The role of lysosomes in human longevity and aging

International Congress on Healthy Aging

May 10-12, 2022

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Thomas Jefferson University
Philadelphia

LYSOSOMAL STORAGE DISEASES

LIPIDOSIS

- NIEMANN-PICK DISEASE*
- GAUCHER DISEASE*
- METACHROMATIC LEUKODYSTROPHY*
- KRABBE DISEASE*
- FABRY DISEASE*
- WOLMAN DISEASE*

GLYCO-PROTEINOSIS

- GM1 GANGLIOSIDOSIS*
- GM2 GANGLIOSIDOSIS*
- FUCOSIDOSIS*
- α -MANNOSDOSIS*
- β -MANNOSDOSIS*
- ASPARTYLGLUCOSAMINURIA
- SIALIDOSIS*

MUCOPOLY-SACCHARIDOSIS

- I-HURLER -SCHEIE*
- II-HUNTER
- III-SANFILIPPO A, B*, C, D
- IV-MORQUIO A, B*
- VI-MAROTEAUX-LAMY*
- VII- β -GLUCURONIDASE DEFICIENCY*

MISCELLANEOUS

- MUCOLIPIDOSIS II (I-CELL)*
- MUCOLIPIDOSIS III*
- MUCOLIPIDOSIS IV
- POMPE DISEASE
- SIALURIA*

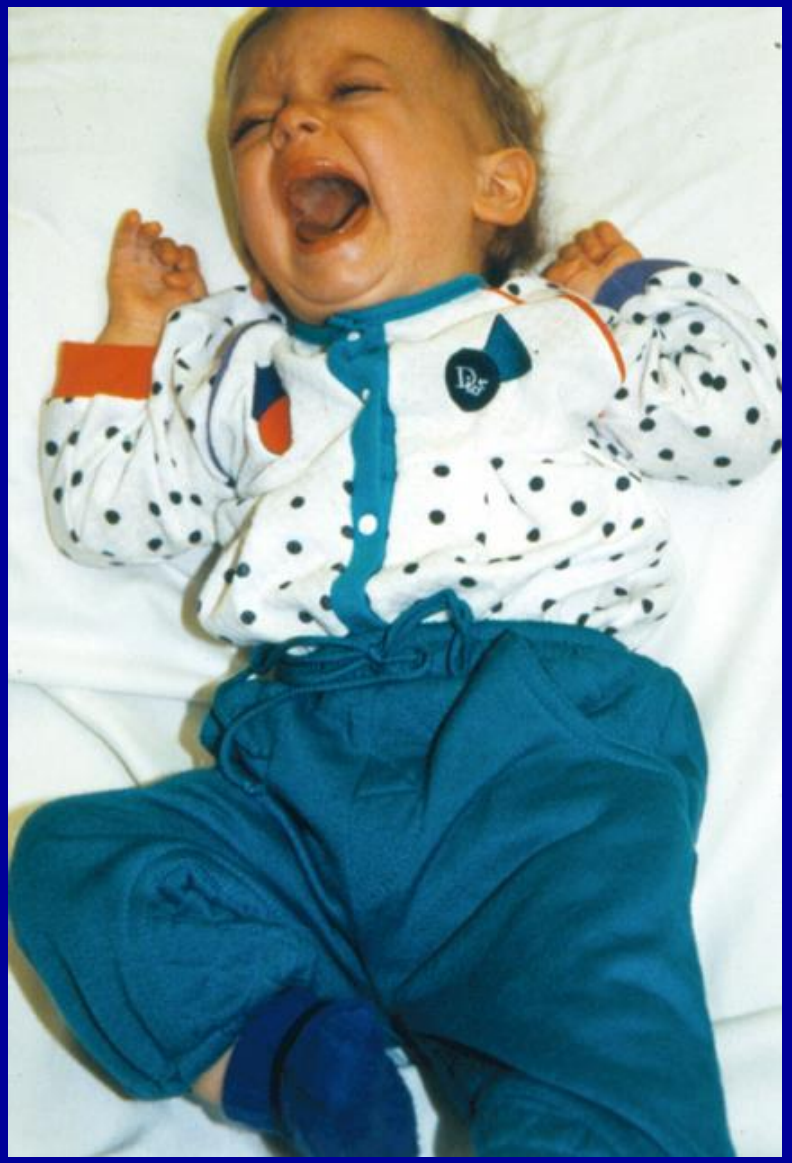
* DIAGNOSABLE IN THIS LABORATORY

What is Krabbe disease?

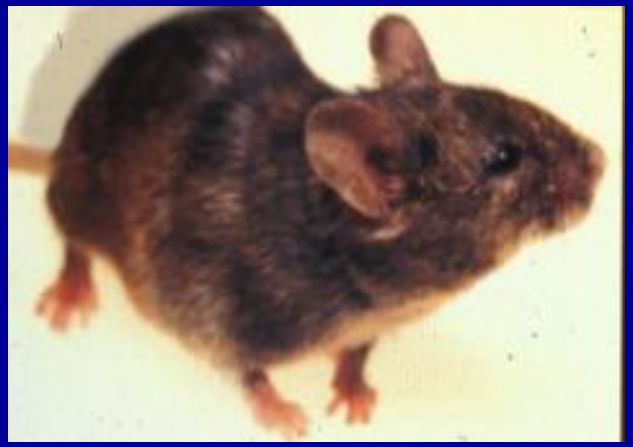
A lysosomal disorder,
With neurodegeneration

Symptoms include:

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

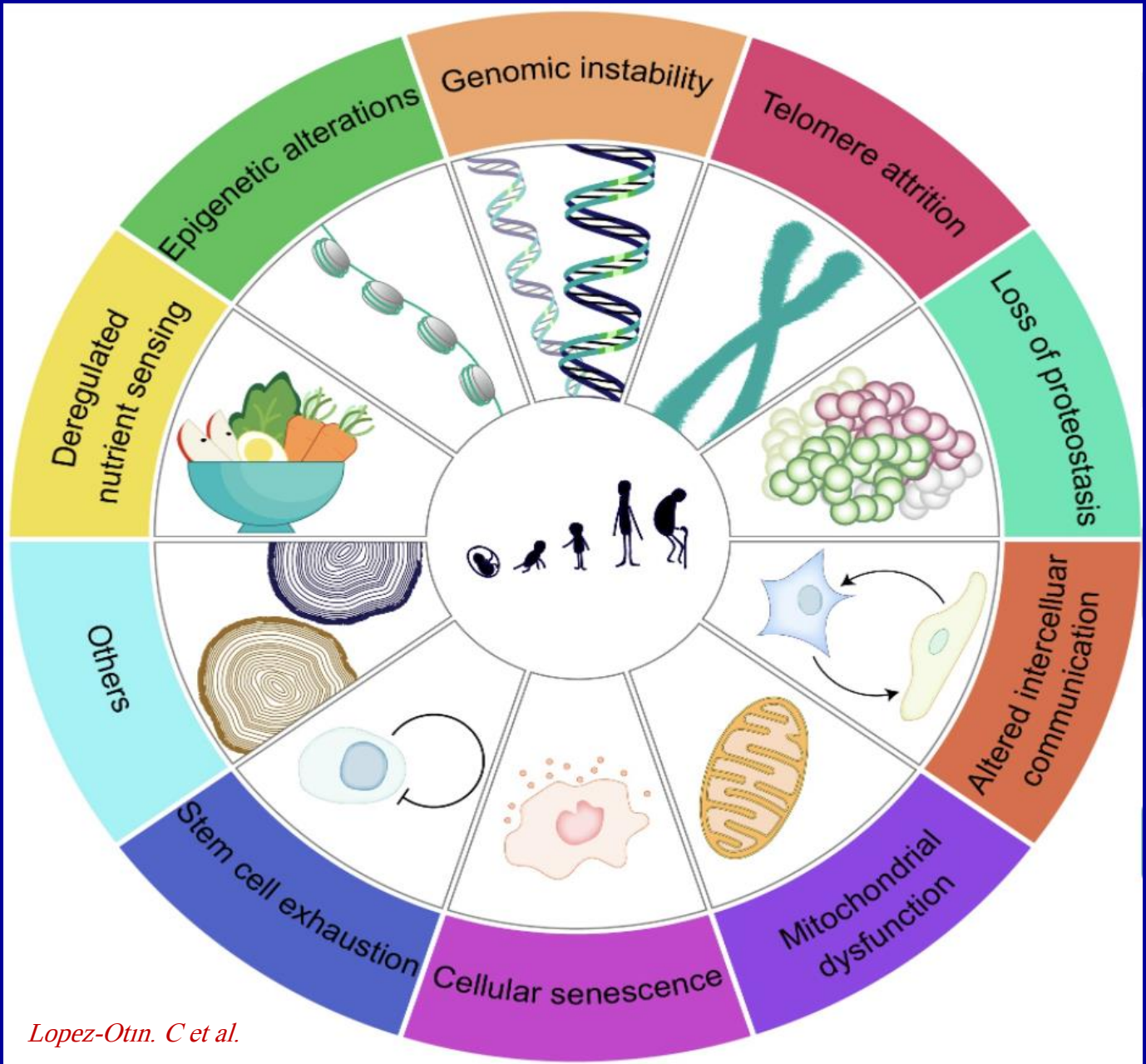


Animal models for Krabbe disease



Wildtype mouse and 200-days-old Twitcher mouse

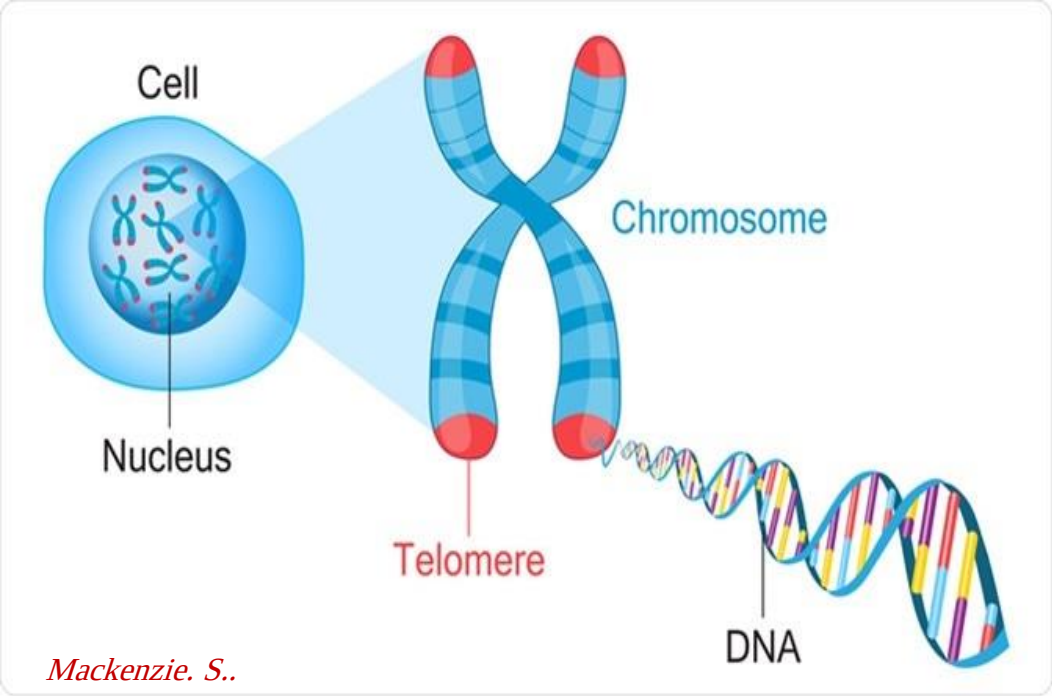
Some theories on human aging & longevity



Lopez-Otın. C et al.

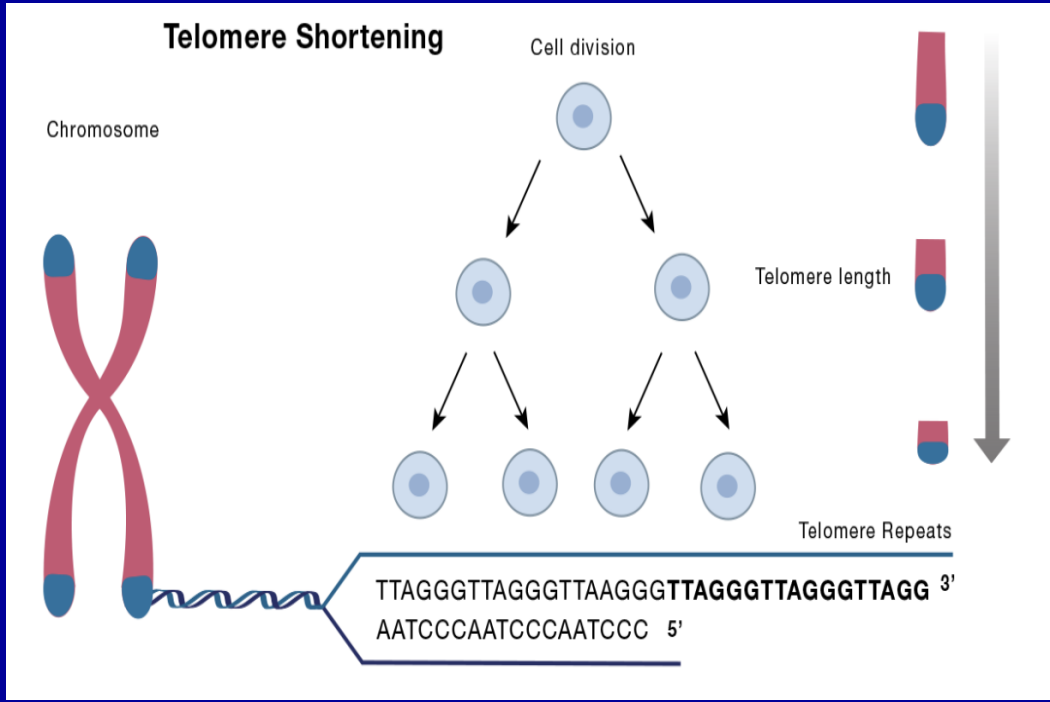
Chromosomal telomere shortening

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



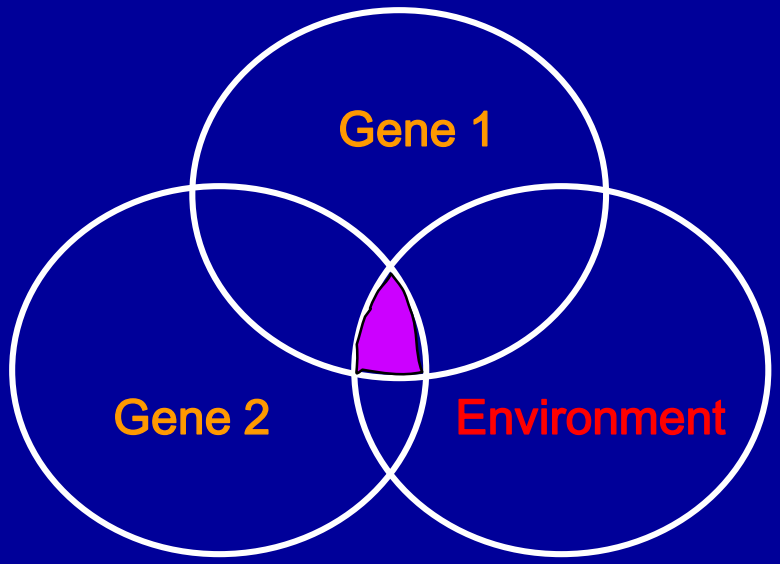
Mackenzie. S..

