Mekanisme Autophagy pada Puasa Ramadhan

Agung Dwi Wahyu Widodo
Departemen Mikrobiologi dan Parasitologi Kedokteran FK Unair
Unit Laboratorium Medis Terpadu FK Unair

Subyek

- Pendahuluan Puasa Ramadhan
- Autophagy
- Macam Autophagy
- Mekanisme Autophagy
- Rahasia Puasa
- Rahasia Sahur
- Rahasia Berbuka Puasa
- Rahasia Puasa Sebulan Penuh
- Kesimpulan

Puasa Ramadhan

Puasa Ramadhan

- “Wahai orang-orang yang beriman! Diwajibkan atas kalian berpuasa sebagaimana diwajibkan atas orang sebelum kalian, agar kalian bertakwa.”
- QS Al-Baqarah ayat 183.

Puasa Ramdhan: Puasa seluruh Tubuh

- Puasa berarti juga mempuasakan seluruh organ tubuh kita mulai mulut, otak, telinga, mata, saluran pencernaan, saluran nafas dan lain-lain
- Imam Ali ibn Abi Thalib As

Rahasia Puasa Ramadhan

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Contents lists available at ScienceDirect

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Original article

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Table 3
Changes in anthropometric variables before and after RIF (n = 51).

Parameter	T1		T2		Significance As compared to the baseline
	Mean	SD	Mean	SD	
Weight (kg)	88.11	16.20	86.64	15.78	**<0.001** **
BMI (kg/m^2)	29.75	5.04	29.28	4.97	**<0.001** **
BFP (%)	29.47	7.05	28.49	7.24	**<0.001** **
FM (kg)	26.41	9.53	25.15	9.37	**<0.001** **
FFM (kg)	61.70	10.31	60.90	11.11	0.173
MM (kg)	58.62	9.82	58.41	9.59	0.287
TBW (kg)	43.94	7.28	43.87	7.09	0.741
BM (kg)	3.08	0.49	3.07	0.47	0.595
VFAR	10.06	4.99	9.76	4.72	0.364
VFAT (cm^2)	100.78	49.95	97.61	47.23	0.325
WC (cm)	98.85	14.24	97.17	13.41	**0.011***
HC (cm)	110.08	9.53	108.59	8.96	**<0.001** **
WHR	0.90	0.09	0.89	0.09	0.541

A paired t-test was used to compare after RIF (T2) with the pre-fasting baseline (T1). BMI, Body mass index; BFP, Body fat percent; FM, Fat mass; BFP, Body fat percent; FFM, Fat-free mass; MM, Muscle mass; TBW, Total body water; BM, Bone mass; VFAR, Visceral fat rating measured by DSM-BIA; VFAT, Visceral fat surface area; WC, Waist circumference; HC, Hip circumference; WHR, Waist: hip ratio; SBP, Systolic blood pressure; DBP, Diastolic blood pressure.

*P < 0.05, a significant difference.

**P < 0.001, a highly significant difference.

NS, no significant difference.

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Table 4
Changes in glucose homeostasis, lipid profile, and inflammatory markers before and after RIF (n = 51).

Parameter	T1		T2		Significance as compared to the baseline
	Mean	SD	Mean	SD	
Glucose homeostasis and lipid profile marker					
SBP (mmHg)	124.0	12.09	126.06	12.89	0.154
DBP (mmHg)	72.43	8.79	73.57	10.10	0.366
FBG (mg/dl)	99.55	21.23	104.71	24.63	0.248
TC (mg/dl)	175.67	39.52	177.12	37.34	0.676
HDL (mg/dl)	45.88	6.78	58.20	12.16	**<0.001** **
TG (mg/dl)	94.64	54.67	98.04	44.96	0.446
LDL (mg/dl)	89.67	39.97	78.92	44.02	0.006*
Inflammatory markers					
IL-6 (pg/dl)	30.46	17.55	18.20	1.35	**<0.001** **
TNF-α (pg/dl)	28.30	4.60	21.23	1.57	**<0.001** **
IL-10 (pg/dl)	18.27	0.75	19.53	1.23	**<0.001** **
CD163 (μg/ml)	188.304	105.336	228.472	114.222	**0.023***
Hp (mg/dl)	131.62	43.76	122.11	54.12	0.064

A paired t-test was used to compare after RIF (T2) with the pre-fasting baseline (T1).
CD163: Scavenger receptor; DBP: Diastolic blood pressure; FBG: Fasting blood glucose; HDL: High-density lipoprotein; Hp: Haptoglobin; IL-10: Interleukin-10; IL-6: Interleukin-6; LDL: Low-density lipoprotein; SBP: Systolic blood pressure; TC: Total cholesterol; TG: Triglycerides; TNF-α: Tumor necrosis factor-α.
*$P < 0.05$, a significant difference.
**$P < 0.001$, a highly significant difference.
NS, no significant difference.

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Table 5
Changes in dietary intake of macro- and micronutrients before and after RIF (n = 51).

Parameter	T1		T2		Significance as compared to the baseline
	Mean	SD	Mean	SD	
Energy (kcal/d)	2120.29	780.21	2113.64	845.09	0.962
Fat calories (kcal/day)	696.71	416.07	673.13	373.07	0.723
Protein (g/d)	107.79	37.88	88.20	40.82	**0.003****
Total carbohydrates (g/d)	253.30	96.49	278.99	120.05	0.150
Total sugars (g/d)	66.40	32.24	107.00	53.34	**<0.001** **
Total fats (g/d)	77.57	46.27	75.21	41.88	0.751
Saturated fat (g/d)	23.57	13.16	22.54	12.65	0.636
Total water (ml/d)	1374.61	713.00	1488.51	764.97	0.406
MUFA (g/d)	20.11	11.50	22.53	13.51	0.281
PUFA (g/d)	10.40	8.30	15.75	16.84	**0.041***
Trans fat (g/d)	0.56	0.83	0.64	1.43	0.801
Cholesterol (mg/d)	392.89	184.55	266.75	177.20	**<0.001** **
Vitamin C (mg/d)	73.48	50.84	95.64	66.58	0.020*
α-Carotene (μg/d)	16.45	27.81	23.98	40.54	0.395
β-Carotene (μg/d)	409.95	686.01	586.71	983.55	0.275
Omega-3 fatty acids (mg/d)	0.65	0.57	1.72	2.27	**0.002***
Omega-6 fatty acids (mg/d)	7.75	7.24	9.54	10.67	0.304
Lycopene (μg/d)	1407.65	2564.12	7213.44	12,084.38	0.057
Selenium (μg/d)	83.73	49.25	69.21	48.90	0.144
Vitamin E (mg/d)	5.91	3.66	8.41	9.87	0.093

A paired t-test was used to compare after RIF (T2) with the pre-fasting baseline (T1).
MUFA, Monounsaturated fat; PUFA, polyunsaturated fat.
*P < 0.05, a significant difference.
**P < 0.001, a highly significant difference.
NS, no significant difference.

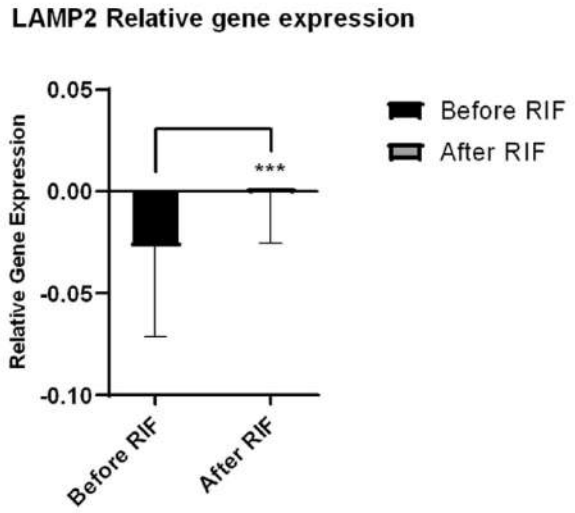


Fig. 1. Relative (in comparison with healthy participants with normal BMI) *LAMP2* gene expression before (T1) and after RIF (T2) for overweight/obese participants. ***$P < 0.0001$.

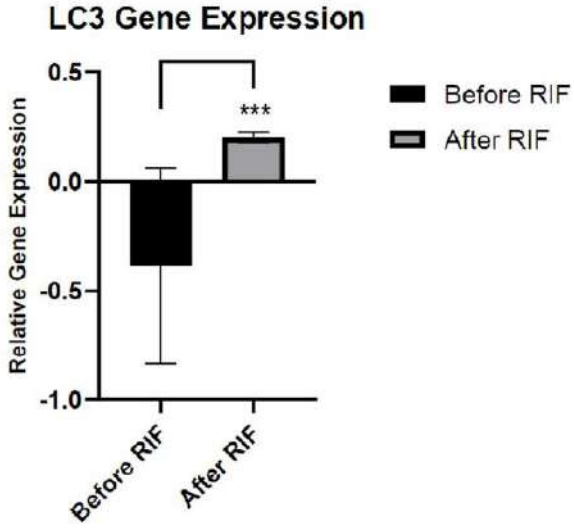


Fig. 2. Relative (in comparison with healthy participants with normal BMI) *LC3B* gene expression before (T1) and after RIF (T2) for the overweight/obese participants.***$P < 0.0001$.

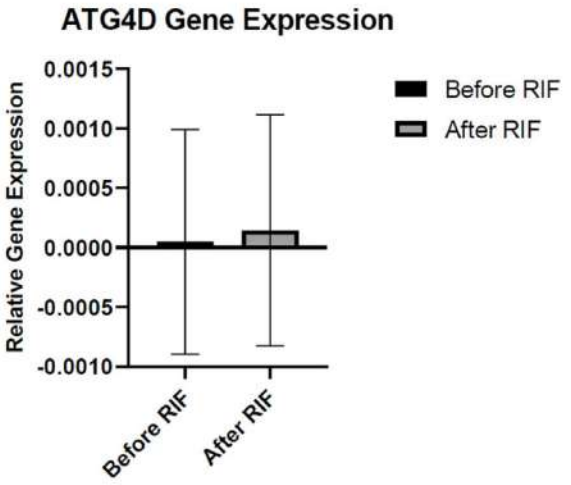


Fig. 4. Relative (in comparison with healthy participants with normal BMI) *ATG4D* gene expression before (T1) and after RIF (T2) for overweight/obese participants.

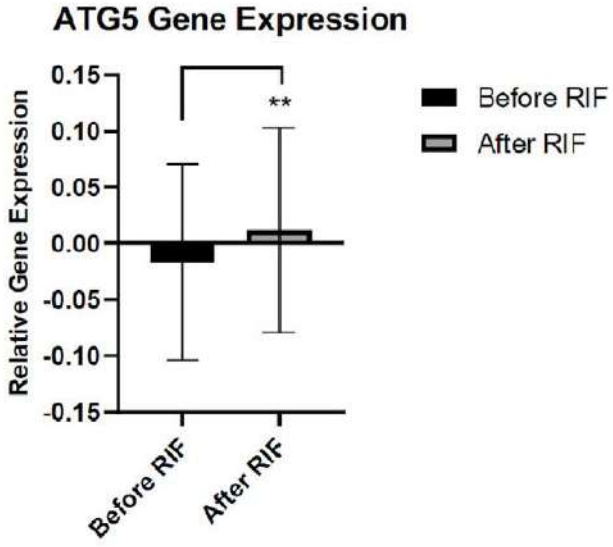


Fig. 3. Relative (in comparison with healthy participants with normal BMI) *ATG5* gene expression before (T1) and after RIF (T2) for overweight/obese participants. **$P < 0.001$.

History of Autophagy

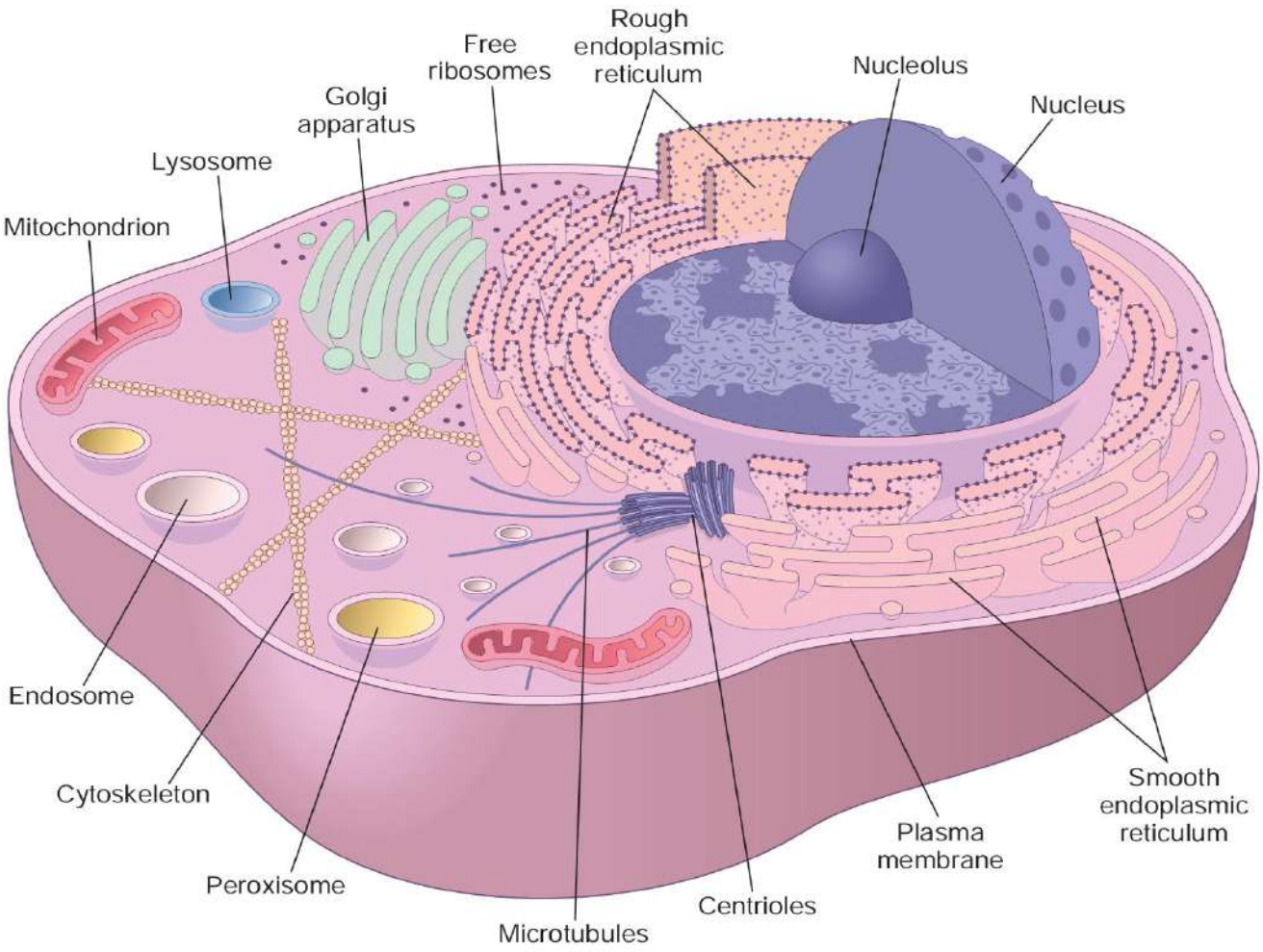
- 1860- **M Auselmier**, used term ‘autophagy’.
- 1963- **C de Duve**, coined the term **Autophagy**
- 1992- **Ohsumi**, induction autophagy in yeast
- 1993- **Ohsumi**, identified first Autophagy gene in yeast
- 1998- **Mizushima** , identified first autophagy genes in mamals ATG 5 and ATG12
- 2000- **Yoshimori**, identified Atg8 homolog (LC3)
- 2003- **the autophagy community** adopted a unified gene and protein nomenclature based on the atg acronym, which stands for “ autophagy-related”

Autophagy Definition

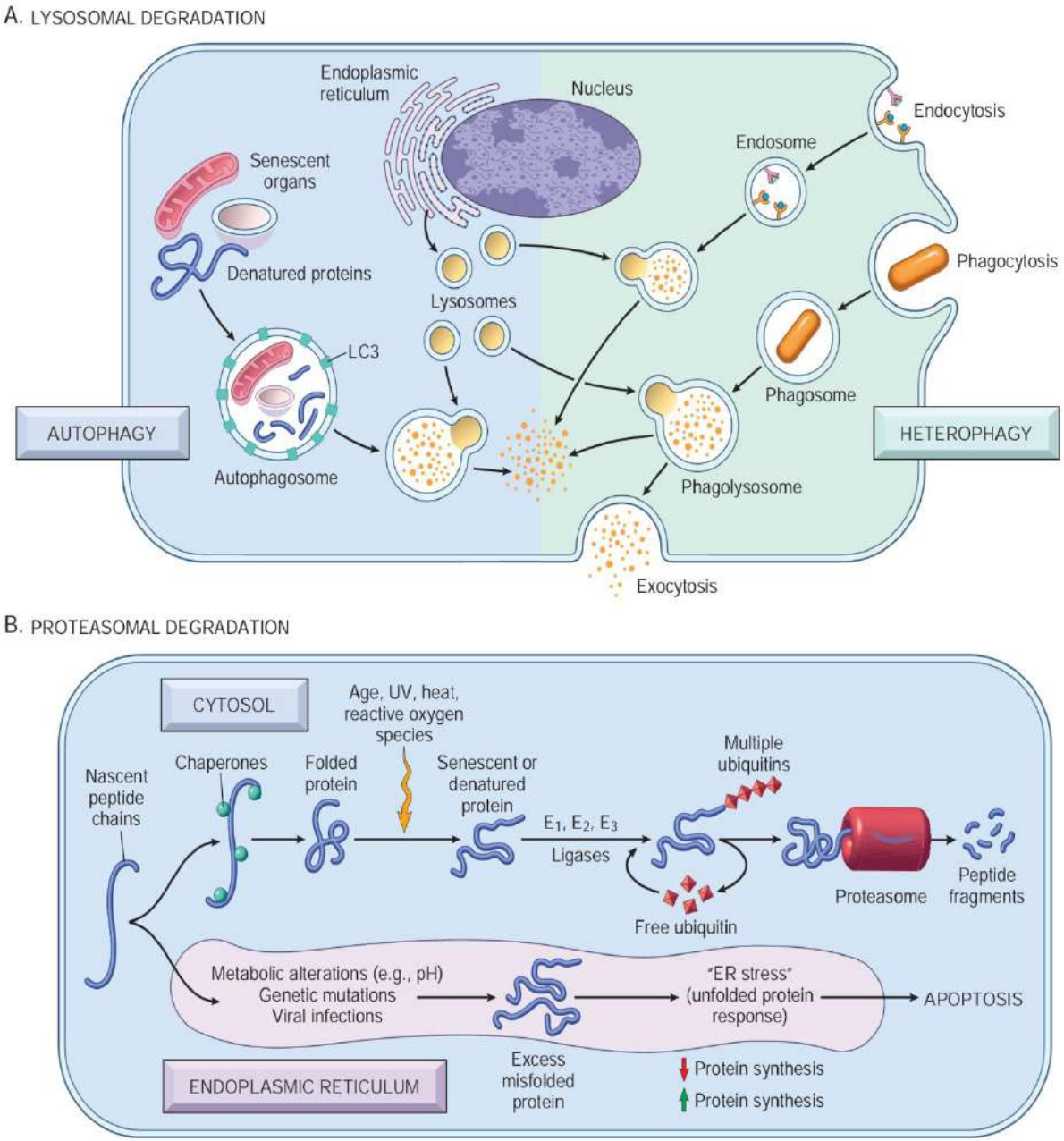
- **Autophagy**: A catabolic pathway involving the degradation of cellular components through the lysosomal machinery, the major subtype of which is ***macroautophagy***.
- ***Macroautophagy***: A cellular process that involves the sequestration of cytoplasmic components into double-membrane auto phagosomes that fuse with lysosomes, where their cargoes are delivered for degradation and recycling.
- ***Microautophagy*** involves the direct assimilation of cargo into lysosomes by invagination of the membrane without the intermediacy of autophagosomes.
- ***Chaperone-mediated autophagy***, molecular chaperones (i.e., heat-shock cognate proteins) facilitate the transfer of proteins to the lysosomes.

Relative volumes of intracellular organelles (hepatocyte)

Compartment	% total volume	number/cell	role in the cell
Cytosol	54%	1	metabolism, transport, protein translation
Mitochondria	22%	1700	energy generation, apoptosis
Rough ER	9%	1*	synthesis of membrane and secreted proteins
Smooth ER, Golgi	6%	1*	protein modification, sorting, catabolism
Nucleus	6%	1	cell regulation, proliferation, DNA transcription
Endosomes	1%	200	intracellular transport and export, ingestion of extracellular substances
Lysosomes	1%	300	cellular catabolism
Peroxisomes	1%	400	very long-chain fatty acid metabolism



Intracellular Catabolism



Autophagy

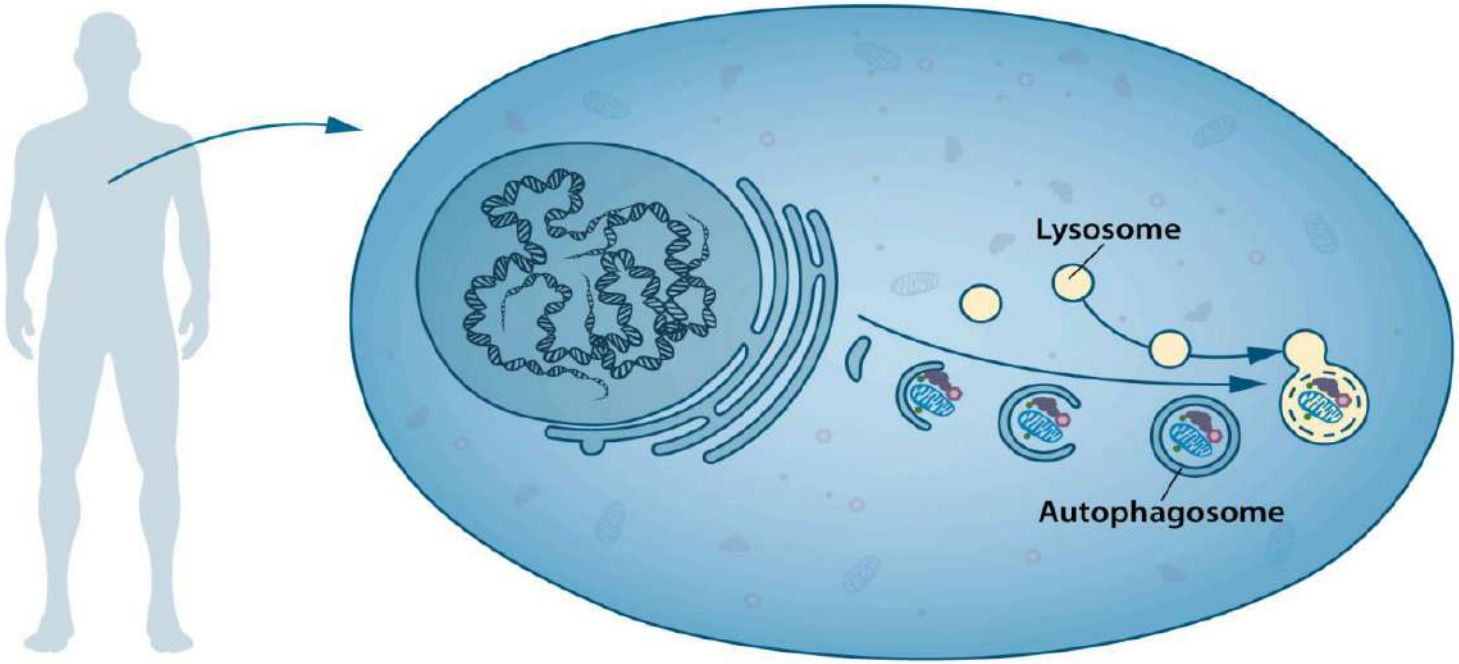


Figure 1: Our cells have different specialized compartments. Lysosomes constitute one such compartment and contain enzymes for digestion of cellular contents. A new type of vesicle called *autophagosome* was observed within the cell. As the autophagosome forms, it engulfs cellular contents, such as damaged proteins and organelles. Finally, it fuses with the lysosome, where the contents are degraded into smaller constituents. This process provides the cell with nutrients and building blocks for renewal.

