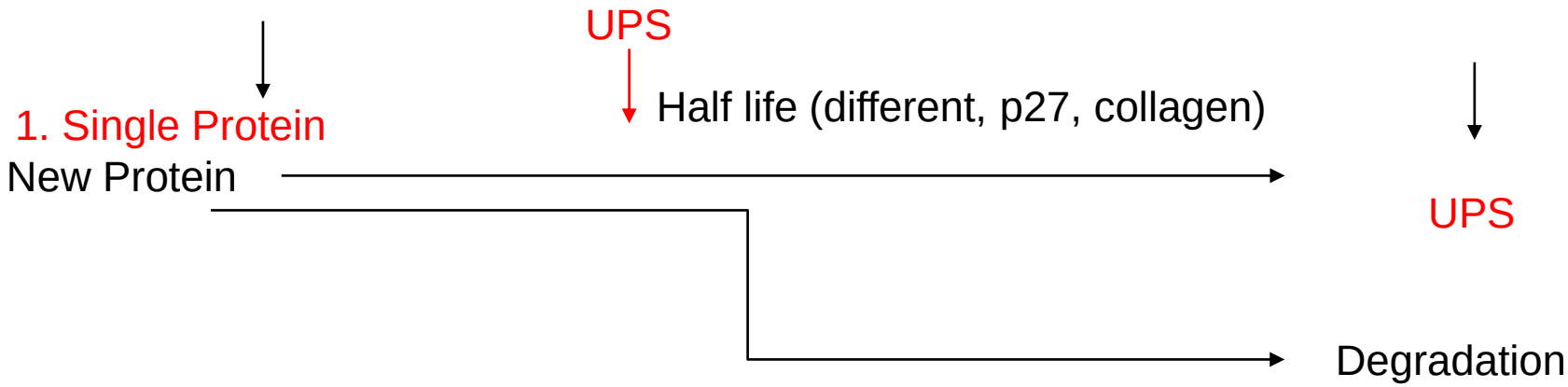
INSTITUT FÜR
EXPERIMENTELLE
INNERE MEDIZIN

Die Vorlesung „Autophagie“ findet am 17. Oktober um 15.30 im Haus 5 (4. Stock, Seminarraum) in unserem Institut statt!

Willkommen!
D. Dubiel

Protein (Eiweß)_Turnover

Definition: In cell biology, protein turnover refers to the **replacement of older proteins as they are broken down within the cell by new synthesized protein**.
Different types of proteins have very different turnover rates.
A rate of new synthesized protein is equal to rate of degrading protein: Steady state !!!!

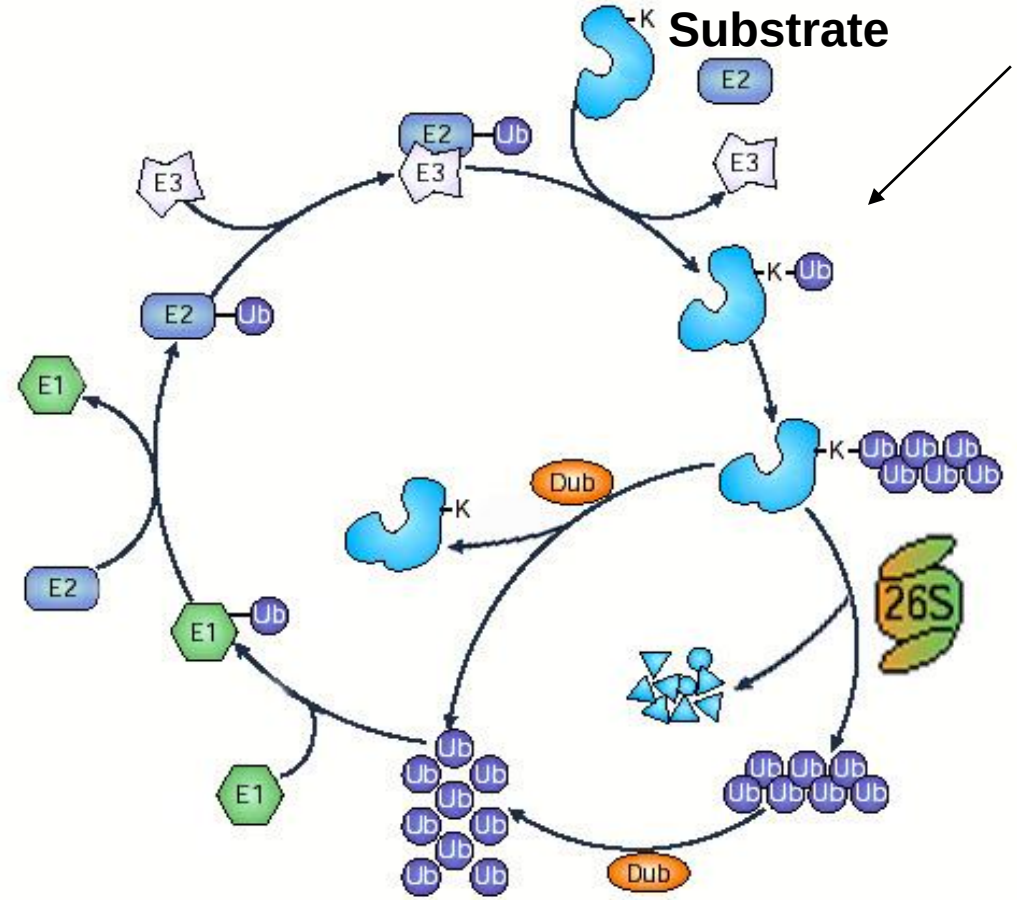


Single proteins: from amino acids (peptide bond)

Cleaved by enzymes: proteases

The Ubiquitin (Ub) Proteasome System (UPS)

-Major proteolytic system in eukaryotic cells
-Ub is a signal for proteolysis



Ub binds to Lys-Substrate

Components of the UPS

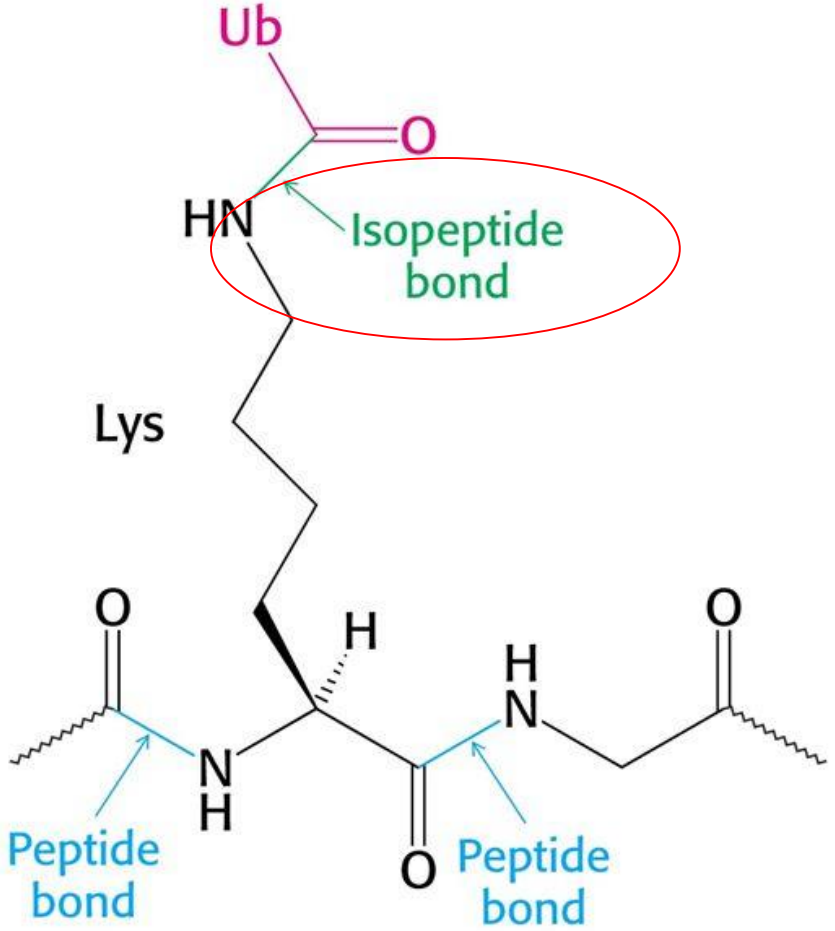
- E1 – Ub activating enzymes
- E2 – family of Ub conjugating enzymes
- E3 – families of Ub ligating enzymes
- The 26S proteasome
- Family of deubiquitinating enzymes (DUBs)

Modified from Sullivan et al., 2003

The peptide bond

Ubiquitin covalently binds to ε-amino group of lysine residue on a protein destined to be degraded.

Isopeptide bond is formed.



Components of the UPS

Ubiquitin: from Latin *ubique* (“everywhere”), from *ubi* (“where”)

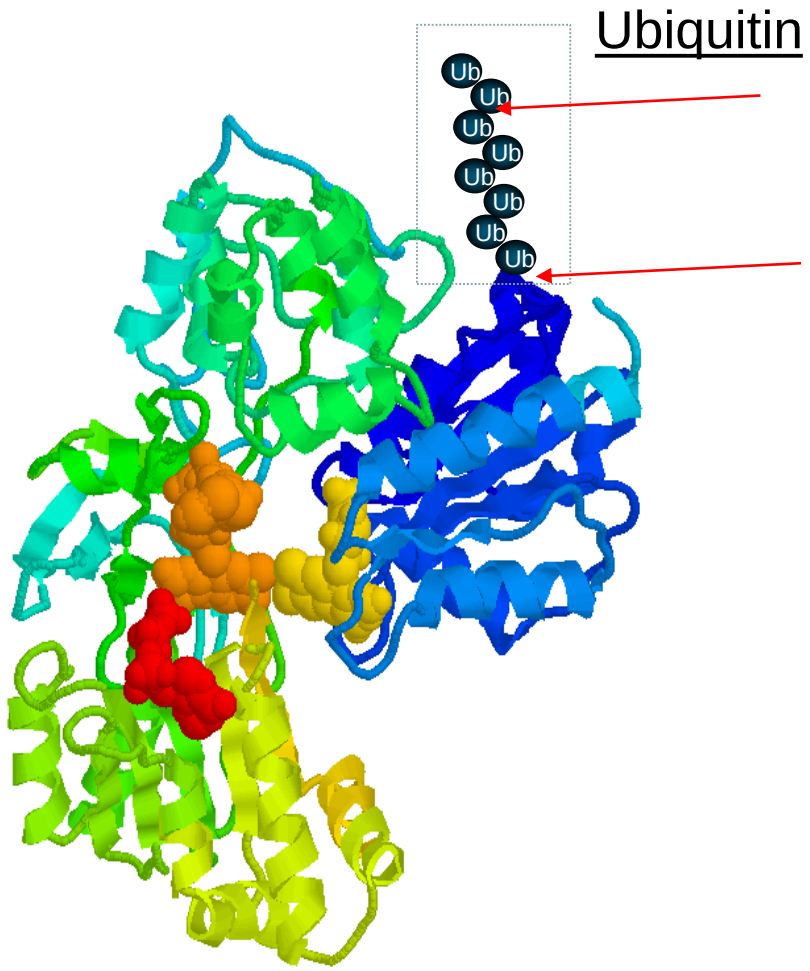
Ubiqutin: Covalent bond between:

Ub- Lys-Substrates

Ub- Lys48-Ub

-Ubiquitination/Ubiquitylation:

- a posttranslational modification



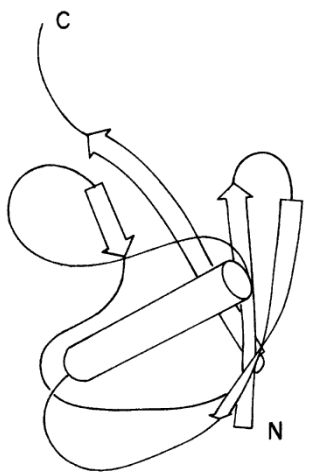
Ubiquitin (Ub)

Amino acid sequence of Ub

Met – Gln – Ile – Phe – Val – Lys – Thr – Leu – Thr – Gly –
Lys – Thr – Ile – Thr – Leu – Glu – Val – Glu – Pro – Ser –
Asp – Thr – Ile – Glu – Asn – Val – Lys – Ala – Lys – Ile –
Gln – Asp – Lys – Glu – Gly – Ile – Pro – Pro – Asp – Gln –
Gln – Arg – Leu – Ile – Phe – Ala – Gly – Lys – Gln – Leu –
Glu – Asp – Gly – Arg – Thr – Leu – Ser – Asp – Tyr – Asn –
Ile – Gln – Lys – Glu – Ser – Thr – Leu – His – Leu – Val –
Leu – Arg – Leu – Arg – Gly – Gly

5, 10, 15, 20, 25, 30, 35, 40, 45, 48, 50, 55, 60, 63, 65, 70, 75

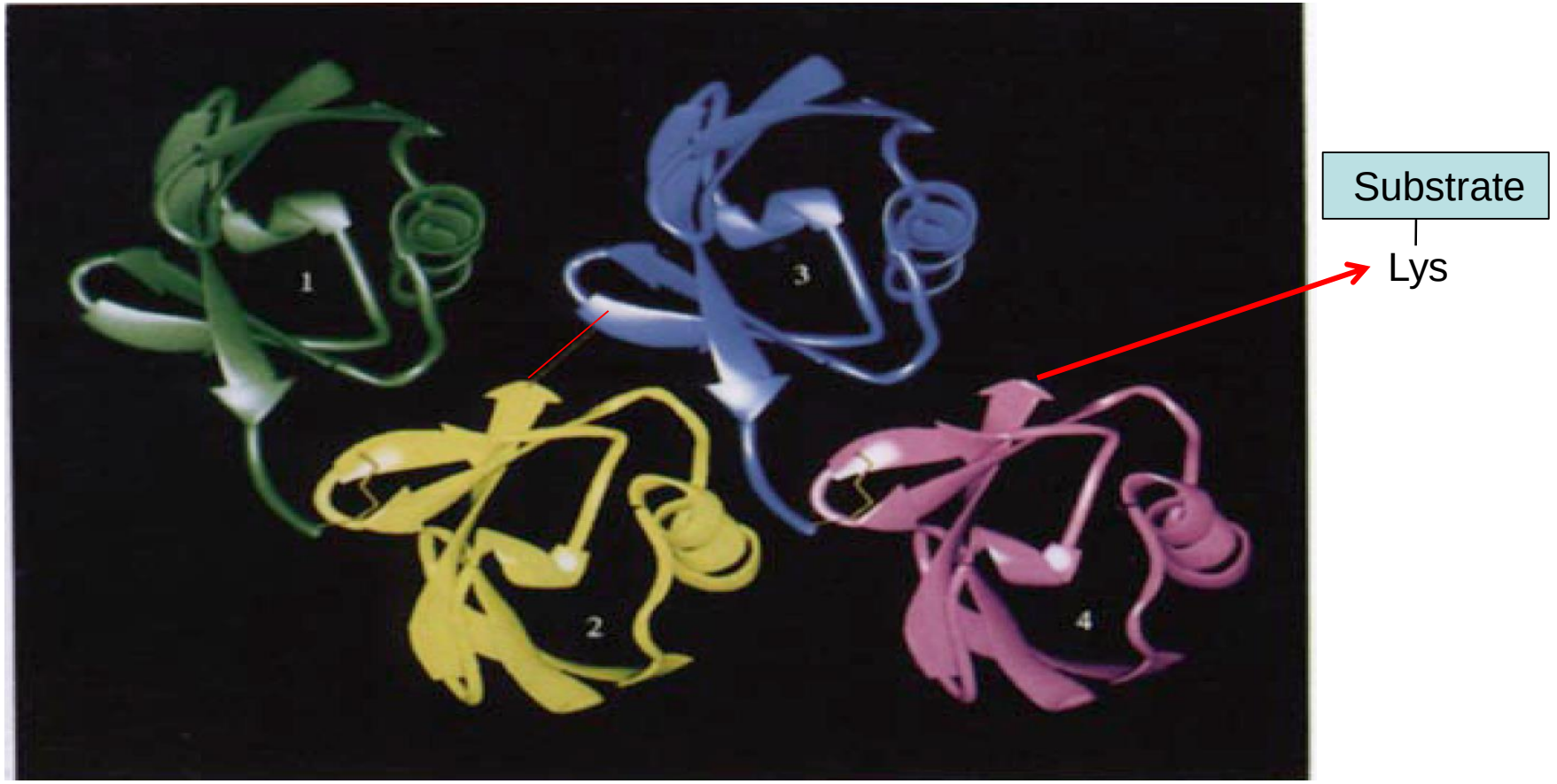
Formation of Ub-chain



Alpha-helix (cylinders) and beta-strands (ribbons) of Ub structure

Ubiquitin-like proteins:
SUMO - small ubiquitin-like modifier
Nedd8 - neural-precursor-cell-expressed developmentally down-regulated 8

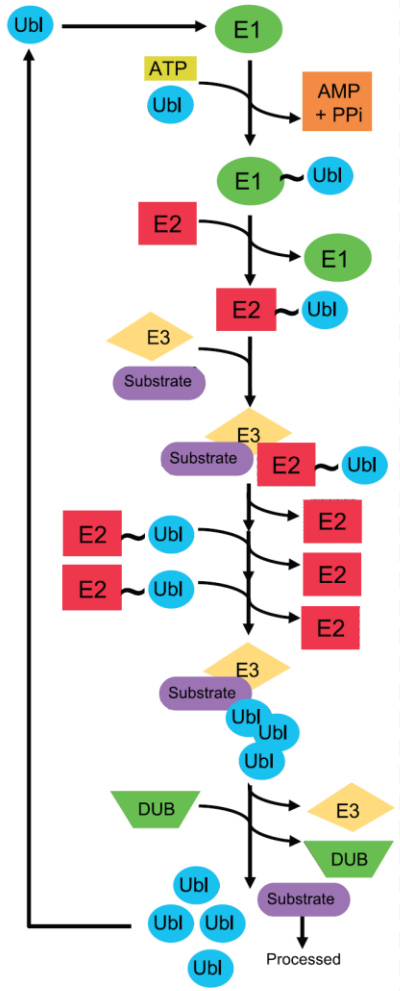
Poly-Ub chains are the signals for proteolysis



In tetra-Ub molecules of Ub are linked via isopeptide bond between the Ub-Gly-COOH and Ub-Lys48-NH2.

Ub conjugates = branched proteins

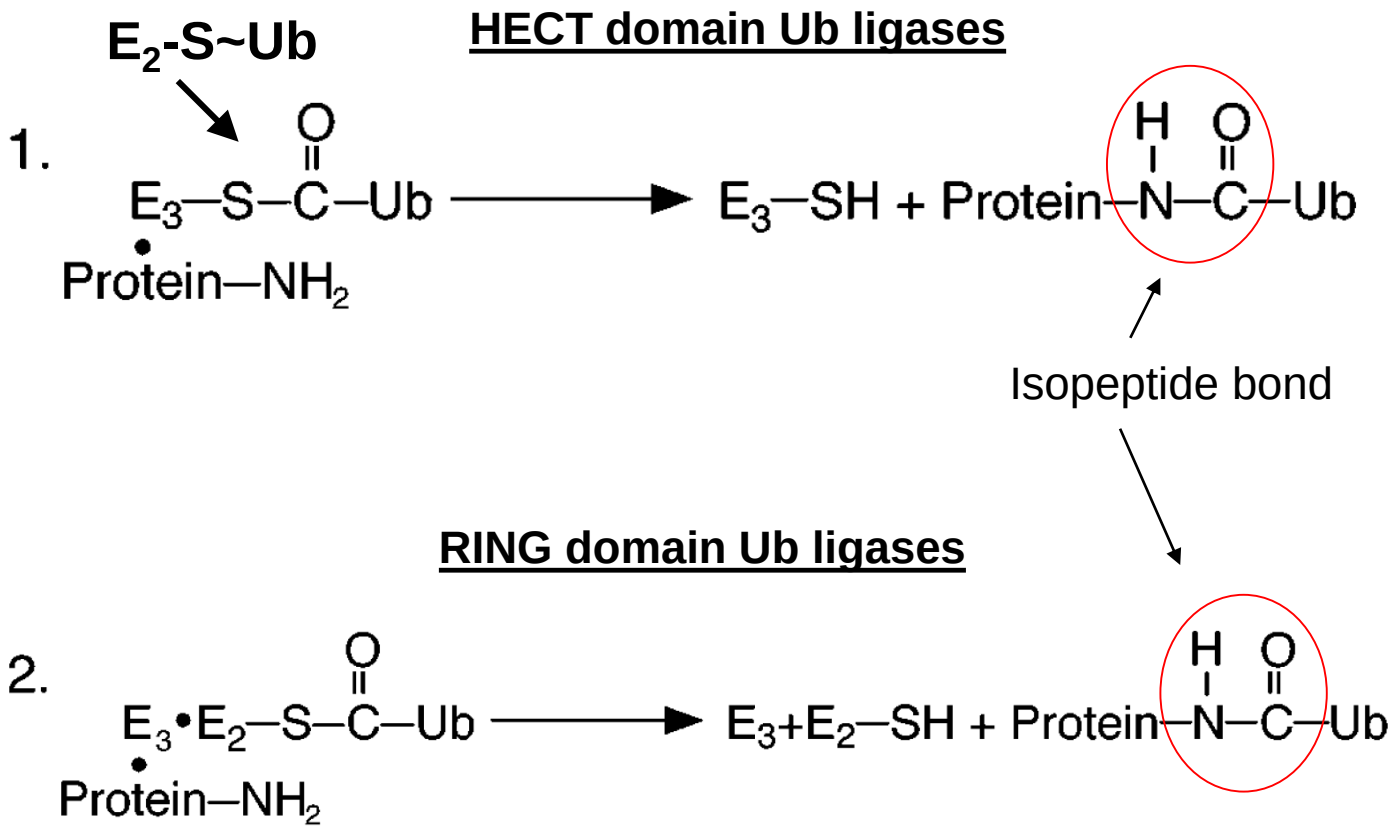
The UPS



Ubiquitin	SUMO	NEDD8	ISG15
E1 (2):	E1 (1):	E1 (1):	E1 (1):
Uba1 Uba6	Aos1/Uba2	APPBP1/Uba3	UBE1L
E2 (30):	E2 (1):	E2 (2):	E2 (3):
UBE2A(hHR6A) UBE2B(hHR6B) UBE2C(UbcH10) UBE2D1(UbcH5A) UBE2D2(UbcH5B) UBE2D3(UbcH5C) UBE2D4(HBUCE1) UBE2E1(UbcH6) ± UBE2E2 UBE2E3(UbcH9) UBE2G1(UBE2G) UBE2G2(UBC7) UBE2H(UBCH) UBE2J1(NCUBE1) UBE2J2(NCUBE2) UBE2K(HIP2) UBE2L3(UbcH7) UBE2L6(UbcH8) ± UBE2N(Ubc13) UBE2O(E2-230K) UBE2Q1(NICE-5) UBE2Q2 UBE2R1(CDC34) UBE2R2(CDC34B) UBE2S(E2-EPF) UBE2T(HSPC150) UBE2U* UBE2V1(UEV-1A) UBE2V2(MMS2) UBE2W UBE2Z(Use1) BIRC6(apollon)	UBE2I(Ubc9)	UBE2M(Ubc12) UBE2F(NCE2)	UBE2L6(UbcH8) : UBE2E1(UbcH6) : UBE2E2 ±
E3 (>1000):	E3 (4):	E3 (2):	E3 (2):
Single/multiple subunit RING, HECT, U-box, PHD	RanBP2, Pc2, PIAS-proteins, Topors	Rbx1 Rbx2	HERC5 EFP

Ub ligases (E3s)

The Ub ligases (E3s) ligate specifically Ub to protein substrates. They determine the specificity of the UPS.



Poly-ubiquitinated proteins are recognized and degraded by the 26S proteasome (proteolytic machinery)

Composition of the 26S proteasome

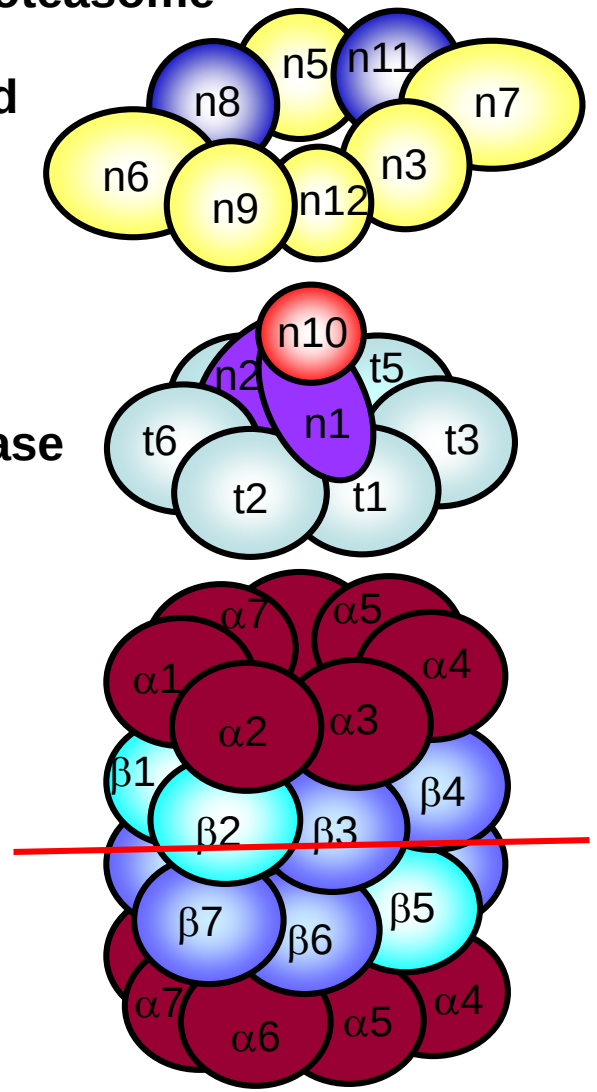
19S regulatory complex

Lid

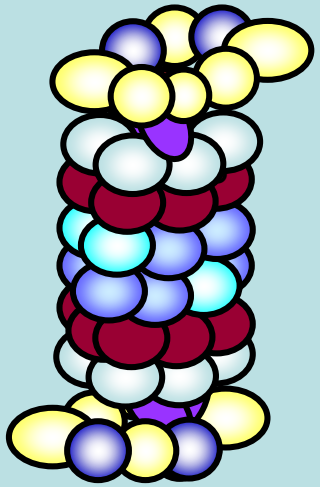
Base

n = Rpn
t = Rpt

20S proteasome



26S proteasome



In vivo!

