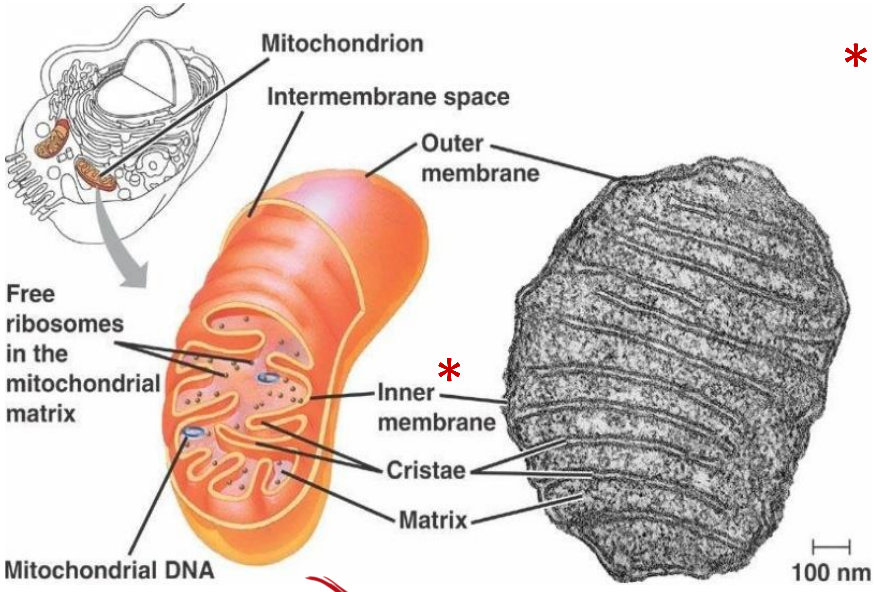
Mitochondrial Supercomplexes

Biological Macromolecules - Prof. Francesco Bernardi

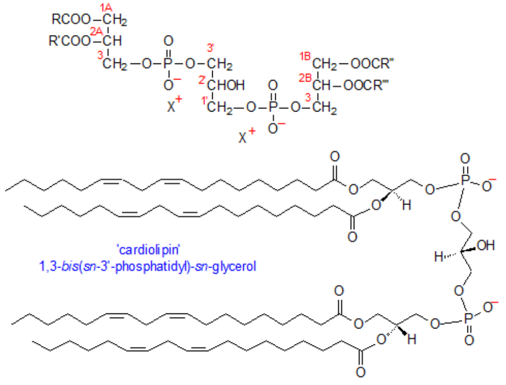
Natascia Caroccia, PhD student

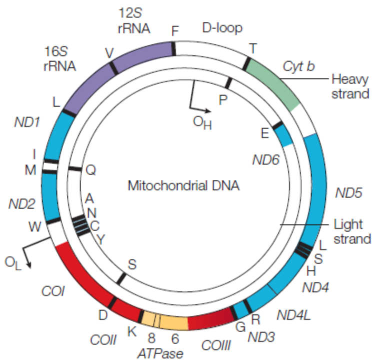
2nd May 2017

Mitochondria and energy production



* Cardiolipin

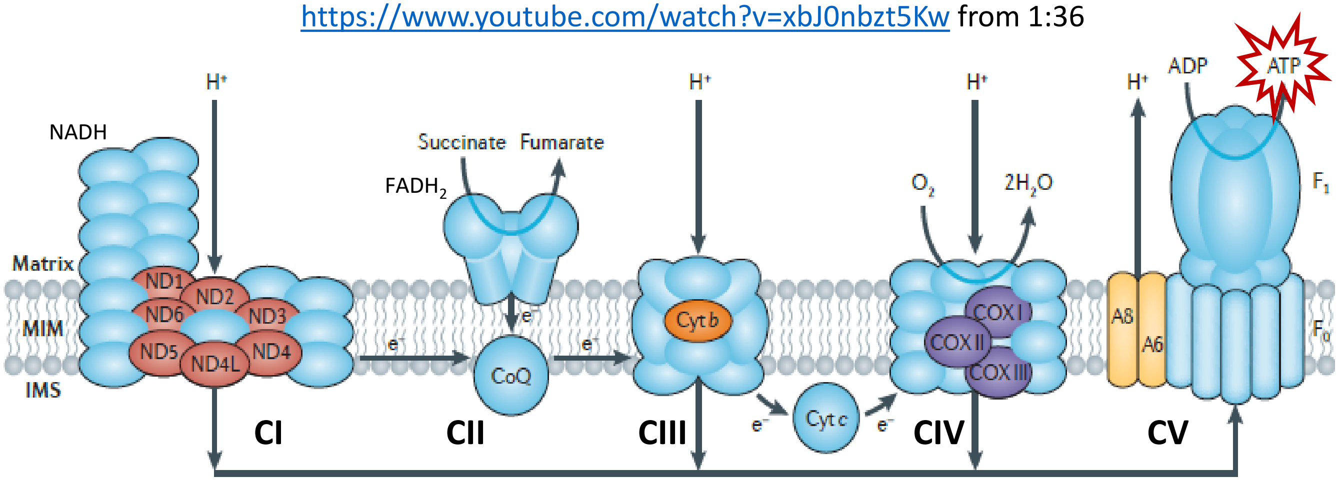




