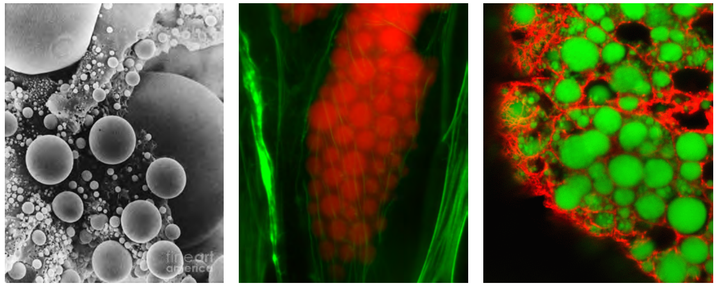
Distribucija in dinamika lipidov v celici: lipidne kapljice in uravnavanje membranske sestave

Toni Petan

Institut Jožef Stefan, Ljubljana, Slovenija

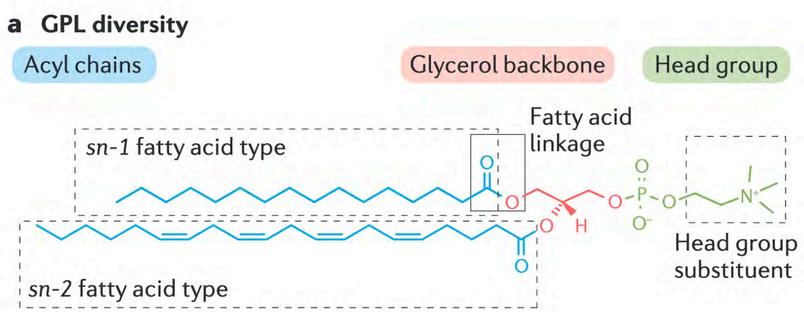


FKKT
22. april 2025

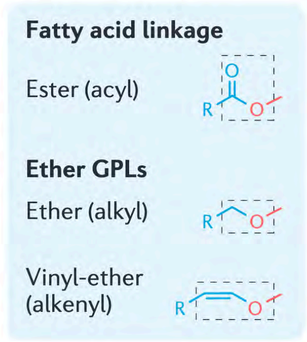
Jožef Stefan Institute

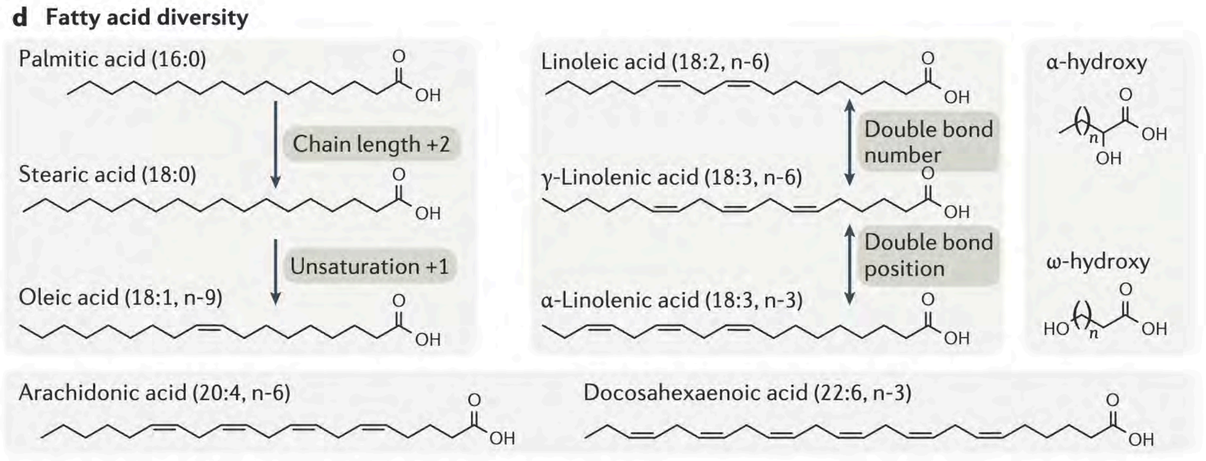
David M. Phillips - Fine Art America
Ana Temprano, Toni Petan
Matthias Beller

Raznolikost membranskih (glicero)fosfolipidov



GPL	Head group substituent
Phosphatidic acid	–
PtdCho	Choline
PtdEtn	Ethanolamine
PtdSer	Serine
PtdIns	Inositol
PtdGro	Glycerol
Cardiolipin	PtdGro
LBPA	LPA
PtdGlc	Glucose

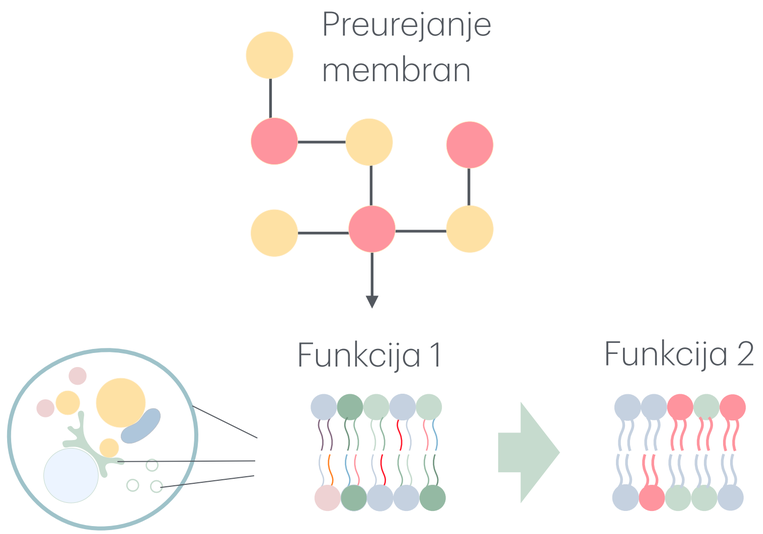




>1500 različnih vrst fosfolipidov

Harayama & Riezman Nat Rev Mol Cell Biol 2018

Izzivi na področju celične in molekularne biologije lipidov



Kakšna je funkcija posameznih lipidov ali skupkov lipidov v membrani ali organelu? Kako se funkcije posameznih lipidov seštevajo?

Kakšna je lipidna sestava organelov in kako se spremeni pri določenem procesu? Ali se funkcija organelov spremeni z njihovo sestavo?

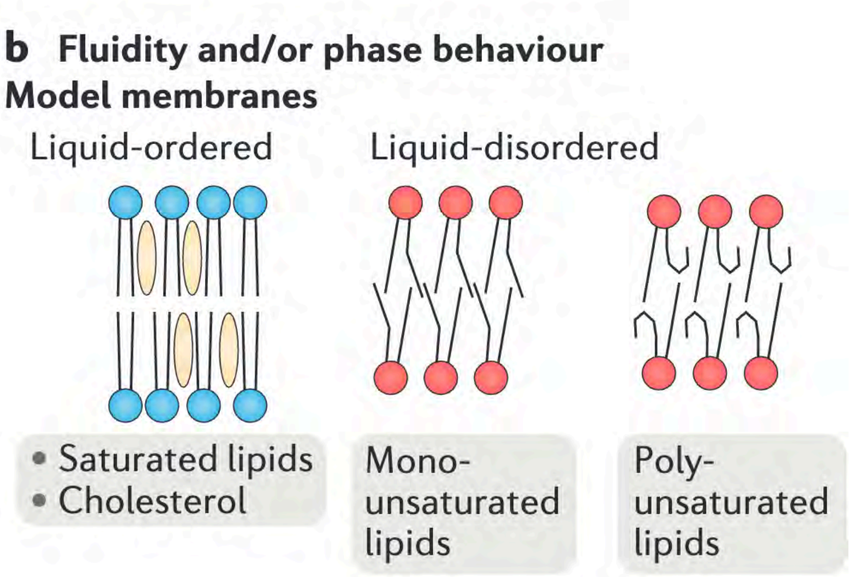
Kateri mehanizmi uravnavajo sestavo in s tem funkcijo posameznih membranskih domen in organelov?

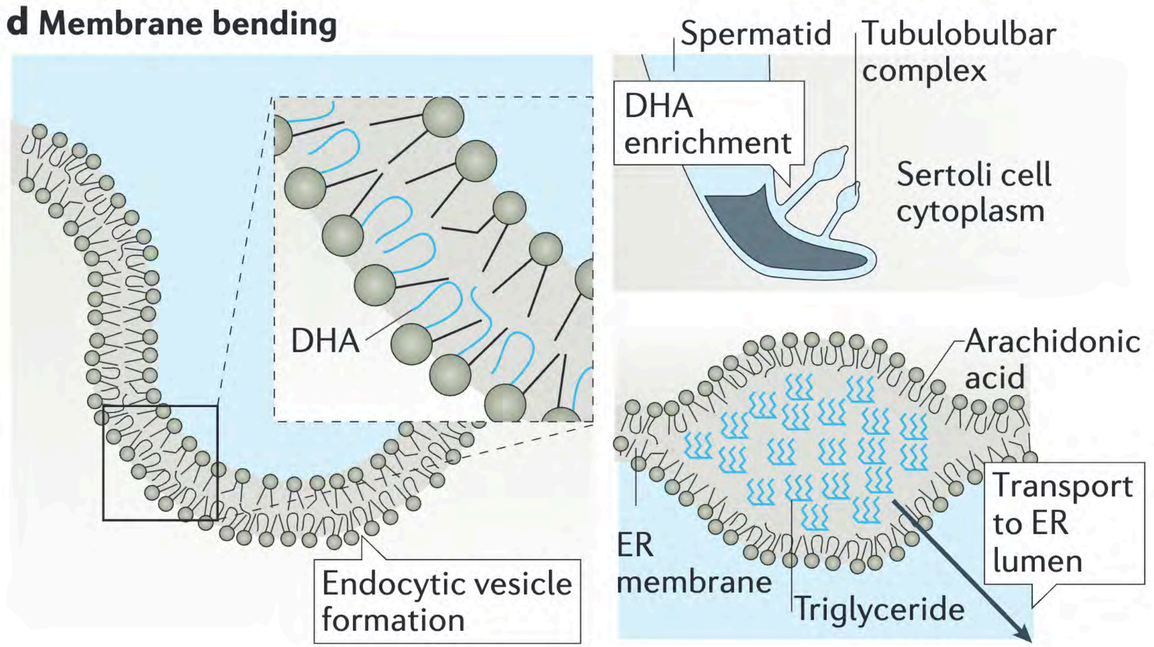
Dinamika in distribucija lipidov v celici ter njihova funkcija v določenem kontekstu ostajajo velike neznanke.

Stopnja nenasičenosti določa bistvene membranske lastnosti

Fluidnost

Ukrivljanje

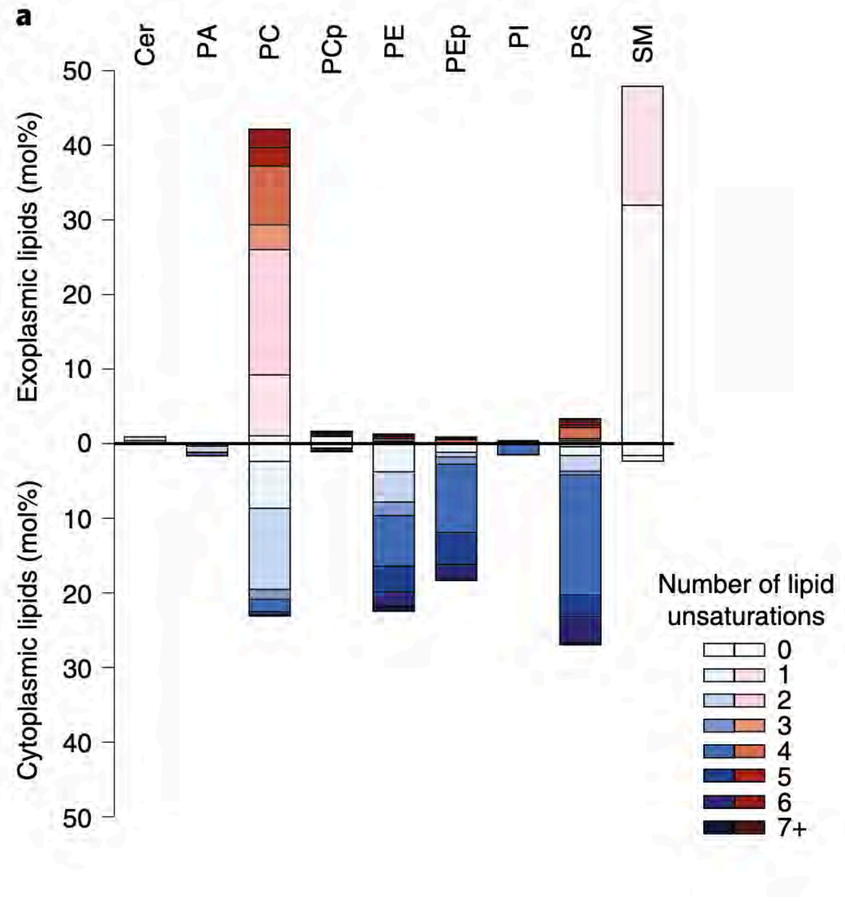




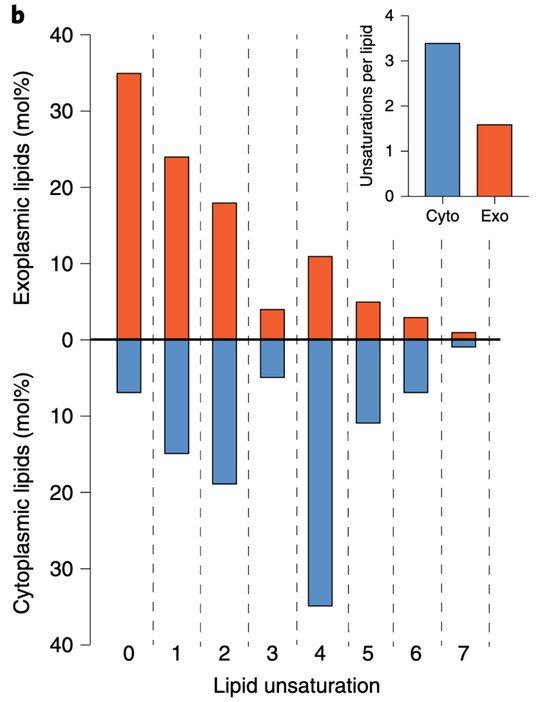
Harayama & Riezman Nat Rev Mol Cell Biol 2018

Asimetrična razporeditev lipidov - in njihove nenasičenosti

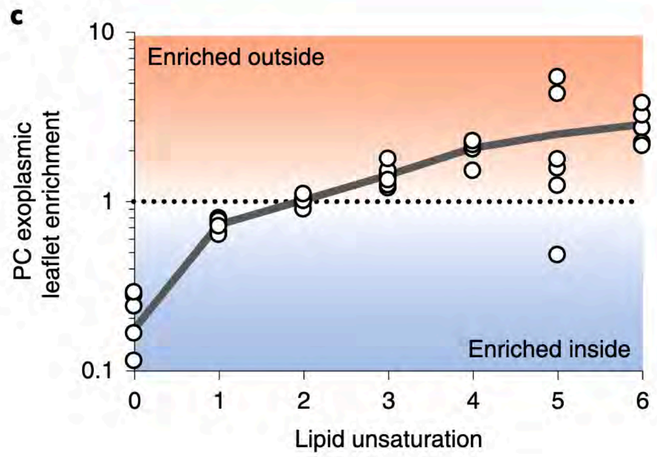
Lipidna sestava plazemske membrane



Nenasičenost plazemske membrane



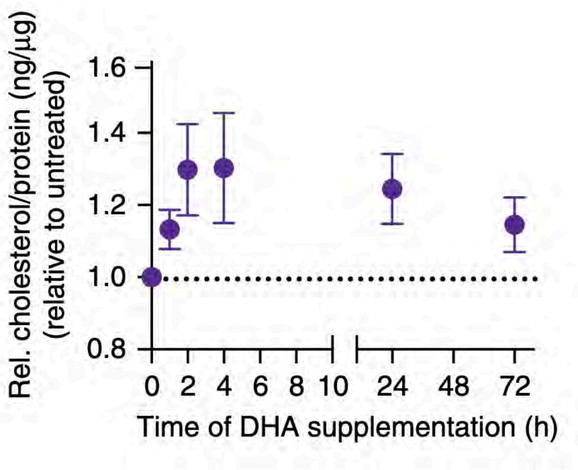
Nenasičenost in razporeditev PC



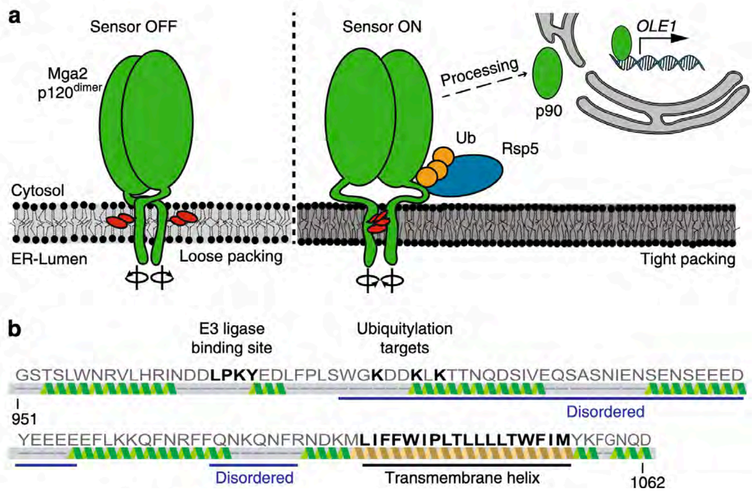
Asimetrija nenasičenosti se ohranja po endocitozi.

Lorent et al., *Nat Chem Biol* 2020.

Celice ohranjajo stopnjo membranske nenasičenosti v ozkem območju



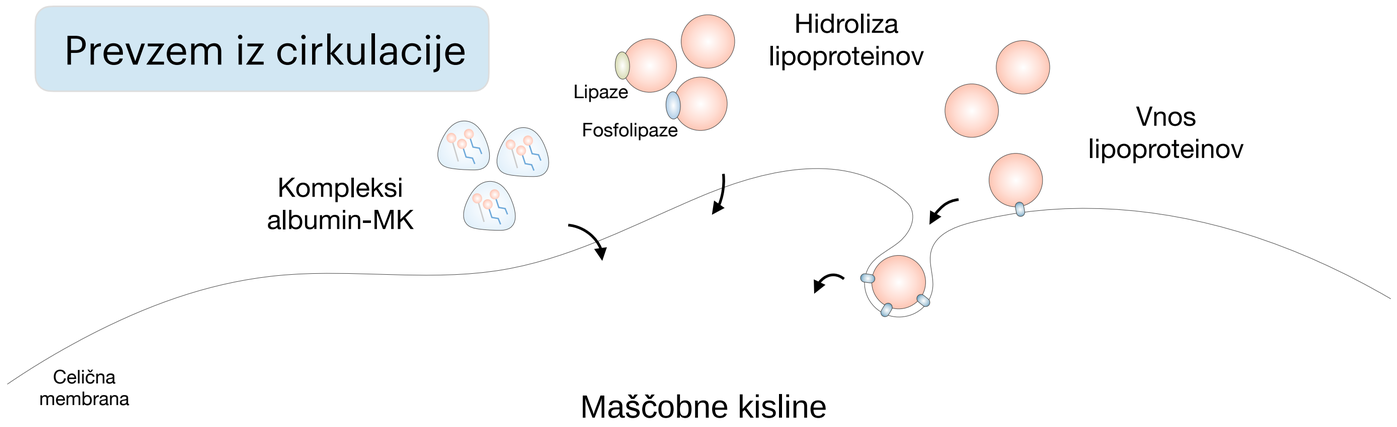
Prevelika nenasičenost membrane sproži sintezo holesterola in nasičenih maščobnih kislin



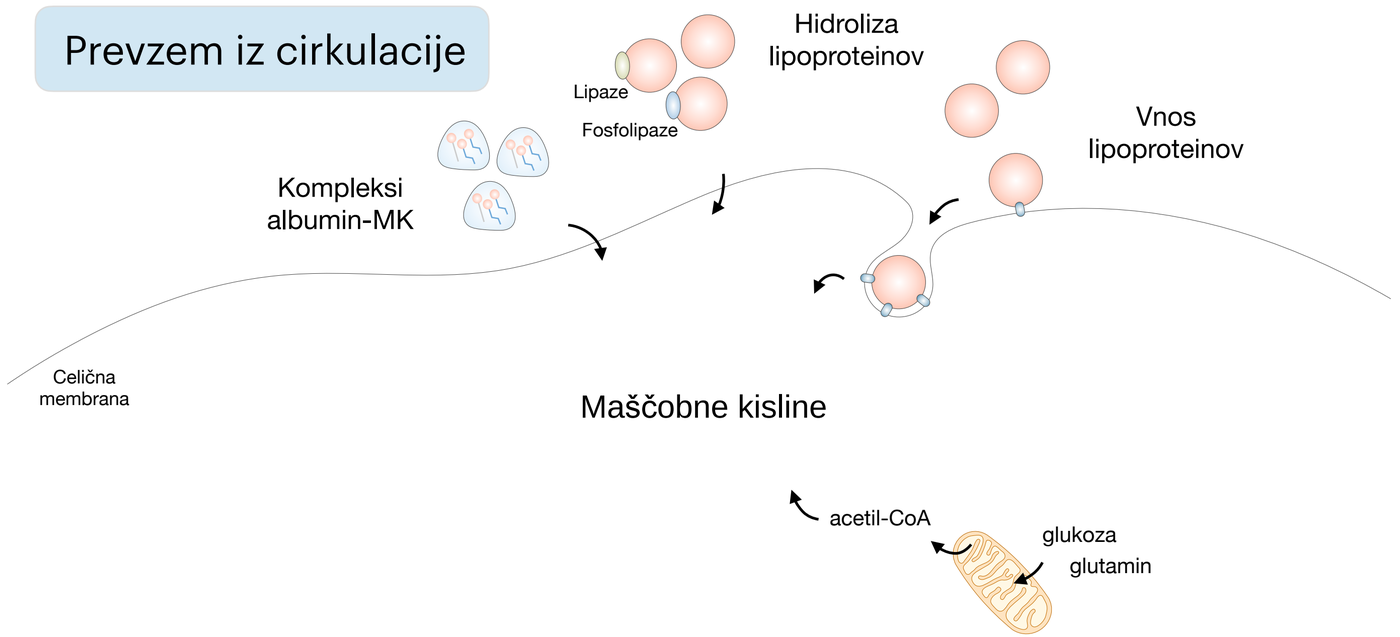
Prevelika nasičenost: senzorski protein detektira povečano pakiranje membrane ER in aktivira sintezo nenasičenih MK

Levental et al., *Nat Comm* 2020.
Ballweg et al., *Nat Comm* 2020.