Telomeres are locater at the both ends of the chromosomes

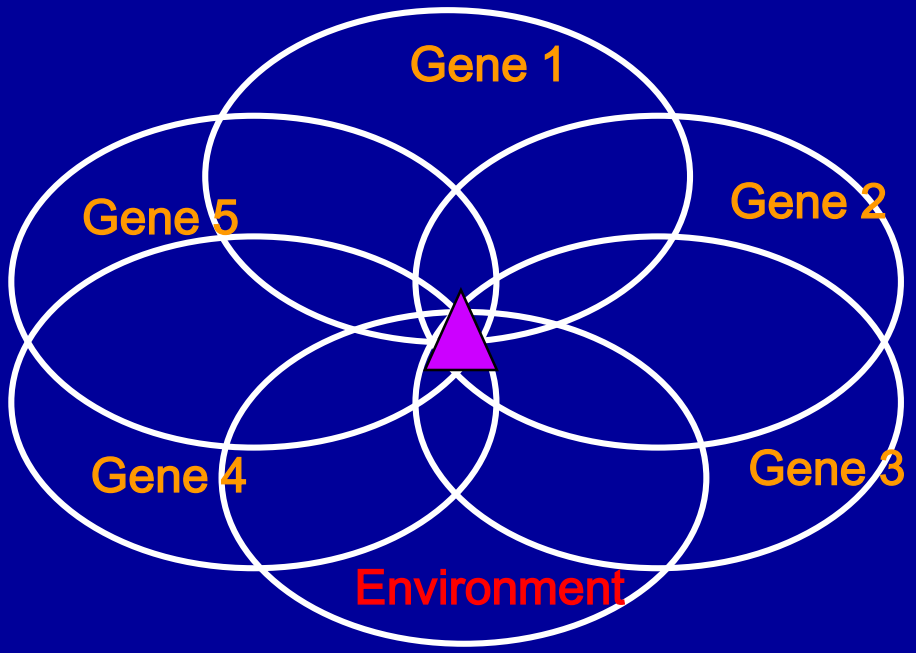


Telomeres get shorter each time at cell division

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

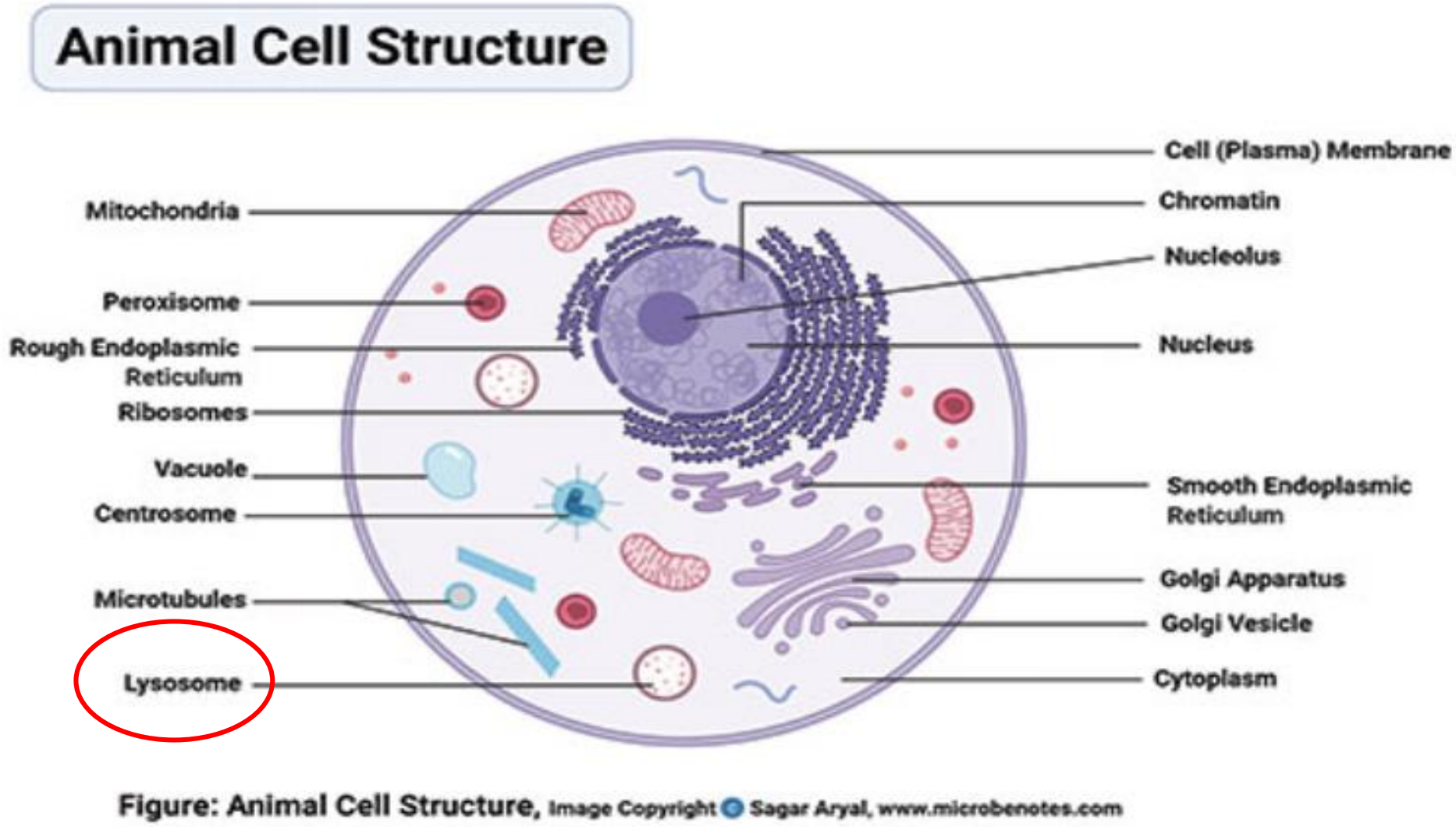
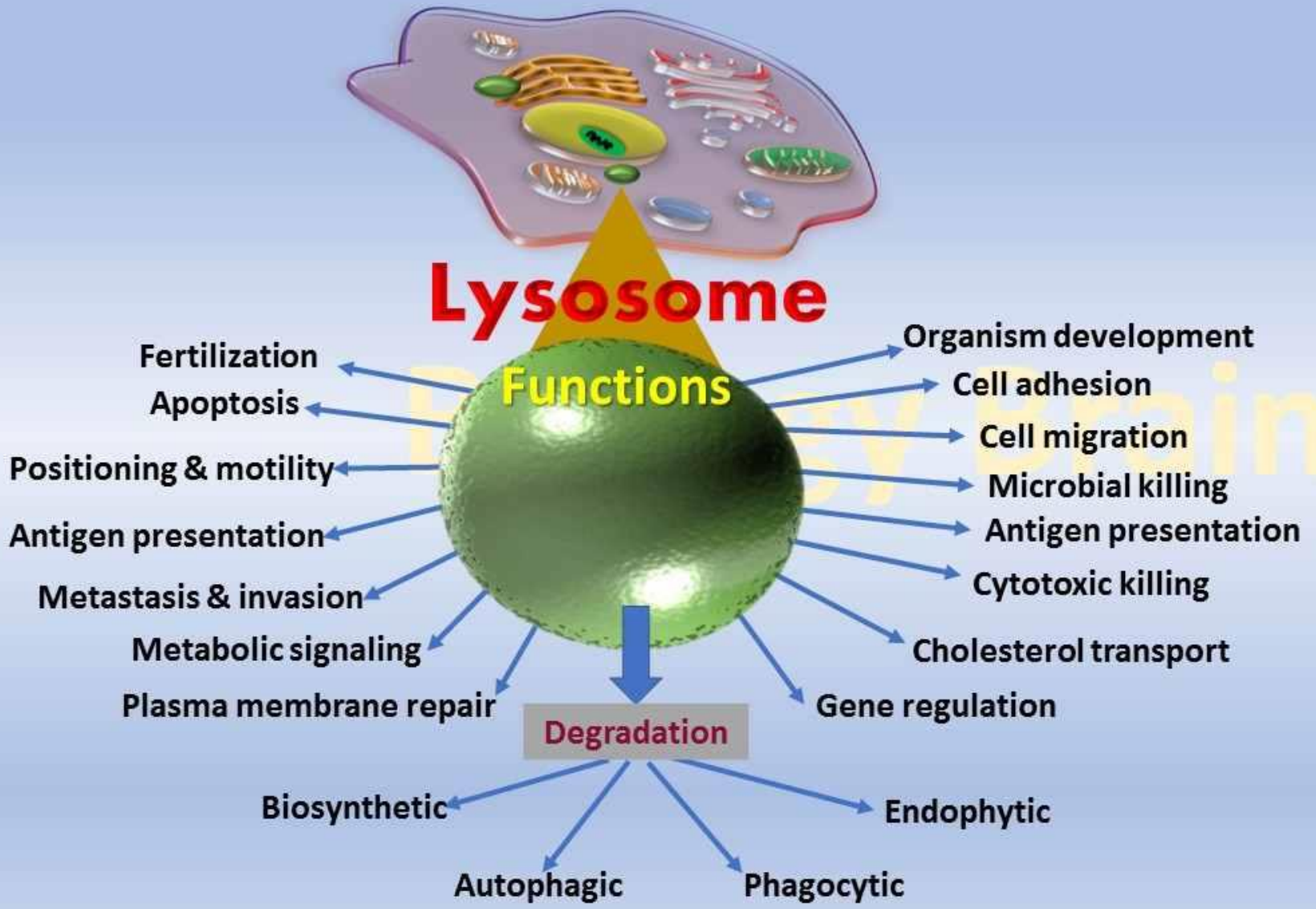


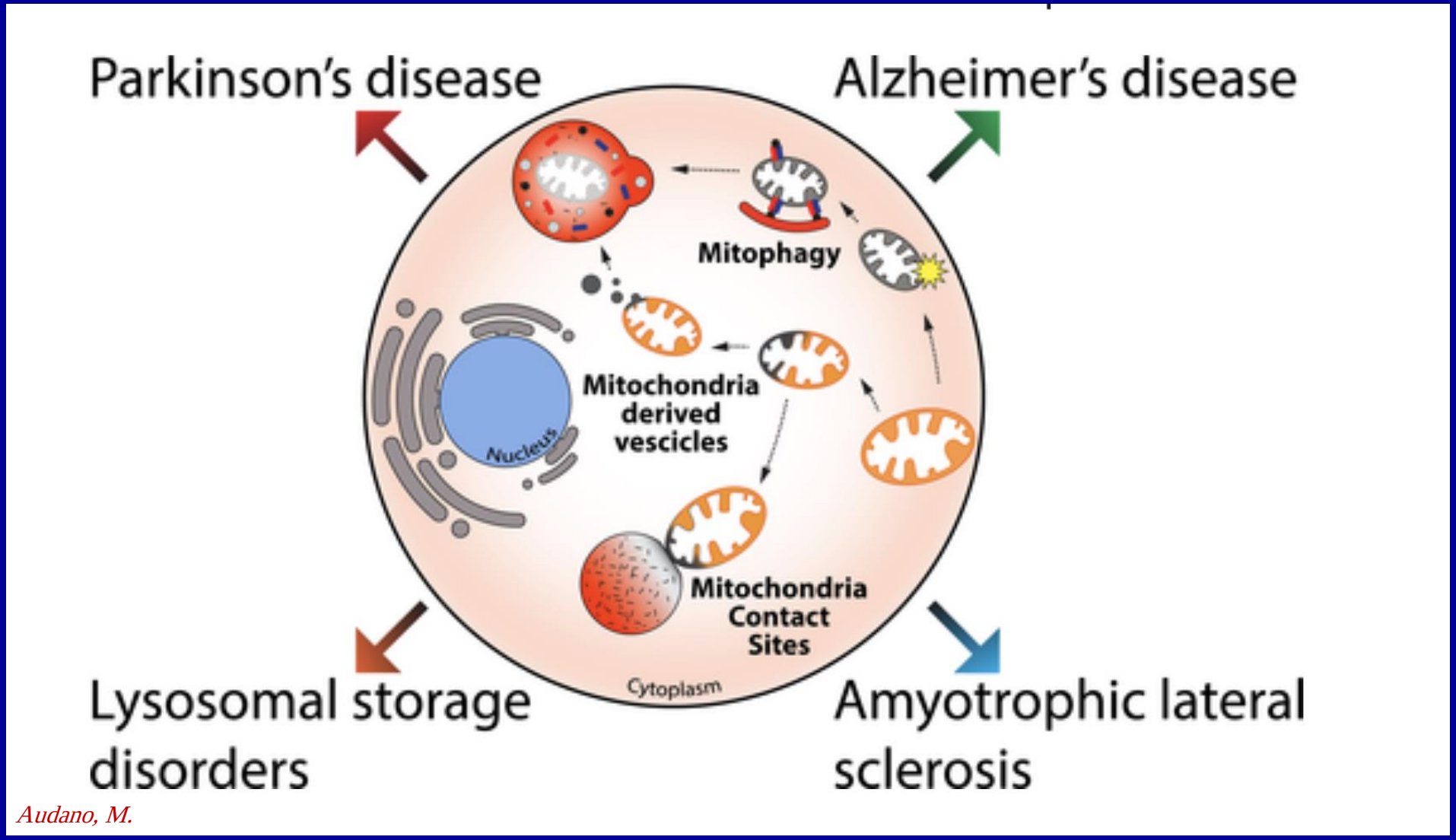
Figure: Animal Cell Structure, Image Copyright © Sagar Aryal, www.microbenotes.com

Supkota, A.