The Nobel Prize in Physiology or Medicine 1974

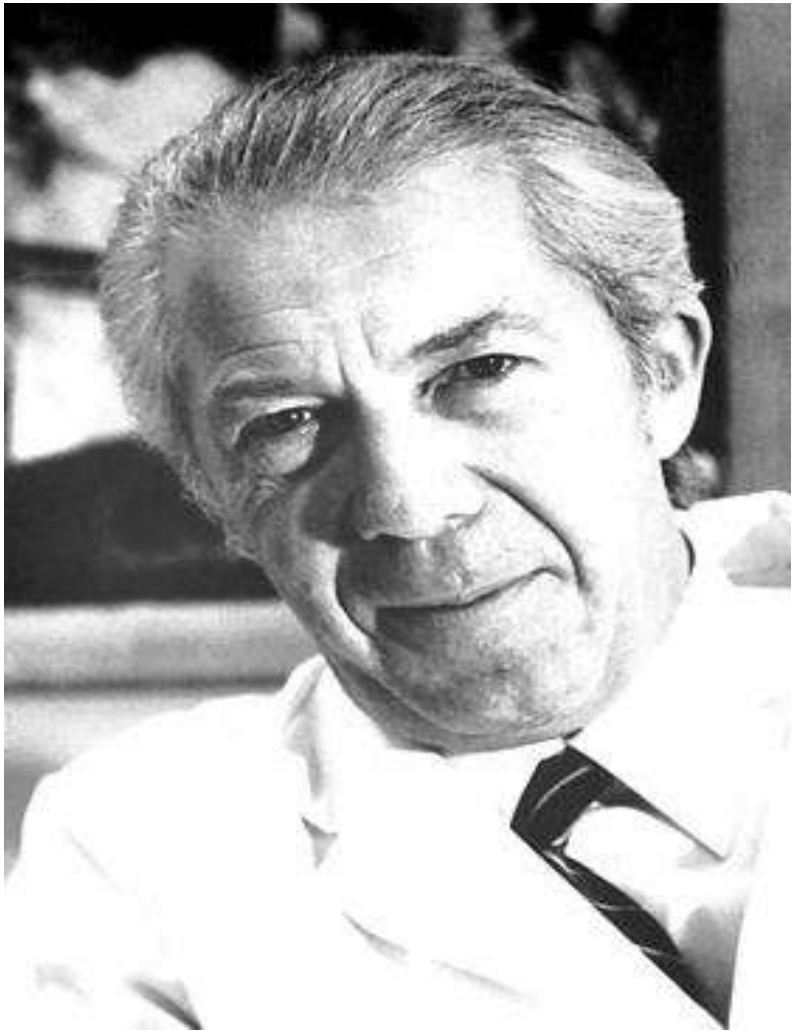
Albert Claude
Prize share: 1/3

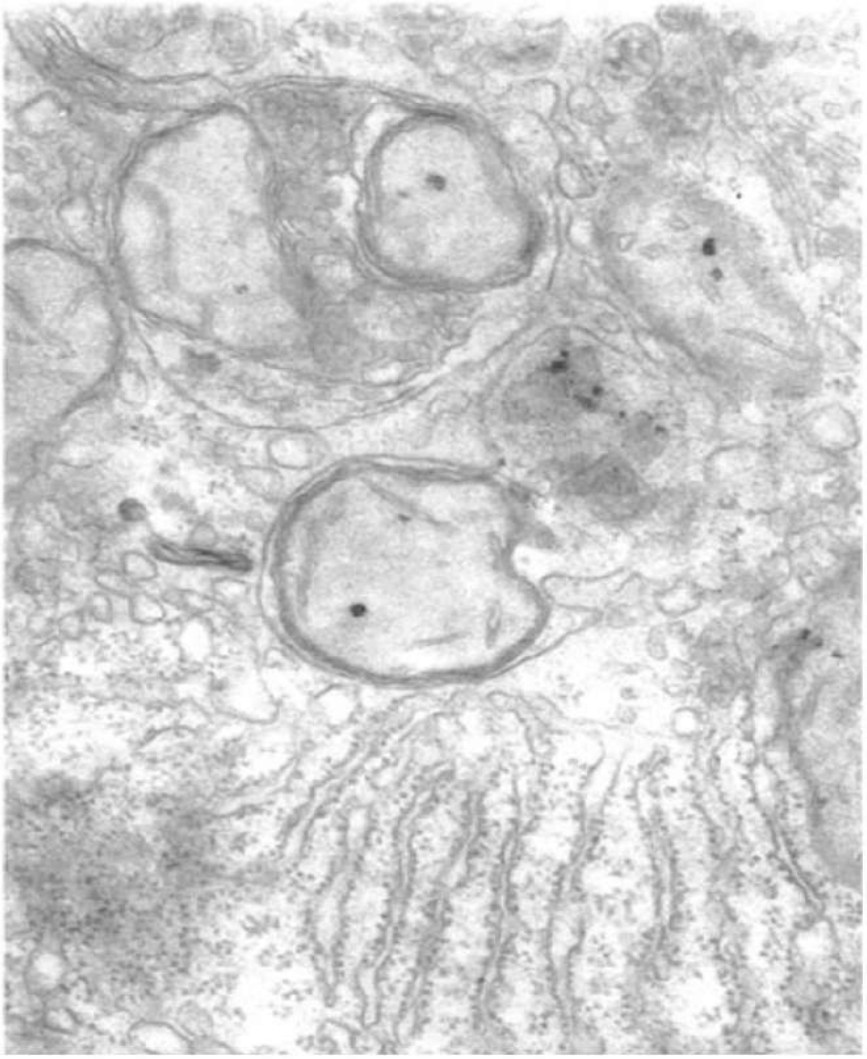
Christian de Duve
Prize share: 1/3

George E. Palade
Prize share: 1/3

The Nobel Prize in Physiology or Medicine 1974 was awarded jointly to Albert Claude, Christian de Duve and George E. Palade *"for their discoveries concerning the structural and functional organization of the cell"*.

de Duve and Autophagy





The Nobel Prize in Chemistry 2004

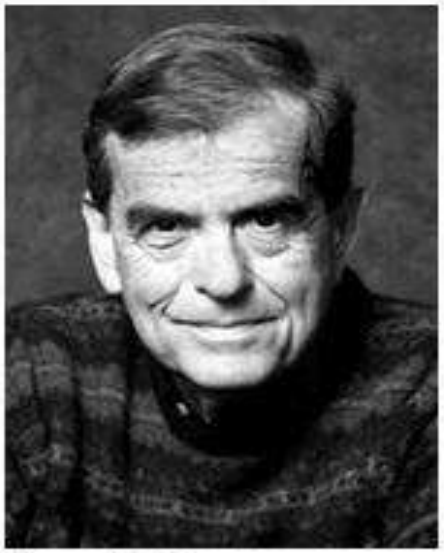


Photo: D. Porges

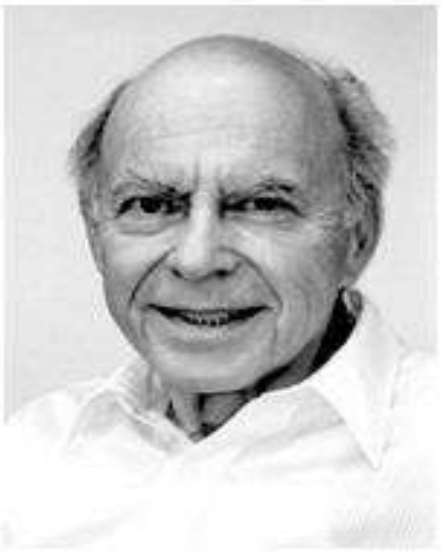
Aaron Ciechanover

Prize share: 1/3

Photo: D. Porges

Avram Hershko

Prize share: 1/3



Irwin Rose

Prize share: 1/3

The Nobel Prize in Chemistry 2004 was awarded jointly to Aaron Ciechanover, Avram Hershko and Irwin Rose *"for the discovery of ubiquitin-mediated protein degradation"*.

NATURE | **NEWS**

Medicine Nobel for research on how cells 'eat themselves'

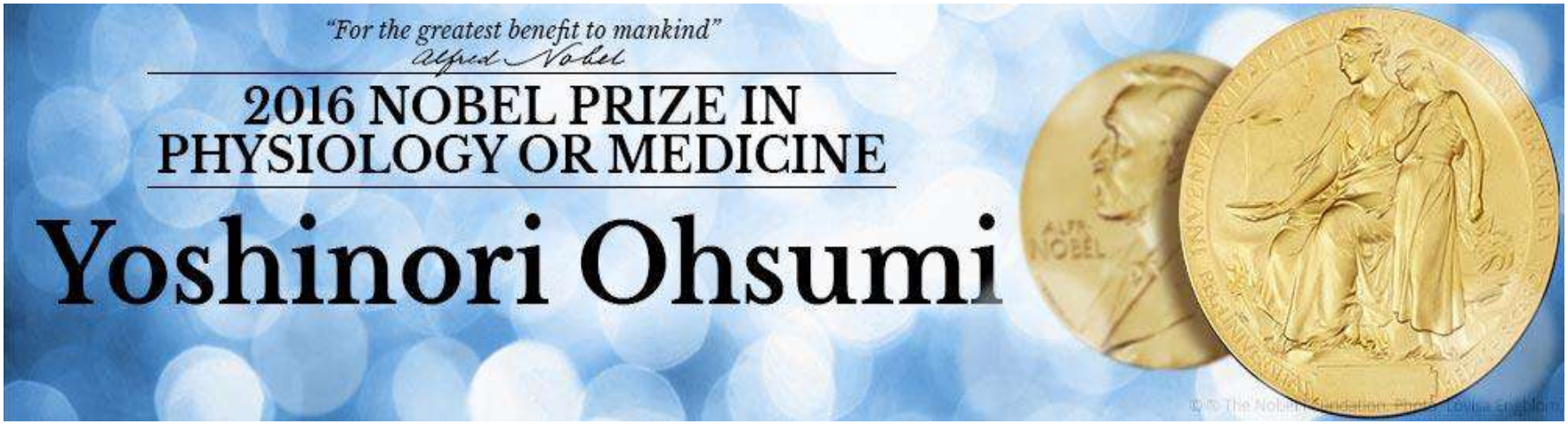
Japanese biologist Yoshinori Ohsumi recognized for work on autophagy.

Richard Van Noorden & **Heidi Ledford**

03 October 2016

Tokyo Institute of Technology/Reuters

Yoshinori Ohsumi, winner of the 2016 Nobel Prize in Physiology or Medicine.



The Nobel Prize in Physiology or Medicine 2016

Photo: Mari Honda
Yoshinori Ohsumi
Prize share: 1/1

The Nobel Prize in Physiology or Medicine 2016 was awarded to Yoshinori Ohsumi *"for his discoveries of mechanisms for autophagy"*.

The Nobel Prize in Physiology or Medicine 2016

Photo: Mari Honda

Yoshinori Ohsumi

Prize share: 1/1

The Nobel Prize in Physiology or Medicine 2016 was awarded to Yoshinori Ohsumi *"for his discoveries of mechanisms for autophagy"*.

Yoshinori Ohsumi was born 1945 in Fukuoka, Japan. He received a Ph.D. from University of Tokyo in 1974. After spending three years at Rockefeller University, New York, USA, he returned to the University of Tokyo where he established his research group in 1988. He is since 2009 a professor at the Tokyo Institute of Technology.

Ohsumi Key Publication

Key publications:

Takeshige, K., Baba, M., Tsuboi, S., Noda, T. and Ohsumi, Y. (1992). Autophagy in yeast demonstrated with proteinase-deficient mutants and conditions for its induction. Journal of Cell Biology 119, 301-311

Tsukada, M. and Ohsumi, Y. (1993). Isolation and characterization of autophagy-defective mutants of *Saccharomyces cervisiae*. FEBS Letters 333, 169-174

Mizushima, N., Noda, T., Yoshimori, T., Tanaka, Y., Ishii, T., George, M.D., Klionsky, D.J., Ohsumi, M. and Ohsumi, Y. (1998). A protein conjugation system essential for autophagy. Nature 395, 395-398

Ichimura, Y., Kirisako T., Takao, T., Satomi, Y., Shimonishi, Y., Ishihara, N., Mizushima, N., Tanida, I., Kominami, E., Ohsumi, M., Noda, T. and Ohsumi, Y. (2000). A ubiquitin-like system mediates protein lipidation. Nature, 408, 488-492

Autophagy in Yeast

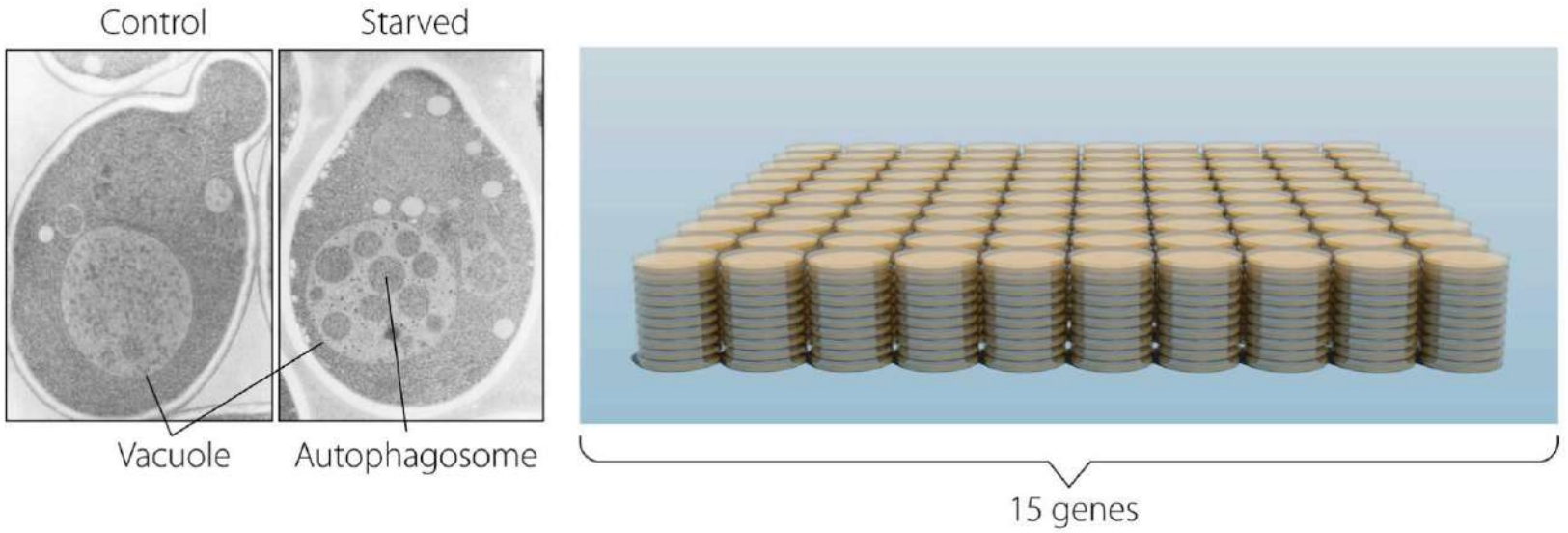
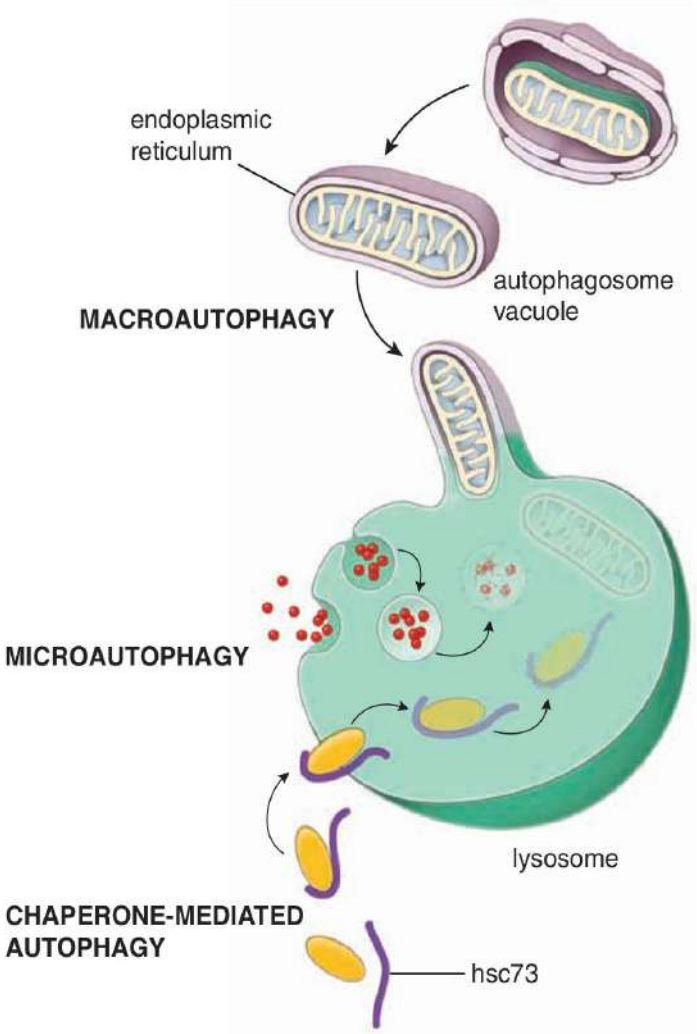


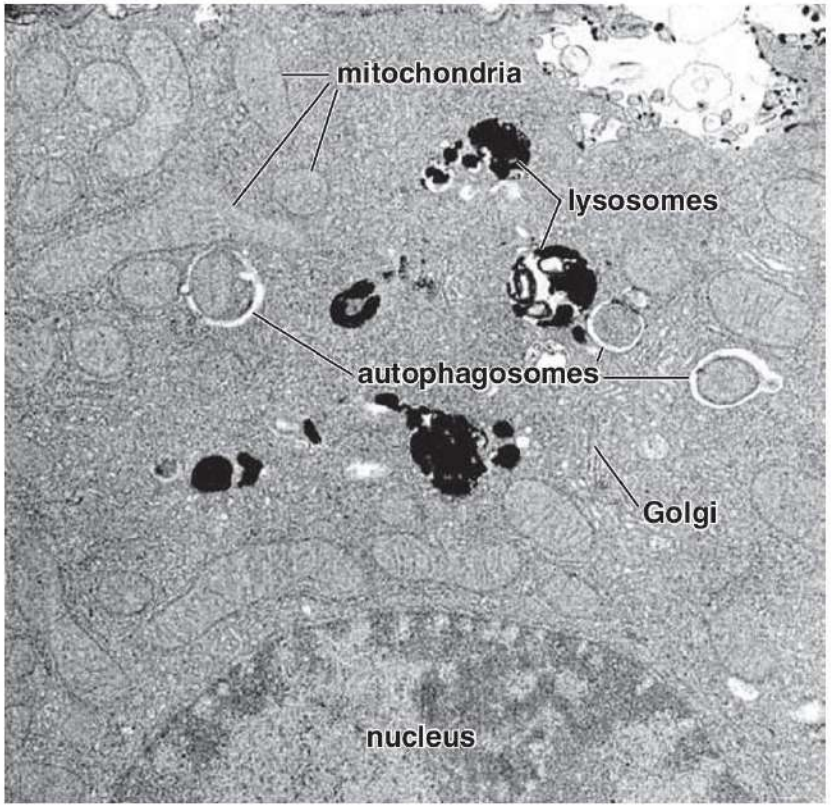
Figure 2: In yeast (left panel) a large compartment called the *vacuole* corresponds to the lysosome in mammalian cells. Ohsumi generated yeast lacking vacuolar degradation enzymes. When these yeast cells were starved, autophagosomes rapidly accumulated in the vacuole (middle panel). His experiment demonstrated that autophagy exists in yeast. As a next step, Ohsumi studied thousands of yeast mutants (right panel) and identified 15 genes that are essential for autophagy.

Type of Autophagy

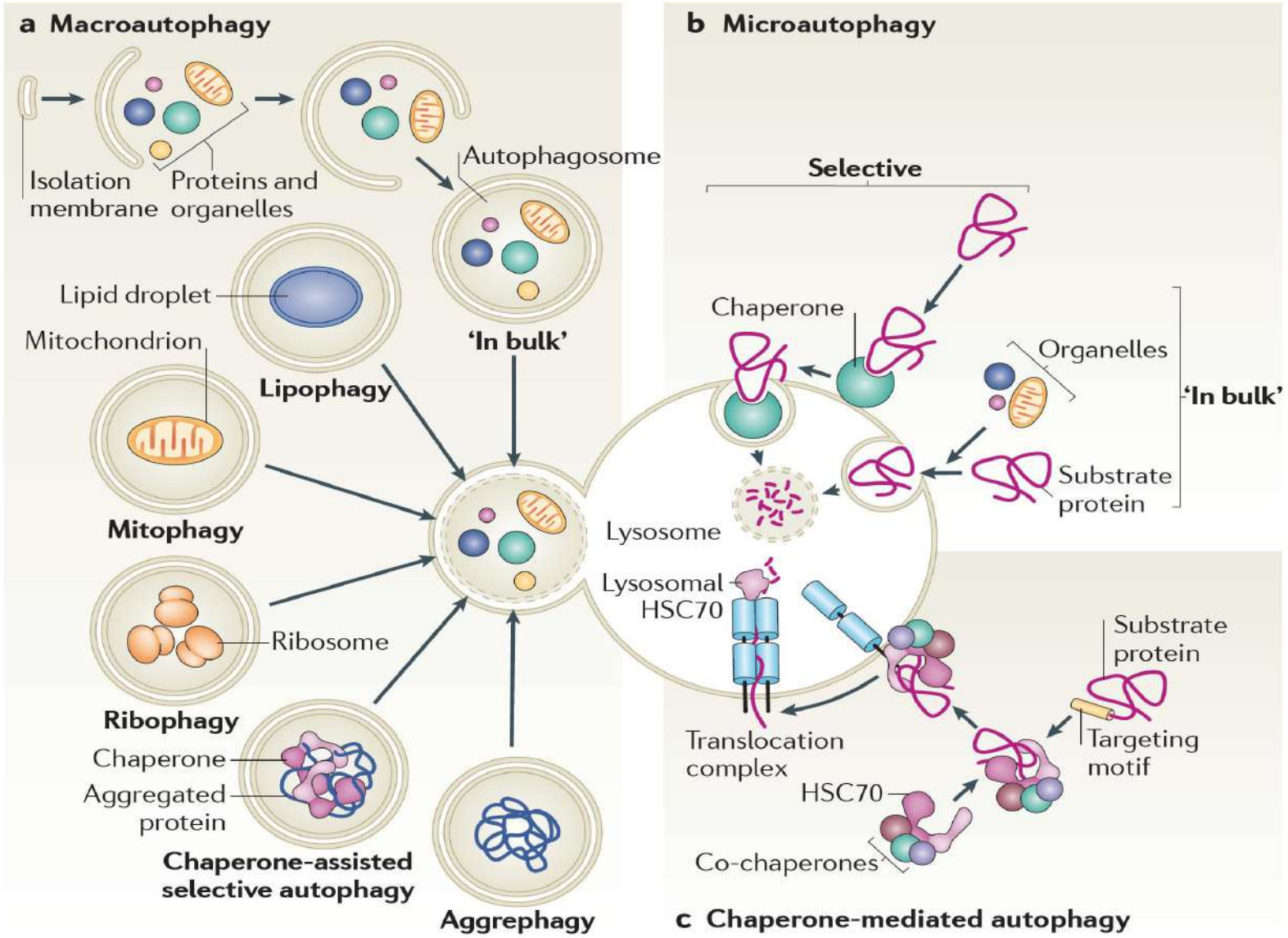
- **Autophagy** is a process in which a cell eats its own contents (Greek: auto, self; phagy, eating).
- It involves the delivery of cytoplasmic materials to the lysosome for degradation. Autophagy can be categorized into **three types**:
- **Chaperone-mediated autophagy** (direct translocation across the lysosomal membrane by chaperone proteins)
- **Microautophagy** (inward invagination of lysosomal membrane for delivery)
- **Macroautophagy** (hereafter referred to as **autophagy**), the major form of autophagy involving the sequestration and transportation of portions of cytosol in a double-membrane bound autophagic vacuole (**autophagosome**)

