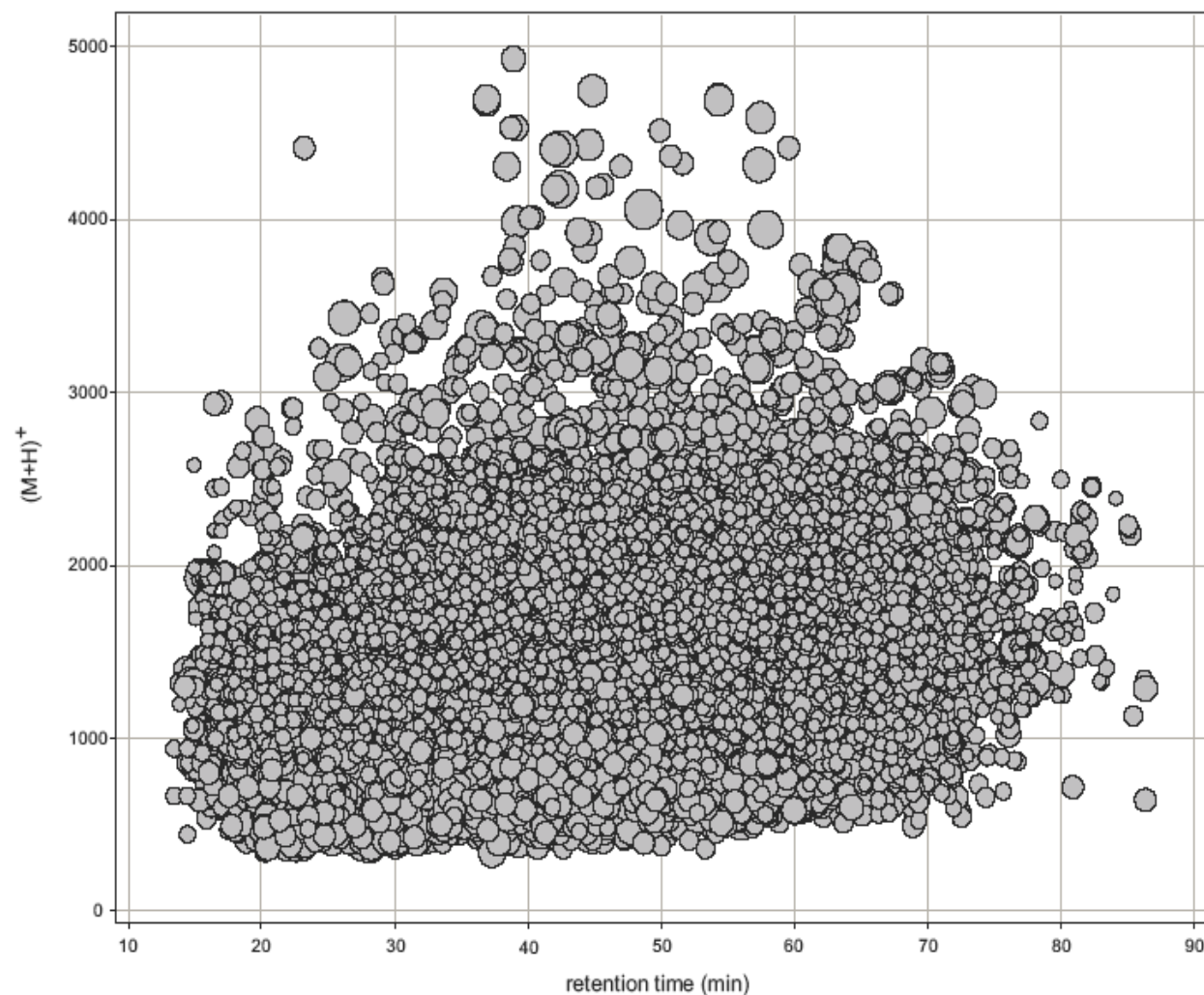
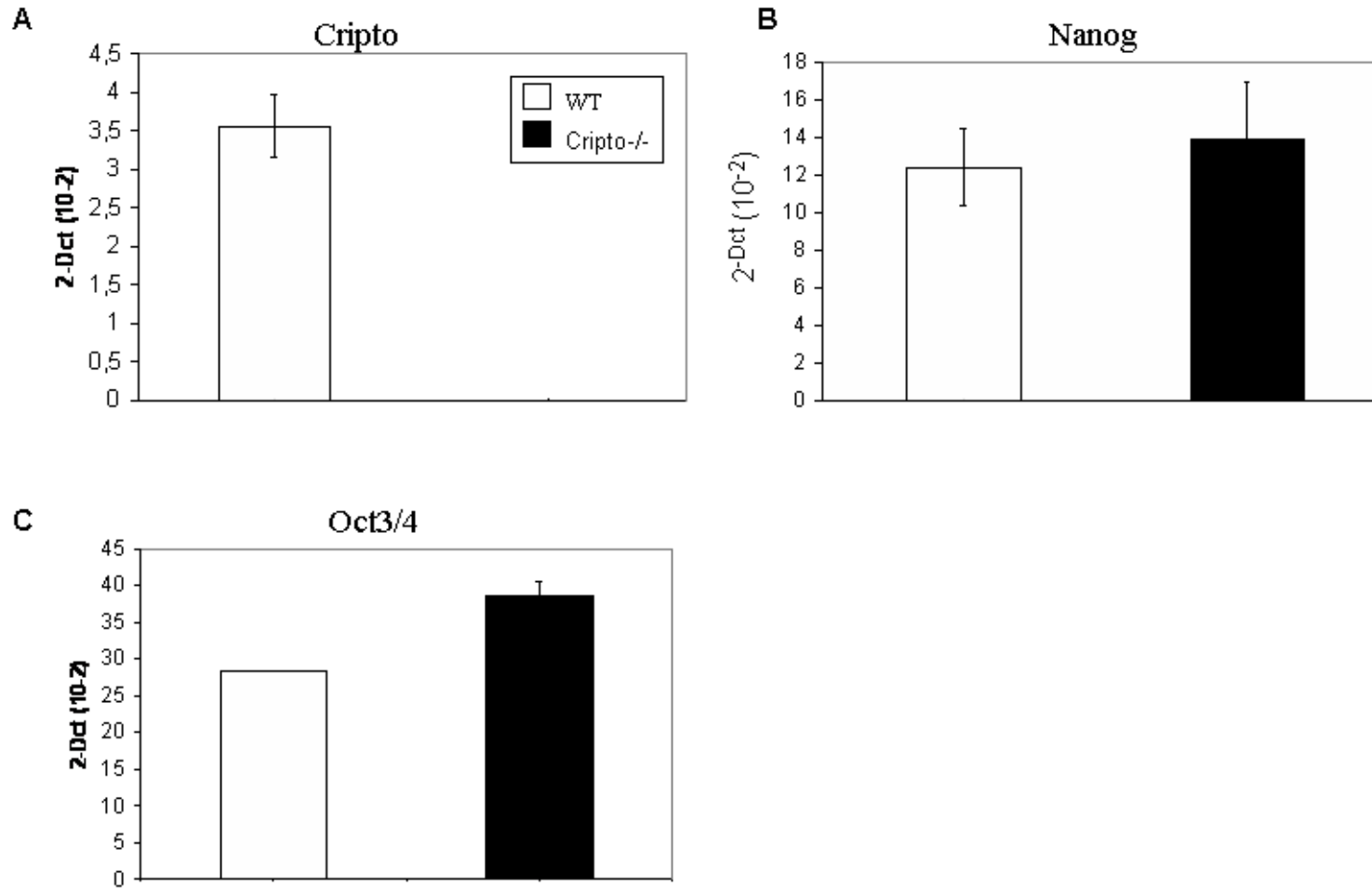