Lysosome as a multi-functional organelle

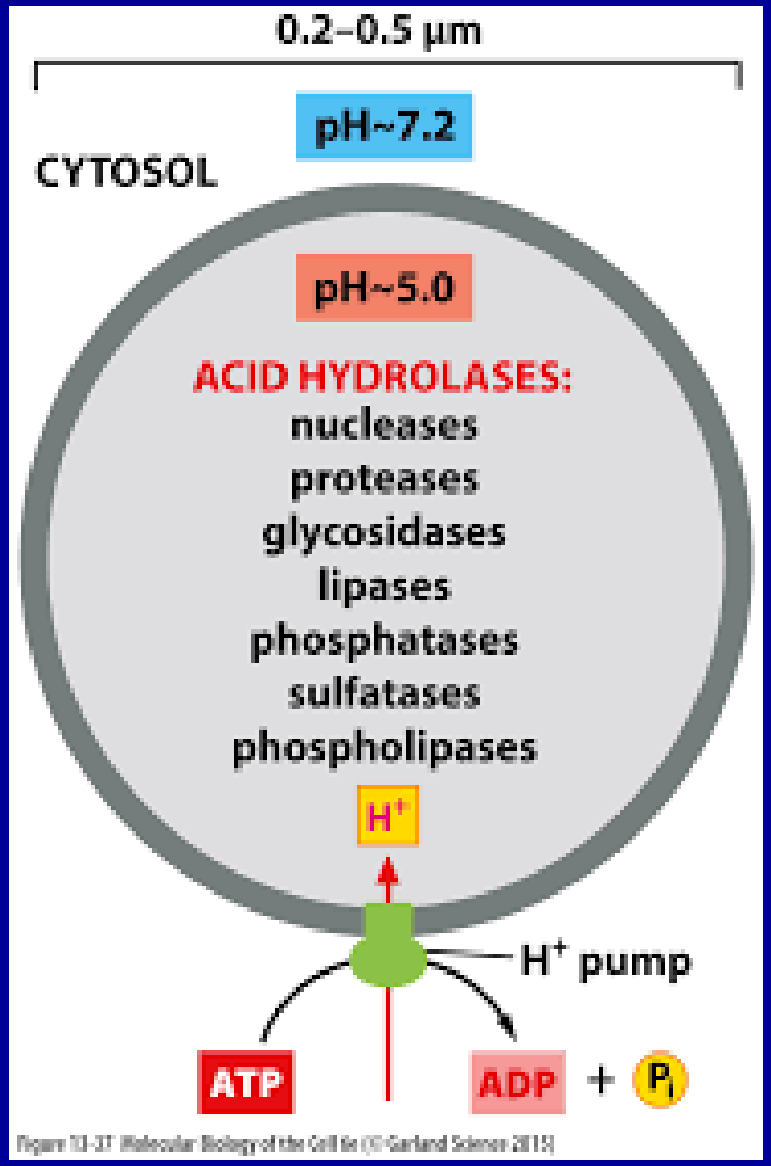


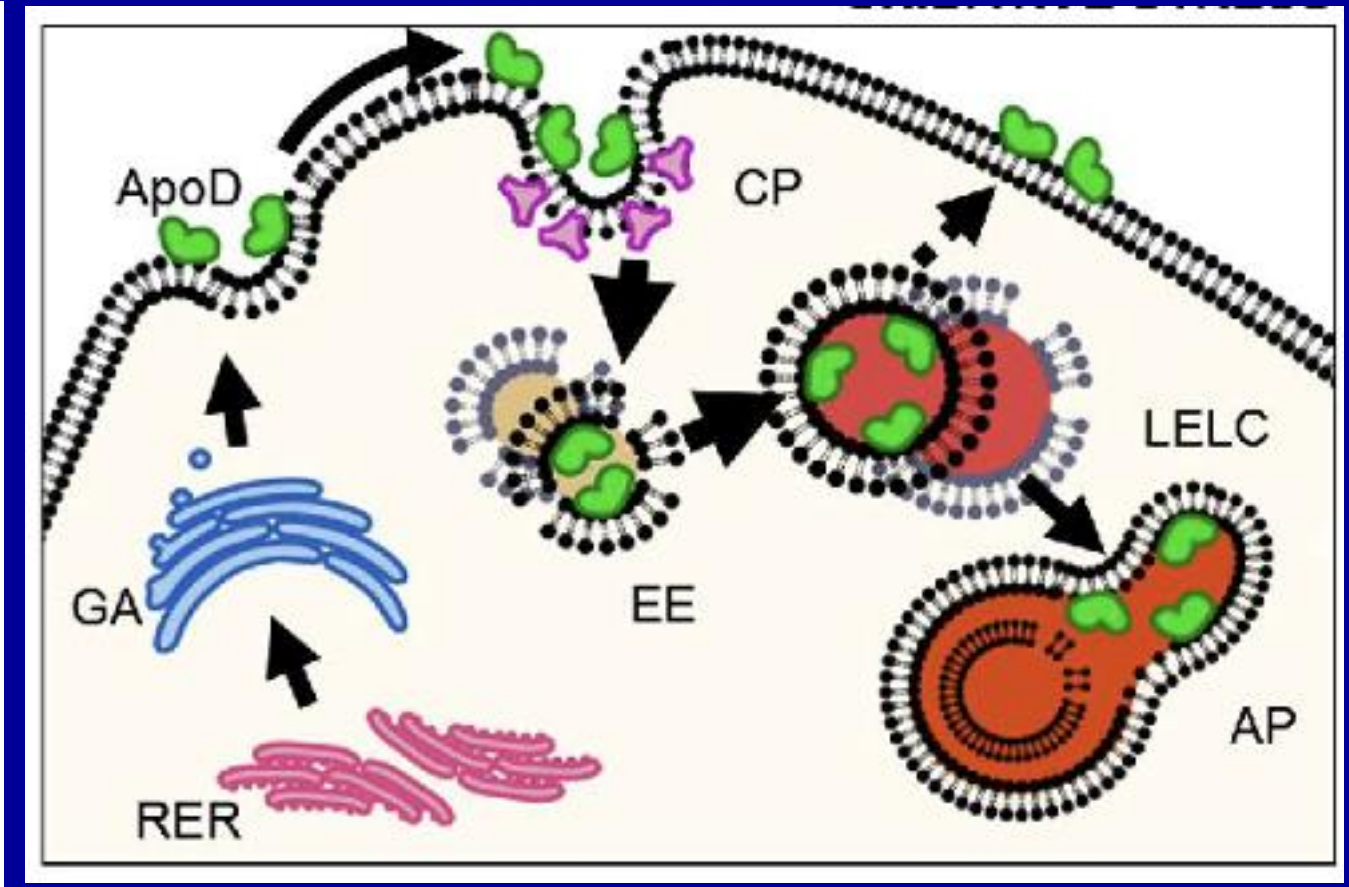
Lysosomal Role in Aging Diseases



Audano, M.

Lysosomal acidic milieu





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

Axnx, M.

Lillo, C et al.

