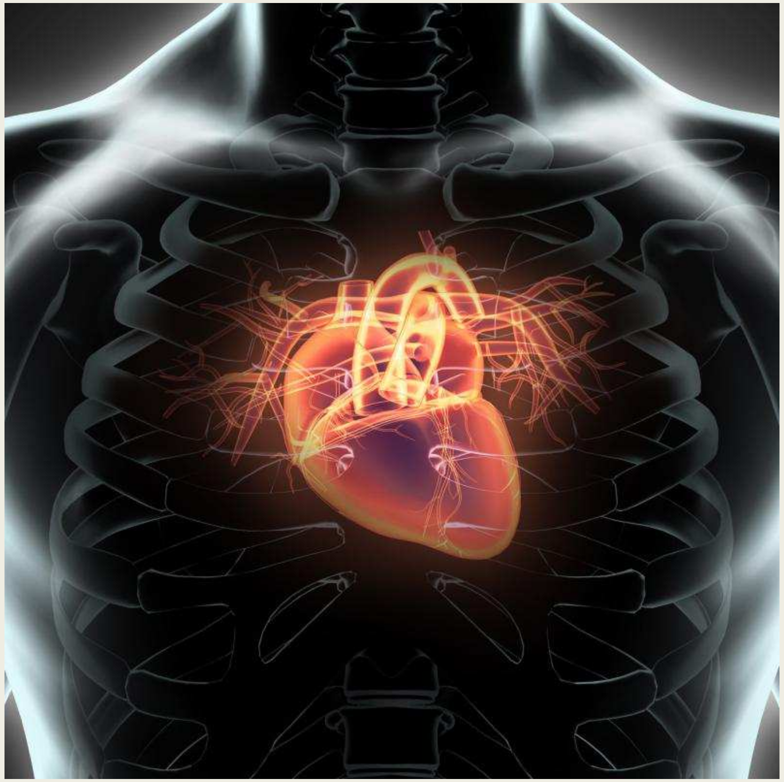


CARDIAC ENERGY METABOLISM

Master1

Jérôme Piquereau

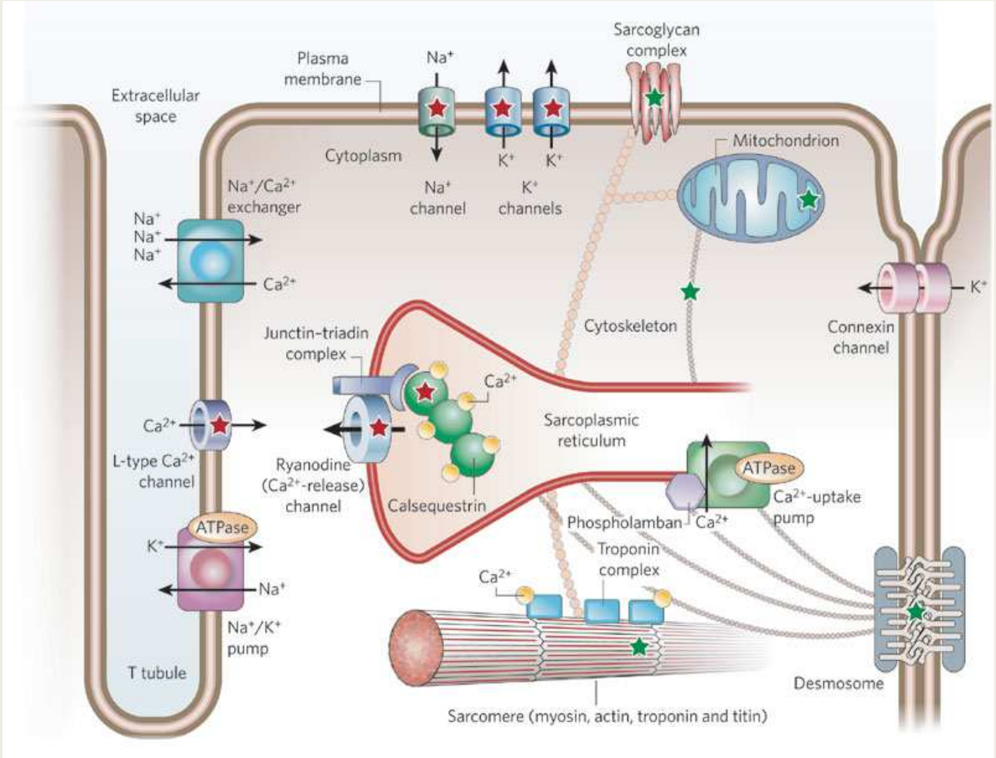
Contractile activity and energy cunsomption

Main energy consumers in the cardiomyocyte:

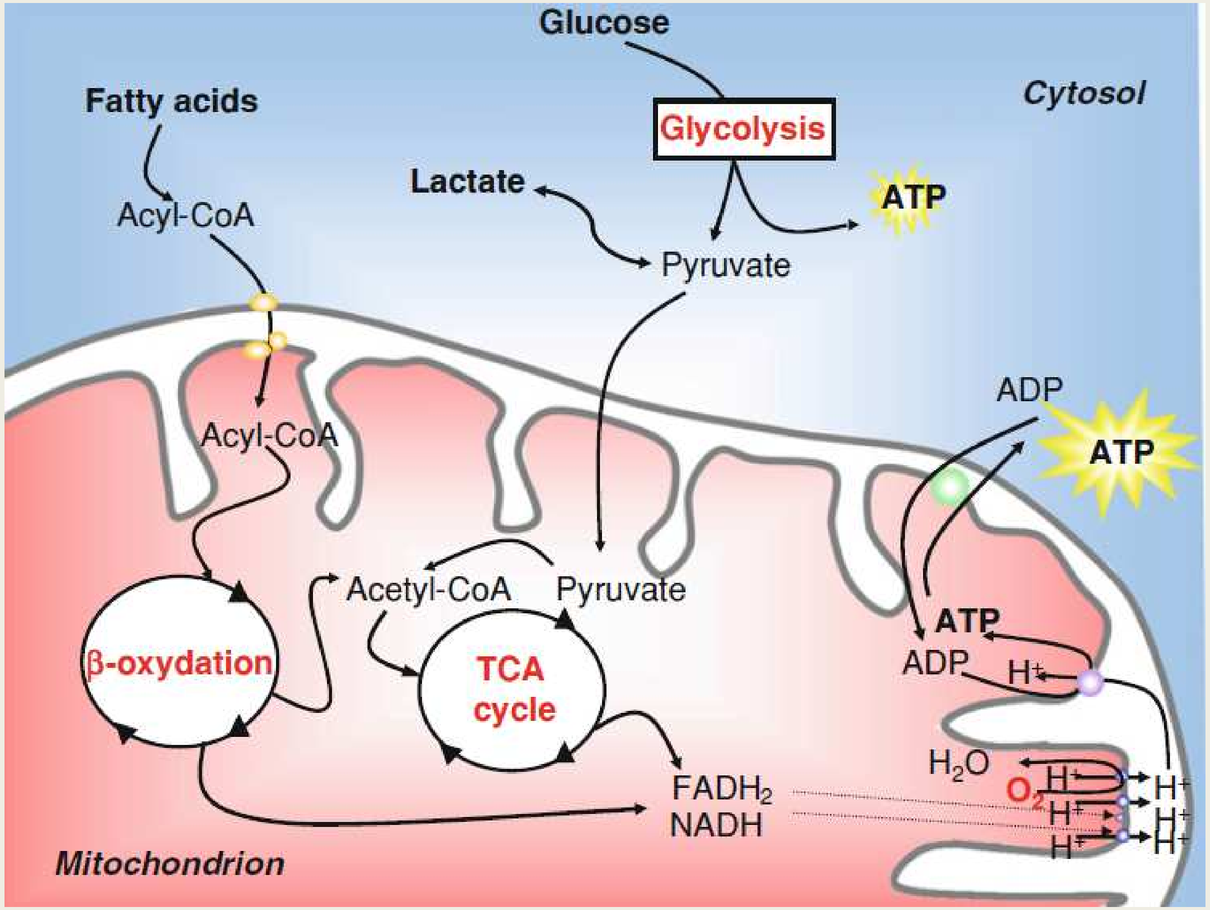
- Myosin ATPase
- SERCA
- Membrane transporters

Heart :
- High energy demand (1mM ATP/s) : one of the major energy consumer
- Low energy stock (8mM ATP and 15 mM PCr)
- Requires a constant energy production

Contraction of the cardiomyocyte and energy



Energy substrates of the myocardium

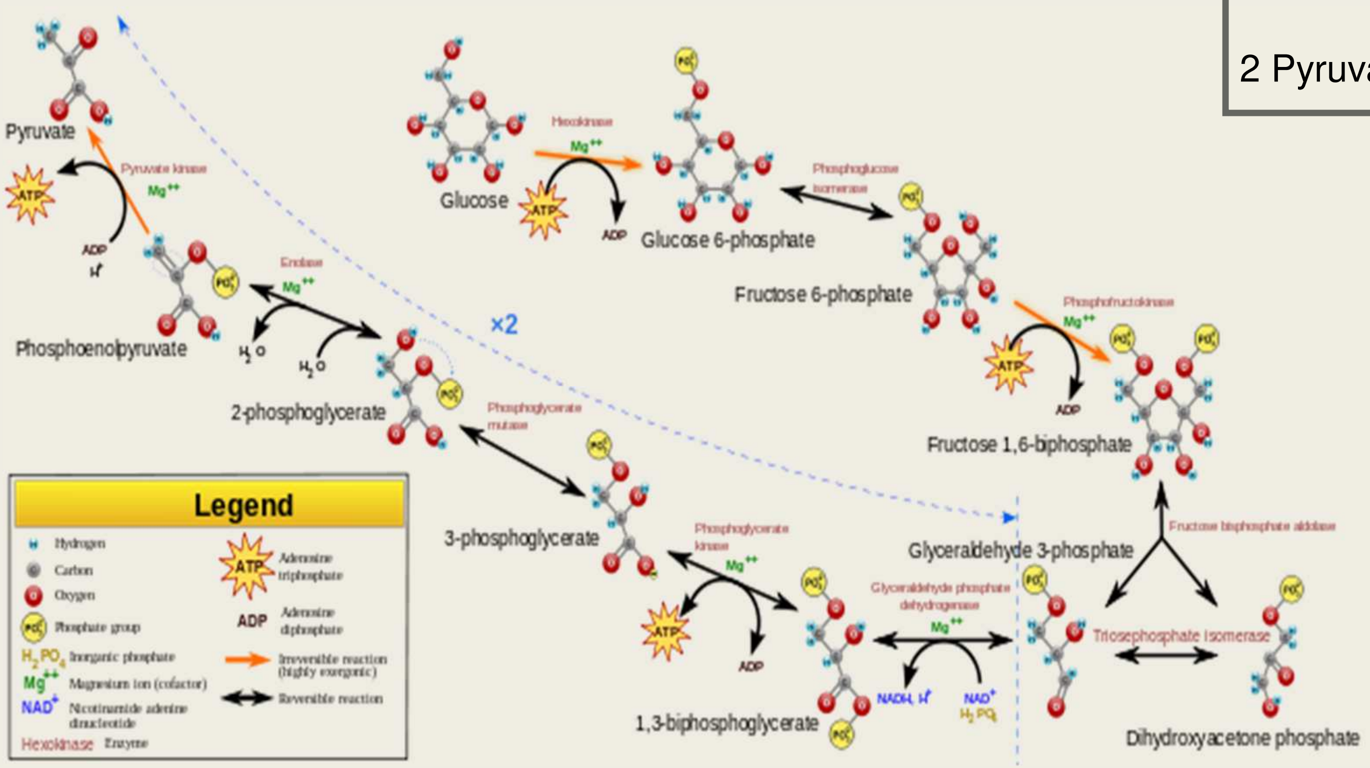


myocardium can use many kinds of substrates

Normal conditions: fatty acids

Mitochondria produce 90-95% of energy

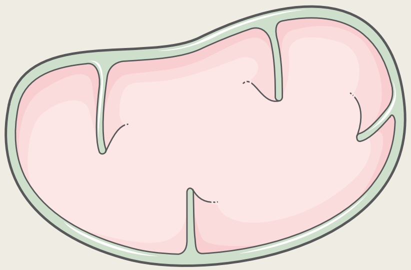
Glycolysis



Anaerobic glycolysis production:

2 Pyruvate, 2 NADH, 2 ATP

Mitochondria: at the heart of cardiac energetics

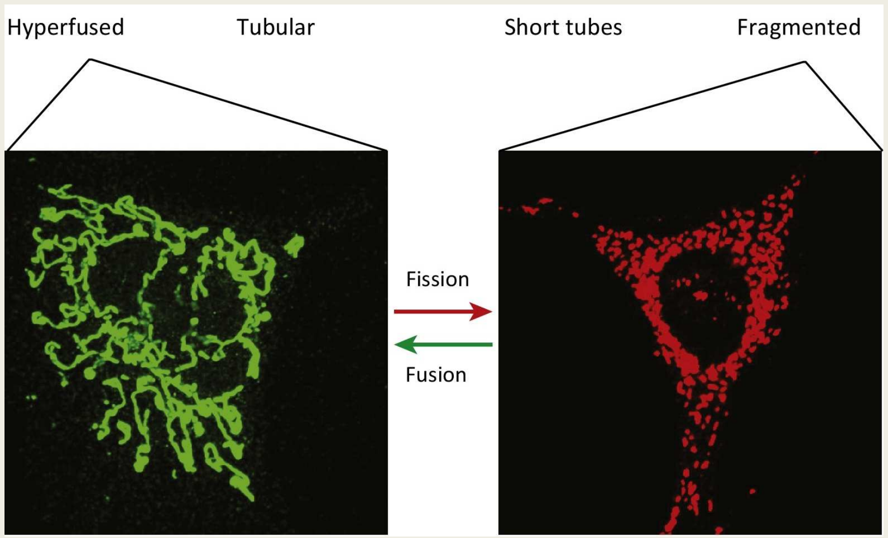


- outer membrane
- Intermembrane space
- Inner membrane with cristae
- Matrix

Mitochondrion

Mitos
« filament »

Chondros
« seed »

