Avtofagija, nevroglija in promet mešičkov

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za možgane
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TEDEN MOŽGANOV

Kako so nastali evkarionti?

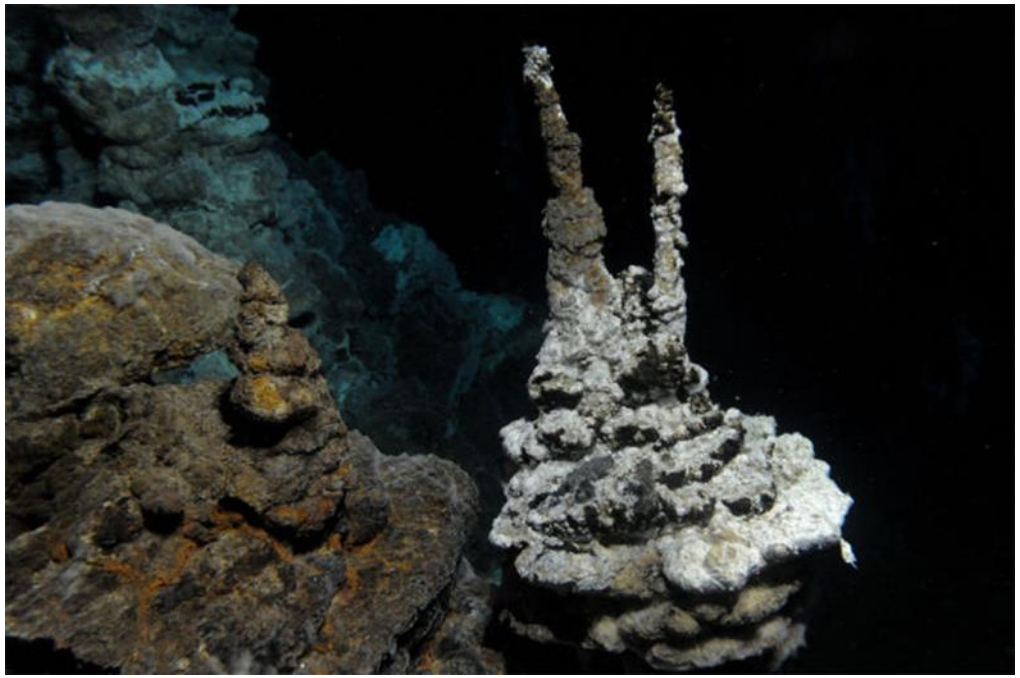
Evkarionti imajo večji celični volumen kot prokarionti in vsebujejo organele.

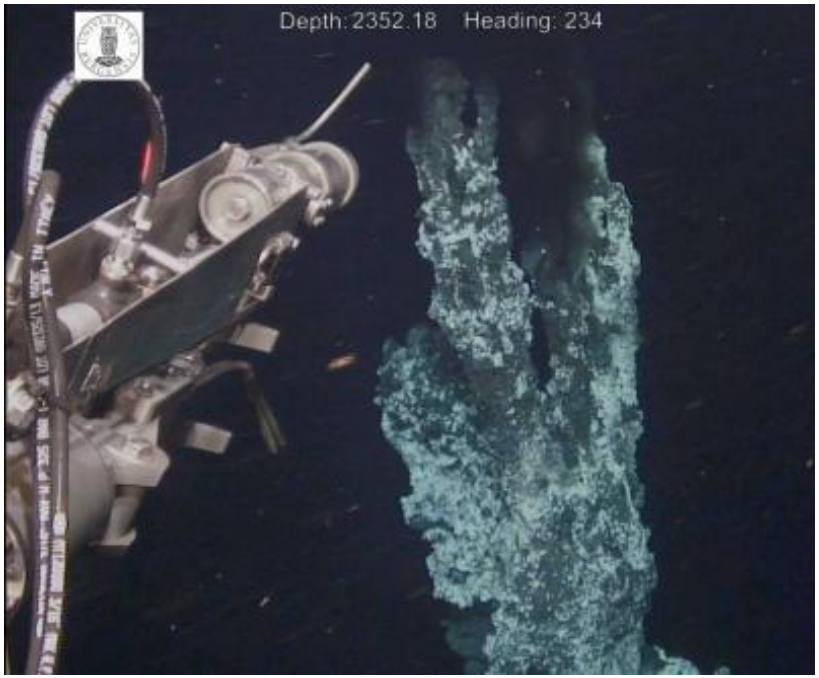
Endosimbiontska hipoteza o nastanku evkariontov.

Pred ~3 bilijoni let naj bi že obstajal organizem, predhodnik evkariontov? Starost zemlje ~4,5 bilijonov let.

Lokiarchaeota: organizmi, ki so jih odkrili pred kratkim(Spang et al., 2015, Nature 2015).

Dimniki „Loki's Castle“ 3000 m pod gladino morja





Desno: zgornji meter dimnika (12 m) hidrotermalnega vrelca (Loki's Castle sredi julija, 2008). Na levi je vidna robotska roka podmornice, s katero so zajeli vzorec vode.
https://en.wikipedia.org/wiki/Loki%27s_Castle

Lizosomi

- Endolizosomi so bili verjetno prvi organeli (Spang et al., 2015, Nature 2015).
- Lizosome je opisal Christian De Duve (1955).
- Poimenoval iz grščine: λύσις (lusis) – litični ali prebavni organel, vsebujejo hidrolitične encime.

Lizosomi

- Lizosom ima osrednjo vlogo v znotrajceličnem delovanju celice.
- Tudi v povezavi z avtofagijo: tudi ta termin je uvedel C. de Duve (1963, kongres v Londonu, ki ga je organiziral Danieli).

The Nobel Prize in Physiology or Medicine 1974
Albert Claude, Christian de Duve, George E. Palade