Human mtDNA. Taylor, R.W. and Turnbull, D.M. (2005), *Nature Reviews.*

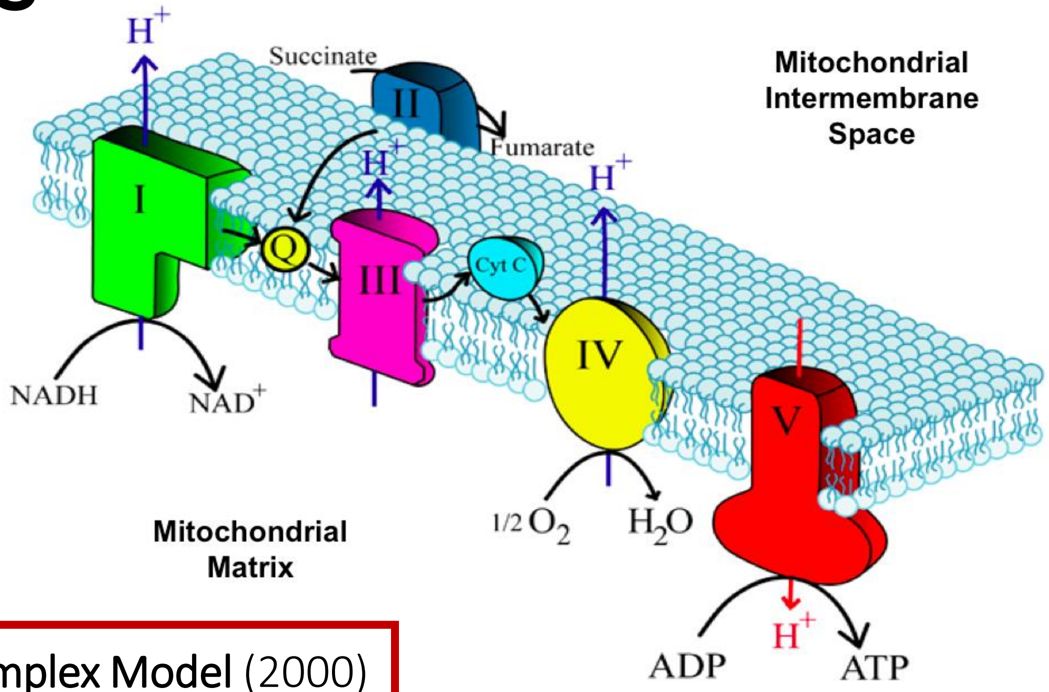
Oxidative phosphorylation (OXPHOS)

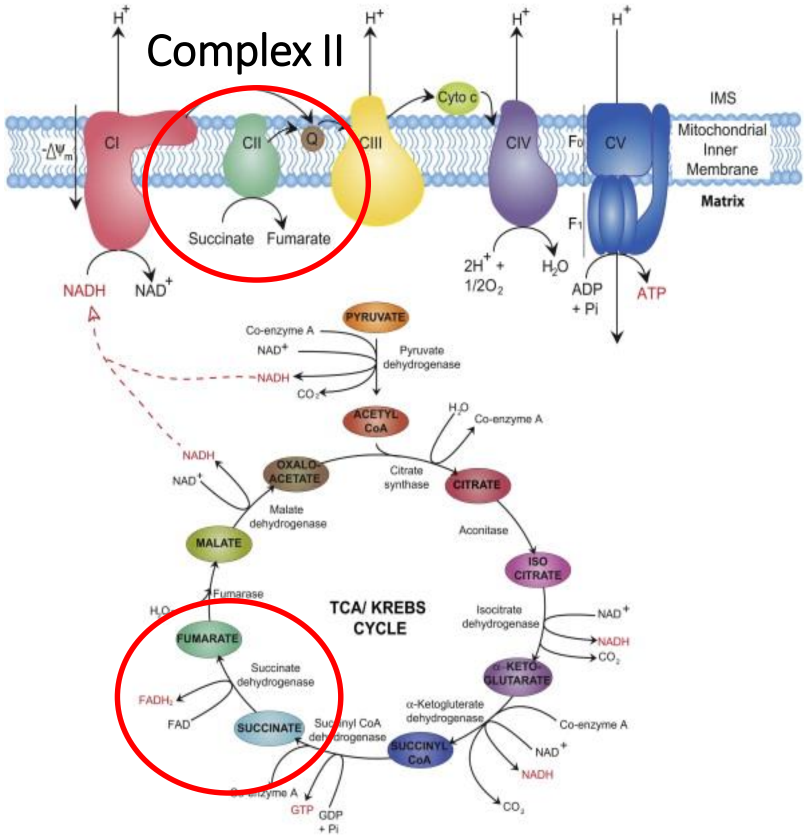
https://www.youtube.com/watch?v=xbJ0nbzt5Kw from 1:36



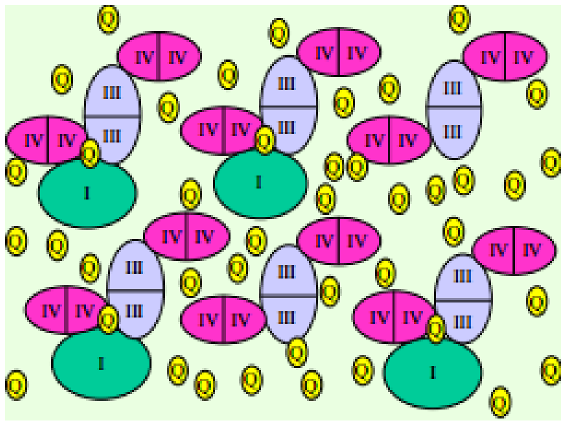
Oxidative phosphorylation. Image modified from Schon et al. (2012), *Nature Reviews*.

