Cours du 17-11-2014

Mitochondria: in sickness and in health

Cell
2012 vol. 148 (6) pp. 1145-59

Nunnari J, Suomalainen A

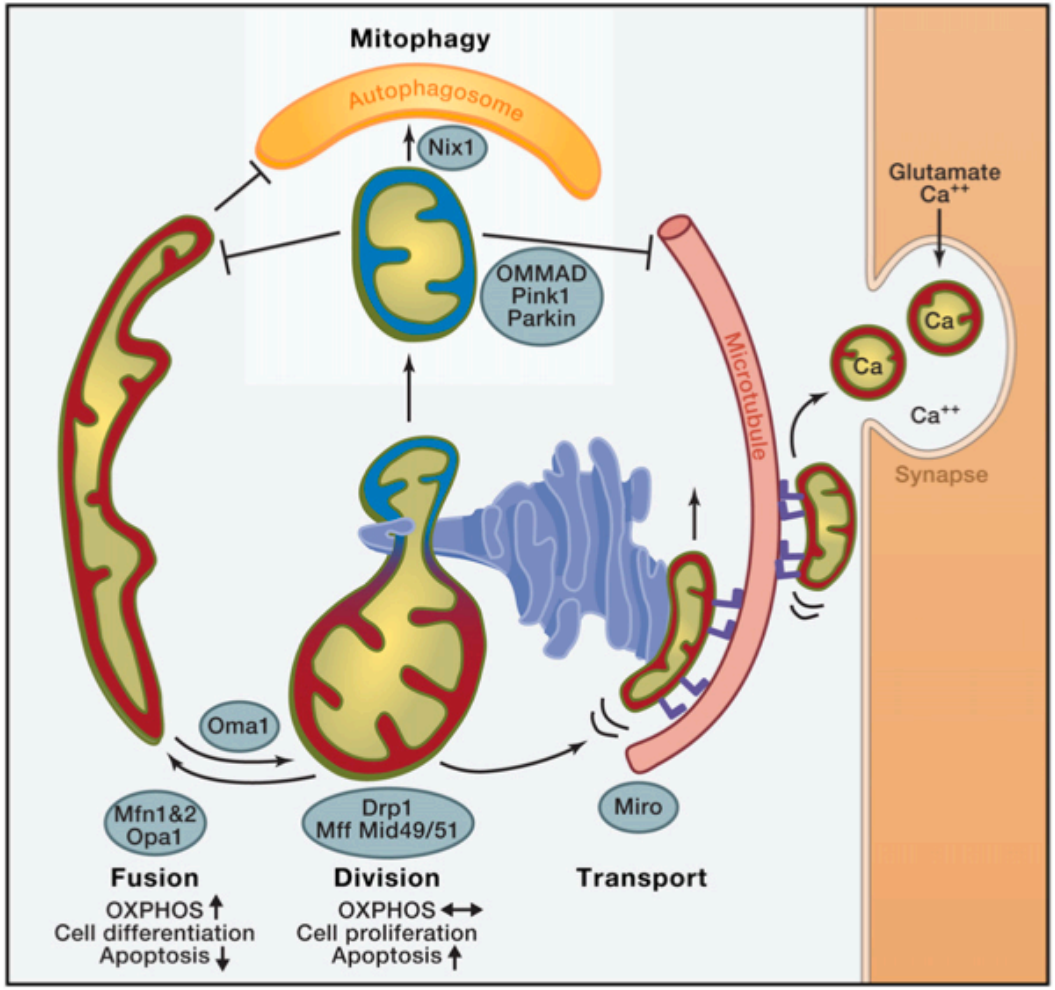

Figure 2. Roles of Mitochondrial Dynamics

Red: mitochondria with high membrane potential, with high oxidative phosphorylation (OXPHOS) activity. Blue: Mitochondria with low membrane potential. Mitofusin 1 or 2 (MFN1, MFN2) mediate mitochondrial outer-membrane fusion in a tissue-specific manner, and OPA1 (optic atrophy gene 1) mediates inner-membrane fusion. The zinc metalloprotease OMA1 proteolytically cleaves OPA1 under low membrane potential conditions, promoting fission. Mitochondrial dynamics factors 49 and 51 or mitochondrial fission factor (Mff) recruit DRP1 onto mitochondria at sites marked by endoplasmic reticulum tubules (ER), and DRP1 mediates mitochondrial division. In cultured cells, upon a decrease in mitochondrial membrane potential, PINK1 kinase recruits Parkin, a ubiquitin E3 ligase, which ubiquitinates several mitochondrial targets, including MFN1 and Miro, to facilitate the degradation of mitochondria via mitophagy. Parkin-mediated ubiquitination triggers OMMAD, outer-mitochondrial membrane-associated degradation—a proteosomal pathway that degrades ubiquinated OM proteins in a CDC48-dependent manner. OMMAD is probably cell type-dependent and may also function in quality control. In erythrocytes, mitophagy receptor Nix1 is involved in autophagosome recruitment. ER forms close contacts with mitochondria, essential for calcium regulation in cellular microcompartments. Miro (blue feet) is a mitochondrial receptor for kinesin via Milton that facilitates the transport of mitochondria on microtubules in a Ca^{2+}-regulated manner. Upon synaptic activity in neurons, influx of glutamate and Ca^{2+} halts mitochondrial transport via Miro to position them at sites of synaptic activity that require Ca^{2+} uptake and ATP.

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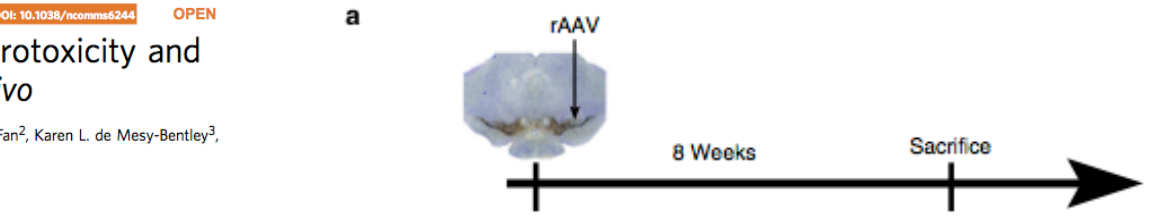
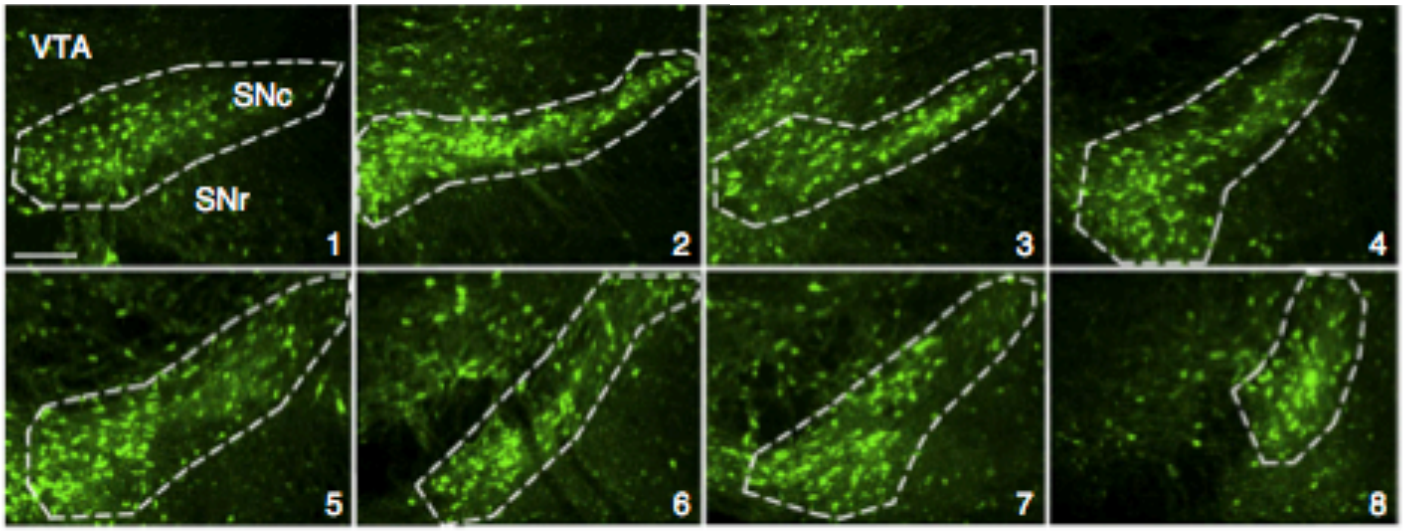
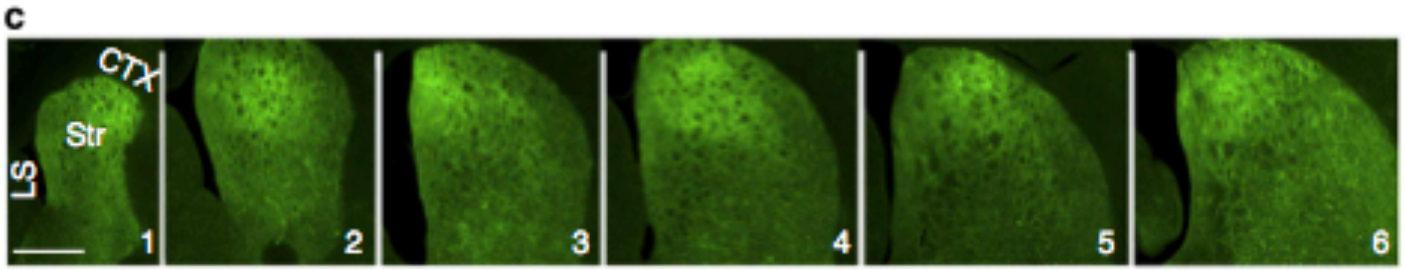
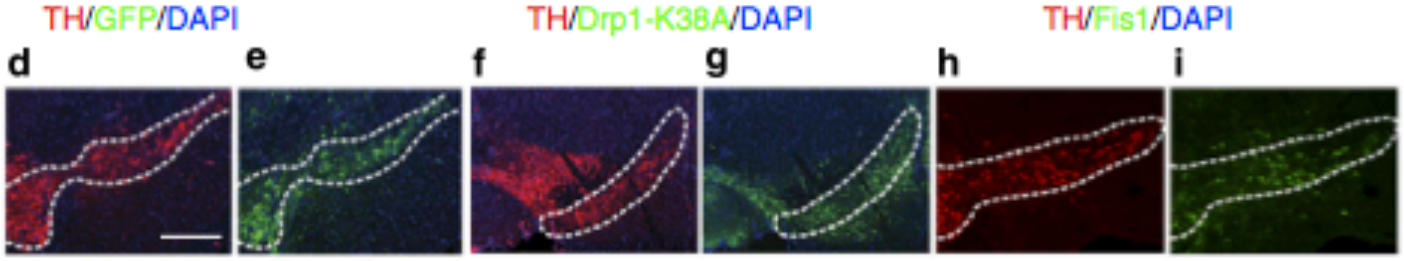




eGFP rostro-caudal



Striatum rostro-caudal



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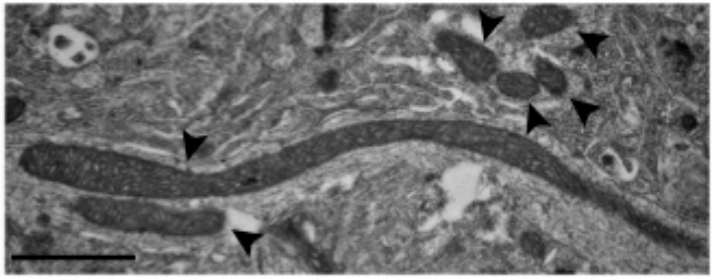