Supplementary Fig 1. LC-MS^E accurate mass-retention time clusters detected throughout the analysis for both RI and *cripto*^{-/-} samples. An appreciation of the sample complexity is readily obtained by visualising the total number – after de-isotoping and charge-state reduction – of detected clusters (approximately 33,000) from the replicates of each condition. The scatter plot reports the distribution of the number of detected clusters according to their monoisotopic masses ($M+H^+$) vs. the retention time measurements. The size of the spots represents the intensity of the cluster (peptide) on the ²log scale.



Supplementary Figure 1

Supplementary Fig 2. RTQ-PCR expression profiles of Oct3/4, Nanog and Cripto in RI and Cr^{-/-} mESc. mRNA expression levels of Cripto (A), Nanog (B) and Oct3/4 (C) were normalized to gapdh expression; data are mean $\pm$ SE, n $\geq$ 3.



Supplementary Figure 2

Supplementary Table 1. Common proteins identified to the RI and cripto^{-/-} (Cr^{-/-}) cell lines by qualitative 2D LC-MS/MS and label-free LC-MS^E.

accession #	description	RI			Cr ^{-/-}			experiment
		# peptides*	coverage (%)*	n (replicate identifications)**	# peptides*	coverage (%)*	n (replicate identifications)**	
P62259	14 3 3 protein epsilon	7	29.9	4	7	34.1	4	both
P61982	14 3 3 protein gamma	4	20.4	4	5	24.3	4	both
P63101	14 3 3 protein zeta/delta	7	35.6	4	10	43.9	4	both
P60710	Actin cytoplasmic 1	13	36.3	4	11	30.7	4	both
P63268	Actin gamma enteric smooth muscle	5	16.3	4	5	14.2	4	both
P05064	Fructose biphosphate aldolase A	9	31.6	4	11	39.9	4	both
Q03265	ATP synthase subunit alpha mitochondrial	7	14.8	4	8	14.4	4	both
Q922D8	C1 tetrahydrofolate synthase cytoplasmic C1	7	8.9	4	9	12.2	4	both
P63038	60 kDa heat shock protein mitochondrial	10	23.1	4	15	34.4	4	both
P10126	Elongation factor 1-alpha 1	7	20.3	4	8	17.5	4	both
P57776	Elongation factor 1-delta	6	27.2	4	10	45.7	4	both
P58252	Elongation factor 2	13	13.8	4	18	21.7	4	both
P17182	Alpha enolase (NNE)	13	31.8	4	17	45.4	4	both
P08113	Endoplasmic	9	12.5	4	12	17.2	4	both
P30416	FK506 binding protein 4	6	19.3	4	9	24.7	4	both
P56959	RNA binding protein FUS	4	8.6	4	8	12.2	3	both
P16858	Glyceraldehyde 3 phosphate dehydrogenase	9	24	4	11	30.7	4	both
Q99PT1	Rho GDP dissociation inhibitor 1	3	23	4	5	26.6	4	both
P38647	Stress-70 protein mitochondrial	9	16	4	14	25.4	4	both
P20029	78 kDa glucose-regulated protein (GRP 78)	11	22.8	4	15	25.2	4	both
P15864	Histone H12	6.3	27.7	4	3	17	2	both
Q64475	Histone H2B type 1 B	3.7	31.5	4	2	15.9	2	both
P62806	Histone H4	2	21.4	4	3	24.6	4	both
P61979	Heterogeneous nuclear ribonucleoprotein K	7	16.4	4	8	19.4	4	both
P07901	Heat shock protein HSP 90-alpha	16	26.6	4	21	33.3	4	both
P11499	Heat shock protein HSP 90-beta	18	30.3	4	23	34.4	4	both
P63017	Heat shock cognate 71 kDa protein	17	31.3	4	17	32.8	4	both
P14602	Heat shock protein beta-1	3	18.2	4	4	16.7	3	both
P60843	Eukaryotic initiation factor 4A-I	9	20.6	4	11	25	4	both
P52480	Pyruvate kinase isozymes M1/M2	16	33.8	4	18	39.9	4	both
P06151	L lactate dehydrogenase A chain	5	16.3	4	9	29.4	4	both
P16125	L lactate dehydrogenase B chain	4	16.2	2	6	20.3	4	both