Models



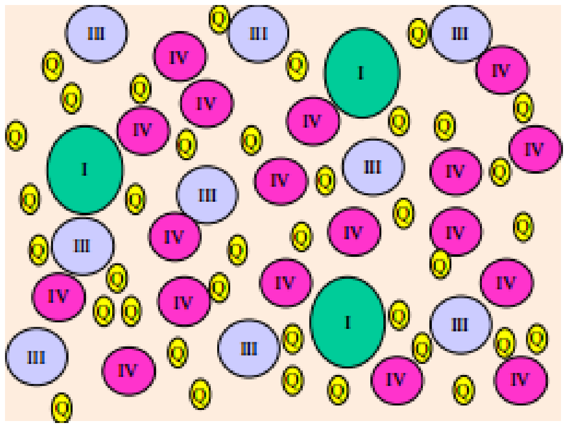


Schagger's **Supercomplex Model** (2000)

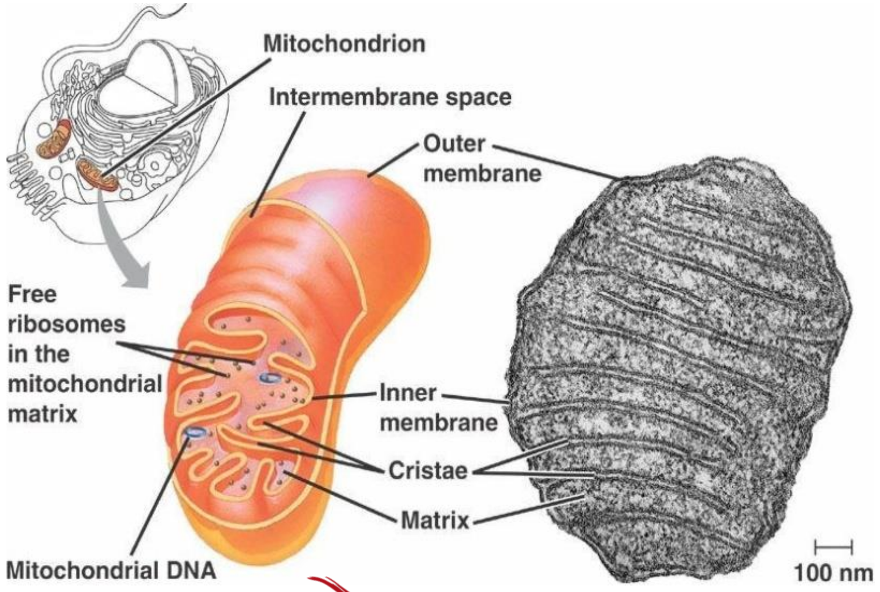


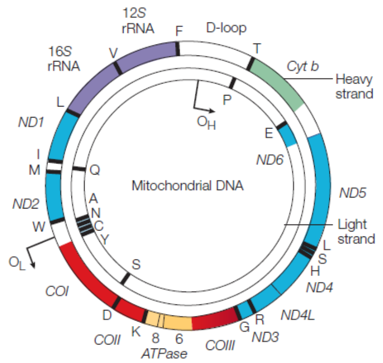
Solid state *vs* Fluid state

Hackenbrock's **Random Collision Model** (1986)