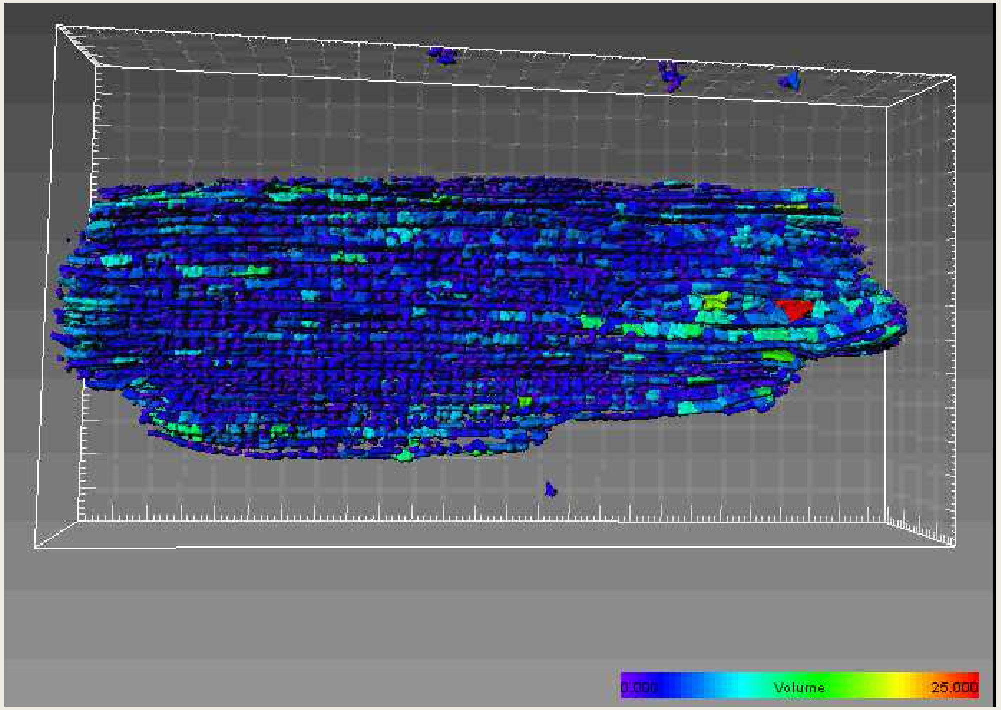


Mitochondria in adult cardiomyocytes

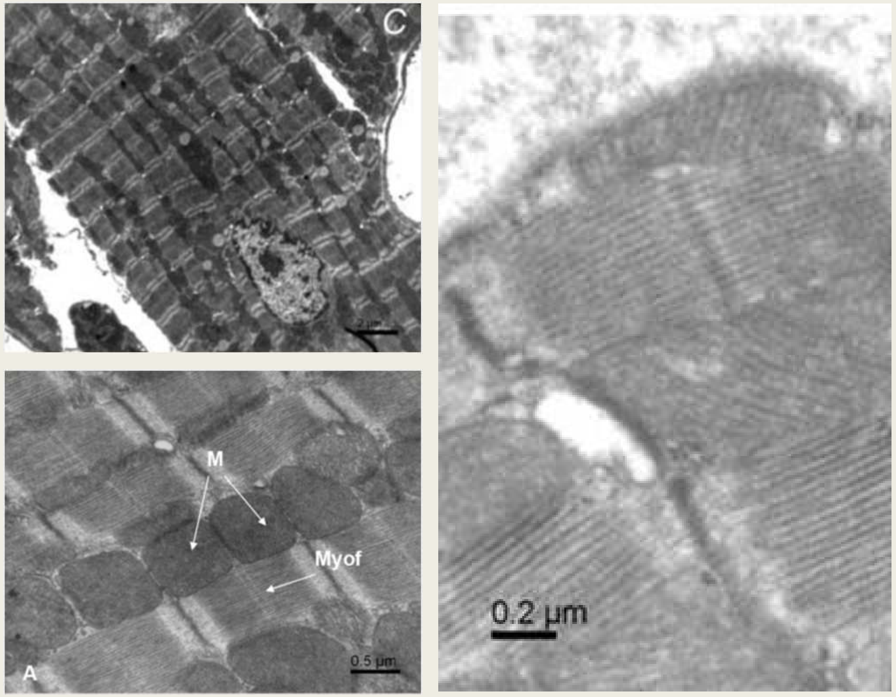
5000 to 10000 mitochondria per cell

Mean volume 1 µm3

Mitochondria occupy 30-40 % of the cell volume



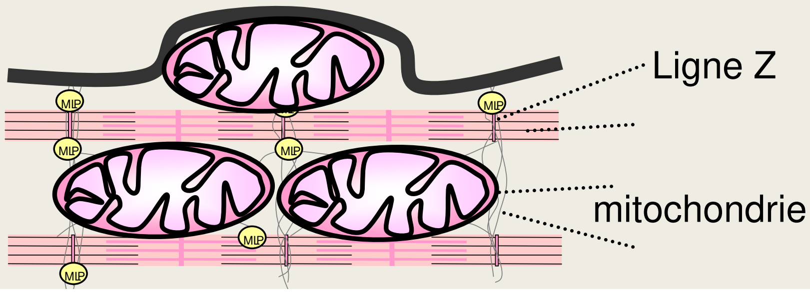
Mitochondria and cardiomyocyte cytoarchitecture



Precise arrangement of the components within the cytosol:

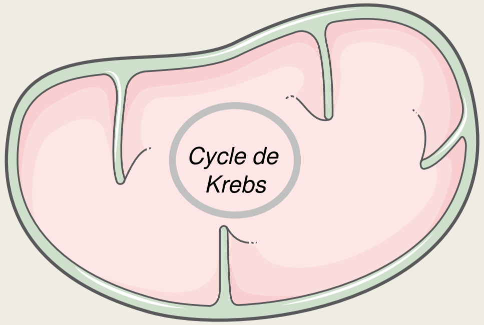
- emergence of microdomain
  - between mitochondria and myofilament
  - between mitochondria and SR

- Involvement of a highly specialized cytoskeleton
  - Microtubule
  - actin
  - Intermediate filaments (desmin)



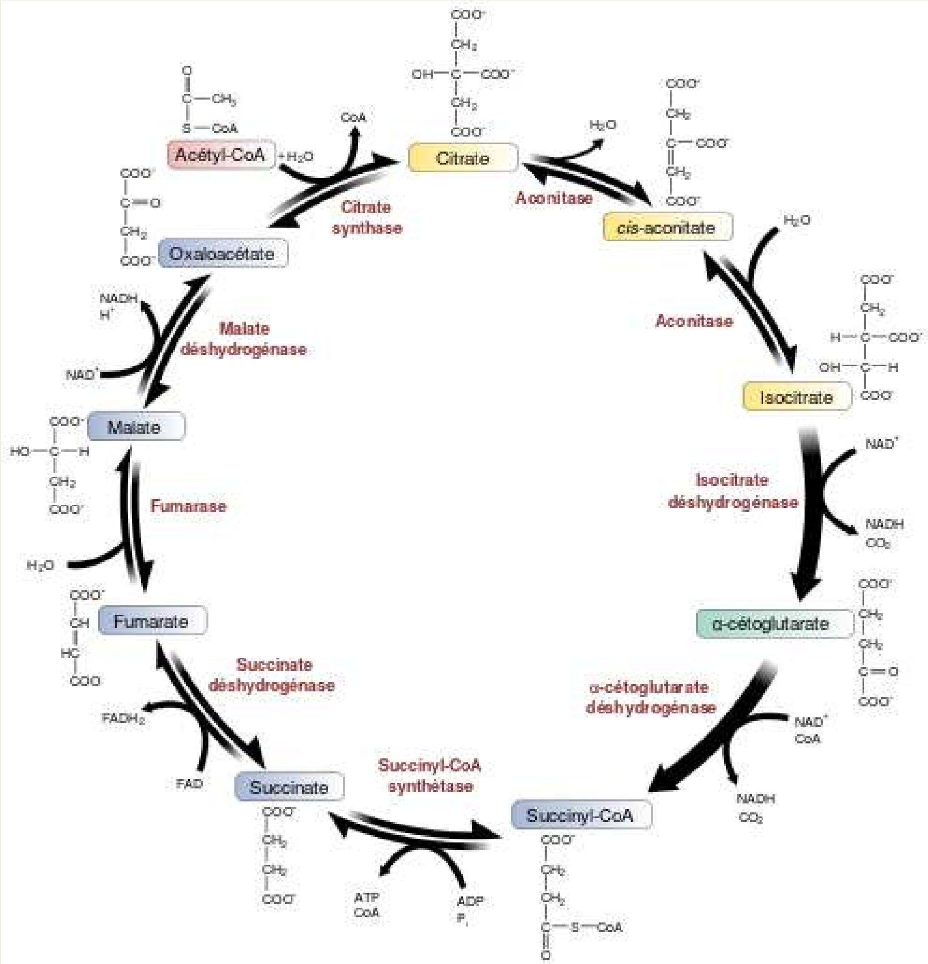
Krebs cycle

- Takes place in the mitochondrial matrix
- Citric acid cycle (CAC), tricarboxylic acid cycle (TAC)
- Series of chemical reactions from acetyl-CoA
- Release of reducing agent (NADH, FADH2)



Described by Sir Hans Krebs (1900 – 1981) during the 30's – Nobel Prize 1953

Krebs cycle

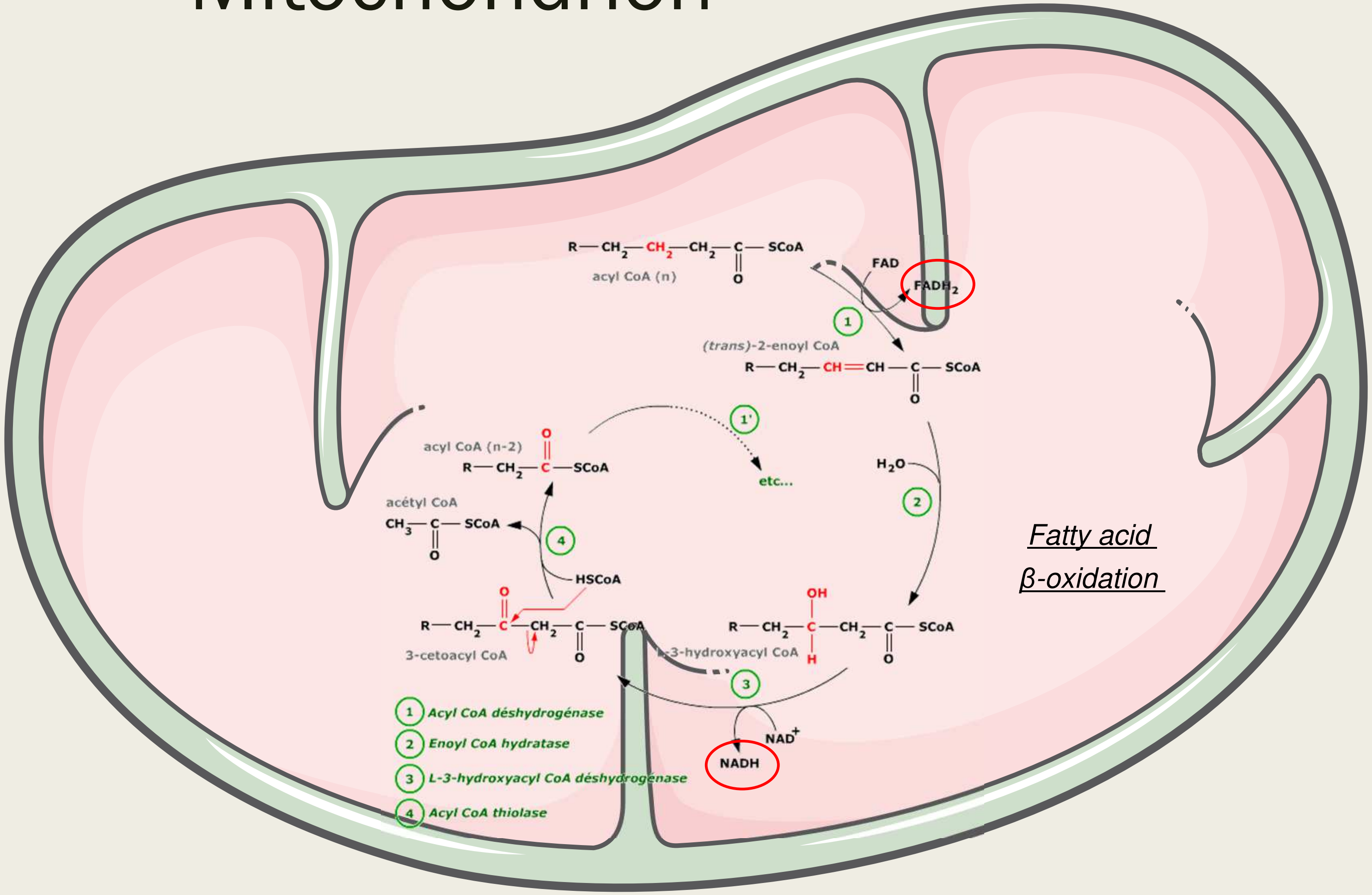


Output of the cycle

1 ATP
3 NADH
1 FADH2

Mitochondrial electron transfer chain (ETC)