accession #	description	RI			Cr ^{-/-}			experiment
		# peptides*	coverage (%)*	n (replicate identifications)**	# peptides*	coverage (%)*	n (replicate identifications)**	
Q7TPV4	Myb-binding protein 1A	10	9.5	4	12	10.3	4	both
P08249	Malate dehydrogenase mitochondrial	5	17.9	4	8	23.6	4	both
P28667	MARCKS related protein	2	14	2	4	38.3	4	both
Q60817	Nascent polipeptide-associated complex subunit alpha	4	19.5	3	2	13	4	both
Q99MD9	Nuclear autoantigenic sperm protein	10	16.9	4	15	25.5	4	both
Q01768	Nucleoside diphosphate kinase B	4	31.4	4	4	30	4	both
Q61937	Nucleophosmin	6	28.2	4	7	27.1	4	both
P09405	Nucleolin	10	15.3	4	14	27	4	both
Q9CY58	Plasminogen activator inhibitor 1	6	21.6	4	12	29.8	4	both
Q922R8	Protein disulfide-isomerase A6	7	17.5	4	9	21.8	3	both
Q9DBJ1	Phosphoglycerate mutase 1	5	32.8	4	5	26.5	4	both
P09411	Phosphoglycerate kinase 1	8	26	4	11	39.2	4	both
P17742	Peptidyl-prolyl cis-trans isomerase A	7	40.9	4	6	34.3	4	both
P35700	Peroxiredoxin-1	6	36.9	4	6	36.9	4	both
P26350	Prothymosin alpha	3	20.1	4	5	35.1	4	both
P67984	60S ribosomal protein L22	3	21.9	4	3	20.3	4	both
P62830	60S ribosomal protein L23	2	21.4	2	3	29.5	4	both
P27659	60S ribosomal protein L3	4	11.8	4	6	17.4	4	both
Q9D8E6	60S ribosomal protein L4	4	11.3	4	9	18.5	4	both
P47911	60S ribosomal protein L6	5	9.1	4	4	11.3	4	both
P14148	60S ribosomal protein L7	6	20.7	4	6	17	4	both
P12970	60S ribosomal protein L7a	5	17.7	4	7	22.9	4	both
P14869	60S acidic ribosomal protein P0	6	25.3	4	8	37.6	4	both
P99027	60S acidic ribosomal protein P2	4	55.9	4	5	80.3	4	both
O88569	Heterogeneous nuclear ribonucleoproteins A2/B1	6	21	4	6	22.5	4	both
Q8BG05	Heterogeneous nuclear ribonucleoprotein A3	5	13.5	4	6	17.2	4	both
P62270	40S ribosomal protein S18	4	19.7	2	6	32	4	both
P25444	40S ribosomal protein S2	5	14.5	3	6	17.1	4	both
P62858	40S ribosomal protein S28	2	35.7	4	3	37.7	4	both
P62908	40S ribosomal protein S3	8	35.7	4	9	32.8	4	both
P62754	40S ribosomal protein S6	4	15.1	4	3	17.9	4	both
P62242	40S ribosomal protein S8	4	18.3	4	6	27.6	4	both
P14206	40S ribosomal protein SA	3	13.9	4	5	19.8	4	both
Q9EQU5	Protein SET	6	23.1	4	7	27.7	4	both
P68373	Tubulin alpha-6 chain	6	17.8	4	8	22.3	4	both
P68372	Tubulin beta-2C chain	6	16.6	4	6	18.3	4	both

accession #	description	RI			Cr ^{-/-}			experiment
		# peptides*	coverage (%)*	n (replicate identifications)**	# peptides*	coverage (%)*	n (replicate identifications)**	
P99024	Tubulin beta-5 chain	5	12.7	4	8	24.8	4	both
P80315	T complex protein 1 subunit delta	6	14.2	4	9	19.3	4	both
Q01853	Transitional endoplasmic reticulum ATPase	4	6.9	3	9	13.6	3	both
Q62318	Transcription intermediary factor 1-beta	13	27.8	4	12	25.5	4	both
P17751	Triosephosphate isomerase	5	27.7	4	7	34.1	4	both
Q02053	Ubiquitin activating enzyme E1	9	9.6	4	12	13	2	both
P62991	Ubiquitin	5	52	3	6	62.3	4	both
P20152	Vimentin	8	14.9	3	9	21.4	4	both
P68510	14 3 3 protein eta	4	16.3	3	5	24.3	4	both
P68254	14 3 3 protein theta	4	20.3	4	7	35.8	4	both
P57780	Alpha-actinin-4	11	14.5	4	15	17.9	3	both
O70251	Elongation factor 1-beta	3	17.2	4	6	32.6	4	both
P28656	Nucleosome assembly protein 1 like 1	3	10.5	3	3	10.8	4	both
P17918	Proliferating cell nuclear antigen PCNA	5	24.1	3	6	30.9	4	both
P35979	60S ribosomal protein L12	4	37.6	4	7	53.3	4	both
Q9WTX5	S phase kinase associated protein 1A	3	16.9	3	2	15.3	3	both
P80318	T complex protein 1 subunit gamma	6	11.4	4	12	25.1	4	both
P62737	Actin aortic smooth muscle	6	17.2	3	5	15.8	3	LC-MS ^E
P68033	Actin alpha cardiac muscle 1	6	17.7	3	5	15.7	3	LC-MS ^E
P63260	Actin cytoplasmic 2	12	34.5	3	11	33.8	3	LC-MS ^E
P68134	Actin alpha skeletal muscle	6	16.3	3	5	14.1	3	LC-MS ^E
P47738	Aldehyde dehydrogenase mitochondrial	6	15.7	3	6	15.4	3	LC-MS ^E
P56480	ATP synthase subunit beta mitochondrial	8	19.7	3	7	17.8	3	LC-MS ^E
P18760	Cofilin-1	5	35.7	3	4	29.9	3	LC-MS ^E
P62631	Elongation factor 1-alpha 2 (Statin S1)	3	6.8	3	3	7.7	3	LC-MS ^E
P17183	Gamma-enolase (NSE)	5	13.1	3	5	16.8	3	LC-MS ^E
O35737	Heterogeneous nuclear ribonucleoprotein H	4	12.4	3	5	18.8	3	LC-MS ^E
Q9Z2X1	Heterogeneous nuclear ribonucleoprotein F	3	13.2	3	5	16.2	3	LC-MS ^E
Q61696	Heat shock 70 kDa protein 1A	3	5.4	3	6	11.9	3	LC-MS ^E
P17879	Heat shock 70 kDa protein 1B	3	4.8	3	4	8.9	3	LC-MS ^E
P16627	Heat shock 70 kDa protein 1L	4	6.2	3	7	12.3	3	LC-MS ^E
P17156	Heat shock-related 70 kDa protein 2	9	16	3	7	14.6	3	LC-MS ^E
Q61316	Heat shock 70 kDa protein 4	7	14.8	3	12	21.8	3	LC-MS ^E
P10630	Eukaryotic initiation factor 4A-II	4	10.4	3	4	8.1	3	LC-MS ^E
P60335	Poly(rC)-binding protein 1	5	20.1	3	5	18.1	3	LC-MS ^E