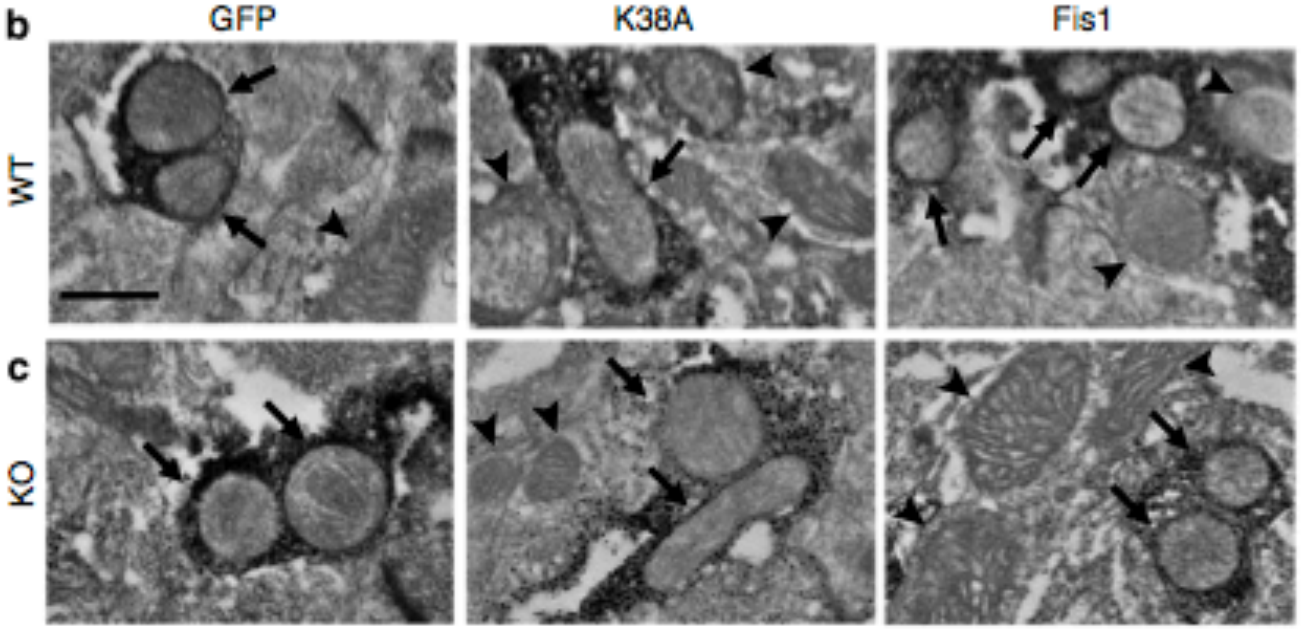

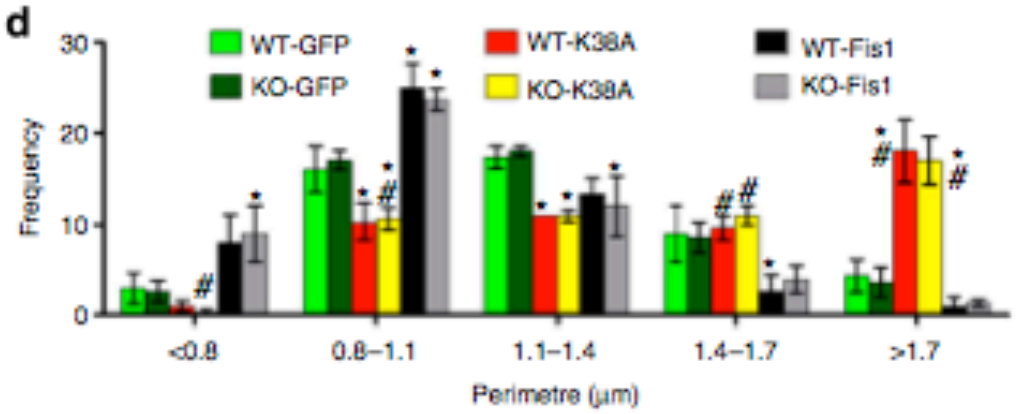

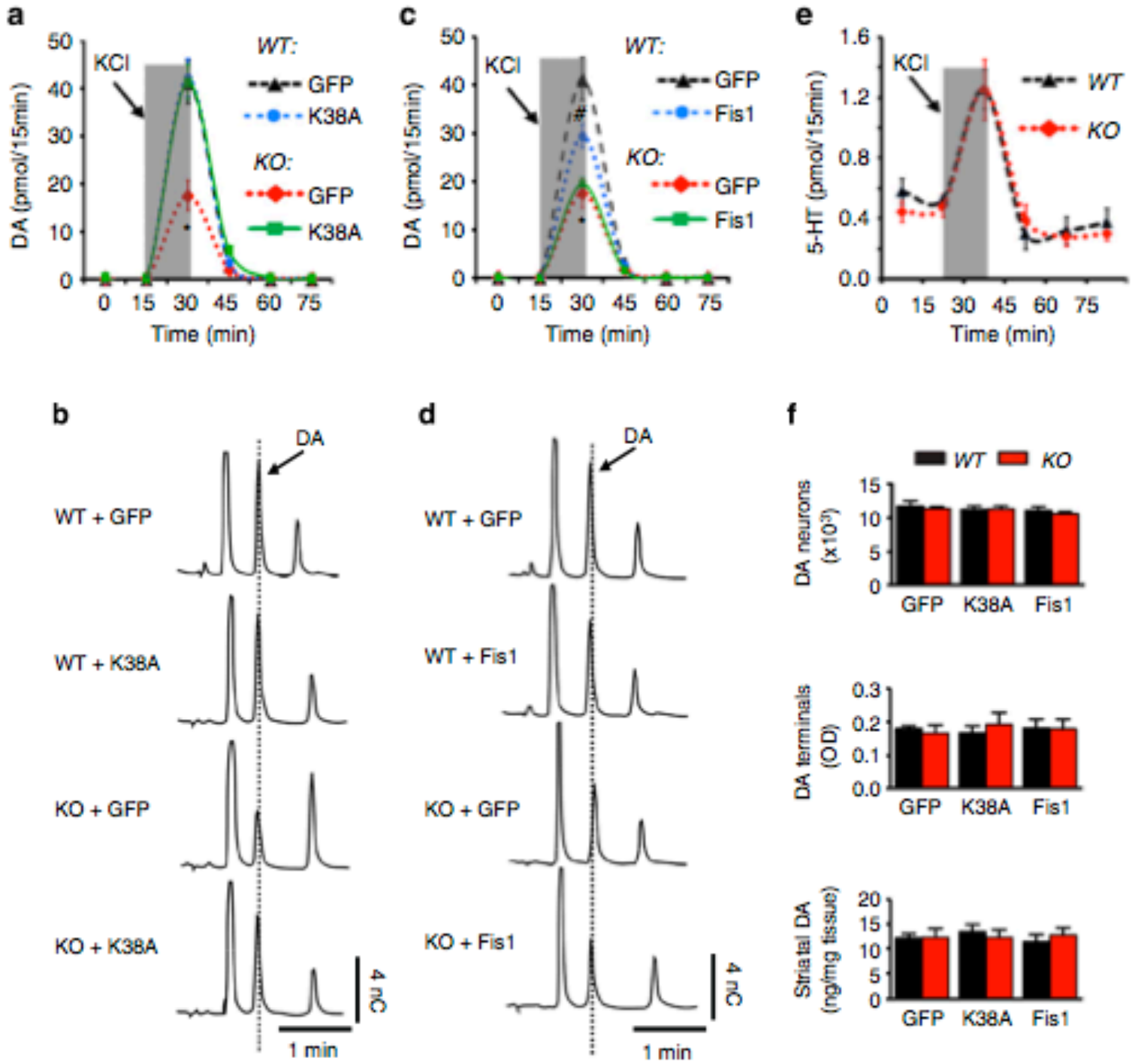
a
DA (pmol/15min)
KCl
WT:
GFP
K38A
KO:
GFP
K38A
Time (min)
c
DA (pmol/15min)
KCl
WT:
GFP
Fis1
KO:
GFP
Fis1
Time (min)
e
5-HT (pmol/15min)
KCl
WT
KO
Time (min)
b
DA
WT + GFP
WT + K38A
KO + GFP
KO + K38A
4 nC
1 min
d
DA
WT + GFP
WT + Fis1
KO + GFP
KO + Fis1
4 nC
1 min
f
WT
KO
DA neurons (x10³)
GFP
K38A
Fis1
DA terminals (OD)
GFP
K38A
Fis1
Striatal DA (ng/mg tissue)
GFP
K38A
Fis1

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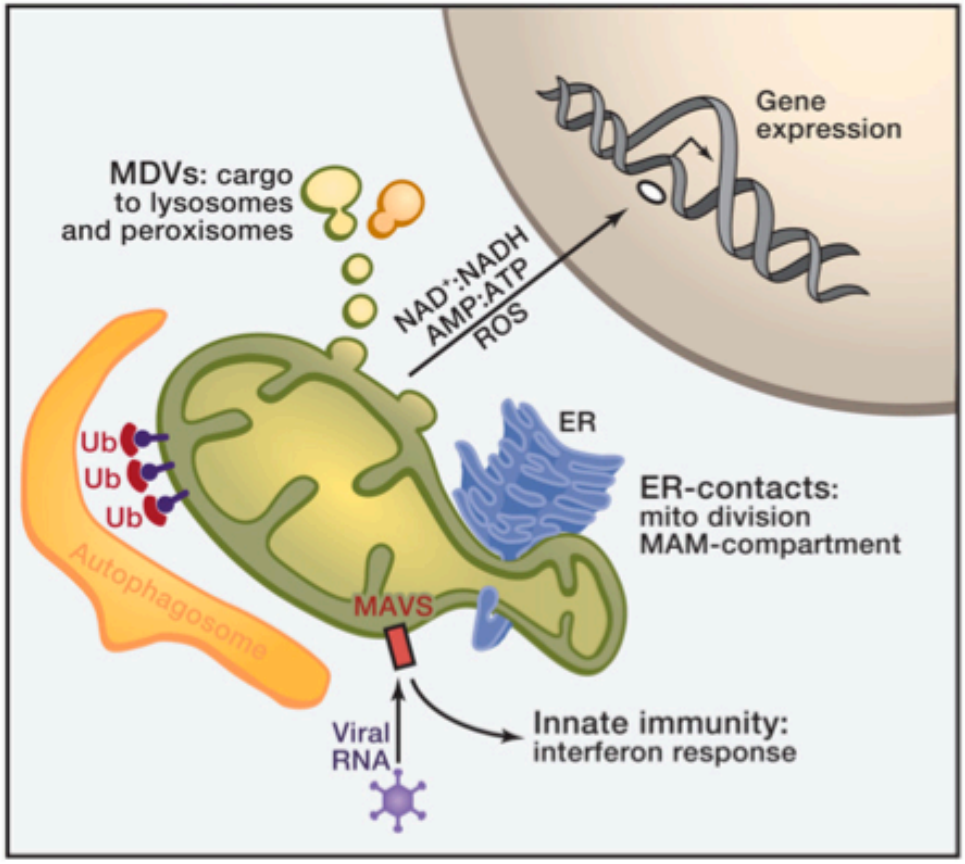
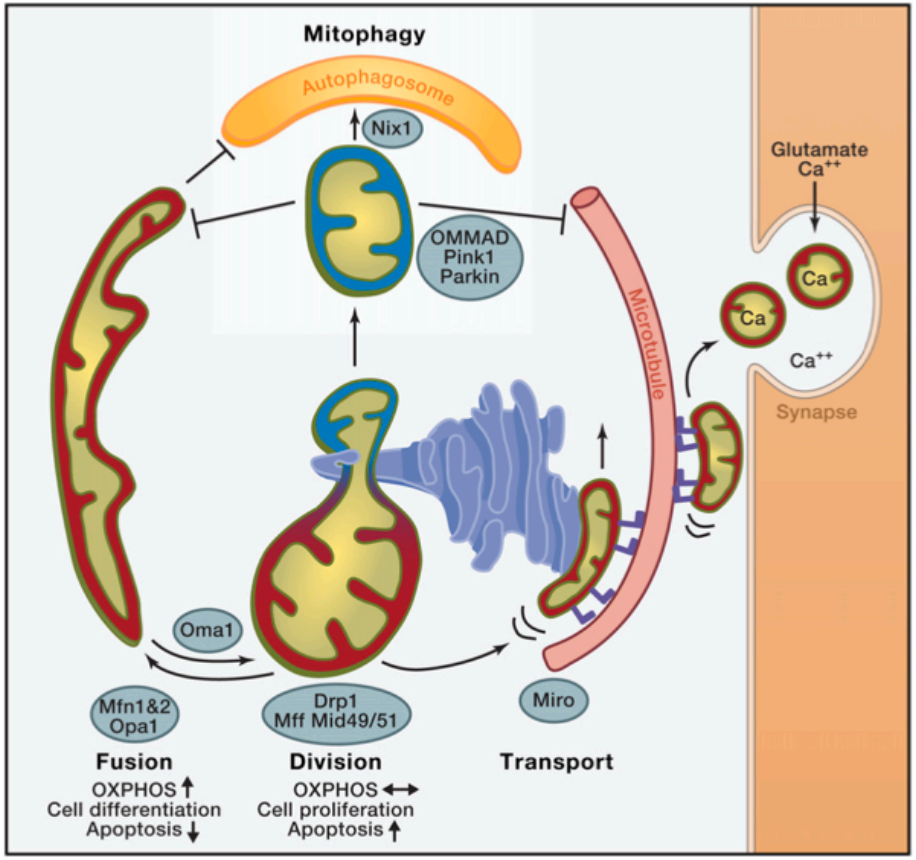




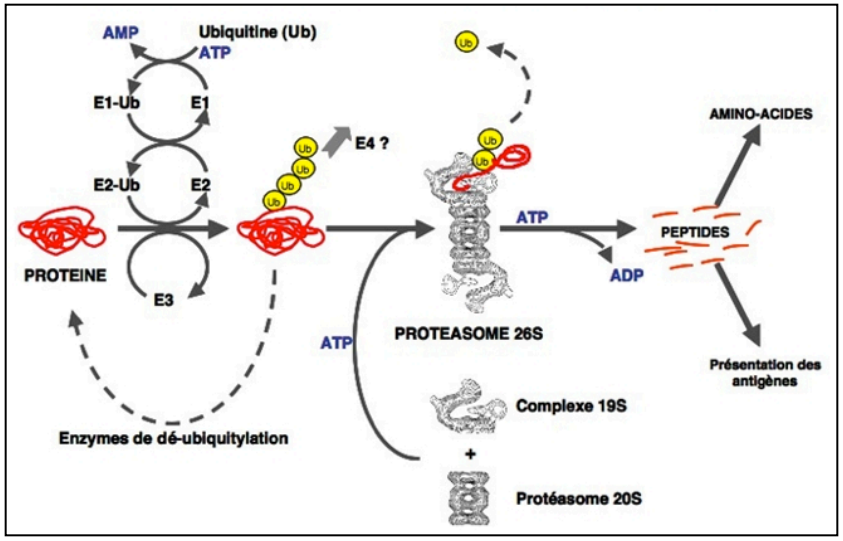


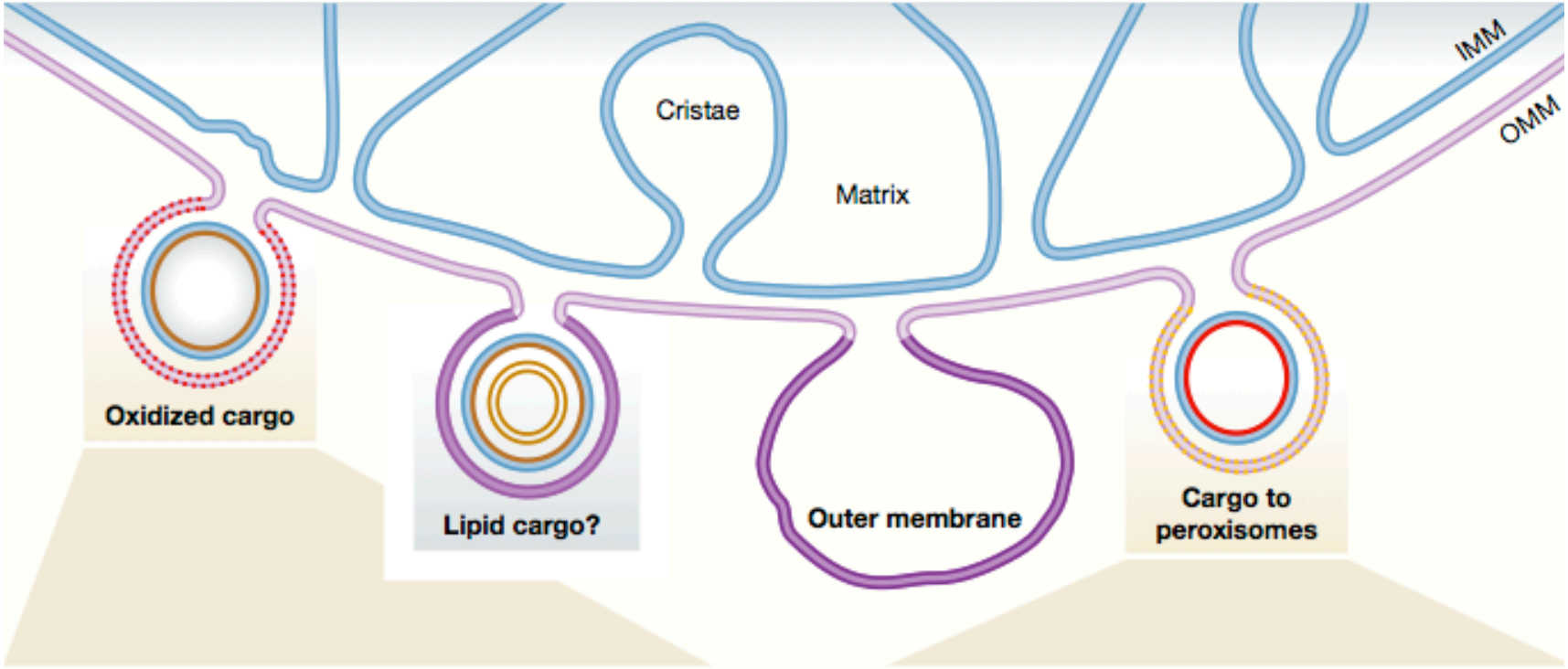
Figure 3. Interorganellar Communication

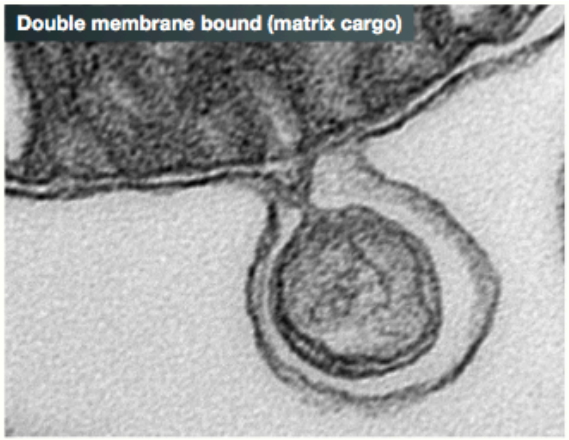
Ub, ubiquitin; red and blue, proteins in mitochondrial outer membrane are PINK1, a mitochondrial kinase, and the E3 ubiquitin ligase Parkin, recruited onto mitochondria by PINK1; MDV, mitochondria-derived vesicle; NAD, nicotinamide adenine dinucleotide, oxidized form; NADH, nicotinamide adenine dinucleotide, reduced form; AMP, adenosine monophosphate; ATP, adenosine triphosphate; ER, endoplasmic reticulum, tubules of which are marking sites of mitochondrial division; MAVS, mitochondrial antiviral signaling, which is activated by viral RNA; MAM, mitochondrial-associated endoplasmic reticulum membrane.

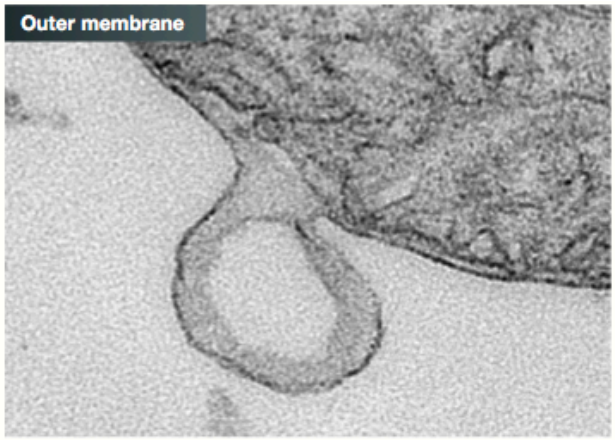
A new pathway for mitochondrial quality control: mitochondrial-derived vesicles

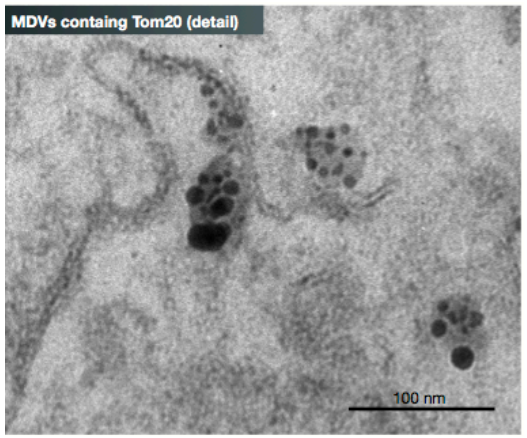
The EMBO Journal
2014 pp.

