Da and a maximum of 2 missed cleavages. The software was instructed to use the following variable modifications during the search: carbamidomethylation of cysteine, oxidation of methionine, and SILAC labeled [$^{13}C_6$]-lysine. Peptide peaks were annotation using the PeptideProphet algorithm in Elucidator configured to use 5% FDR. SILAC labeled pairs were detected using up to three [$^{13}C_6$]-lysine labels with a 20 ppm m/z tolerance and 0.2 minute retention time tolerance. Light/heavy ratios were calculated for each labeled pair and the peptide rations were merged into protein ratios for each mouse group using Elucidator's weighted statistics.

In the labeled-pair pipeline, Elucidator was designed to report differences between a pair of labeled and unlabeled groups. In our study, we used the SILAC labeled animal as an internal standard to normalize the data and compare the normalized ratios across the experimental conditions. To compare ND, STZ-I and STZ+I groups, a z-statistic was calculated from the difference between two log-ratios divided by the pooled error, and used to calculate a p-value as a measure of significance for the difference between any two groups. Peptide pairs with the highest detector signal had highest impact on the estimation of L/H protein ratio. Only the proteins present in all experimental animals with at least one "light" (unlabeled) and "heavy" ([$^{13}C_6$]-lysine labeled) peptide pair were used in the analysis. The L/H protein ratio value was calculated for each animal, and used to calculate the intragroup ratio estimation error (σ) of a given protein.

$$\sigma_{\mathbf{x}} = \frac{\log_{10} \frac{L}{H} protein\ x\ ratio}{\frac{I_H x - I_L x}{\sqrt{\boldsymbol{\sigma}_H{}^2 x + \boldsymbol{\sigma}_L{}^2 x}}}$$

Where:

$\sigma_{\mathbf{x}}$ – ratio estimation error for the protein x, $\log_{10}$ scale.

$\log_{10} \frac{L}{H} protein\ x\ ratio$ - "light" (sample) to "heavy" (reference) ratio of the protein x, $\log_{10}$ scale.

$I_L x$ – mean detector intensity of "light" (sample) version of protein x.

$I_H x$ – mean detector intensity of "heavy" (reference) version of protein x.

$\sigma_L{}^2 x$ – error value for "light" (sample) version of protein x.

$\sigma_H{}^2 x$ – error value for "heavy" (reference) version of protein x.

SUPPLEMENTARY DATA

The group ratio estimation error (σ) of a given protein, together with intragroup ratio values were used to calculate individual protein p-value according to the equations:

$$s_p\ (A,B) = \sqrt[2]{\frac{(2 * (\sigma_x\ A)^2) + (2 * (\sigma_x\ B)^2)}{n-2}}$$

$$Z - test = \left|\frac{\left(\log_{10}\frac{L}{H} protein\ x\ ratio\ A\right) - \left(\log_{10}\frac{L}{H} protein\ x\ ratio\ B\right)}{s_p\ (A,B)}\right|$$

$$p - value\ = 2 * \left(1 - \frac{1}{\sqrt{2\pi}} e^{\frac{z-test^2}{2}}\right)$$

Where:

s_p (A,B) – sample standard deviation between groups A and B, calculated from pooled variance.

$E\ protein\ x\ A$ – Ratio estimation error for the protein x in group A

$E\ protein\ x\ B$ – Ratio estimation error for the protein x in group B

n – total number of animals in both groups

$\frac{L}{H} protein\ x\ ratio\ A$ – mean sample (light) to reference (heavy) ratio of the protein X in group A

The difference in the protein expression between the groups was calculated as a “ratio of the ratios” giving the relative change in the expression of the given protein between the experimental groups:

$$Protein\ x\ ratio\ \left({}^{A}/_{B}\right) = \frac{\frac{L}{H} protein\ x\ ratio\ A}{\frac{L}{H} protein\ x\ ratio\ B}$$

where “L/H protein x ratio A” is mean, weighted, L/H ratio of protein x in group A and “L/H protein x ratio B” is mean, weighted, L/H ratio of protein x in group B.

Supplementary Table S1. Results of MS/MS analysis of Vinculin (VINC) loading control/housekeeping protein expression in experimental animals. The even mixing of experimental samples (light, L) with SILAC reference sample (heavy, H), is confirmed by the lack of statistical difference in Light/Heavy ratio value between animals (based on 5 L/H peptide pairs for each animal). The even loading of samples was proven by the analysis of light only (experimental) peptides (value based on mean signal intensity of 15 VINC light peptides per animal), which shows no statistical difference. N=6 per group.

	VINC L (experimental)/H (reference) peptide ratio		VINC light (experimental) peptides intensity	
Group	**Mean**	**SD**	**Mean**	**SD**
ND	0.966	0.063	2.26E+05	2.54E+04
STZ-I	0.958	0.061	2.27E+05	3.31E+04
STZ+I	0.992	0.066	2.21E+05	3.70E+04

ANOVA	**SS**	**df**	**MS**	**F**	**p**	**SS**	**df**	**MS**	**F**	**p**
Effect	0	2	0	0.477	0.629	1.04E+8	2	5.22E+7	0.050	0.951
Error	5.98E-02	15	3.99E-03			1.56E+10	15	1.04E+9		

Supplementary Table S2A. Individual protein differential expression data from figure **2A volcano plot (STZ-I vs. ND comparison)** of 149 significantly affected proteins implicated in skeletal muscle energy metabolism. Table lists protein symbols, names and accession numbers as given by UniProt database, together with their expression ratio (in log2 scale), p-value (base and in –log10 scale) and Ingenuity IPA protein group affiliation (Group). Proteins are listed in the alphabetical order by their respective symbols.

Symbol	Entrez Gene Name	Accession #	Log2 (STZ-I vs ND)	p-value (STZ-I vs ND)	-log10 p-value (STZ-I vs ND)	Group
ACAA2	acetyl-CoA acyltransferase 2	Q8BWT1	-0.672	1.8E-42	41.738	FA metabolism
ACAD9	acyl-CoA dehydrogenase family, member 9	Q3ULL9	-0.418	2.3E-02	1.631	FA metabolism
ACADL	acyl-CoA dehydrogenase, long chain	P51174	-0.461	4.7E-19	18.330	FA metabolism
ACADM	acyl-CoA dehydrogenase, C-4 to C-12 straight chain	Q91WS8	-0.512	8.0E-13	12.096	FA metabolism
ACADVL	acyl-CoA dehydrogenase, very long chain	B1AR27	-0.246	2.2E-16	15.654	FA metabolism
ACAT1	acetyl-CoA acetyltransferase 1	Q8QZT1	-0.44	7.9E-25	24.103	FA metabolism
ACO2	aconitase 2, mitochondrial	Q99KI0	0.073	3.8E-08	7.420	Respiratory chain/TCA cycle
ACSL1	acyl-CoA synthetase long-chain family member 1	P41216	-0.235	5.8E-19	18.236	FA metabolism
ADCK3	aarF domain containing kinase 3	Q60936	0.285	3.6E-03	2.444	
AGL	amylo-alpha-1, 6-glucosidase, 4-alpha-glucanotransferase	Q8CE68	-0.125	4.5E-02	1.345	Glycolysis/Glycogen degradation
AIFM1	apoptosis-inducing factor, mitochondrion-associated, 1	Q9Z0X1	-0.32	4.9E-03	2.309	
ALDH2	aldehyde dehydrogenase 2 family (mitochondrial)	P47738	-0.156	9.1E-03	2.040	FA metabolism
ALDOA	aldolase A, fructose-bisphosphate	Q5FWB7	0.187	4.2E-06	5.381	Glycolysis/Glycogen degradation
ATP5A1	ATP synthase, H+ transporting, mitochondrial F1 complex, alpha subunit 1, cardiac muscle	Q03265	-0.185	1.0E-07	7.001	Respiratory chain/TCA cycle
ATP5B	ATP synthase, H+ transporting, mitochondrial F1 complex, beta polypeptide	P56480	-0.202	4.4E-16	15.353	Respiratory chain/TCA cycle
ATP5C1	ATP synthase, H+ transporting, mitochondrial F1 complex, gamma polypeptide 1	A2AKV3	-0.15	5.2E-05	4.286	Respiratory chain/TCA cycle
ATP5F1	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit B1	Q80W36	-0.238	6.7E-08	7.171	Respiratory chain/TCA cycle
Atp5h	ATP synthase, H+ transporting, mitochondrial F0 complex, subunit d	Q9DCX2	-0.3	5.1E-12	11.292	Respiratory chain/TCA cycle
ATP5I	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit E	Q06185	-0.211	2.9E-04	3.532	Respiratory chain/TCA cycle

ATP5L	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit G	Q9CQY3	-0.286	1.3E-04	3.876	Respiratory chain/TCA cycle
ATP5O	ATP synthase, H+ transporting, mitochondrial F1 complex, O subunit	Q9DB20	-0.201	2.9E-05	4.544	Respiratory chain/TCA cycle
CAPZA2	capping protein (actin filament) muscle Z-line, alpha 2	P47754	0.707	5.6E-22	21.251	
CASQ1	calsequestrin 1 (fast-twitch, skeletal muscle)	O09165	0.446	1.9E-04	3.712	
CAT	catalase	P24270	1.398	1.5E-09	8.818	
CD36	CD36 molecule (thrombospondin receptor)	Q08857	0.729	3.2E-14	13.495	FA transport and uptake
CHCHD3	coiled-coil-helix-coiled-coil-helix domain containing 3	Q9D9P1	-0.315	2.0E-04	3.699	
CISD1	CDGSH iron sulfur domain 1	Q91WS0	-0.13	2.6E-02	1.578	
CKMT2	creatine kinase, mitochondrial 2 (sarcomeric)	Q6P8J7	-0.646	4.5E-88	87.347	
COQ9	coenzyme Q9 homolog (S. cerevisiae)	Q8K1Z0	-0.337	2.5E-09	8.595	Respiratory chain/TCA cycle
COX1	cytochrome c oxidase subunit I	Q9MD68	-0.392	2.6E-09	8.588	Respiratory chain/TCA cycle
COX2	cytochrome c oxidase subunit II	P00405	-0.331	1.6E-05	4.790	Respiratory chain/TCA cycle
COX4I1	cytochrome c oxidase subunit IV isoform 1	P19783	-0.321	2.6E-04	3.588	Respiratory chain/TCA cycle
COX5A	cytochrome c oxidase subunit Va	P12787	-0.386	1.3E-02	1.876	Respiratory chain/TCA cycle
COX5B	cytochrome c oxidase subunit Vb	P19536	-0.374	1.5E-04	3.824	Respiratory chain/TCA cycle
COX6C	cytochrome c oxidase subunit VIc	Q9CPQ1	-0.398	3.3E-02	1.487	Respiratory chain/TCA cycle
CPT1B	carnitine palmitoyltransferase 1B (muscle)	Q3UIM5	-0.226	1.4E-10	9.842	FA metabolism
CPT2	carnitine palmitoyltransferase 2	P52825	-0.345	1.0E-04	4.000	FA metabolism
CRAT	carnitine O-acetyltransferase	P47934	-0.268	1.2E-10	9.907	
CS	citrate synthase	Q9CZU6	-0.211	3.0E-10	9.526	Respiratory chain/TCA cycle
CYC1	cytochrome c-1	Q9D0M3	-0.365	1.3E-05	4.903	Respiratory chain/TCA cycle
CYCS	cytochrome c, somatic	P62897	-0.259	7.8E-09	8.111	Respiratory chain/TCA cycle
DECR1	2,4-dienoyl CoA reductase 1, mitochondrial	Q9CQ62	-0.296	2.3E-07	6.646	
DLAT	dihydrolipoamide S-acetyltransferase	Q8BMF4	-0.251	3.6E-19	18.439	
DLD	dihydrolipoamide dehydrogenase	O08749	-0.114	1.6E-04	3.801	Respiratory chain/TCA cycle
DLST	dihydrolipoamide S-succinyltransferase (E2 component of 2-oxo-glutarate complex)	Q9D2G2	-0.318	1.1E-05	4.979	Respiratory chain/TCA cycle
ECHS1	enoyl CoA hydratase, short chain, 1, mitochondrial	Q8BH95	-0,310	7,98E-03	2,098	FA metabolism
ECI1	enoyl-CoA delta isomerase 1	Q8QZV3	-0.289	6.8E-08	7.166	FA metabolism

ENO1	enolase 1, (alpha)	P17182	0.167	1.8E-08	7.750	Glycolysis/Glycogen degradation
ENO2	enolase 2 (gamma, neuronal)	P17183	0.121	3.2E-04	3.498	Glycolysis/Glycogen degradation
ENO3	enolase 3 (beta, muscle)	P21550	0.113	5.8E-13	12.238	Glycolysis/Glycogen degradation
ETFA	electron-transfer-flavoprotein, alpha polypeptide	Q99LC5	-0.286	3.8E-10	9.421	Respiratory chain/TCA cycle
ETFB	electron-transfer-flavoprotein, beta polypeptide	Q9DCW4	-0.373	3.6E-14	13.447	Respiratory chain/TCA cycle
FABP3	fatty acid binding protein 3, muscle and heart (mammary-derived growth inhibitor)	Q5EBJ0	0.29	1.6E-06	5.807	FA transport and uptake
FABP4	fatty acid binding protein 4, adipocyte	Q542H7	0.53	3.9E-26	25.411	FA transport and uptake
FBP2	fructose-1,6-bisphosphatase 2	Q3TKP4	0.431	1.8E-07	6.745	Glycolysis/Glycogen degradation
FH	fumarate hydratase	Q3UIA9	-0.237	3.2E-04	3.498	Respiratory chain/TCA cycle
Gapdh/LOC100042025	glyceraldehyde-3-phosphate dehydrogenase	P16858	0.102	1.3E-14	13.893	Glycolysis/Glycogen degradation
GBAS	glioblastoma amplified sequence	Q3TD78	-0.304	1.2E-04	3.928	
GLUD1	glutamate dehydrogenase 1	P26443	0.206	2.4E-02	1.613	
GOT2 (FABPpm)	glutamic-oxaloacetic transaminase 2, mitochondrial (aspartate aminotransferase 2)	P05202	-0.377	1.1E-19	18.963	FA transport and uptake
GPD1	glycerol-3-phosphate dehydrogenase 1 (soluble)	P13707	0.136	1.1E-13	12.971	Glycolysis/Glycogen degradation
GPD2	glycerol-3-phosphate dehydrogenase 2 (mitochondrial)	Q64521	0.11	1.8E-02	1.745	Glycolysis/Glycogen degradation
GPI	glucose-6-phosphate isomerase	P06745	0.145	4.3E-14	13.369	Glycolysis/Glycogen degradation
GSTM5	glutathione S-transferase mu 5	P10649	0.303	3.2E-07	6.495	
HADH	hydroxyacyl-CoA dehydrogenase	Q61425	-0.334	8.7E-05	4.060	FA metabolism
HADHA	hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), alpha subunit	Q8BMS1	-0,213	1,58E-12	11,802	FA metabolism
HADHB	hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), beta subunit	Q99JY0	-0.162	2.1E-13	12.688	FA metabolism
HIBADH	3-hydroxyisobutyrate dehydrogenase	Q99L13	-0.38	4.8E-03	2.316	
HIBCH	3-hydroxyisobutyryl-CoA hydrolase	Q8QZS1	-0.255	1.7E-03	2.767	
HSD17B10/M/SCHAD	hydroxysteroid (17-beta) dehydrogenase 10 / short chain L-3-hydroxyacyl-CoA dehydrogenase	Q99N15	-0.162	3.3E-03	2.479	FA metabolism
HSP90AB1	heat shock protein 90kDa alpha (cytosolic), class B member 1	Q71LX8	-0.291	1.4E-13	12.854	
HSPA9	heat shock 70kDa protein 9	P38647	-0.423	9.3E-20	19.030	

