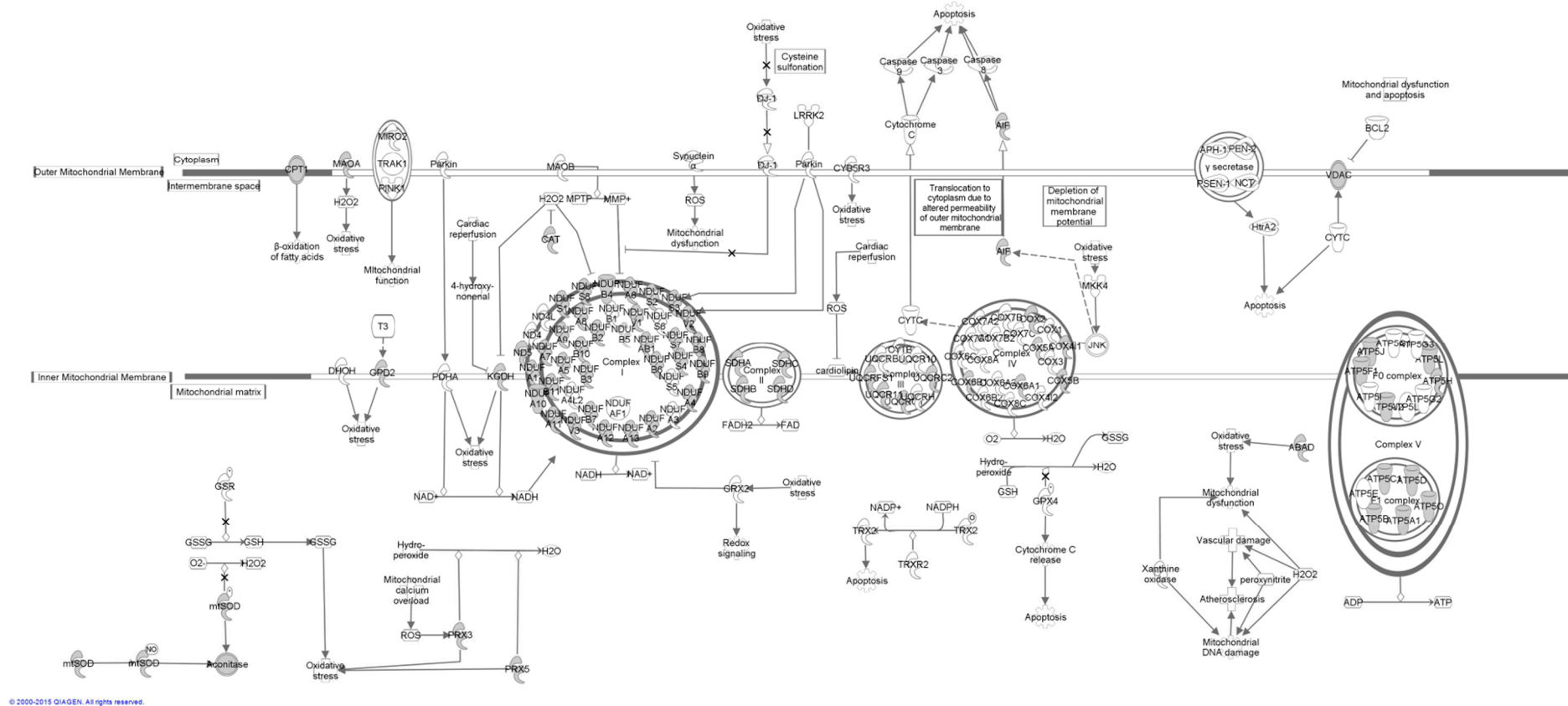




## Supplementary Information



**Figure S1.** IPA representation of mitochondrial pathways. The complete list of identified proteins was submitted to IPA. Almost all the mitochondrial functional proteins were mapped (shown in grey).

**Table S1.** Differentially expressed proteins involved in cell death and mitochondrial quality control in response to stress.

