Supplementary Information

"Autophagy-dependent survival is controlled with a unique regulatory network upon various cellular stress events"

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I. Mathematical codes for computational simulations

Although the complexity of the cellular system makes really difficult to make mathematical models of a biological regulatory network, with a proper reduction approach a simple wiring diagram can be created containing the key components of the control network (1, 2). Our wiring diagrams are based on the relevant system level feedback loops, while they are independent form can be independent of the identity of molecular players. With this mathematical modelling, the qualitative features of the dynamical system behind autophagy regulation can be easily explored by using both computational simulations and signal-response curves. A biological regulatory network can be translated into a set of ordinary differential equation (ODE) to describe how the concentration/activity of each control element in the network changes with the time (3, 4). A generic differential equation depicting the temporal changes of a regulatory element is composed of two parts: production and consumption terms. In a cellular protein-protein regulatory network the production can be given by protein synthesis (i.e. transcription and translation) and/or an activation (i.e. post-translational modification) term, while the consumption can be given by protein degradation and/or inactivation term. Usually synthesis and degradation reactions are described by mass action kinetics, whereas protein activity can be described either by mass action or Michaelis-Menten kinetics (1, 5-7). Solving a set of non-linear ODEs gives the time evolution of the relative protein concentration/activity (time courses).

The temporal profiles were computed numerically using *XPP-AUT*, which is freely available from http://www.math.pitt.edu/~bard/xpp/xpp.html. All the simulations presented in the text are based on the following XPP codes which contains ODEs. The rate constants (k) have the dimension of min^{-1} and Michaelis constants (*J*) are dimensionless. The proteins levels/activities are given in arbitrary units (a.u).

The code for a general model simulating time series

```
# a model to simulate autophagy induction with XPP-AUT

# initial conditions
```

