

The role of lysosomes in human longevity and aging

International Congress on Healthy Aging
May 10-12, 2022

Mohammad Bagher Rafi, Ph.D.

*Emeritus Professor of Neurology
Thomas Jefferson University
Philadelphia*

LYSOSOMAL STORAGE DISEASES



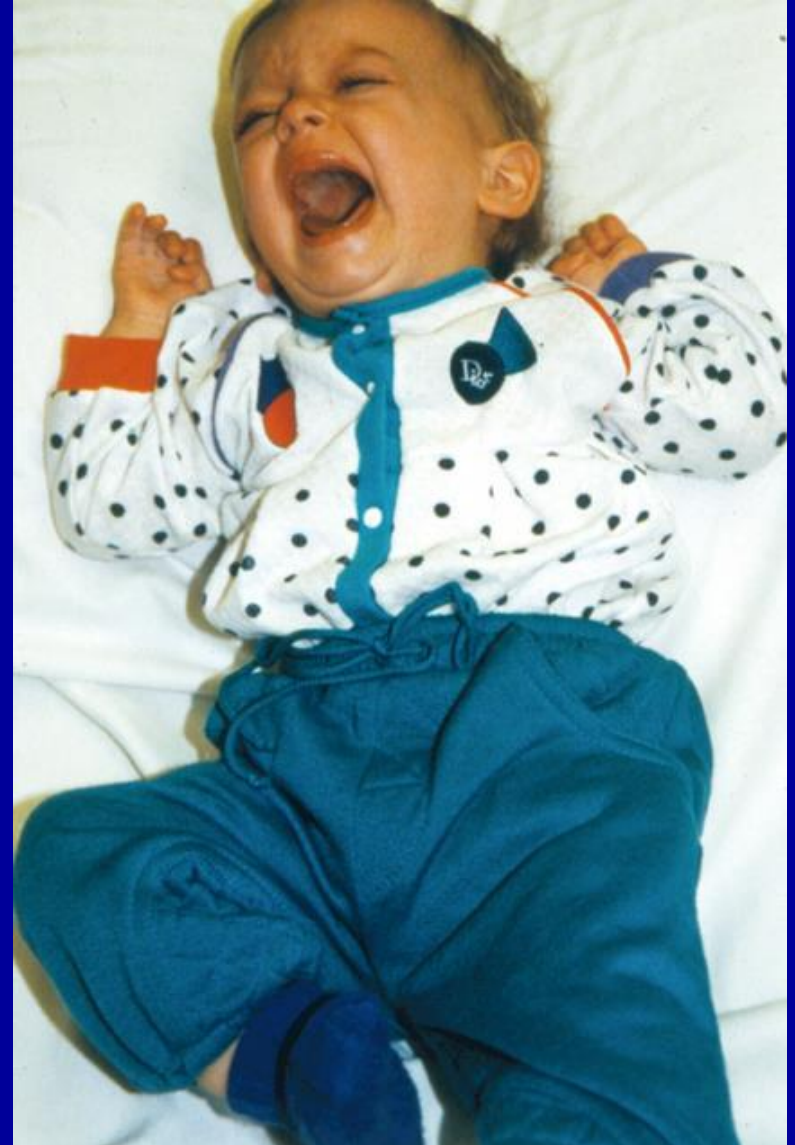
* DIAGNOSABLE IN THIS LABORATORY

What is Krabbe disease?

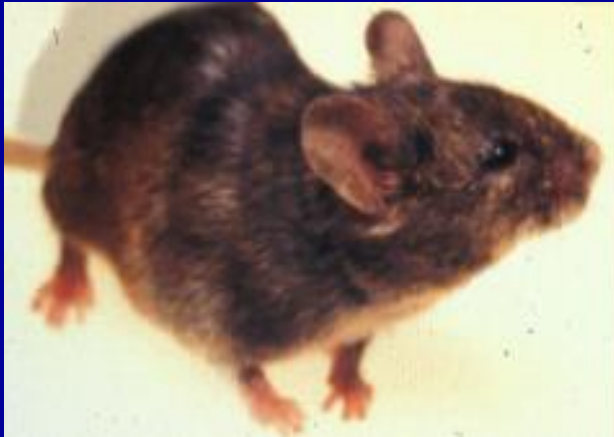
A lysosomal disorder,
With neurodegeneration

Symptoms include:

- *Irritability,*
- *Fevers,*
- *Limb stiffness,*
- *Seizures,*
- *Feeding difficulties*



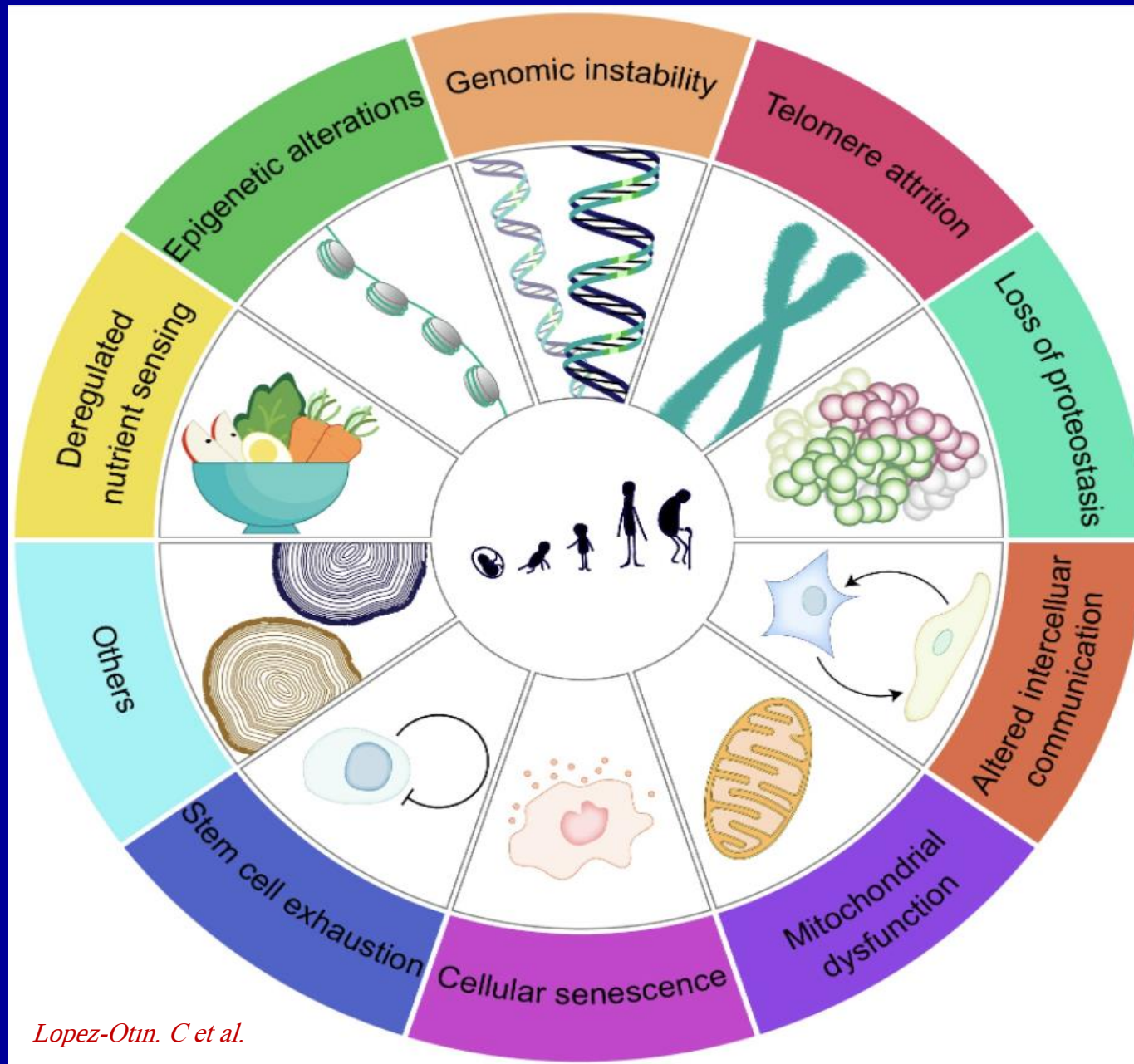
Animal models for Krabbe disease



Wildtype mouse and 200-days-old Twitcher mouse

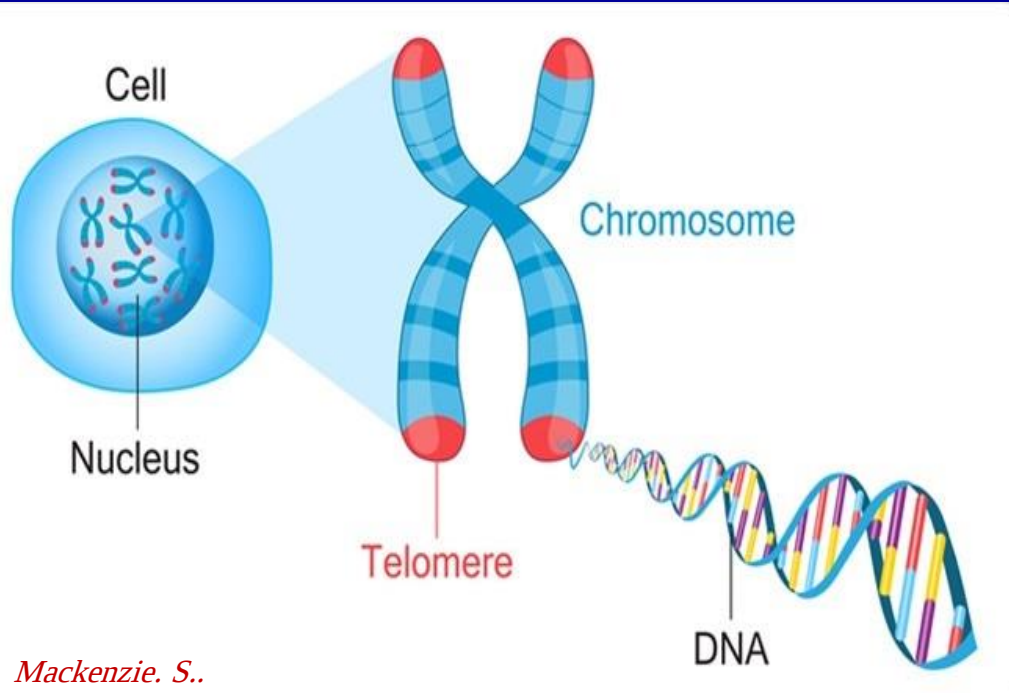


Some theories on human aging & longevity

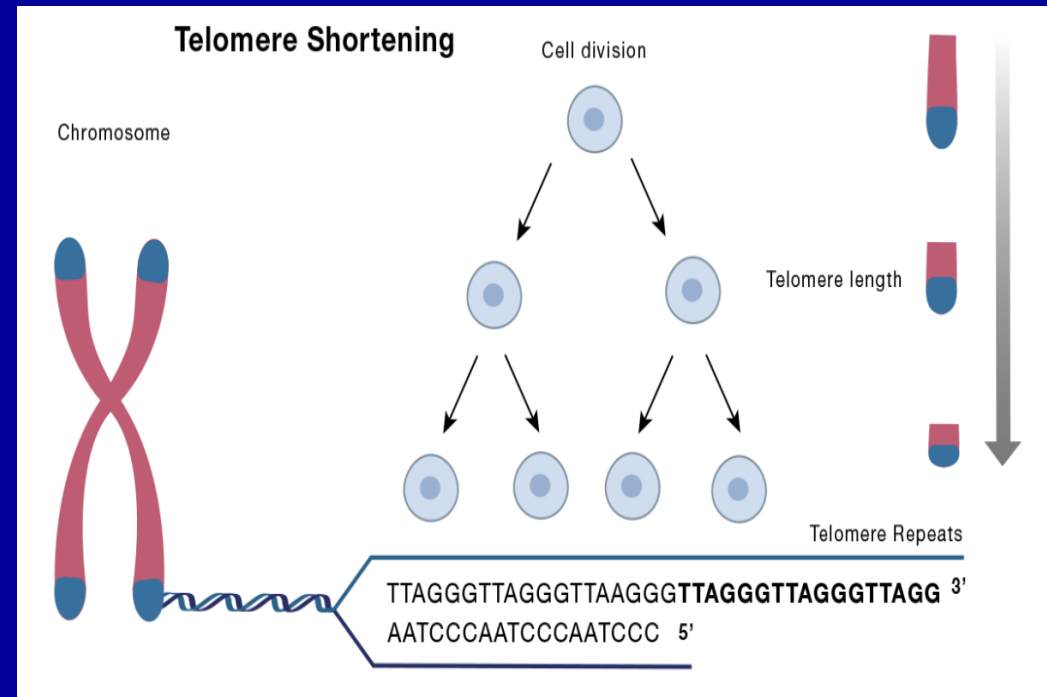


Chromosomal telomere shortening

Telomeres are crucial parts of the chromosome that act to protect them and ensure DNA replication is performed effectively.