accession #	description	RI			Cr ^{-/-}			experiment
		# peptides*	coverage (%)*	n (replicate identifications)**	# peptides*	coverage (%)*	n (replicate identifications)**	
P63276	40S ribosomal protein S17	3	34.3	3	4	34.1	3	LC-MS ^E
P08228	Superoxide dismutase	5	36.6	3	5	24	3	LC-MS ^E
P68369	Tubulin alpha-1 chain	7	22.3	3	8	26.9	3	LC-MS ^E
P05213	Tubulin alpha-2 chain	7	23.3	3	9	29.4	3	LC-MS ^E
P05214	Tubulin alpha-3/alpha-7 chain	6	17.8	3	6	21.3	3	LC-MS ^E
P68368	Tubulin alpha-4 chain	4	13.5	3	5	15.4	3	LC-MS ^E
Q9JJZ2	Tubulin alpha-8 chain	3	9.9	3	4	12.3	3	LC-MS ^E
Q7TMM9	Tubulin beta-2A chain	5	15.7	3	6	19.9	3	LC-MS ^E
Q9CWF2	Tubulin beta-2B chain	7	20.4	3	5	16.5	3	LC-MS ^E
Q9ERD7	Tubulin beta-3 chain	3	9.6	3	4	11.9	3	LC-MS ^E
Q9D6F9	Tubulin beta-4 chain	4	9.8	3	6	17.2	3	LC-MS ^E
P42932	T-complex protein 1 subunit theta	4	8.9	3	8	18.4	3	LC-MS ^E
Q9CQV8	14-3-3 protein beta/alpha	6	28.7	2	5	27.8	2	LC-MS ^E
Q8VDN2	Sodium/potassium-transporting ATPase alpha-1 chain	7	10.1	2	6	8.7	2	LC-MS ^E
Q6PIC6	Sodium/potassium-transporting ATPase alpha-3 chain	9	12	2	8	9.9	2	LC-MS ^E
P31001	Desmin	6	14.5	2	10	20.7	2	LC-MS ^E
P53657	Pyruvate kinase isozymes R/L	4	7.5	2	6	14.5	2	LC-MS ^E
P15532	Nucleoside diphosphate kinase A	4	26.3	2	5	36.8	2	LC-MS ^E
P47962	60S ribosomal protein L5	2	8.4	2	5	14.1	2	LC-MS ^E
Q99LX0	Protein DJ-1	3	24.3	2	3	25.4	3	LC-MS ^E
Q9CWI9	Bifunctional purine biosynthesis protein PURH	6	14.2	2	8	21.2	3	LC-MS ^E
Q64433	10 kDa heat shock protein mitochondrial	4	35.3	3	3	23.5	2	LC-MS ^E
Q9D2U9	Histone H2B type 3-A	4	33.1	3	2	17.5	2	LC-MS ^E
Q8CGP0	Histone H2B type 3-B	3	27.8	3	3	22.6	2	LC-MS ^E
P14211	Calreticulin	4	10.8	3	10	27.2	1	LC-MS ^E
P43277	Histone H13	4	20.1	3	2	9.5	1	LC-MS ^E
P70696	Histone H2B type 1 A	3	21.3	3	2	15.7	1	LC-MS ^E
Q6ZWY9	Histone H2B type 1 C	4	31.5	3	2	15.9	1	LC-MS ^E
P10853	Histone H2B type 1 F	5	31.5	3	2	15.9	1	LC-MS ^E
Q64478	Histone H2B type 1 H	4	31.5	3	2	15.9	1	LC-MS ^E
Q8CGP1	Histone H2B type 1 K	5	33.1	3	2	15.9	1	LC-MS ^E
P10854	Histone H2B type 1 M	4	31.5	3	2	15.9	1	LC-MS ^E
Q8CGP2	Histone H2B type 1 P	4	31.5	3	2	15.9	1	LC-MS ^E
Q64525	Histone H2B type 2 B	4	31.5	3	3	15.9	1	LC-MS ^E
Q64524	Histone H2B type 2 E	3	27.8	3	4	30.2	1	LC-MS ^E
P62827	GTP binding nuclear protein Ran GTPase	4	19.4	3	4	24.5	1	LC-MS ^E

accession #	description	RI			Cr ^{-/-}			experiment
		# peptides*	coverage (%)*	n (replicate identifications)**	# peptides*	coverage (%)*	n (replicate identifications)**	
P62889	60S ribosomal protein L30	2	24.3	3	5	45.2	1	LC-MS ^E
P62918	60S ribosomal protein L8	3	11.7	3	2	10.5	1	LC-MS ^E
Q8BP47	Asparaginyl tRNA synthetase cytoplasmic	4	9.5	3	5	11.5	1	LC-MS ^E
P70333	Heterogeneous nuclear ribonucleoprotein H	3	8.7	1	3	13.4	3	LC-MS ^E
Q04447	Creatine kinase B type	6	18.4	1	5	18.5	3	LC-MS ^E
Q6ZWV3	60S ribosomal protein L10	2	11.7	1	4	19.9	3	LC-MS ^E
Q60864	Stress induced phosphoprotein 1 STI1	4	7.7	1	8	18	3	LC-MS ^E
P07724	Serum albumin	1	2.14	1	1	2.3	1	DDA
Q9EST5	Acidic leucine rich nuclear phosphoprotein 32	1	3.68	1	1	3.3	1	DDA
O55143	Sarcoplasmic endoplasmic reticulum calcium ATPase 2	2	2.68	1	1	1.3	1	DDA
P47757	F actin capping protein subunit beta CapZ beta	1	3.61	1	1	3.6	1	DDA
P23198	Chromobox protein homolog 3	1	6.01	1	2	13.7	1	DDA
Q68FD5	Clathrin heavy chain	4	2.15	1	1	0.9	1	DDA
P26231	Catenin alpha 1	1	1.1	1	1	1.1	1	DDA
Q9JIK5	Nucleolar RNA helicase 2	2	2.7	1	2	3.4	1	DDA
P62204	Calmodulin CaM	2	16.8	1	2	16.8	1	DDA
Q9CXU9	Eukaryotic translation initiation factor 1b	2	27.4	1	1	14.2	1	DDA
P62869	Transcription elongation factor B	1	7.6	1	1	7.6	1	DDA
Q3UMY5	Echinoderm microtubule associated protein like 4	1	0.9	1	1	0.9	1	DDA
P21550	Beta enolase Muscle specific enolase	2	7.6	1	2	7.6	1	DDA
Q62446	FK506 binding protein 3	1	3.6	1	1	4.9	1	DDA
P68040	Guanine nucleotide binding protein subunit beta 2	1	3.2	1	1	3.2	1	DDA
P24472	Glutathione S transferase A4	1	5.9	1	1	5.9	1	DDA
P43276	Histone H15 H1 VAR5 H1b	1	5.4	1	1	5.4	1	DDA
Q8CGP6	Histone H2A type 1 H	1	14.8	1	2	21.9	1	DDA
Q3THW5	Histone H2AV H2AF Z	1	7.8	1	2	18.0	1	DDA
P68433	Histone H31	3	16.2	1	2	11.8	1	DDA
P02301	Histone H3 like Embryonic	1	11.1	1	1	11.1	1	DDA
P63158	High mobility group protein B1	1	6.1	1	2	12.1	1	DDA
Q9Z204	Heterogeneous nuclear ribonucleoproteins C1 C2	1	2.9	1	1	3.2	1	DDA
Q99L45	Eukaryotic translation initiation factor 2 subunit 2	1	3.6	1	1	3.6	1	DDA
Q9Z0N1	Eukaryotic translation initiation factor 2 subunit 3	1	3.0	1	1	3.0	1	DDA
Q9CXY6	Interleukin enhancer binding factor 2	1	3.6	1	1	3.6	1	DDA
Q9Z1X4	Interleukin enhancer binding factor 3	1	1.1	1	1	1.1	1	DDA
P70168	Importin beta 1 subunit	1	1.5	1	1	1.8	1	DDA