The funstions of 26S proteasome subcomplexes

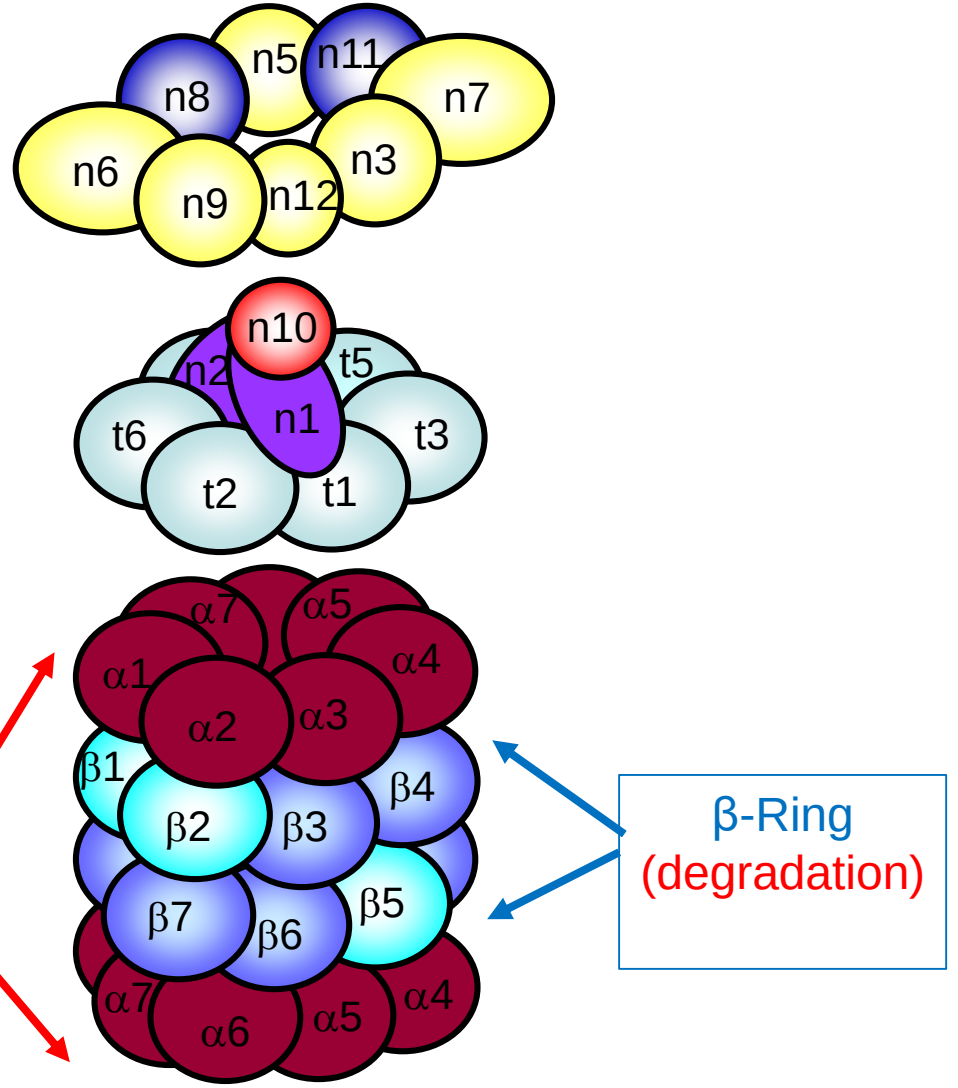
Lid

(recognition of poly-Ub, cleavage of Ub molecules)

Base

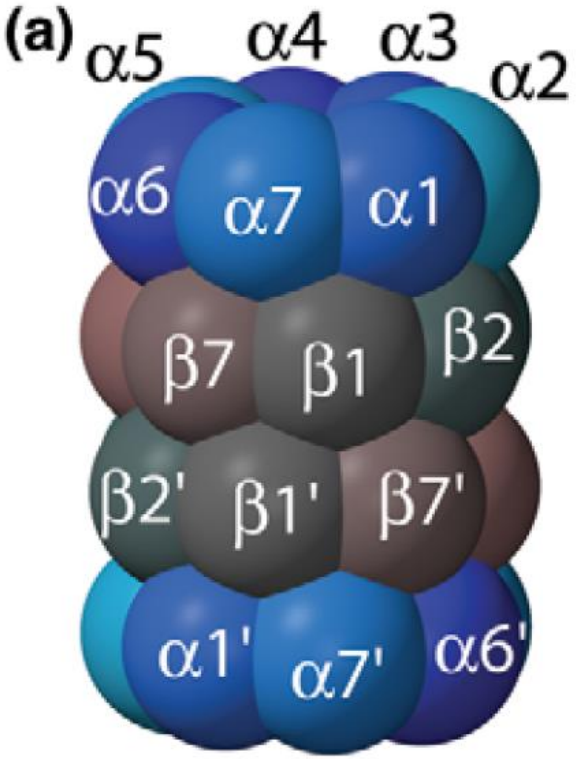
(folding of proteins, gate opening)

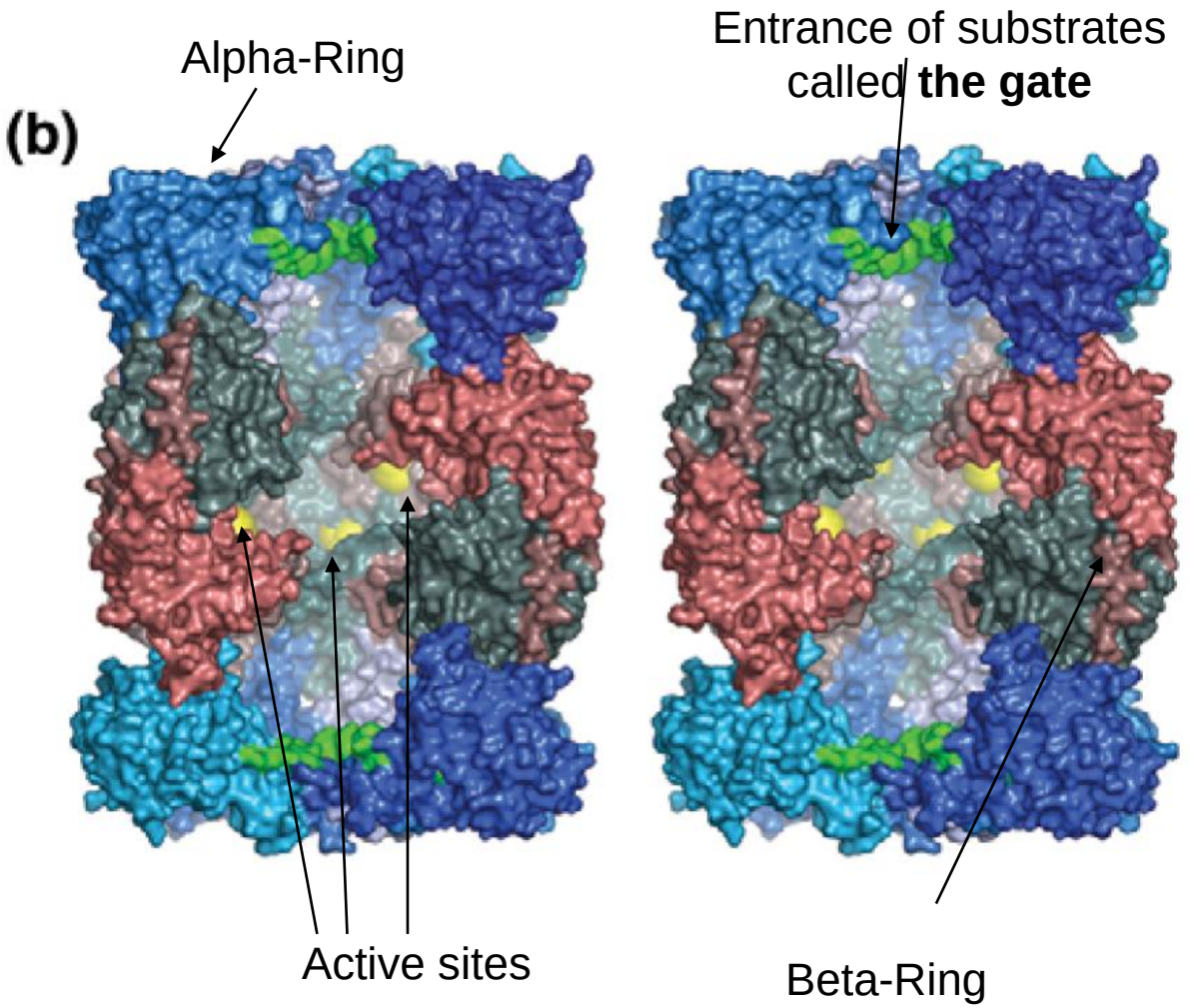
α-Ring (gate opening)



β-Ring (degradation)

Structure of the 20S core proteasome

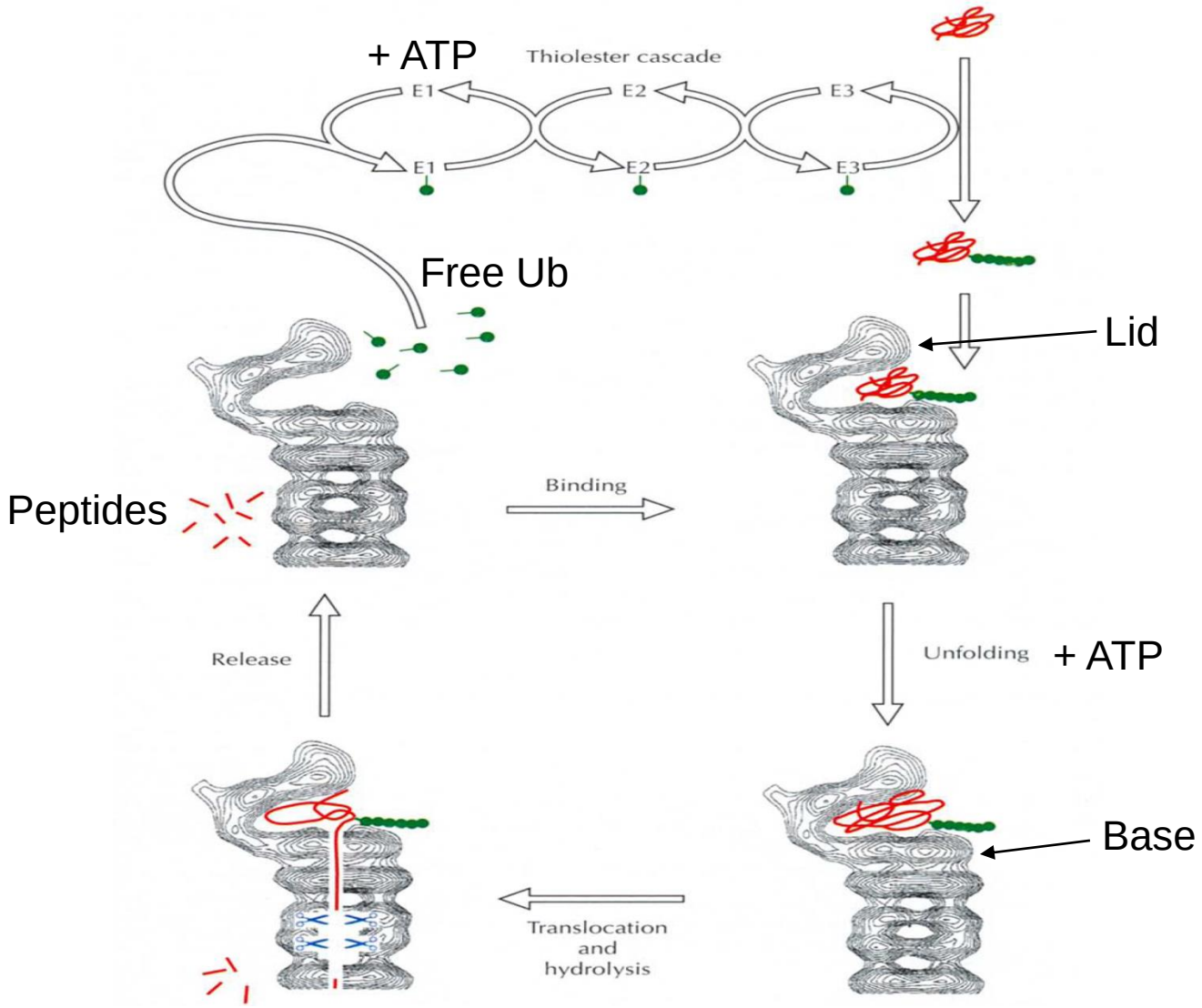




Threonine: Thr

How much active sites contain one molecul 20S proteasome?

Why do we need ATP in the UPS?



ATP is needed to make the process more specific.

Questions

What is proteolysis? What are endo- and exo-peptidases?

-20S Proteasome: endopeptidases

Which type of protease is the 20S proteasome?

- Cystein-protease
- Threonin-protease
- Metalloprotease

Are DUBs specific?
Yes

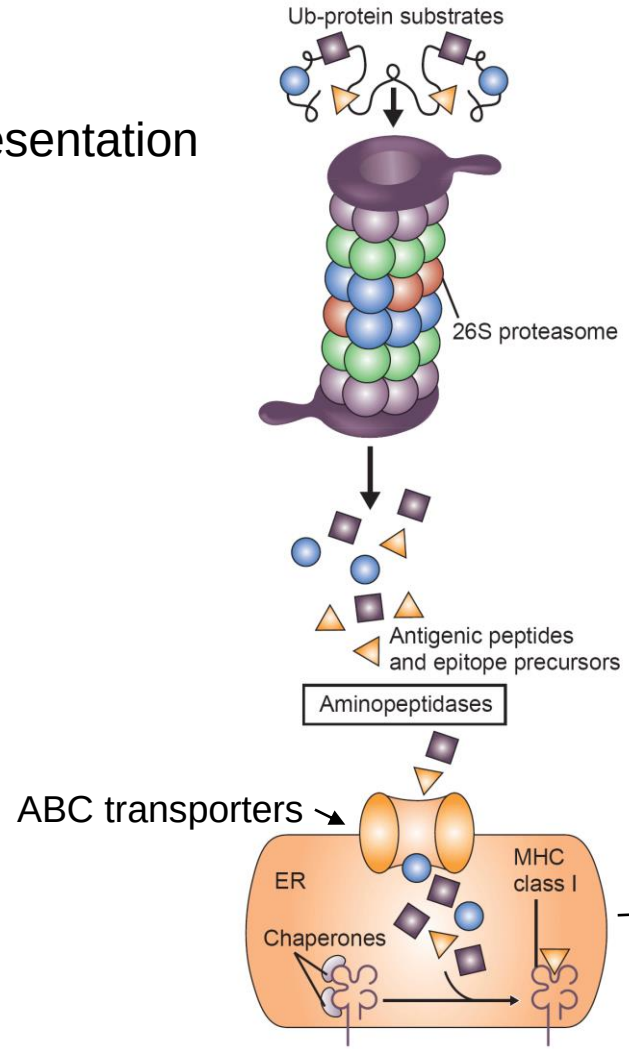
What about the UPS?
Yes (Poly-Ub proteine, E3 Ub Ligases are specific)

Are the 20S proteasome and the 26S proteasome specific?
No/Yes

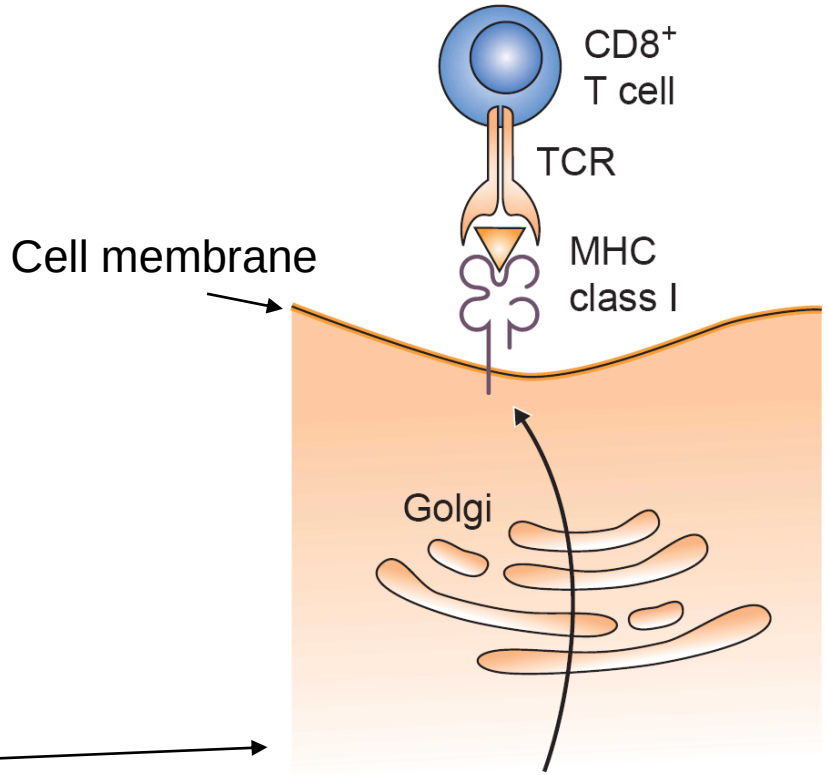
1. Antigen processing by the 26S proteasome

-antigens
-antigene presentation

Processing of viral proteins

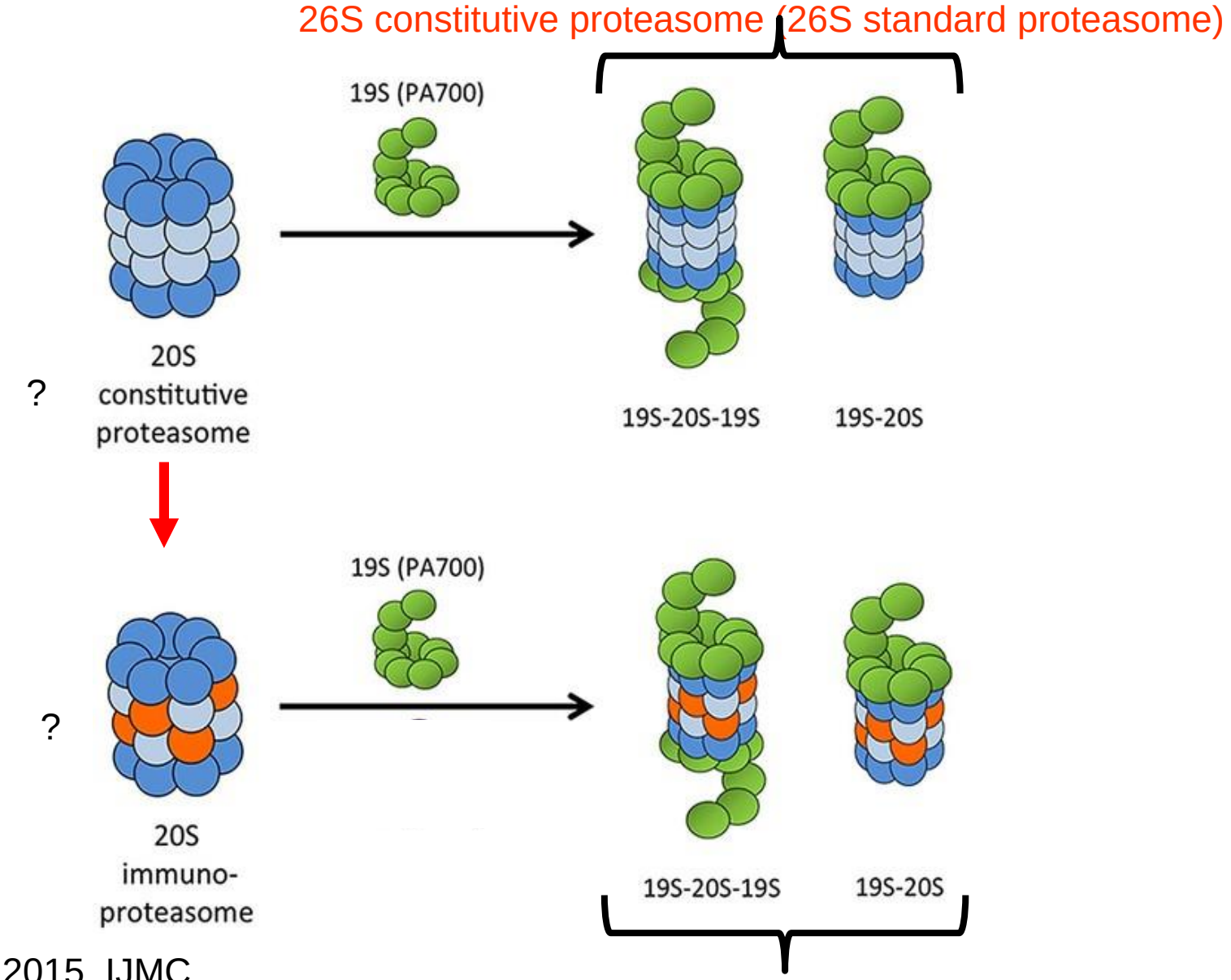


Presentation of antigenic peptides
by infected somatic cells



Kloetzel, P.-M. (2004) Nature Immunology

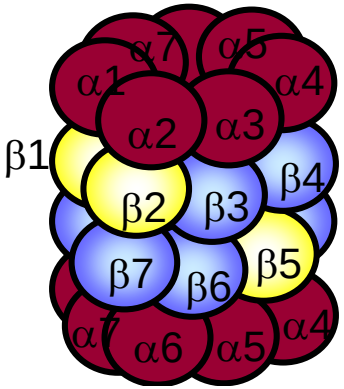
Proteasome populations in infected or cytokine stimulated cells



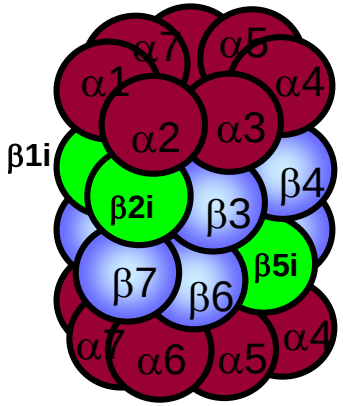
McCarthy et al. 2015, IJMC

Function of immunoproteasomes

- Efficient MHC class I antigen presentation
- Degradation of oxidized proteins



20S constitutive proteasome



20S immunoproteasome

26S or 20S immunoproteasome

Reasons:

Production of epitops:

1. some preferences e.g. more digestion after hydrophobic amino acids, high binding affinity to MHC class I molecule, more nonamers (qualitative change), but no formation of neoantigens!

9 amino acids

2. Immunoproteasome is more active? (quantitative change)!!!!

Components of the UPS

Ubiquitin: from Latin *ubique* (“everywhere”), from *ubi* (“where”)

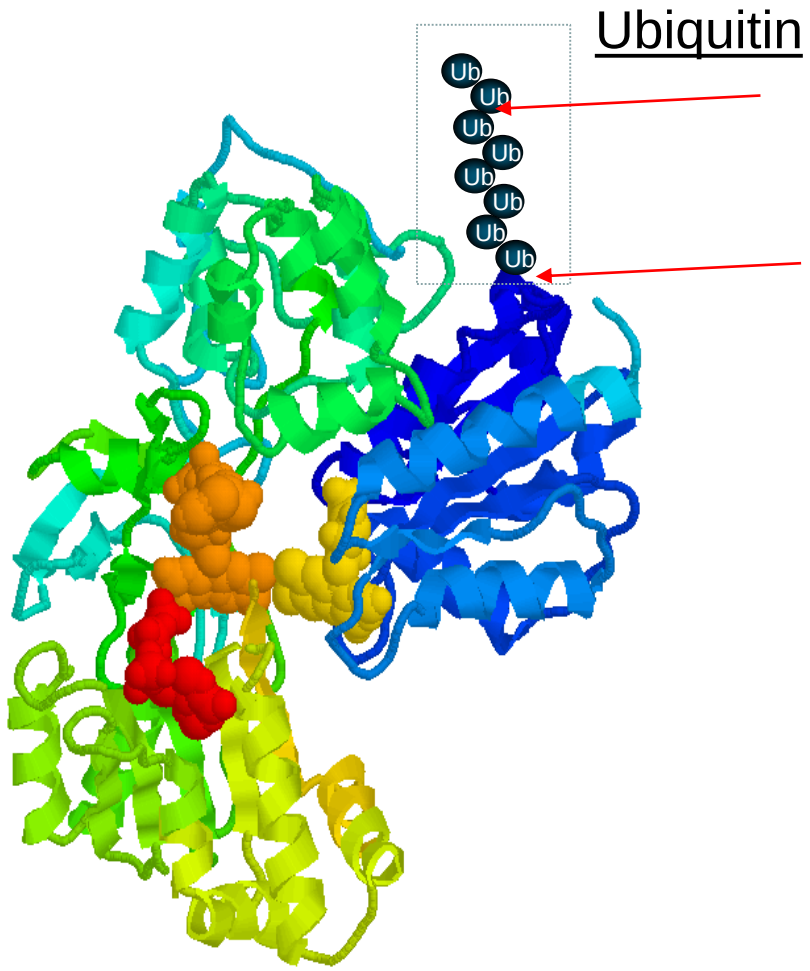
Ubiqutin: Covalent bond between:

Ub-Ub

Ub-Substrates

-Ubiquitination/Ubiquitylation:

a posttranslational modification



Ub-like proteins (Ubl)

Posttranslational Modifications

Covalent-conjugated proteins:

-Ubiquitin

-NEDD8

-Sumo

-FAT10

-ISG15

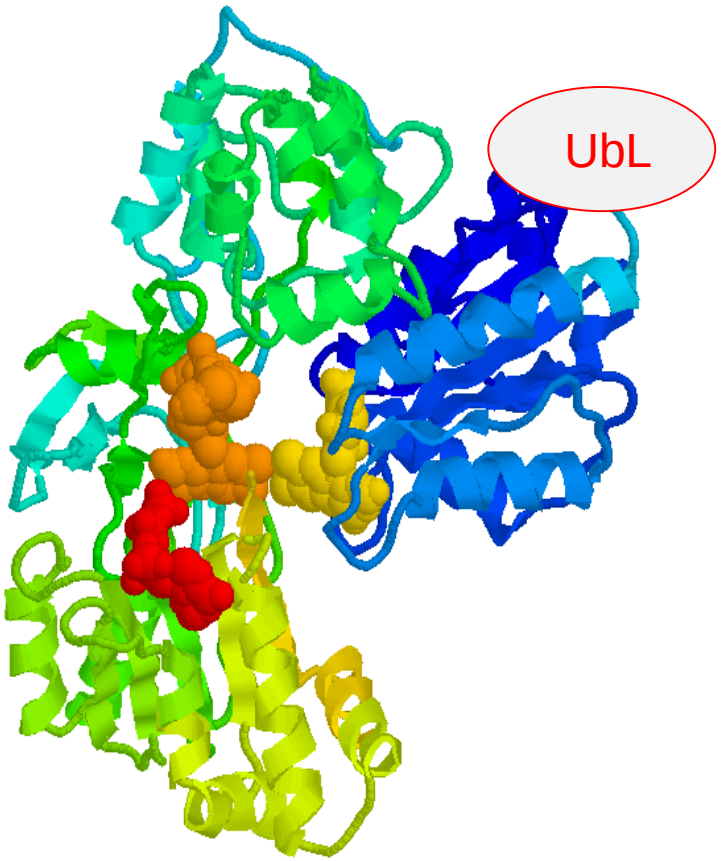
-UFM1

-UBL5

-ATG8=LC3

-ATG12

Ubiquitin-like proteins (Ubl)



Why is a protein ubiquitin-like?