	(mortalin)					
HSPD1	heat shock 60kDa protein 1 (chaperonin)	P63038	-0.248	3.1E-18	17.509	
HSPE1	heat shock 10kDa protein 1 (chaperonin 10)	Q64433	-0.348	7.8E-04	3.107	
IDH2	isocitrate dehydrogenase 2 (NADP+), mitochondrial	P54071	0.472	3.9E-19	18.409	
IDH3A	isocitrate dehydrogenase 3 (NAD+) alpha	Q9D6R2	-0.303	4.2E-15	14.375	Respiratory chain/TCA cycle
IDH3B	isocitrate dehydrogenase 3 (NAD+) beta	Q91VA7	-0.319	3.5E-24	23.457	Respiratory chain/TCA cycle
IDH3G	isocitrate dehydrogenase 3 (NAD+) gamma	P70404	-0.392	2.1E-10	9.688	Respiratory chain/TCA cycle
IMMT	inner membrane protein, mitochondrial	Q3TVZ5	-0.321	3.7E-39	38.431	
IVD	isovaleryl-CoA dehydrogenase	Q9JHI5	-0.343	3.3E-03	2.481	FA metabolism
LETM1	leucine zipper-EF-hand containing transmembrane protein 1	Q9Z2I0	-0.5	9.4E-05	4.028	
LRPPRC	leucine-rich pentatricopeptide repeat containing	Q99KF9	-0.711	4.6E-04	3.339	
MDH1	malate dehydrogenase 1, NAD (soluble)	P14152	0.155	6.9E-03	2.161	Glycolysis/Glycogen degradation/TCA Cycle
MDH2	malate dehydrogenase 2, NAD (mitochondrial)	P08249	-0.198	9.9E-14	13.004	Respiratory chain/TCA cycle
MPC2	mitochondrial pyruvate carrier 2	Q9D023	-0.514	3.4E-06	5.474	
ND5	NADH dehydrogenase, subunit 5 (complex I)	Q9MD82	-0.447	2.1E-03	2.682	Respiratory chain/TCA cycle
NDUFA10	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 10, 42kDa	Q99LC3	-0.334	4.9E-09	8.311	Respiratory chain/TCA cycle
NDUFA12	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 12	Q5M9K5	-0.375	1.7E-02	1.759	Respiratory chain/TCA cycle
NDUFA13	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 13	Q9ERS2	-0.367	3.2E-05	4.498	Respiratory chain/TCA cycle
NDUFA2	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 2, 8kDa	Q9CQ75	-0.485	8.4E-04	3.077	Respiratory chain/TCA cycle
NDUFA5	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 5, 13kDa	Q9CPP6	-0.414	3.0E-08	7.527	Respiratory chain/TCA cycle
NDUFA6	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 6, 14kDa	Q9CQZ5	-0.371	6.0E-12	11.223	Respiratory chain/TCA cycle
NDUFA7	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 7, 14.5kDa	Q9Z1P6	-0.432	4.7E-02	1.325	Respiratory chain/TCA cycle
NDUFA8	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 8, 19kDa	Q9DCJ5	-0.363	1.3E-05	4.879	Respiratory chain/TCA cycle
NDUFA9	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 9, 39kDa	Q9DC69	-0.435	1.6E-07	6.785	Respiratory chain/TCA cycle
NDUFB11	NADH dehydrogenase	B1AV40	-0.521	3.9E-02	1.405	Respiratory chain/TCA

	(ubiquinone) 1 beta subcomplex, 11, 17.3kDa					cycle
NDUFB3	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 3, 12kDa	Q9CQZ6	-0.432	1.8E-03	2.757	Respiratory chain/TCA cycle
NDUFB4	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15kDa	Q9DBH2	-0.395	1.4E-02	1.863	Respiratory chain/TCA cycle
NDUFB5	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 16kDa	Q9CQH3	-0.332	4.4E-10	9.353	Respiratory chain/TCA cycle
NDUFB7	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 7, 18kDa	Q9CR61	-0.581	1.6E-02	1.788	Respiratory chain/TCA cycle
NDUFB8	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 8, 19kDa	Q9D6J5	-0.301	3.9E-02	1.407	Respiratory chain/TCA cycle
NDUFC2	NADH dehydrogenase (ubiquinone) 1, subcomplex unknown, 2, 14.5kDa	Q9D846	-0.267	4.8E-02	1.316	Respiratory chain/TCA cycle
NDUFS1	NADH dehydrogenase (ubiquinone) Fe-S protein 1, 75kDa (NADH-coenzyme Q reductase)	Q91VD9	-0.333	2.0E-15	14.699	Respiratory chain/TCA cycle
NDUFS2	NADH dehydrogenase (ubiquinone) Fe-S protein 2, 49kDa (NADH-coenzyme Q reductase)	Q91WD5	-0.327	2.9E-09	8.536	Respiratory chain/TCA cycle
NDUFS3	NADH dehydrogenase (ubiquinone) Fe-S protein 3, 30kDa (NADH-coenzyme Q reductase)	Q9DCT2	-0.399	2.9E-02	1.536	Respiratory chain/TCA cycle
NDUFS4	NADH dehydrogenase (ubiquinone) Fe-S protein 4, 18kDa (NADH-coenzyme Q reductase)	Q9CXZ1	-0.312	3.0E-05	4.529	Respiratory chain/TCA cycle
NDUFS5	NADH dehydrogenase (ubiquinone) Fe-S protein 5, 15kDa (NADH-coenzyme Q reductase)	Q99LY9	-0.415	2.8E-03	2.561	Respiratory chain/TCA cycle
NDUFS6	NADH dehydrogenase (ubiquinone) Fe-S protein 6, 13kDa (NADH-coenzyme Q reductase)	P52503	-0.418	1.4E-02	1.851	Respiratory chain/TCA cycle
NDUFV1	NADH dehydrogenase (ubiquinone) flavoprotein 1, 51kDa	Q91YT0	-0.325	9.3E-14	13.032	Respiratory chain/TCA cycle
NDUFV2	NADH dehydrogenase (ubiquinone) flavoprotein 2, 24kDa	Q9D6J6	-0.41	1.8E-02	1.742	Respiratory chain/TCA cycle
OGDH	oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide)	Q60597	-0.215	6.7E-08	7.171	Respiratory chain/TCA cycle
OXCT1	3-oxoacid CoA transferase 1	Q9D0K2	-0.52	1.9E-21	20.726	
PARK7	parkinson protein 7	Q99LX0	0.218	2.1E-05	4.682	

PDHA1	pyruvate dehydrogenase (lipoamide) alpha 1	Q3UFJ3	-0.392	3.5E-04	3.457	Respiratory chain/TCA cycle
PDK4	pyruvate dehydrogenase kinase, isozyme 4	O70571	3.148	9.8E-05	4.011	
PDPR	pyruvate dehydrogenase phosphatase regulatory subunit	Q7TSQ8	-0.412	2.1E-10	9.686	
PFKM	phosphofructokinase, muscle	P47857	0.072	2.5E-04	3.609	Glycolysis/Glycogen degradation
PGAM2	phosphoglycerate mutase 2 (muscle)	Q5NCI4	0.085	2.5E-06	5.602	Glycolysis/Glycogen degradation
PGK1	phosphoglycerate kinase 1	P09411	0.242	2.4E-15	14.613	Glycolysis/Glycogen degradation
PGM1	phosphoglucomutase 1	Q3UGE3	0.205	9.2E-09	8.034	Glycolysis/Glycogen degradation
PHB	prohibitin	Q5SQG5	-0.248	1.2E-04	3.917	
Pkm	pyruvate kinase, muscle	P52480	0.097	6.8E-05	4.168	Glycolysis/Glycogen degradation
PRDX5	peroxiredoxin 5	Q9D6X2	-0.299	4.8E-08	7.315	
PYGB	phosphorylase, glycogen; brain	Q3UGT5	0.285	8.5E-07	6.073	Glycolysis/Glycogen degradation
PYGM	phosphorylase, glycogen, muscle	Q9WUB3	0.256	1.1E-15	14.955	Glycolysis/Glycogen degradation
SDHA	succinate dehydrogenase complex, subunit A, flavoprotein (Fp)	Q8K2B3	-0.298	6.2E-21	20.211	Respiratory chain/TCA cycle
SDHB	succinate dehydrogenase complex, subunit B, iron sulfur (Ip)	A2AA77	-0.302	1.4E-09	8.848	Respiratory chain/TCA cycle
SDHC	succinate dehydrogenase complex, subunit C, integral membrane protein, 15kDa	Q5XK33	-0.522	3.2E-03	2.498	Respiratory chain/TCA cycle
SLC25A11	solute carrier family 25 (mitochondrial carrier; oxoglutarate carrier), member 11	Q5SX48	-0.388	7.8E-10	9.109	
SLC25A12	solute carrier family 25 (aspartate/glutamate carrier), member 12	Q8BH59	-0.176	8.5E-19	18.070	
SLC25A3	solute carrier family 25 (mitochondrial carrier; phosphate carrier), member 3	Q8VEM8	-0.348	8.6E-17	16.068	
SLC25A4	solute carrier family 25 (mitochondrial carrier; adenine nucleotide translocator), member 4	P48962	-0.233	1.0E-04	3.987	
SLC25A5	solute carrier family 25 (mitochondrial carrier; adenine nucleotide translocator), member 5	P51881	-0.209	4.9E-05	4.313	
SLC27A1 (FATP1)	solute carrier family 27 (fatty acid transporter), member 1	Q3TP13	0.413	2.0E-03	2.693	FA transport and uptake
SOD1	superoxide dismutase 1, soluble	Q8C355	0.213	9.2E-07	6.038	
SOD2	superoxide dismutase 2, mitochondrial	P09671	-0.305	8.3E-07	6.081	Respiratory chain/TCA cycle
SUCLA2	succinate-CoA ligase, ADP-forming, beta subunit	Q3U6C7	-0.24	3.2E-11	10.492	Respiratory chain/TCA cycle

SUCLG1	succinate-CoA ligase, alpha subunit	Q9WUM5	-0.246	2.1E-11	10.680	Respiratory chain/TCA cycle
TPI1	triosephosphate isomerase 1	P17751	0.172	3.9E-18	17.413	Glycolysis/Glycogen degradation
TRAP1	TNF receptor-associated protein 1	Q9CQN1	-0.462	4.5E-02	1.352	
TUFM	Tu translation elongation factor, mitochondrial	Q8BFR5	-0.179	1.6E-05	4.801	
UQCRB	ubiquinol-cytochrome c reductase binding protein	Q9D855	-0.399	2.1E-09	8.684	Respiratory chain/TCA cycle
UQCRC1	ubiquinol-cytochrome c reductase core protein I	Q3THM1	-0.23	8.3E-07	6.082	Respiratory chain/TCA cycle
UQCRC2	ubiquinol-cytochrome c reductase core protein II	Q9DB77	-0.254	1.2E-19	18.914	Respiratory chain/TCA cycle
UQCRFS1	ubiquinol-cytochrome c reductase, Rieske iron-sulfur polypeptide 1	Q9CR68	-0.331	5.3E-31	30.276	Respiratory chain/TCA cycle
VDAC1	voltage-dependent anion channel 1	Q60932	-0.159	2.1E-05	4.680	
VDAC2	voltage-dependent anion channel 2	Q60930	-0.165	3.6E-04	3.450	
YWHAE	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon polypeptide	A2ACM8	0.132	2.9E-04	3.533	
YWHAZ	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide	Q8BWN0	0.139	4.3E-03	2.366	

SUPPLEMENTARY DATA

Supplementary Table S2B. Individual protein differential expression data from figure **2B volcano plot (STZ+I vs. STZ-I comparison)** of 77 significantly affected proteins implicated in skeletal muscle energy metabolism. Table lists protein symbols, names and accession numbers as given by UniProt database, together with their expression ratio (in log2 scale), p-value (base and in –log10 scale) and Ingenuity IPA protein group affiliation (Group). Proteins are listed in the alphabetical order by their respective symbols.

Symbol	Entrez Gene Name	Accession #	Log2 (STZ+I vs STZ-I)	p-value (STZ+I vs STZ-I)	-log10 p-value (STZ+I vs STZ-I)	Group
ACAA2	acetyl-CoA acyltransferase 2	Q8BWT1	0.149	3.7E-03	2.431	FA metabolism
ACADL	acyl-CoA dehydrogenase, long chain	P51174	-0.196	2.9E-04	3.538	FA metabolism
ACADVL	acyl-CoA dehydrogenase, very long chain	B1AR27	-0.110	3.1E-02	1.509	FA metabolism
ACAT1	acetyl-CoA acetyltransferase 1	Q8QZT1	0.145	4.4E-04	3.361	FA metabolism
ACSL1	acyl-CoA synthetase long-chain family member 1	P41216	-0.221	3.4E-10	9.466	FA metabolism
ADCK3	aarF domain containing kinase 3	Q60936	-0.270	2.0E-02	1.701	
ADH5	alcohol dehydrogenase 5 (class III), chi polypeptide	Q6P5I3	-0.139	3.9E-02	1.415	FA metabolism
ALDH2	aldehyde dehydrogenase 2 family (mitochondrial)	P47738	-0.297	5.1E-06	5.297	FA metabolism
ALDOA	aldolase A, fructose-bisphosphate	Q5FWB7	-0.161	5.6E-05	4.249	Glycolysis/Glycogen degradation
ATP5A1	ATP synthase, H+ transporting, mitochondrial F1 complex, alpha subunit 1, cardiac muscle	D3Z6F5	0.067	3.8E-02	1.425	Respiratory chain/TCA cycle
ATP5B	ATP synthase, H+ transporting, mitochondrial F1 complex, beta polypeptide	P56480	0.075	1.0E-03	2.991	Respiratory chain/TCA cycle
CASQ1	calsequestrin 1 (fast-twitch, skeletal muscle)	O09165	-0.427	3.0E-04	3.524	
CAT	catalase	P24270	-1.341	8.7E-09	8.062	
CD36	CD36 molecule (thrombospondin receptor)	Q08857	-0.615	6.0E-17	16.223	FA uptake and transport
CKMT2	creatine kinase, mitochondrial 2 (sarcomeric)	Q6P8J7	0.267	2.2E-16	15.654	
CS	citrate synthase	Q9CZU6	0.088	9.3E-03	2.031	Respiratory chain/TCA cycle
DECR1	2,4-dienoyl CoA reductase 1, mitochondrial	Q9CQ62	-0.135	2.5E-02	1.607	
ECH1	enoyl CoA hydratase 1, peroxisomal	O35459	-0.427	3.5E-02	1.460	FA metabolism
ECI1	enoyl-CoA delta isomerase 1	Q8QZV3	-0.151	3.2E-04	3.492	FA metabolism
ENO1	enolase 1, (alpha)	P17182	-0.201	3.6E-13	12.447	Glycolysis/Glycogen degradation
ENO2	enolase 2 (gamma, neuronal)	P17183	-0.365	1.1E-05	4.967	Glycolysis/Glycogen degradation
ENO3	enolase 3 (beta, muscle)	P21550	-0.417	8.2E-34	33.085	Glycolysis/Glycogen degradation