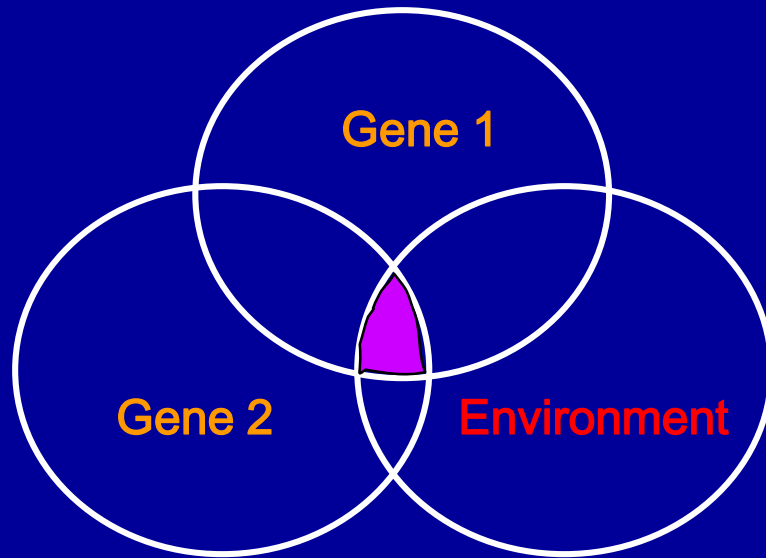


Telomeres are located at the both ends of the chromosomes

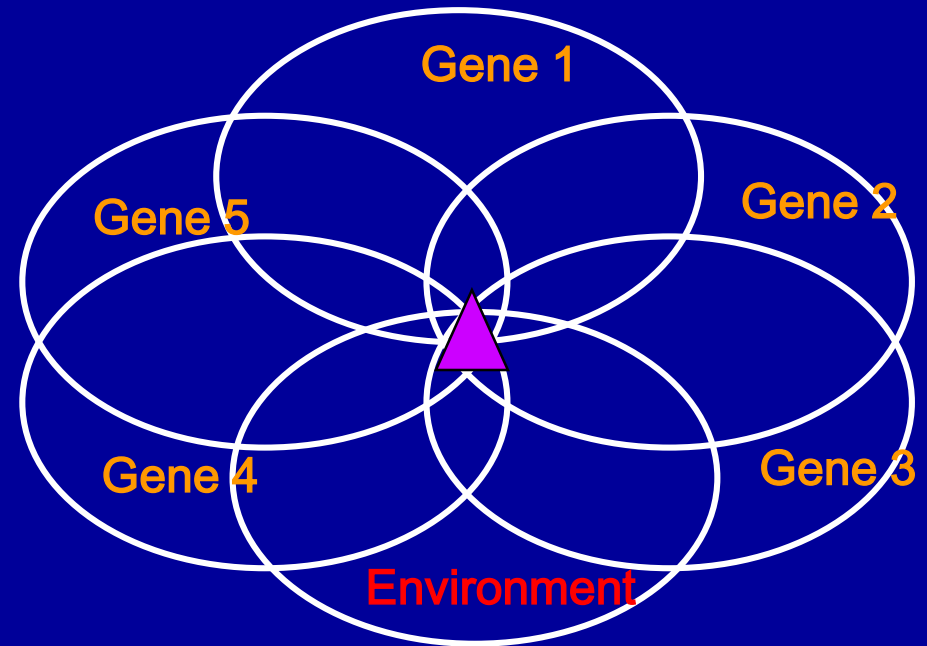


Telomeres get shorter each time at cell division

Interaction of Genes & Environment



Few genes and environmental factors each contributing a large risk.



Many genes and environmental factors each contributing a small risk.

Lysosome as a Cellular Organelle

Animal Cell Structure

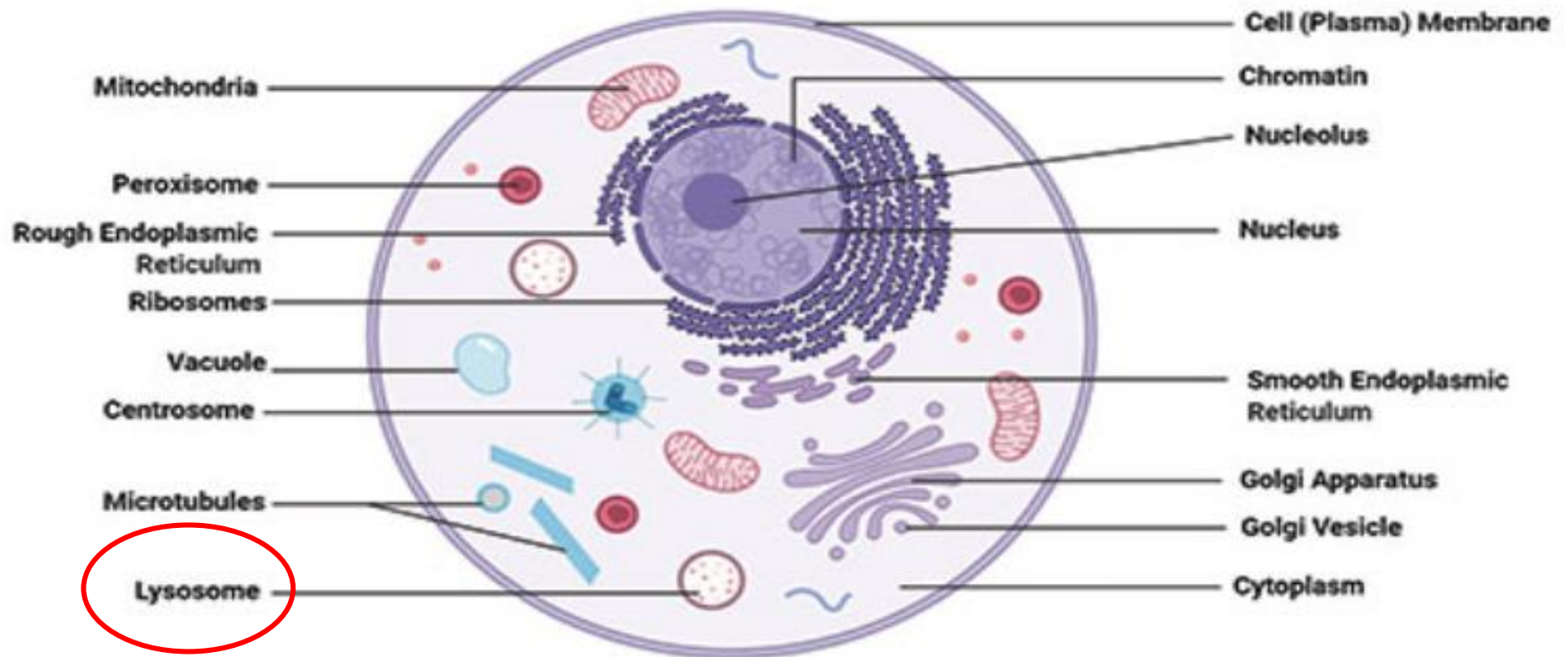
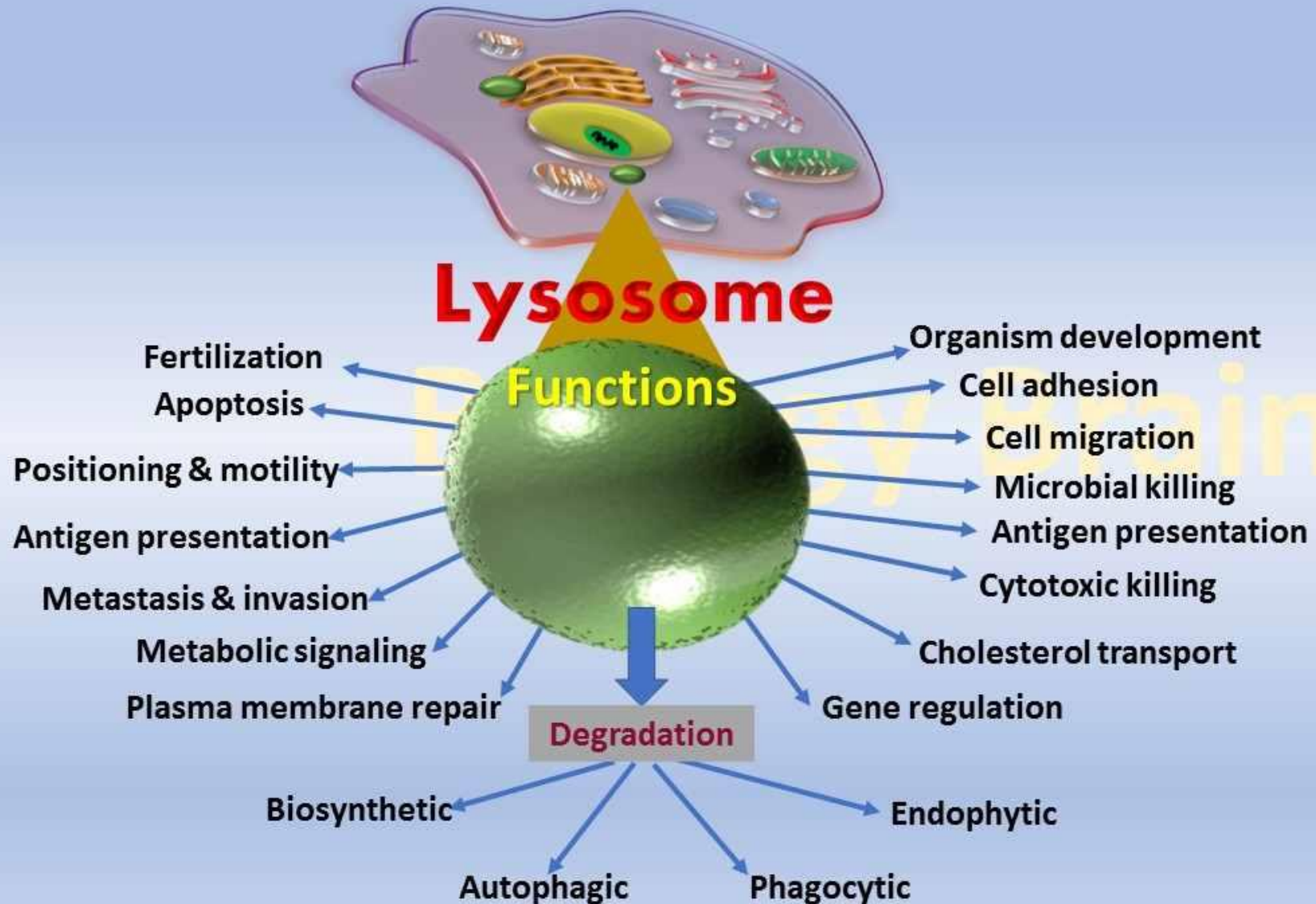
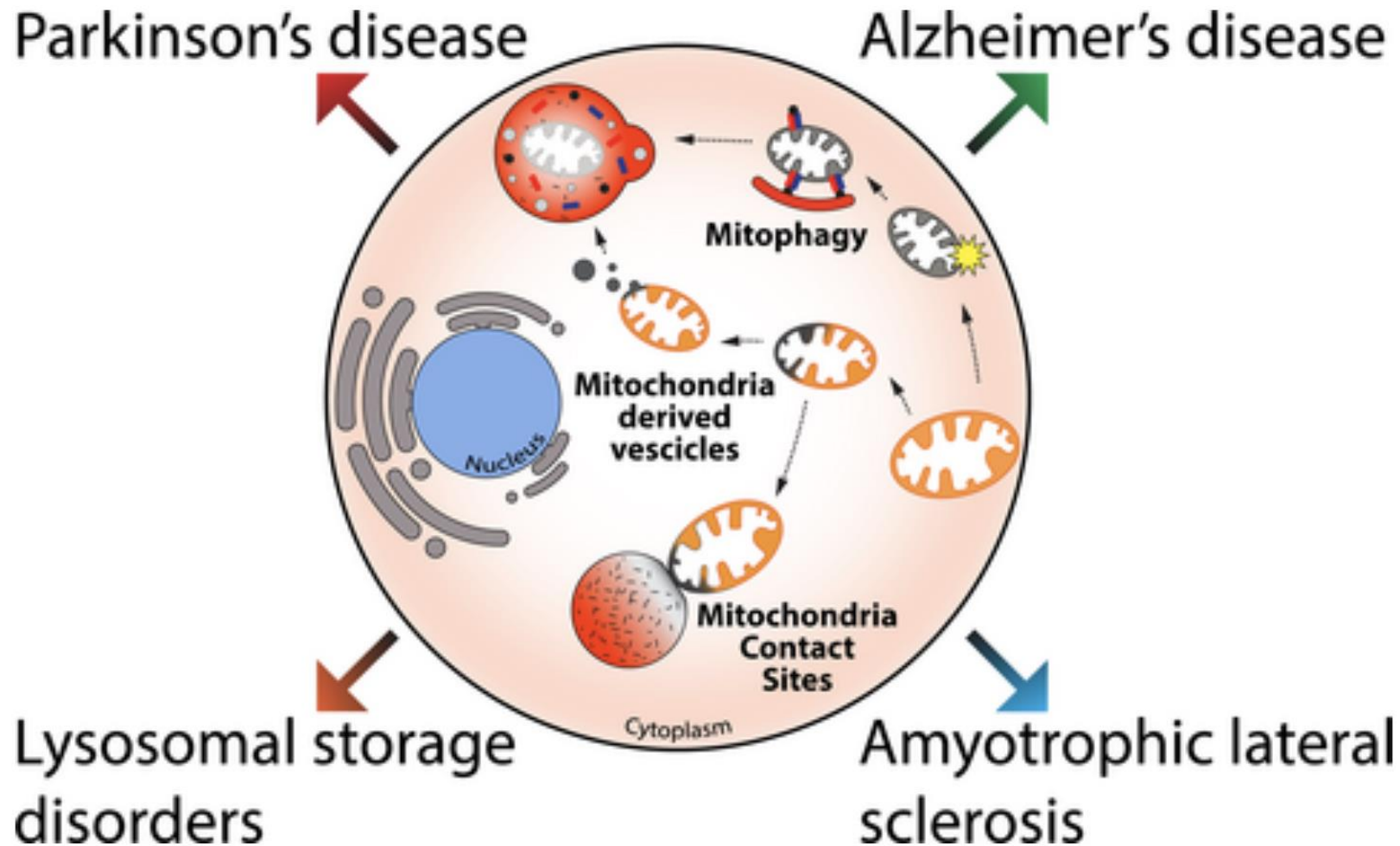


