Paris NASH Meeting

International Think Tank

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9th edition

The central role of mitochondrion in the metabolic health of the hepatocyte

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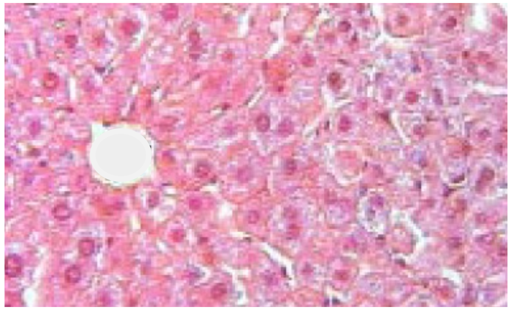
Inserm U1317 (NuMeCan), Rennes, France

Paris
NASH
Meeting
International Think Tank

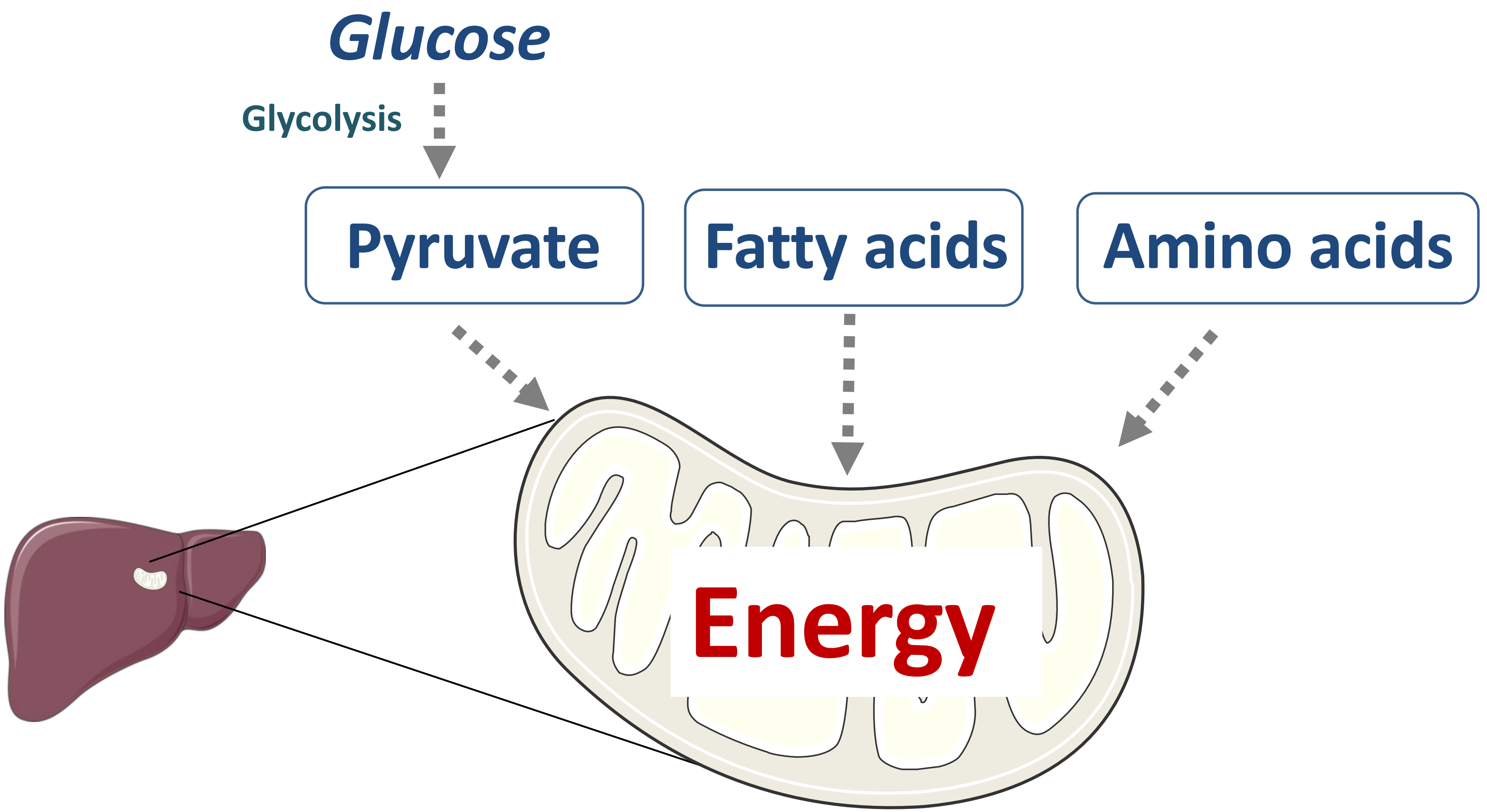
Conflict of interest disclosure

I have no actual or potential conflict of interest in relation to this presentation.

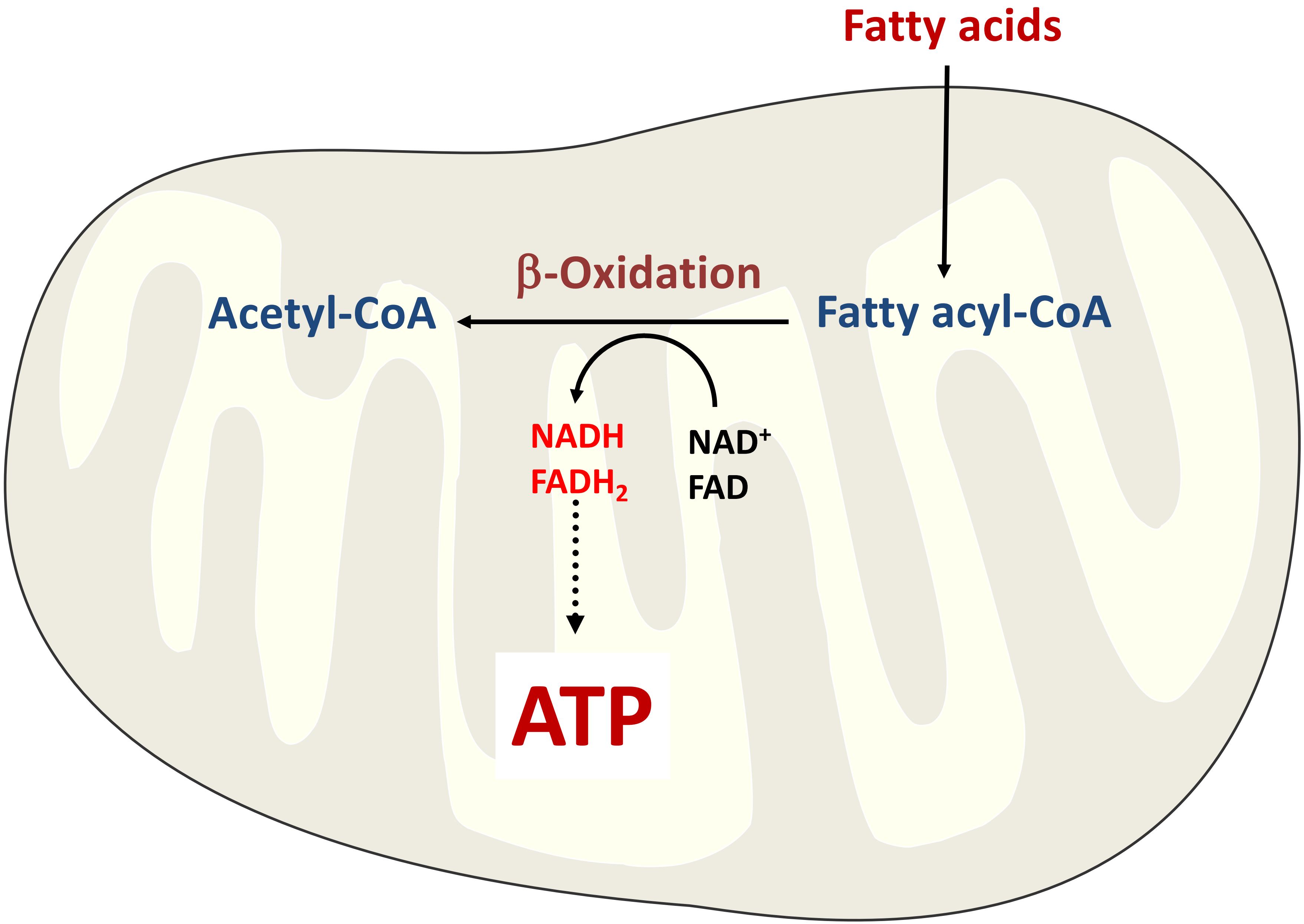
Main mitochondrial functions in healthy hepatocytes



Liver mitochondria need fuel to produce energy



Fuel oxidation provides the reducing equivalents NADH and $FADH_2$



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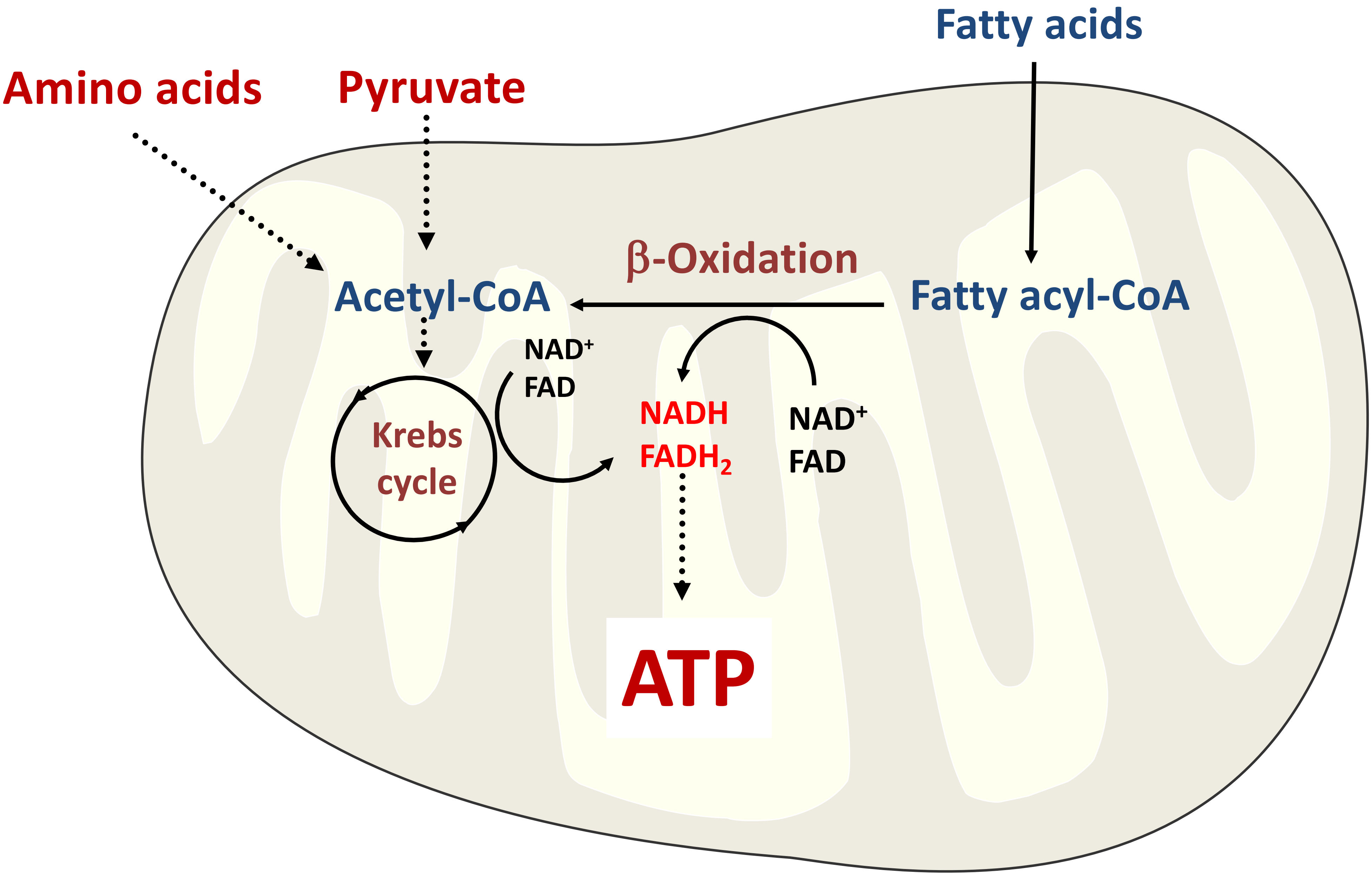
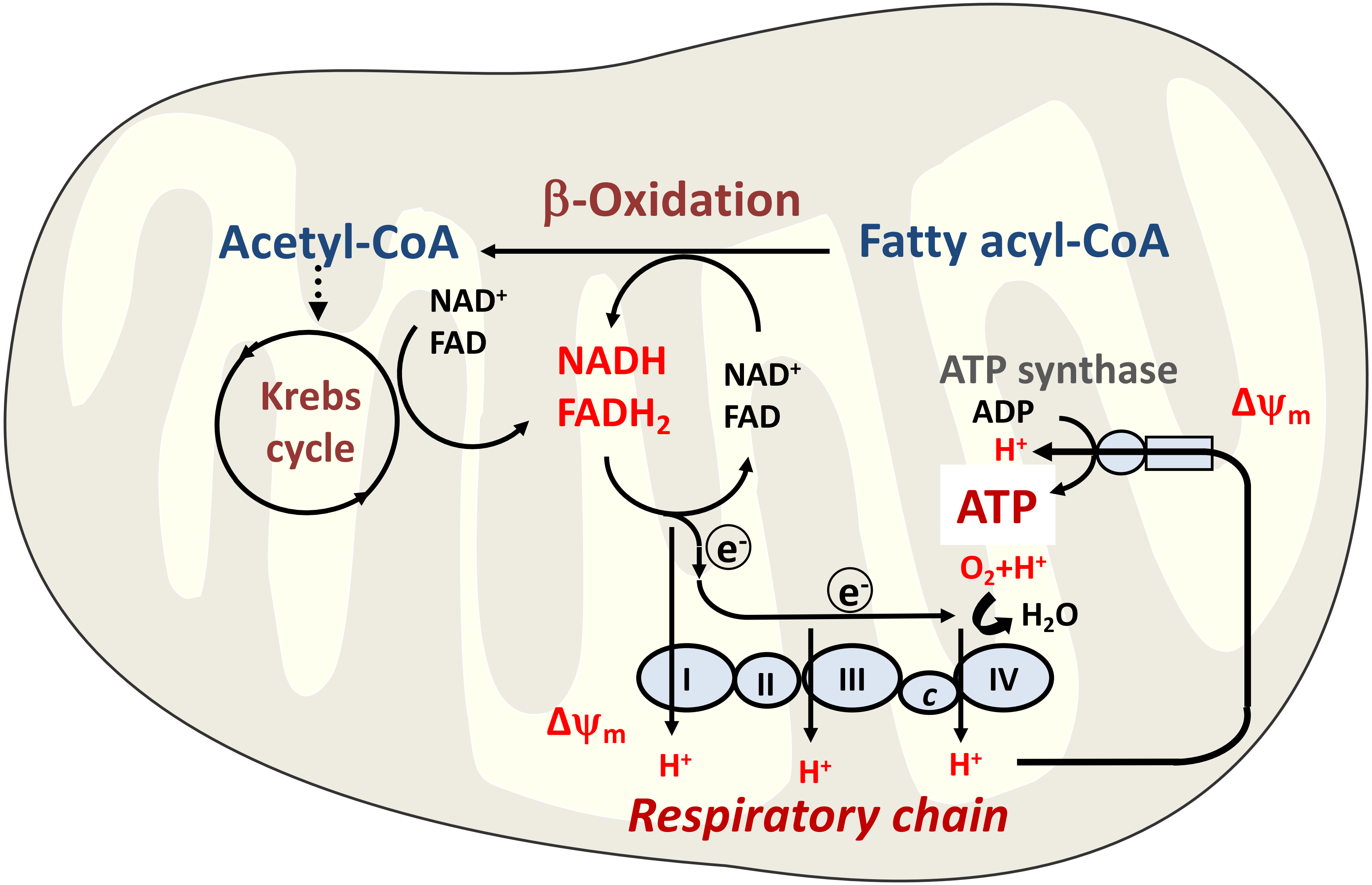
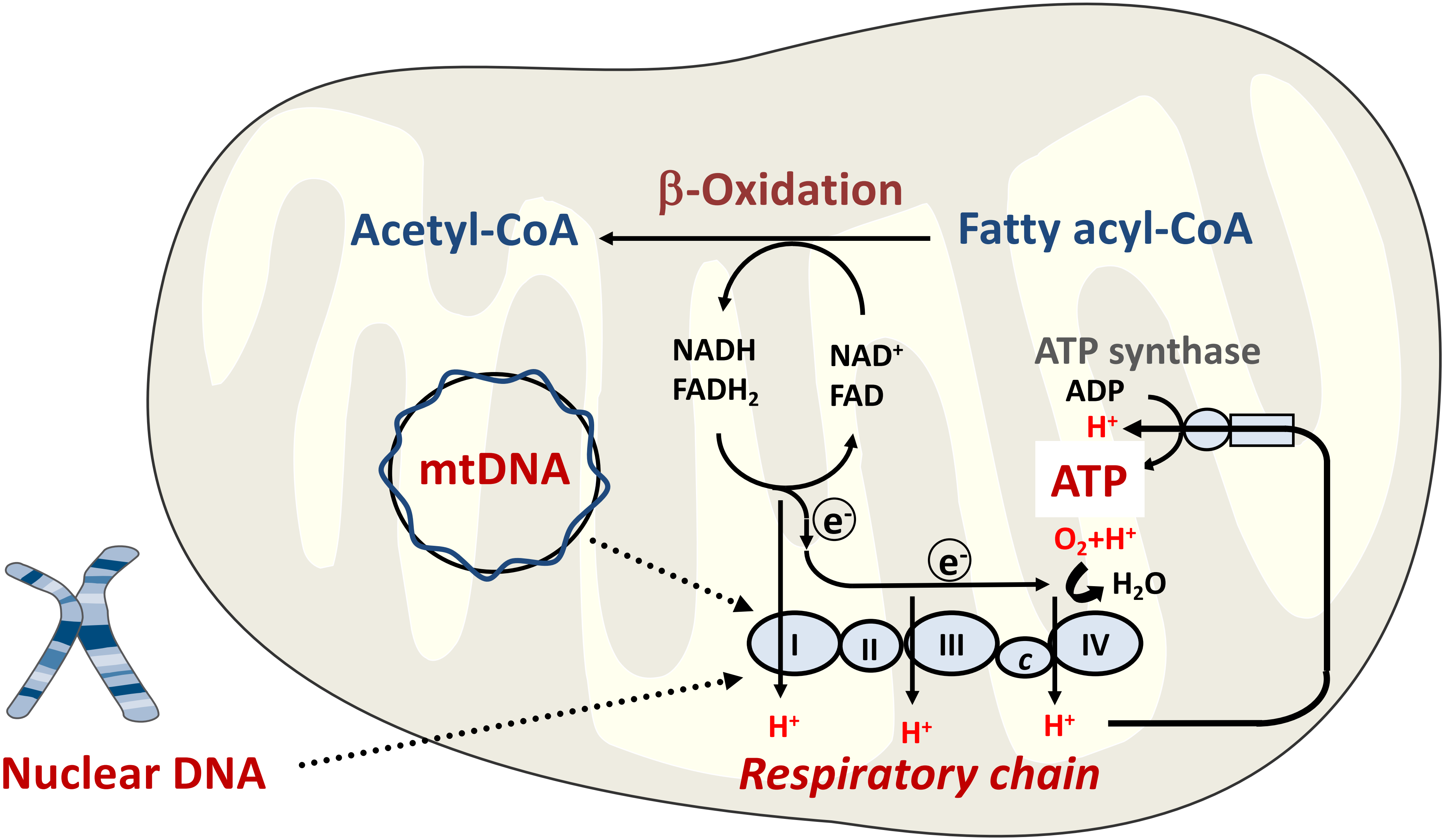


