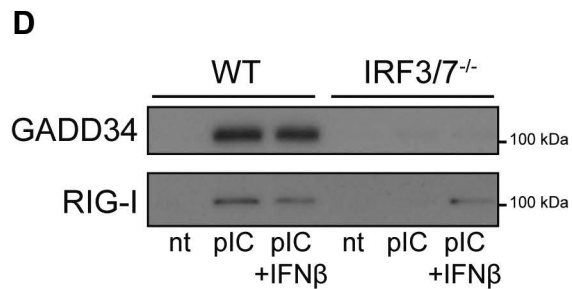
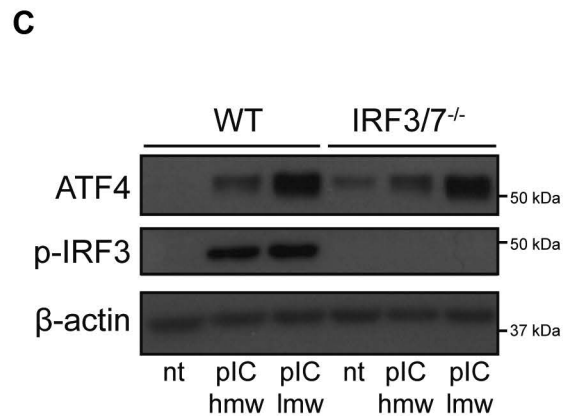
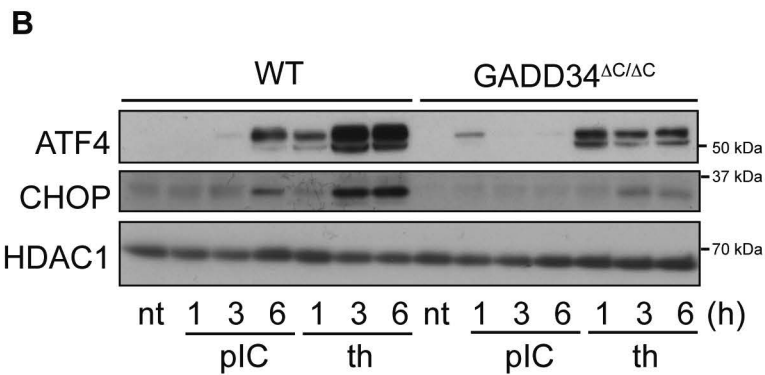
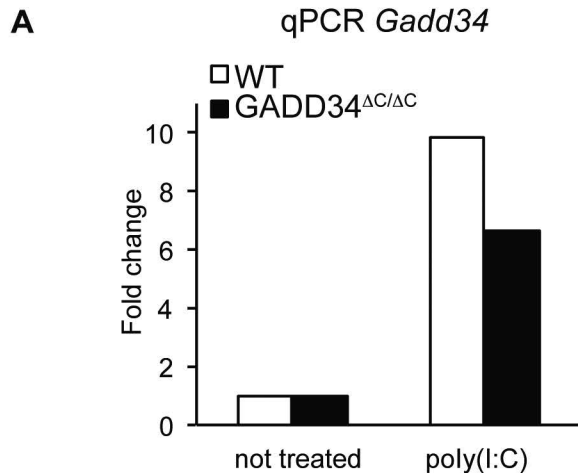


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Supplementary figure S1



Appendix figure legend

Appendix Figure S1.

- A- Gadd34 mRNA was quantified by qPCR after 6h of HMW poly(I:C) treatment in WT and GADD34^{ΔC/ΔC} MEFs. mRNA levels are expressed as fold change compared to untreated condition.
- B- WT and GADD34^{ΔC/ΔC} MEFs were treated with HMW poly(I:C) (pIC) or thapsigargin (th) for 1, 3 and 6h. ATF4 and CHOP expression in nuclear extracts were detected by immunoblot. HDAC1 expression was used as equal loading control. (nt: non treated condition)
- C- WT and IRF3/7^{-/-} MEFs were left untreated (nt), or treated with HMW- or LMW poly(I:C) for 6h. ATF4 and p-IRF3 levels in nuclear extracts were detected by immunoblot β-actin was used as equal loading control.
- D- WT and IRF3/7^{-/-} MEFs were treated with HMW poly(I:C) during 8h in the presence or not of 1 ng/ml of recombinant mouse IFNβ. GADD34 and RIG-I expression were detected by immunoblot on whole cell lysates. Expression of RIG-I is used as a positive control of recombinant IFNβ effect.