Accession Number	Gene Name	Protein Name	Function, Process	IR-LT3S (FC)	IR-NT3 (FC)
<i>Mitochondria-mediated cell death:</i>					
G3V741	<i>Slc25a3</i>	Phosphate carrier protein	Mitochondria permeability transition (cell death)	NS	-2.2 *
Q9WVJ6	<i>Tgm2</i>	Protein Tgm2	Clearance of damaged mitochondria	7.0	39 *
Q9Z2L0	<i>Vdac1</i>	Voltage-dependent anion-selective channel protein 1	Apoptosis, necrosis	3.4	NS *
P81155	<i>Vdac2</i>	Voltage-dependent anion-selective channel protein 2	Apoptosis, necrosis	3.4	1.80
Q9R1Z0	<i>Vdac3</i>	Voltage-dependent anion-selective channel protein 3	Apoptosis, necrosis	3.5	2.05
<i>Mitochondria quality control:</i>					
G3V913	<i>Hspb1</i>	Heat shock 27 kDa protein 1	Chaperone, negative regulation of oxidative stress	42	67 *
P63018	<i>Hspa8</i>	Heat shock cognate 71 kDa	Chaperone-mediated protein folding	NS	20 *
P97541	<i>Hspb6</i>	Heat shock protein $\beta$ -6	Chaperone, protein homodimerization	NS	3.1 *
P34058	<i>Hsp90ab1</i>	Heat shock protein HSP 90- $\beta$	Chaperone, maturation, structural maintenance and proper regulation of target proteins	7.5	24 *
P63039	<i>Hspd1</i>	Heat shock protein 60 kDa	Mitochondrial protein import and macromolecular assembly	4.4	4.1
P97576	<i>Grpel1</i>	GrpE protein homolog 1	Proteins translocation from the inner membrane into the mitochondrial matrix	4.9	7.3
P23928	<i>Cryab</i>	$\alpha$ -crystallin B chain	Chaperone-like activity, preventing aggregation of various proteins under stress conditions	14	27 *
Q5XIM0	<i>Bcs1l</i>	BCS1-like (Yeast)	Chaperone-like protein essential for mitochondrial complex assembly	4.2	5.3
Q5BJQ0	<i>Adck3</i>	Chaperone activity of bc1 complex-like	Chaperone-like. Proper conformation and functioning of protein complexes in the respiratory chain	5.6	6.2
D4AC73	<i>Chchd7</i>	Protein Chchd7	Assembly of mitochondrial respiratory complex COX23 Cytochrome C Oxidase Assembly Homolog	7.3	1.4 *
P85834	<i>Tufm</i>	Elongation factor Tu	Mitochondrial protein biosynthesis	5.1	3.7 *
Q68FT1	<i>Coq9</i>	Ubiquinone biosynthesis protein	Cofactor biosynthesis	2.4	8.0 *
P62076	<i>Timm13</i>	Mitochondrial import inner membrane translocase subunit Tim13	Chaperone-like, protein folding and guiding through the mitochondrial intermembrane space	NS	1.3 *
P62909	<i>Rps3</i>	40S ribosomal protein S3	Repair of damaged DNA	8.7	28 *
G3V8V6	<i>MacroD1</i>	O-acetyl-ADP-ribose deacetylase MACROD1	Cellular response to DNA damage stimulus	7.3	15 *
P31044	<i>Pebp1</i>	Phosphatidylethanolamine-binding protein 1	Serine protease inhibitor, response to oxidative stress and wounding	3.7	14 *
F1LM33	<i>Lrpprc</i>	Leucine-rich PPR	Translation or stability of mitochondrially encoded cytochrome c oxidase subunits	2.9	4.4
P13437	<i>Acaa2</i>	3-ketoacyl-CoA thiolase	Abolishes mitochondrial damage and BNIP3-mediated apoptosis	13	15

Table S1. Cont.