ETFA	electron-transfer-flavoprotein, alpha polypeptide	Q99LC5	-0.117	1.1E-03	2.943	Respiratory chain/TCA cycle
ETFB	electron-transfer-flavoprotein, beta polypeptide	Q9DCW4	-0.119	3.4E-04	3.467	Respiratory chain/TCA cycle
FABP3	fatty acid binding protein 3, muscle and heart (mammary-derived growth inhibitor)	Q5EBJ0	-0.318	1.2E-07	6.939	FA uptake and transport
FABP4	fatty acid binding protein 4, adipocyte	Q542H7	-0.873	6.7E-81	80.177	FA uptake and transport
FBP2	fructose-1,6-bisphosphatase 2	Q3TKP4	-0.378	2.8E-06	5.554	Glycolysis/Glycogen degradation
Gapdh/LOC100042025	glyceraldehyde-3-phosphate dehydrogenase	P16858	-0.105	9.6E-08	7.016	Glycolysis/Glycogen degradation
GARS	glycyl-tRNA synthetase	Q9CZD3	-0.182	4.0E-02	1.397	
GOT2	glutamic-oxaloacetic transaminase 2, mitochondrial (aspartate aminotransferase 2)	P05202	0.126	1.4E-03	2.870	FA uptake and transport
GPD1	glycerol-3-phosphate dehydrogenase 1 (soluble)	P13707	-0.169	3.9E-07	6.411	Glycolysis/Glycogen degradation
GPD2	glycerol-3-phosphate dehydrogenase 2 (mitochondrial)	Q64521	0.115	3.4E-02	1.469	Respiratory chain/TCA cycle
GPI	glucose-6-phosphate isomerase	P06745	-0.143	6.7E-14	13.173	Glycolysis/Glycogen degradation
GSTM5	glutathione S-transferase mu 5	P10649	-0.255	1.9E-03	2.730	
HADH	hydroxyacyl-CoA dehydrogenase	Q61425	-0.169	3.1E-02	1.510	FA metabolism
HADHA	hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), alpha subunit	Q8BMS1	-0.134	4.4E-13	12.358	FA metabolism
HADHB	hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), beta subunit	Q99JY0	-0.150	1.9E-08	7.730	FA metabolism
HK2	hexokinase 2	O08528	0.238	2.0E-02	1.693	
HSP90AB1	heat shock protein 90kDa alpha (cytosolic), class B member 1	Q71LX8	0.257	3.9E-13	12.411	
HSPA9	heat shock 70kDa protein 9 (mortalin)	P38647	0.158	3.1E-04	3.506	
HSPD1	heat shock 60kDa protein 1 (chaperonin)	P63038	0.063	4.7E-02	1.332	
IDH2	isocitrate dehydrogenase 2 (NADP+), mitochondrial	P54071	-0.333	3.5E-18	17.452	
IDH3A	isocitrate dehydrogenase 3 (NAD+) alpha	Q9D6R2	0.141	9.7E-04	3.011	Respiratory chain/TCA cycle
IDH3B	isocitrate dehydrogenase 3 (NAD+) beta	Q91VA7	0.130	7.0E-04	3.152	Respiratory chain/TCA cycle
IDH3G	isocitrate dehydrogenase 3 (NAD+) gamma	P70404	0.157	3.4E-02	1.469	Respiratory chain/TCA cycle
IVD	isovaleryl-CoA dehydrogenase	Q9JHI5	0.282	3.7E-03	2.433	FA metabolism
MDH2	malate dehydrogenase 2, NAD (mitochondrial)	P08249	0.081	1.6E-06	5.799	Respiratory chain/TCA cycle
ME1	malic enzyme 1, NADP(+)-dependent, cytosolic	Q921S3	-0.221	2.3E-05	4.648	Glycolysis/Glycogen degradation

MPC2	mitochondrial pyruvate carrier 2	Q9D023	0.251	2.0E-02	1.710	
NDUFS1	NADH dehydrogenase (ubiquinone) Fe-S protein 1, 75kDa (NADH-coenzyme Q reductase)	Q91VD9	0.112	6.7E-03	2.175	Respiratory chain/TCA cycle
NDUFV1	NADH dehydrogenase (ubiquinone) flavoprotein 1, 51kDa	Q91YT0	0.119	2.8E-03	2.554	Respiratory chain/TCA cycle
OXCT1	3-oxoacid CoA transferase 1	Q9D0K2	0.308	1.2E-09	8.921	
PARK7	parkinson protein 7	Q99LX0	-0.238	7.0E-07	6.157	
PDK4	pyruvate dehydrogenase kinase, isozyme 4	O70571	-2.468	4.7E-07	6.333	
PDPR	pyruvate dehydrogenase phosphatase regulatory subunit	Q7TSQ8	0.301	2.3E-02	1.638	
PFKM	phosphofructokinase, muscle	P47857	0.104	2.0E-08	7.701	Glycolysis/Glycogen degradation
PGAM2	phosphoglycerate mutase 2 (muscle)	Q5NCI4	-0.139	2.9E-04	3.533	Glycolysis/Glycogen degradation
PGM1	phosphoglucomutase 1	Q3UGE3	-0.207	9.2E-09	8.034	Glycolysis/Glycogen degradation
Pkm	pyruvate kinase, muscle	P52480	-0.110	1.6E-05	4.796	Glycolysis/Glycogen degradation
PYGB	phosphorylase, glycogen; brain	Q3UGT5	-0.280	2.5E-06	5.599	Glycolysis/Glycogen degradation
PYGM	phosphorylase, glycogen, muscle	Q9WUB3	-0.271	3.4E-17	16.475	Glycolysis/Glycogen degradation
SDHA	succinate dehydrogenase complex, subunit A, flavoprotein (Fp)	Q8K2B3	0.101	9.2E-04	3.035	Respiratory chain/TCA cycle
SDHB	succinate dehydrogenase complex, subunit B, iron sulfur (Ip)	A2AA77	0.135	6.4E-03	2.194	Respiratory chain/TCA cycle
SLC25A11	solute carrier family 25 (mitochondrial carrier; oxoglutarate carrier), member 11	Q5SX48	0.168	7.4E-03	2.134	
SLC25A12	solute carrier family 25 (aspartate/glutamate carrier), member 12	Q8BH59	0.049	6.6E-03	2.180	
SLC25A3	solute carrier family 25 (mitochondrial carrier; phosphate carrier), member 3	Q8VEM8	0.100	7.3E-03	2.137	
SLC25A4	solute carrier family 25 (mitochondrial carrier; adenine nucleotide translocator), member 4	P48962	0.082	2.1E-03	2.686	
SLC27A1 (FATP1)	solute carrier family 27 (fatty acid transporter), member 1	Q3TP13	-0.800	2.7E-07	6.577	FA uptake and transport
SOD1	superoxide dismutase 1, soluble	Q8C355	-0.284	2.4E-10	9.614	
SOD2	superoxide dismutase 2, mitochondrial	P09671	0.132	3.3E-02	1.487	
SUCLA2	succinate-CoA ligase, ADP-forming, beta subunit	Q3U6C7	0.079	7.7E-03	2.116	Respiratory chain/TCA cycle
TPI1	triosephosphate isomerase 1	P17751	-0.152	4.4E-16	15.353	Glycolysis/Glycogen degradation
UQCRC2	ubiquinol-cytochrome c reductase core protein II	Q9DB77	0.089	4.2E-04	3.382	Respiratory chain/TCA cycle

UQCRFS1	ubiquinol-cytochrome c reductase, Rieske iron-sulfur polypeptide 1	Q9CR68	0.119	1.1E-03	2.951	Respiratory chain/TCA cycle
VDAC2	voltage-dependent anion channel 2	Q60930	0.072	2.0E-02	1.708	
YWHAE	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon polypeptide	A2ACM8	-0.171	2.4E-04	3.627	
YWHAZ	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide	Q8BWN0	-0.229	2.0E-06	5.703	

Supplementary Table S2C. Individual protein differential expression data from **Figure 2C volcano plot (STZ+I vs. ND comparison)** of 104 significantly affected proteins implicated in skeletal muscle energy metabolism. Table lists protein symbols, names and accession numbers as given by UniProt database, together with their expression ratio (in log2 scale), p-value (base and in –log10 scale) and Ingenuity IPA protein group affiliation (Group). Proteins are listed in the alphabetical order by their respective symbols.

Symbol	Entrez Gene Name	Accesion #	Log2 (STZ+I vs ND)	p-value (STZ+I vs ND)	-log10 p-value (STZ+I vs ND)	Group
ACAA2	acetyl-CoA acyltransferase 2	Q8BWT1	-0.523	1.1E-27	26.947	FA metabolism
ACADL	acyl-CoA dehydrogenase, long chain	P51174	-0.510	3.7E-23	22.434	FA metabolism
ACADM	acyl-CoA dehydrogenase, C-4 to C-12 straight chain	Q91WS8	-0.454	1.3E-13	12.876	FA metabolism
ACADVL	acyl-CoA dehydrogenase, very long chain	P50544	-0.301	4.4E-16	15.353	FA metabolism
ACO2	aconitase 2, mitochondrial	Q99KI0	0.050	1.4E-04	3.842	Respiratory chain/TCA cycle
ACSL1	acyl-CoA synthetase long-chain family member 1	P41216	-0.318	1.9E-42	41.728	FA metabolism
ALDH2	aldehyde dehydrogenase 2 family (mitochondrial)	P47738	-0.453	2.4E-13	12.629	FA metabolism
ALDOA	aldolase A, fructose-bisphosphate	Q5FWB7	0.100	2.8E-04	3.561	Glycolysis/Glycogen degradation
ATP5A1	ATP synthase, H+ transporting, mitochondrial F1 complex, alpha subunit 1, cardiac muscle	D3Z6F5	-0.118	7.0E-05	4.154	Respiratory chain/TCA cycle
ATP5B	ATP synthase, H+ transporting, mitochondrial F1 complex, beta polypeptide	P56480	-0.127	4.3E-07	6.368	Respiratory chain/TCA cycle
ATP5C1	ATP synthase, H+ transporting, mitochondrial F1 complex, gamma polypeptide 1	A2AKU9	-0.144	2.4E-06	5.620	Respiratory chain/TCA cycle
ATP5F1	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit B1	Q5I0W0	-0.200	2.5E-06	5.599	Respiratory chain/TCA cycle

ATP5H	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit d	Q9DCX2	-0.250	4.0E-11	10.394	Respiratory chain/TCA cycle
ATP5L	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit G	Q9CPQ8	-0.261	2.7E-05	4.565	Respiratory chain/TCA cycle
ATP5O	ATP synthase, H+ transporting, mitochondrial F1 complex, O subunit	Q9DB20	-0.161	9.0E-05	4.047	Respiratory chain/TCA cycle
ECHS1	enoyl CoA hydratase, short chain, 1, mitochondrial	Q8BH95	-0,292	1,21E-02	1.918	FA metabolism
CD36	CD36 molecule (thrombospondin receptor)	Q08857	-0.261	1.9E-03	2.728	FA uptake and transport
CHCHD3	coiled-coil-helix-coiled-coil-helix domain containing 3	Q9D9P1	-0.231	3.0E-02	1.524	Mitochondrial protein
CISD1	CDGSH iron sulfur domain 1	Q91WS0	-0.145	3.8E-03	2.426	Mitochondrial protein
COX1	cytochrome c oxidase subunit I	Q9MD68	-0.269	1.8E-04	3.757	Respiratory chain/TCA cycle
COX2	cytochrome c oxidase subunit II	P00405	-0.213	3.3E-04	3.479	Respiratory chain/TCA cycle
COX4I1	cytochrome c oxidase subunit IV isoform 1	P19783	-0.211	4.7E-03	2.328	Respiratory chain/TCA cycle
COX5A	cytochrome c oxidase subunit Va	P12787	-0.267	4.7E-03	2.330	Respiratory chain/TCA cycle
COX5B	cytochrome c oxidase subunit Vb	P19536	-0.256	4.4E-03	2.360	Respiratory chain/TCA cycle
CPT1B	carnitine palmitoyltransferase 1B (muscle)	Q3UIM5	-0.246	3.0E-12	11.520	FA metabolism
CPT2	carnitine palmitoyltransferase 2	P52825	-0.324	3.8E-04	3.420	FA metabolism
CRAT	carnitine O-acetyltransferase	P47934	-0.253	1.1E-06	5.975	Mitochondrial protein
CS	citrate synthase	Q9CZU6	-0.123	2.2E-04	3.666	Respiratory chain/TCA cycle
CYC1	cytochrome c-1	Q9D0M3	-0.266	1.9E-03	2.726	Respiratory chain/TCA cycle

CYCS	cytochrome c, somatic	Q56A15	-0.229	5.1E-06	5.291	Respiratory chain/TCA cycle
DECR1	2,4-dienoyl CoA reductase 1, mitochondrial	Q9CQ62	-0.327	3.1E-10	9.507	Mitochondrial protein
DLAT	dihydrolipoamide S-acetyltransferase	Q8BMF4	-0.257	6.8E-20	19.170	Glycolysis/Glycogen degradation
DLD	dihydrolipoamide dehydrogenase	O08749	-0.127	8.1E-06	5.092	Respiratory chain/TCA cycle
DLST	dihydrolipoamide S-succinyltransferase (E2 component of 2-oxo-glutarate complex)	Q9D2G2	-0.295	2.8E-04	3.551	Respiratory chain/TCA cycle
ECI1	enoyl-CoA delta isomerase 1	Q8QZV3	-0.268	2.4E-08	7.625	FA metabolism
ENO3	enolase 3 (beta, muscle)	P21550	-0.309	5.2E-25	24.287	Glycolysis/Glycogen degradation
ETFA	electron-transfer-flavoprotein, alpha polypeptide	Q99LC5	-0.272	6.4E-30	29.193	Respiratory chain/TCA cycle
ETFB	electron-transfer-flavoprotein, beta polypeptide	Q9DCW4	-0.315	5.1E-18	17.296	Respiratory chain/TCA cycle
FABP3	fatty acid binding protein 3, muscle and heart (mammary-derived growth inhibitor)	Q5EBJ0	-0.398	1.5E-33	32.830	FA uptake and transport
FABP4	fatty acid binding protein 4, adipocyte	Q542H7	-0.343	5.0E-18	17.298	FA uptake and transport
FH	fumarate hydratase	Q3UIA9	0.097	2.3E-03	2.638	Respiratory chain/TCA cycle
GAPDH	glyceraldehyde-3-phosphate dehydrogenase	P16858	0.073	2.2E-13	12.650	Glycolysis/Glycogen degradation
GOT2	glutamic-oxaloacetic transaminase 2, mitochondrial (aspartate aminotransferase 2)	P05202	-0.251	9.7E-13	12.014	FA uptake and transport
GPD1	glycerol-3-phosphate dehydrogenase 1 (soluble)	P13707	0.094	3.8E-07	6.418	Glycolysis/Glycogen degradation
GPD2	glycerol-3-phosphate dehydrogenase 2	Q64521	0.225	3.5E-07	6.462	Glycolysis/Glycogen degradation

	(mitochondrial)					
HADH	hydroxyacyl-CoA dehydrogenase	Q61425	-0.361	2.4E-06	5.616	FA metabolism
HADHA	hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), alpha subunit	Q8BMS1	-0.255	6.9E-25	24.164	FA metabolism
HADHB	hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), beta subunit	Q99JY0	-0.235	8.5E-27	26.071	FA metabolism
HIBADH	3-hydroxyisobutyrate dehydrogenase	Q99L13	-0.445	9.2E-04	3.035	Mitochondrial protein
HSD17B10	hydroxysteroid (17-beta) dehydrogenase 10	Q99N15	-0.137	3.1E-02	1.504	FA metabolism
HSPA9	heat shock 70kDa protein 9 (mortalin)	P38647	-0.265	8.5E-10	9.072	Mitochondrial protein
HSPD1	heat shock 60kDa protein 1 (chaperonin)	P63038	-0.216	5.1E-13	12.292	Mitochondrial protein
HSPE1	heat shock 10kDa protein 1 (chaperonin 10)	Q64433	-0.238	4.1E-02	1.389	Mitochondrial protein
IDH2	isocitrate dehydrogenase 2 (NADP+), mitochondrial	P54071	-0.242	2.9E-13	12.541	Respiratory chain/TCA cycle
IDH3A	isocitrate dehydrogenase 3 (NAD+) alpha	Q9D6R2	-0.181	7.4E-09	8.131	Respiratory chain/TCA cycle
IDH3B	isocitrate dehydrogenase 3 (NAD+) beta	Q91VA7	-0.212	1.7E-11	10.762	Respiratory chain/TCA cycle
IDH3G	isocitrate dehydrogenase 3 (NAD+) gamma	P70404	-0.235	1.1E-03	2.975	Respiratory chain/TCA cycle
LETM1	leucine zipper-EF-hand containing transmembrane protein 1	Q9Z2I0	-0.402	1.3E-03	2.893	Mitochondrial solute transport
LRPPRC	leucine-rich pentatricopeptide repeat containing	Q99KF9	-0.439	3.4E-02	1.471	Mitochondrial protein

MDH2	malate dehydrogenase 2, NAD (mitochondrial)	P08249	-0.152	5.0E-11	10.303	Respiratory chain/TCA cycle
ME1	malic enzyme 1, NADP(+)-dependent, cytosolic	Q9DBF9	-0.347	3.9E-07	6.405	Glycolysis/Glycogen degradation

Supplementary Table S2D. Individual differential expression from **Figure 2D (STZ-I vs. ND comparison)** of 60 significantly affected proteins implicated in protein synthesis, protein degradation and oxidative stress response. Table lists protein symbols, names and accession numbers as given by UniProt database database, together with their expression ratio (in log2 scale), p-value (base and in –log10 scale) and Ingenuity IPA protein group affiliation (Group). Proteins are listed in the alphabetical order by their respective symbols.