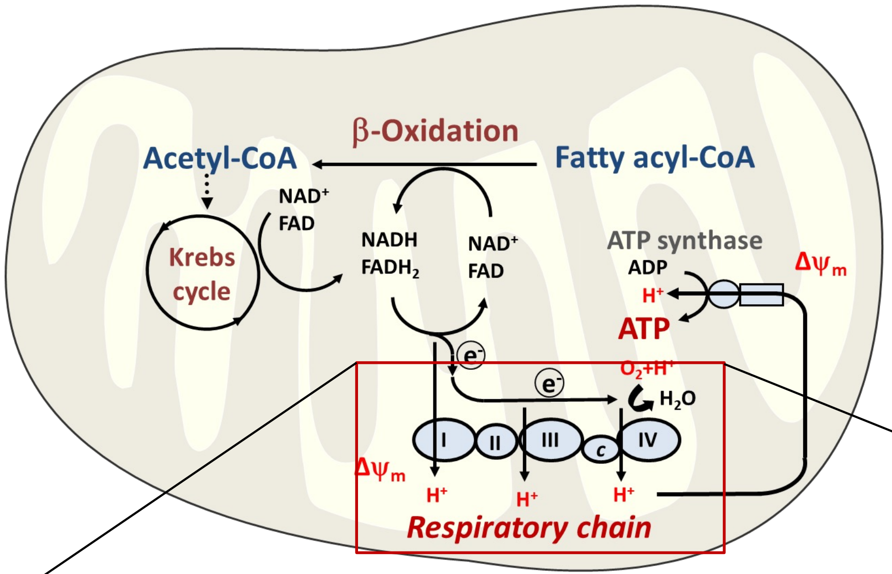
NADH and $FADH_2$ provide electrons and protons to the respiratory chain for ATP synthesis



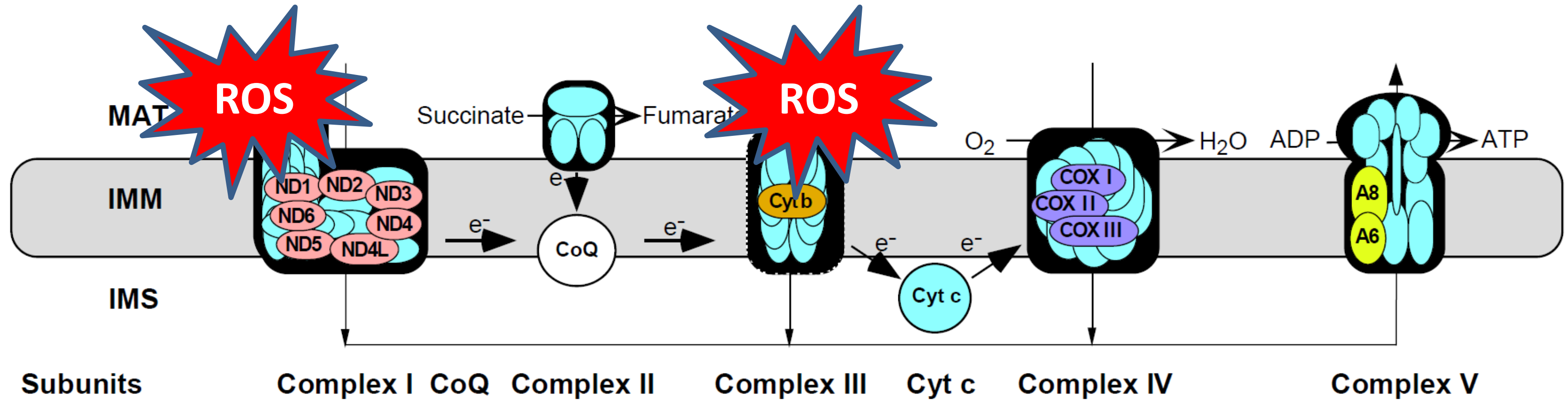
The respiratory chain requires two genomes



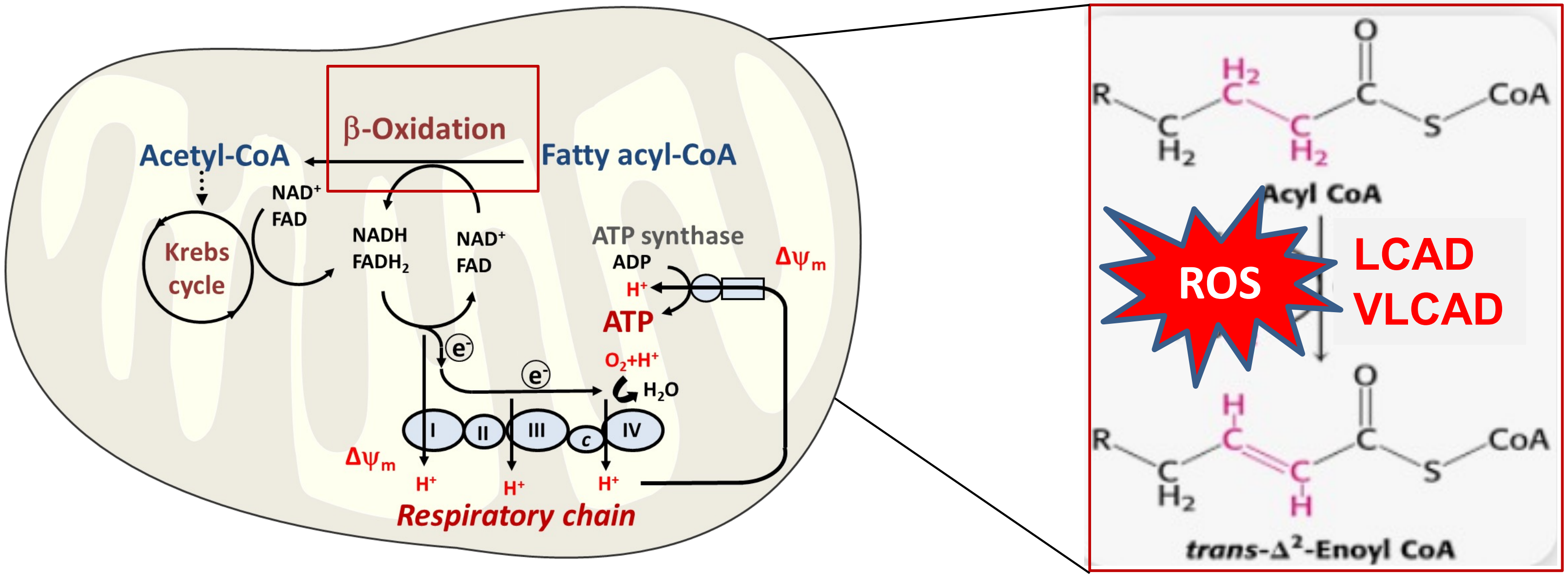
The respiratory chain constantly produces ROS



Leakage of electrons within complexes I and III with generation of superoxide anion ($O_2^{\cdot-}$)



Mitochondrial fatty acid oxidation also produces ROS



Redox Biology 4 (2015)

H_2O_2 release from the very long chain acyl-CoA dehydrogenase

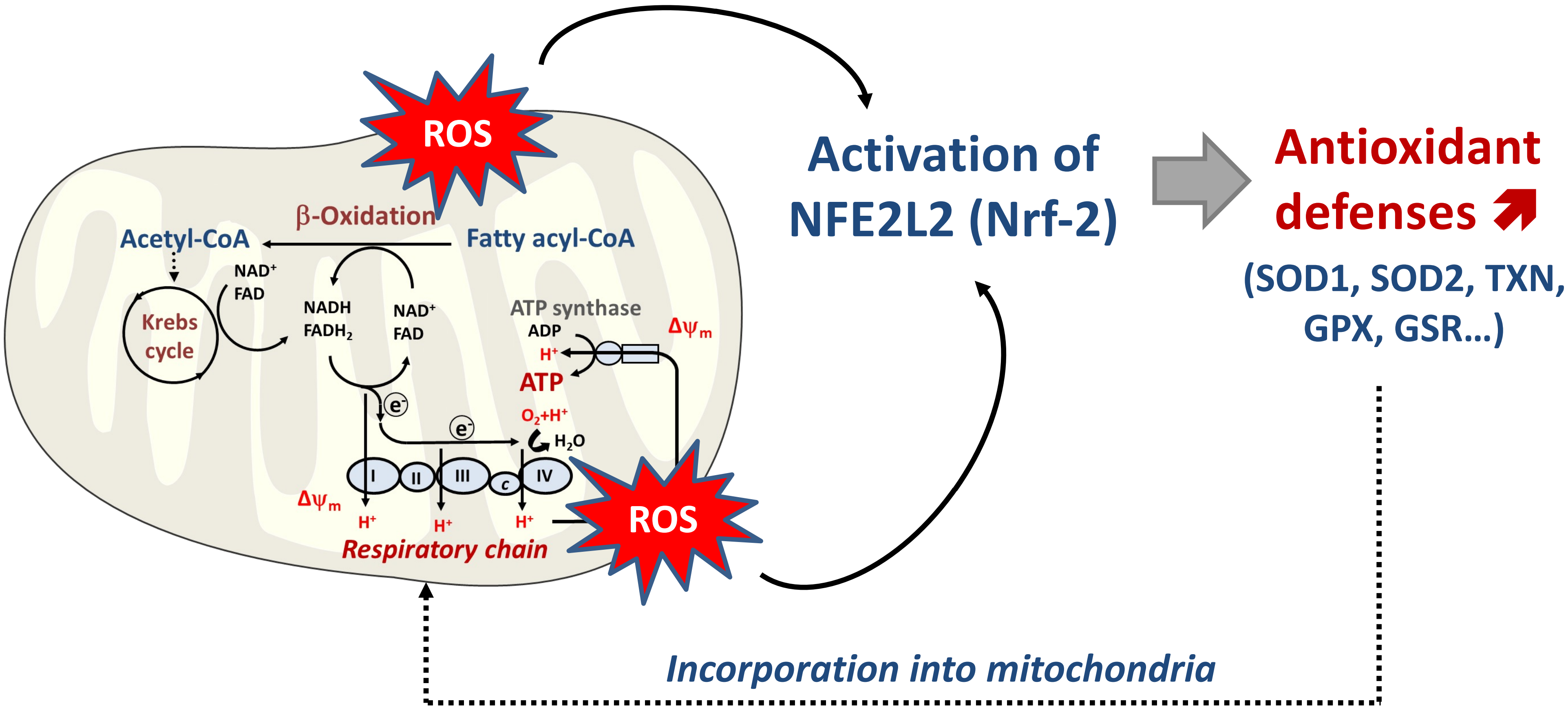
Pâmela A.H.B. Kakimoto, Fábio K. Tamaki, Ariel R. Cardoso, Sandro R. Marana, Alicia J. Kowaltowski*

Redox Biology 26 (2019)

The fatty acid oxidation enzyme long-chain acyl-CoA dehydrogenase can be a source of mitochondrial hydrogen peroxide

Yuxun Zhang, Sivakama S. Bharathi, Megan E. Beck, Eric S. Goetzman*

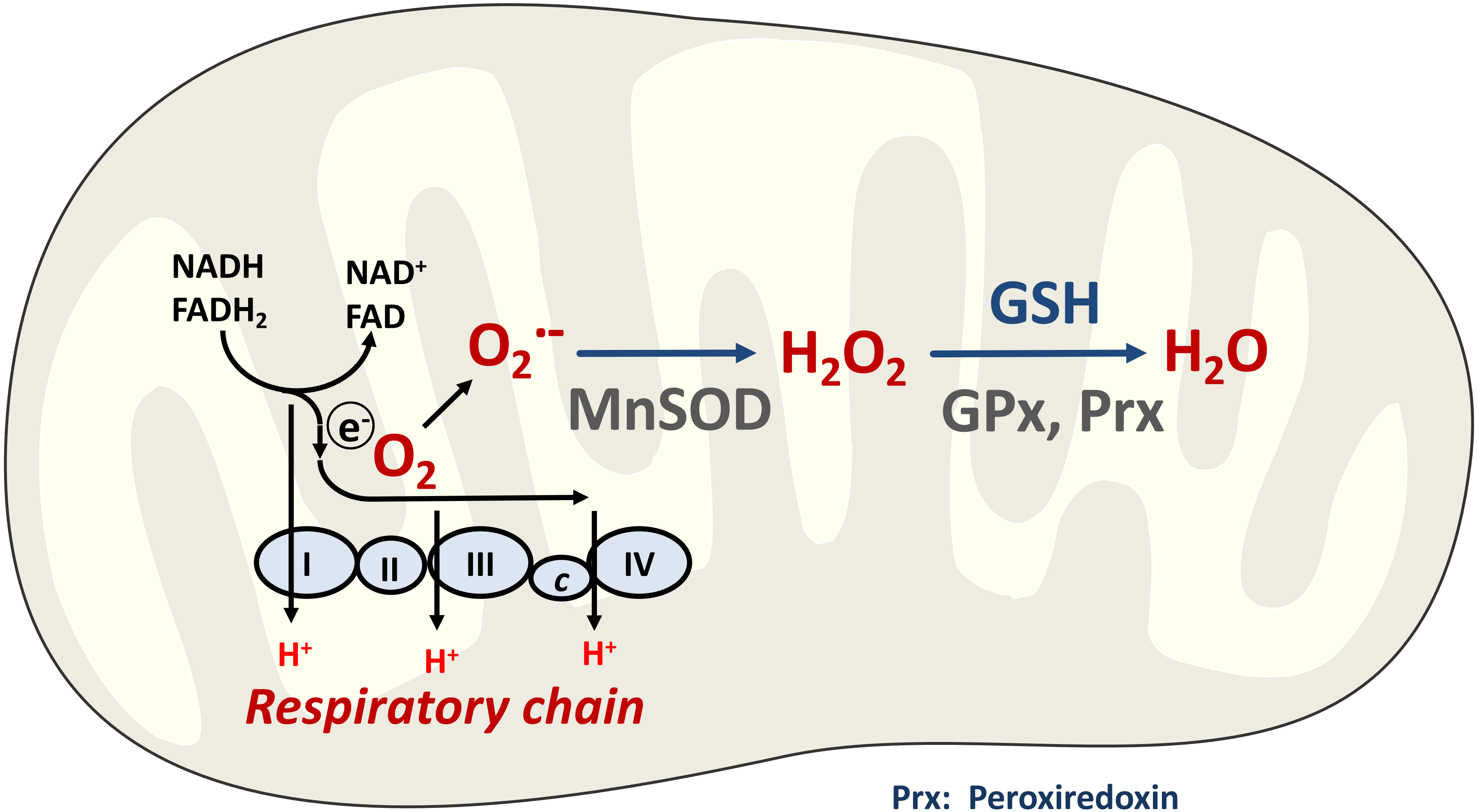
Physiological role of mitochondrial ROS



NFE2L2: NFE2 like bZIP transcription factor 2

SOD: superoxide dismutase
TXN: Thioredoxin
GPX: Glutathione peroxidase
GSR: Glutathione-disulfide reductase

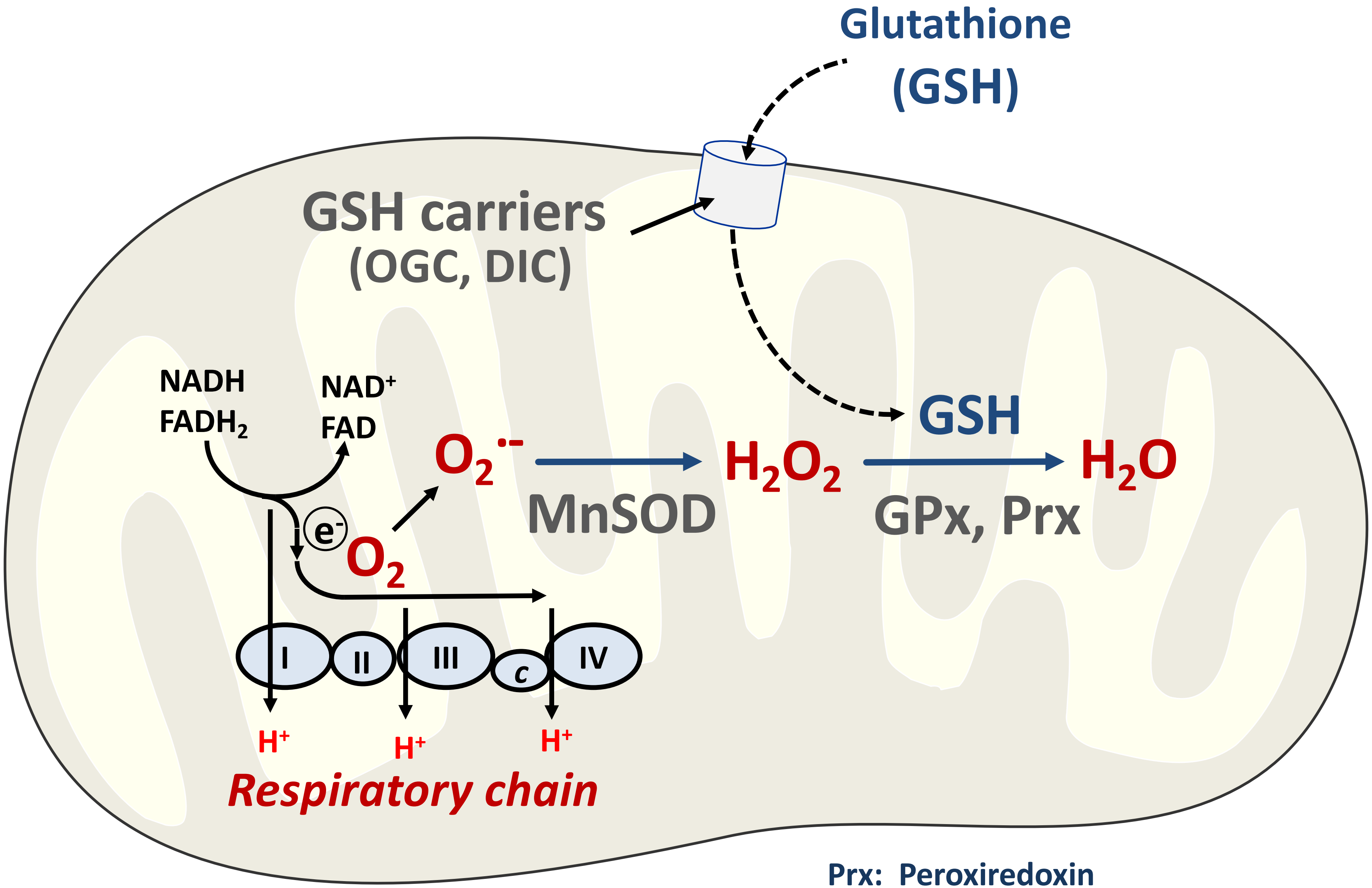
Mitochondrial antioxidant defenses



OGC: Oxoglutarate carrier
DIC: Dicarboxylate carrier

Prx: Peroxiredoxin
GPx: Glutathione peroxidase
MnSOD (SOD2): Mn superoxide dismutase