Figure: Animal Cell Structure, Image Copyright Sagar Aryal, www.microbenotes.com

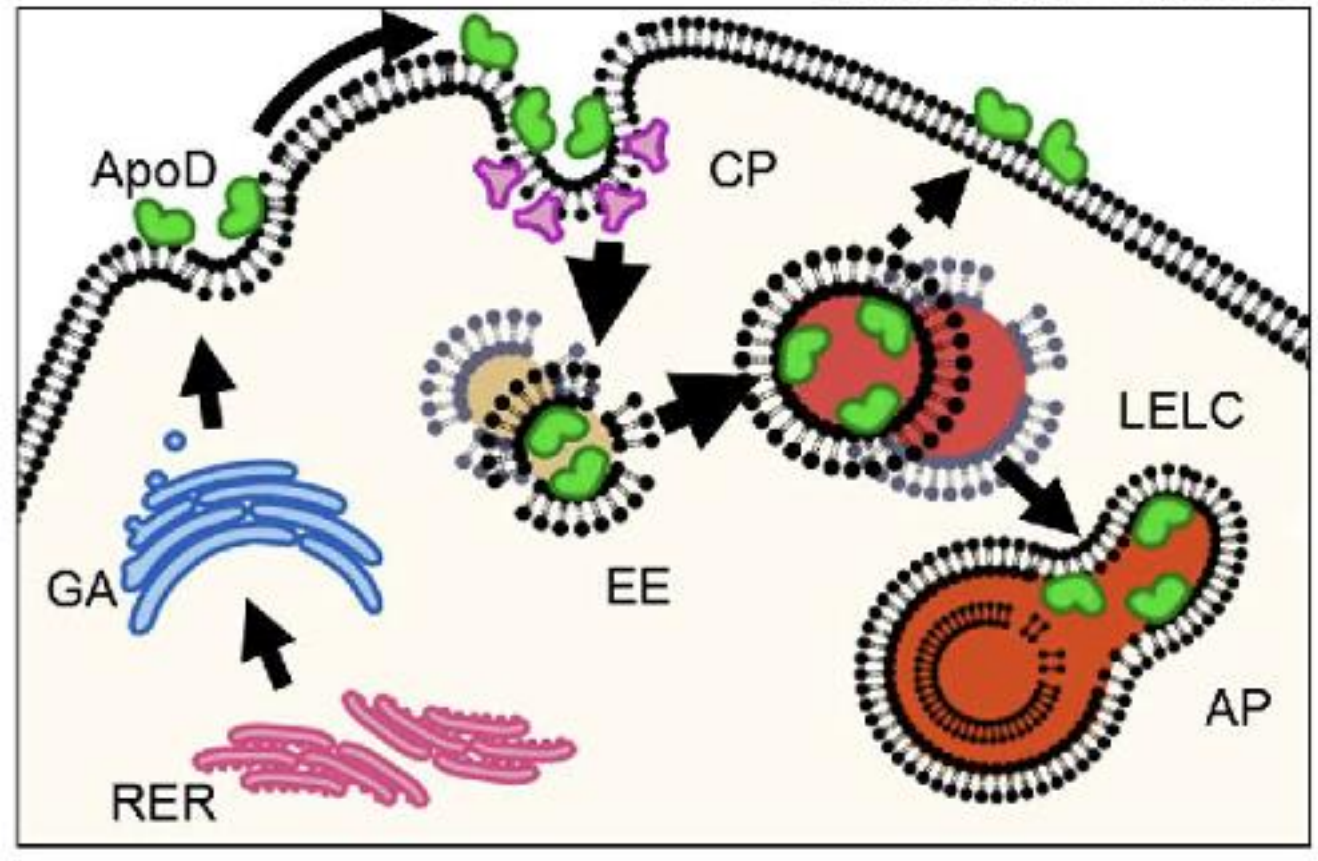
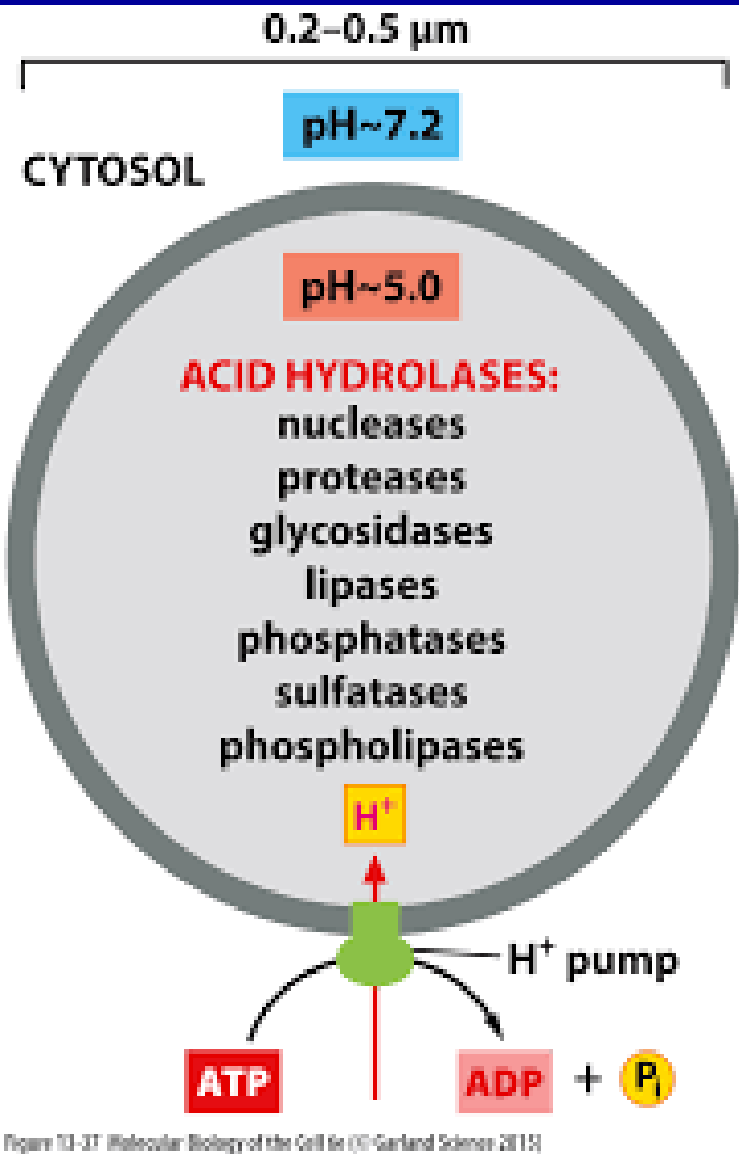
Lysosome as a multi-functional organelle



Lysosomal Role in Aging Diseases



Lysosomal acidic milieu

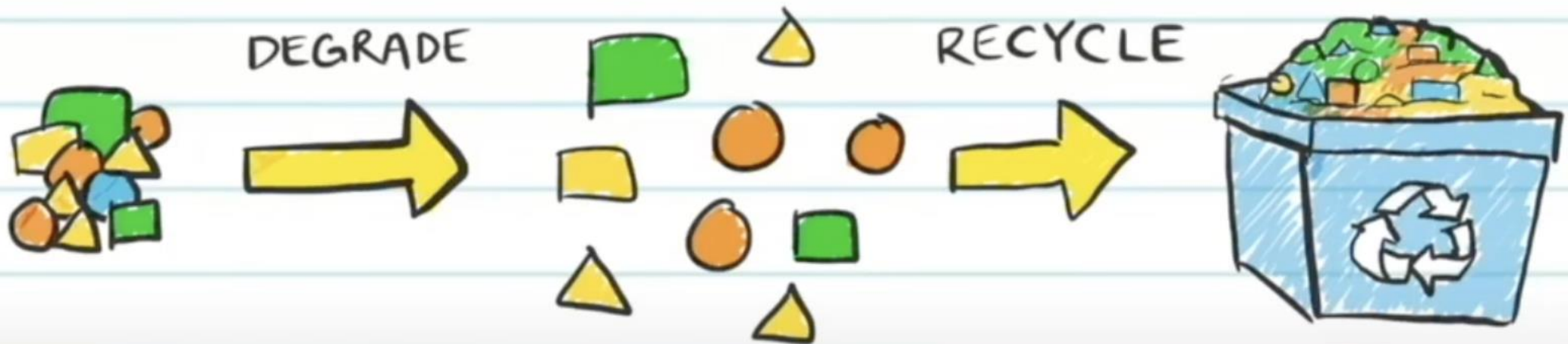


Apolipoprotein D (ApoD)'s role in neutralizing anti-oxidative stress effects: restoring membrane permeability

Lysosomal role in cell biology

- I. **Autophagy and longevity**
- II. **Lysosomes and nutrient homeostasis**
- III. **Lysosomes and mitochondrial function**

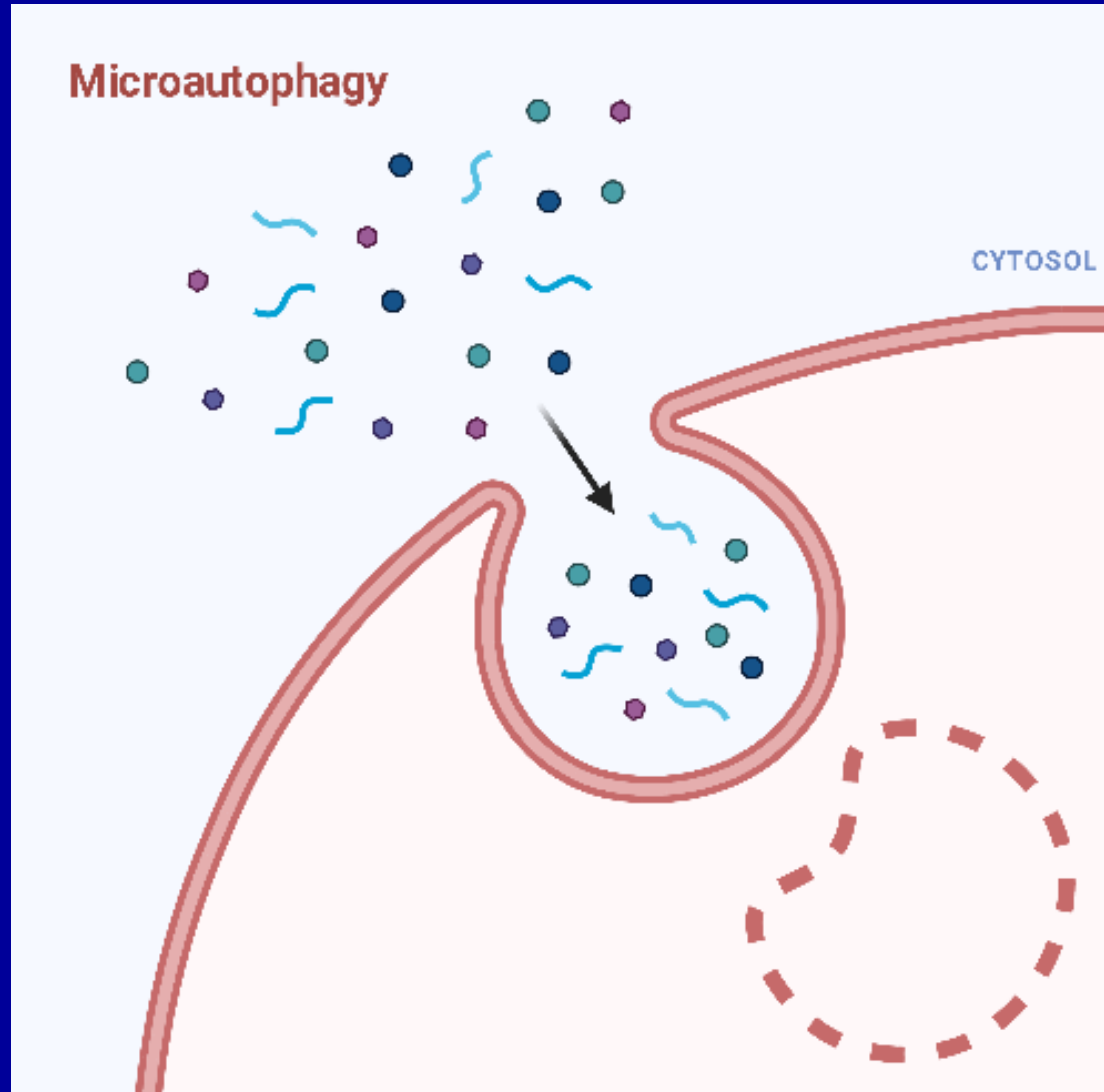
Autophagy



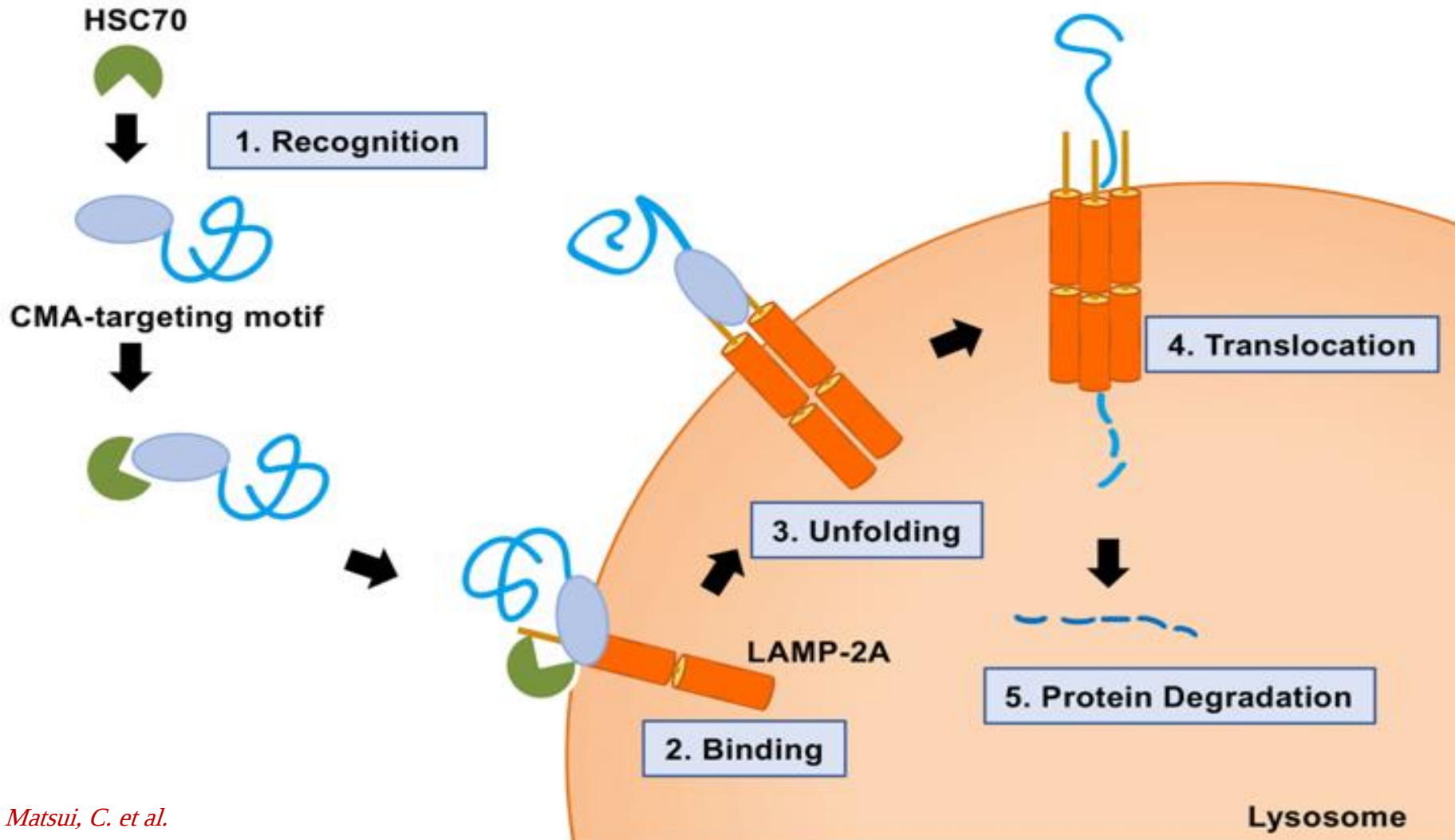
Autophagy

- Microautophagy,
- Chaperone-mediated autophagy (CMA)
- Macroautophagy.