Standardni viri maščobnih kislin



Standardni viri maščobnih kislin



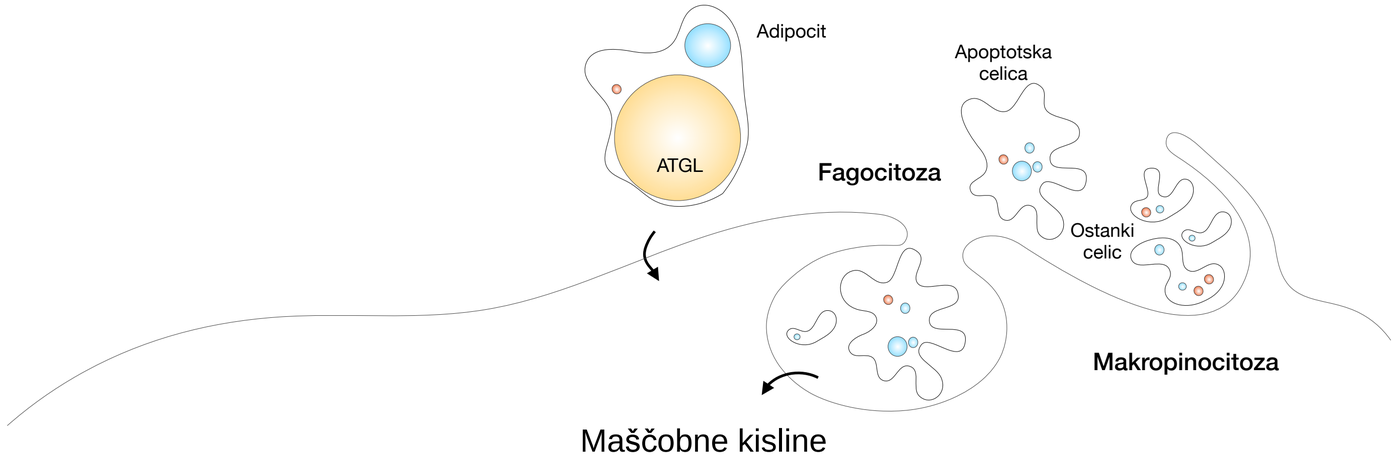
Alternativni viri maščobnih kislin

Alternativni zunajcelični viri

Petan et al., *Molecules* 2018

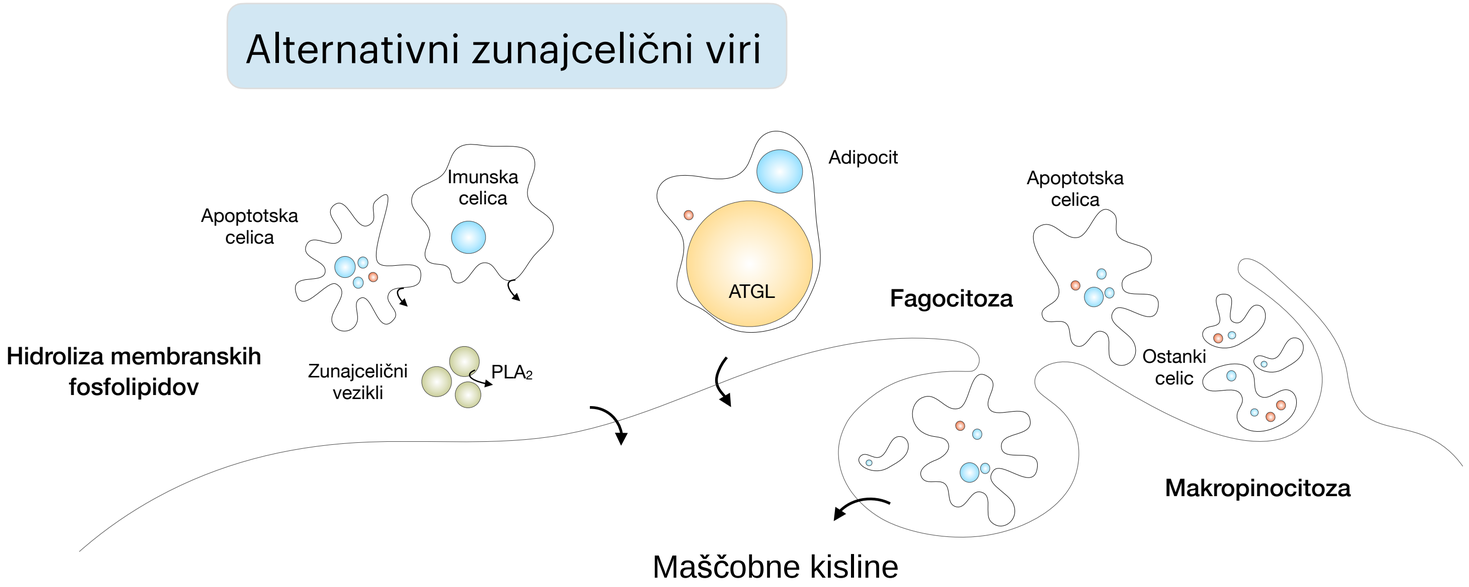
Alternativni viri maščobnih kislin

Alternativni zunajcelični viri



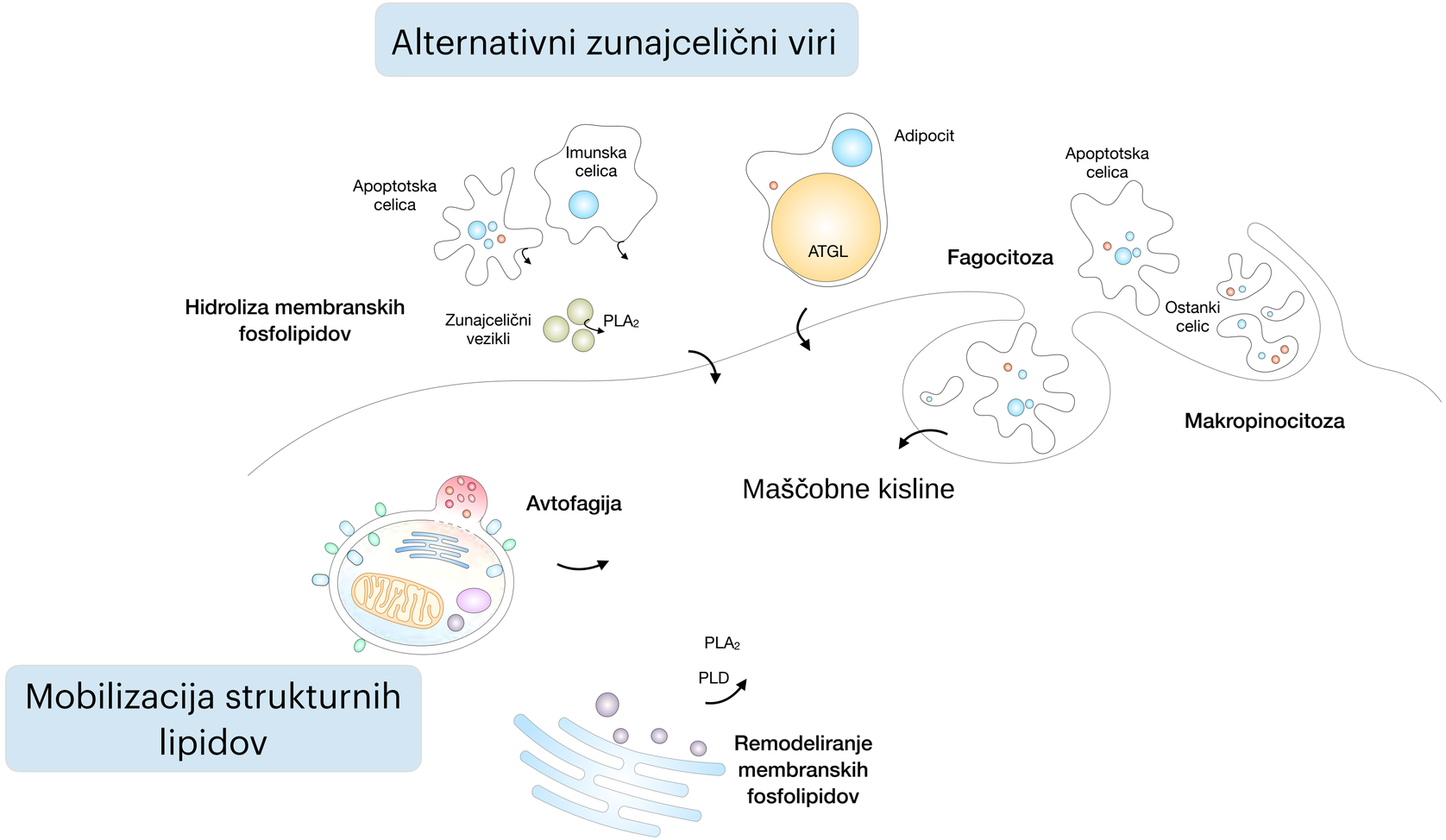
Petan et al., *Molecules* 2018

Alternativni viri maščobnih kislin



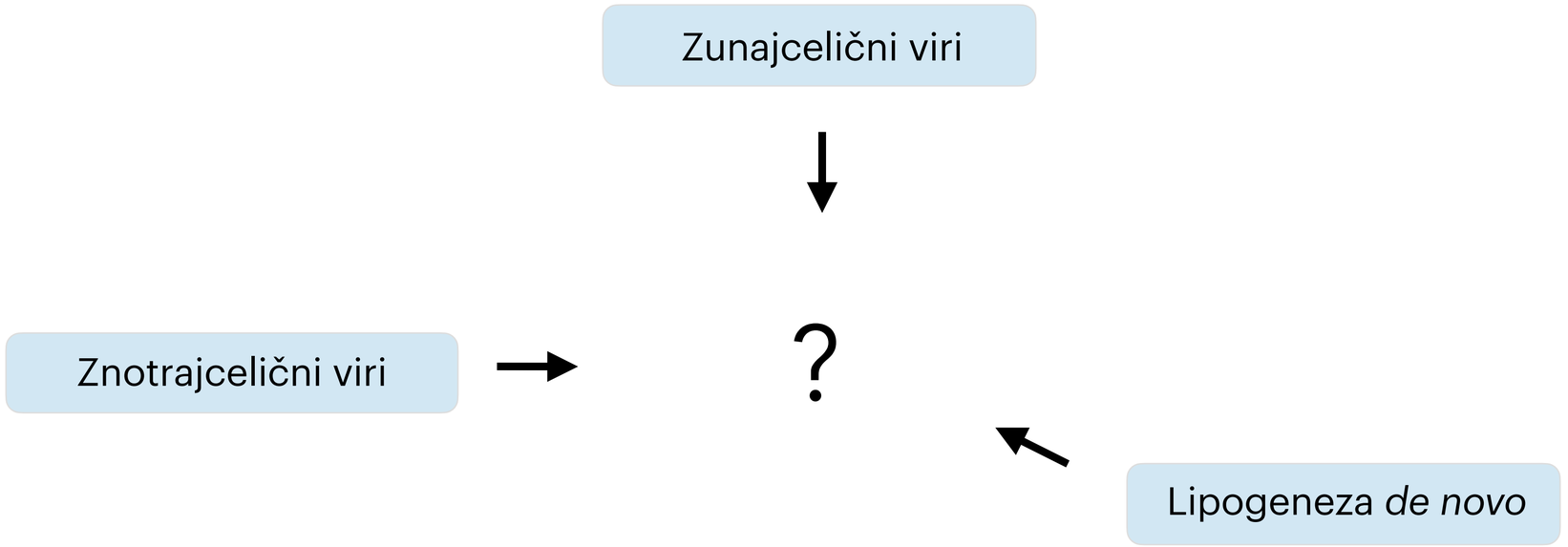
Petan et al., *Molecules* 2018

Alternativni viri maščobnih kislin

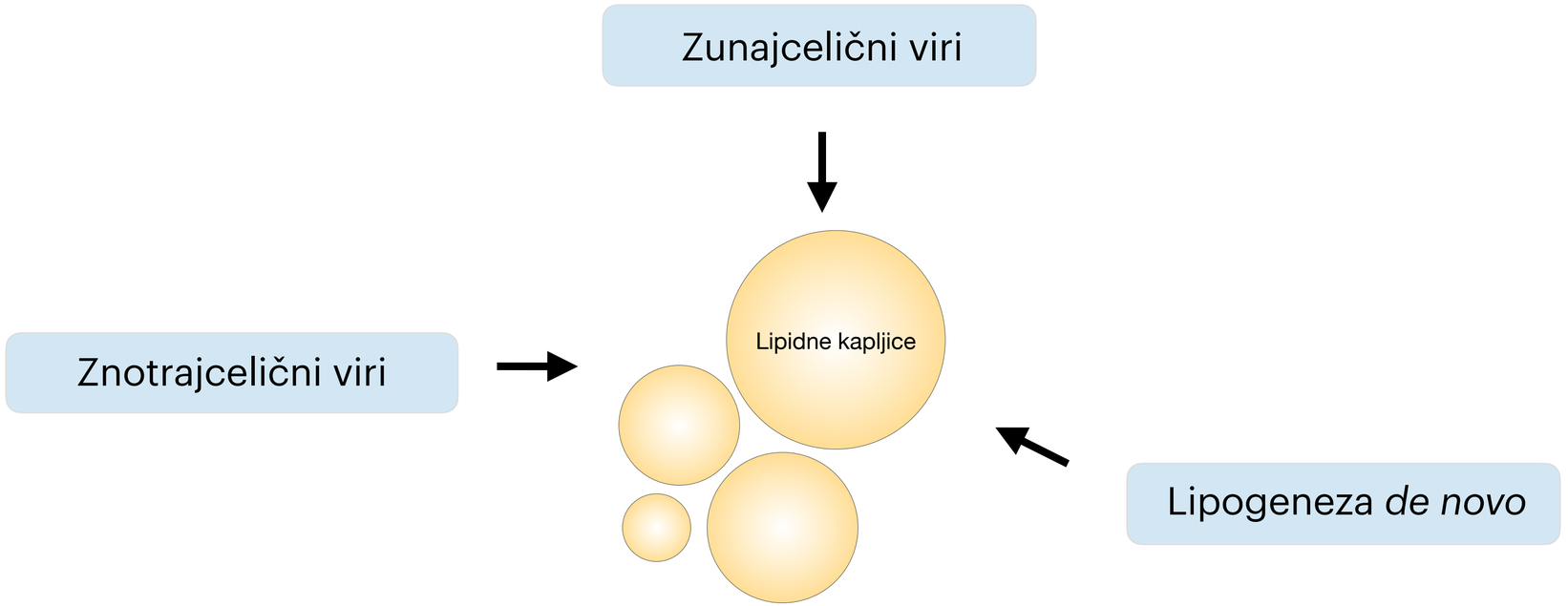


Petan et al., *Molecules* 2018

Ali obstaja centralni sistem za upravljanje z viri MK in njihovo presnovo?



Ali obstaja centralni sistem za upravljanje z viri MK in njihovo presnovo?



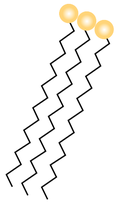
Maščobne celice hranijo maščobe v lipidnih kapljicah

Maščobne celice

Hursting et al, The Scientist 2015.

Trigliceridi so najbolj učinkovit način shranjevanja energije

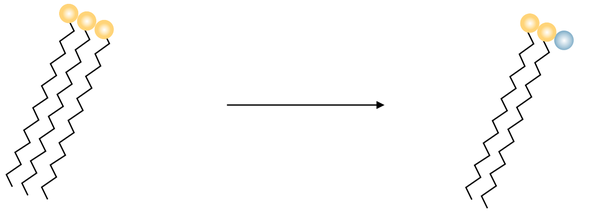
Lipoliza



Triacilglicerol
(TAG)

Trigliceridi so najbolj učinkovit način shranjevanja energije

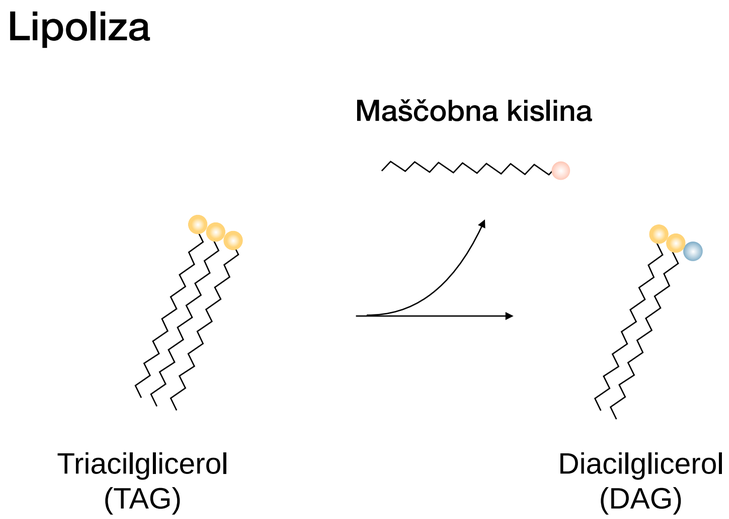
Lipoliza



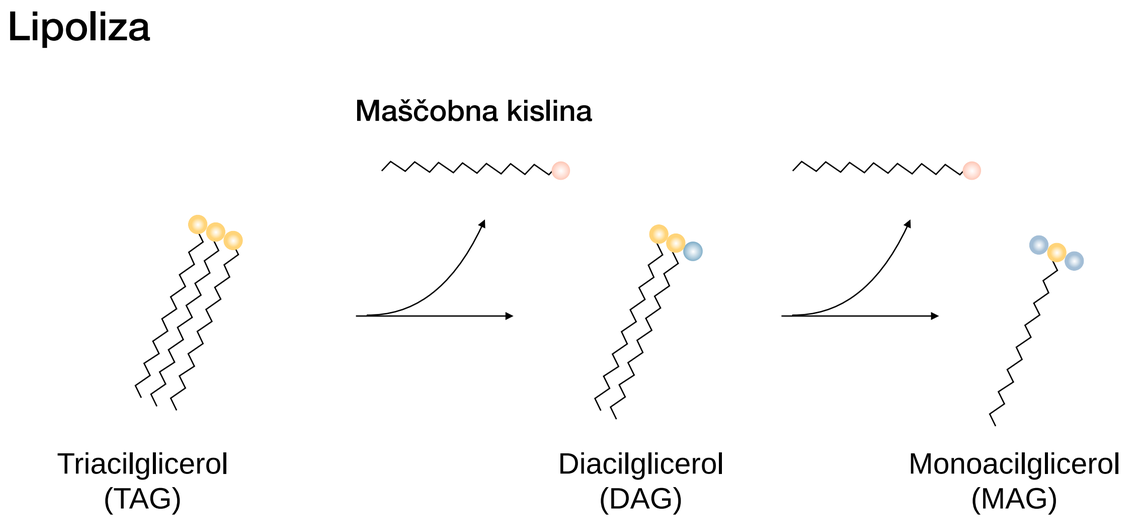
Triacilglicerol
(TAG)

Diacilglicerol
(DAG)

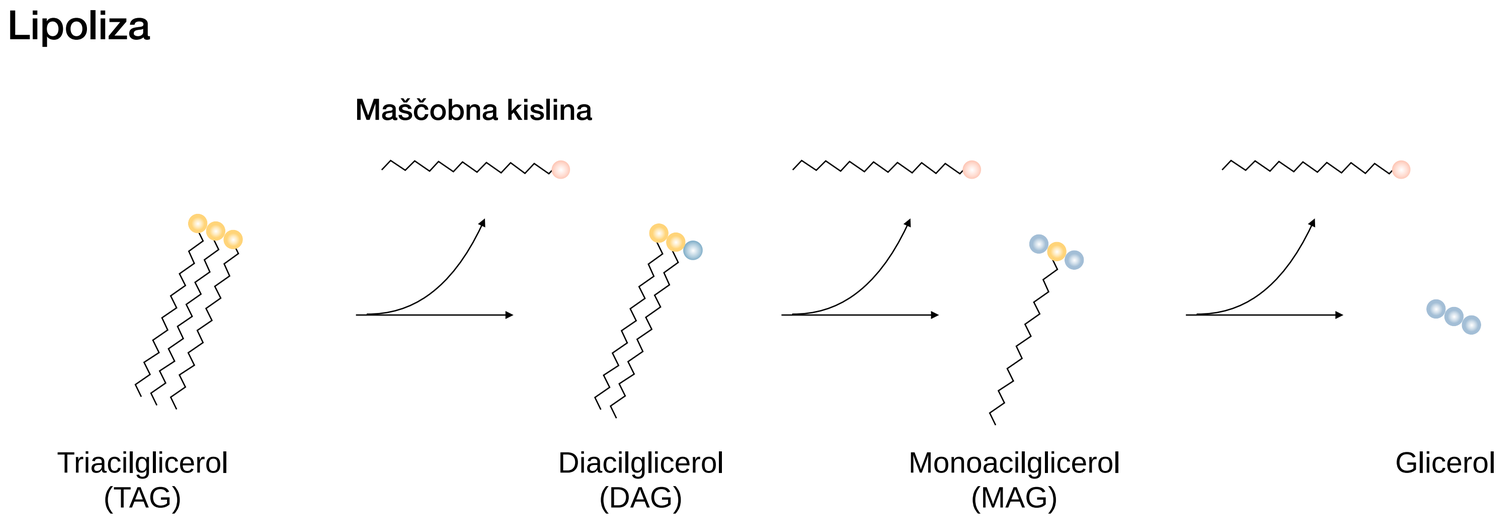
Trigliceridi so najbolj učinkovit način shranjevanja energije



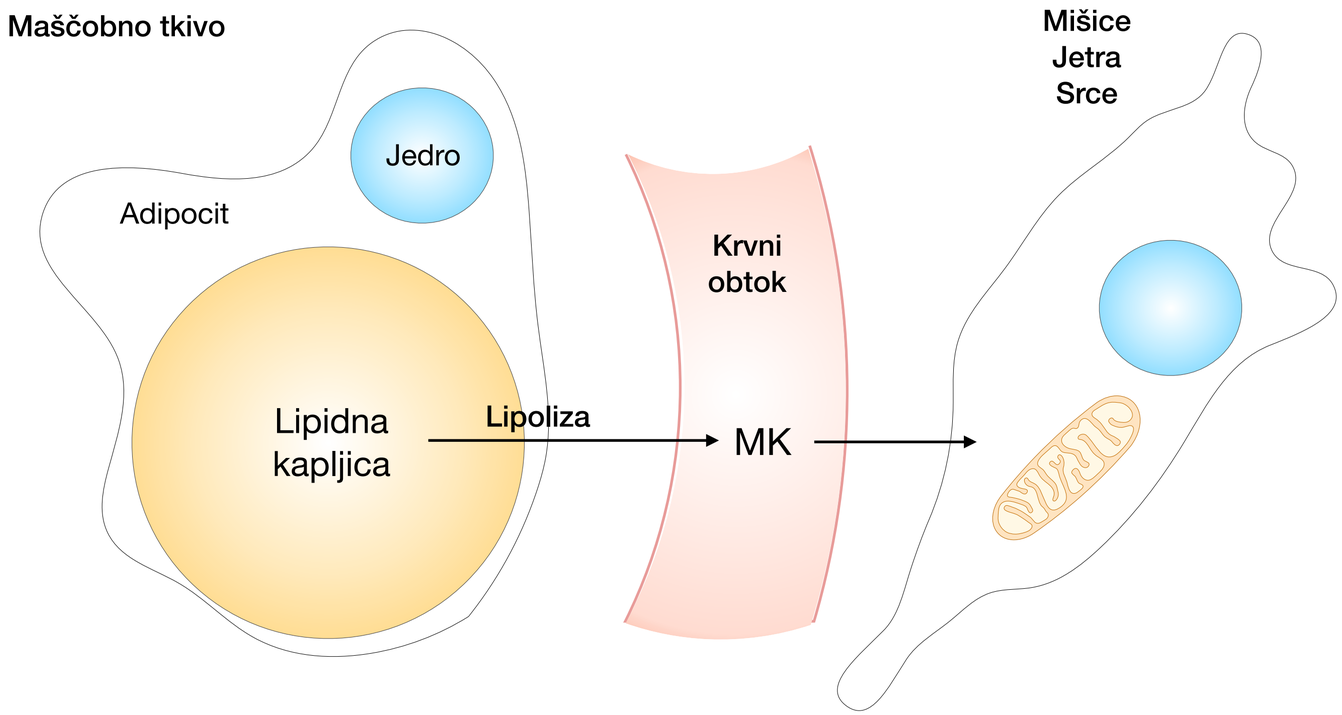
Trigliceridi so najbolj učinkovit način shranjevanja energije



Trigliceridi so najbolj učinkovit način shranjevanja energije

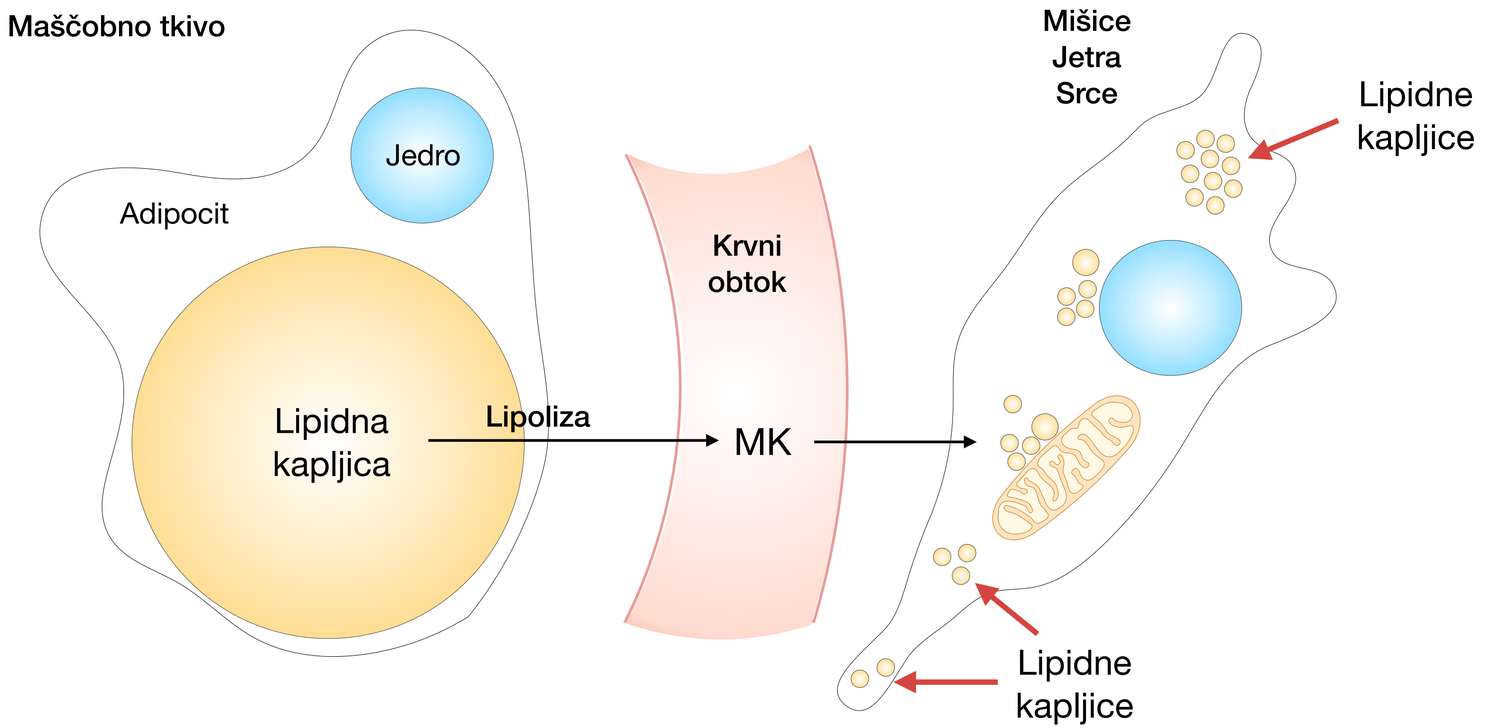


Adipociti sproščajo maščobne kisline v krvni obtok



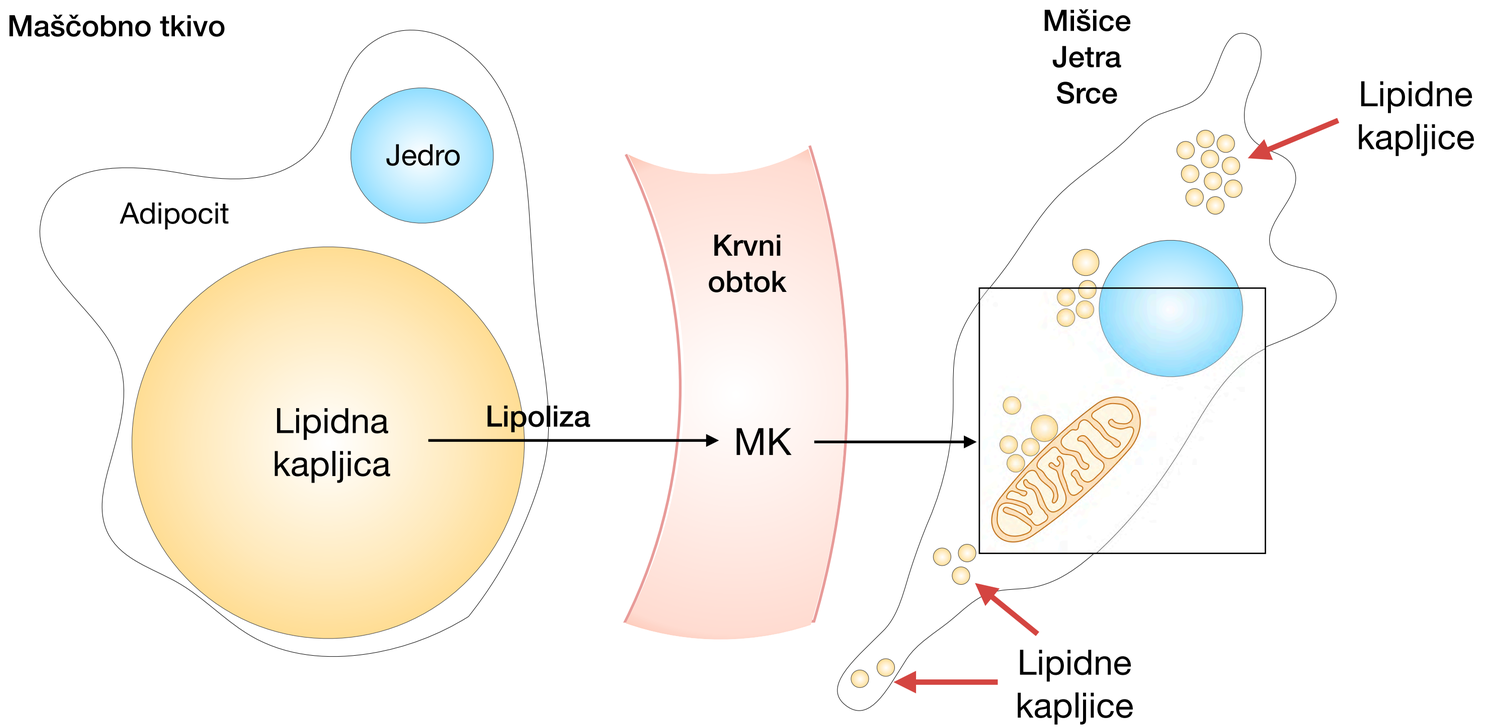
Zimmermann et al., *Science* 2004.
Schoiswohl et al., *J Lipid Res* 2010.
Haemmerle et al., *Nature Med* 2011.