- The ability to be conjugated? Enzyme-cascade (E1-E3)
- The structure? Similarity
- The amino acid composition? Sequence Homology

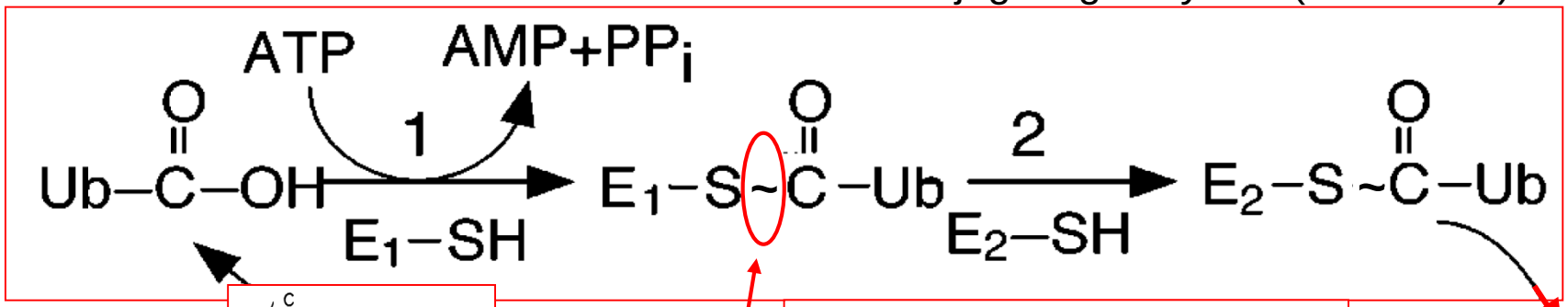
Activation and transfer of Ub

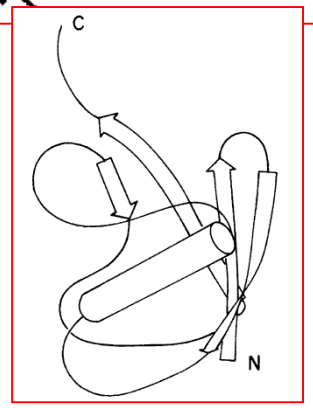
E1 – Ub activating enzyme

There are few Ub activating enzymes in eukaryotic cells

E2s – UBCs – Ub conjugating enzymes

There is a large family of Ub conjugating enzymes (~50 UBCs).

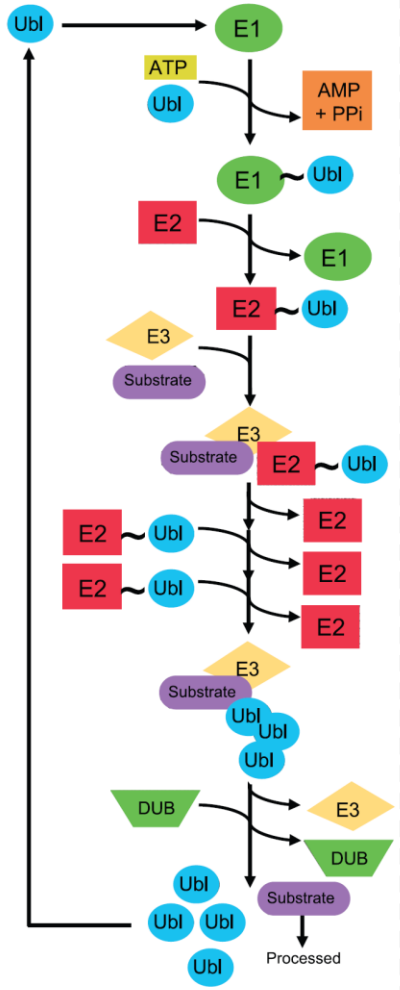




Transthiolation reaction from E1-S-Ub to E2-S-Ub.

Thioester bond

The UPS



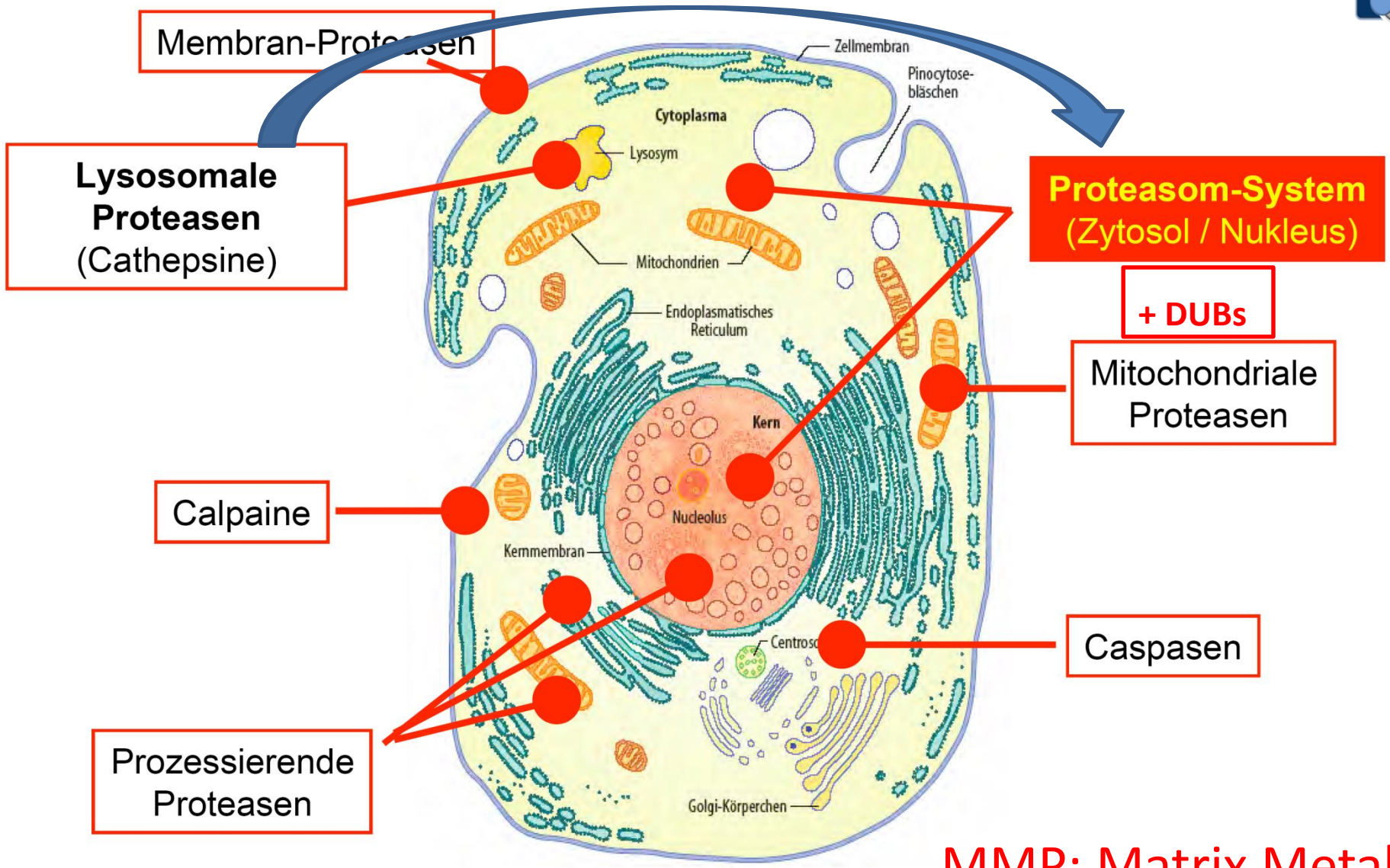
Ubiquitin	SUMO	NEDD8	ISG15
E1 (2):	E1 (1):	E1 (1):	E1 (1):
Uba1 Uba6	Aos1/Uba2	APPBP1/Uba3	UBE1L
E2 (30):	E2 (1):	E2 (2):	E2 (3):
UBE2A(hHR6A) UBE2B(hHR6B) UBE2C(UbcH10) UBE2D1(UbcH5A) UBE2D2(UbcH5B) UBE2D3(UbcH5C) UBE2D4(HBUCE1) UBE2E1(UbcH6) ± UBE2E2 UBE2E3(UbcH9) UBE2G1(UBE2G) UBE2G2(UBC7) UBE2H(UBCH) UBE2J1(NCUBE1) UBE2J2(NCUBE2) UBE2K(HIP2) UBE2L3(UbcH7) UBE2L6(UbcH8) ± UBE2N(Ubc13) UBE2O(E2-230K) UBE2Q1(NICE-5) UBE2Q2 UBE2R1(CDC34) UBE2R2(CDC34B) UBE2S(E2-EPF) UBE2T(HSPC150) UBE2U* UBE2V1(UEV-1A) UBE2V2(MMS2) UBE2W UBE2Z(Use1) BIRC6(apollon)	UBE2I(Ubc9)	UBE2M(Ubc12) UBE2F(NCE2)	UBE2L6(UbcH8) : UBE2E1(UbcH6) : UBE2E2 ±
E3 (>1000):	E3 (4):	E3 (2):	E3 (2):
Single/multiple subunit RING, HECT, U-box, PHD	RanBP2, Pc2, PIAS-proteins, Topors	Rbx1 Rbx2	HERC5 EFP

Institut für Experimentelle Innere Medizin
Medizinische Fakultät
Otto-von-Guericke-Universität Magdeburg

VL 2 (Dr. Dawadschargal Dubiel)

Autophagy/Autophagie

Cellular proteases



MMP: Matrix Metalloproteasen

Outlines:

- Definition
- History & Discovery
- Functions
- Autophagy types
- Transcription factors
- Macroautophagy signals
- Macroautophagy steps
- Selective macroautophagy
- Substrates of autophagy
- Impairment of autophagy
- Comparison of UPS and selective Macroautophagy

Autophagy (Definition)

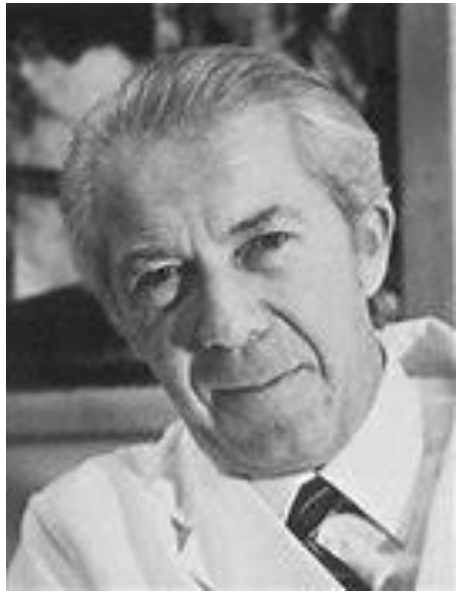
- **Autophagy** (or *autophagocytosis*) (from the Ancient Greek αὐτόφαγος *autóphagos*, meaning "self-devouring„)

- In all eucaryotic cells (animal and plants): **lysosome** (from Ancient Greek *λύσις*, from *lysis* and *σῶμα sṓma* 'body‘) and **vacuole** (from latin ´vacuus‘: Vacuum or empty room)

Lysosome (Cell organelle)

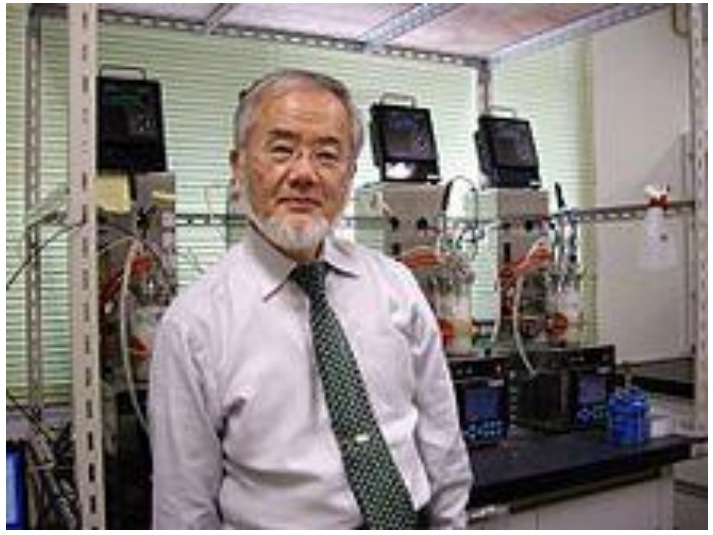
- Vesicle with membrane originally formed from ER
- The vesicle contains 60 hydrolytic enzymes and 50 membrane proteins
- Enzymes are active on low pH
- The vesicle contains membrane proteins, among them ATPase complexes for maintaining low pH (proton pumps)
- Substrates: cell organelles, proteins, lipids and nucleic acids (RNAs and DNAs)

History & Discovery



Prof. Christian René de Duve: 1974 Nobel Prize in Physiology or Medicine

-1950: Lysosome as a vesicle with hydrolytic Enzymes
-Peroxisomes



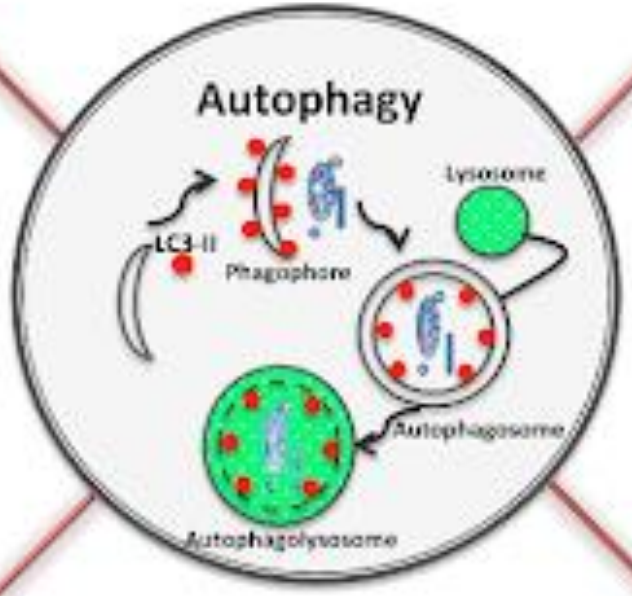
Prof. Dr. Yoshinori Ohsumi: 2016 Nobel Prize in Physiology or Medicine

-1990: Autophagy ATG-Gens in yeast and mammalia
-Functions of Autophagy

Functions of autophagy

METABOLISM
Carbon metabolism
Lipid metabolism
Protein metabolism
Nutrient mobilization
Energy production

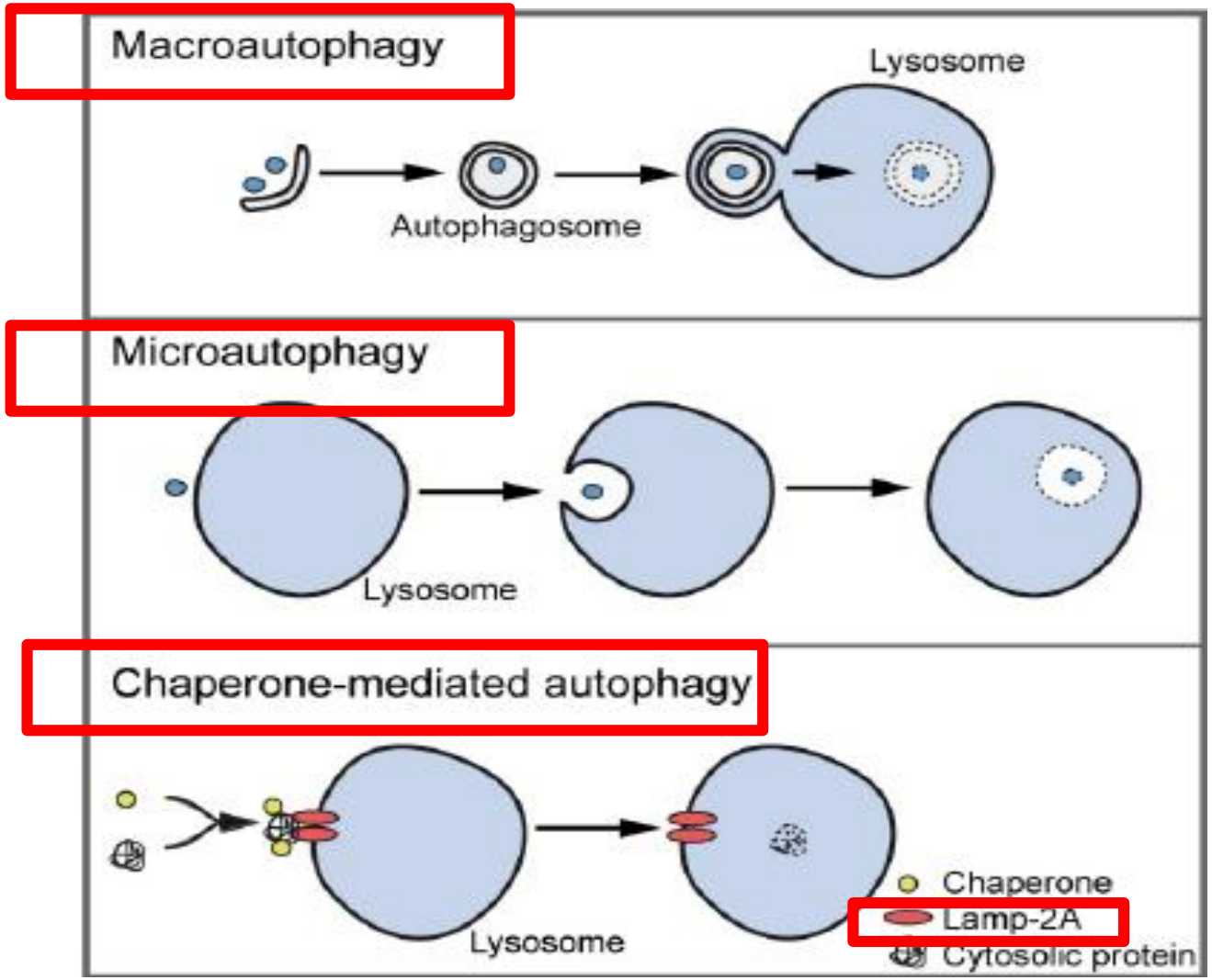
SUBVERSION
(Bacteria, virus…)
Microorganism replication
Survival/Apoptosis response
Nutrient mobilization
Energy production



QUALITY CONTROL
Survival/Apoptosis response
Response to ER stress
Protein quality control
Organelle degradation
Cell destruction

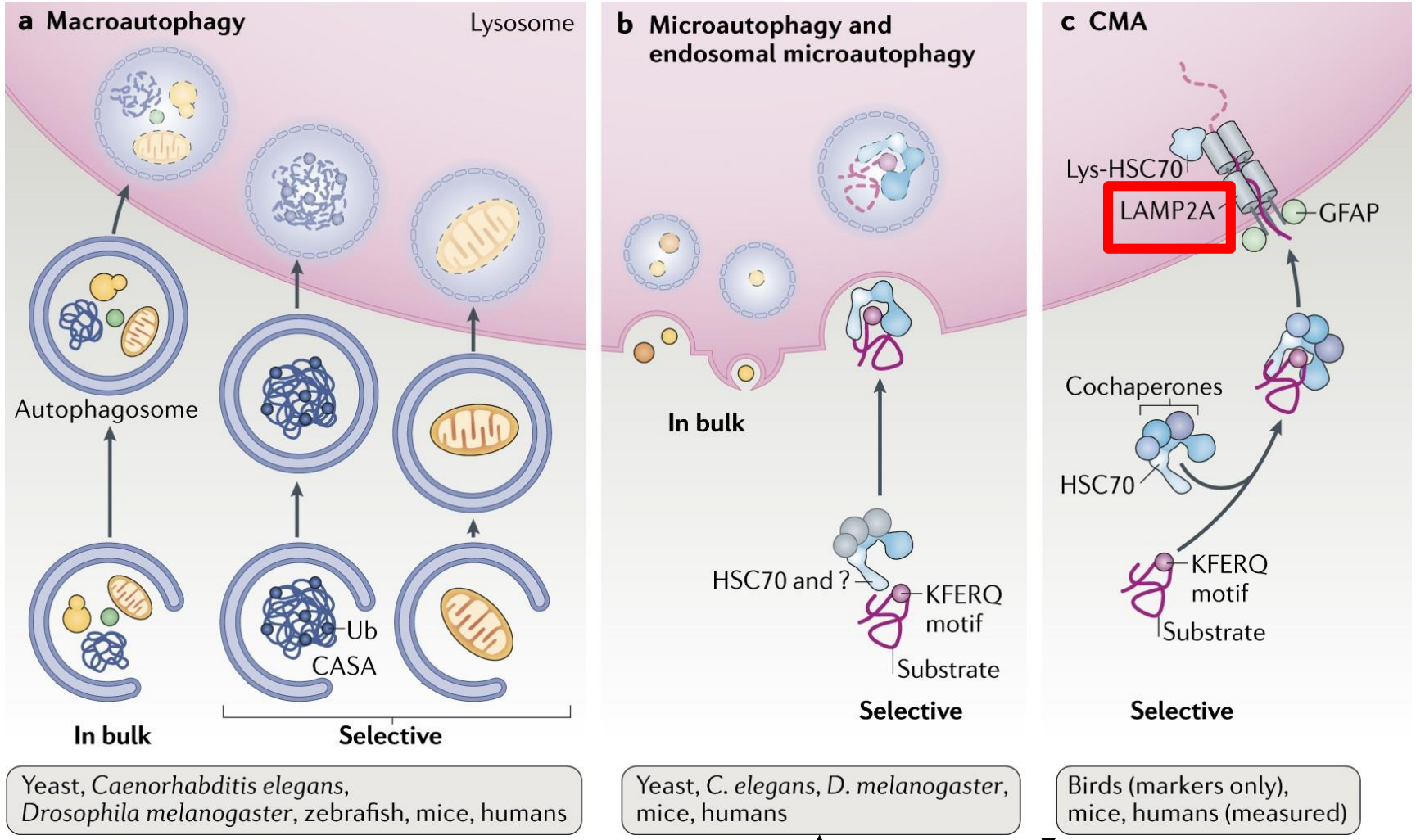
CELL DEFENSE
Antigen presentation
TLR recognition
Microorganism
degradation

Autophagy types



Aburto et al. *Cells* 2012

Autophagy types

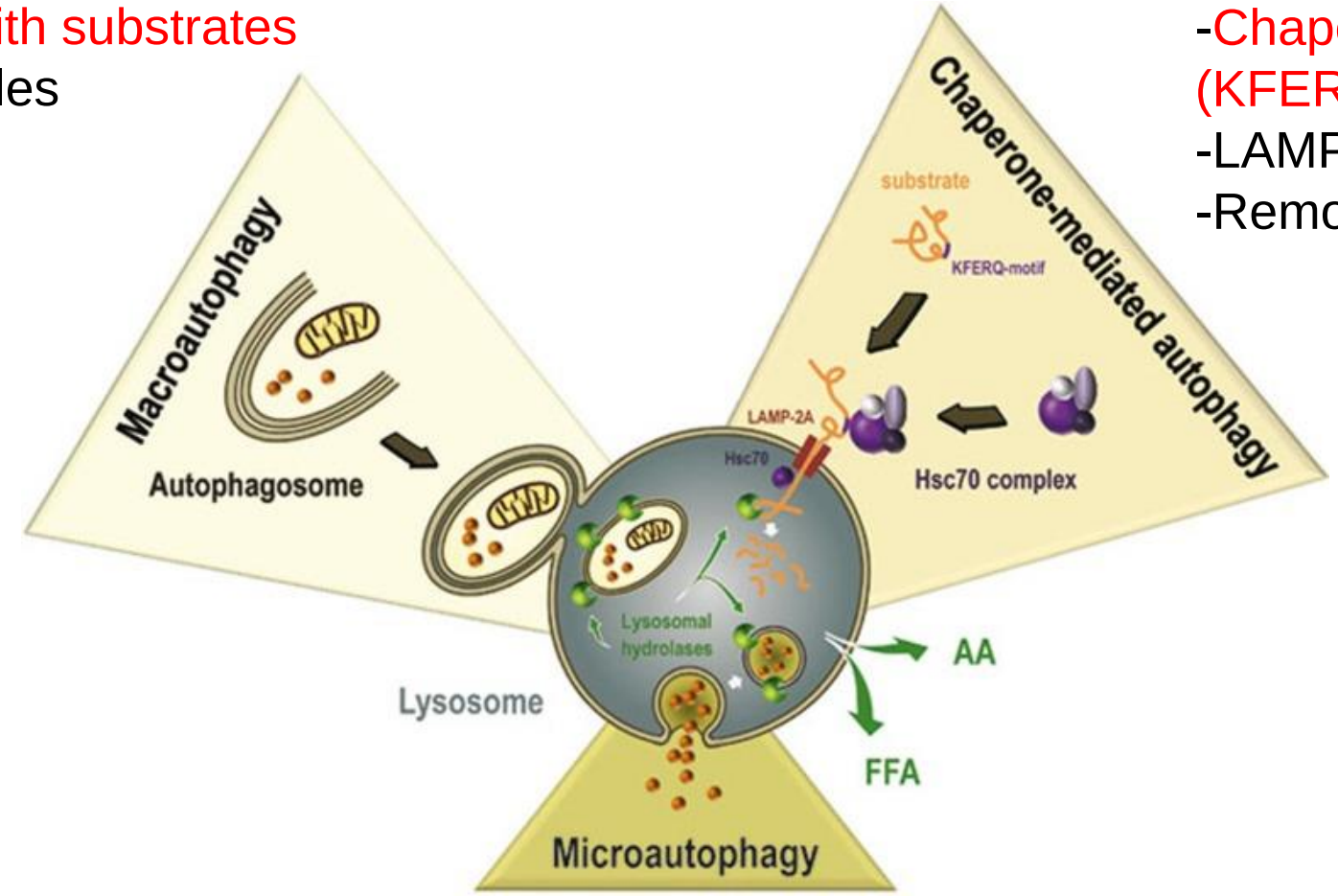


KFERQ motive

Kaushik et al. *Nature Reviews Molecular Cell Biology* 2018

Autophagy types

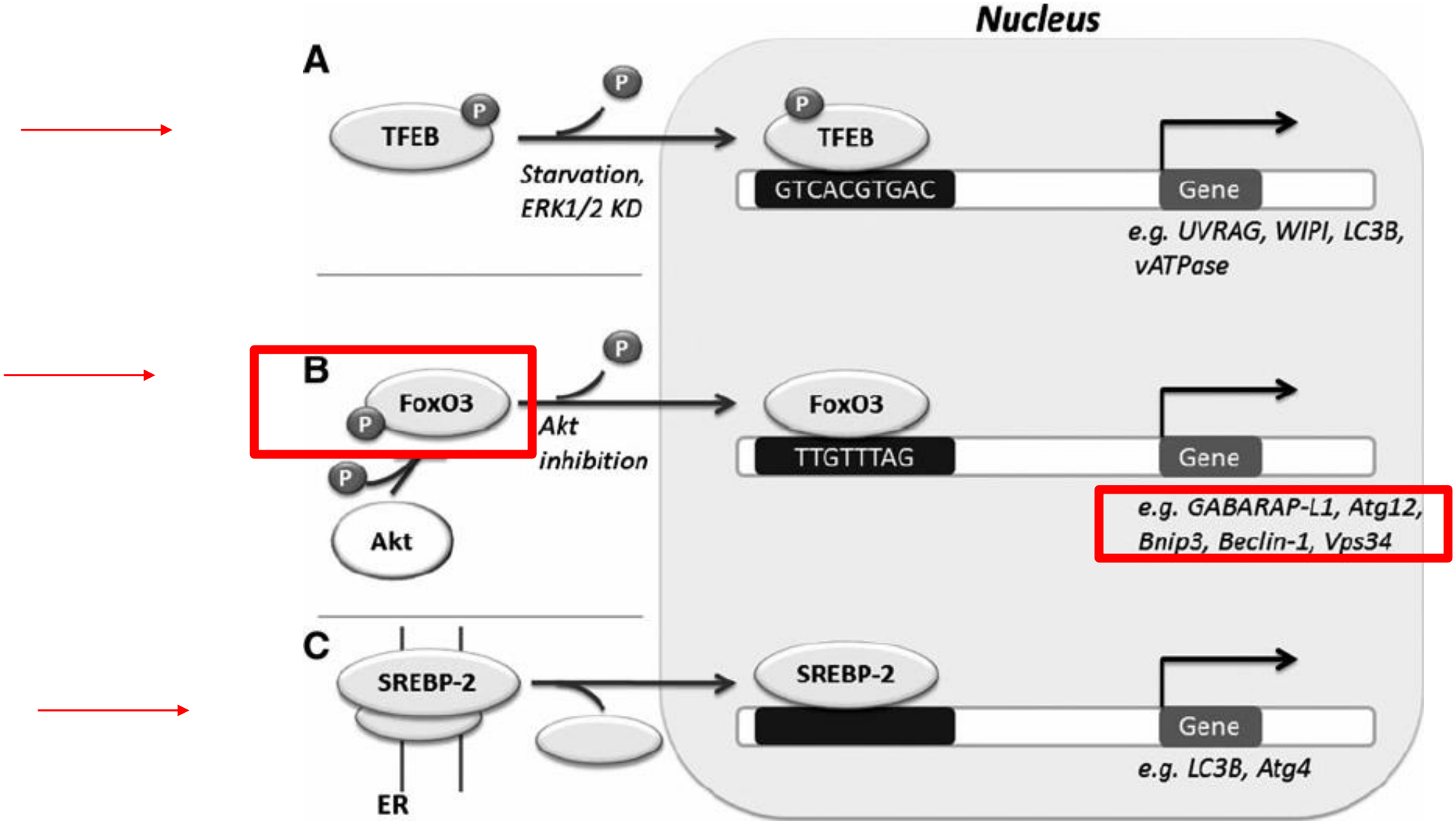
-Formation of vesicles with substrates
-Removal of cell organelles
-Removal of pathogens
-Removal of proteins