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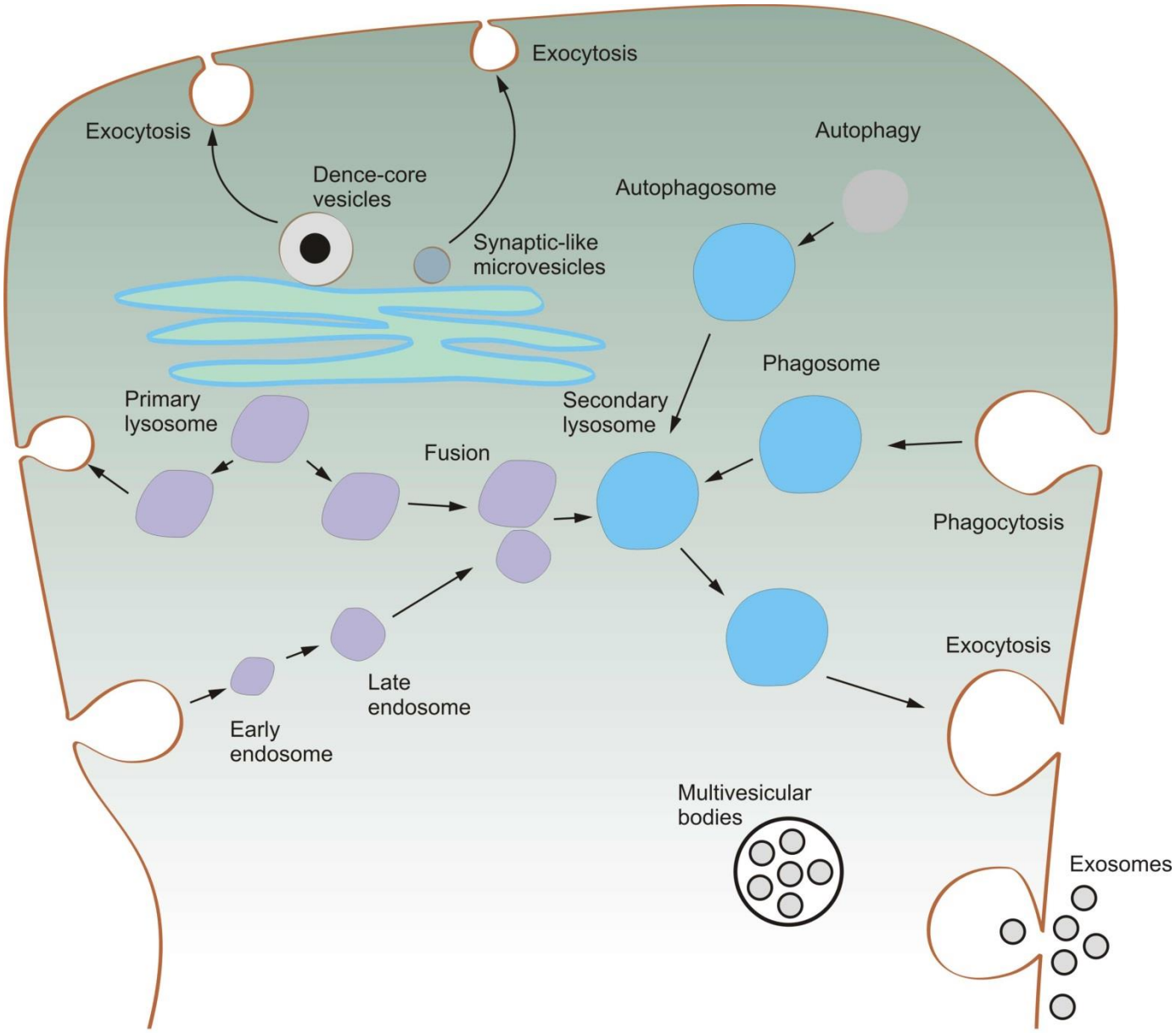
The Nobel Prize in Physiology or Medicine 1974

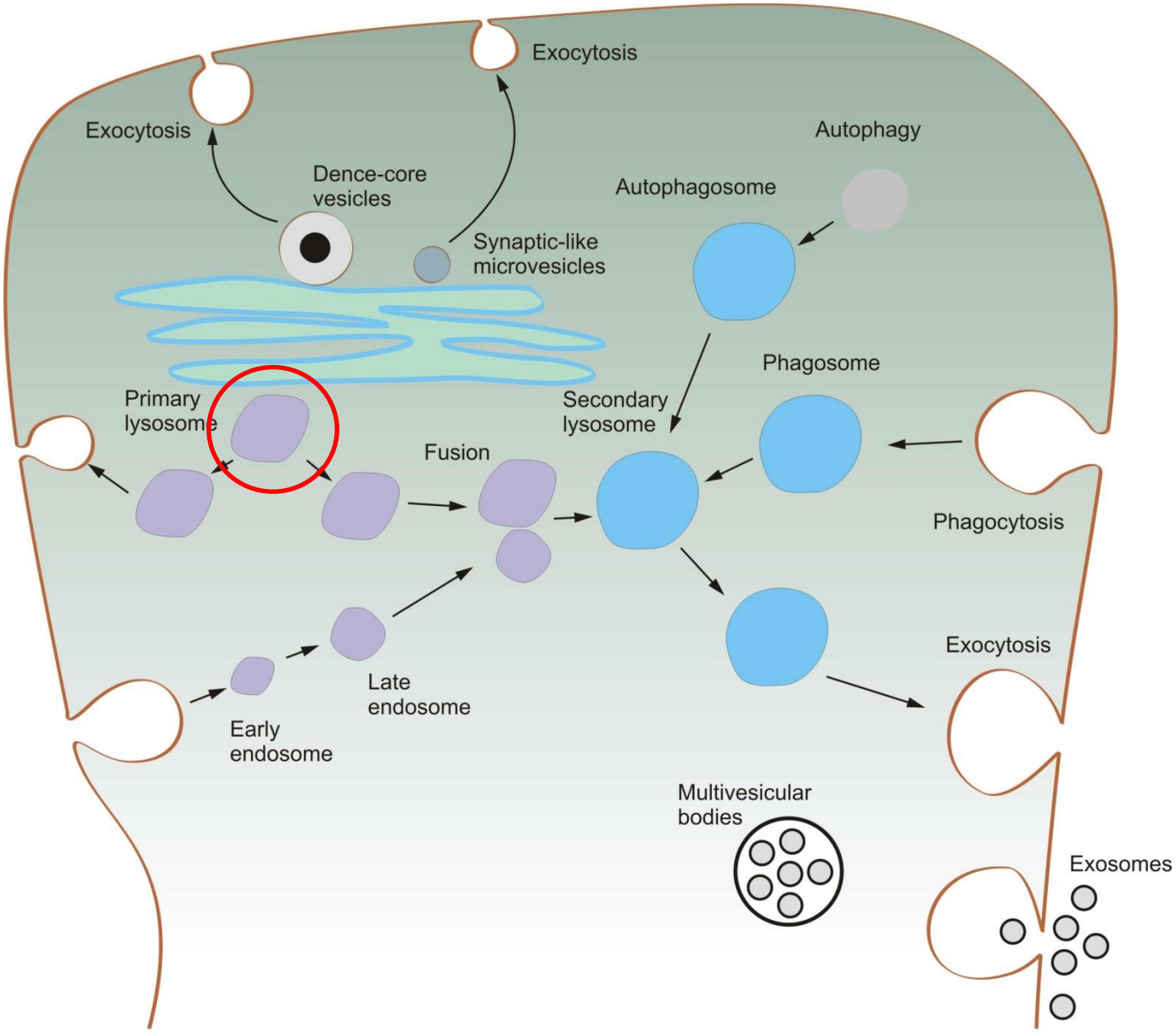
Albert Claude
Prize share: 1/3

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"*.