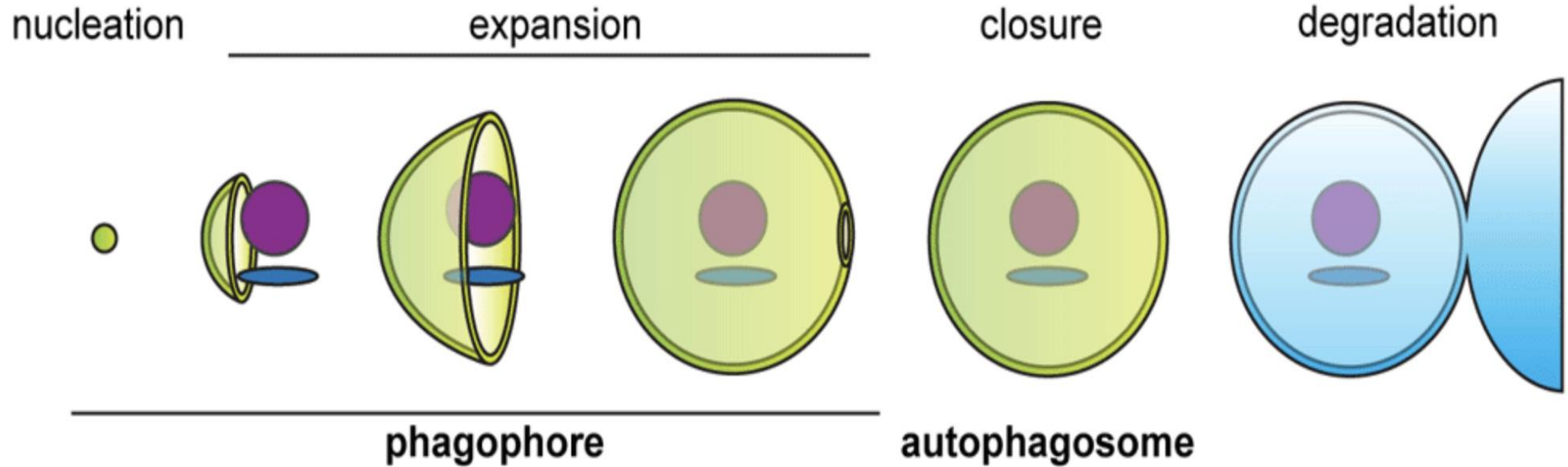
Microautophagy



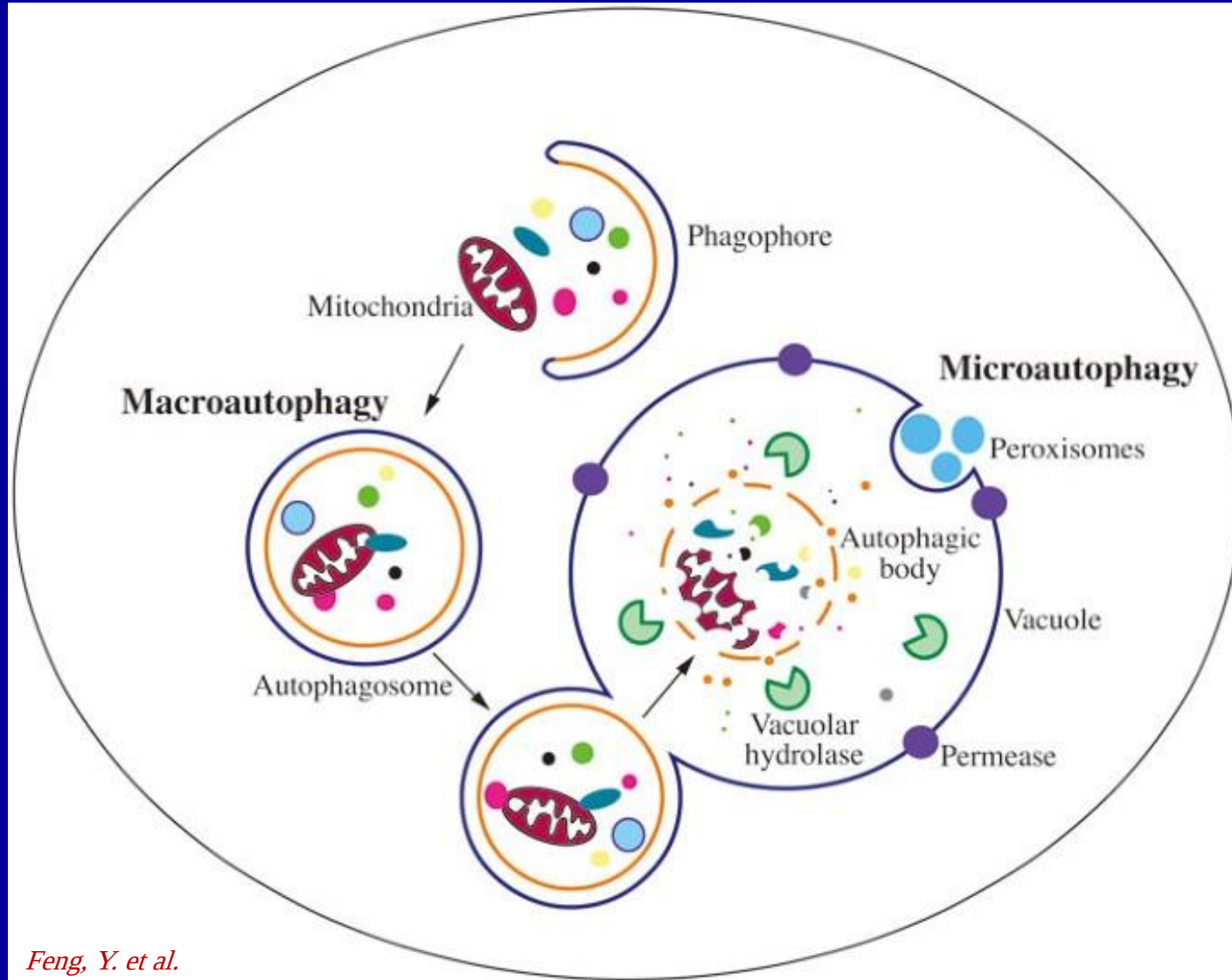
Chaperone-mediated autophagy (CMA)