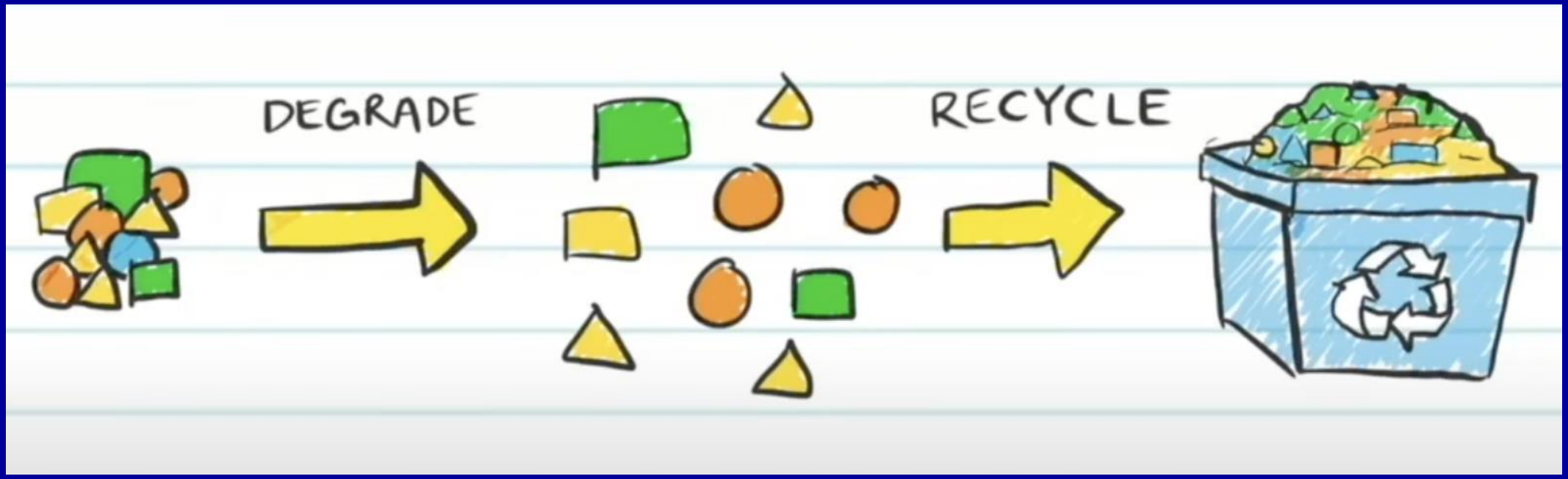
Lysosomal role in cell biology

I. **Autophagy and longevity**

II. **Lysosomes and nutrient homeostasis**

III. **Lysosomes and mitochondrial function**

Autophagy



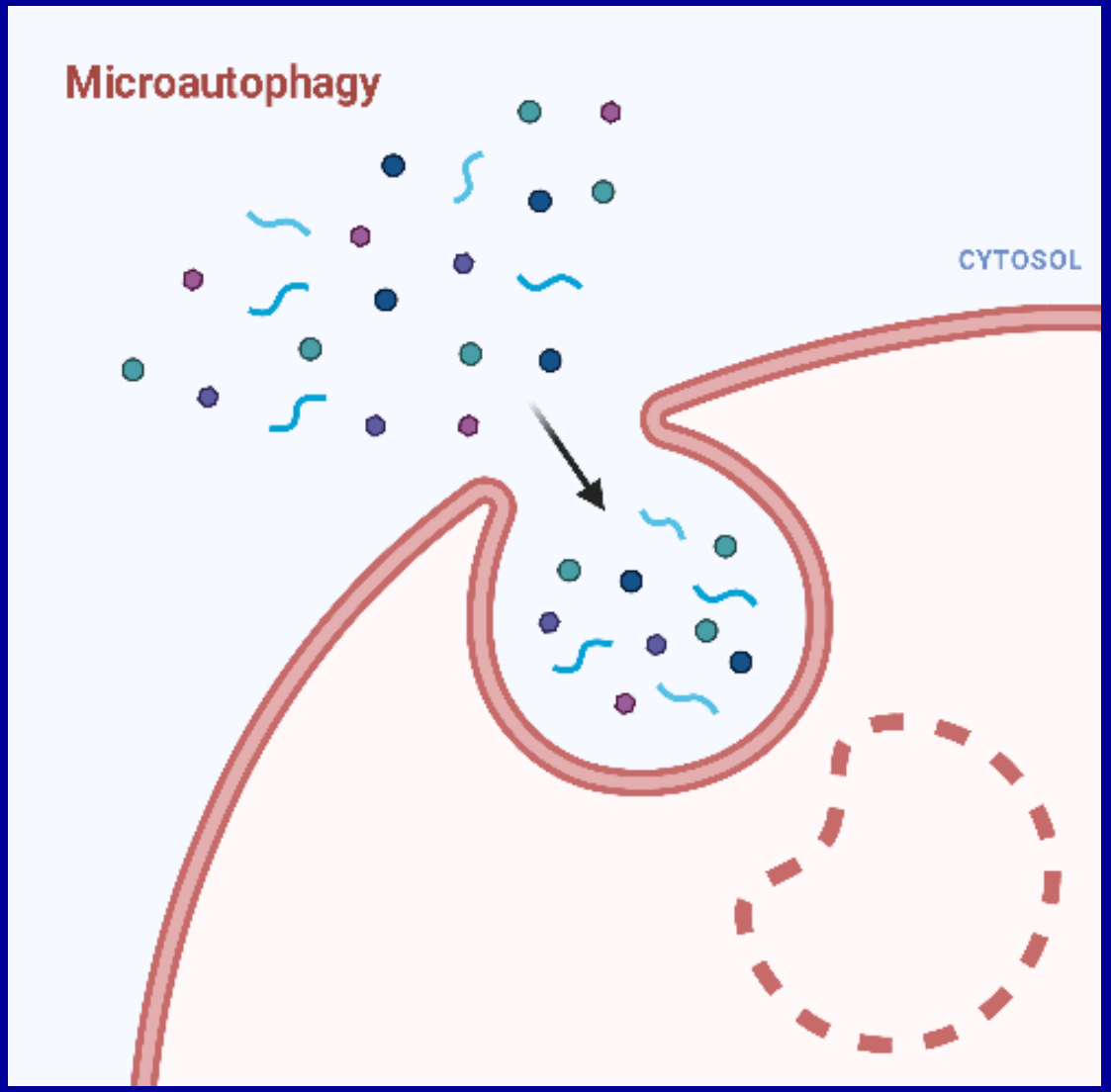
Autophagy

-Microautophagy,

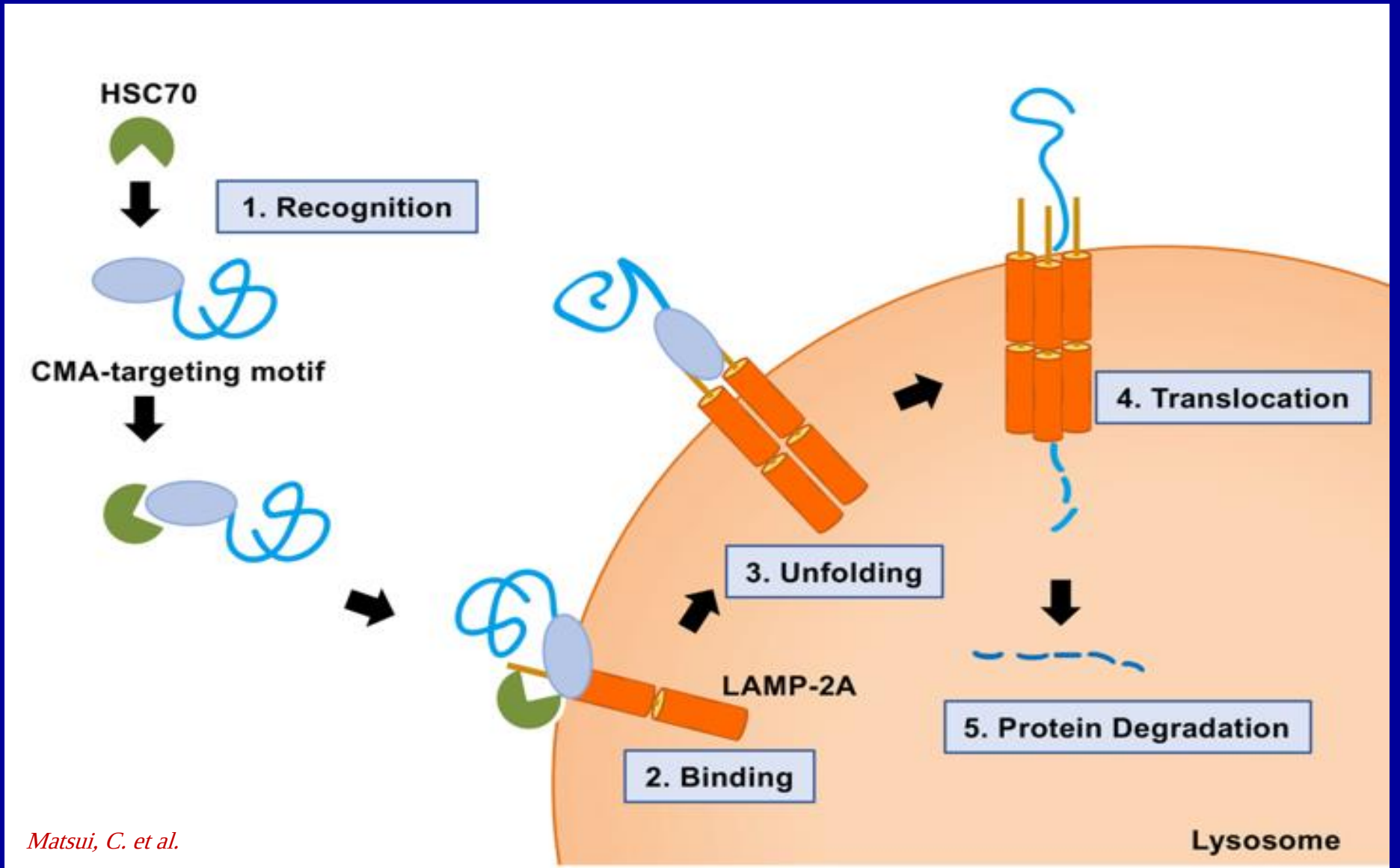
-Chaperone-mediated autophagy (CMA)

-Macroautophagy.

Microautophagy

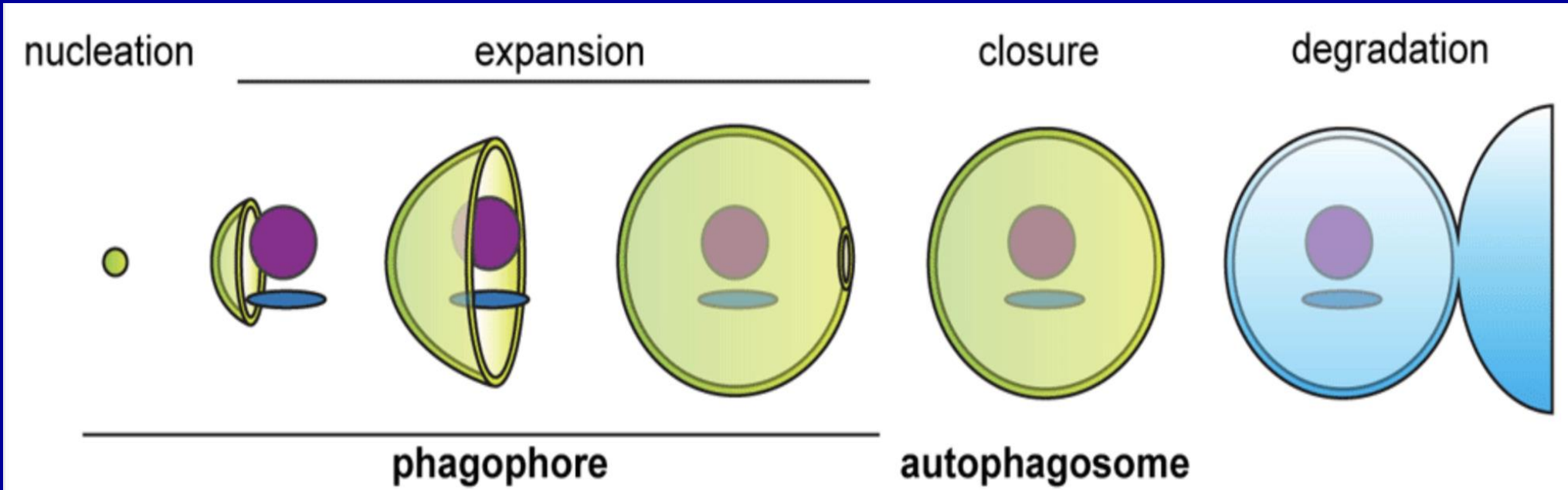


Chaperone-mediated autophagy (CMA)



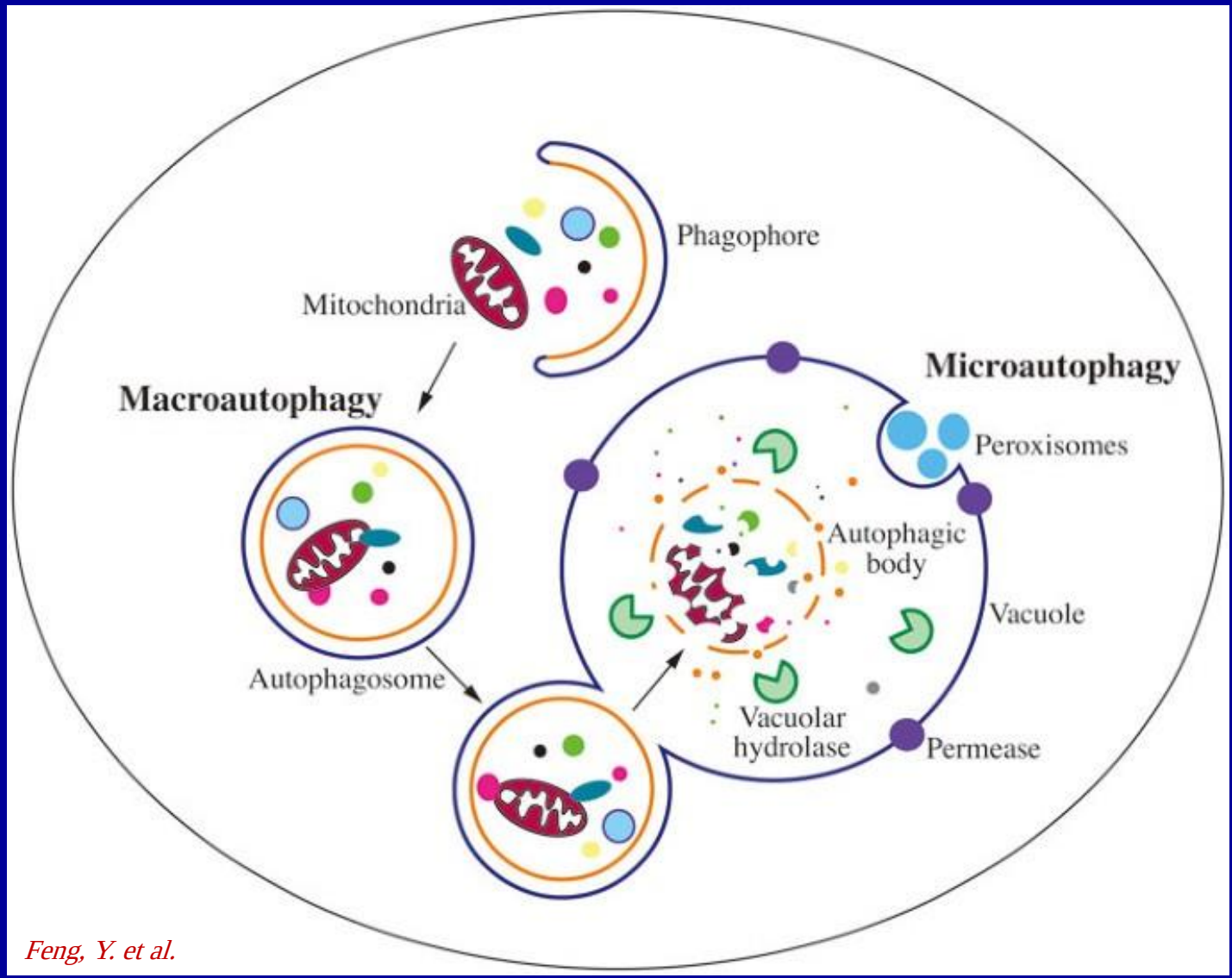
Matsui, C. et al.

Macroautophagy: autophagosome formation



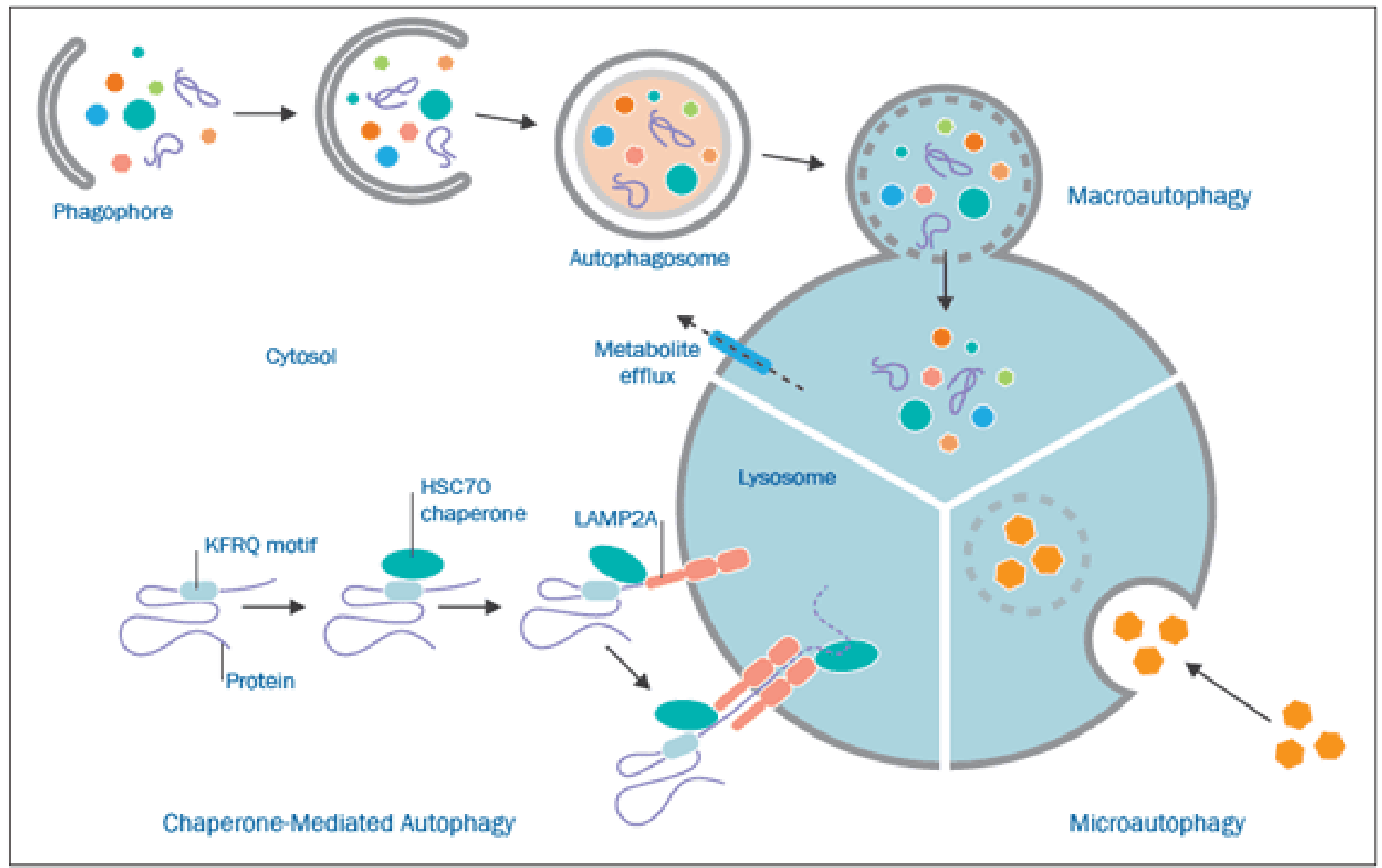
Graef, M.