Exocytosis
Exocytosis
Dence-core
vesicles
Synaptic-like
microvesicles
Autophagy
Autophagosome
Phagosome
Primary
lysosome
Secondary
lysosome
Fusion
Phagocytosis
Late
endosome
Early
endosome
Exocytosis
Multivesicular
bodies
Exosomes


Exocytosis
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Late
endosome
Early
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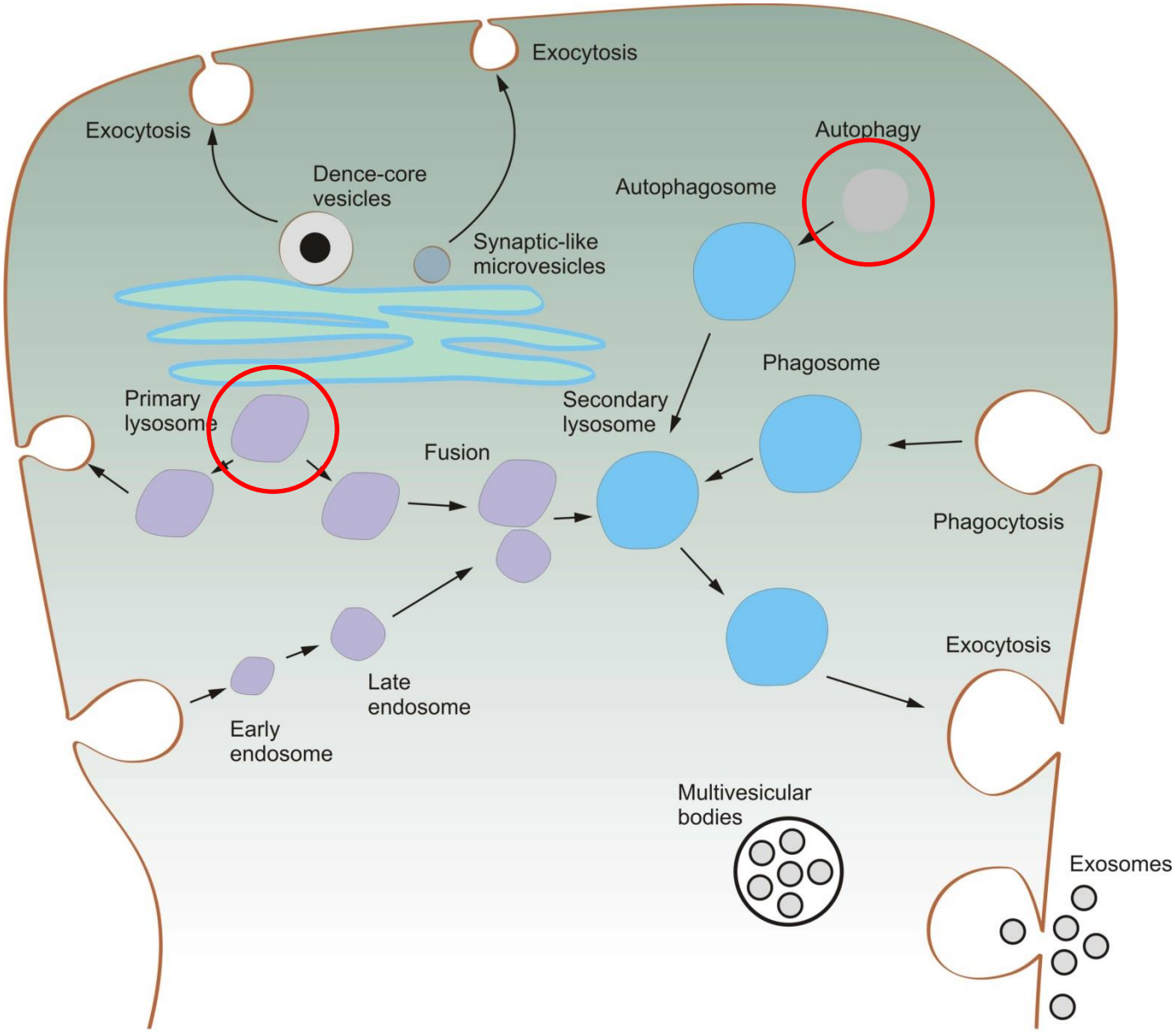
Multivesicular
bodies
Exosomes


Exocytosis
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The Nobel Prize in Physiology or Medicine 2016
Yoshinori Ohsumi

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The Nobel Prize in Physiology or Medicine 2016

Photo: A. Mahmoud
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"*.

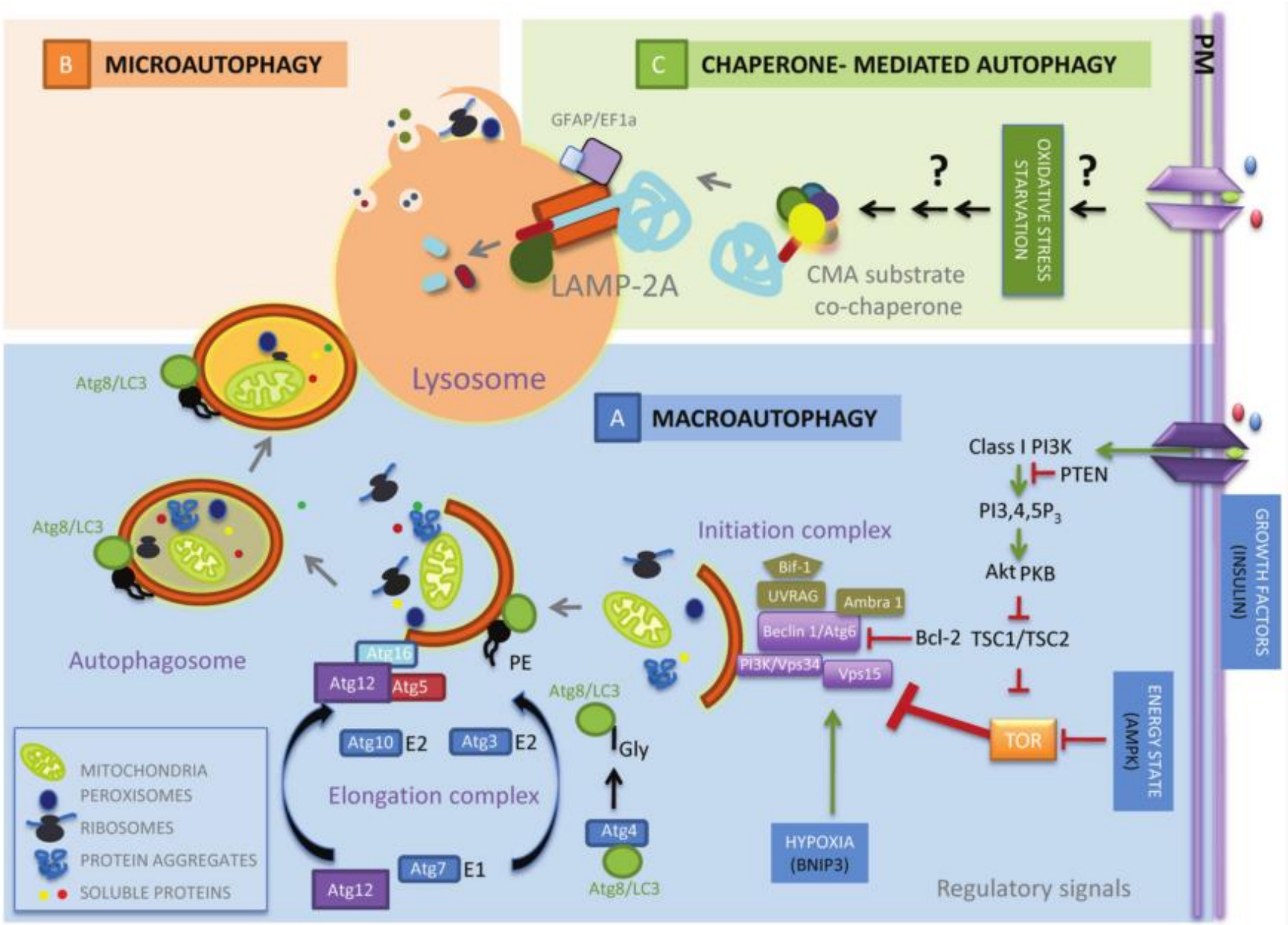
Autophagy mediates the **digestion and recycling of non-essential parts of the cell** during starvation and participates in a variety of physiological processes where cellular components must be removed to leave space for new ones.