Mitochondrial antioxidant defenses



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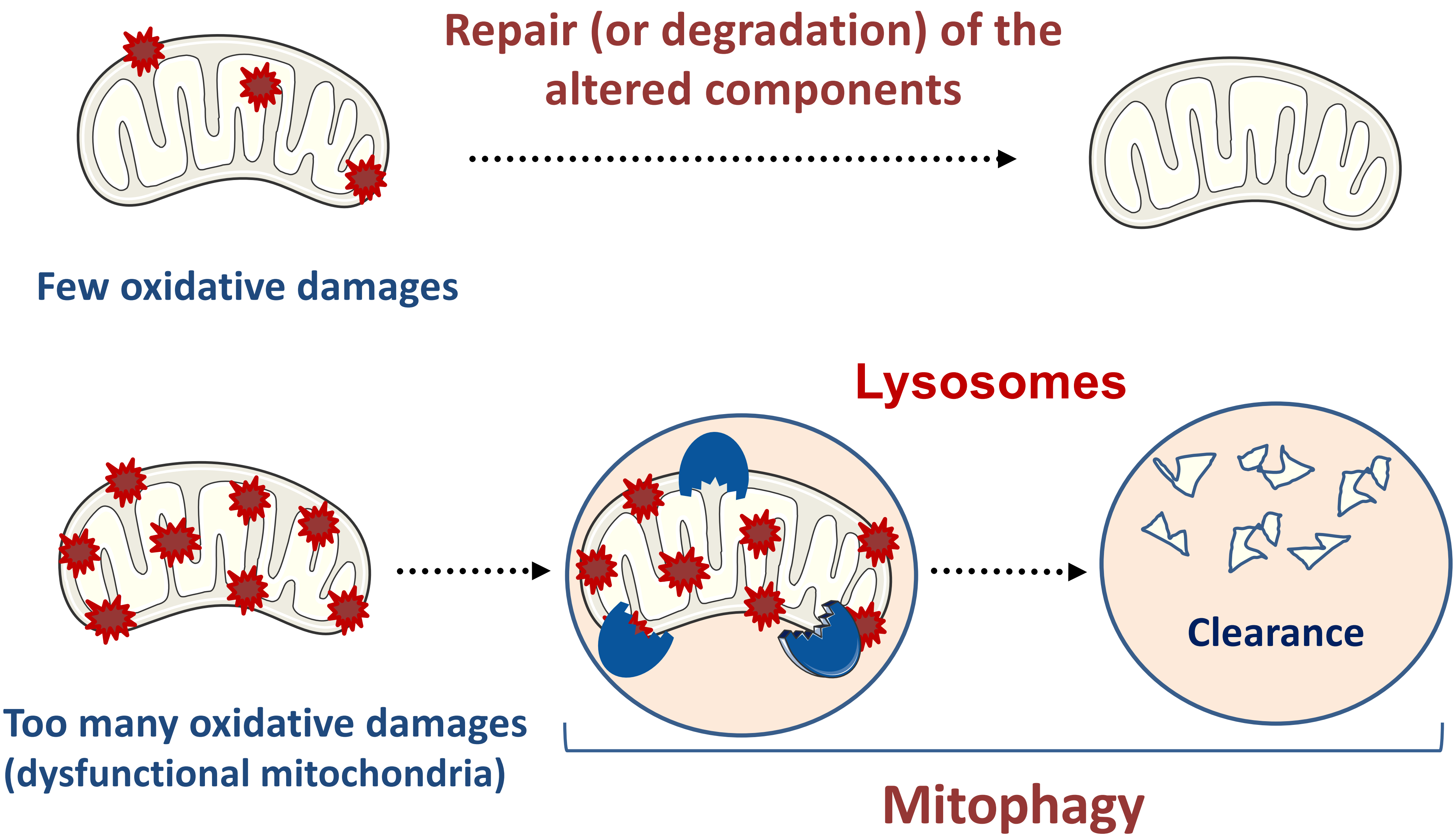
DIC: Dicarboxylate carrier

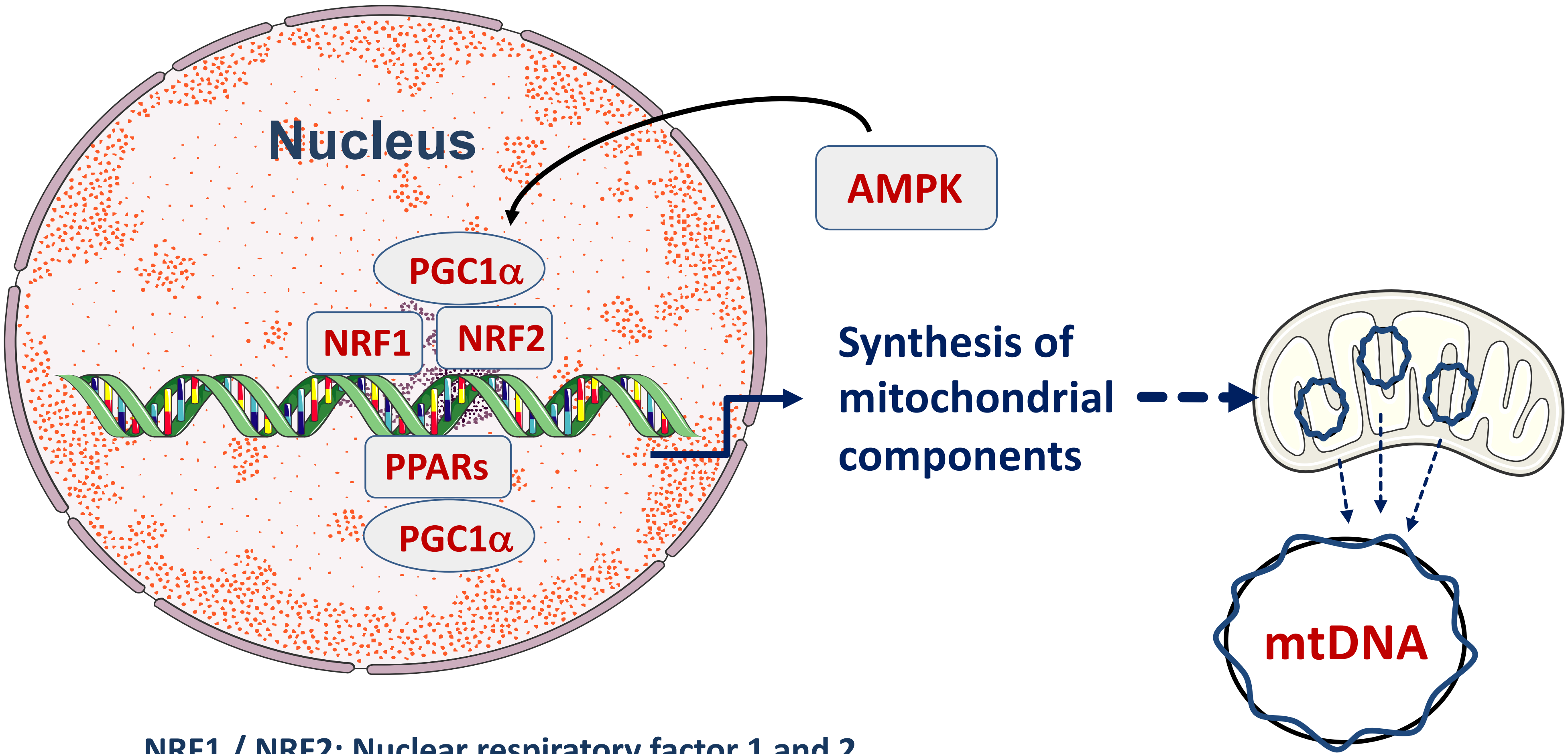
Prx: Peroxiredoxin
GPx: Glutathione peroxidase
MnSOD (SOD2): Mn superoxide dismutase

Systems of mitochondrial quality control

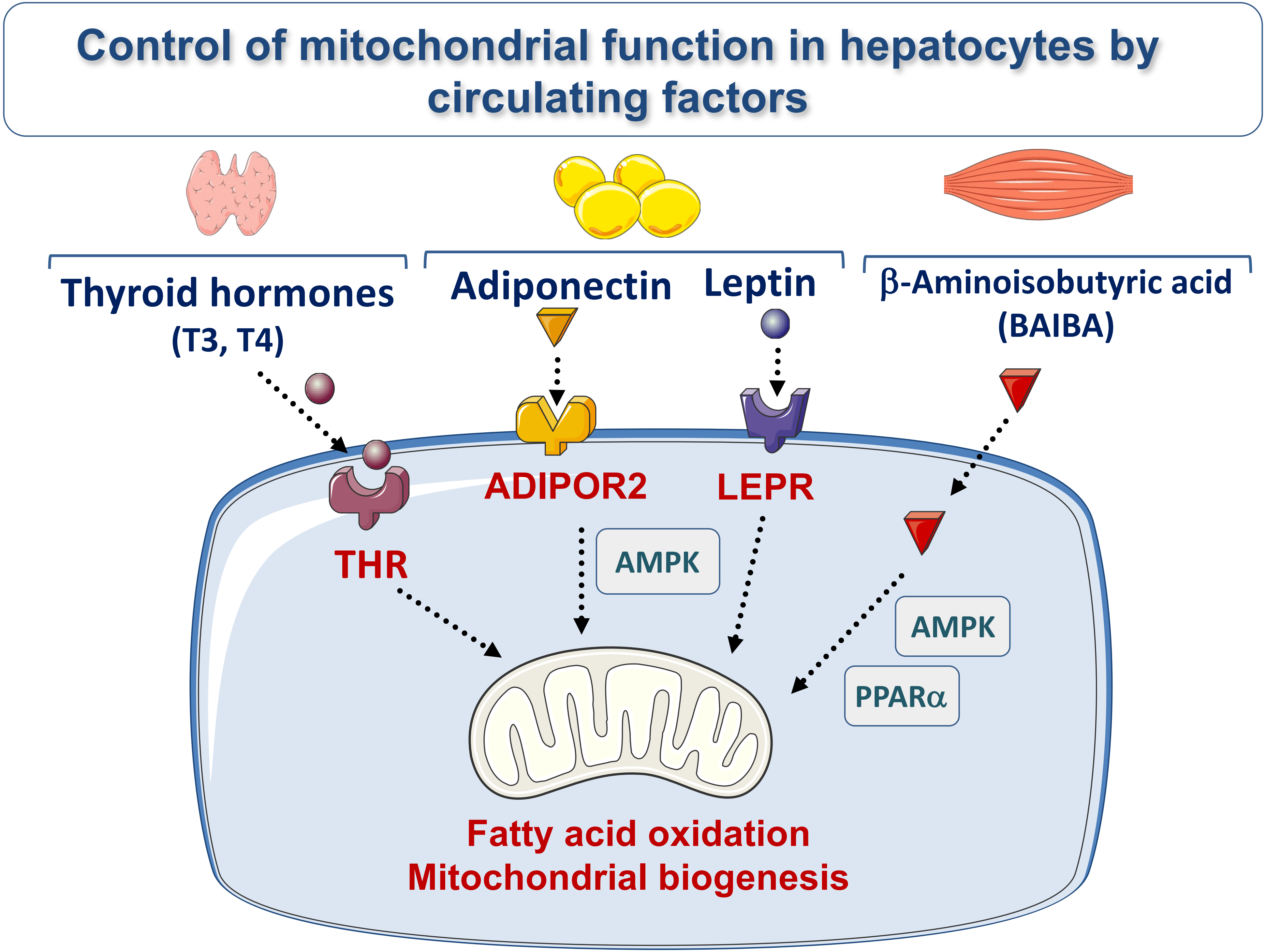


Regulation of mitochondrial biogenesis

When cells require new (healthy) mitochondria

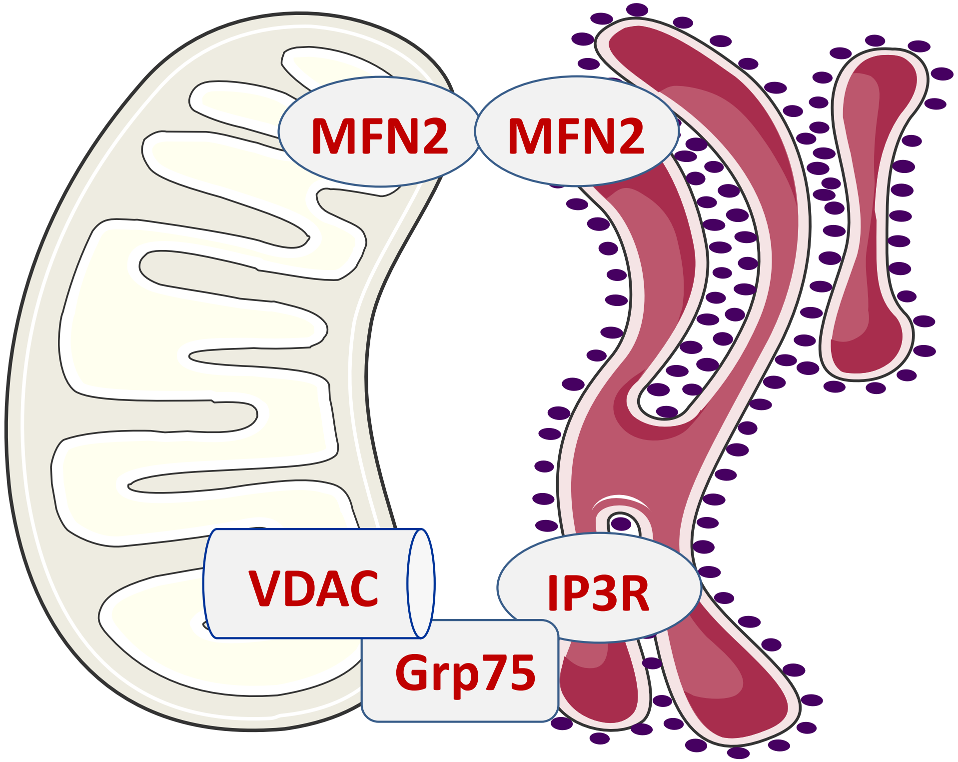


NRF1 / NRF2: Nuclear respiratory factor 1 and 2
AMPK: AMP-activated protein kinase
PPARs: Peroxisome proliferator-activated receptors
PGC1α: Peroxisome proliferator-activated receptor-γ coactivator 1α


Control of mitochondrial function in hepatocytes by circulating factors
Thyroid hormones
(T3, T4)
Adiponectin
Leptin
β-Aminoisobutyric acid
(BAIBA)
ADIPOR2
LEPR
THR
AMPK
AMPK
PPARα
Fatty acid oxidation
Mitochondrial biogenesis

Interactions between mitochondria and endoplasmic reticulum

Mitochondria-associated ER membranes (MAMs)

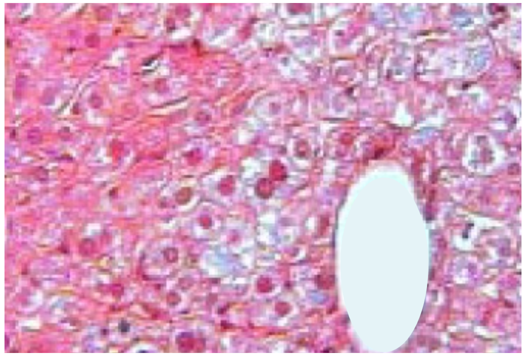


MFN2: Mitofusin 2
VDAC: Voltage-dependent anion channel
Grp75: Glucose-related protein 75
IP3R : Inositol triphosphate receptor

Physiological roles in:

- Exchange of calcium
- Lipid and glucose homeostasis
- Insulin signaling

Origins of mitochondrial alterations in NAFLD

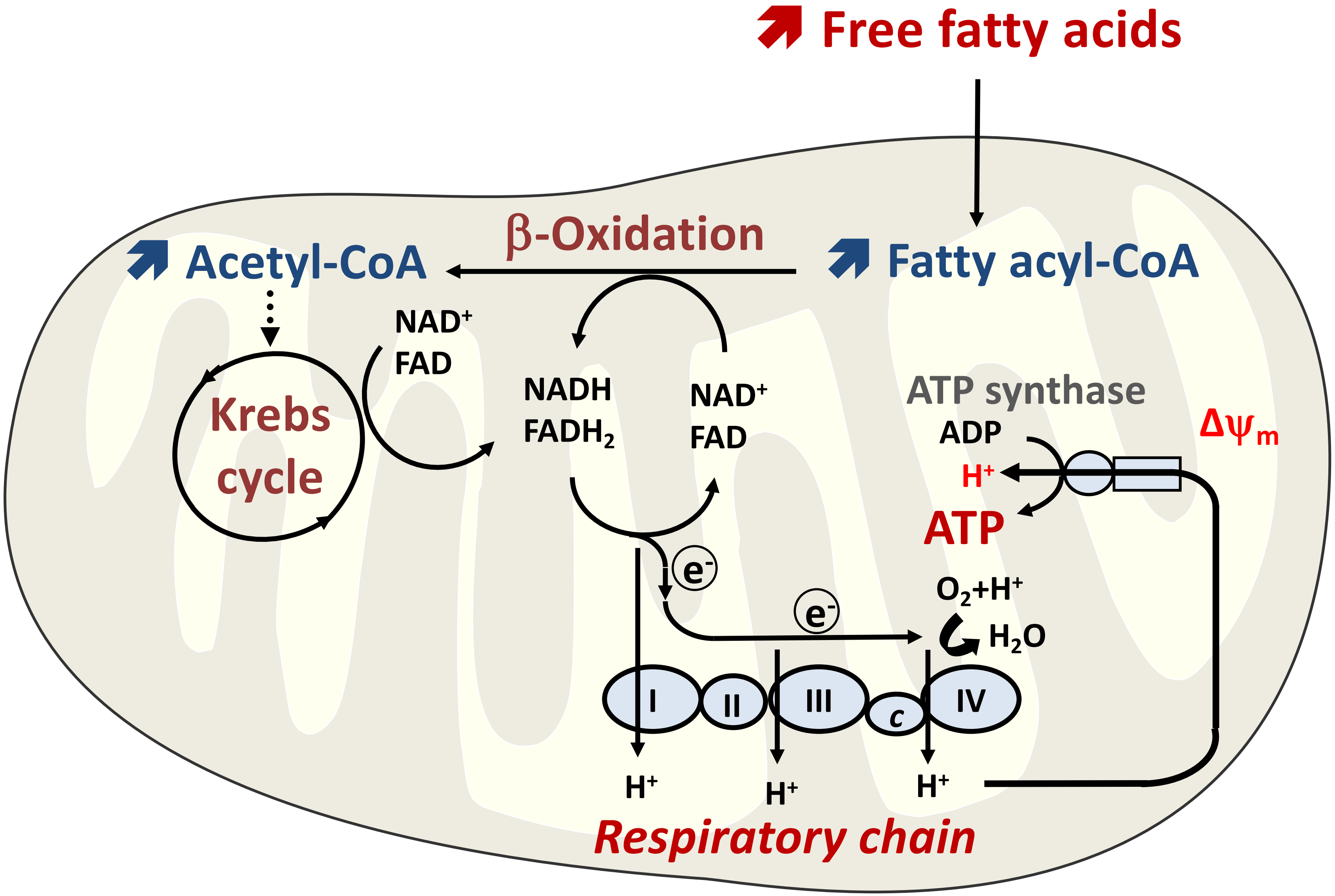


☑ Experimental studies ✚ ✚ ✚
☑ Clinical investigations ✚

NAFL is associated with increased mitochondrial oxidative metabolism

Sunny *et al.*, Trends Endocrinol Metab 2017

Fromenty & Roden, J Hepatol 2023



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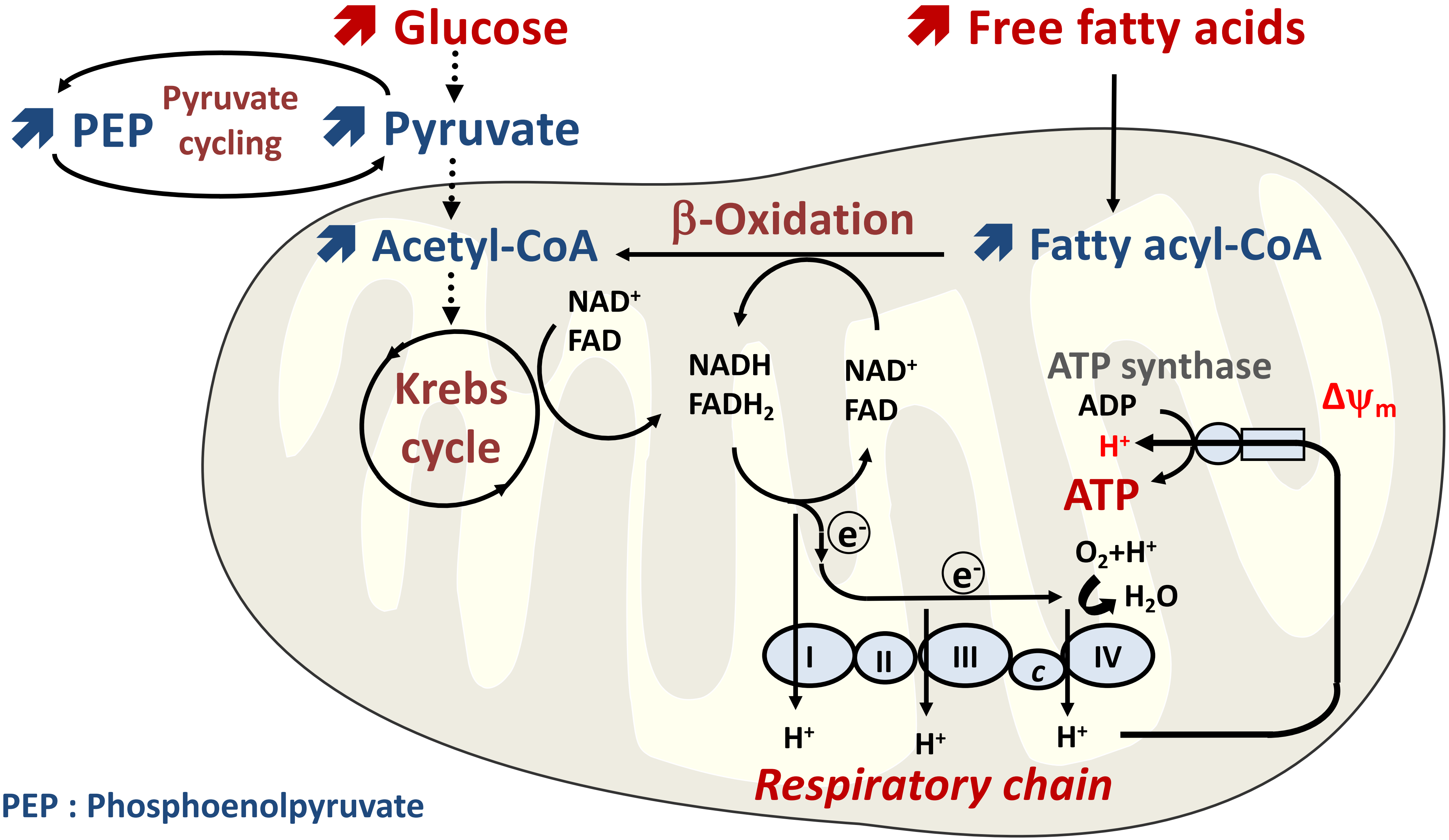
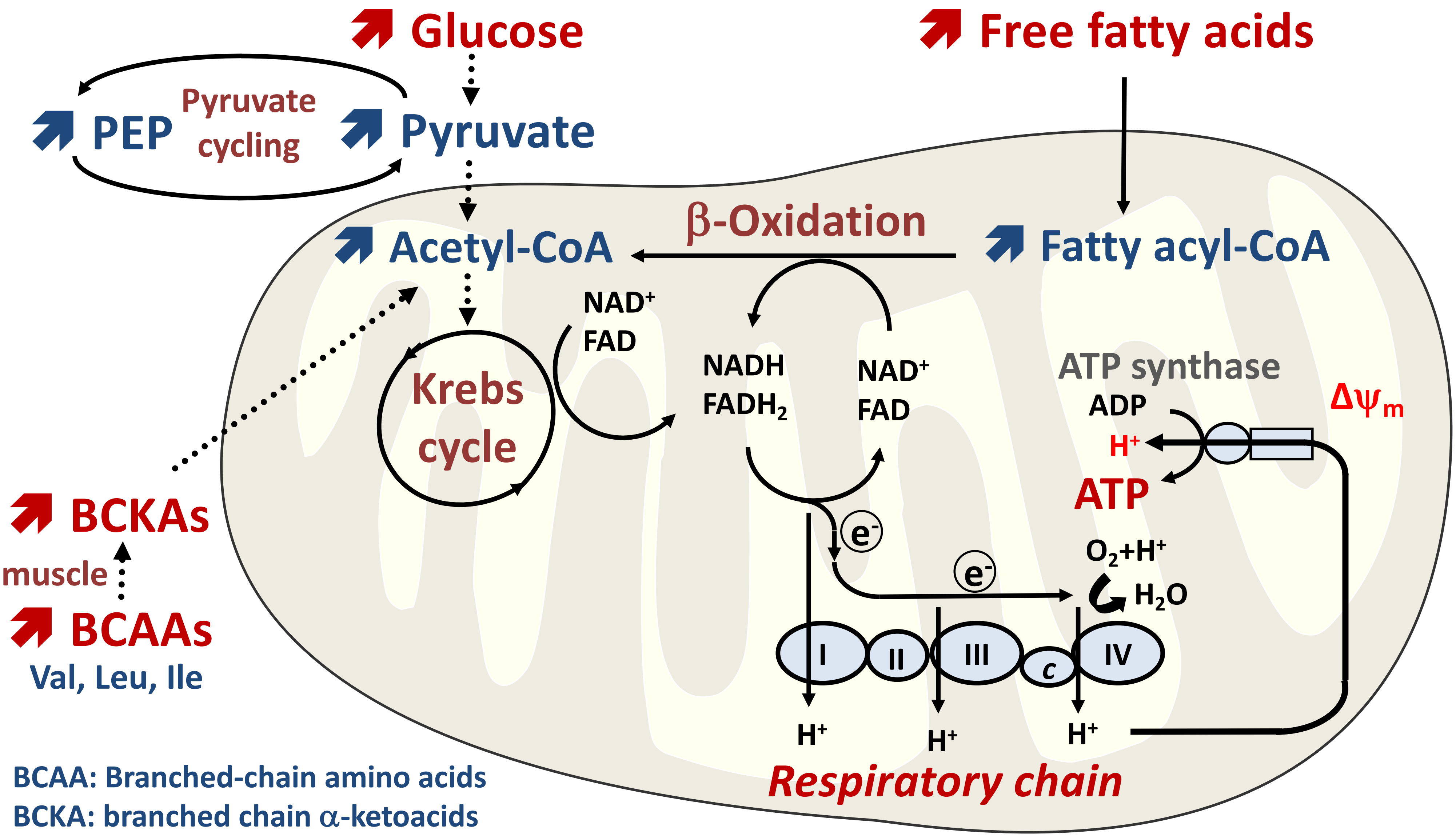


PEP : Phosphoenolpyruvate

NAFL is associated with increased mitochondrial oxidative metabolism

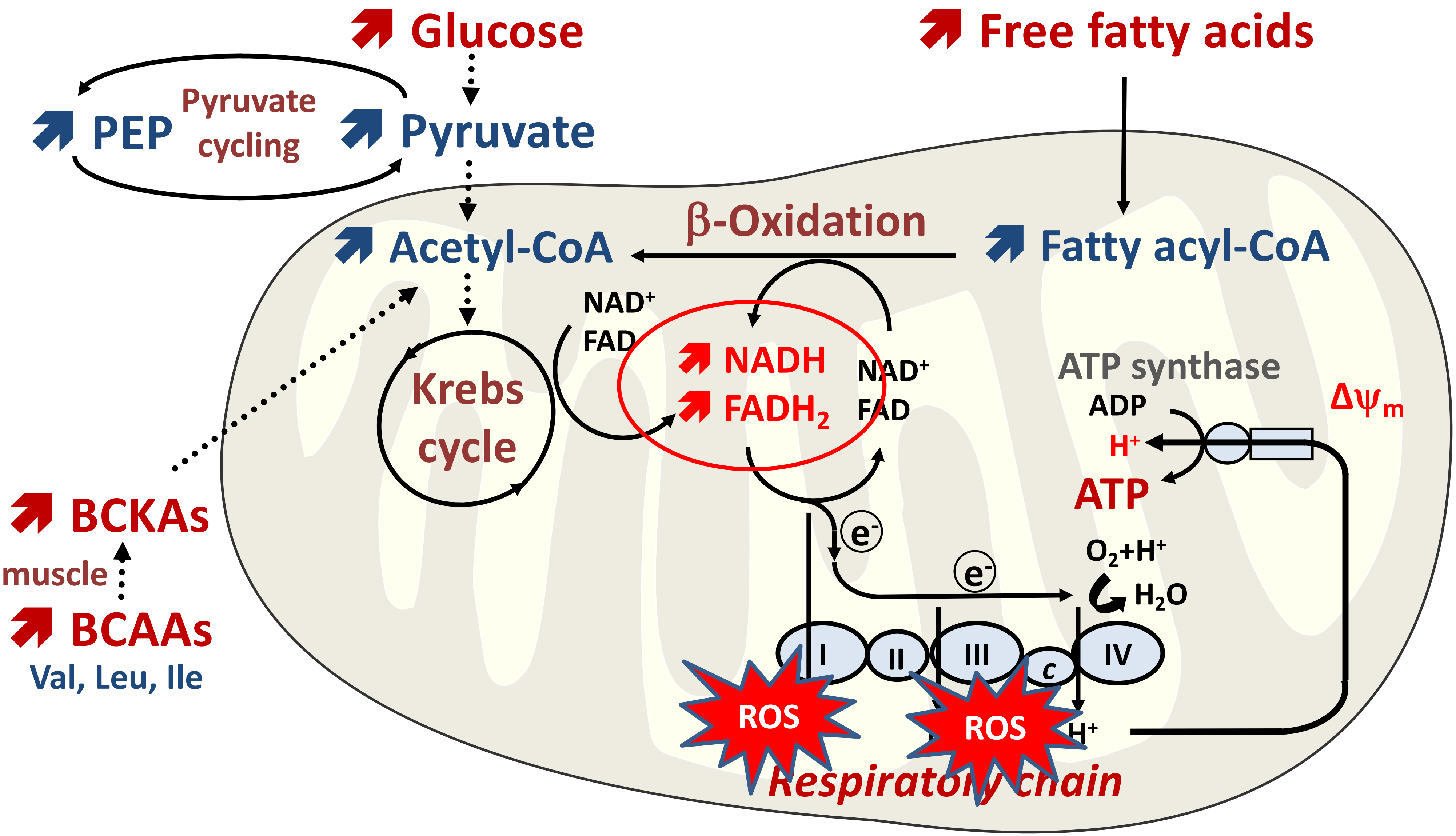
Sunny *et al.*, Trends Endocrinol Metab 2017 Fromenty & Roden, J Hepatol 2023



BCAA: Branched-chain amino acids
BCKA: branched chain α-ketoacids

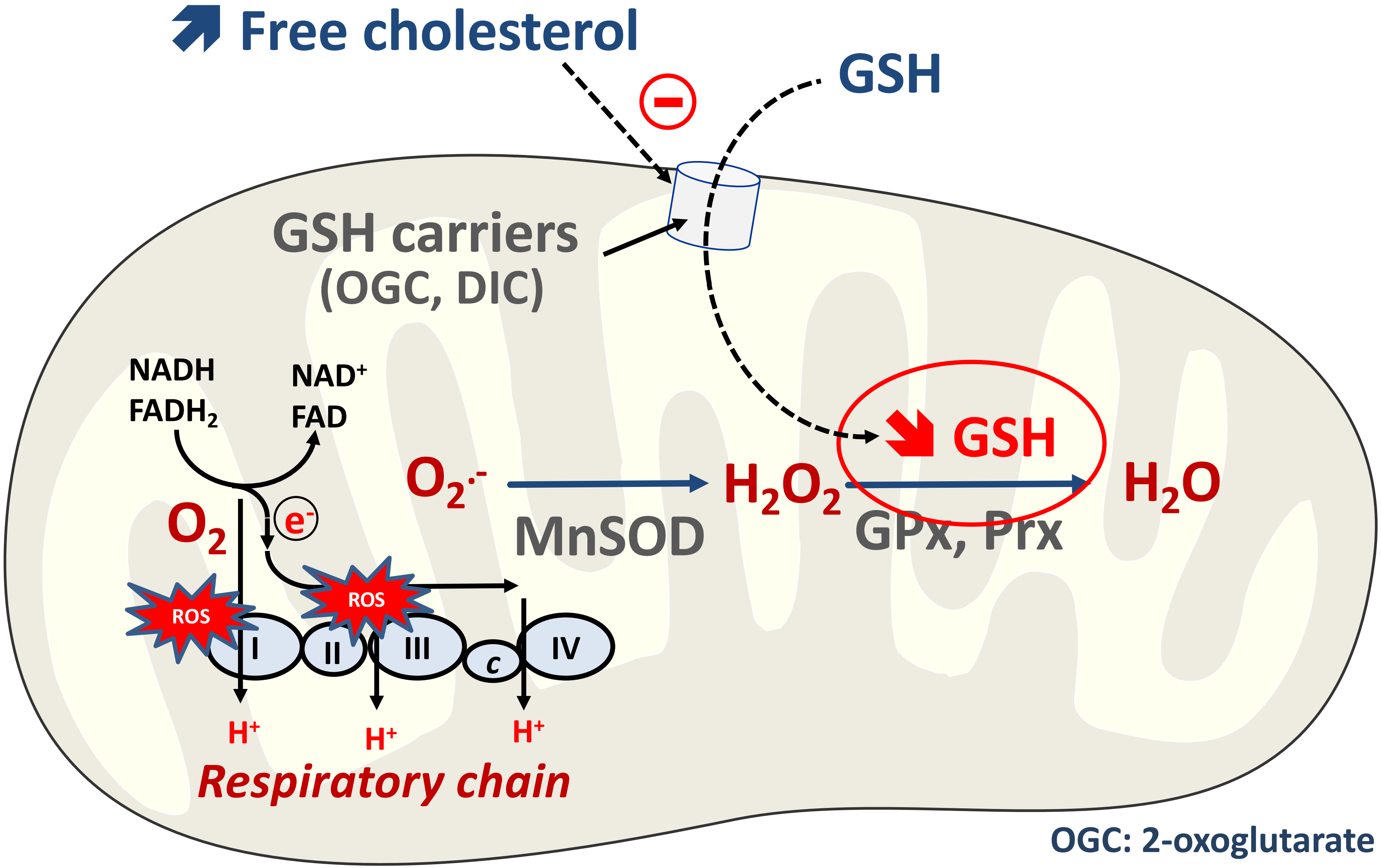
NAFL is associated with increased mitochondrial oxidative metabolism