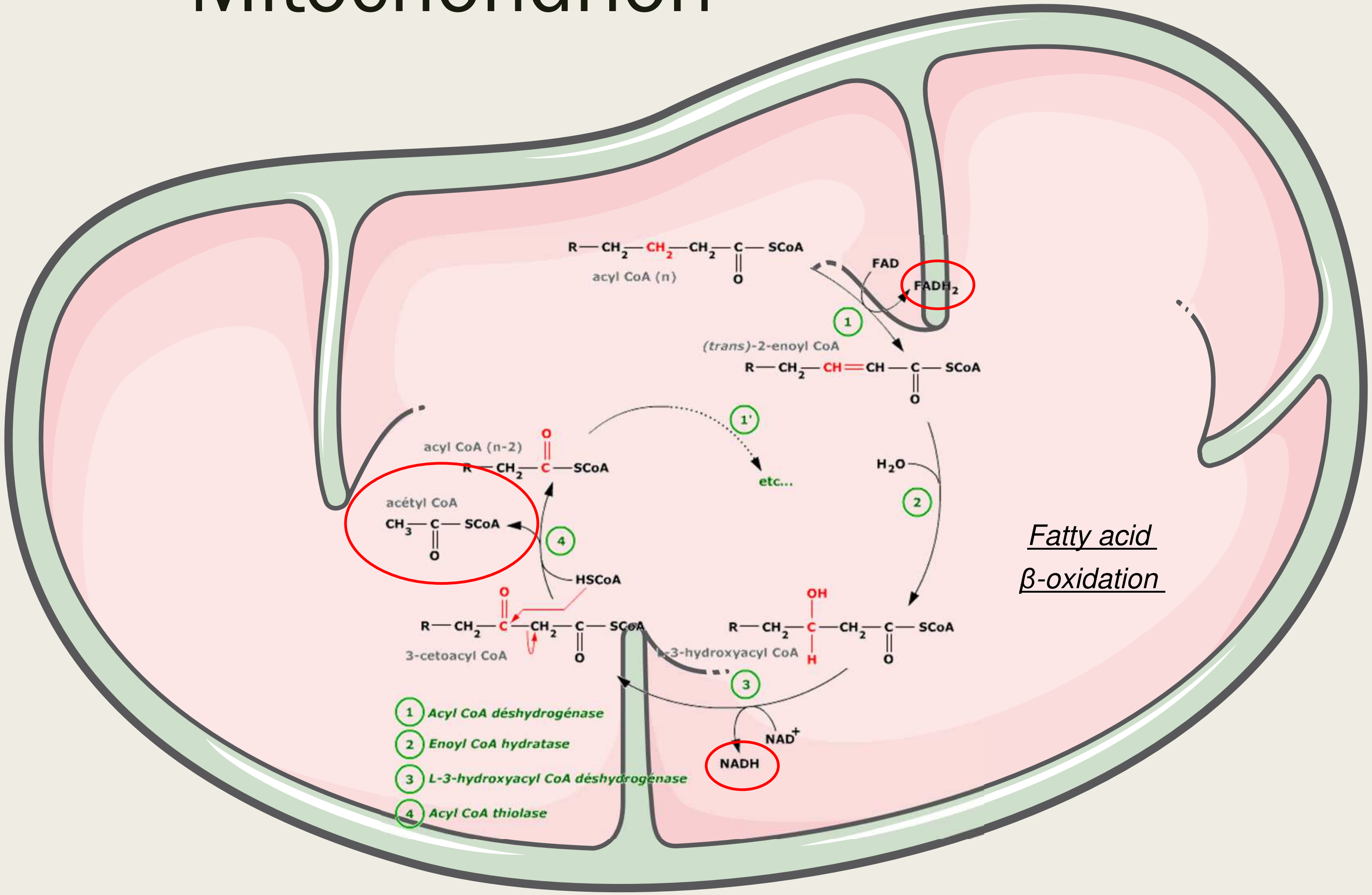
Mitochondrion



the powerhouse of the cardiac muscle cell

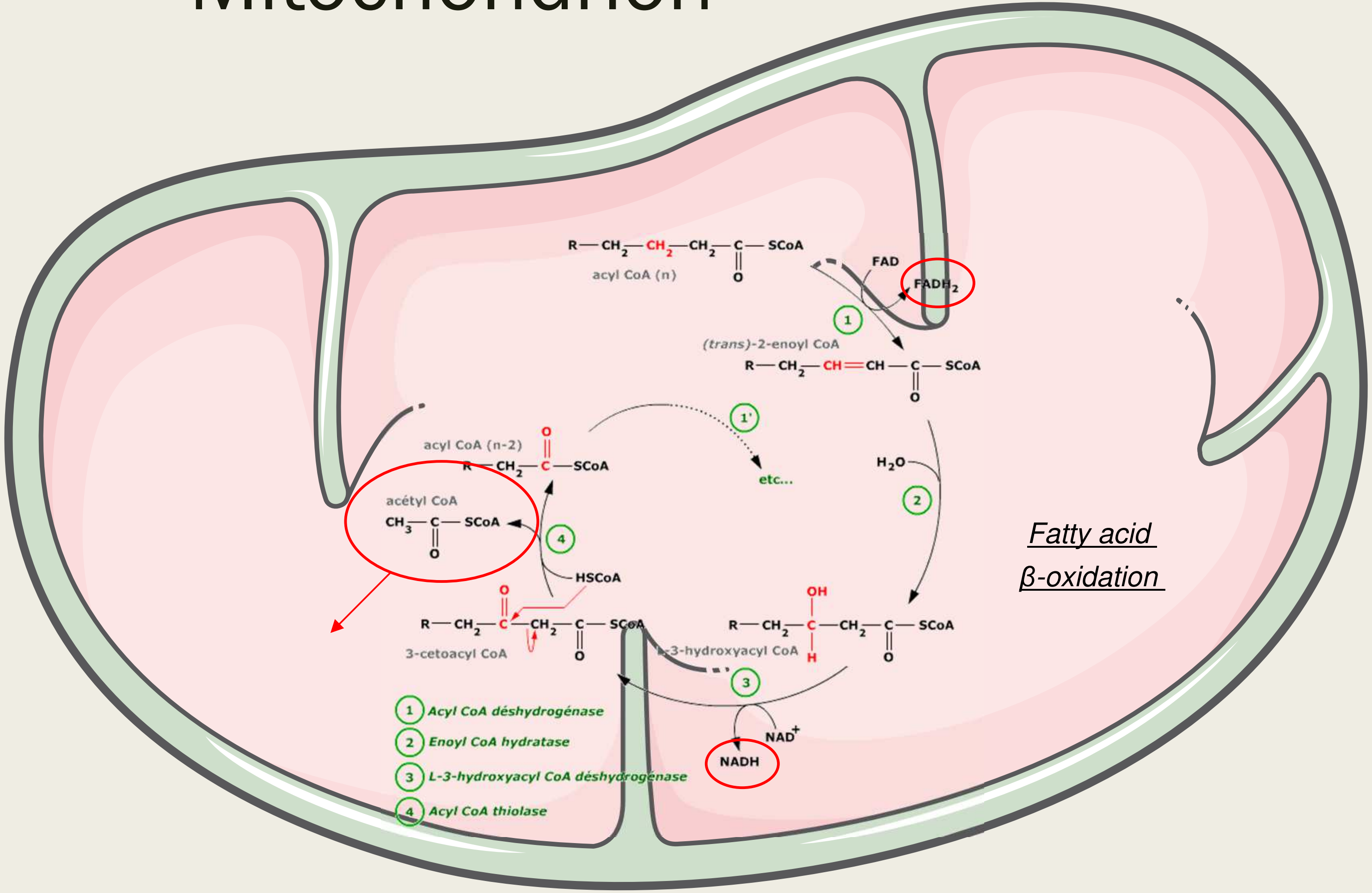
Mitochondrion

the powerhouse of the cardiac muscle cell

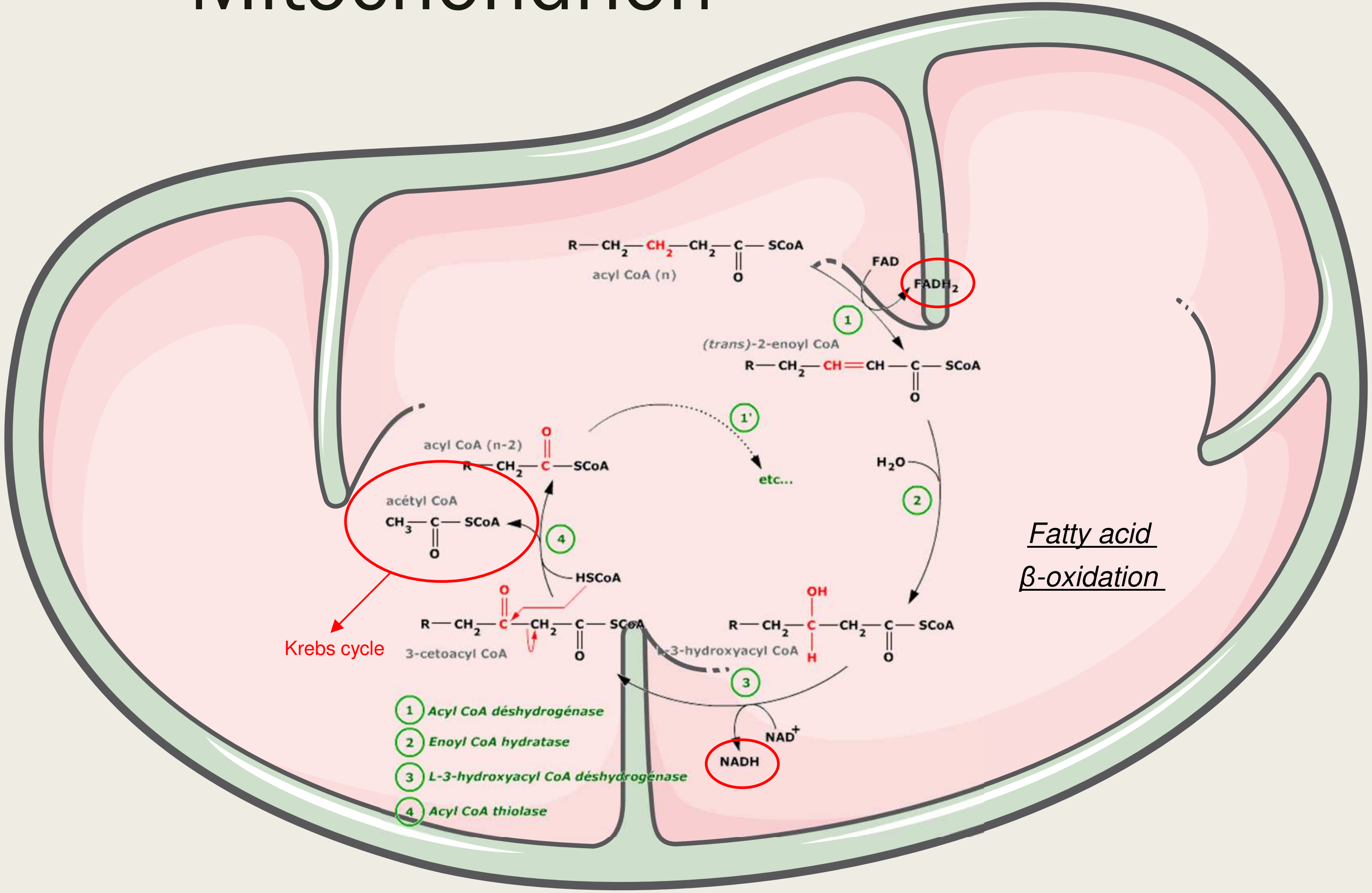


Mitochondrion

the powerhouse of the cardiac muscle cell



Mitochondrion



the powerhouse of the cardiac muscle cell

ETC and oxidative phosphorylation

Proton translocation:

Electron transfer in the chain → proton translocation to mitochondrial intermembrane space.

Proton translocation:

Accumulation of H+ in intermembrane space

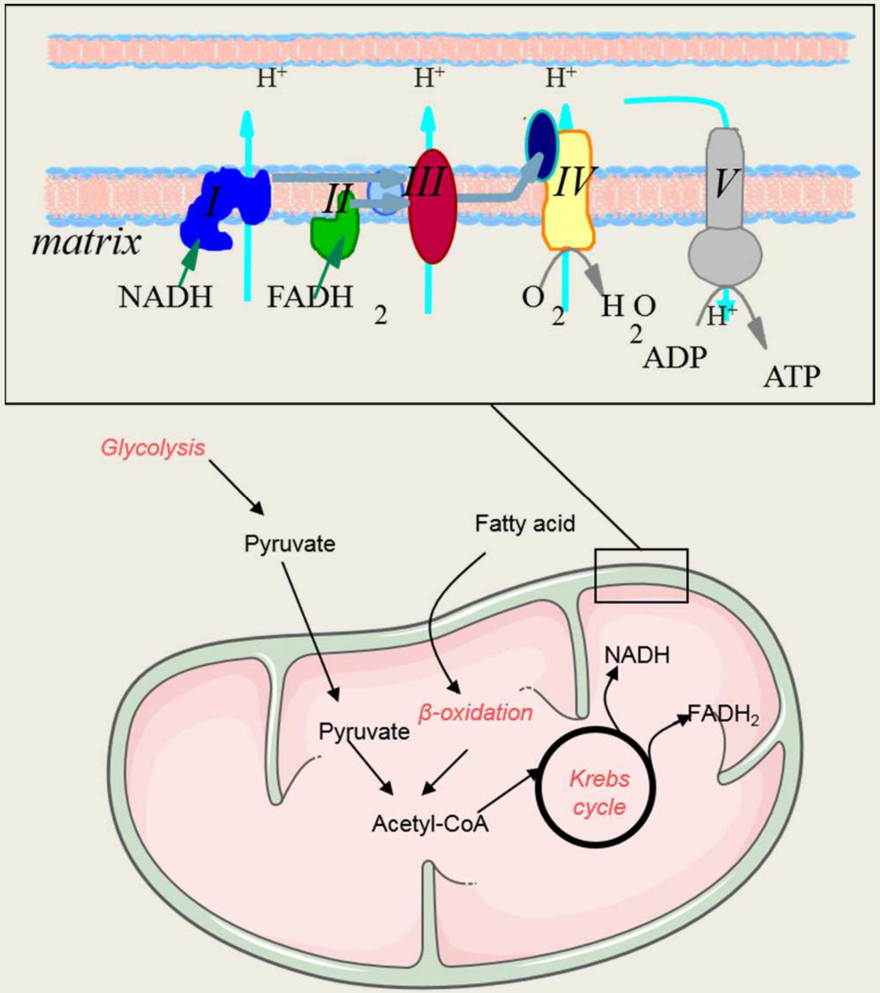
Concentration gradient: proton concentration is more important in intermembrane space (0.5 pH unit).