Adipociti sproščajo maščobne kisline v krvni obtok



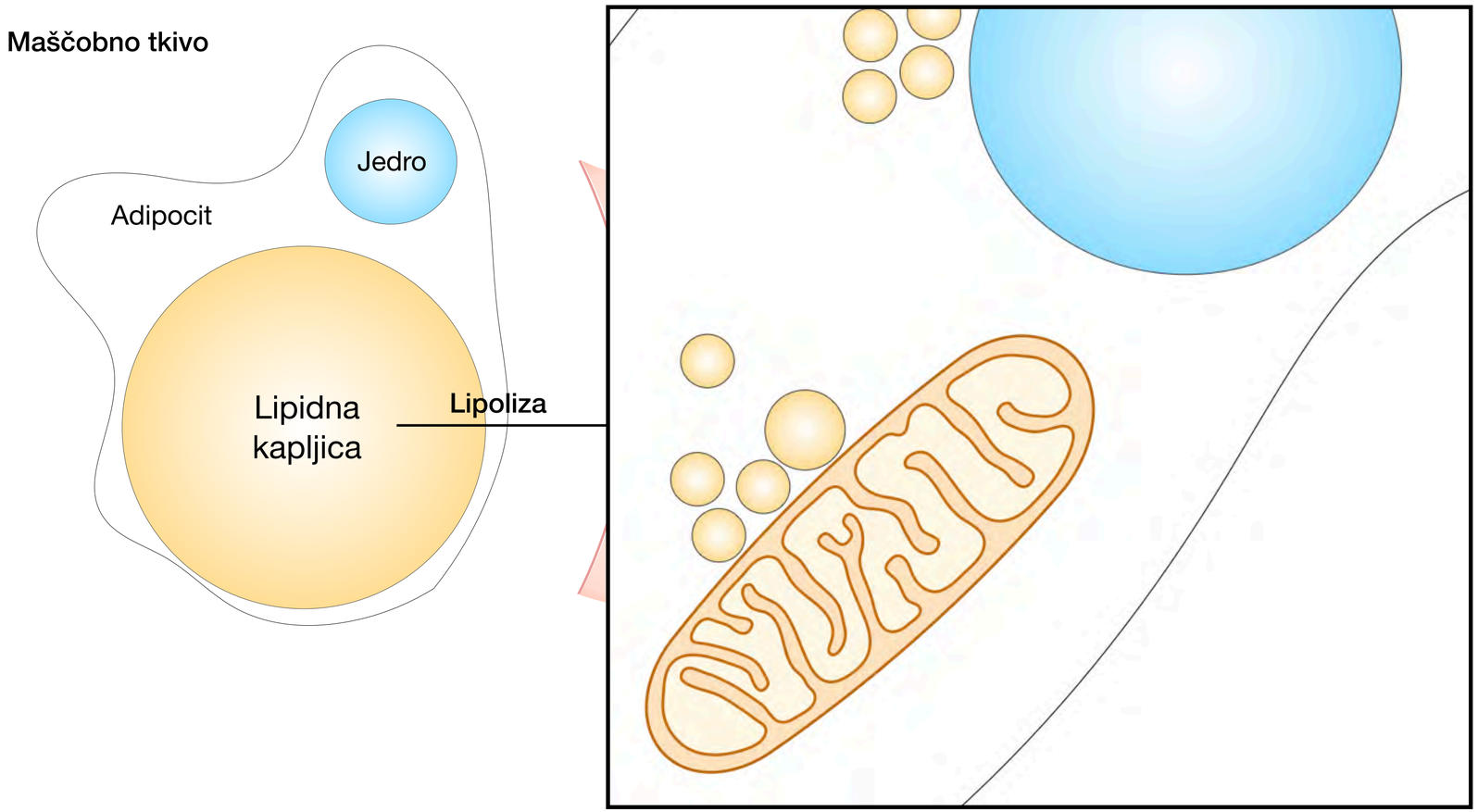
Zimmermann et al., *Science* 2004.
Schoiswohl et al., *J Lipid Res* 2010.
Haemmerle et al., *Nature Med* 2011.

Adipociti sproščajo maščobne kisline v krvni obtok



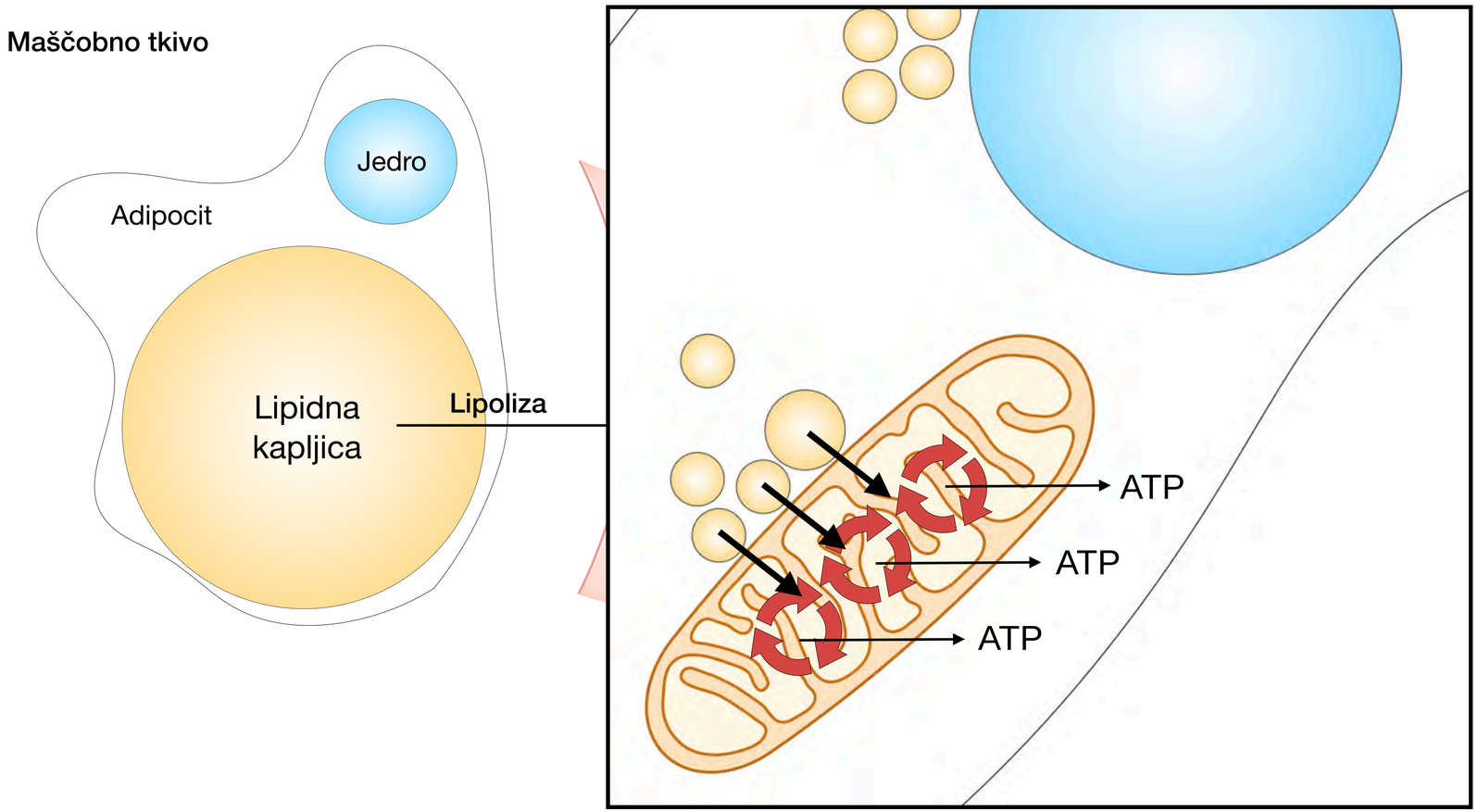
Zimmermann et al., *Science* 2004.
Schoiswohl et al., *J Lipid Res* 2010.
Haemmerle et al., *Nature Med* 2011.

Adipociti sproščajo maščobne kisline v krvni obtok



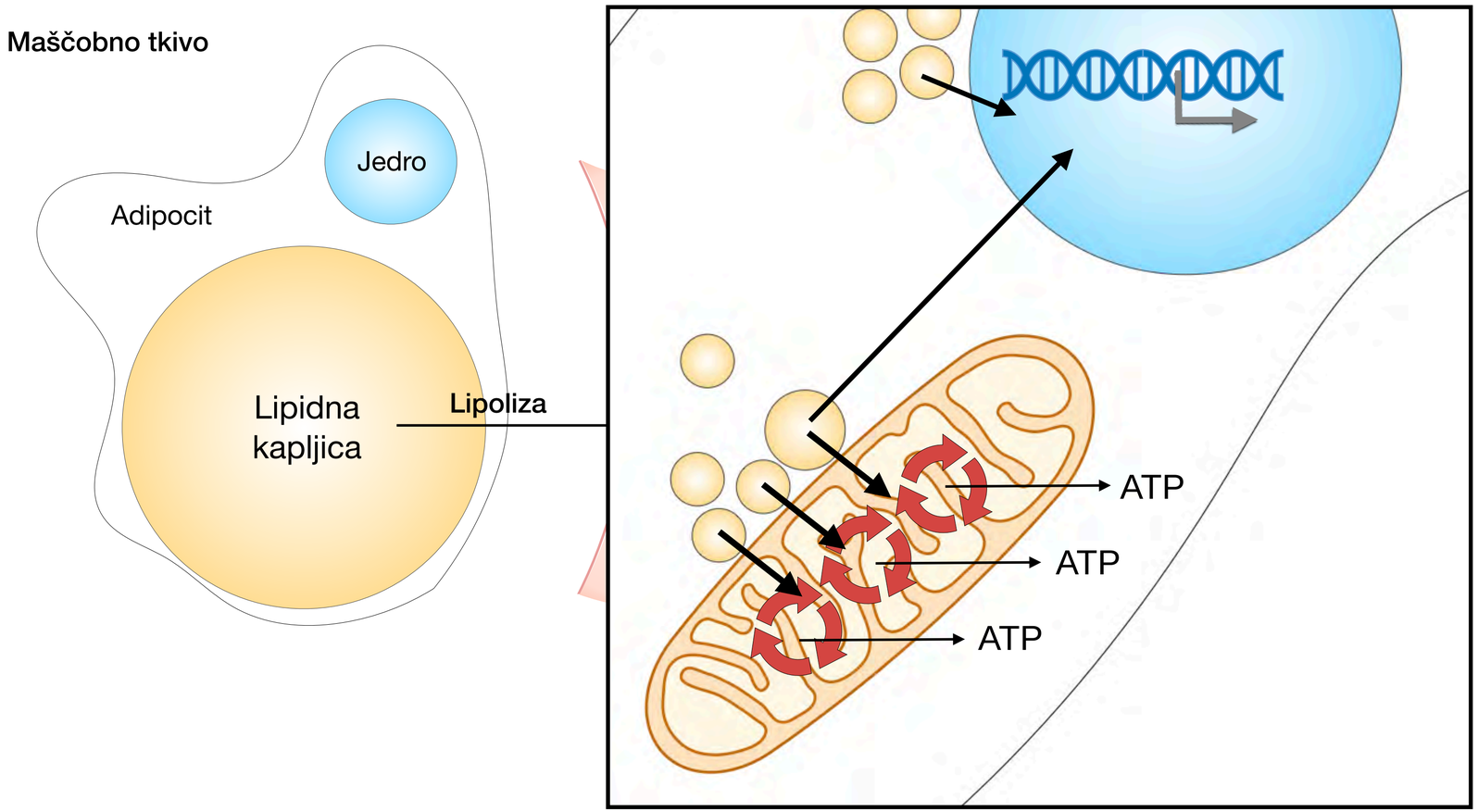
Zimmermann et al., *Science* 2004.
Schoiswohl et al., *J Lipid Res* 2010.
Haemmerle et al., *Nature Med* 2011.

Adipociti sproščajo maščobne kisline v krvni obtok



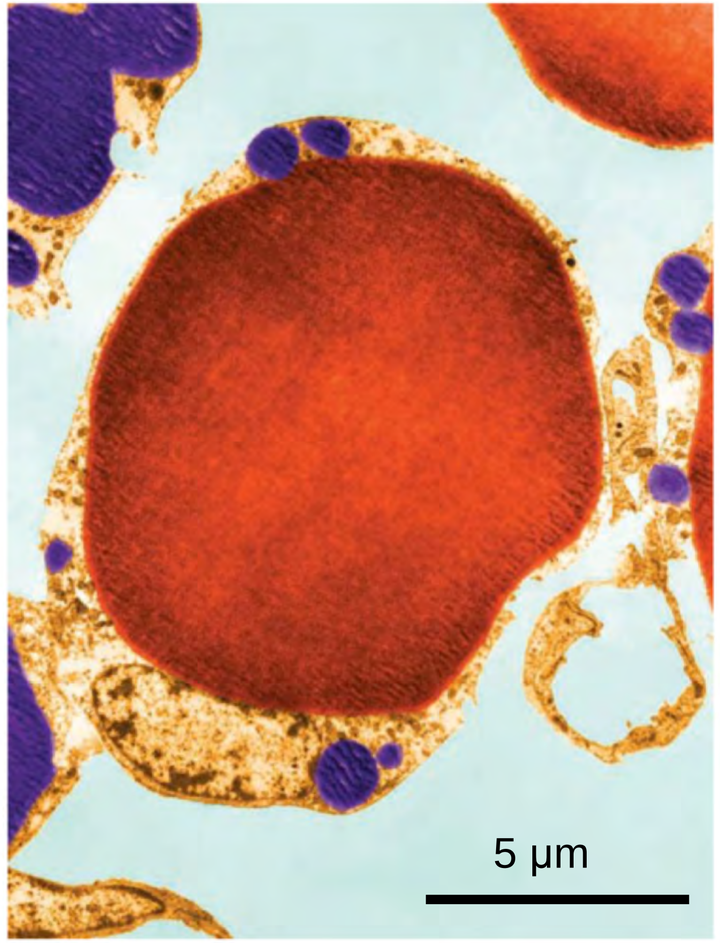
Zimmermann et al., *Science* 2004.
Schoiswohl et al., *J Lipid Res* 2010.
Haemmerle et al., *Nature Med* 2011.

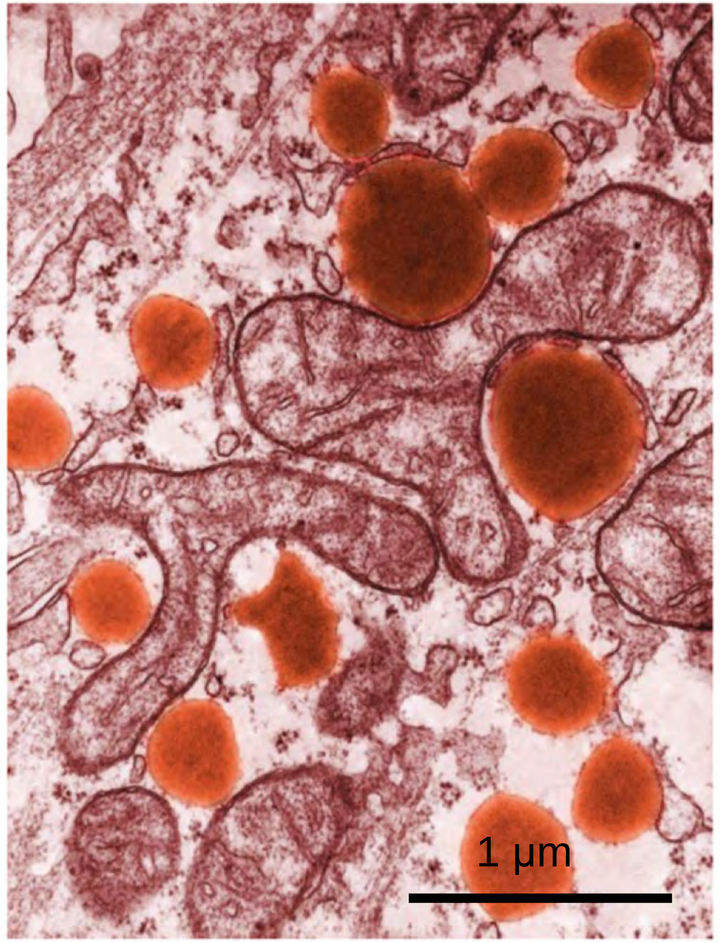
Adipociti sproščajo maščobne kisline v krvni obtok



Zimmermann et al., *Science* 2004.
Schoiswohl et al., *J Lipid Res* 2010.
Haemmerle et al., *Nature Med* 2011.

Lipidne kapljice so prisotne tudi v drugih tkivih

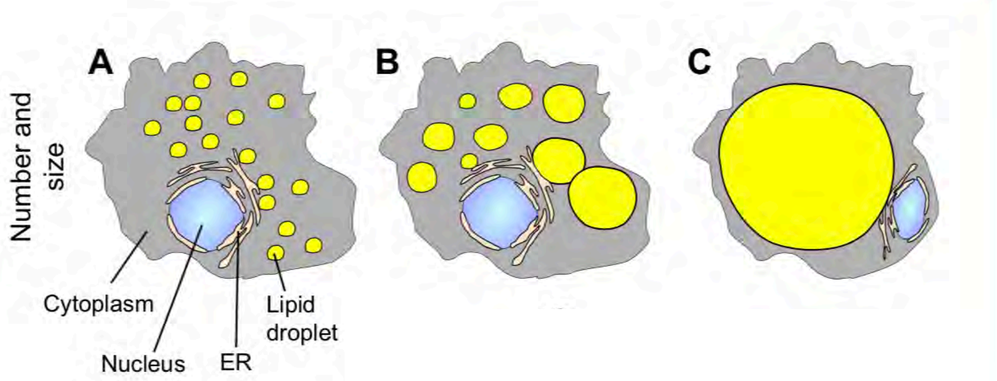




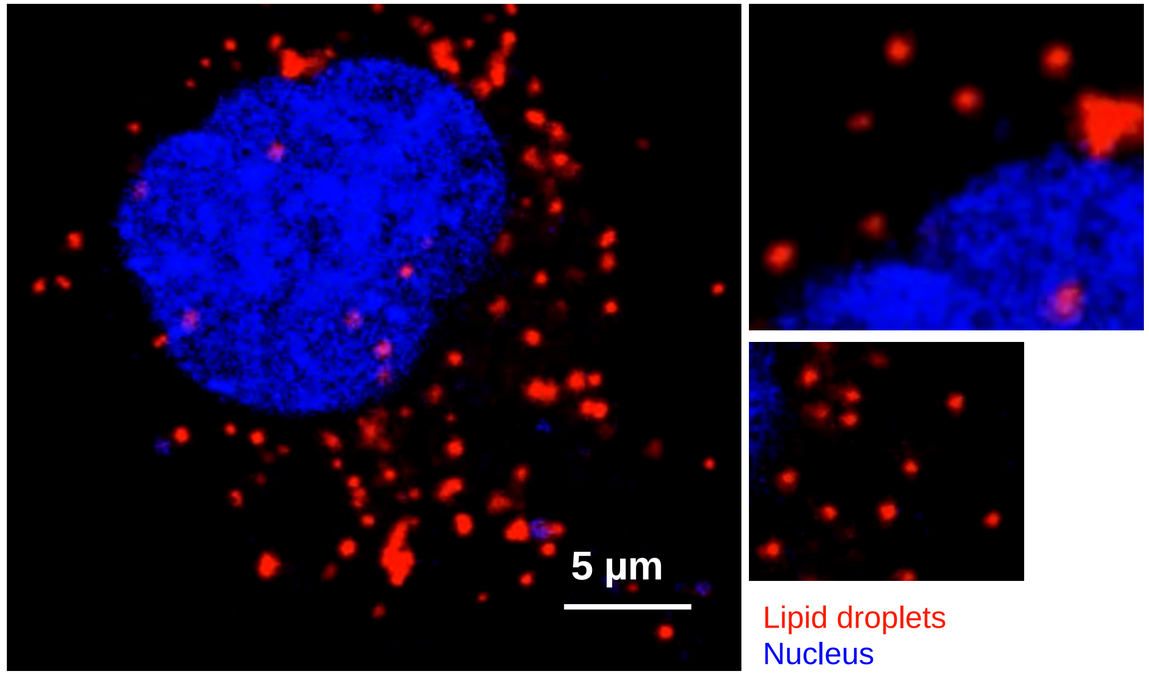
Hursting et al, The Scientist 2015.

V večini celic so lipidne kapljice majhne, številčne in zelo dinamične

Number and size heterogeneity



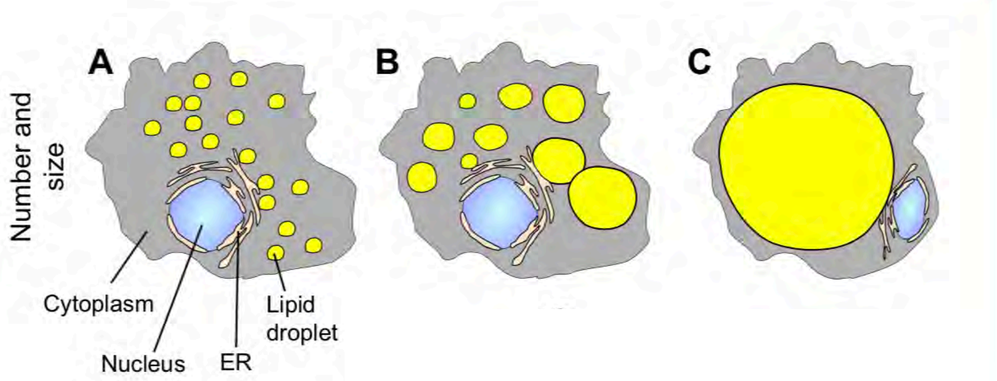
Starving fibroblasts



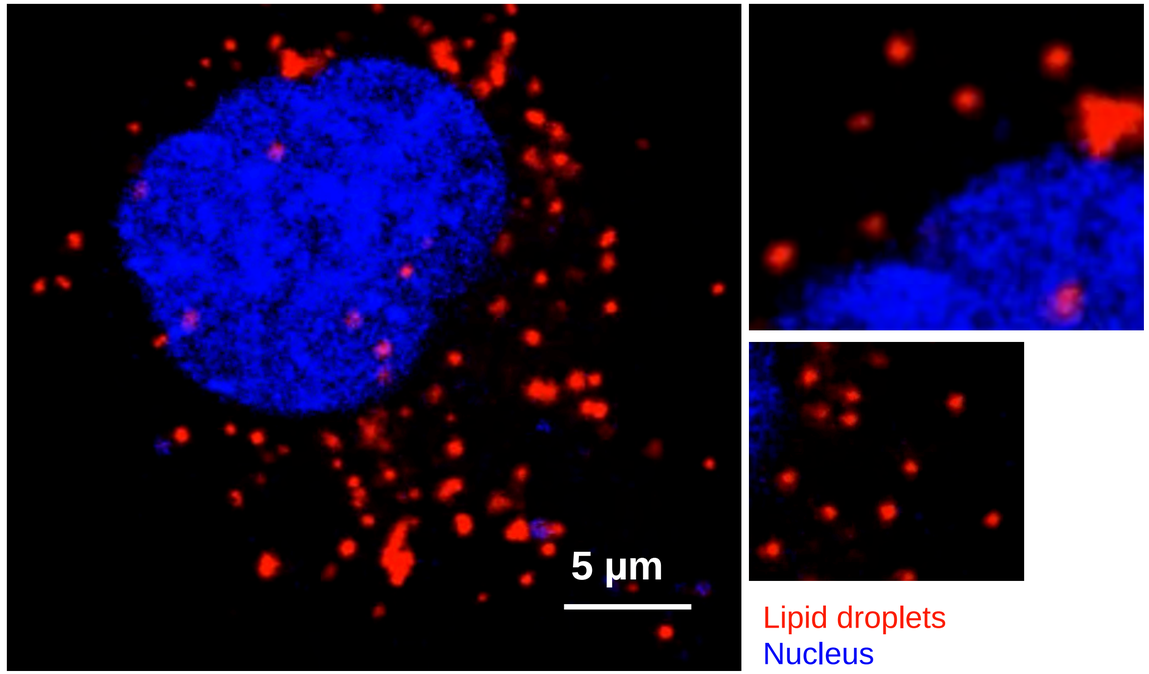
Thiam et al., J Cell Sci 2017.
Herms et al., Nat Commun 2015
Hursting et al, The Scientist 2015

V večini celic so lipidne kapljice majhne, številčne in zelo dinamične

Number and size heterogeneity

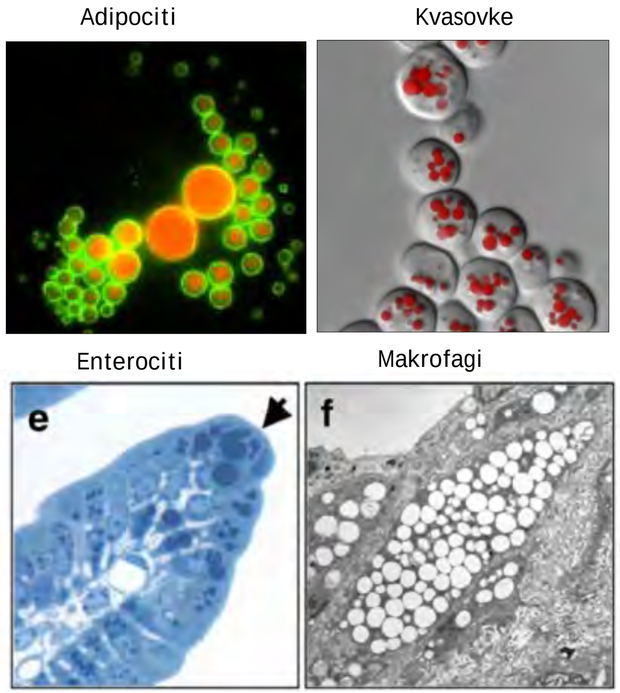


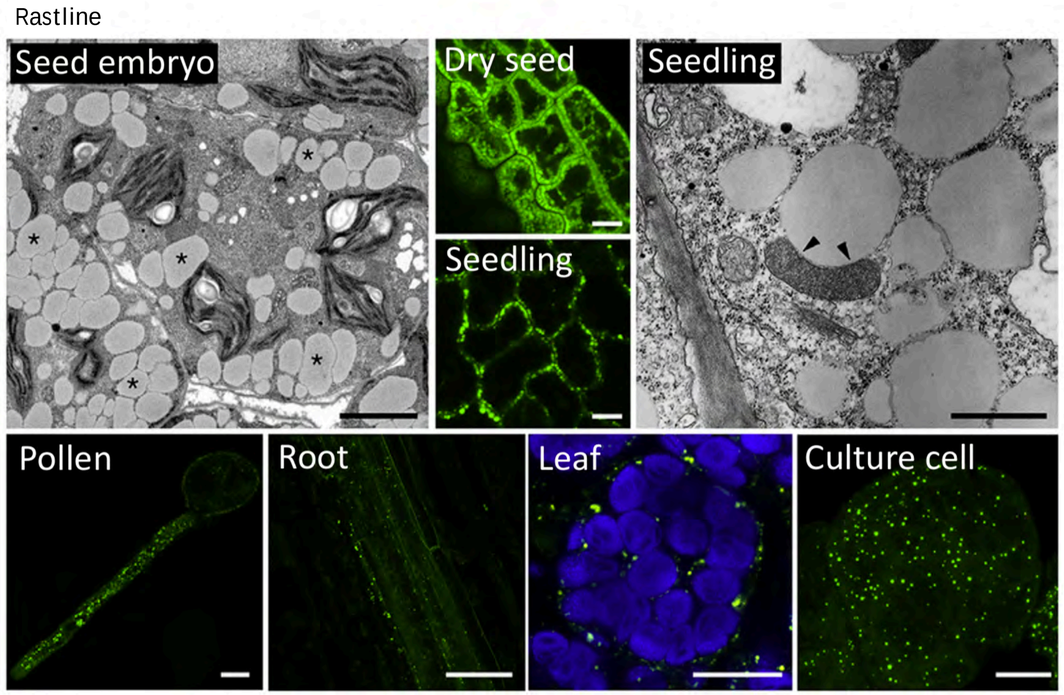
Starving fibroblasts



Thiam et al., J Cell Sci 2017.
Herms et al., Nat Commun 2015
Hursting et al, The Scientist 2015

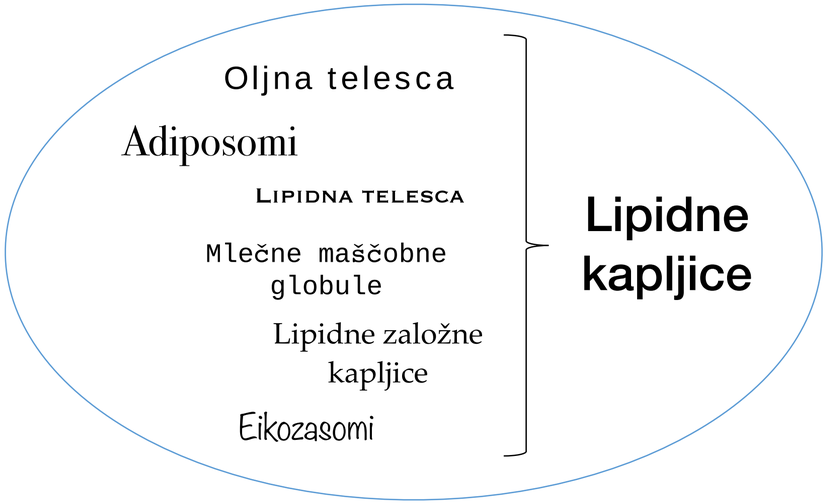
Lipidne kapljice so prisotne v vseh evkariontskih celicah





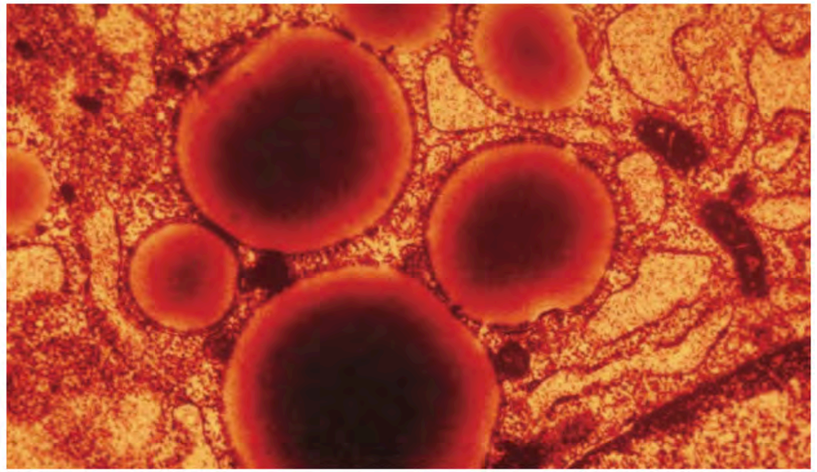
Dawn Brasaemle
Sepp Kowhlwein
Walther & Farese
Pyc et al., *Trends Plant Sci.* 2017.