-Chaperone recognition (KFERQ-Motive)
-LAMP2 internalisation
-Removal of cytosolic proteins

-lysosomal membrane invagination, vesicle formation into lysosome
-Removal of cytoplasmatic materials e.g. lipids

Transcription factors



Macroautophagy: cellular proccess

- Extracellular or intracellular signals

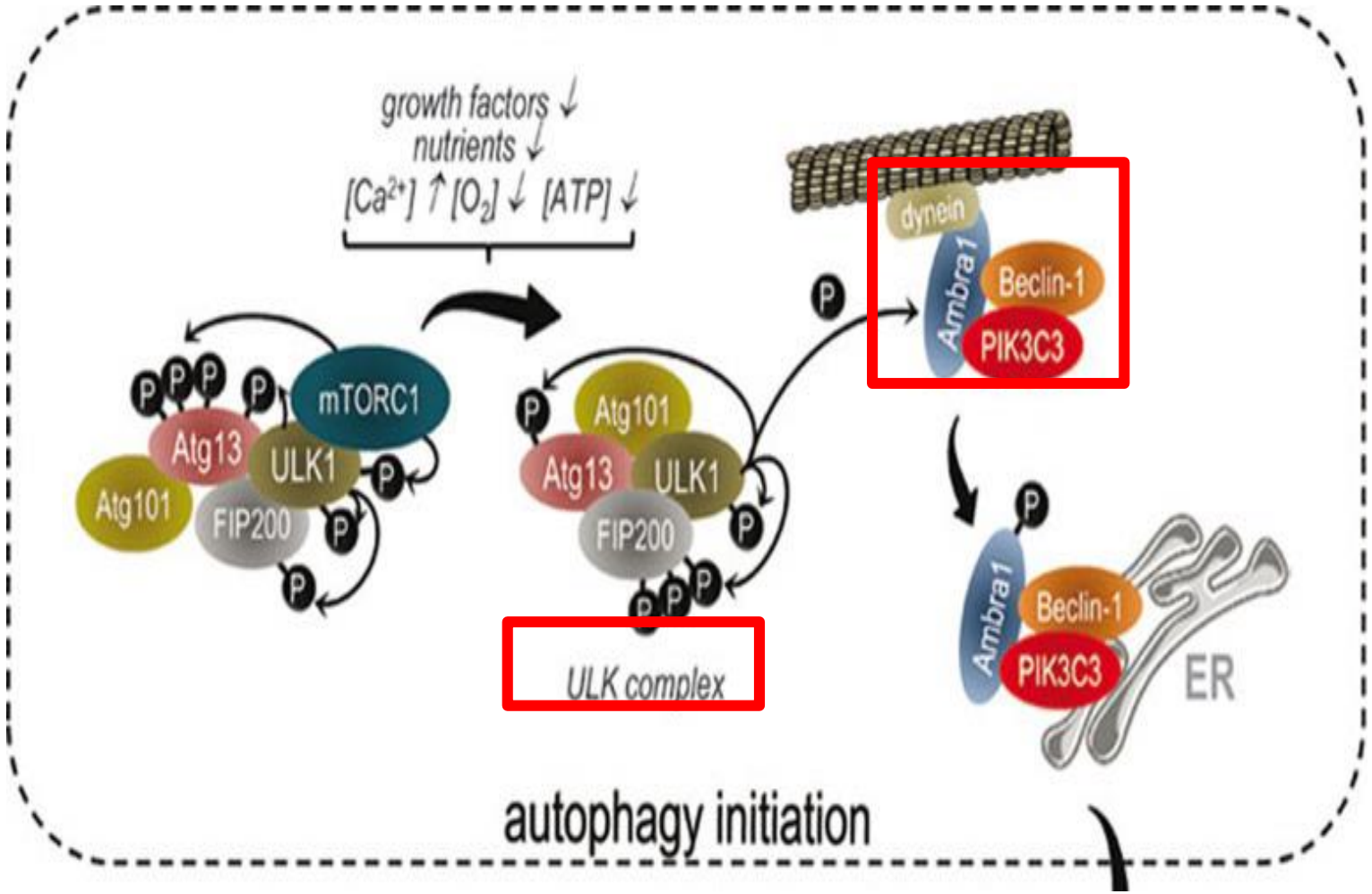
Macroautophagy-steps in cells

- 1. Initiation
- 2. Nucleation
- 3. Elongation
- 4. Maturation
- 5. Fusion
- 6. Degradation

Extra- and intracellular signals:

- 1. Extracellular signals:
  - Serum starvation (e. g. low energy)
  - Amino acid limitation
  - Growth factor limitation
  - Radiation
  - Hypoxia
  - Infection
- 2. Intracellular signals:
  - Defects in organelles
  - Accumulation of non-functional protein complexes
  - Misfolded proteins and protein aggregates

1. Initiation



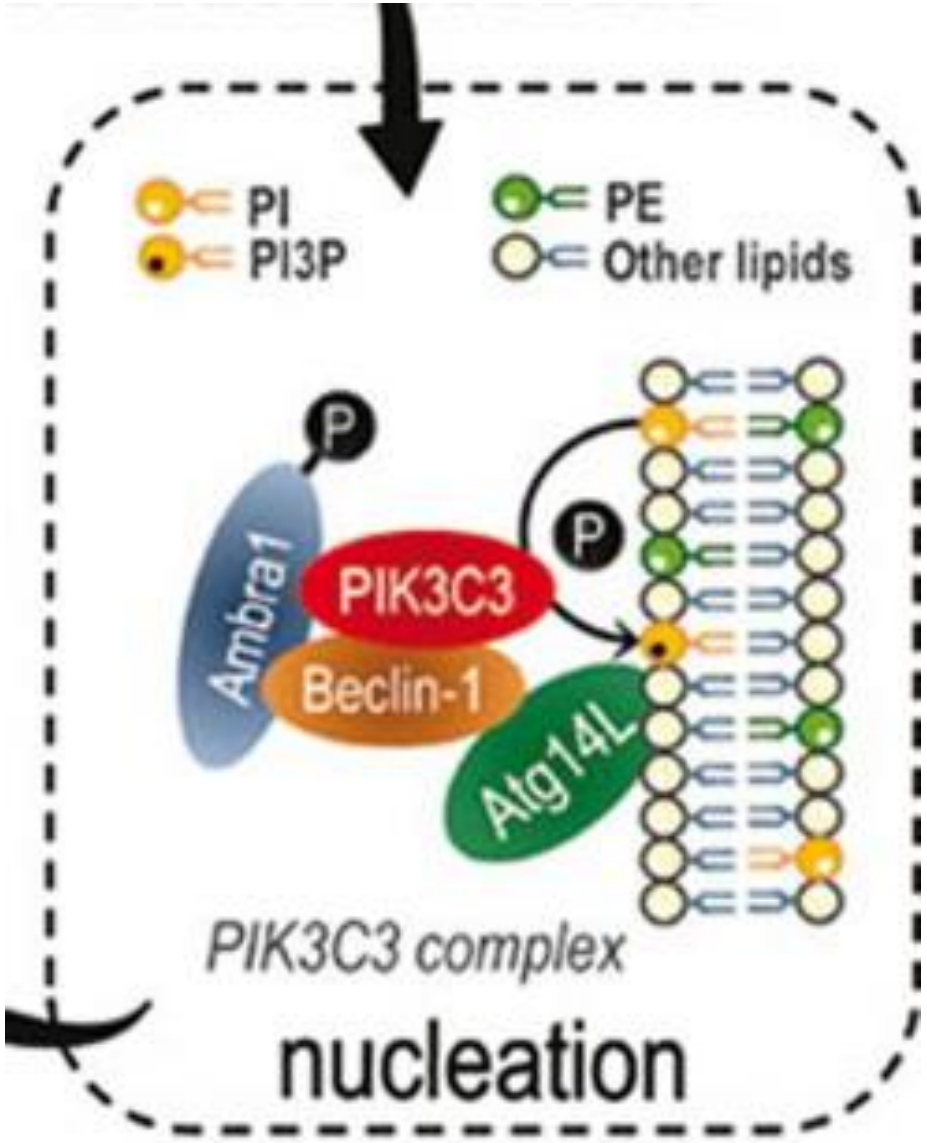
-Inhibition of mTORC1,
(dissociation of mTORC1 from ULK)

-Activation of ULK complex

-ULK phosphorylates PIKC3 complex
(release of PIKC3 complex
from microtubules and recruit onto ER)

Wirawan et al. *Cell Research* 2012

2. Nucleation

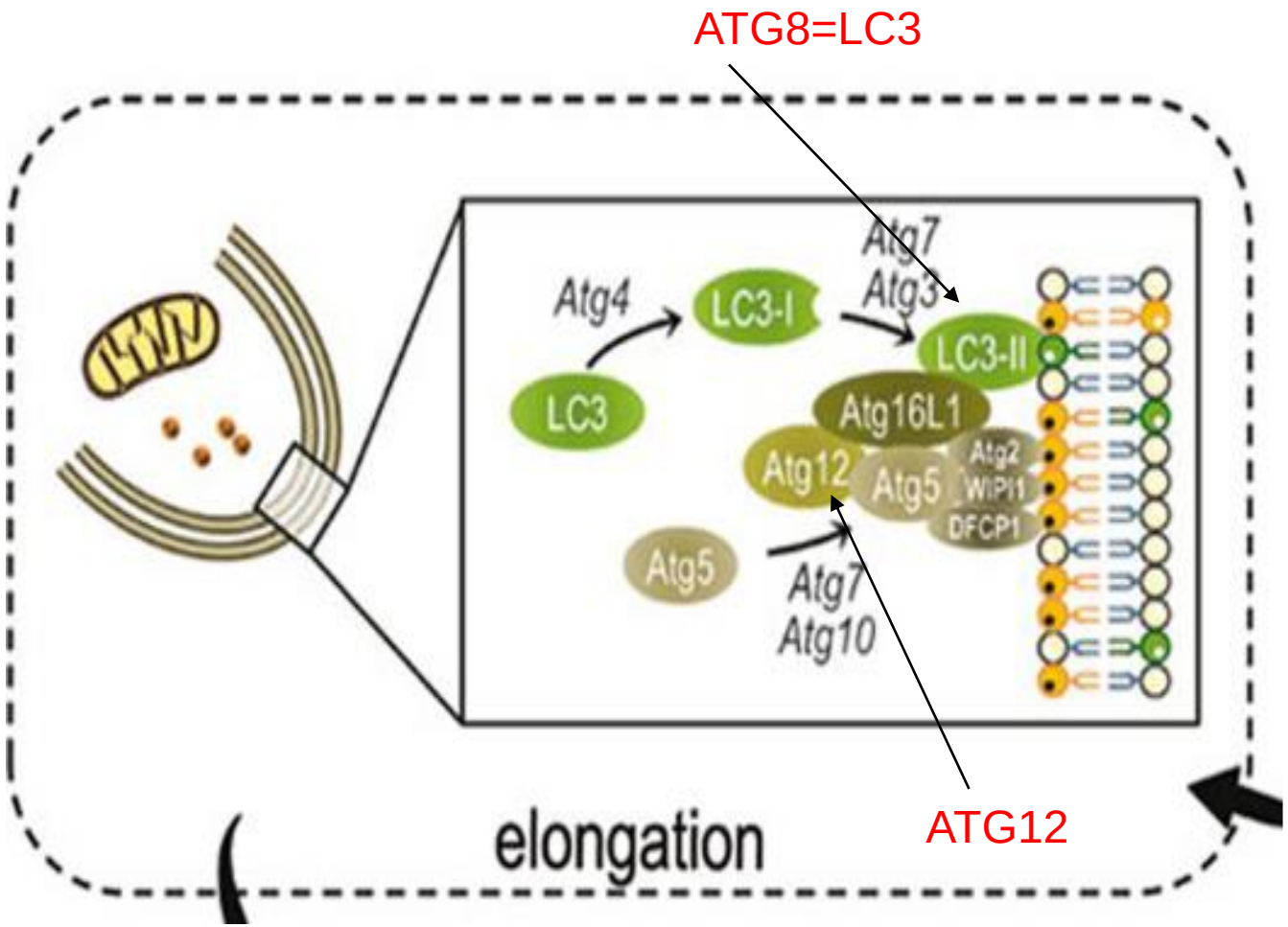


-PIK3C3 complex generates PI3P

-PI3P recruits ATG proteins
to the side of autophagosome

Wirawan et al. *Cell Research* 2012

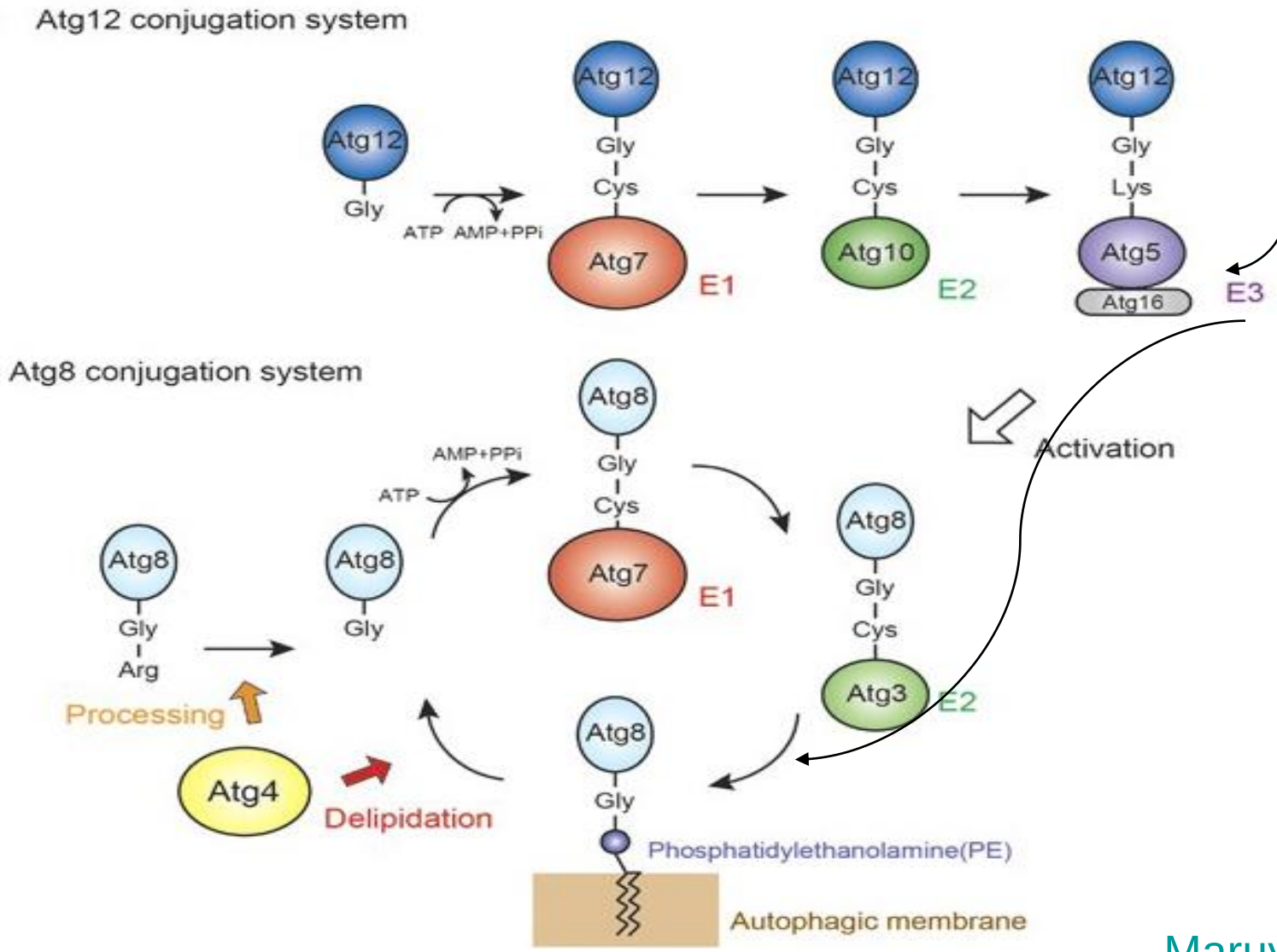
3. Elongation



-Phagophore membrane expansion and shaping
by ATG12 conjugation (outer side of membrane)
ATG8 conjugation system (inner and outer side membrane)

Wirawan et al. *Cell Research* 2012

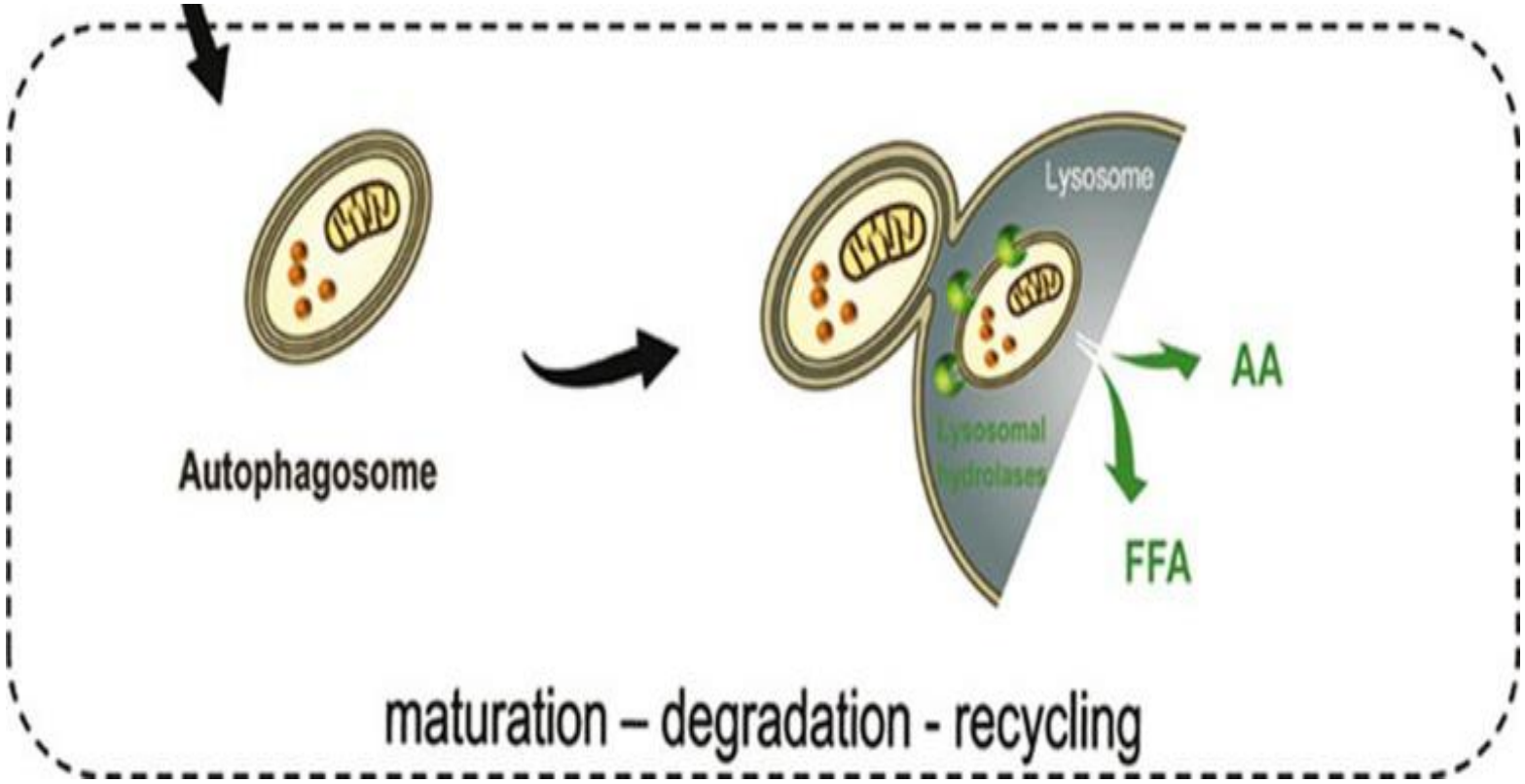
Macroautophagy needs ATGylation: ATG8 and ATG12 Conjugation



-ATP consumption
-Enzyme cascade: E1,E2, E3
-Ub-lilke proteins:ATG12, ATG8

Maruyama et al. *Journal of Antibiotics* 2017

4. Maturation-5. Fusion-6. Degradation



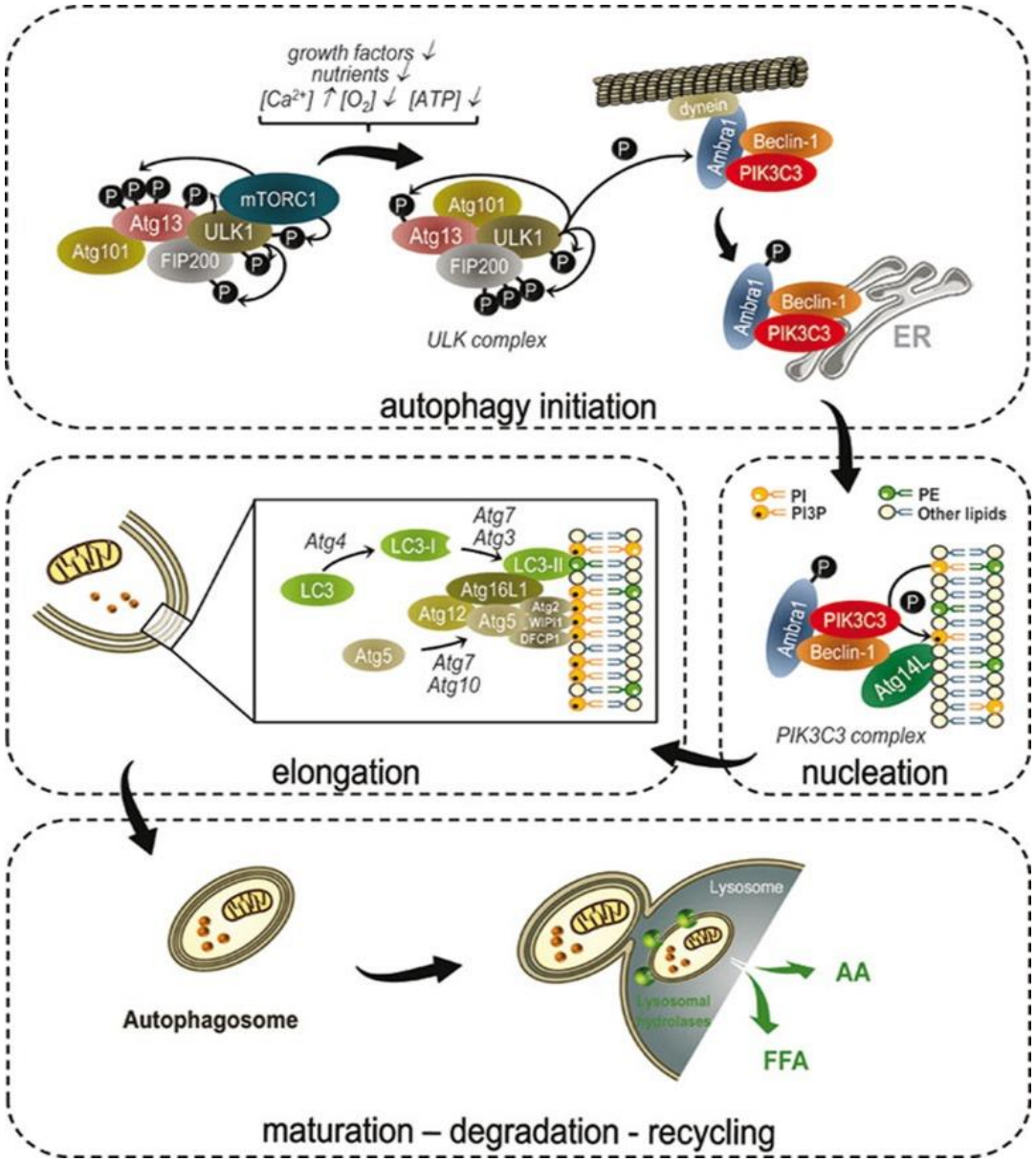
-Recruitment of substrates (cargos) into the membrane
-Closure of phagophore membrane (Autophagosome)

Fusion with lysosome

Degradation by lysosome (lysosomal enzymes work at low pH)