Symbol	**Entrez Gene Name**	**Accesion #**	**Log2 (STZ-I vs ND)**	**p-value (STZ-I vs ND)**	**-log10 p-value (STZ-I vs ND)**	**Group**
ACTA1	actin, alpha 1, skeletal muscle	P68134	0.241	1.8E-06	5.740	Oxidative stress and cellular damage
CAT	catalase	P24270	1.398	1.5E-09	8.818	Oxidative stress and cellular damage
CRYAB	crystallin, alpha B	Q52L78	-0.561	8.9E-13	12.053	Protein synthesis and chaperones
DARS	aspartyl-tRNA synthetase	Q3TF87	-0.419	3.9E-06	5.408	Protein synthesis and chaperones
EEF1D	eukaryotic translation elongation factor 1 delta (guanine nucleotide exchange protein)	P57776	-0.514	2.3E-02	1.638	Protein synthesis and chaperones
EEF1G	eukaryotic translation elongation factor 1 gamma	Q4FZK2	-0.651	2.6E-14	13.578	Protein synthesis and chaperones
EPRS	glutamyl-prolyl-tRNA synthetase	Q8CGC7	-0.363	3.6E-05	4.445	Protein synthesis and chaperones
FTH1	ferritin, heavy polypeptide 1	P09528	0.567	1.5E-04	3.812	Oxidative stress and cellular damage
GSTM1	glutathione S-transferase mu 1	P15626	0.521	4.7E-05	4.327	Oxidative stress and cellular damage
GSTM4	glutathione S-transferase mu 4	Q8R5I6	0.415	1.0E-03	2.983	Oxidative stress and cellular damage

GSTM5	glutathione S-transferase mu 5	P10649	0.303	3.2E-07	6.495	Oxidative stress and cellular damage
GSTP1	glutathione S-transferase pi 1	P19157	0.269	4.0E-06	5.399	Oxidative stress and cellular damage
HSP90AB1	heat shock protein 90kDa alpha (cytosolic), class B member 1	Q71LX8	-0.291	1.4E-13	12.854	Protein synthesis and chaperones
HSP90AB1	heat shock protein 90kDa alpha (cytosolic), class B member 1	Q71LX8	-0.291	1.4E-13	12.854	Oxidative stress and cellular damage
HSP90B1	heat shock protein 90kDa beta (Grp94), member 1	P08113	-0.267	5.7E-02	1.243	Protein synthesis and chaperones
HSPA4	heat shock 70kDa protein 4	Q61316	-0.182	6.5E-02	1.185	Protein synthesis and chaperones
HSPA9	heat shock 70kDa protein 9 (mortalin)	P38647	-0.423	9.3E-20	19.030	Protein synthesis and chaperones
HSPB1	heat shock 27kDa protein 1	P14602	-0.514	9.1E-13	12.042	Protein synthesis and chaperones
HSPB6	heat shock protein, alpha-crystallin-related, B6	Q5EBG6	-0.827	3.0E-12	11.519	Protein synthesis and chaperones
HSPD1	heat shock 60kDa protein 1 (chaperonin)	P63038	-0.248	3.1E-18	17.509	Protein synthesis and chaperones
HSPE1	heat shock 10kDa protein 1 (chaperonin 10)	Q4KL76	-0.348	7.8E-04	3.107	Protein synthesis and chaperones
MAP2K6	mitogen-activated protein kinase kinase 6	P70236	-0.322	7.3E-03	2.140	Oxidative stress and cellular damage
PPP1CB	protein phosphatase 1, catalytic subunit, beta isozyme	P62141	-0.191	1.4E-02	1.860	Protein synthesis and chaperones
PRDX1	peroxiredoxin 1	P35700	0.136	8.5E-03	2.072	Oxidative stress and cellular damage
PRDX2	peroxiredoxin 2	Q61171	0.085	8.6E-03	2.066	Oxidative stress and cellular damage
PRDX5	peroxiredoxin 5	P99029	-0.299	4.8E-08	7.315	Oxidative stress and cellular damage
PSMA5	proteasome (prosome, macropain) subunit, alpha type, 5	Q9Z2U1	0.342	1.1E-06	5.979	Protein ubiquitination-related
RPL10A	ribosomal protein L10a	P53026	-0.694	1.9E-05	4.721	Protein synthesis and

						chaperones
RPL11	ribosomal protein L11	A2BH07	-0.643	1.0E-05	4.983	Protein synthesis and chaperones
RPL12	ribosomal protein L12	Q5BLK0	-0.573	1.2E-03	2.939	Protein synthesis and chaperones
RPL13	ribosomal protein L13	P47963	0.57	1.4E-02	1.866	Protein synthesis and chaperones
RPL23	ribosomal protein L23	P62830	-0.382	9.8E-03	2.009	Protein synthesis and chaperones
RPL35A	ribosomal protein L35a	O55142	-0.701	3.4E-03	2.469	Protein synthesis and chaperones
RPL9	ribosomal protein L9	P51410	-0.719	5.5E-04	3.256	Protein synthesis and chaperones
RPLP0	ribosomal protein, large, P0	Q5M8R8	-0.674	5.8E-10	9.240	Protein synthesis and chaperones
RPLP2	ribosomal protein, large, P2	P99027	-0.234	1.3E-03	2.900	Protein synthesis and chaperones
RPS10	ribosomal protein S10	Q3U9P0	-0.492	3.5E-02	1.456	Protein synthesis and chaperones
RPS11	ribosomal protein S11	Q3UC02	-0.461	2.2E-02	1.652	Protein synthesis and chaperones
RPS18	ribosomal protein S18	P62270	-0.328	1.1E-02	1.951	Protein synthesis and chaperones
RPS19	ribosomal protein S19	Q9CZX8	-0.514	9.9E-04	3.007	Protein synthesis and chaperones
RPS2	ribosomal protein S2	P25444	-0.583	5.3E-04	3.276	Protein synthesis and chaperones
RPS3	ribosomal protein S3	Q5YLW3	-0.544	3.8E-04	3.425	Protein synthesis and chaperones
RPS4Y1	ribosomal protein S4, Y-linked 1	P62702	-0.607	5.3E-03	2.278	Protein synthesis and chaperones
RPS7	ribosomal protein S7	P62082	-0.197	2.9E-02	1.538	Protein synthesis and chaperones
RPSA	ribosomal protein SA	B2CY77	-0.605	1.7E-05	4.783	Protein synthesis and chaperones

SOD1	superoxide dismutase 1, soluble	P08228	0.213	9.2E-07	6.038	Oxidative stress and cellular damage
SOD2	superoxide dismutase 2, mitochondrial	P09671	-0.305	8.3E-07	6.081	Oxidative stress and cellular damage
STIP1	stress-induced-phosphoprotein 1	Q60864	-0.186	5.2E-03	2.287	Oxidative stress and cellular damage
TARSL2	threonyl-tRNA synthetase-like 2	Q8BLY2	-0.415	3.7E-06	5.437	Protein synthesis and chaperones
TPT1	tumor protein, translationally-controlled 1	P63028	-0.188	8.3E-03	2.079	Protein synthesis and chaperones
TUFM	Tu translation elongation factor, mitochondrial	Q8BFR5	-0.179	1.6E-05	4.801	Protein synthesis and chaperones
UBA1	ubiquitin-like modifier activating enzyme 1	Q02053	0.16	5.4E-03	2.265	Protein ubiquitination-related
UBC	ubiquitin C	A5JUZ1	0.351	1.3E-15	14.876	Protein ubiquitination-related
UBE2L3	ubiquitin-conjugating enzyme E2L 3	P68037	0.16	3.9E-02	1.415	Protein ubiquitination-related
USP35	ubiquitin specific peptidase 35	NP_001170883	0.721	2.8E-03	2.548	Protein ubiquitination-related
YWHAB	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, beta polypeptide	Q9CQV8	0.514	1.3E-03	2.873	Oxidative stress and cellular damage
YWHAE	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon polypeptide	Q5SS40	0.132	2.9E-04	3.533	Oxidative stress and cellular damage
YWHAG	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, gamma polypeptide	A8IP69	0.136	7.2E-06	5.143	Oxidative stress and cellular damage
YWHAZ	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide	P63101	0.139	4.3E-03	2.366	Oxidative stress and cellular damage

Supplementary Table S2E. Individual differential expression from **Figure 2E (STZ+I vs. STZ-I comparison)** of 60 significantly affected proteins implicated in protein synthesis, protein degradation and oxidative stress response. Table lists protein symbols, names and accession numbers as given by UniProt database, together with their expression ratio (in log2 scale), p-value (base and in –log10 scale) and Ingenuity IPA protein group affiliation (Group). Proteins are listed in the alphabetical order by their respective symbols.

Symbol	**Entrez Gene Name**	**Accesion #**	**Log2 (STZ+I vs STZ-I)**	**p-value (STZ+I vs STZ-I)**	**-log10 p-value (STZ+I vs STZ-I)**	**Group**
ACTA1	actin, alpha 1, skeletal muscle	P68134	0.212	3.8E-05	4.419	Oxidative stress and cellular damage
CAT	catalase	P24270	-1.341	8.7E-09	8.062	Oxidative stress and cellular damage
DARS	aspartyl-tRNA synthetase	Q3TF87	0.733	3.6E-05	4.445	Protein synthesis and chaperones
EEF1A2	eukaryotic translation elongation factor 1 alpha 2	P62631	0.049	3.2E-02	1.498	Protein synthesis and chaperones
EEF1D	eukaryotic translation elongation factor 1 delta (guanine nucleotide exchange protein)	P57776	0.541	2.5E-02	1.609	Protein synthesis and chaperones
EEF1G	eukaryotic translation elongation factor 1 gamma	Q4FZK2	0.584	4.5E-09	8.344	Protein synthesis and chaperones
Eif5a	eukaryotic translation initiation factor 5A	P63242	-0.138	1.7E-02	1.780	Protein synthesis and chaperones
EPRS	glutamyl-prolyl-tRNA synthetase	Q8CGC7	0.262	1.3E-03	2.900	Protein synthesis and chaperones
FTH1	ferritin, heavy polypeptide 1	P09528	-0.702	1.0E-09	9.002	Oxidative stress and cellular damage
GARS	glycyl-tRNA synthetase	Q9CZD3	-0.182	4.0E-02	1.397	Protein synthesis and chaperones
GPX3	glutathione peroxidase 3 (plasma)	P46412	-0.586	1.2E-02	1.939	Oxidative stress and cellular damage
GSTM1	glutathione S-transferase mu 1	P15626	-0.250	4.0E-02	1.398	Oxidative stress and cellular damage
GSTM4	glutathione S-transferase mu 4	Q8R5I6	-0.244	2.7E-02	1.565	Oxidative stress and cellular damage
GSTM5	glutathione S-transferase mu 5	P10649	-0.255	1.9E-03	2.730	Oxidative stress and cellular damage
GSTP1	glutathione S-transferase pi 1	P19157	-0.274	2.8E-06	5.550	Oxidative stress and cellular damage
HSP90AB1	heat shock protein 90kDa alpha (cytosolic), class B member 1	Q71LX8	0.257	3.9E-13	12.411	Oxidative stress and cellular damage
HSP90AB1	heat shock protein 90kDa alpha (cytosolic), class B member 1	Q71LX8	0.257	3.9E-13	12.411	Protein synthesis and chaperones
HSPA9	heat shock 70kDa protein 9 (mortalin)	P38647	0.158	3.1E-04	3.506	Protein synthesis and chaperones

HSPB1	heat shock 27kDa protein 1	P14602	0.244	4.2E-04	3.375	Protein synthesis and chaperones
HSPB6	heat shock protein, alpha-crystallin-related, B6	Q5EBG6	0.600	6.0E-05	4.223	Protein synthesis and chaperones
HSPD1	heat shock 60kDa protein 1 (chaperonin)	P63038	0.063	4.7E-02	1.332	Protein synthesis and chaperones
ME1	malic enzyme 1, NADP(+)-dependent, cytosolic	Q921S3	-0.221	2.3E-05	4.648	Oxidative stress and cellular damage
PPP1CA	protein phosphatase 1, catalytic subunit, alpha isozyme	P62137	0.189	4.6E-02	1.334	Protein synthesis and chaperones
PPP2R2A	protein phosphatase 2, regulatory subunit B, alpha	Q6P1F6	-0.172	2.9E-03	2.539	Protein synthesis and chaperones
PRDX1	peroxiredoxin 1	B1AXW5	-0.211	1.6E-09	8.796	Oxidative stress and cellular damage
PRDX2	peroxiredoxin 2	Q61171	-0.152	4.2E-06	5.375	Oxidative stress and cellular damage
PSMA5	proteasome (prosome, macropain) subunit, alpha type, 5	Q9Z2U1	-0.215	2.7E-03	2.573	Protein ubiquitination-related
PSMC4	proteasome (prosome, macropain) 26S subunit, ATPase, 4	Q3TFA5	-0.204	1.5E-02	1.821	Protein ubiquitination-related
RPL10A	ribosomal protein L10a	P53026	0.693	1.2E-04	3.936	Protein synthesis and chaperones
RPL11	ribosomal protein L11	A2BH07	0.626	1.7E-07	6.770	Protein synthesis and chaperones
RPL12	ribosomal protein L12	Q5BLK0	0.628	7.7E-05	4.114	Protein synthesis and chaperones
RPL22	ribosomal protein L22	P67984	0.544	4.9E-02	1.308	Protein synthesis and chaperones
RPL23	ribosomal protein L23	P62830	0.505	7.9E-04	3.101	Protein synthesis and chaperones
RPL27	ribosomal protein L27	P61358	0.800	3.5E-02	1.460	Protein synthesis and chaperones
RPL35A	ribosomal protein L35a	O55142	0.665	1.3E-03	2.893	Protein synthesis and chaperones
RPL9	ribosomal protein L9	P51410	0.813	1.2E-05	4.932	Protein synthesis and chaperones
RPLP0	ribosomal protein, large, P0	Q5M8R8	0.710	3.4E-11	10.466	Protein synthesis and chaperones
RPLP2	ribosomal protein, large, P2	P99027	0.240	1.8E-03	2.757	Protein synthesis and chaperones
RPS10	ribosomal protein S10	Q3U9P0	0.575	9.4E-03	2.027	Protein synthesis and chaperones
RPS11	ribosomal protein S11	Q3UC02	0.723	8.0E-04	3.096	Protein synthesis and chaperones
RPS13	ribosomal protein S13	Q5BLJ7	0.592	1.9E-02	1.726	Protein synthesis and chaperones
RPS15A	ribosomal protein S15a	P62245	0.505	1.3E-02	1.886	Protein synthesis and chaperones
RPS16	ribosomal protein S16	A4FUS1	0.659	2.1E-02	1.678	Protein synthesis and chaperones
RPS18	ribosomal protein S18	P62270	0.318	2.2E-02	1.650	Protein synthesis and chaperones

RPS19	ribosomal protein S19	Q9CZX8	0.571	1.4E-04	3.851	Protein synthesis and chaperones
RPS2	ribosomal protein S2	P25444	0.331	2.7E-02	1.565	Protein synthesis and chaperones
RPS3	ribosomal protein S3	Q5YLW3	0.800	2.6E-08	7.588	Protein synthesis and chaperones
RPS4Y1	ribosomal protein S4, Y-linked 1	P62702	0.963	4.4E-05	4.354	Protein synthesis and chaperones
RPSA	ribosomal protein SA	B2CY77	0.656	9.7E-06	5.015	Protein synthesis and chaperones
SOD1	superoxide dismutase 1, soluble	P08228	-0.284	2.4E-10	9.614	Oxidative stress and cellular damage
SOD2	superoxide dismutase 2, mitochondrial	P09671	0.132	3.3E-02	1.487	Oxidative stress and cellular damage
TARSL2	threonyl-tRNA synthetase-like 2	Q8BLY2	0.247	2.8E-03	2.554	Protein synthesis and chaperones
TKT	transketolase	P40142	-0.280	4.1E-02	1.393	Oxidative stress and cellular damage
UBA1	ubiquitin-like modifier activating enzyme 1	Q02053	-0.115	2.9E-02	1.538	Protein ubiquitination-related
UBC	ubiquitin C	A5JUZ1	-0.244	1.1E-06	5.947	Protein ubiquitination-related
VCP	valosin containing protein	Q01853	-0.123	1.4E-08	7.860	Oxidative stress and cellular damage
YWHAB	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, beta polypeptide	Q9CQV8	-0.439	4.2E-03	2.378	Oxidative stress and cellular damage
YWHAE	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon polypeptide	Q5SS40	-0.171	2.4E-04	3.627	Oxidative stress and cellular damage
YWHAG	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, gamma polypeptide	A8IP69	-0.174	4.9E-11	10.310	Oxidative stress and cellular damage
YWHAZ	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide	P63101	-0.229	2.0E-06	5.703	Oxidative stress and cellular damage

Supplementary Table S2F. Individual differential expression from **Figure S2F (STZ+I vs. ND comparison)** of 32 significantly affected proteins implicated in protein synthesis, protein degradation and oxidative stress response. Table lists protein symbols, names and accession numbers as given by UniProt database, together with their expression ratio (in log2 scale), p-value (base and in –log10 scale) and Ingenuity IPA protein group affiliation (Group). Proteins are listed in the alphabetical order by their respective symbols.