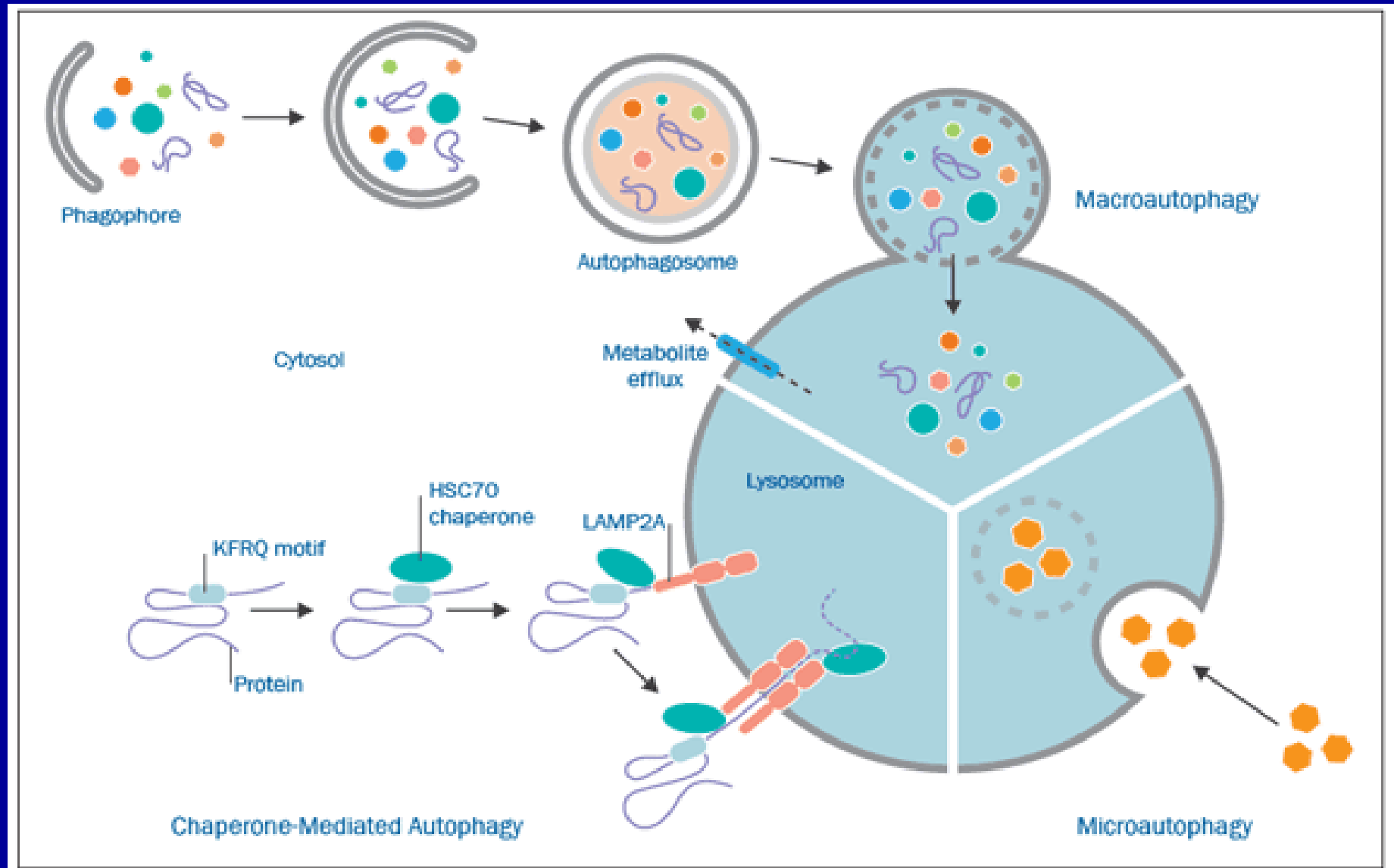
Macroautophagy: autophagosome formation



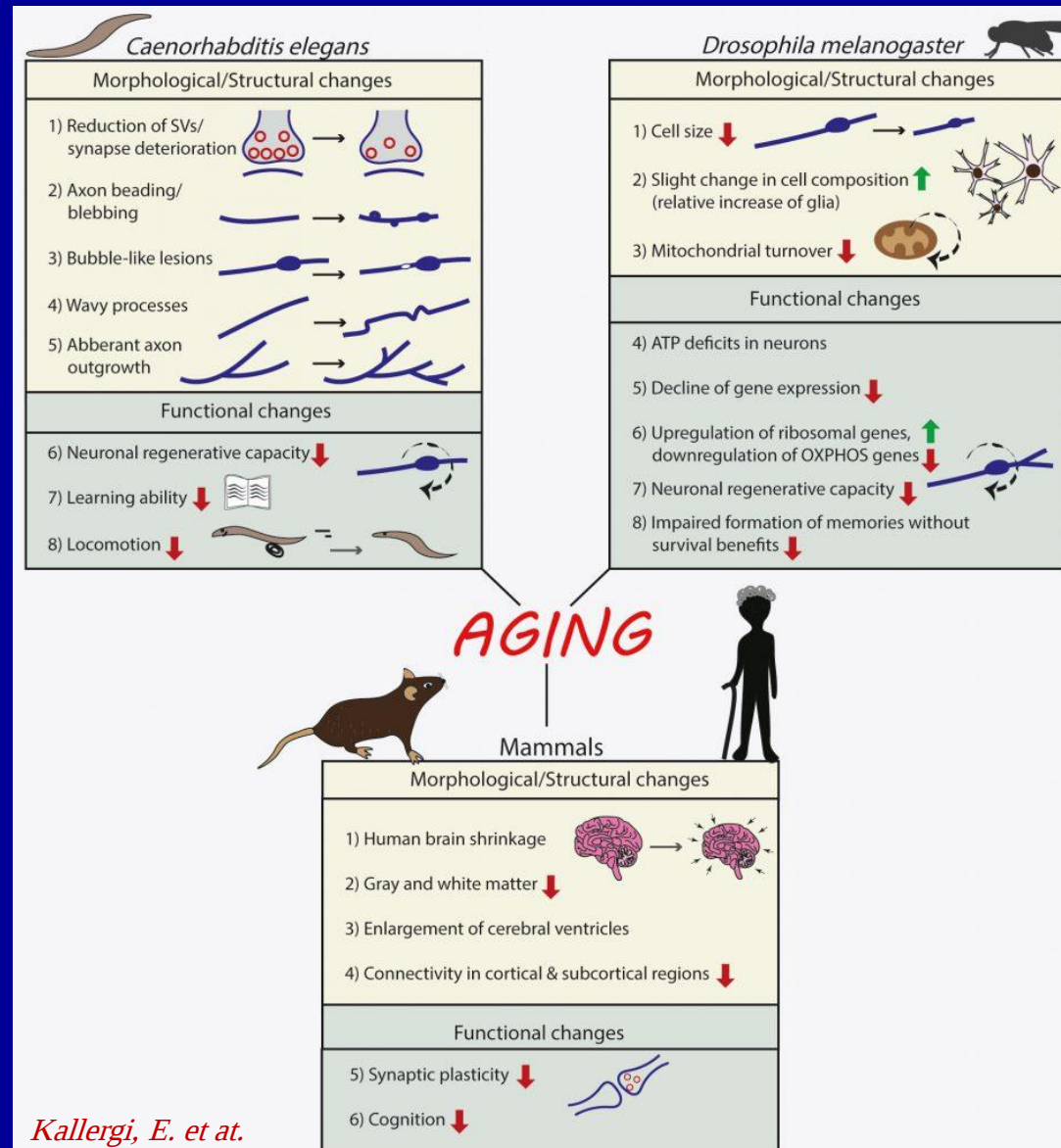
Macroautophagy & Microautophagy



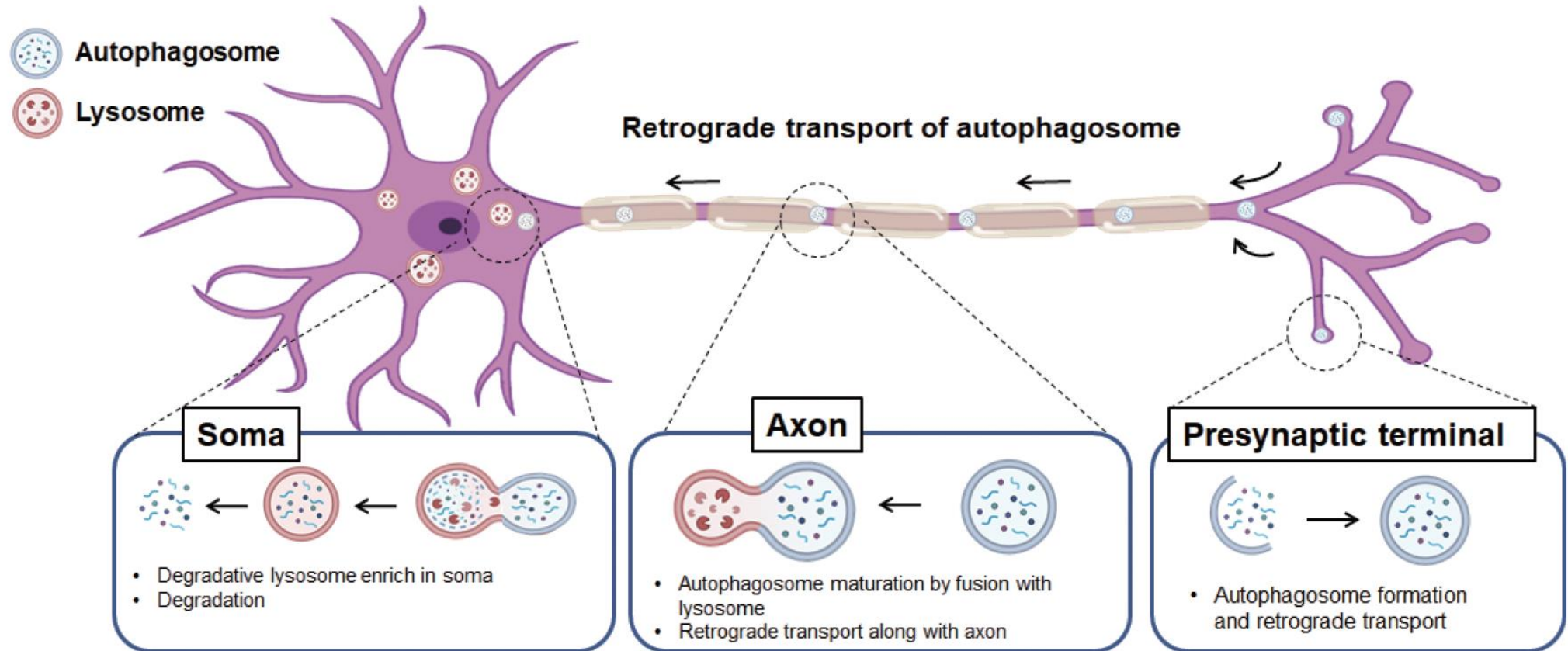
All three types of autophagy



Macroautophagy machinery in animal kingdom



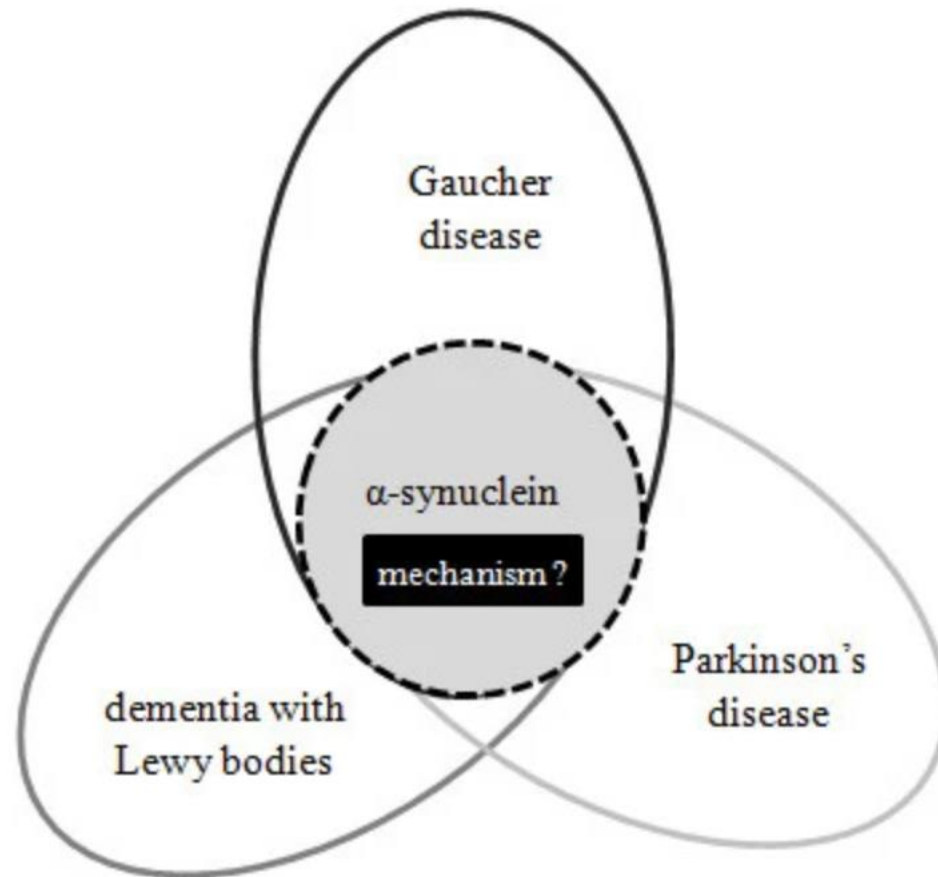
Autophagy in nervous systems



LYSOSOMAL HYDROLYSIS

Disorder	Enzyme Deficiency	Storage Product(s)	Major Organs Involved
Mucopolysaccharidoses			
MPS / Hurler and Scheie syndromes	α -iduronidase	Dermatan sulfate, heparan sulfate	Central nervous system, connective tissue, heart, skeleton, cornea
MPSII Hunter syndrome	Iduronate sulfatase	Dermatan sulfate, heparan sulfate	Central nervous system, connective tissue, heart, skeleton, cornea
Sphingolipidoses			
GM, gangliosidosis	β -Galactosidase	GM, ganglioside, oligosaccharides	Central nervous system, skeleton, viscera
Krabbe's disease	Galactosylcerebrosidase β -Galactosidase	Galactosylsphingosine	Central nervous system
Tay-Sachs disease	Hexosaminidase A	GM ₂ , ganglioside	Central nervous system
Fabry disease	α -Galactosidase A	Gb ₃ , globotriaosylceramide	Kidney, heart, cornea
Lipidoses			
Wolman's disease	Acid lipase	Triglycerides, cholesteryl esters	Liver, spleen, adrenal
Cholesteryl ester storage disease	Acid lipase	Triglycerides, cholesteryl esters	Liver, spleen, heart
Disorders of Glycoprotein Degradation			
Fucosidosis	α -Fucosidase	Fragments of glycoproteins and glycolipids	Central nervous system
Mannosidosis	α -Mannosidase	Fragments of glycoproteins	Central nervous system, skeleton, liver, spleen
Sialidosis (mucopolipidosis I)	Oligosaccharide neuraminidase	Fragments of glycoproteins	Central nervous system, skeleton, liver, spleen
Disorders of Enzyme Localization			
Mucopolipidosis II (I-cell disease)	N-Acetylglucosaminyl-phosphotransferase	Mucopolysaccharidoses, lipids, glycoproteins	Central nervous system, connective tissue, skeleton, heart
Mucopolipidosis III (Pseudo-Hurler polydystrophy)	N-Acetylglucosaminyl-phosphotransferase	Mucopolysaccharidoses, lipids, glycoproteins	Joint and connective tissue problems predominantly

Gaucher disease, dementia & Parkinson's Disease



Synucleinopathies demonstrating a relationship with Gaucher disease.

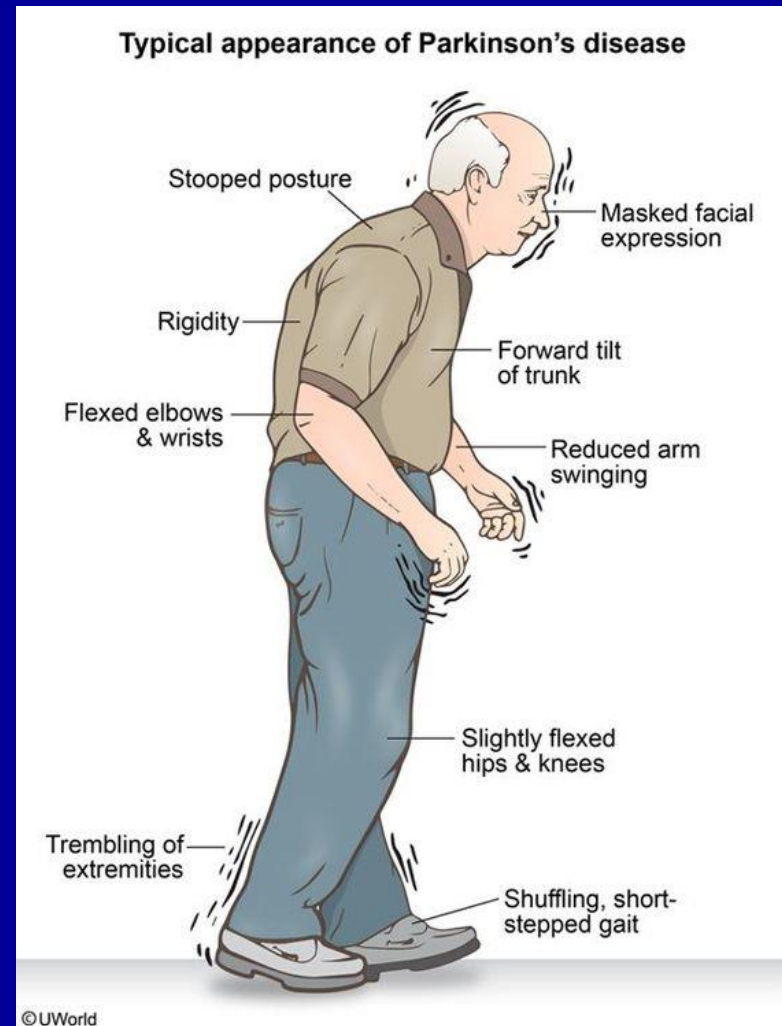
Campbell, TN. et al.