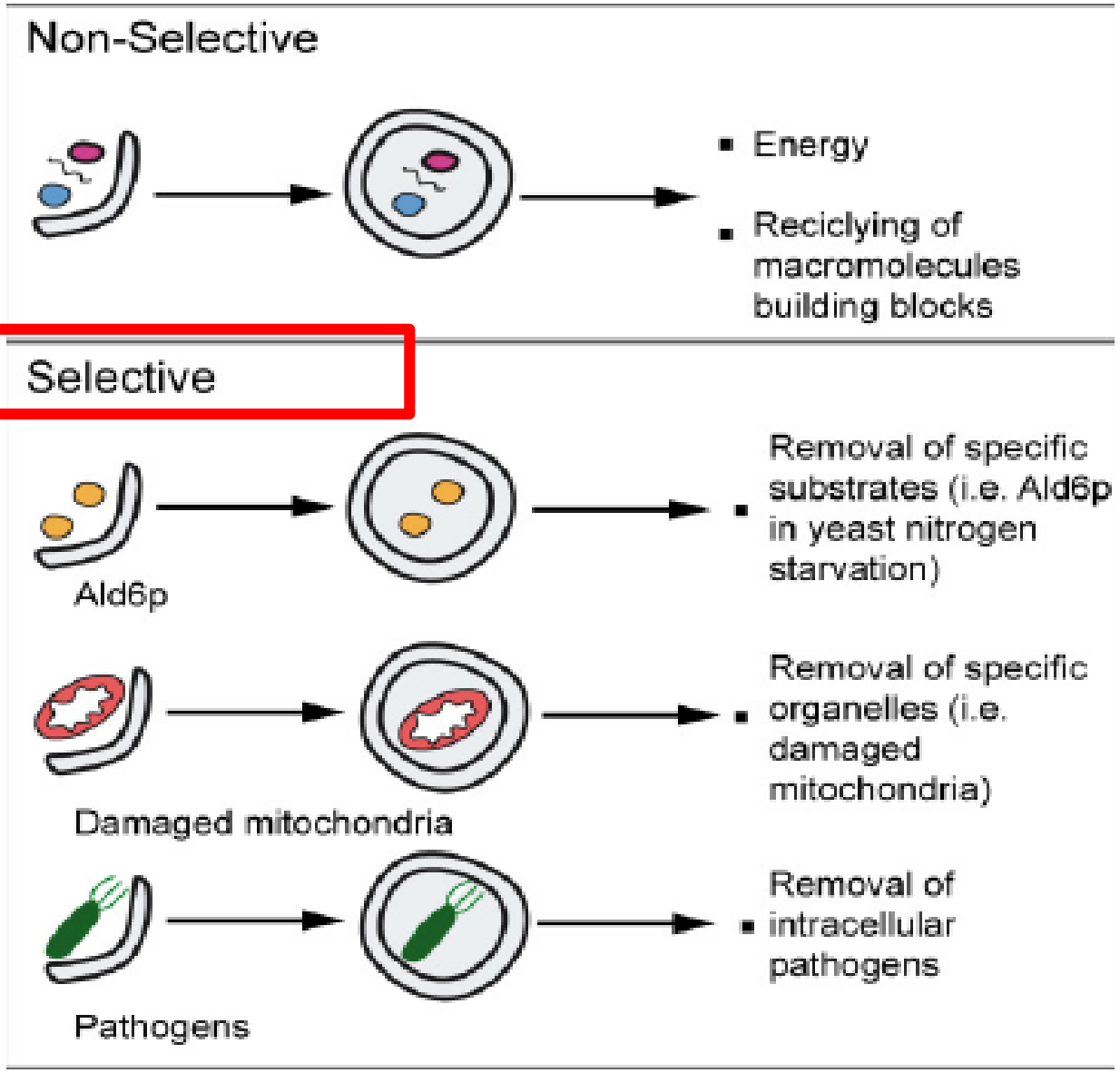
Wirawan et al. *Cell Research* 2012

Macroautophagy steps



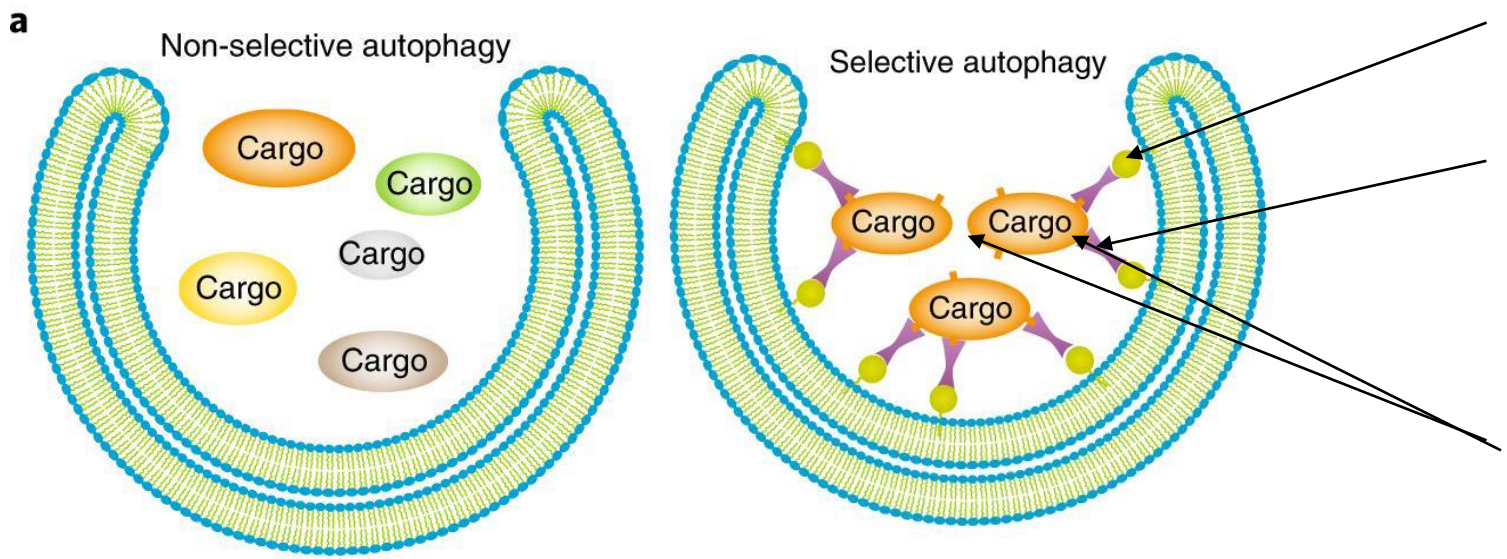
Wirawan et al. *Cell Research* 2012

Macroautophagy types



Aburto et al. *Cells* 2012

Selective macroautophagy



ATG8/LC3 (yellow)

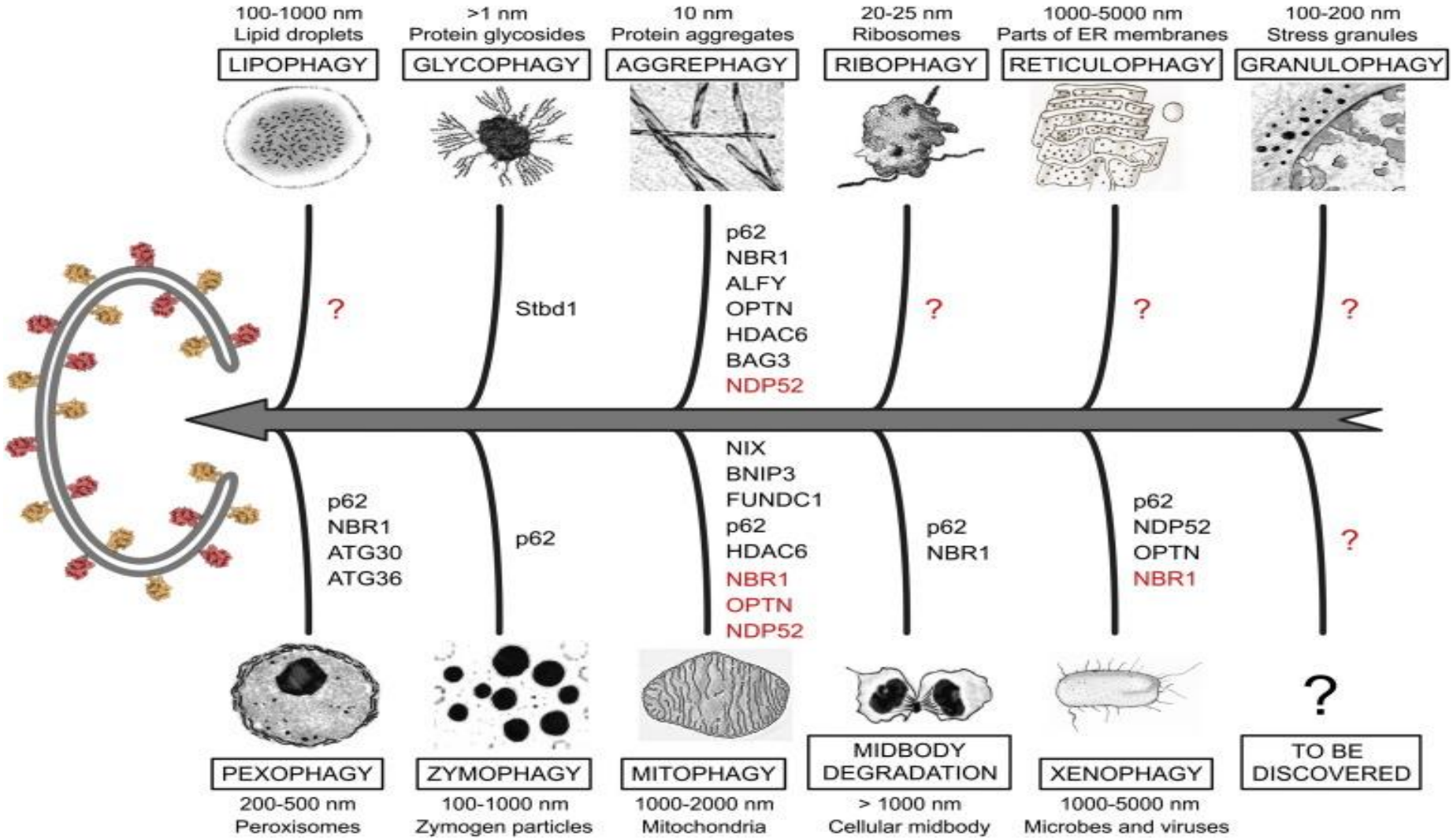
Receptors: ATG8/LC3 and Ub (pink)

Ubiquitin: Mono or Chains

Selectivity is determined by

1. Ubiquitination (Mono-Ub or Di-Ub: Lys 63, 6)
2. Specific Receptors: binding to ATG8 and Ub
3. ATG8

Specific receptors



Rogov et al. *Molecular Cell* 2014

Substrates of autophagy

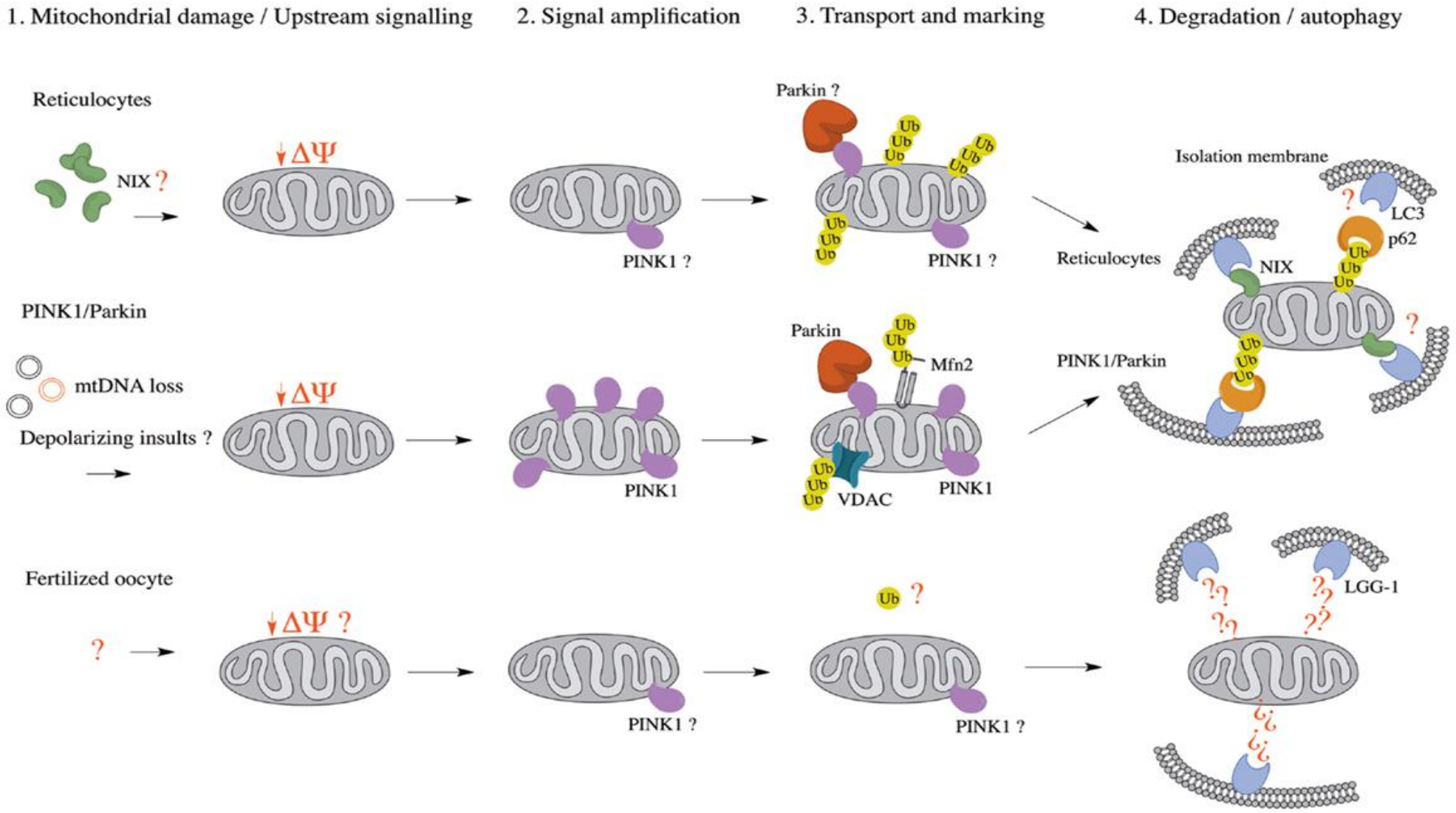
- Organelles: Mitochondria (Mitophagy)
  Perixosomes (Pexophagy)
  Lipid Droplets (Lipophagy)
- Misfolded proteins
- Protein aggregates
- Protein complexes e.g. 26S Proteasome

} Proteaphagy

- Pathogens (Xenophagy): Bacteria (Bacteriophagy) Virus (Virophagy), Fungi (fungal autophagy)

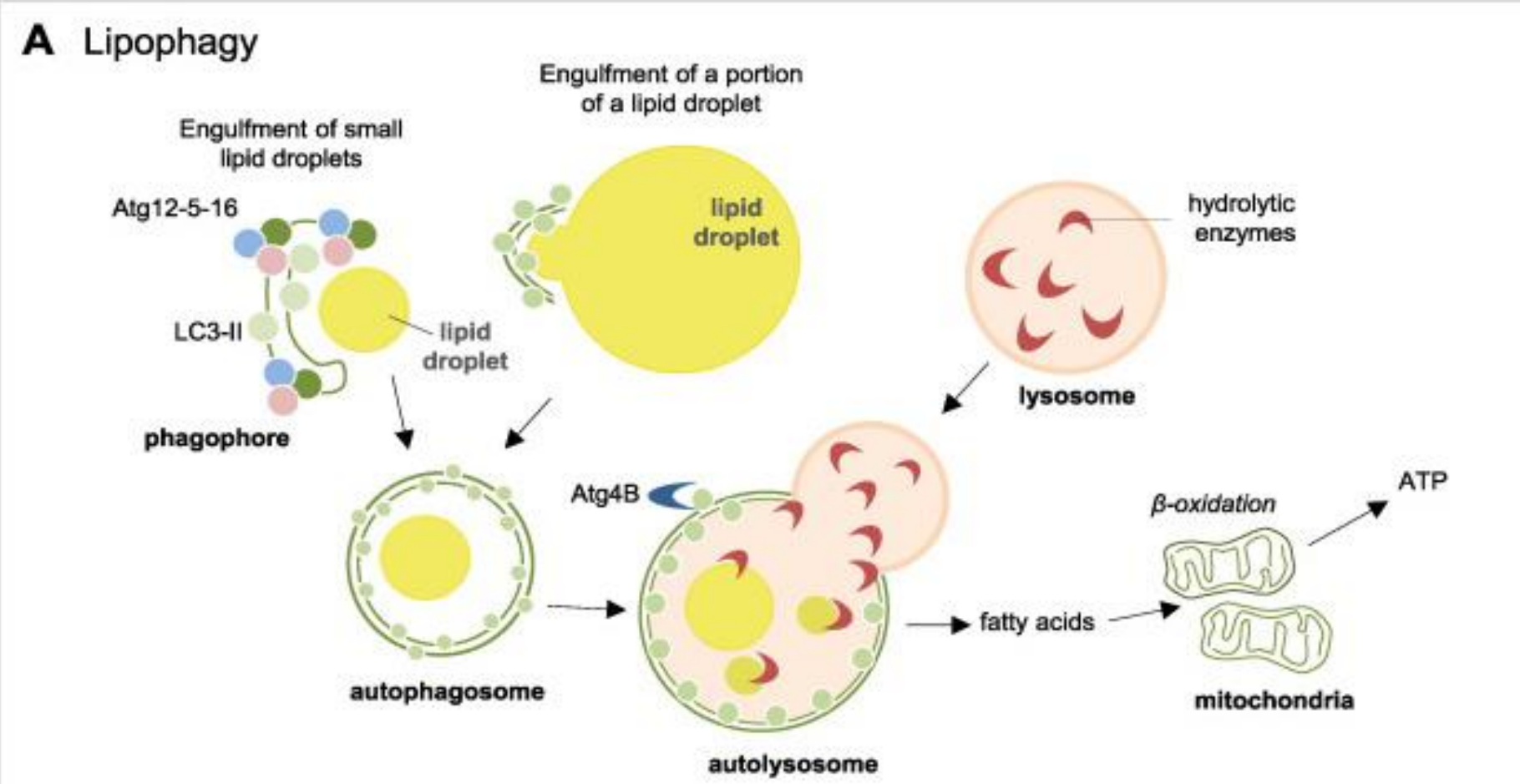
1. Mitochondria: Mitophagy

Substrates of autophagy



Grenier et al. *Frontiers Neurology* 2013

2. Lipophagy

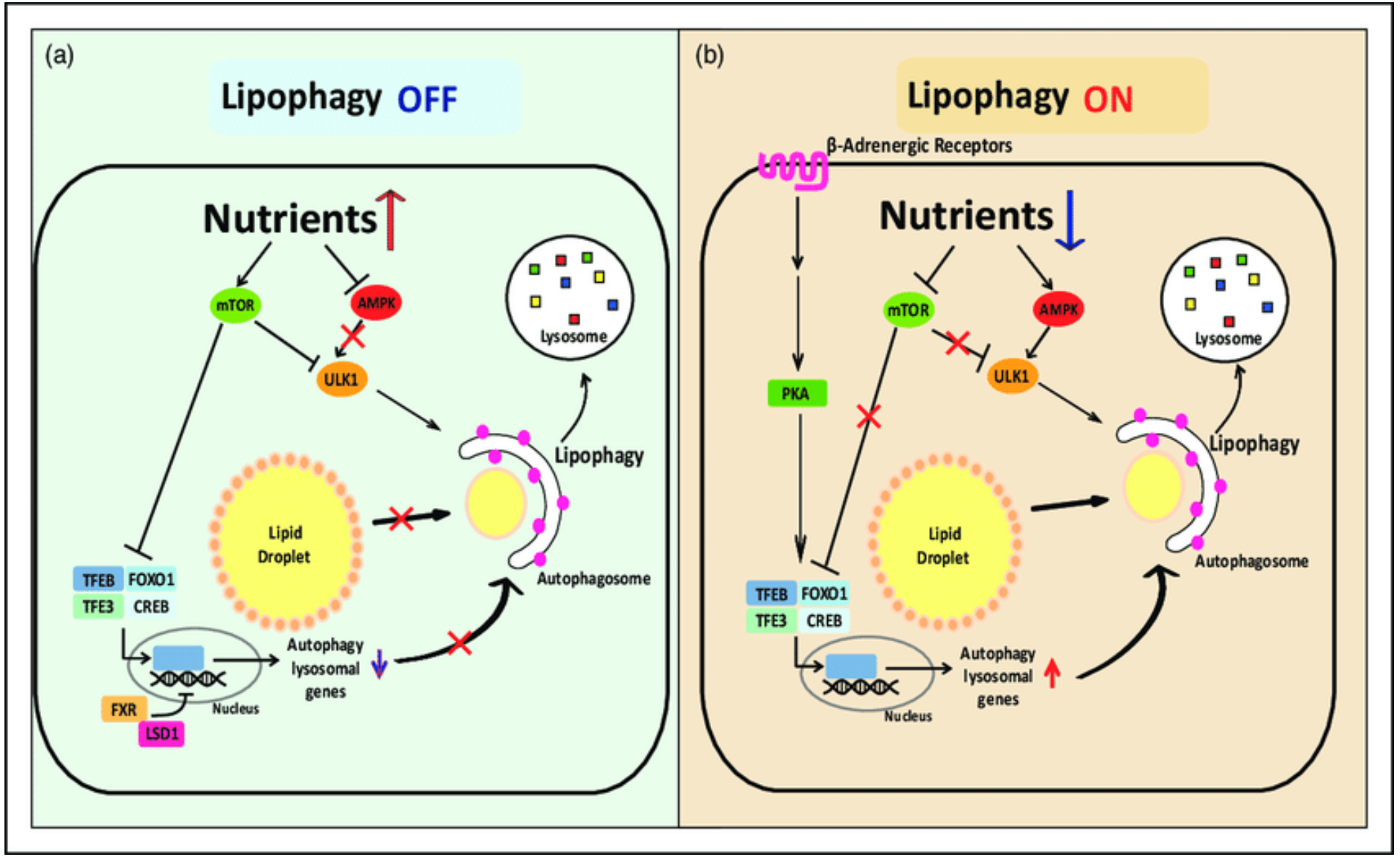


Ubiquitin E3 Ligase: unknown

Specific receptor: unknown

???

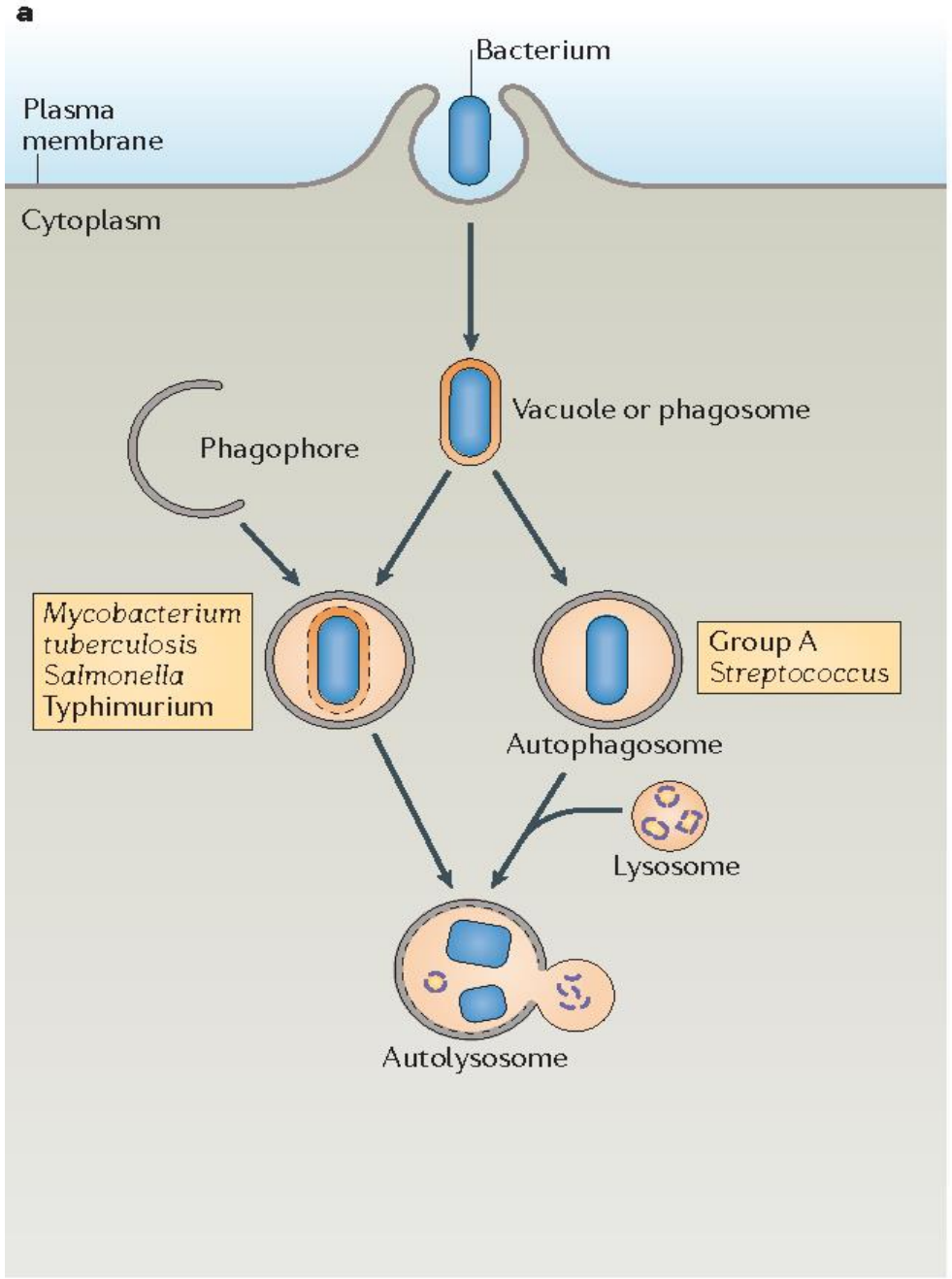
2. Lipophagy



Zhang et al. *Current Opinion* 2018

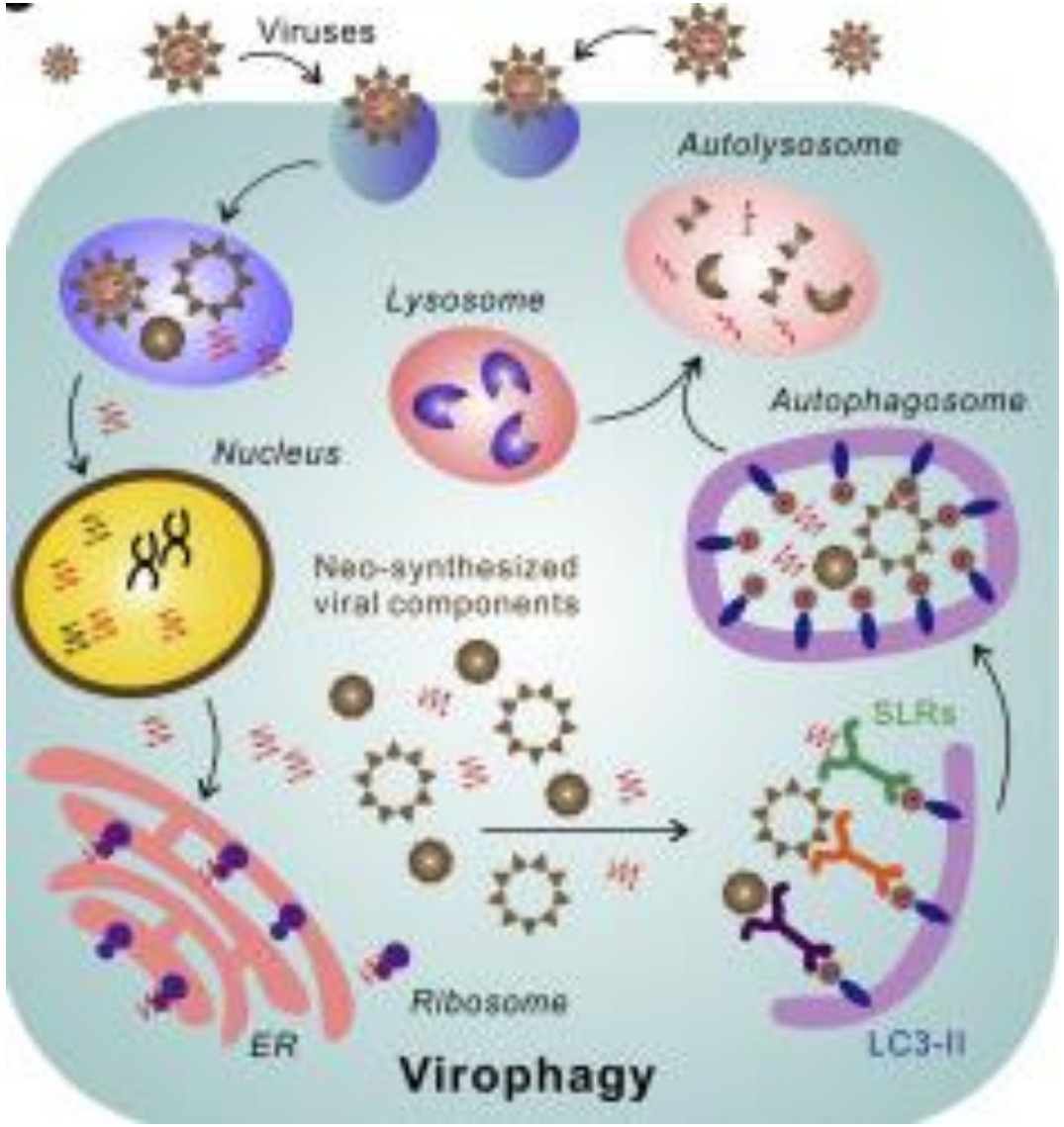
3. Bacteriophagy

Ubiquitin E3 Ligase: unknown
Specific receptors: e. g. p62, NDP52, Optineurin, NBR1