Autophagy is a key cellular process capable of clearing **invading microorganisms** and **toxic protein aggregates**, and therefore plays an important role during infection, in ageing and in the pathogenesis of many human diseases.

Autofagy was defined in 1960‘s as a process (C. De Duve), but in 1993, Ohsumi published his seminal discovery of 15 genes of key importance for autophagy in budding yeast.

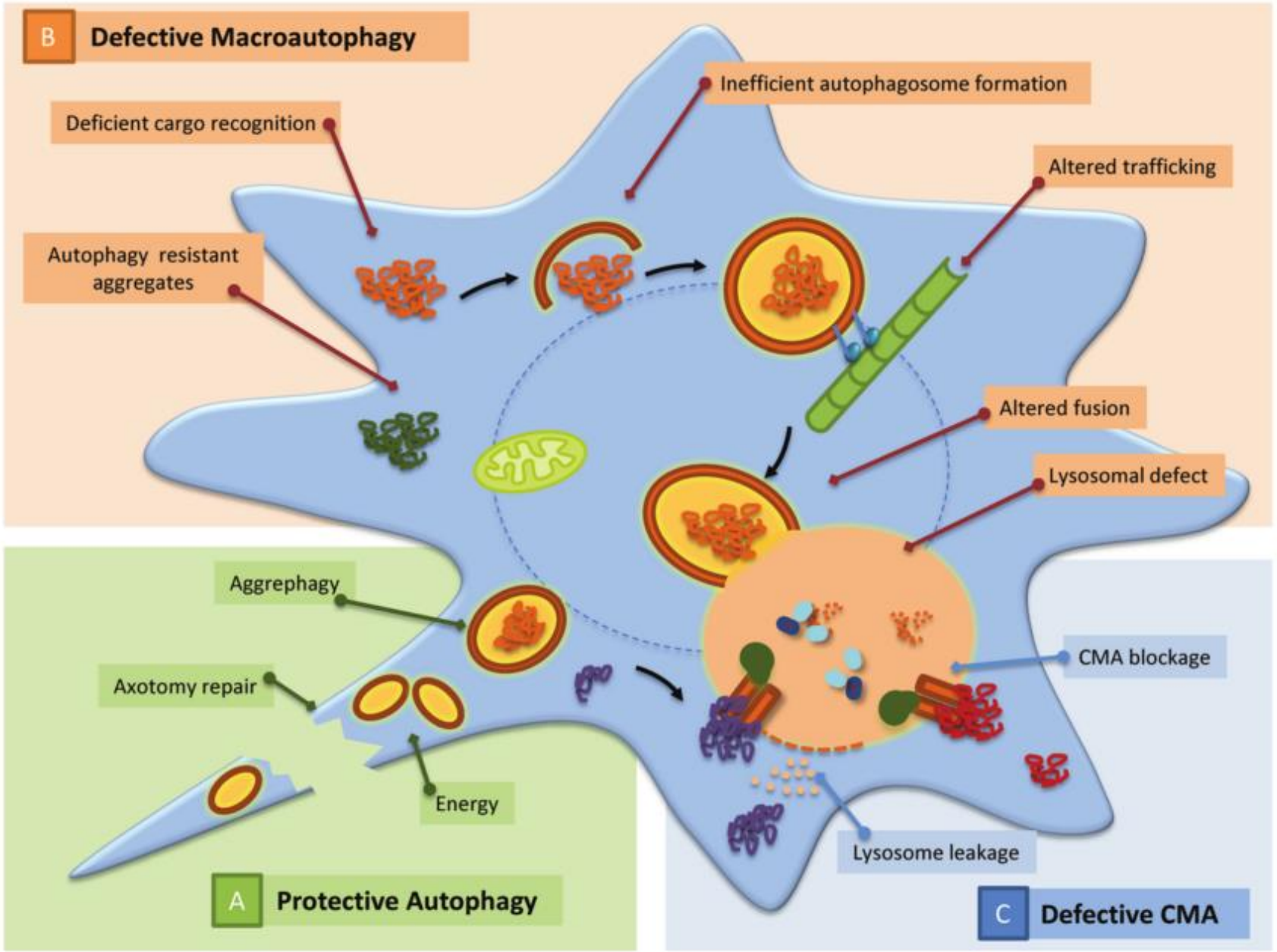
Tsukada M, Ohsumi Y (1993) Isolation and characterization of autophagy-defective mutants of Saccharomyces cerevisiae. FEBS Lett. 333(1-2):169-74.

Sridhar et al 2012, J Pathology



Autophagy was known to occur at a low basal level, and to increase during **differentiation** and **remodeling** in a variety of tissues, including brain, intestine, kidney, lung, liver, prostate, skin and thyroid gland. It was speculated that autophagy might be a mechanism for coping with **metabolic stress** in response to starvation and that it might have roles in **the pathogenesis of disease: cancer, cardiopathology, infection/immune diseases, neurodegeneration,**