Appendix Table S1

Common genes upregulated in WT and GADD34 ^{ΔC/ΔC}				Genes ONLY upregulated in WT				Genes ONLY upregulated in GADD34 ^{ΔC/ΔC}			
1190002H23Rik	Ddx58	Hpx	Parp14	0610040B10Rik	Bst2	Gm11517	Hyal3	Nfil3	Sh3gl3	1110065H08Rik	Nr13
1810011O10Rik	Ddx60	Hsd17b13	Parp9	1700055D18Rik	Cacna1h	Gm11563	Icam1	Nfkbb1	Six1	1500012F01Rik	Nts
2310026L22Rik	Dhx58	Hsh2d	Pdzrn4	1700094D03Rik	Cap2	Gm12185	l04	Ng23	Slc16a9	1700091H14Rik	Olf512
2610018G03Rik	Dtx3l	I830012O16Rik	Phf11	1700125H20Rik	Casp4	Gm12250	Ifi203	Nlrc5	Slc23a3	2610035D17Rik	Olf543
4921517L17Rik	Dub1	Ifi204	Pmaip1	1810007D17Rik	Ccdc81	Gm12655	Ifi35	Nmi	Slc25a22	4932438H23Rik	Paip1
4922505G16Rik	Efnb3	Ifi44	Popdc2	2010002M12Rik	Ccl1	Gm13083	Ifi47	Nod2	Slc2a6	4933416M07Rik	Pkd11
4930412F09Rik	Egr1	Ifih1	Ppm1a	2010005H15Rik	Ccrn4l	Gm13105	Ifi2	Nppc	Slfn10-ps	4933437F05Rik	Plk3
4930488B22Rik	Egr2	Ifit1	Pram1	2310001H17Rik	Cd209g	Gm13391	Ifitm3	Nrip1	Slfn2	5830415F09Rik	Plscr2
8030451A03Rik	Egr4	Ifit3	Ptpn22	2310042D19Rik	Cd40	Gm14137	Ifitm6	Nrip3	Slfn9	9430008C03Rik	Prdm11
9130015A21Rik	Errf1	Ifna12	Pvt1	3110043O21Rik	Cfb	Gm1966	Ifna1	Nub1	Slpi	9530018H14Rik	Prm3
A530032D15Rik	Fam110c	Ifna13	Rasgef1b	3230401D17Rik	Ch25h	Gm17019	ligp1	Nufip1	Smcr8	A430089I19Rik	Rad52
A530040E14Rik	Fam46a	Ifna2	Rbm43	4930459C07Rik	Chka	Gm17757	ll15ra	Oas1e	Soat2	A930027P06Rik	Relt
Abcc8	Fam84b	Ifna4	Relb	4930512H18Rik	Clec2d	Gm1966	ll28a	Oas3	Socs1	Abr	Rf4
AC125149.2	Fcgr1	Ifna5	Rnd1	4930523C07Rik	Clec2h	Gm20627	Impg2	Ogdh	Spr1a	AC140325.4	Rgs2
AC132444.2	Fos	Ifnab	Rnf213	4930528F23Rik	Ccl5	Gm20665	Inpp1	Ogfr	Spy2d1	AC153928.3	Rnd3
AC133103.6	Frmr3	Ifnb1	Rsad2	4930599N23Rik	Cln3	Gm2582	Ipo11	Olf985	Stfa211	AC163653.5	Sdk1
AC168977.1	Gadd45a	Igtp	Rtp4	4933422A05Rik	Cnksr1	Gm3099	lrak3	Ovpg1	Taf7	AC168977.2	Sele
Acox1	Gbp2	Il15	Saa3	4933433H22Rik	Creb3l4	Gm3455	lr2	Oxct2b	Tap1	Aim1	Sla