Sugiura A, McLelland GL, Fon EA, McBride HM





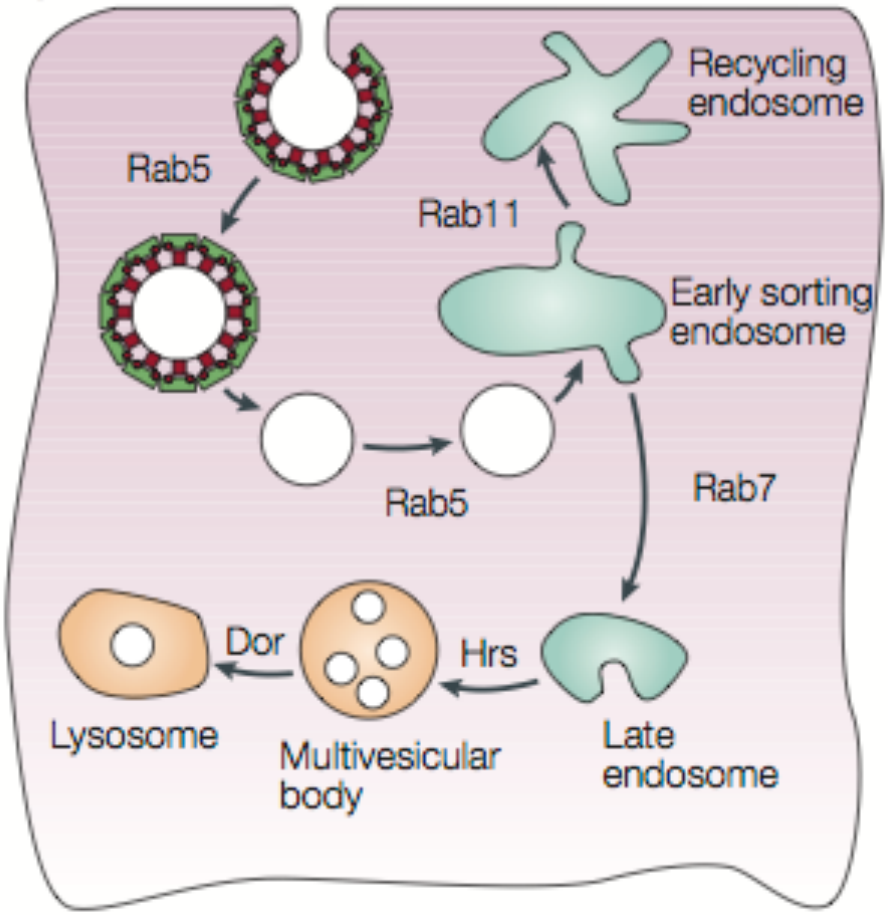




Signal dispersal and transduction through the endocytic pathway

Nat Rev Mol Cell Biol
2003 vol. 4 (3) pp. 213-24

González-Gaitán M



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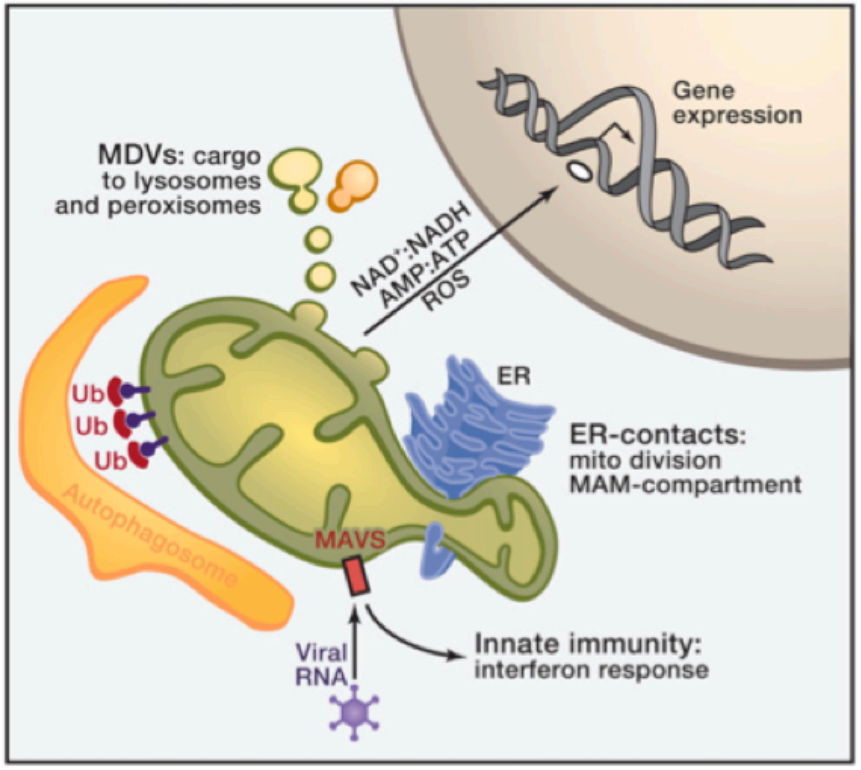

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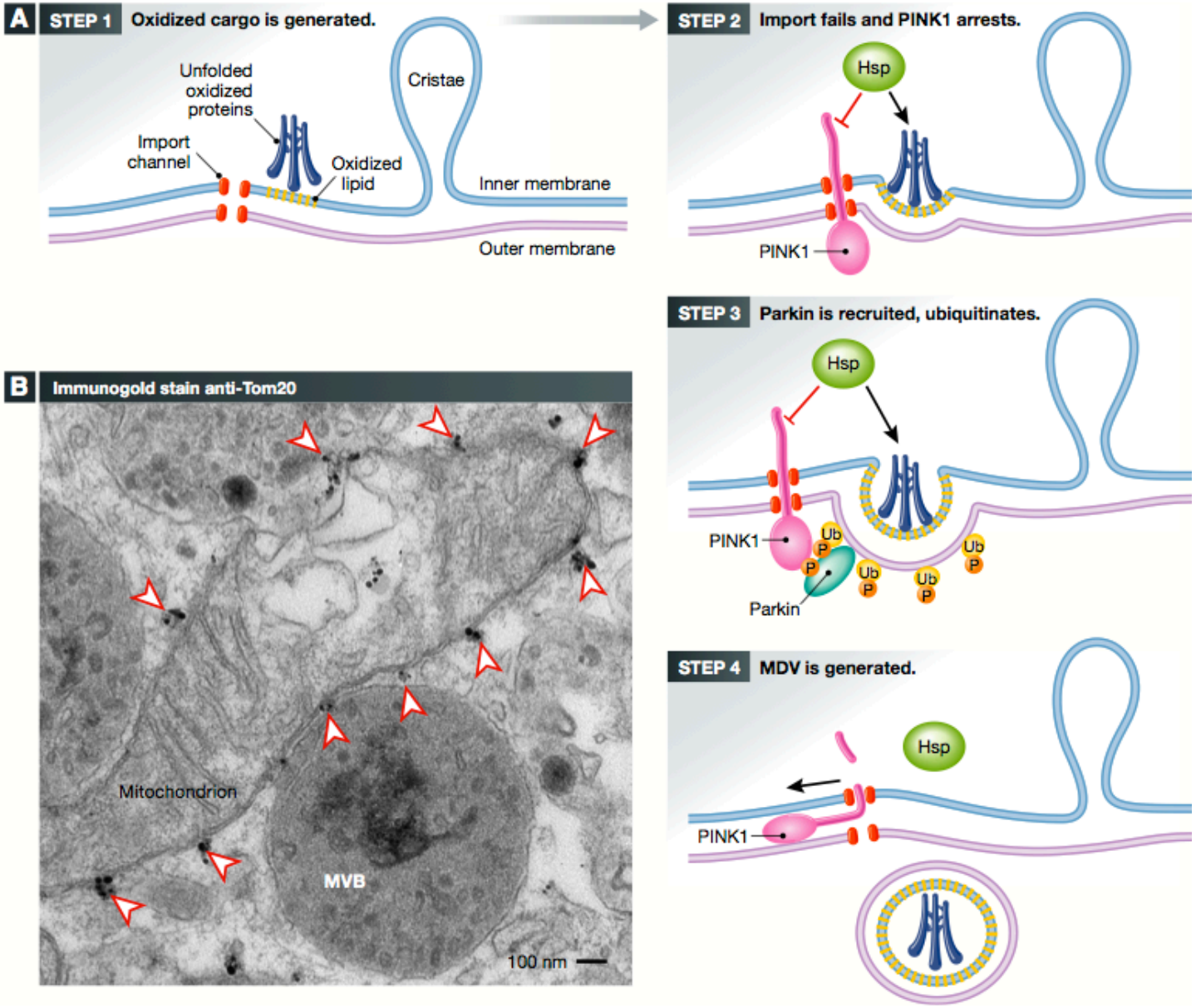

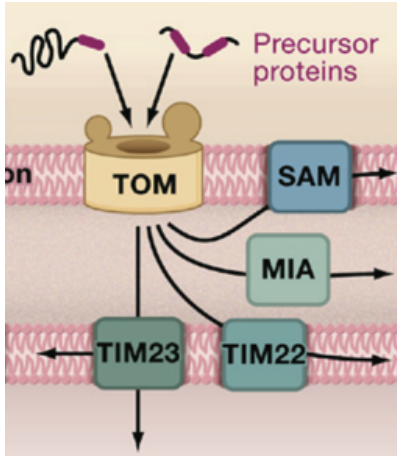

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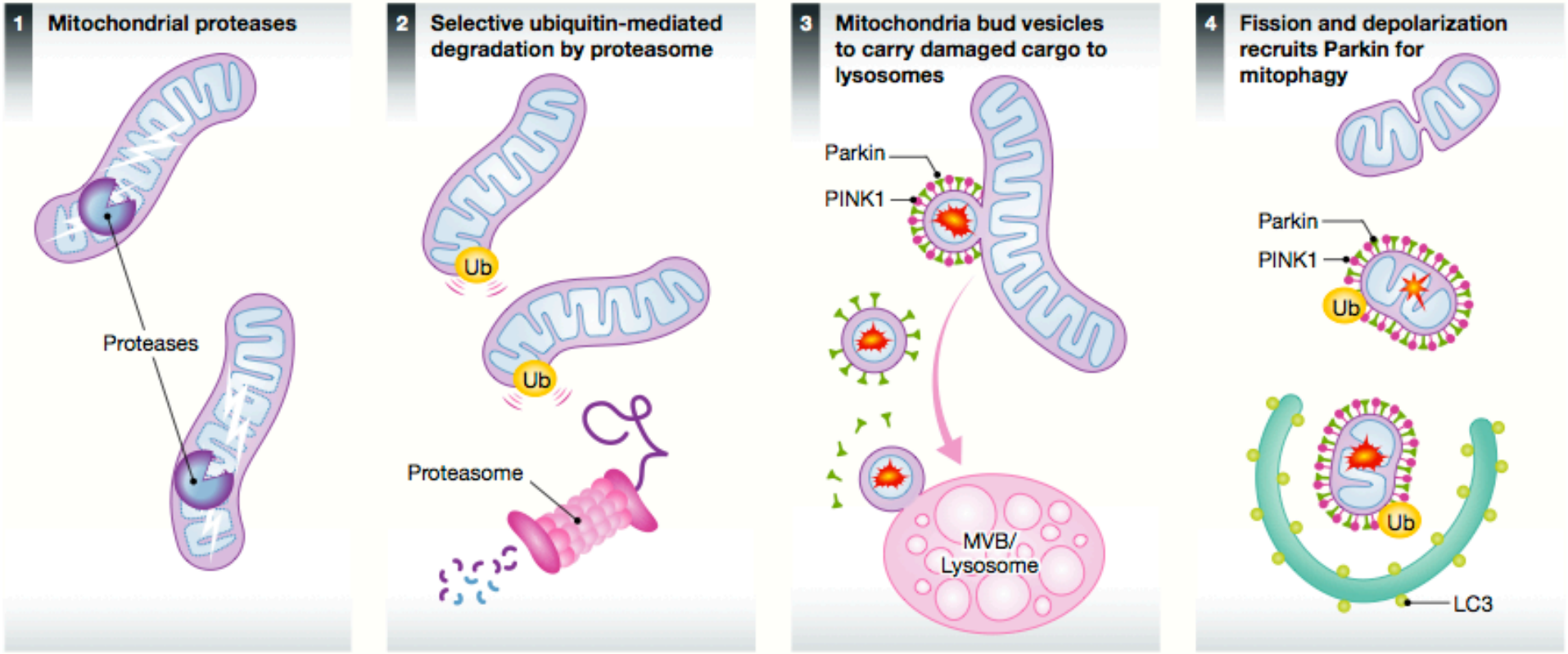
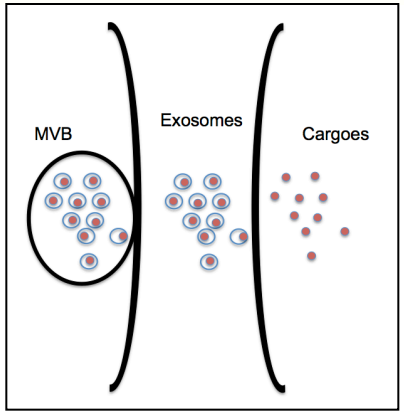
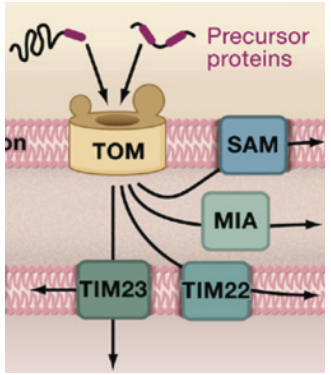


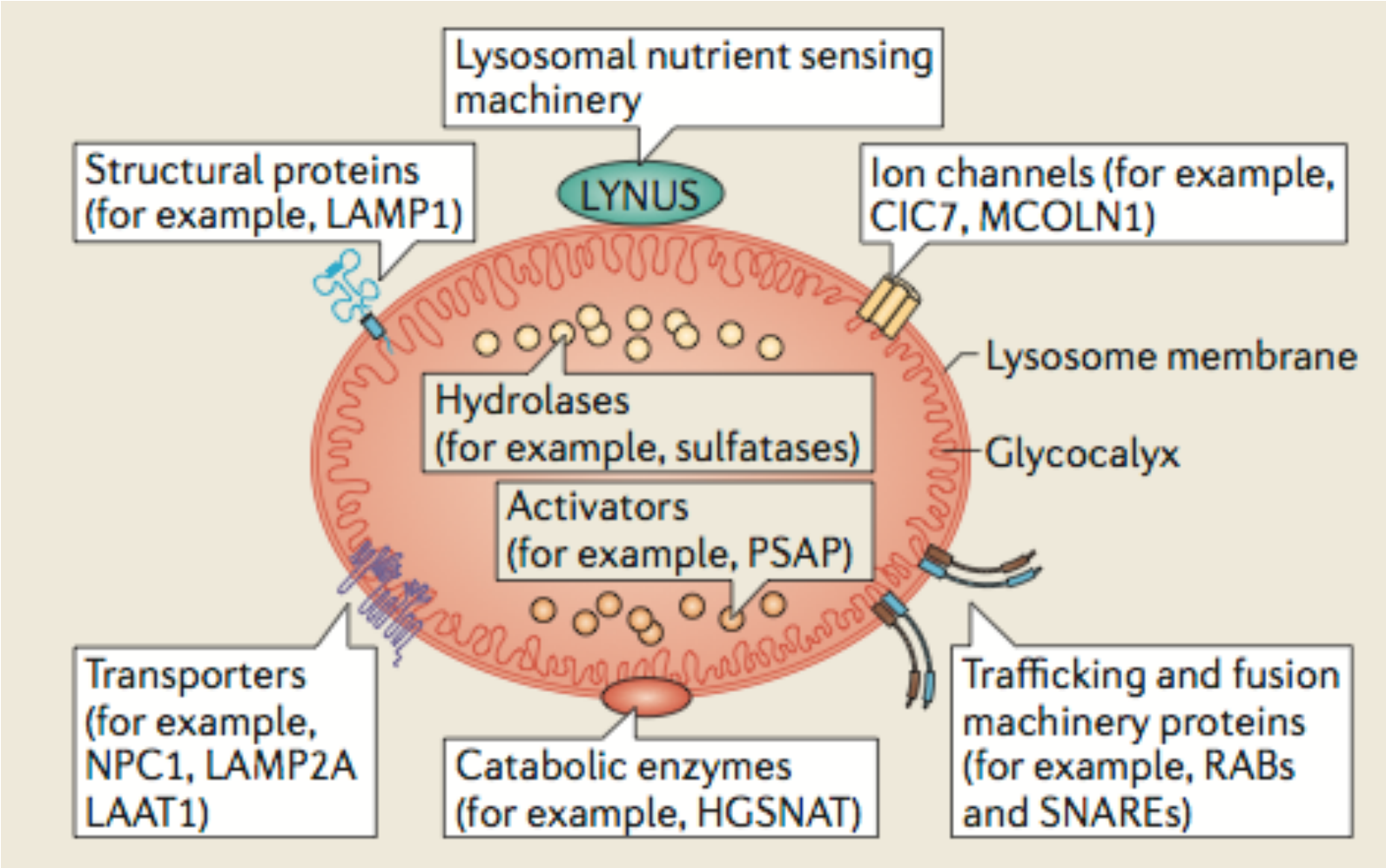




Signals from the lysosome: a control centre for cellular clearance and energy metabolism