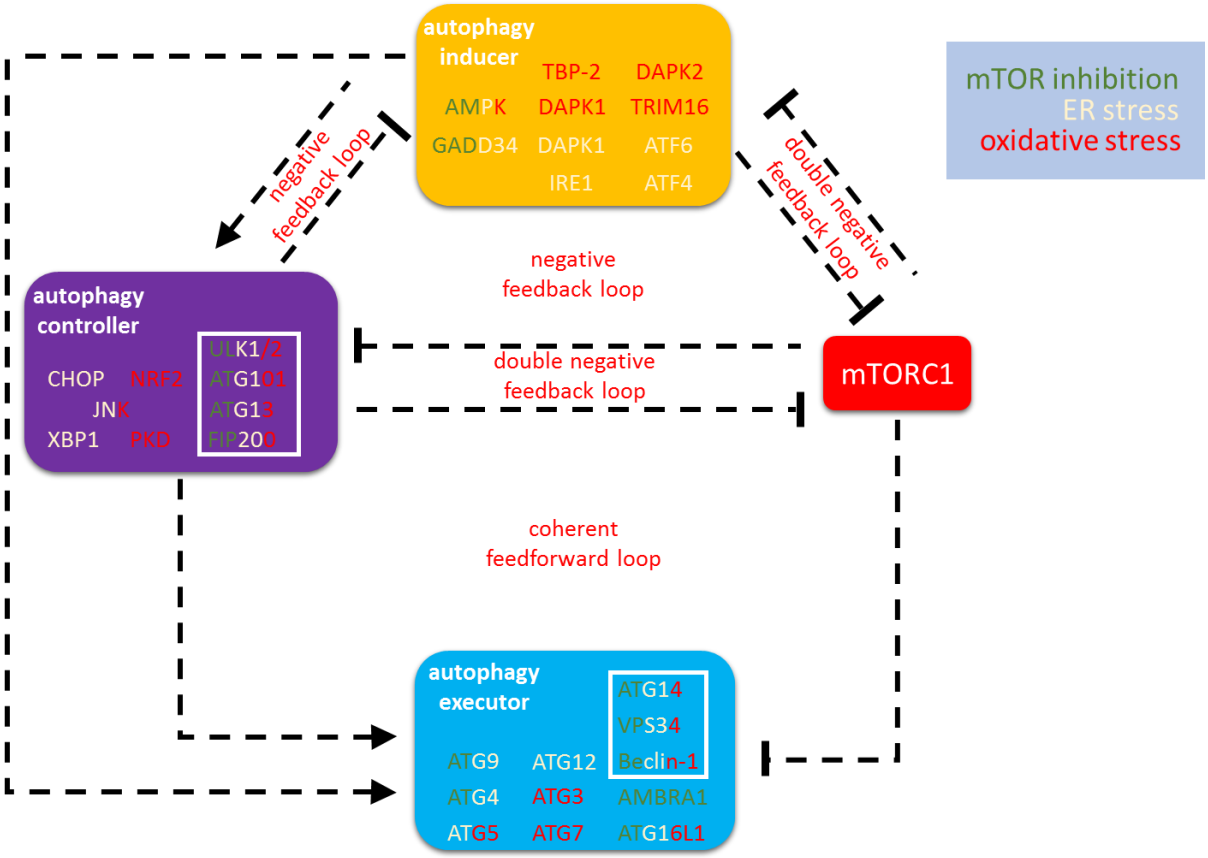
```
init AUCO=1.3381e-005, PAUIN=0.0717, AUIN=0.0382, mTOR=0.6370, AUEX=0.0019,
DEATH=0.0044

# differential equations
# AUCO represents the active form of autophagy controller
AUCO' = (kaac + kaac'*AUIN)*(AUCOT-AUCO)/(JAUCO + AUCOT-AUCO) - (kiac +
kiac'*mTOR)*AUCO/(JAUCO + AUCO)

# pAUIN represents the active, pre-form of autophagy inducer
pAUIN' = (kapai + kapai'*stress/(1+stress))*(pAUINT-pAUIN) - (kipai +
kipai'*AUCO + kipai"*mTOR + kipai'"*DEATH)*pAUIN

# AUIN represents the active form of autophagy inducer
AUIN' = kaai*pAUIN*(AUINT-AUIN)/(JAUIN + AUINT-AUIN) - (kiai +
kiai'*mTOR)*AUIN/(JAUIN + AUIN)

# mTOR represents the active form of mTORC1
mTOR' = (kamtor + kamtor'*stress/(1+stress) + kamtor"*DEATH)*(mtoT-mTOR) -
(kimtor + kimtor'*AUIN + kimtor"*AUCO)*mTOR

# AUEX represents the active AUEX genes; when AUEX is active we assume that
autophagy is also active
AUEX' = (kaax + kaax'*AUCO + kaax"*AUIN)*(AUEXT- AUEX)/(JAUEX + AUEXT-
AUEX) - (kiax + kiax'*mTOR + kiax"*DEATH)* AUEX /(JAUEX + AUEX)

# DEATH represents the possible cell death of the cell
DEATH' =(kade + kade'*AUCO + kade"*stress + kade'"*mTOR)*(1-DEATH)/(Jdea +
1-DEATH) - (kide + kide'*AUEX)*DEATH/(Jdea + DEATH)

# parameters
# simulating rapamycin treatment: stress=0.75
# simulating high stress with GADD34 depletion: stress=9, AUIT=0.1
# simulating high stress with CHOP depletion: stress=9, AUCOT=0.1
# simulating high stress with GADD34 over-expression: stress=9, AUIT=2
# simulating high stress with CHOP over-expression: stress=9, AUCOT=1.25
# simulating high stress with KEAP1 depletion: stress=7.5, kaac=5
# simulating EGCG treatment: kaai=50, kimtor=50
# simulating EGCG treatment with high stress: kaai=50, kimtor=50, stress=5
# simulating EGCG treatment with high stress and GADD34 depletion: kaai=50,
kimtor=50, stress=5, AUINT=0.1
p stress=0
p kaac=0.05, kaac'=2, kiac=0.01, kiac'=15, JAUCO=0.001, AUCOT=1
p kapai=0.02, kapai'=1, kipai=0.25, kipai'=20, kipai"=0, kipai'"=2, pAUIT=1
p kaai=7.5, kiai=1.5, kiai'=2, AUINT=1, JAUIN=0.2
p kamtor=0.05, kamtor'=0.03, kamtor"=0.3, kimtor=0.01, kimtor'=0.5,
kimtor"=10, mtoT=1
p kaax=0.075, kaax'=0.15, kaax"=2, kiax=0.1, kiax'=20, kiax"=20, AUEXT=1,
JAUEX=0.2
p kade=0, kade’=0.5, kade”=0.05, kade’”=0.005, kide=0.01, kide’=30,
Jdea=0.1

done
```