Huang et al. *Nature Reviews Microbiology* 2014

4. Virophagy

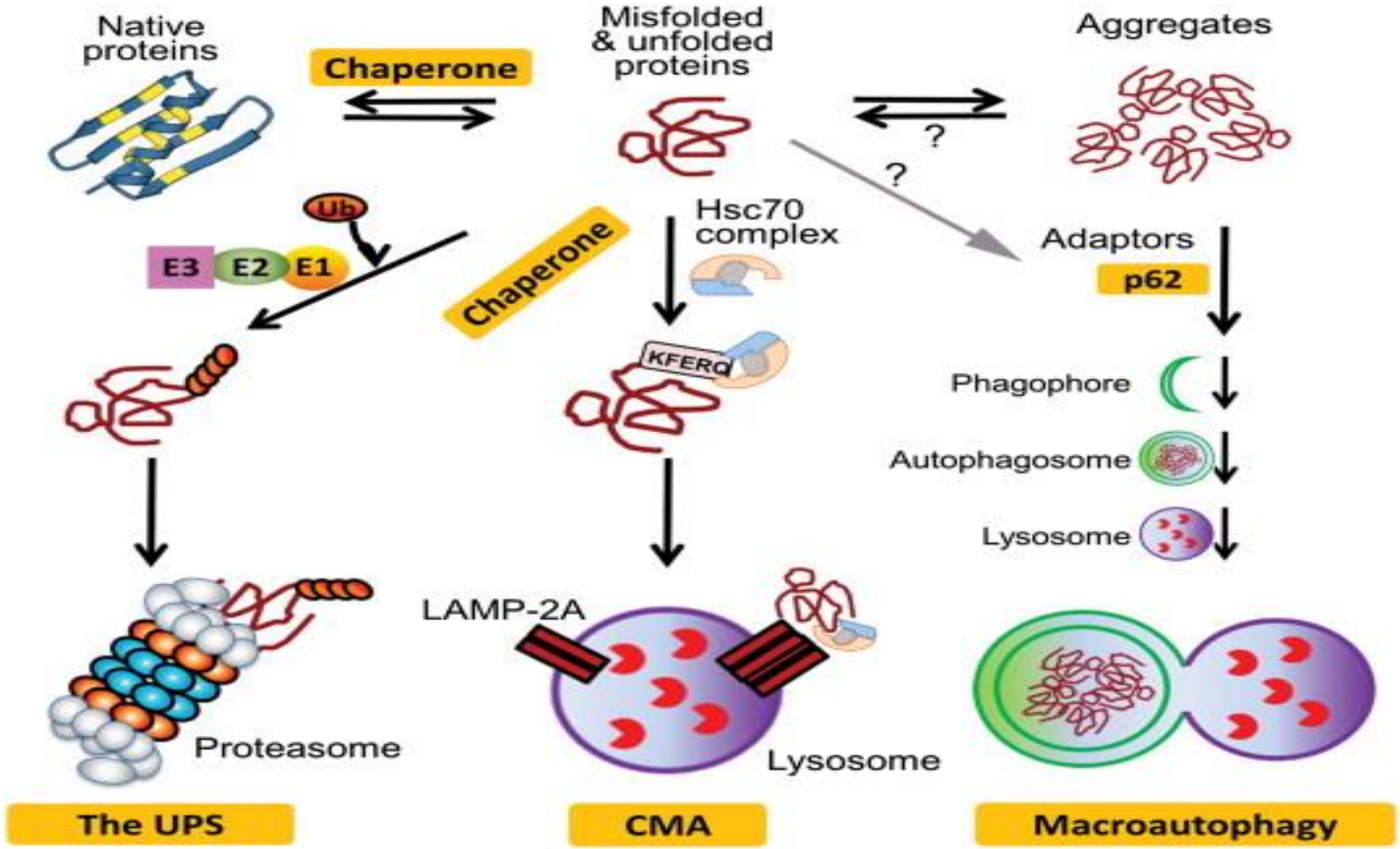


Ubiquitin E3 Ligase: unknown

Specific receptors: Beclin1???

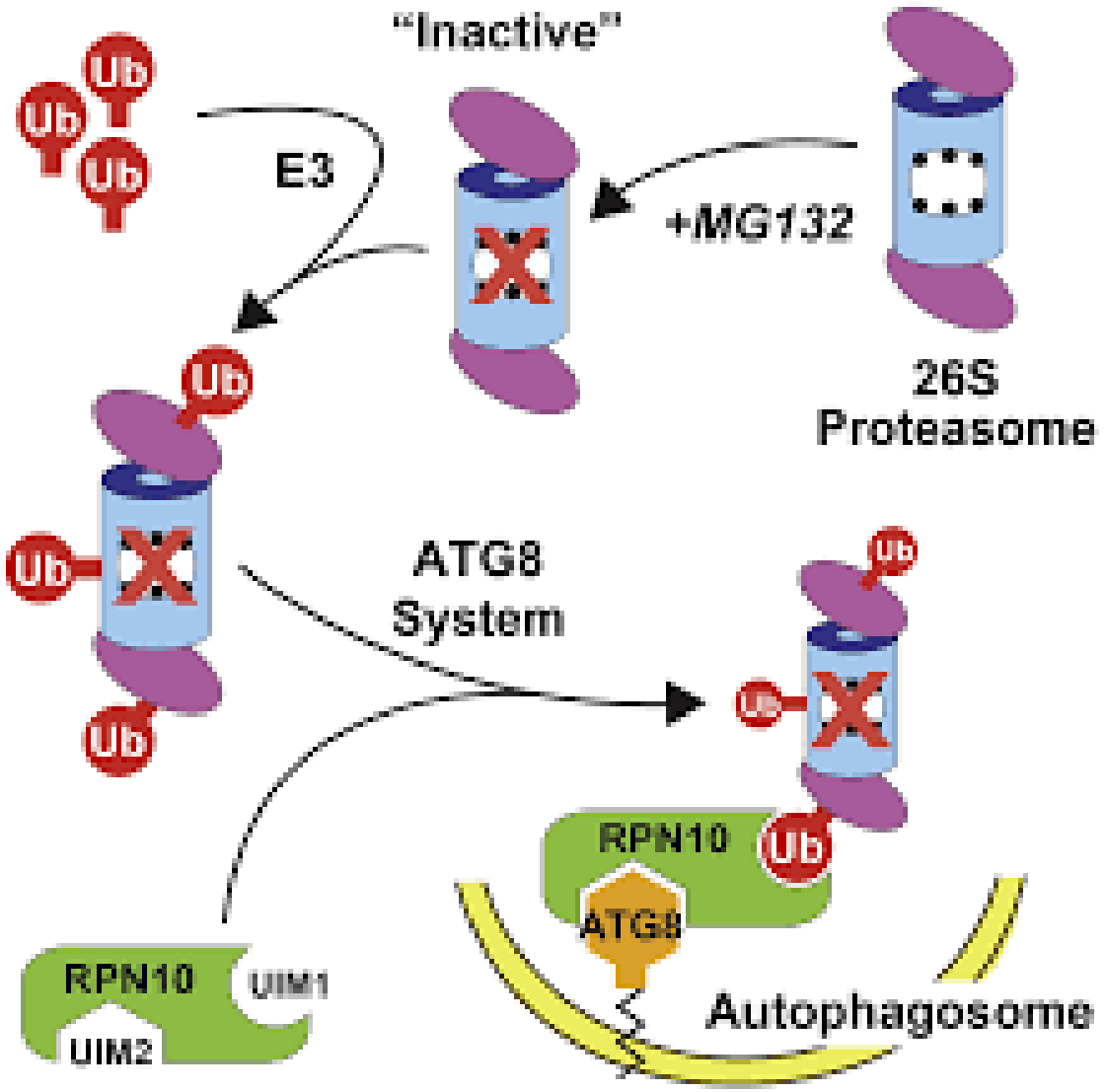
???

5. Misfolded Proteins & Proteinaggregates



???

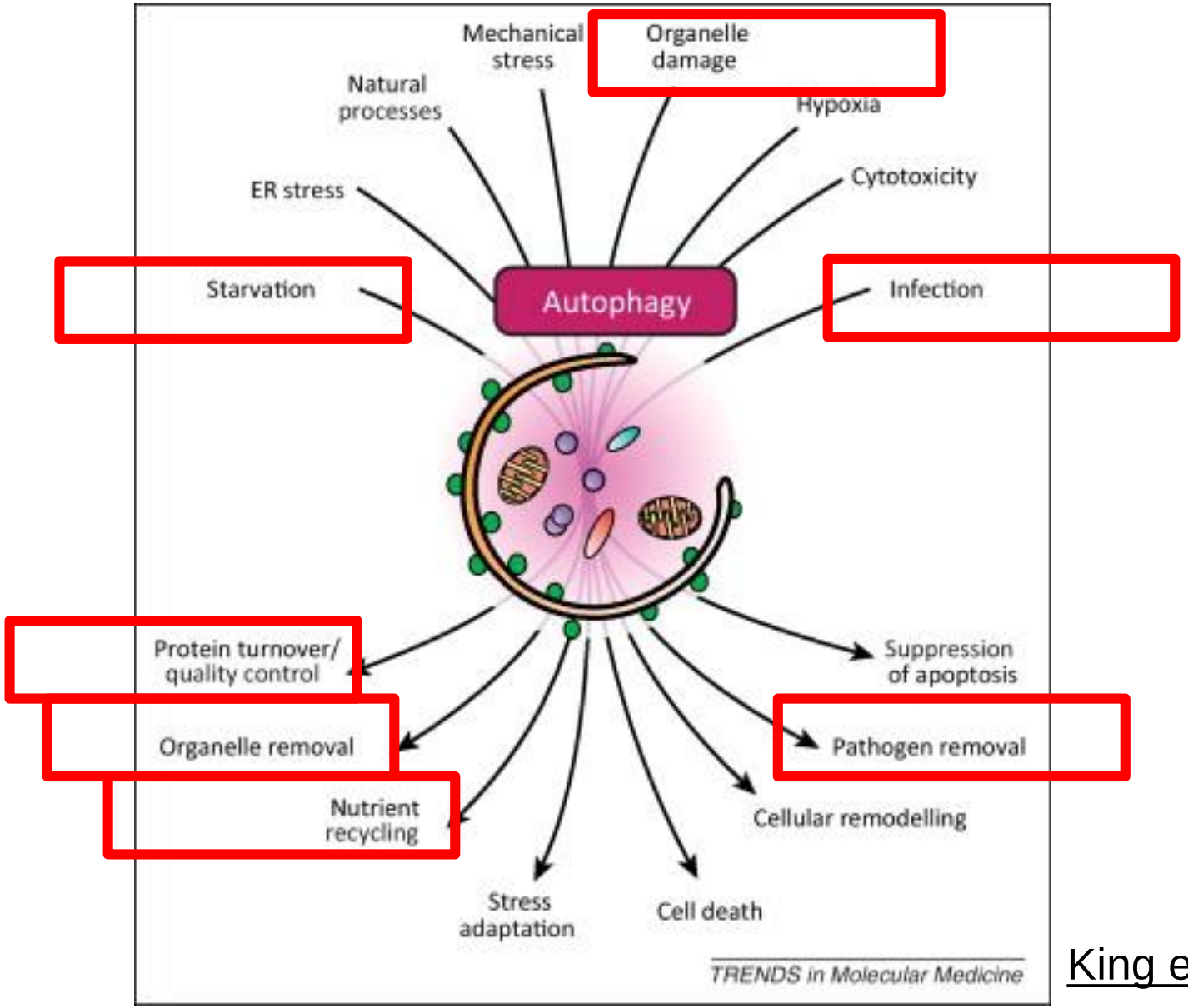
6. Protein complexes: Proteasome & CSN complex



Is non-functional CSN complex
a substrate of autophagy?

Marshall et al. *Molecular Cell* 2015

Functions of autophagy

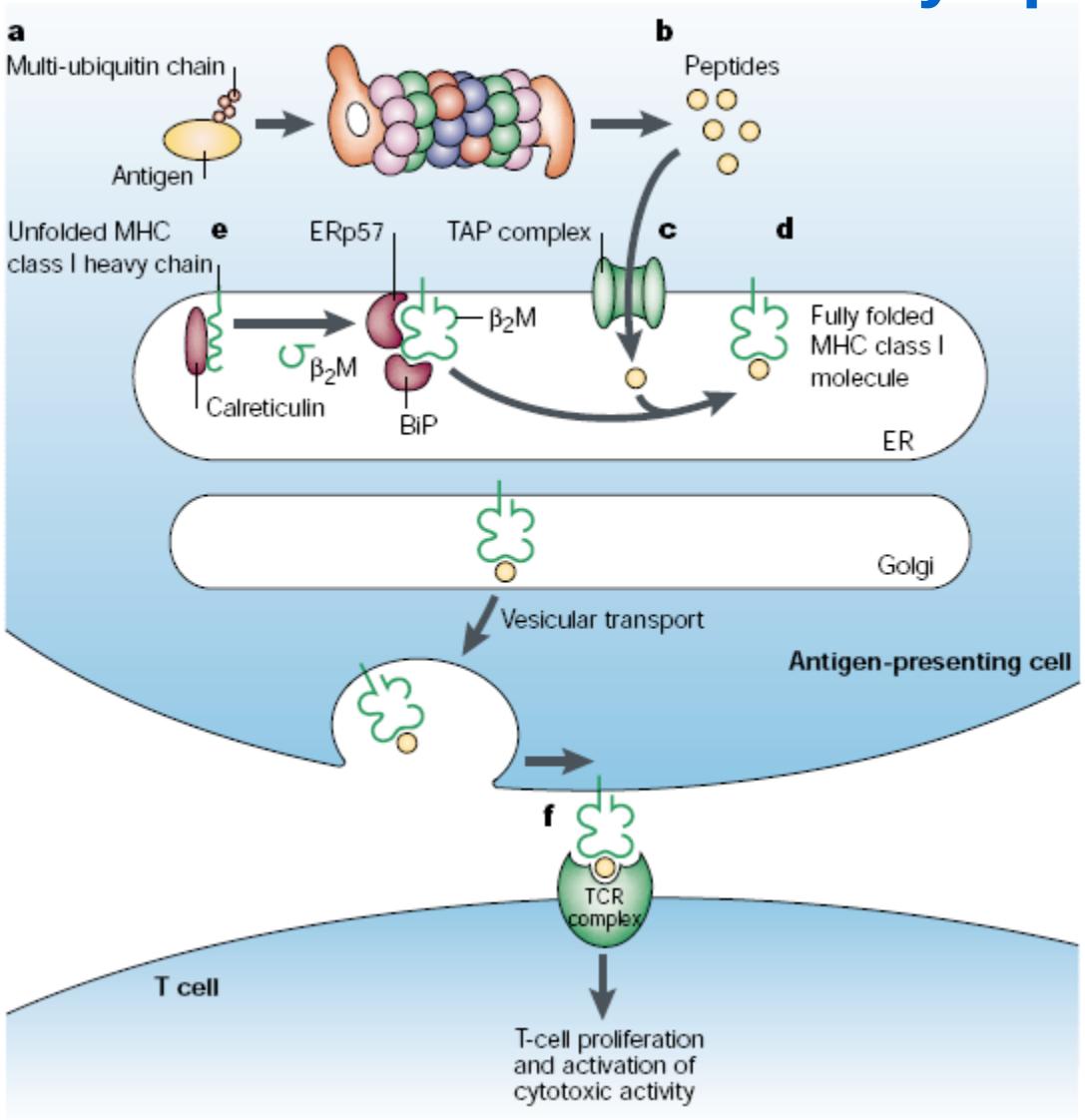


← Stimuli

← **Functions**

King et al. *Trends in Molecular Medicine 2012*

Antigen presentation by MHC class I is essential to defend against viral infection and leads to destruction of the infected cell by apoptosis

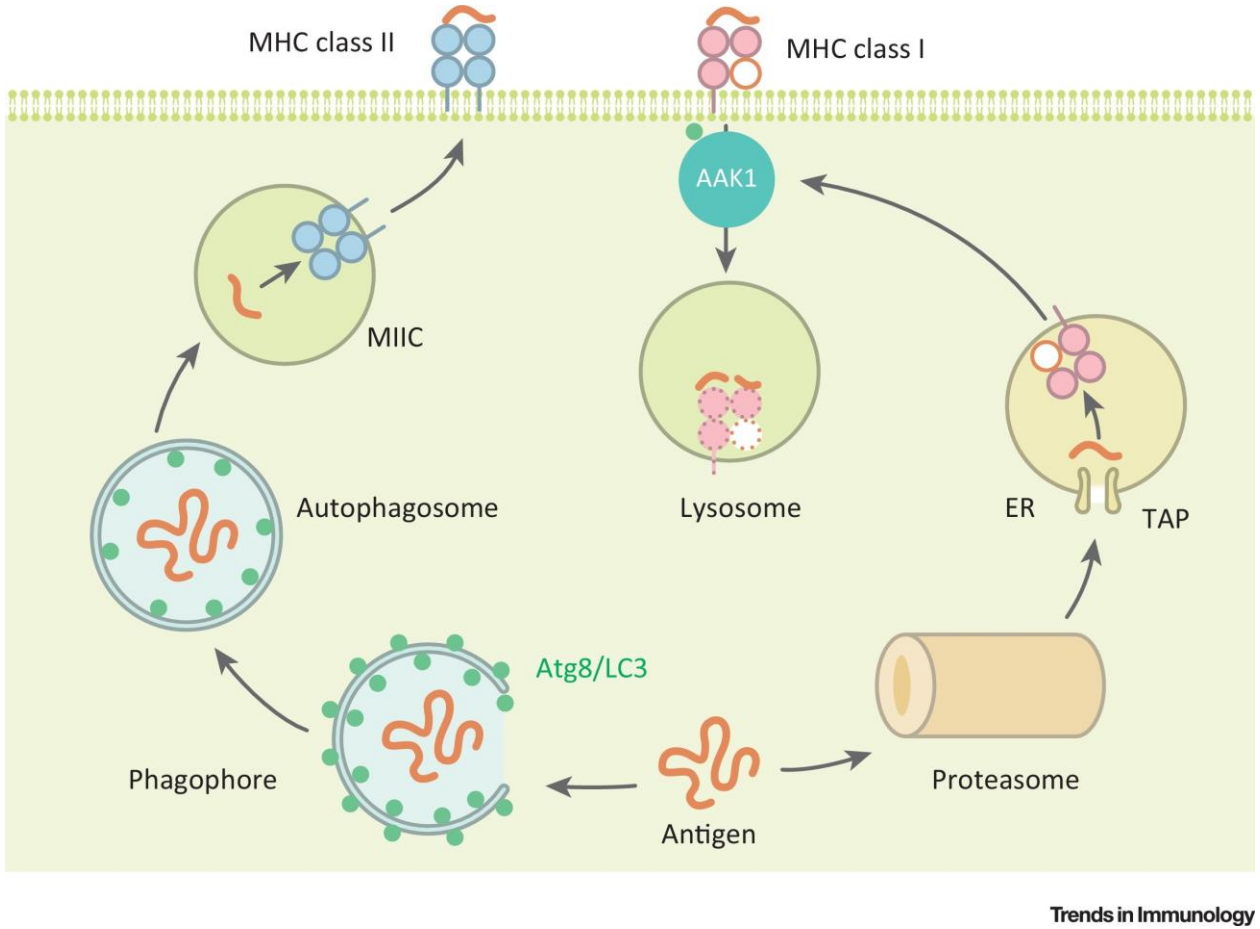


UPS

MHC class I and II presentation

Lysosome

Antigens



UPS

Antigens

Which cells are involved in antigen presentation?

Which cells express MHC class I molecules?

All nucleated cells, all somatic cells.

Which cells express MHC class II molecules?

All professional antigen presentig cells including macrophages, Dentritic cells and B cells.

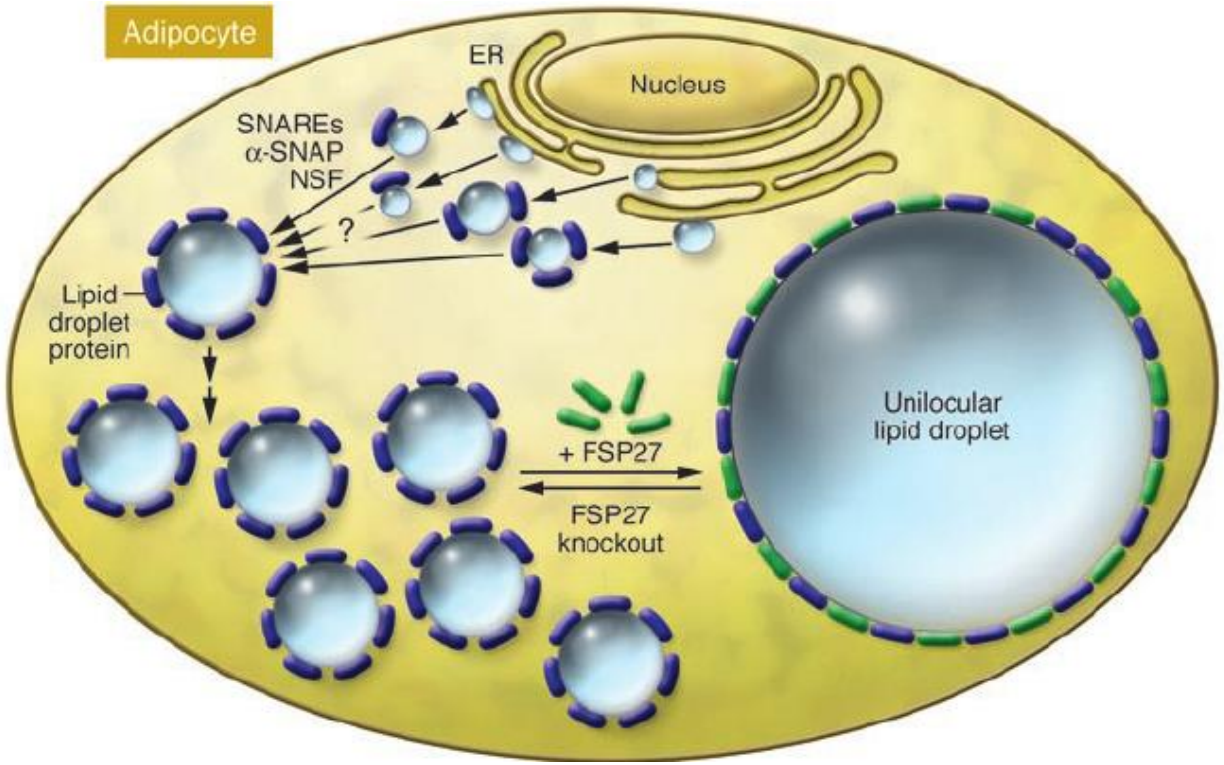
Impaired autophagy and their consequences

- Lipid metabolism dysregulation
- Neurodegenerative diseases
- Immun-defects
- Cancer??

1. Lipid Droplet-associated diseases

Obesity

Fatty liver



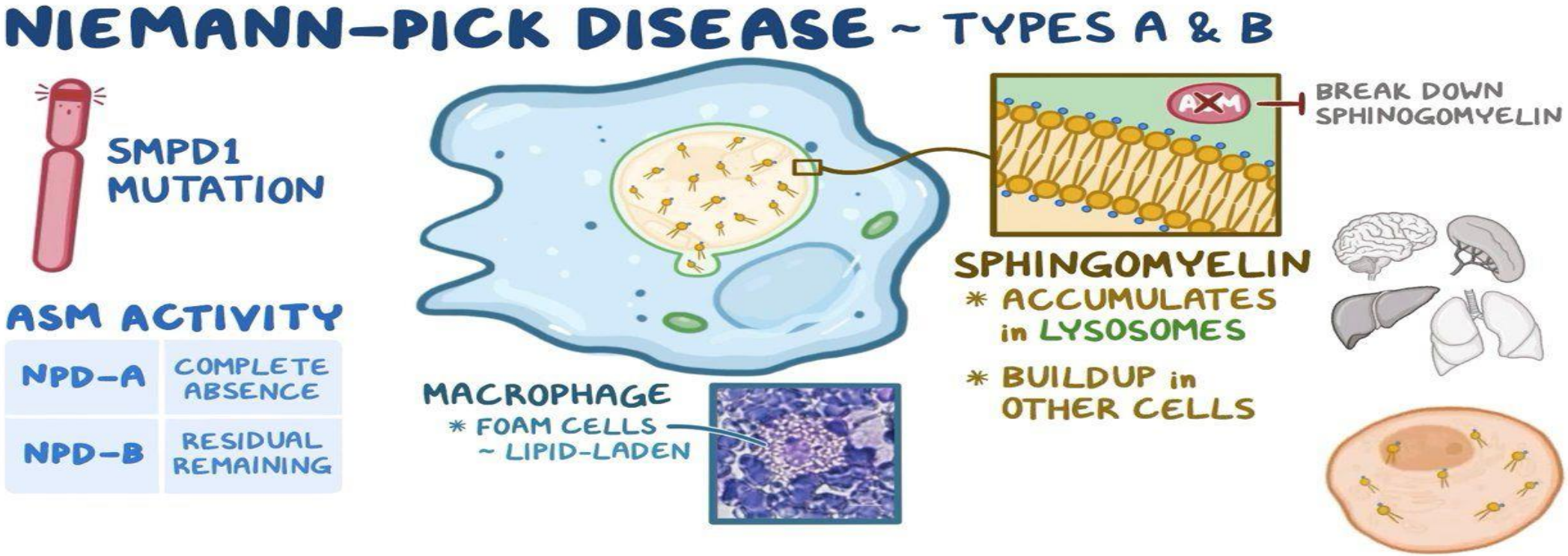
Accumulation of lipid droplets due to failed lipophagy during fatty liver and obesity?