Al607873	Gbp3	Il5	Samd7	4933439G12Rik	Cxcl9	Gm4107	lr5	P2rx7	Tap2	Angpt4	Slc6a4
AL592187.1	Gbp5	Il6	Samd9l	5430410E06Rik	Cyct	Gm4123	lr8	Padi4	Tapbp	Anxa13	SNORD26
Amhr2	Gbp7	Irf1	Sez6l	5830416P10Rik	Cyp26c1	Gm4134	lrg1	Parp12	Tbc1d2	BB287469	Socs2
Ankrd33b	Gem	Irf7	Sgms2	6230427J02Rik	Cyth4	Gm44	lta6	Pcdh8	Tbx21	BC061212	Speer4b
Apobec3	Gm11202	Irf9	Skor1	9130017N09Rik	D730005E14Rik	Gm4632	Jakmp1	Pdcd1	Tcstv3	BE949265	Syce1l
Apol	Gm11274	Irgm1	Slc25a25	9330175E14Rik	Daxx	Gm4841	Kdr	Piwil4	Tdrd7	C2cd4b	Taf1d
Apol7a	Gm11545	Irgm2	Slfn8	9530082P21Rik	Dcp2	Gm4902	Khdrbs1	Plcx2d	Tespa1	Cdkn1a	Tas2r104
Apol7b	Gm11597	Isg15	Snhg12	9930023K05Rik	Ddx24	Gm4955	Klf4	Plekha4	Tr3	Crxos1	Tnfaip2
Apol7c	Gm11974	Isg20	snoR38	9930105H17Rik	Dll1	Gm4992	Klkb1	Plekha6	Tm6sf1	Cyp4f14	Tnfsf15
Apol9a	Gm13271	Isoe2a	SNORA71	9930111J21Rik2	Dusp8	Gm5431	Krt16	Plekhf2	Tmem184a	D130020L05Rik	Trim15
Apol9b	Gm13272	Itg6	Sp140	A530064D06Rik	Duxbl	Gm5483	Lama3	Plk2	Tmem198	Dusp1	Tslp
Arid5a	Gm13275	Junb	Stat1	AA474408	Dync1h1	Gm5595	Lck	Plip	Tmem212	E230008N13Rik	Zbtb46
Atf3	Gm13280	Klf6	Stat2	Abcb1a	Dync1i1	Gm5622	Lct	Pml	Tmem229b	Esm1	Zc3h12a
AW011738	Gm13284	Klk1b3	Stx11	AC074329.1	Dyrk3	Gm5970	Lgals3bp	Pnpla7	Tmprs2	Fam102b	Zfp423
BC006779	Gm13286	Klrb1a	Tacr2	AC122425.1	E330016A19Rik	Gm6264	Lgals8	Pnpt1	Tnfsf10	Fam36a	
BC049762	Gm14010	Krt17	Tex19.1	AC132444.1	E330037I15Rik	Gm6401	Lgals9	Ppmlk	Tnfsf18	Fam59b	
Btbd16	Gm14446	LOC100505112	Tgif1	AC211878.1	Efhb	Gm8127	Lif	Prdm9	Tor1aip1	Fhad1	
Btg2	Gm15753	Lpar3	Tgtp1	Adamts1	Ehd4	Gm8815	LOC100044874	Prr5l	Tor1aip2	Gm12346	
C130026I21Rik	Gm16340	Ltb	Tiparp	Adar	Eif2ak2	Gm8909	LOC547349	Tor3a	Tor3a	Gm13078	
Ccdc147	Gm16506	March4	Tlr2	Agri	F3	Gm9574	LOC552877	Psmb9	Trem3	Gm13180	
Ccl2	Gm4189	Mir147	Tmem140	Ahr	F830016B08Rik	Gm9877	LOC640793	Psme2b-ps	Trim12c	Gm13496	
Ccl4	Gm4951	Mnda	Tnf	Apobec1	Fam110b	Gna13	Lpxn	Ptgs2	Trim14	Gm14636	