Lipidne kapljice niso le inertne zaloge maščob



Lipidne kapljice niso le inertne zaloge maščob

3 MARCH 2006 VOL 311 **SCIENCE** www.sciencemag.org
Published by AAAS



CELL BIOLOGY

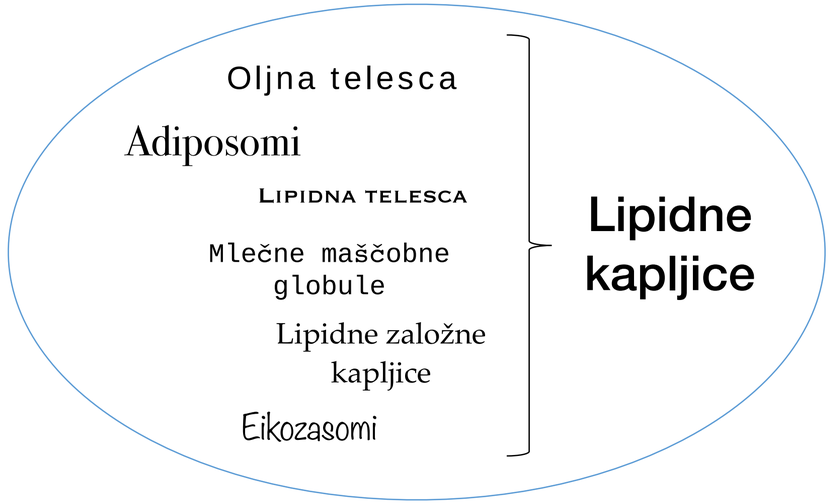
Great Balls of Fat

Lipid droplets, long-ignored globules inside cells, are earning recognition as possible organelles involved in cholesterol synthesis and much more

In the breast cells that produce milk, they're called milk fat globules. In plants, they go by the name oil bodies. In fruit flies, lipid storage droplets. Yeast, lipid particles. Cell biologist Richard Anderson prefers the name adiposomes. Immunologist Peter

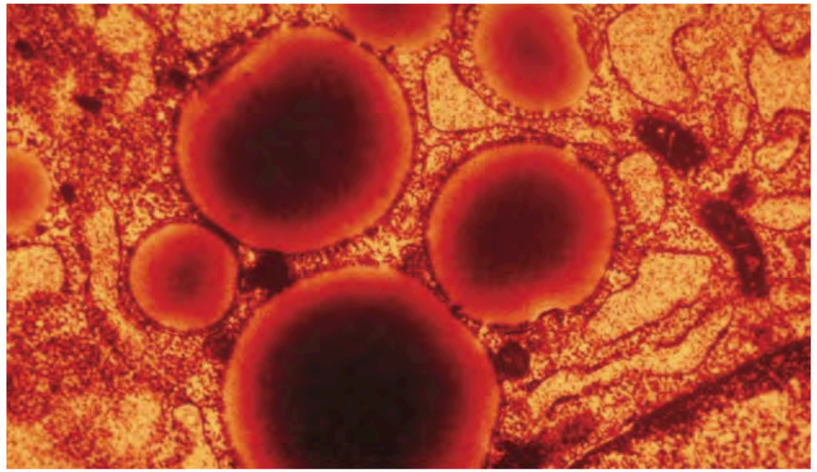
eases, diabetes, cardiovascular trouble, and liver problems.

This is a far cry from earlier perceptions of lipid droplets, the name most scientists use for the particles. Biologists once considered lipid droplets just inert storage vessels for energy-



Lipidne kapljice niso le inertne zaloge maščob

3 MARCH 2006 VOL 311 **SCIENCE** www.sciencemag.org
Published by AAAS



CELL BIOLOGY

Great Balls of Fat

Lipid droplets, long-ignored globules inside cells, are earning recognition as possible organelles involved in cholesterol synthesis and much more

In the breast cells that produce milk, they're called milk fat globules. In plants, they go by the name oil bodies. In fruit flies, lipid storage droplets. Yeast, lipid particles. Cell biologist Richard Anderson prefers the name adiposomes. Immunologist Peter

eases, diabetes, cardiovascular trouble, and liver problems.

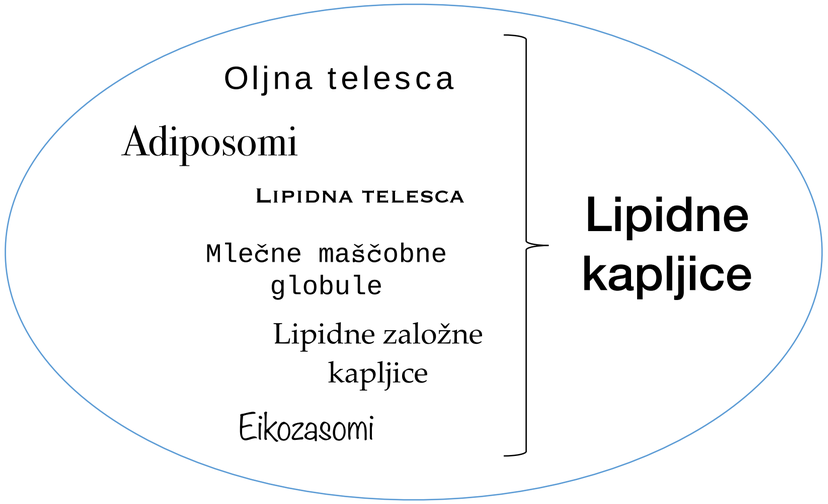
This is a far cry from earlier perceptions of lipid droplets, the name most scientists use for the particles. Biologists once considered lipid droplets just inert storage vessels for energy-

Leading Edge
Essay
Cell *139*, November 25, 2009 ©2009 Elsevier Inc.
Cell

Lipid Droplets Finally Get a Little R-E-S-P-E-C-T

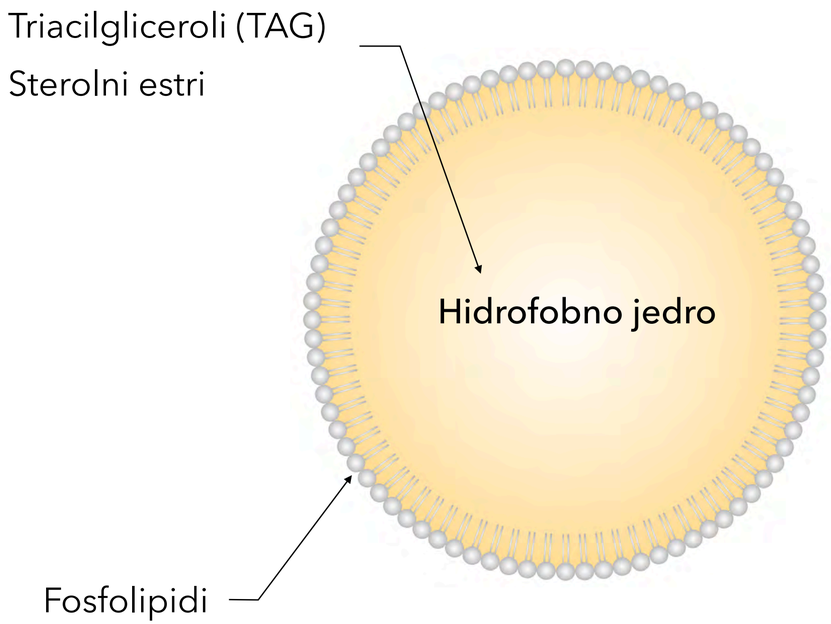
Robert V. Farese, Jr.[1,2,*] **and Tobias C. Walther**[3,*]
[1]Gladstone Institute of Cardiovascular Disease
[2]Departments of Medicine and Biochemistry & Biophysics, University of California
San Francisco, CA 94158, USA
[3]Organelle Architecture and Dynamics, Max Planck Institute of Biochemistry, Martinsried 82152, Germany
*Correspondence: bfarese@gladstone.ucsf.edu (R.V.F.), twalther@biochem.mpg.de (T.C.W.)
DOI 10.1016/j.cell.2009.11.005

Long underappreciated as important cellular organelles, lipid droplets are finally being recognized as dynamic structures with a complex and interesting biology. In light of this newfound respect, we discuss emerging views on lipid droplet biology and speculate on the major advances to come.

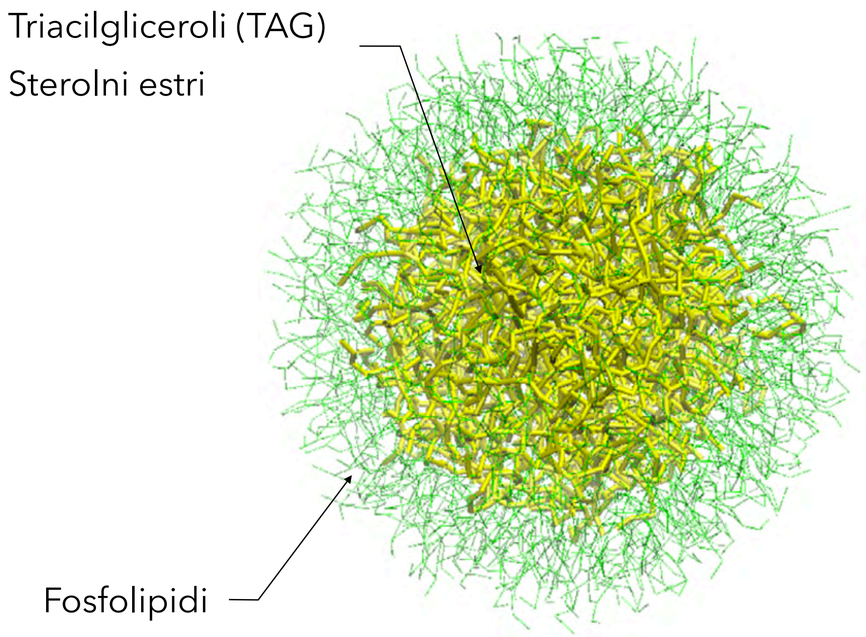


Lipidne kapljice so organeli

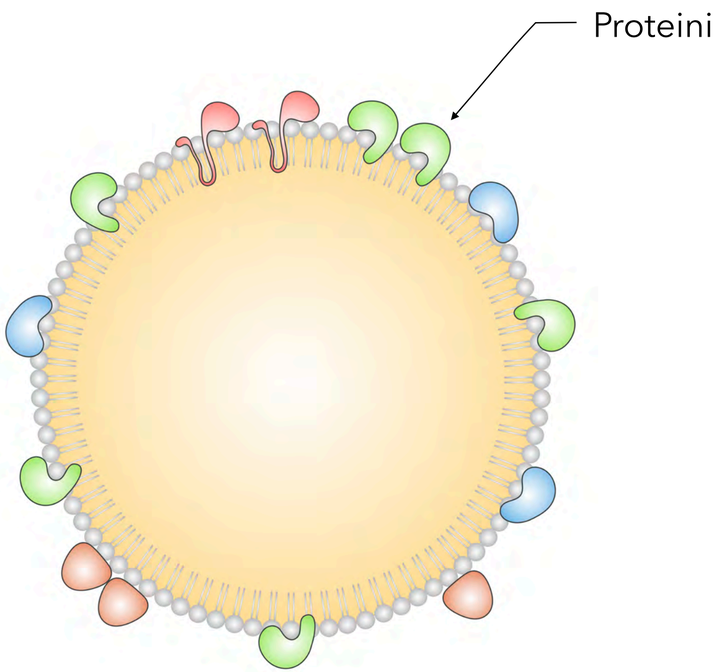
Lipidne kapljice so organeli



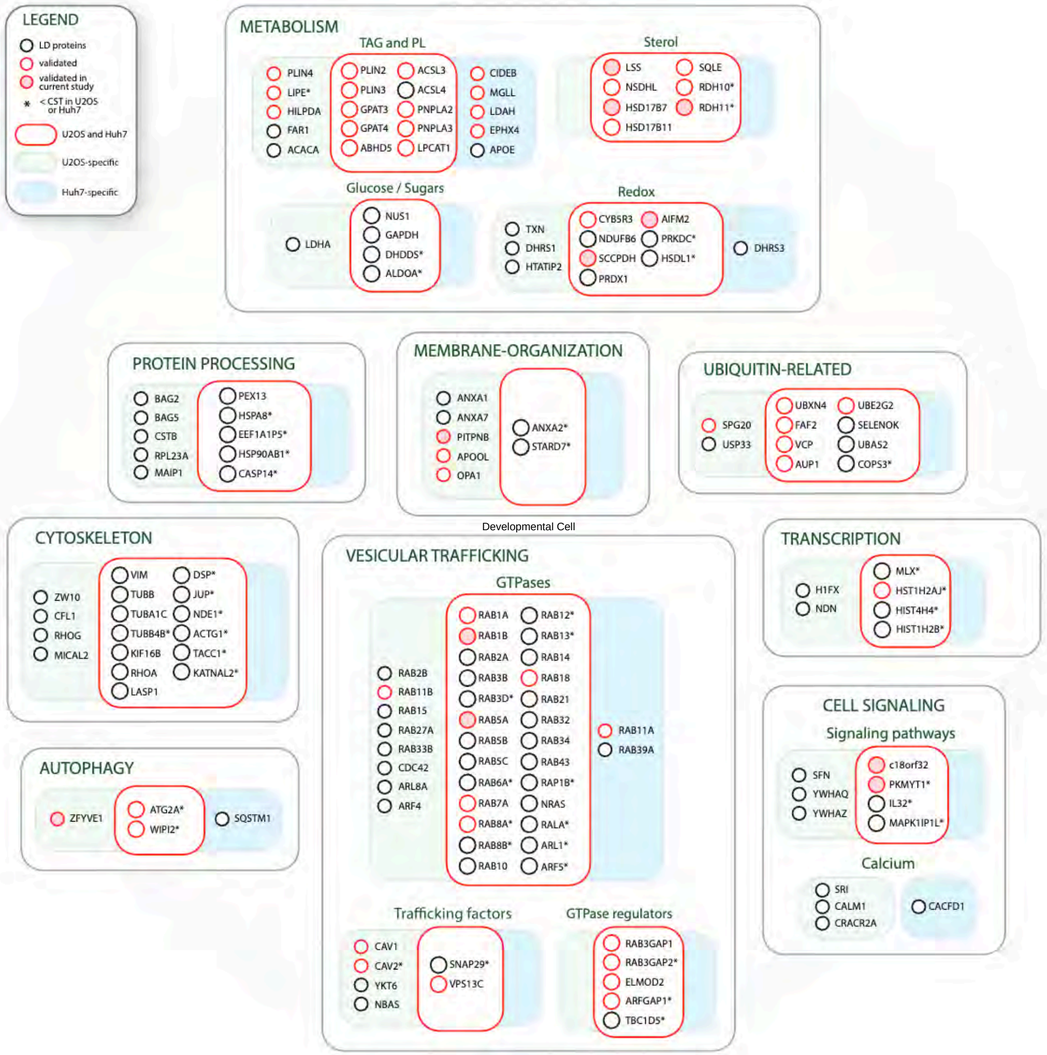
Lipidne kapljice so organeli



Številni proteini so vgrajeni v površinski fosfolipidni sloj

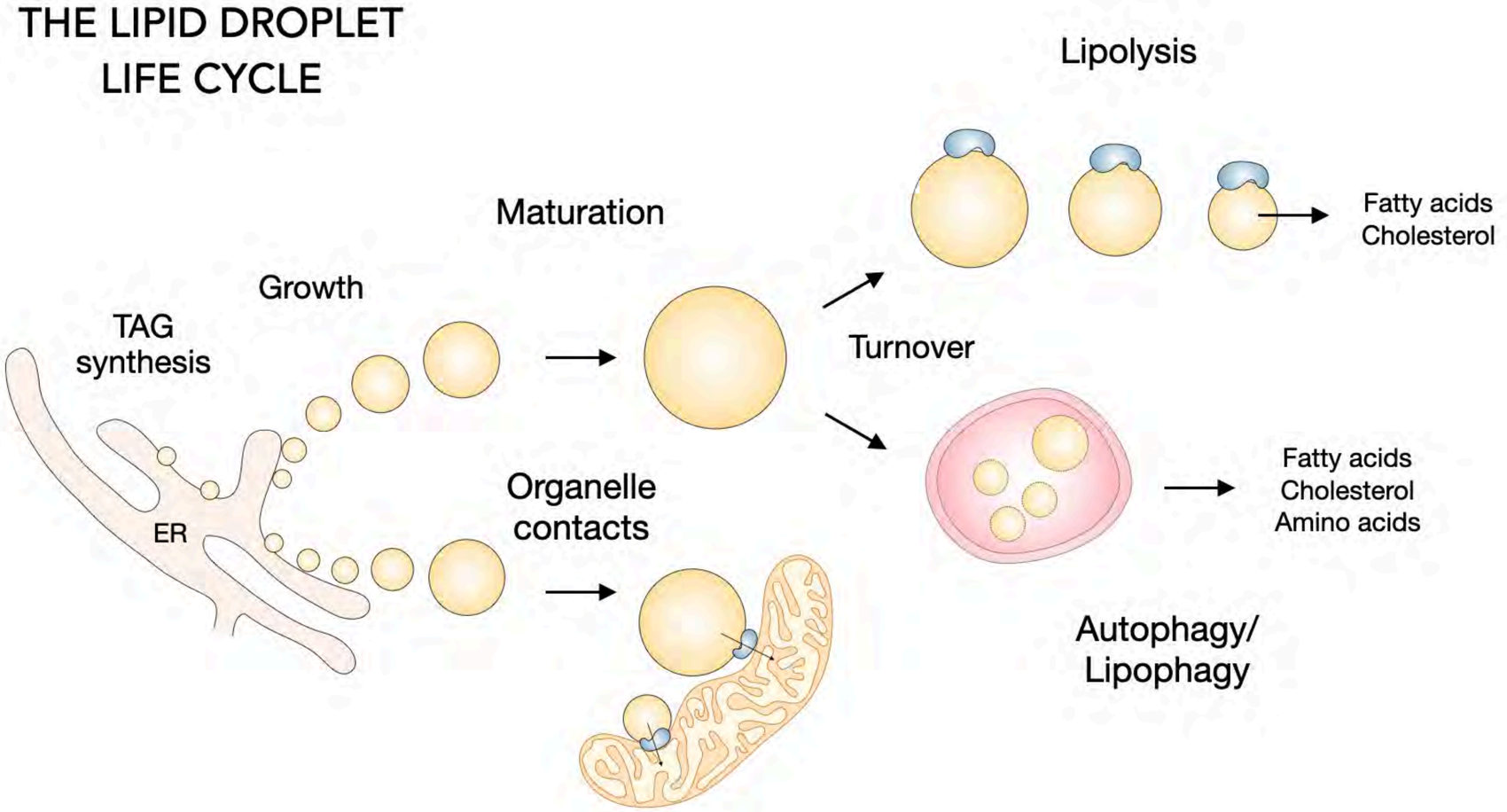


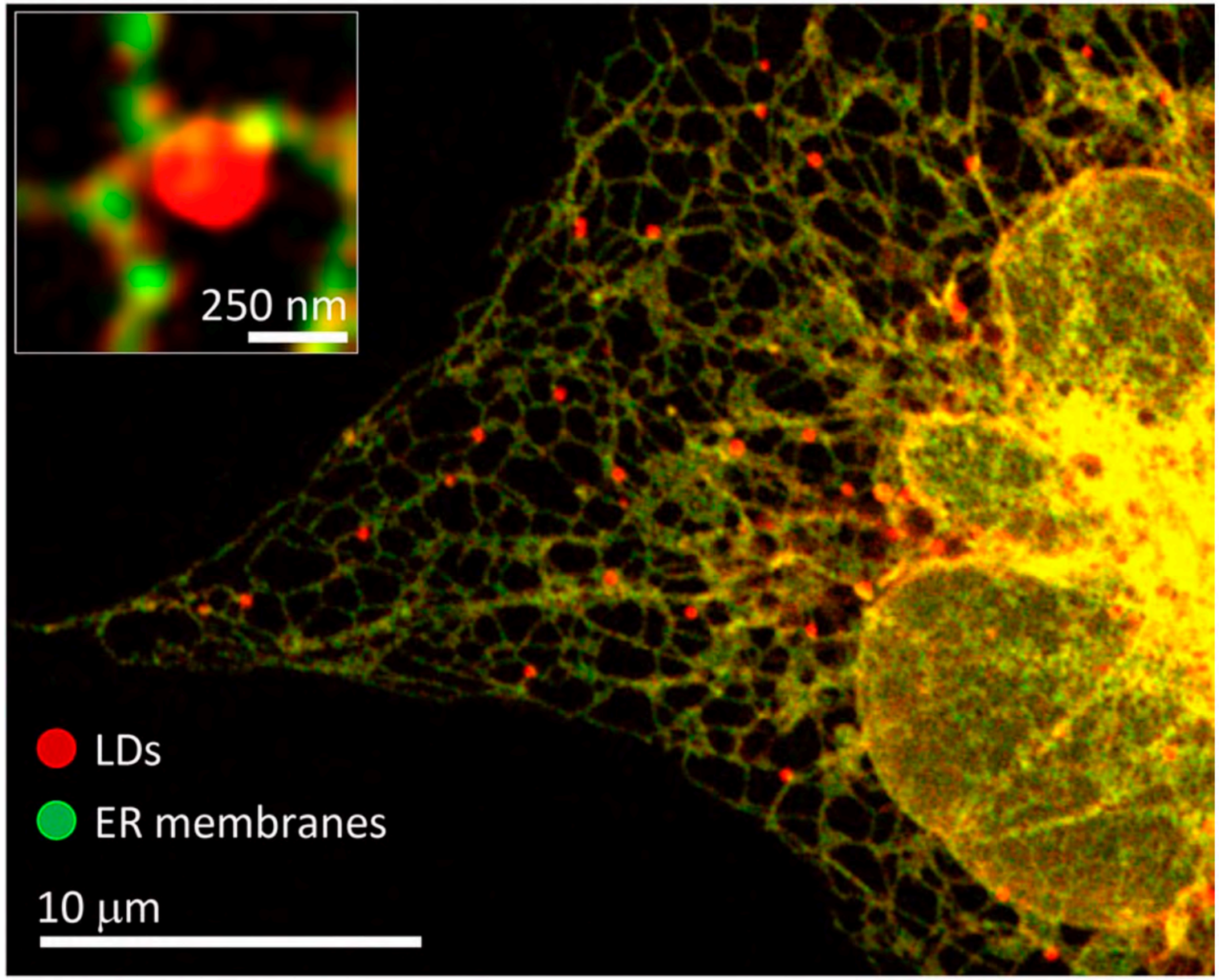
Proteini LK imajo zelo raznolike funkcije



Developmental Cell

Bersuker et al Dev Cell 2018

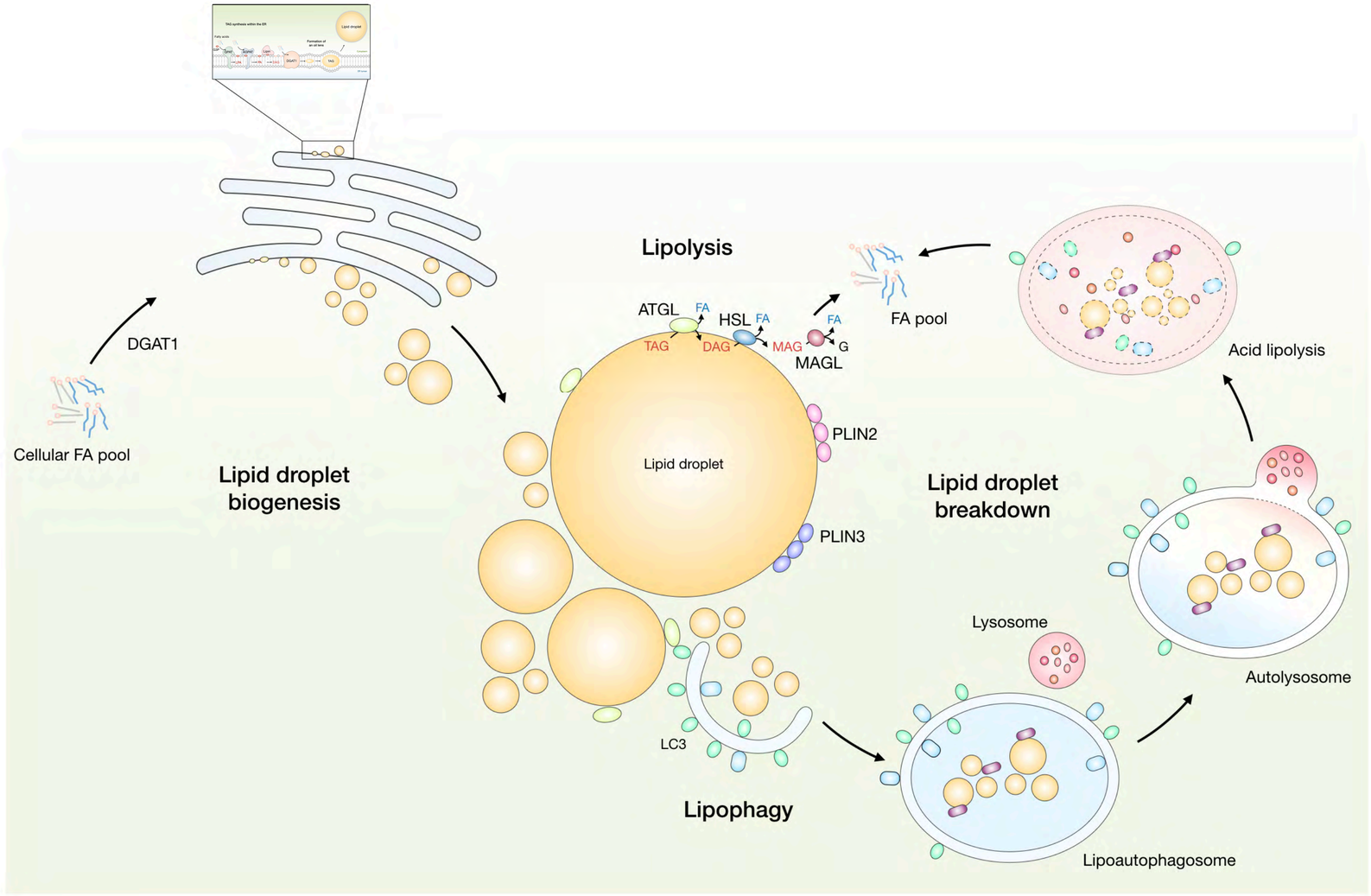

THE LIPID DROPLET
LIFE CYCLE
Lipolysis
Maturation
Growth
TAG
synthesis
Fatty acids
Cholesterol
Turnover
ER
Organelle
contacts
Fatty acids
Cholesterol
Amino acids
Autophagy/
Lipophagy