Macroautophagy, Microautophagy and Chaperone-Mediated Autophagy

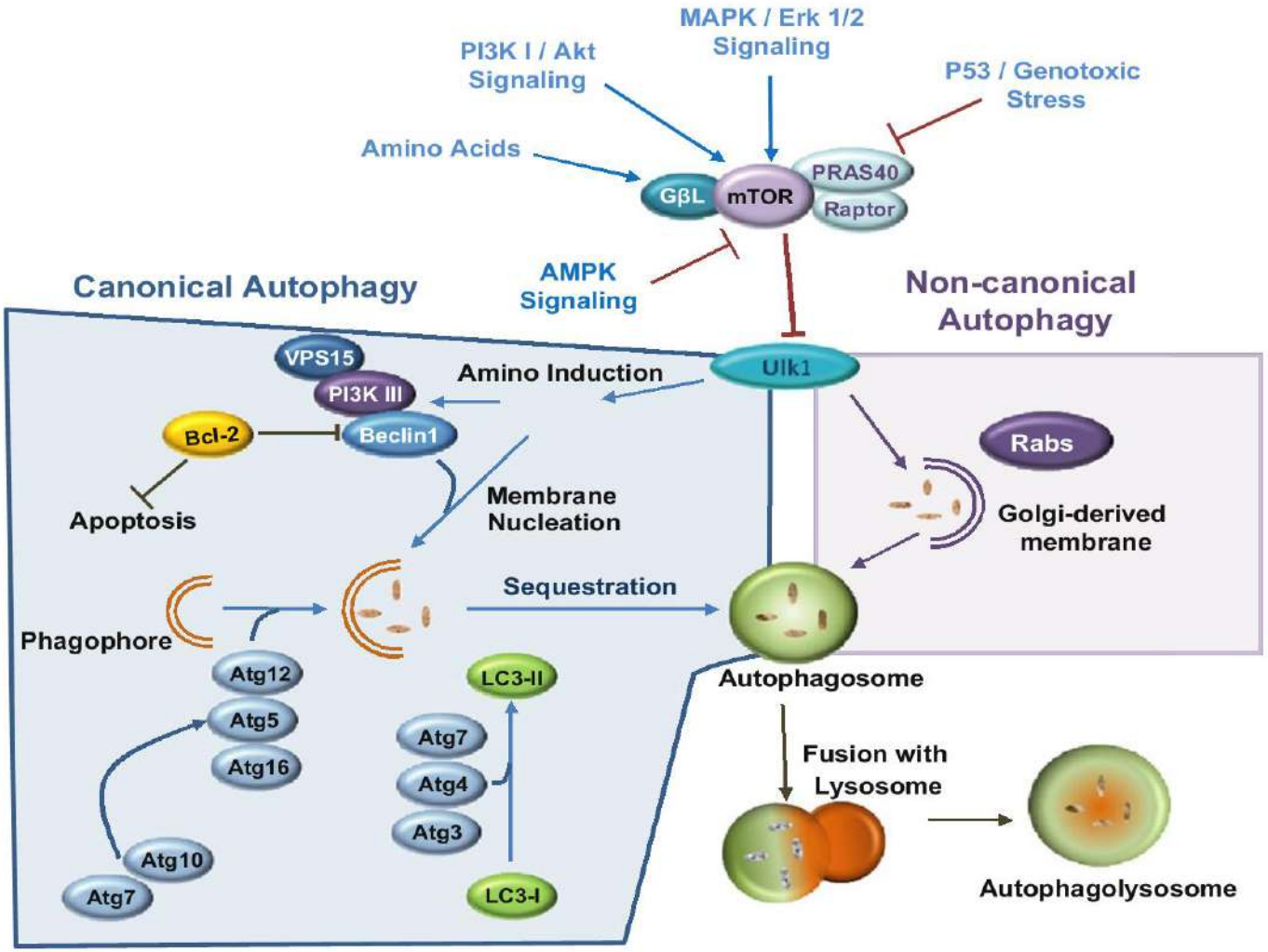




Distinct types of autophagy



Overview Macroautophagy



Selective Autophagy

- There are specific types of autophagy in which specific proteins or cell organelles are delivered to the autophagosome/lysosome for degradation. These autophagy types are enu-merated below.
- 1. **Aggrephagy** : selective degradation of cellular aggregates, especially proteins (Overbye et al ., 2007)
- 2. **Axophagy**: degradation of axons (Yue, 2007)
- 3. **Glyophagy**: degradation of glycogen particles (Jiang et al ., 2011)
- 4. **Lipophagy**: selective degradation of lipid droplets (Singh et al ., 2009)
- 5. **Mitophagy**: selective degradation of mitochondria (Kanki, 2010; Coto-Montes et al ., 2012)
- 6. **Nucleophagy**: selective degradation of parts of the nucleus (Mijaljica et al ., 2010)
- 7. **Pexophagy**: selective degeneration of peroxisomes; dependent on PEX3 and PEX4 proteins (Klionsky, 1997)
- 8. **Reticulophagy** : selective degradation of rough endoplasmic reticulum to balance its expansion by unfolded proteins (Klionsky et al ., 2007)
- 9. **Ribophagy**: selective degradation of the 60S ribosomal subunit (Kraft et al ., 2008)
- 10. **Xenophagy**: defense against intracellular pathogens (Shpilka and Elazar, 2012)
- 11. **Zymophagy** : degradation of zymogen granules (Vaccaro, 2012).

Autophagy in *Guyton* and *Hall*, 2016

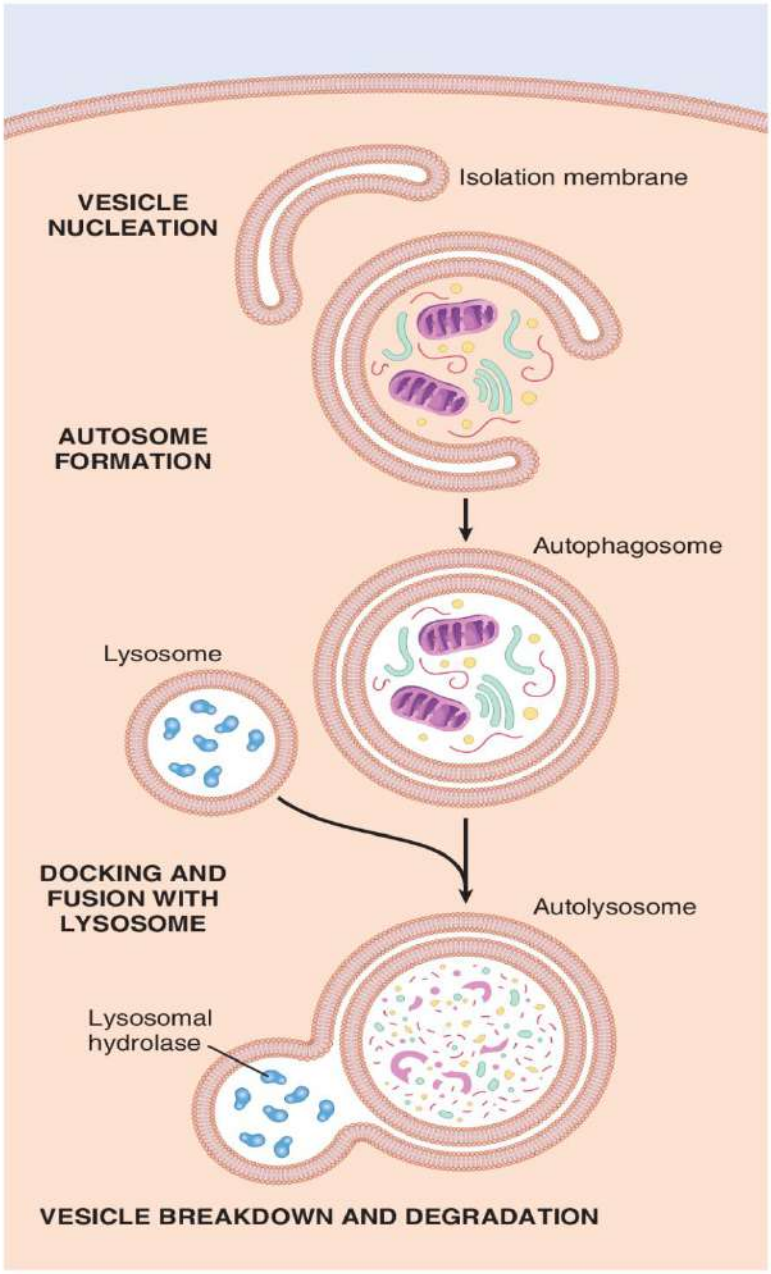


Figure 2-13. Schematic diagram of autophagy steps.

Recycling of Cell Organelles—Autophagy. Lysosomes play a key role in the process of *autophagy*, which literally means "to eat oneself." Autophagy is a housekeeping process by which obsolete organelles and large protein aggregates are degraded and recycled (**Figure 2-13**). Worn-out cell organelles are transferred to lysosomes by double membrane structures called *autophagosomes* that are formed in the cytosol. Invagination of the lysosomal membrane and the formation of vesicles provides another pathway for cytosolic structures to be transported into the lumen of the lysosomes. Once inside the lysosomes, the organelles are digested and the nutrients are reused by the cell. Autophagy contributes to the routine turnover of cytoplasmic components and is a key mechanism for tissue development, for cell survival when nutrients are scarce, and for maintaining homeostasis. In liver cells, for example, the average mitochondrion normally has a life span of only about 10 days before it is destroyed.

Autophagy Mechanism

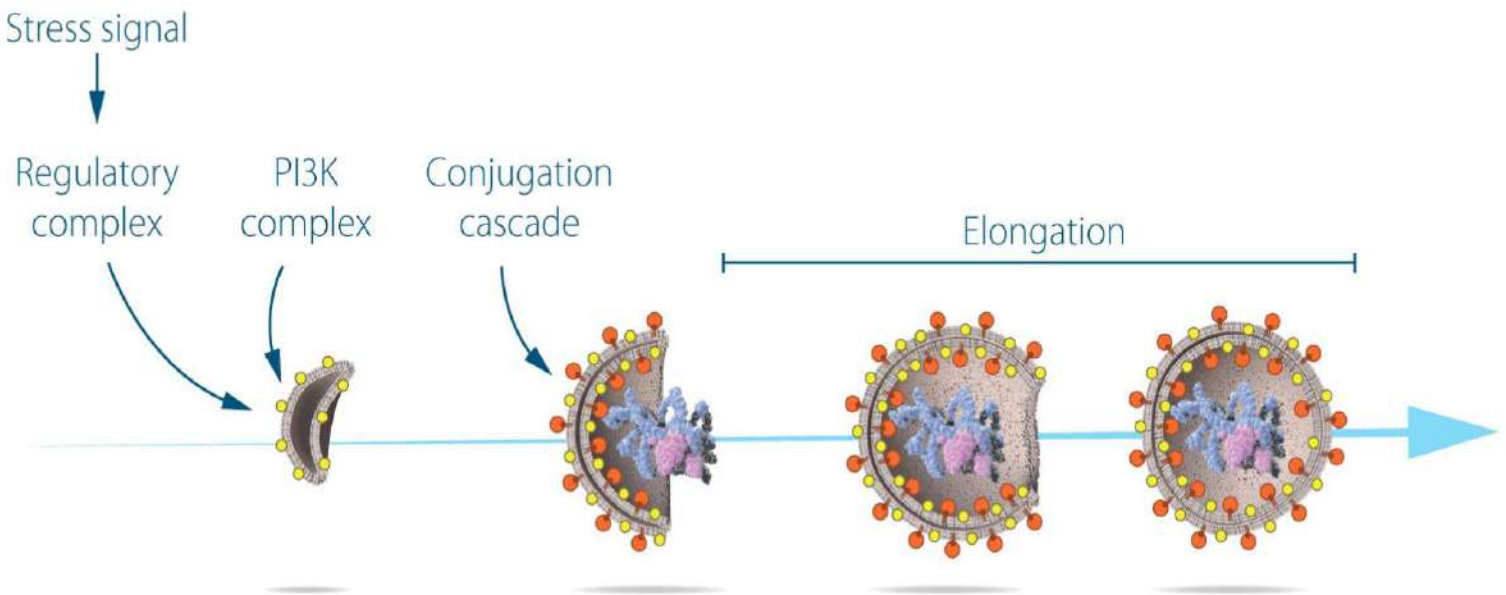


Figure 3: Ohsumi studied the function of the proteins encoded by key autophagy genes. He delineated how stress signals initiate autophagy and the mechanism by which proteins and protein complexes promote distinct stages of autophagosome formation.

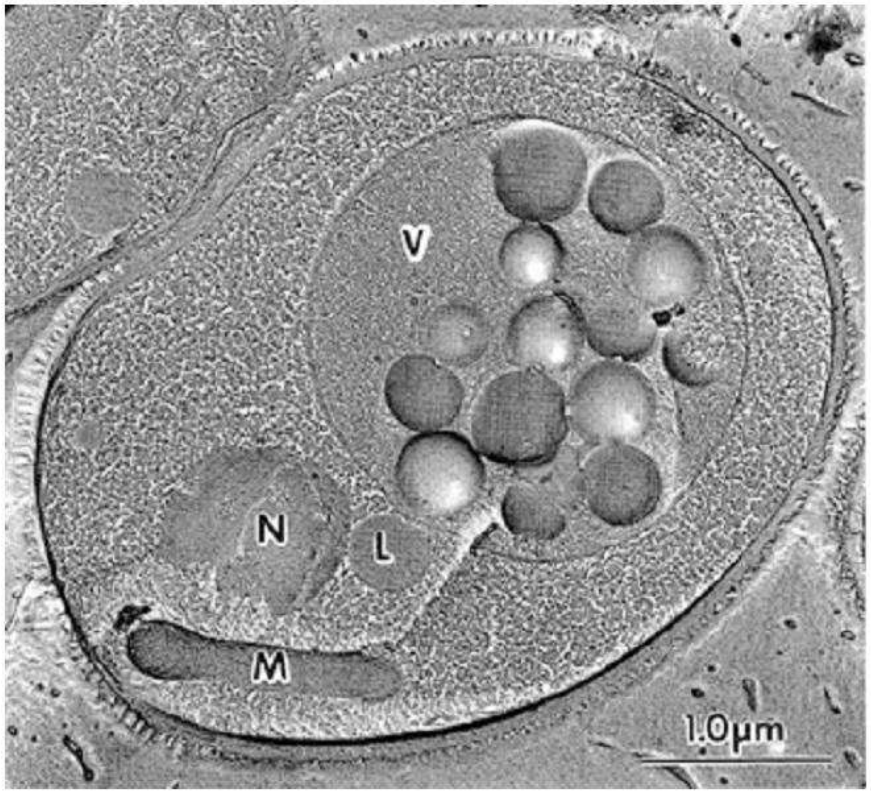


Fig. 2.2 Autophagic bodies in yeast. Autophagic bodies accumulating in the vacuole of a yeast cell that has been starved of nitrogen for 3 h and contains a mutation inactivating lysosomal/vacuolar function. Under these conditions, autophagosomes fuse with the vacuole but are not destroyed. This assay allowed identification of autophagy mutants in yeast by the work of Ohsumi and colleagues. Image was produced by rapid freezing of unfixed cells followed by freeze etching. This figure first appeared in Baba et al. (1995). Reproduced with permission of Japan Society for Cell Biology

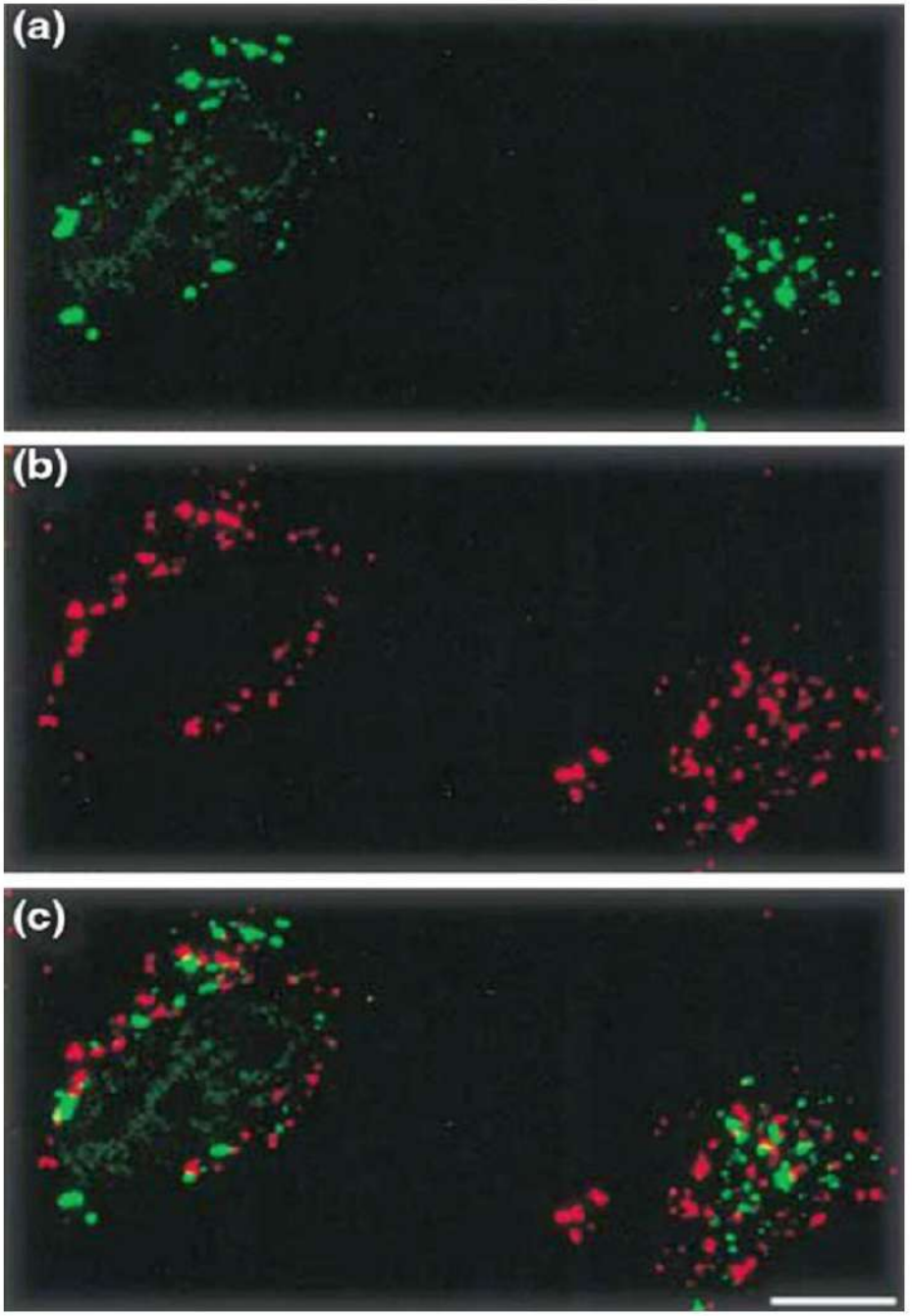
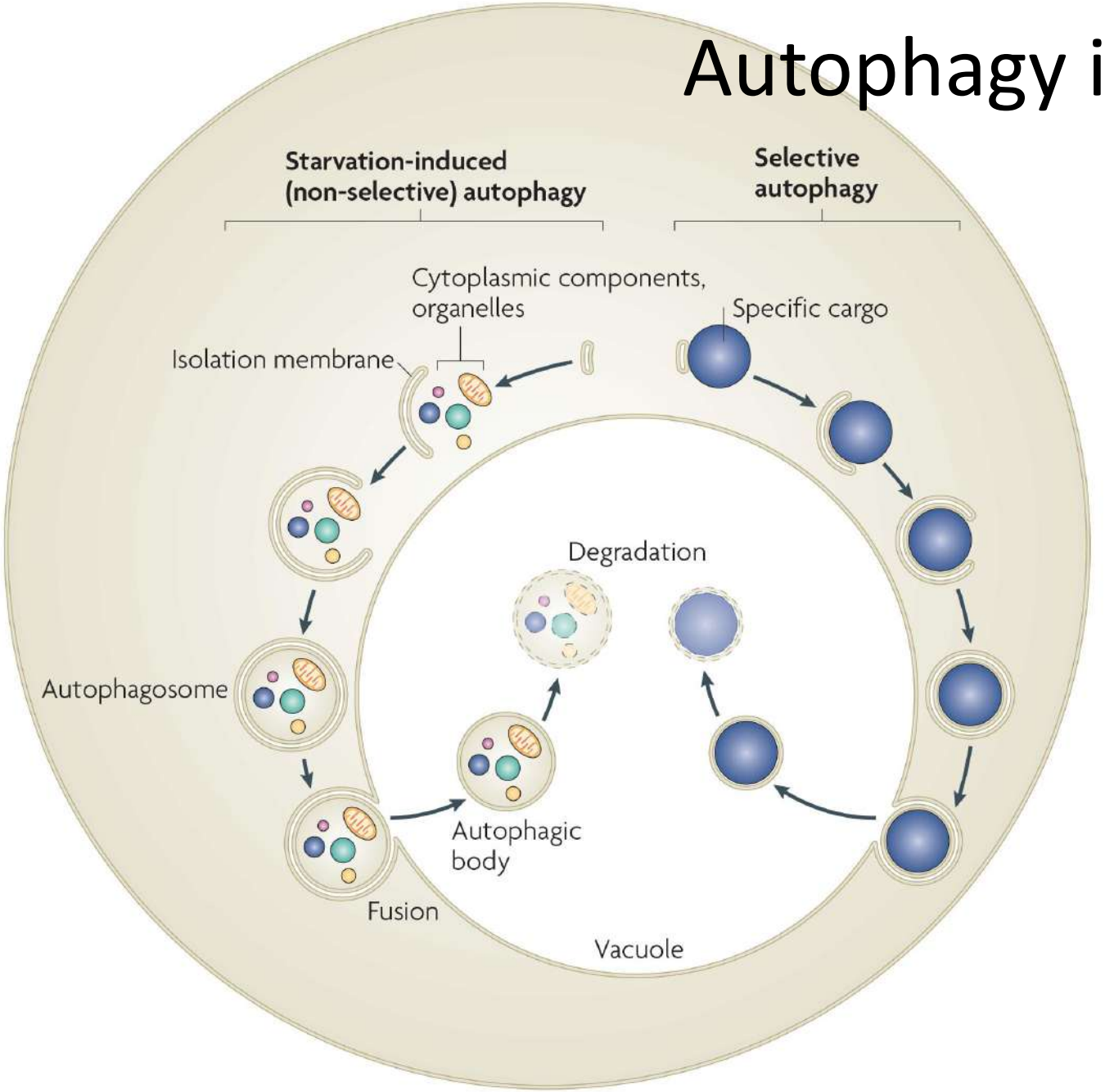
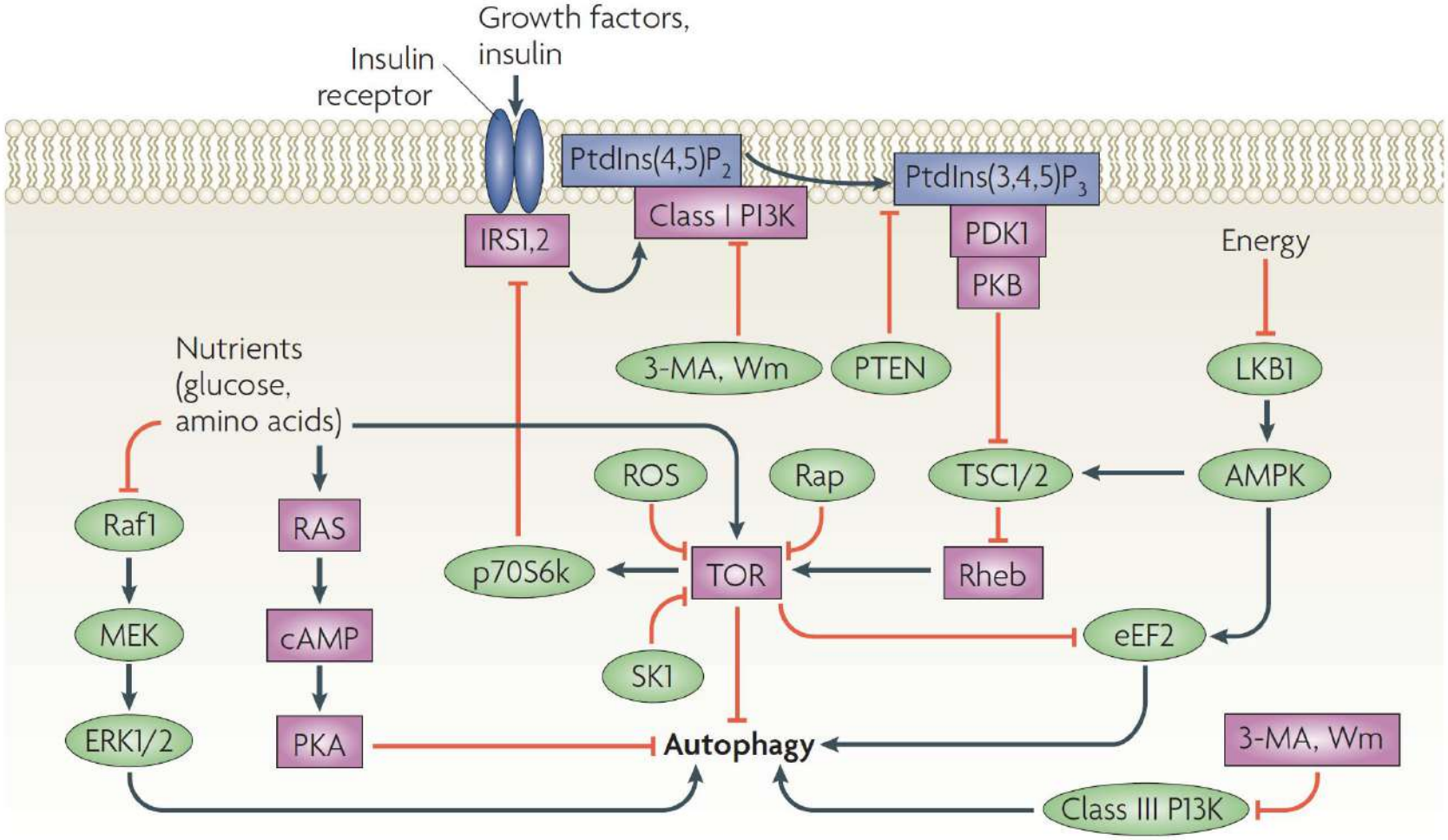