Glucocerebrosidase deficiency & Parkinson

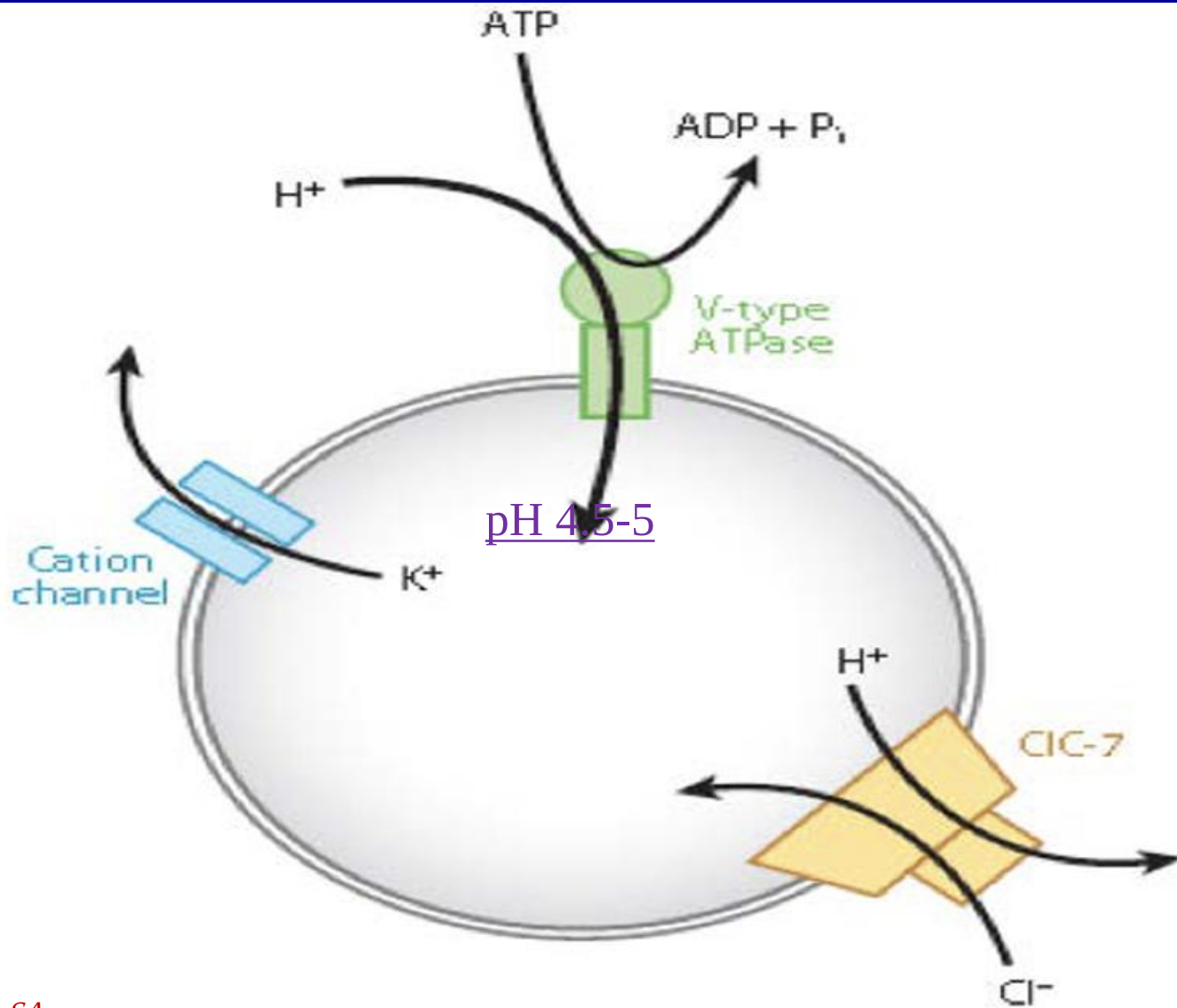
Gaucher's disease



Parkinson's disease



ATPase pump & PH regulation

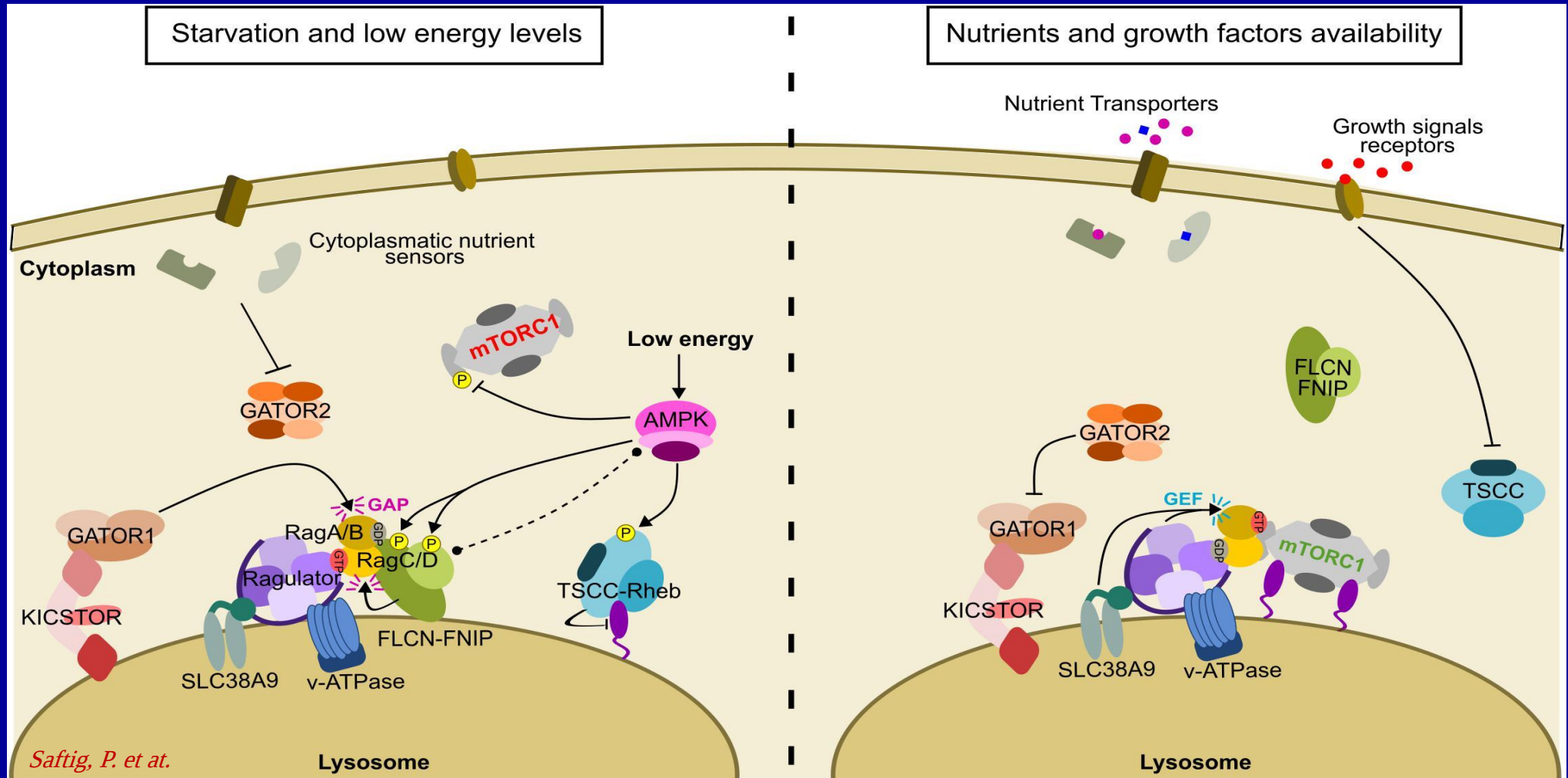


Lysosomal role in cell biology

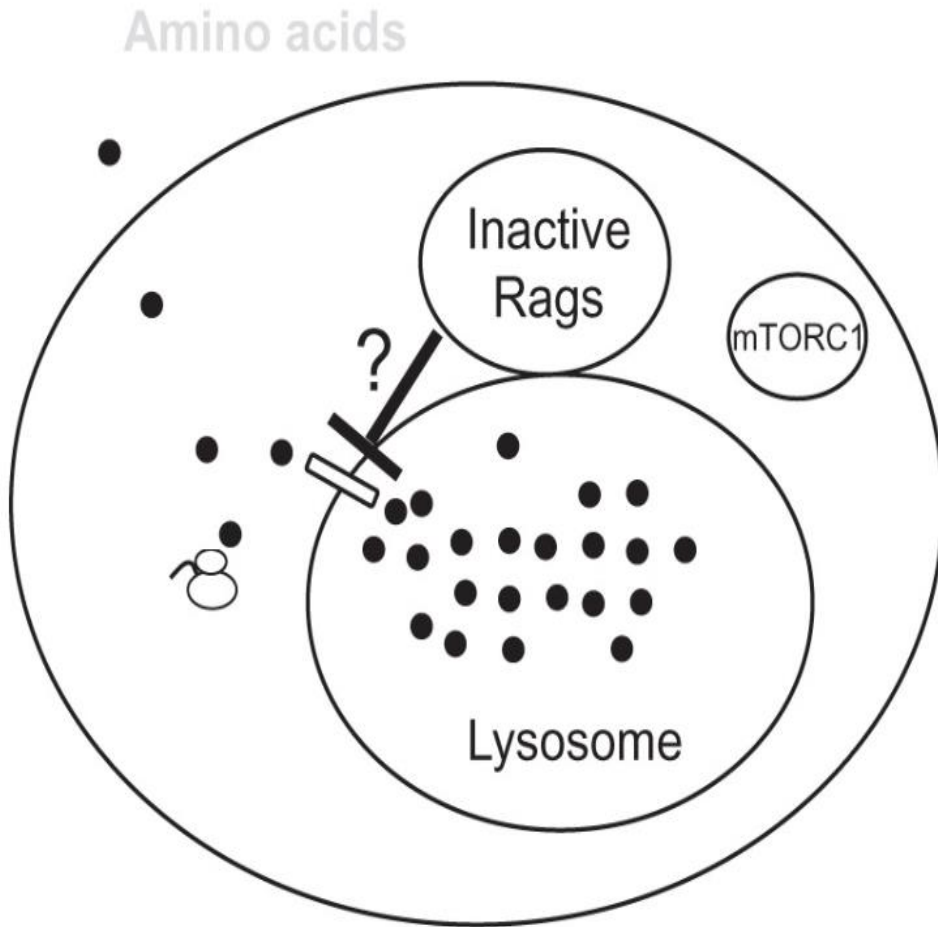
- I. Autophagy and longevity
- II. **Lysosomes and nutrient homeostasis**
- III. Lysosomes and mitochondrial function

Conclusion

Nutrient Sensing & Homeostasis

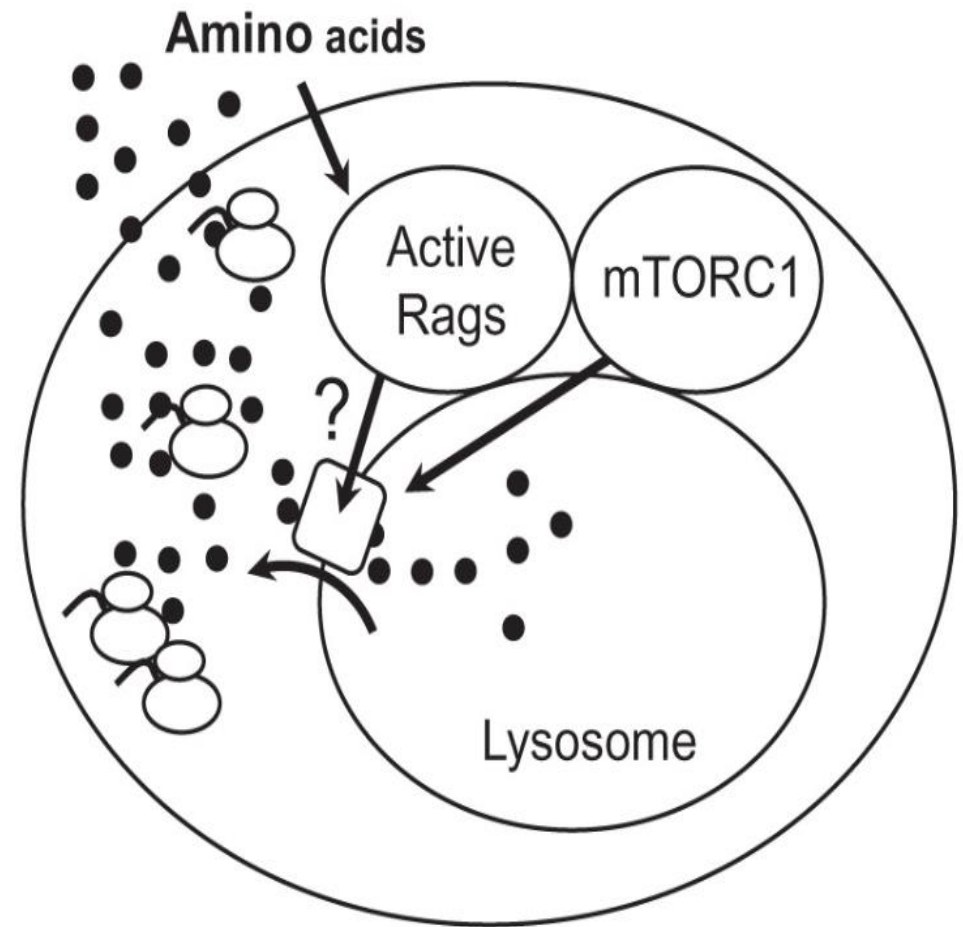


Amino acids storage in lysosomes



Inoki, K. et al.