accession #	description	RI			Cr ^{-/-}			experiment
		# peptides*	coverage (%)*	n (replicate identifications)**	# peptides*	coverage (%)*	n (replicate identifications)**	
P24547	Inosine 5 monophosphate dehydrogenase 2	1	2.5	1	2	6.8	1	DDA
Q9WTP6	Adenylate kinase isoenzyme 2 mitochondrial	1	4.3	1	1	4.3	1	DDA
P25206	DNA replication licensing factor MCM3	1	1.2	1	1	1.6	1	DDA
P97311	DNA replication licensing factor MCM6	1	1.2	1	1	1.2	1	DDA
Q61881	DNA replication licensing factor MCM7	2	4.6	1	1	2.4	1	DDA
Q8VEM8	Phosphate carrier protein mitochondrial	1	2.2	1	1	2.8	1	DDA
Q9D6Z1	Nucleolar protein 5A	1	2.8	1	1	2.8	1	DDA
P11103	Poly ADP ribose polymerase 1	3	4.6	1	2	3.2	1	DDA
P27773	Protein disulfide isomerase A3	2	4.4	1	2	4.0	1	DDA
P70296	Phosphatidylethanolamine binding protein 1	3	28.3	1	1	7.0	1	DDA
P24369	Peptidyl prolyl cis trans isomerase B	2	8.7	1	1	4.3	1	DDA
O08709	Peroxiredoxin 6	2	16.5	1	1	4.5	1	DDA
P62962	Profilin 1	1	11.4	1	2	21.4	1	DDA
O88685	26S protease regulatory subunit 6A Proteasome 26S	1	2.3	1	1	2.3	1	DDA
Q8BG32	26S proteasome non ATPase regulatory subunit 11	1	3.1	1	2	5.7	1	DDA
Q99JF8	PC4 and SFRS1 interacting protein	1	2.8	1	1	2.8	1	DDA
P61290	Proteasome activator complex subunit 3	1	5.9	1	1	5.9	1	DDA
Q60972	Histone binding protein RBBP4 RetinoblastomaBP4	1	2.8	1	1	2.8	1	DDA
P53026	60S ribosomal protein L10a	1	6.0	1	3	14.3	1	DDA
P47963	60S ribosomal protein L13	2	8.5	1	3	13.7	1	DDA
Q9CPR4	60S ribosomal protein L17	1	7.6	1	1	7.6	1	DDA
P84099	60S ribosomal protein L19	1	8.7	1	1	8.7	1	DDA
Q8BP67	60S ribosomal protein L24	1	8.3	1	1	8.3	1	DDA
P61255	60S ribosomal protein L26	2	6.2	1	2	11.0	1	DDA
P14115	60S ribosomal protein L27a	1	7.4	1	1	7.4	1	DDA
O55142	60S ribosomal protein L35a	1	8.2	1	1	8.2	1	DDA
P49312	Heterogeneous nuclear ribonucleoprotein A1	1	4.7	1	1	4.7	1	DDA
Q8BHD7	Regulator of differentiation 1 Rod1	1	1.9	1	1	1.9	1	DDA
P62301	40S ribosomal protein S13	1	8.0	1	1	8.0	1	DDA
P62264	40S ribosomal protein S14	1	8.6	1	1	8.6	1	DDA
P60867	40S ribosomal protein S20	1	10.1	1	1	9.2	1	DDA
P97351	40S ribosomal protein S3a	1	4.9	1	1	4.9	1	DDA
P62702	40S ribosomal protein S4 X isoform	1	6.5	1	1	6.5	1	DDA
P62082	40S ribosomal protein S7	1	6.2	1	1	6.2	1	DDA
P60122	RuvB like 1	1	4.0	1	1	4.0	1	DDA
Q8K4Z5	Splicing factor 3 subunit 1	2	5.4	1	1	2.5	1	DDA

accession #	description	RI			Cr ^{-/-}			experiment
		# peptides*	coverage (%)*	n (replicate identifications)**	# peptides*	coverage (%)*	n (replicate identifications)**	
Q6PDM2	Splicing factor arginine serine rich 1	1	5.7	1	1	5.7	1	DDA
P62317	Small nuclear ribonucleoprotein	1	15.3	1	1	8.5	1	DDA
Q91WM1	Spermatid perinuclear RNA binding protein	1	1.5	1	1	1.5	1	DDA
P58771	Tropomyosin 1 alpha chain	1	3.5	1	2	6.7	1	DDA
Q9CQN1	Heat shock protein 75 kDa mitochondrial	1	2.0	1	1	2.0	1	DDA
Q9CQM9	Thioredoxin like protein 2	1	3.0	1	1	3.0	1	DDA
P62960	Nuclease sensitive element binding protein 1	1	5.3	1	1	5.3	1	DDA
P50580	Proliferation associated protein 2G4	6	18.5	1	2	7.1	1	DDA
P62852	40S ribosomal protein S25	3	23.2	1	1	7.2	1	DDA
P11983	T complex protein 1 subunit alpha	8	15.8	1	1	1.8	1	DDA