The code for a general model calculating balance curves

```
# a model to simulate autophagy induction with XPP-AUT

# initial conditions
init AUCO=0, AUI=0


# differential equations

# AUCO represents the active form of autophagy inducer
AUCO' = (kaac + kaac'*AUIN)*(AUCOT-AUCO)/(JAUCO + AUCOT-AUCO) - (kiac +
kiac'*mTOR)*AUCO/(JAUCO + AUCO)

# AUI represents the active form of autophagy inducer
AUI' = kaai*pAUIN*(AUINT-AUIN)/(JAUI + AUINT-AUIN) - (kiai +
kiai'*mTOR)*AUI/(JAUI + AUIN)
# steady state function

# mTOR represents the active form of mTOR
mTOR = (kamtor + kamtor'*stress/(1+stress) + kamtor"*DEATH)*mtoT/(kamtor +
kamtor'*stress/(1+stress) + kamtor"*DEATH + kimtor + kimtor'*AUIN +
kimtor"*AUCO)

# pAUIN represents the active, pre-form of autophagy inducer
pAUIN = (kapai + kapai'*stress/(1+stress))*pAUINT/(kapai +
kapai'*stress/(1+stress) + kipai + kipai'*AUCO + kipai"*mTOR +
kipai'"*DEATH)

# AUEX represents the active AUEX genes; when AUEX is active we assume that
autophagy is also active
AUEX = AUEXT*GK(kaax + kaax'*AUCO + kaax"*AUIN,kiax + kiax'*mTOR +
kiax"*DEATH,JAUEX,JAUEX)

# DEATH represents the possible cell death of the cell
DEATH = GK(kade + kade'*AUCO + kade"*stress + kade"'*mTOR,kide +
kide'*AUTA,Jdea,Jdea)

# 'Goldbeter-Koshand' function (GK)
GB(arg1,arg2,arg3,arg4) = arg2-arg1+arg2*arg3+arg1*arg4
GK(arg1,arg2,arg3,arg4) =
2*arg1*arg4/(GB(arg1,arg2,arg3,arg4)+sqrt(GB(arg1,arg2,arg3,arg4)^2-
4*(arg2-arg1)*arg1*arg4))

# parameters
# simulating rapamycin treatment: stress=0.75
p stress=0
p kaac=0.05, kaac'=2, kiac=0.01, kiac'=15, jAUCO=0.001, AUCOT=1
p kapai=0.02, kapai'=1, kipai=0.25, kipai'=20, kipai"=0, kipai'"=2,
pAUINT=1
p kaai=7.5, kiai=1.5, kiai'=2, AUINT=1, JAUIN=0.201
p kamtor=0.05, kamtor'=0.03, kamtor"=0.3, kimtor=0.01, kimtor'=0.5,
kimtor"=10, mtoT=1
```

```
p kaax=0.075, kaax'=0.15, kaax"=2, kiax=0.1, kiax'=20, kiax"=20, AUEXT=1,
JAUEX=0.2
p kade=0, kade’=0.5, kade”=0.05, kade’”=0.005, kide=0.01, kide’=30,
Jdea=0.1

done
```

II. Figures



Supplementary Figure 1. The possible regulatory components and their inter-connections in various cellular stress induced autophagy. The autophagy inducer, the autophagy controller, the autophagy executor and mTORC1 are grouped together in isolated orange, purple, red and blue, respectively. Solid arrows represent biochemical reactions, dashed line shows how the molecules can influence each other. Blocked end lines denote inhibition.