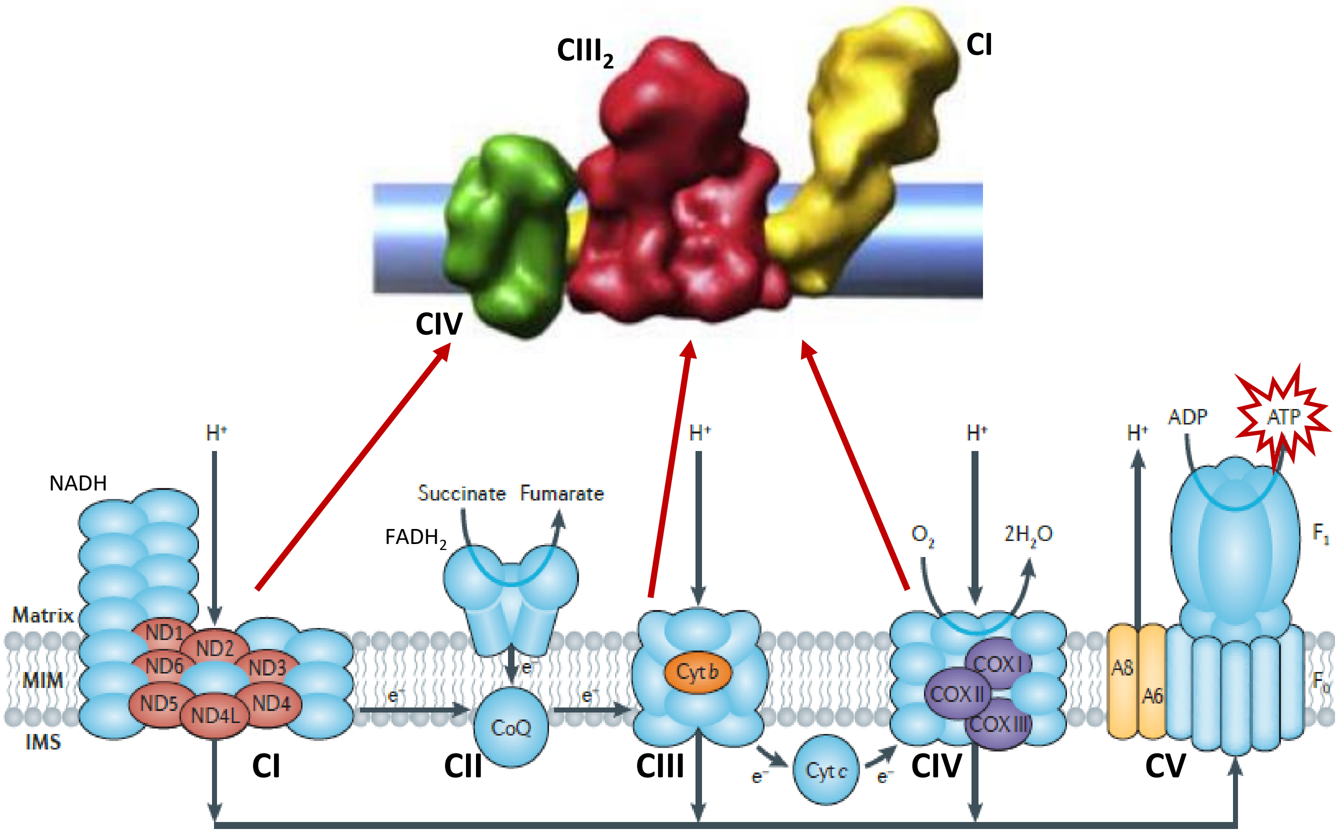
Mitochondria and energy production





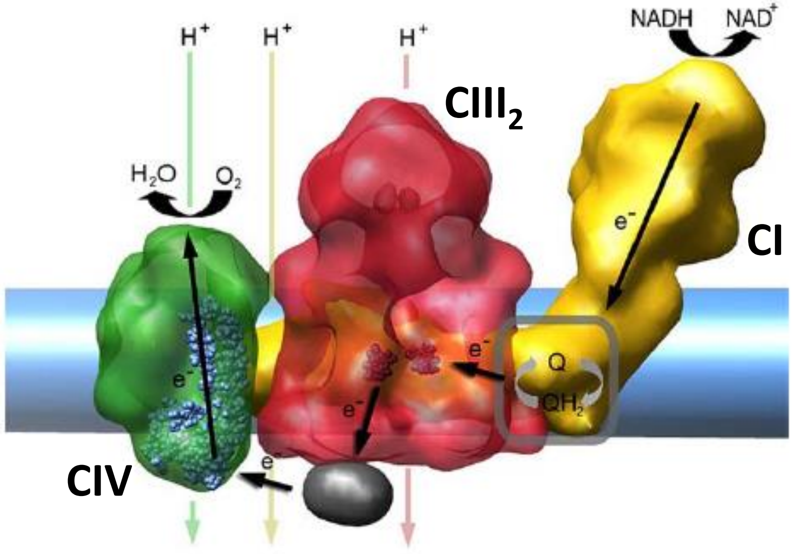
Human mtDNA. Taylor, R.W. and Turnbull, D.M. (2005), *Nature Reviews.*

Supercomplex or Respirasome

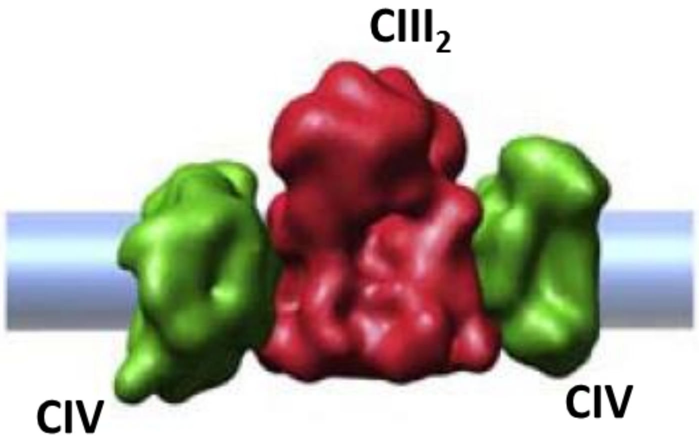


Oxidative phosphorylation. Image modified from Schon et al. (2012), *Nature Reviews*.

Mitochondrial supercomplexes in mammals



High molecular weight supercomplexes
CI_1+$CIII_2$+CIV_n (where n= 0-4)