Macroautophagy & Microautophgy

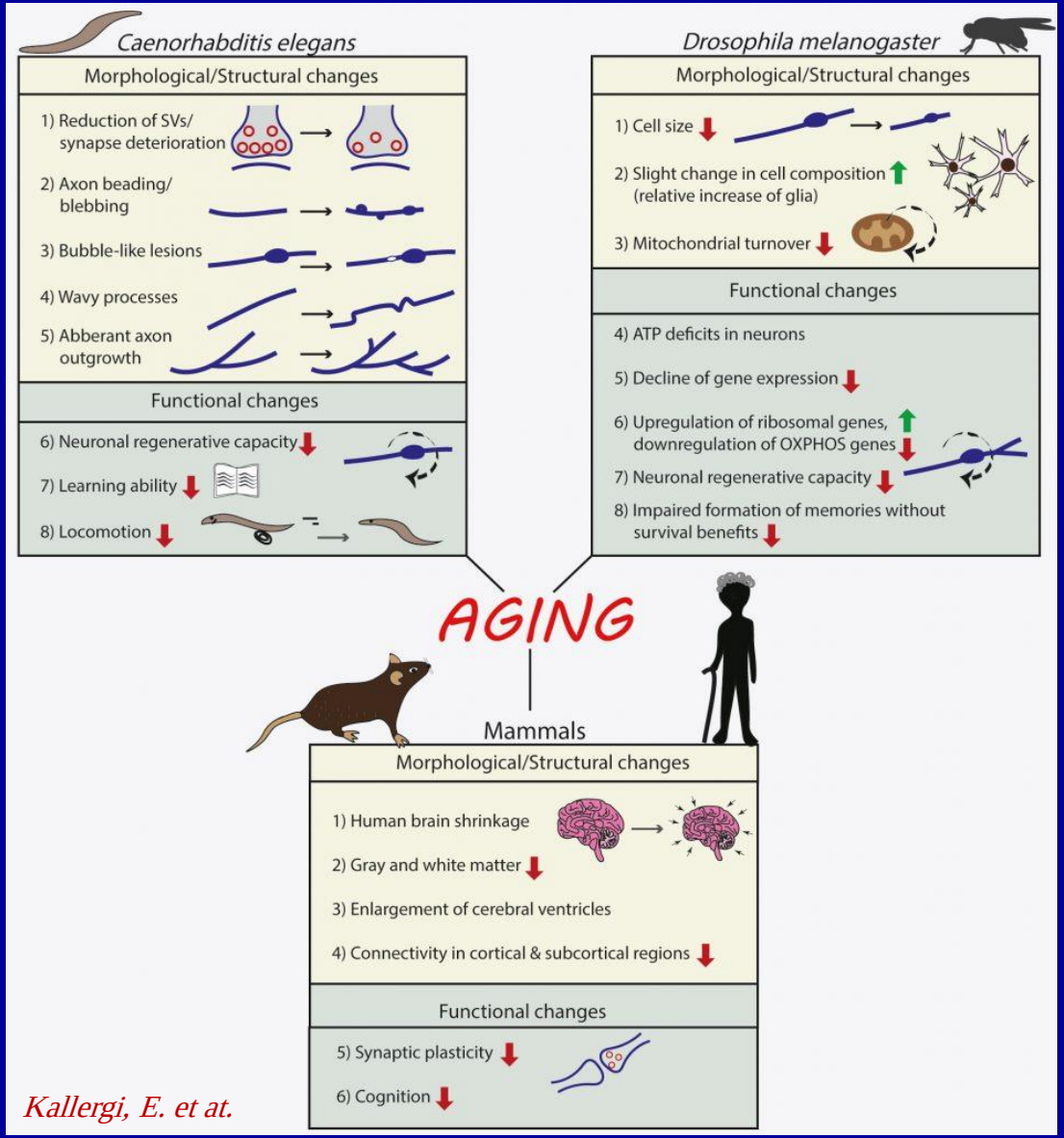


Feng, Y. et al.

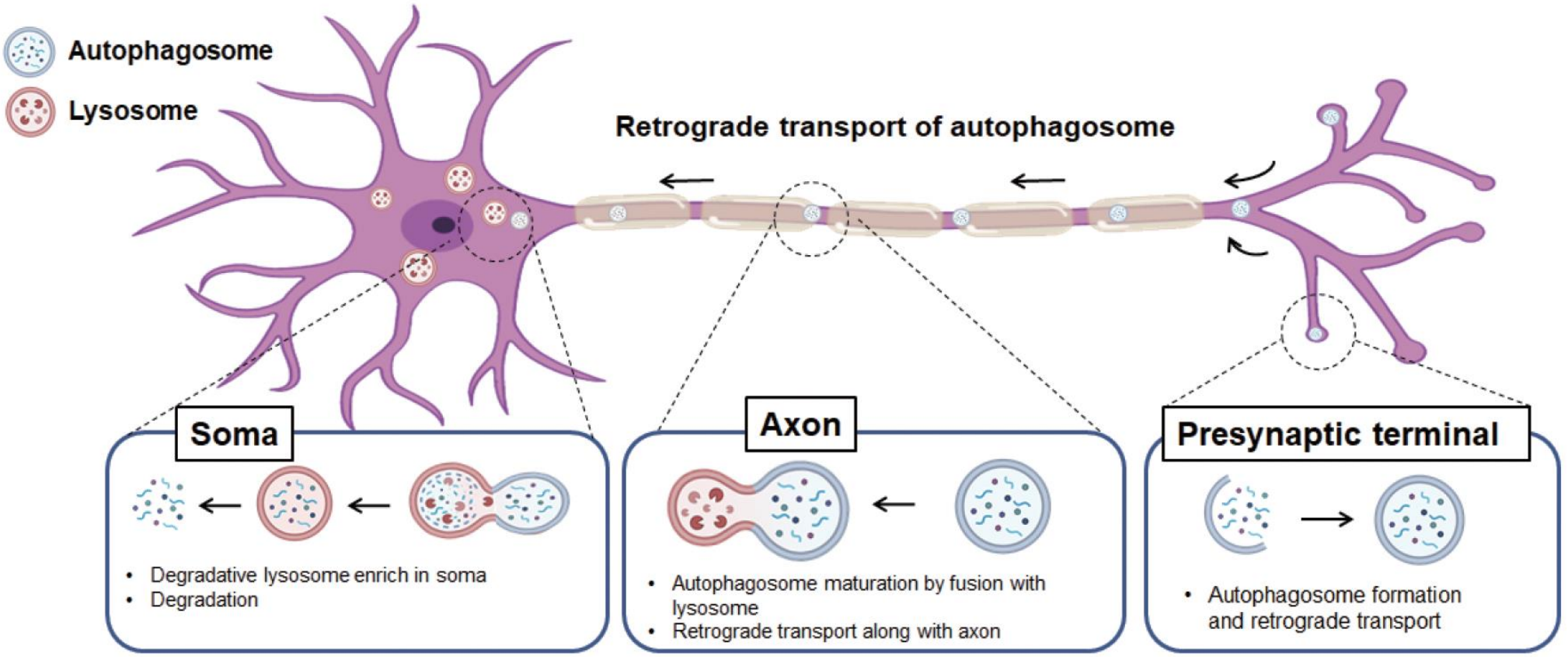
All three types of autophagy



Macroautophagy machinery in animal kingdom



Autophagy in nervous systems

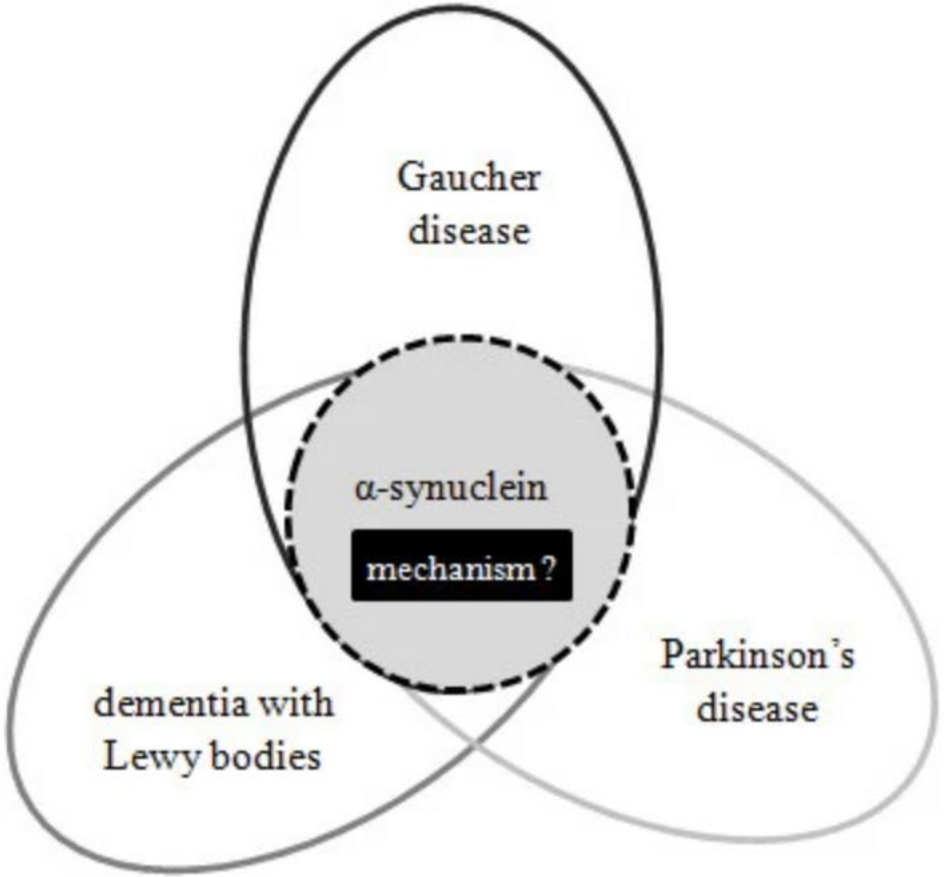


Valencia, M. et at.

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	Galactosylcerebroside 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-Fucosidosis	Fragments of glycoproteins and glycolipids	Central nervous system
Mannosidosis	α-Mannosidase	Fragments of glycoproteins	Central nervous system, skeleton, liver, spleen
Sialidosis (mucolipidosis I)	Oligosaccharide neuramindase	Fragments of glycoproteins	Central nervous system, skeleton, liver, spleen
Disorders of Enzyme Localization			
Mucolipidosis II (I-cell disease)	*N*-Acetylglucosaminyl-phosphotransferase	Mucopolysaccharidoses, lipids, glycoproteins	Central nervous system, connective tissue, skeleton, heart
Mucolipidosis III (Pseudo-Hurler polydystrophy	*N*-Acetylglucosaminyl-phosphotransferase	Mucopolysaccharidoses, lipids, glycoproteins	Joint and connective tissue problems predominantly

Gaucher disease, dementia & Parkinson's Disease



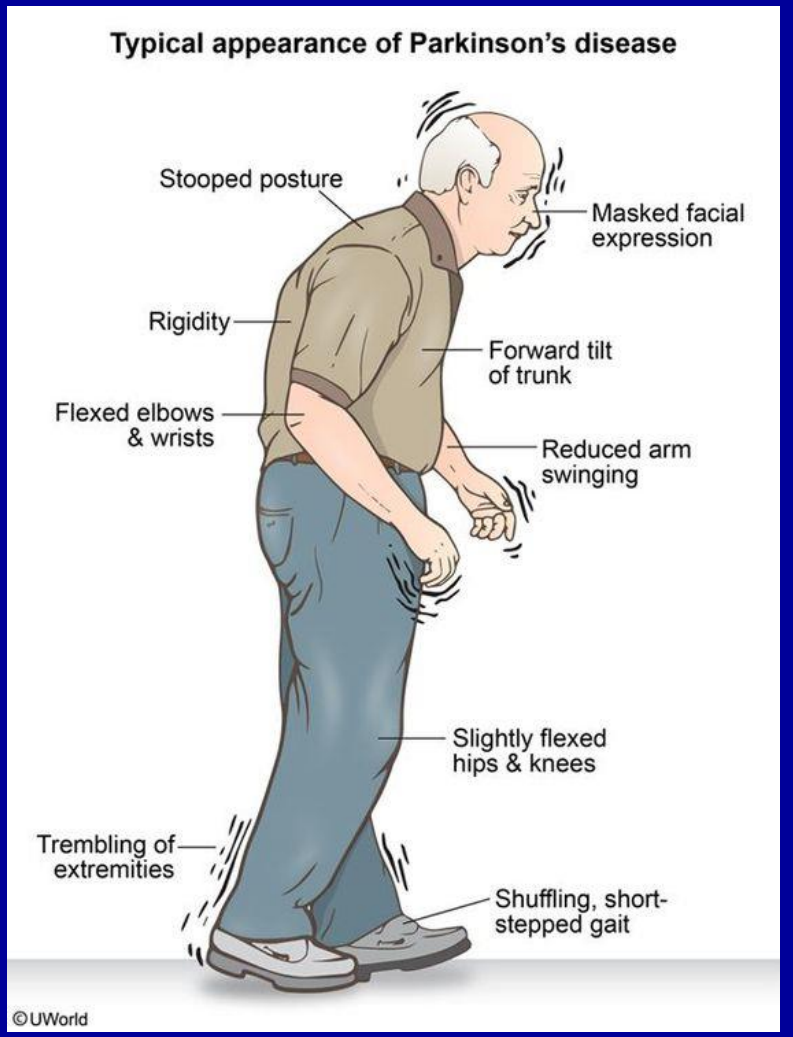
Synucleinopathies demonstrating a relationship with Gaucher disease.