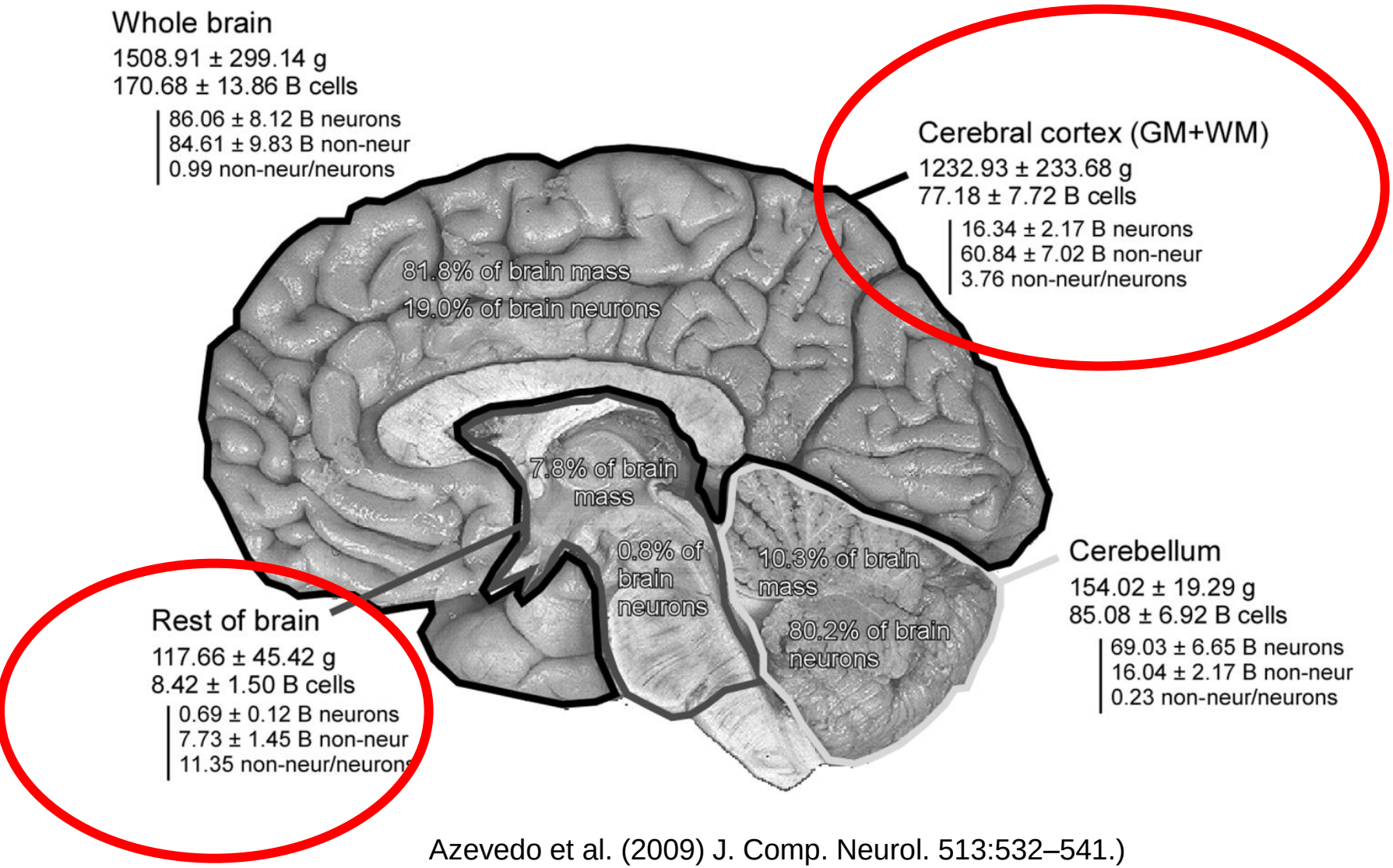
Vloga avtofagije v nevrodegeneraciji
Sridhar et al 2012 J Pathology



Možgani delujejo ne le zaradi nevronov, pač pa tudi zaradi nevroglije.

Pri nevrodegeneraciji so vpletene tudi druge celice v možganih- astrociti.

82% mase možganov predstavlja neokorteks, v katerem je 4 krat več ne-nevronov (med temi so tudi astrociti)



Azevedo et al. (2009) J. Comp. Neurol. 513:532–541.)

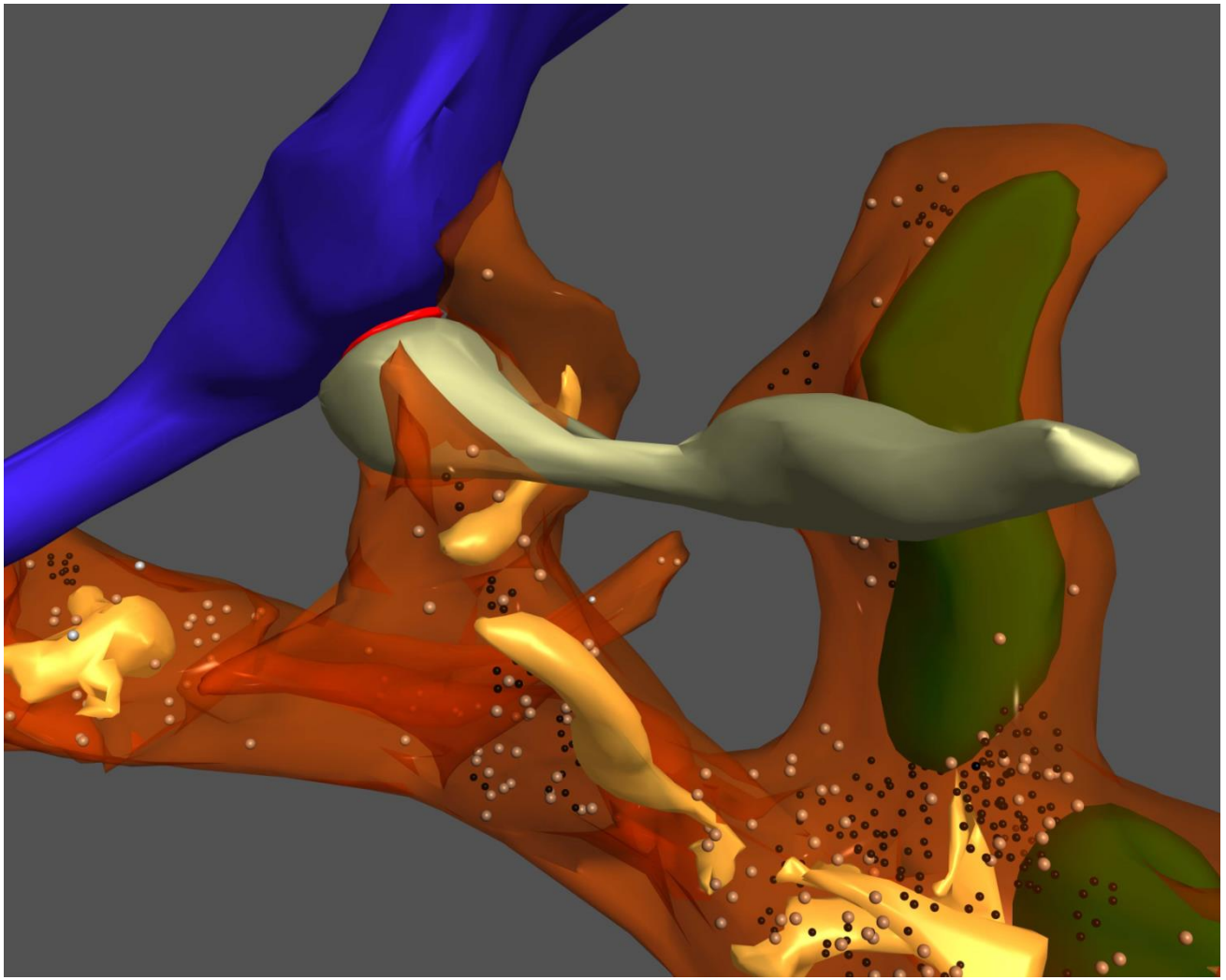
Vloga nevroglije v nervoloških boleznih vključno z nevrodegeneracijo temelji na:

Astrociti, tip nevroglije, so edinstvene celice:

- **prekašajo nevrone po številu v neokorteksu,**
- **oblikujejo tesne stike (plastične) s sinapsami (tripartitna sinapsa),**
- **delujejo v časovni domeni, ki je počasnejša kot pri nevronih,**
- **vsebujejo glikogen**
- **uporabljajo mešičke za komunikacijo.**

Poskusi na živalskih modelih kažejo na osrednjo vlogo astrocitov v Alzheimerjevi bolezni, umski manjzmožnosti, nevroinflamatornih stanjih,.....