Fig. 2.3 Expression of GFP-LC3 in mammalian cells. This image showed for the first time the localization of mammalian LC3 tagged with GFP and expressed in mammalian cells. The cells were also treated with bafilomycin A1 to enhance accumulation of autophagosomes before they fuse with lysosomes (stained here for Lamp-1 in the red channel). This figure first appeared in Kabeya (2000). Reproduced with permission of John Wiley and Sons

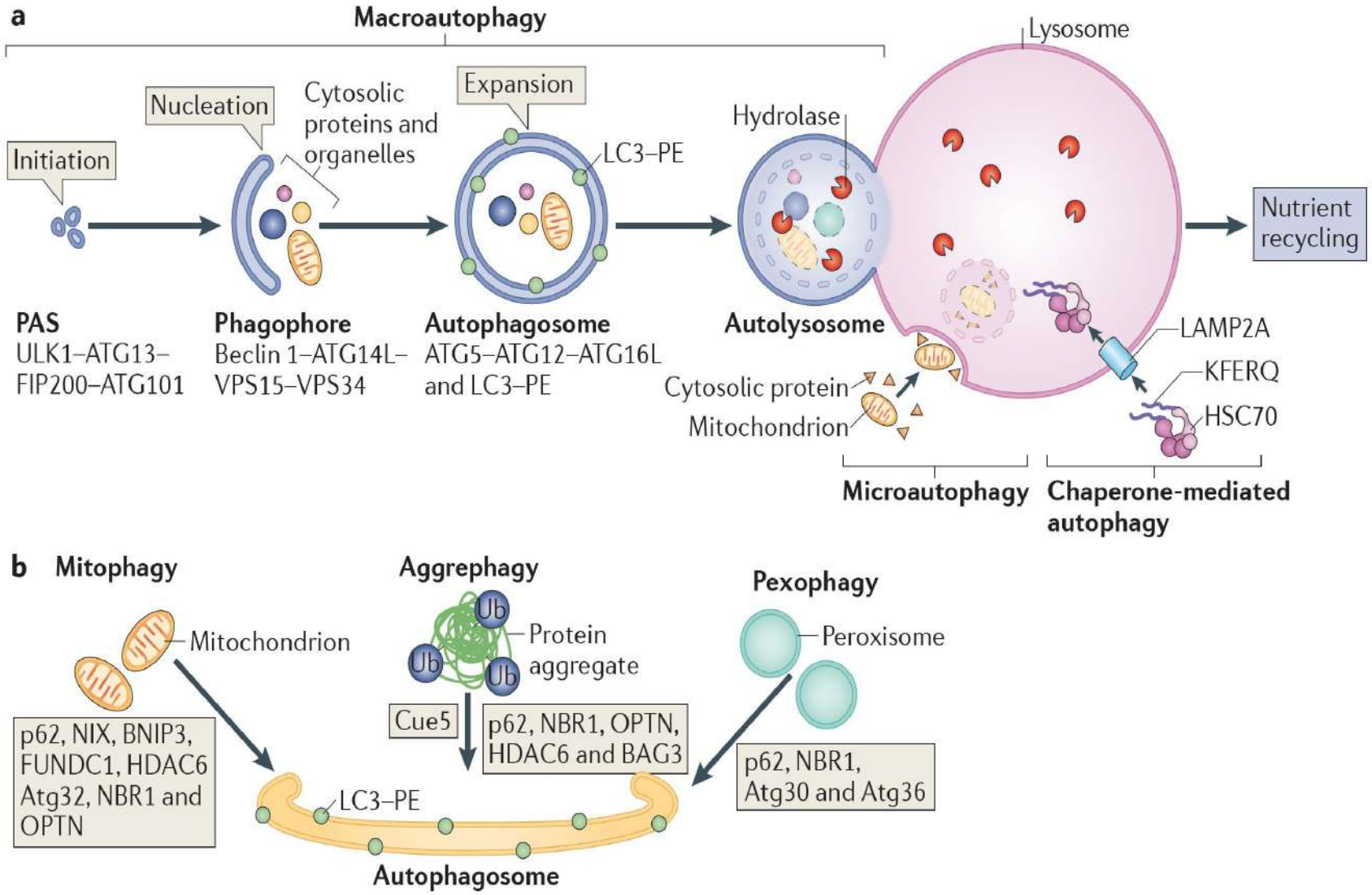
Autophagy in yeast



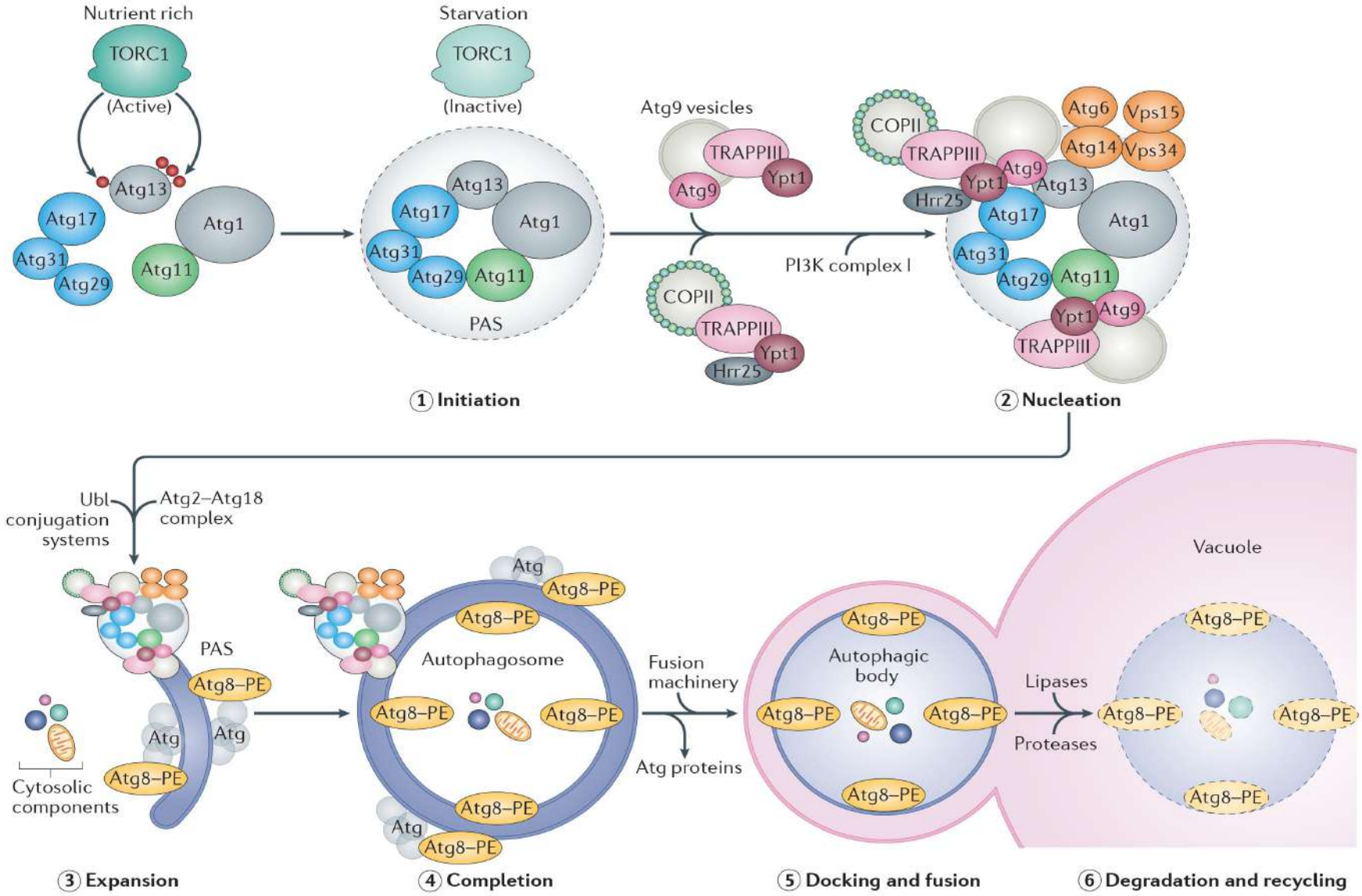
Regulation of autophagy in mammalian cells



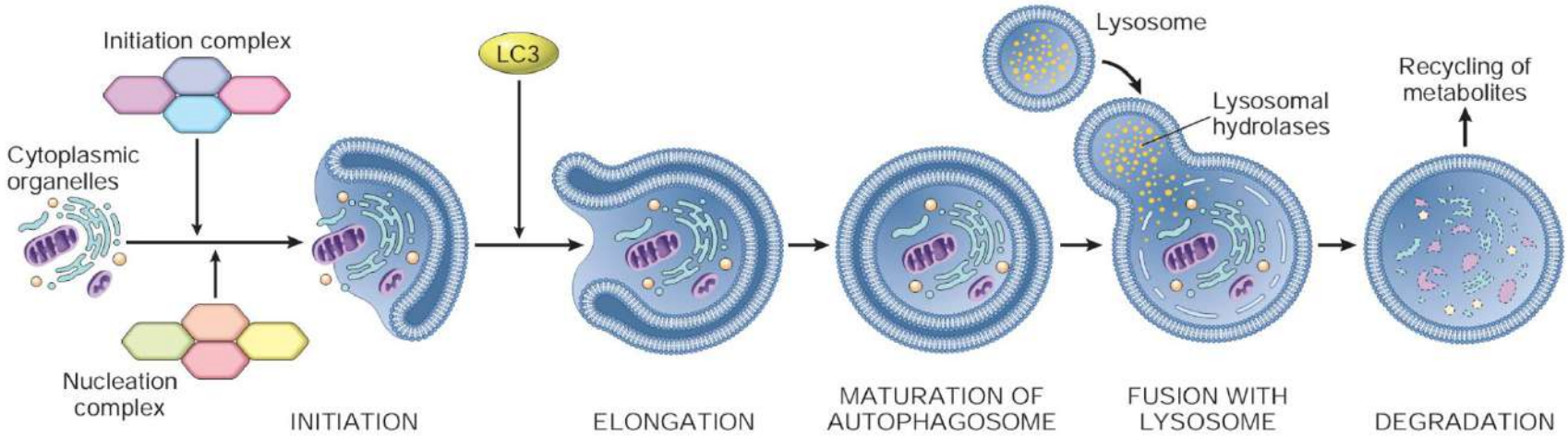
Overview of mammalian autophagy pathways



Steps in autophagy



Phases of The Autophagic Pathway



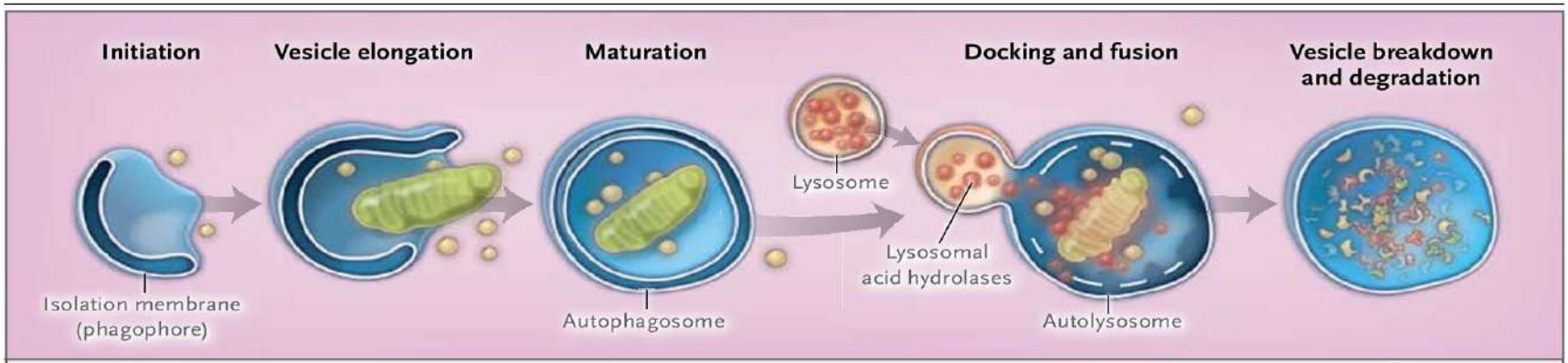


Figure 1. Phases of the Autophagic Pathway.

The autophagic pathway proceeds through several phases, including initiation (formation of a preautophagosomal structure leading to an isolation membrane, or phagophore), vesicle elongation, autophagosome maturation and cargo sequestration, and autophagosome–lysosome fusion. In the final stage, autophagosomal contents are degraded by lysosomal acid hydrolases and the contents of the autolysosome are released for metabolic recycling.

Table 1. Major Mammalian Autophagic Proteins.

Autophagic Protein	Gene	Yeast Homologue	Function in Autophagic Regulation
Unc-51–like kinase 1	*ULK1*	Atg1	Interfaces with mTORC1; major initiator of the regulation of autophagy
ATG3	*ATG3*	Atg3	Ubiquitin (E2)-like enzyme; acts as ligase for ATG8 and ATG12, catalyzes the conjugation of ATG8-like proteins to phosphatidylethanolamine (PE)
ATG4B	*ATG4B*	Atg4b	ATG8 cysteine peptidase; converts pro-LC3 (ATG8) to LC3-I, delipidates autophagosomal LC3-II
ATG5	*ATG5*	Atg5	Forms a complex with ATG12; assists in autophagosomal elongation
Beclin 1	*BECN1*	Atg6/Vps30	BCL-2–binding protein; forms a regulatory complex with class III phosphatidylinositol-3-kinase (VPS34)
ATG7	*ATG7*	Atg7	E1 ubiquitin conjugase–like enzyme; facilitates conjugation of ATG8 proteins to PE, acts as an E1 enzyme for ATG12 conjugation to ATG5 and ATG3
Microtubule-associated protein 1 light chain 3B	*MAP1LC3B*	Atg8	Ubiquitin-like modifier; stably associates with autophagosomal membrane
ATG9A	*ATG9A*	Atg9	Associates with preautophagosomal structure in yeast, assists in autophagosomal assembly
ATG10	*ATG10*	Atg10	E2 ubiquitin ligase-like enzyme; catalyzes the conjugation of ATG5 and ATG12
ATG12	*ATG12*	Atg12	Forms a complex with ATG5; assists in autophagosomal elongation
ATG14L	*ATG14*	Atg14	Autophagy-specific subunit of Beclin 1–class III phosphatidylinositol complex
ATG16L1	*ATG16*	Atg16	Associates with isolation membrane in complex with ATG5–ATG12; assists in autophagosomal elongation

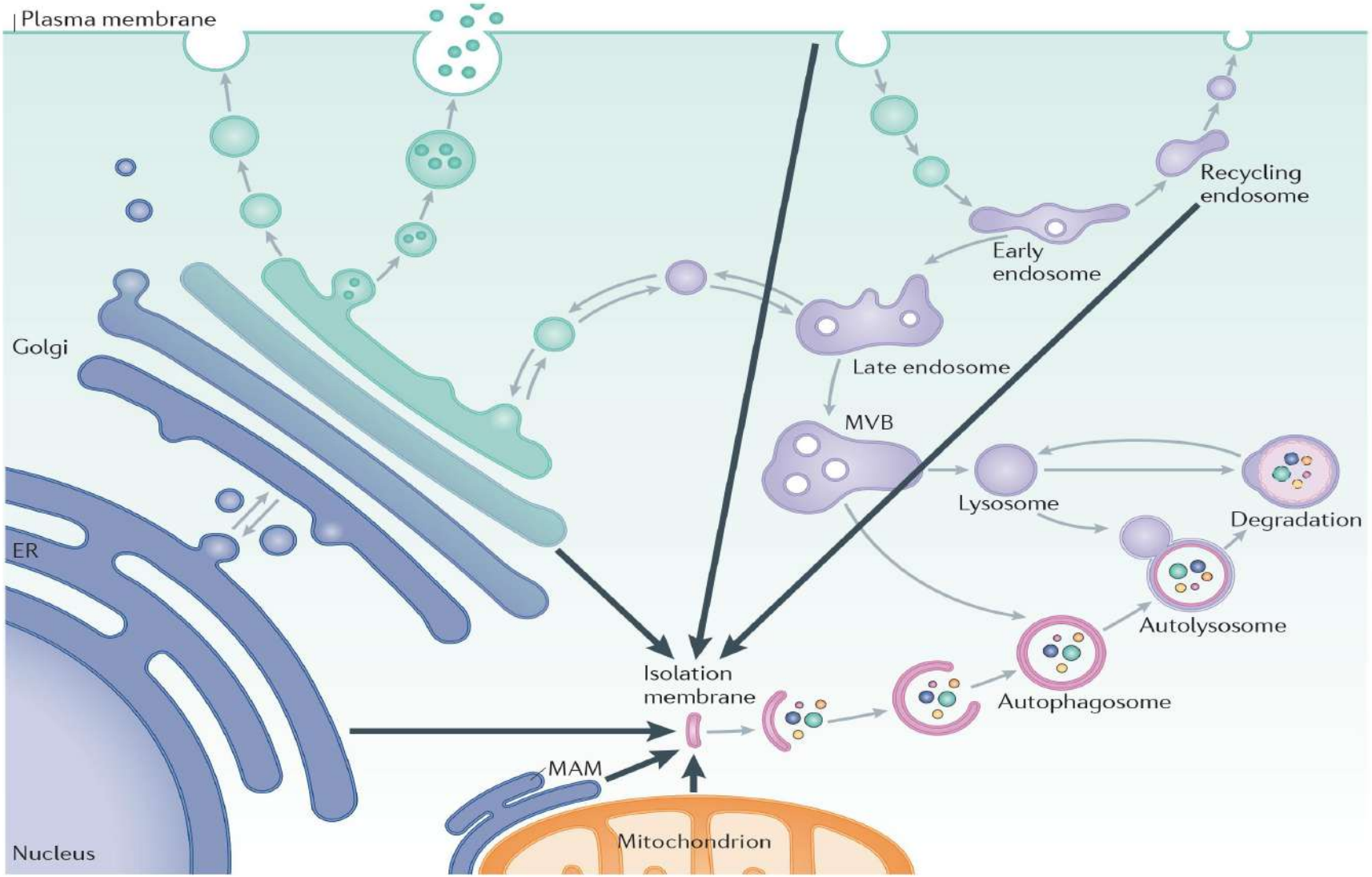
Molecular Regulation of Autophagy

- The mammalian (or mechanistic) target of rapamycin (mTOR), which resides in a macromolecular complex, **mTORC1** inhibit UNC-51–like kinase 1 (ULK1), ATG13, ATG101, and FIP200 complexs (**initition autophagy**).
- **The Beclin 1–interacting complexs** include Beclin 1, BCL-2 family proteins (which inhibit autophagy), the class III phosphatidylinositol 3-kinase (VPS34), and ATG14L (required for autophagy) activated **phosphatidylinositol-3-phosphate**, which promotes autophagosomal membrane nucleation.
- Autophagosomal elongation requires two ubiquitin-like conjugation systems: **the ATG5–ATG12** conjugation system and the microtubule-associated protein **light chain 3 (LC3–ATG8)** conjugation system.

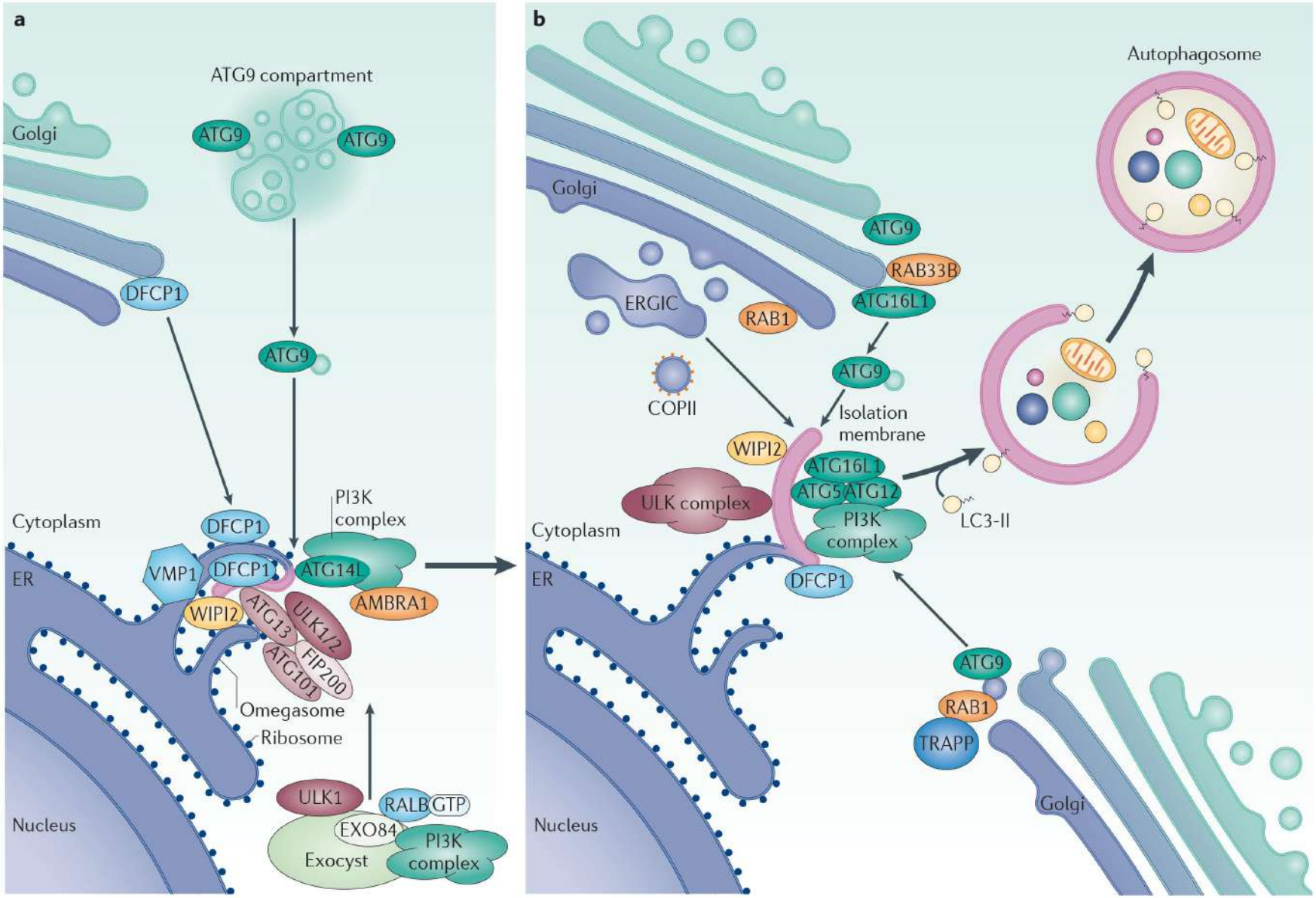
Function of Autophagy

- Autophagy participates in the turnover of mitochondria (through the selective process of **mitophagy**) and other organelles.
- Autophagy is involved in the clearance of polyubiquitinated protein aggregates (i.e., **aggrephagy)**.
- Autophagy has also been implicated as a regulator of lipid metabolism (i.e., **lipophagy**)
- Autophagy primarily acts as a protective mechanism that may prevent cell death (BCL2).
- Autophagy assists in the immune response by degrading intracellular bacte-ria and viruses (i.e., **xenophagy**)
- Autophagy can also play crucial roles **in adaptive immune responses** such as antigen presentation and lymphocyte development