Sunny *et al.*, Trends Endocrinol Metab 2017   Fromenty & Roden, J Hepatol 2023



NAFL can be associated with reduced mitochondrial glutathione levels

Mari *et al.*, Antioxidants 2020 Horn *et al.*, Hepatol Commun 2022



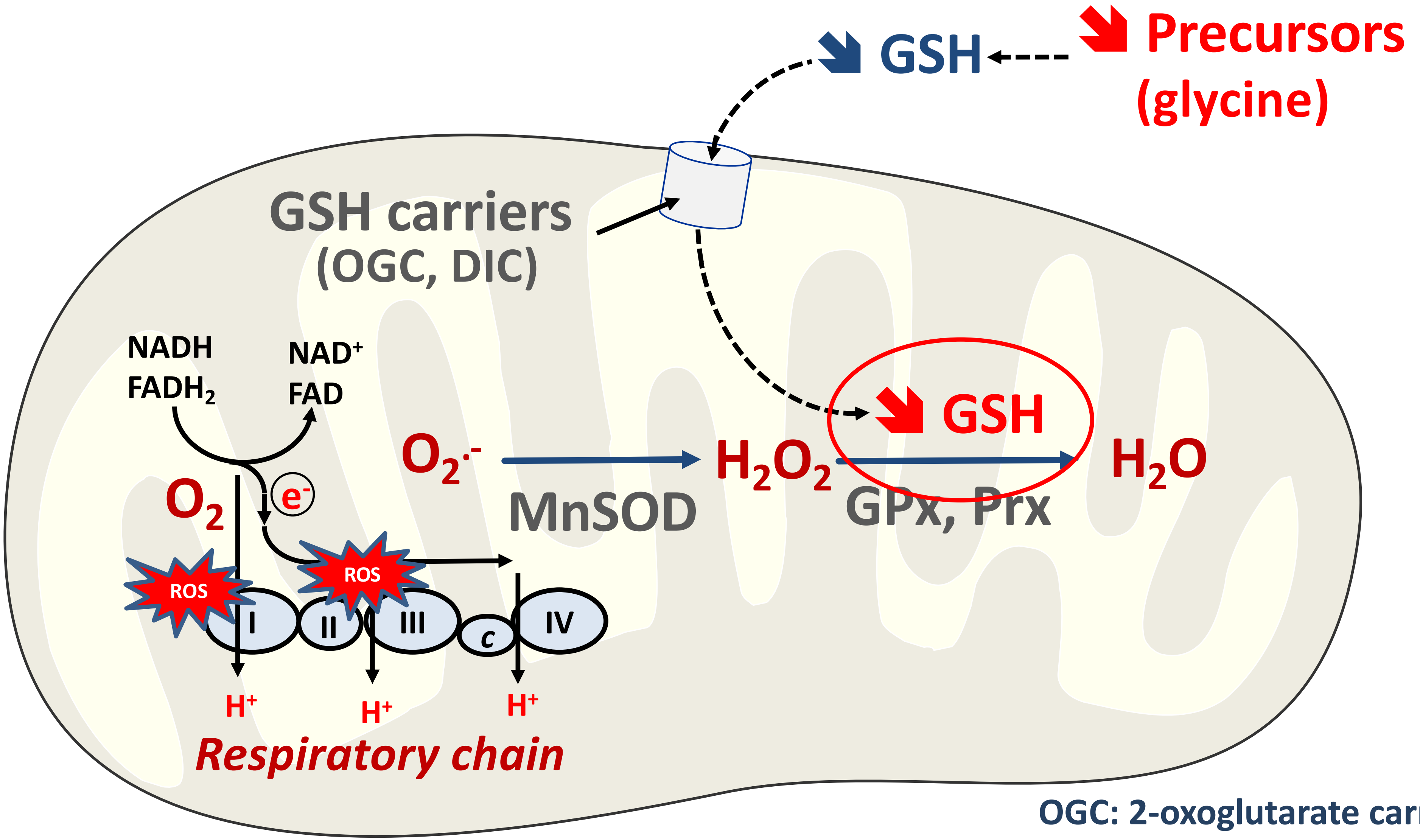
OGC: 2-oxoglutarate carrier
DIC : dicarboxylate carrier

• 2020

NAFL can be associated with reduced mitochondrial glutathione levels

Rom *et al.*, Sci Transl Med 2020

Ghrayeb *et al.*, bioRxiv 2023

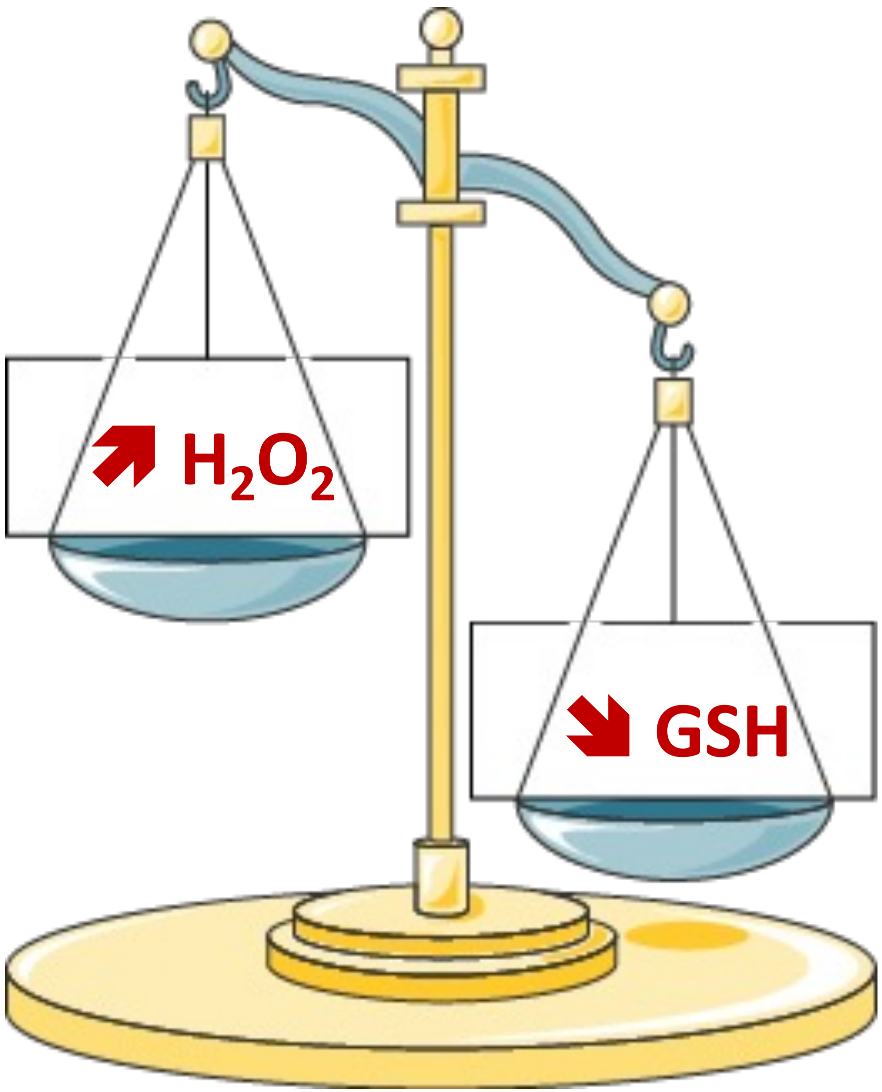


OGC: 2-oxoglutarate carrier

DIC : dicarboxylate carrier

Unbalance between ROS production and GSH levels

Seika *et al.*, Cell Mol Gastroenterol Hepatol 2022   Podszun *et al.*, J Histochem Cytochem 2020



NAFL and impairment of antioxidant defenses

Yang *et al.*, Arch Biochem Biophys 2000
Lazarin *et al.*, Exp Mol Pathol 2011
Nadal-Casellas *et al.*, Cell Physiol Biochem 2010
Videla *et al.*, Clin Sci 2004
Robin *et al.*, Hepatology 2005
Besse-Patin *et al.*, Gastroenterology 2017

NAFL can also be associated with reduced expression and activity of different antioxidant enzymes (*mitochondrial):

- ☒ **Cu/Zn superoxide dismutase (SOD1)**
- ☒ **Mn superoxide dismutase (SOD2)***
- ☒ **Glutathione peroxidase (GPx)***
- ☒ **Glutathione S-transferase (GST)***

NAFL and impairment of antioxidant defenses

Li *et al.*, Oxid Med Cell Longev 2016

Wang *et al.*, Can J Physiol Pharmacol 2017

Yang *et al.*, Food Funct 2019

Piñeiro-Ramil *et al.*, Antioxidants 2022

Mateus & Prip-Buus, Eur J Clin Invest 2022

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- ☒ Mn superoxide dismutase (SOD2)*
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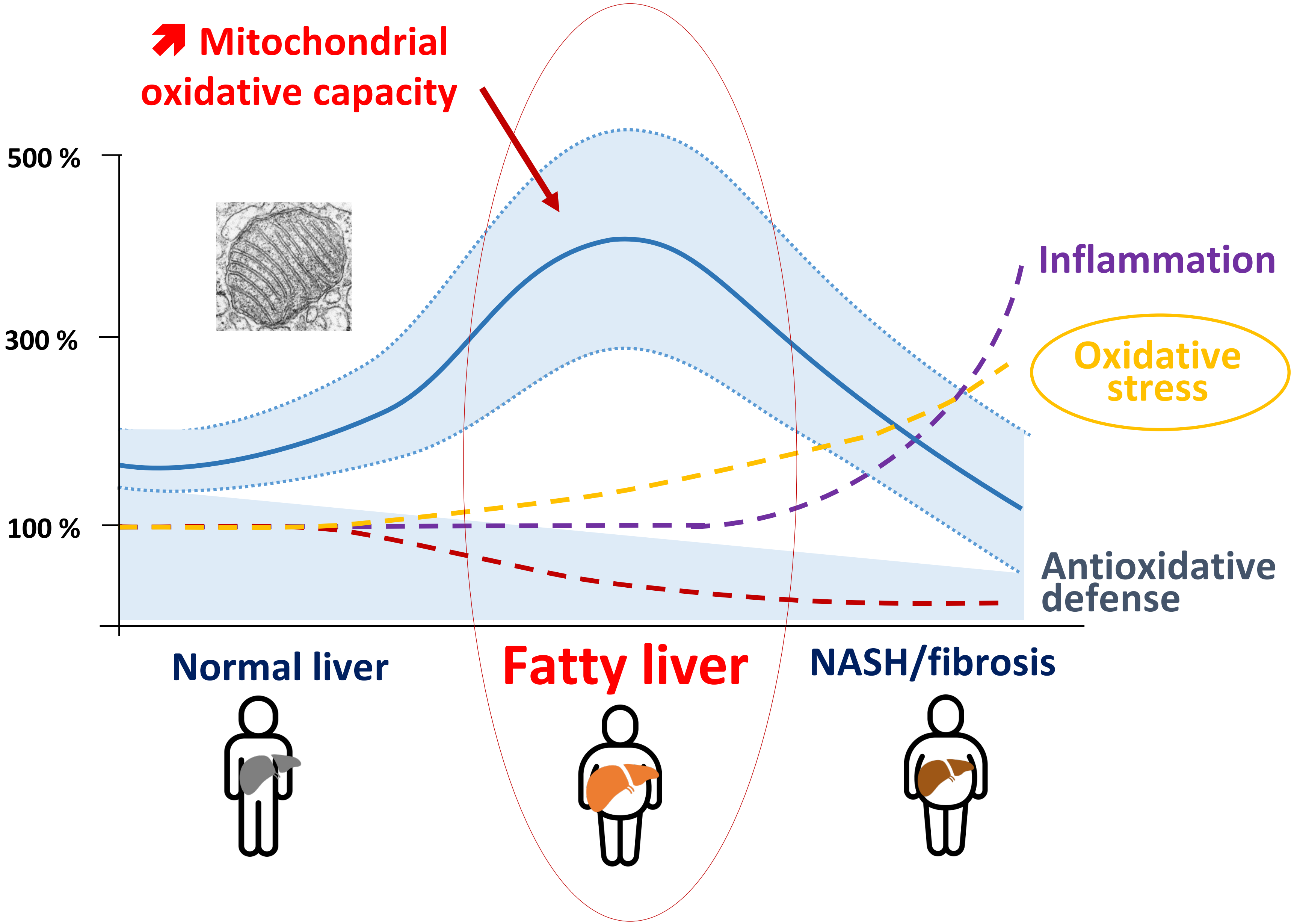
↘ H_2S

↓ ?

↘ Nrf-2

Mitochondrial oxidative capacity during NAFLD

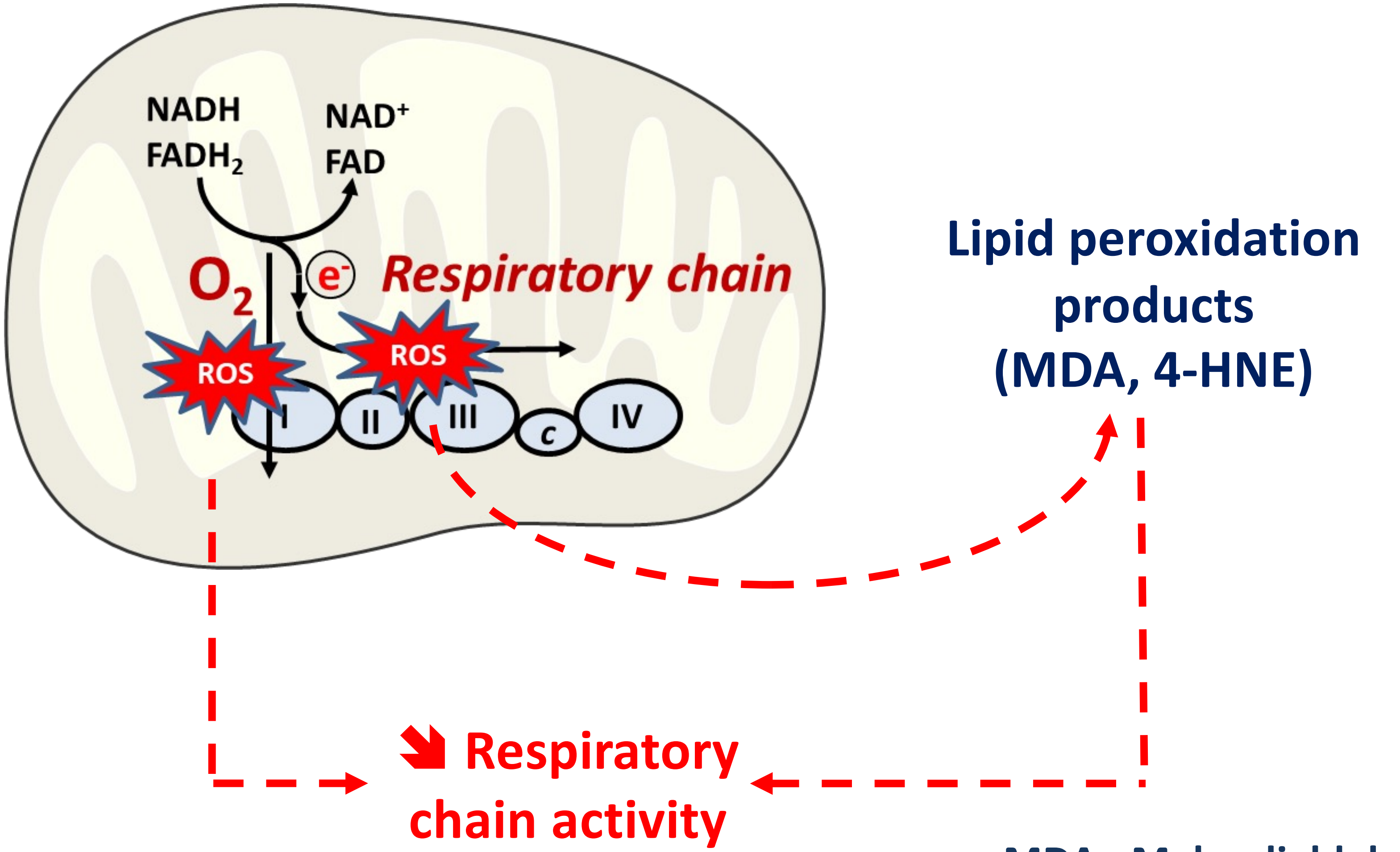


Adapted from Fromenty and Roden, J Hepatol 2023

Mitochondrial alterations in the NAFL to NASH transition: the vicious circle hypothesis

Begriche *et al.*, Hepatology 2013 Dornas & Schuppan, Am J Physiol 2020

Mansouri *et al.*, Gastroenterology 2018



MDA: Malondialdehyde
4-HNE: 4-Hydroxynonenal

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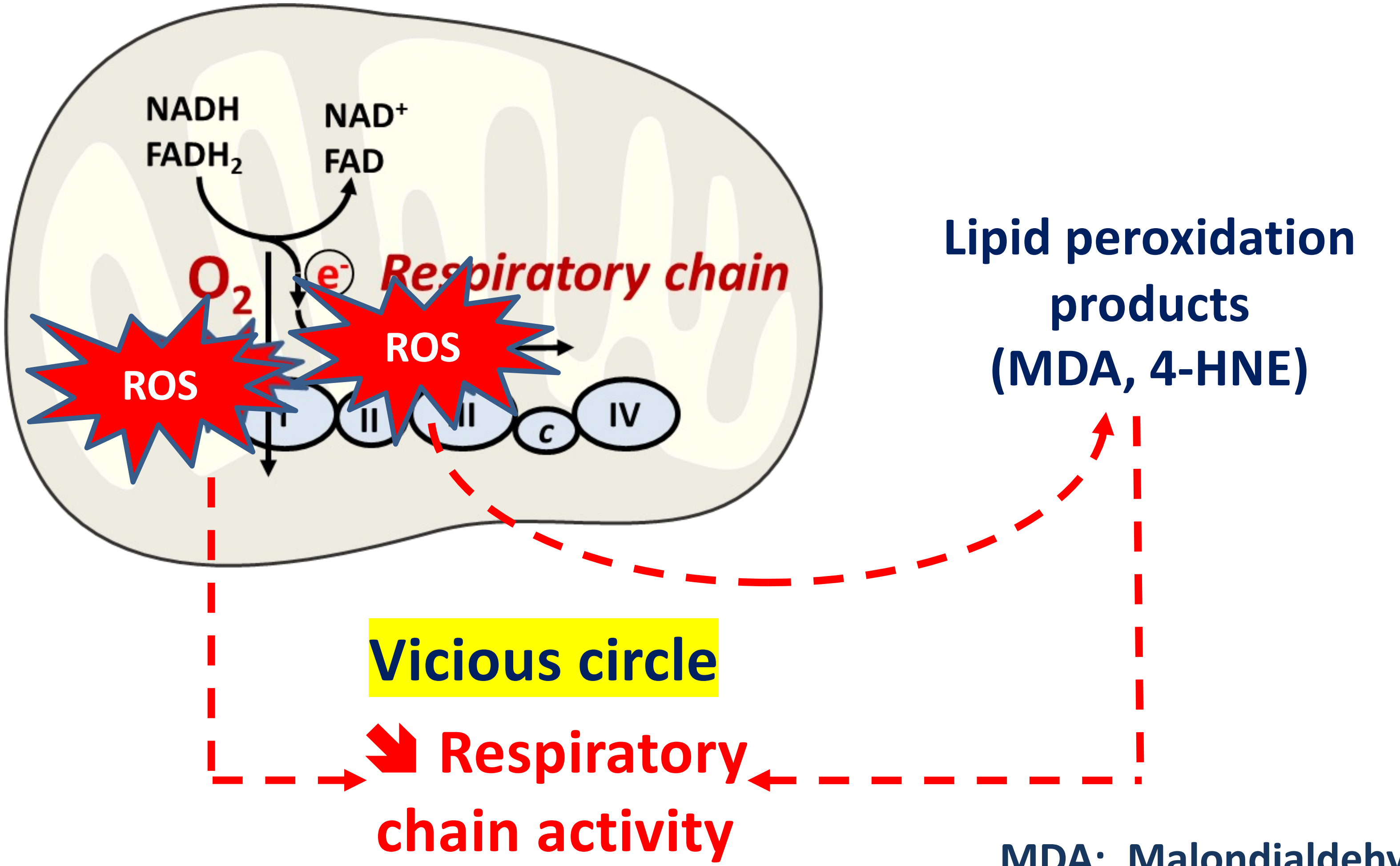