Symbol	Entrez Gene Name	Accesion #	Log2 (STZ+I vs ND)	p-value (STZ+I vs ND)	-log10 p-value (STZ+I vs ND)	Group
ACTA1	actin, alpha 1, skeletal muscle	P68134	0.452	2.8E-30	29.558	Oxidative stress and cellular damage
ACTC1	actin, alpha, cardiac muscle 1	Q3UIJ3	0.558	7.5E-06	5.126	Oxidative stress and cellular damage
CRYAB	crystallin, alpha B	Q52L78	-0.312	4.5E-12	11.343	Protein ubiquitination-related
DNAJA2	DnaJ (Hsp40) homolog, subfamily A, member 2	Q9QYJ0	-0.230	3.4E-02	1.472	Oxidative stress and cellular damage
EEF1G	eukaryotic translation elongation factor 1 gamma	Q4FZK2	-0.146	1.4E-02	1.863	Protein synthesis and chaperones
FTH1	ferritin, heavy polypeptide 1	P09528	-0.290	1.7E-02	1.764	Oxidative stress and cellular damage
GARS	glycyl-tRNA synthetase	Q9CZD3	-0.203	5.6E-03	2.251	Protein synthesis and chaperones
GSTM1	glutathione S-transferase mu 1	P15626	0.270	4.0E-02	1.394	Oxidative stress and cellular damage
GSTM5	glutathione S-transferase mu 5	P10649	0.149	1.2E-02	1.907	Oxidative stress and cellular damage
HSP90AB1	heat shock protein 90kDa alpha (cytosolic), class B member 1	Q71LX8	-0.110	4.1E-04	3.389	Protein synthesis and chaperones
HSPA4	heat shock 70kDa protein 4	Q61316	-0.254	1.3E-02	1.876	Protein synthesis and chaperones
HSPA9	heat shock 70kDa protein 9 (mortalin)	P38647	-0.265	8.5E-10	9.072	Protein synthesis and chaperones
HSPB1	heat shock 27kDa protein 1	P14602	-0.270	4.5E-04	3.346	Protein synthesis and chaperones

HSPD1	heat shock 60kDa protein 1 (chaperonin)	P63038	-0.216	5.1E-13	12.292	Protein synthesis and chaperones
HSPE1	heat shock 10kDa protein 1 (chaperonin 10)	Q4KL76	-0.238	4.1E-02	1.389	Protein synthesis and chaperones
ME1	malic enzyme 1, NADP(+)-dependent, cytosolic	Q9DBF9	-0.347	3.9E-07	6.405	Oxidative stress and cellular damage
MGST3	microsomal glutathione S-transferase 3	Q9CPU4	-0.313	1.8E-02	1.757	Oxidative stress and cellular damage
PRDX1	peroxiredoxin 1	P35700	-0.150	6.5E-06	5.190	Oxidative stress and cellular damage
PRDX2	peroxiredoxin 2	Q61171	-0.104	5.8E-03	2.237	Oxidative stress and cellular damage
PRDX3	peroxiredoxin 3	P20108	-0.127	4.6E-02	1.341	Oxidative stress and cellular damage
PRDX5	peroxiredoxin 5	P99029	-0.258	5.1E-06	5.292	Oxidative stress and cellular damage
PSMA5	proteasome (prosome, macropain) subunit, alpha type, 5	Q9Z2U1	-0.160	2.4E-02	1.625	Protein ubiquitination-related
PSMB3	proteasome (prosome, macropain) subunit, beta type, 3	Q545G0	-0.296	4.6E-03	2.338	Protein ubiquitination-related
SOD1	superoxide dismutase 1, soluble	P08228	-0.118	2.0E-02	1.701	Oxidative stress and cellular damage
SOD2	superoxide dismutase 2, mitochondrial	P09671	-0.173	6.3E-04	3.199	Oxidative stress and cellular damage
STIP1	stress-induced phosphoprotein 1	Q60864	-0.184	1.7E-02	1.764	Oxidative stress and cellular damage
TARSL2	threonyl-tRNA synthetase-like 2	Q8BLY2	-0.167	4.6E-02	1.335	Protein synthesis and chaperones
TUFM	Tu translation elongation factor, mitochondrial	Q8BFR5	0.107	7.9E-03	2.104	Protein synthesis and chaperones
UBC	ubiquitin C	A5JUZ1	0.107	1.5E-02	1.824	Protein ubiquitination-related
VCP	valosin containing protein	Q01853	-0.140	2.0E-09	8.706	Oxidative stress and

						cellular damage
YWHAG	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, gamma polypeptide	A8IP69	-0.095	4.1E-02	1.383	Oxidative stress and cellular damage
YWHAZ	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide	P63101	-0.146	7.9E-03	2.102	Oxidative stress and cellular damage

Supplementary Table S3A. Canonical pathways significantly affected by insulin deprivation (STZ-I vs. ND comparison). Table lists pathway names as given by Ingenuity Pathway Analysis software, pathway p-value (score, as –Log10 p-value derivative) and significantly affected molecular members of a given pathway.

Pathway Name	Score	Significantly affected proteins
Mitochondrial Dysfunction	36	HSD17B10,SDHB,NDUFA9,NDUFA10,PRDX5,CPT1B,NDUFB5,NDUFB4,COX2,NDUFA2,PDHA1,NDUFA5,NDUFS1,SOD2,PARK7,GPD2,NDUFS6,UQCRFS1,NDUFS2,OGDH,COX4I1,NDUFS4,AIFM1,NDUFA8,SDHA,COX1,NDUFV1,NDUFB3,CYCS,ATP5A1,COX6C,NDUFS3,NDUFA13,ATP5C1,NDUFS5,ND5,NDUFV2,ATP5B,NDUFA6,CAT,UQCRC2,NDUFB7,COX5A,NDUFA12,CYC1,UQCRC1,COX5B,NDUFA7
TCA Cycle II (Eukaryotic)	17,6	SDHA,SDHB,IDH3G,ACO2,SUCLA2,CS,SUCLG1,DLST,DLD,IDH3A,FH,MDH2,OGDH,IDH3B
Glycolysis I	8,44	Pkm,PGK1,GPI,TPI1,ENO3,PGAM2,ALDOA,PFKM,FBP2
Calcium Signaling	8,29	MYH4,TNNT1,MYL2,TNNI2,TNNC2,MYH8,TNNC1,ATP2A1,TPM3,TPM2,Tpm1,MYH7,ATP2A2,MYL1,MYH2,TNNT3,CASQ1,MYL4,RYR1,ACTC1,ACTA1,MYH1
Fatty Acid β-oxidation I	7,01	HSD17B10,HADHB,SLC27A1,ACADM,ACAA2,ECI1,ACSL1,HADHA,HADH
Glycolysis II	5,68	PGK1,GPI,ENO3,PGAM2,ALDOA,MDH2,FBP2
Actin Cytoskeleton Signaling	5,11	MYH4,PFN1,MYL2,MYH8,MYLPF,ACTN2,MYLK2,PPP1CB,MYH7,GSN,TTN,MYL1,MYH2,CFL2,MYL4,ACTC1,ACTA1,ACTN3,MYH1
Cellular Effects of Sildenafil (Viagra)	4,88	MYH4,MYH2,MYL2,MYH8,MYLPF,MYL4,PPP1CB,MYH7,ACTC1,MYL1,ACTA1,MYH1
Glycogen Degradation II	4,65	PYGM,PGM1,PYGB,AGL
Glycogen Degradation III	4,19	PYGM,PGM1,PYGB,AGL
Valine Degradation I	4,11	HIBCH,HADHB,HIBADH,DLD,HADHA
2-ketoglutarate Dehydrogenase Complex	4	DLST,DLD,OGDH
Ketolysis	4	HADHB,OXCT1,HADHA
Aspartate Degradation II	4	GOT1,MDH2,GOT2
Isoleucine Degradation I	3,84	HSD17B10,HADHB,DLD,HADHA
Epithelial Adherens Junction Signaling	3,8	MYH4,MYL2,MYH8,ACTN2,TUBA4A,MYH7,TUBB,MYL1,MYH2,MYL4,ACTC1,ACTN3,ACTA1,MYH1
RhoA Signaling	3,63	PFN1,CFL2,MYL2,MYLPF,MYLK2,MYL4,PPP1CB,ACTC1,TTN,MYL1,ACTA1
ILK Signaling	3,58	MAP2K6,MYH4,MYL2,MYH8,ACTN2,MYH7,MYL1,MYH2,CFL2,FLNC,MYL4,ACTC1,ACTA1,ACTN3,MYH1
Glutaryl-CoA Degradation	3,55	HSD17B10,HADHB,HADHA,HADH
Tryptophan Degradation III (Eukaryotic)	3,55	HSD17B10,HADHB,HADHA,HADH

Regulation of Actin-based Motility by Rho	3,44	PFN1,MYL2,MYLPF,MYL4,PPP1CB,GSN,ACTC1,MYL1,ACTA1
Acetyl-CoA Biosynthesis I (Pyruvate Dehydrogenase Complex)	3,41	PDHA1,DLAT,DLD
Mitochondrial L-carnitine Shuttle Pathway	2,93	CPT1B,CPT2,SLC27A1,ACSL1
Superoxide Radicals Degradation	2,74	SOD1,SOD2,CAT
Methylglyoxal Degradation III	2,74	Akr1b10,FAM213B,AKR1B1
Creatine-phosphate Biosynthesis	2,66	CKMT2,CKM
Pyruvate Fermentation to Lactate	2,66	Ldhb,LDHA
Glycerol Degradation I	2,66	GPD1,GPD2
Glycerol-3-phosphate Shuttle	2,66	GPD1,GPD2
Glutamate Degradation II	2,66	GOT1,GOT2
Aspartate Biosynthesis	2,66	GOT1,GOT2
Protein Kinase A Signaling	2,61	H1F0,MYH4,YWHAG,YWHAE,MYL2,TNNI2,YWHAB,MYLPF,MYLK2,GNB2L1,YWHAZ,PPP1CB,PYGB,TTN,MYL1,MYH2,PYGM,FLNC,MYL4,RYR1
EIF2 Signaling	2,58	RPS7,RPS4Y1,RPS10,RPS18,RPS19,RPLP2,PPP1CB,RPL12,RPS3,RPLP0,RPL10A,RPSA
Phenylalanine Degradation IV (Mammalian, via Side Chain)	2,33	ALDH2,GOT1,GOT2
Superpathway of Methionine Degradation	2,27	DLD,GOT1,MAT2A,GOT2
Phenylethylamine Degradation I	2,2	AOC3,ALDH2
L-cysteine Degradation I	2,2	GOT1,GOT2
Ethanol Degradation IV	2,17	ALDH2,CAT,ACSL1
Stearate Biosynthesis I (Animals)	2,07	FAM213B,FASN,SLC27A1,ACSL1
Mevalonate Pathway I	1,91	HADHB,HADHA
Cell Cycle: G2/M DNA Damage Checkpoint Regulation	1,76	YWHAG,YWHAE,YWHAB,YWHAZ
Tight Junction Signaling	1,73	MYH4,MYH2,MYL2,MYH8,MYL4,MYH7,ACTC1,MYL1,ACTA1,MYH1
Remodeling of Epithelial Adherens Junctions	1,72	ACTN2,TUBA4A,TUBB,ACTC1,ACTA1,ACTN3
Ketogenesis	1,71	HADHB,HADHA
Sucrose Degradation V (Mammalian)	1,71	TPI1,ALDOA
Superpathway of Geranylgeranyldiphosphate Biosynthesis I (via Mevalonate)	1,71	HADHB,HADHA
NRF2-mediated Oxidative Stress Response	1,7	MAP2K6,GSTM1,SOD1,SOD2,GSTM5,PRDX1,STIP1,CAT,ACTC1,ACTA1,FTH1
Ethanol Degradation II	1,6	HSD17B10,ALDH2,ACSL1
Hepatic Fibrosis / Hepatic Stellate Cell Activation	1,6	COL1A2,MYH4,MYH2,MYL2,MYH8,MYL4,MYH7,MYL1,MYH1
PPARα/RXRα Activation	1,47	MAP2K6,ACADL,GPD1,HSP90AB1,GPD2,FASN,CPT1B,CD36,SLC27A1,GOT2
Fatty Acid Activation	1,41	SLC27A1,ACSL1
Calcium Transport I	1,41	ATP2A1,ATP2A2
Colanic Acid Building Blocks Biosynthesis	1,41	GPI,UGP2
Oxidative Ethanol Degradation	1,41	ALDH2,ACSL1

III		
Myc Mediated Apoptosis Signaling	1,39	YWHAG,YWHAE,CYCS,YWHAB,YWHAZ
Glucose and Glucose-1-phosphate Degradation	1,33	PGM1
Protein Citrullination	1,33	PADI2
Palmitate Biosynthesis I (Animals)	1,33	FASN
Fatty Acid Biosynthesis Initiation II	1,33	FASN
GDP-glucose Biosynthesis	1,33	PGM1
Glutamate Biosynthesis II	1,33	GLUD1
Glutamate Degradation X	1,33	GLUD1

Supplementary Table S3B. Canonical pathways significantly affected by insulin treatment of STZ-animals (STZ+I vs. STZ-I comparison). Table lists pathway names as given by Ingenuity Pathway Analysis software, pathway p-value (score, as –Log10 p-value derivative) and significantly affected molecular members of a given pathway.