III. Tables

	autophagy inducer		autophagy controller		autophagy executors	
	protein name	reference	protein name	reference	protein name	reference
mTOR inhibition	AMPK	Kim et al, 2011 Egan et al, 2011 Leprivier et al, 2020 Filomeni et al, 2015	ULK1/2	Ganley et al, 2009 Hosokawa et al, 2009 Jung et al, 2009 Filomeni et al, 2015	AMBRA1	Egan, 2015 Di Bartolomeo et al, 2010
	GADD34	Ito et al, 2015 Uddin et al, 2011 Watanabe et al, 2007 Leprivier et al, 2020	FIP200	Ganley et al, 2009 Hosokawa et al, 2009 Jung et al, 2009 Filomeni et al, 2015	ATG14	Wold et al, 2016
			ATG13	Ganley et al, 2009 Hosokawa et al, 2009 Jung et al, 2009 Puente et al, 2016 Filomeni et al, 2015	ATG4	Pengo et al, 2017
			ATG101	Zachari et al, 2017 Hosokawa et al, 2009 Mercer et al, 2009	Vps34	Kim et al, 2013 Russel et al, 2013 Egan et al, 2015
					Beclin1	Russel et al, 2013 Kim et al, 2013 Kim et al, 2013
					ATG9	Zhou et al, 2017 Weerasekara et al, 2014
					ATG16L1	Dooley et al, 2014 Gammoh et al, 2013
oxidative stress	AMPK	Kosztelnik et al, 2018 Gao, 2019 Shiomi et al, 2014 Filomeni et al, 2015 Navarro-Yepes et al, 2014 Wang et al, 2011	NRF2	Jena et al, 2018 Filomeni et al, 2015 Navarro-Yepes et al, 2014 Medvedev et al, 2016 Kosztelnik et al, 2018	Beclin1	Liu et al, 2015 Lerner et al, 2012
	TBP-2	Zhou et al, 2016	JNK	Liu et al, 2015 Lerner et al, 2007	VPS34	Lerner et al, 2012 Lerner et al, 2012
	DAPK1	Lerner et al, 2012 Lerner et al, 2007 Lerner et al, 2012	ULK1/2	Filomeni et al, 2015 Navarro-Yepes et al, 2014 Jena et al, 2018	ATG14	Geering, 2015
	DAPK2	Schlegel et al, 2015 Geering, 2015	FIP200	Navarro-Yepes et al, 2014 Filomeni et al, 2015	ATG16L	Jena et al, 2018
	TRIM16	Jena et al, 2018	ATG13	Navarro-Yepes et al, 2014 Filomeni et al, 2015	ATG 5	Wang et al, 2015
			ATG101	Navarro-Yepes et al, 2014 Filomeni et al, 2015	ATG7	Wang et al, 2015 Burgoyne et al, 2018
			PKD	Lerner et al, 2012 Lerner et al, 2012 Lerner et al, 2007	ATG3	Burgoyne et al, 2018
					ATG4	Scherz-Shouval et al, 2007 Filomeni et al, 2015 Navarro-Yepes et al, 2014
ER stress	AMPK	Kandala et al, 2012 Liu et al, 2018 Qi et al, 2015 Xi et al, 2013	ULK1/2	Song et al, 2018 Lin et al, 2019	Beclin-1	Song et al, 2018 Cheng et al, 2014 Margariti et al, 2013 B'chir et al, 2013 Lin et al, 2019
	GADD34	Hyrskyluoto et al, 2012 Holczer et al, 2016	FIP200	Song et al, 2018 Lin et al, 2019	VPS34	Song et al, 2018
	DAPK1	Song et al, 2018	ATG13	Song et al, 2018 Lin et al, 2019	ATG14	Song et al, 2018
	IRE1	Song et al, 2018 Ogata et al, 2006 Cheng et al, 2014 Margariti et al, 2013 Lin et al, 2019	ATG101	Song et al, 2018 Lin et al, 2019	ATG16L	Song et al, 2018 B'chir et al, 2013
	ATF4	B'chir et al, 2013 Lin et al, 2019 Song et al, 2018	CHOP	Song et al, 2018 B'chir et al, 2013 Guo et al, 2014 Lin et al, 2019	ATG5	Song et al, 2018 B'chir et al, 2013 Lin et al, 2019
	ATF6	Song et al, 2018 Guo et al, 2014 Lin et al, 2019	JNK	Song et al, 2018 Ogata et al, 2006 Cheng et al, 2014 Lin et al, 2019	ATG12	B'chir et al, 2013 Lin et al, 2019 Song et al, 2018
					ATG9	Lin et al, 2019
			XBP1	Song et al, 2018 Hetz et al, 2009 Margariti et al, 2013 Guo et al, 2014	ATG4	Chen et al, 2012

Supplementary Table 1. Collecting data from literature about possible regulatory components of autophagy induction upon various cellular stress.