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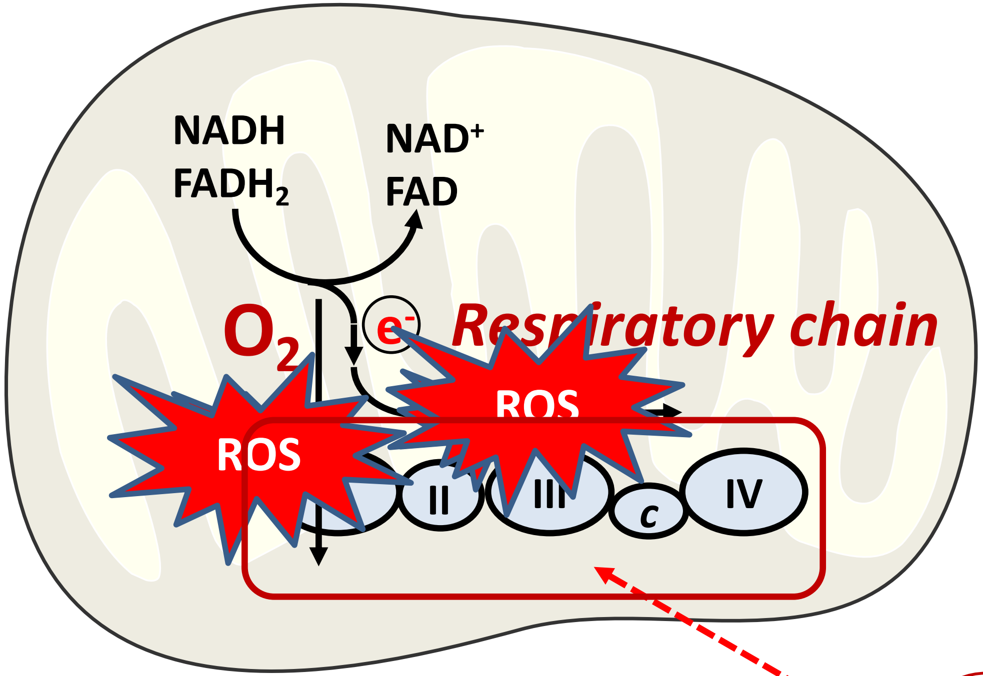


ROS and lipid peroxidation products

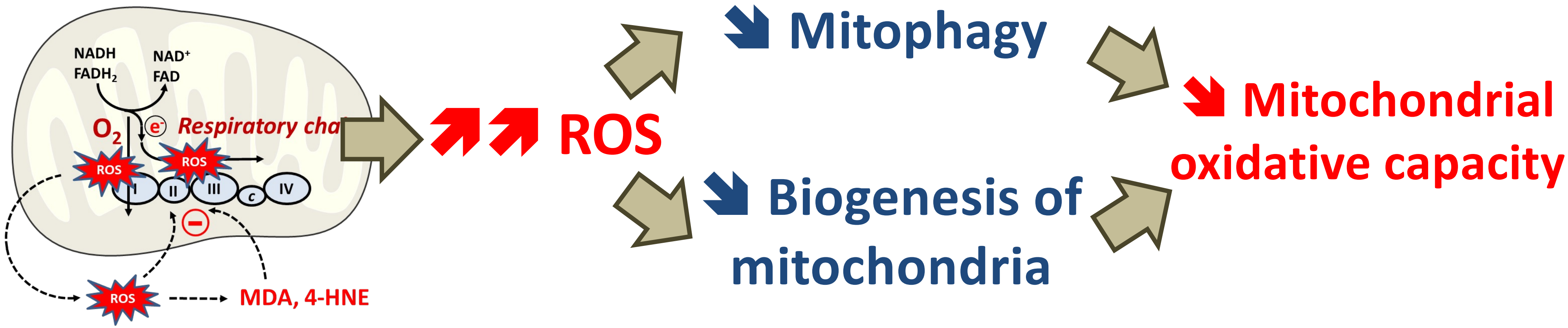
☑ Direct oxidative inactivation of respiratory chain complexes (Fe-S)

☑ Oxidative damages to mtDNA (mutations, deletions)

Other causes of mitochondrial alterations in NAFL/NASH

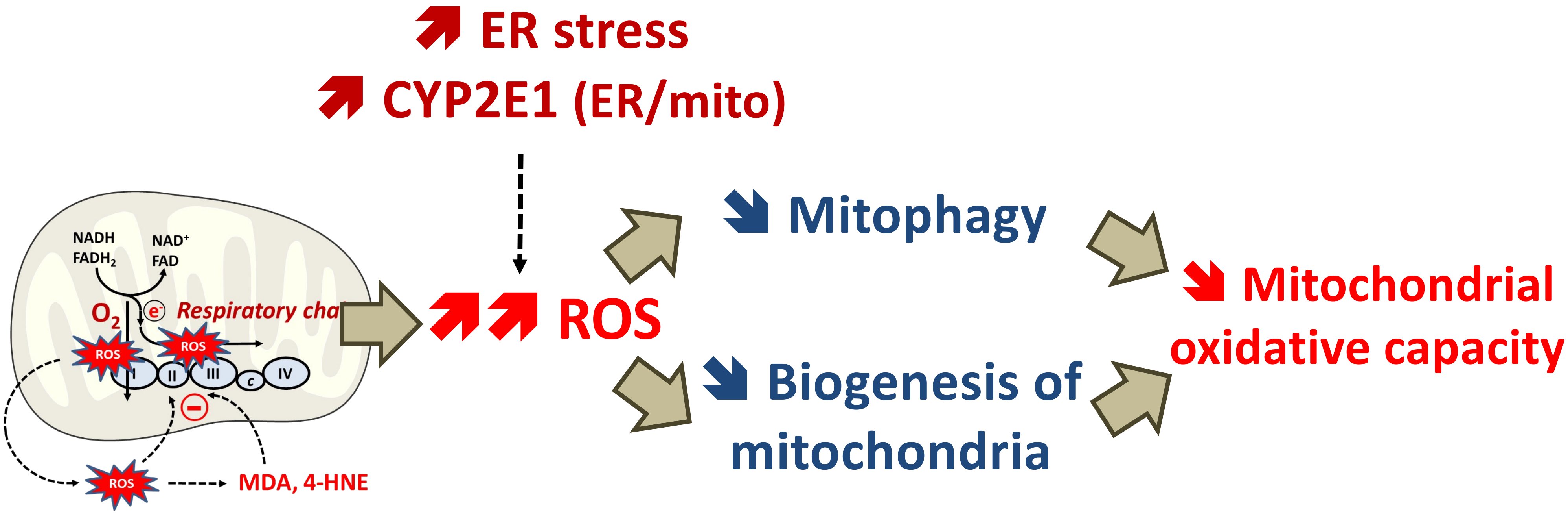
Koliaki *et al*., Cell Metab 2015 Moore *et al*., Hepatology 2022 Fromenty & Roden, J Hepatol 2023

Undamatla *et al*., Sci Rep 2023 Jin *et al*., J Hepatol 2023



Other causes of mitochondrial alterations in NAFL/NASH

Wang *et al.*, Lipids Health Dis. 2020 Correia & Kwon, Biology 2020 Massart *et al.*, Cells 2022

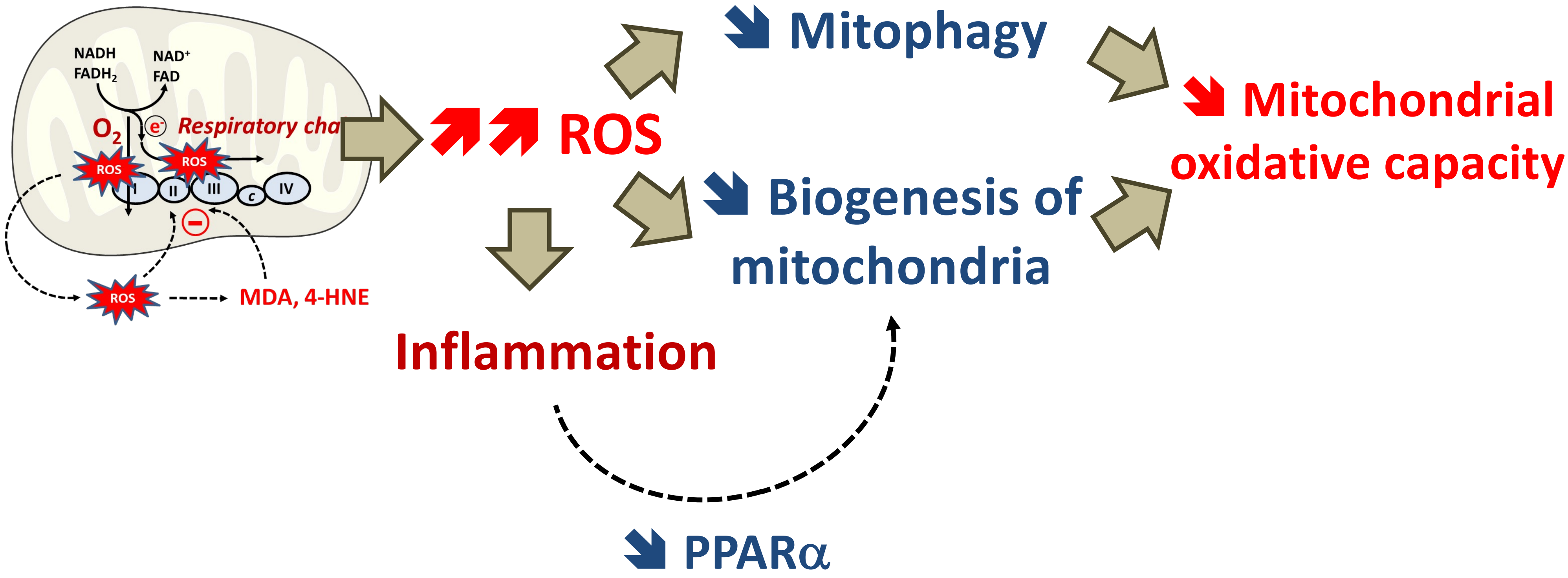


ER: endoplasmic reticulum
CYP2E1 : cytochrome P450 2E1

Other causes of mitochondrial alterations in NAFL/NASH

Koliaki *et al.*, Cell Metab 2015 Moore *et al.*, Hepatology 2022 Fromenty & Roden, J Hepatol 2023