Pathway Name	Score	Significantly affected proteins
Glycolysis I	9,55	Pkm,PGK1,GPI,TPI1,ENO3,PGAM2,ALDOA,PFKM,FBP2
TCA Cycle II (Eukaryotic)	7,99	SDHA,SUCLA2,SDHB,CS,IDH3G,IDH3A,MDH2,IDH3B
Glycolysis II	7,99	PGK1,GPI,ENO3,PGAM2,ALDOA,ME1,MDH2,FBP2
Fatty Acid β-oxidation I	5,51	HADHB,SLC27A1,ACAA2,ECI1,ACSL1,HADHA,HADH
Calcium Signaling	5,21	TNNT1,TNNI2,MYL2,TNNC2,ATP2A1,PRKAR2A,Tpm1,MYH7,ATP2A2,TNNT3,CASQ1,RYR1,ASPH,ACTA1,MYH1
EIF2 Signaling	4,98	RPS4Y1,RPL22,RPL27,RPS18,RPS19,RPLP0,RPL10A,RPS10,RPS16,RPLP2,RPL12,RPS3,PPP1CA,RPSA
Ketolysis	4,37	HADHB,OXCT1,HADHA
Aspartate Degradation II	4,37	GOT1,MDH2,GOT2
Mitochondrial Dysfunction	3,52	SDHA,NDUFV1,SDHB,NDUFS1,SOD2,ATP5B,PARK7,GPD2,ATP5A1,UQCRC2,CAT,UQCRFS1
Glycogen Degradation II	3,4	PYGM,PGM1,PYGB
Glycogen Degradation III	3,11	PYGM,PGM1,PYGB
Superoxide Radicals Degradation	3,11	SOD1,SOD2,CAT
Creatine-phosphate Biosynthesis	2,91	CKMT2,CKM
Pyruvate Fermentation to Lactate	2,91	Ldhb,LDHA
Glycerol Degradation I	2,91	GPD1,GPD2
Glycerol-3-phosphate Shuttle	2,91	GPD1,GPD2
Glutamate Degradation II	2,91	GOT1,GOT2
Aspartate Biosynthesis	2,91	GOT1,GOT2
Actin Cytoskeleton Signaling	2,73	PFN1,CFL2,MYL2,MYLPF,ACTN2,MYLK2,MYH7,GSN,TTN,ACTA1,ACTN3,MYH1
Glutaryl-CoA Degradation	2,68	HADHB,HADHA,HADH
Phenylalanine Degradation IV (Mammalian, via Side Chain)	2,68	ALDH2,GOT1,GOT2
Tryptophan Degradation III (Eukaryotic)	2,68	HADHB,HADHA,HADH
RhoA Signaling	2,66	PFN1,CFL2,MYL2,MYLPF,MYLK2,Pfn2,TTN,ACTA1

Ethanol Degradation IV	2,52	ALDH2,CAT,ACSL1
Protein Kinase A Signaling	2,45	H1F0,YWHAG,YWHAE,TNNI2,MYL2,YWHAB,MYLPF,MYLK2,YWHAZ,PRKAR2A,PYGB,TTN,PYGM,PHKB,RYR1,PPP1CA
Phenylethylamine Degradation I	2,45	AOC3,ALDH2
L-cysteine Degradation I	2,45	GOT1,GOT2
tRNA Charging	2,43	TARSL2,GARS,DARS,EPRS
Nitric Oxide Signaling in the Cardiovascular System	2,4	HSP90AB1,CACNA1S,ATP2A1,CAV1,PRKAR2A,ATP2A2
Cellular Effects of Sildenafil (Viagra)	2,37	MYL2,MYLPF,CACNA1S,PRKAR2A,MYH7,ACTA1,MYH1
Cell Cycle: G2/M DNA Damage Checkpoint Regulation	2,19	YWHAG,YWHAE,YWHAB,YWHAZ
Mevalonate Pathway I	2,16	HADHB,HADHA
Ketogenesis	1,94	HADHB,HADHA
Sucrose Degradation V (Mammalian)	1,94	TPI1,ALDOA
Superpathway of Geranylgeranyldiphosphate Biosynthesis I (via Mevalonate)	1,94	HADHB,HADHA
Ethanol Degradation II	1,94	ADH5,ALDH2,ACSL1
Regulation of eIF4 and p70S6K Signaling	1,83	RPS4Y1,RPS10,PPP2R2A,RPS16,RPS18,RPS19,RPS3,RPSA
PPARα/RXRα Activation	1,81	ACADL,GPD1,HSP90AB1,GPD2,ADIPOQ,PRKAR2A,CD36,SLC27A1,GOT2
Superpathway of Methionine Degradation	1,77	GOT1,MAT2A,GOT2
Epithelial Adherens Junction Signaling	1,68	TUBA1A,MYL2,TUBB4B,ACTN2,MYH7,ACTA1,ACTN3,MYH1
NRF2-mediated Oxidative Stress Response	1,68	GSTM1,SOD1,SOD2,GSTM5,PRDX1,CAT,VCP,ACTA1,FTH1
Remodeling of Epithelial Adherens Junctions	1,67	TUBA1A,TUBB4B,ACTN2,ACTA1,ACTN3
Fatty Acid Activation	1,64	SLC27A1,ACSL1
Isoleucine Degradation I	1,64	HADHB,HADHA
Calcium Transport I	1,64	ATP2A1,ATP2A2
Colanic Acid Building Blocks Biosynthesis	1,64	GPI,UGP2
Oxidative Ethanol Degradation III	1,64	ALDH2,ACSL1
Regulation of Actin-based Motility by Rho	1,56	PFN1,MYL2,MYLPF,GSN,ACTA1
Cardiomyocyte Differentiation via BMP Receptors	1,53	MYL2,MYH7
Glucose and Glucose-1-phosphate Degradation	1,46	PGM1
Spermine Biosynthesis	1,46	SMS
GDP-glucose Biosynthesis	1,46	PGM1
Formaldehyde Oxidation II (Glutathione-dependent)	1,46	ADH5
14-3-3-mediated Signaling	1,46	YWHAG,TUBA1A,YWHAE,TUBB4B,YWHAB,YWHAZ
γ-linolenate Biosynthesis II (Animals)	1,43	SLC27A1,ACSL1
Cardiac β-adrenergic Signaling	1,38	PPP2R2A,CACNA1S,ATP2A1,PRKAR2A,PPP1CA,ATP2A2
ILK Signaling	1,32	CFL2,MYL2,PPP2R2A,ACTN2,MYH7,ACTA1,ACTN3,MYH1

Supplementary Table S3C. Canonical pathways significantly different between insulin treated and non-diabetic animals (STZ+I vs. ND comparison). Table lists pathway names as given by Ingenuity Pathway Analysis software, pathway p-value (score, as –Log10 p-value derivative) and significantly affected molecular members of a given pathway.

Pathway Name	Score	Significantly affected proteins
Mitochondrial Dysfunction	27	HSD17B10,SDHB,NDUFA9,NDUFA10,PRDX5,CPT1B,NDUFB5,COX2,NDUFA2,PDHA1,NDUFA5,NDUFS1,SOD2,GPD2,UQCRFS1,NDUFS2,OGDH,COX4I1,NDUFS4,NDUFA8,COX1,SDHA,NDUFV1,NDUFB3,CYCS,ATP5A1,NDUFA13,ATP5C1,NDUFS5,PRDX3,ATP5B,NDUFA6,UQCRC2,COX5A,CYC1,UQCRC1,COX5B
TCA Cycle II (Eukaryotic)	19.3	SDHA,SDHB,IDH3G,ACO2,SUCLA2,CS,SUCLG1,DLST,DLD,IDH3A,FH,MDH2,OGDH,IDH3B
Calcium Signaling	9.65	MYH4,TNNT1,MYL2,TNNI2,TNNC2,MYH8,TNNC1,ATP2A1,PRKAR2A,TPM3,TPM2,Tpm1,ATP2A2,MYL1,MYH2,TNNT3,MYL4,RYR1,ACTC1,ACTA1,MYH1
Fatty Acid β-oxidation I	8.01	HSD17B10,HADHB,SLC27A1,ACADM,ACAA2,ECI1,ACSL1,HADHA,HADH
Cellular Effects of Sildenafil (Viagra)	5.23	MYH4,MYH2,MYL2,MYH8,MYLPF,PRKAR2A,MYL4,ACTC1,MYL1,ACTA1,MYH1
Valine Degradation I	4.66	HIBCH,HADHB,HIBADH,DLD,HADHA
2-ketoglutarate Dehydrogenase Complex	4.34	DLST,DLD,OGDH
Ketolysis	4.34	HADHB,OXCT1,HADHA
Aspartate Degradation II	4.34	GOT1,MDH2,GOT2
Isoleucine Degradation I	4.29	HSD17B10,HADHB,DLD,HADHA
Glutaryl-CoA Degradation	4	HSD17B10,HADHB,HADHA,HADH
Tryptophan Degradation III (Eukaryotic)	4	HSD17B10,HADHB,HADHA,HADH
Gluconeogenesis I	3.9	PGK1,ENO3,ALDOA,ME1,MDH2
Epithelial Adherens Junction Signaling	3.76	MYH4,MYH2,MYL2,MYH8,ACTN2,TUBA4A,MYL4,ACTC1,MYL1,ACTA1,ACTN3,MYH1
Acetyl-CoA Biosynthesis I (Pyruvate Dehydrogenase Complex)	3.75	PDHA1,DLAT,DLD
Actin Cytoskeleton Signaling	3.69	MYH4,MYL2,MYH8,MYLPF,ACTN2,GSN,TTN,MYL1,MYH2,MYL4,ACTC1,ACTN3,ACTA1,MYH1
ILK Signaling	3.67	MYH4,MYL2,MYH8,ACTN2,MYL1,PPP2R1A,MYH2,FLNC,MYL4,ACTC1,ACTA1,ACTN3,MYH

		1
Mitochondrial L-carnitine Shuttle Pathway	3.36	CPT1B,CPT2,SLC27A1,ACSL1
Tight Junction Signaling	3.05	MYH4,PPP2R1A,MYH2,MYL2,MYH8,PRKAR2A,MYL4,ACTC1,MYL1,ACTA1,MYH1
NRF2-mediated Oxidative Stress Response	3.04	GSTM1,SOD1,SOD2,GSTM5,PRDX1,STIP1,VCP,DNAJA2,ACTC1,ACTA1,MGST3,FTH1
Pyruvate Fermentation to Lactate	2.89	Ldhb,LDHA
Glycerol Degradation I	2.89	GPD1,GPD2
Glycerol-3-phosphate Shuttle	2.89	GPD1,GPD2
Glutamate Degradation II	2.89	GOT1,GOT2
Aspartate Biosynthesis	2.89	GOT1,GOT2
Glycolysis I	2.8	PGK1,ENO3,ALDOA,PFKM
Regulation of Actin-based Motility by Rho	2.79	MYL2,MYLPF,MYL4,GSN,ACTC1,MYL1,ACTA1
Phenylalanine Degradation IV (Mammalian, via Side Chain)	2.65	ALDH2,GOT1,GOT2
L-cysteine Degradation I	2.43	GOT1,GOT2
PPARα/RXRα Activation	2.21	ACADL,GPD1,HSP90AB1,GPD2,FASN,CPT1B,PRKAR2A,CD36,SLC27A1,GOT2
Mevalonate Pathway I	2.14	HADHB,HADHA
Glutathione-mediated Detoxification	2.11	GSTM1,GSTM5,MGST3
RhoA Signaling	2.02	MYL2,MYLPF,MYL4,ACTC1,TTN,MYL1,ACTA1
Ketogenesis	1.93	HADHB,HADHA
Glycogen Degradation II	1.93	PYGM,PGM1
Superpathway of Geranylgeranyldiphosphate Biosynthesis I (via Mevalonate)	1.93	HADHB,HADHA
Ethanol Degradation II	1.91	HSD17B10,ALDH2,ACSL1
Hepatic Fibrosis / Hepatic Stellate Cell Activation	1.8	COL1A2,MYH4,MYH2,MYL2,MYH8,MYL4,MYL1,MYH1

Glycogen Degradation III	1.76	PYGM,PGM1
Superoxide Radicals Degradation	1.76	SOD1,SOD2
Superpathway of Methionine Degradation	1.75	DLD,GOT1,GOT2
LPS/IL-1 Mediated Inhibition of RXR Function	1.71	GSTM1,GSTM5,CPT1B,CPT2,FABP4,SLC27A1,FABP3,ACSL1,MGST3
Protein Kinase A Signaling	1.65	MYH4,YWHAG,MYL2,TNNI2,MYLPF,YWHAZ,PRKAR2A,TTN,MYL1,MYH2,PYGM,FLNC,MYL4,RYR1
Remodeling of Epithelial Adherens Junctions	1.63	ACTN2,TUBA4A,ACTC1,ACTA1,ACTN3
Fatty Acid Activation	1.62	SLC27A1,ACSL1
Calcium Transport I	1.62	ATP2A1,ATP2A2
Oxidative Ethanol Degradation III	1.62	ALDH2,ACSL1
Stearate Biosynthesis I (Animals)	1.61	FASN,SLC27A1,ACSL1
Glucose and Glucose-1-phosphate Degradation	1.45	PGM1
Protein Citrullination	1.45	PADI2
Palmitate Biosynthesis I (Animals)	1.45	FASN
Fatty Acid Biosynthesis Initiation II	1.45	FASN
GDP-glucose Biosynthesis	1.45	PGM1
TR/RXR Activation	1.43	SLC16A3,COL6A3,FASN,ATP2A1,ME1
γ-linolenate Biosynthesis II (Animals)	1.41	SLC27A1,ACSL1
Ethanol Degradation IV	1.41	ALDH2,ACSL1

SUPPLEMENTARY DATA

Supplementary Table S4. Individual mitochondrial protein data from **Figure S3**. Table lists 111 mitochondrial proteins, protein symbols, names and accession numbers as given by UniProt database, together with their expression ratio (in log2 scale), p-value (base and in –log10 scale) and Ingenuity IPA protein group affiliation (Group). Proteins are listed in alphabetical order by their symbols. Mitochondrial localization according to MitoCarta mitochondrial proteome database.