Accession Number	Gene Name	Protein Name	Function, Process	IR-LT3S (FC)	IR-NT3 (FC)
<i>Antioxidant defence:</i>					
G3V7J0	<i>Aldh6a1</i>	Aldehyde dehydrogenase family 6, isoform CRA	Aldehyde clearance, prevents aldehyde mediated oxidative stress	4.2	10 *
F1LN88	<i>Aldh2</i>	Aldehyde dehydrogenase	Aldehyde clearance, prevents aldehyde mediated oxidative stress	NS	9.6 *
P35704	<i>Prdx2</i>	Peroxiredoxin-2	Antioxidant	NS	19 *
Q9R063	<i>Prdx5</i>	Peroxiredoxin-5	Antioxidant	NS	39 *
P07632	<i>Sod1</i>	Superoxide dismutase [Cu-Zn]	Antioxidant	NS	8.8 *
P07895	<i>Sod2</i>	Superoxide dismutase [Mn]	Antioxidant	NS	12 *

Comparison among groups was performed as described in statistical analysis. FC = fold change with respect to sham group; NS = not significantly different from sham group; \* *p* vs. IR-LT3S < 0.017.

Table S2. Differentially expressed proteins involved in electron transport and oxidative phosphorylation.

Accession Number	Gene Name	Protein Name	Function, Process	IR-LT3S (FC)	IR-NT3 (FC)
P11608	<i>Mt-atp8</i>	ATP synthase protein 8	ATP synthesis complex V	-55	-40
P15999	<i>Atp5a1</i>	ATP synthase subunit $\alpha$	ATP synthesis complex V	-4.5	-5.2
G3V6D3	<i>Atp5b</i>	ATP synthase subunit $\beta$	ATP synthesis complex V	-3.0	-2.7
P31399	<i>Atp5h</i>	ATP synthase subunit d	ATP synthesis complex V	-10	-15
G3V7Y3	<i>Atp5d</i>	ATP synthase subunit $\delta$	ATP synthesis complex V	-6.4	-7.7
P29419	<i>Atp5i</i>	ATP synthase subunit e	ATP synthesis complex V	-9.2	-13
F7FFJ9	<i>Atp5c1</i>	ATP synthase subunit $\gamma$	ATP synthesis complex V	-1.92	-2.5
Q06647	<i>Atp5o</i>	ATP synthase subunit O	ATP synthesis complex V	-3.6	-3.3
P21571	<i>Atp5j</i>	ATP synthase-coupling factor 6	ATP synthesis complex V	-4.4	-16
Q68FY0	<i>Uqcrc1</i>	Cytochrome b-c1 complex subunit 1	Electron transport complex III	-3.1	-4.7 *
P32551	<i>Uqcrc2</i>	Cytochrome b-c1 complex subunit 2	Electron transport complex III	-2.0	-2.4
Q5M9I5	<i>Uqcrh</i>	Cytochrome b-c1 complex subunit 6	Electron transport complex III	1.30	-15 *
Q7TQ16	<i>Uqcrcq</i>	Cytochrome b-c1 complex subunit 8	Electron transport complex III	-4.3	-3.9
P20788	<i>Uqcrcfs1</i>	Cytochrome b-c1 complex subunit Rieske	Electron transport complex III	-5.6	-6.0
Q8SEZ5	<i>Mt-co2</i>	Cytochrome c oxidase subunit 2	Electron transport complex IV	NS	-3.6 *
P10888	<i>Cox4i1</i>	Cytochrome c oxidase subunit 4 isoform 1	Electron transport complex IV	-1.7	-6.2 *
P11240	<i>Cox5a</i>	Cytochrome c oxidase subunit 5A	Electron transport complex IV	NS	-3.4 *

Table S2. Cont.