* average number of matching peptides and coverage involving an LC-MS^E identification

** summed identification replication number for both acquisitions methods

Supplementary Table 2. Single based peptide DDA identification overview. Search criteria: precursor mass tolerance, 25 ppm; fragment ion tolerance, 0.05 Da; allowed number of missed cleavage sites up to 1; fixed modification CAM-cysteine; variable modification methionine oxidation, peptide identification probability > 95%, the presence of a consecutive y'' ion series of at least 3 amino acids per MS/MS fragmentation spectrum. See section Experimental for more database search identification details.

accession #	peptide sequence	mW	Cr ^{-/-}					RI				
			m/z	z	Δ (Da)	y'' and b ions**	log likelihood*	m/z	z	Δ (Da)	y'' and b ions**	log likelihood*
O55142	DETEFYLGK	1100.503	551.260	2	0.002	0.725	143.8	551.259	2	0.000	0.647	112.3
O88685	VDILDPALLR	1123.660	562.837	2	-0.002	0.579	99.3	562.838	2	0.000	0.772	103.9
P02301	VGLFEDTNLCAIHAK	1686.840	563.284	3	-0.010	0.805	205.5	563.283	3	-0.015	0.690	145.3
P07724	ECCHGDLLECADDR	1748.655	583.878	3	-0.044	0.358	92.7					
	LGEYGFQNAILVR	1478.788						740.397	2	-0.009	0.720	212.9
P14115	TGVAPIIDVVR	1138.671	570.346	2	0.006	0.619	120.3	570.344	2	0.001	0.651	106.2
P24472	KPPPDGPYVEVVR	1451.777	484.927	3	-0.019	0.747	180.9	484.932	3	-0.004	0.760	115.9
P25206	DIQPAFSADIAK	1389.678	695.851	2	0.008	0.680	135.5					
	GVVCIDEFDK	1180.544						591.279	2	-0.001	0.632	100.2
P26231	SDALNSAIDK	1032.509	517.258	2	-0.009	0.596	127.2	517.265	2	0.005	0.596	61.6
P43276	ATGPPVSELITK	1211.676	606.846	2	0.001	0.623	275.4	606.839	2	-0.015	0.797	297.9
P47757	STLNEIYFGK	1170.592	586.301	2	-0.005	0.684	125.9	586.300	2	-0.008	0.649	146.2
P49312	GFAFVTFDDHDSVDK	1698.752	567.261	3	0.008	0.644	74.9	567.254	3	-0.013	0.701	109.8
P60122	GTEDITSPHGIPLDLLDR	1947.990	650.340	3	0.007	0.448	80.8	650.332	3	-0.018	0.495	162.7
P60867	TPVEPEVAIHR	1246.667	416.558	3	-0.015	0.873	203.0					
	LIDLHSPSEIVK	1349.755						450.920	3	-0.020	0.594	73.0
P61290	ITSEAEDLVANFFPK	1679.841	840.936	2	0.015	0.667	114.8	840.932	2	0.008	0.483	54.5
P62082	AIIIFVPVPQLK	1336.848	669.434	2	0.005	0.725	63.1	669.436	2	0.008	0.594	63.9
P62264	IEDVTPIPSDSTR	1428.710	715.368	2	0.010	0.773	274.5	715.360	2	-0.006	0.733	159.4
P62301	GLTPSQIGVILR	1252.750	627.378	2	-0.009	0.681	179.0	627.382	2	-0.002	0.594	195.6
P62317	SEMTPEELQK	1190.549	596.284	2	0.003	0.719	127.1					
	EEEEFNTGPLSVLTQSVK	2005.984						1004.000	2	0.000	0.419	72.5
P62702	TDITYPAGFMDVISIDK	1884.918	943.476	2	0.018	0.485	210.0	943.463	2	-0.007	0.616	238.2
P62869	DDQLLDDGK	1017.461	509.739	2	0.001	0.608	132.8	509.742	2	0.006	0.569	121.5
P62960	SVGDGETVEFDVVEGEK	1794.816	898.419	2	0.007	0.657	191.0	898.418	2	0.005	0.606	183.8
P68040	DETNYGIPQR	1191.552	596.785	2	0.002	0.789	142.3	596.782	2	-0.004	0.860	150.9
P70168	GDQENVHPDVMLVQPR	1832.884	611.966	3	-0.009	0.527	96.3					
	SNEILTAIIQGM	1444.771						723.409	2	0.033	0.733	53.6
P84099	VWLDPNETNEIANANSR	1941.918	971.968	2	0.003	0.586	153.5	971.966	2	-0.002	0.586	159.8