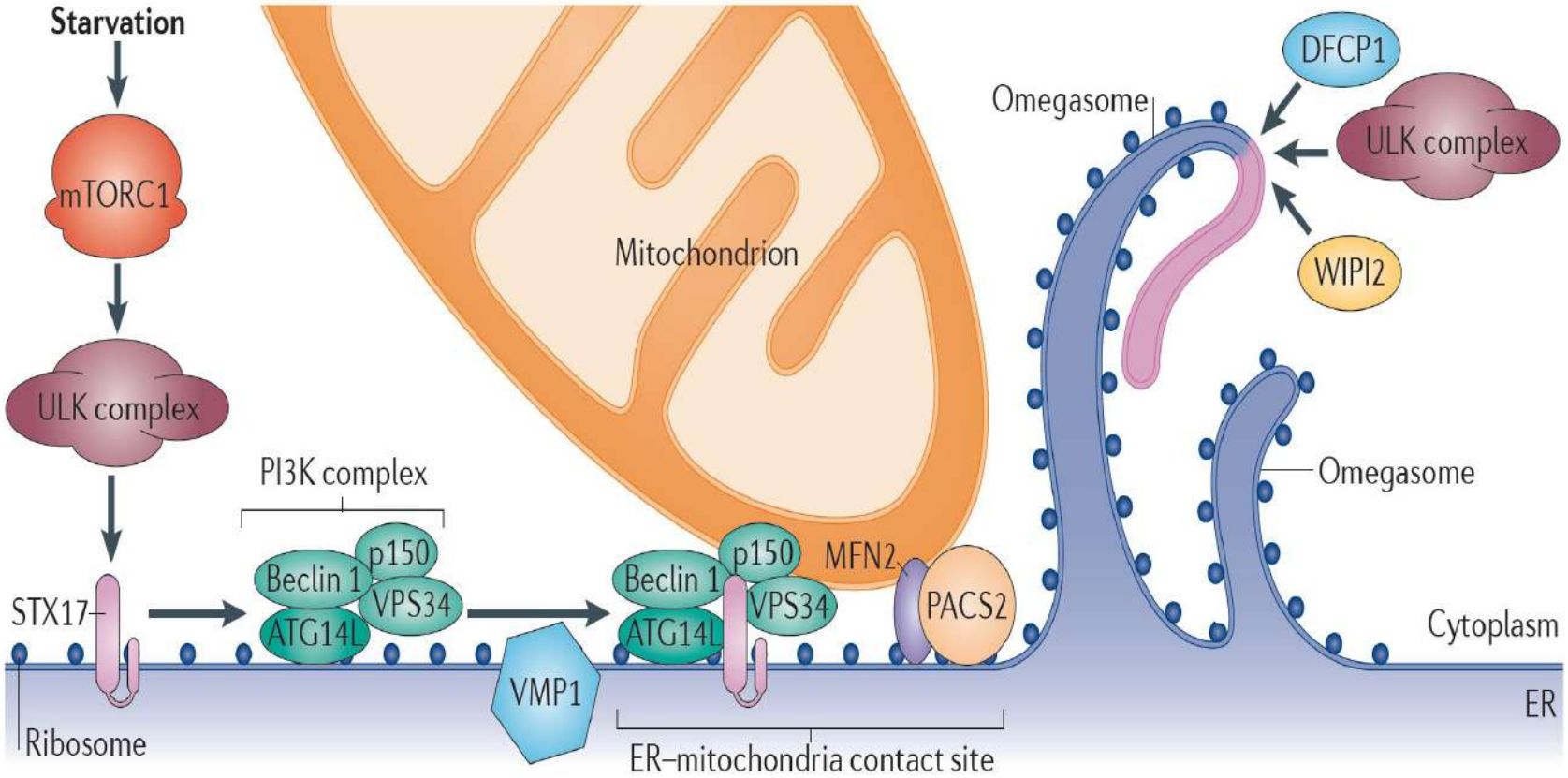
Overview of the autophagic pathway and organelles that might contribute to autophagosome biogenesis.



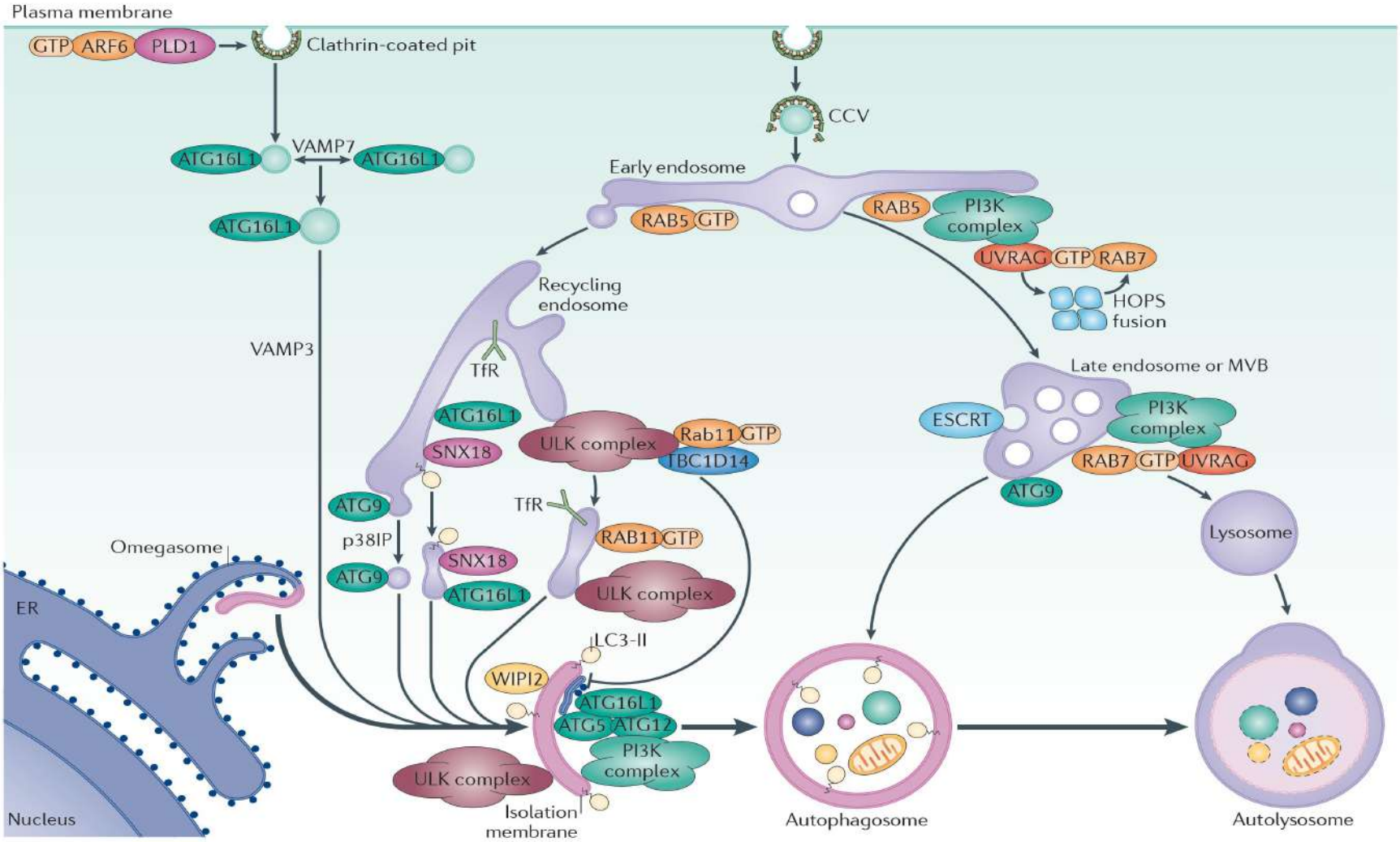
Formation and expansion of the isolation membrane



Autophagosome formation at the ER–mitochondria contact site



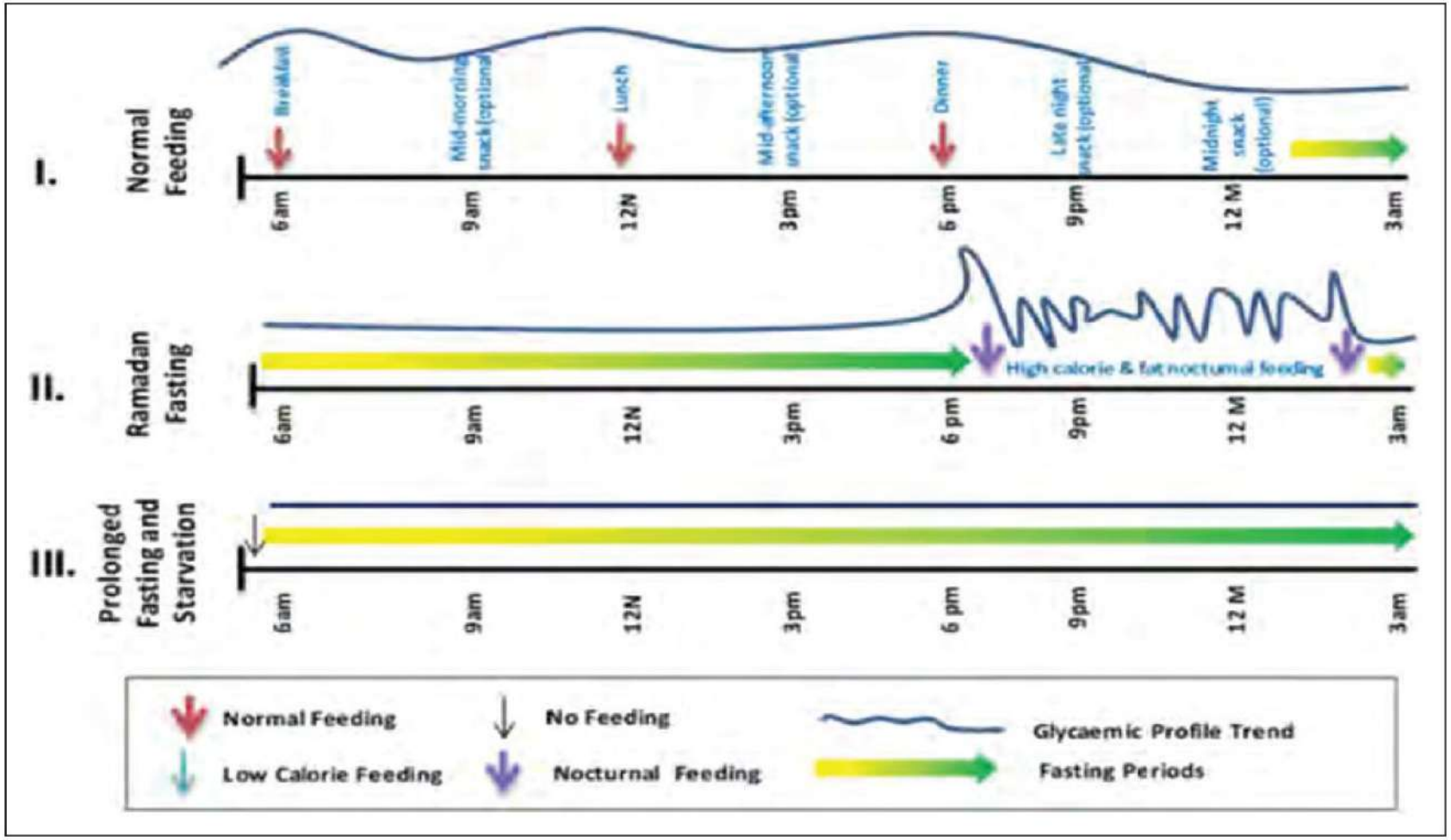
Endocytic contributions to the growing Autophagosome



Rahasia Sahur

- Rasulullah SAW bersabda, "Sahurlah, karena sesunggguhnya di dalam sahur itu terdapat keberkahan.”
- Rasulullah SAW bersabda,'Perbedaan antara puasa kita dan puasa Ahlikitab adalah makan sahur'.
- Sunan Ad-Darimi Hadits no 1696 dan 1697

Eating Habits and Energy Intake on RF



Rahasia Berbuka Puasa

- Nabi SAW bersabda, "Jika salah seorang di antara kalian berbuka, maka ia sebaiknya berbuka dengan kurma. Jika dia tidak menemukon kurma, moka ia sebaiknya berbuka dengan air bersih, karena sesungguhnya air itu suci."
- Sunan Ad-Darimi hadits no 1701

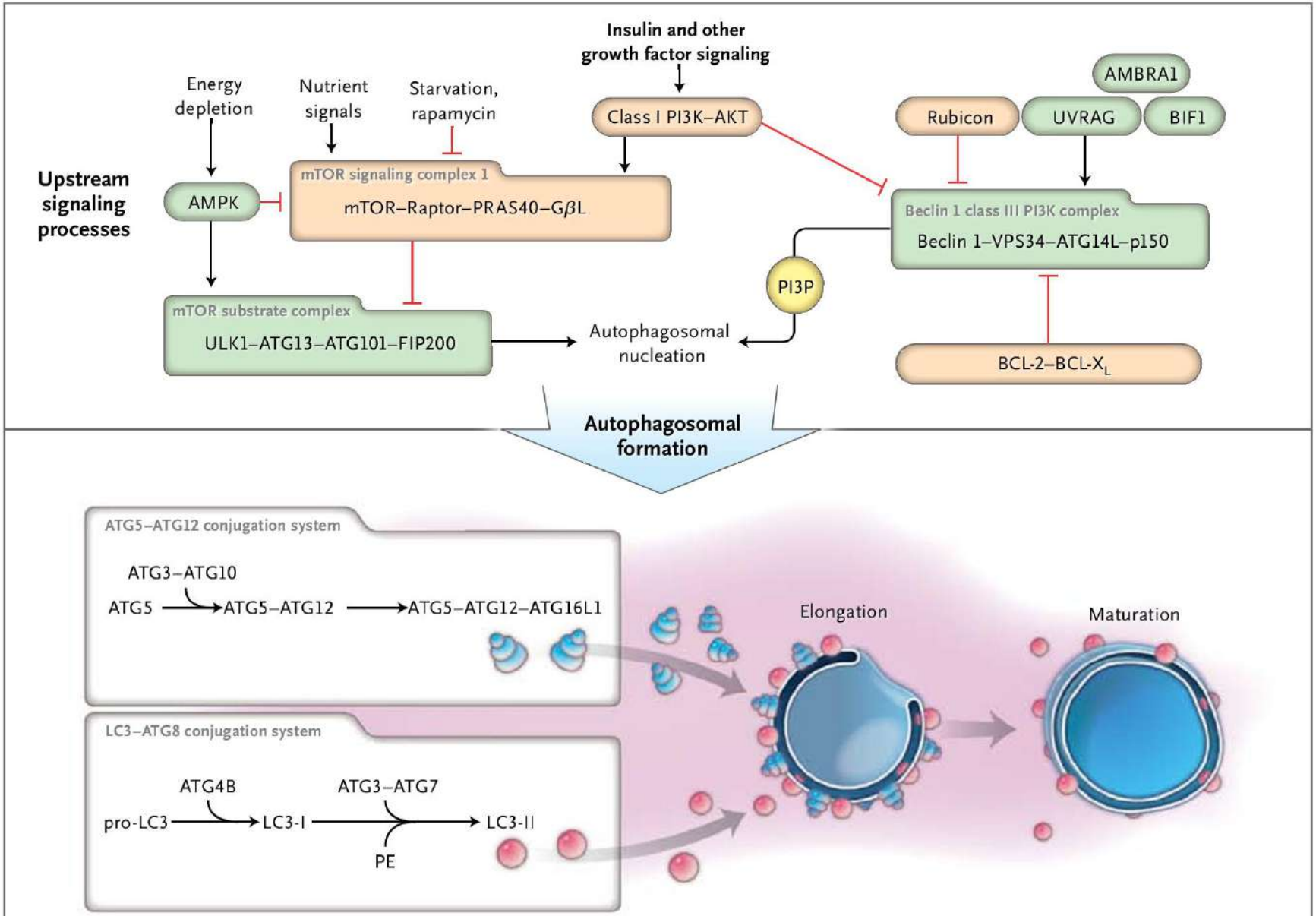
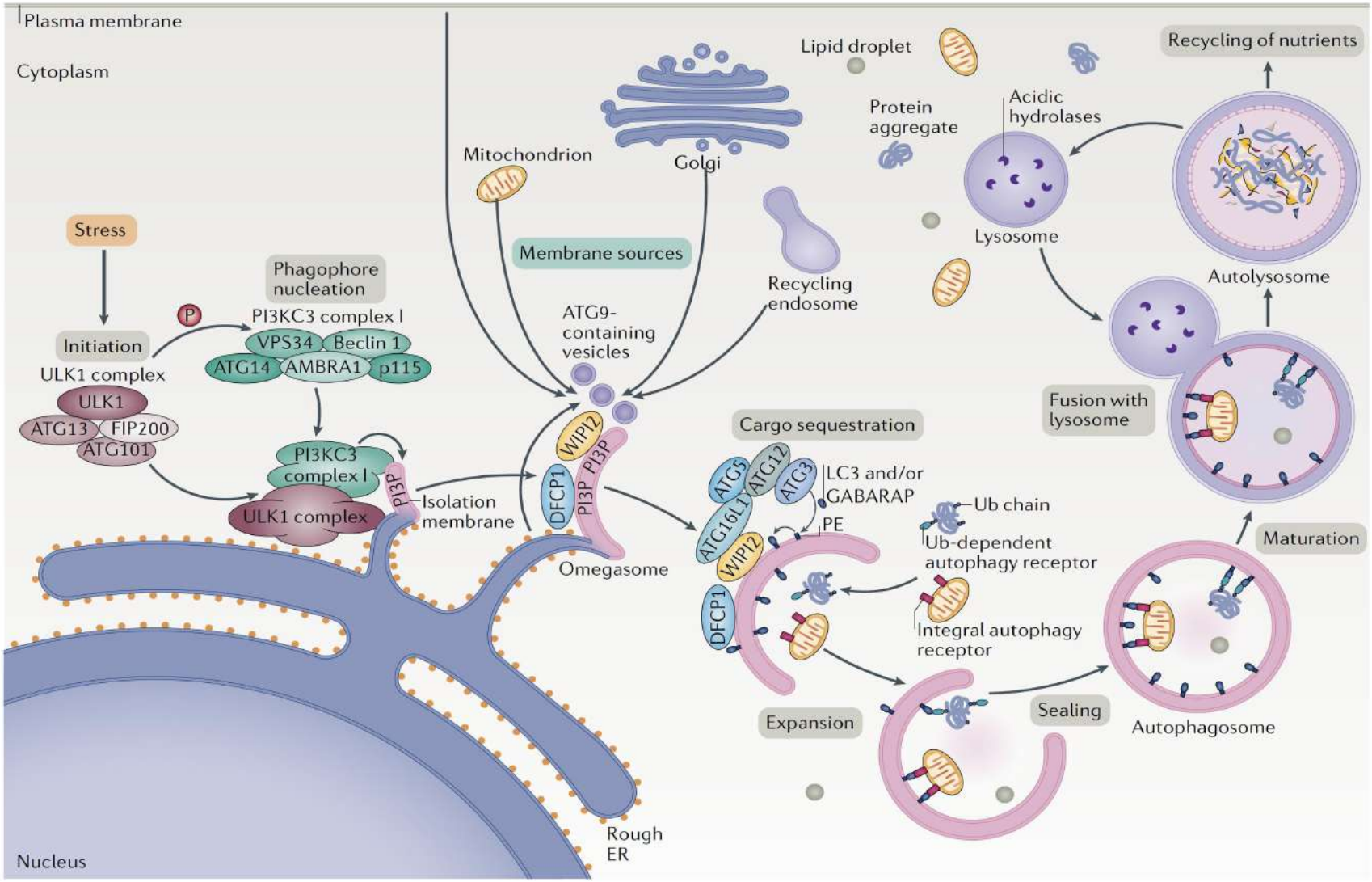
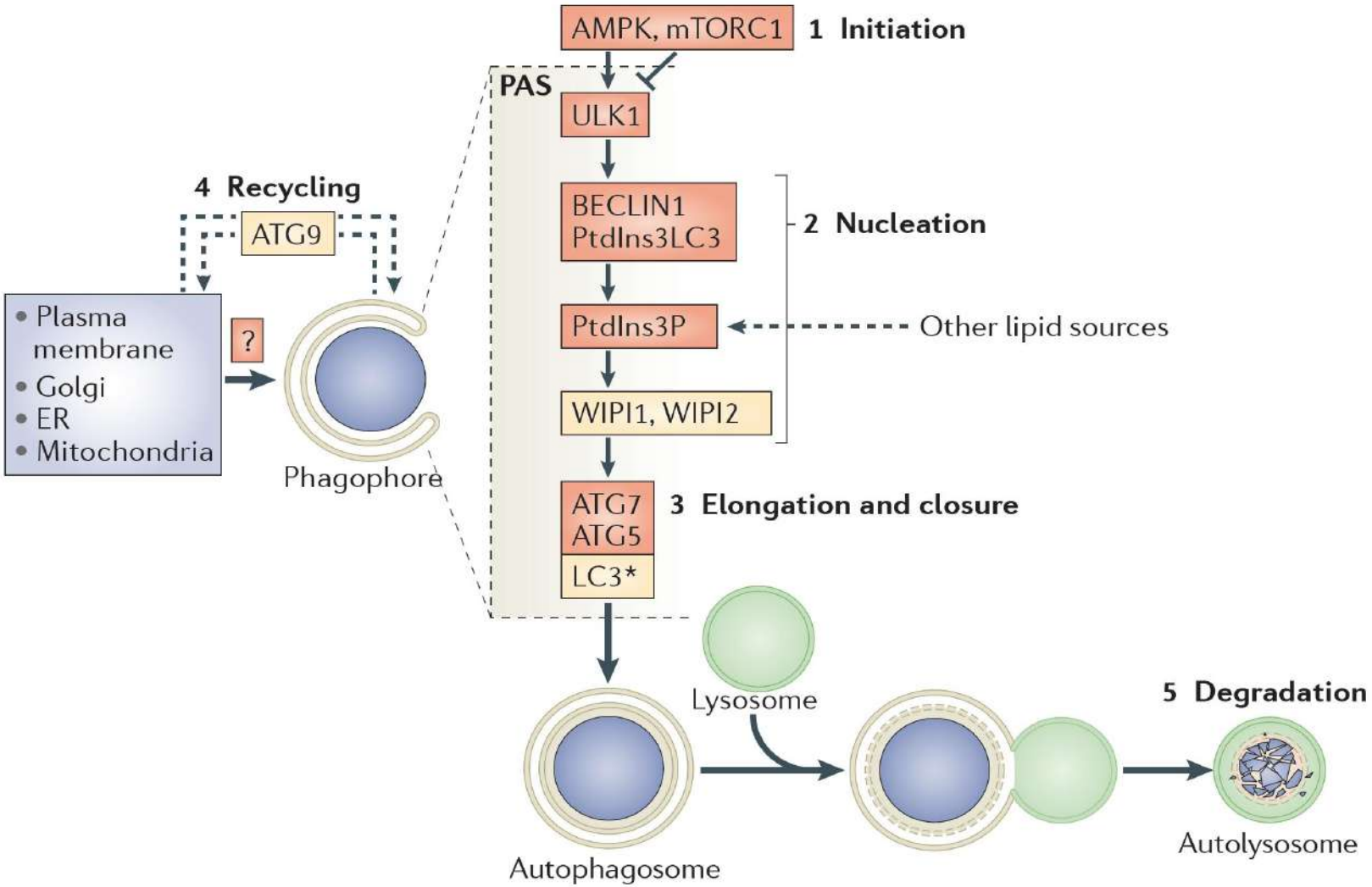


Figure 2. Regulation of the Autophagic Pathway.