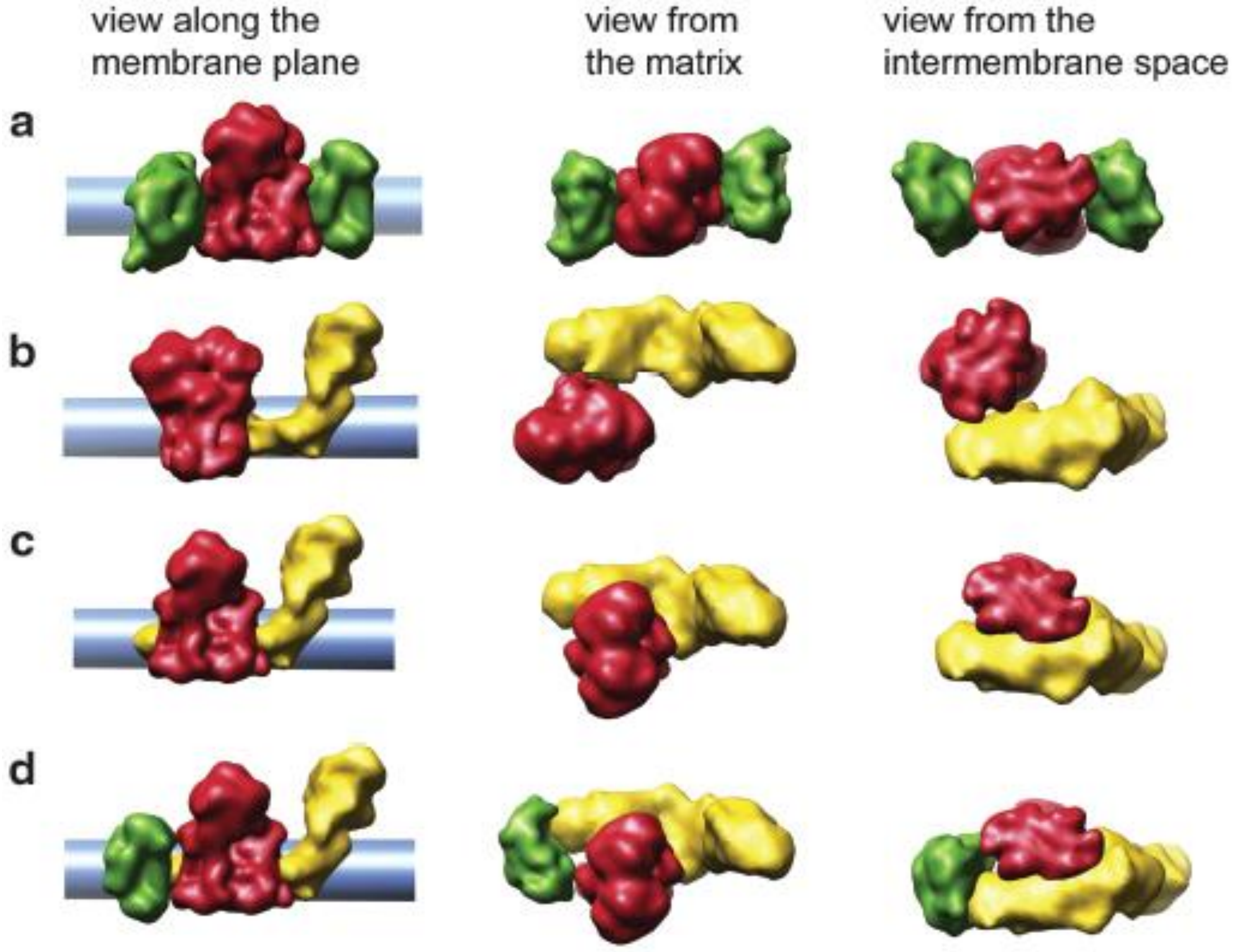


Low molecular weight supercomplexes
$CIII_2$+CIV_n (where n= 1-4)

- **functional advantages**
- **structural advantages**

Images modified from Vonck, J. and Schäfer, E. (2009) *Biochim. Biophys. Acta*

Supercomplex models



$CIII_2$+CIV_2 from *Saccharomyces cerevisiae*

CI_1+$CIII_2$ from *Arabidopsis thaliana*

CI_1+$CIII_2$ from *Bos taurus*

CI_1+$CIII_2$+CIV_1 from *Bos taurus*

Vonck, J. e Schäfer, E. (2009) *Biochim. Biophys. Acta*

ARTICLE

doi:10.1038/nature19774

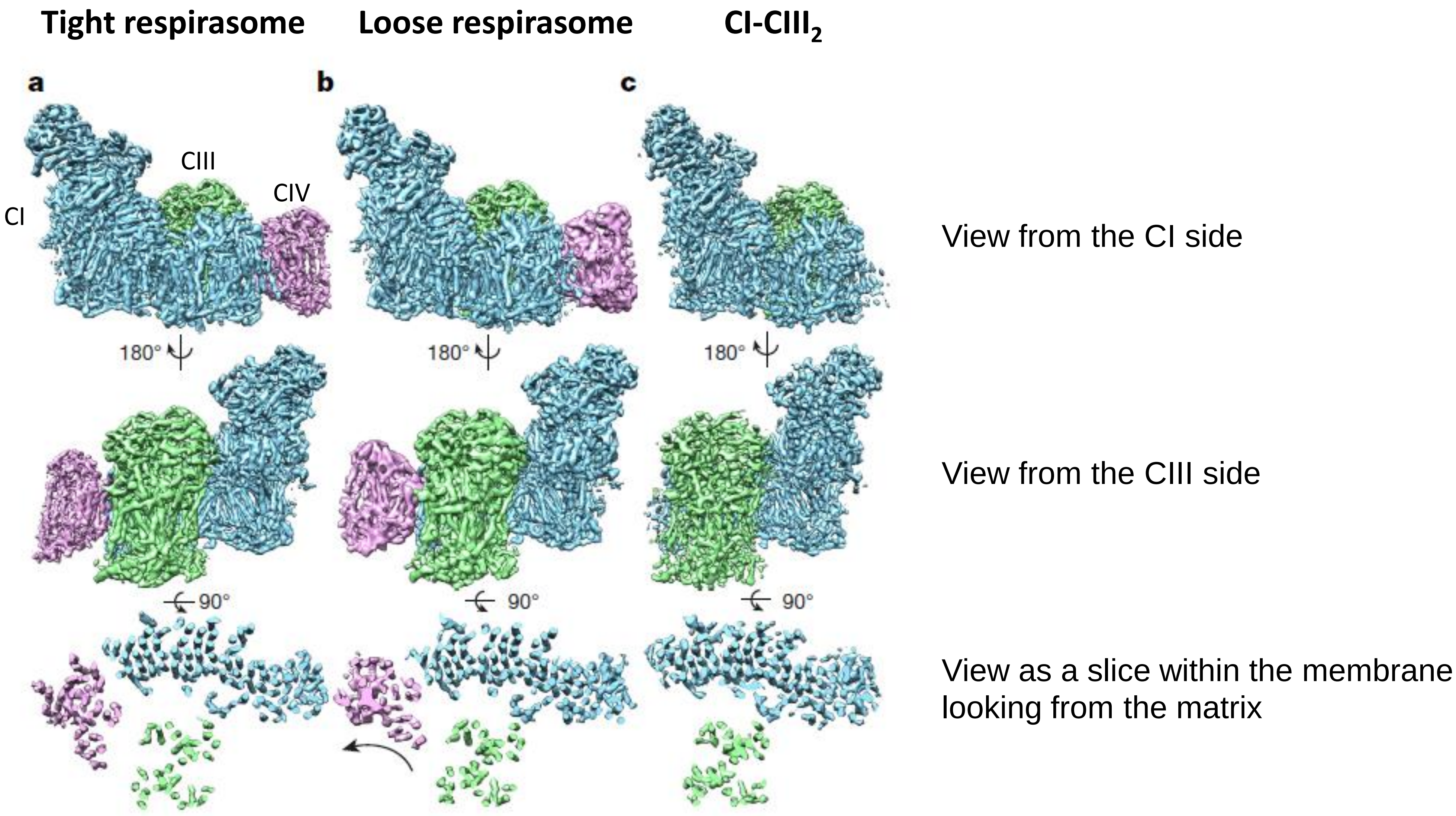
The architecture of respiratory supercomplexes