Accession Number	Gene Name	Protein Name	Function, Process	IR-LT3S (FC)	IR-NT3 (FC)
D3ZD09	<i>Cox6b1</i>	Cytochrome c oxidase subunit 6B1	Electron transport complex IV	-3.6	-5.6
P11951	<i>Cox6c2</i>	Cytochrome c oxidase subunit 6C-2	Electron transport complex IV	-3.3	-8.8 *
P35171	<i>Cox7a2</i>	Cytochrome c oxidase subunit 7A2	Electron transport complex IV	-4.0	-4.4
D3ZYX8	<i>Cox7a2l</i>	Cytochrome c oxidase subunit VIIa polypeptide 2 like	Electron transport complex IV	-27	-12.5
D3ZFQ8	<i>Cyc1</i>	Cytochrome c-1 (Predicted), isoform CRA_b	Electron carrier protein	NS	-3.8 *
Q66HF3	<i>Etfdh</i>	Electron transfer flavoprotein-ubiquinone oxidoreductase	Electron carrier protein	NS	-2.3 *
Q5RK08	<i>Gbas</i>	Glioblastoma amplified sequence	Oxidative phosphorylation	9.00	6.5 *
F1LXA0	<i>Ndufa12</i>	NADH dehydrogenase (Ubiquinone) 1 $\alpha$ subcomplex, 12	Electron transport complex I	-2.4	-2.7
B2RYS8	<i>Ndufb8</i>	NADH dehydrogenase (Ubiquinone) 1 $\beta$ subcomplex 8	Electron transport complex I	1.24	-5.4 *
D4A565	<i>Ndufb5</i>	NADH dehydrogenase (Ubiquinone) 1 $\beta$ subcomplex, 5	Electron transport complex I	NS	-2.1 *
D3ZZ21	<i>Ndufb6</i>	NADH dehydrogenase (Ubiquinone) 1 $\beta$ subcomplex, 6	Electron transport complex I	NS	-4.7 *
D3ZLT1	<i>Ndufb7</i>	NADH dehydrogenase (Ubiquinone) 1 $\beta$ subcomplex, 7	Electron transport complex I	-1.71	-1.29
B2RYW3	<i>Ndufb9</i>	NADH dehydrogenase (Ubiquinone) 1 $\beta$ subcomplex, 9	Electron transport complex I	NS	-6.2 *
D3ZG43	<i>Ndufs3</i>	NADH dehydrogenase (Ubiquinone) Fe-S protein 3	Electron transport complex I	1.73	-2.2
Q5RJN0	<i>Ndufs7</i>	NADH dehydrogenase (Ubiquinone) Fe-S protein 7	Electron transport complex I	2.07	NS *
B0BNE6	<i>Ndufs8</i>	NADH dehydrogenase (Ubiquinone) Fe-S protein 8	Electron transport complex I	4.0	NS *
Q5XIH3	<i>Ndufv1</i>	NADH dehydrogenase (Ubiquinone) flavoprotein 1	Electron transport complex I	1.43	-2.2 *
Q561S0	<i>Ndufa10</i>	NADH dehydrogenase (Ubiquinone) 1 $\alpha$ subcomplex subunit 10	Electron transport complex I	-3.1	-1.8 *
D3ZS58	<i>Ndufa2</i>	NADH dehydrogenase (Ubiquinone) 1 $\alpha$ subcomplex subunit 2	Electron transport complex I	1.37	-4.2 *
Q63362	<i>Ndufa5</i>	NADH dehydrogenase (Ubiquinone) 1 $\alpha$ subcomplex subunit 5	Electron transport complex I	2.7	-2.7 *
Q5BK63	<i>Ndufa9</i>	NADH dehydrogenase (Ubiquinone) 1 $\alpha$ subcomplex subunit 9	Electron transport complex I	2.8	NS *
Q5PQZ9	<i>Ndufc2</i>	NADH dehydrogenase (Ubiquinone) 1 subunit C2	Electron transport complex I	-25	-29
P19234	<i>Ndufv2</i>	NADH dehydrogenase (Ubiquinone) flavoprotein 2	Electron transport complex I	NS	-3.1 *
Q641Y2	<i>Ndufs2</i>	NADH dehydrogenase (Ubiquinone) iron-sulfur protein 2	Electron transport complex I	1.97	-1.4 *
Q5XIF3	<i>Ndufs4</i>	NADH dehydrogenase (Ubiquinone) iron-sulfur protein 4	Electron transport complex I	3.30	NS *
Q66HF1	<i>Ndufs1</i>	NADH-ubiquinone oxidoreductase 75 kDa subunit	Electron transport complex I	1.44	-3.1
Q8SEZ0	<i>Mt-nd5</i>	NADH-ubiquinone oxidoreductase chain 5	Electron transport complex I	-3.0	-5.4
A9UMV9	<i>Ndufa7</i>	Ndufa7 protein	Electron transport complex I	-7.9	-5.2
D4A5L9	<i>LOC679794</i>	Protein LOC679794	Electron carrier protein	-11	NS *
D4A4P3	<i>Ndufa3</i>	Protein LOC100361144	Electron carrier protein	2.14	-6.2 *
F1LPG5	<i>Ndufa4</i>	Protein LOC688963	Electron carrier protein	-2.4	-2.4