Connections	References
AMPK -> ULK1/2	Bach et al, 2011 Egan et al, 2011 Kim et al, 2011 Roach, 2011 Shang et al, 2011 Urano et al, 2018 Cardaci et al, 2012 Kaushal et al, 2019 Holczer et al, 2018 Zhao et al, 2016 Lee et al, 2010 Behrends et al, 2010 Tamargo-Gómez et al, 2018
ULK1/2 -I AMPK	Löffler et al, 2011 Dite et al, 2017
ULK1/2 -I mTORC1	Dunlop et al, 2011 Jung et al, 2011
AMPK -I mTORC1	Gwinn et al, 2008 Inoki et al, 2003 Kaushal et al, 2019 She et al, 2014 Alexander et al, 2010 Zhao et al, 2016 Meley et al, 2006 Tamargo-Gómez et al, 2018
mTORC1 -I ULK1/2	Ganley et al, 2009 Hosokawa et al, 2009 Kim et al, 2011 Jung et al, 2009 Zhao et al, 2016
mTORC1 -I AMPK	Holczer et al, 2019 Ling et al, 2020
AMPK -> autophagy	Meijer et al, 2015 Abada et al, 2014 Xi et al, 2013 Zhao et al, 2016 Meley et al, 2006 Tamargo-Gómez et al, 2018
ULK1/2 -> autophagy	Kim et al, 2011 Russel et al, 2013 Urano et al, 2018 Zhao et al, 2016 Zachari et al, 2017
mTOR -I autophagy	Nazio et al, 2013 Yuan et al, 2013 Settembre et al, 2012 Martina et al, 2012 Settembre et al, 2013 Kim et al, 2015
GADD34 -I mTORC1	Uddin et al, 2011 Watanabe et al, 2007 Hyrskyluoto et al, 2012 Holczer et al, 2016
AMPK -> NRF2	Salminen et al, 2012 Joo et al, 2016 Lin et al, 2018
NRF2 -I AMPK	Kosztelnik et al, 2018
GADD34 -> autophagy	Ito et al, 2015 Uddin et al, 2011
CHOP -> autophagy	B'chir et al, 2013 Rouschop et al, 2010
IRE1 -> autophagy	Song et al, 2018 Ogata et al, 2006

mTOR inhibition (starvation, rapamycin treatment, etc.)
oxidative stress
ER stress
oxidative stress + mTOR inhibition
ER stress + mTOR inhibition
none of them

Supplementary Table 2. Collecting data from literature about the proved regulatory connections during cellular stress induced autophagy regulation.

IV. Introducing the theoretical analysis of phosphorylation site search on NRF2

The potential Ser and Thr phosphorylation sites of ULK1/2 were identified on NRF2 sequence by Group-based Prediction System 5.0 (http://gps.biocuckoo.cn/). The sequence of NRF2 was downloaded from UniProt (https://www.uniprot.org/). The threshold was high under prediction. Table 3. includes the position of Ser and Thr amino acids, the catalytic subunits of ULK1/2, the peptid sequence in the near of Ser and Thr amino acids and the score values. The score value is calculated by GPS algorithm to evaluate the potential of phosphorylation. The higher the value, the more potential the residue is phosphorylated (http://gps.biocuckoo.cn/).

The phosphorylation sites were verified by NetPhos 3.1 (http://www.cbs.dtu.dk/services/NetPhos). Those phosphorylation sites were collected and checked where the phosphorylation kinase was unknown (see the NetPhos column in the Table 3.). The score above 0.500 indicates positive predictions.