Campbell, TN. et at.

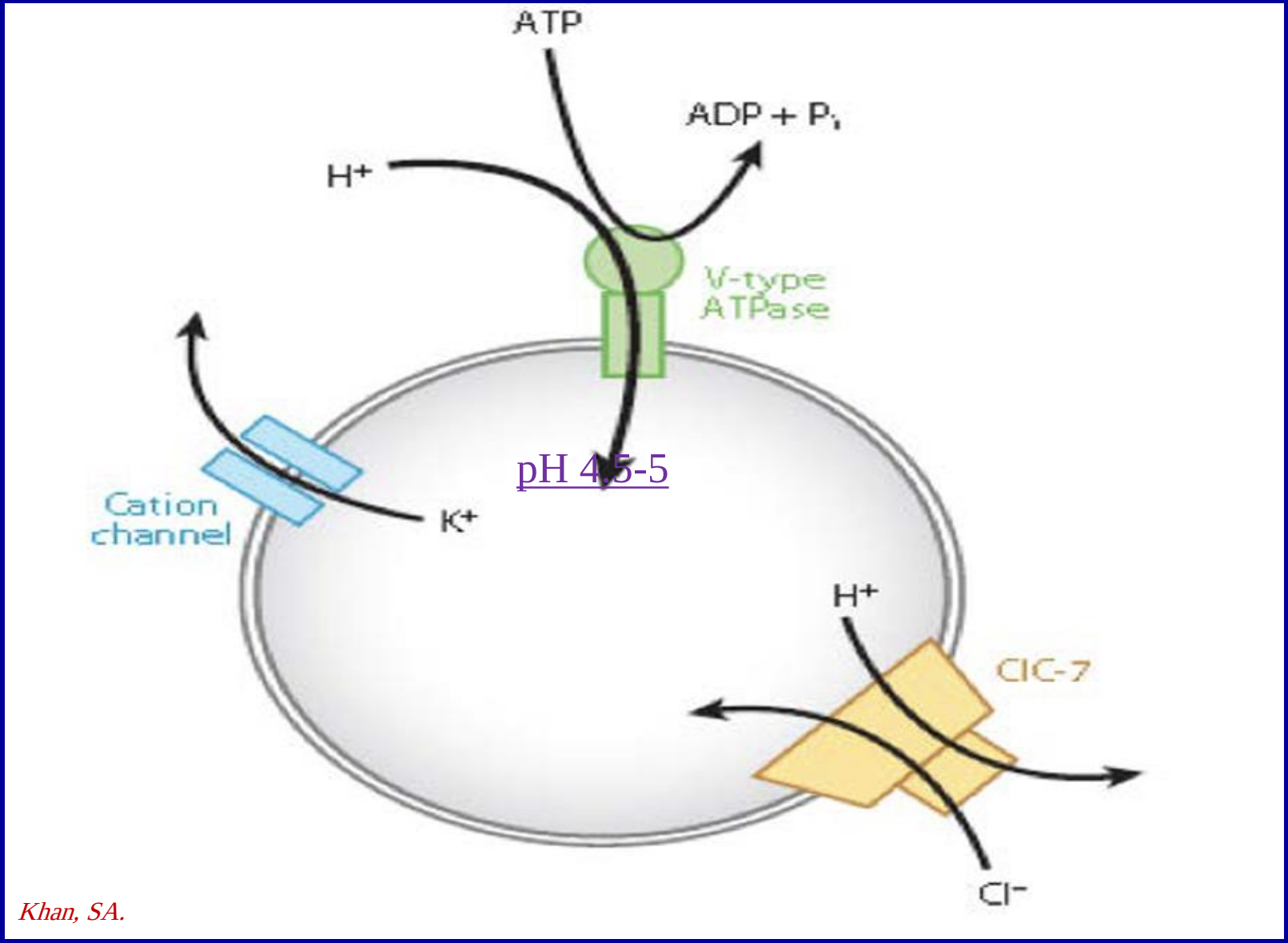
Glucocerebrosidase deficiency & Parkinson

Gaucher's disease

Parkinson's disease



ATPase pump & PH regulation



Khan, SA.

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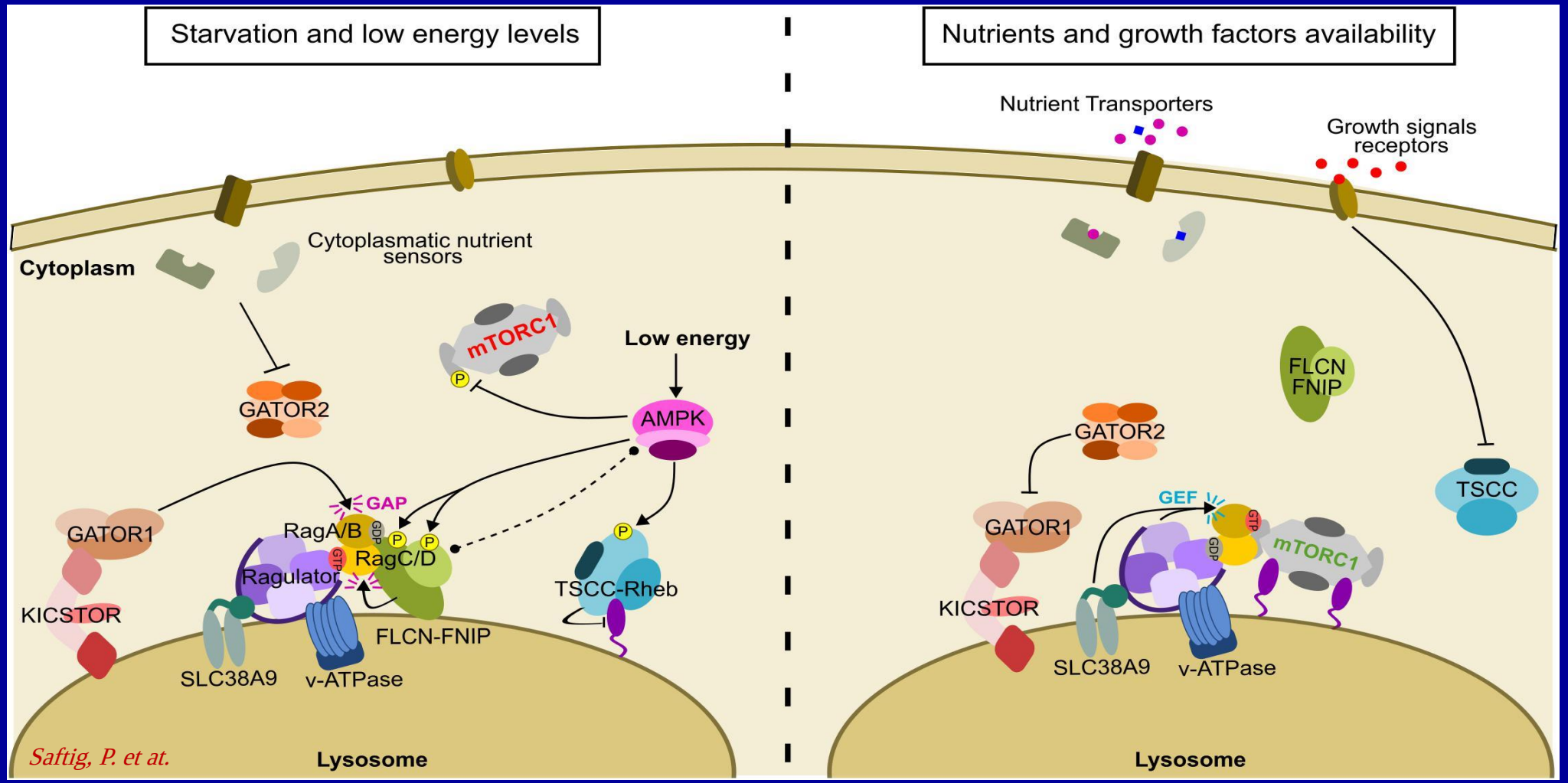
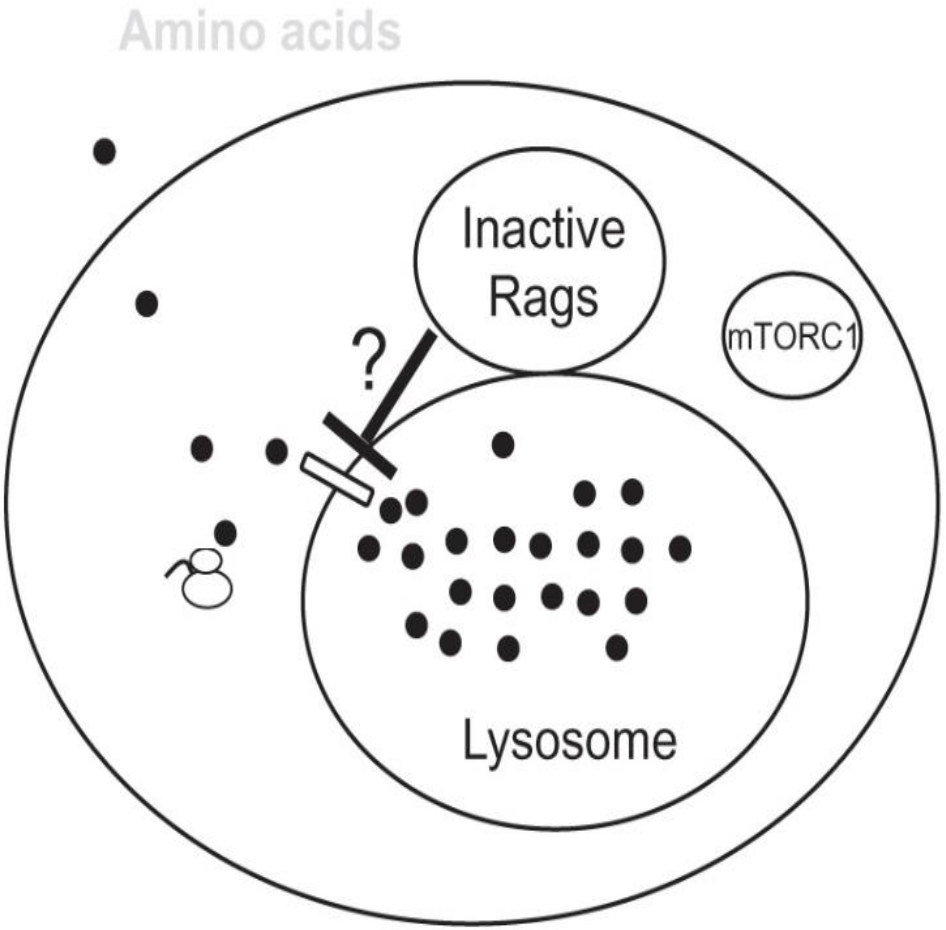
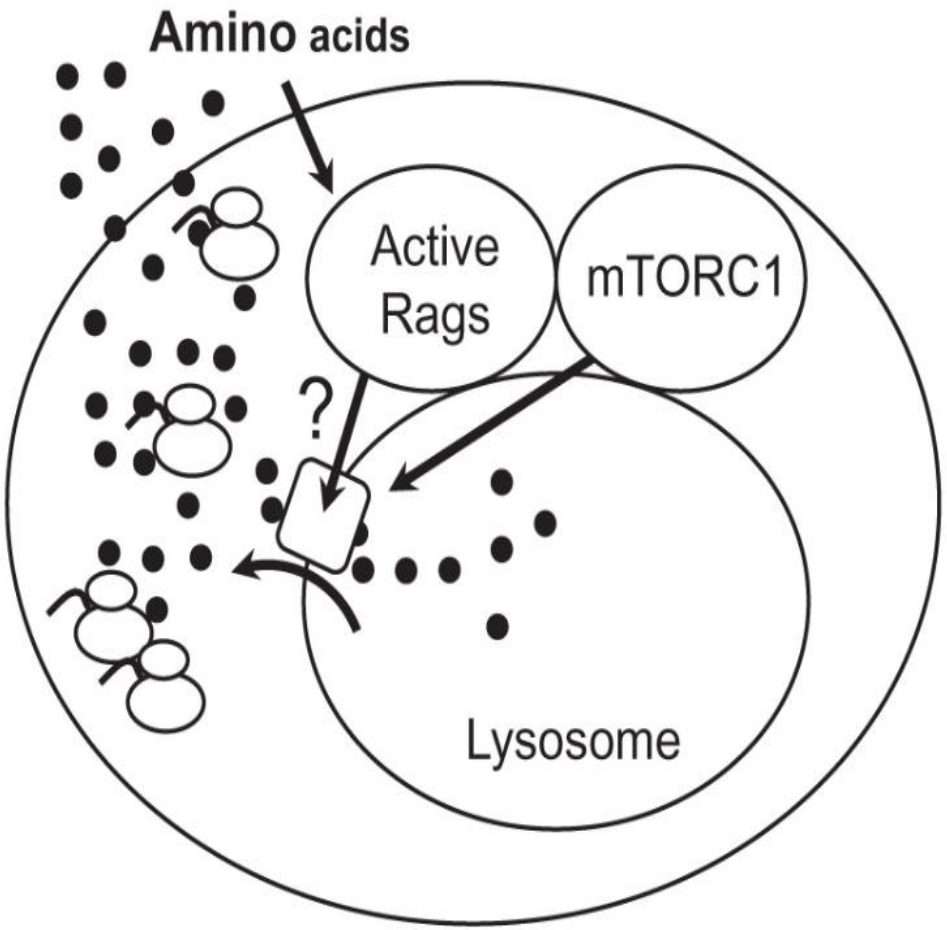
Conclusion

Nutrient Sensing & Homeostasis



Amino acids storage in lysosomes





Inoki, K. et at.