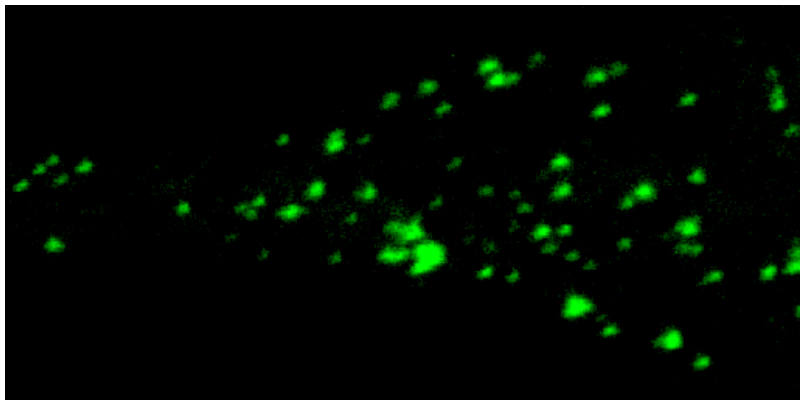
Ostroff et al. (2014) Synapses Lacking Astrocyte Appear in the Amygdala During Consolidation of Pavlovian Threat Conditioning. J. Comp. Neurol. 522:2152–2163, 2014.

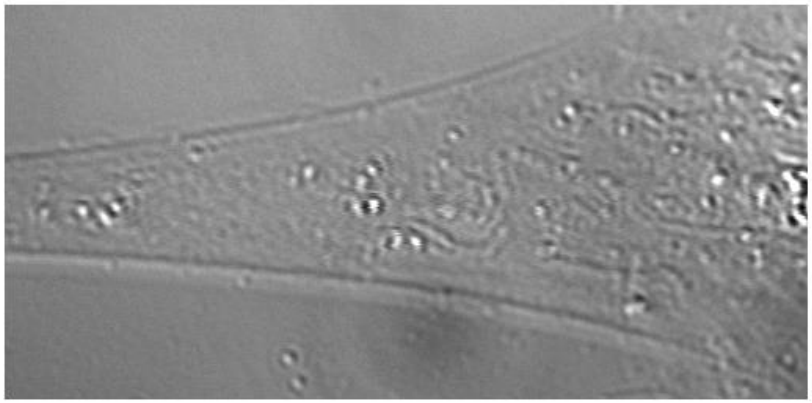


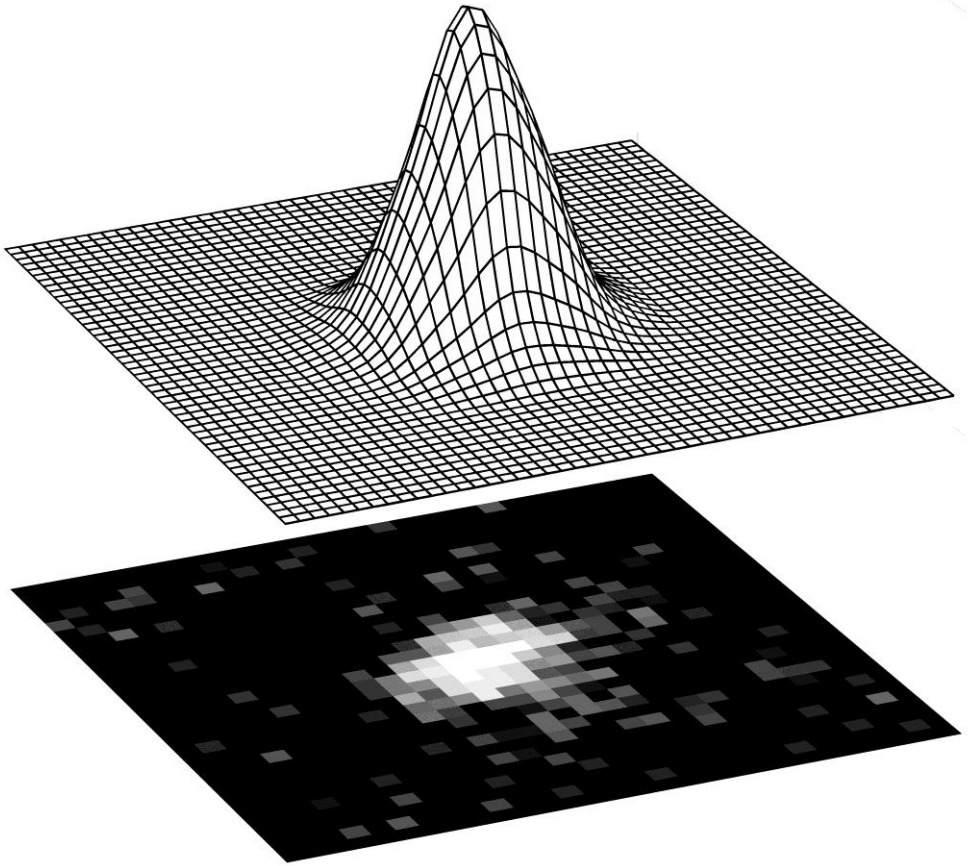
http://www.cns.nyu.edu/ledoux/SFN2011/L.%20OSTROFF.htm

Mobilnost mešičkov

Potokar et al., BBRC, 2005
Confocal microscopy

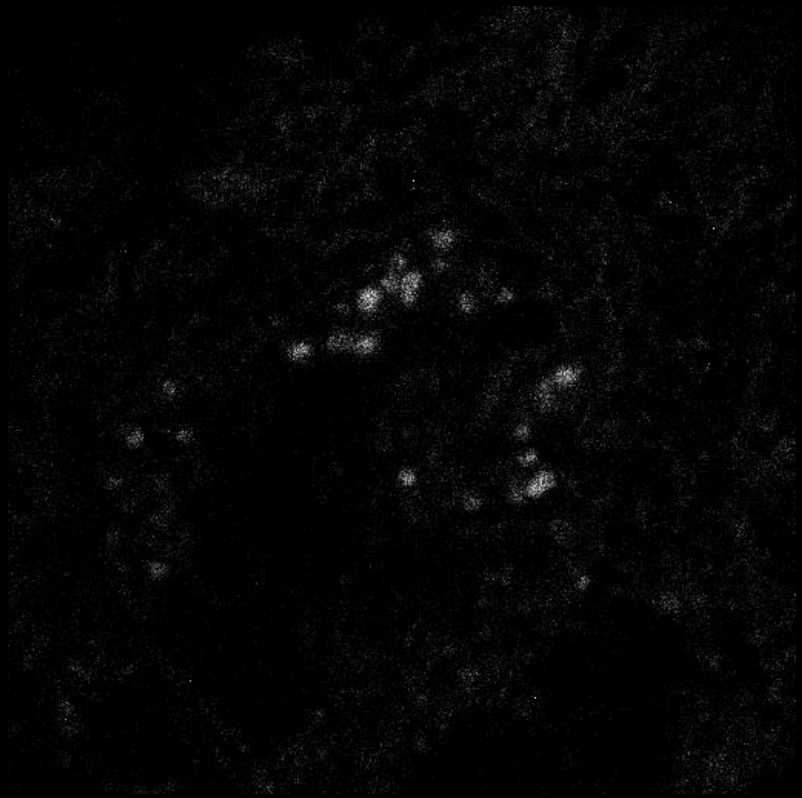






The mobility of fluorescent VGLUT1 puncta differs in non-stimulated and stimulated cells