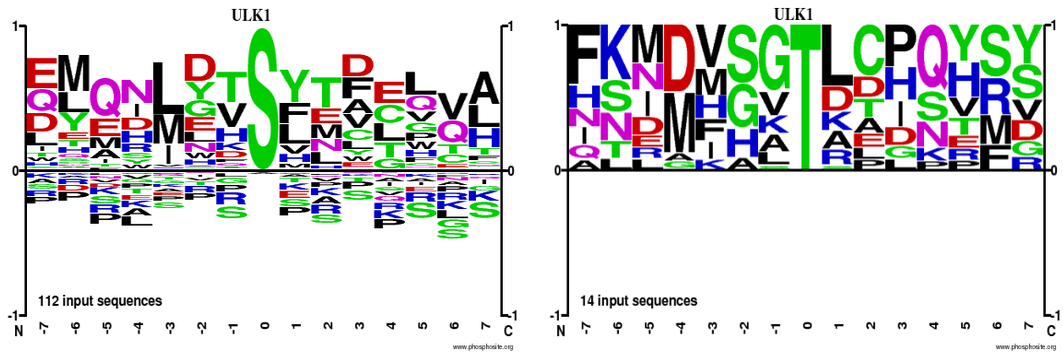
The phosphorylation sites were also searched with the help of PhosphositePlus (https://www.phosphosite.org/homeAction.action). In this database, the consensus phosphorylation motif of ULK1 is used, which is created with the help of several well-known phosphorylated sequences of ULK1 substrates. The same amino acids within the identified potential ULK1 phosphorylation sequences were marked with red colour (see the Peptid column of Table 3.).

Detailed description the legend of Supplementary Table 3.

ULK1/2 phosphorylation sites on NRF2					NetPhos
Position	**Code**	**Enzyme**	**Peptide**	**Score**	**Score - kinase (unknown)**
the position number # of S/T P'ion site	Ser (S) or Thr (T) P'ion site	name of the kinase	consensus P'ion sequence with red letters	evaluate the potential of P'ion site	evaluate the potential of P'ion site

Consensus ULK1-dependent phosphorylation sites

PhosphoSite Plus shows the preferred Ser and Thr phosphorylation sites of ULK1 kinase:
https://www.phosphosite.org/proteinAction.action?id=796&showAllSites=true



The preferred Ser and Thr phosphorylation sites of ULK2 kinase is not known yet, however the protein sequence identity is 78% within the kinase domains of ULK1 and ULK2 (8).

Table 3. *ULK1/2 phosphorylation sites on different isoforms of NRF2*

ULK1/2 phosphorylation sites on NRF2 Isoform 1					NetPhos
Position	**Code**	**Enzyme**	**Peptide**	**Score**	**Score - kinase (unknown)**
351	S	ULK1	SGISLNTSPSVASPE	38.529	0.981 unsp
410	S	ULK1	MVQPLSPSQGQSTHV	42.467	
231	S	ULK2	DNYHFYSSIPSMEKE	4.744	
320	S	ULK2	LNGPIDVSDLSLCKA	4.537	
414	S	ULK2	LSPSQGQSTHVHDAQ	5.696	0.638 unsp
447	S	ULK2	PFTKDKHSSRLEAHL	4.241	0.992 unsp
ULK1/2 phosphorylation sites on NRF2 Isoform 2					**NetPhos**
Position	**Code**	**Enzyme**	**Peptide**	**Score**	**Score - kinase (unknown)**
335	S	ULK1	SGISLNTSPSVASPE	38.529	0.981 unsp
394	S	ULK1	MVQPLSPSQGQSTHV	42.467	
17	S	ULK2	QDIDLGVSREVFDFS	4.638	0.971 unsp
215	S	ULK2	DNYHFYSSIPSMEKE	4.744	
304	S	ULK2	LNGPIDVSDLSLCKA	4.537	
398	S	ULK2	LSPSQGQSTHVHDAQ	5.696	0.638 unsp
431	S	ULK2	PFTKDKHSSRLEAHL	4.241	0.992 unsp
ULK1/2 phosphorylation sites on NRF2 Isoform 3					**NetPhos**
Position	**Code**	**Enzyme**	**Peptide**	**Score**	**Score - kinase (unknown)**
328	S	ULK1	SGISLNTSPSVASPE	38.529	0.981 unsp
387	S	ULK1	MVQPLSPSQGQSTHV	42.467	
17	S	ULK2	QDIDLGVSREVFDFS	4.638	0.971 unsp
208	S	ULK2	DNYHFYSSIPSMEKE	4.744	
297	S	ULK2	LNGPIDVSDLSLCKA	4.537	
391	S	ULK2	LSPSQGQSTHVHDAQ	5.696	0.638 unsp
424	S	ULK2	PFTKDKHSSRLEAHL	4.241	0.992 unsp

V. References

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