Nat Rev Mol Cell Biol
2013 vol. 14 (5) pp. 283–96

Settembre C, Fraldi A, Medina DL, Ballabio A



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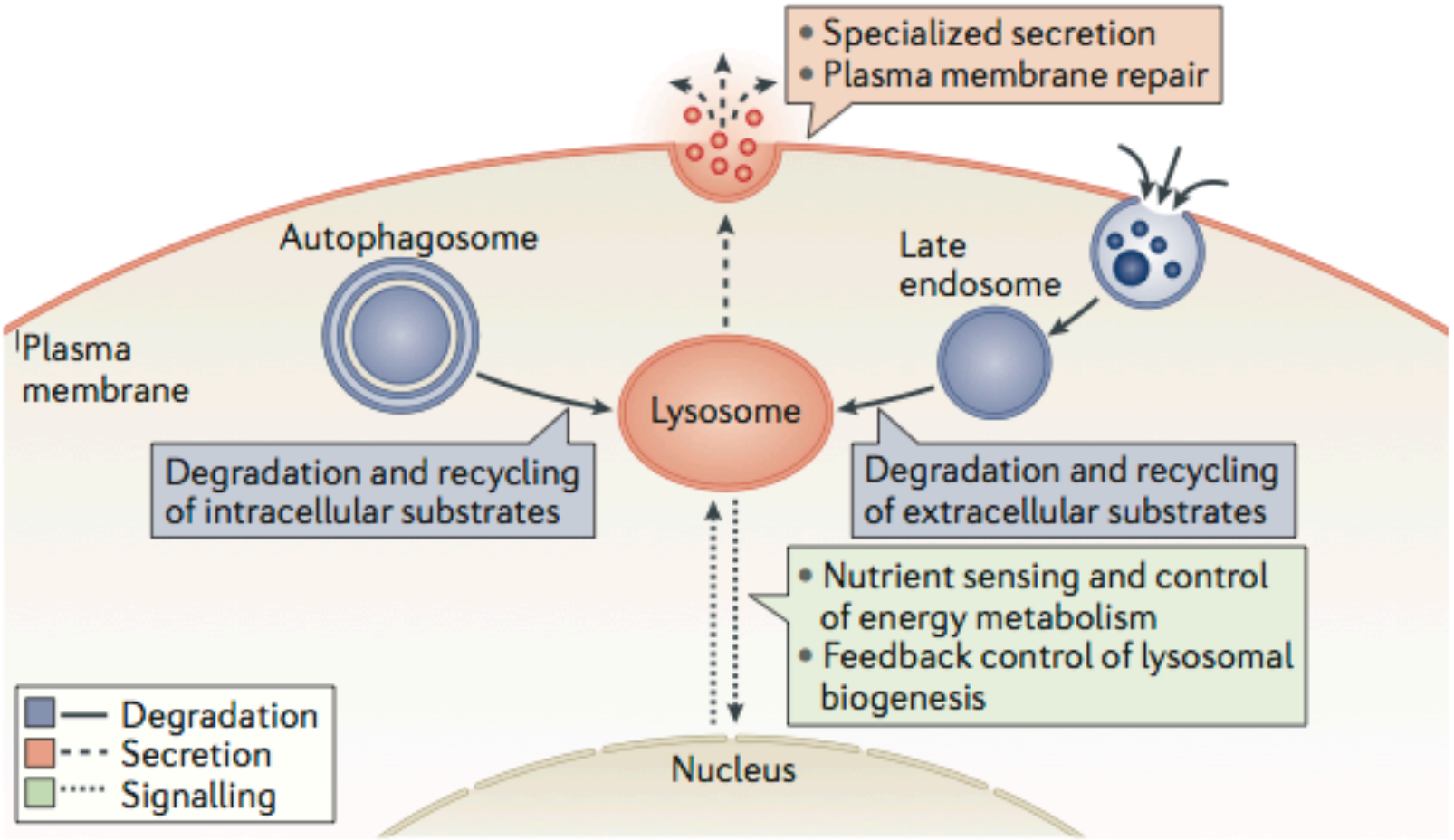
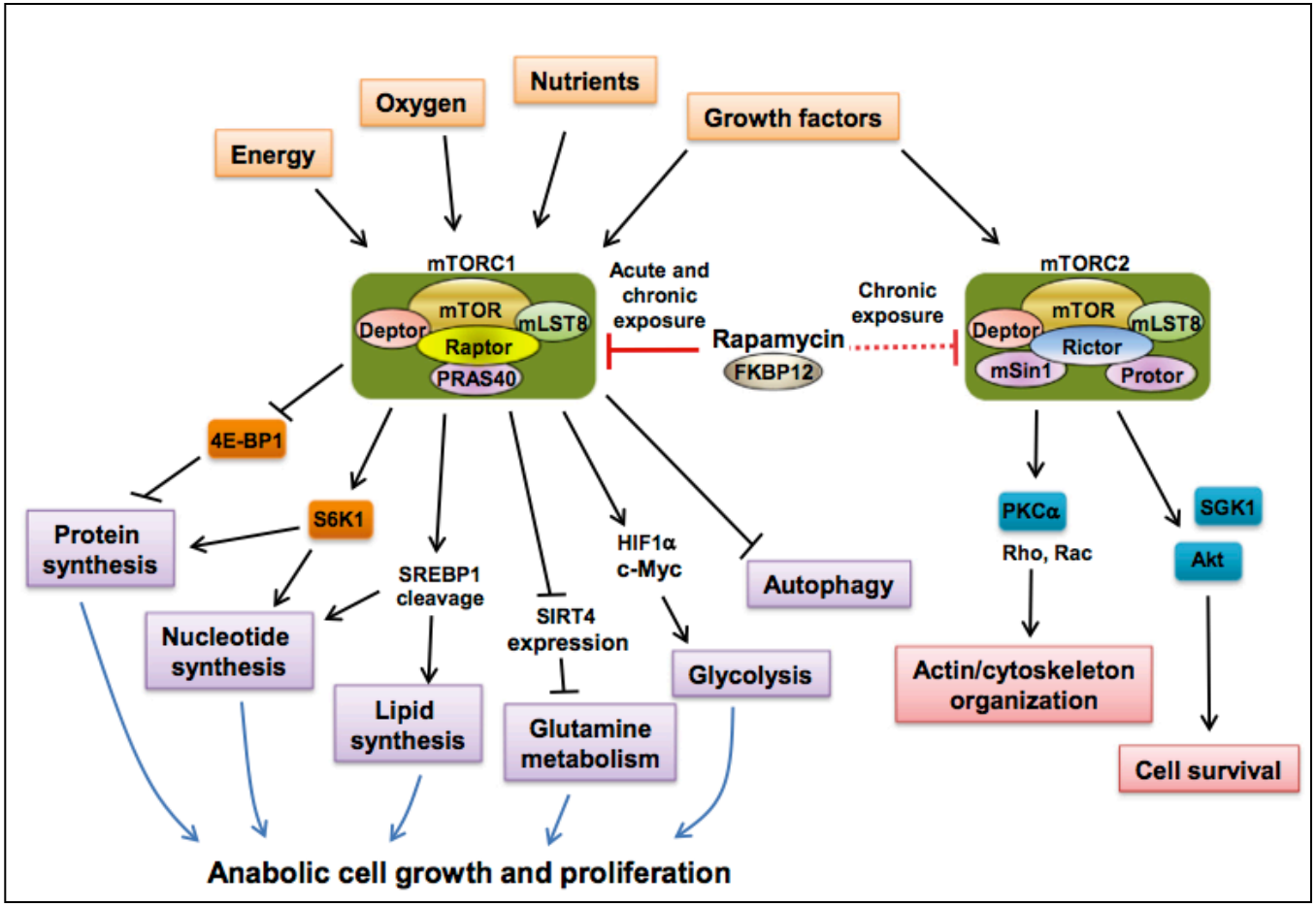


Rapamycin: One Drug, Many Effects

Cell Metabolism
2014 vol. 19 (3) pp. 373-379

Li J, Kim SG, Blenis J



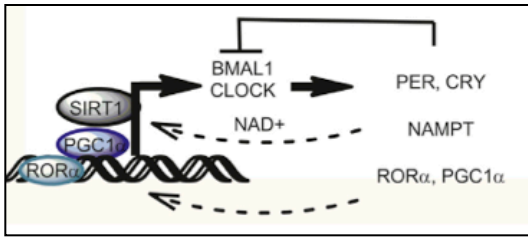


Figure 1. The Two mTOR Complexes and the Regulation of Key Cellular Processes

mTOR exists in two functionally distinct complexes, termed mTORC1 and mTORC2. mTORC1 integrates multiple signals from growth factors, oxygen, energy levels, and nutrients such as amino acids to promote cell growth and proliferation by activation of anabolic processes such as protein, lipid, and nucleotide synthesis; stimulation of energy metabolism such as glycolysis and glutaminolysis; and inhibition of catabolic process such as autophagy. Unlike mTORC1, mTORC2 only responds to growth factors and regulates actin/cytoskeleton organization and cell survival through the pathways as shown above. Rapamycin acutely inhibits mTORC1, whereas chronic exposure to rapamycin can also inhibit mTORC2.

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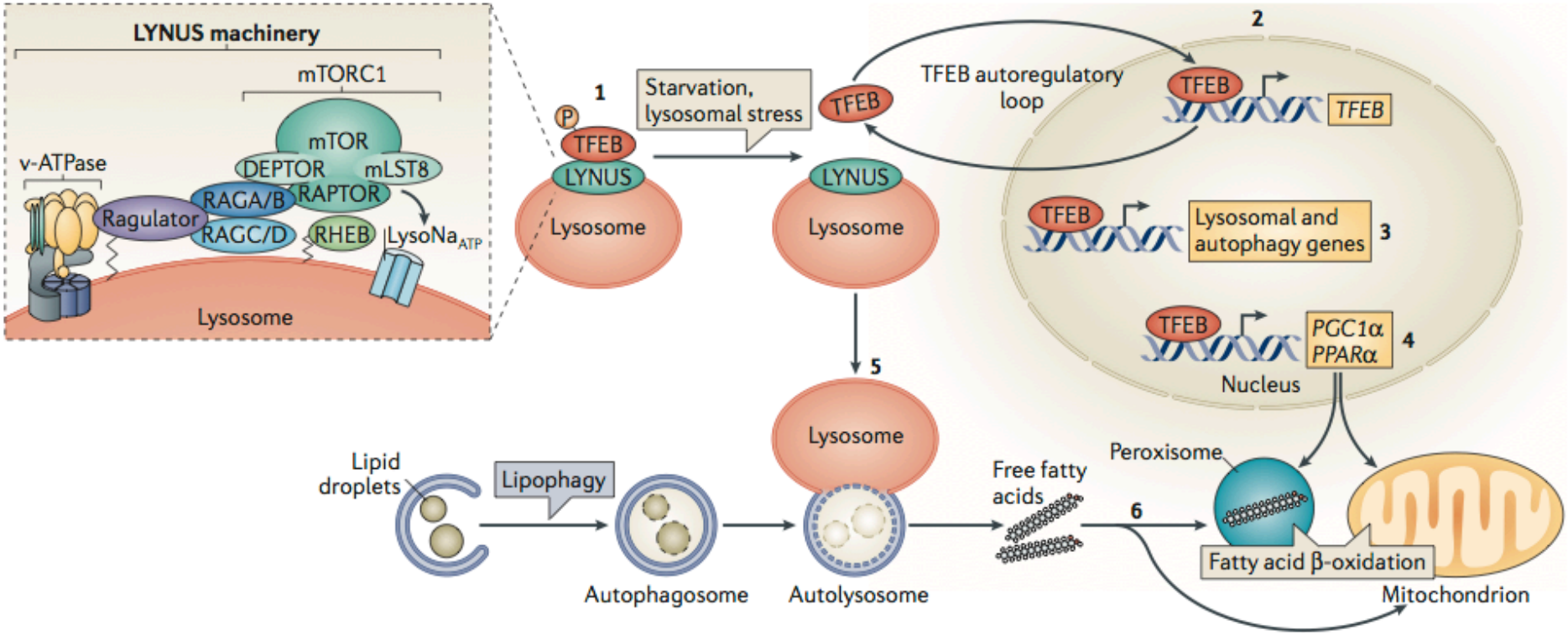

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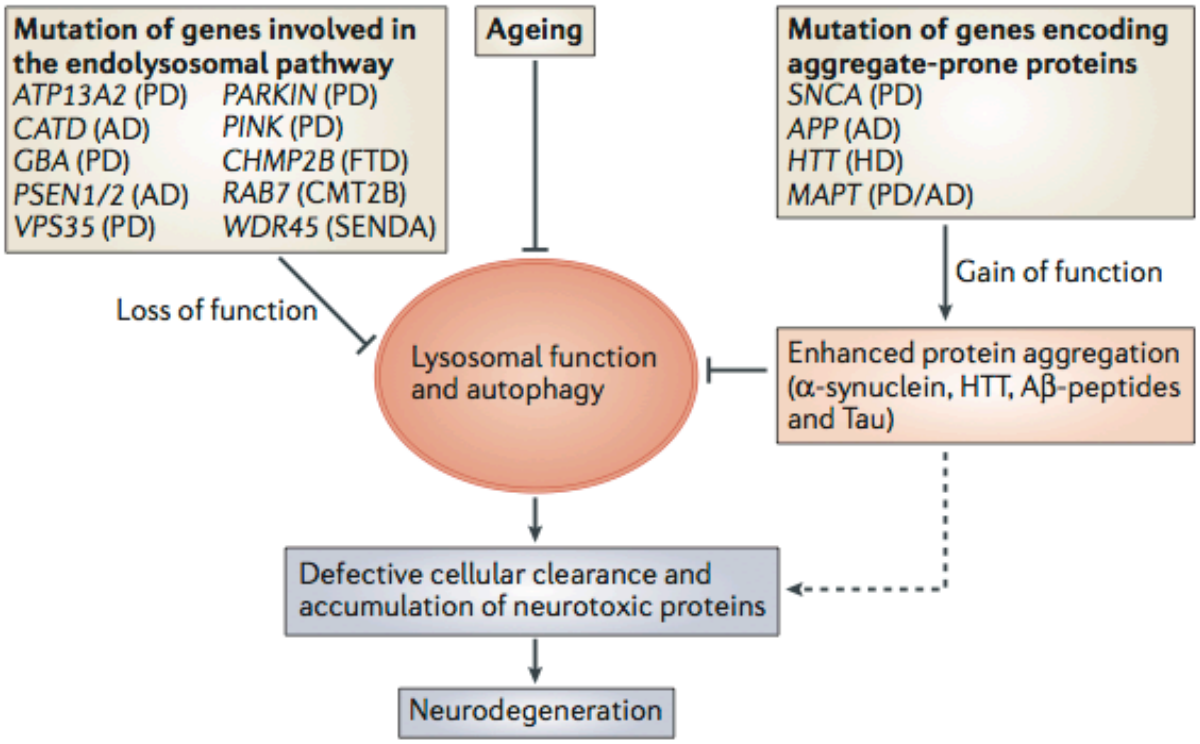

