Table S1: Yeast strains and plasmids used in this study

Strain	Genotype	Source
Y7092	*MATα can1Δ::STE2pr-HIS5 lyp1Δ ura3Δ0 leu2Δ0 his3Δ1*	Boone lab, University of Toronto
Y9230	*MATα can1Δ::STE2pr-URA3 lyp1Δ ura3Δ0 leu2Δ0 his3Δ1*	Boone lab, University of Toronto
yCG192	*MATα can1Δ::STE2pr-HIS5 lyp1Δ ura3Δ0 leu2Δ0 his3Δ1 ire1Δ::natMX4*	This study
yCG215	*MATα can1Δ::STE2pr-URA3 ura3Δ0::NLS-RedStar2-natNT2 leu2Δ0 his3Δ1 met15Δ0*	This study
yCG241	*MATα can1Δ::STE2pr-HIS5 lyp1Δ ura3Δ0 leu2Δ0 his3Δ1 hac1Δ::natMX4*	This study
yCG251	*MATα can1Δ::STE2pr-URA3 ura3Δ0::NLS-RedStar2-hphNT1 leu2Δ0 his3Δ1 met15Δ0*	This study
yCG253	*MATα can1Δ::STE2pr-URA3 lyp1Δ:: mCherry-natMX4 ura3Δ0::NLS-RedStar2-hphNT1 leu2Δ0 his3Δ1 met15Δ0*	This study
yCG266	*MATα can1Δ::STE2pr-Sp_HIS5; his3Δ1 leu2Δ0 ura3Δ0 met15Δ::4xUPRE-GFP-URA3 lyp1Δ::TEF2pr_mCherry-natMX4*	This study
yCG312	*MATα CEN::LEU can1Δ::STE2pr-URA3 lyp1Δ:: mCherry-natMX4 ura3Δ0::NLS-RedStar2-hphNT1*	This study
yCG 321	*MATα MRH1-GFP-HIS3MX6 can1Δ::STE2pr-URA3 lyp1Δ::mCherry-natMX4 ura3Δ0::NLS-RedStar2-hphNT1 leu2Δ met15Δ0 his3Δ1*	This study
P4339	Plasmid; natMX4	Tong et al, 2001
pMJ002	Plasmid; mCherry	David Breslow, University of California, San Francisco
pFA6a-hph	Plasmid; hphNT1	Janke et al, 2004
pYM43	Plasmid; Redstar2 natNT2	Janke et al, 2004
pYM-N19	Plasmid; natNT2 TEF2pr	Janke et al, 2004

Table SII: Genes negatively epistatic with *IRE1* as a query gene

ORF	GENE	SESA Score	Genetic interaction by tetrad
YBL082C	ALG3/RHK1	-0.5153	SL
YPL227C	ALG5	-0.58807	SL
YOR002W	ALG6	-0.56612	SL
YOR067C	ALG8	-0.50898	SL
YNL219C	ALG9	-0.50958	SL
YNR030W	ALG12/ECM39	-0.49693	SL
YLR242C	ARV1	-0.43792	SL
YNL259C	ATX1	-0.04165	NI
YPL069C	BTS1	-0.13992	ND
YGR157W	CHO2	-0.14417	NI
YLR087C	CSF1	-0.58620	SSL
YMR264W	CUE1	-0.54903	SL
YGR227W	DIE2	-0.50556	SL
YNL080C	EOS1	-0.26267	SL
YDR414C	ERD1	-0.27198	SSL
YJR054W	ERM6	-0.12261	ND
YGL054C	ERV14	-0.38737	NI
YML012W	ERV25	-0.33518	SSL
YGR284C	ERV29	-0.09176	NI
YBR041W	FAT1	-0.06392	SSL
YOL013C	HRD1	-0.46648	SL
YLR207W	HRD3	-0.37837	SL
YIL090W	ICE2	-0.22327	NI
YJR118C	ILM1	-0.43344	NI
YDR123C	INO2	-0.06872	NI
YOL108C	INO4	-0.21090	NI
YNL322C	KRE1	-0.07092	NI
YJL062W	LAS21	-0.41616	SSL
YKL073W	LHS1	-0.52158	SL