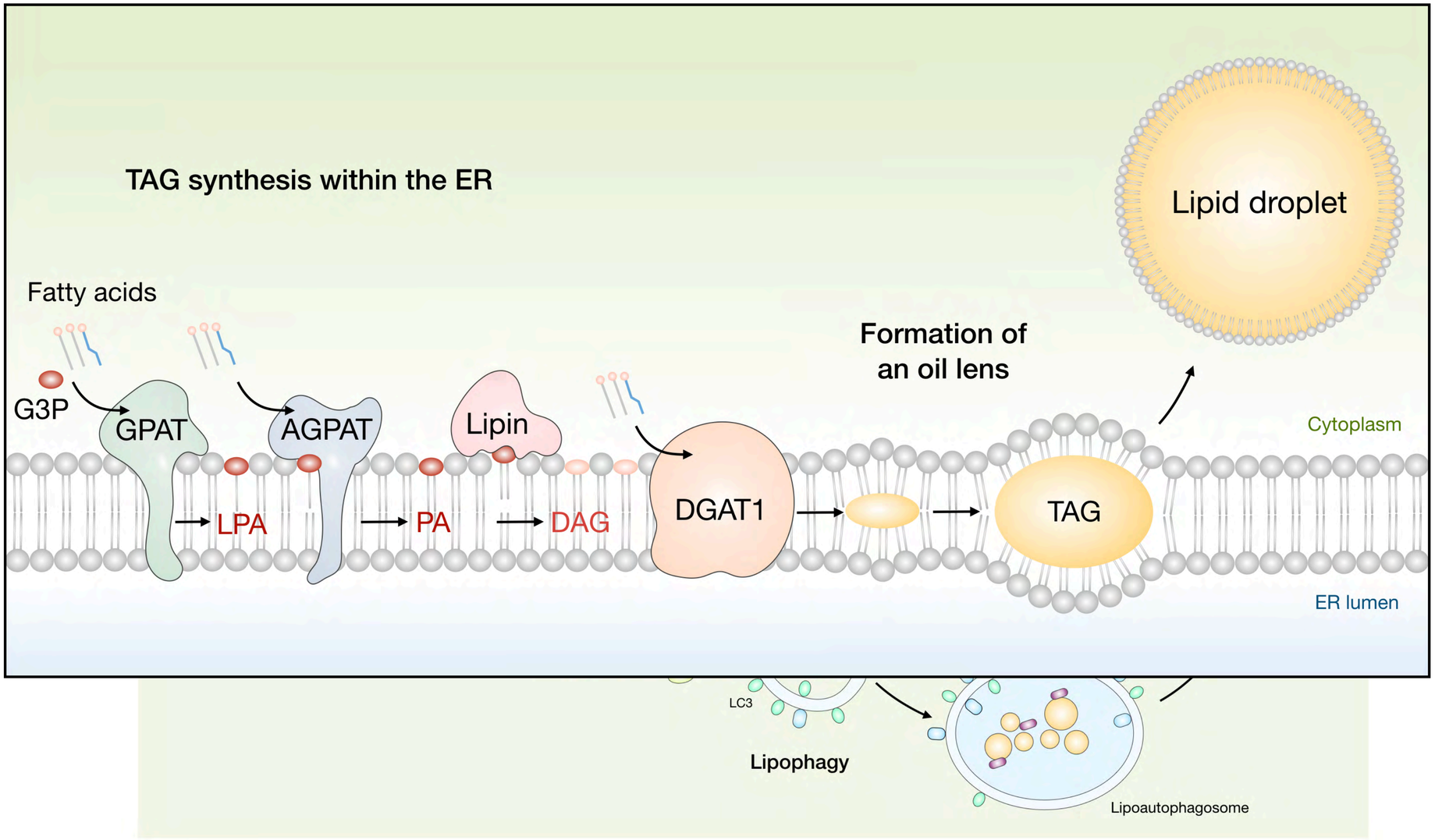
Nastanek novih LK v celici – le nekaj minut po dodatku maščobnih kislin

Pol et al., *J Cell Blol.* 2014.

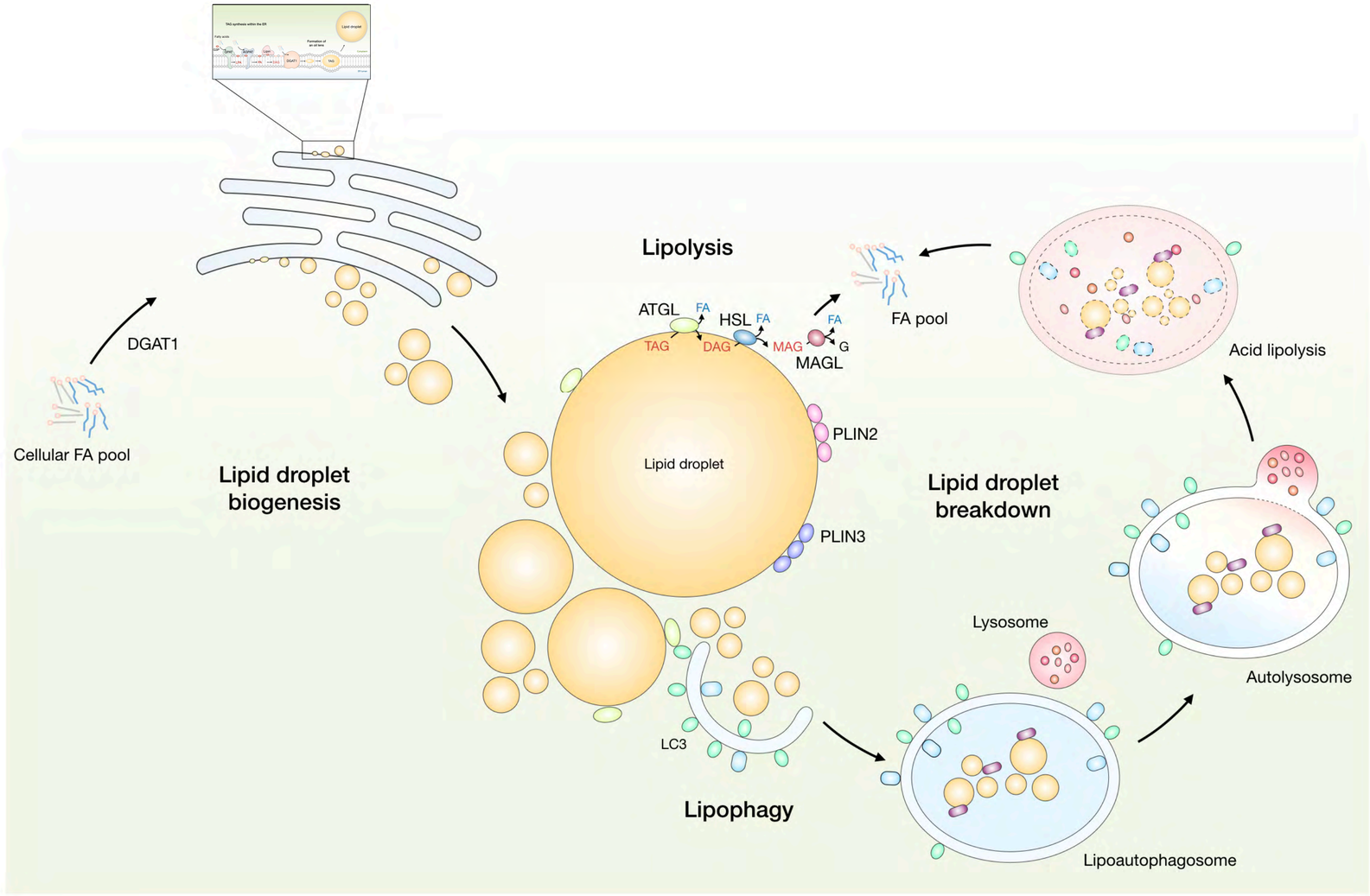
Biosinteza in razgradnja lipidnih kapljic



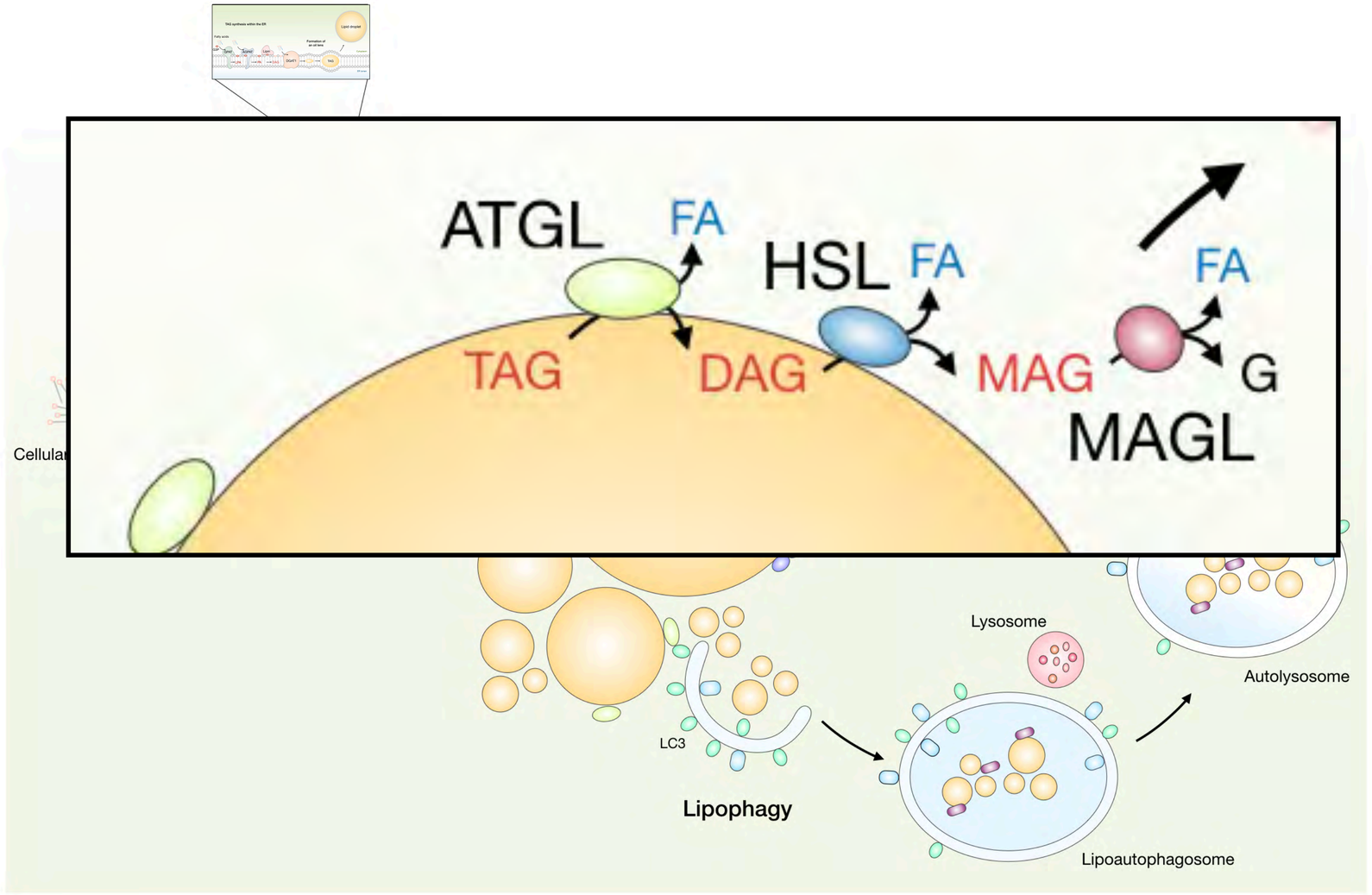
Biosinteza in razgradnja lipidnih kapljic



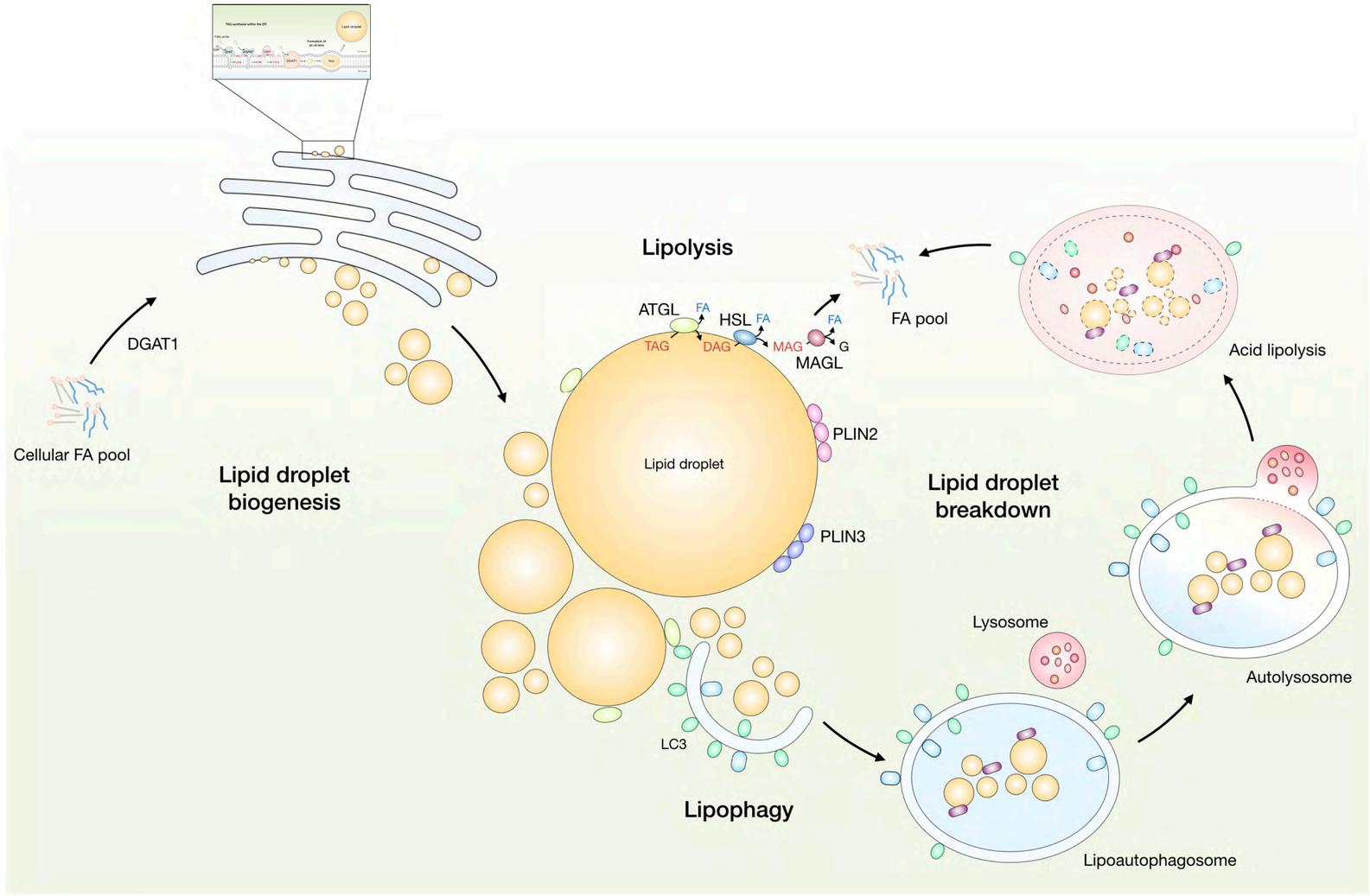
Biosinteza in razgradnja lipidnih kapljic



Biosinteza in razgradnja lipidnih kapljic

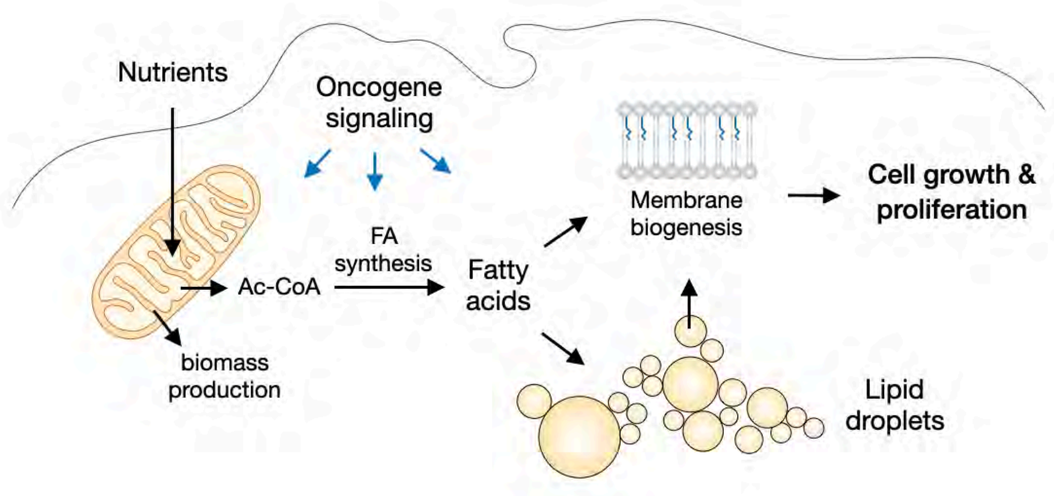


Biosinteza in razgradnja lipidnih kapljic



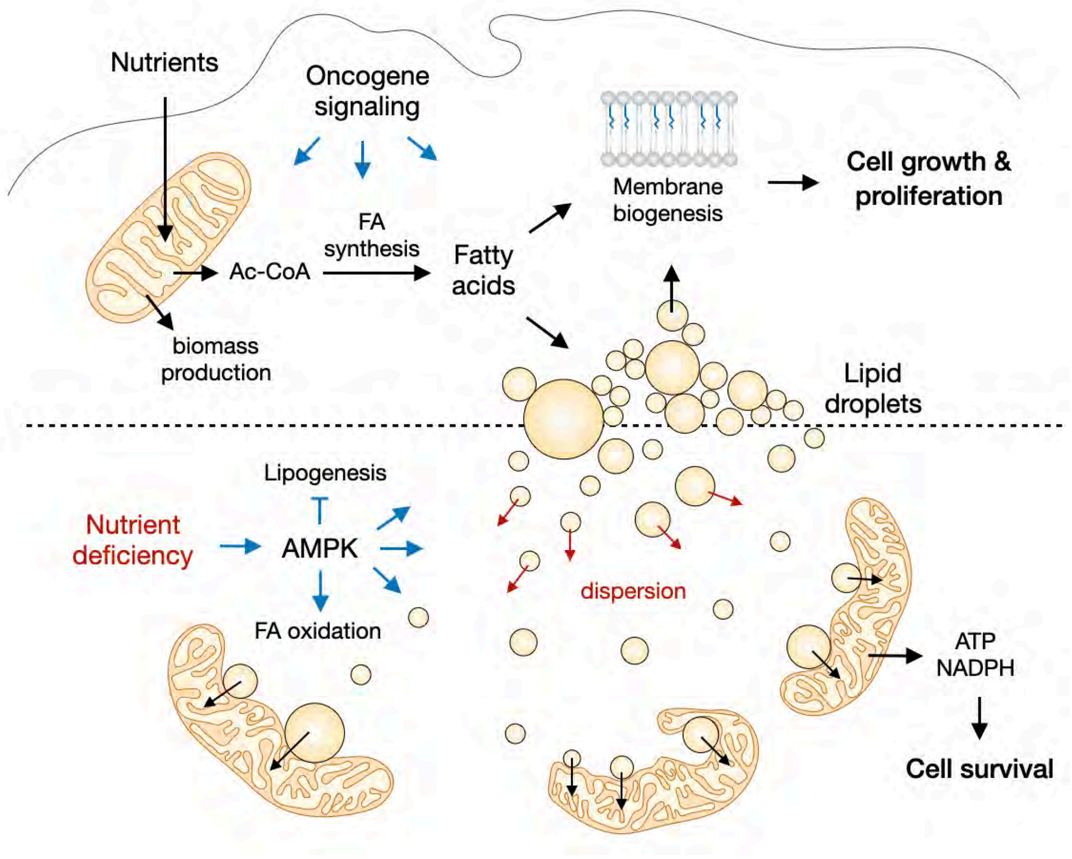
Kakšne so vloge kapljic v celici?