Lipid-associated diseases (Lipid storage diseases)

Lysosomal storage disease

Niemann-Pick A/ disease:

Mutation on Lipase: Sphingomyelinase ⟶ Defect on degradation of Sphingomyelin



2. Neurodegenerative diseases

AD: Alzheimer‘s Disease:
Accumulation of amyloid precursor proteins (APP),Presenilins and
tau proteins forms Lewy bodies and neurofibrillary tangles in neurons
Mutation: APP, Tau, Presenilin1 and 2

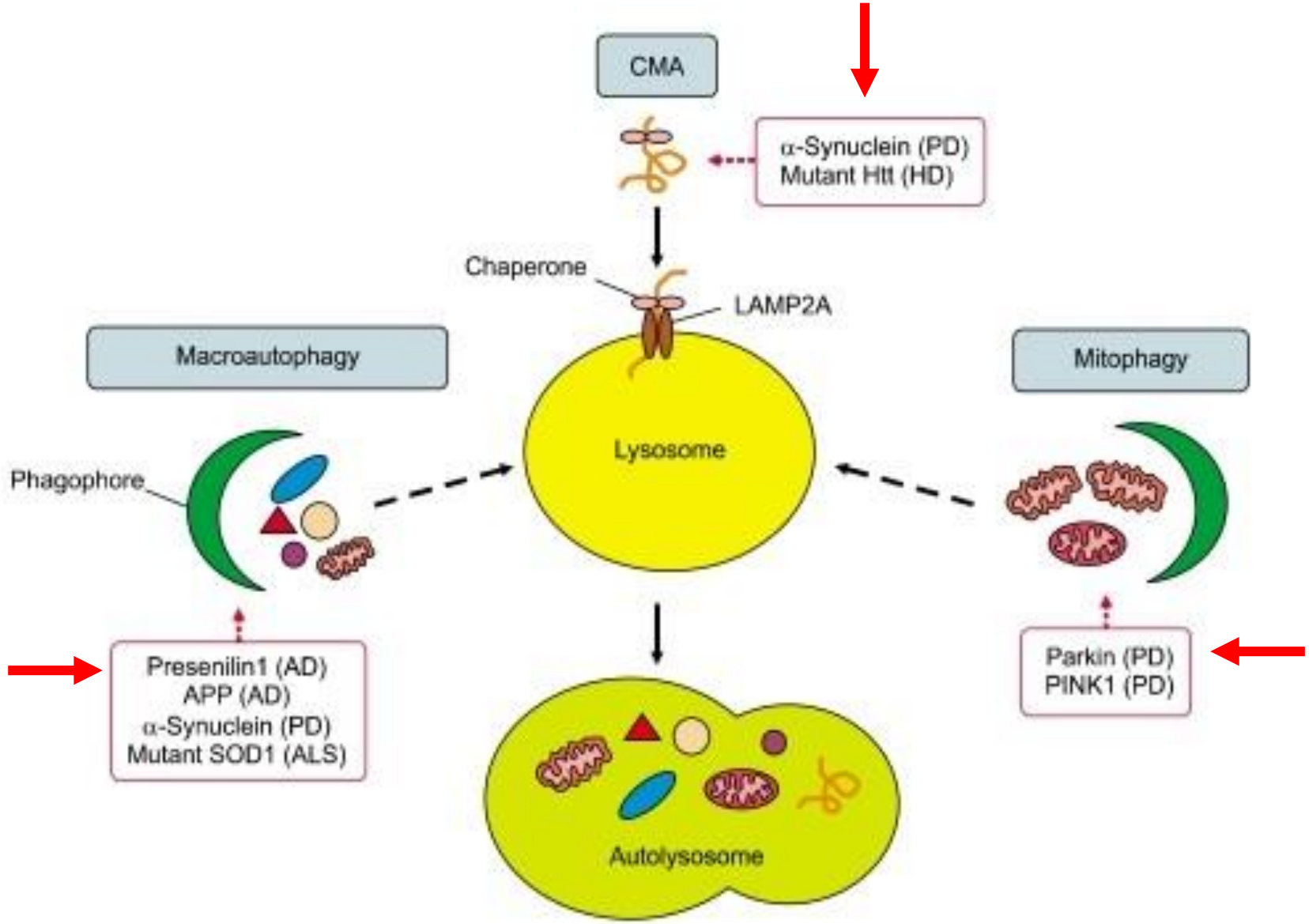
PD: Parkinson‘s Disease:
Accumulation of disordered cell organelles and alpha-synuclein forms Lewy bodies in neurons
Mutations e.g. Parkin

ALS: Amyotrophic lateral sclerosis:
death of neurons controlling voluntary muscles
Mutation: e. g. superoxid dismutase 1 (SOD1)

HD: Huntington‘s Disease:
death of brain cells
Mutation: repeats of triplenucleotides (CAG) in Huntington protein DNA which form polyQ regions

Neurodegenerative diseases

Impaired autophagy



Son et al. *EXPERIMENTAL and MOLECULAR MEDICINE* 2012

Neurodegenerative diseases:

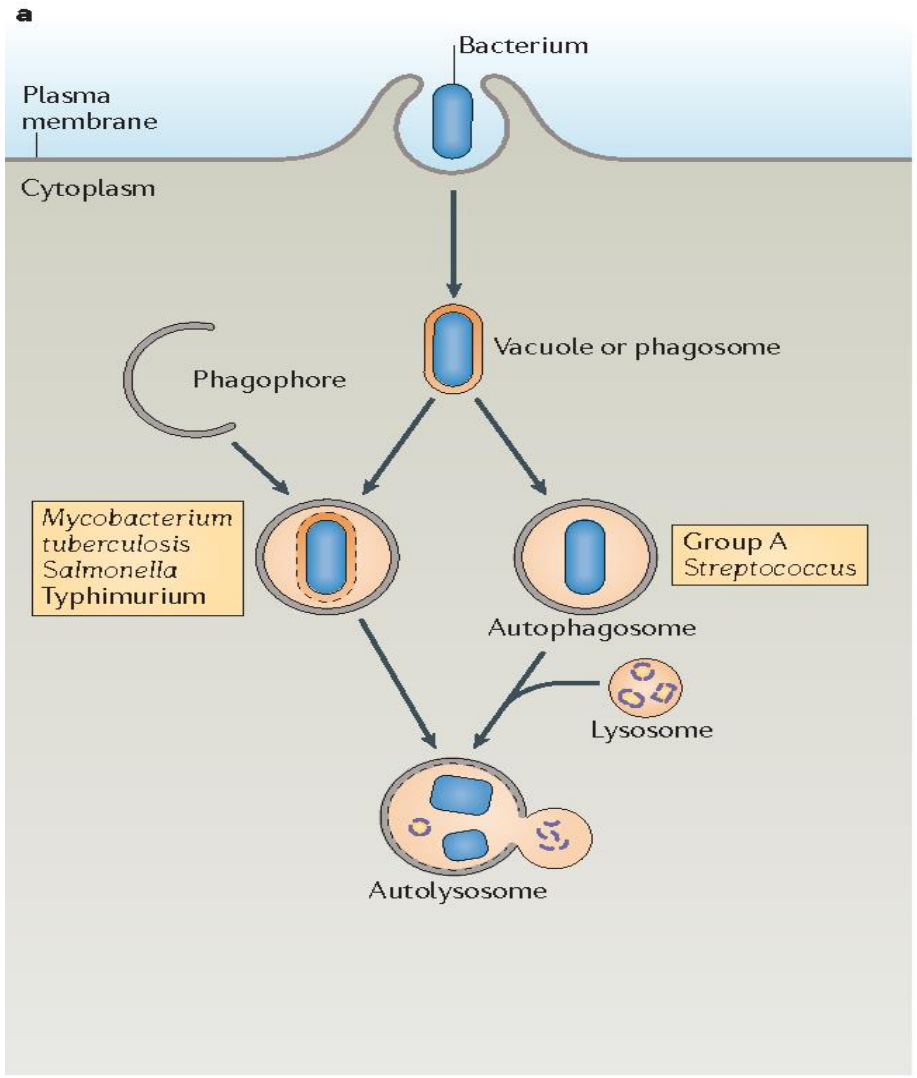
Mutations of proteins implicated in aggresome formation lead to neurodegenerative diseases

Table 1. Proteins Implicated in Aggresome Formation

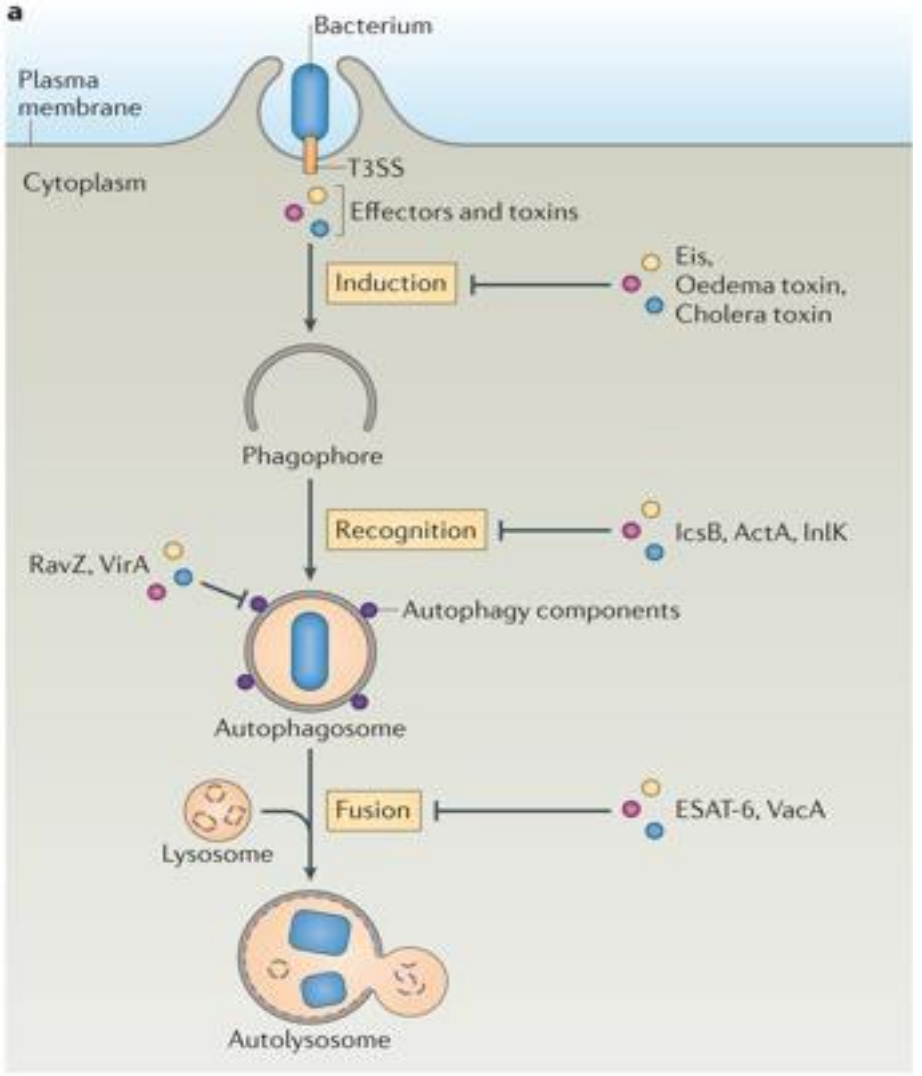
Protein	Function	Wild-type protein localized to inclusion bodies	Mutations associated with disease	Ref.
Histone deacetylase 6	Deacetylase, adaptor protein	Lewy bodies	Unknown	[46]
Parkin	E3 ubiquitin-protein ligase	Lewy bodies	Parkinson's disease	[34, 38]
Ataxin-3	Deubiquitinating enzyme	SCA type-1 and 2 DRPLA intranuclear inclusions	SCA type-3	[37]
Dynein motor complex	Retrograde microtubule motor	Unknown	Motor neuron degeneration	[87, 88]
Ubiquilin-1	Folding of amyloid precursor protein (APP)	Lewy bodies and neurofibrillary tangles	Alzheimer's disease (potential risk factor)	[147, 154]

SCA, spinocerebellar ataxia; *DRPLA*, dentatorubral-pallidoluysian atrophy; ALS, amyotrophic lateral sclerosis.

3. Impaired bacteriophagy



Normal defence

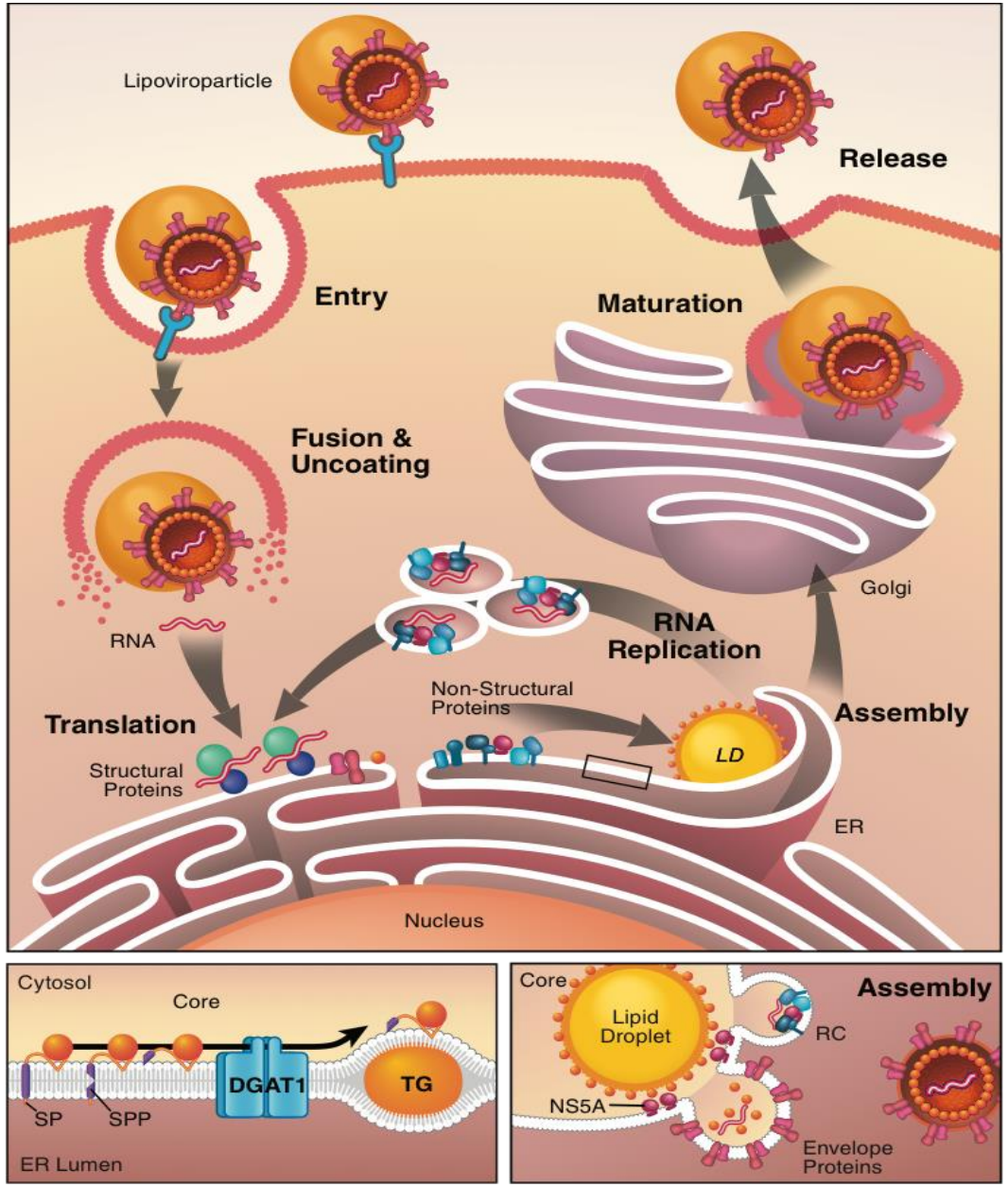


Impaired defence

-Toxine
-Effectors

Huang et al. *Nature Reviews Microbiology* 2014

4. Impaired virophagy



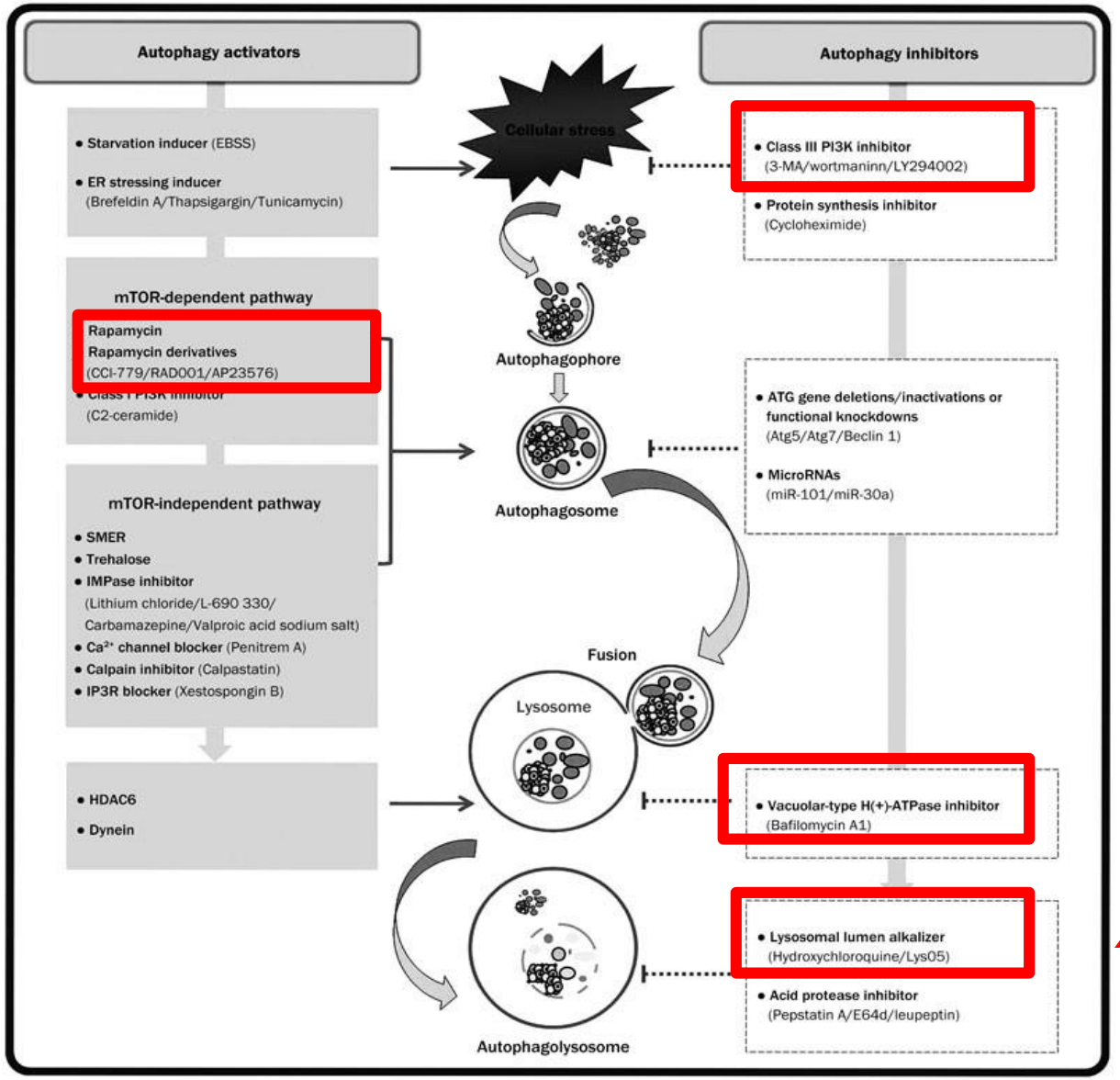
Endocytosis
Virus replication,
Virus assembly,
Exocytosis

Inhibition or activation of autophagy?

- Neurodegenerative diseases: Activators

- Virus infection: Inhibitors

Inhibitors of autophagy

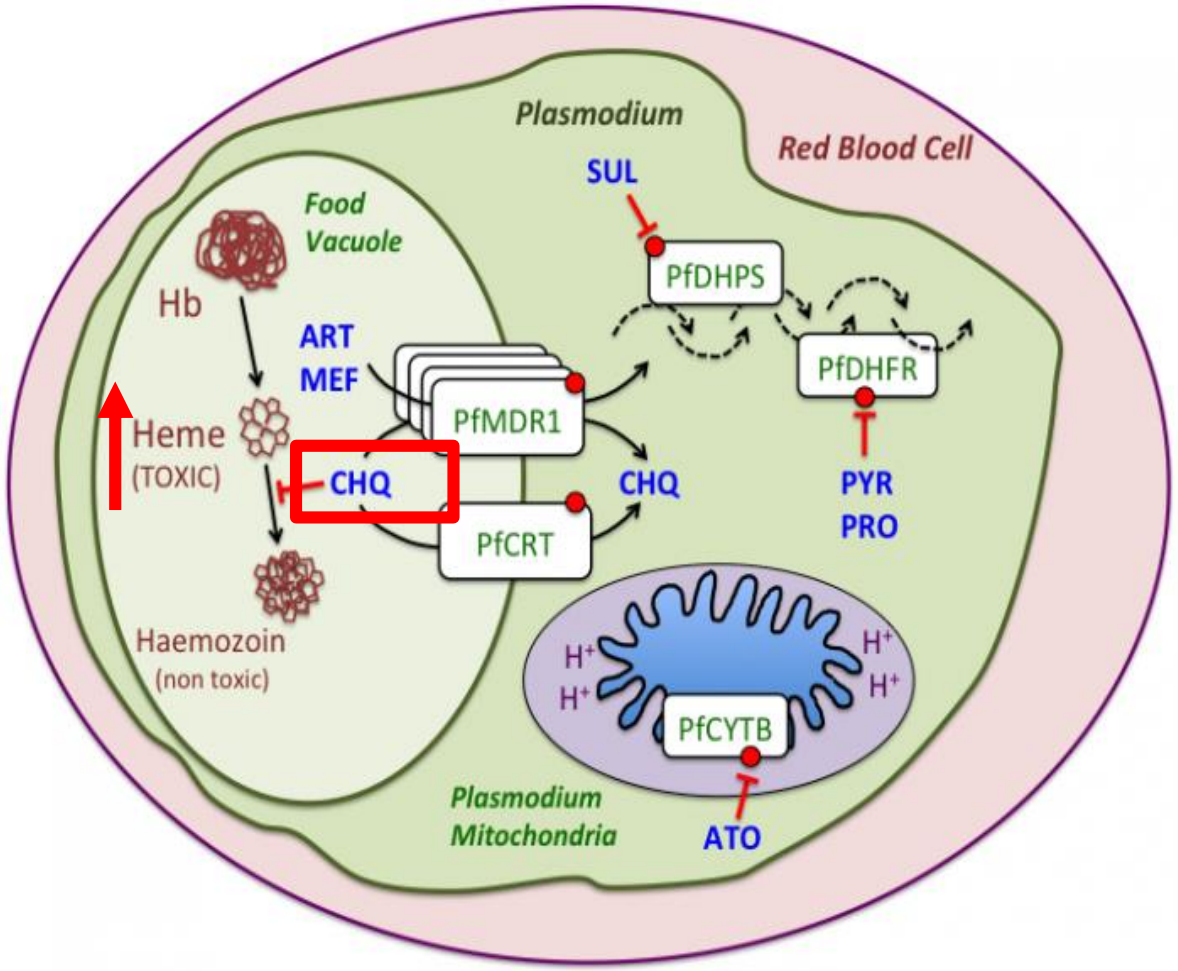


Chloroquine

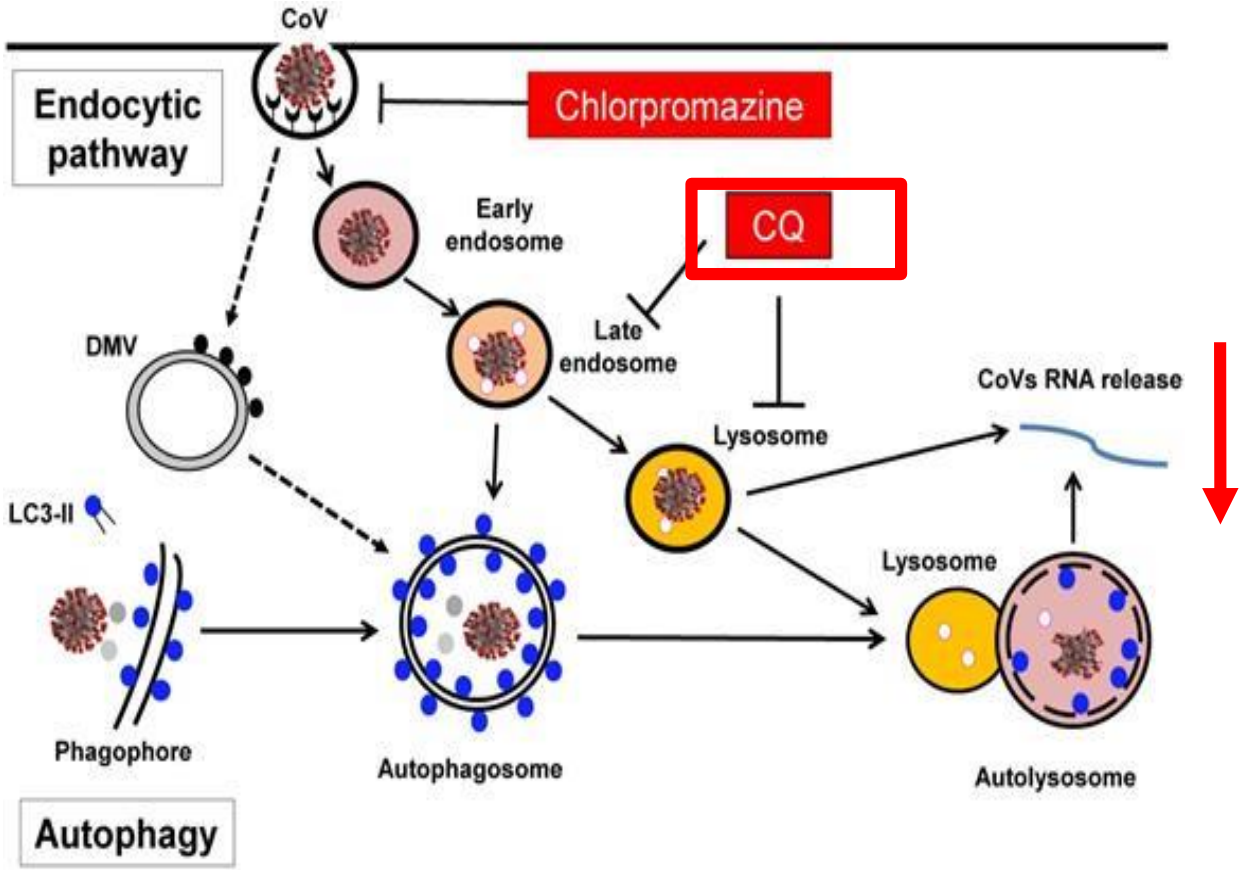
Yabg et al. *Acta Pharmacologica Sinica* 2013

Chloroquine (Hydrochloroquine): CHQ/CQ

Malaria



Virus???