Comparison among groups was performed as described in statistical analysis. FC = fold change with respect to sham group; NS = not significantly different from sham group; \*  $p$  vs. IR-LT3S < 0.017.

**Table S3.** Differentially expressed proteins involved in pyruvate metabolism and tricarboxylic acid cycle.

Accession Number	Gene Name	Protein Name	Function, Process	IR-LT3S (FC)	IR-NT3 (FC)
P00507	<i>Got2</i>	Aspartate aminotransferase	Pre TCA, anaplerotic reaction	NS	10 *
P38718	<i>Mpc2</i>	Mitochondrial pyruvate carrier 2	Mitochondrial pyruvate transport (pre TCA)	16	25
D4A5G8	<i>Pdha11</i>	Protein Pdha1/1	Conversion of pyruvate to acetyl-CoA (pre TCA)	2.8	5.0 *
P49432	<i>Pdhb</i>	Pyruvate dehydrogenase E1 component subunit $\beta$	Conversion of pyruvate to acetyl-CoA (pre TCA)	1.7	3.6
F1MA54	<i>Pdk1</i>	Pyruvate dehydrogenase (acetyl-transferring) kinase isozyme 1	Conversion of pyruvate to acetyl-CoA (pre TCA)	11	15 *
Q64536	<i>Pdk2</i>	Pyruvate dehydrogenase (acetyl-transferring) kinase isozyme 2	Conversion of pyruvate to acetyl-CoA (pre TCA)	6.7	13 *
Q8VHF5	<i>Cs</i>	Citrate synthase	TCA	NS	7.2 *
Q9ER34	<i>Aco2</i>	Aconitate hydratase	TCA	2.0	4.9 *
F1LNF7	<i>Idh3a</i>	Isocitrate dehydrogenase (NAD) subunit $\alpha$	TCA	4.2	4.5
Q68FX0	<i>Idh3B</i>	Isocitrate dehydrogenase (NAD) subunit $\beta$	TCA	5.1	7.0
P56574	<i>Idh2</i>	Isocitrate dehydrogenase (NADP)	TCA	5.8	10 *
Q5XIJ3	<i>Idh3g</i>	Isocitrate dehydrogenase 3 (NAD), $\gamma$	TCA	10	15
Q5XI78	<i>Ogdh</i>	2-oxoglutarate dehydrogenase	TCA	N.S	4.0 *
G3V6P2	<i>Dlst</i>	Dihydrolipoamide S-succinyltransferase	TCA, (E2 component of 2-oxo-glutarate complex)	NS	2.3 *
Q6P6R2	<i>Dld</i>	Dihydrolipoyl dehydrogenase	TCA, (E3 component of 2-oxo-glutarate complex)	-1.8	4.7 *
F1LM47	<i>Sucla2</i>	Protein Sucla2	TCA (succinyl-CoA synthetase)	12	18 *
P13086	<i>Suclg1</i>	Succinyl-CoA synthetase (ADP/GDP-forming) subunit $\alpha$	TCA	3.1	5.3 *
Q641Z9	<i>Sdhc</i>	Succinate dehydrogenase complex, subunit c, integral membrane	TCA (succinate dehydrogenase activity)	1.6	1.7
Q6PCT8	<i>Sdhd</i>	Succinate dehydrogenase (ubiquinone) cytochrome b small subunit	TCA	3.0	3.3
Q920L2	<i>Sdha</i>	Succinate dehydrogenase (ubiquinone) flavoprotein subunit	TCA	1.4	-1.4 *
P21913	<i>Sdhb</i>	Succinate dehydrogenase (ubiquinone) iron-sulfur subunit	TCA	1.4	NS *
Q5M964	<i>Fh</i>	Fumarate hydratase 1	TCA	NS	3.4 *
P04636	<i>Mdh2</i>	Malate dehydrogenase	TCA	-7.7	NS *