Lipidne kapljice delujejo kot pufri za maščobne kisline



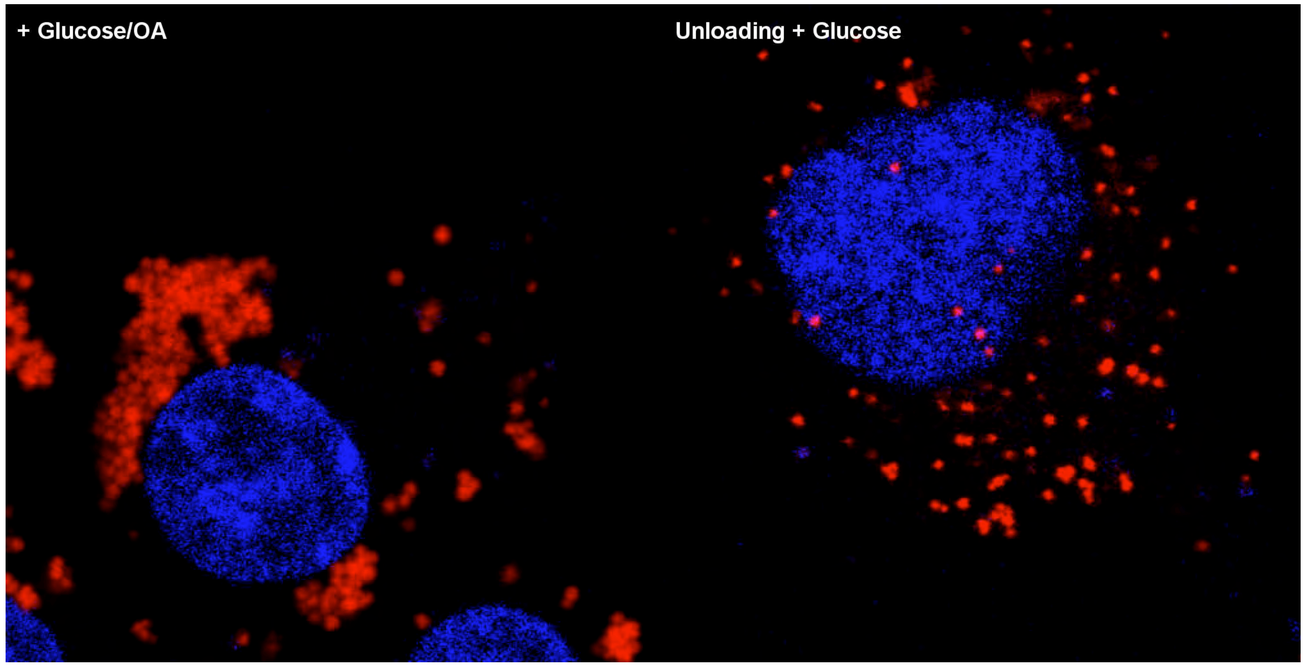
Petan, *Rev Phys Pharm Biochem* 2020

Lipidne kapljice delujejo kot pufri za maščobne kisline



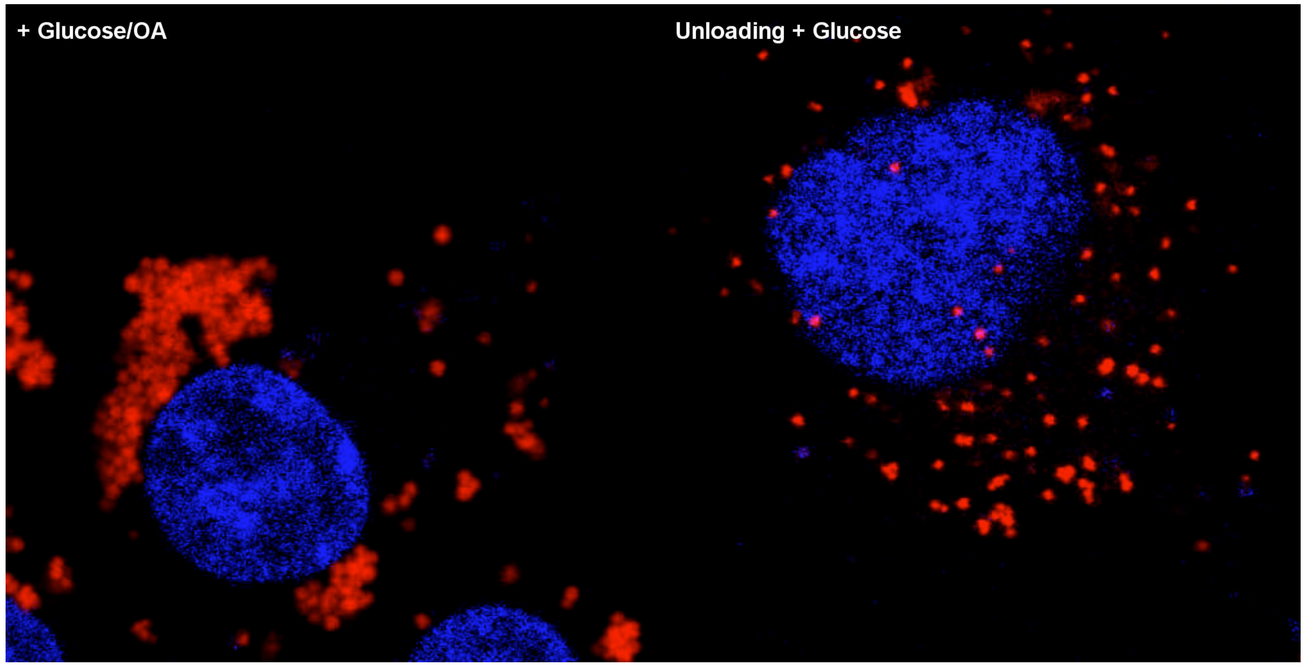
Petan, *Rev Phys Pharm Biochem* 2020

V stradanih celicah se LK razpršijo in hitro premikajo po celici



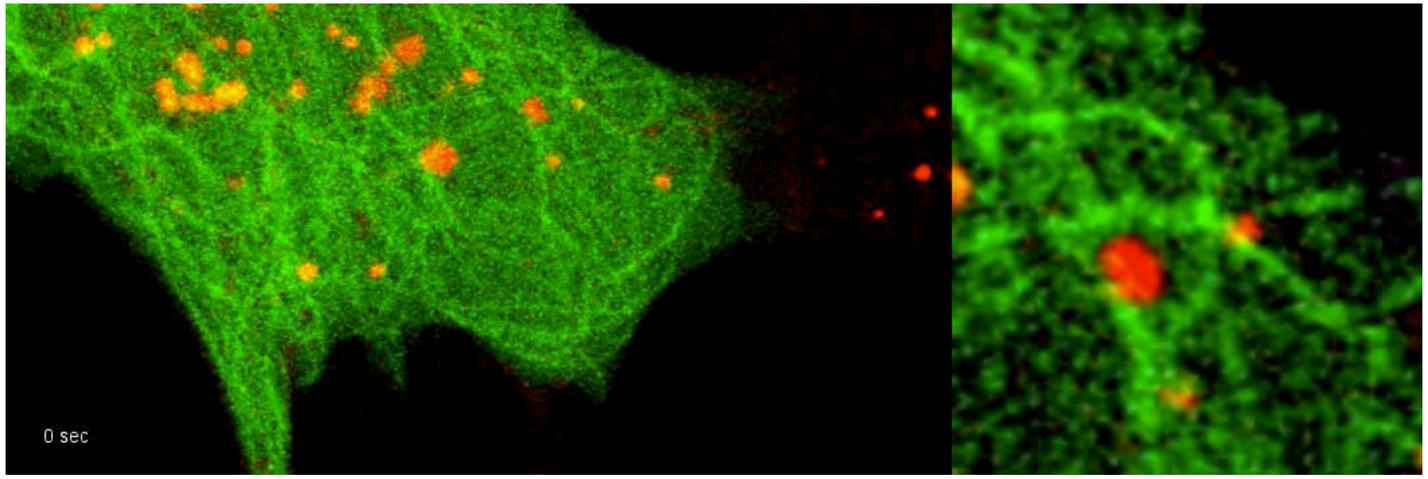
Herms et al, *Nat Comm.* 2015

V stradanih celicah se LK razpršijo in hitro premikajo po celici



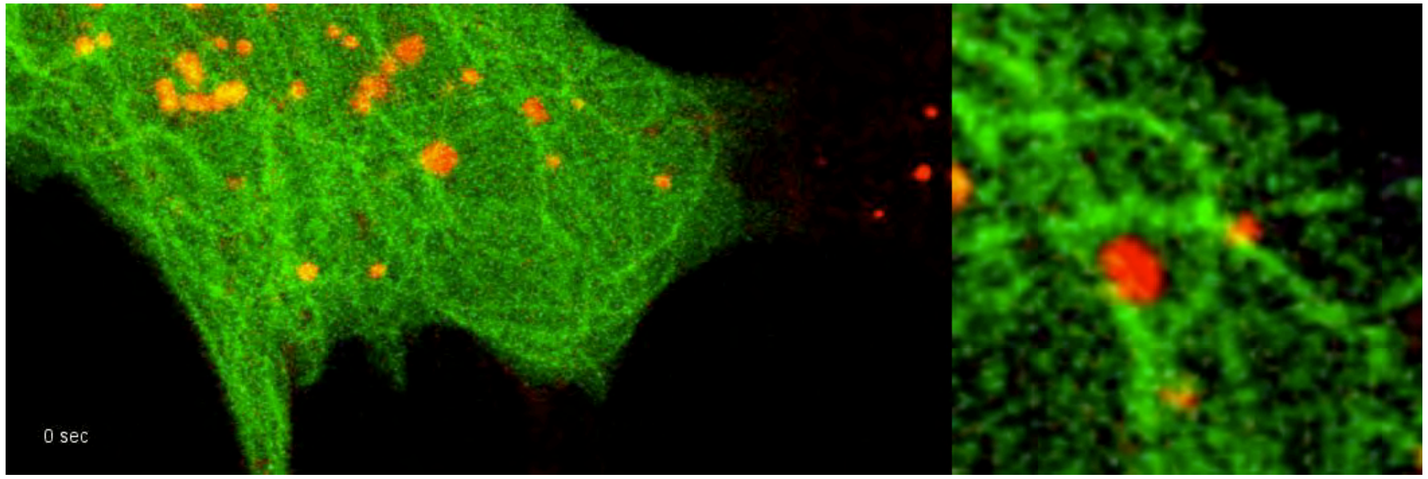
Herms et al, *Nat Comm.* 2015

LK se premikajo po mikrotubulih



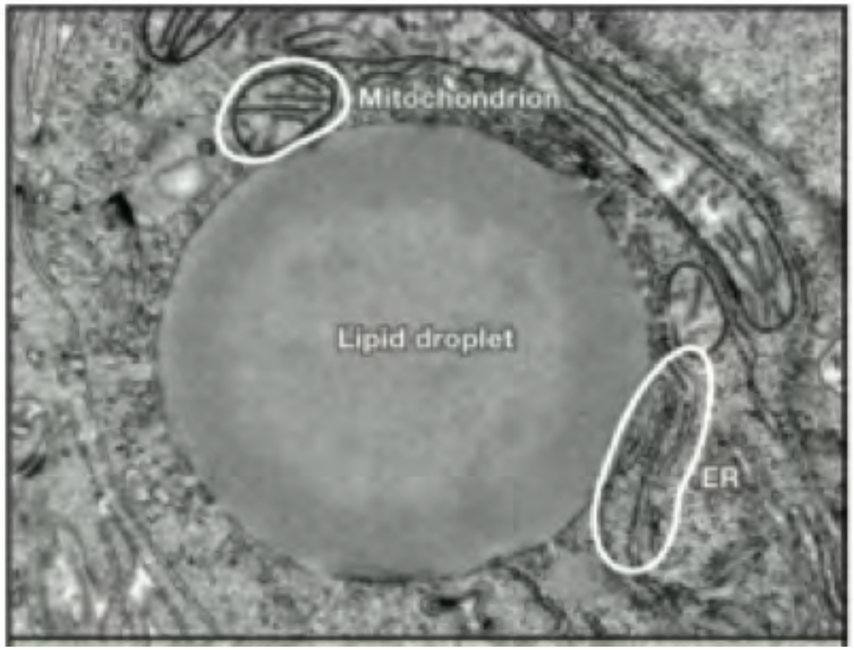
Herms et al, *Nat Comm*. 2015

LK se premikajo po mikrotubulih



Herms et al, *Nat Comm*. 2015

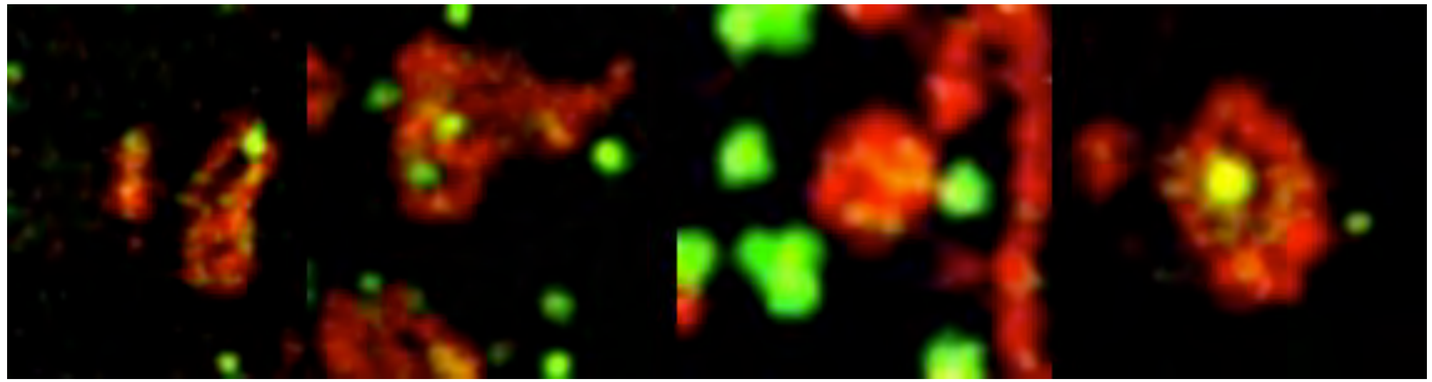
LK interagirajo z mitohondriji



Farese & Walther, Cell. 2009

LK interagirajo z mitohondriji

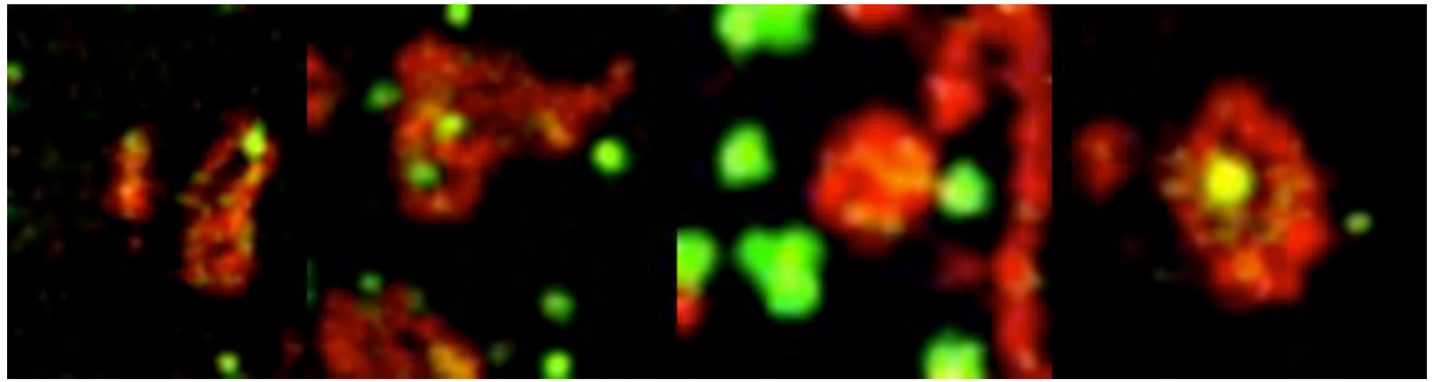
Dinamične interakcije med mitohondriji in LK



Herms et al, *Nat Comm.* 2015

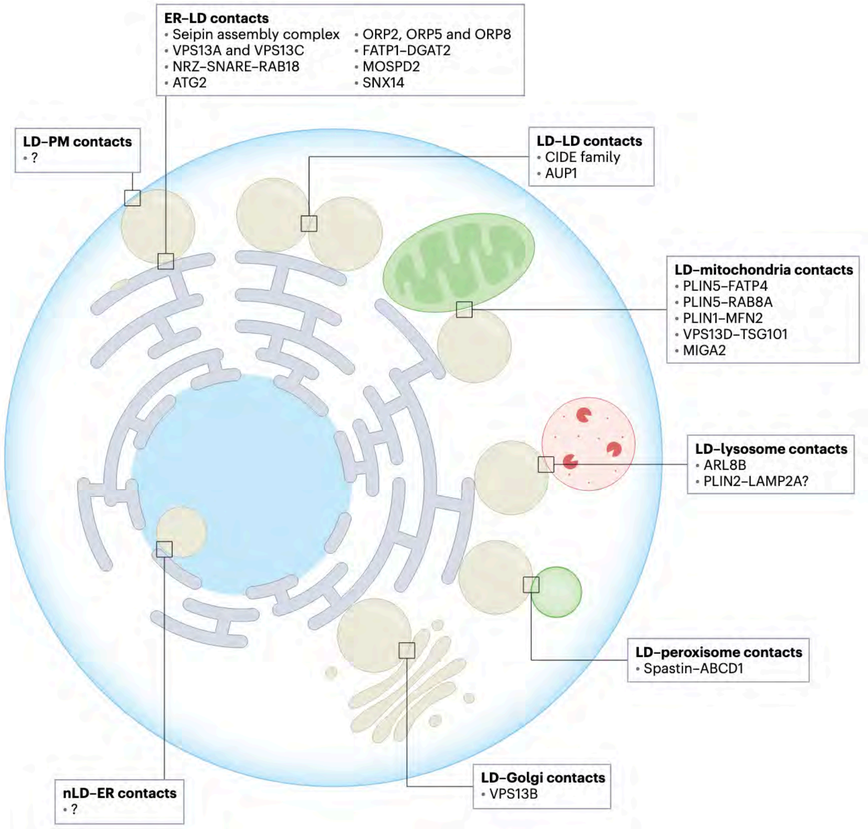
LK interagirajo z mitohondriji

Dinamične interakcije med mitohondriji in LK



Herms et al, *Nat Comm.* 2015

Lipidne kapljice tvorijo reverzibilne kontakte z vsemi organeli

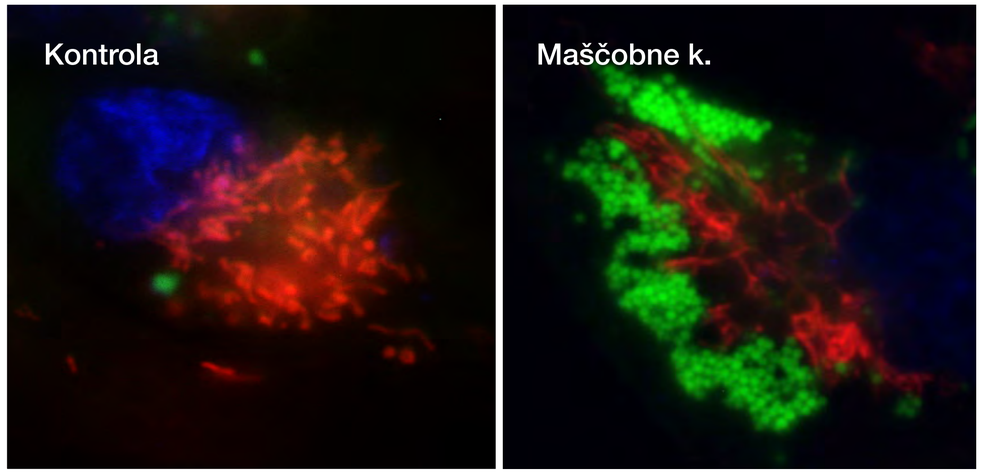


Mathiowetz & Olzmann Nat Cell Biol 2024

Stres inducira biogenezo lipidnih kapljic

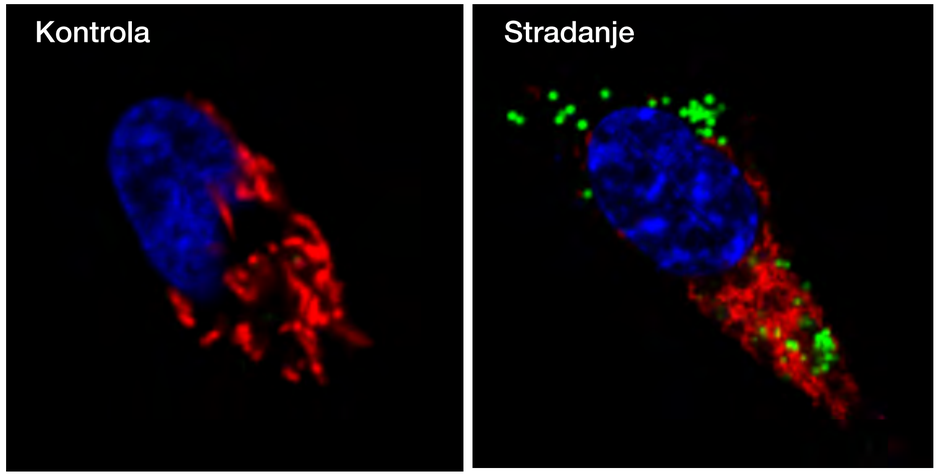
Presežek hranil

Mitohondriji = rdeča
Lipidne kapljice = zelena



Celice raka dojke

Pomanjkanje hranil

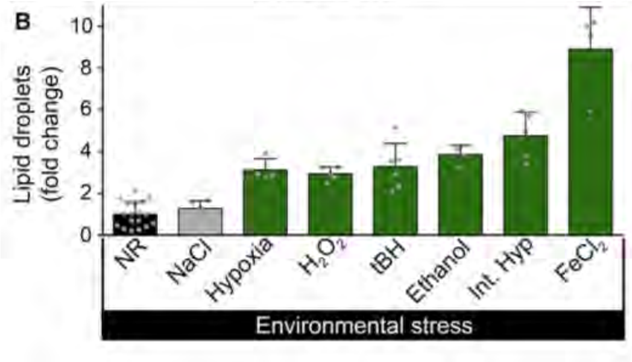


Celice raka dojke, akutno stradanje *in vitro*

Jarc et al, BBA 2018
Jusovič et al., Cancers 2023

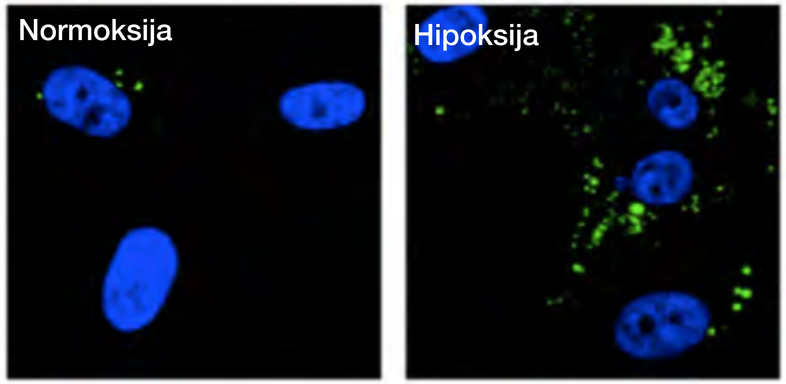
Stres inducira biogenezo lipidnih kapljic

Oksidativni stres



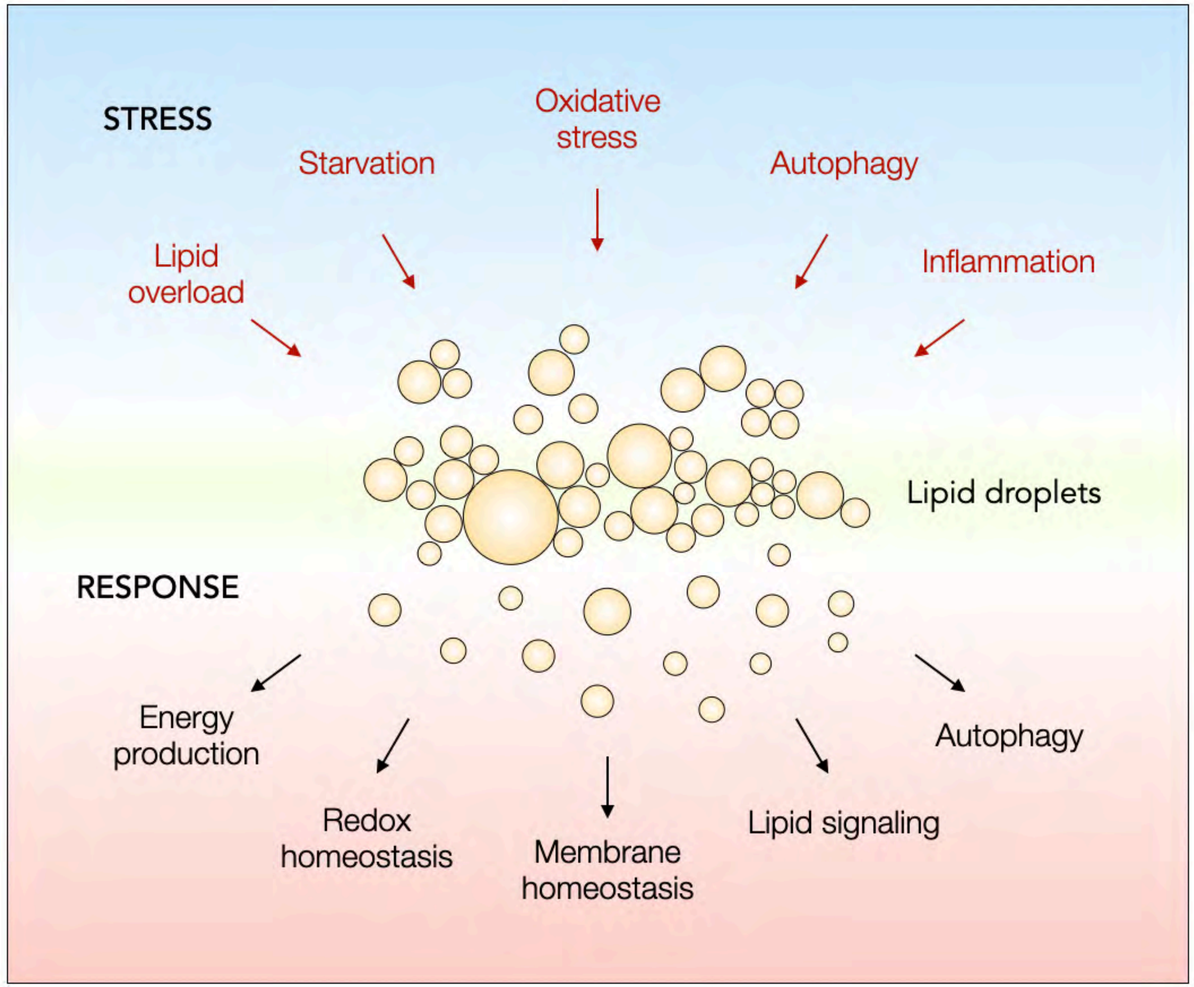
Centralno živčevje, *Drosophila*
Bailey et al, Cell 2015

Hipoksija



Celice glioblastoma U87
Bensaad et al., *Cell Rep* 2014

Lipidne kapljice so nujne za odgovor in adaptacijo celic na stres



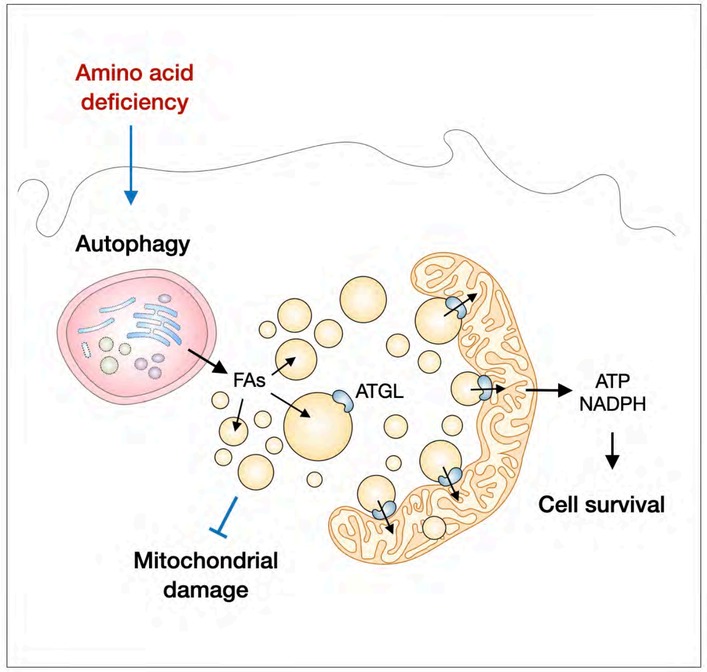
Jusovič et al., *in preparation*
Petan, *Rev Phys Pharm Biochem* 2020

Zakaj se kapljice tvorijo v popolni odsotnosti hranil?

LK prevzamejo presežek MK,
ki se sprostijo z avtofagijo

in natančno regulirajo prenos
teh MK v mitohondrije.

S tem obenem preprečijo
poškodbe mitohondrijev



Lipidne kapljice ublažijo stres, ki nastane ob sproščanju prekomernih količin MK v celici

Rambold et al., *Dev Cell* 2015
Nguyen et al., *Dev Cell* 2017
Petan, *Rev Physiol Biochem Pharm* 2020

Celične funkcije lipidnih kapljic v različnih stresnih pogojih ostajajo večinoma neznane ali slabo razumljene.

Ali lipidne kapljice določajo usodo različnih vrst lipidov?

Je dostava specifičnih lipidov na specifična mesta v celici ena od njihovih temeljnih nalog?

Ali je ohranjanje membranskega ravnovesja v celici ena od osnovnih funkcij LK?

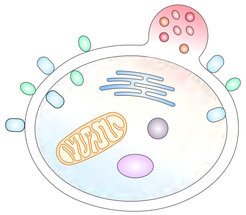
Lipid mediator production

Lipases

Energy balance & Stress resistance

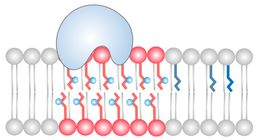
Inflammation & Tumour growth

Lipid droplets



Autophagy

Phospholipases

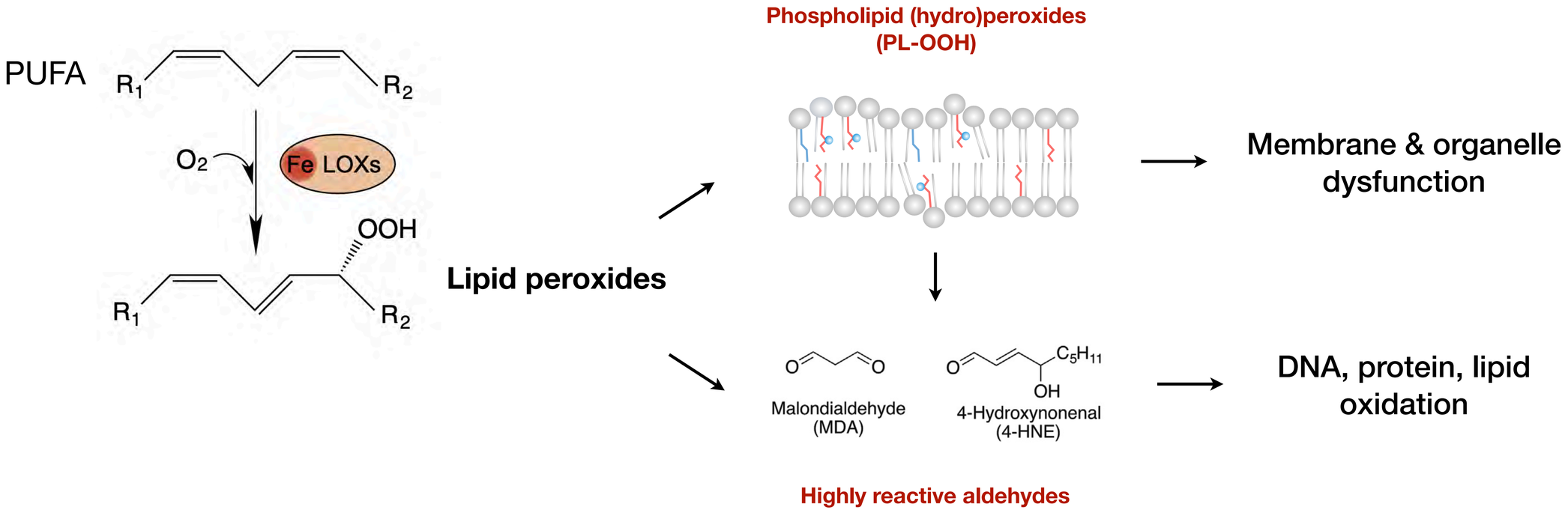


Membrane remodelling & Lipid peroxidation

Redox homeostasis & Ferroptosis

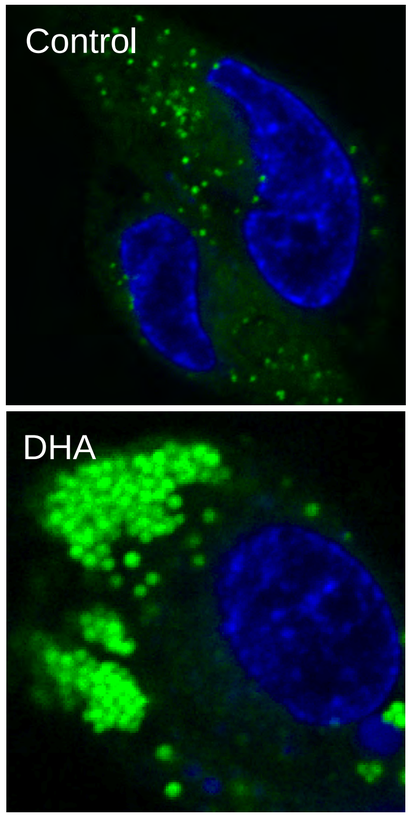
Lipidne kapljice in regulacija membranske sestave pri feroptozi

Polinenasičene MK (PUFA) se lahko oksidirajo v toksične lipidne perokside

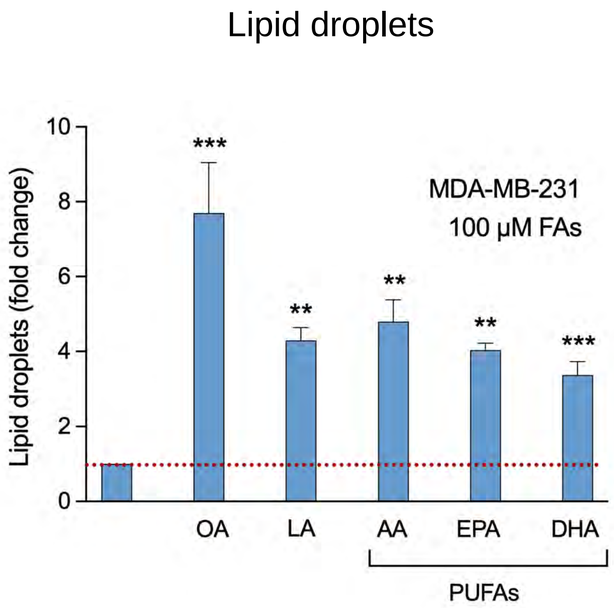


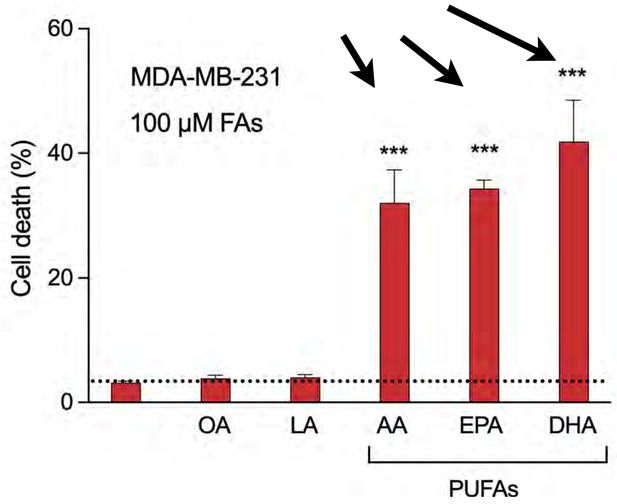
Yang et al., *PNAS* 2016.