Ccl5	Gm5123	Mndal	Tnfaip3	Apobec4	Fam129a	Gpr98	Lrp2	Ptpn13	Trim25	Gm15340	
Ccl7	Gm6482	Mob3c	Traf1	Apol10b	Fap	Gsg1	Lta	Ptpre	Trim26	Gm15863	
Ccn1	Gm7945	Mx1	Trex1	Apol8	Fbxl2	Gvin1	Lypd6b	Pydc3	Trim30a	Gm8005	
Ccr12	Gm8220	Mx2	Trim12a	Apon	Fbxo15	H2-BI	Maff	Pyhin1	Trim30b	Gm9694	
Cd274	Gm8232	Myc	Trim21	Arc	Fgd4	H2-D1	Mageb2	Rab8b	Trim56	Gm9758	
Cd44	Gm8247	Mylk	Trim30c	Arhgef3	Foxf1a	H2-K1	Mapt	Rad23b	Trim6	Gpr119	
Cd52	Gm9706	Neur13	Trim30d	Arl5c	Fpr2	H2-K2	March11	Rasl11b	Tspan33	Hist1h2ba	
Cd74	Grlh1	Nfkbia	Trim34a	Armcx6	Fzd5	H2-M11	Mep1a	Rbmy1a1	U6atac	Hist2h4	
Cd83	H2-M2	Nfkbie	Trim5	Asap3	Gabrp	H2-M3	Mir101a	Rdh5	Uba7	Hivep2	
Celf3	Has2	Nfkbiz	Trim69	Ascc3	Gadd45g	H2-M9	Mitd1	Rel	Ubd	Hspbap1	
Cish	Hdc	Niacr1	Trpm1	Atp8b3	Gata3	H2-Q1	Milki	Rfx5	Unc80	Ier2	
Cmpk2	Herc6	Nr1h5	Txnip	B230307C23Rik	Gbp1	H2-Q10	Mov10	Rgs22	Vnn1	Jun	
Creg2	Hist1h1c	Nrg4	Ube2l6	Bai2	Gbp10	H2-Q2	Mpeg1	Rhob	Vwf	Klk1b24	
Csf1	Hist1h2bc	Nudt13	Ucma	Batf2	Gbp4	H2-Q3	Mpo	Ripk2	Wdfy4	Lag3	
Csf2	Hist1h2bg	Oas1a	Usp-ps	BB157357	Gcg	H2-Q5	Msc	Rnasel	Zbp1	Lmcd1	
Csrnp1	Hist1h2bp	Oas1b	Usp17l5	BC005561	Gdap10	H2-Q6	Mtmr7	Rnaset2a	Zbtb10	LOC402769	
Cxcl1	Hist1h2bq	Oas1c	Usp18	BC016423	Gdf15	H2-T10	Myd88	Rnf19b	Zbtb3	LOC641136	
Cxcl10	Hist1h3g	Oas1f	Vcam1	BC023105	Gdnf	H2-T22	Myom1	Rnf31	Zbtb5	Lrrc30	
Cxcl16	Hist1h4i	Oas1g	Xaf1	BC057022	Glis3	H2-T23	N4bp1	RP23-53N8.2	Zc3h6	Lrrc3b	
Cxcl2	Hist1h4m	Oas2	Zc3hav1	BC061194	Glp2r	Hfm1	Naip6	S1pr1	Zfhh4	Madcam1	
Cyp26a1	Hist2h2aa2	Oas1	Zfp36	BC100530	Gm10092	Hist1h1d	Nceh1	Scn10a	Zfp202	Map3k8	
Cyp26b1	Hist2h2bb	Oas2	Zfp945	Bcl2l11	Gm106	Hist3h2ba	Nckap1l	Sema5b	Zfp296	Mcoln1	
D14Erd668e	Hist2h3c2-ps	Ovol1	Zmynd15	Bglap-rs1	Gm10775	Hkdc1	Ndrgr1	Serpinb9c	Zfp382	Mfsd6l	
D730045A05Rik	Hist3h2a	Parp10	Znf1	Bglap2	Gm10839	Hmha1		Serpinb9d	Zfr2	Myo18b	
				Bmyc	Gm11127	Hmox1		Sfxn2	Zmynd12	Nfkbid	
					Gm11435	Hoxb5			Zufsp		