Amino acid limited conditions



Amino acid sufficient conditions

Lysosomal role in cell biology

- I. Autophagy and longevity
- II. Lysosomes and nutrient homeostasis
- III. Lysosomes and mitochondrial function

Lysosomes and mitochondrial interactions

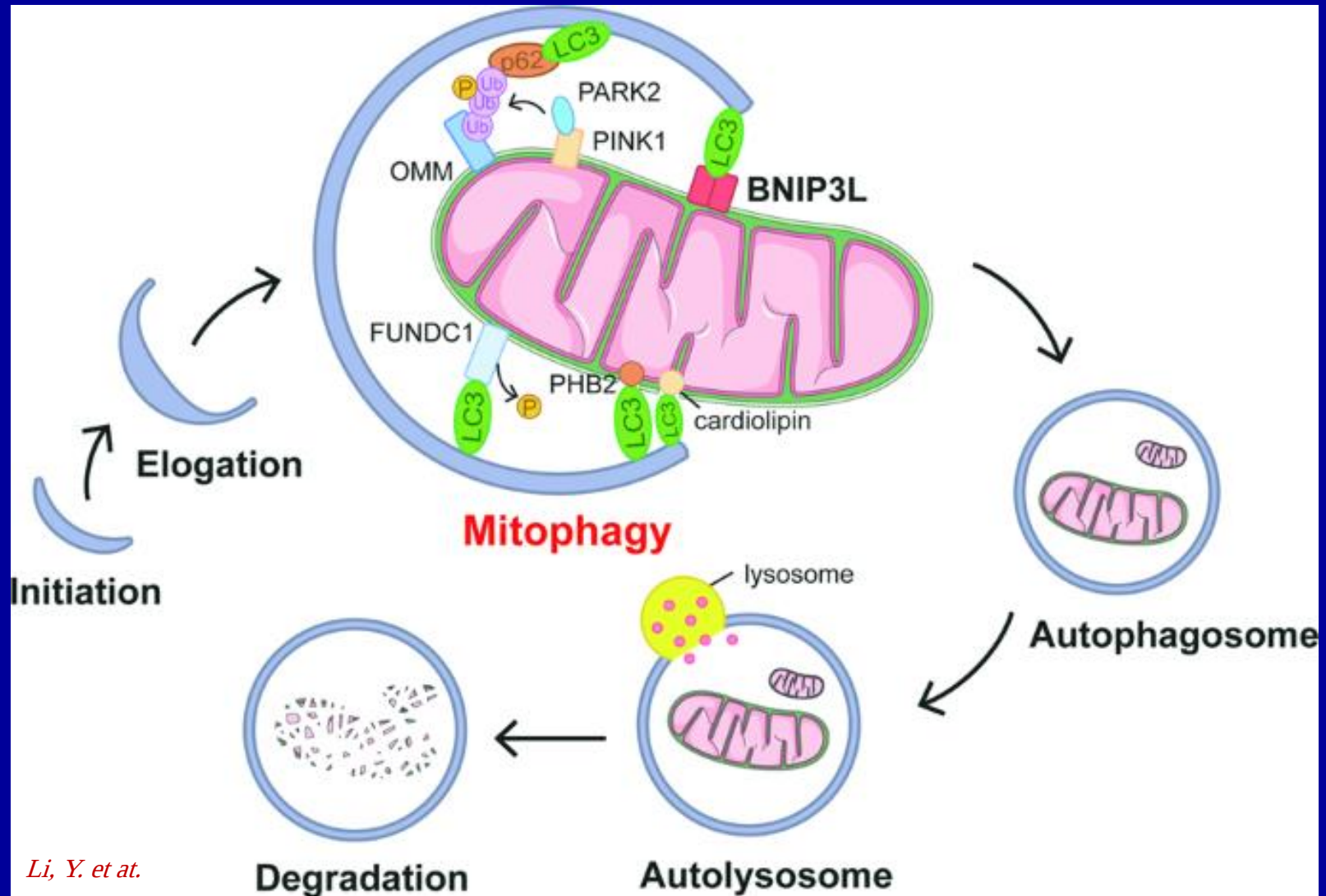
I. Degradative process

- Mitophagy

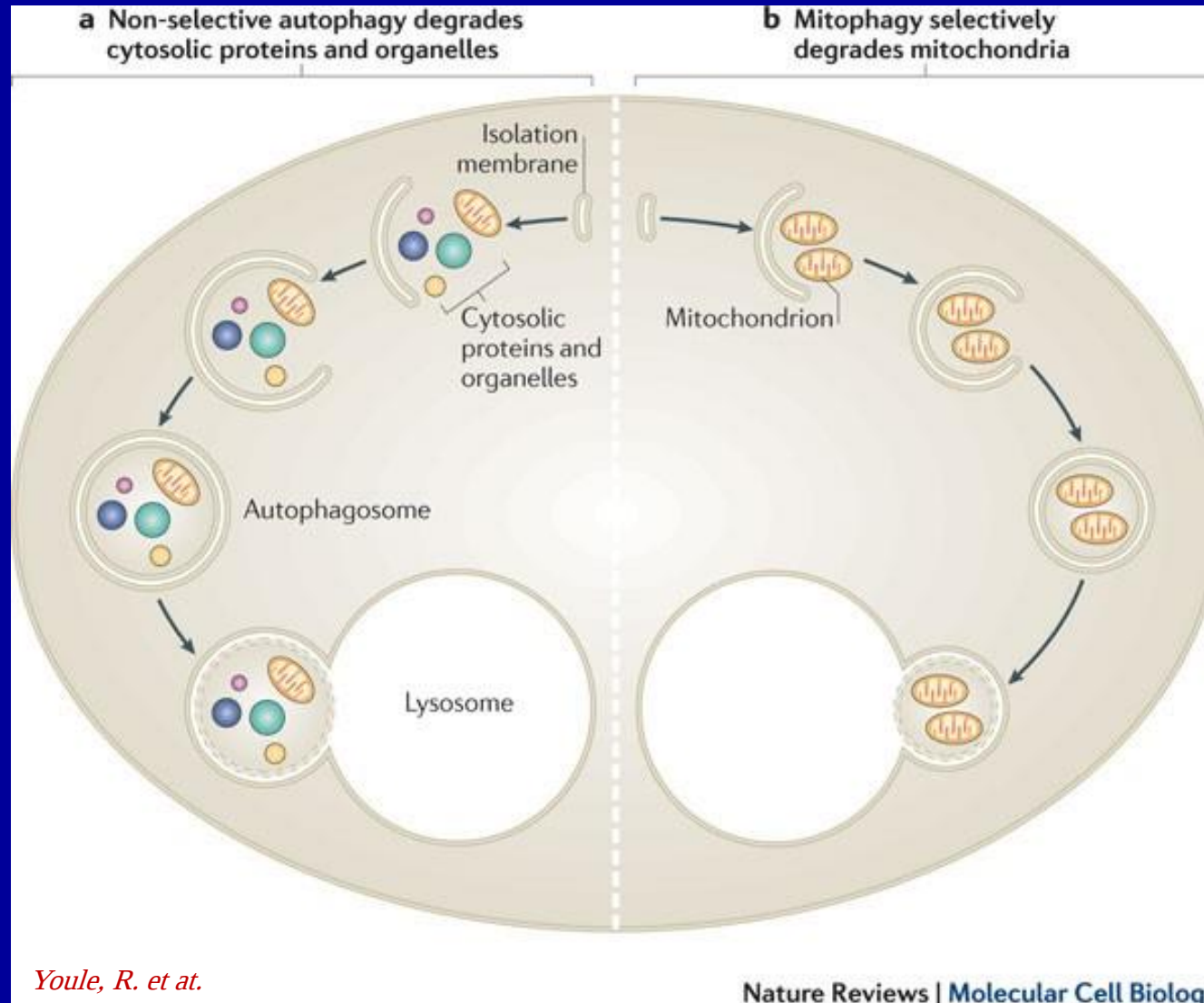
- Mitochondrial delivered vesicles (MDV)

II. Non-degradative process

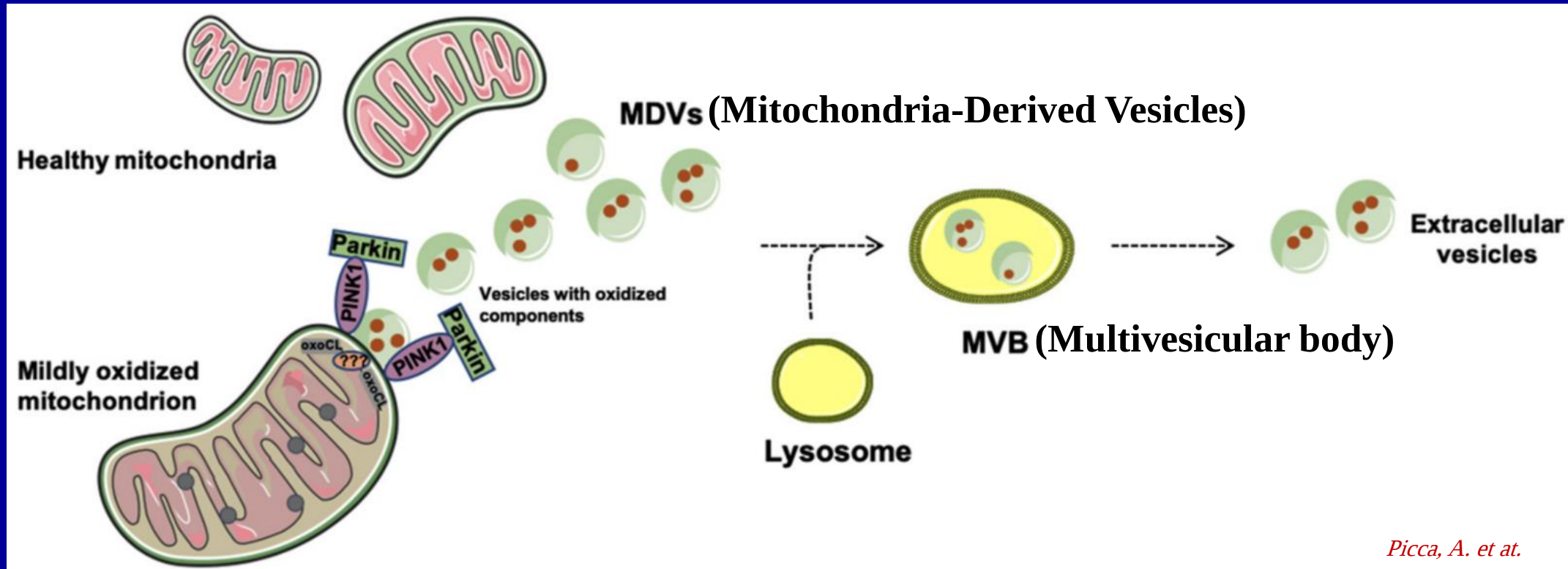
Mitophagy



Selective & Non-selective Mitophagy

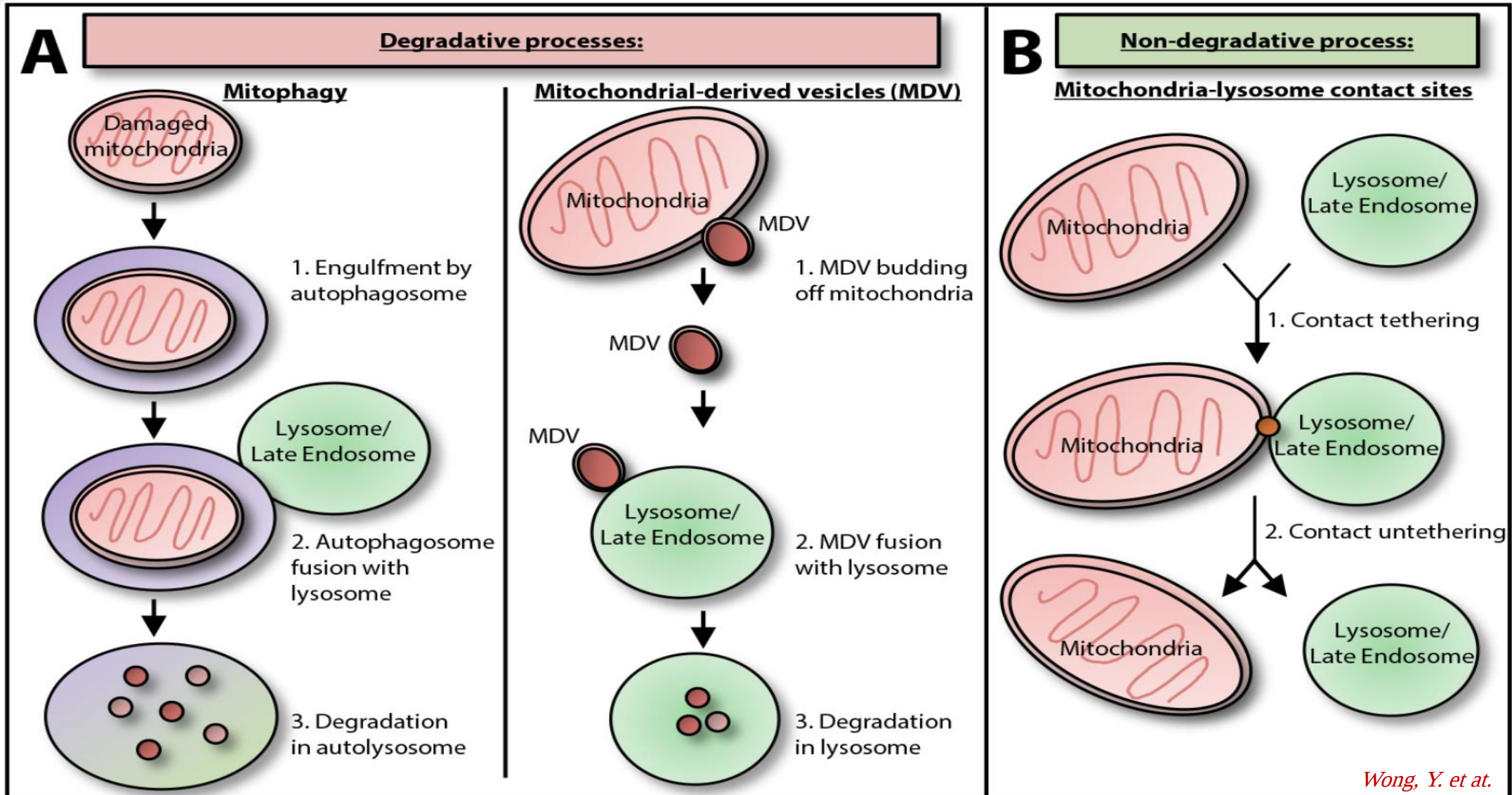


Mitochondria-Derived Vesicles (MDVs)



Picca, A. et al.

Lysosomal & Mitochondrial Interactions



Conclusion

The role of lysosomes in human longevity and aging

- *Cellular housekeeping duty*
- *Nutrient sensing and homeostasis*
- *Inter-organelle cross-talks*

Is it possible to improve healthy lifespan by promoting lysosomal function?