accession #	peptide sequence	mW	Cr ^{-/-}					RI				
			m/z	z	Δ (Da)	y'' and b ions**	log likelihood*	m/z	z	Δ (Da)	y'' and b ions**	log likelihood*
P97311	DEEQTAESIK	1148.520	575.266	2	-0.004	0.737	70.3	575.267	2	-0.001	0.526	71.6
P97351	NCLTNFHGMDLTR	1577.708	526.908	3	-0.009	0.680	95.9	526.903	3	-0.024	0.480	72.4
Q3UMY5	WFLVDAETR	1135.566	568.793	2	0.005	0.490	47.0	568.792	2	0.001	0.412	39.3
Q60972	GEFGGFGSVSGK	1127.525	564.771	2	0.002	0.667	152.5	564.768	2	-0.004	0.667	133.3
Q62446	SEETLDEGPPK	1200.551	601.283	2	-0.001	0.651	174.4					
	AWTVEQLR	1001.530						501.771	2	-0.003	0.733	76.0
Q6PDM2	GGPPFAFVEFEDPR	1563.736	782.882	2	0.014	0.815	124.1	782.879	2	0.007	0.605	105.7
Q8BHD7	EGQEDQGLTK	1103.509	552.766	2	0.007	0.579	56.1	552.759	2	-0.007	0.561	90.9
Q8BP67	AITGASLADIMAK	1260.675	631.347	2	0.003	0.800	170.9	631.344	2	-0.003	0.827	233.9
Q8VEM8	GSTASQVLQR	1045.552	523.782	2	-0.004	0.807	143.1					
	FGFYEVFK	1035.507						518.760	2	-0.003	0.711	93.7
Q91WM1	GWPLELICEK	1243.627	622.822	2	0.001	0.667	49.6	622.821	2	-0.001	0.614	70.0
Q99JF8	VDEVDPDGAVKPPTNK	1564.810	522.604	3	-0.022	0.586	84.2	522.603	3	-0.023	0.540	69.3
Q99L45	IFDIDEAEEAIK	1391.682	696.850	2	0.002	0.565	109.1	696.850	2	0.003	0.812	177.5
Q9CPR4	EQIVPKPEEEVAQK	1622.851	541.955	3	-0.011	0.704	170.4	541.947	3	-0.034	0.642	106.3
Q9CQM9	DNGELLPIK	1110.628	556.322	2	0.000	0.737	129.0	556.321	2	-0.003	0.754	124.3
Q9CQN1	GVVDSEDIPLNLSR	1512.778	757.398	2	0.003	0.852	200.3	757.398	2	0.003	0.778	181.7
Q9CXY6	ILPTLEAVAALGNK	1408.829	705.421	2	-0.002	0.593	100.0	705.418	2	-0.008	0.741	118.2
Q9D6Z1	EELASDLEEMATSSAK	1709.767	855.897	2	0.011	0.677	168.4	855.891	2	0.000	0.731	169.8
Q9EST5	DISTLEPLK	1014.560	508.288	2	0.000	0.549	114.7					
	DISTLEPLKR	1170.661						586.336	2	-0.004	0.561	66.4
Q9WTP6	NGFLLDGFPR	1134.582	568.304	2	0.011	0.509	60.2	568.300	2	0.002	0.737	95.3
Q9Z0N1	IVLTNPVCTEVGEK	1557.807	779.907	2	-0.009	0.704	182.9	779.907	2	-0.010	0.568	142.7
Q9Z1X4	GWPLELLCEK	1243.627	622.822	2	0.001	0.667	49.6	622.821	2	-0.001	0.614	70.0
Q9Z204	VDSLLESLEK	1131.602	566.812	2	0.006	0.702	180.3					
	SDVEAIFSK	994.497						498.257	2	0.000	0.510	115.6
P23198	DSDEADLVLAKE	1174.572						588.295	2	0.003	0.635	110.3
P24547	EDLVVAPAGVTLK	1310.745						656.382	2	0.005	0.707	163.5
P53026	AVDIPHMDIEALK	1450.749						484.585	3	-0.017	0.627	67.5
P58771	IQLVEEELDR	1242.646						622.330	2	-0.001	0.860	161.5
P62962	TFVSITPAEVGVLVGK	1615.918						808.965	2	-0.005	0.720	251.7
P63158	GEHPGLSIGDVAKE	1278.657						427.223	3	-0.012	0.707	170.2
Q3THW5	GDEELDSLIIK	1117.550						559.782	2	-0.003	0.632	162.9
Q8BG32	EQSILELGSLLAKE	1399.792						700.902	2	-0.003	0.613	51.9
Q8CGP6	VTIAQGGVLPNIQAVLLPK	1930.162						644.388	3	-0.022	0.802	389.7

accession #	peptide sequence	mW	Cr ^{-/-}					RI				
			m/z	z	Δ (Da)	y'' and b ions**	log likelihood*	m/z	z	Δ (Da)	y'' and b ions**	log likelihood*
O08709	DDNNMPVTAR	1131.498	566.756	2	-0.001	0.579	101.0					
O55143	ISLPVILMDETLK	1470.837	736.437	2	0.022	0.467	71.8					
P11983	SSFPGVGLDK	1005.513	503.763	2	-0.003	0.737	158.5					
P24369	DVIIVDSGK	944.518	473.267	2	0.000	0.608	38.3					
P62852	AALQELLSK	971.565	486.789	2	-0.003	0.765	167.4					
P70296	VDYAGVTVDDELGK	1364.682	683.351	2	0.005	0.747	130.0					
Q61881	SDDDVSGAGELSSEELK	1736.759	869.394	2	0.014	0.475	101.8					
Q68FD5	EDKLECSEELGDLVK	1762.830	588.615	3	-0.008	0.586	85.9					
Q8K4Z5	EDPTPSKPVVGIIYPPPEVR	2189.173	730.734	3	0.007	0.419	122.8					
Q9CXU9	GDDLTPAGTEDYIHIR	1783.874	595.634	3	0.004	0.452	79.3					

* The peptide score reflects the natural log scale probability of a fragment spectrum given the peptide sequence. The fragmentation characteristics of peptides at low energy collisional induced dissociation are encoded into a Markov model that incorporates a, b, y and z immonium ions, fragment ions from modifications, and internal ions from proline. The algorithm calculates the probability of a correct sequence assignment as the product of the probability of assigning a peptide sequence before evaluating the experimental data (prior) and of the likelihood of the specific peptide fragmentation divided by the normalization factor obtained from the experimental spectra. The model also considers the number of possible sequences and is tuned for tight matches. Additional information on the peptide scoring scheme has been described by Skilling et al. (ProbSeq - A fragmentation model for interpretation of electrospray tandem mass spectrometry data (2004) *Comp. Funct. Genom.* 5, 61-68).