Lists of genes found statistically up-regulated in WT and GADD34^{ΔC/ΔC} MEFs upon HMW poly(I:C) treatment during 6h as compared to their untreated counterparts. Probes were classified with Venn diagram. 257 genes were up-regulated in both WT and GADD34^{ΔC/ΔC} MEFs, 391 were only up-regulated in WT and 97 only in GADD34^{ΔC/ΔC} MEFs.

Appendix Table S2

Genes upregulated only in WT (vs ATF4 ^{-/-}) MEFs upon tunicamycin					
Car6	4932422M17Rik	Osbpl2	Hagh	Dym	Asph
Derl3	Gpt2	4930431P03Rik	Dusp18	Usp31	Ppiib
Cox6a2	Rab38	Slc5a6	Erlin1	Rrbp1	D6Wsu116e
Acox2	S100a7a	Lims2	Camk1	Gm10734	Gtf2a1
Csn3	Mtm1	2610528E23Rik	2210008F06Rik	1810010H24Rik	Cyb5b
Slc6a12	Sbtd1	Klra5	Kctd4	MLlt4	Zfp945
Angptl6	Slc7a1	Tmcc3	Camk1d	Cdv3	Pusl1
2310002L13Rik	Ptrh1	Sft2d2	Tle1	Plcx2	Ssr4
Chchd10	Shmt2	XM_124146	Uprt	Ahnak	Gpr85
Soat2	NAP112914-1	Mapk6	Serpib9g	Tmem97	A630033H20Rik
Slc6a9	Chka	Slc1a5	Otud1	Ddr2	Aup1
Chac1	Gtpbp2	Mthfd2	Pard3	Mtdh	2310046K23Rik
B4galnt2	Hoxa1	Fam195a	Xpot	Eif1a	4732491K20Rik
Odz4	Areg	Eps8	2310058N22Rik	Sertad2	Mal
Cth	Clic5	Cobl	Arhgap33	Atp2a2	Gale
Tacr2	Dhrs9	Tbp1	Coasy	Pard6a	A630012P03Rik
Cnfn	5330431K02Rik	Sh3bgrl2	Slc43a3	Nfkbib	Hs1bp3
Avil	Firt3	Gpr124	Svip	Timm8a1	Kdm6a
Cdsn	Ppef1	Dpysl3	Lrrc8b	Gtf2h1	Thyn1
Gm10639	Gpr137b-ps	Akna	2700007P21Rik	Rnh1	Gnat2
Gpr137b	Sh3tc2	Them4	Mfsd11	LOC100044193	Camk2d
Fgf21	Sgcd	Nars	Bcl2l1	Gls	Fip1l1
Msln	Mamdc2	Aap5	Tcea1	Slc26a6	Gm13238
Tmem179	Asns	XM_485592	BC022687	Slc2a5	Klk10
Vipr2	Dennd4a	Slc25a29	Slc25a37	Ahi1	2210011C24Rik
Cyb5r2	Kcnt2	Gm12060	Zfand2a	Lym4	Cln6
Akr1b7	Mei4	Stt3b	Gmppb	Bend6	Ogt
Sh2d6	Phgdh	Ormdl2	Calcb	Zbtb7b	Kcnma1
Gm3776	Aig1	Mpp6	Stard5	Sphk2	Mrps18b
Stc2	Cpeb1	Amot1	Pck2	Mtss1	Fads2
Tmem47	Renbp	Zfp57	1810029B16Rik	Slc35c2	4922501C03Rik
Gm8709	Mtap1b	Larp1b	Insig1	Crebl2	H2-M10.3
Fibin	Ecel1	Siah2	Sh3bp2	LOC100504608	Far1
Adm2	Klrg2	XM_910588	Cebpg	Twistnb	Nnmt
Nrcam	Gm129	Atp6v0b	AK086332	AA467197	Pppde2