The New York Times

- https://www.nytimes.com/2021/04/08/health/coronavirus-mrna-kariko.html?utm_source=Nature+Briefing&utm_campaign=e1ed2e8872-briefing-dy-20210413&utm_medium=email&utm_term=0_c9dfd39373-e1ed2e8872-45216894

Dr. Kariko

Similarities and Differences of UPS and selective Macroautophagy

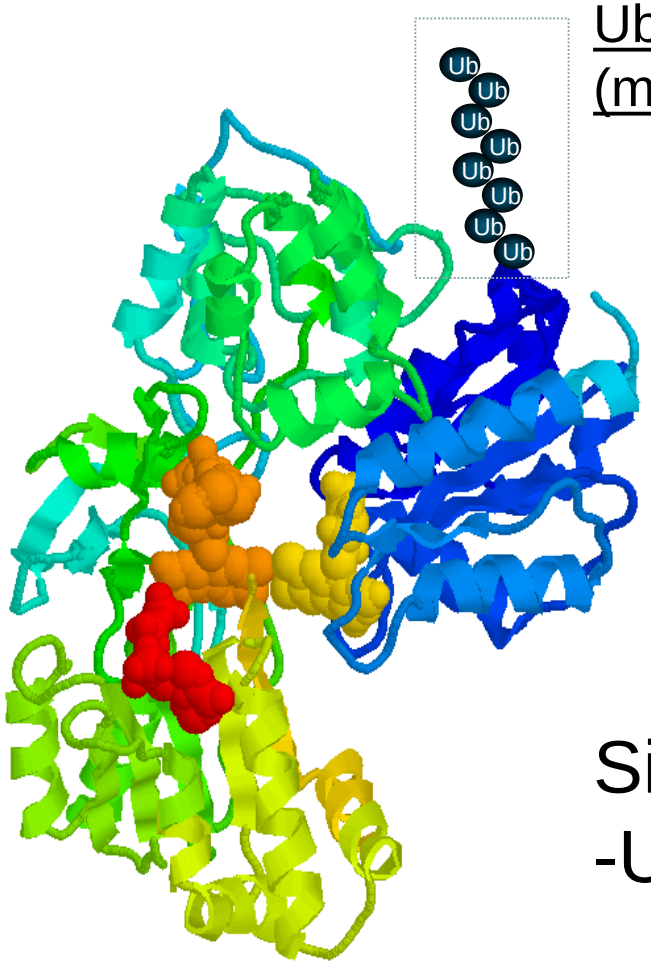
	UPS	Selective Macroautophagy
Abundance	All eucaryotic cells	All eucaryotic cells
Signal	Ubiquitin-Chain via Lys48 (min 4 Ub molecules)	Ubiquitin, ATG8
ATP consumption	Yes	Yes
Ub-like modifier conjugation system	Ubiquitination (Ub-conjugation, Ub.chain)	Ubiquitination, ATGylation: ATG8, ATG12-conjugation
Proteolytic machinery	Protein complex	Cell organelle: Lysosome
Enzymes	Protease: 26S proteasome	Proteases, Nucleases, Lipases
Selectivity	E3	Specific receptors, E3
Substrates	Proteins	Proteins, Protein complexes, Lipids, Nucleic acids, Cell organelles, Pathogens
Function	Proteolysis Antigenpresentation	Proteolysis, Lipolysis, Antigenpresentation

Crosstalk between UPS and selective macroautophagy

- Ubiquitin-like proteins: Ubiquitin, ATG8, ATG12
- Ub-like protein conjugation system
- Ub or Ub-chains
- Ub E3 Ligases

Signal of substrates:

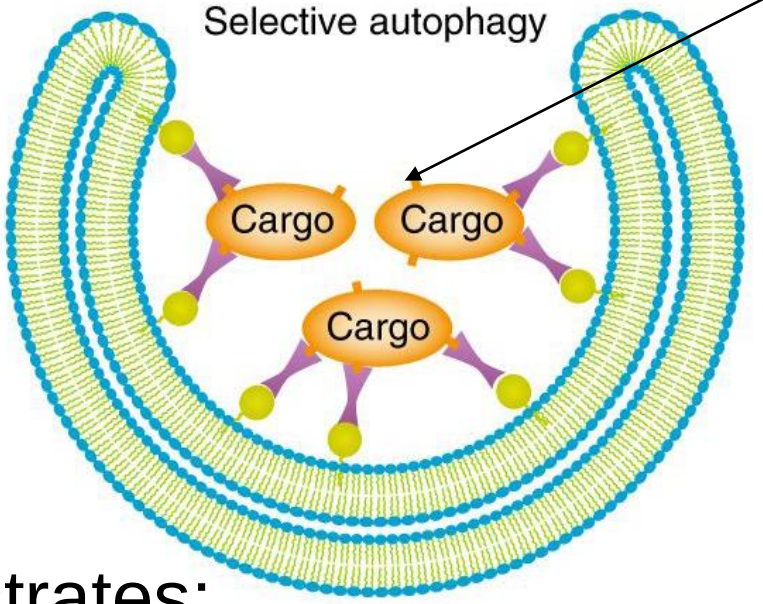
UPS



Ubiquitination
(min. 4 molecules)

(Lys 48 chain)

Selective macroautophagy



Ubiquitination
(1 or 2 molecules)

(Lys 63 chain)

Signal of substrates:
-Ubiquitination (Ub-chain or Mono-Ub, Di-Ub)

PE: Phosphatidylethanolamine

UPS

Selective macroautophagy

E3?

The Ub ligases (E3s) ligate specifically Ub to protein substrates. They determine the specificity of the UPS.

HECT domain Ub ligases

1. E_2-S~Ub → E_3–S–C(=O)–Ub + Protein–NH_2 → E_3–SH + Protein–NH–C(=O)–Ub

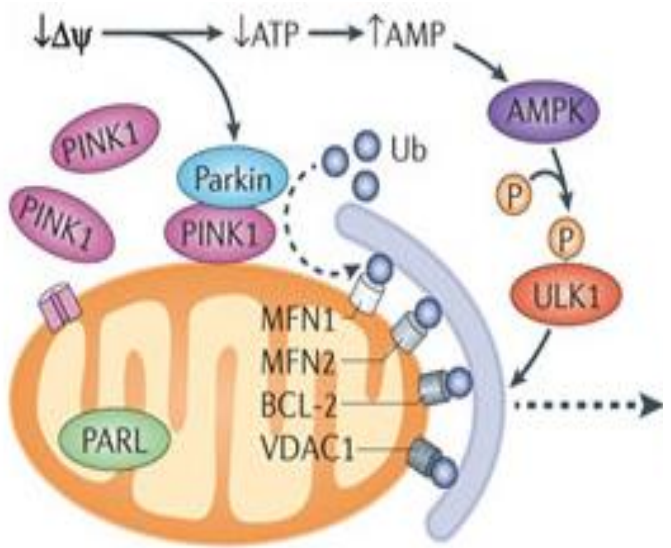
Isopeptide bond

RING domain Ub ligases

2. E_3•E_2–S–C(=O)–Ub + Protein–NH_2 → E_3+E_2–SH + Protein–NH–C(=O)–Ub

Hundreds E3s are known

Parkin: HECT-RING E3



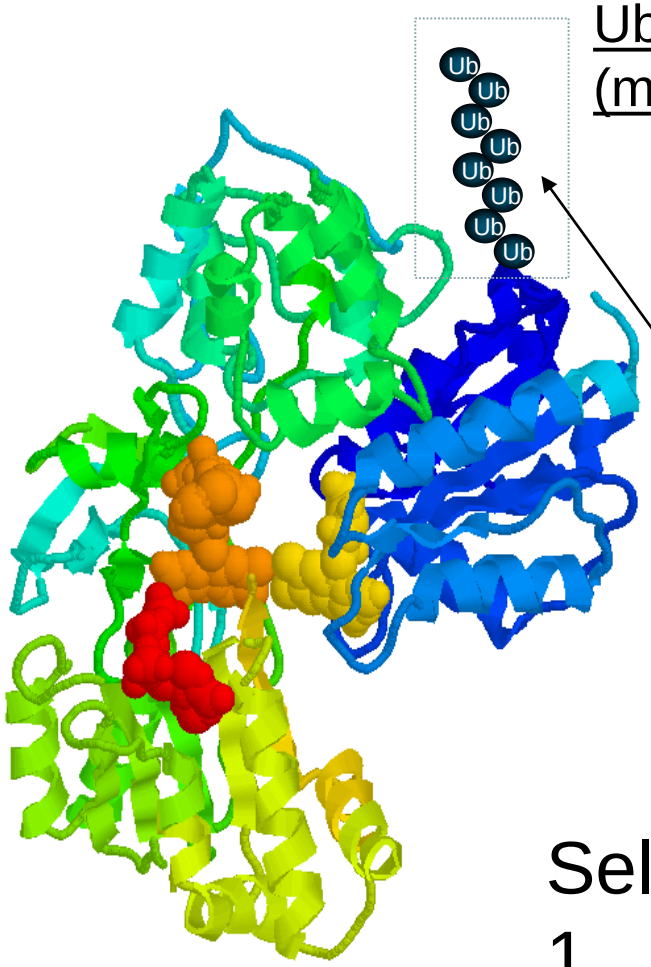
Very rare known about E3 ligases in auotphagy

Comparison between UPS and selective Macroautophagy

Selectivity of substrates:

Comparison between UPS and selective Macroautophagy

UPS

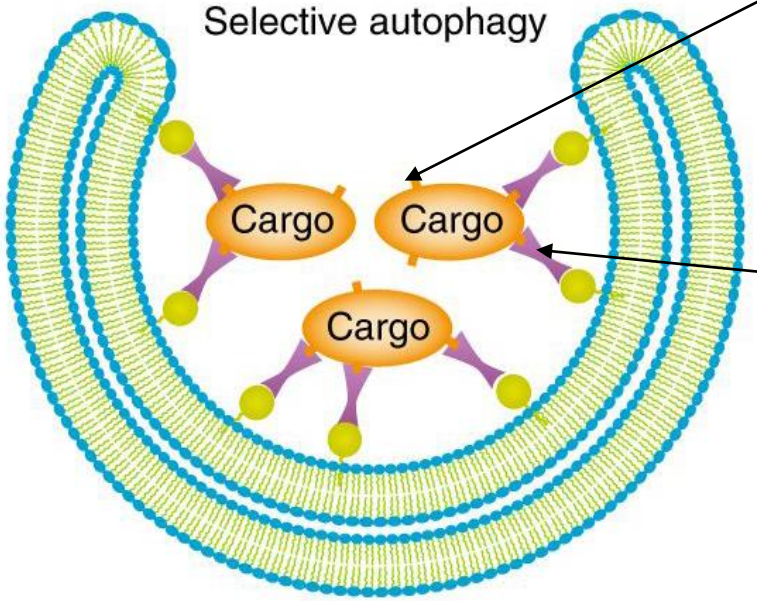


Ubiquitination
(min. 4 molecules)

Receptors
(Ub-chain and
Proteasome)

Selective macroautophagy

Ubiquitination
(1 or 2 molecules)



Receptors
(Ub and ATG8)

Selectivity is determined by

1. Ub ligase E3s
2. Specific Receptors: binding to Ubl or Ub-chains

ATP consumption

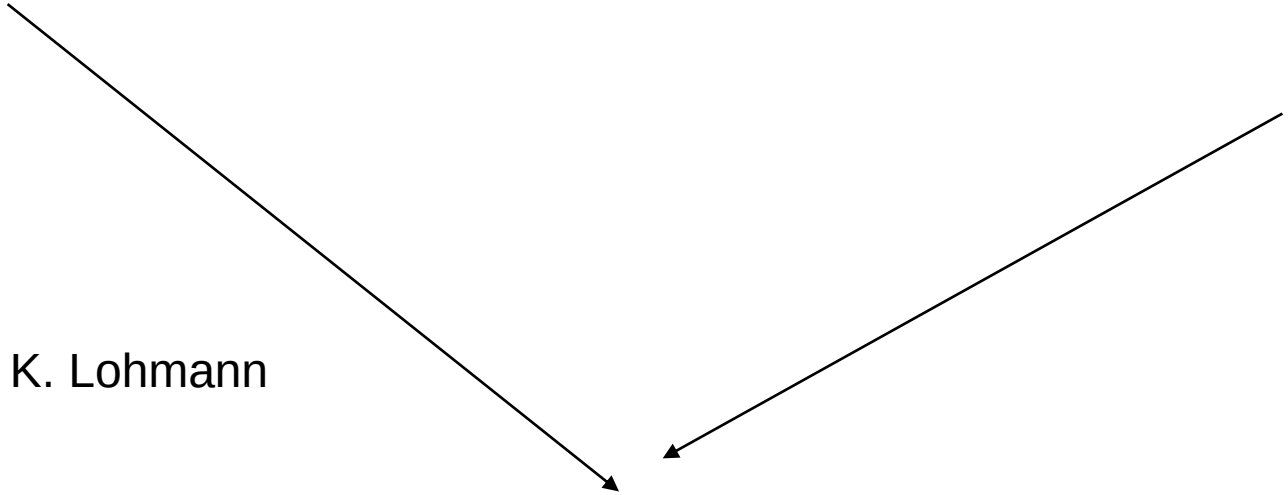
- UPS

Ubiquitination

- Selective macroautophagy

Ubiquitination

ATGylation



ATP consumption

ATP: is discovered by K. Lohmann

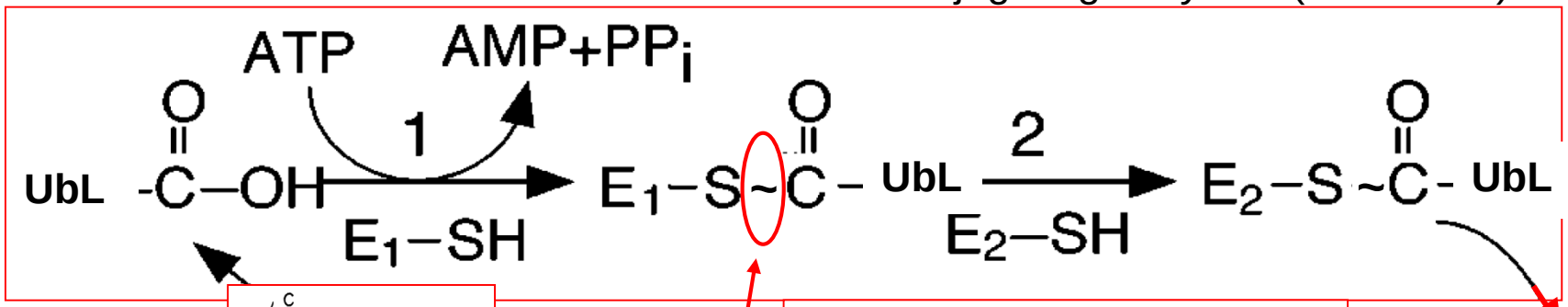
Activation and transfer of UbLs like Ub

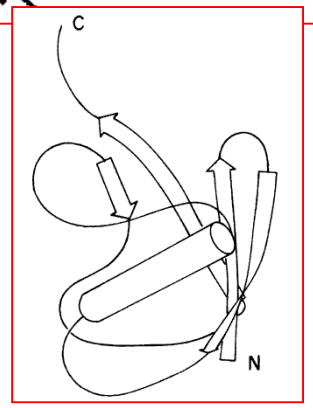
E1 – UbL activating enzyme

There are few Ub activating enzymes in eukaryotic cells

E2s – UBCs – UbL conjugating enzymes

There is a large family of UbL conjugating enzymes (~50 UBCs).





Transthiolation reaction from E1-S-UbL to E2-S-UbL.

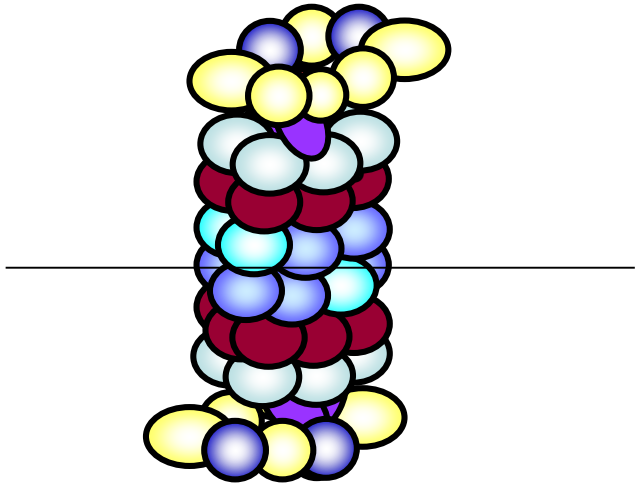
Thioester bond

proteolytic machineries

Comparison between UPS and selective Macroautophagy

UPS

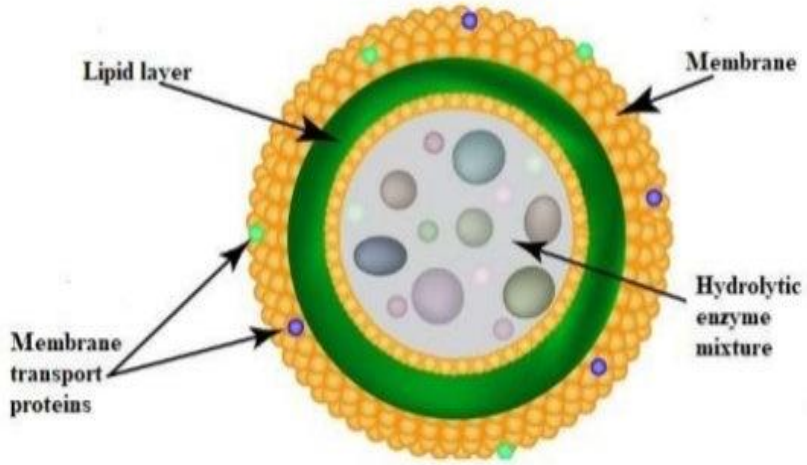
26S proteasome



Protein complex
Protease: 20S one molecule contains
6 active centres
(DUB activity)
Active sides occur at inner cavity
Why?
pH 7-7.5

Selective macroautophagy

Lysosomes



Organelle
Proteases, nucleases and lipases (60 enzymes)
enzymes are at inner of lysosomes, why?
pH 4.5-5

Substrates

UPS	Selective macroautophagy
-Poly-Ub Proteins	-Organelles: Mitochondria Perixosomes Lipid Droplets
	-Pathogens (Xenophagy): Bacteria (Bacteriophagy) Virus (Virophagy), Fungi (fungal autophagy)
	-Misfolded proteins, protein aggregates, protein complexes e.g. 26S Proteasome
	-Lipids

Stimulis and functions:

Comparison between UPS and selective Macroautophagy

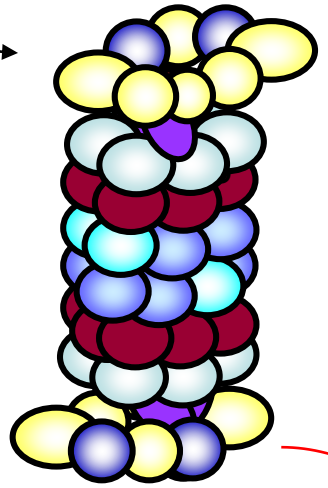
UPS

Hypoxia

ER stress

26S proteasome

Infection



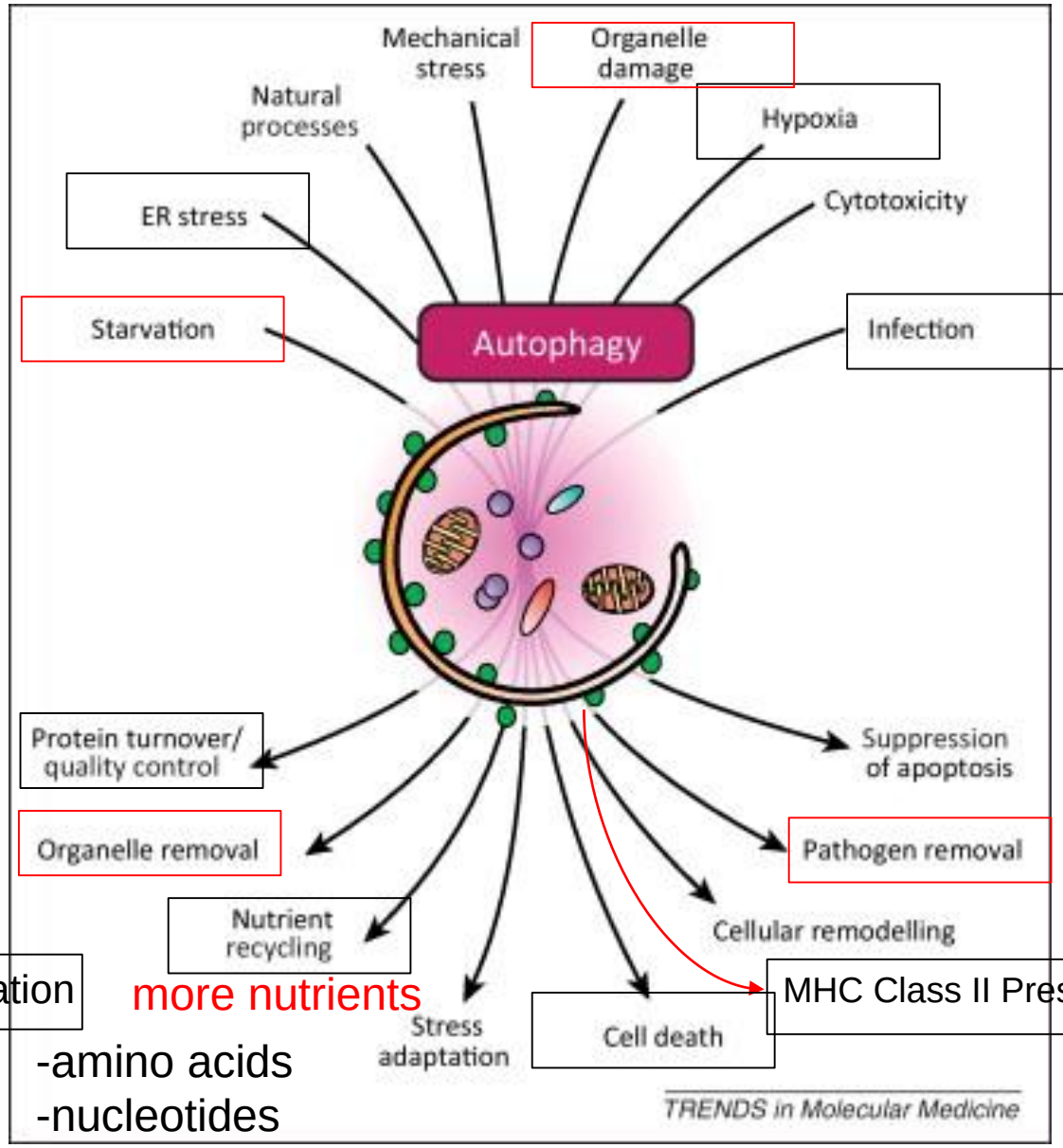
Protein turnover/ quality control

Nutrient recycling

Cell death

MHC Class I Presentation

Selective macroautophagy



more nutrients

-amino acids
-nucleotides
-Kohlenstoff

MHC Class II Presentation

1. All nucleated cells, all somatic cells.

2. Endogenous antigenes
Viral proetins endogenous?

3. Peptide size: nonamer
Proteasome

4. apoptosis in infected or mutated cells

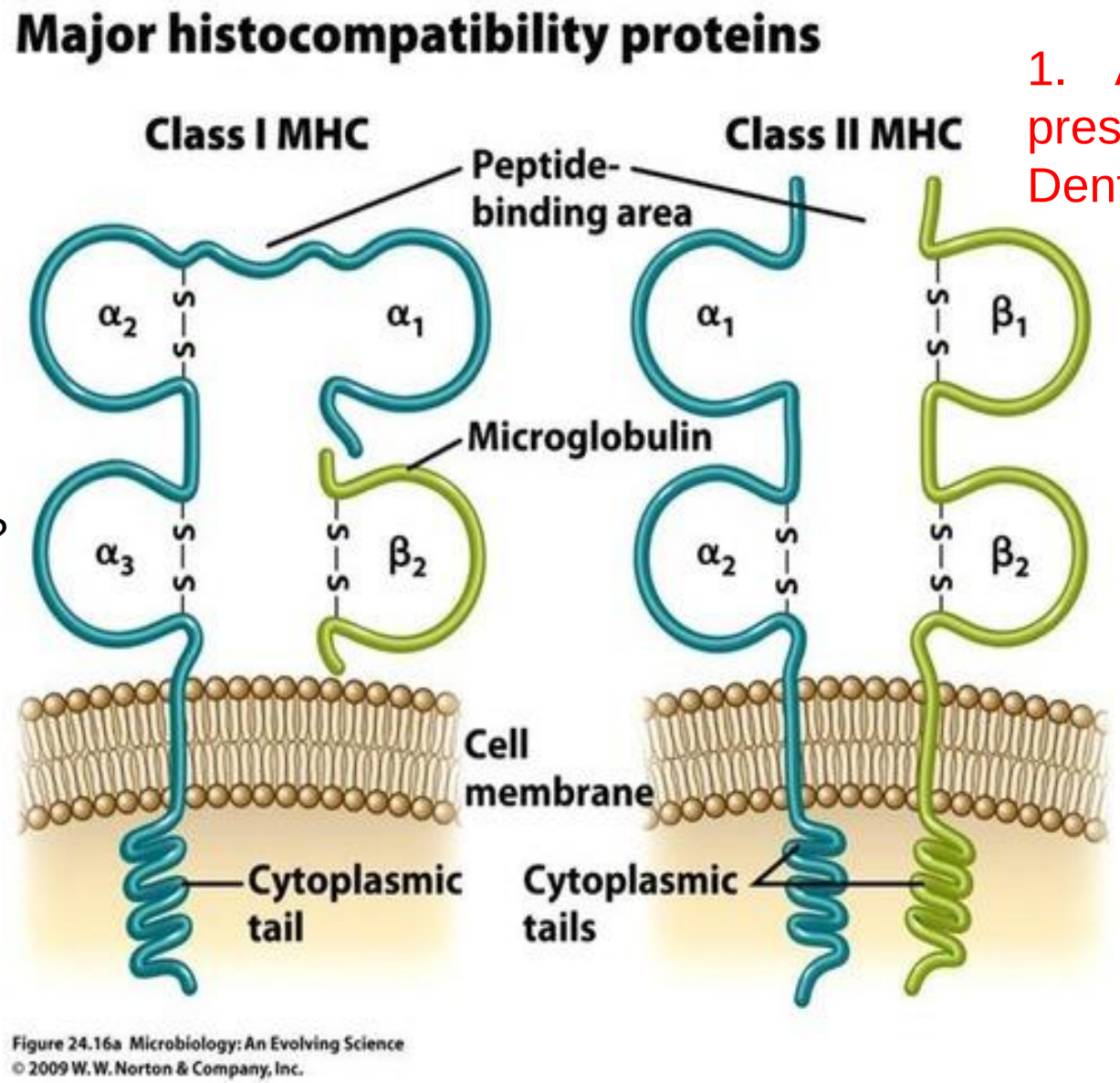


Figure 24.16a Microbiology: An Evolving Science
© 2009 W. W. Norton & Company, Inc.

1. All professional antigen presentig cells e.g. macrophages, Dentritic cells and B cells.

2.Exogenous antigenes

3. 18-20-mer
Lysosome

4. specific immune reaction: production of antibodies, formation of memory cells, apoptosis