Dodatek PUFA inducira tvorbo LK in celično smrt v rakavih celicah



Lipid droplets (green)

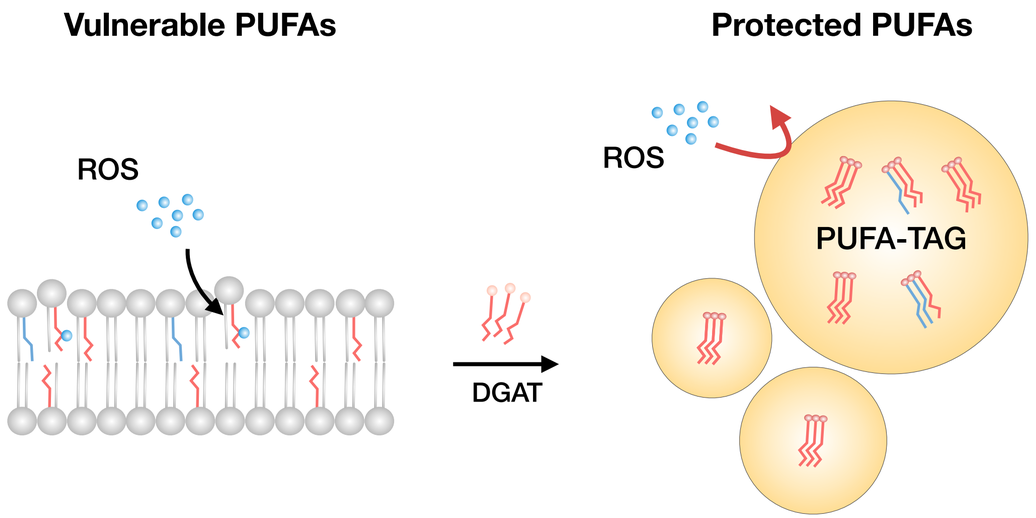




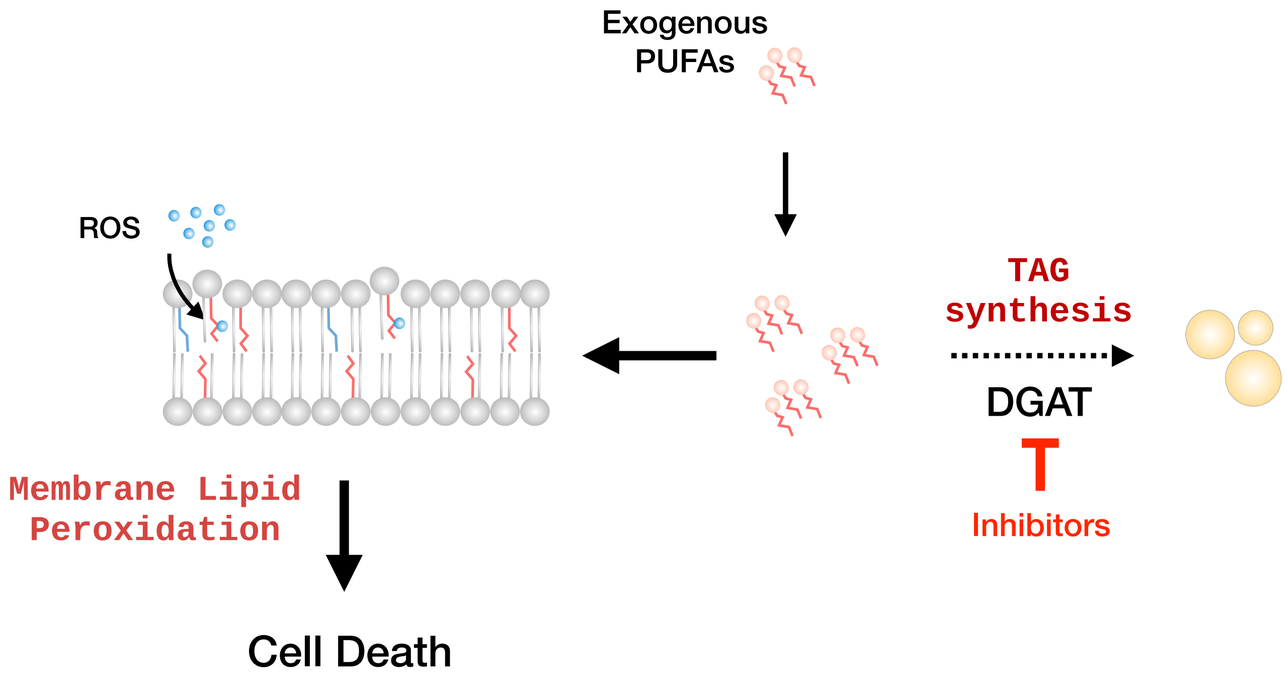
OA = oleic acid (C18:1)
LA = linoleic acid (C18:2)
AA = arachidonic acid (C20:4)
EPA = eicosapentaenoic acid (C20:5)
DHA = docosahexaenoic acid (C22:6)

Jarc et al., BBA 2018

Ali lipidne kapljice ščitijo PUFA pred oksidacijo?

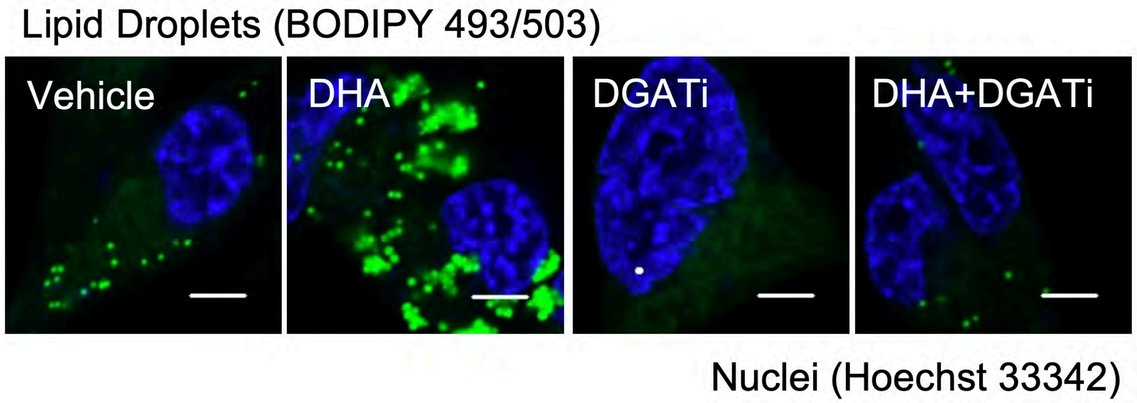


Ali inhibicija tvorbe LK potencira toksičnost PUFA?

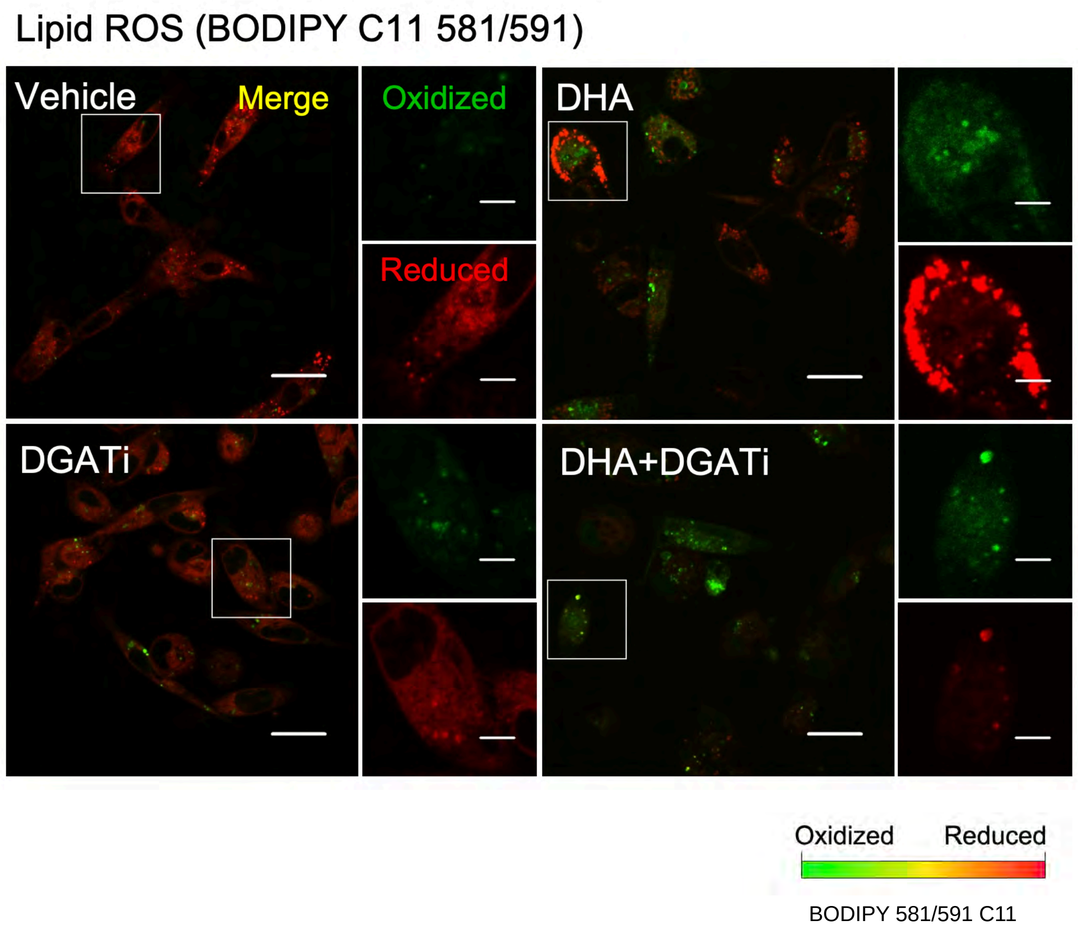


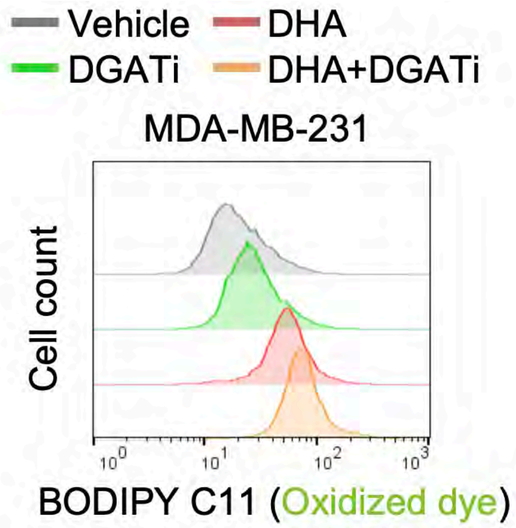
Kump et al., *in preparation*

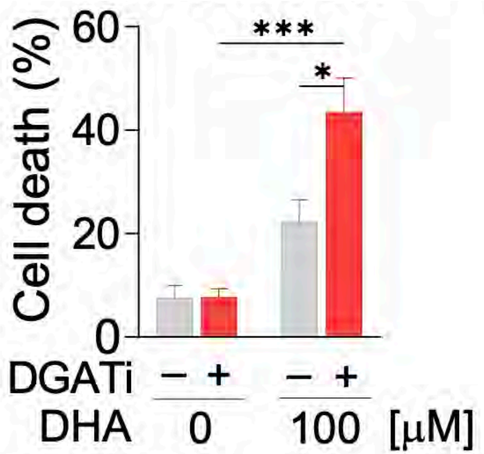
Inhibicija DGAT prepreči tvorbo lipidnih kapljic ob dodatku PUFA



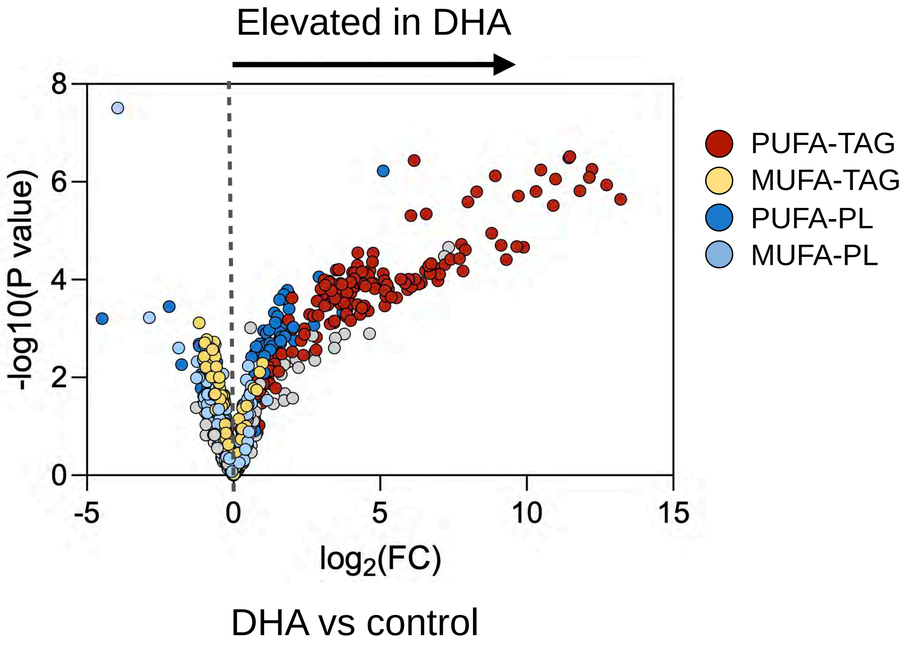
Inhibicija DGAT poveča lipidno peroksidacijo in smrt celic ob dodatku PUFA



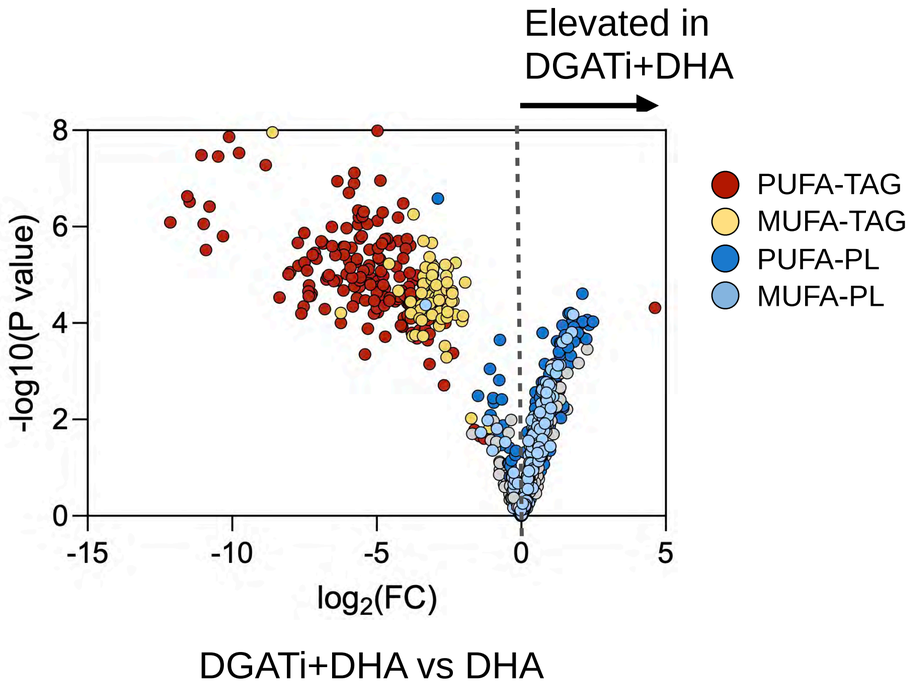




Inhibicija DGAT preusmeri PUFA v membranske fosfolipide

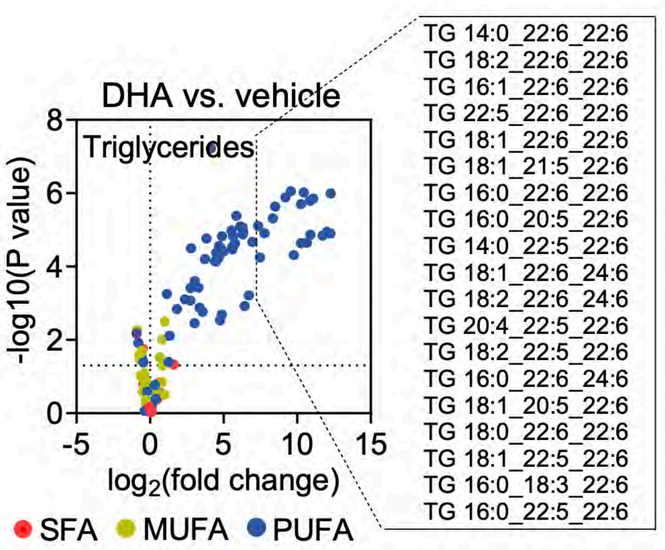


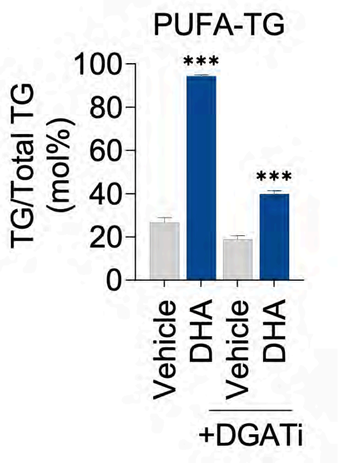
DHA vs control

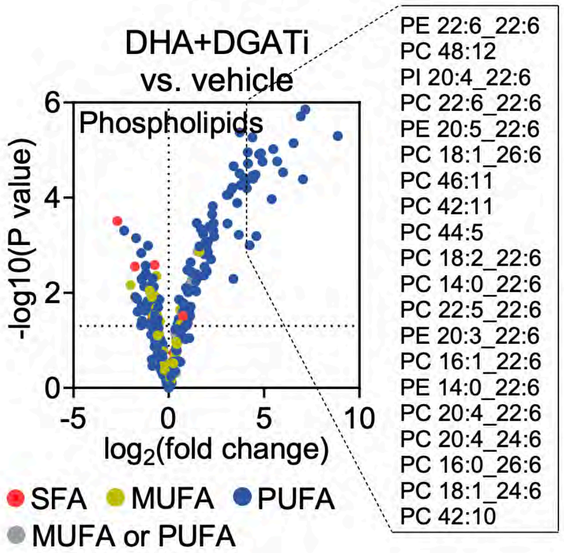


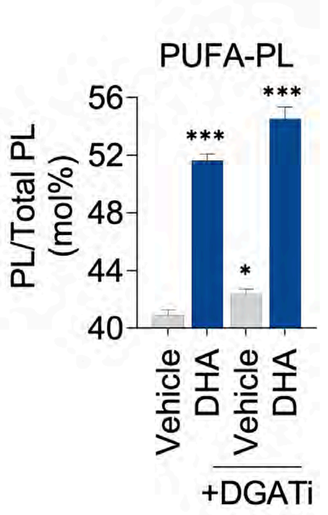
DGATi+DHA vs DHA

Inhibicija DGAT preusmeri PUFA v membranske fosfolipide



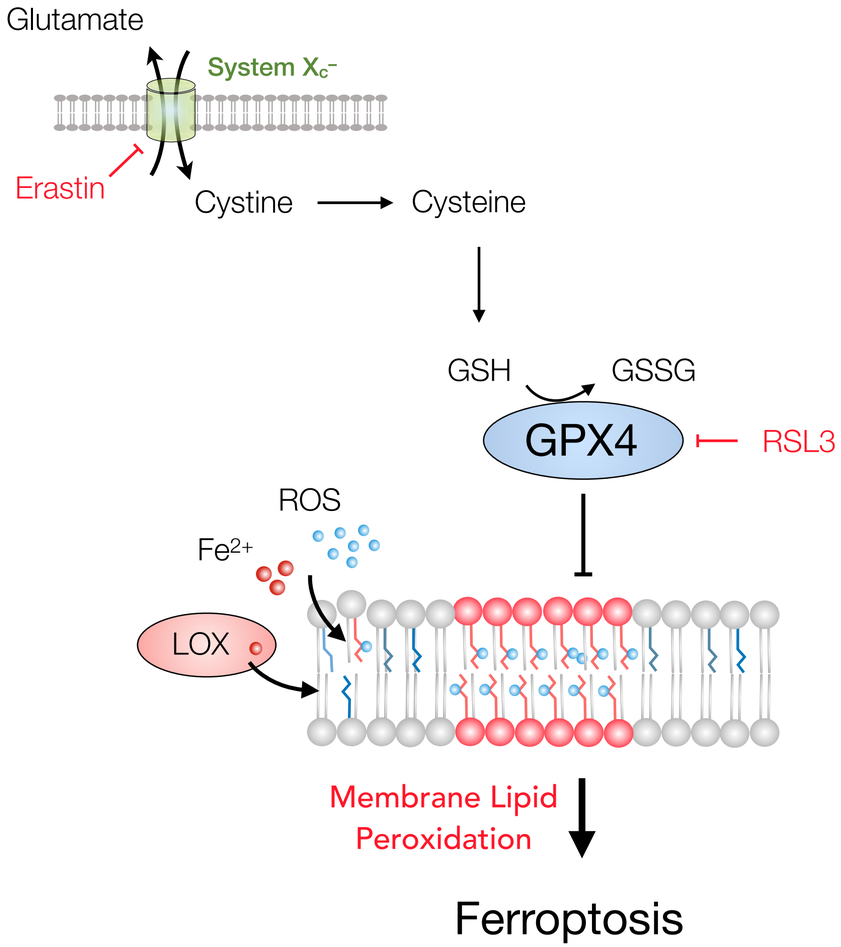






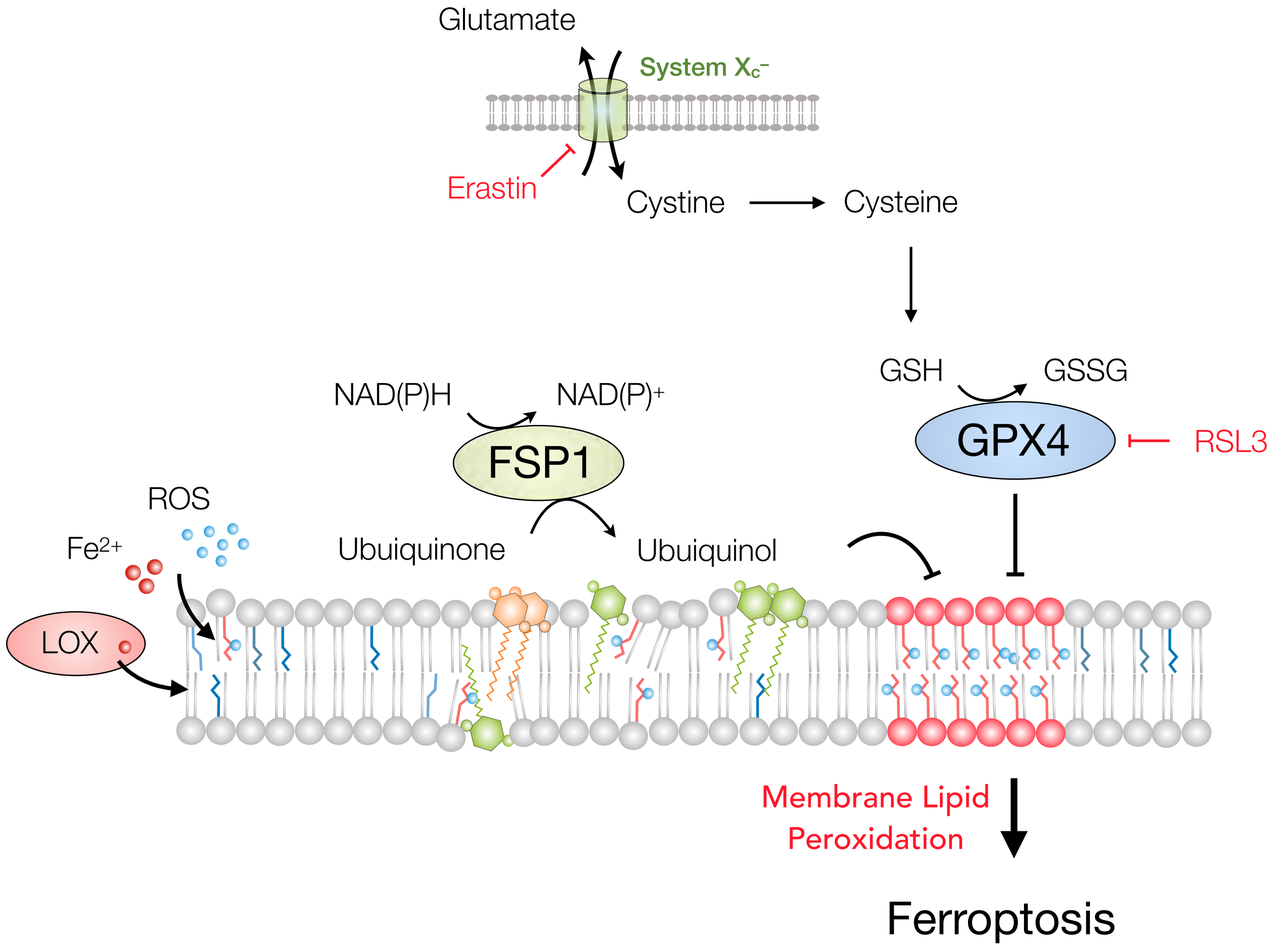
Povečana nenasičenost membran bi lahko pojasnila povečano lipidno peroksidacijo ob inhibiciji tvorbe LK

Feroptoza je celična smrt odvisna od membranske lipidne peroksidacije



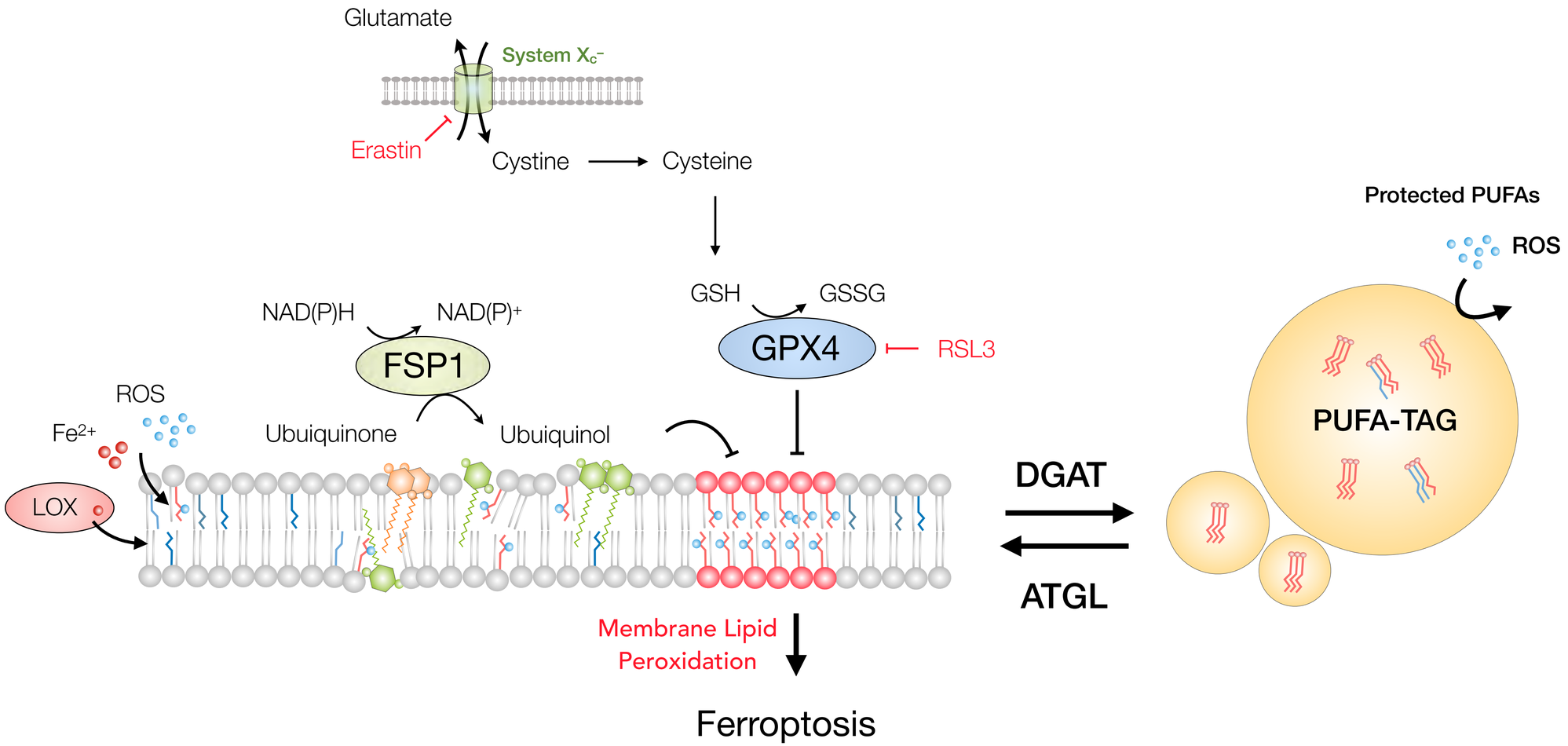
Dixon et al., *Cell* 2012.
Stockwell et al., *Cell* 2017.
Feng & Stockwell, *Plos Biol.* 2018.