James A. Letts[1], Karol Fiedorczuk[1,2] & Leonid A. Sazanov[1]

Mitochondrial electron transport chain complexes are organized into supercomplexes responsible for carrying out cellular respiration. Here we present three architectures of mammalian (ovine) supercomplexes determined by cryo-electron microscopy. We identify two distinct arrangements of supercomplex $CICIII_2CIV$ (the respirasome)—a major 'tight' form and a minor 'loose' form (resolved at the resolution of 5.8 Å and 6.7 Å, respectively), which may represent different stages in supercomplex assembly or disassembly. We have also determined an architecture of supercomplex $CICIII_2$ at 7.8 Å resolution. All observed density can be attributed to the known 80 subunits of the individual complexes, including 132 transmembrane helices. The individual complexes form tight interactions that vary between the architectures, with complex IV subunit COX7a switching contact from complex III to complex I. The arrangement of active sites within the supercomplex may help control reactive oxygen species production. To our knowledge, these are the first complete architectures of the dominant, physiologically relevant state of the electron transport chain.

[1]Institute of Science and Technology Austria, Klosterneuburg 3400, Austria. [2]MRC Mitochondrial Biology Unit, Cambridge CB2 0XY, UK.

The respirasome adopts two distinct architectures



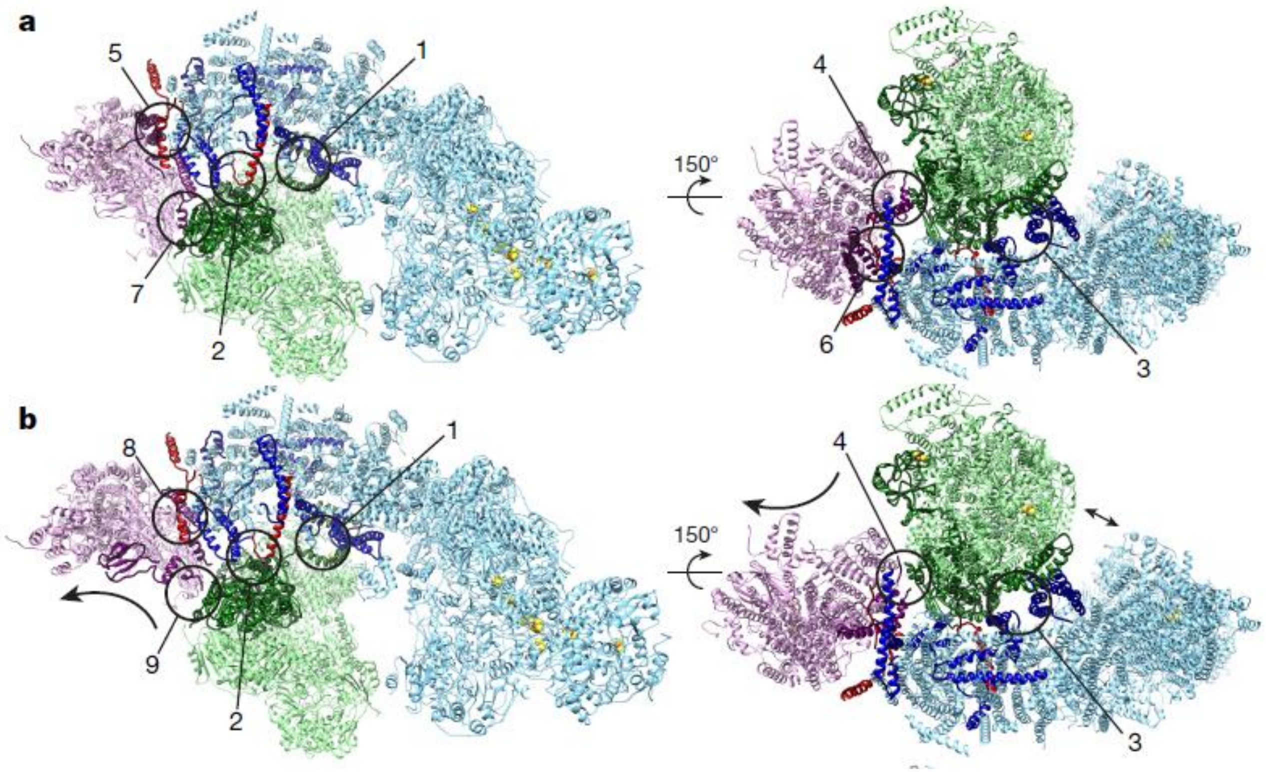
Cryo-EM density maps of mammalian supecomplexes from *Ovis aries* heart. Image from Letts et al. (2016), *Nature*.