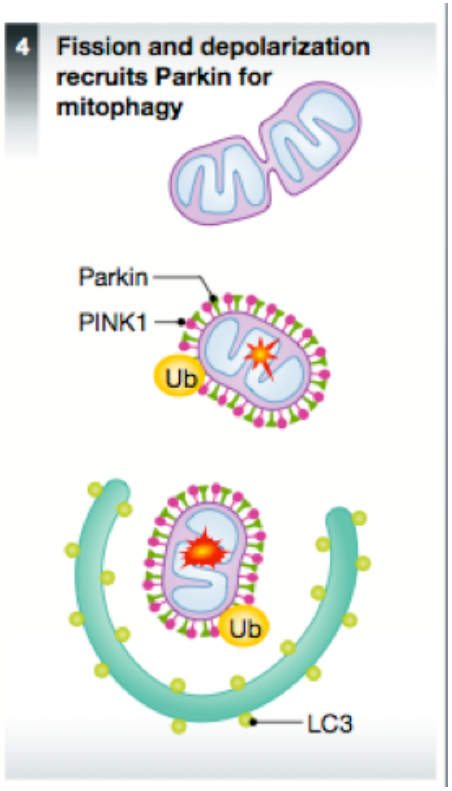

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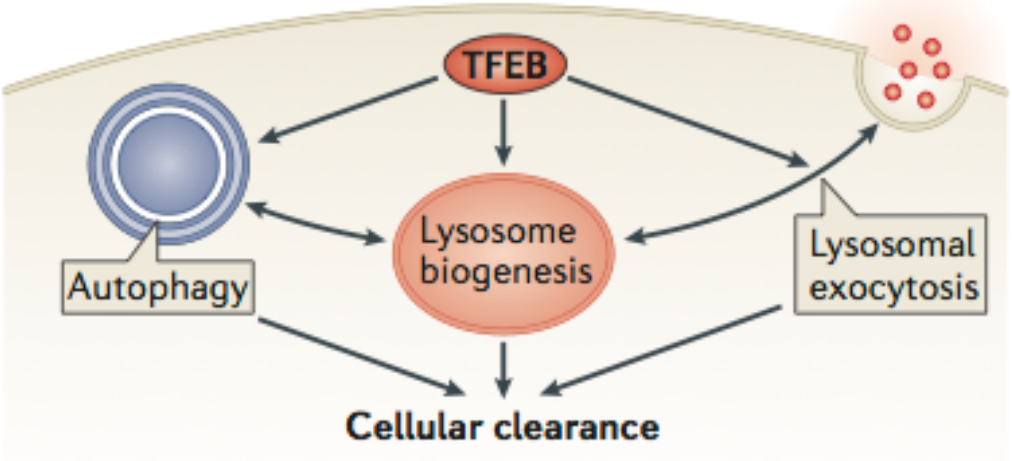

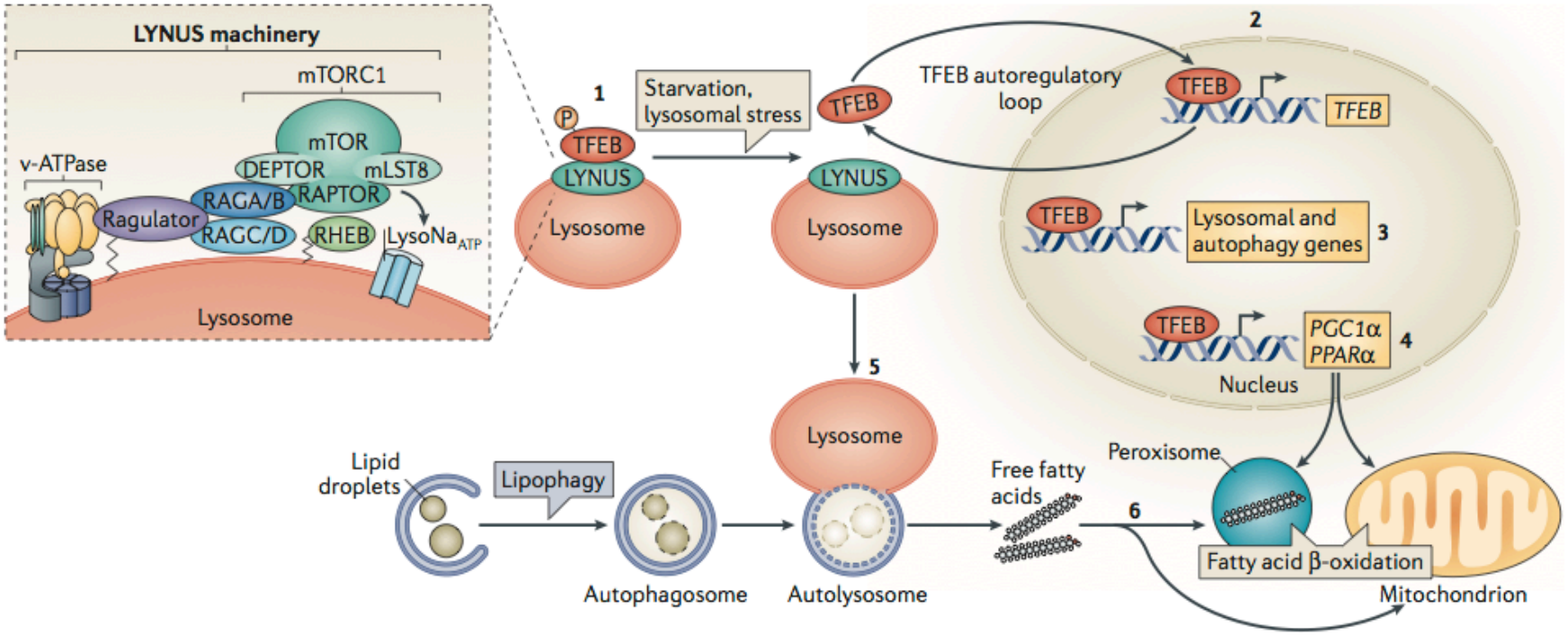

Autophagy in mammalian development and differentiation

Nature Cell Biology
2010 vol. 12 (9) pp. 823-30

Mizushima N, Levine B

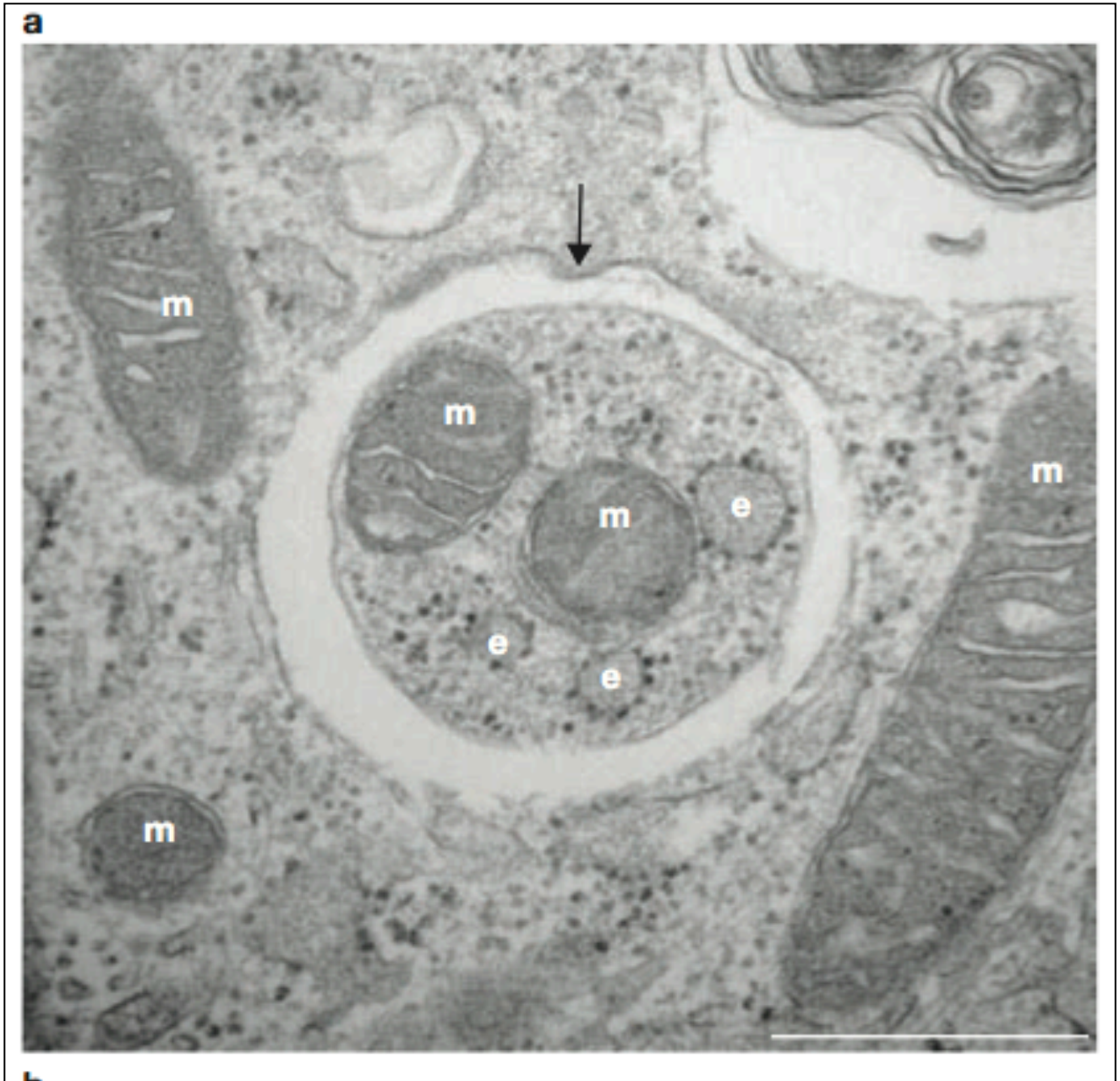

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Table 1 The roles of autophagy in development and differentiation of model organisms

Organism	Role	Reference
Saccharomyces cerevisiae	Spore formation	93
Schizosaccharomyces pombe	Spore formation	94, 95
Dictyostelium discoideum	Fruiting body formation	96, 97
Sordaria macrospora	Essential for growth; fruiting body formation	98
Podospora anserina	Development of aerial hyphae; differentiation of female reproductive organs	99
Leishmania major	Differentiation into metacyclic promastigote	100
Trypanosoma cruzi	Differentiation into metacyclic trypomastigotes	101
Caenorhabditis elegans	Larval development; dauer formation; degradation of germline P granules in somatic cells	10, 102, 103
Drosophila melanogaster	Larval development; degradation of larval tissues (for example midgut and salivary gland)*; synaptic development	104–107
Arabidopsis thaliana	Dispensable	108–110
Mus musculus	See Tables 2 and 3	

The development-related roles of autophagy are listed. Autophagy may have other roles in each organism. For example, autophagy is important for starvation adaptation in all of these organisms.
*Metamorphosis seems almost normal in the *Drosophila atg7* mutant, although the pupal period is prolonged[111].

Table 2 Phenotypes of systemic knockout mice of *ATG*-related genes

Genes	Phenotype	References
Atg3$^{-/-}$, *Atg5*$^{-/-}$, *Atg7*$^{-/-}$, *Atg9*$^{-/-}$, *Atg16L1*$^{-/-}$	Neonatal lethal with reduced amino acid levels, suckling defect (Atg9 has an additional role in innate immune responses induced by double-stranded DNA)	17–21
beclin 1$^{-/-}$	Early embryonic lethal (E7.5 or earlier) with defects in proamniotic canal closure (heterozygous mice show increased susceptibility to spontaneous tumours)	28, 29
FIP200$^{-/-}$	Embryonic lethal (E13.5–E16.5) due to defective heart and liver development	32
Ambra1$^{gt/gt}$	Embryonic lethal (~E14) with defects in neural tube development, and hyperproliferation of neural tissues	30
ULK1$^{-/-}$	Increased reticulocyte number with delayed mitochondrial clearance	51
Atg4C$^{-/-}$	Viable, fertile, increased susceptibility to carcinogen-induced fibrosarcoma	112
LC3B$^{-/-}$	Normal phenotype	113
GABARAP$^{-/-}$	Normal phenotype	114

The phenotypes of conventional systemic knockout mice of *ATG*-related genes are listed. *gt*, gene-trapped allele.

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Table 3 Phenotypes of tissue-specific knockout mice of *ATG*-related genes

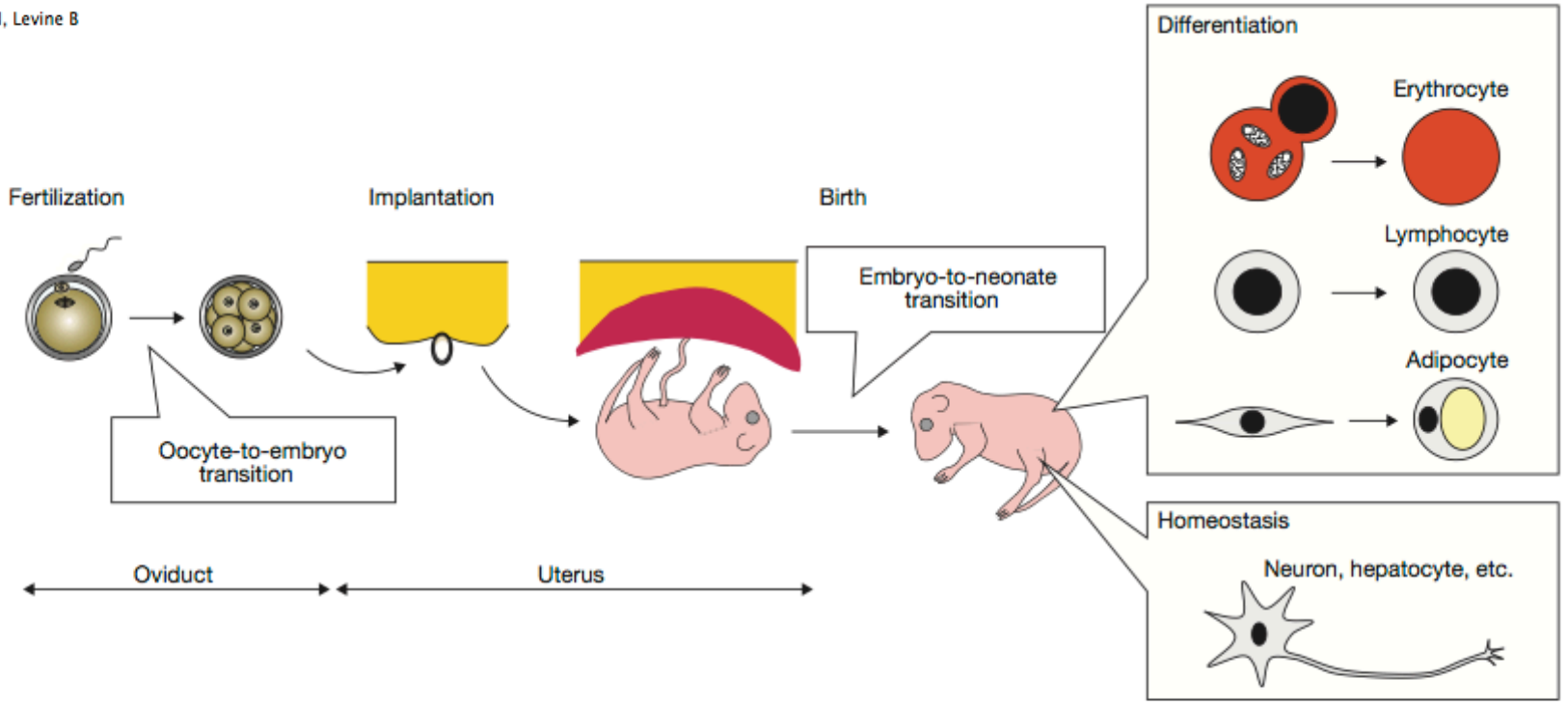
Mouse model	Target tissue/cell	Major phenotype	References
Atg5 F/F; Nestin-*Cre*, *Atg7 F/F;* Nestin-*Cre*	Neural cell	Neurodegeneration; accumulation of ubiquitin and p62	70, 71, 80
FIP200 F/F; Nestin-*Cre*	Neural cell	Neurodegeneration; accumulation of ubiquitin, p62 and mitochondria (more severe than *Atg5/7 F/F;* Nestin-*Cre*)	72
Atg5 F/F; Pcp2-*Cre*, *Atg7 F/F;* Pcp2-*Cre*	Purkinje cell	Axonal degeneration; accumulation of p62	115, 116
Atg5 F/F; Mx1-*Cre*, *Atg7 F/F;* Mx1-*Cre*, *Atg7 F/F;* Alb-*Cre*	Hepatocyte	Hepatic failure, hepatomegaly; accumulation of ubiquitin, p62 and mitochondria	19, 67, 70, 80
Atg5 F/F; MLC2v-*Cre*	Cardiomyocyte	Minimal abnormal phenotype (sensitive to pressure overload-cardiac failure)	73
Atg5 F/F; Mer*Cre*Mer	Cardiomyocyte	Cardiac hypertrophy and dysfunction; accumulation of ubiquitin, p62 and mitochondria	73
Atg5 F/F; HSA-*Cre*	Skeletal muscle	Atrophy of fast muscle fibres; accumulation of ubiquitin and p62	74
Atg5 F/F; Mlc1-*Cre*	Skeletal muscle	Muscle atrophy and weakness; accumulation of ubiquitin, p62 and mitochondria	75
Atg7 F/F; Ap2-*Cre*	Adipocyte	Decreased white adipose tissue mass, resistant to obesity; accumulation of p62 and mitochondria	60, 62
Atg5 F/F; EL-*Cre*	Pancreatic acinar cell	No abnormal phenotype (resistant to acute pancreatitis)	117
Atg7 F/F; Rip-*Cre*	Pancreatic β-cell	Impaired β-cell function, reduced β-cell mass; accumulation of ubiquitin, p62 and mitochondria	76, 77
Atg5 F/F; Zp3-*Cre*	Oocyte	Embryonic lethal at 4–8-cell stage (if fertilized with *Atg5*$^{-}$ sperm)	11
Atg5 F/F; Lck-*Cre*, *Atg7 F/F;* Lck-*Cre*	T cell	Decreased T-cell numbers; accumulation of mitochondria	55, 56
Atg5 F/F; CD19-*Cre*	B cell	Reduced B-1a B-cell numbers	59
Atg7 F/F; Vav-*Cre*	Haematopoietic cell	Severe anaemia, lymphopenia (T and B cells); accumulation of mitochondria	53
Atg5 F/F; CD11c-*Cre*	Dendritic cell	(Succumbed to viral infection due to defects in antigen presentation)	118
Atg5 F/F; Podocin-*Cre*	Podocyte	Late-onset glomerulosclerosis; accumulation of ubiquitin, p62 and mitochondria	78