Symbol	Entrez Gene Name	Accession #	Log2 (STZ-I vs ND)	p-value (STZ-I vs ND)	Log2 (STZ+I vs ND)	p-value (STZ+I vs ND)	Group
ACAA2	acetyl-CoA acyltransferase 2	Q8BWT1	-0.672	1.8E-42	-0.523	1.1E-27	Lipid metabolism
ACADL	acyl-CoA dehydrogenase, long chain	P51174	-0.461	4.7E-19	-0.510	3.7E-23	Lipid metabolism
ACADM	acyl-CoA dehydrogenase, C-4 to C-12 straight chain	Q91WS8	-0.512	8.0E-13	-0.454	1.3E-13	Lipid metabolism
ACADVL	acyl-CoA dehydrogenase, very long chain	B1AR27	-0.246	2.2E-16	-0.301	4.4E-16	Lipid metabolism
ACAT1	acetyl-CoA acetyltransferase 1	Q8QZT1	-0.440	7.89E-25	-0.295	1.12E-12	Lipid metabolism
ACO2	aconitase 2, mitochondrial	Q99KI0	0.073	3.8E-08	0.050	1.4E-04	TCA Cycle
ACSL1	acyl-CoA synthetase long-chain family member 1	P41216	-0.235	5.8E-19	-0.318	1.9E-42	Lipid metabolism
ADCK3	aarF domain containing kinase 3	Q60936	0.285	3.6E-03	-0.288	3.2E-02	Respiratory chain, realted
ALDH2	aldehyde dehydrogenase 2 family (mitochondrial)	P47738	-0.156	9.1E-03	-0.453	2.4E-13	Ethanol degradation
ATP5A1	ATP synthase, H+ transporting, mitochondrial F1 complex, alpha subunit 1, cardiac muscle	D3Z6F5	-0.185	1.0E-07	-0.118	7.0E-05	Respiratory chain
ATP5B	ATP synthase, H+ transporting, mitochondrial F1 complex, beta polypeptide	P56480	-0.202	4.4E-16	-0.127	4.3E-07	Respiratory chain
ATP5C1	ATP synthase, H+ transporting, mitochondrial F1 complex, gamma polypeptide 1	A2AKU9	-0.150	5.2E-05	-0.144	2.4E-06	Respiratory chain
ATP5F1	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit B1	Q5I0W0	-0.238	6.7E-08	-0.200	2.5E-06	Respiratory chain

Atp5h	ATP synthase, H+ transporting, mitochondrial F0 complex, subunit d	Q9DCX2	-0.300	5.1E-12	-0.250	4.0E-11	Respiratory chain
ATP5I	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit E	Q5EBI8	-0.211	2.9E-04	-0.177	1.4E-03	Respiratory chain
ATP5L	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit G	Q9CPQ8	-0.286	1.3E-04	-0.261	2.7E-05	Respiratory chain
ATP5O	ATP synthase, H+ transporting, mitochondrial F1 complex, O subunit	Q9DB20	-0.201	2.9E-05	-0.161	9.0E-05	Respiratory chain
CAPZA2	capping protein (actin filament) muscle Z-line, alpha 2	Q5DQJ3	0.707	5.6E-22	0.763	4.2E-23	
CHCHD3	coiled-coil-helix-coiled-coil-helix domain containing 3	Q9CRB9	-0.315	2.0E-04	-0.231	3.0E-02	Mitochondrial cristae integrity
CISD1	CDGSH iron sulfur domain 1	Q91WS0	-0.130	2.6E-02	-0.145	3.8E-03	Mitochondrial
CKMT2	creatine kinase, mitochondrial 2 (sarcomeric)	Q6P8J7	-0.646	4.5E-88	-0.379	2.6E-54	Mitochondrial transport
COQ9	coenzyme Q9 homolog (S. cerevisiae)	Q8K1Z0	-0.337	2.5E-09	-0.245	2.0E-05	Ubiquinone biosynthesis
COX1	cytochrome c oxidase subunit I	Q9MD68	-0.392	2.6E-09	-0.269	1.8E-04	Respiratory chain
COX2	cytochrome c oxidase subunit II	P00405	-0.331	1.6E-05	-0.213	3.3E-04	Respiratory chain
COX4I1	cytochrome c oxidase subunit IV isoform 1	P19783	-0.321	2.6E-04	-0.211	4.7E-03	Respiratory chain
COX5A	cytochrome c oxidase subunit Va	P12787	-0.386	1.3E-02	-0.267	4.7E-03	Respiratory chain
COX5B	cytochrome c oxidase subunit Vb	P19536	-0.374	1.5E-04	-0.256	4.4E-03	Respiratory chain
CPT1B	carnitine palmitoyltransferase 1B (muscle)	Q3UIM5	-0.226	1.4E-10	-0.246	3.0E-12	Lipid metabolism
CPT2	carnitine palmitoyltransferase 2	P52825	-0.345	1.0E-04	-0.324	3.8E-04	Lipid metabolism

CRAT	carnitine O-acetyltransferase	Q3V1Y3	-0.268	1.2E-10	-0.253	1.1E-06	Lipid metabolism
CS	citrate synthase	Q9CZU6	-0.211	3.0E-10	-0.123	2.2E-04	TCA Cycle
CYC1	cytochrome c-1	Q9D0M3	-0.365	1.3E-05	-0.266	1.9E-03	Respiratory chain
CYCS	cytochrome c, somatic	Q56A15	-0.259	7.8E-09	-0.229	5.1E-06	Respiratory chain
DECR1	2,4-dienoyl CoA reductase 1, mitochondrial	Q4FJK0	-0.296	2.3E-07	-0.327	3.1E-10	Lipid metabolism
DLAT	dihydrolipoamide S-acetyltransferase	Q8BMF4	-0.251	3.6E-19	-0.257	6.8E-20	Lipid metabolism
DLD	dihydrolipoamide dehydrogenase	O08749	-0.114	1.6E-04	-0.127	8.1E-06	Lipid metabolism
DLST	dihydrolipoamide S-succinyltransferase (E2 component of 2-oxo-glutarate complex)	Q9D2G2	-0.318	1.1E-05	-0.295	2.8E-04	Lipid metabolism
ECI1	enoyl-CoA delta isomerase 1	Q8QZV3	-0.289	6.8E-08	-0.268	2.4E-08	Lipid metabolism
ECHS1	enoyl CoA hydratase, short chain, 1, mitochondrial	Q8BH95	-0,310	7,98E-03	-0,292	1,21E-02	Lipid metabolism
ETFA	electron-transfer-flavoprotein, alpha polypeptide	Q99LC5	-0.286	3.8E-10	-0.272	6.4E-30	Respiratory chain
ETFB	electron-transfer-flavoprotein, beta polypeptide	Q9DCW4	-0.373	3.6E-14	-0.315	5.1E-18	Respiratory chain
ETFDH	electron-transferring-flavoprotein dehydrogenase	Q6PF96	-0.422	3.78E-08	-0.386	2.69E-07	Respiratory chain
FH	fumarate hydratase	P97807	-0.237	3.2E-04	0.097	2.3E-03	TCA Cycle
Gapdh	glyceraldehyde-3-phosphate dehydrogenase	P16858	0.102	1.28E-14	0.073	2.24E-13	Glycolysis/Glycogen degradation
GOT2	glutamic-oxaloacetic transaminase 2, mitochondrial (aspartate aminotransferase 2)	P05202	-0.377	1.1E-19	-0.251	9.7E-13	Lipid metabolism
GPD2	glycerol-3-phosphate dehydrogenase 2 (mitochondrial)	Q64521	0.110	1.8E-02	0.225	3.5E-07	Lipid metabolism

GSTM5	glutathione S-transferase mu 5	P10649	0.303	3.2E-07	0.149	1.2E-02	Free Radical Scavenging/Protein ubiquitination/Protein Folding
HADH	hydroxyacyl-CoA dehydrogenase	Q61425	-0.334	8.7E-05	-0.361	2.4E-06	Lipid metabolism
HADHA	hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), alpha subunit	Q8BMS1	0.179	4.4E-16	-0.255	6.9E-25	Lipid metabolism
HADHB	hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), beta subunit	Q99JY0	-0.162	2.1E-13	-0.235	8.5E-27	Lipid metabolism
HIBADH	3-hydroxyisobutyrate dehydrogenase	Q99L13	-0.380	4.8E-03	-0.445	9.2E-04	Valine Degradation
HIBCH	3-hydroxyisobutyryl-CoA hydrolase	Q8QZS1	-0.255	1.7E-03	-0.179	4.2E-02	Valine Degradation
HSD17B10 ; M/SCHAD	hydroxysteroid (17-beta) dehydrogenase 10	Q99N15	-0.162	3.3E-03	-0.137	3.1E-02	Lipid metabolism
HSP90AB1	heat shock protein 90kDa alpha (cytosolic), class B member 1	Q71LX8	-0.291	1.4E-13	-0.110	4.1E-04	Free Radical Scavenging/Protein ubiquitination/Protein Folding
HSPA9	heat shock 70kDa protein 9 (mortalin)	P38647	-0.423	9.3E-20	-0.265	8.5E-10	Free Radical Scavenging/Protein ubiquitination/Protein Folding
HSPD1	heat shock 60kDa protein 1 (chaperonin)	P63038	-0.248	3.1E-18	-0.216	5.1E-13	Free Radical Scavenging/Protein ubiquitination/Protein Folding
HSPE1	heat shock 10kDa protein 1 (chaperonin 10)	Q4KL76	-0.348	7.8E-04	-0.238	4.1E-02	Free Radical Scavenging/Protein ubiquitination/Protein Folding
IDH2	isocitrate dehydrogenase 2	P54071	0.472	3.9E-19	-0.242	2.9E-13	TCA Cycle

	(NADP+), mitochondrial						
IDH3A	isocitrate dehydrogenase 3 (NAD+) alpha	Q9D6R2	-0.303	4.2E-15	-0.181	7.4E-09	TCA Cycle
IDH3B	isocitrate dehydrogenase 3 (NAD+) beta	Q91VA7	-0.319	3.5E-24	-0.212	1.7E-11	TCA Cycle
IDH3G	isocitrate dehydrogenase 3 (NAD+) gamma	P70404	-0.392	2.1E-10	-0.235	1.1E-03	TCA Cycle
IMMT	inner membrane protein, mitochondrial	Q3TEY5	-0.321	3.7E-39	-0.287	1.5E-31	Free Radical Scavenging/Protein ubiquitination/Protein Folding
LRPPRC	leucine-rich pentatricopeptide repeat containing	Q6PB66	-0.711	4.6E-04	-0.439	3.4E-02	Lipid metabolism
LETM1	leucine zipper-EF-hand containing transmembrane protein 1	Q9Z2I0	-0.5	9.38E-05	-0.402	1.28E-03	Putative mitochondrial Ca(2+)/H(+) antiporter
MDH2	malate dehydrogenase 2, NAD (mitochondrial)	P08249	-0.198	9.9E-14	-0.152	5.0E-11	TCA Cycle
MPC2	mitochondrial pyruvate carrier 2	Q9D023	-0.514	3.4E-06	-0.262	9.6E-03	Mitochondrial transport
NDUFA10	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 10, 42kDa	Q99LC3	-0.334	4.9E-09	-0.226	2.1E-03	Respiratory chain
NDUFA13	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 13	Q9ERS2	-0.367	3.2E-05	-0.213	2.3E-03	Respiratory chain
NDUFA2	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 2, 8kDa	Q9CQ75	-0.485	8.4E-04	-0.281	2.1E-02	Respiratory chain
NDUFA5	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 5, 13kDa	Q9CPP6	-0.414	3.0E-08	-0.296	1.8E-05	Respiratory chain
NDUFA6	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 6, 14kDa	Q9CQZ5	-0.371	6.0E-12	-0.319	4.4E-07	Respiratory chain
NDUFA8	NADH dehydrogenase (ubiquinone) 1 alpha	Q9DCJ5	-0.363	1.3E-05	-0.256	1.1E-03	Respiratory chain

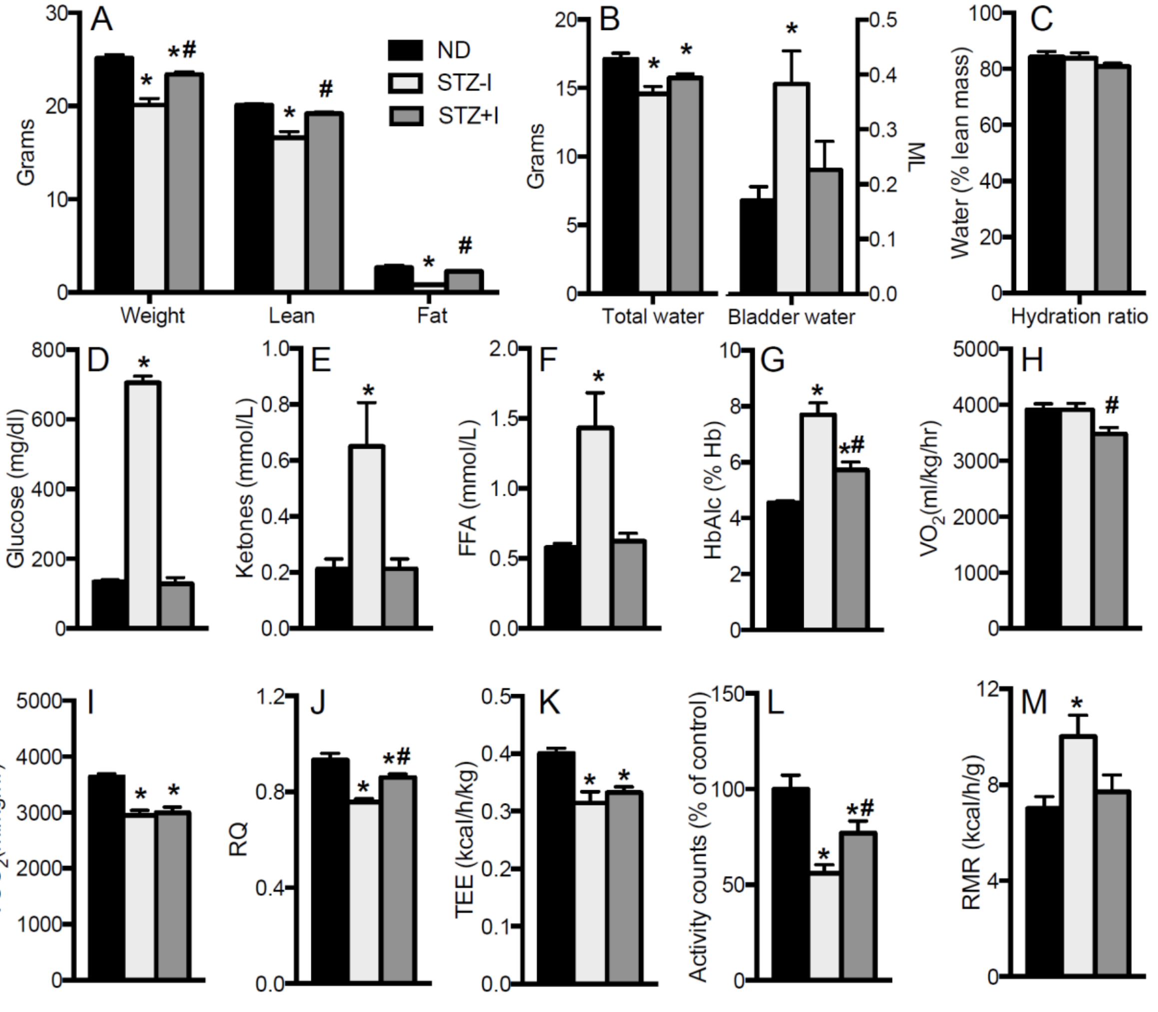
	subcomplex, 8, 19kDa						
NDUFA9	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 9, 39kDa	Q6GTD3	-0.435	1.6E-07	-0.317	3.9E-06	Respiratory chain
NDUFB3	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 3, 12kDa	Q9D6H6	-0.432	1.8E-03	-0.311	2.0E-02	Respiratory chain
NDUFB5	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 16kDa	Q8BU20	-0.332	4.4E-10	-0.250	1.8E-05	Respiratory chain
NDUFS1	NADH dehydrogenase (ubiquinone) Fe-S protein 1, 75kDa (NADH-coenzyme Q reductase)	Q91VD9	-0.333	2.0E-15	-0.221	1.8E-10	Respiratory chain
NDUFS2	NADH dehydrogenase (ubiquinone) Fe-S protein 2, 49kDa (NADH-coenzyme Q reductase)	Q91WD5	-0.327	2.9E-09	-0.248	5.9E-05	Respiratory chain
NDUFS4	NADH dehydrogenase (ubiquinone) Fe-S protein 4, 18kDa (NADH-coenzyme Q reductase)	Q923F9	-0.312	3.0E-05	-0.201	3.5E-03	Respiratory chain
NDUFS5	NADH dehydrogenase (ubiquinone) Fe-S protein 5, 15kDa (NADH-coenzyme Q reductase)	Q99LY9	-0.415	2.8E-03	-0.319	1.5E-02	Respiratory chain
NDUFV1	NADH dehydrogenase (ubiquinone) flavoprotein 1, 51kDa	Q91YT0	-0.325	9.3E-14	-0.206	1.0E-05	Respiratory chain
OGDH	oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide)	Q60597	-0.215	6.7E-08	-0.212	1.0E-08	TCA Cycle
OXCT1	3-oxoacid CoA transferase 1	Q9D0K2	-0.520	1.9E-21	-0.212	2.5E-06	Lipid metabolism
PDHA1	pyruvate dehydrogenase (lipoamide) alpha 1	Q3UFJ3	-0.392	3.5E-04	-0.347	2.2E-03	Glycolysis, TCA Cycle
PDHB	pyruvate dehydrogenase (lipoamide) beta	Q9D051	-0.233	2.71E-06	-0.189	2.45E-05	Glycolysis, TCA Cycle
PDHX	pyruvate dehydrogenase	Q8BKZ9	-0.304	4.41E-09	-0.26	4.91E-07	Glycolysis, TCA Cycle

	complex, component X						
PDPR	pyruvate dehydrogenase phosphatase regulatory subunit	Q7TSQ8	-0.412	2.1E-10	-0.283	2.4E-06	Glycolysis, TCA Cycle
PHB	prohibitin	P67778	-0.248	1.2E-04	-0.217	2.7E-04	Free Radical Scavenging/Protein ubiquitination/Protein Folding
PRDX5	peroxiredoxin 5	P99029	-0.299	4.8E-08	-0.258	5.1E-06	Free Radical Scavenging/Protein ubiquitination/Protein Folding
SAMM50	sorting and assembly machinery component 50 homolog (S. cerevisiae)	Q8BGH2	-0.229	3.70E-03	-0.129	4.73E-02	Mitochondrial protein complexes assembly
SDHA	succinate dehydrogenase complex, subunit A, flavoprotein (Fp)	Q8K2B3	-0.298	6.2E-21	-0.197	4.2E-12	Respiratory chain
SDHB	succinate dehydrogenase complex, subunit B, iron sulfur (Ip)	A2AA77	-0.302	1.4E-09	-0.167	3.6E-04	Respiratory chain
SDHC	succinate dehydrogenase complex, subunit C, integral membrane protein, 15kDa	Q5XK33	-0.522	3.18E-03	-0.378	2.13E-02	Respiratory chain
SLC25A11	solute carrier family 25 (mitochondrial carrier; oxoglutarate carrier), member 11	Q5SX53	-0.388	7.8E-10	-0.220	2.5E-04	Mitochondrial transport
SLC25A12	solute carrier family 25 (aspartate/glutamate carrier), member 12	Q8BH59	-0.176	8.5E-19	-0.126	6.0E-12	Mitochondrial transport
SLC25A3	solute carrier family 25 (mitochondrial carrier; phosphate carrier), member 3	Q3THU8	-0.348	8.6E-17	-0.248	3.0E-12	Mitochondrial transport
SLC25A4	solute carrier family 25 (mitochondrial carrier; adenine nucleotide translocator), member 4	Q8BVI9	-0.233	1.0E-04	-0.138	4.3E-03	Mitochondrial transport