Electrical gradient: accumulation of positive electric charge (electrical potential difference : -150mV)

Proton motive force:

Electrochemical gradient → the passage of protons to the matrix through ATP synthase allows the production of ATP

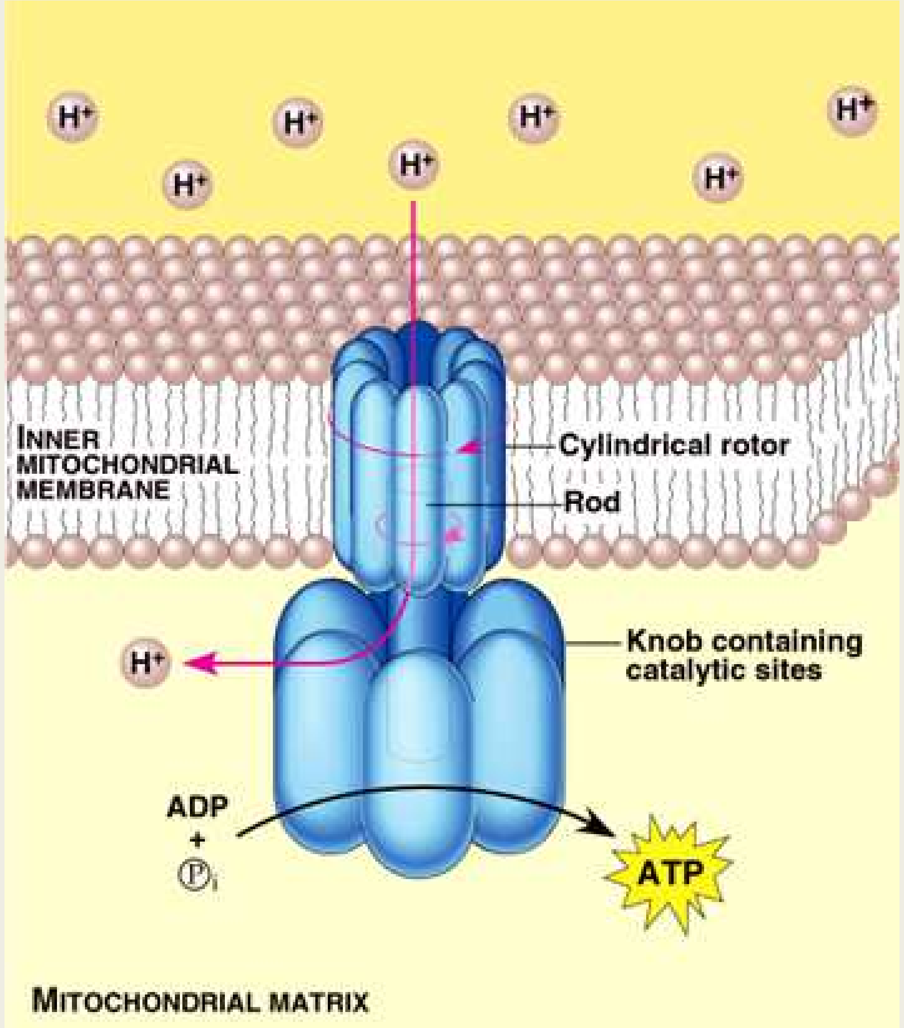
Energy production in the cardiomyocyte



ATP synthase

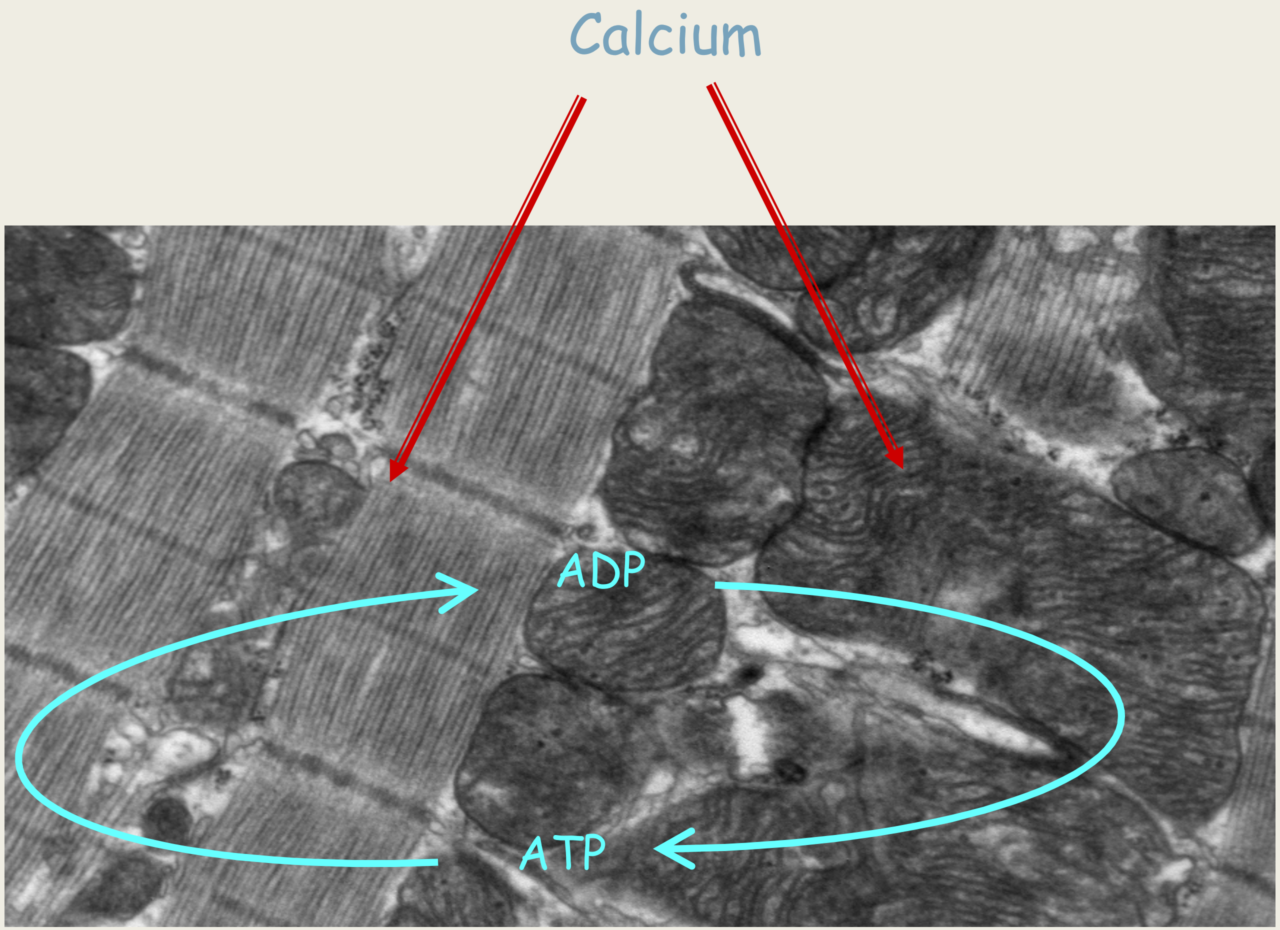
Protons flow through a channel in the ATP synthesis, the movement spins the protein and the mechanical movement of this rotor provides the energy to add an inorganic phosphate group to ADP to form ATP.

ATP synthase = a nanomotor (turbine).



Energy production in the cardiomyocyte

Regulation of energy production



Workload increase :

Increase in cytosolic Calcium
→ calcium in mitochondrial matrix increases
→ stimulation of mt dehydrogenases and ATP synthase
→ Higher production of NADH and ATP

Increase in cytosolic ADP
→ stimulation ATP production by ATP synthase

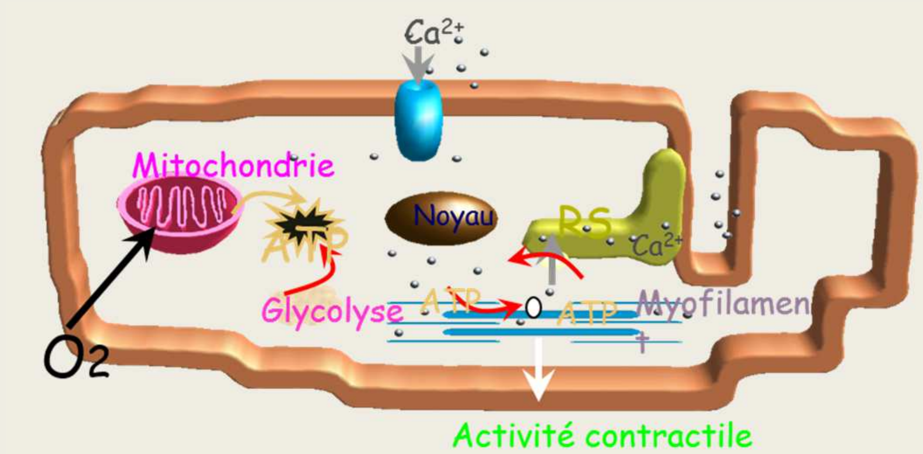
From energy producers to energy consumers

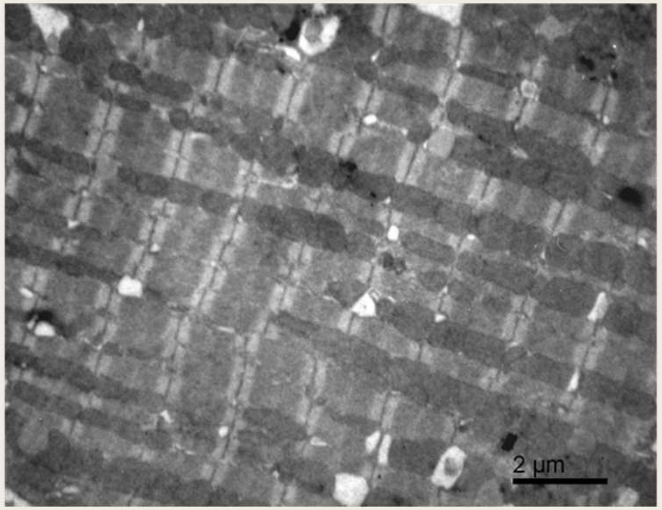
High density of myofilaments and mitochondria

Low efficiency of energy diffusion

☞ Energy transfer systems are required

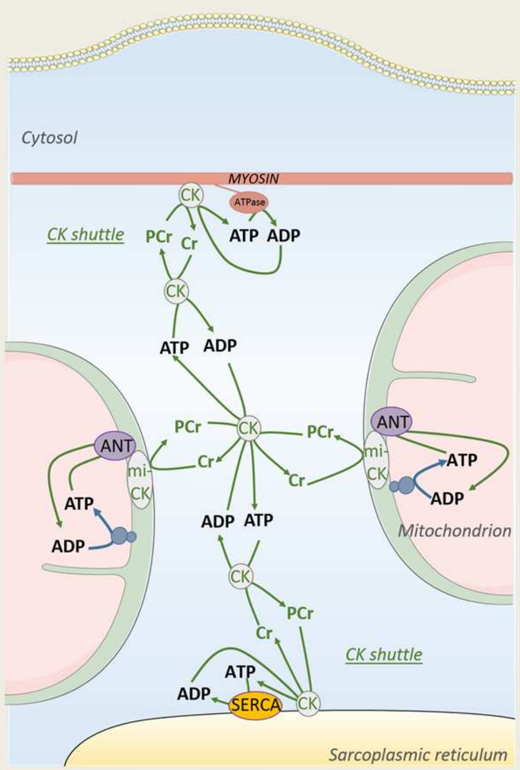
Energy transfer within the cardiomyocyte