YIR033W	MGA2	-0.14475	NI
YGL136C	MRM2	-0.10622	ND
YJR073C	OPI3	-0.47901	NI
YOR085W	OST3	-0.53328	SL
YDL232W	OST4	-0.42975	NI
YGL226C-A	OST5	-0.13472	SL
YCR044C	PER1	-0.25242	NI
YOL001W	PHO80	-0.39188	SSL
YAL023C	PMT2	-0.44881	SSL
YNL169C	PSD1	-0.38584	ND
YMR201C	RAD14	-0.09608	SSL
YCL001W	RER1	-0.11307	ND
YDL020C	RPN4	-0.49929	SL
YKL212W	SAC1	-0.18441	NI
YMR214W	SCJ1	-0.48491	SSL
YBR171W	SEC66	-0.45898	SL
YOL031C	SIL1	-0.20836	SSL
YOR154W	SLP1	-0.01222	ND
YML055W	SPC2	-0.59309	SL
YJR117W	STE24	-0.50635	SL
YIL039W	TED1	-0.04067	ND
YBR082C	UBC4	-0.36349	NI
YMR022W	UBC7/QRI8	-0.55025	SL
YML013W	UBX2/SEL1	-0.52930	SL
YML029W	USA1	-0.23973	NI
YGR105W	VMA21	-0.11099	ND
YLR346C		-0.46639	NI

Tetrad Analysis; SL=synthetic lethal; SSL=synthetic sick; NI=no interacton; ND=not determined

Table SIII: Genes negatively epistatic with *HAC1* as a query gene

ORF	GENE	SESA Score
YBL082C	ALG3/RHK1	-0.40976
YPL227C	ALG5	-0.57687
YOR002W	ALG6	-0.56211
YOR067C	ALG8	-0.53580
YNL219C	ALG9	-0.42172
YNR030W	ALG12/ECM39	-0.53039
YLR242C	ARV1	-0.45570
YNL275W	BOR1	-0.07301
YPL069C	BTS1	-0.10034
YLR062C	BUD28	-0.09233
YGR157W	CHO2	-0.09136
YLR087C	CSF1	-0.60154
YMR264W	CUE1	-0.50142
YGR092W	DBF2	-0.06769
YBR201W	DER1	-0.03397
YGR227W	DIE2	-0.46141
YNL080C	EOS1	-0.22353
YDR414C	ERD1	-0.18519
YGL054C	ERV14	-0.19788
YML012W	ERV25	-0.29462
YGR284C	ERV29	-0.04990
YBR041W	FAT1	-0.02386
YNL274C	GOR1	-0.19229
YOL013C	HRD1	-0.44479
YLR207W	HRD3	-0.29978
YIL090W	ICE2	-0.18522
YJR118C	ILM1	-0.33541
YDR123C	INO2	-0.08561
YOL108C	INO4	-0.23215
YNL322C	KRE1	-0.03476

YJL062W	LAS21	-0.29362
YKL073W	LHS1	-0.50670
YLR104W	LCL2	-0.07108
YIR033W	MGA2	-0.11734
YJR073C	OPI3	-0.47489
YOR085W	OST3	-0.53988
YDL232W	OST4	-0.41983
YGL226C-A	OST5	-0.01659
YCR044C	PER1	-0.19100
YOL001W	PHO80	-0.33921
YAL023C	PMT2	-0.40223
YNL169C	PSD1	-0.33891
YMR022W	UBC7/QRI8	-0.52816
YGL147C	RPL9A	-0.07853
YDL020C	RPN4	-0.27814
YKL212W	SAC1	-0.05150
YDR159W	SAC3	-0.21699
YMR214W	SCJ1	-0.43950
YBR171W	SEC66	-0.24270
YML013W	SEL1/UBX2	-0.50304
YOL031C	SIL1	-0.09694
YML055W	SPC2	-0.58049
YHL007C	STE20	-0.04567
YJR117W	STE24	-0.50816
YDR126W	SWF1	-0.15695
YIL039W	TED1	-0.04345
YBR082C	UBC4	-0.39076
YML029W	USA1	-0.20885
YGR105W	VMA21	-0.11086
YLR262C	YPT6	-0.01033

Table SIV: Genes compensating tunicamycin stress in absence of *IRE1* or *HAC1*

	TM & *ire1Δ*	**TM & *hac1Δ***	**FUNCTION**
YKL207W		AIM27/EMC3	Protein folding ER
YJR032W	CPR7		Peptide prolyl-transisomerase
YGR092W	DBF2		Cell cycle stress response
YCL045C		EMC1	Protein folding ER
YGL231C		EMC4	Protein folding ER
YFR041C		ERJ5	Protein folding ER
YOR246C		ENV9	Redox vacuole-endosome
YER083C		GET2	Golgi ER retrograde
YIL027C		KRE27/EMC5	Protein folding ER
YOL064C		MET22	Methionine biosynth
YGL167C		PMR1	Ca2+ ATPase Golgi sorting
YER120W		SCS2	ER Phospholipid synthesis
YGL126W		SCS3	Insositol prototrophy
YLR268W		SEC22	Golgi ER retrograde
YIL076W		SEC28	Golgi ER retrograde
YKL184W	SPE1		Ornithine decarboxylase
YOR242C		SSP2	Sporulation & mitosis
YHL007C	STE20		Signal transduction kinase
YBR061C		TRM7	tRNA methyl transferase
YGL212W	VAM7/VPS43		Vacuolar SNARE complex
YOL095C		HMI1	Mitochondrial DNA helicase
YGL115W		SNF4	
YPL212W	ALG5		