Amino acid limited conditions

Amino acid sufficient conditions

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Lysosomes and mitochondrial interactions

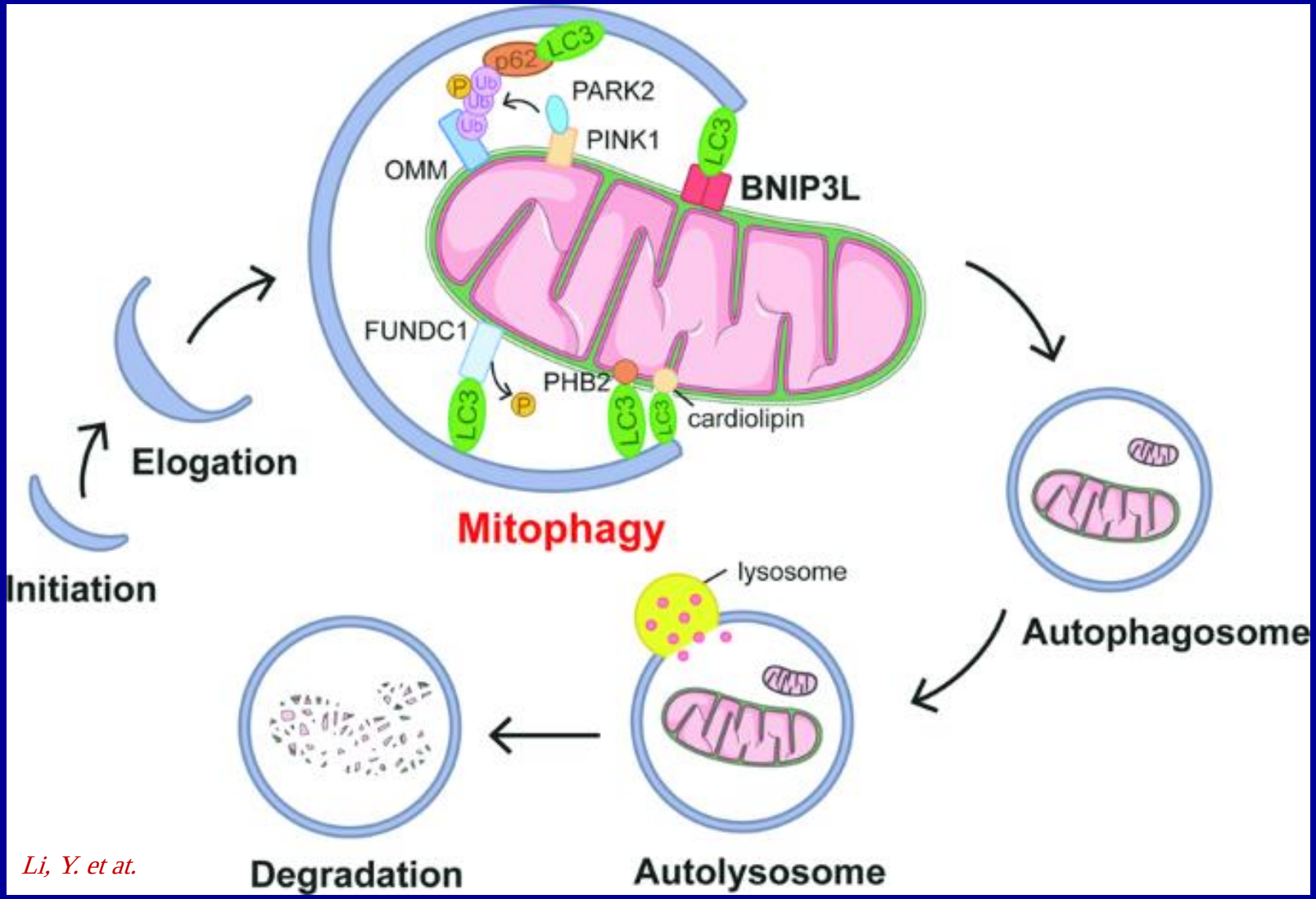
I. Degradative process

-Mitophagy

-Mitochondrial delivered vesicles (MDV)

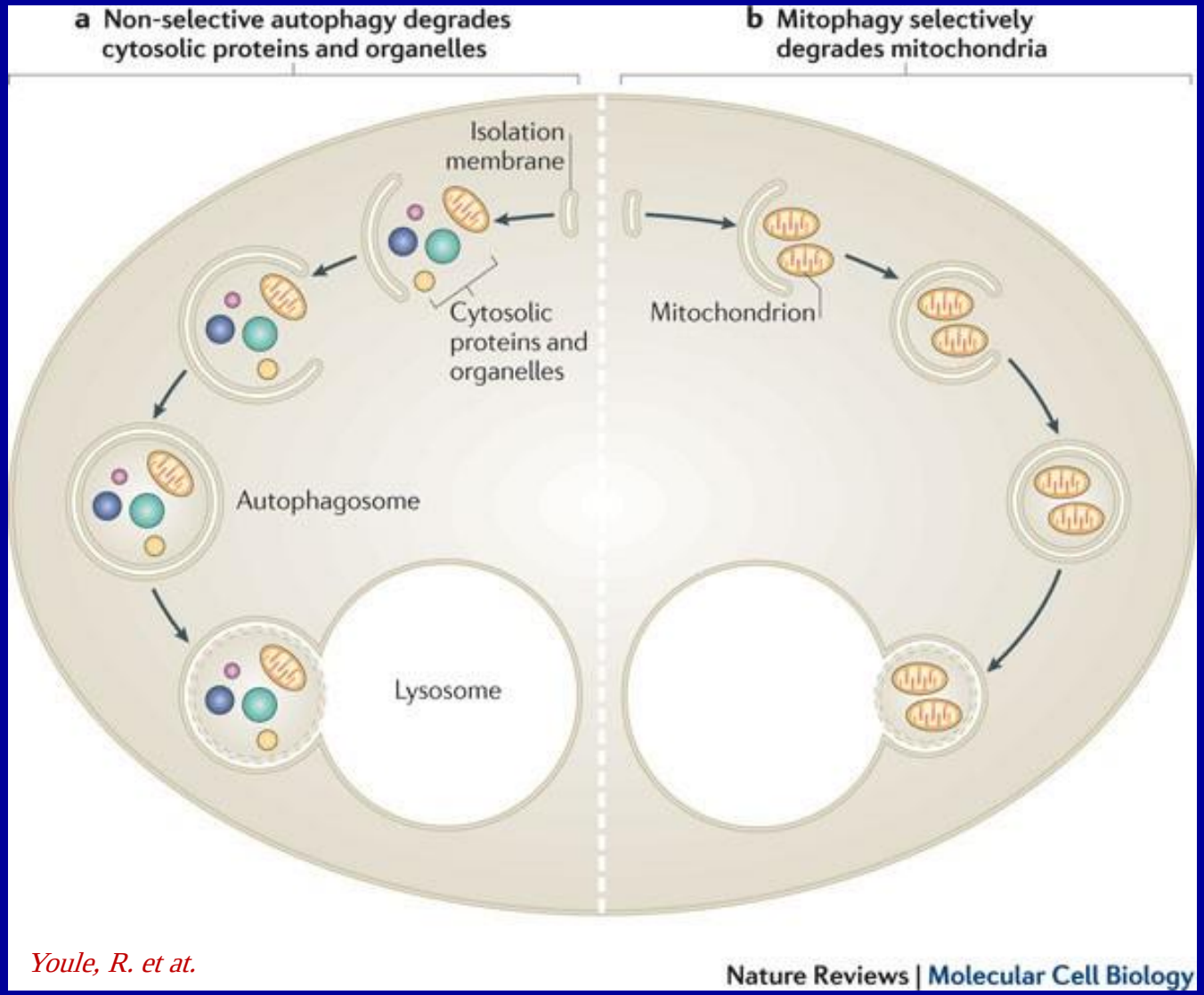
II. Non-degradative process

Mitophagy

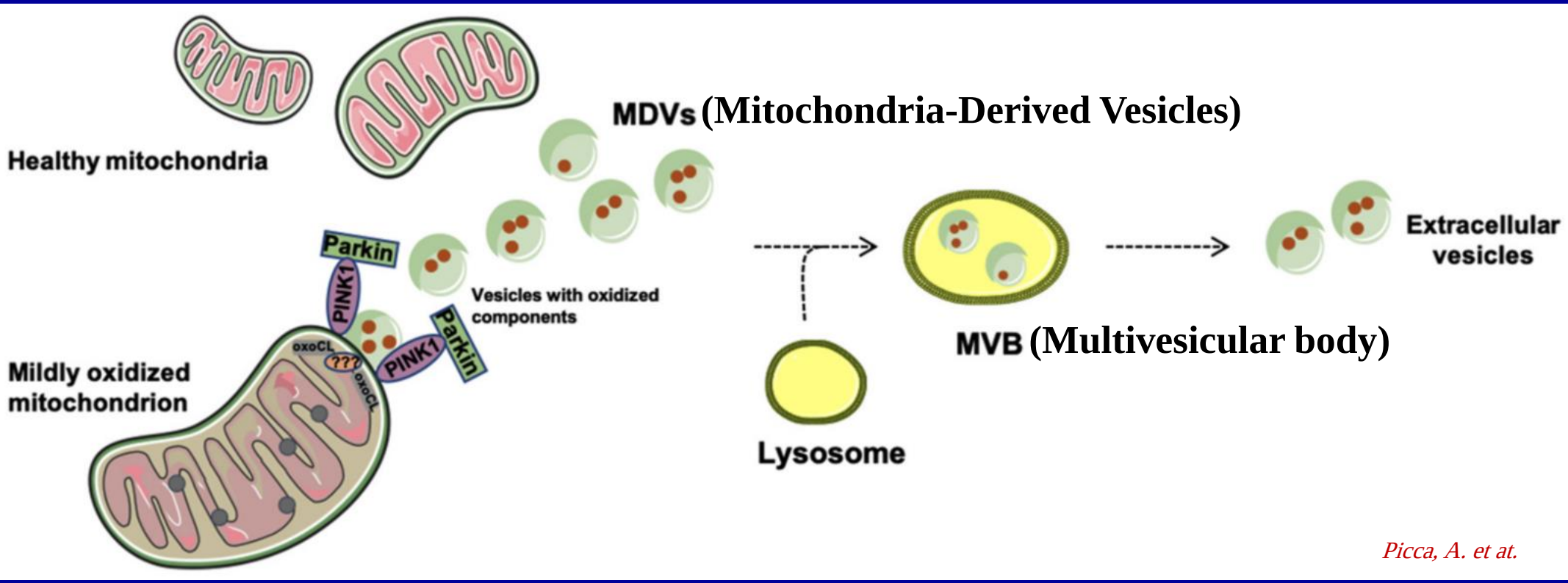


Li, Y. et at.