Energy transfer systems

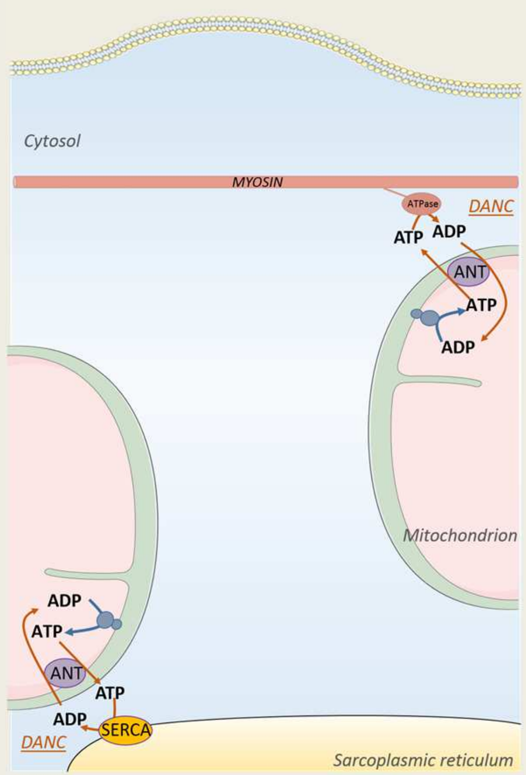
Creatine Kinase shuttle

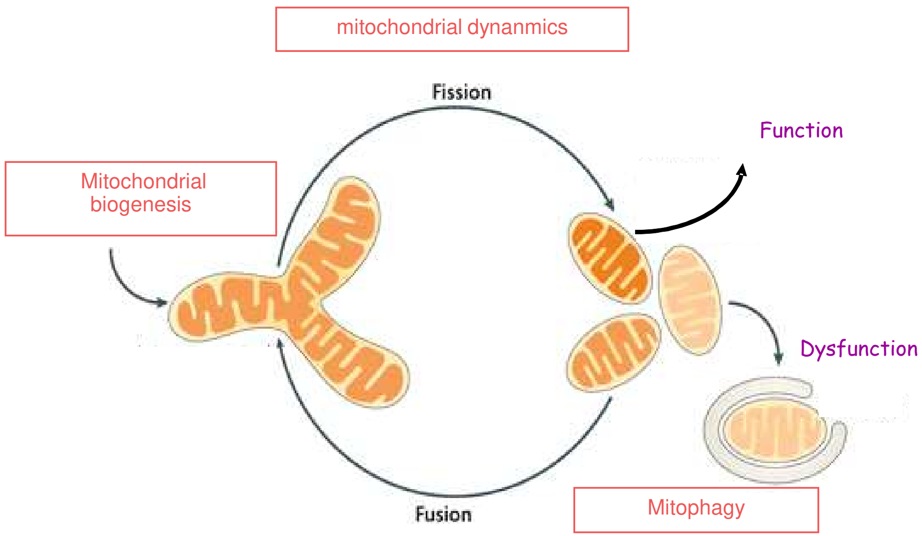


CK

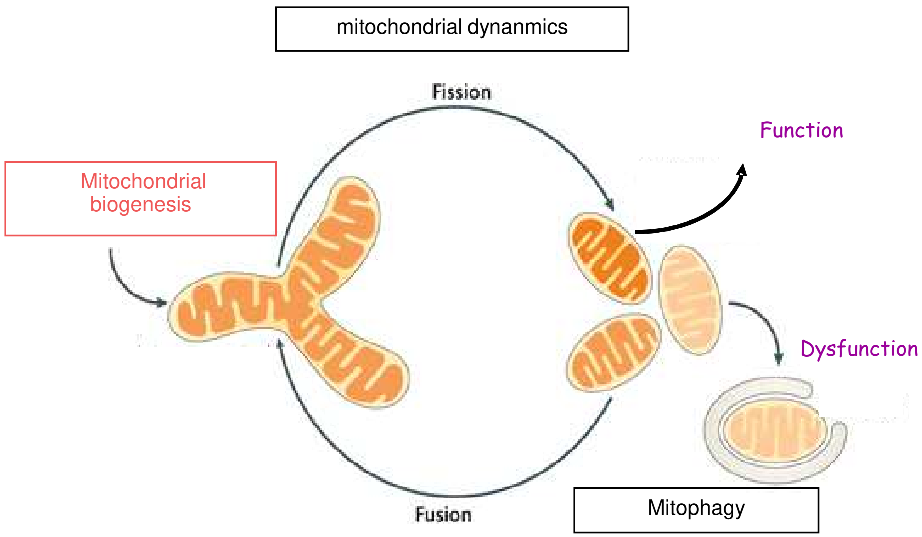
creatine + ATP ⟷ phosphocreatine + ADP

Direct adenine nucleotide channeling





Mitochondrial life cycle



Mitochondrial life cycle

Mitochondrial biogenesis

Proliferation of mitochondria through division

Mitochondrial DNA replication

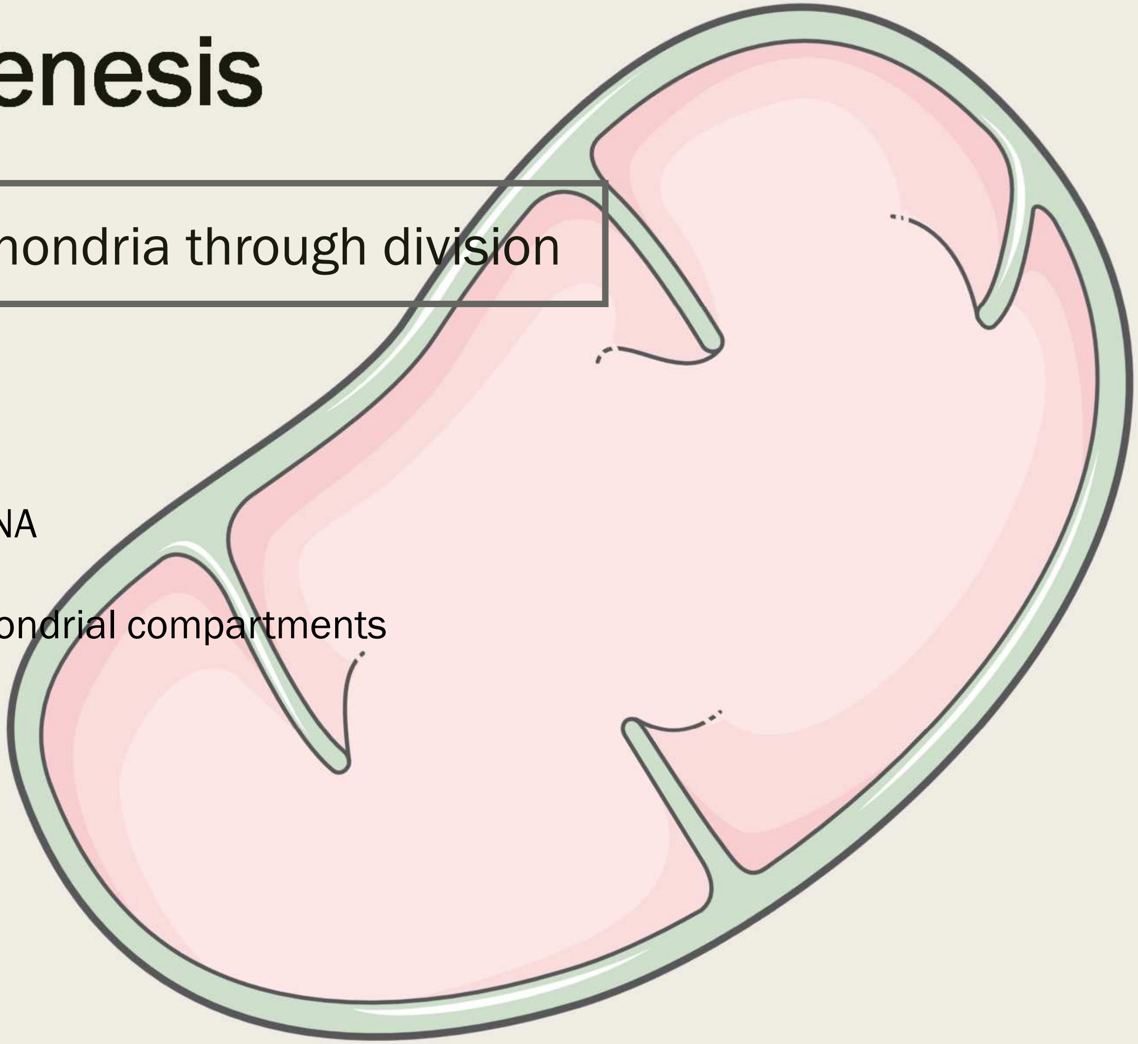
Transcription of nuclear DNA and mitochondrial DNA

Import of precursors produced in cytosol to mtochondrial compartments

Complex assembly

Lipid and phospholipid synthesis

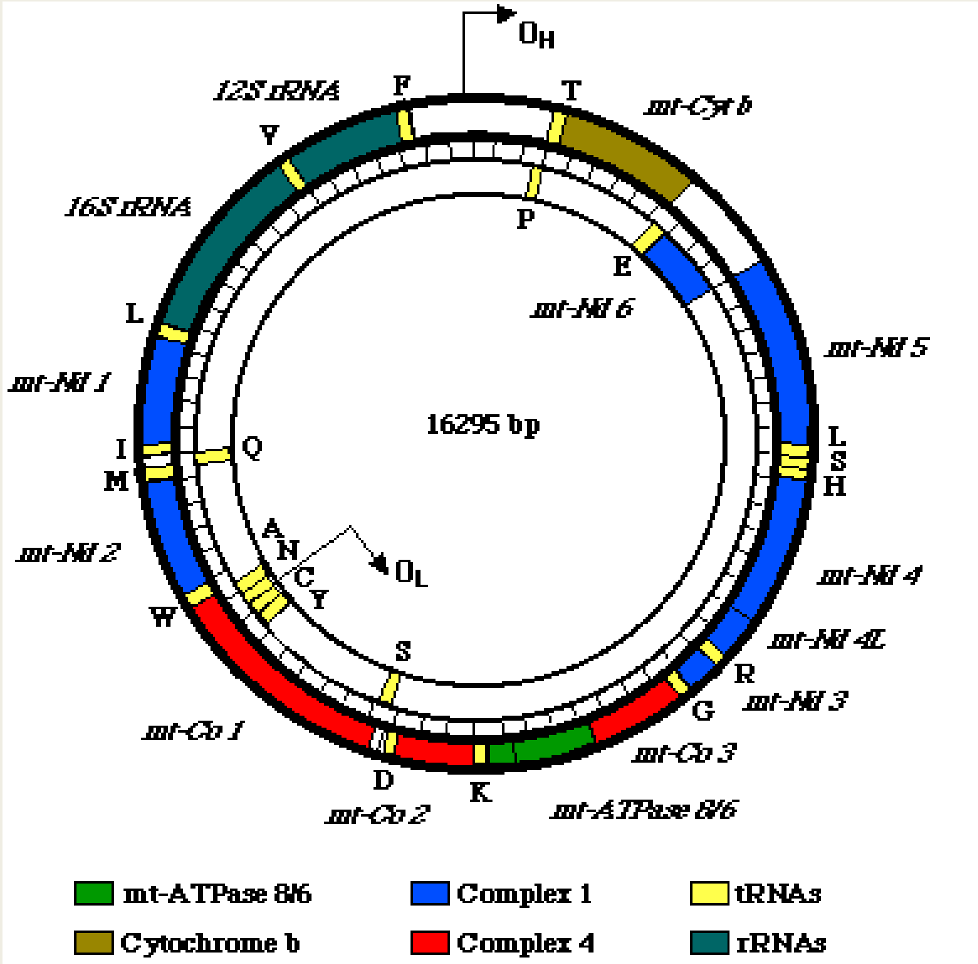
Mitochondrial dynamics



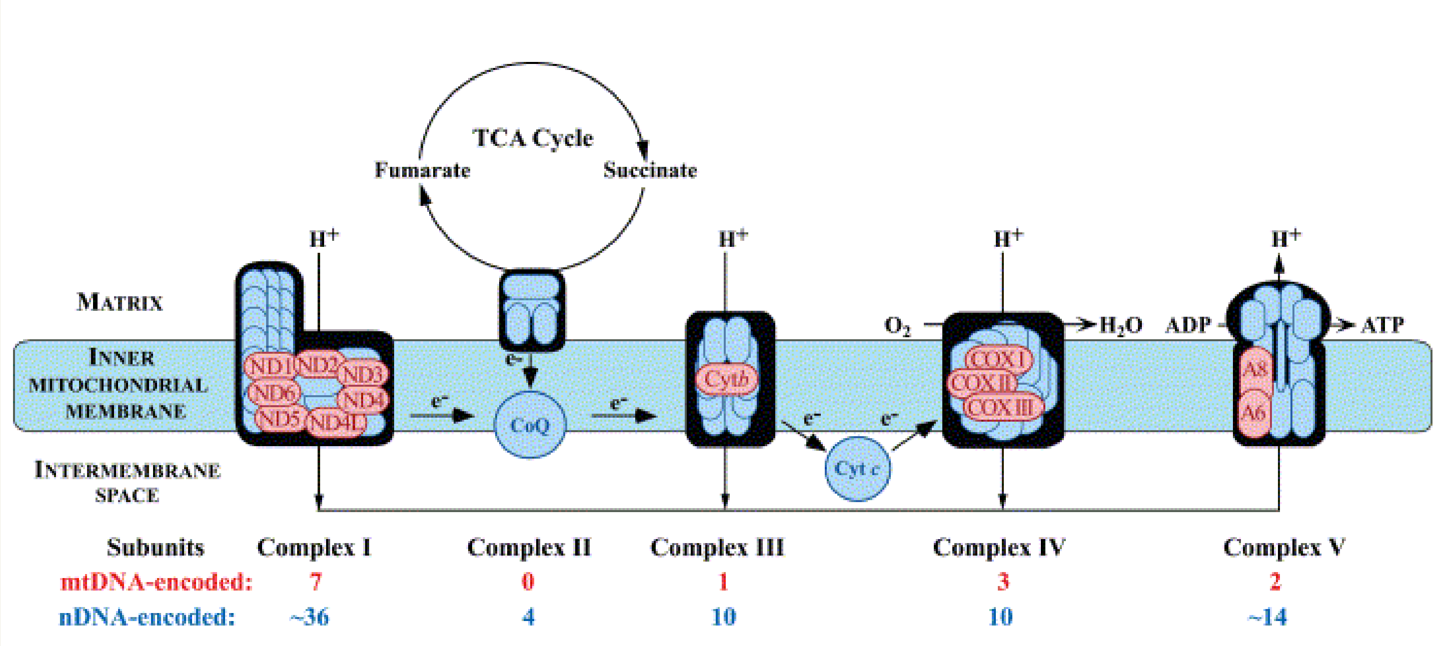
Mitochondrial genes

Mitochondrial DNA
- circular
- 16 569 nucleotide pairs
- 13 proteins (ETC)
- 22 transfert ARN
- 2 ribosomal ARN