Undamatla *et al.*, Sci Rep 2023 Jin *et al.*, J Hepatol 2023

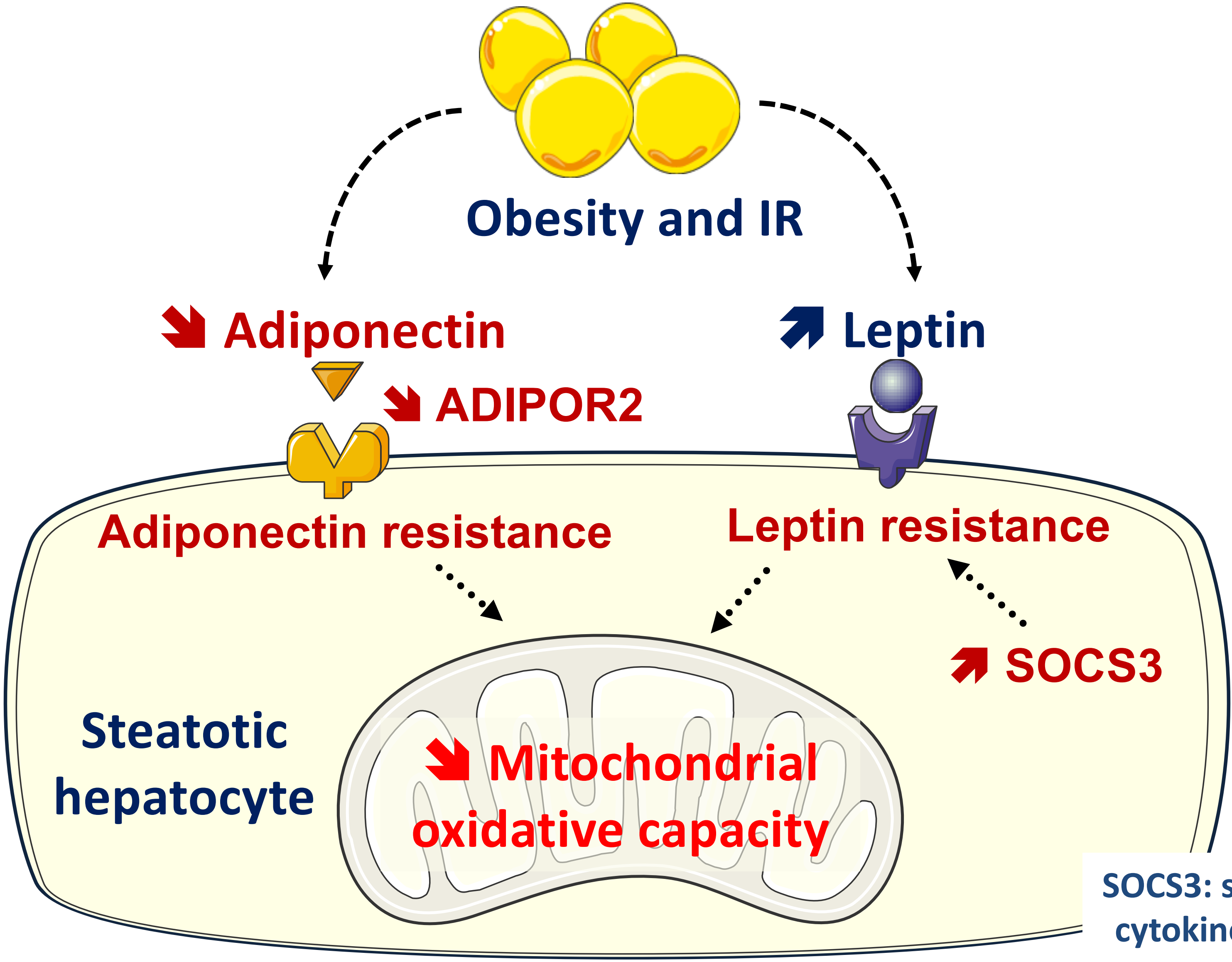


PPARα: peroxisome proliferator-activated receptor-alpha

Other causes of mitochondrial alterations in NAFL/NASH

Moschen *et al*., Current Med Chem 2012
Francisco *et al*., Biology 2022

Sangüesa *et al*., Mol Nutr Food Res 2018
Zhang *et al*., Plos One 2015

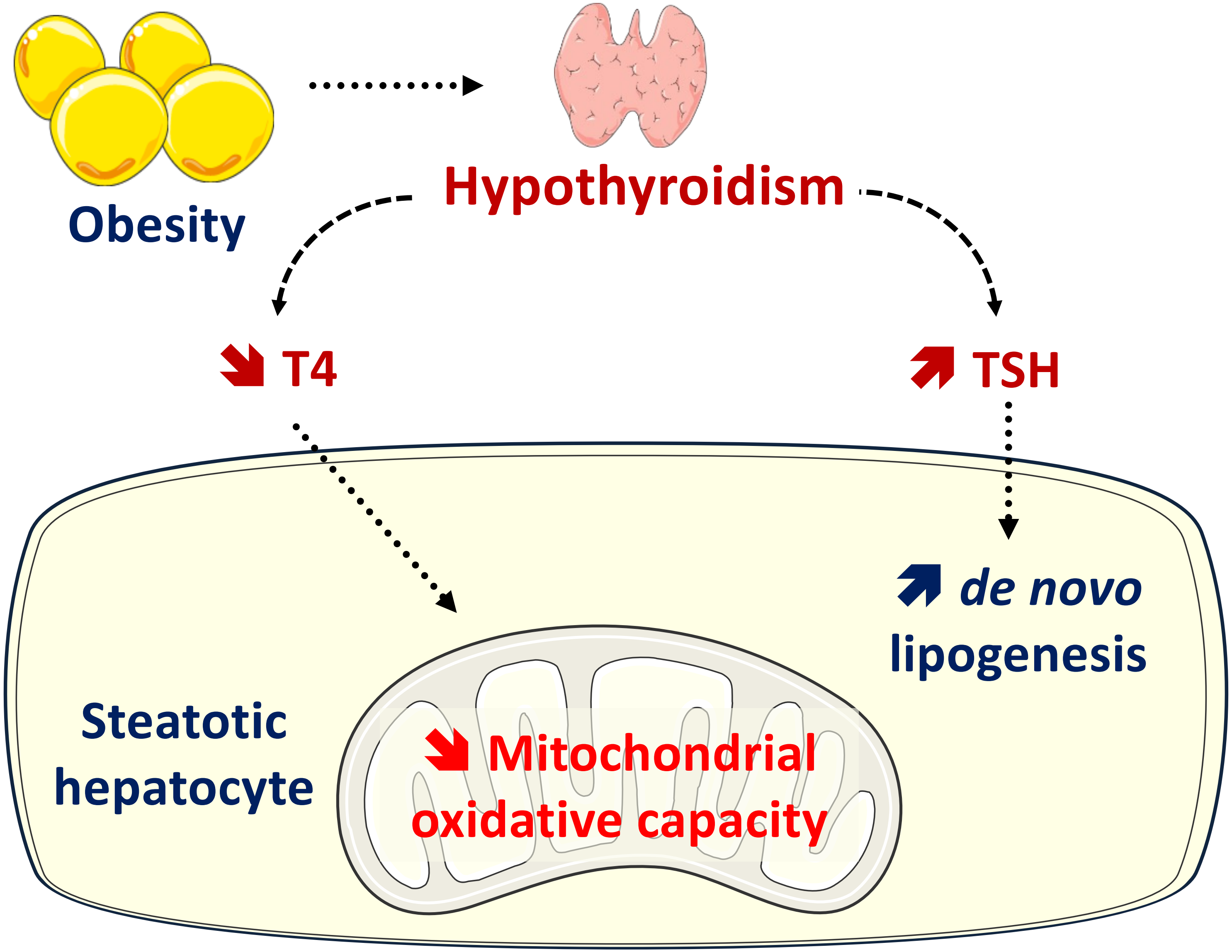


SOCS3: suppressor of cytokine signaling 3

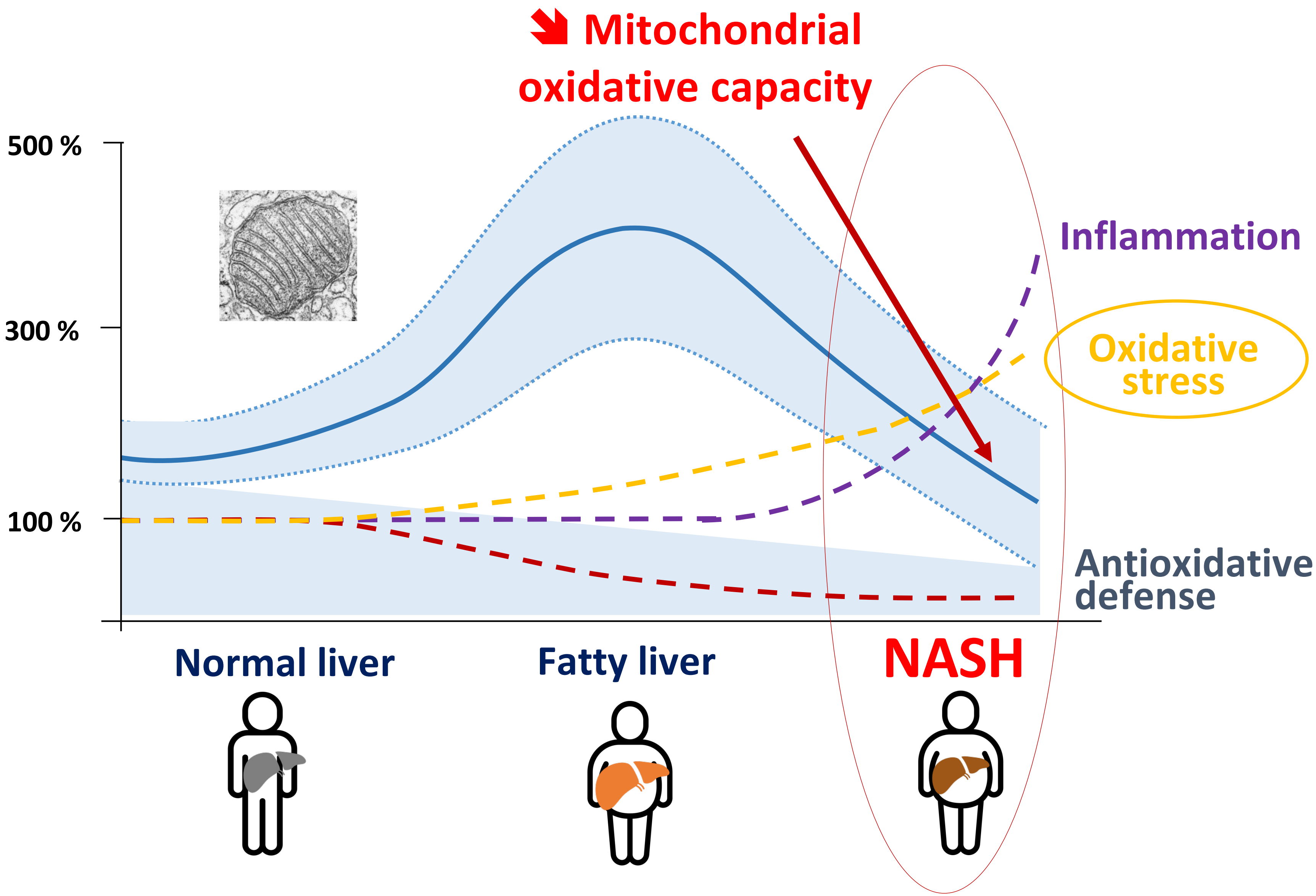
Other causes of mitochondrial alterations in NAFL/NASH

Song *et al.*, Front Immunol 2019

Hatziagelaki *et al.*, Trends Endocr Metab 2022
Zeng *et al.*, Medicine 2021

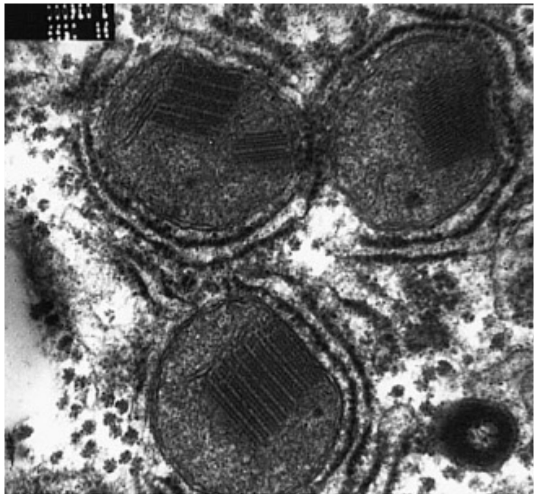


Mitochondrial oxidative capacity during NAFLD



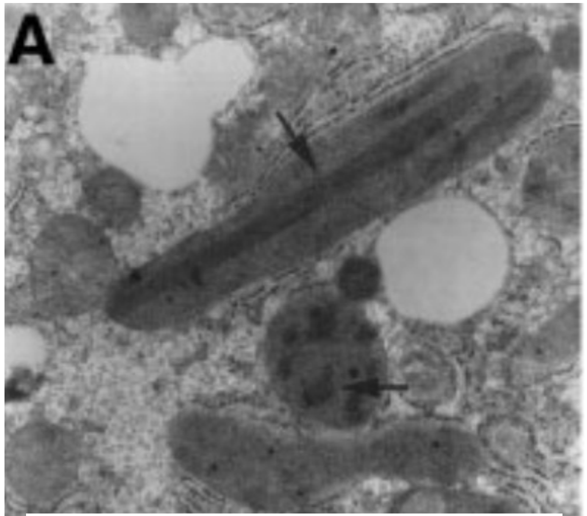
Adapted from Fromenty and Roden, J. Hepatol. 2023

Sanyal *et al.*,
Gastroenterology 2001



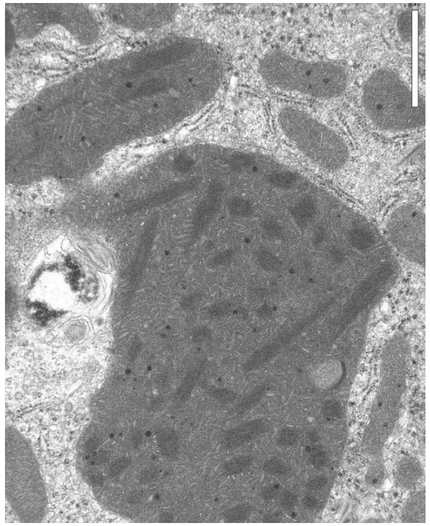
Swollen mitochondria with multi-lamellar membranes

Le *et al.*, Hepatology 2004

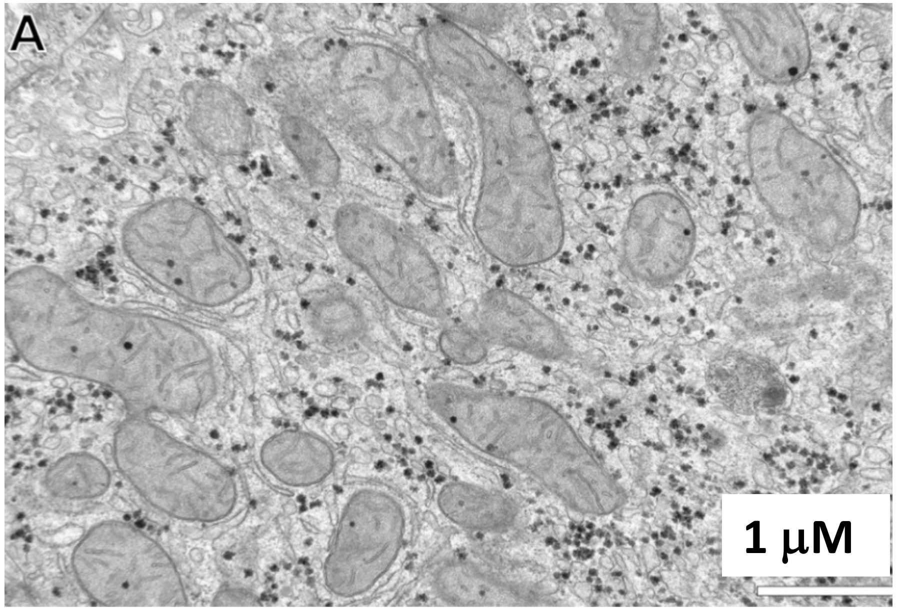


Megamitochondrion with crystalline inclusions

Shami *et al.*, Sci Rep 2021



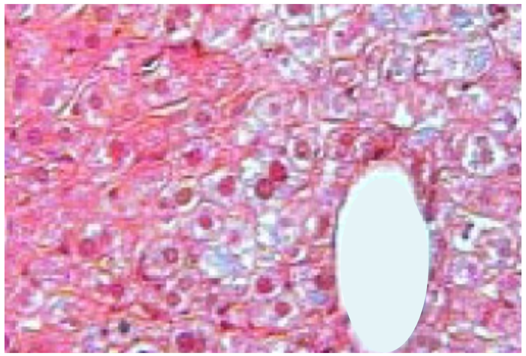
Giant mitochondrion with disrupted cristae



Shami *et al.*, Sci Rep 2021

Liver mitochondria from a healthy individual

Consequences of mitochondrial dysfunction in NAFLD



Hepatocellular consequences of mitochondrial alterations

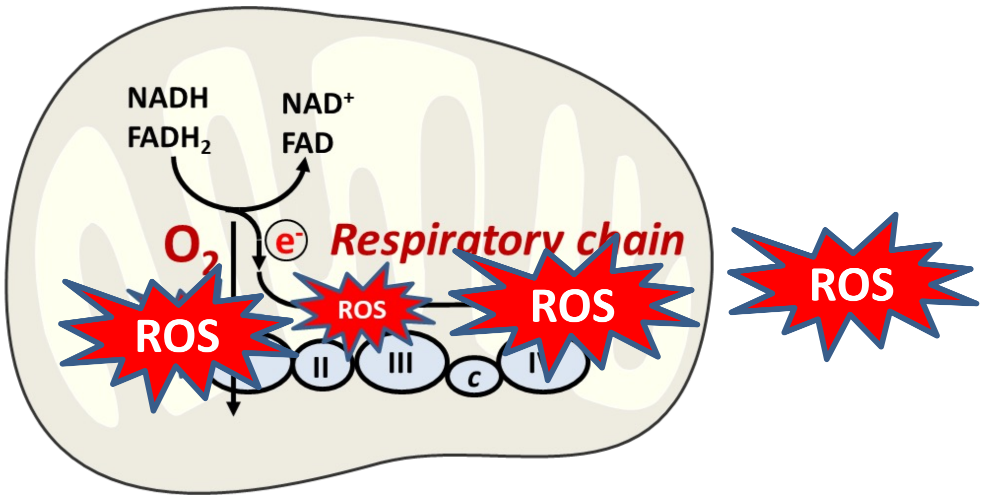
Lim *et al.*, Cell Signal 2009

Rieusset, Cell Death Dis 2018

Guan *et al.*, Exp Gerontol 2013

Guo *et al.*, J Cell Mol Med 2018

Mitochondrial alterations



↗ JNK

↗ p38MAPK

Impairment of insulin signaling

JNK : c-Jun N-terminal kinase

MAPK: mitogen activated protein kinase

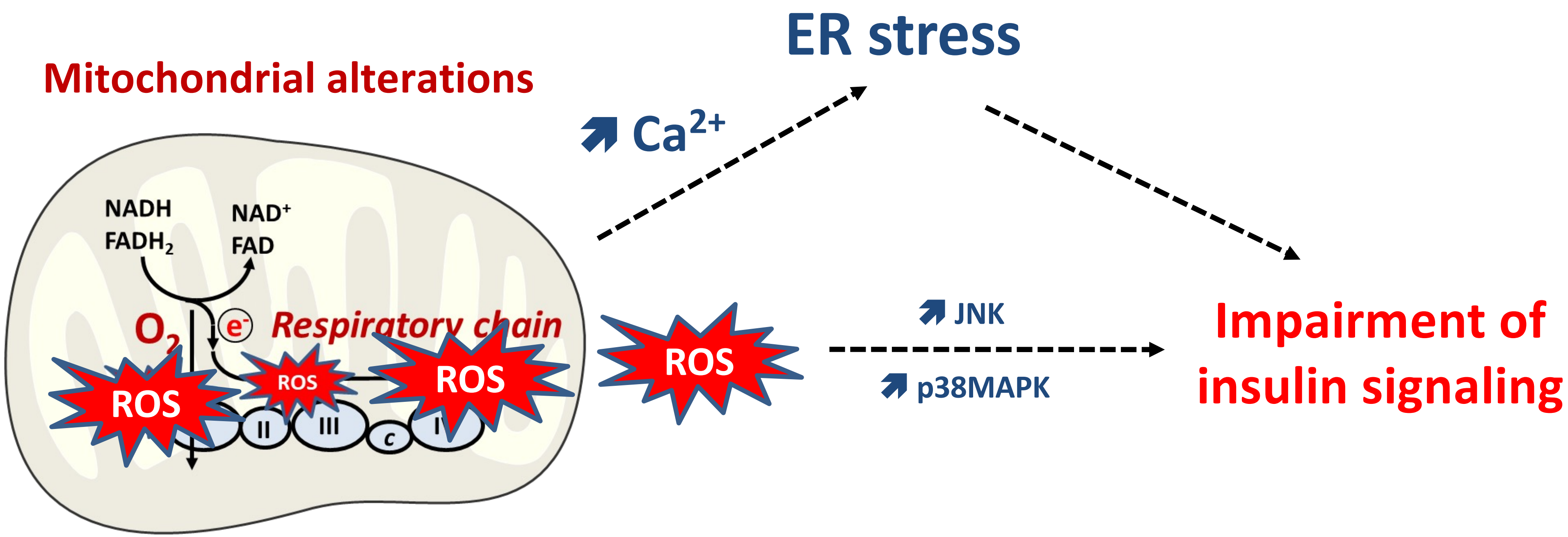
Hepatocellular consequences of mitochondrial alterations