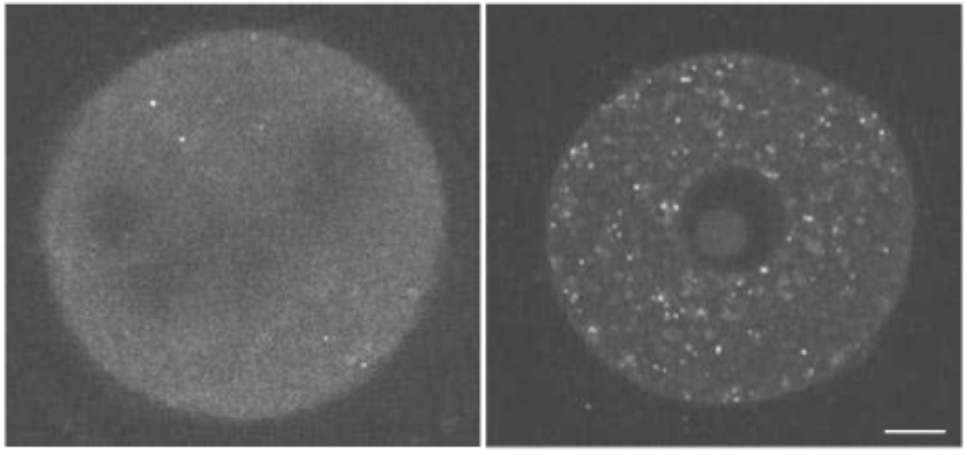
Phenotypes of tissue-specific knockout mice of *ATG*-related genes are listed. *F*, floxed allele; MLC2v, myosin light chain 2v; Mlc1, myosin light chain 1; HAS, human skeletal actin; EL, elastase I; Rip, rat insulin promoter. 'Accumulation of ubiquitin' refers to the accumulation of either ubiquitylated proteins or ubiquitin aggregates. 'Accumulation of p62' refers to the accumulation of either p62 protein or p62-positive aggregates.

Autophagy in mammalian development and differentiation

Nature Cell Biology
2010 vol. 12 (9) pp. 823-30

Mizushima N, Levine B

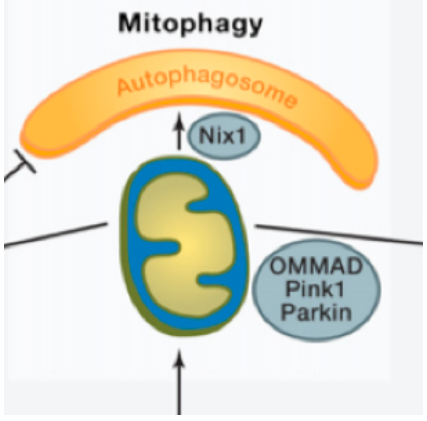




Mitochondria: in sickness and in health

Cell
2012 vol. 148 (6) pp. 1145-59

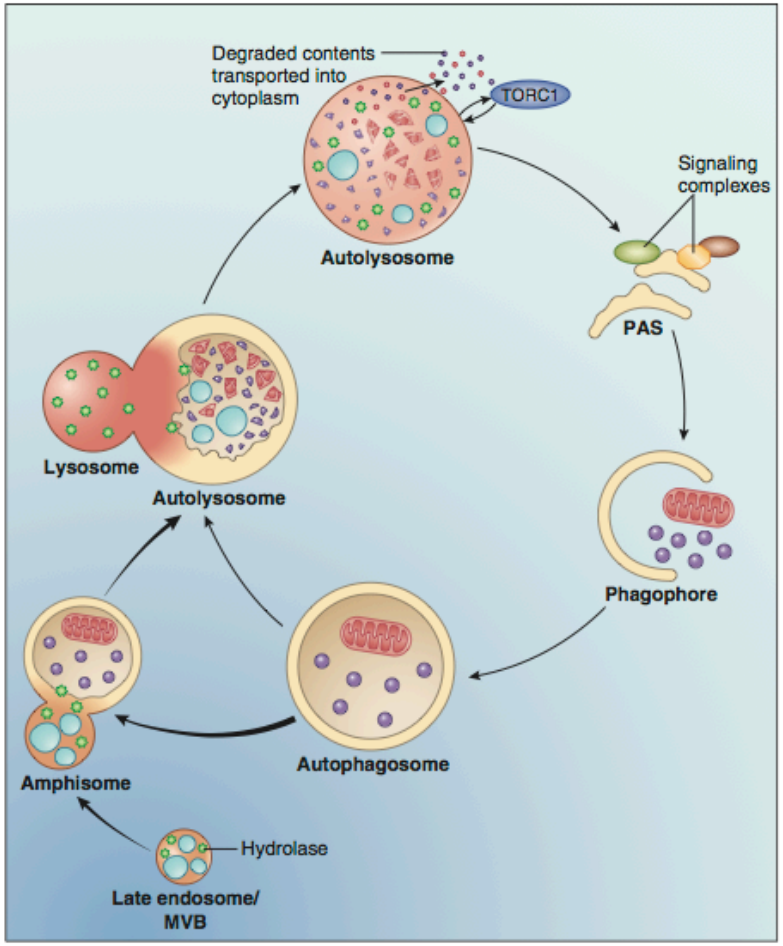
Nunnari J, Suomalainen A

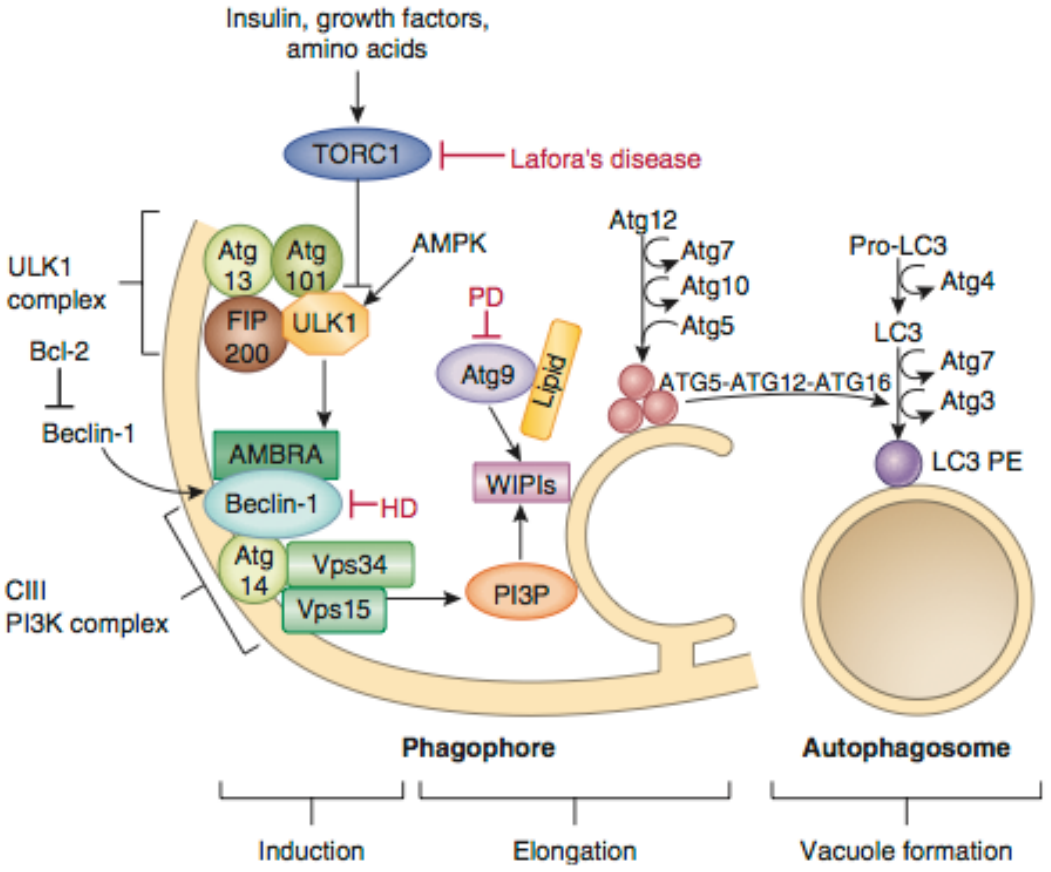


The role of autophagy in neurodegenerative disease

Nixon RA

Nature Medicine
2013 vol. 19 (8) pp. 983-97





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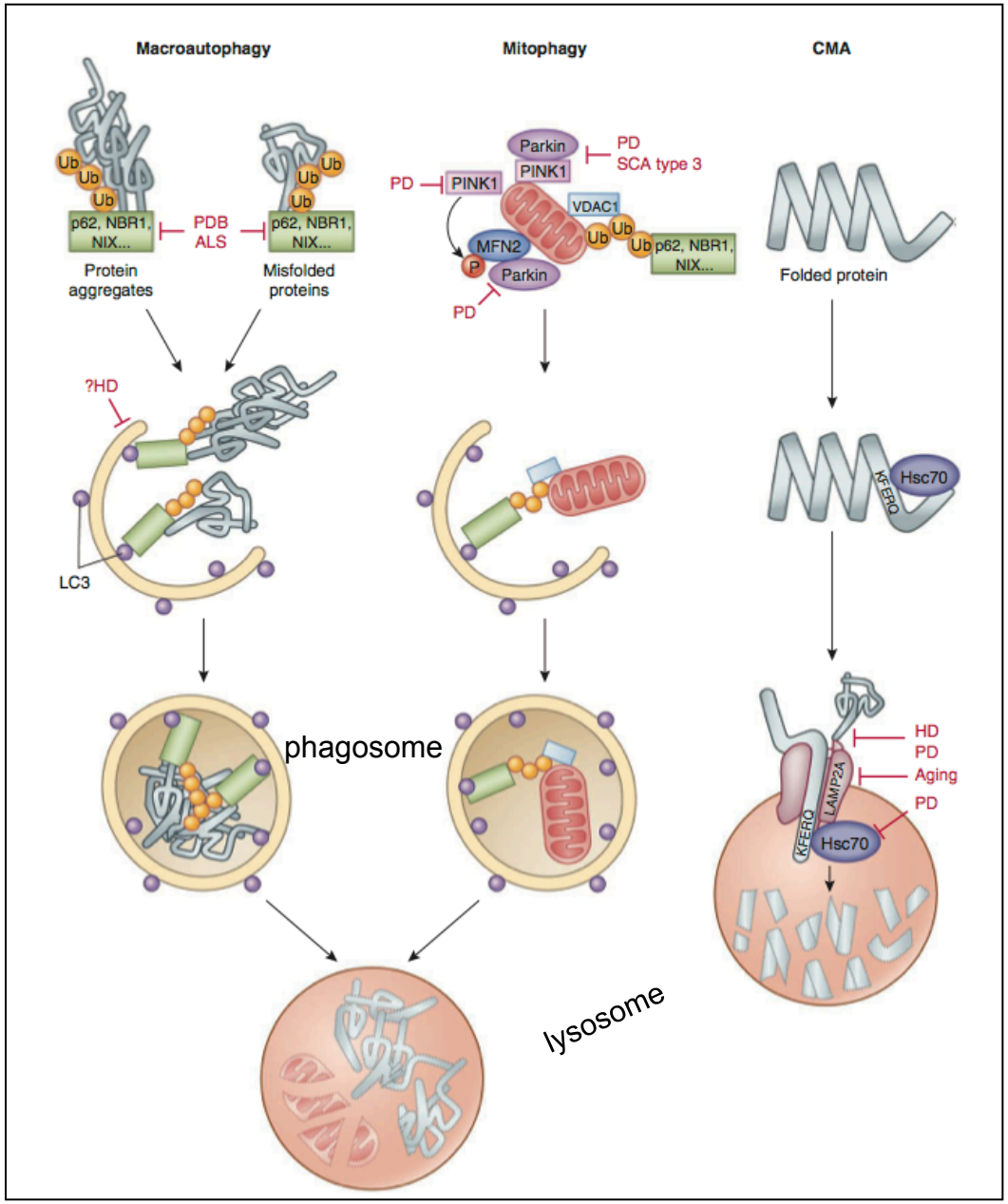

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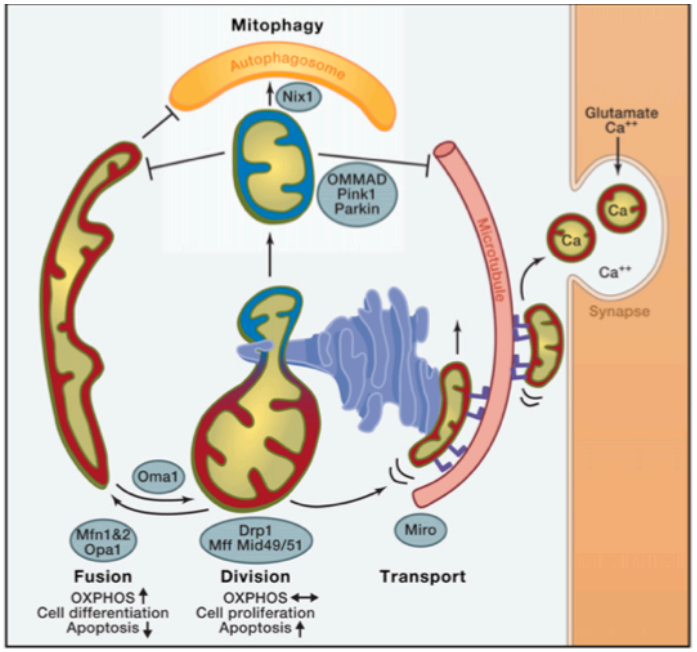