NON-STIMULATED



STIMULATED

Promet mešičkov (tudi tistih avtofagosomnih), ki transportirajo različne molekule, se spremeni v patoloških razmerah.

CB1 receptor (Osborne et al., 2009 ASN Neuro)

Notch signals (Wilhelmsson et al. 2012, Stem Cells)

tPA (Casse et al., 2012; J. Neurosci)

AQP4 (Potokar et al. 2013, Glia)

MHC II antigen presenting molecules (Vardjan et al., 2012, J. Neuroinflamation)

Tick-borne encephalitis virus (Potokar et al., 2014, Plos ONE)

Reactive astrogliosis (Potokar et al., Traffic, 2007)

Fingolimod (Gilenya, Novartis) (Trkov et al., Glia 2012)

Ketamine (anaesthetic and antidepressive) (Lasic et al., J. Neurochem, 2016; Stenovec et al. (2016) Mol. Neurobiol.)

Alzheimer‘s disease (Stenovec et al., Glia 2016)

Intellecutal dissability (Potokar et al., 2016)

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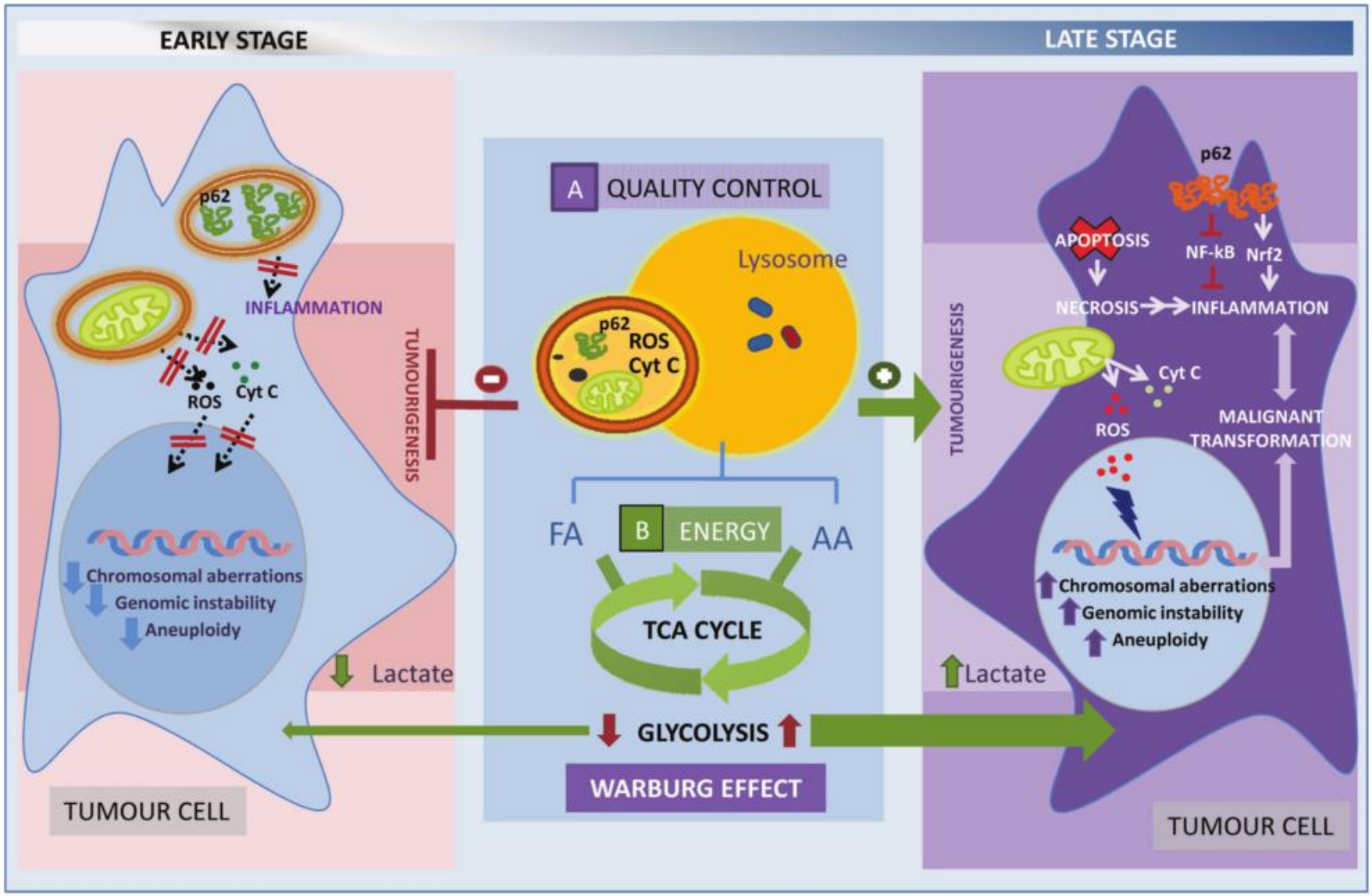
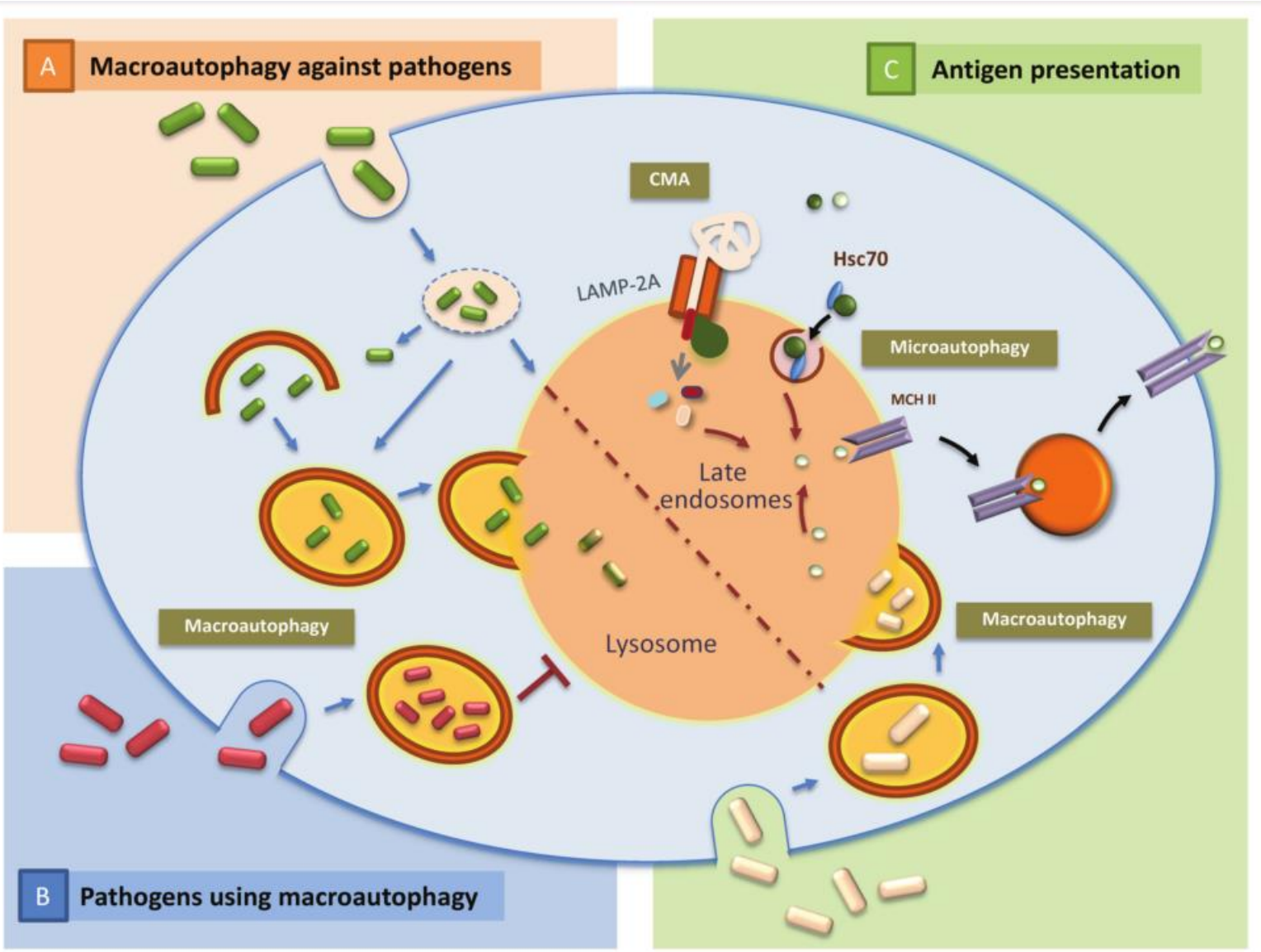
Ophrys insectifera L., Kršičevec (1091m), Vardjanščica (865m)