TCA = tricarboxylic acid cycle. Comparison among groups was performed as described in statistical analysis. FC = fold change with respect to sham group; NS = not significantly different from sham group; \*  $p$  vs. IR-LT3S < 0.017.

**Table S4.** Differentially expressed proteins involved in fatty acid transport, biosynthesis and oxidation.

Accession Number	Gene Name	Protein Name	Function, Process	IR-LT3S (FC)	IR-NT3 (FC)
G3V734	<i>Decr1</i>	2,4-dienoyl CoA reductase 1	Auxiliary enzyme of $\beta$ oxidation	2.6	13 *
D3ZA93	<i>Acot13</i>	Protein Acot13	Regulate intracellular levels of acyl-CoAs, free fatty acids and CoASH	6.1	10 *
G3V796	<i>Acadm</i>	Acetyl-Coenzyme A dehydrogenase, medium chain	Fatty acid $\beta$ oxidation	3.5	5.9 *
Q6IMX3	<i>Acads</i>	Acetyl-Coenzyme A dehydrogenase, short chain	Fatty acid $\beta$ oxidation	4.8	6.1 *
D3ZF13	<i>Ndufab1</i>	Acyl carrier protein	Fatty acid biosynthesis	1.4	-3.4 *
Q499N5	<i>Acsf2</i>	Acyl-CoA synthetase family member 2	Fatty acid metabolism	7.3	15 *
Q6IMX8	<i>Acot2</i>	Acyl-CoA thioesterase 2	Increases the utilization of fatty acid substrate	NS	7.1 *
Q5M9H2	<i>Acadol</i>	Acyl-Coenzyme A dehydrogenase, very long chain	Fatty acid $\beta$ oxidation	4.0	2.4
Q63704	<i>Cpt1b</i>	Carnitine <i>O</i> -palmitoyltransferase 1	Fatty acid $\beta$ oxidation	2.9	1.6 *
P18886	<i>Cpt2</i>	Carnitine <i>O</i> -palmitoyltransferase 2	Fatty acid $\beta$ oxidation	3.0	3.0
Q62651	<i>Ech1</i>	$\Delta(3,5)$ - $\Delta(2,4)$ -dienoyl-CoA isomerase	Lipid metabolism, fatty acid $\beta$ oxidation	NS	6.2 *
Q68G41	<i>Eci1</i>	Dodecenoyl-Coenzyme A $\delta$ isomerase (3,2 <i>trans</i> -enoyl-Coenzyme A isomerase)	Fatty acid $\beta$ oxidation	NS	2.1 *
P13803	<i>Etfa</i>	Electron transfer flavoprotein subunit $\alpha$	Lipid metabolism	4.04	3.76
Q68FU3	<i>Etfb</i>	Electron transfer flavoprotein subunit $\beta$	Lipid metabolism	2.30	2.72
Q5XIC0	<i>Eci2</i>	Enoyl-CoA $\delta$ isomerase 2	Fatty acid $\beta$ oxidation	3.7	6.0
P14604	<i>Echs1</i>	Enoyl-CoA hydratase	Fatty acid $\beta$ oxidation	NS	6.4 *
P07483	<i>Fabp3</i>	Fatty acid-binding protein	Long chain fatty acid transport, fatty acid $\beta$ oxidation	NS	49 *
Q9WVK7	<i>Hadh</i>	Hydroxyacyl-coenzyme A dehydrogenase	Lipid metabolism; fatty acid $\beta$ -oxidation	NS	22 *
P15650	<i>Acadl</i>	Long-chain specific acyl-CoA dehydrogenase	Fatty acid $\beta$ oxidation	2.2	5.0 *
P14882	<i>Pcca</i>	Propionyl-CoA carboxylase $\alpha$ chain	Lipid metabolism	5.2	5.2
Q68FZ8	<i>Pccb</i>	Propionyl coenzyme A carboxylase, $\beta$ polypeptide	Lipid metabolism	2.8	4.5
M0R7V3	<i>Apoa</i>	Protein Apoa	Lipid transport	-1.4	-3.1