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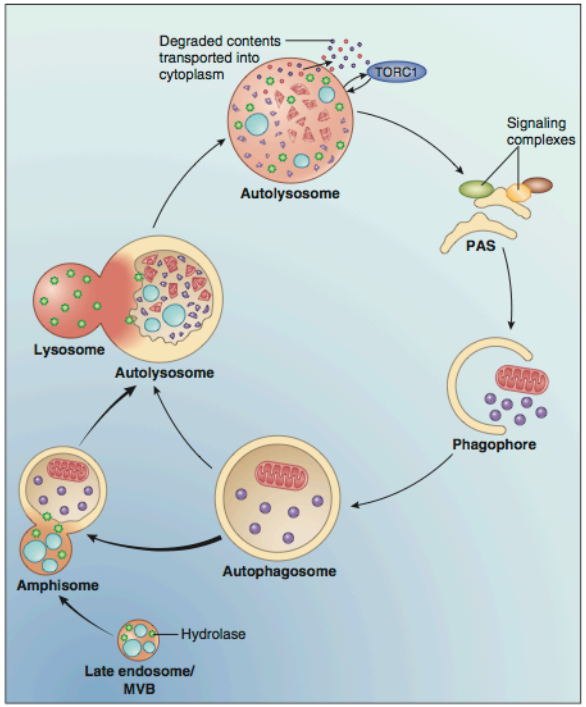
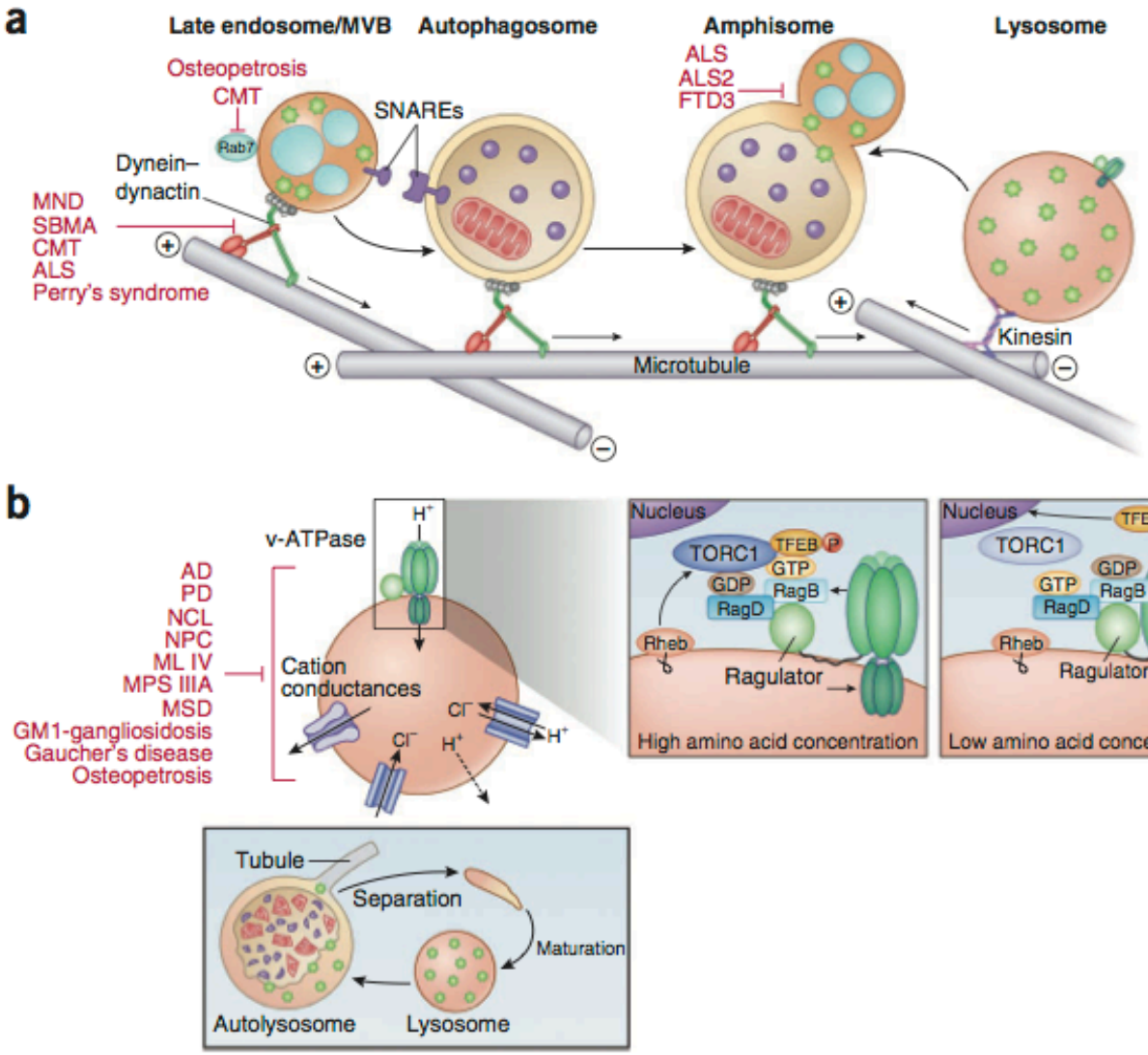
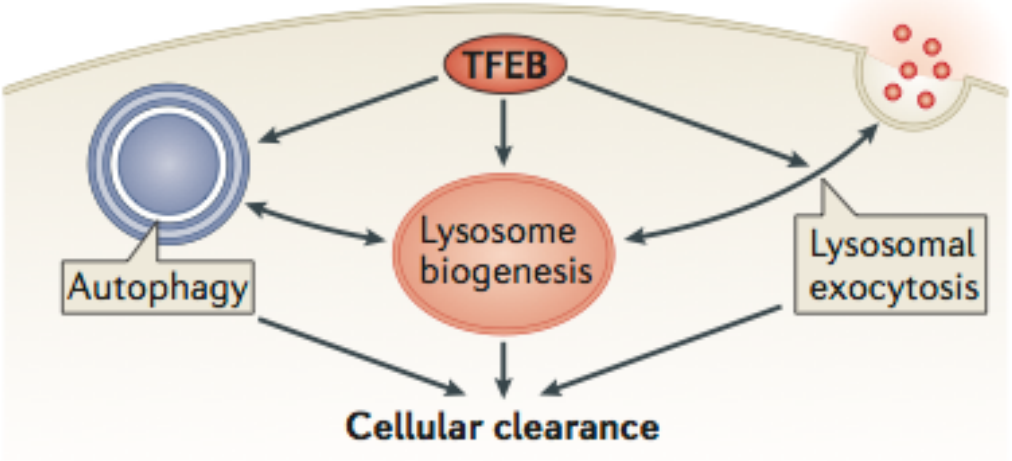


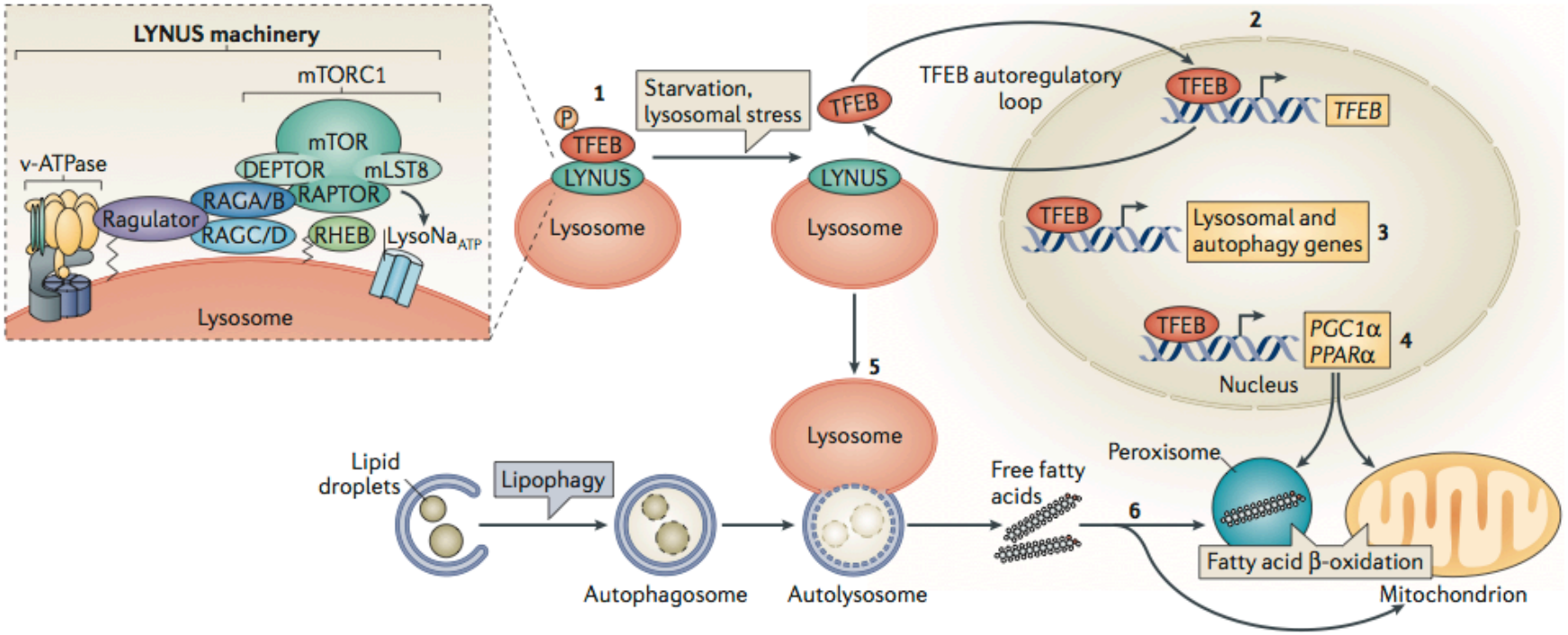


Signals from the lysosome: a control centre for cellular clearance and energy metabolism

Nat Rev Mol Cell Biol
2013 vol. 14 (5) pp. 283–96

Settembre C, Fraldi A, Medina DL, Ballabio A

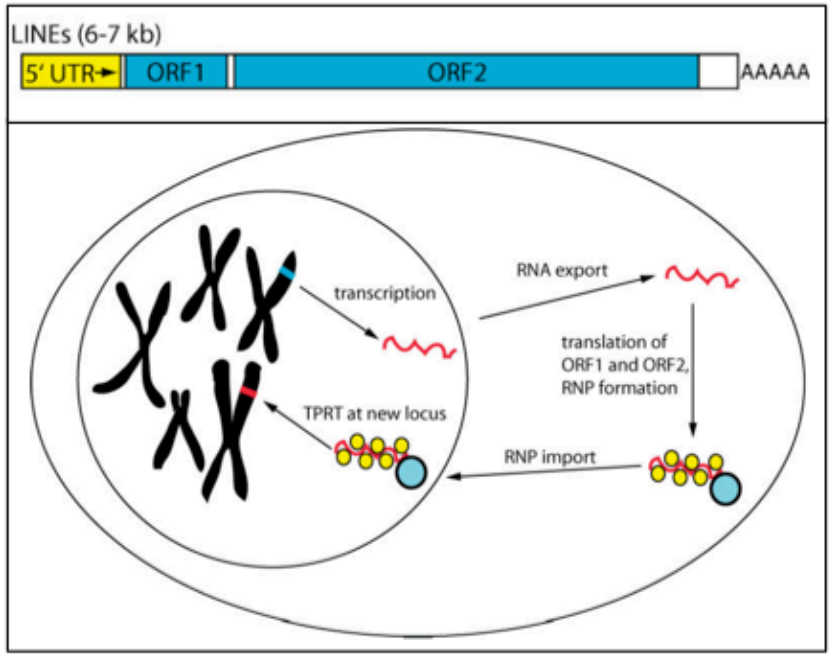




LINE-1 retrotransposons: modulators of quantity and quality of mammalian gene expression?

Jeffrey S. Han and Jef D. Boeke*

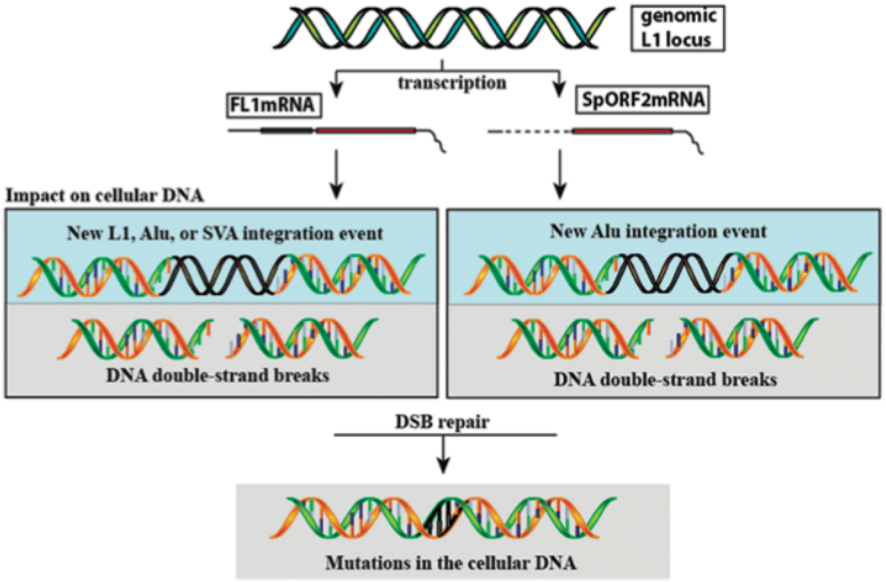
BioEssays 27:775–784, © 2005

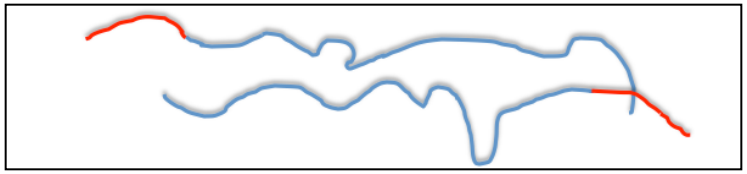


Somatic expression of LINE-1 elements in human tissues

Belancio VP, Roy-Engel AM, Pochampally RR, Deininger P

Nucleic Acids Research
2010 vol. 38 (12) pp. 3909-22

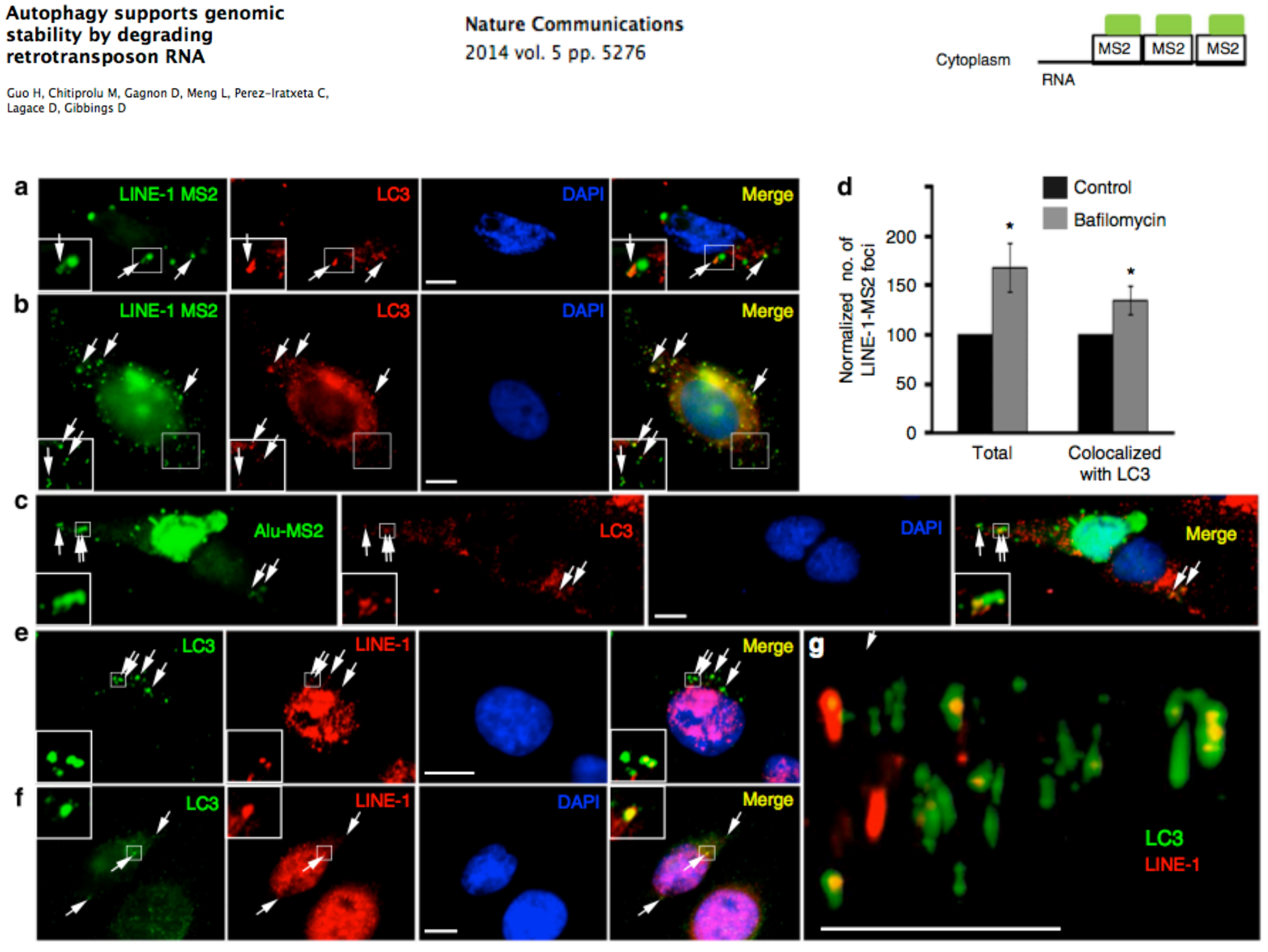




Autophagy supports genomic stability by degrading retrotransposon RNA

Guo H, Chitiprolu M, Gagnon D, Meng L, Perez-Iratxeta C, Lagace D, Gibbings D

Nature Communications
2014 vol. 5 pp. 5276



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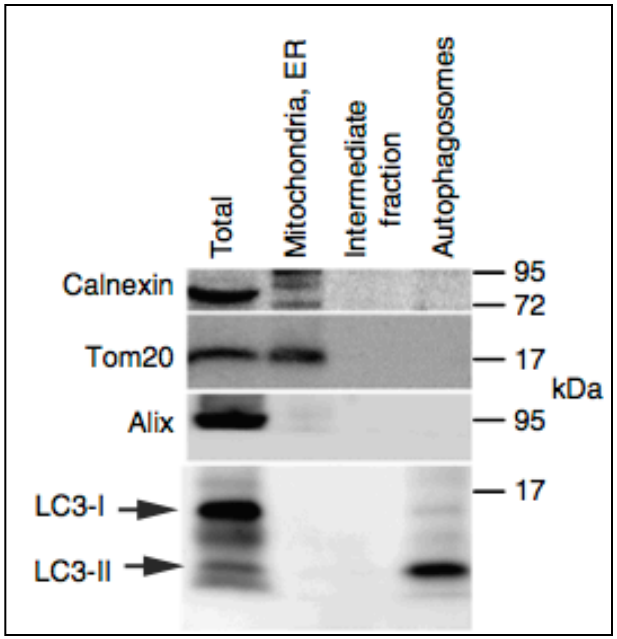