Nuclear DNA
- 1000 mitochondrial proteins
- Precursors

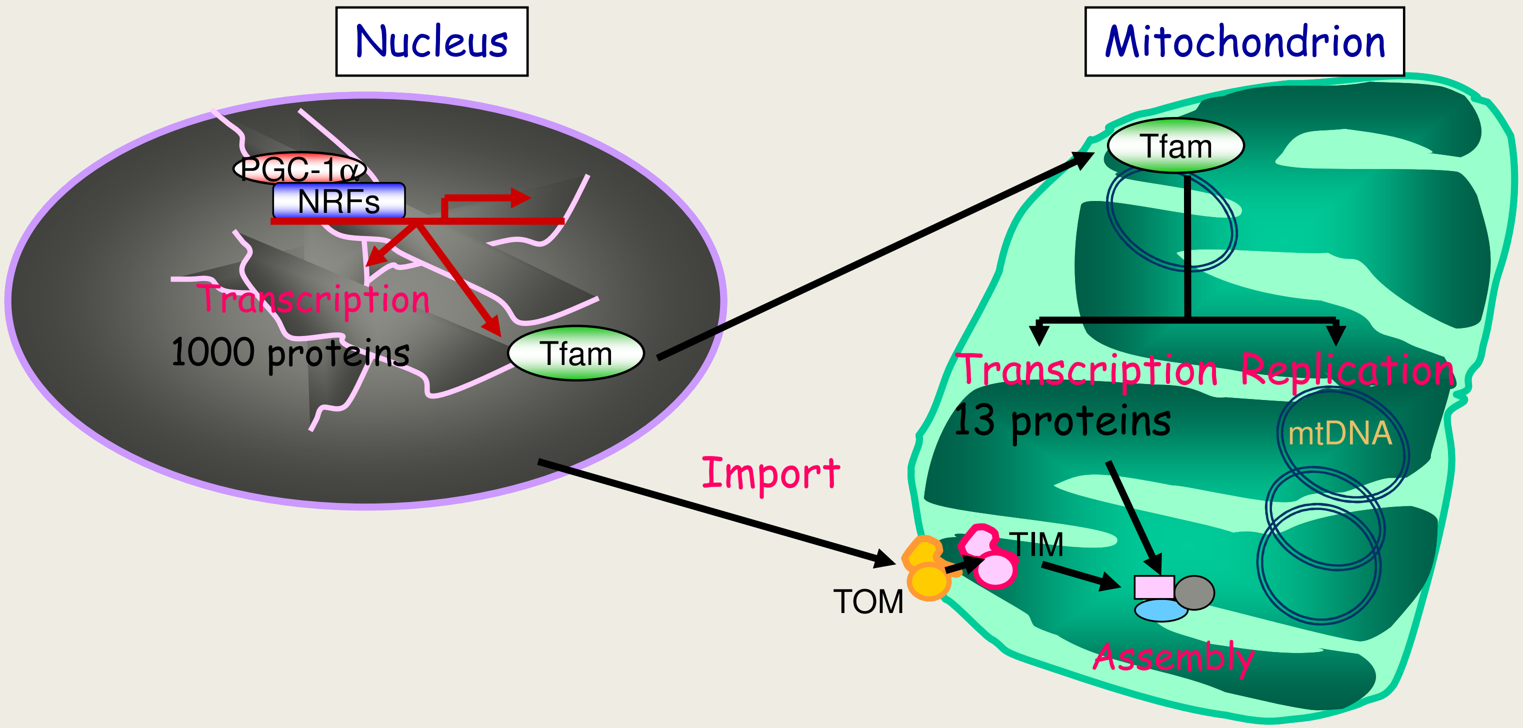


Mitochondrial genes and ETC

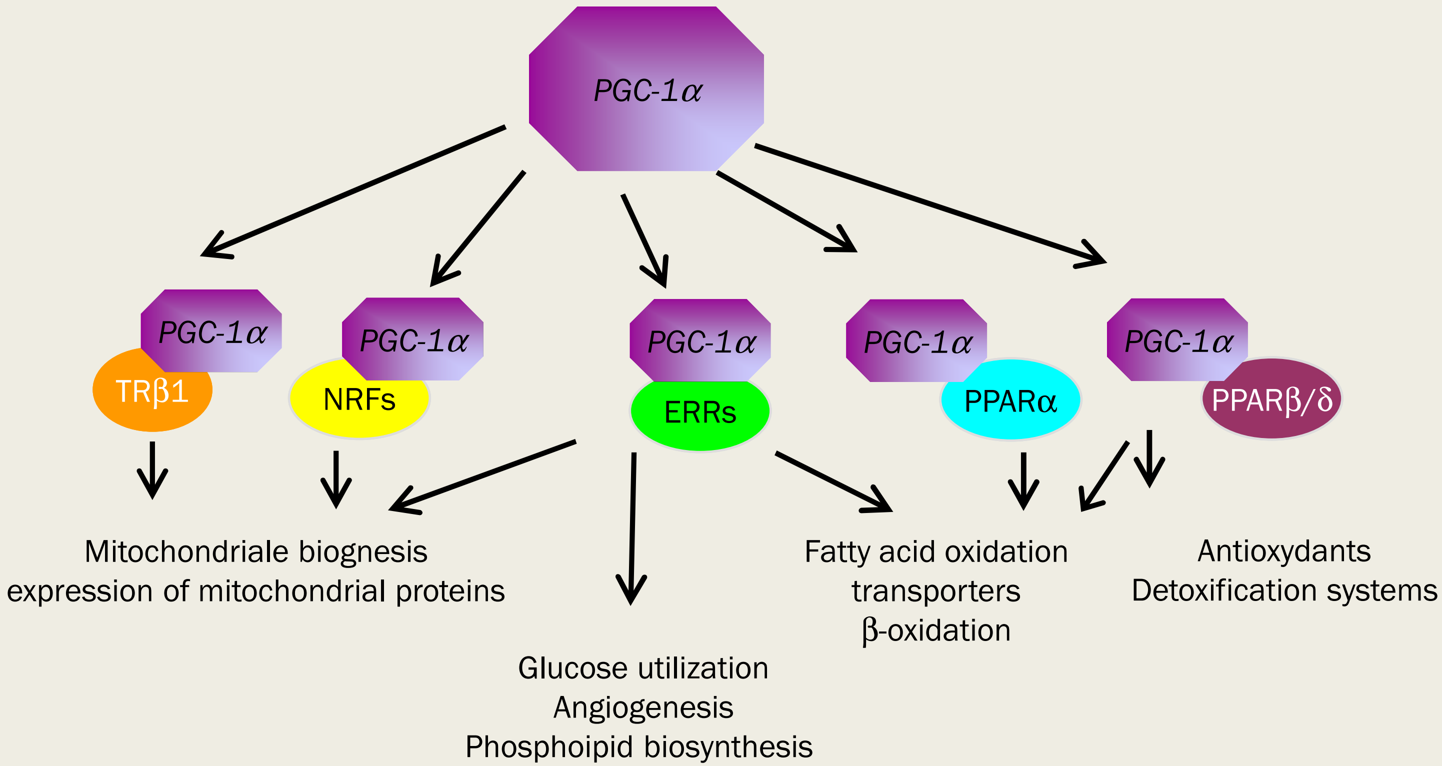


Complex I: NADH coQ oxydoreductase
Complex II: Succinate dehydrogenase
Complex III: Cytochrome c reductase
Complex IV: Cytochrome oxydase (COX)
Complex V: ATP synthase

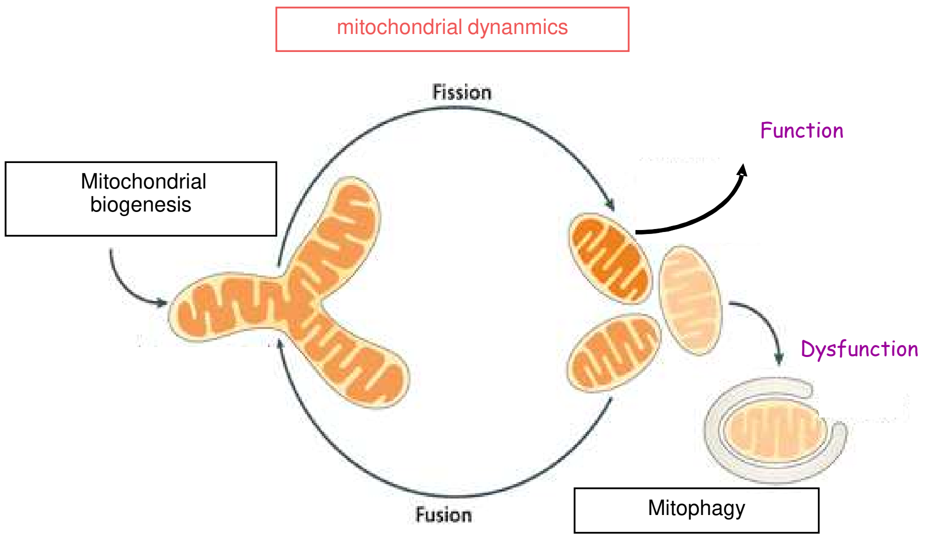
Regulation of transcription



Regulation of transcription



Ventura-Clapier et al Cardiovasc Res 2008



Mitochondrial life cycle

Mains actors

<u>Fission:</u>

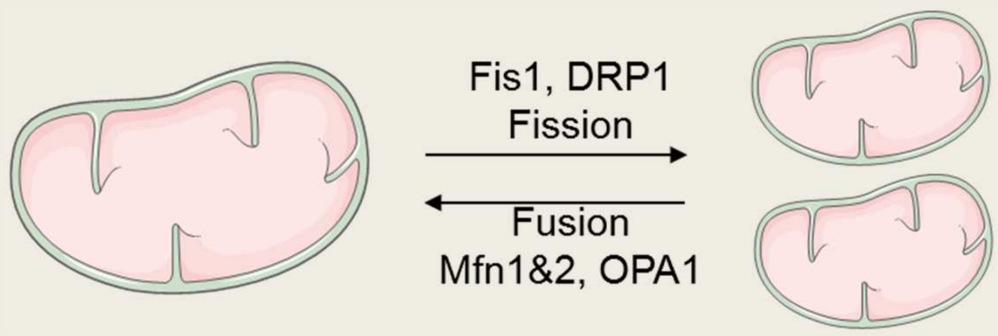
Division of a mitochondrion into several daughter mitochondria

Main regulators: DRP1 and Fis1

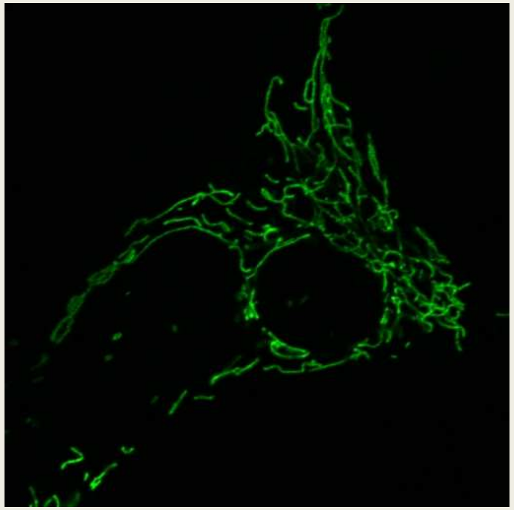
<u>Fusion</u>

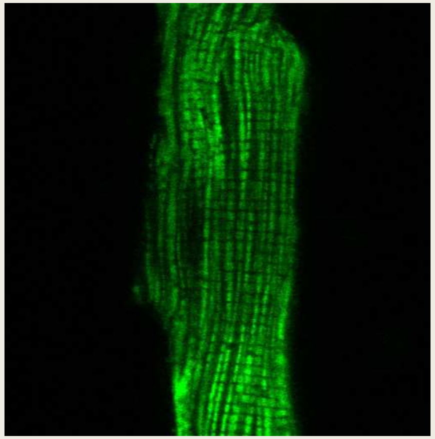
Physical merging of outer and inner membranes of two originally distinct mitochondria.

Main regulators: Mitofusins (Mfn1 et Mfn2) and OPA1



Mitochondrial network





Fused or fragmented mitochondrial network

According to :
- Cellular environment (energetics, ROS…)
- Cell cycle life (mitosis, apotposis)
- Cell type

Regulated by
- Pro-fusion and pro-fission proteins expression balance
- Dynamin activity modulation (post-translational modulations)

Consequences on
- Cell death resistance
- Bioenergetic efficiency

Mitochondrial dynamics in adult cardiomyocyte

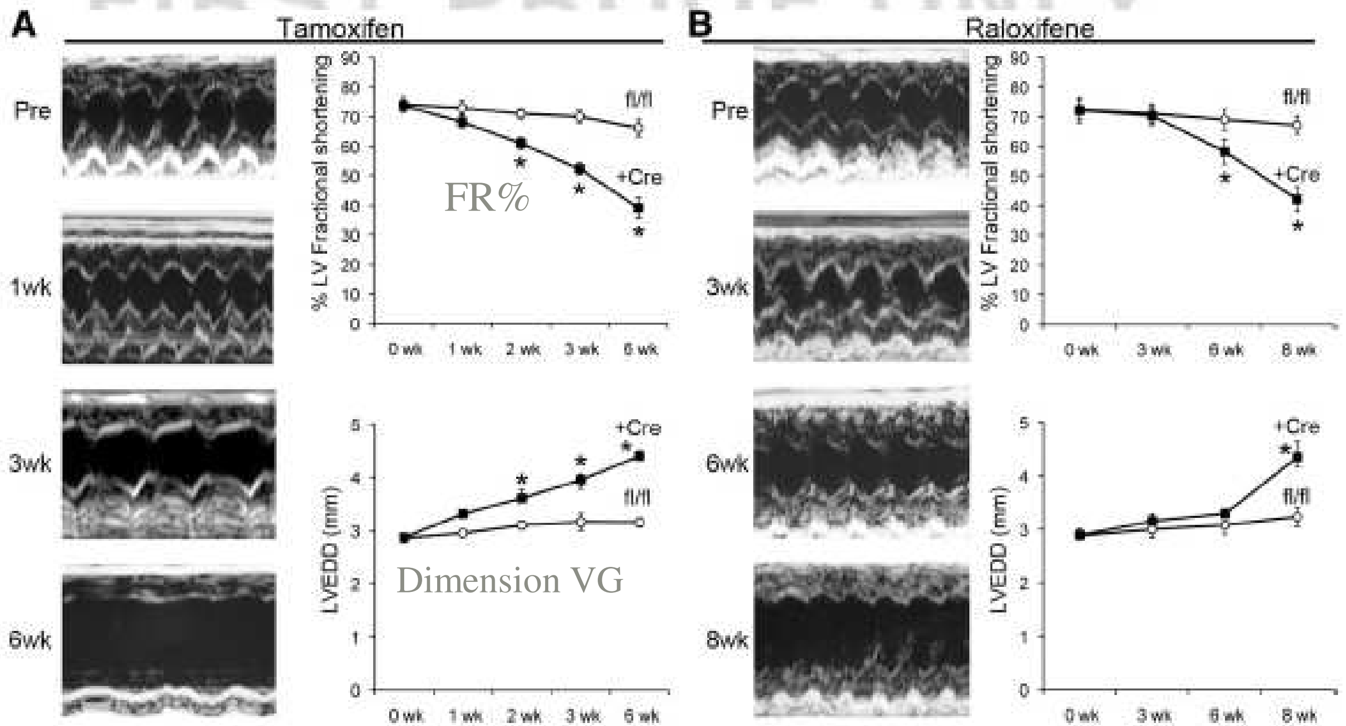


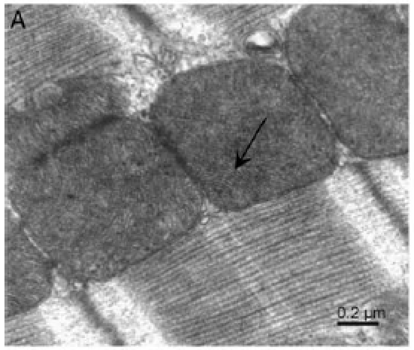
Figure 4. Combined mitofusins 1 (Mfn1) and 2 (Mfn2) ablation in adult hearts induces rapidly progressive dilated cardiomyopathy. A, Representative M-mode echocardiograms of unanesthetized mouse left ventricles before (Pre) and at intervals after conditional ablation of Mfn1 and Mfn2 with tamoxifen. Group data for fractional shortening (**top**) and LV end diastolic dimension (LVEDD, **bottom**) are to the right (n=4–5 per group). **B**) Same as in (**A**), but using Raloxifene to activate MER-Cre-MER (n=4 per group).

Chen Y. et al, 2011 Circ. Res.

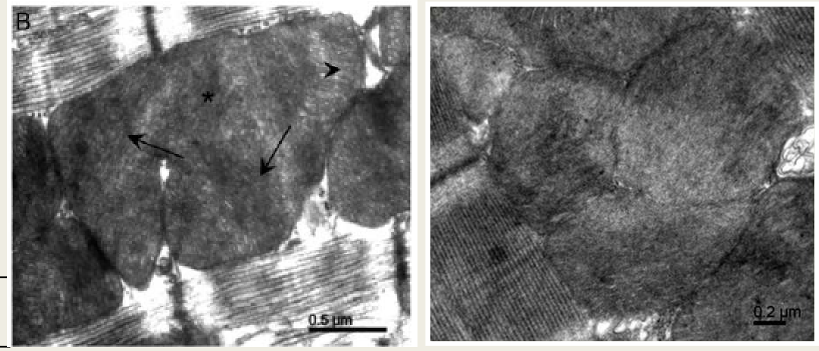
Mice die 8 weeks after Mfns deletion

Mitochondrial dynamics in adult cardiomyocyte

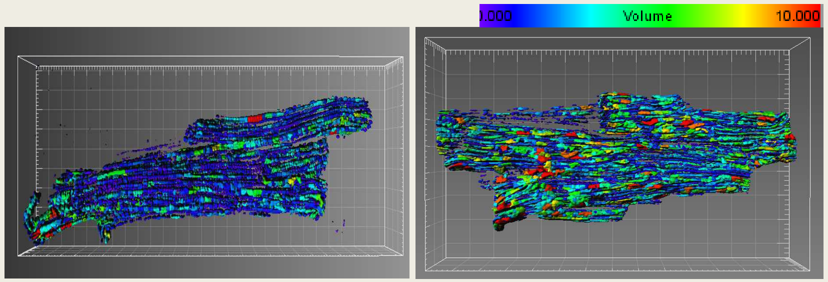
OPA1$^{+/+}$



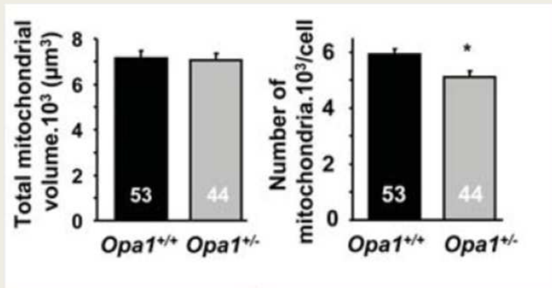
OPA1$^{+/-}$

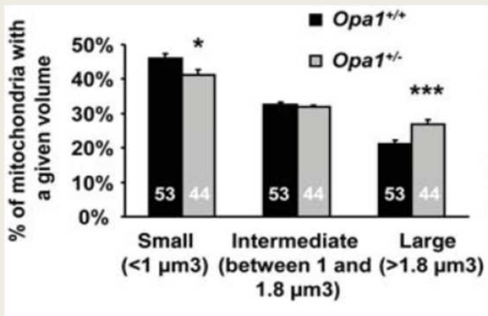


Mitochondrial volume analysis



Souris OPA1$^{+/+}$ Souris OPA1$^{+/-}$





Piquereau J. et al, 2012 Cardiovasc. Res.

Role of mitochondrial dynamics

Mitochondrial quality control

Metabolites and DNA exchanges

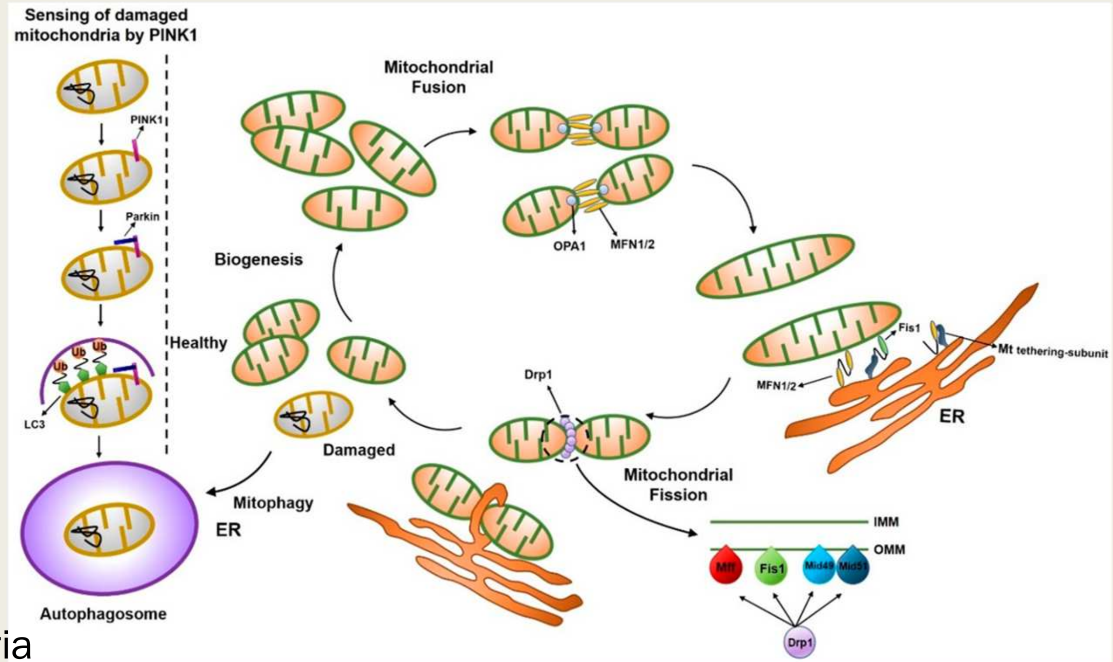
Network architecture

Mitchondrial biogenesis

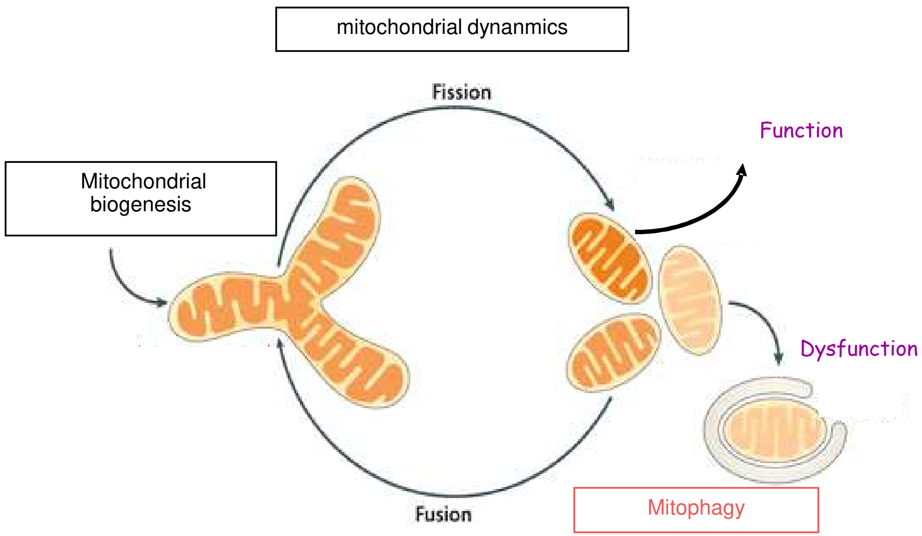
Apoptosis

Stress response

Selective autophagy of mitochondria



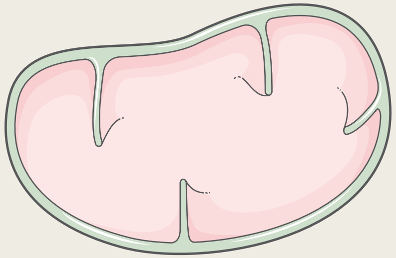
Mitochondrial life cycle



Molecular mechanism

Mitophagy

selective autophagy of mitochondria
involvment of a specific protein machinery



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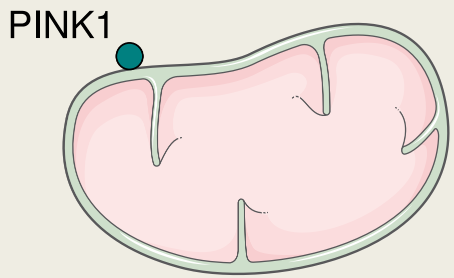

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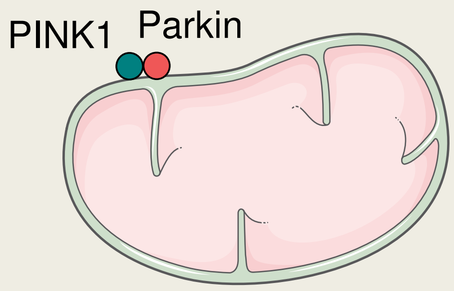

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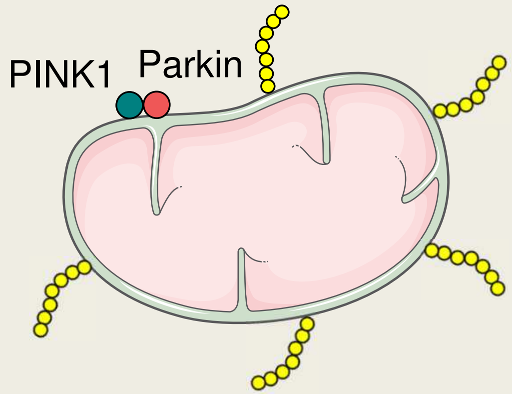

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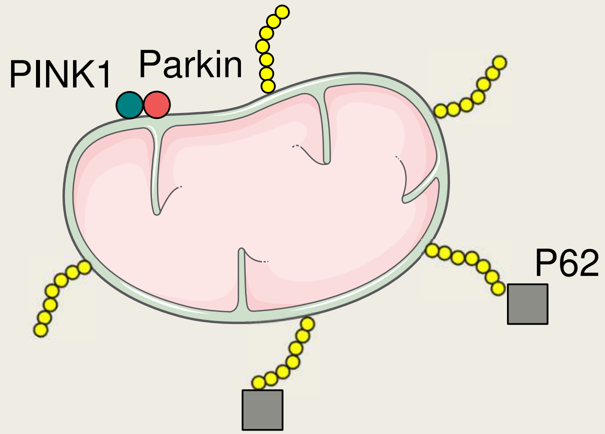

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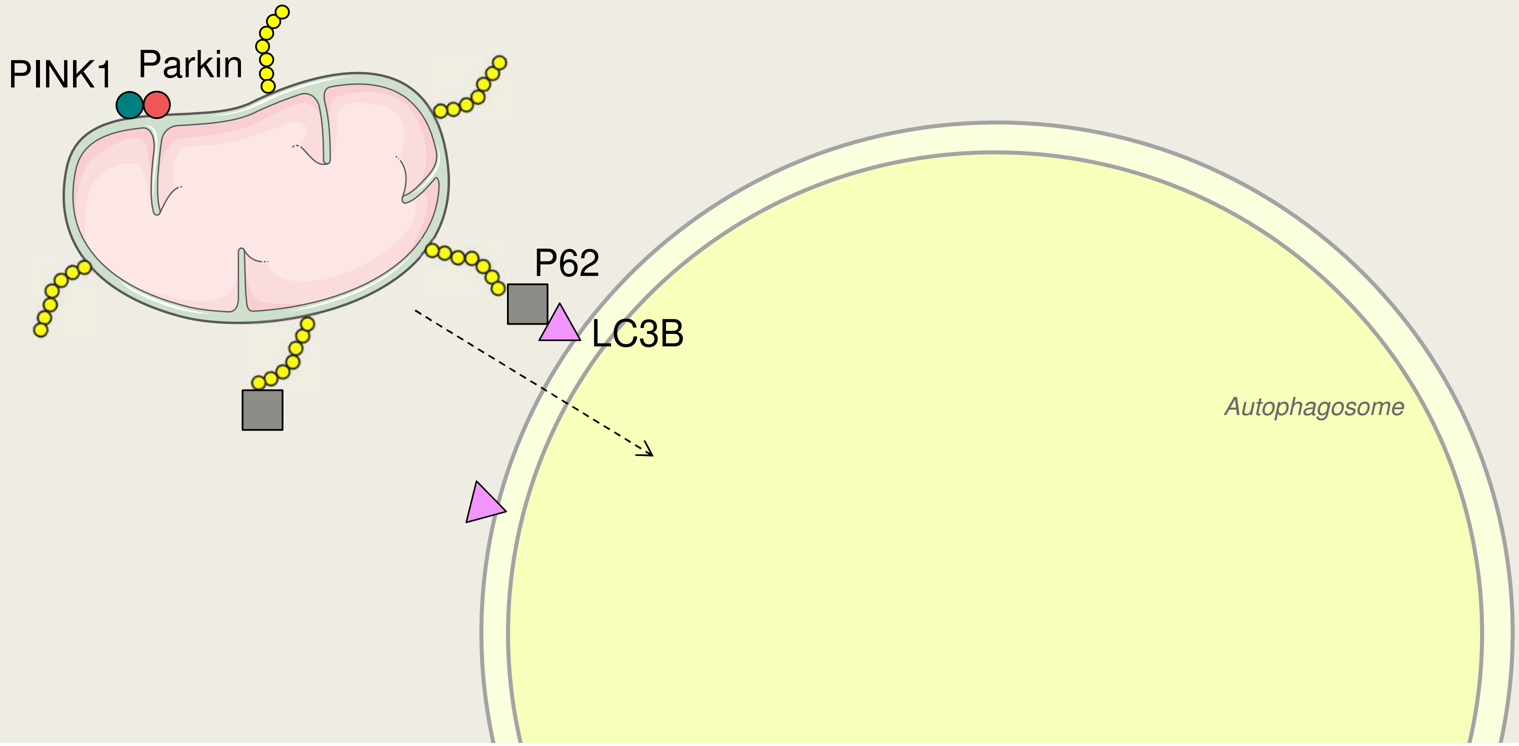
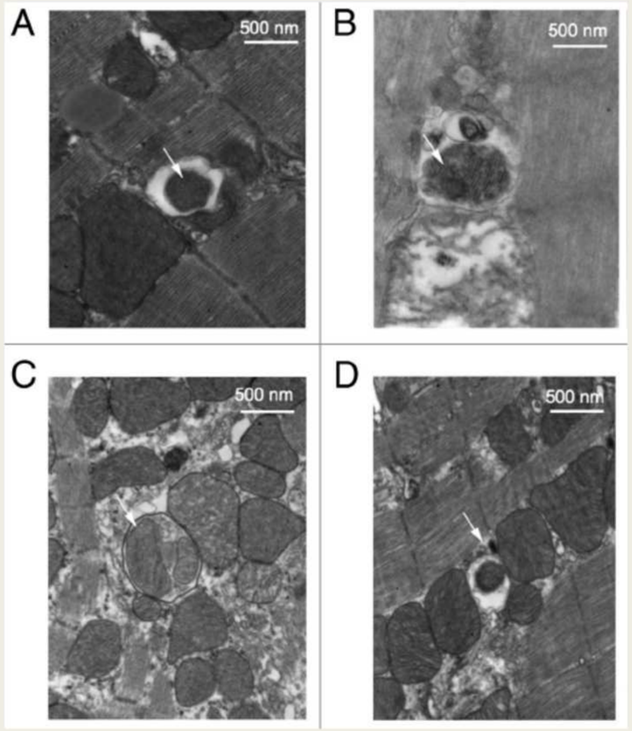
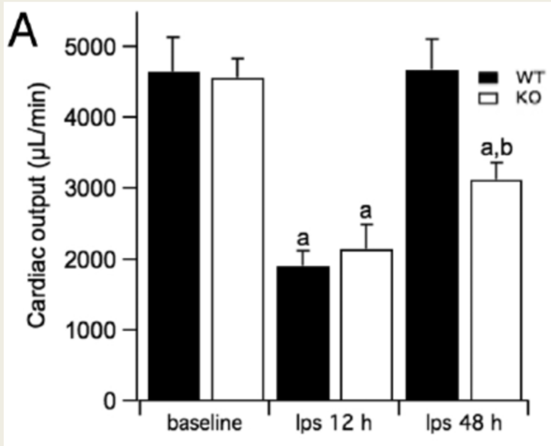


Mitophagy in the heart

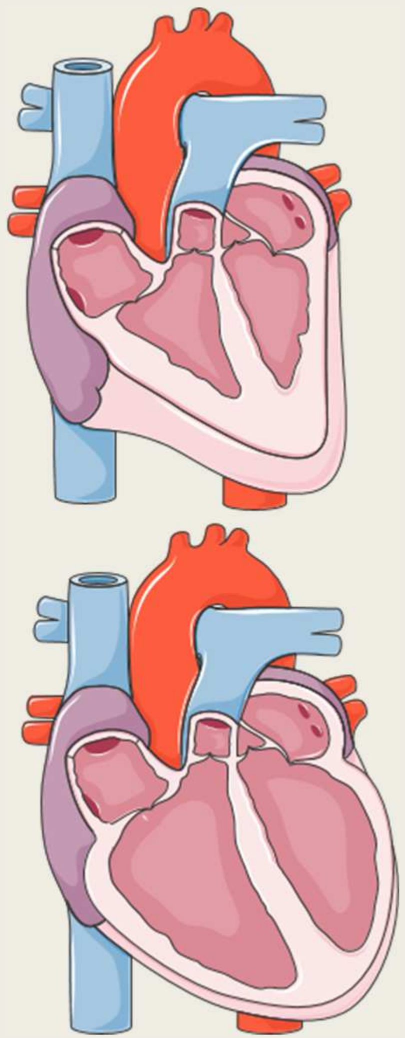


Identification of mitophagy in stressed heart in the early 2010's.



Mitophagy is required to fully recover after sepsis.

Piquereau et al,2013 Autophagy.



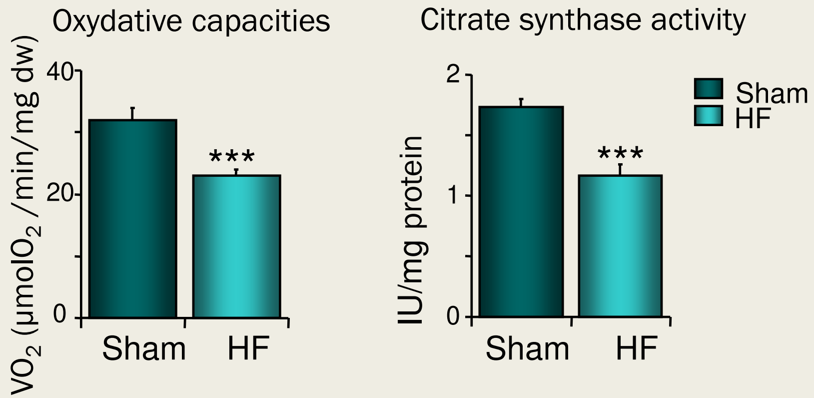
Heart failure

Inability of the heart to provide adequate blood flow to meet the needs of the organism

Associated with energy metabolism alterations

Bioenergetics modulations in heart failure

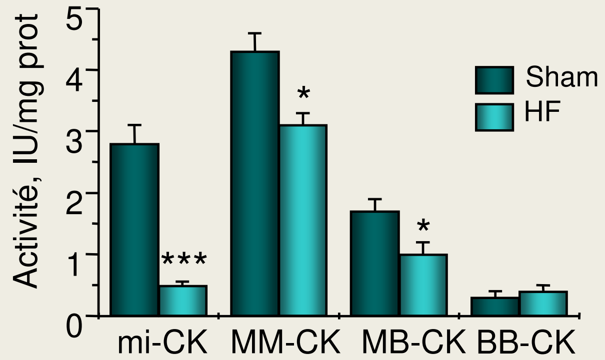
Mtochondrial energy production

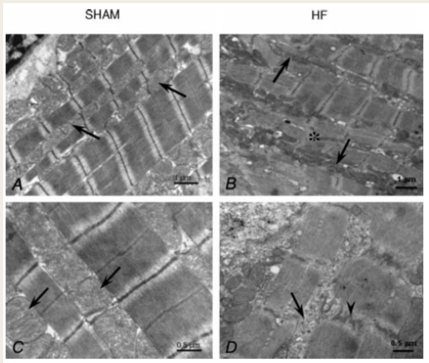


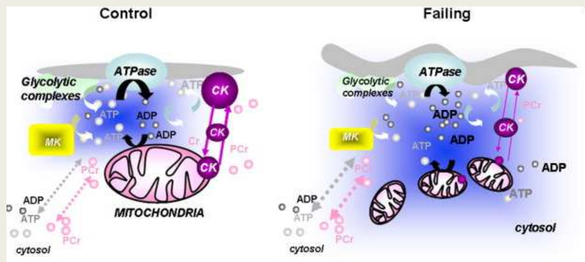
Decrease in mitochondrial energy production

Close link between energetics and HF stage

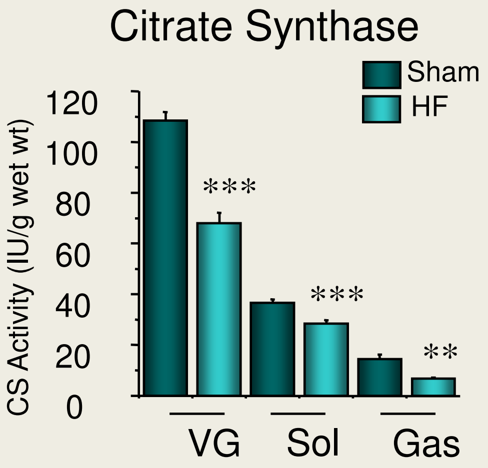
Energy transfer

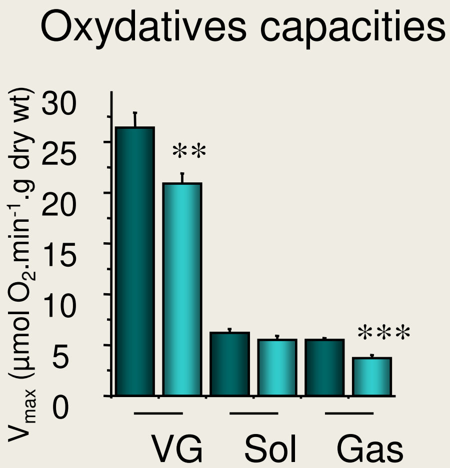




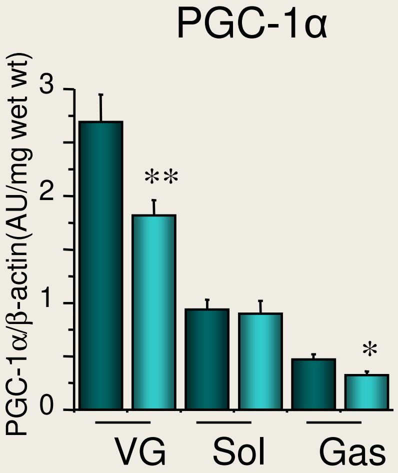


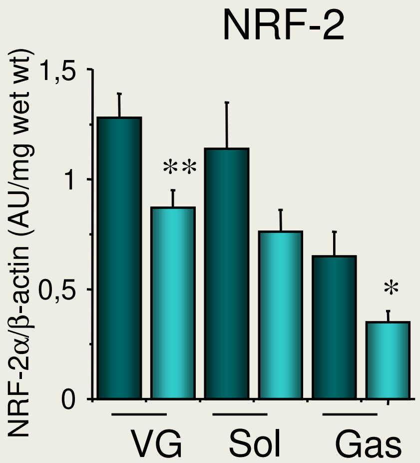
Bioenergetics modulations in heart failure

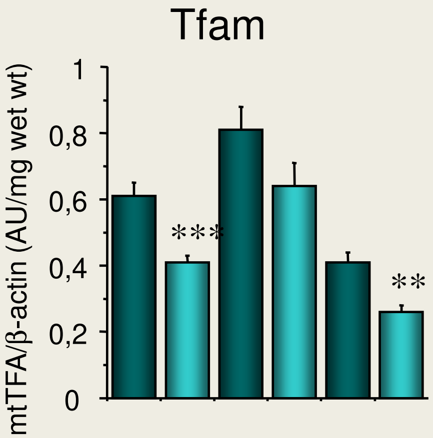




Alteration of production capacities

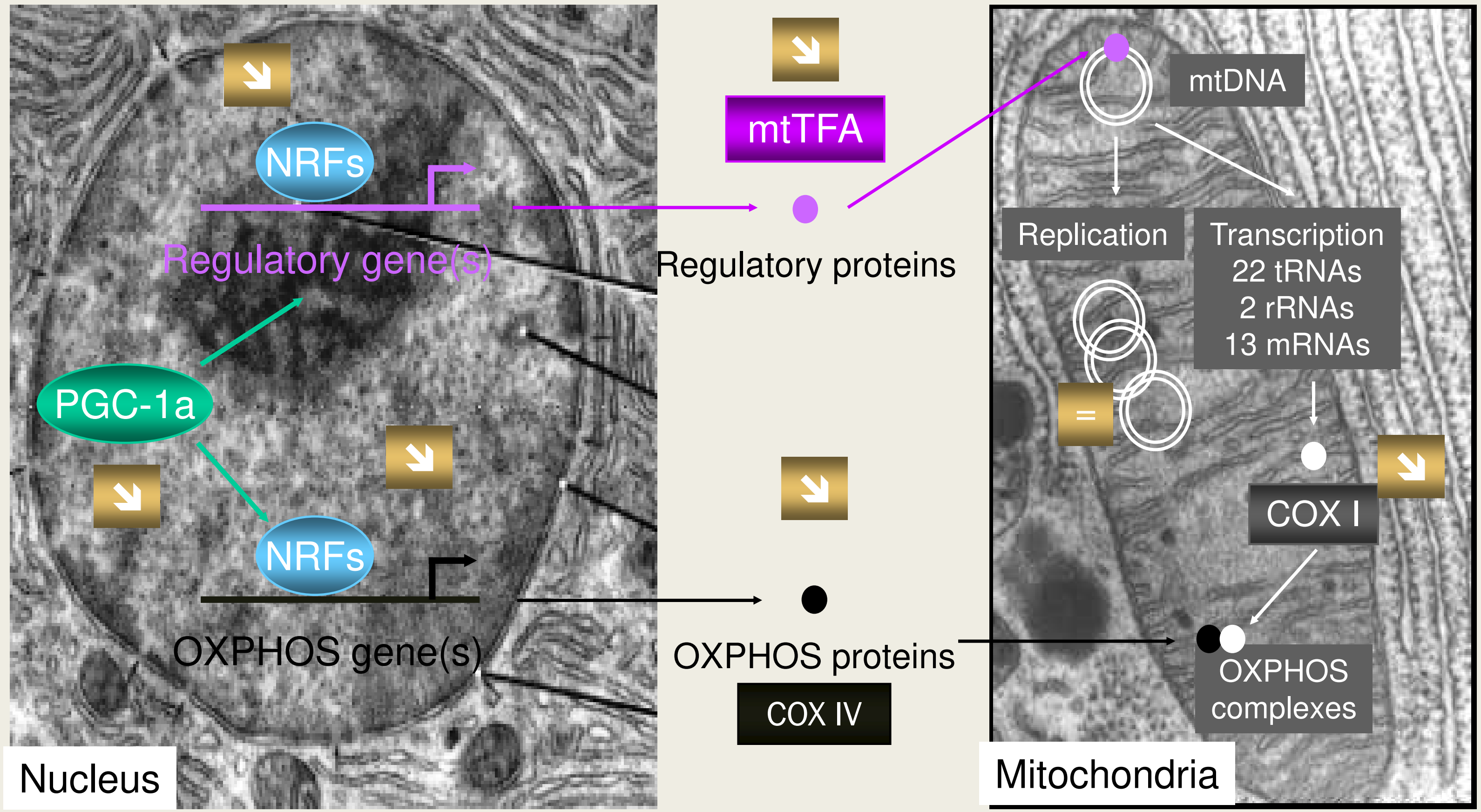






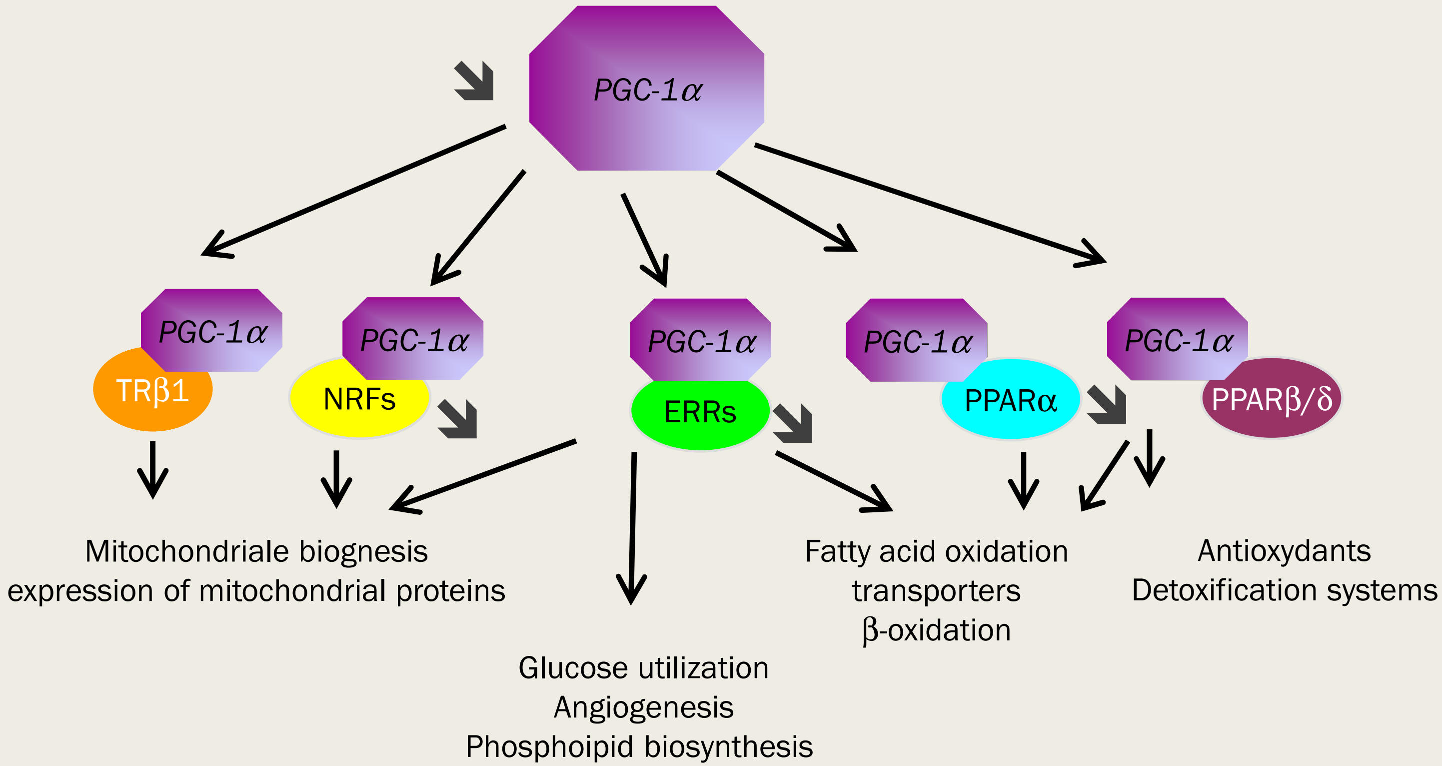
Weakening of mitochondrial biogenesis processes

Mitochondrial biogenesis in heart failure



Garnier et al J Physiol 2003 551:491

Dysregulation of the master regulator



Ventura-Clapier et al Cardiovasc Res 2008