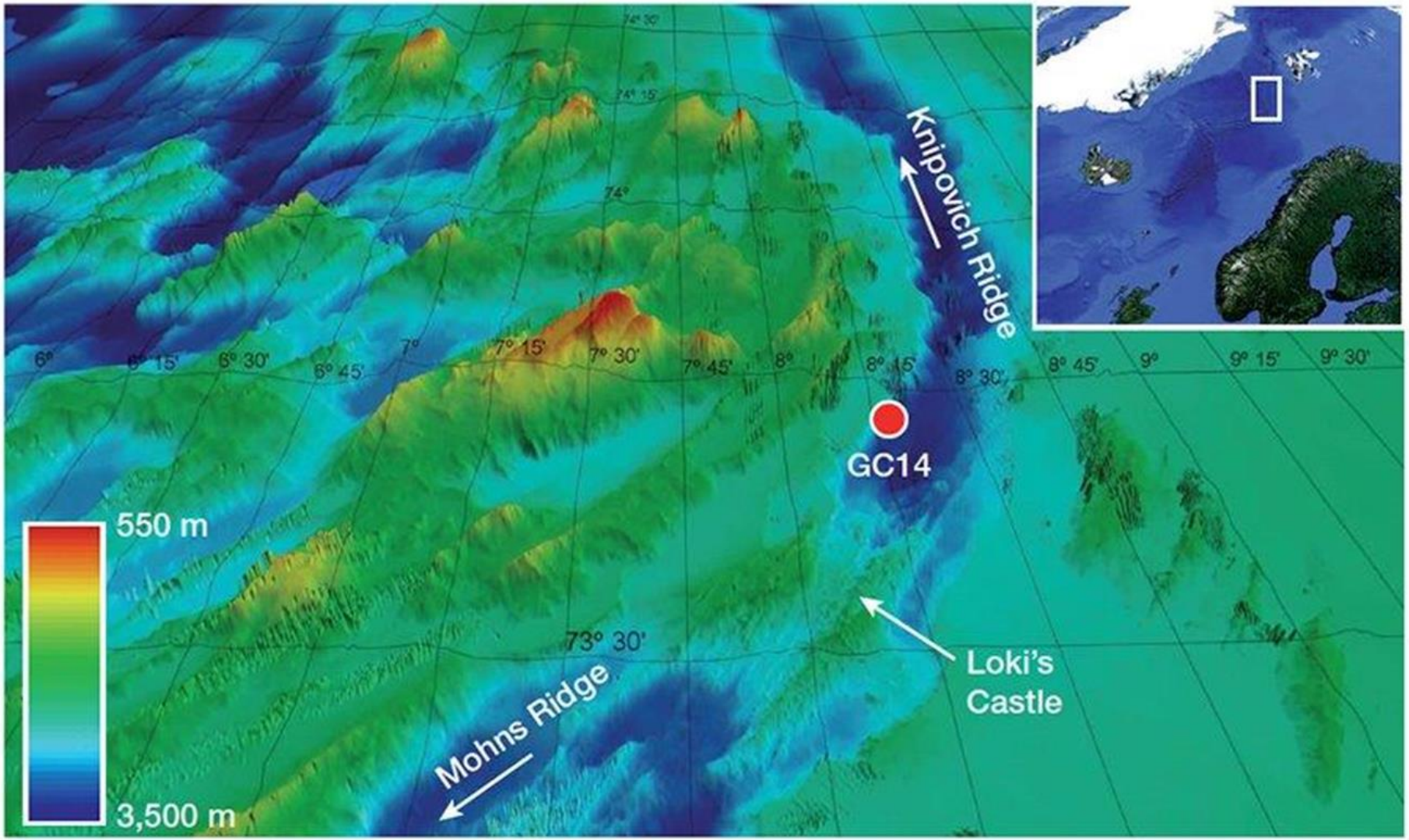
Vloga avtofagije v tumorigenezi
Sridhar et al 2012 J Pathology



Vloga avtofagije pri infekciji
Sridhar et al 2012 J Pathology



Norveški mitološki lik: Loki


Knipovich Ridge
GC14
550 m
3,500 m
73° 30'
Mohns Ridge
Loki's
Castle
6°
6° 15'
6° 30'
6° 45'
7°
7° 15'
7° 30'
7° 45'
8°
8° 15'
8° 30'
8° 45'
9°
9° 15'
9° 30'