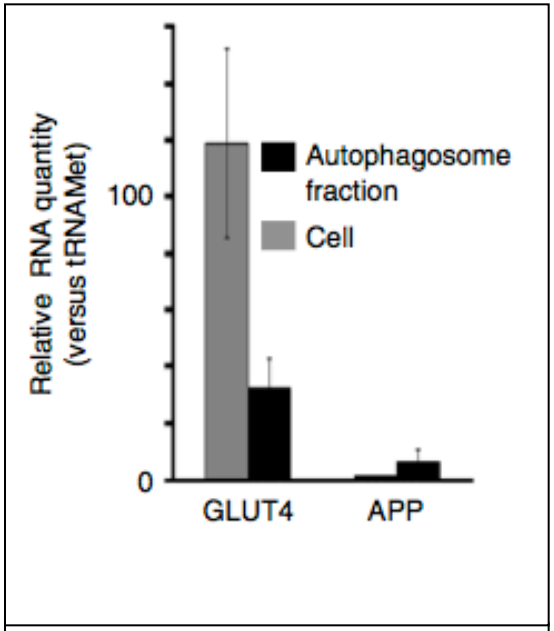

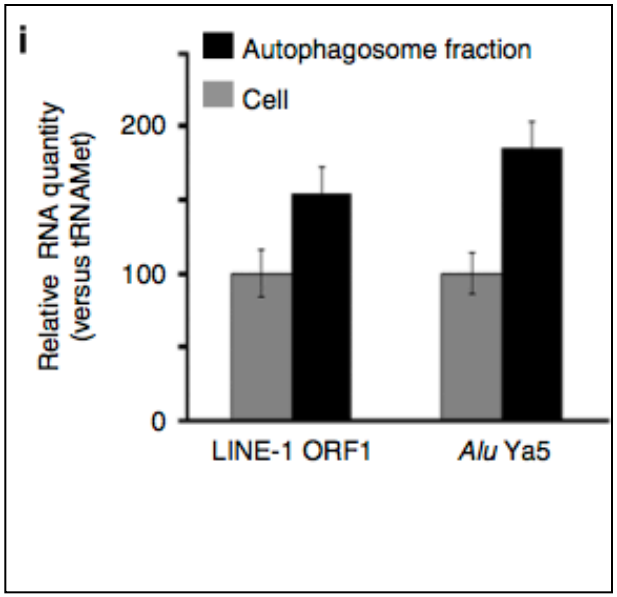

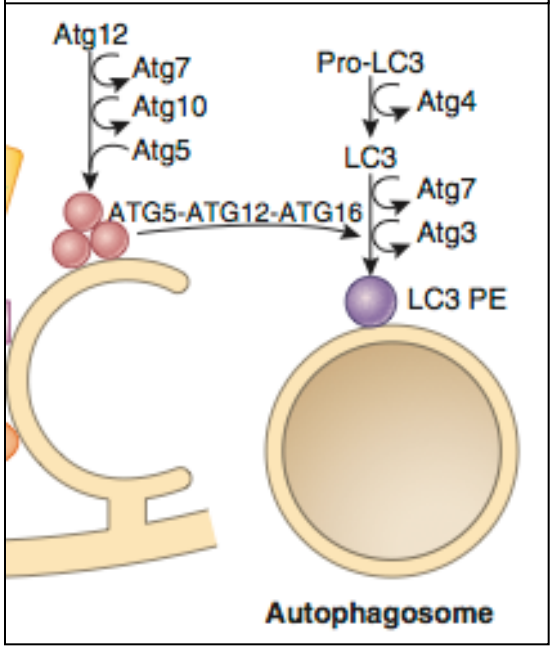

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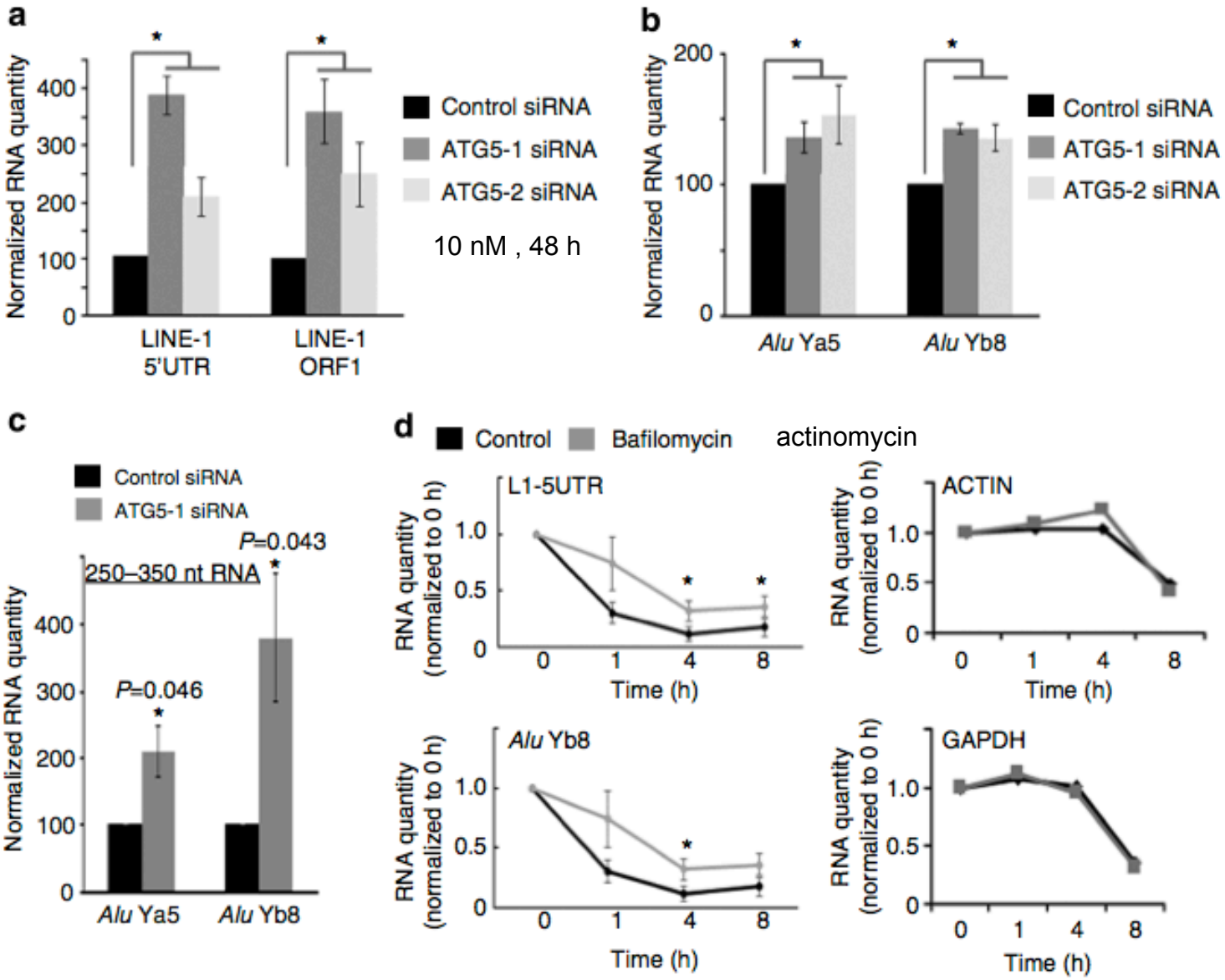

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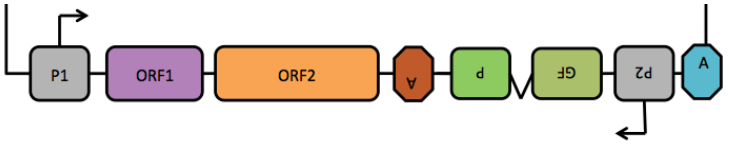

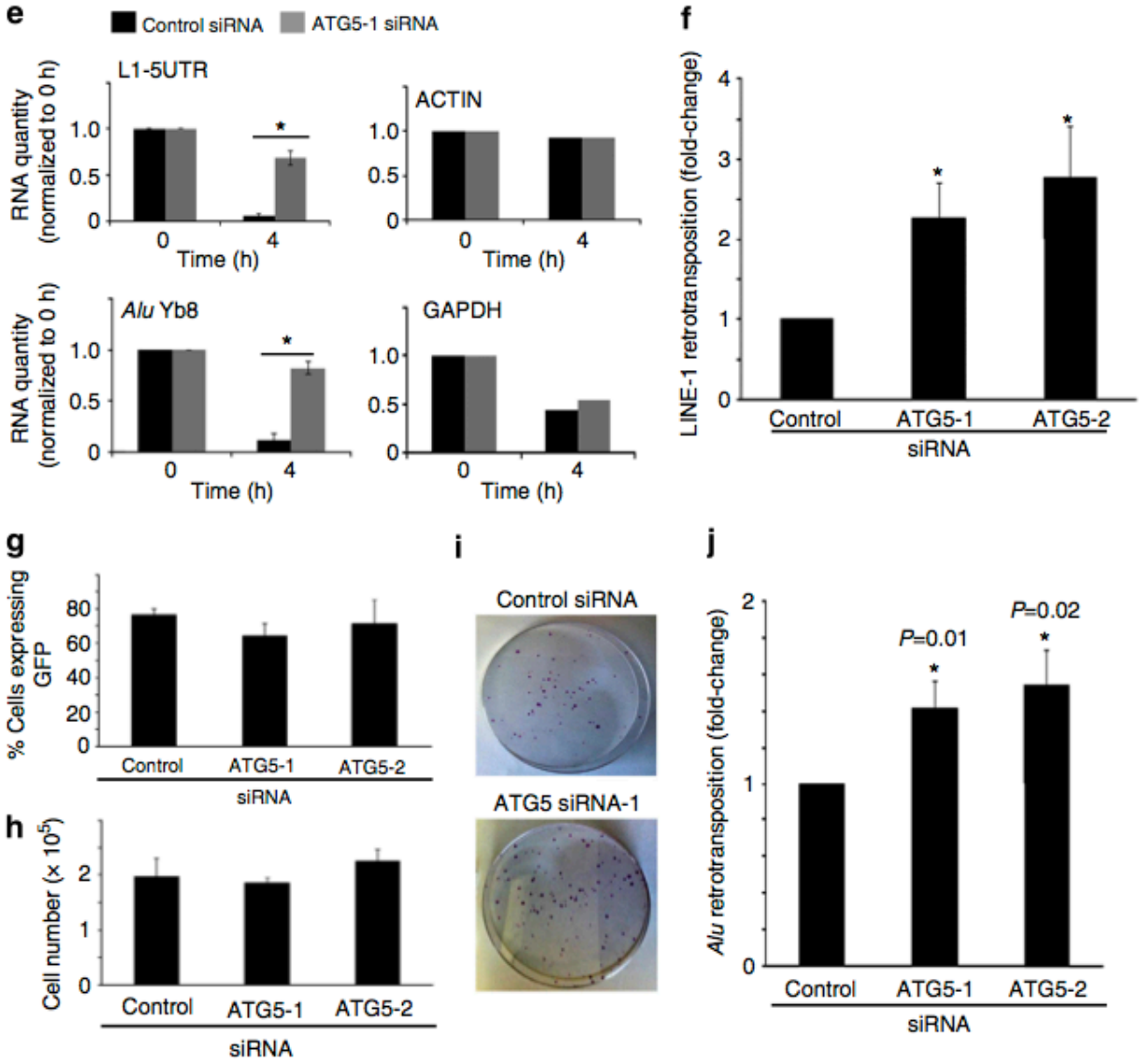

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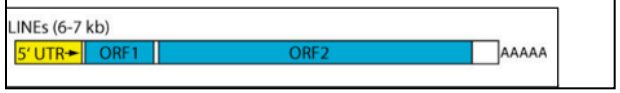

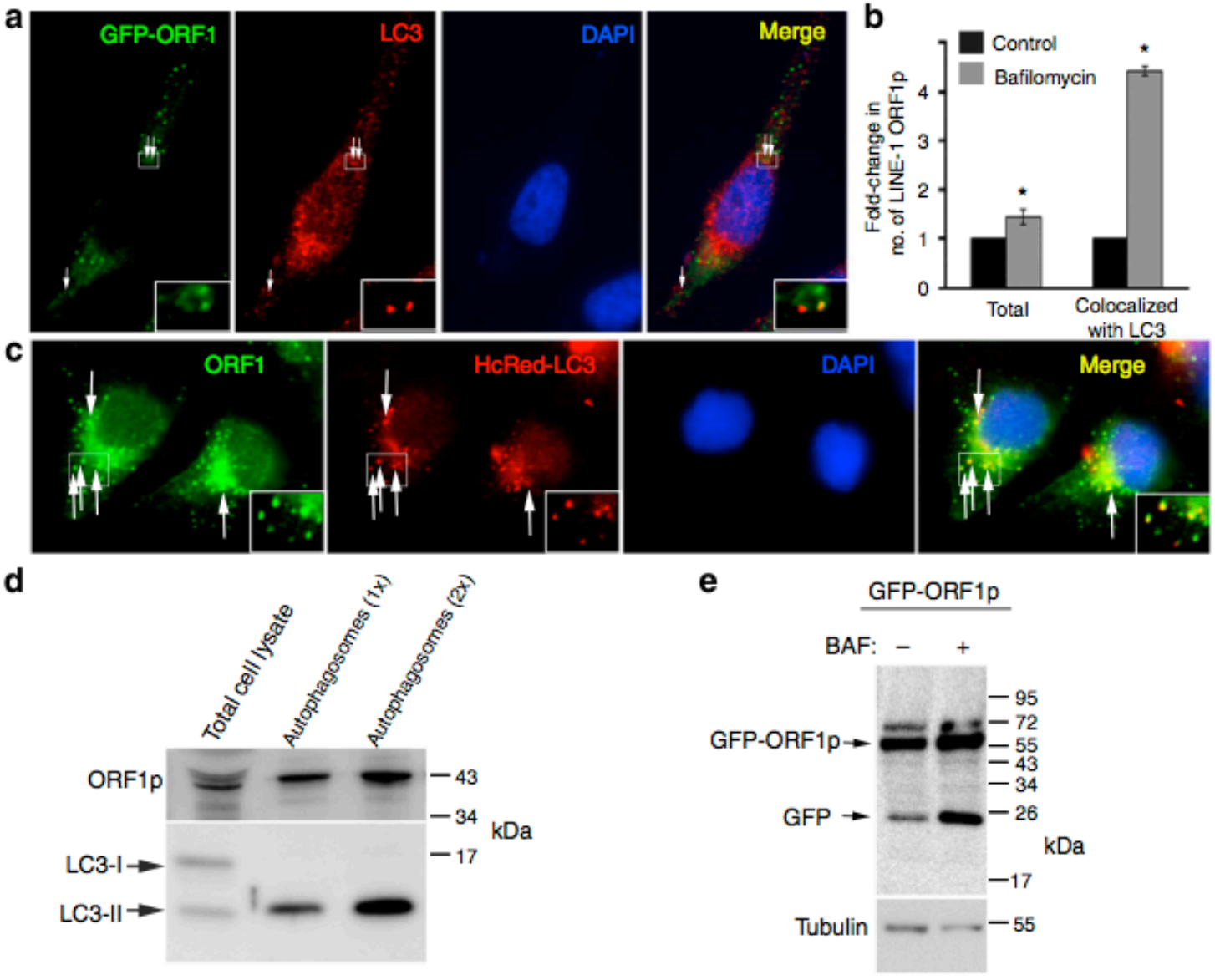

The Hallmarks of Aging

Cell *153*, June 6, 2013 ©2013 Elsevier Inc.

Carlos López-Otín,[1] Maria A. Blasco,[2] Linda Partridge,[3,4] Manuel Serrano,[5,*] and Guido Kroemer[6,7,8,9,10]

Figure 1. The Hallmarks of Aging
The scheme enumerates the nine hallmarks described in this Review: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication.