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Functions and Malfunction of Mitochondria and tRNA synthase Made Easy

Aleksandra Trifunovic

Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Germany

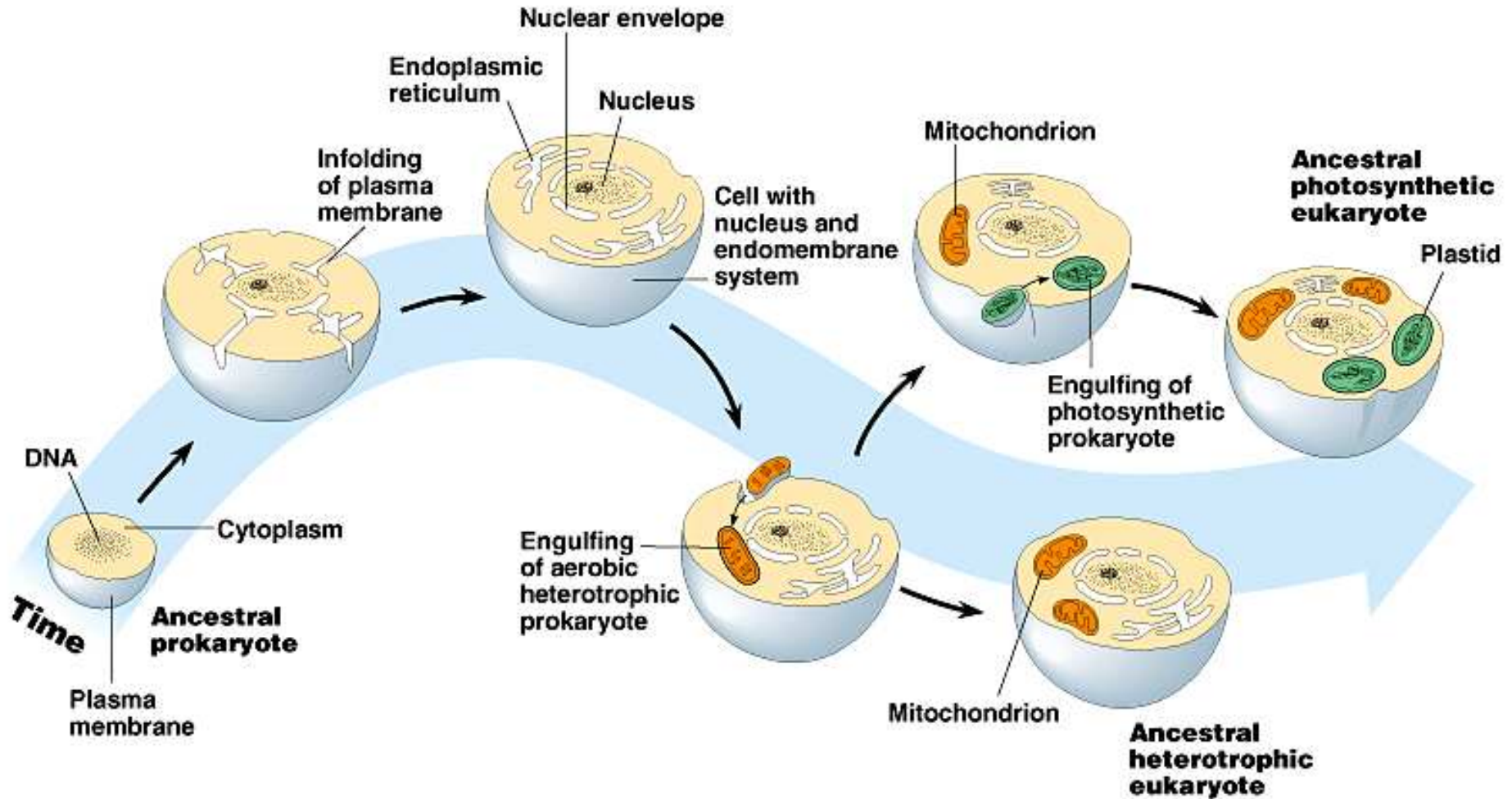
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The amazing world of nature's longest invasion

Aleksandra Trifunovic

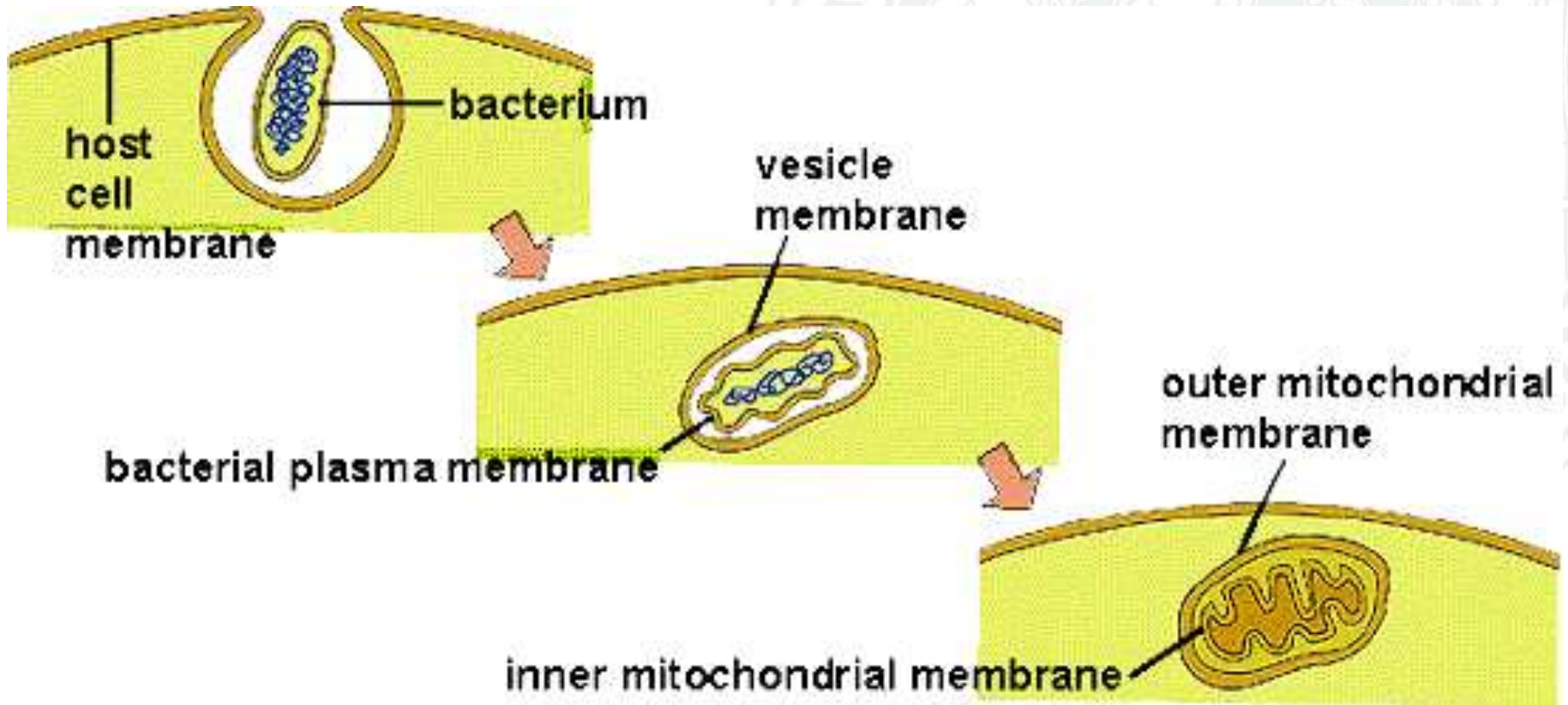
Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Germany

Origin of mitochondria



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Origin of mitochondria



Some facts.....

- Without mitochondria, there would be no multicellular organisms
- To function properly, when resting, our body needs 3×10^{18} molecules of ATP in every second
- During one day we produce on average 70kg of ATP
- 70% of this energy is consumed by brain

Mitochondria – the powerplant of the cell

Mitochondria Inner Structure

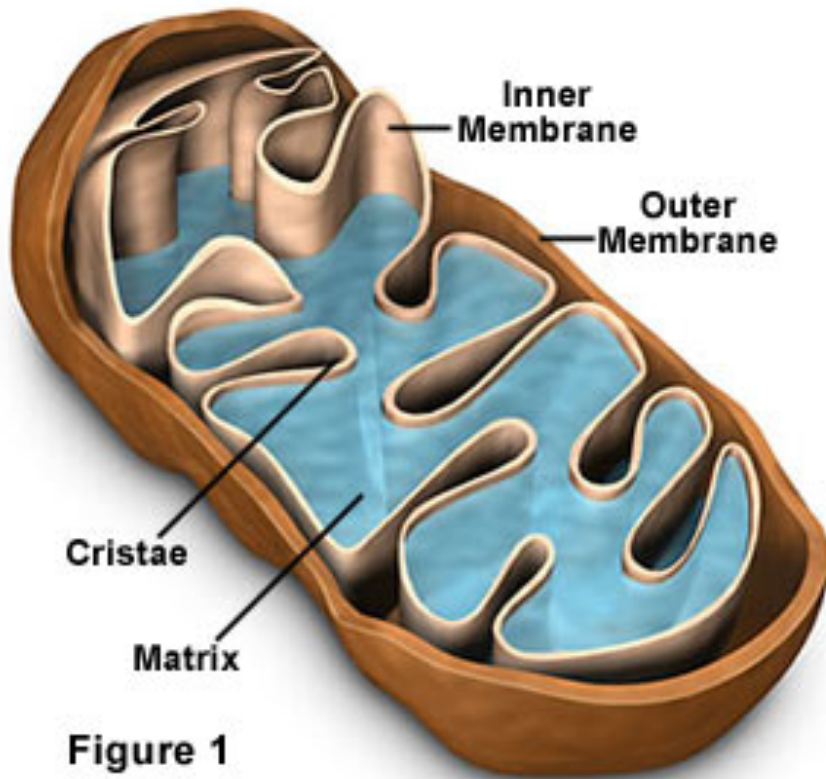
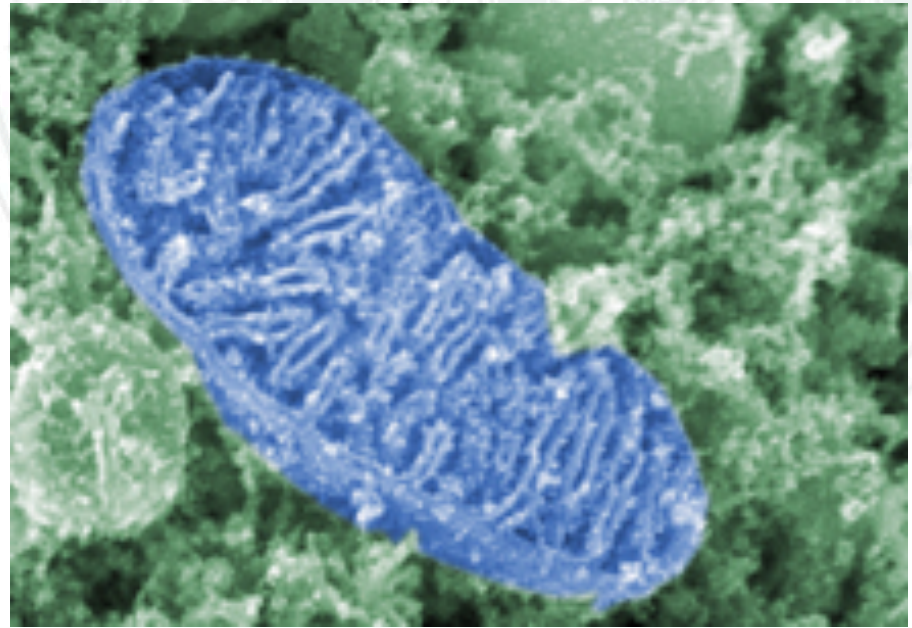


Figure 1



Midichlorians – power to the Jedi



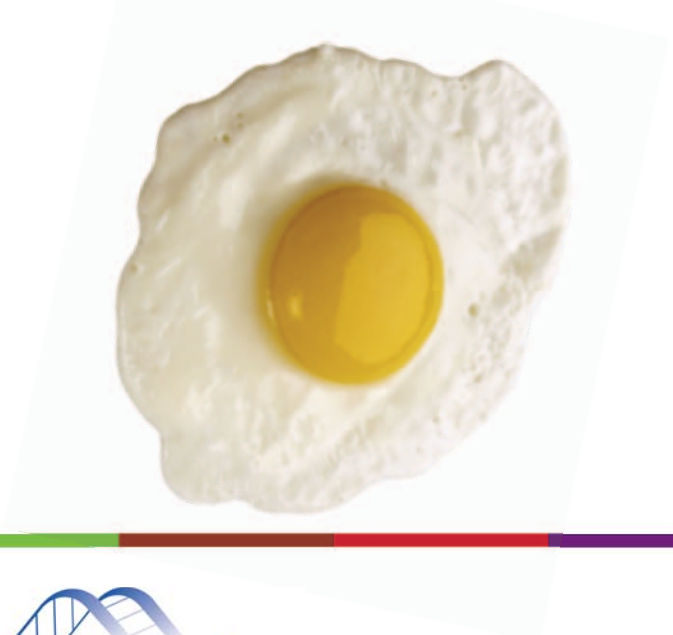
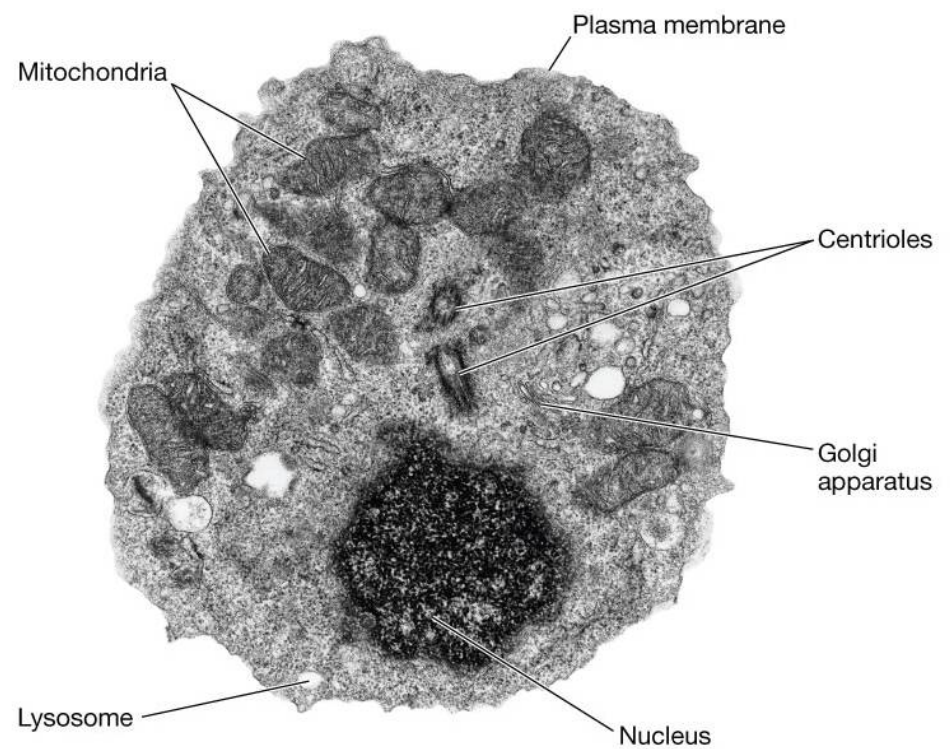
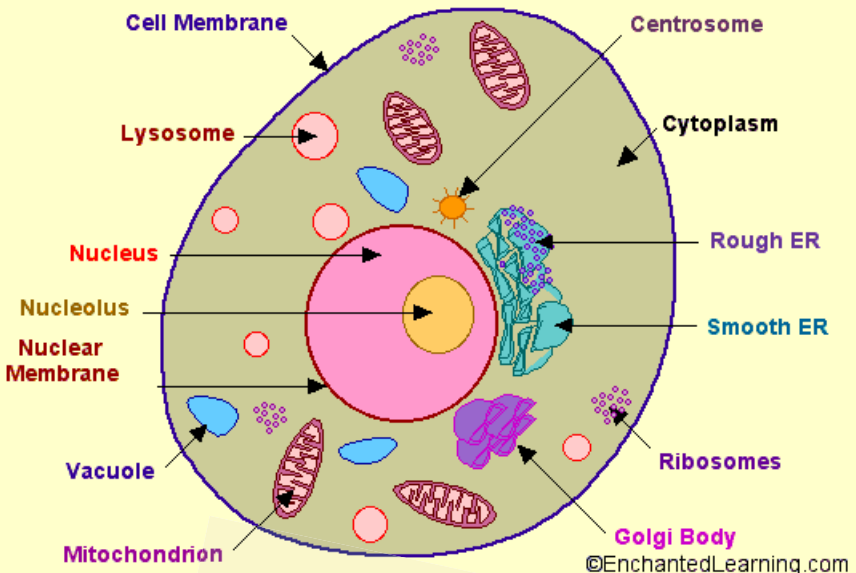
HIGHEST MUDI-CHLORIAN COUNT IN STAR WARS HISTORY

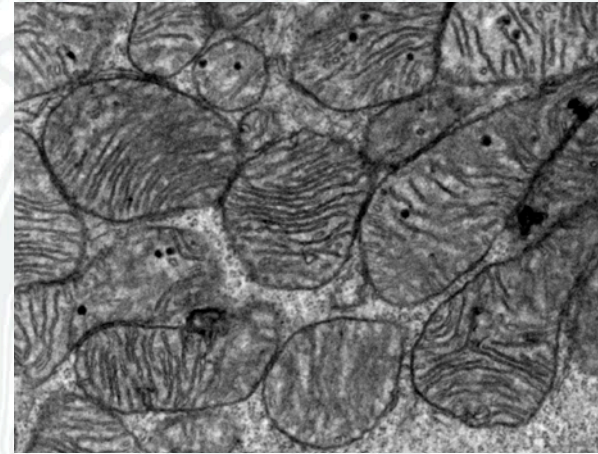
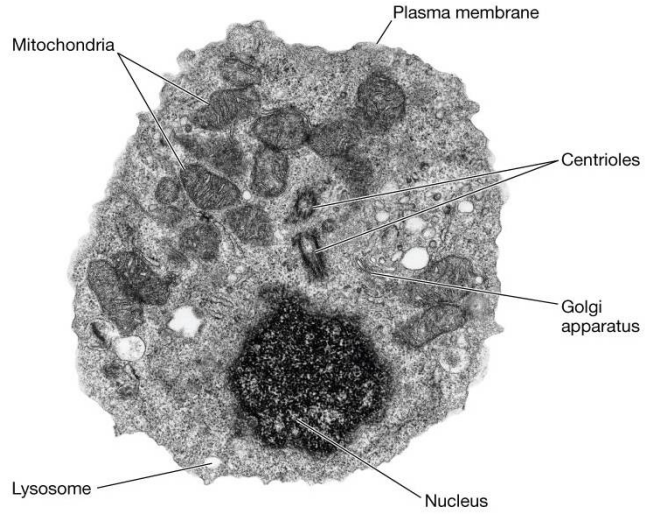


"Without the midi-chlorians, life could not exist, and we would have no knowledge of the Force. They continually speak to us, telling us the will of the Force. When you learn to quiet your mind, you'll hear them speaking to you."

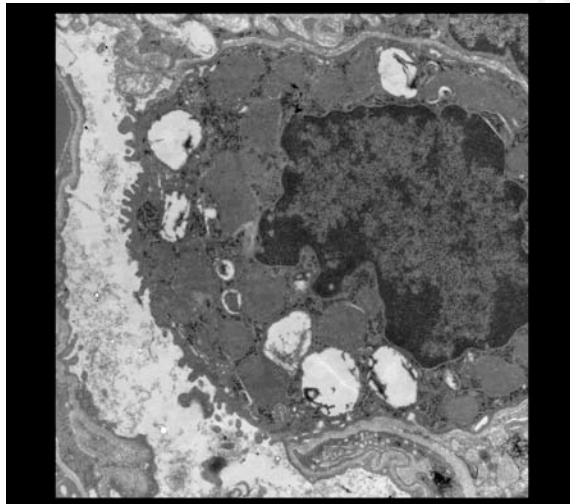
Qui-Gon Jinn, to Anakin Skywalker – Star Wars Ep.1

Cross-Section of an Animal Cell

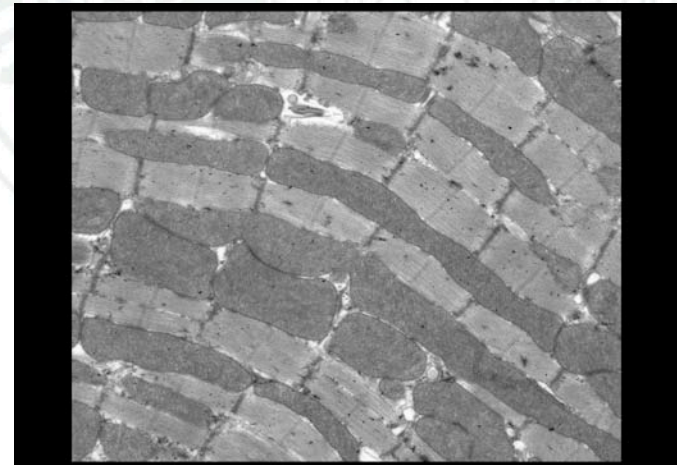




Human fibroblasts

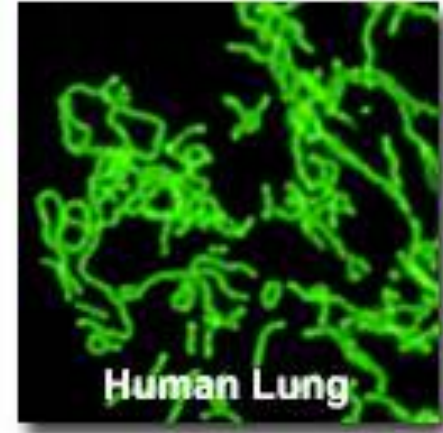
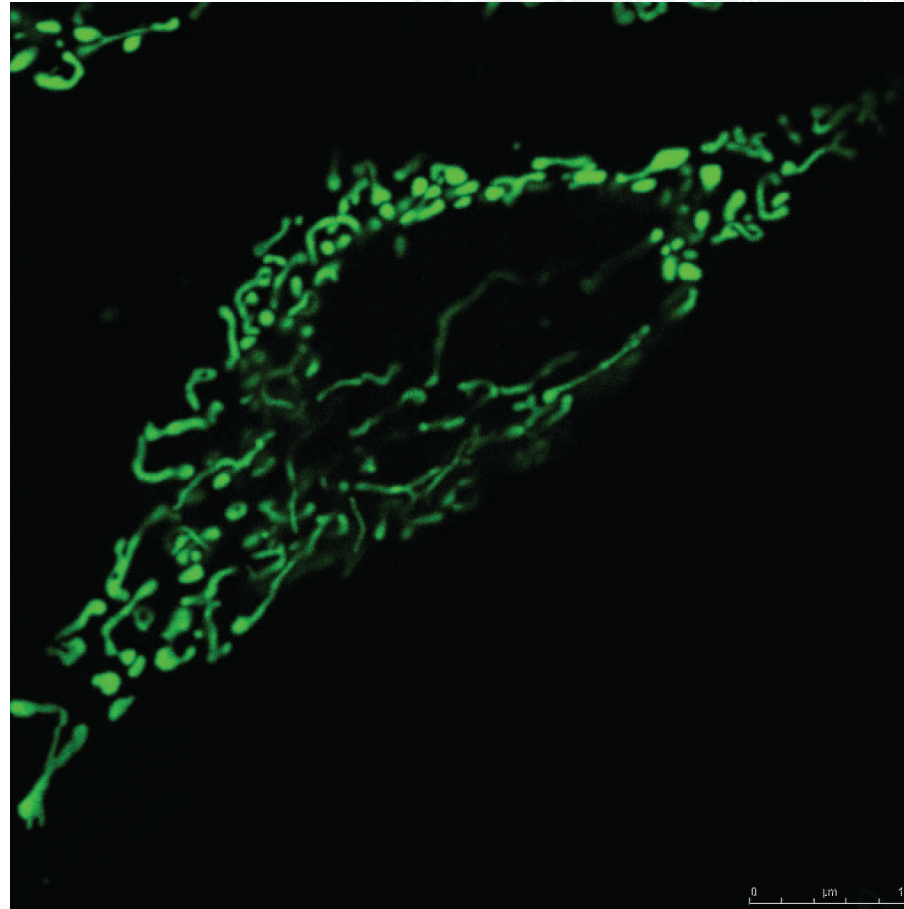


Mouse lung

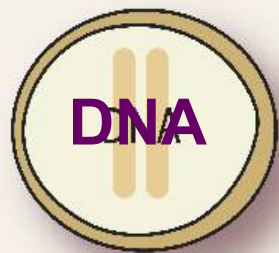


Mouse heart

Mitochondria form a network and are very dynamic



Nucleus



33.000

DNA

RNA

1.500

Proteins

Mitochondrion

factors for replication and transcription of mtDNA

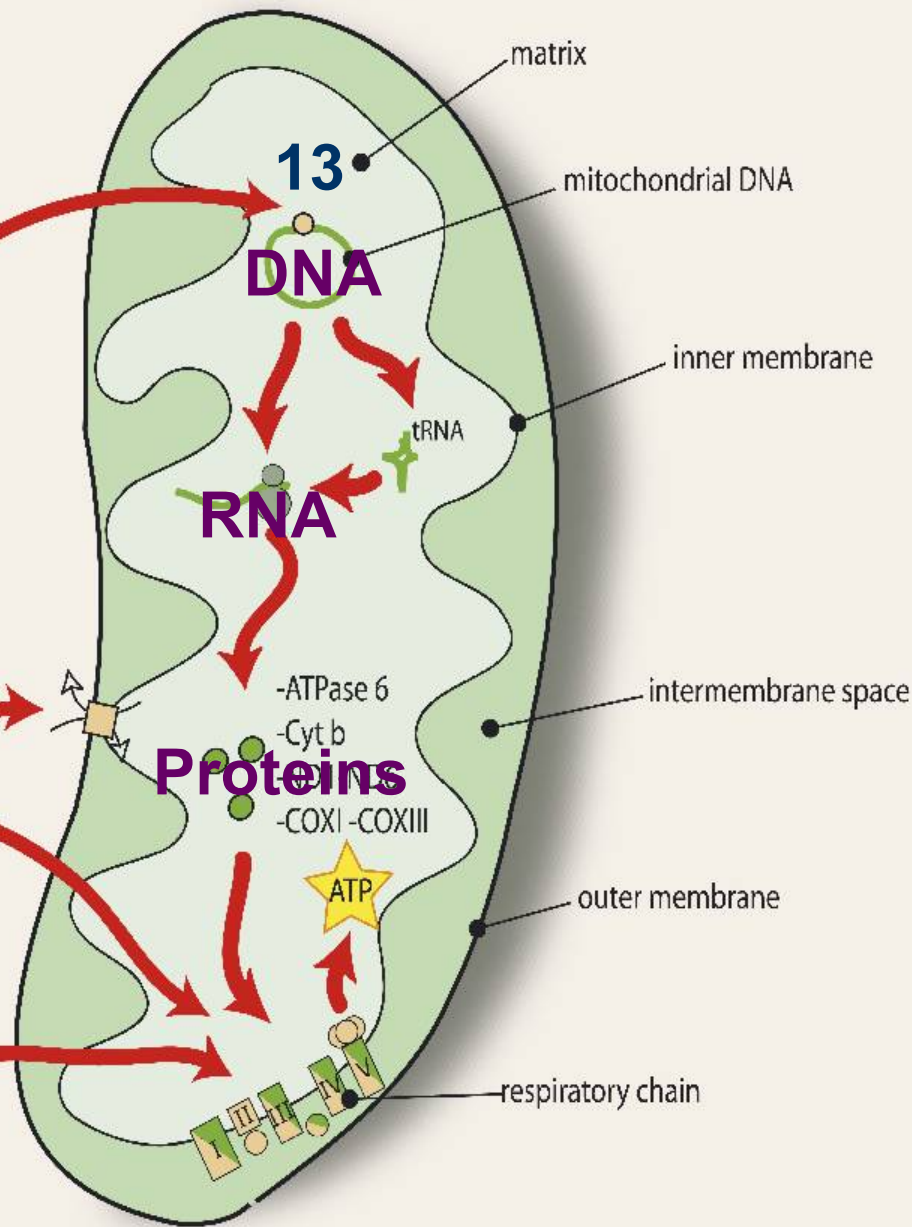
- POLG
- TWINKLE
- ANT1
- TFAM
- TFB1M
- TFB2M
- POLRTM

proteins for membrane transport and OXPHOS assembly

- SURF1
- BCS1L
- SCO1
- SCO1
- etc.

respiratory chain subunits

- NDUFS1
- NDUFS4
- SDHA
- SDHB
- etc.



matrix

13

DNA

mitochondrial DNA

inner membrane

tRNA

RNA

Proteins

-ATPase 6

-Cyt b

-COXI -COXIII

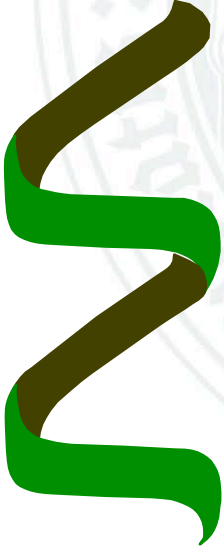
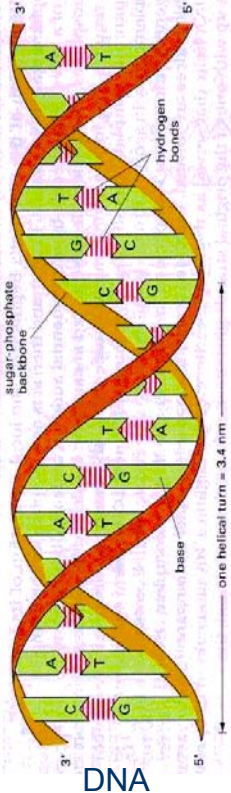
ATP

intermembrane space

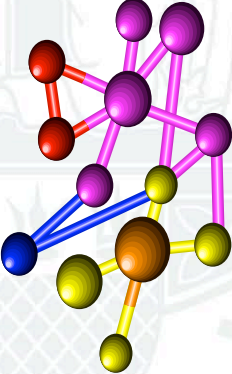
outer membrane

respiratory chain

The central dogma of biology

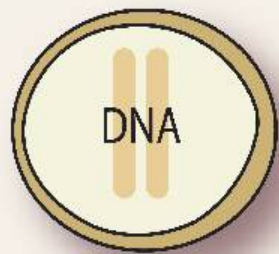


RNA

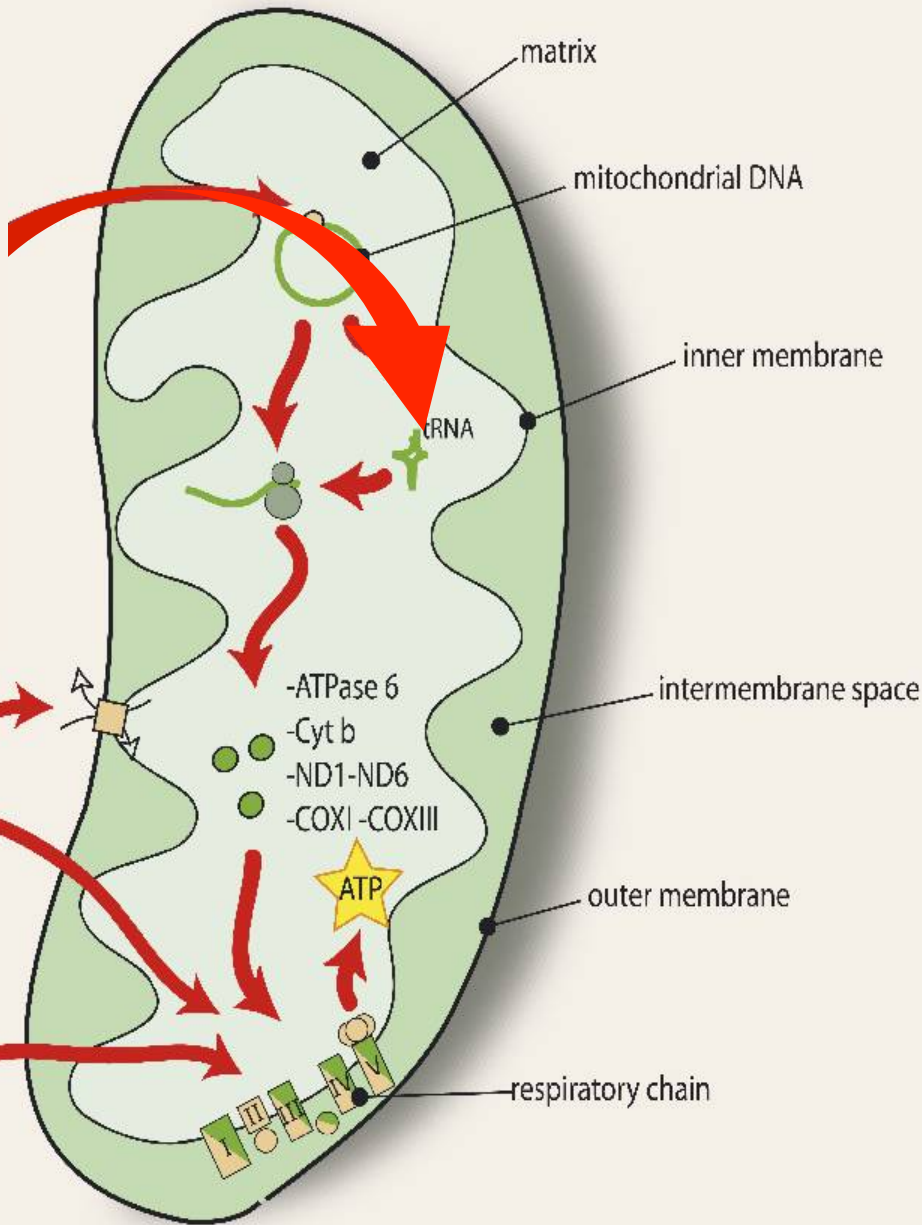


Protein

Nucleus



Mitochondrion

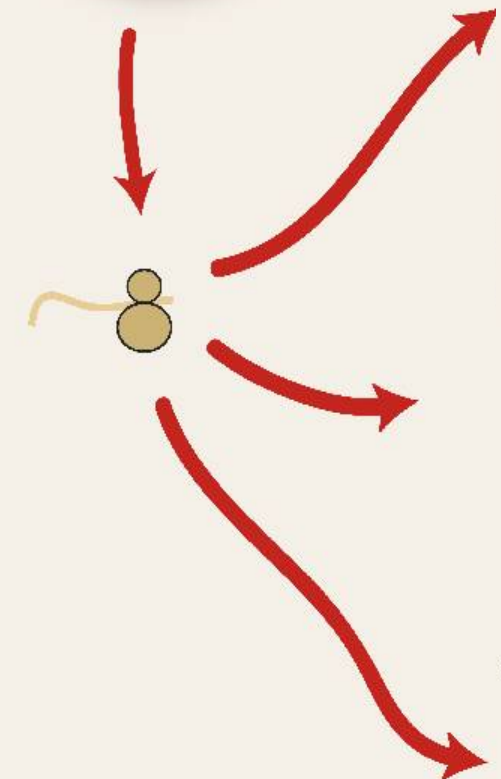


Factors for mitochondrial translation

DARS2,
VAR2,
IARS2,
SARS2....

-SURF1
-BCS1L
-SCO1
-SCO1
etc.

respiratory chain subunits
-NDUFS1
-NDUFS4
-SDHA
-SDHB
etc.

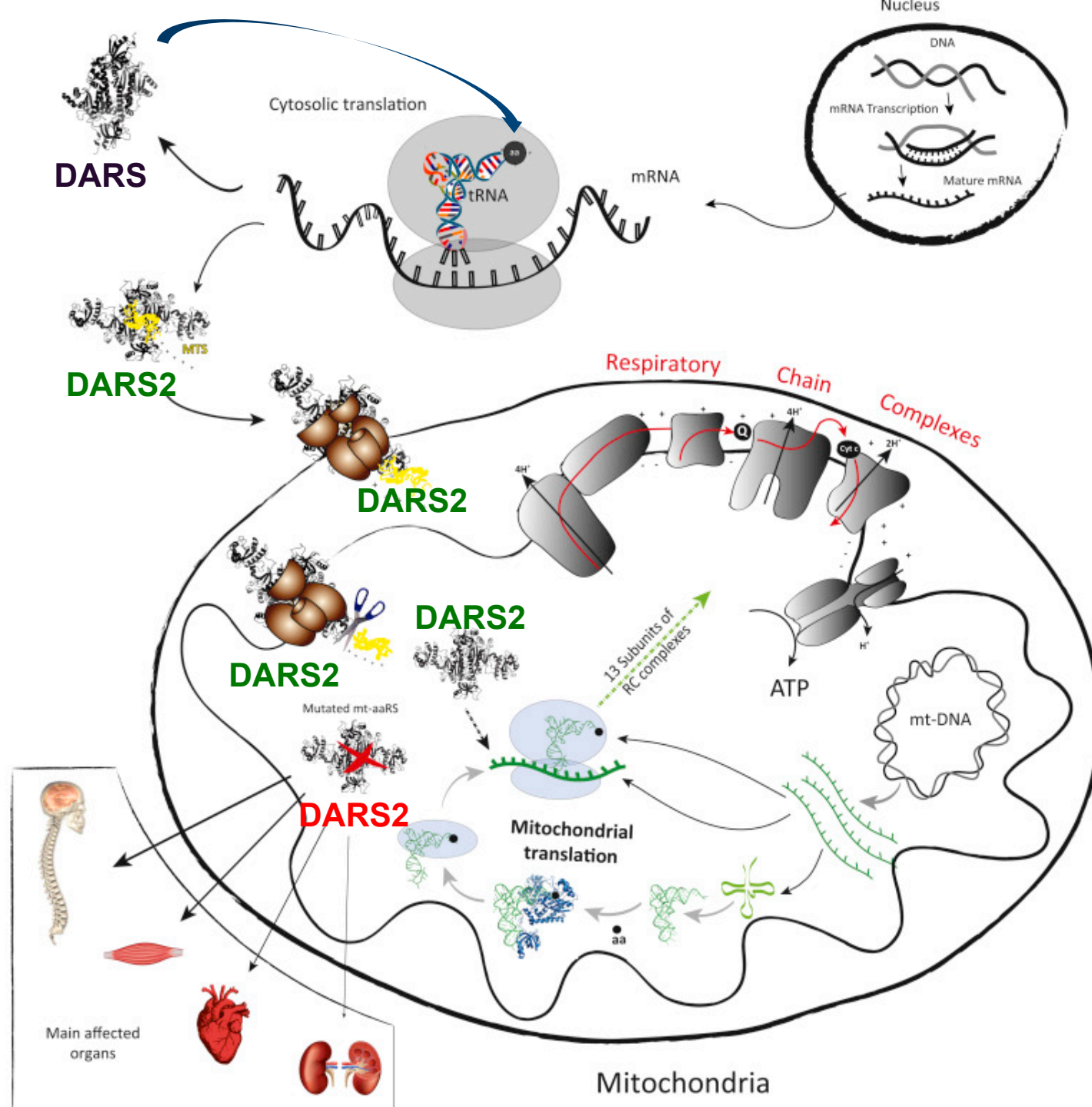


tRNA

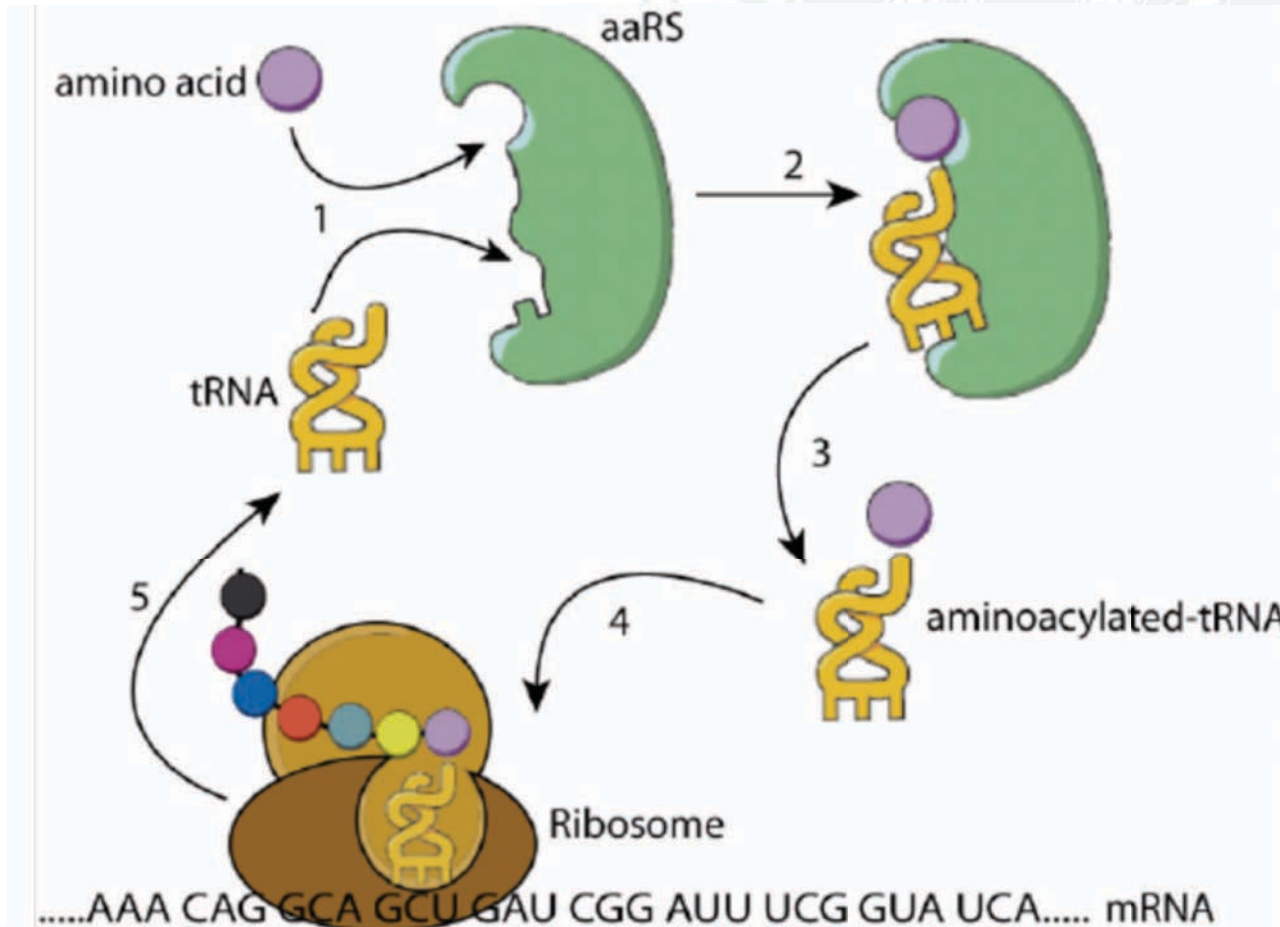
-ATPase 6
-Cyt b
-ND1-ND6
-COXI -COXIII

ATP

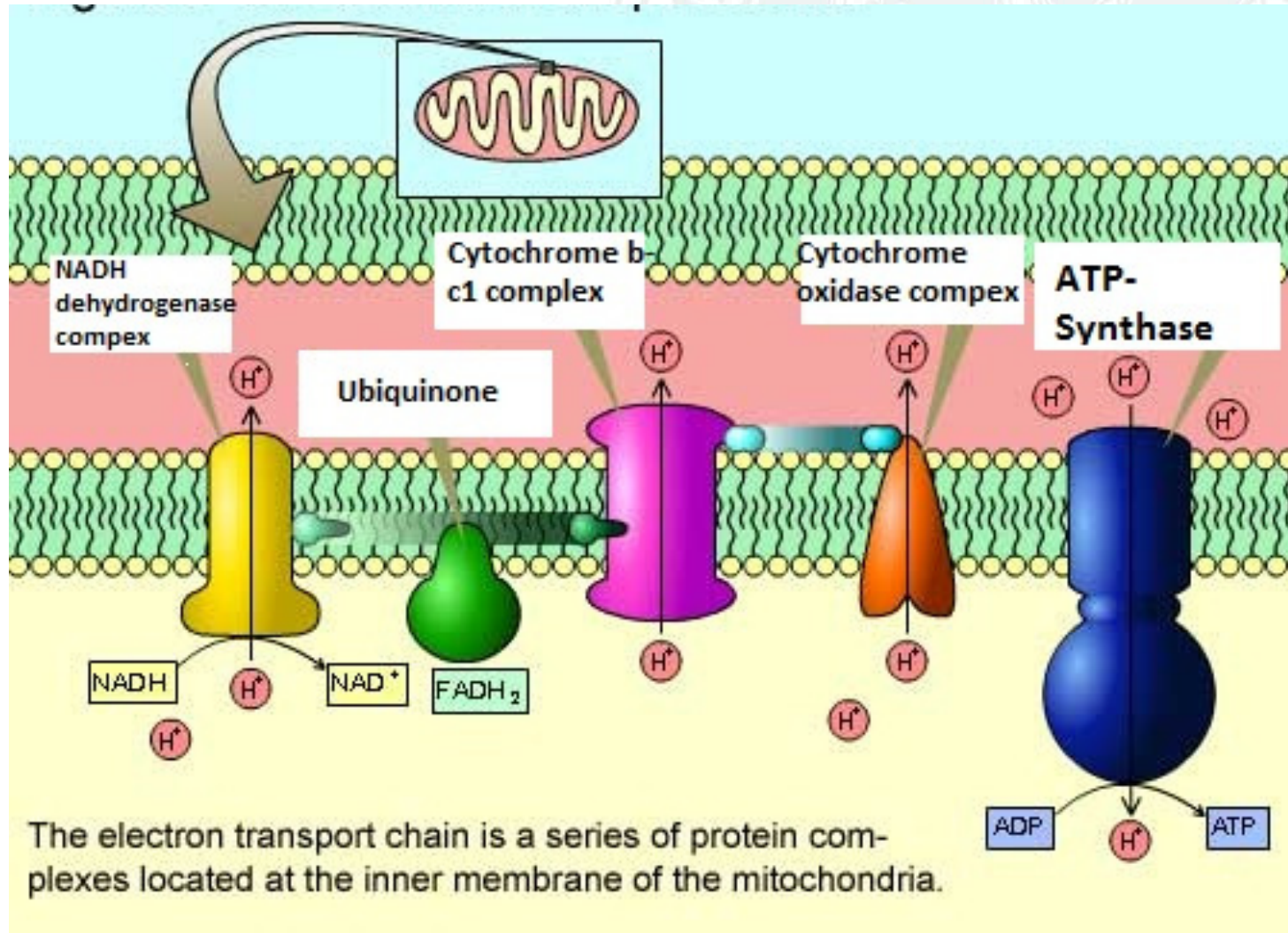
respiratory chain



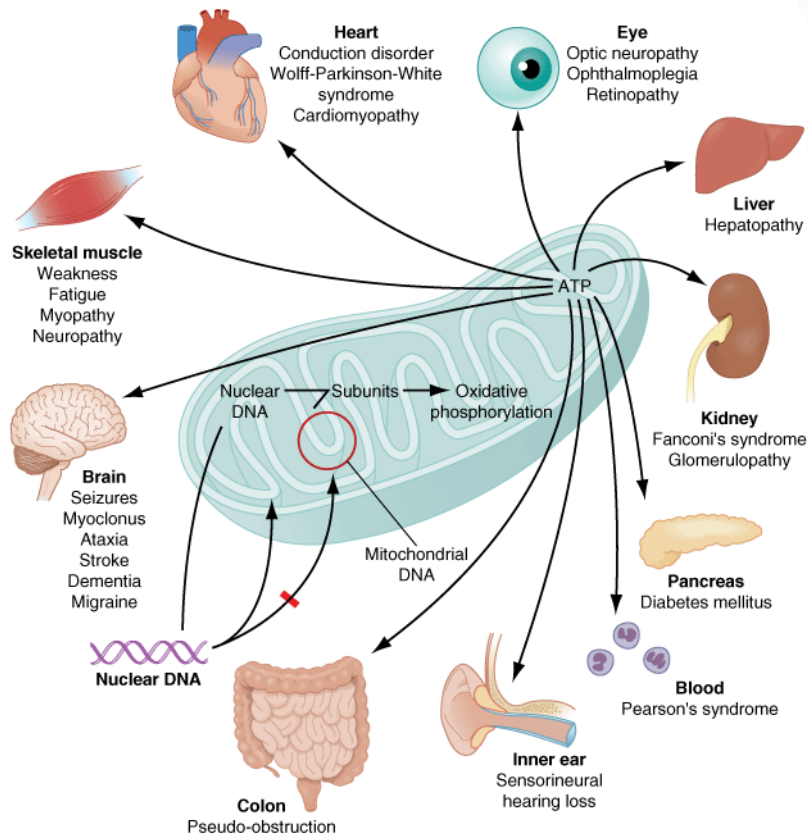
The role of amino acid tRNA synthetase



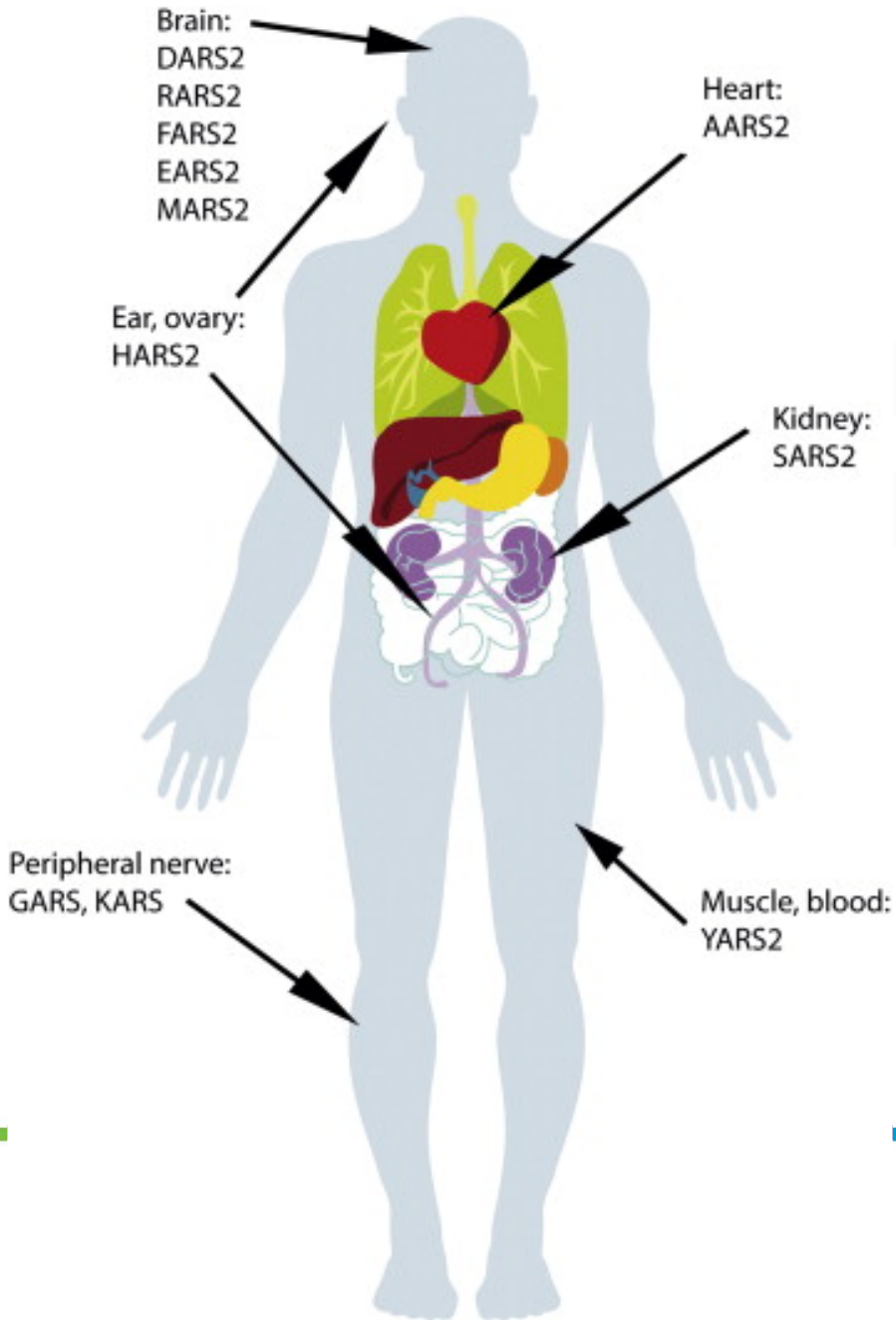
Mitochondrial Respiratory Chain (MRC)



Mitochondrial Diseases




- Every 30 minutes a child is born who will develop a mitochondrial disease by age 10.
- At least 1 in 200 individuals in the general public have a mitochondrial DNA mutation that may lead to development of disease.
- Mitochondrial diseases should be considered in any patient with unexplained multi-system involvement with a progressive course.
- 100s of different diseases genetically
- Even in individuals with the same mutation, there are different symptoms that can change over time
- Challenging to diagnose and even more to treat



Mitochondrial aaARS genes

- Mutations in all mitochondrial tRNA synthetases cause devastating diseases
- The incredible variety in disease presentation is not understood
- Unfortunately there is no treatment



Correlative studies
versus
“Intervention” studies

New evidence for the Theory of the Stork

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Summary

Data from Berlin (Germany) show a significant correlation between the increase in the stork population around the city and the increase in deliveries outside city hospitals (out-of-hospital deliveries). However, there is no correlation between deliveries in hospital buildings (clinical deliveries) and the stork population. The decline in the number of pairs of storks in the German state of Lower Saxony between 1970 and 1985 correlated with the decrease of deliveries in that area. The nearly constant number of deliveries from 1985 to 1995 was associated with an unchanged stork population (no statistical significance). However, the relevance of the stork for the birth rate in that part of Germany remains unclear, because the number of out-of-hospital deliveries in this area is not well documented. A lack of statistical information on out-of-hospital deliveries in general is a severe handicap for further proof for the Theory of the Stork.

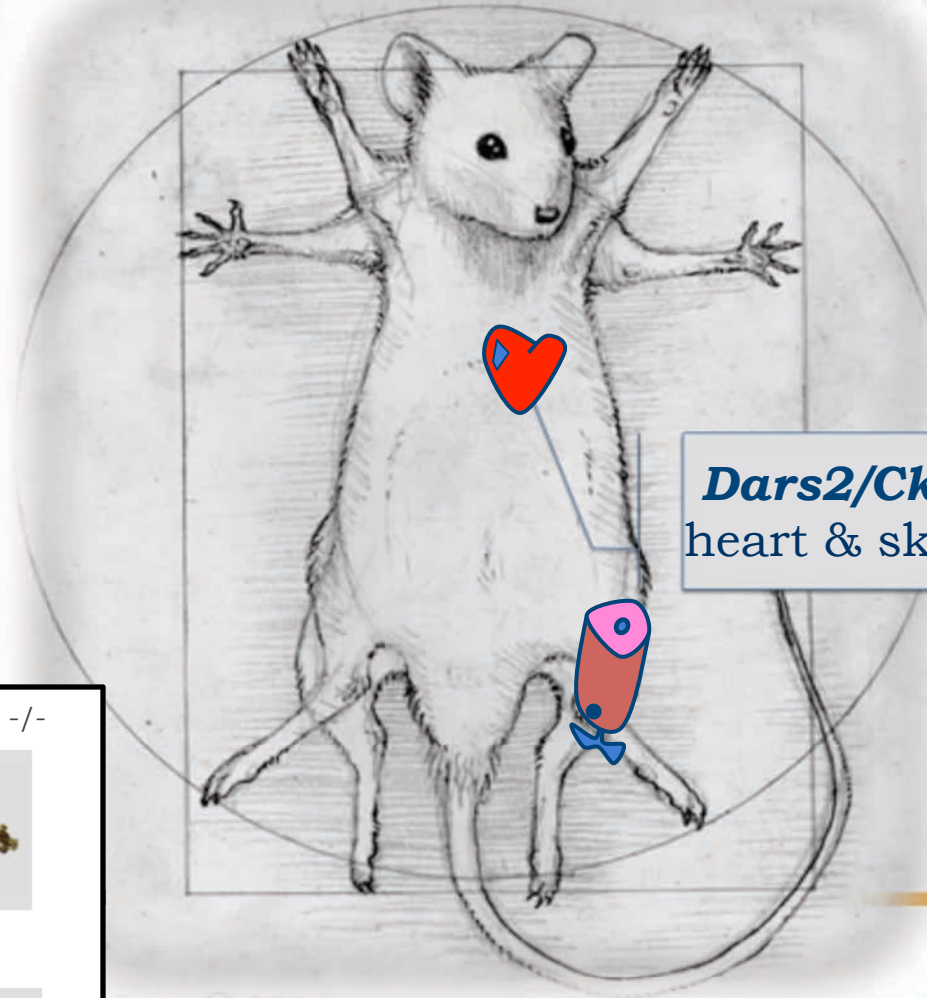
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Paediatric and Perinatal Epidemiology, (2004) 18(1):88 - 92

The intended value (disclaimer): This article is not intended to disprove the value of serious epidemiological investigations. It is an example of how studies based on popular belief and unsubstantiated theory, seconded by low quality references and supported by coincidental statistical association could lead to apparent scientific endorsement. Insofar it is a humorous case study for education in perinatal epidemiology.

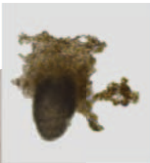
DARS2-deficient mice



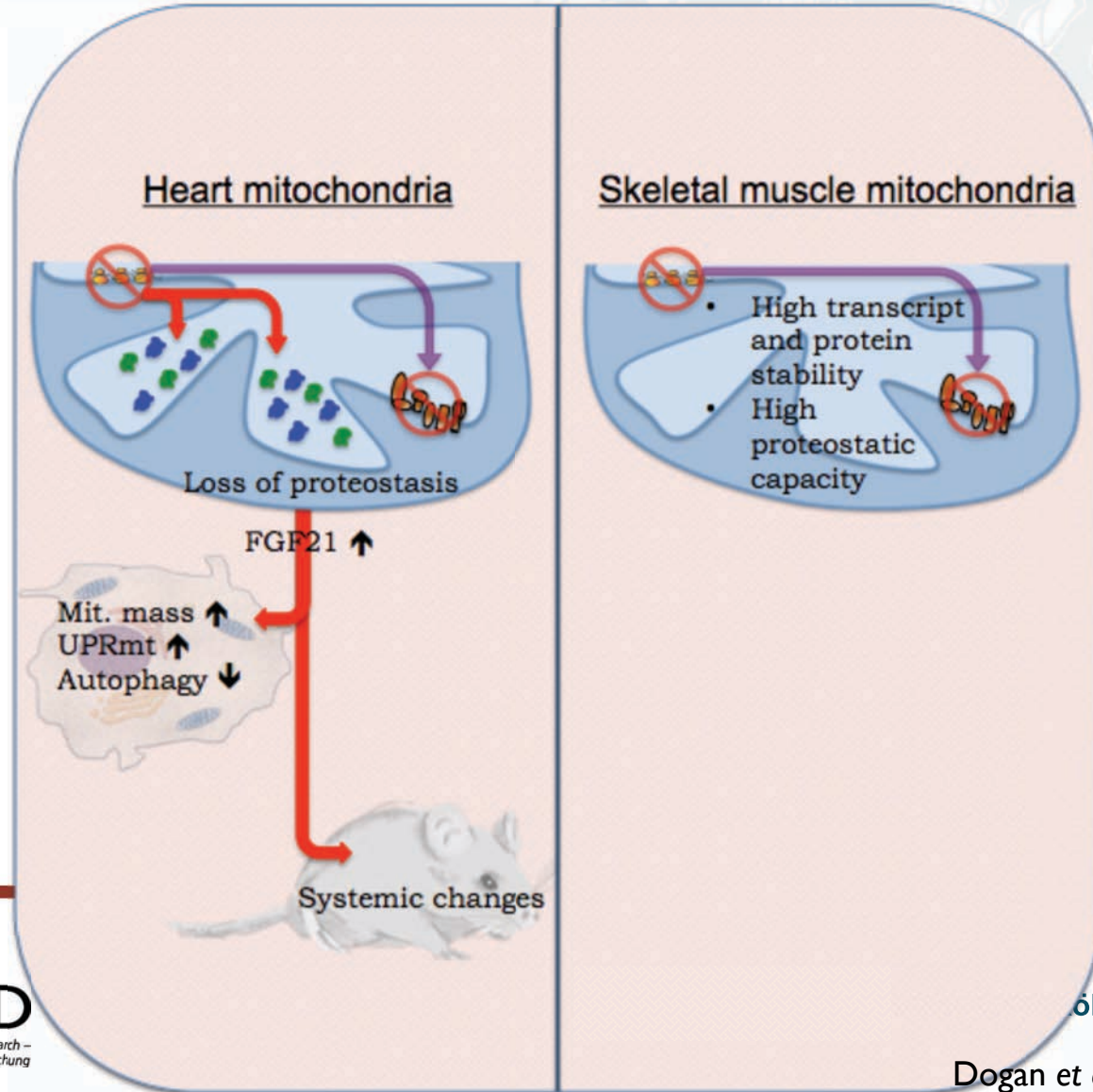
***Dars2/Ckmm-Cre* mice:**
heart & skeletal muscle

Dars2^{+/+}

Dars2^{-/-}



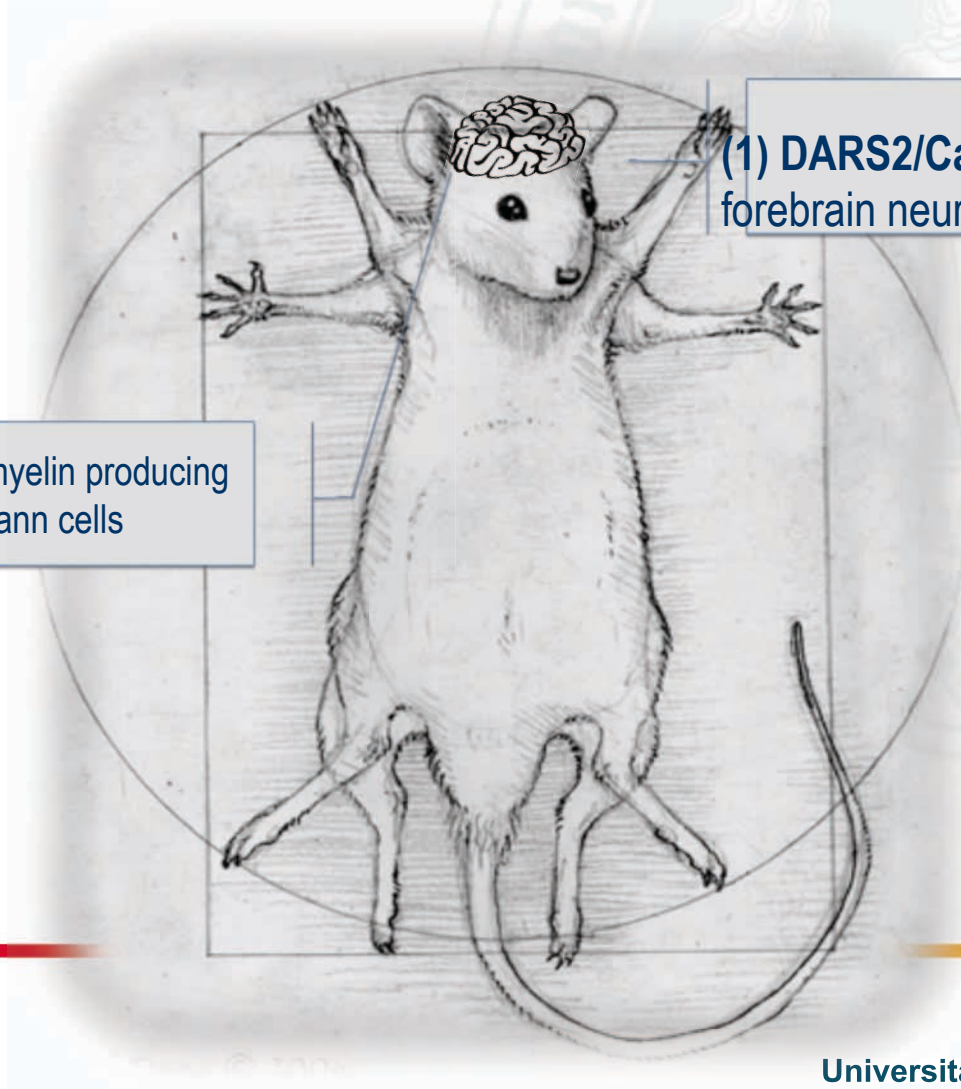
Summary of Dars2 deficiency



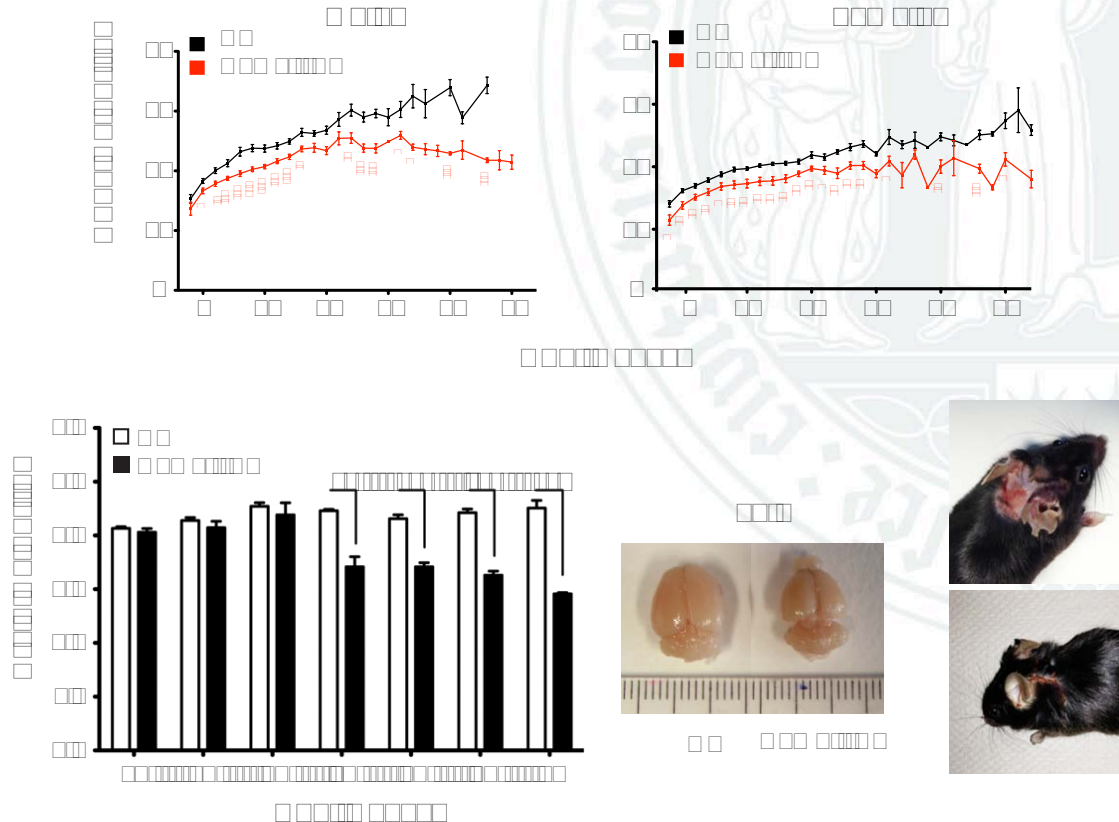
DARS2-deficient mice

(1) DARS2/CaMKII-Cre mice: adult forebrain neurons

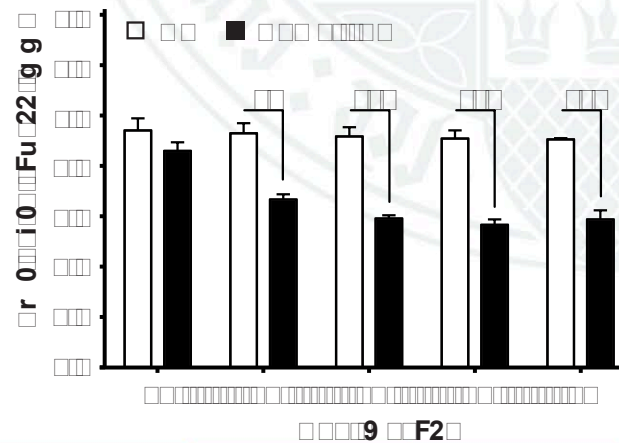
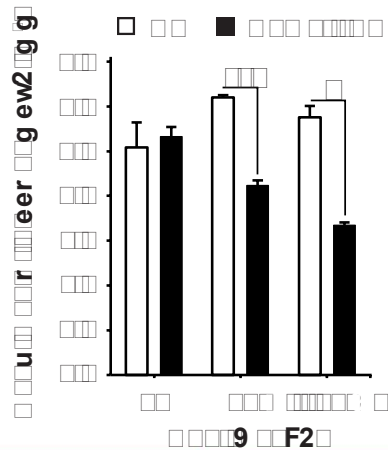
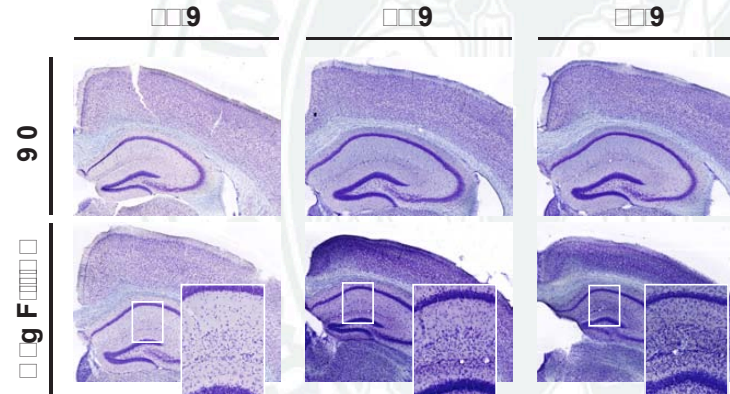
(2) DARS2/Plp-Cre mice: myelin producing oligodendrocytes and Schwann cells



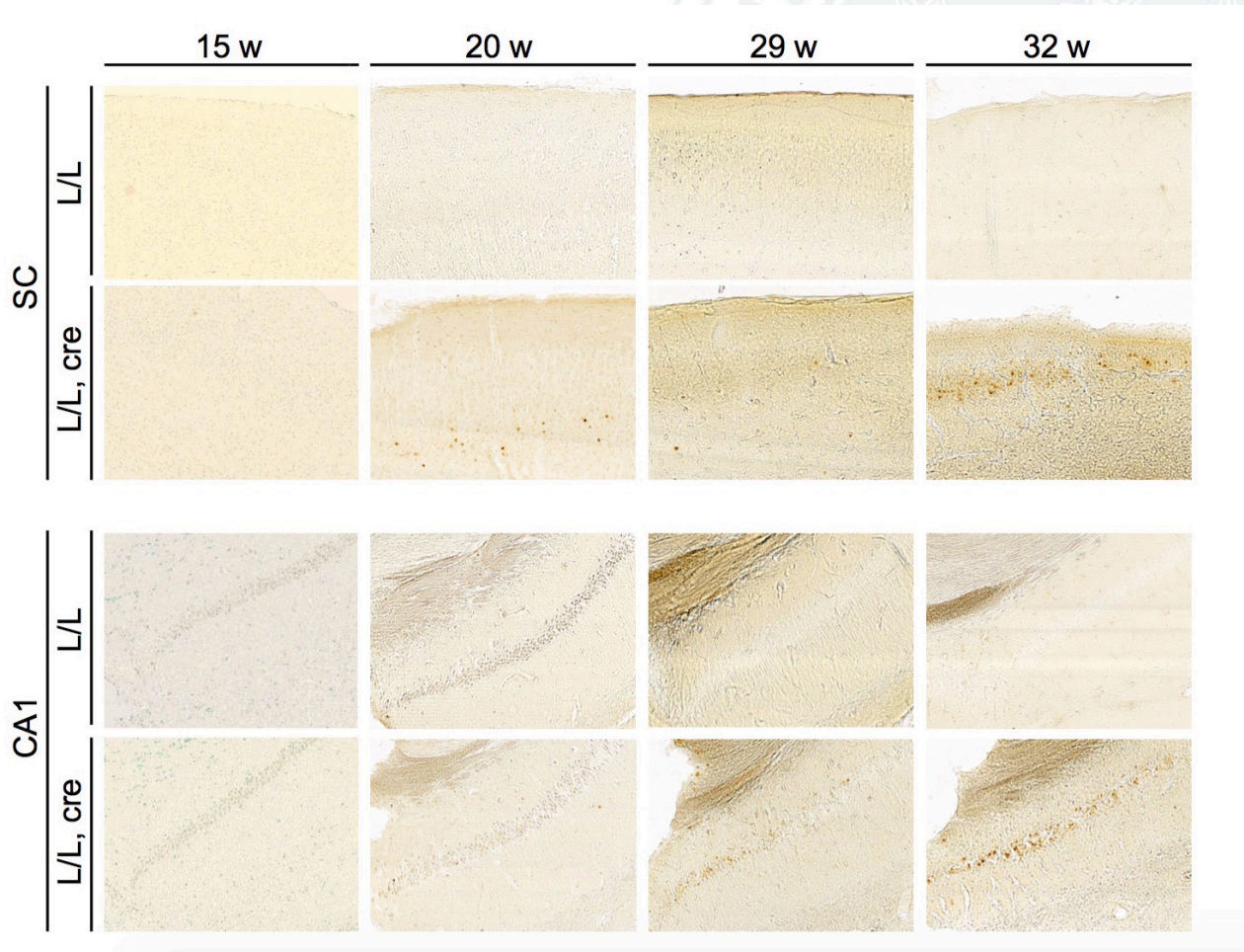
Strong neurodegeneration after 25 weeks – CaMKII-cre



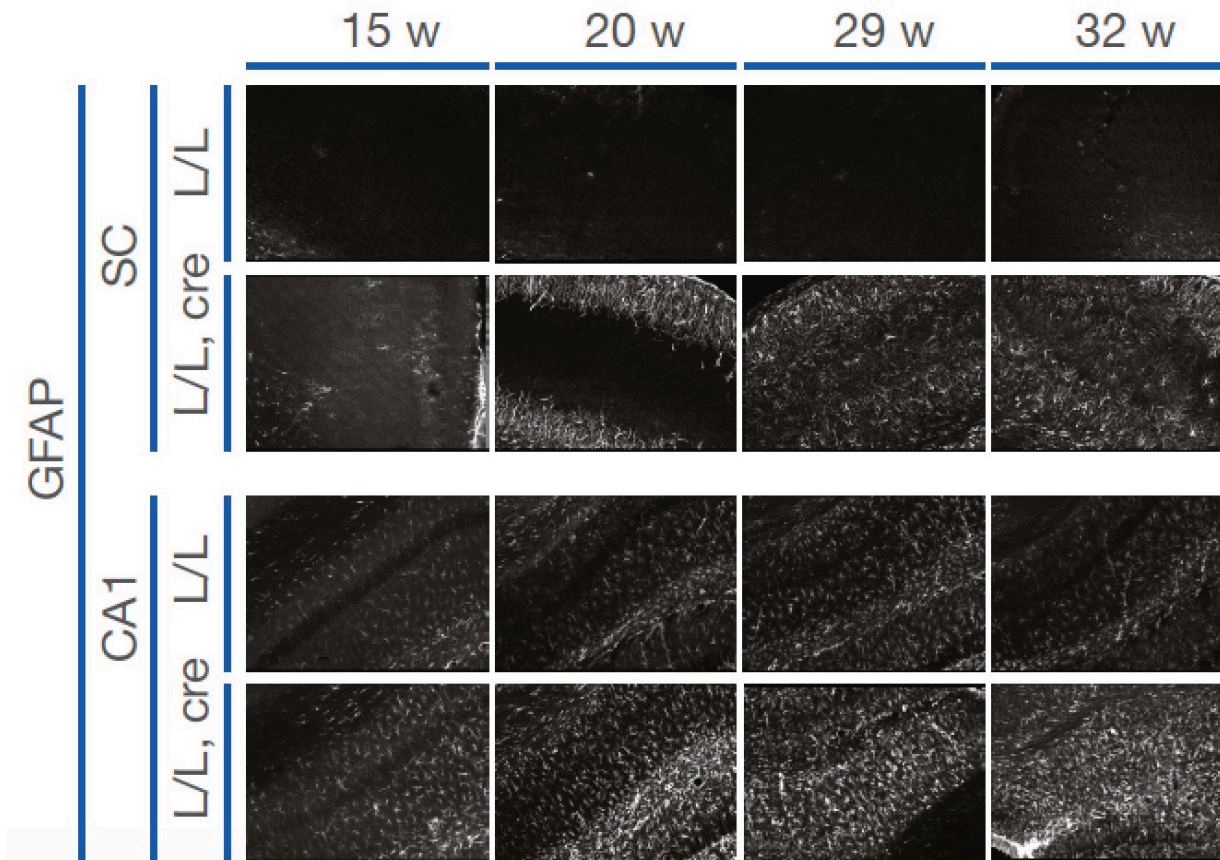
Loss of neurons after 25w – CaMKII-cre



DARS2 depletion leads to the neuronal loss

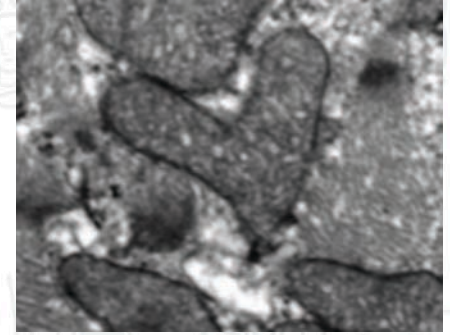


Loss of neurons is followed by strong neuroinflammation





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