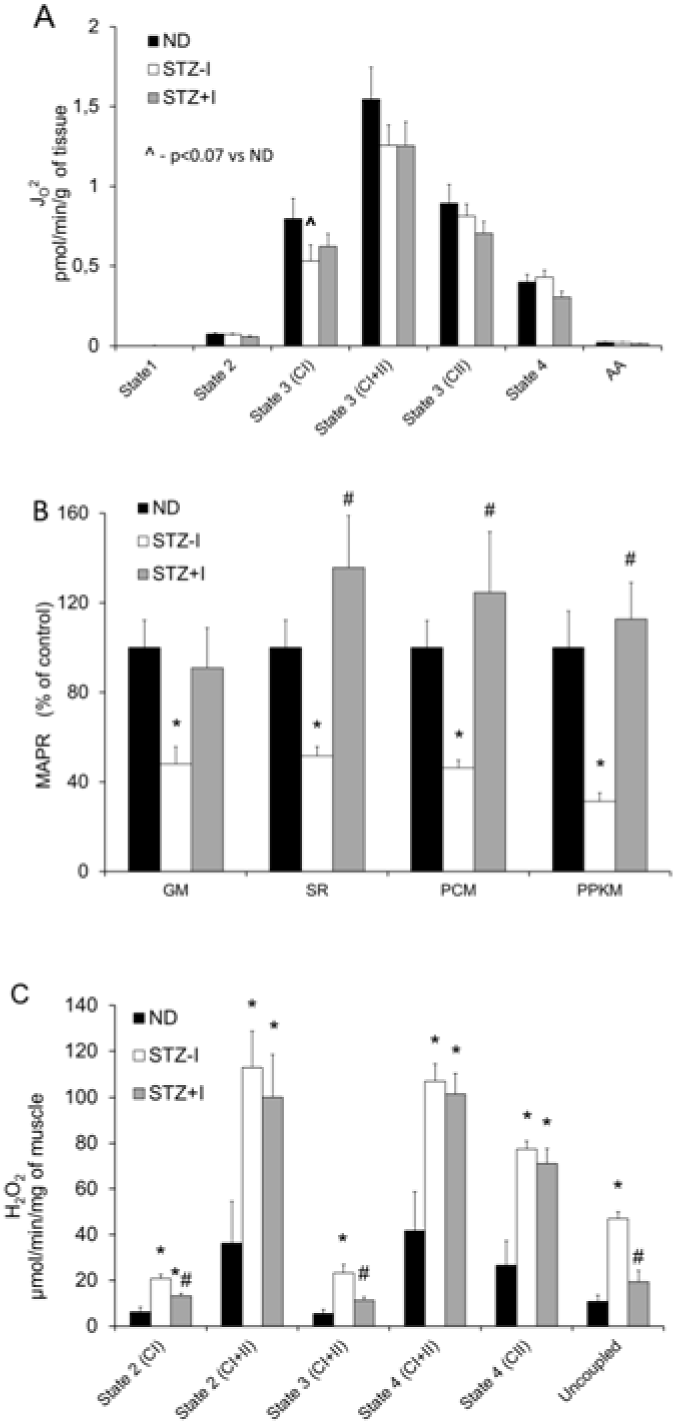
SLC25A5	solute carrier family 25 (mitochondrial carrier; adenine nucleotide translocator), member 5	P51881	-0.209	4.86E-05	-0.149	6.23E-04	Mitochondrial transport
SOD1	superoxide dismutase 1, soluble	P08228	0.213	9.2E-07	-0.118	2.0E-02	Free Radical Scavenging/Protein ubiquitination/Protein Folding
SOD2	superoxide dismutase 2, mitochondrial	P09671	-0.305	8.3E-07	-0.173	6.3E-04	Free Radical Scavenging/Protein ubiquitination/Protein Folding
SUCLA2	succinate-CoA ligase, ADP-forming, beta subunit	Q3U6C7	-0.240	3.2E-11	-0.186	6.3E-10	TCA Cycle
SUCLG1	succinate-CoA ligase, alpha subunit	Q9WUM5	-0.246	2.1E-11	-0.214	1.4E-07	TCA Cycle
TUFM	Tu translation elongation factor, mitochondrial	Q8BFR5	-0.179	1.6E-05	0.107	7.9E-03	Mitochondrial protein translation
UQCRB	ubiquinol-cytochrome c reductase binding protein	Q9D855	-0.399	2.07E-09	-0.336	2.25E-07	Respiratory chain
UQCRC1	ubiquinol-cytochrome c reductase core protein I	Q3TIC8	-0.230	8.3E-07	-0.169	9.2E-05	Respiratory chain
UQCRC2	ubiquinol-cytochrome c reductase core protein II	Q9DB77	-0.254	1.2E-19	-0.165	1.5E-12	Respiratory chain
UQCRFS1	ubiquinol-cytochrome c reductase, Rieske iron-sulfur polypeptide 1	Q9CR68	-0.331	5.3E-31	-0.211	1.4E-10	Respiratory chain
VDAC1	voltage-dependent anion channel 1	Q60932-2	-0.159	2.1E-05	-0.112	6.0E-03	Mitochondrial transport
VDAC2	voltage-dependent anion channel 2	Q60930	-0.165	3.6E-04	-0.119	1.0E-02	Mitochondrial transport
YWHAZ	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide	P63101	0.139	4.3E-03	-0.146	7.9E-03	Free Radical Scavenging/Protein ubiquitination/Protein Folding/Mitochondrial protein import

SUPPLEMENTARY DATA

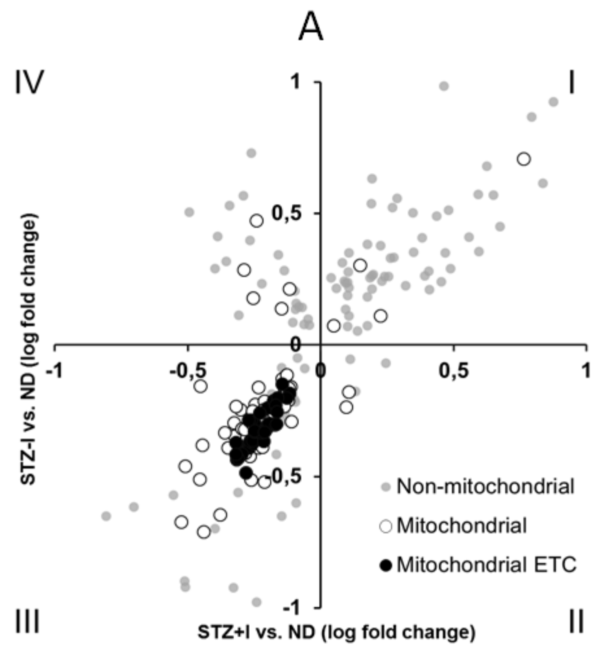
Supplementary Figure S1. **Effects of insulin on body composition, blood parameters, and whole-body energy metabolism.** Insulin replacement restored body weight, lean mass, and fat mass in STZ-induced diabetic mice (A). Insulin replacement also corrected changes in total body water and bladder water volume observed with insulin deprivation (B), while not affecting body hydration ratio (C). Plasma glucose (D), ketones (E), free fatty acids (F) and percentage of HbA1C (G) were elevated by insulin deprivation and corrected by insulin treatment. Results of 24h indirect calorimetry indicate that although insulin treatment was unable to fully compensate for the decrease in respiratory quotient (RQ, J), total 24h energy expenditure (TEE, K) and physical activity (L), it was able to decrease resting metabolic rate (RMR, M). Both oxygen and carbon dioxide flux (H,I) lower in STZ+I and VO_2 was lower in STZ-I than in ND. Data are means ±SEM. N=8 per group. * denotes p<0.05 vs. non-diabetic, # denotes p<0.05 vs. STZ-I group.



Supplementary Figure S2. The effect of insulin deprivation and treatment on mitochondrial oxygen consumption (**Panel A**) ATP production (**Panel B**) and H2O2 emission **(Panel C)** as calculated per muscle tissue weight. Substrate combinations explained under materials and methods section. * - p<0.05 vs. ND group, # - p<0.05 vs. STZ+I group. Values are means +/- SEM N=13 (except panel C, N=8).

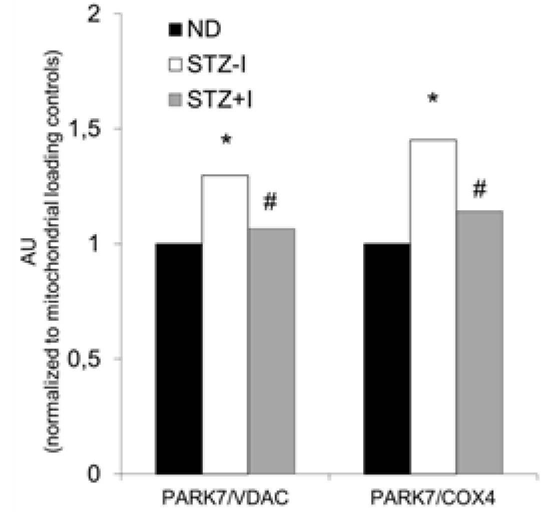


Supplementary Figure S3. **Insulin treatment does not fully corrects mitochondrial proteome changes induced by insulin deprivation.** Panel A shows expression of 242 proteins significantly ($p<0.05$) different from non-diabetic (ND) group in both the STZ-I and STZ+I animals. Proteins not corrected by insulin treatment are located in quadrant III (down-regulated in both STZ-I and STZ+I, n=118) and in quadrant I (up-regulated in both STZ-I and D+,I n=58). Proteins in quadrants II (n=5) and IV (n=27) have the opposite expression pattern and are therefore regulated by insulin. Values from STZ+I vs. ND and STZ-I vs. ND comparison are given on X and Y axis, respectively. Panel B presents significantly altered pathways ($p<0.05$, -log10 p-value >1.3) associated with proteins from respective I-IV quadrants. Detailed expression data for individual mitochondrial proteins is presented in **Table S4**.

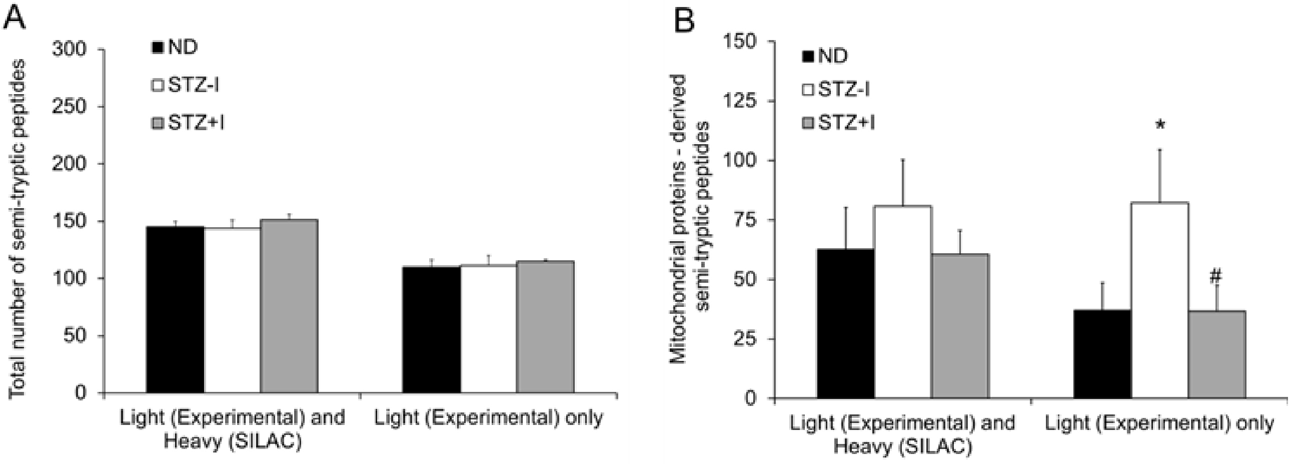


Upregulated in STZ-I **Downregulated in STZ+I**	**Upregulated in STZ-I** **Upregulated in STZ+I**
NRF2 Oxidative Stress Response DNA Damage Regulation Fatty Acids Transport Glucose and GP1 Degradation	Calcium Signaling* Actin Cytoskeleton Signaling Glycerol-3-P Shuttle
Downregulated in STZ-I **Downregulated in STZ+I**	**Downregulated in STZ-I** **Upregulated in STZ+I**
Mitochondrial Dysfunction TCA Cycle Fatty Acid β-oxidation Mitochondrial L-carnitine Shuttle	Actin Cytoskeleton Signaling

Supplementary Figure S4. PPARK7 protein responsible for ROS-related mitophagy is up regulated within mitochondria of STZ-diabetic mice, despite overall decrease in mitochondrial protein content. Mitochondrial loading VDAC1 (non-selective mitochondrial anion channel) or COX41 (subunit of mitochondrial electron transport chain) was used to normalize mitochondrial expression of PARK7 across experimental groups. N=6 per group.



Supplementary Figure S5. Insulin deprivation increases the abundance of semi-tryptic peptides from mitochondrial proteins, which is corrected by insulin treatment. **Panel A** presents total number of semi-tryptic peptides from all skeletal muscle proteins, from both the experimental (light) and SILAC (heavy, graph bars to left) animals and from experimental animals only (light, bar graphs to right). **Panel B** presents total number of semi-tryptic peptides from proteins of mitochondrial origin. The increase in the number of semi-tryptic peptides is visible only for experimental animals in insulin-deprived group N=3 per group. Values represent mean +/- SEM. * -p<0.0001 compared to non-diabetic (ND) group values; # -p<0.0001 as compared to diabetic, insulin treated group (STZ+I).



Supplementary Figure S6. Insulin deprivation in STZ-diabetic animals significantly decreases mixed muscle protein (MMP) fractional synthesis rate (FSR) in different skeletal muscles, which is partially corrected by insulin treatment. Values are expressed as a mean % /day (N=3 per group), +/- SEM * - p<0.05 compared to non-diabetic (ND) group values; # -p<0.05 as compared to diabetic, insulin treated group (STZ+I).