Interactions between the complexes

matrix view intermembrane space view

Tight respirasome

Loose respirasome

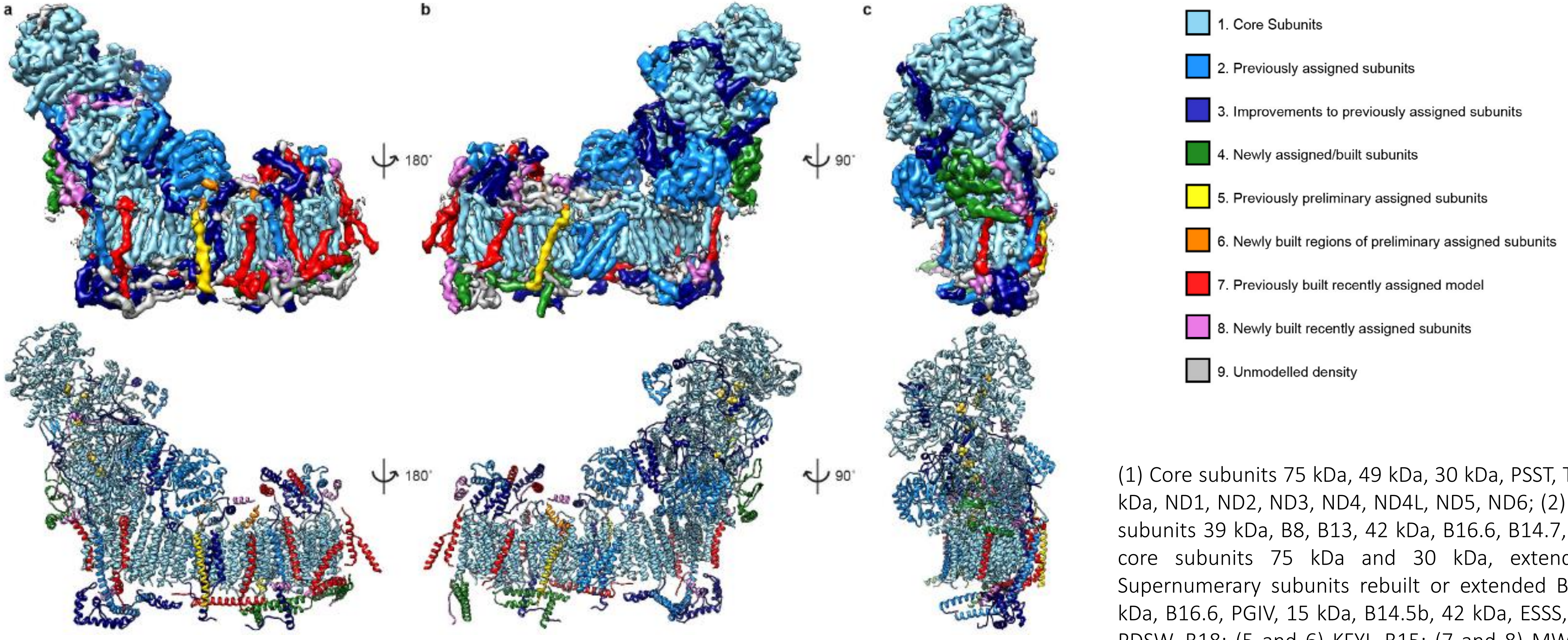


Interaction sites between the electron transport chain complexes. Image from Letts et al. (2016), *Nature*.

Interactions between the supercomplexes can be organized into **nine sites**.

Interacting subunits are darker. Subunits of CI that have been recently assigned are shown in red. Arrows in b indicate the motions of CIII and CIV between the tight and loose respirasomes.

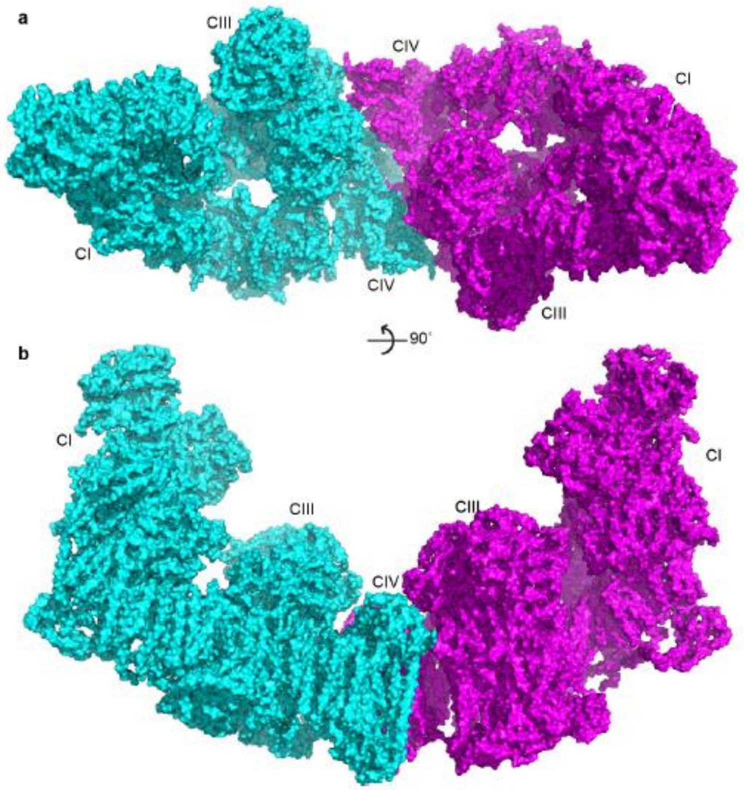
Improved model for CI



CI model and density. Image from Letts et al. (2016), *Nature*.