Comparison among groups was performed as described in statistical analysis. FC = fold change with respect to sham group; NS = not significantly different from sham group; \* *p* vs. IR-LT3S < 0.017.

**Table S5.** Differentially expressed proteins involved in various metabolic process and energy homeostasis.

Accession Number	Gene Name	Protein Name	Function, Pathway	IR-LT3S (FC)	IR-NT3 (FC)
<i>Carbohydrate, amino acid and keton body metabolism:</i>					
P42123	<i>Ldhb</i>	L-lactate dehydrogenase B chain	Glycolysis, lactate clearance	NS	35 *
M0R4B8	<i>N/A</i>	Pyruvate kinase	Glycolysis	2.4	30 *
P16617	<i>Pgk1</i>	Phosphoglycerate kinase 1	Glycolysis	3.8	22 *
G3V6Y6	<i>Pygb</i>	Glycogen phosphorylase	Carbohydrate metabolism	12	40 *
B2GV15	<i>Dbt</i>	Dihydrolipoamide branched chain transacylase E2	Amino acid catabolic process	6.7	5.5
B1WBN3	<i>Bckdha</i>	2-oxoisovalerate dehydrogenase subunit $\alpha$	Amino acid catabolic process	5.8	5.6
P29266	<i>Hibadh</i>	3-hydroxyisobutyrate dehydrogenase	Amino acid degradation	3.2	6.3 *
P12007	<i>Ivd</i>	Isovaleryl-CoA dehydrogenase	Amino acid degradation	3.0	7.3 *
Q5XIT9	<i>Mccc2</i>	Methylcrotonoyl-CoA carboxylase $\beta$ chain	Amino acid degradation	3.4	4.5
F1LP30	<i>Mccc1</i>	Methylcrotonoyl-CoA carboxylase subunit $\alpha$	Amino acid degradation	9.7	7.9
F1LQZ0	<i>Tmem65</i>	Protein Tmem65	Amino acid catabolic process	3.2	2.1
B2GV06	<i>Oxct1</i>	Succinyl-CoA:3-ketoacid coenzyme A transferase 1	Keton body catabolism	NS	4.9 *
P17764	<i>Acat1</i>	Acetyl-CoA acetyltransferase	Ketone body metabolism, lipid metabolism	-1.9	1.6 *
<i>Energy homeostasis:</i>					
Q9WUS0	<i>Ak4</i>	Adenylate kinase 4	Homeostasis of cellular nucleotides, cellular energy homeostasis	1.9	2.3
M0RC66	<i>Ak1</i>	Adenylate kinase isoenzyme 1 (Fragment)	Homeostasis of cellular nucleotides, cellular energy homeostasis	27	50
P09605	<i>Ckmt2</i>	Creatine kinase S-type	Energy transduction in tissues with large, fluctuating energy	-6.1	-2.7 *

Comparison among groups was performed as described in statistical analysis. FC = fold change with respect to sham group; NS = not significantly different from sham group; \*  $p$  vs. IR-LT3S < 0.017.