Amz1	Lck	Cars	B3gnt2	Tmem60	Cgrrf1
Slc4a11	NAP111644-1	Gsta2	9130230N09Rik	Eif3c	Try5
Myom2	Slc25a33	Hdac4	Lrrc16a	Jdp2	Pacs2
Ttc9	Pyhin1	NAP112102-1	Samd12	Cpeb2	Rasal1
Cyb5r1	Nfxl1	Atp2a3	Avpi1	Lrrfip1	Ube2j1
Gadd45a	Dusp5	1110018J18Rik	Lins	4932412D23Rik	Eps15
Aldh1l2	Prkg2	Gm11595	Sco2	5430411K18Rik	Scpep1
Ndrp1	Rtn4r	Fez1	AK5	Cds2	0610007P14Rik
Tmem184a	Ascc2	Tspan15	Lamb3	Plcg2	4932425I24Rik
Ppp1r15a	Cr1l	Duoxa1	Slc38a1	Mdfic	Mtap6
Cyp3a13	Fads3	Akap2	Pde10a	Deb1	Hax1
Wars	Lonrf3	Slc38a7	Slc39a11	XM_909351	Ciapin1
Sspo	Mtap2	BC052688	Cspg4	Krtap4-8	Gcnt1
Atad3a	Ptpn22	Kprp	Uap1l1	Uqcrq	D13Ert608e
Fam171b	Abca8b	Rps6ka2	Entpd5	Mettl22	Slc25a38
Ercc1	Gcat	Ostn	Socs2	Gm7303	Cln8
Mfsd2a	Slc33a1	Tead4	Crls1	Lars	NAP060966-1
Gm8096	NAP114398-1	Meis2	Csnk2b	Rdh11	4930438A08Rik
Tbc1d2	Rnf39	Gm2016	Plagl1	Hapln4	Hspa13
Itpr2	Emp2	Ank2	NAP112224-1	Lphn3	Lman2
Lpin3	Rab39b	Gsto1	Slc35e4	A330009N23Rik	Cdr2l
Pla2g12a	Vat1	Arl5b	Srpb	Timm10	Det1
Tigit	0610010O12Rik	Klra22	Clptm1l	0610007L01Rik	Tmem181a
4930506M07Rik	Tmeff2	Slc20a1	Srm	Pqlc2	D030028A08Rik
Reep6	1700016K19Rik	Recql4	Ipo7	Klf8	Parvb
Itgb7	Slc35f2	LOC236220	Als2cl	P2rx3	Agpat5
Perp	Hmox1	Ass1	Hspa9	Lass6	Tom1
H2-M10.1	Gnpnat1	Pvr	Pecr	Tns3	1110067D22Rik
Pax8	Epha2	Rnf185	Ece2	Trio	Slc36a1
Cyp2c44	Plk3	Suox	Tymp	Yipf6	Sec14l1
Klf5	Spcc3	Fam110c	Tnfaip2	Cyld	Trappc8
Slc7a11	Gm2694	Phf10	Lonp1	Pcca	Zdhhc21
Wfs1	Esy2	Ghitm	Tmem192	Mbtps2	Klra6
Psph	Cpox	Tmem202	Tmem209	Faf1	Pvrl1
Sybu	Ngef	Sars	Eef2k	Gm9079	Grpel2
Plcl2	Mertk	Stau2	Atf6	Serpib9c	BC048403
Ppm1h	Mid1ip1	Ccdc47	Eif5	Eif4g3	Jagn1
Acot2	Strbp	Yrdc	Unc5c	Socs6	Dnaja3
Gch1	Gdap1l1	Eprs	Qdpr	Dgkd	Tm2d3
Ptchd1	Oxsr1	Scfd2	Tmem206	Zyg11b	Ssfa2
Eif4ebp1	Hs3st5	Reep3	Rbm15b	Fut1	Imp3
Slc7a3	Rpp25	Ttl11	Lrp8	LOC100504857	Fam185a
Hmx3	Paqr3	Sgsm1	Snd1	Gfpt1	Krtcap2
Nrip2	Npc1	Tmem120a	Rwdd4a	2810432L12Rik	Homer1
Extl1	Aldh18a1	Ccnd2	Mvd	Pkp1	Cdc42se2
Atf3	Sqstm1	Scly	Slc17a9	Tspyl2	Lnp
Lce1c	Sgms2	Tmem74			