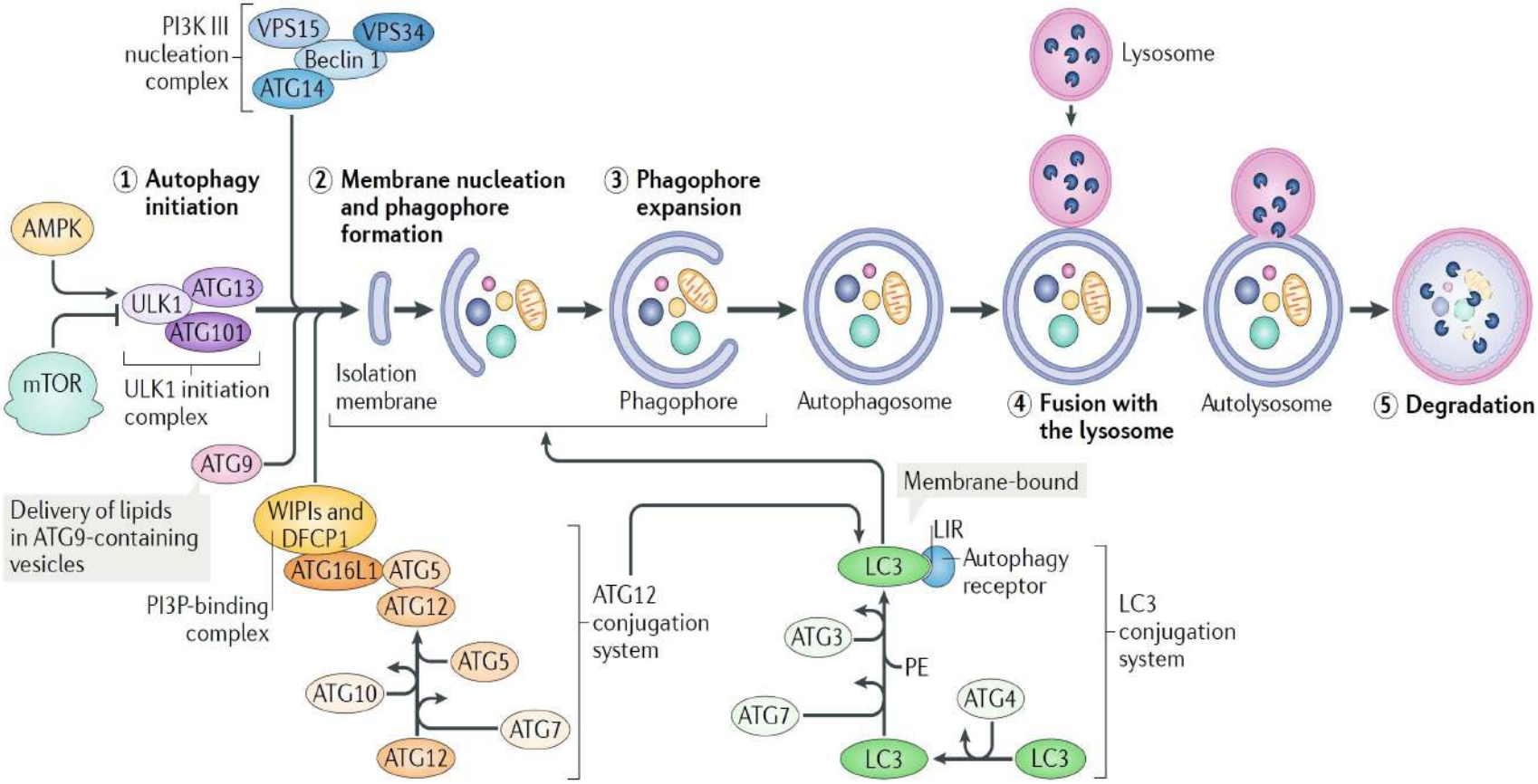
Overview of the autophagy process



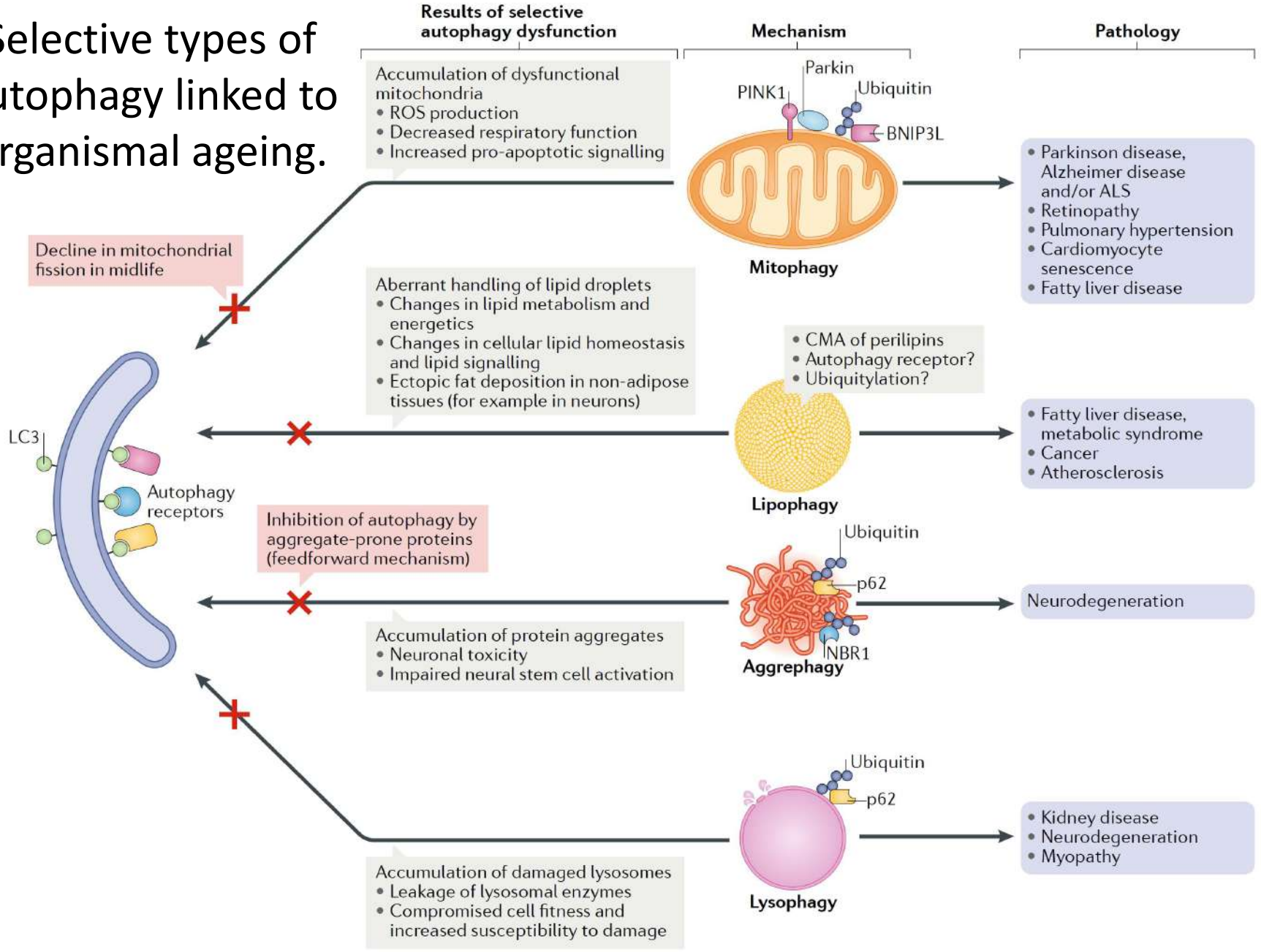
Pathways of canonical and non-canonical autophagy



The macroautophagy process



Selective types of autophagy linked to organismal ageing.



Non Canonical Structures

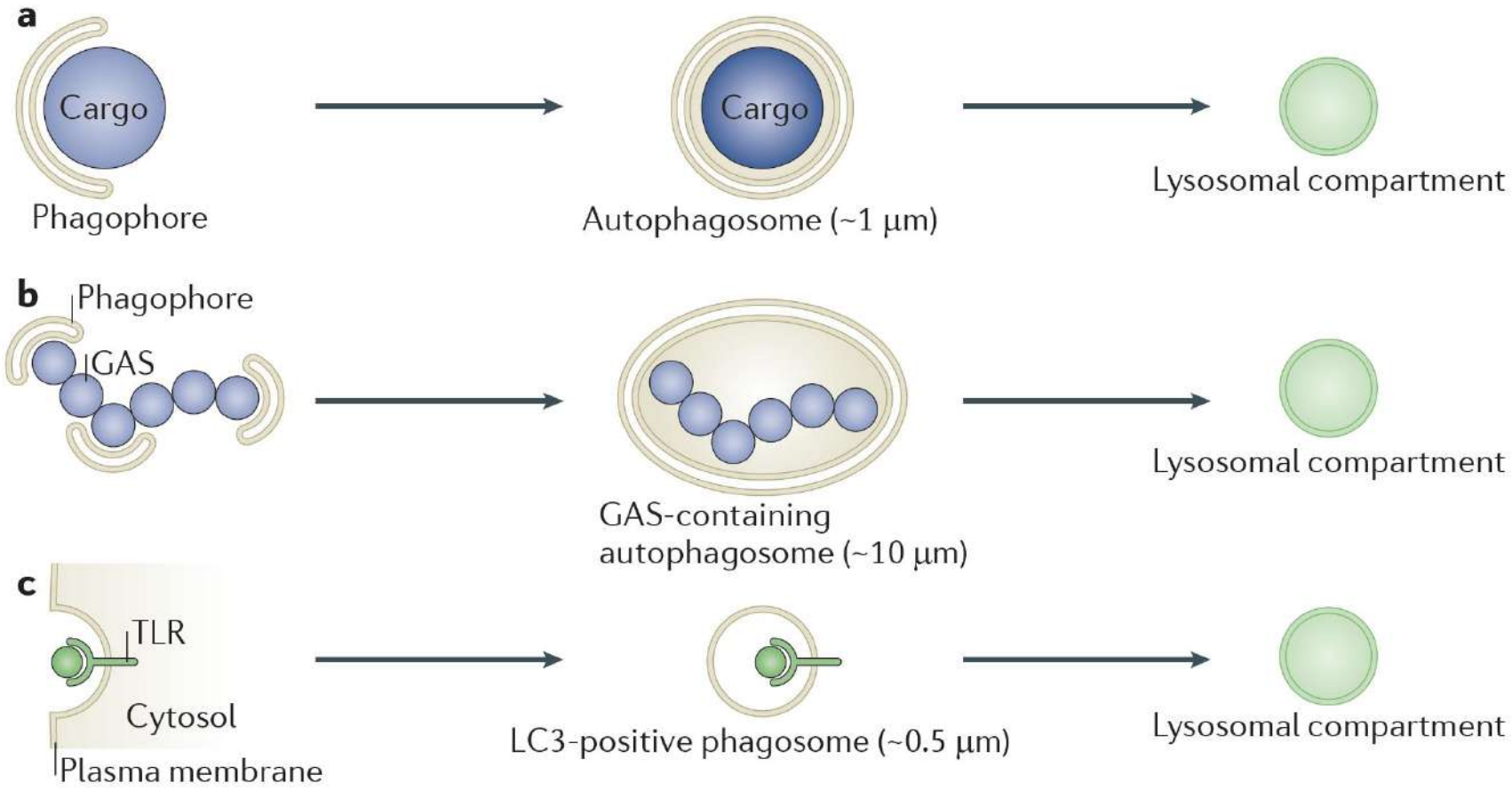


Table 1 | **Effect of autophagy impairment in specific tissues and related pathologies**

Target tissue	Pathologies	Impaired autophagy type	Phenotype
Pancreatic β-cells, whole body (global haploinsuffiency)	Diabetes	Lipophagy, glycophagy, aggrephagy	Impaired insulin secretion, hyperglycaemia and accumulation of protein aggregates
Liver	Obesity	Lipophagy*, glycophagy	Insulin resistance, low blood glucose levels
Liver	Hepatic steatosis	Lipophagy	Increased lipid accumulation
Hypothalamus	Obesity	Hypothalamic lipophagy	Increased food intake, reduced energy expenditure
Skeletal, respiratory and cardiac muscle	Glycogen storage disease type II (Pompe disease)	Glycophagy	Accumulation of glycogen-filled lysosomes
Skeletal and cardiac muscle	Inherited myopathies	Glycophagy, aggrephagy	Accumulation of autophagosomes and glycogen
Liver	Deficiency in α1-antitrypsin	Aggrephagy	Accumulation of inclusions of insoluble enzyme α1-antitrypsin
Brain	Static encephalopathy in childhood with neurodegeneration in adulthood (SENDA)	Ferritinophagy	Iron accumulation in the globus pallidus and substantia nigra of the brain

*Current evidence suggests that the indicated autophagy type is impaired, but it has not been fully proven.

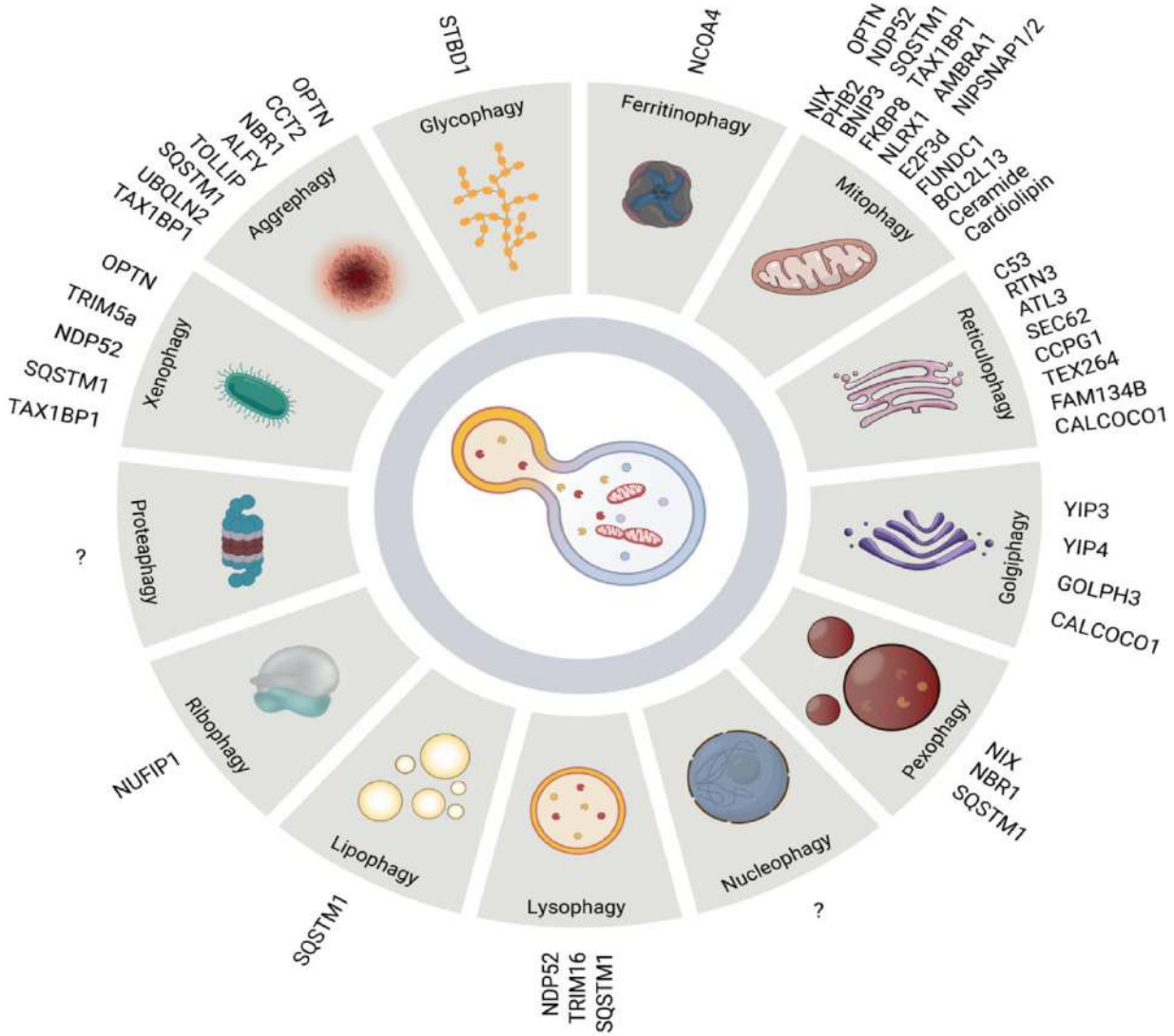


Figure 2. Selective autophagy in mammals and their respective receptors. Schematic representation of the different types of mammalian selective autophagy and the respective selective autophagy receptors (SARs) identified.

Autophagy in Disease

- Cancer
- Neurogenerative Diseases
- Infectious Diseases
- Cardiovascular Diseases
- Metabolic Diseases
- Pulmonary Diseases
- Aging

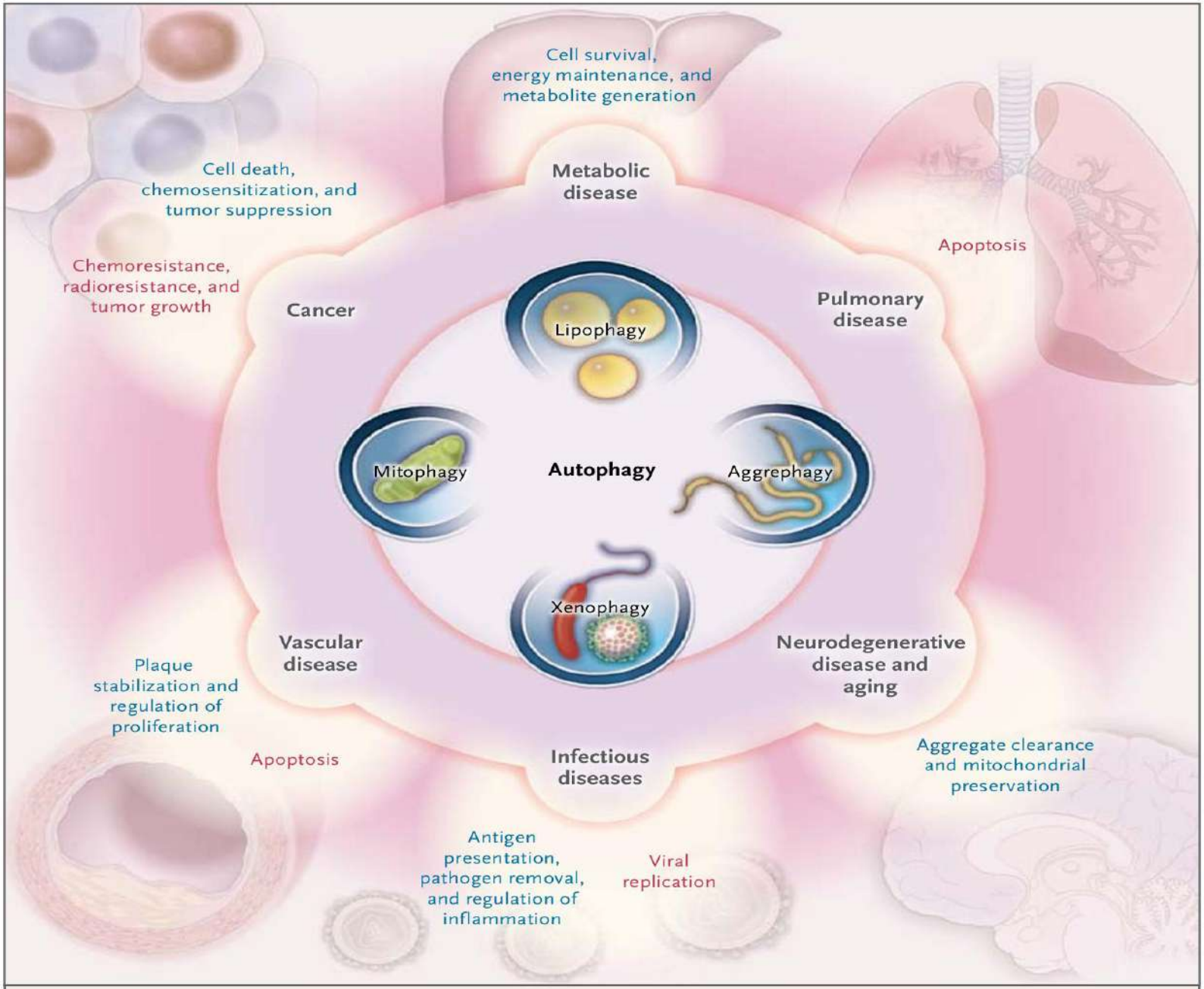


Figure 3. Effects of Autophagy on Disease Progression.

Table 2. Association of Autophagy-Related Factors and Human Disease.*

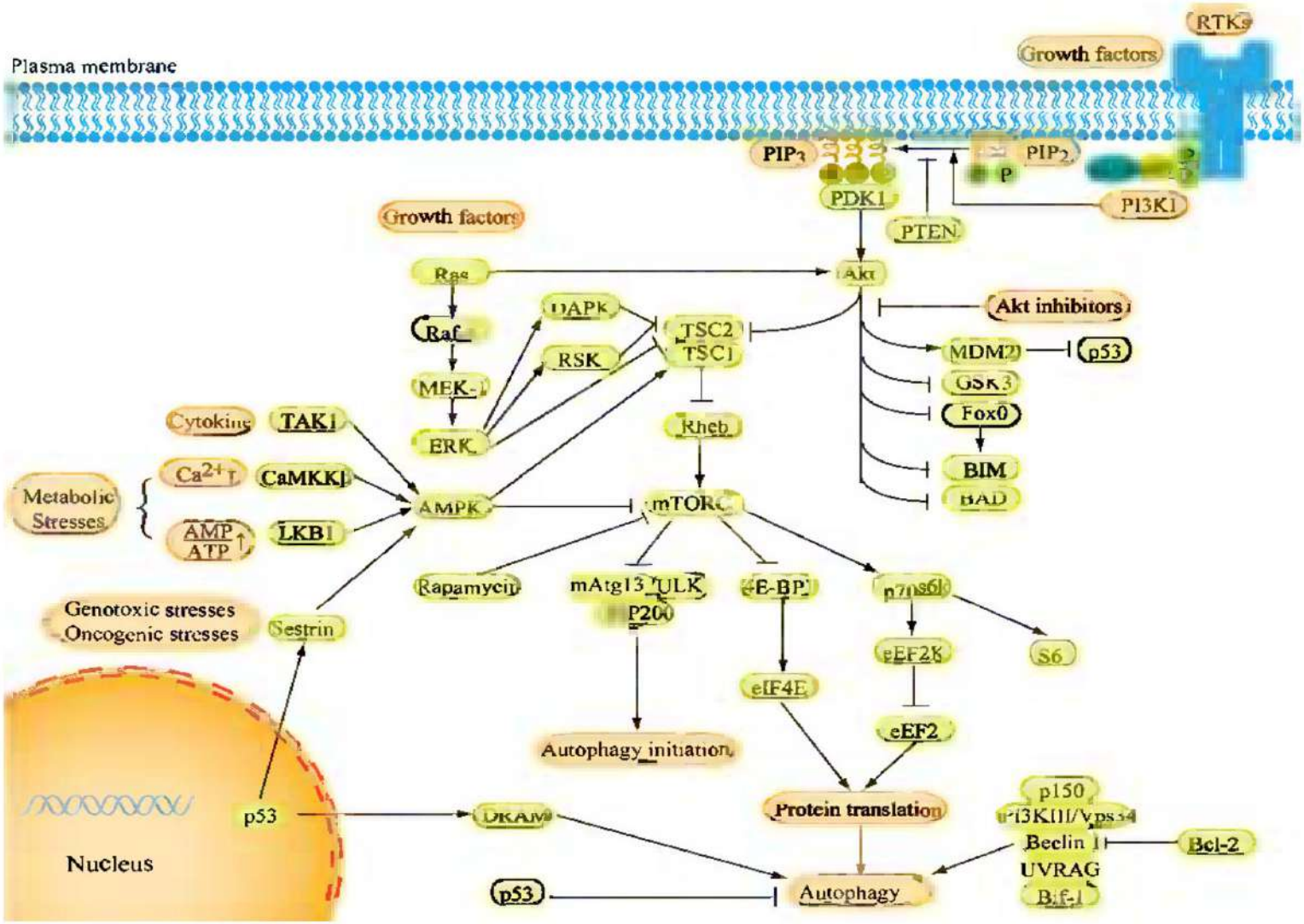
Gene	Association
BECN1	Monoallelically deleted at high frequency in human breast, ovarian, and prostate cancers[5,7-10] Altered expression found in many human tumors[11,12]
UVRAG	Deleted at high frequency in human colon cancers[13]
ATG5	SNPs associated with risk of systemic lupus erythematosus[14] SNPs associated with risk of childhood and adult asthma and decline in lung function[15,16]
ATG16L1	SNPs associated with increased risk of Crohn's disease[17-19]
NOD2	SNPs associated with increased risk of Crohn's disease and susceptibility to *Mycobacterium leprae* infection[14,19,20]
IRGM	SNPs associated with increased risk of Crohn's disease[19,21]; one SNP associated with increased resistance to *M. tuberculosis* infection[22]
LAMP2	X-linked deletion associated with Danon's cardiomyopathy[23]
PARK2	Mutations associated with Parkinson's disease and colon, lung, and brain cancers[7,24]
p62/SQSTM1	Mutations associated with Paget's disease[25]
SMURF1	SNP associated with increased risk of ulcerative colitis[26]

* SNP denotes single-nucleotide polymorphism.