Yes:

- *By preserving lysosomal acidic milieu*
- *By enhancing autophagy*

Conclusion

Lysosomes as the cellular housekeeping staff



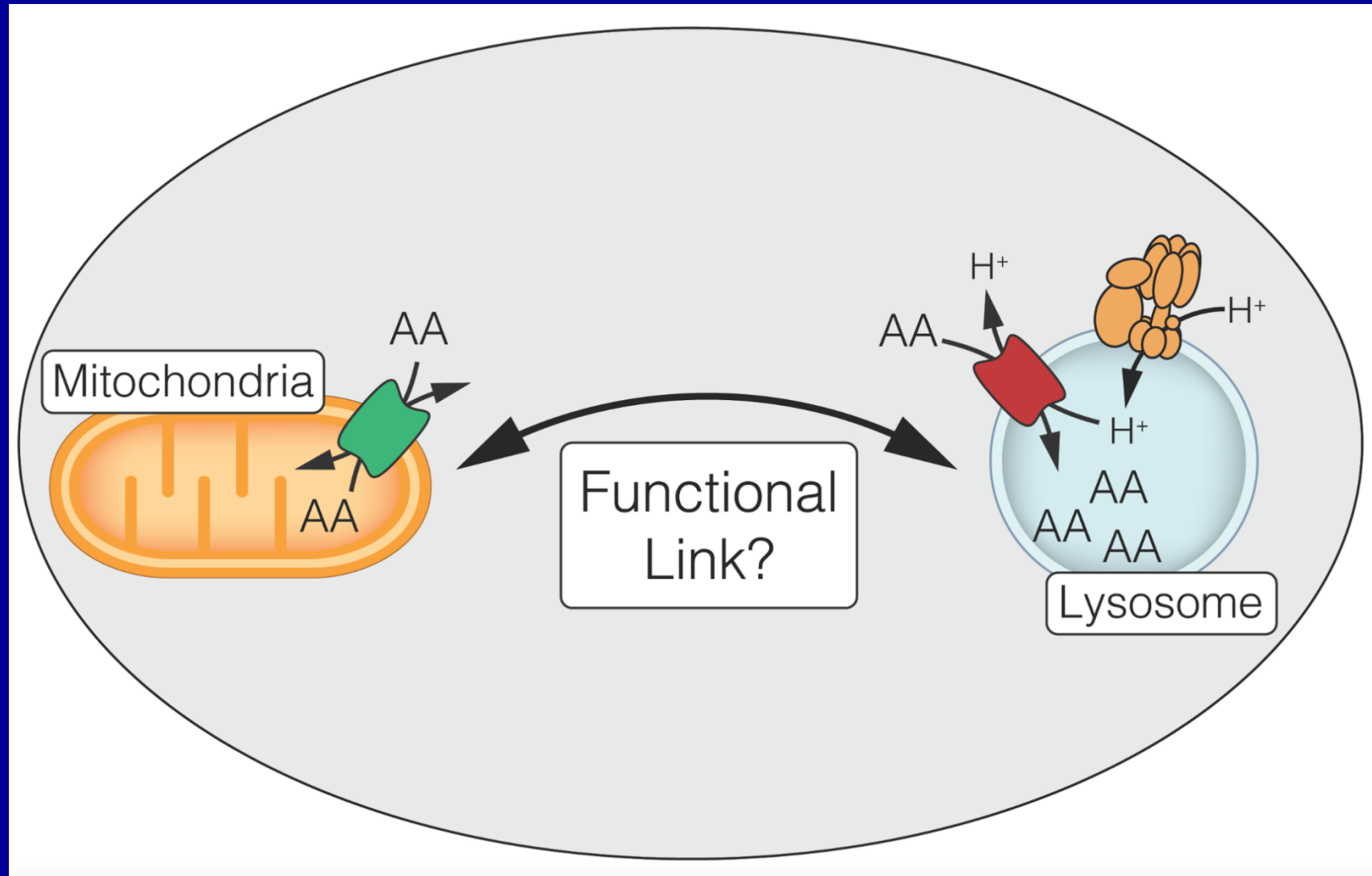
Conclusion

Lysosome as Decision Making Center



Conclusion

Inter-organelle cross-talks



Conclusion

The role of lysosomes in human longevity and aging

- *Cellular housekeeping duty*
- *Nutrient sensing and homeostasis*
- *Inter-organelle cross-talks*

Is it possible to improve healthy lifespan by promoting lysosomal function?

Yes:

- *By preserving lysosomal acidic milieu*
- *By enhancing autophagy*

Conclusion

The role of lysosomes in human longevity and aging

- *Cellular housekeeping duty*
- *Nutrient sensing and homeostasis*
- *Inter-organelle cross-talks*

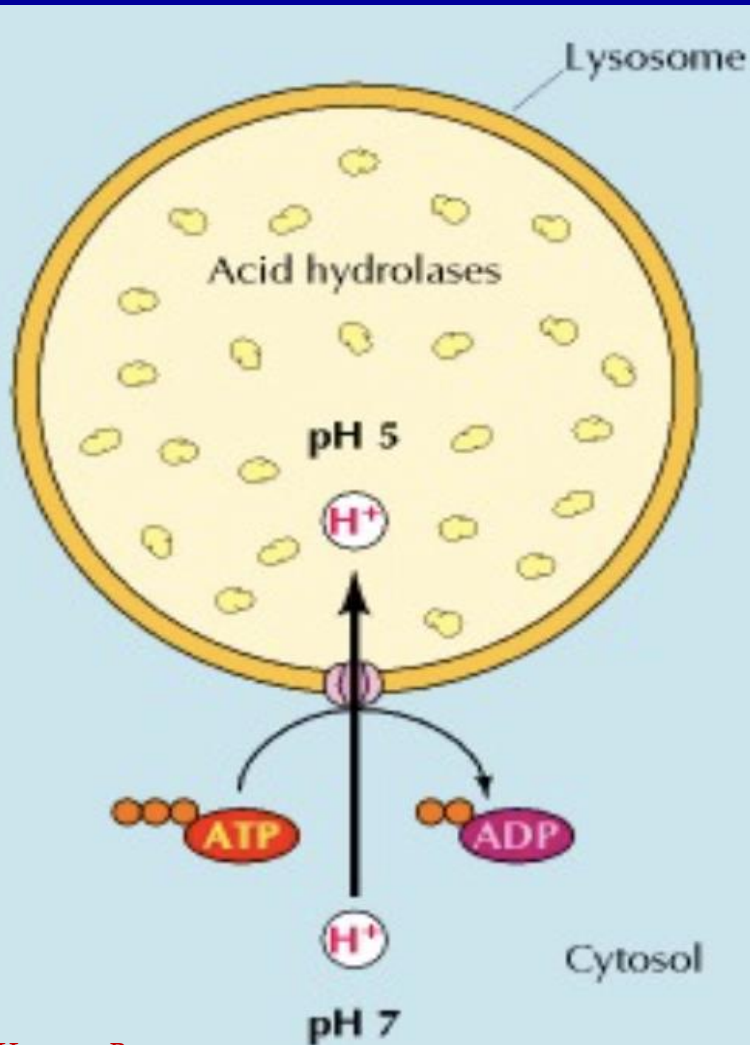
Is it possible to improve healthy lifespan by promoting lysosomal function?

Yes:

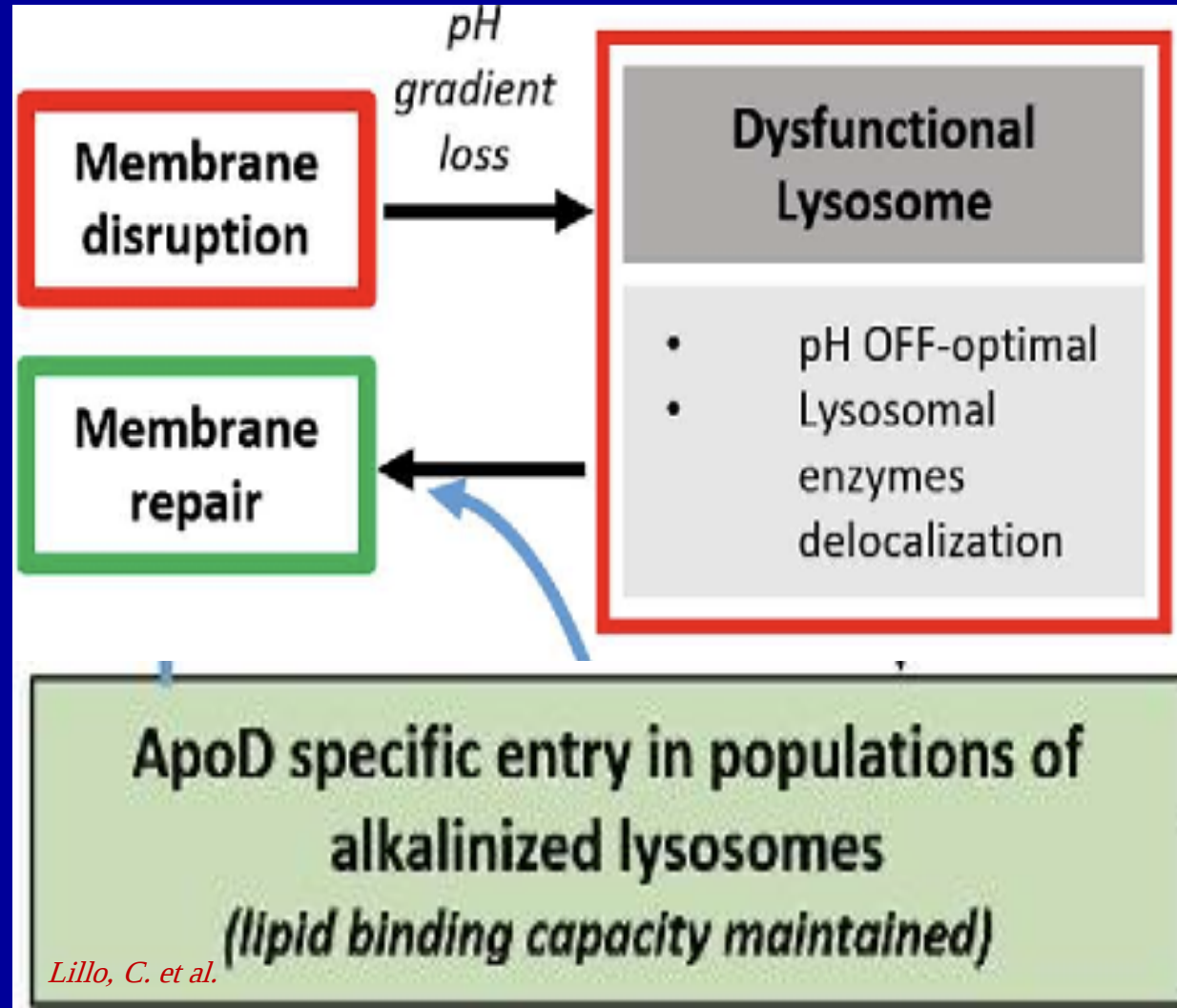
- *By preserving lysosomal acidic milieu*
- *By enhancing autophagy*

Conclusion

Preserving lysosomal acidic milieu



Hanson, P.



Conclusion

The role of lysosomes in human longevity and aging

- *Cellular housekeeping duty*
- *Nutrient sensing and homeostasis*
- *Inter-organelle cross-talks*

Is it possible to improve healthy lifespan by promoting lysosomal function?

Yes:

- *By preserving lysosomal acidic milieu*
- *By enhancing autophagy*

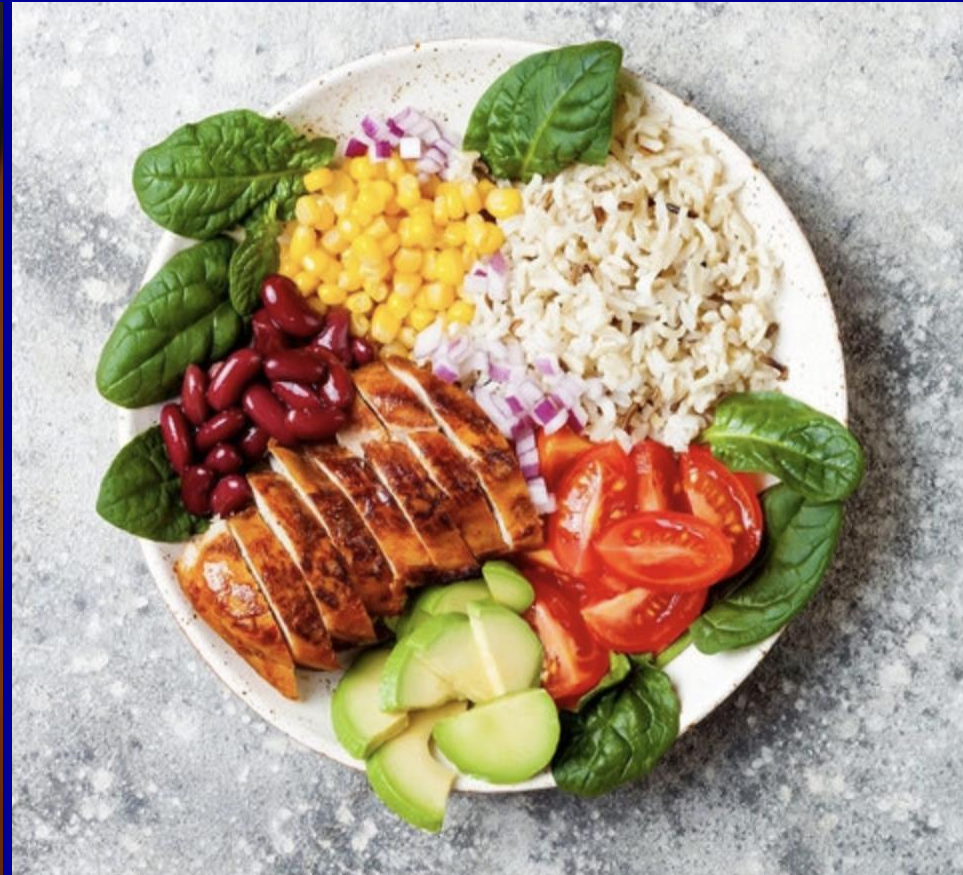
Conclusion

Enhancing Autophagy by Fasting



Conclusion

Enhancing Autophagy by Calorie Restriction (CR)



Bottomline

An organism's survival depends on its ability to maintain a balance between the production of new and the degradation of old materials.

Eat less, live longer!