ATF4 gene expression signature represents the genes that were found up-regulated in WT and not in ATF4^{-/-} MEFs upon tunicamycin during 12h as compared to their untreated counterparts. This list was generated from available public genomic data (GSE49598).

Supplementary Materials and Methods

Microarray analyses

Equal amounts of RNA extract (200 ng) from each replicate were amplified and Cy3 labeled using the Low Input Quick Amp Labeling kit (Agilent Technologies). Hybridizations were performed according to the manufacturer's instructions for One-Color Microarray-Based Gene Expression Analysis using SurePrint G3 Mouse Gene Expression v2 Microarrays (Agilent Technologies). Images were scanned on an Agilent G2505C microarray scanner, and raw images were quantified using the Agilent Feature Extraction 10.7.3.1 software and the GE1_107_Sep09 protocol. Raw gene expression data were background corrected using the "normexp" method and quantile normalized, using the limma package through Bioconductor in the R statistical environment (version 2.15.0). Quality control of the expression data was assessed by boxplots of raw expression data, density plots of the normalized data, and calculation of the Pearson's correlation coefficients between arrays. Genes differentially expressed between each condition were selected as having a fold change (FC) > 2x and a FDR (Benjamini-Hochberg correction) < 0.05 after statistical evaluation through the empirical Bayes method performed with the limma package. The genes that were found upregulated were sorted using Venn diagrams and the gene sets obtained were uploaded into Ingenuity Pathway Analysis (IPA) to test for significant enrichment of functional annotations.

The microarray data have been deposited in the Gene Expression Omnibus (GEO) database under accession number GSE77777. The ATF4 gene expression signature was generated using GEO (GSE49598), on WT and ATF4-deficient MEFs treated or not with tunicamycin for 12h. This ATF4 signature was composed of the genes found statistically up-regulated (FDR < 0.05; FC > 2x according to empirical Bayes method performed with the limma package) in WT MEFs upon tunicamycin treatment as compared to untreated but not found up-regulated in ATF4-deficient MEFs upon tunicamycin treatment as compared to untreated. The GSEA method was used to test whether the ATF4 signature was significantly regulated in the pairwise comparisons between WT or GADD34^{ΔC/ΔC} MEFs treated with poly(I:C) with their untreated counterparts. Graphical output is a bar code. Each bar corresponds to the projection of one probe set of the ATF4 signature gene set on the red-to-blue gradient representing all the probe sets of the gene chip from microarrays analysis, ranked from high expression in non-treated condition to high expression in poly(I:C)-treated condition. The normalized enrichment score (NES) represents the number and differential expression intensity of the genes enriched. The NES is positive if the gene set is enriched in the condition on the left (red) and negative if it is enriched in the condition on the right (blue). The false discovery rate (FDR) is a statistical value representing the likelihood that the enrichment of the gene set represents a false-positive finding (e.g., if FDR = 0.25, a similar enrichment is found in 25% of the random gene sets used as controls). The enrichment was considered significant for FDR < 0.25, as recommended by GSEA developers.

ELISA

IFN-β quantification in culture supernatant was performed using the Mouse Interferon Beta ELISA kit (PBL InterferonSource) according to manufacturer instructions.

Mathematical model (simplification)

The presented mathematical model can be simplified by removing the presence of Ppp1r15a and considering only the regulation of the production of GADD34. This simplification is possible because we decided to represent the decay of the mRNA as triggered by its entering in productive engagement in the ribosome. This mRNA decay model has been chosen for its simplicity (it does not require extra parameters) and the fact it is supported by several publications. From a mathematical point of view, this simple model permits to almost ignore the effect of the production/decay of Ppp1r15a and to inject its participation directly in the equation (6). By the way, we can re-write the model equations like:

1. $P(t) = S1(Ds(t-1))$
2. $Tl(t) = S2(E(t-1))$
3. $Tlg(t) = 1-Tl(t-d1)$
4. $Gp(t) = Gp(t-1) + Tlg(t-d1) * C1 - C2$
5. $E(t) = C3 * P(t-1) - C4 * Gp(t-d2)$

This simplified model has a behavior very similar to the previous model's one (Figure 7B). Moreover, the simulations of virtual cell dynamics does not show any qualitative difference with the ones proposed in Figure 7D. Hence, it seems possible to use this model for the study. However, since the regulation of the *Ppp1r15a* gene seems to be very important from the biological point of view, one can ask if the simplified model will permit to consider the various sources of regulation of this mRNA. For instance, the model of mRNA decay may

be changed for some other models that were discussed in literature in order to estimate their impact on the dynamics. For this study, the presence of the *Ppp1r15a* parameter in the model is therefore important.