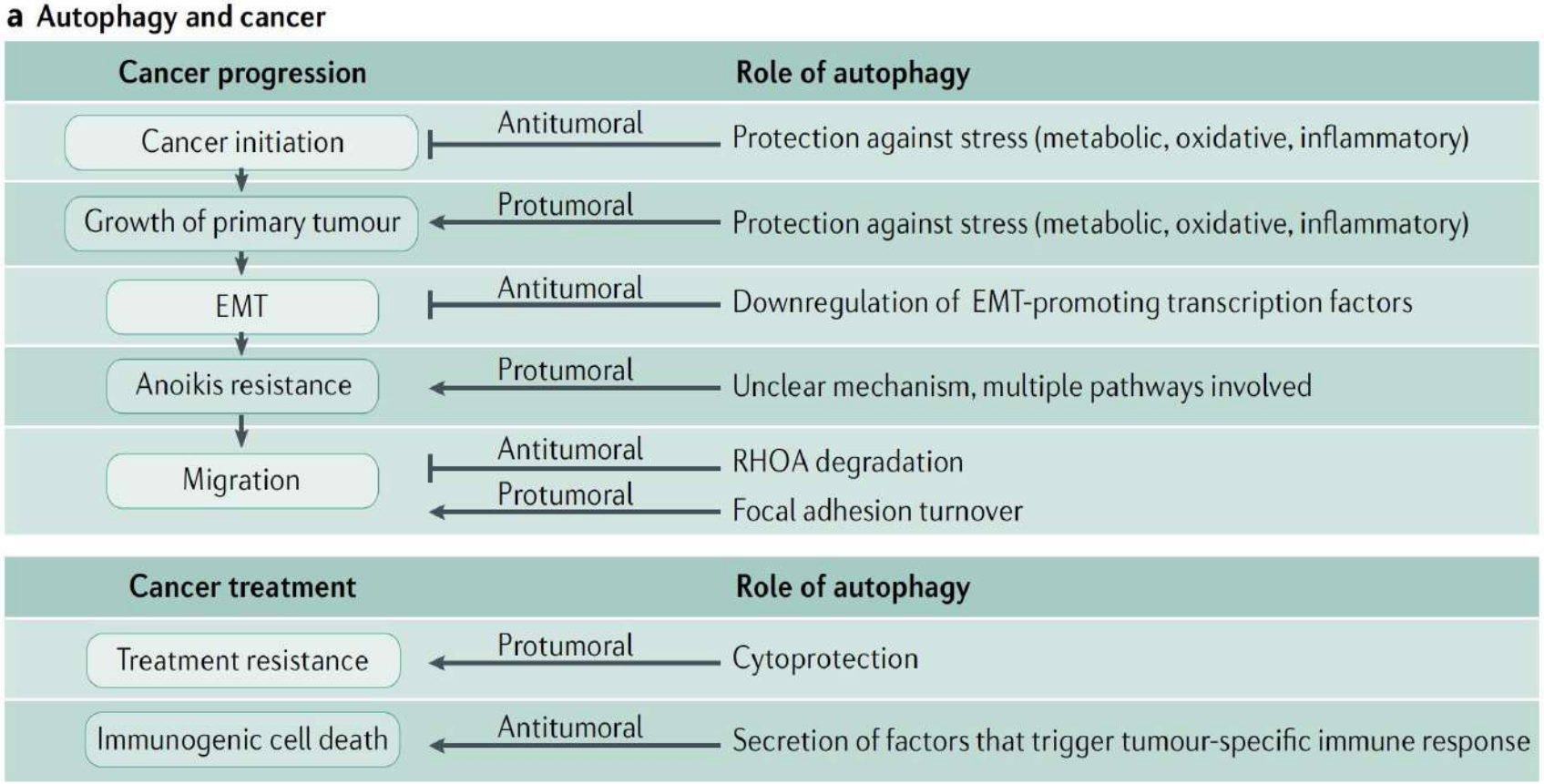
Autophagy and Cancer

- Autophagy may exert a multifactorial influence in cancer.
- Studies in mouse models have assigned **tumor-suppressor function** to additional **autophagy-associated proteins** (i.e., Uvrag and Bif1) and **core autophagy proteins** (i.e., Atg4C, Atg5, and Atg7).
- Autophagy provides an **anticarcinogenic function** in primary cells by safeguarding against metabolic stress through the homeostatic turnover of mitochondria and the clearance of protein aggregates.
- Autophagy may confer a **survival advantage** on tumor cells that are under metabolic stress, as a result of a high proliferation rate and exposure to hypoxia from insufficient vascularization, and that are under selective pressure from therapeutic interventions.

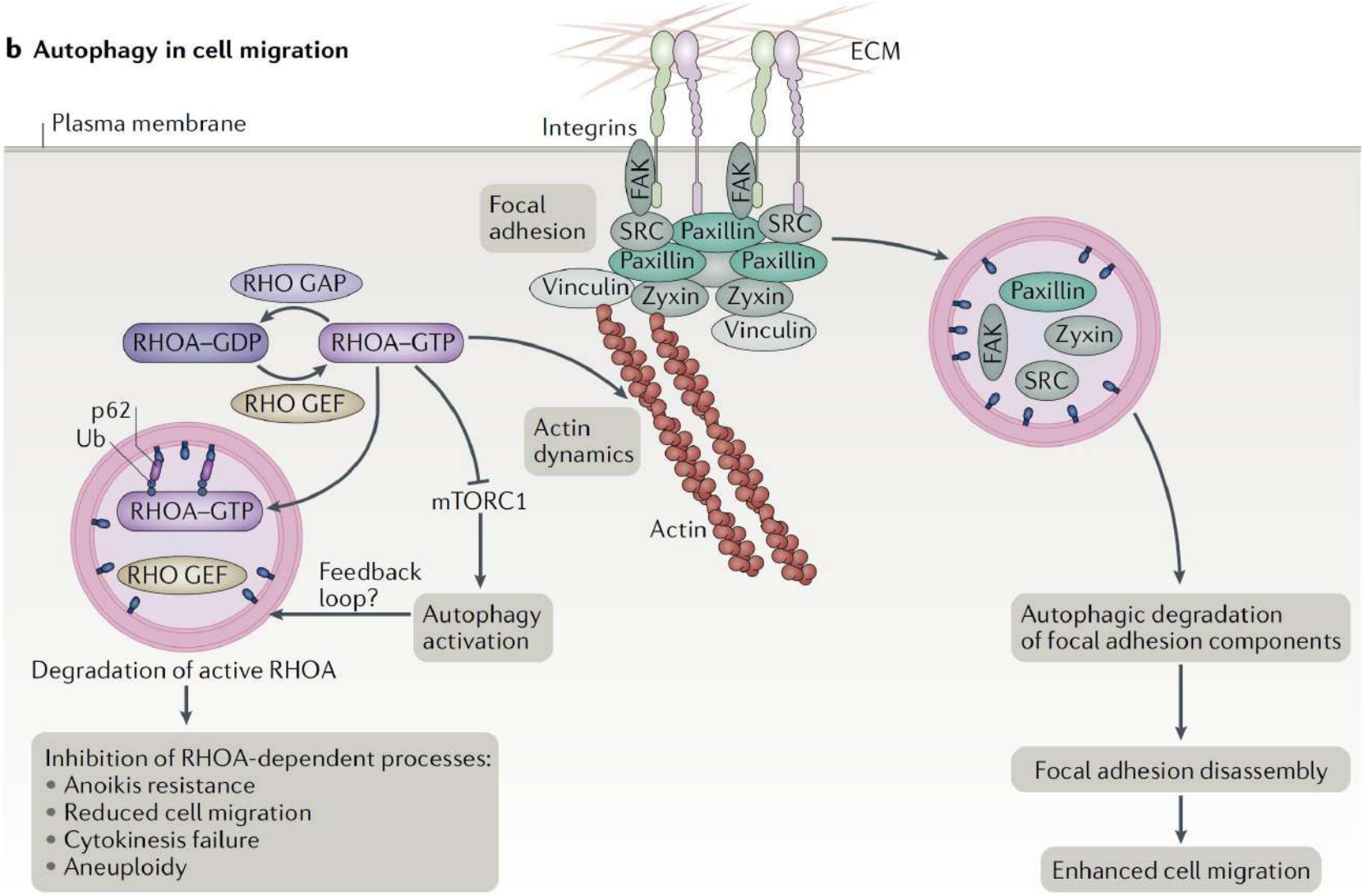
Autophagy and Cancer



Autophagy and cancer



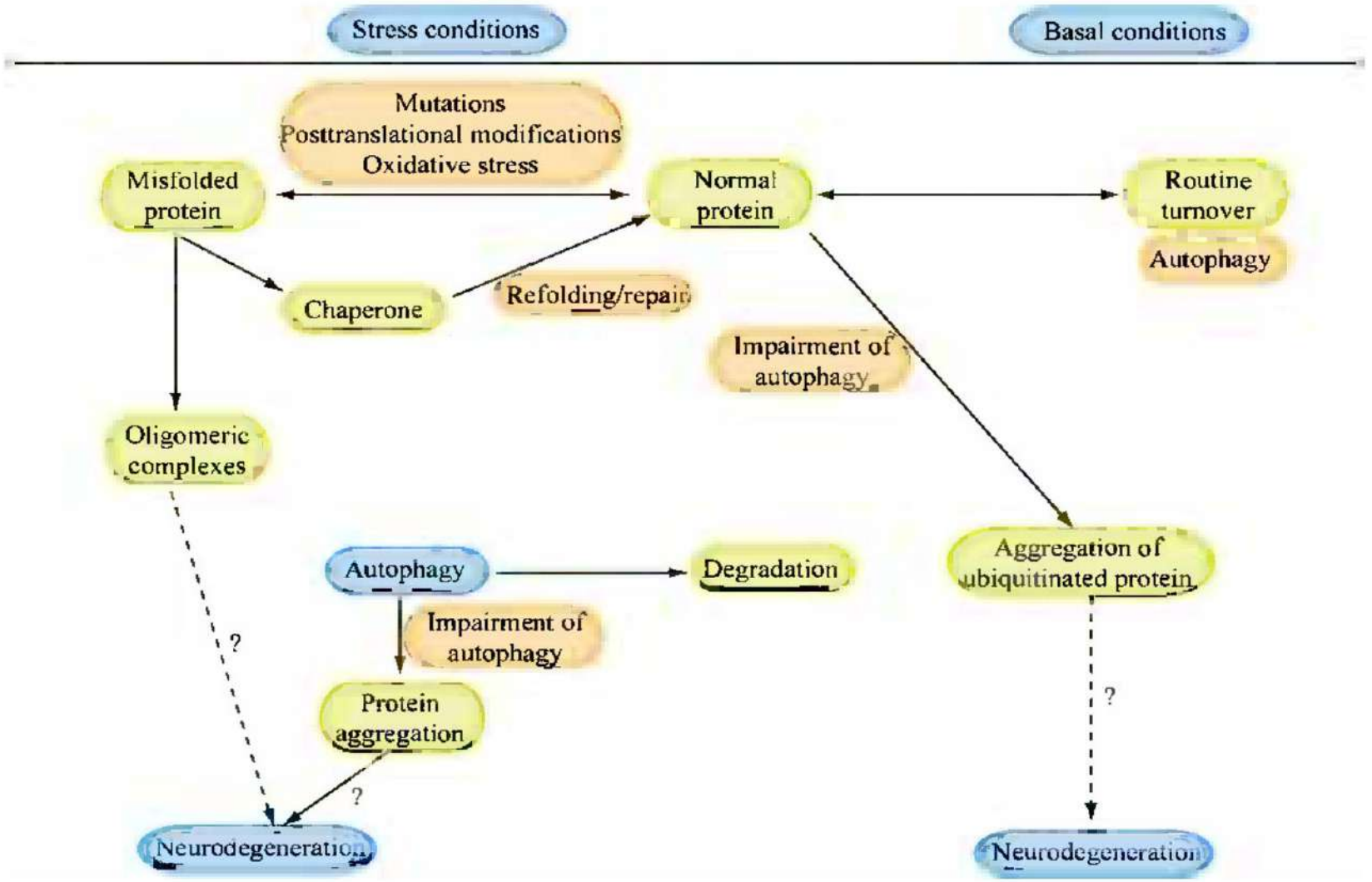
Autophagy in cell migration



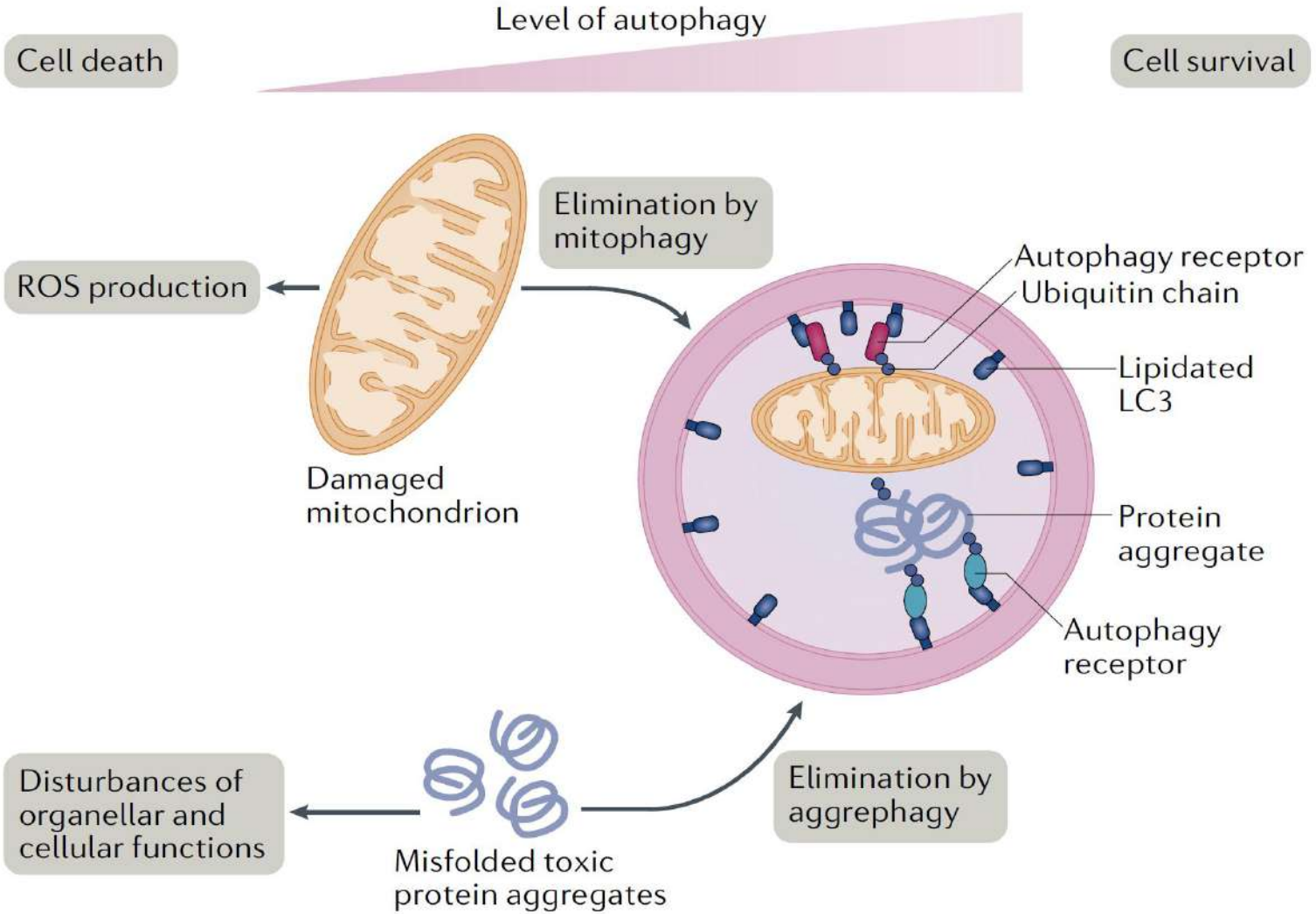
Autophagy and Neurodegeneration

- Autophagy is dysregulated in neurodegenerative disorders.
- **Huntington's disease** and associated polyglutamine disorders involve the accumulation of mutant proteins with polyglutamine-rich extensions (Huntingtin).
- **Alzheimer's disease** involves the aberrant accumulation of hyperphosphorylated forms of microtubule-associated **protein tau**, leading to the formation of neurofibrillary tangles and the accumulation of **beta amyloid peptide (Aβ)** in neural plaques.
- The involvement of **mitochondrial dysfunction** in neurodegeneration is exemplified by **Parkinson's disease**.

Autophagy and Neurodegeneration



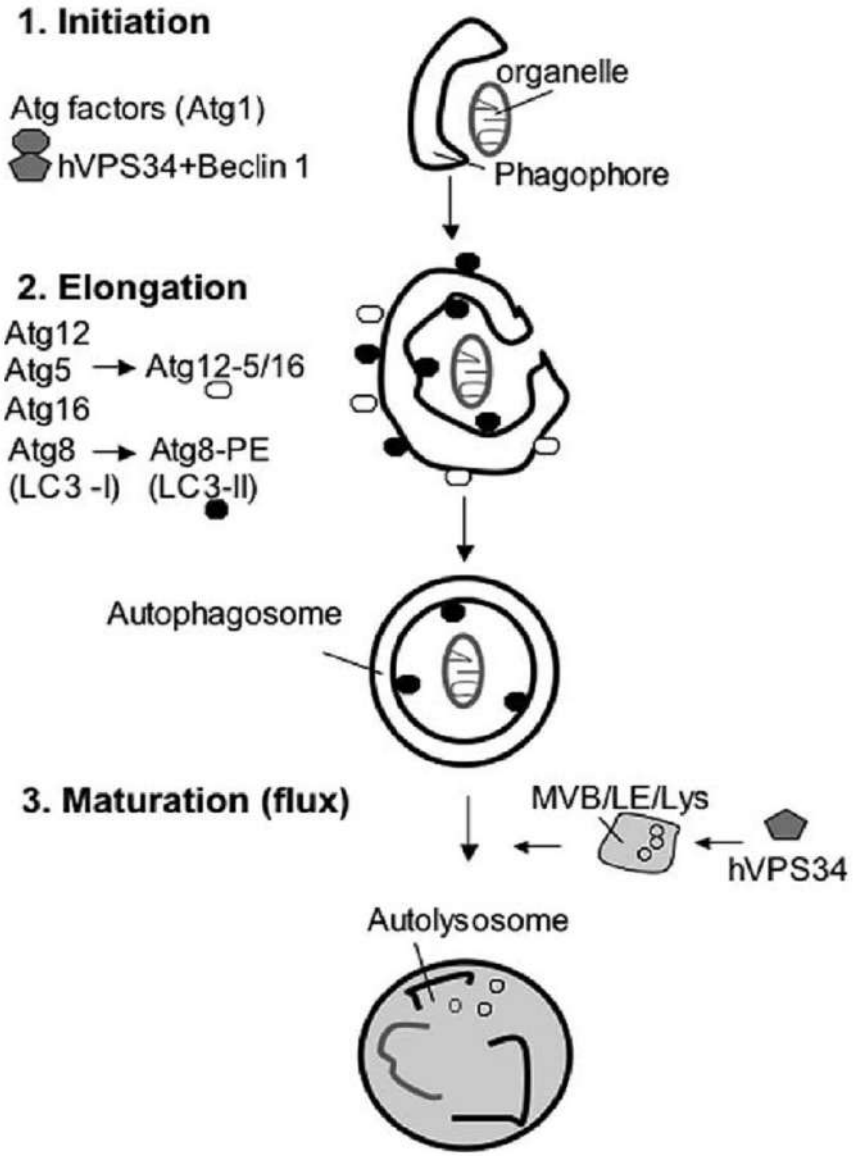
Autophagy in neurodegeneration

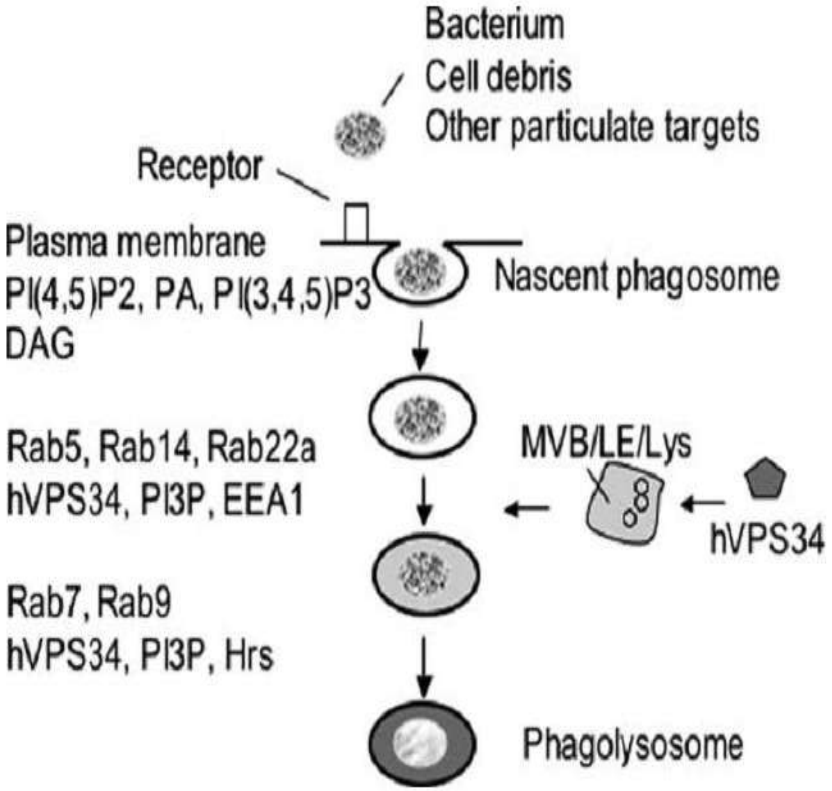


Autophagy and Infectious Diseases

- Autophagy contributes to the regulation and function of **innate and adaptive immune responses**.
- Several medically important human pathogens are degraded in vitro by **xenophagy**, including **bacteria** (e.g., ***group A streptococcus, Mycobacterium tuberculosis , Shigella flexneri , Salmonella enterica, Listeria monocytogenes, and Francisella tularensis***), **viruses** such as ***herpes simplex virus type 1 (HSV-1) and chikungunya virus***, and **parasites** such as ***Toxoplasma gondii*** .
- Pharmacologic up-regulation of autophagy, enhancement of strategies to target intracellular pathogens to autophagosomes, and inhibition of microbial virulence factors that block host autophagy defenses may represent novel strategies for the treatment of certain infectious diseases.