Selective & Non-selective Mitophagy

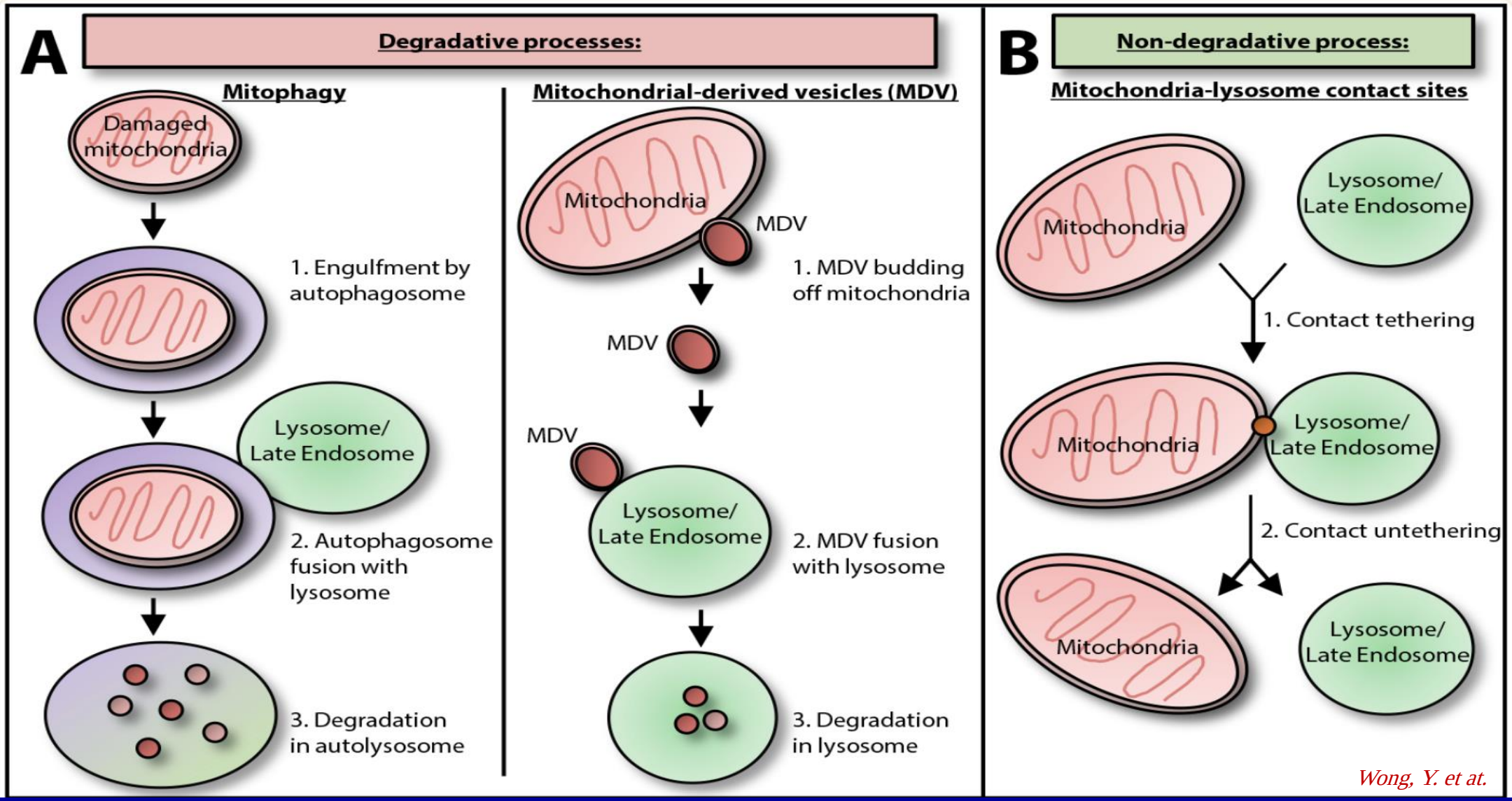


Mitochondria-Derived Vesicles (MDVs)



Picca, A. et at.

Lysosomal & Mitochondrial Interactions



Wong, Y. et at.

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

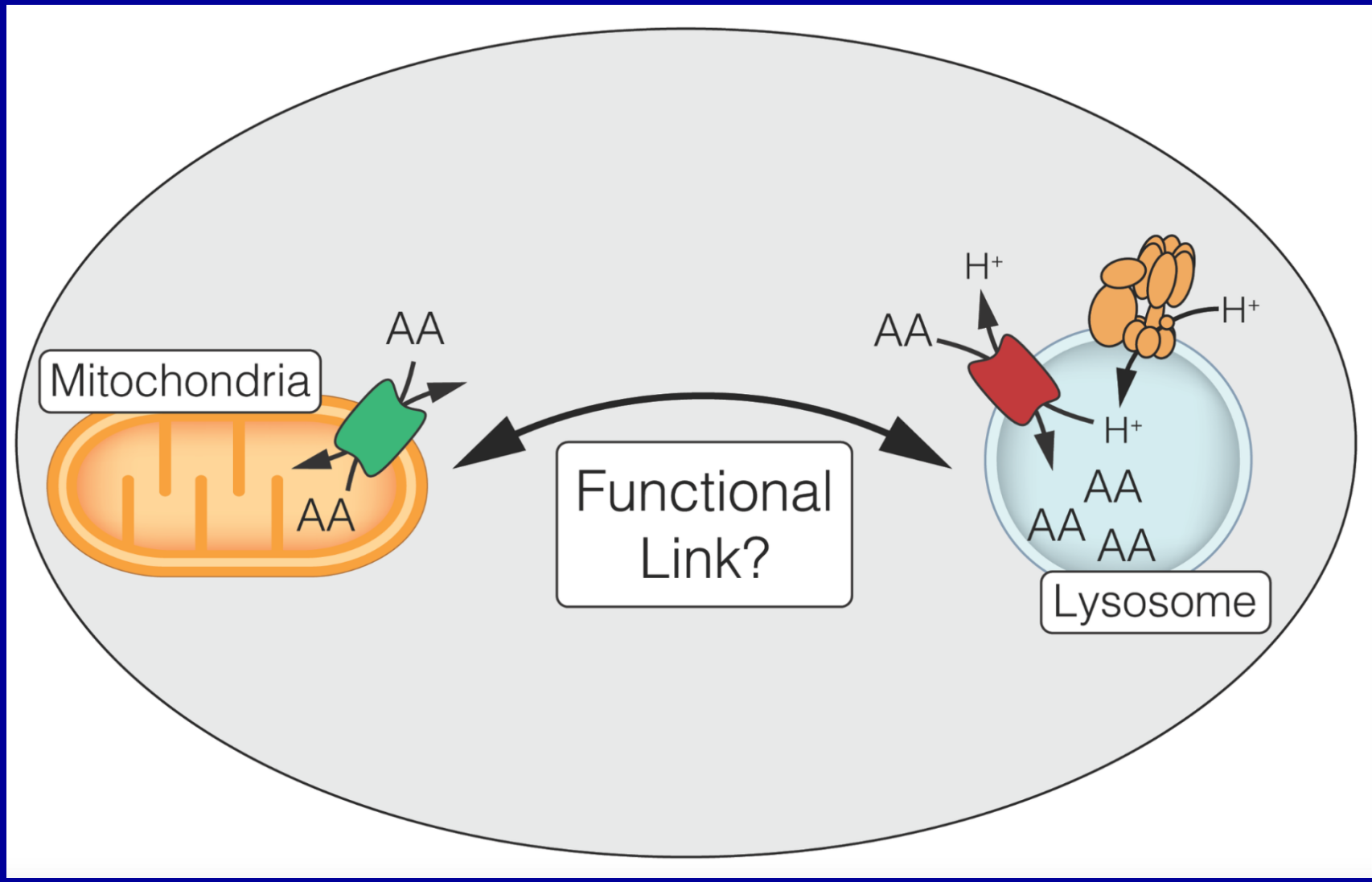
Lysosomes as the cellular housekeeping staff

Conclusion

Lysosome as Decision Making Center

Conclusion

Inter-organelle cross-talks



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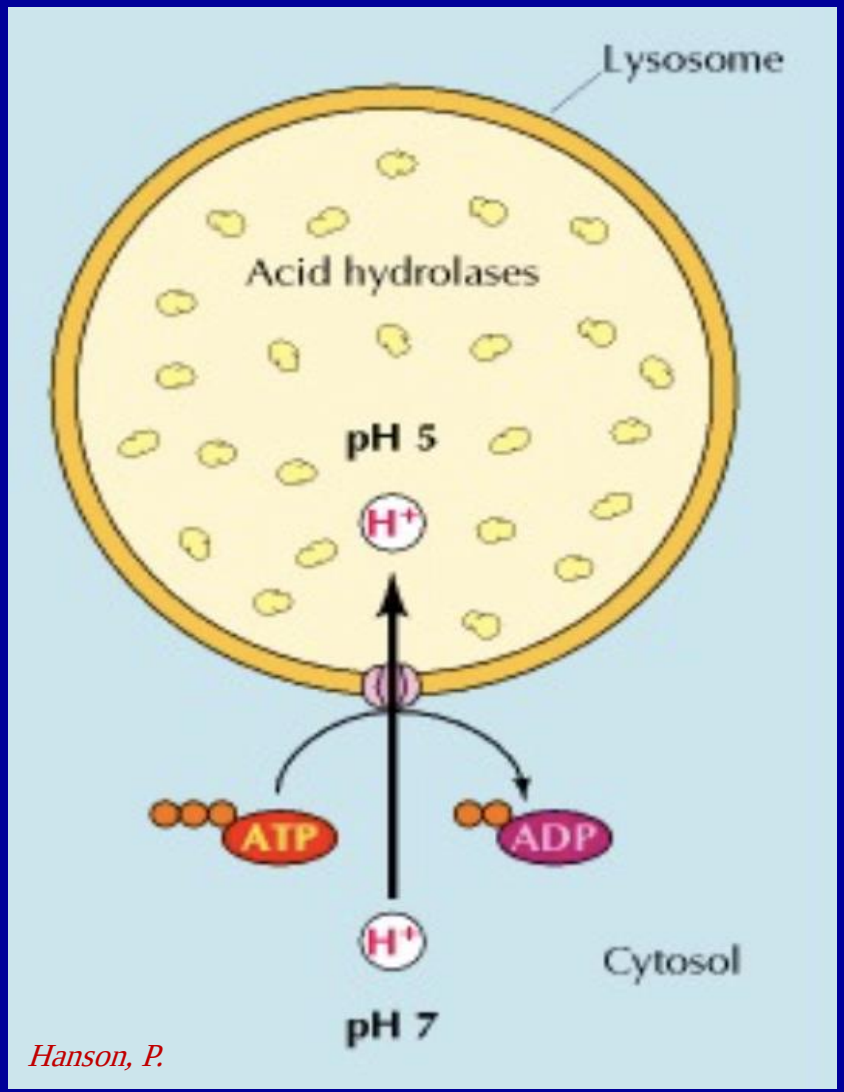
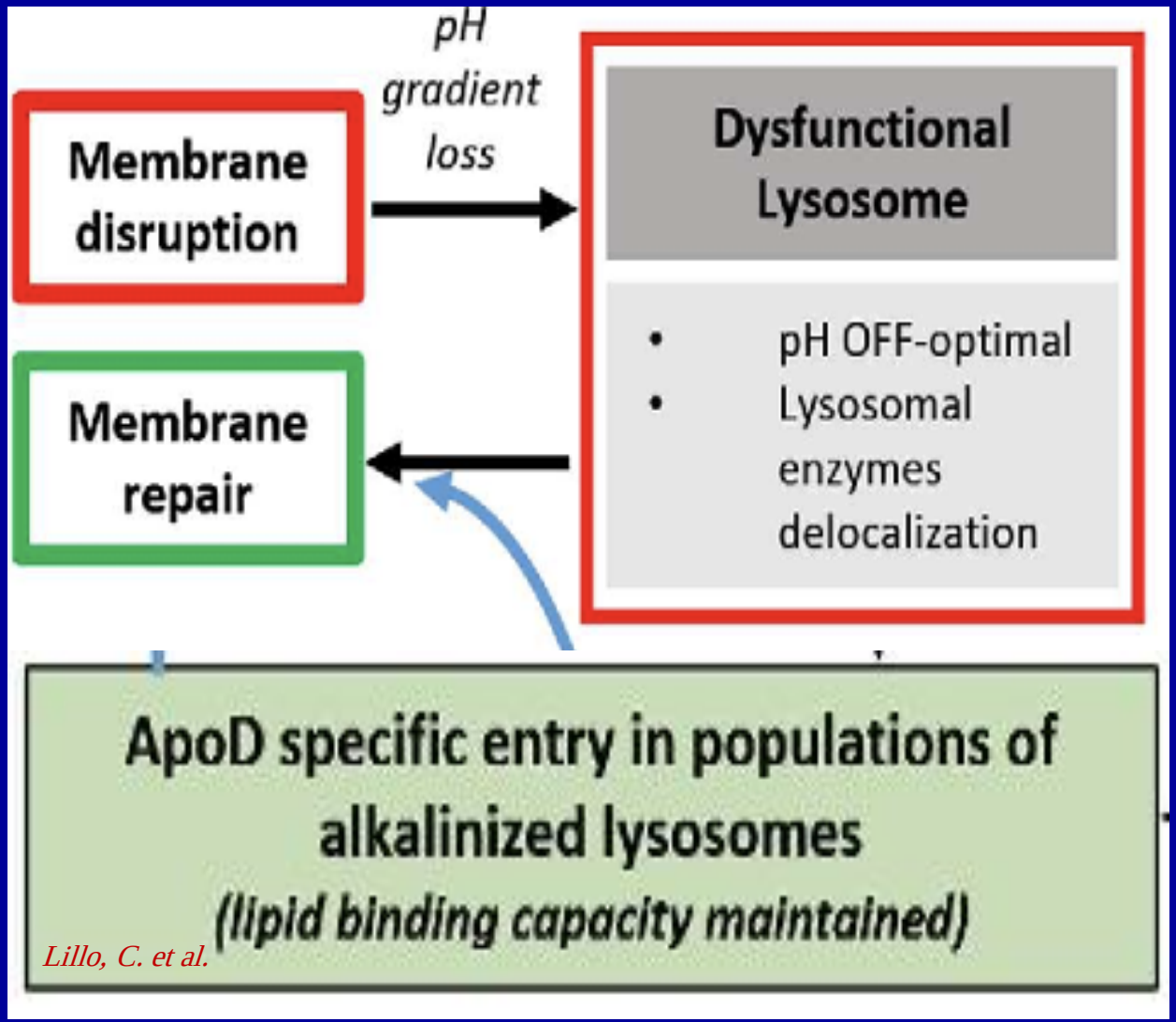
Preserving lysosomal acidic milieu



Hanson, P.



Lillo, C. et al.

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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!