Feroptoza je celična smrt odvisna od membranske lipidne peroksidacije



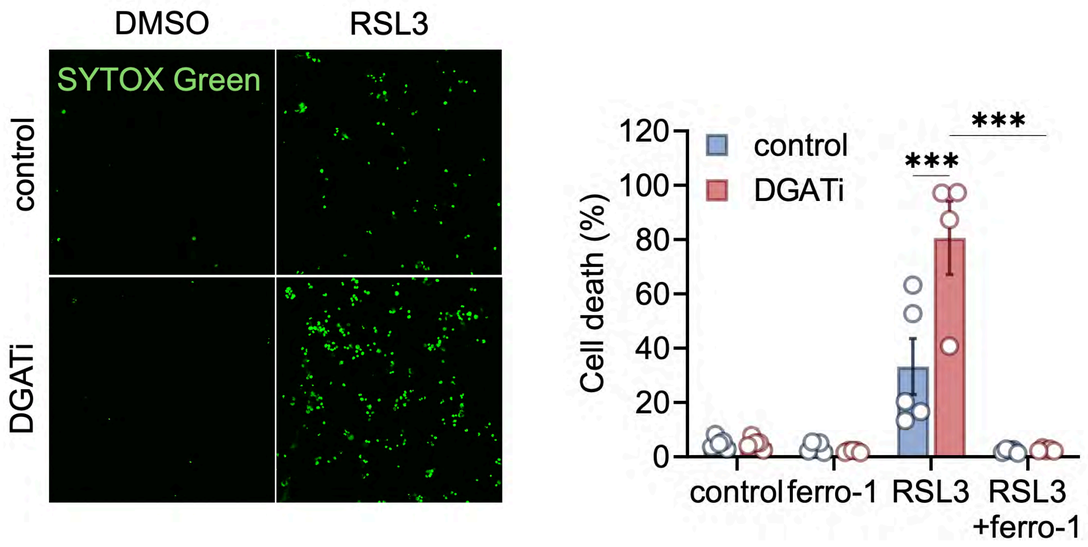
Dixon et al., *Cell* 2012.
Bersuker et al., *Nature* 2019.
Doll et al., *Nature* 2019.

Ali lipidne kapljice lahko uravnavajo feroptozo?

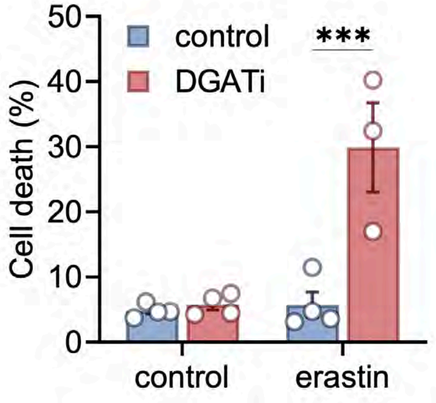


Inhibicija tvorbe LK senzibilizira celice za feroptozo

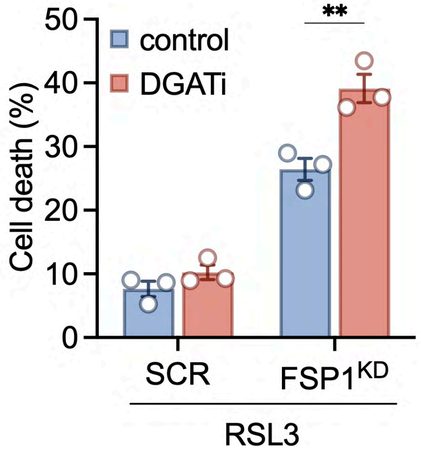
GPX4 inhibition (RSL3)



System Xc– inhibition (Erastin)



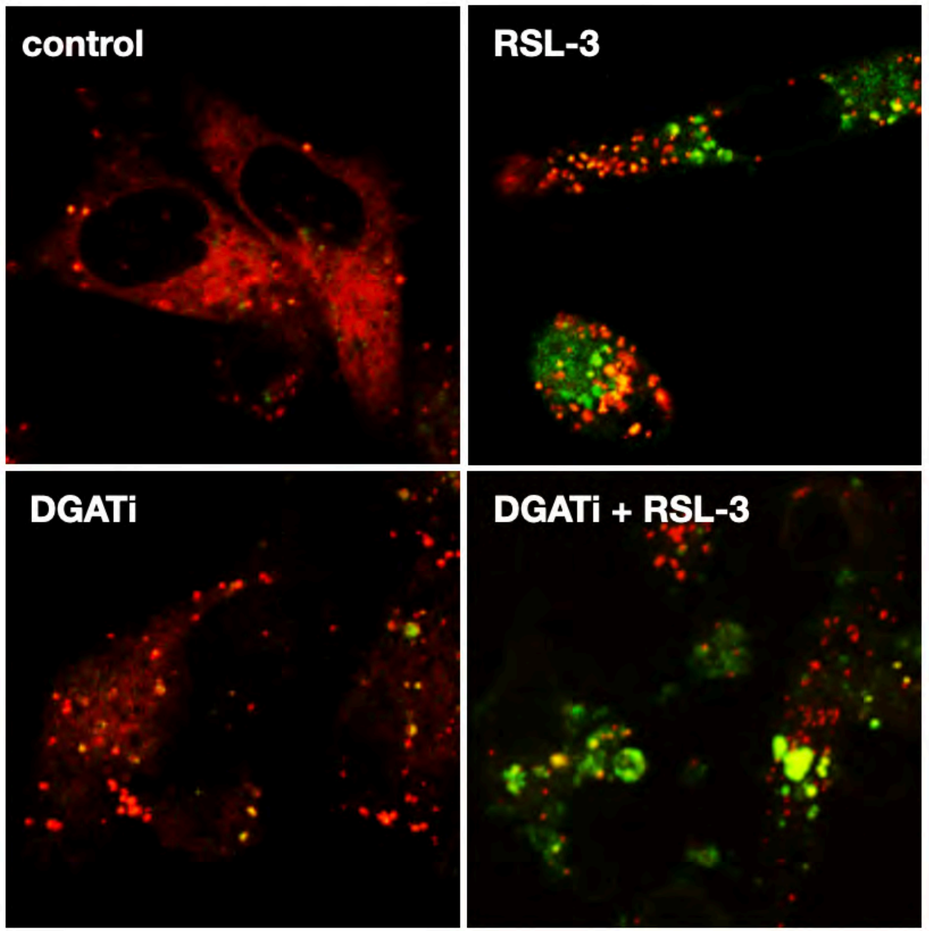
FSP1 knockdown +RSL3



Kump et al., unpublished

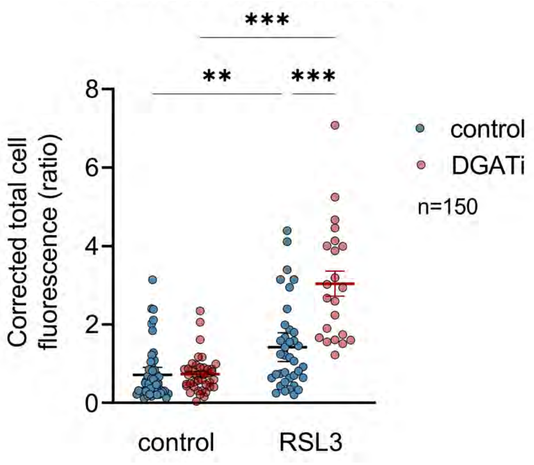
Inhibicija tvorbe LK poveča lipidno peroksidacijo pri feroptozi

BODIPY C11
Oxidized/Reduced



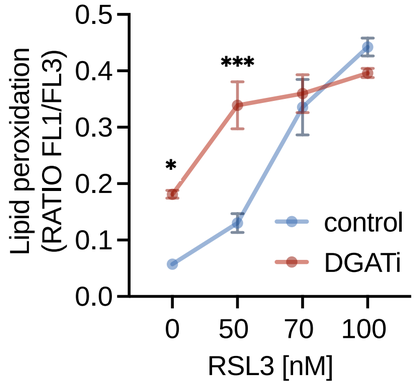
MDA-MB-231

BODIPY C11
Oxidized/Reduced



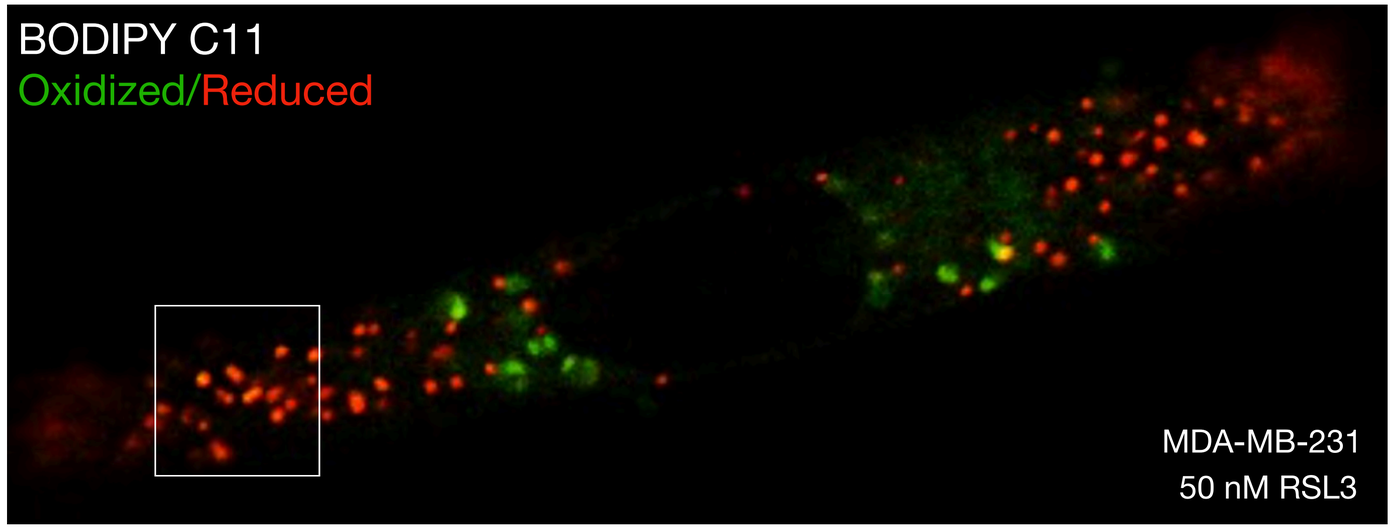
Microscopy
n = 150 cells

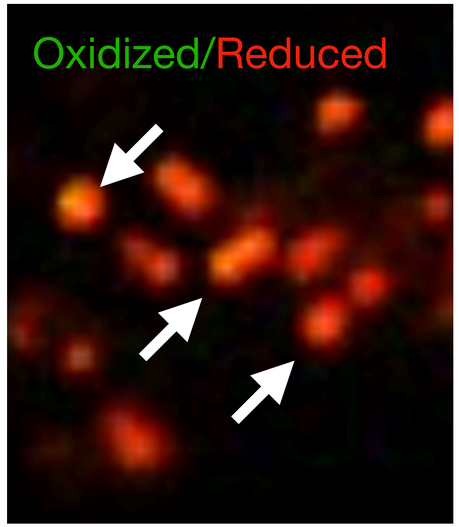
BODIPY C11
Oxidized/Reduced

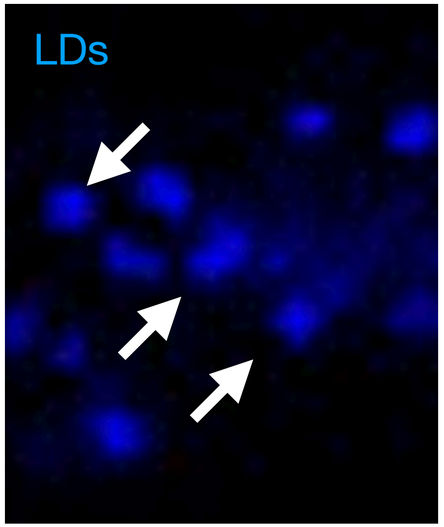


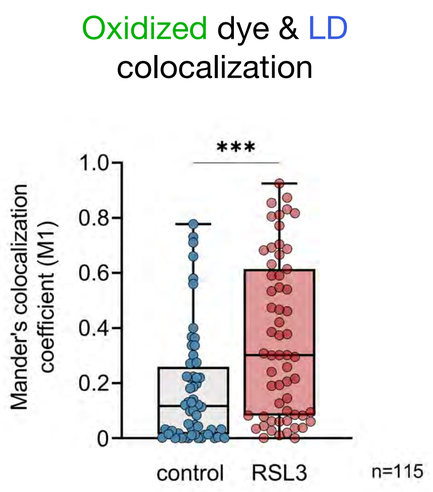
Flow Cytometry
n = 20.000 cells

Perne et al., unpublished









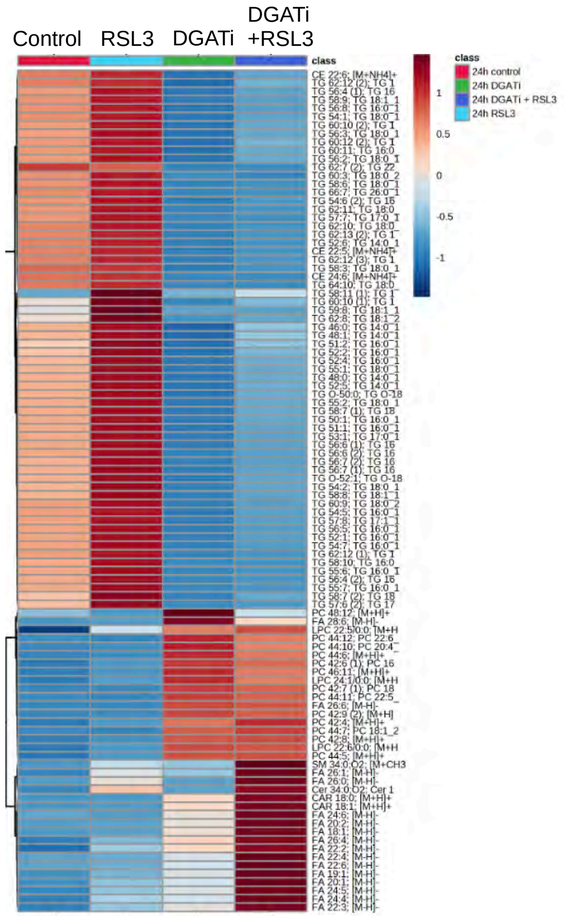
Live cells
n=115

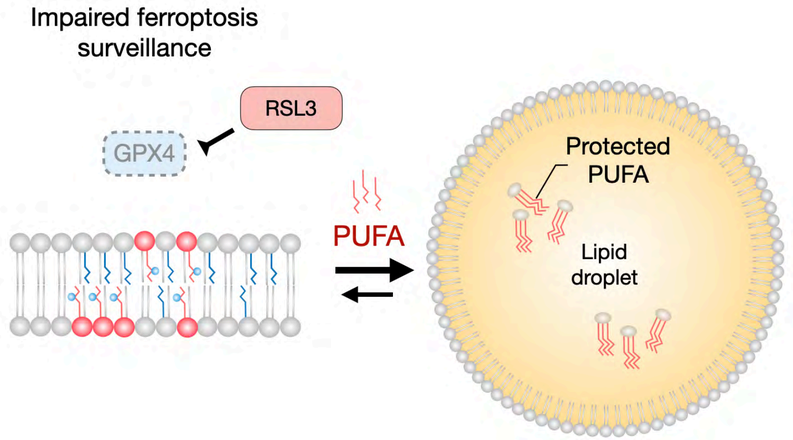
LDs sequester membrane-derived PUFAs?

Perne et al., unpublished

Lipidomika razkriva vlogo LK pri preurejanju membran pri feroptozi

PUFA-TAGs
PUFA-CEs

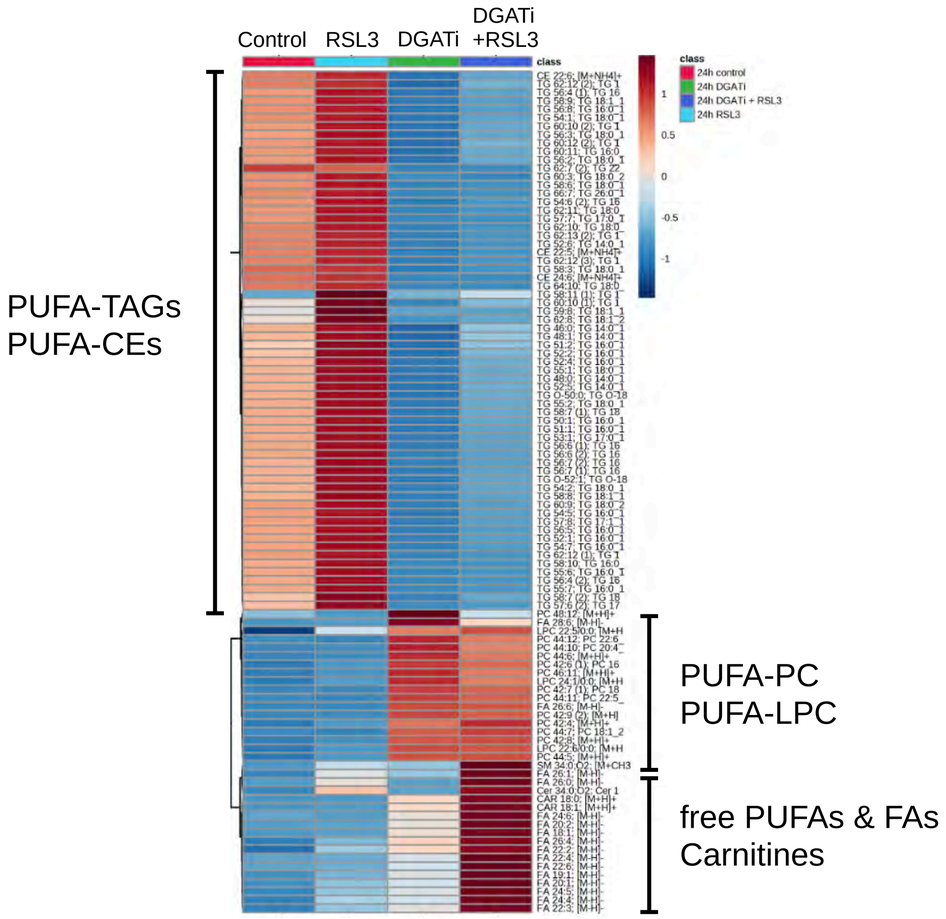


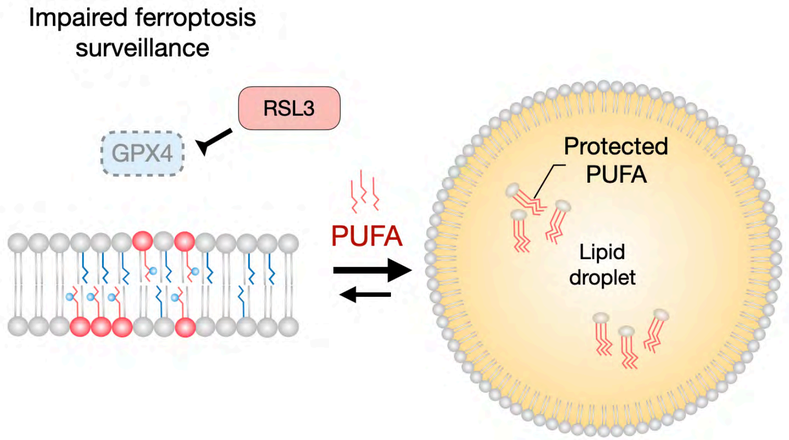


RSL3 obogati LK s PUFA

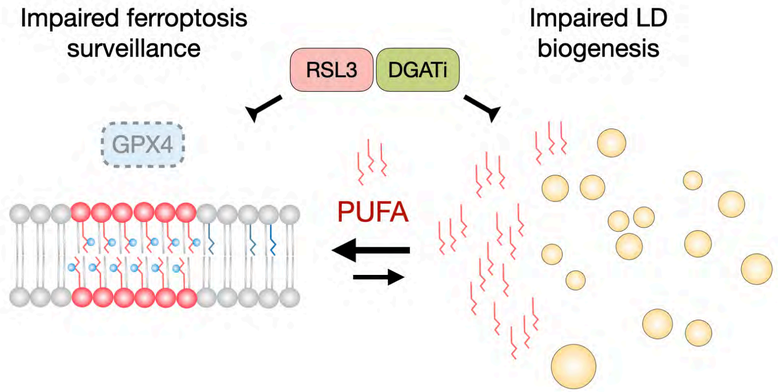
with O. Kuda and M. Fedorova

Lipidomika razkriva vlogo LK pri preurejanju membran pri feroptozi





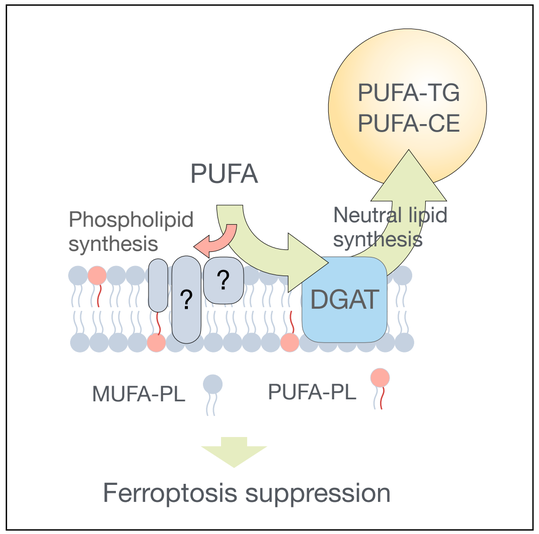
RSL3 obogati LK s PUFA

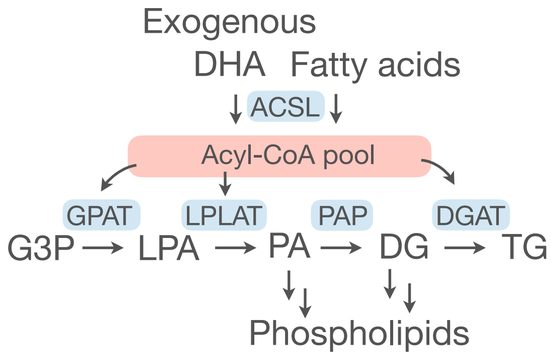


Inhibicija DGAT preusmeri PUFA proti membranskim fosfolipidom

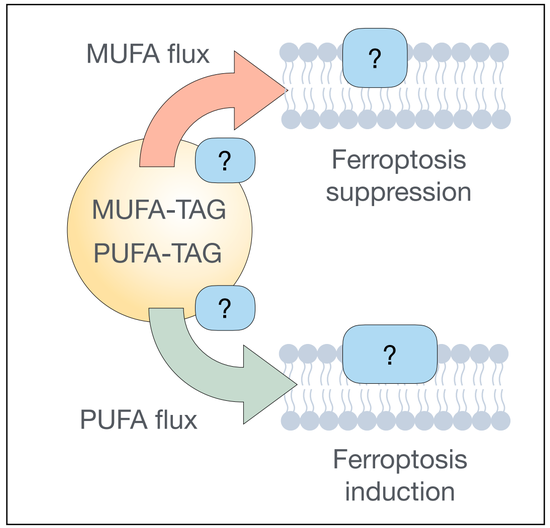
with O. Kuda and M. Fedorova

Zaključki in odprta vprašanja





Zaključki in odprta vprašanja



Zahvala

Ana Kump
Leja Perne
Eva Jarc Jovičić
Špela Koren
Gregor Jazbec
Nastja Feguš

Mauro Danielli
Anja Pucer
Vesna Brglez
Petra Hruševar
Maida Jusović
Petra Malavašič
Toni Nagode
Ema Guštin

Igor Križaj
Adrijana Leonardi
Jernej Šribar

Jožef Stefan Institute
Ljubljana, Slovenia

Robert Zimmermann
Thomas O. Eichmann
IMB & Biotechmed, Uni Graz, Austria

Oliver Werz, Jana Gerstmeier
Paul M. Jordan
Friedrich-Schiller-Universität Jena, Germany

Ondrej Kuda
Kristyna Brejchova
Institute of Physiology, CAS, Prague

Maria Fedorova
TU Dresden, Germany

Mateja Manček Keber
Duško Lainšček
Roman Jerala
National Institute of Chemistry, Ljubljana, Slovenia

Gérard Lambeau
Vesna Brglez
IPMC, CNRS, Valbonne, France

arrs
JAVNA AGENCIJA ZA RAZISKOVALNO DEJAVNOST REPUBLIKE SLOVENIJE

MEDNARODNA PODIPLOMSKA ŠOLA JOŽEFA STEFANA
JOŽEF STEFAN INTERNATIONAL POSTGRADUATE SCHOOL

instruct ERIC
EMBO

epilipidnet
cost
EUROPEAN COOPERATION IN SCIENCE & TECHNOLOGY

Hvala lepa za pozornost!

toni.petan@ijs.si