Autophagy Vs Phagocytosis



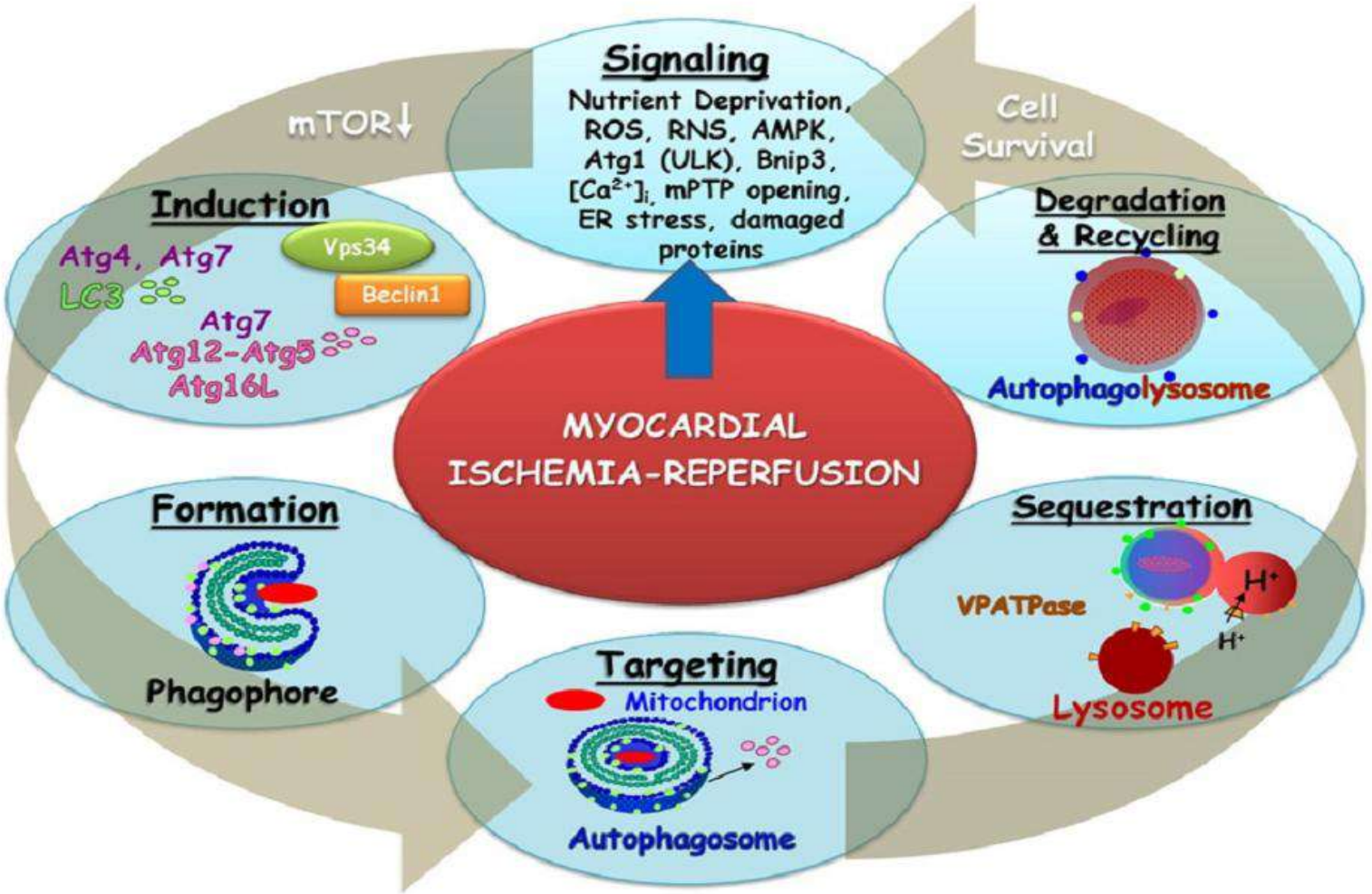


Deretic, 2008

Autophagy and Cardiovascular

- Modulations in autophagy have been associated with diseases of the heart, including cardiomyopathies, cardiac hypertrophy, ischemic heart disease, heart failure, and ischemia–reperfusion injury.
- **Increased numbers of autophagosomes** are evident in macrophages from atherosclerotic plaques.
- Autophagy may **stabilize atherosclerotic plaques** by preventing macrophage apoptosis and plaque necrosis and by preserving efferocytosis.

Autophagy and Cardiovascular



Autophagy and Metabolic Disease

- Autophagy regenerates and releases amino acids, lipids, and other metabolic precursors, which may have a profound effect on tissue metabolism.
- Autophagy acts as a **regulator of lipid metabolism** and **storage**.
- During exercise, **autophagy is increased** in **cardiac and skeletal muscle, adipose tissue**, and **pancreatic beta cells**.
- Exercise-inducedautophagy provides protection against **glucose intolerance** associated with a **high-fat diet**.

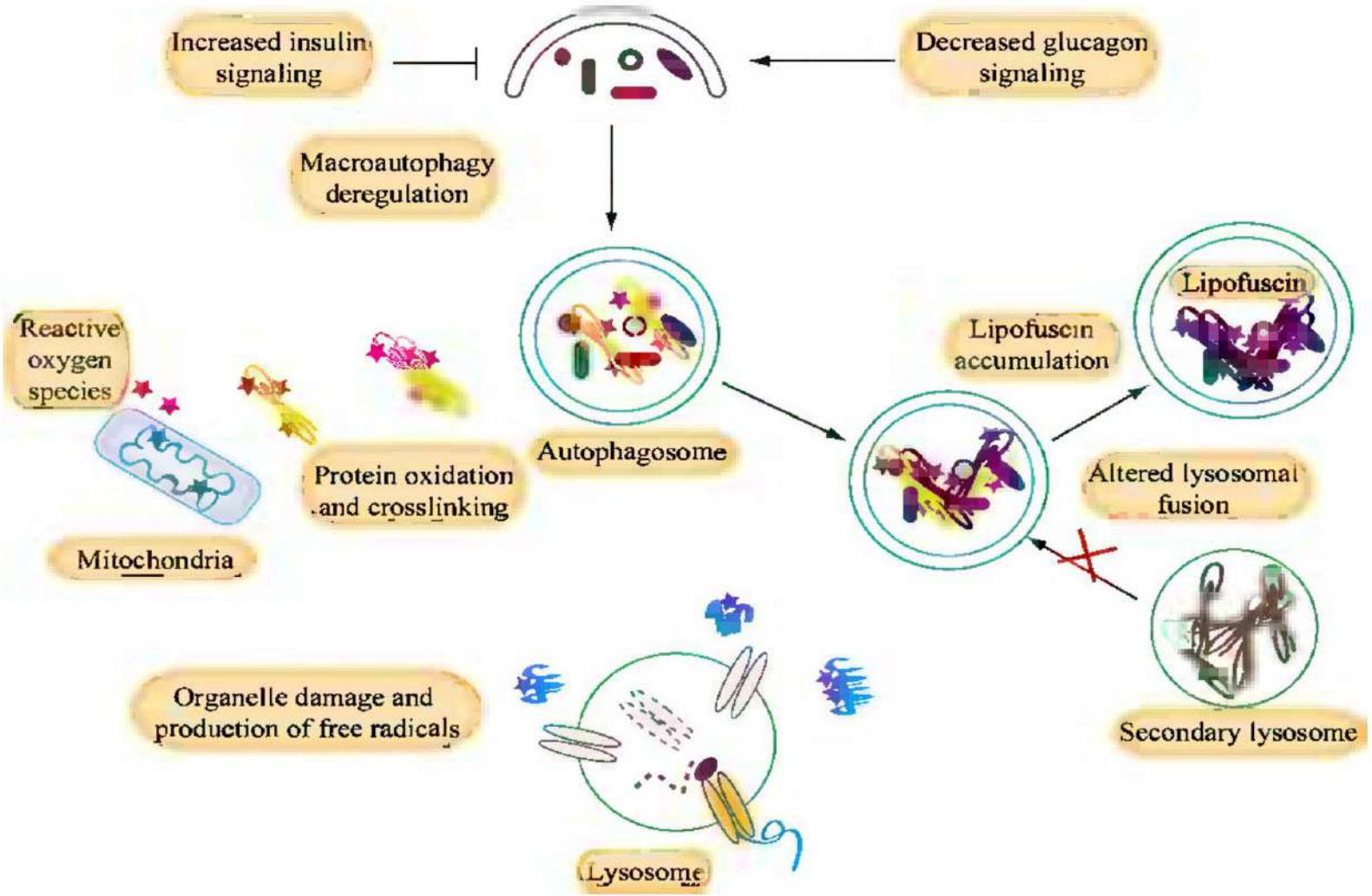
Autophagy and Pulmonary Diseases

- Divergent roles of autophagy have been reported in pulmonary diseases associated with **declining lung function**.
- **Increased autophagy** was associated with a propathogenic and proapoptotic phenotype in chronic obstructive pulmonary disease (**COPD**).
- Lung tissue isolated from patients with **pulmo-nary hypertension** have **increased LC3B activation and autophagosome formation**
- **Increased autophagosomes** have been noted in bronchial-biopsy specimens from patients with **asthma** and **ATG5 expression is elevated** in nasal-biopsy specimens from **children with asthma**

Autophagy and Aging

- The homeostatic functions of autophagy with respect to turnover of long-lived proteins and removal of damaged organelles and cellular debris are believed **to constitute an antiaging process.**
- From animal Models suggests that **modulation of autophagy can influence lifespan**.
- Analysis of gene expression in the brain in old persons as compared with young persons revealed **down-regulation of autophagy genes** (i.e., ATG5 , ATG7 , and BECN1) with age

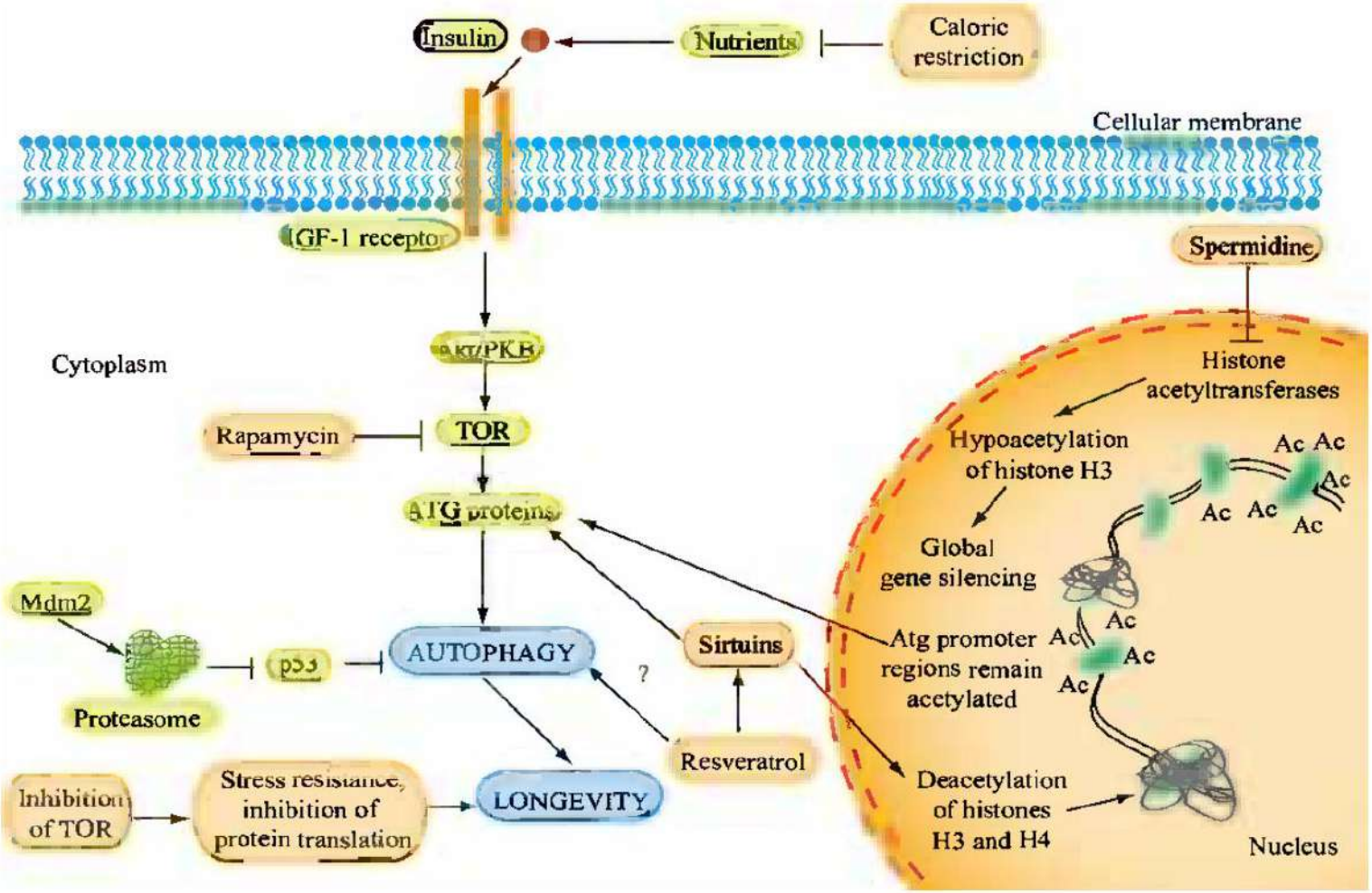
Autophagy and Aging



Autophagy in Clinical Application

- Pharmacologic enhancement of autophagy (i.e., with **vitamin D** or **adenosine 5'-monophosphate–activated protein kinase [AMPK]** activators) promises to benefit certain diseases (i.e ., infectious or neurodegenerative diseases).
- **Sirolimus**, a clinically approved immunosuppressive and anticancer drug that inhibits mTOR and has been used to enhance autophagy in experimental models
- Cytosolic or histone deacetylases (i.e., **sirtuin-1, HDAC1, HDAC2, and HDAC6**) may act as regulators of autophagic initiation and of autophagic flux.
- HDAC inhibitors, or inhibitors of lysosomal acidification (e.g., **chloroquine** and **hydroxychloroquine)** for modulating autophagy.

Autophagy and Clinical Application



Rahasia Puasa Sebulan Penuh

- Rasulullah SAW bersabda, "Sesungguhnya satu bulan itu dua puluh sembilan hari. Karena itu, jonganlah berpuasa kecuali jika telah melihat hilal, dan janganlah berbuka hingga melihat hilal. Jika mendung menghalangi kalian (untuk melihat hilal), mako perkirakantah jumtah hari (Bulan Ramadhon) satu bulan penuh."
- Sunan Ad-Darimi hadits no 1690

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Original Article

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Effect of 30-day Ramadan fasting on autophagy pathway and metabolic health outcome in healthy individuals

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Original Article

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Effect of 30-day Ramadan fasting on autophagy pathway and metabolic health outcome in healthy individuals

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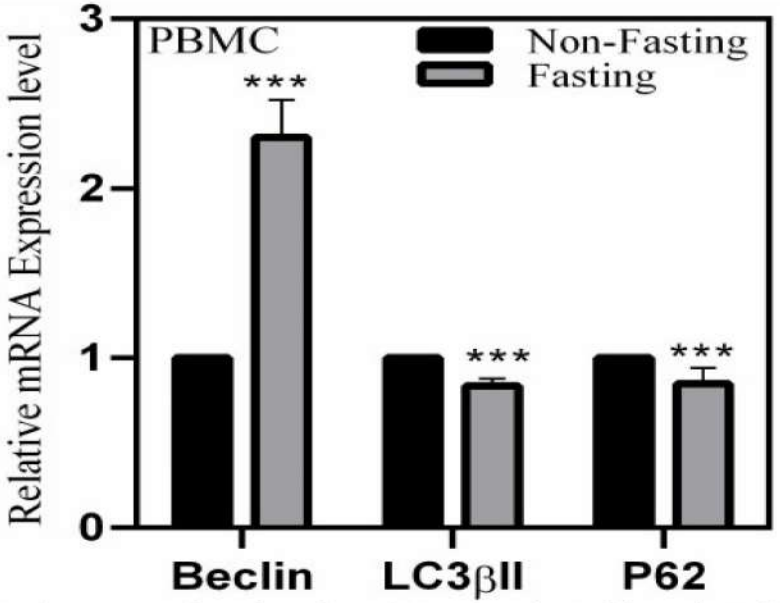
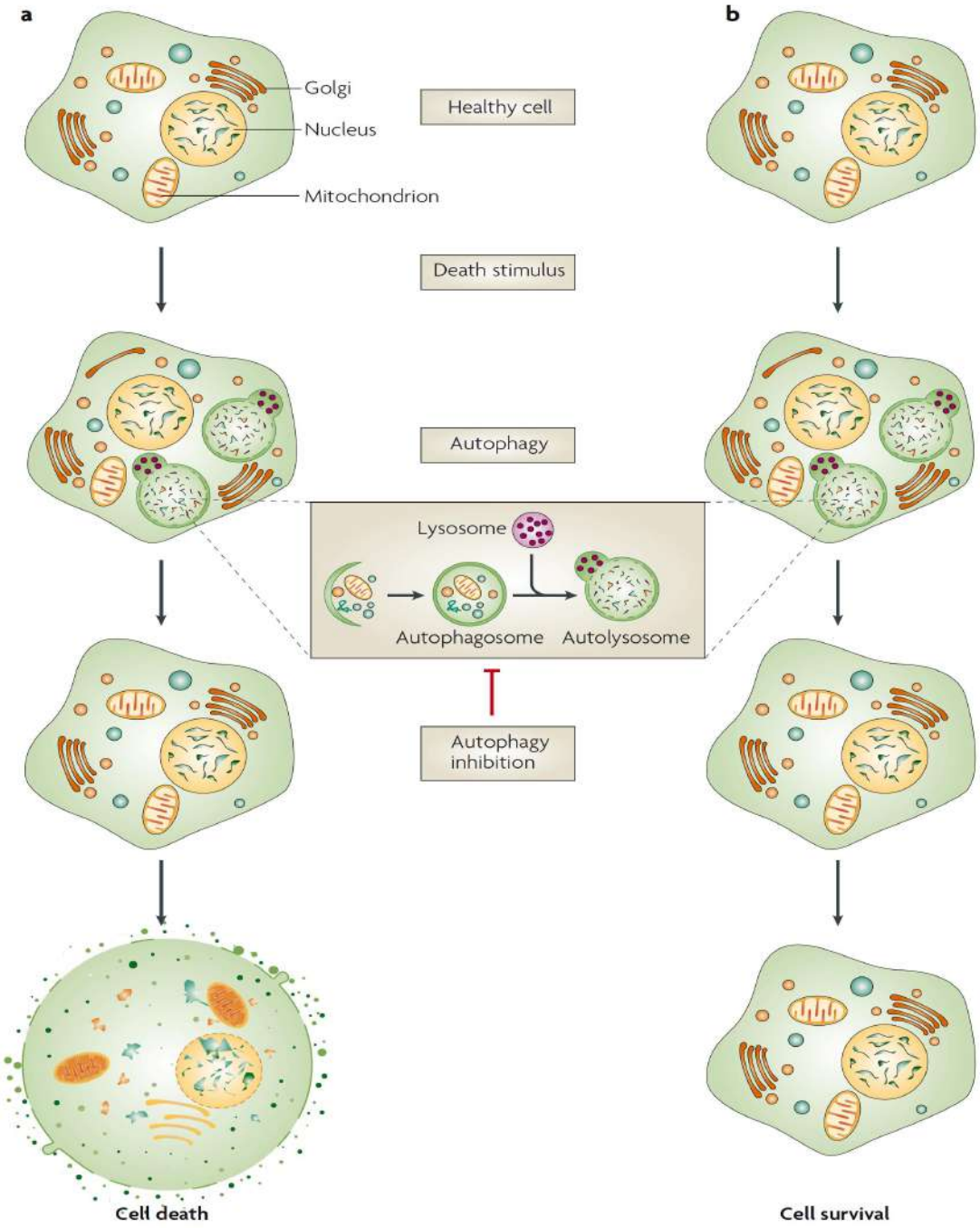


Figure 2: The relative mRNA expression levels of *Beclin-1*, *LC3* and *P62* in fasting and non-fasting groups. The Data are reported as the means ± SD of three independent assays (n=3, ***P<0.001)

Rahasia Puasa Sebulan Penuh

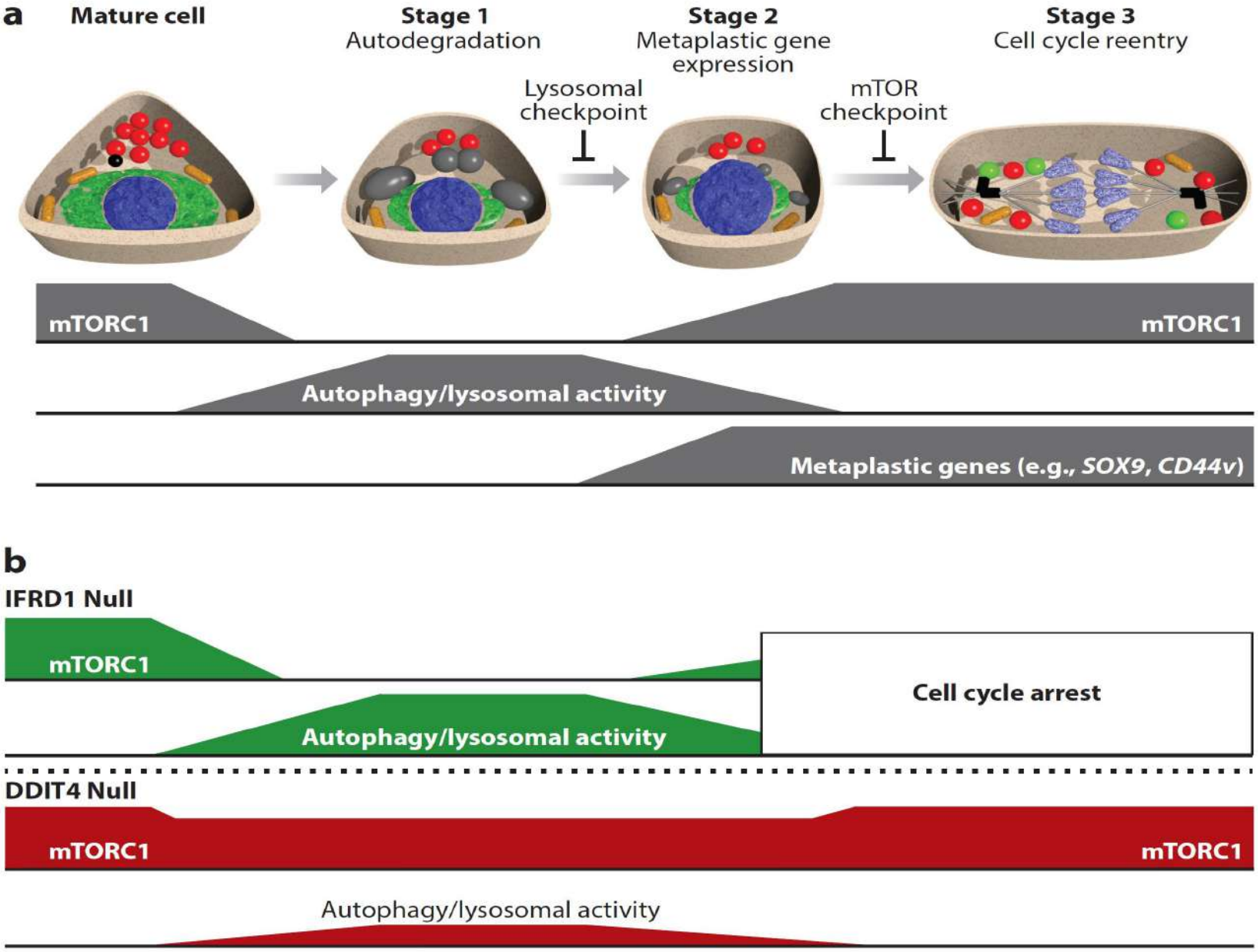
- Rasulullah SAW bersabda, "Hindarilah puasa wishal." (Beliau mengatakan itu) dua kali.
- Para sahabat berkata, "(Tapi) engkau sendiri melakukan puasa wishal?"
- Beliau menjawab, "Sesungguhnya aku tidak seperti kalian. Sesungguhnyaaku tidur, sementara Tuhanku memberikan makan dan minum kepadaku.”
- Sunan Ad-Darimi hadits no 1703



‘cell death with autophagy’
versus
‘cell death by autophagy’

Setelah puasa sebulan seperti bayi yang baru lahir

- Rasulullah SAW bersabda: Sesungguhnya Allah Azza wa Jalla telah mewajibkan puasa Romadhan dan aku telah mensunnahkan menegakkan shalatnya, maka barangsiapa berpuasa dan menegakkannya mengharapkan ridho Allah SWT keluar dari dosa-dosanya seperti hari ibunya melahirkannya.
- HR. Imam Ahmad/1572,
- Nasai /2180,
- Ibnu Majh/ 1318.


a
Mature cell
Stage 1
Autodegradation
Stage 2
Metaplastic gene expression
Stage 3
Cell cycle reentry
Lysosomal checkpoint
mTOR checkpoint
mTORC1
mTORC1
Autophagy/lysosomal activity
Metaplastic genes (e.g., SOX9, CD44v)
b
IFRD1 Null
mTORC1
Autophagy/lysosomal activity
Cell cycle arrest
DDIT4 Null
mTORC1
mTORC1
Autophagy/lysosomal activity

Kesimpulan

- Puasa tidak saja menahan Haus dan Lapar tetapi memiliki rahasia molekuler yang dahsyat
- Rahasia Puasa, Sahur, Iftar dan Puasa Sebulan Penuh dapat di jelaskan secara Ilmiah
- Bila Rahasia sudah terbuka, maukah kita meninggalkan Puasa Ramadhan?

Arigatou
Gozaimasu