** fractions of identified y'' and b ions compared to the theoretical maximum.

Supplementary Table 3. LC-MS^E uniquely identified proteins to the RI and cripto^{-/-} (Cr^{-/-}) cell lines in at least two replication injections.

accession #	Description	n (replicate identifications)	average # peptides	average coverage (%)	condition
Q7TPR4	Alpha-actinin-1	3	8	10.4	RI
P48024	Eukaryotic translation initiation factor 1	3	4	42.8	RI
Q99020	Heterogeneous nuclear ribonucleoprotein A/B	3	3	9.8	RI*
Q922F4	Tubulin beta-6 chain	3	3	8.0	RI
Q6A068	Cell division cycle 5-related protein	2	5	7.0	RI
P43274	Histone H14	2	3	14.4	RI*
P14733	Lamin-B1	2	9	16.8	RI*
P97310	DNA replication licensing factor MCM2	2	7	8.4	RI*
P49717	DNA replication licensing factor MCM4	2	4	5.6	RI
Q99KP6	Pre-mRNA-processing factor 19	2	4	10.6	RI*
Q61820	GTP-binding nuclear protein Ran testis-specific isoform	2	2	11.1	RI*
Q8VIJ6	Splicing factor proline- and glutamine-rich	2	5	8.1	RI
P61089	Ubiquitin-conjugating enzyme E2 N	2	2	17.1	RI
Q5U5Q9	Ubiquitin interaction motif-containing protein 1	2	4	6.3	RI
P51881	ADP/ATP translocase 2	3	3	11.2	Cr ^{-/-} *
P84228	Histone H32	3	3	19.1	Cr ^{-/-}
P84244	Histone H33	3	3	15.0	Cr ^{-/-}
P09041	Phosphoglycerate kinase testis specific	3	5	12.8	Cr ^{-/-}
Q9DCD0	6-phosphogluconate dehydrogenase decarboxylating	2	7	15.5	Cr ^{-/-}
P06745	Glucose-6-phosphate isomerase	2	5	13.1	Cr ^{-/-}
P22752	Histone H2A type 1	2	2	21.5	Cr ^{-/-}
Q8CGP5	Histone H2A type 1-F	2	2	21.5	Cr ^{-/-}
Q8CGP7	Histone H2A type 1-K	2	2	21.5	Cr ^{-/-}
Q6GSS7	Histone H2A type 2-A	2	2	21.5	Cr ^{-/-}
Q64523	Histone H2A type 2-C	2	2	21.7	Cr ^{-/-}
Q8BFU2	Histone H2A type 3	2	2	21.5	Cr ^{-/-}
P51859	Hepatoma-derived growth factor (HDGF)	2	4	22.4	Cr ^{-/-}
Q8BGD9	Eukaryotic translation initiation factor 4B	2	5	10.4	Cr ^{-/-}
P63242	Eukaryotic translation initiation factor 5A-1	2	4	23.4	Cr ^{-/-}
O35685	Nuclear migration protein nudC	2	8	22.0	Cr ^{-/-}
Q9CZX8	40S ribosomal protein S19	2	3	19.7	Cr ^{-/-}
P80317	T-complex protein 1 subunit zeta	2	7	14.5	Cr ^{-/-}
P58774	Tropomyosin beta chain	2	6	18.7	Cr ^{-/-}

* protein also identified by 2D LC-MS/MS analysis.

Supplementary Table 4. Experimental details of MALDI-TOF peptide mass fingerprint used for the 2D-SDS/PAGE spot identifications (see Figure 6) relative to Hsp70 (A) and Hsp25 (B).

A	Spot ID	Protein identified	Accession n°	Coverage	%Pr	Peptide Matches	Theoretical Mr/pI
	25	Stress-70 protein [precursor]	P38647*	37.0	100	22	73.5/5.8
	<i>m/z</i>	Peak Mw	Peptide Mw	Delta (ppm)	Sequence	Modifications[#]	
	958.455	957.447	957.488	-42.7	(K)VLENAEGAR(T)		
	1450.745	1449.737	1449.710	18.5	(R)TTPSVVAFTADGER(L)		
	1149.545	1148.537	1148.546	-8.0	(R)RYDDPEVQK(D)		
	948.487	947.479	947.508	-30.5	(K)DTKNVPFK(I)		
	1341.645	1340.637	1340.611	19.7	(R)ASNGDAWVEAHGK(L)		
	1333.628	1332.621	1332.631	-8.0	(K)ETAENYLGHTAK(N)		
	1694.862	1693.854	1693.842	6.9	(K)NAVITVPAYFNDSQR(Q)		
	1242.681	1241.673	1241.673	0.0	(K)DAGQISGLNVLR(V)		
	2055.961	2054.953	2054.955	-0.7	(K)STNGDTFLGGEDFDQALLR(H)		
	1706.884	1705.877	1705.830	27.0	(R)ETGVDLTKDNMALQR(V)	Oxidation M (11)	
	1489.851	1488.843	1488.830	8.9	(R)AQFEGIVTDLIK(R)		
	973.543	972.535	972.518	17.9	(K)RTIAPCQK(A)	Carbamidomethyl C (6)	
	1446.767	1445.759	1445.755	2.7	(K)SDIGEVLVGGMTR(M)		
	1290.740	1289.732	1289.673	45.7	(K)VQQTVQDLFGR(A)		
	1808.941	1807.933	1807.895	20.7	(K)SQVFSTAADGQTQVEIK(V)		
	1493.714	1492.706	1492.640	44.0	(K)VCQGEREMAGDNK(L)	Carbamidomethyl C (2)	
	979.495	978.488	978.433	55.9	(K)DDIENMVK(N)	Oxidation M (6)	
	938.403	937.395	937.425	-31.9	(K)YAEEDRR(K)		
	2158.091	2157.083	2157.037	21.2	(K)ERVEAVNMAEGIIHDTETK(M)	Oxidation M (8)	
	1020.490	1019.482	1019.452	30.0	(K)DSETGENIR(Q)		
	901.461	900.454	900.442	13.4	(K)LFEMAYK(K)		

B	Spot ID	Protein identified	Accession n°	Coverage	%Pr	Peptide Matches	Theoretical Mr/pI
	42	Heat-shock protein beta-1 (HSP25)	P14602	29.2	99.99	6	22.9/6.1
	1005.497	1004.489	1004.472	17.3	(R)SPSWEPFR(D)		
	1031.482	1030.474	1030.462	11.4	(R)DWYPAHSR(L)		
	1075.574	1074.567	1074.567	-0.5	(R)QLSSGVSEIR(Q)		
	1104.516	1103.508	1103.500	7.9	(R)QDEHGYSR(C)		
	1149.621	1148.613	1148.598	13.3	(R)LFDQAQGVPR(L)		
	1797.958	1796.950	1796.931	10.5	(R)VSLDVNHFAPEELTVK(T)		

* UniProtKB/Swiss-Prot entry belonging to the heat shock protein 70 family (including also the Q61696, P17879 and P16627 entries extracted from the index of similarity lines).

[#] When redundant, peptides with methionine oxidation have been excluded from sequence coverage calculation.