Lim *et al.*, Cell Signal 2009

Rieusset, Cell Death Dis 2018

Guan *et al.*, Exp Gerontol 2013

Guo *et al.*, J Cell Mol Med 2018



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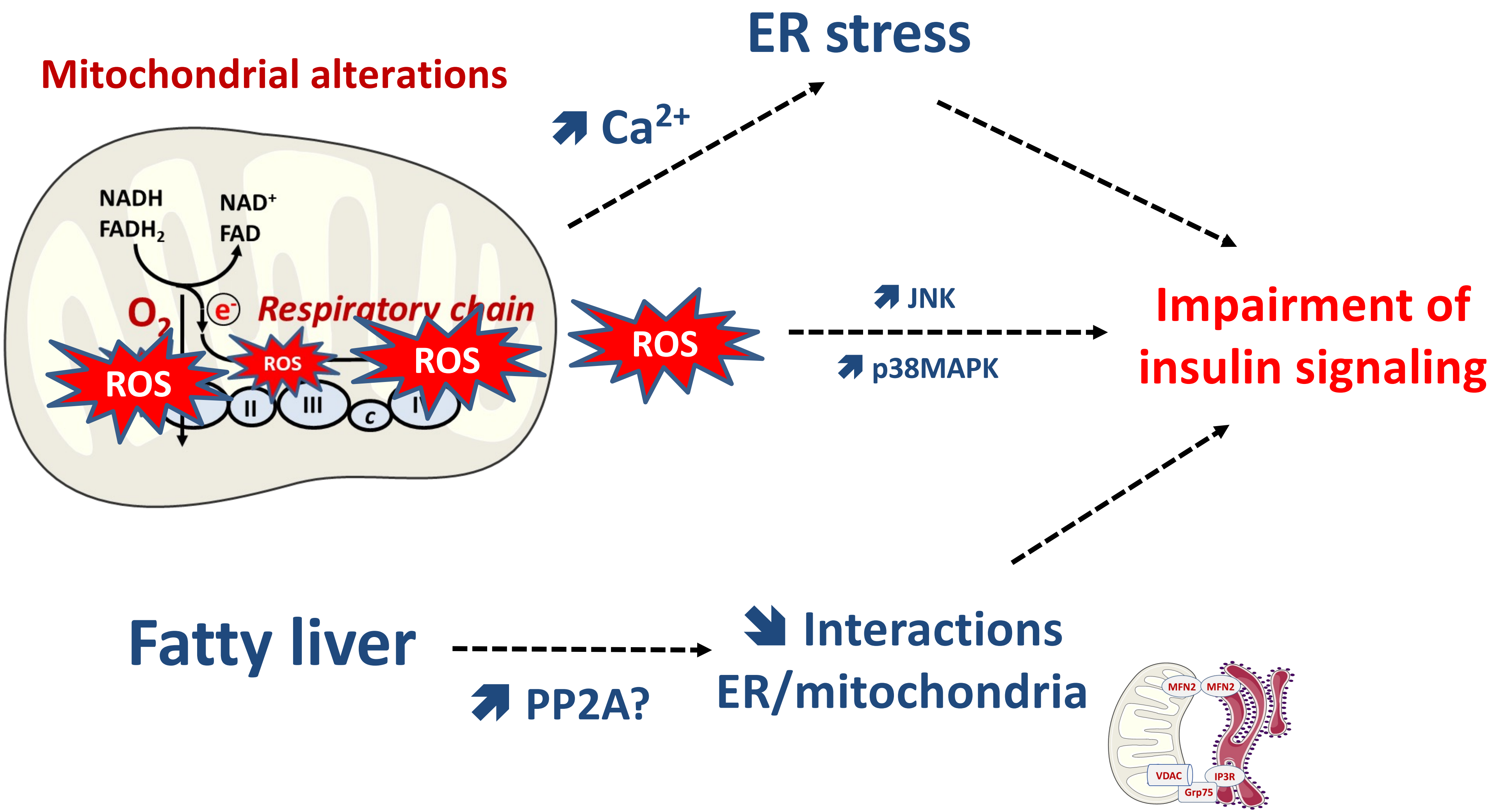
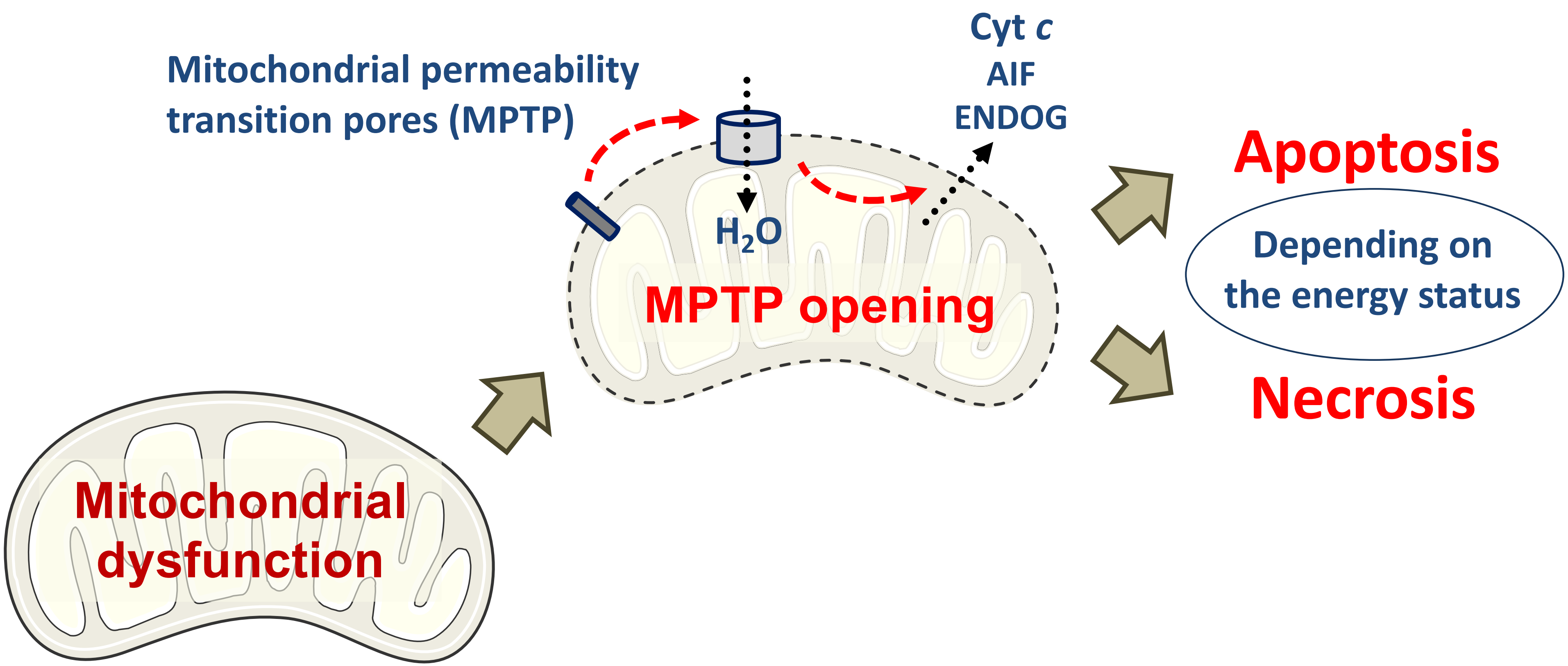


PP2A: protein phosphatase 2A

Hepatocellular consequences of mitochondrial alterations

Bonora *et al.*, Oncogene 2015

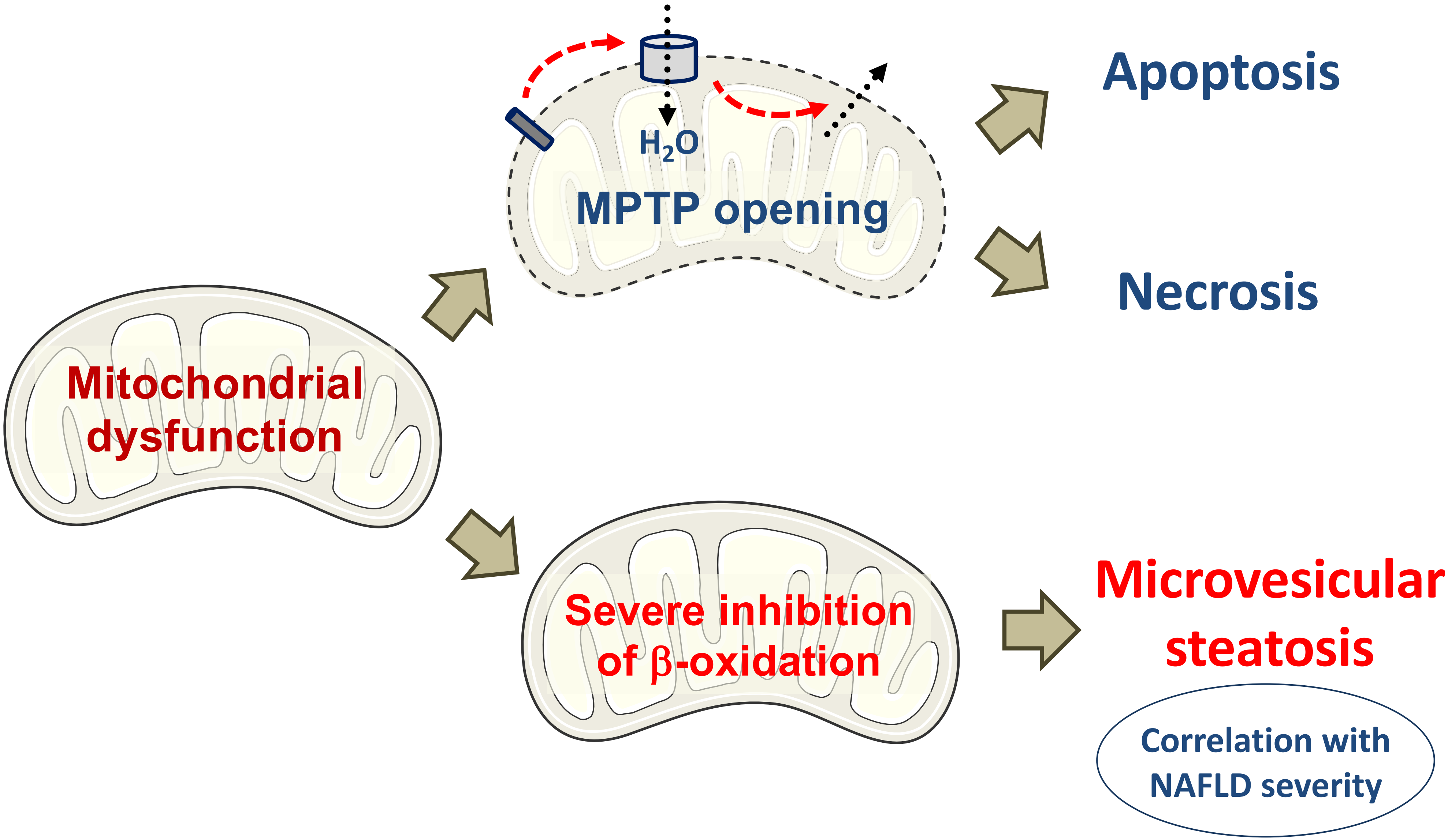
Morciano *et al.*, Biological Reviews 2021



Hepatocellular consequences of mitochondrial alterations

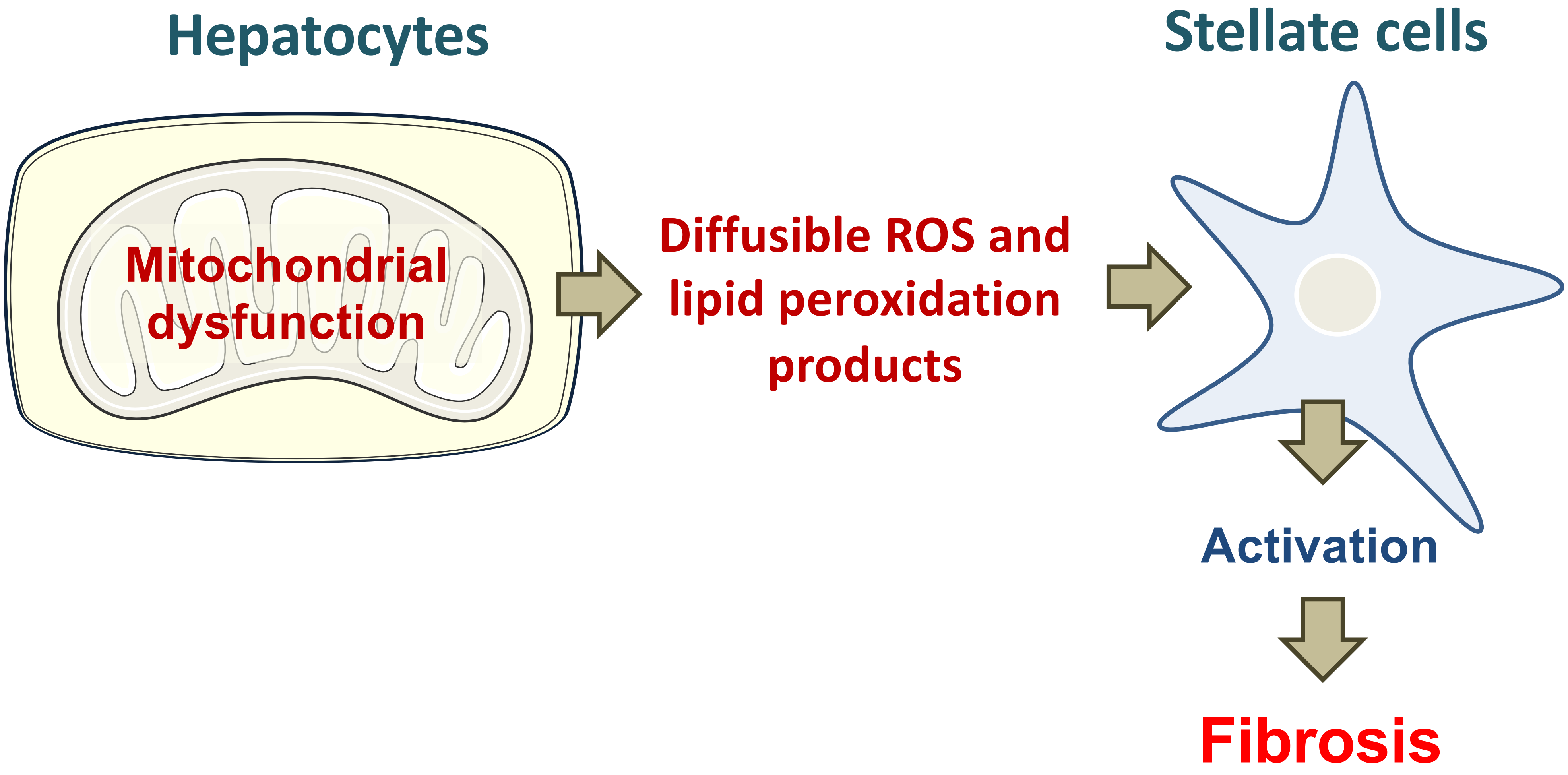
Trak-Smayra *et al*., Int J Exp Pathol 2011
Tandra *et al*., J Hepatol 2011

Celebi *et al*., Acta Gastroenterol Belg 2020
Germano *et al*., Obes Surg 2023



Mitochondrial alterations in hepatocytes and fibrosis

Bedossa *et al.*, Hepatology 1994
Nieto *et al.*, J Biol Chem 2002
Mitchell *et al.*, Am J Pathol 2009
Das *et al.*, J Pineal Res 2017

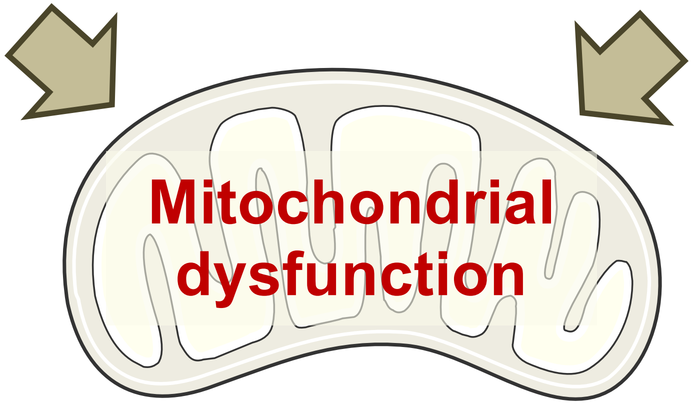


Mitochondrial dysfunction induced by alcohol and drugs

Fromenty & Pessayre, Pharmacol Ther 1995
Porceddu *et al*., Tox Sci 2012

Ramachandran *et al*., J Clin Transl Res 2018
Fromenty, Food Chem Toxicol 2020

Alcohol abuse **Pharmaceuticals**

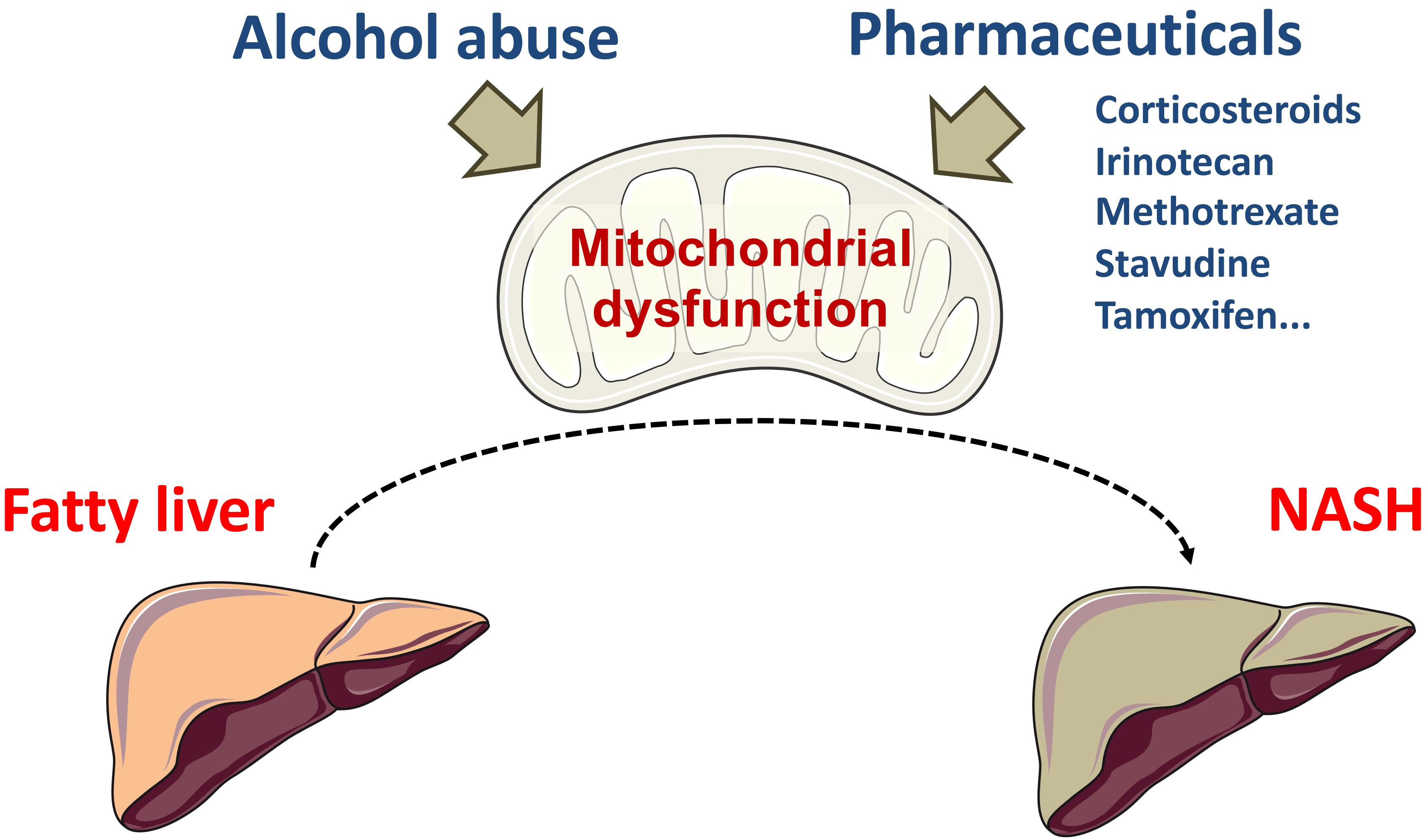


↘ Fatty acid oxidation
↘ Respiratory chain
↘ Mitochondrial DNA
↘ Mitochondrial biogenesis
Activation of MPTP opening

Role of alcohol abuse and drugs in NAFLD aggravation

Larrain & Rinell, Clin Liver Dis 2012
Allard *et al.*, Adv Pharmacol 2019

Massart *et al.*, Int J Mol Sci 2022
Fromenty & Roden, J Hepatol 2023



Thank you for your attention !!

Karima Begriche
Julie Massart
Jacinthe Aubert
Simon Bucher
Dounia Le Guillou
Anaïs Michaut

NuMeCan, Equipe EXPRES, Rennes

Clémence Penhoat
Grégory Pinon
Thomas Gicquel
Anne Corlu
Pierre-Jean Ferron
(réseau PREVITOX)

Dominique Pessayre and other former colleagues in Paris,
M.A. Robin, A. Mansouri, A. Berson, P. Lettéron, E. Fréneaux…