Table SV: Genes compensating DTT stress in absence of *IRE1* or *HAC1*

	DTT & *ire1Δ*	**DTT & *hac1Δ***	**FUNCTION**
YAL058W	CNE1	CNE1	Protein folding ER
YGL027C		CWH41	ER processing glycosidase
YCR017C		CWH43	Cell wall biogenesis
YGR092W	DBF2		Cell cycle stress response
YMR202W	ERG2	ERG2	Ergosterol biosynth
YLR056W	ERG3		Ergosterol biosynth
YFR041C		ERJ5	Protein folding ER
YAR002C-A		ERP1	ER Golgi anterograde
YNL323W		LEM3	ER Phospholipid synth
YCL001W		RER1	Golgi ER retrograde
YBR229C	ROT2	ROT2	ER processing glycosidase
YGL126W	SCS3	SCS3	Insositol prototrophy
YLR268W	SEC22	SEC22	Golgi ER retrograde
YIL076W		SEC28	Golgi ER retrograde
YDR477W	SNF1		Ser/Thr protein kinase
YGL115W	SNF4		AMP-activated protein kinase
YJR010C-A	SPC1	SPC1	Signal peptidase
YIL047C	SYG1		Unknown plasma membrane
YGL115W		SNF4	
YOL052C		SPE2	
YKL184W	SPE1		
YNL064C	YDJ1		
YBR162W	YSY6		

Table SVI: Primers used in this study

Primer	Description	Sequence
144	TEF2pr_NLS forward	TGCGAGGCATATTTATGGTGAAGGATAAGTTT TGACCATCAAGAAGGTTCGTACGCTGCAGGTC GAC
145	TEF2pr_NLS reverse	CTTTCTCTTTTTCTTTGGAGATTCAAATTCAGA ACCATCAGCAGTTCTTTTACCACCAGTCATAGA AGCCATGTCCGGGGGGGATCCACTAG
146	NLS-Redstar2 forward	GAATTTGAATCTCCAAAGAAAAAGAGAAAGGT TGAAGCTTCTGGTTTGGTTCCTAGAGGTTCTGC TTCTTCTGAAGATGTCATC
147	NLS-Redstar2 reverse	CCATGAAGCTTTTTCTTTCCAATTTTTTTTTTTT CGTCATTATAGAAATCCGCTGGCCGGGTGACC CGGCGGGGAC
240	hph marker switch	CGAGAAAATCTGGAAGAGTAAAAAAGGAGTA GAAACATTTTGAAGCTATGAGCTCCGAGCTCG TTAAAGCCTTCGAG
224	mCherry forward	AATTGCATTGTCTATAACGATAACAAAAGACA TCGTATATATATATATATCGTACGCTGCAGGTC GAC
252	mCherry reverse	TCTATTTTTTTATTTTTTTCTATTTTGAAGGCAT GCAAGAGGTTCTGTGAACTATAGGGAGACCGG CAGA
122	IRE1 deletion forward primer	ATACACATTAAAAAAACAGCATATCTGAGGAA TTAATATTTTAGCACTTTGAAAAACATGGAGG CCCAGAATACCCT
123	IRE1 deletion reverse primer	CAAAGTAACATTAATGCAATAATCAACCAAGA AGAAGCAGAGGGGCATGAACATGCAGTATAG CGACCAGCATTCAC
120	IRE1 deletion confirmation reverse primer (used with #118)	TGCAGAACGAAAGCTTTCCA
121	IRE1 deletion confirmation forward primer (used with #119)	GGAGATCAATGAGCCAACTT

118	NatR cassette internal confirmation primer	TGGCTGGAGGTCACCAACGTC
119	NatR cassette internal confirmation primer	TACGAGACGACCACGAAGC
190	HAC1 deletion forward primer	GTCAAACATAACAACCTCCTCCTCCCCCACCTACGACAACAACCGCCACTACATGGAGGCCCAGAATACCCT
191	HAC1 deletion reverse primer	AACAGCGATAATAACGAGAAAAAAAAAATTATACCCTCTTGCGATTGTCTCAGTATAGCGACCAGCATTCAC
188	HAC1 deletion confirmation forward primer (used with #119)	TGGGCAGCGACACTGAACATA
189	HAC1 deletion confirmation reverse primer (used with #118)	ATGAACGTGGTTTTGAACACCT