(1) Core subunits 75 kDa, 49 kDa, 30 kDa, PSST, TYKY, 51 kDa, 24 kDa, ND1, ND2, ND3, ND4, ND4L, ND5, ND6; (2) supernumerary subunits 39 kDa, B8, B13, 42 kDa, B16.6, B14.7, SDAP-α /β ; (3) core subunits 75 kDa and 30 kDa, extended C termini. Supernumerary subunits rebuilt or extended B14, 18 kDa, 13 kDa, B16.6, PGIV, 15 kDa, B14.5b, 42 kDa, ESSS, B22; (4) B17.2, PDSW, B18; (5 and 6) KFYI, B15; (7 and 8) MWFE, B9, B14.5a, MNLL, AGGG, B12, SGDH, B17, ASHI. These subunits have been assigned in our subsequent work32; (9) the unmodelled density, which represents ~ 7% of the total volume of the CI density.

Respiratory strings model

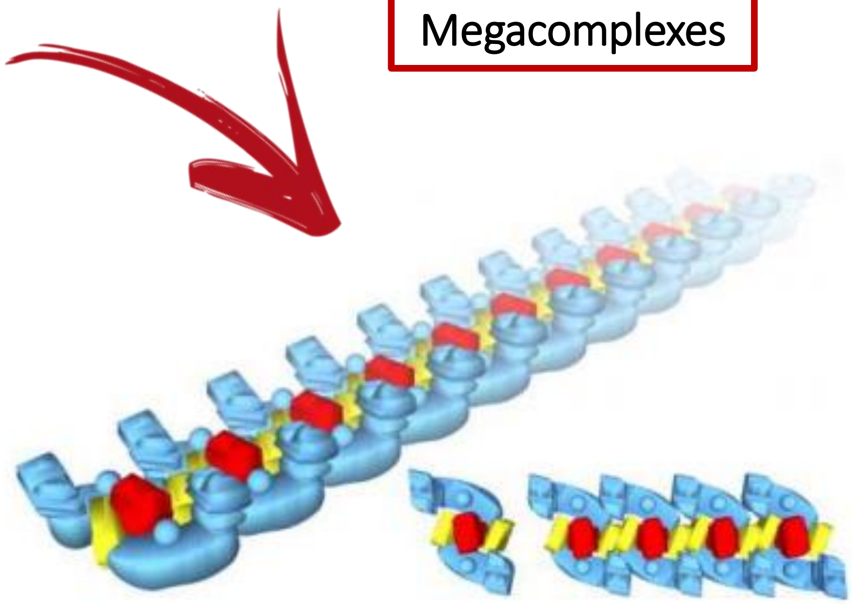


View from the mitochondrial matrix

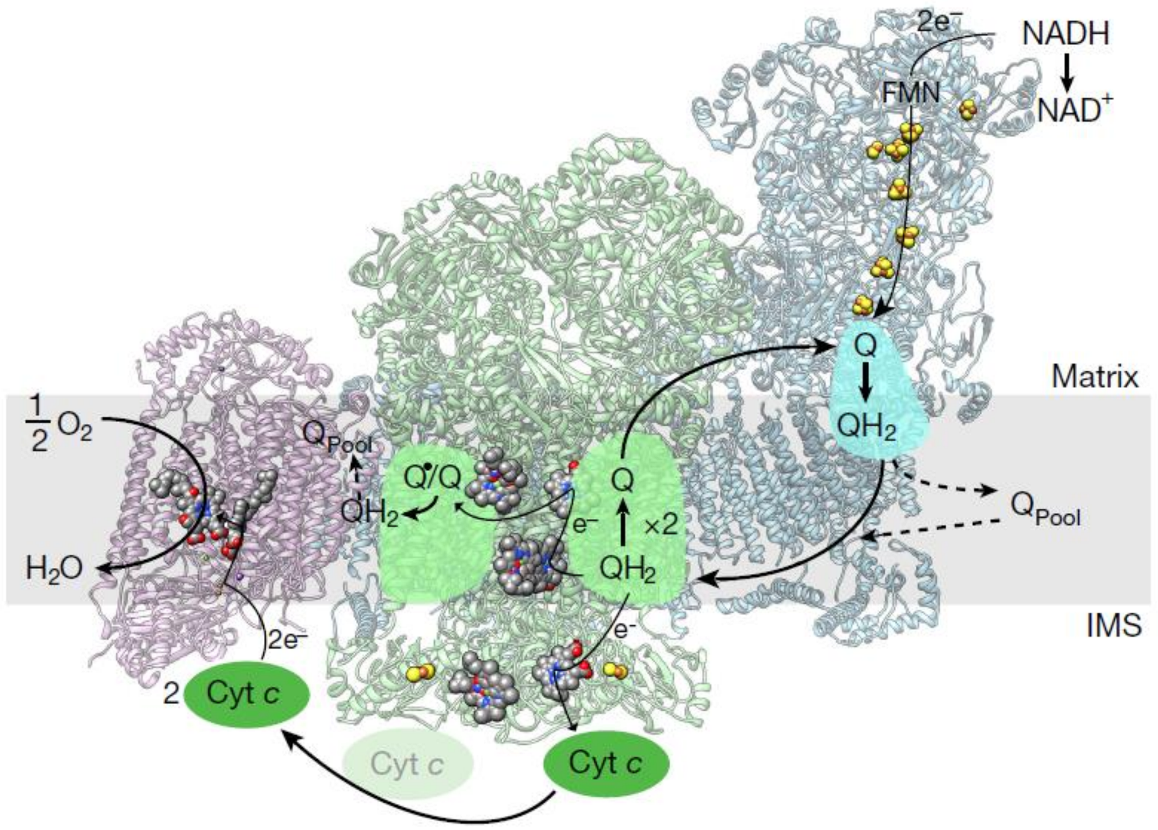
Side view in the membrane plane

Modelling of putative higher-order organization of respiratory chain. Image from Letts et al. (2016), *Nature*.

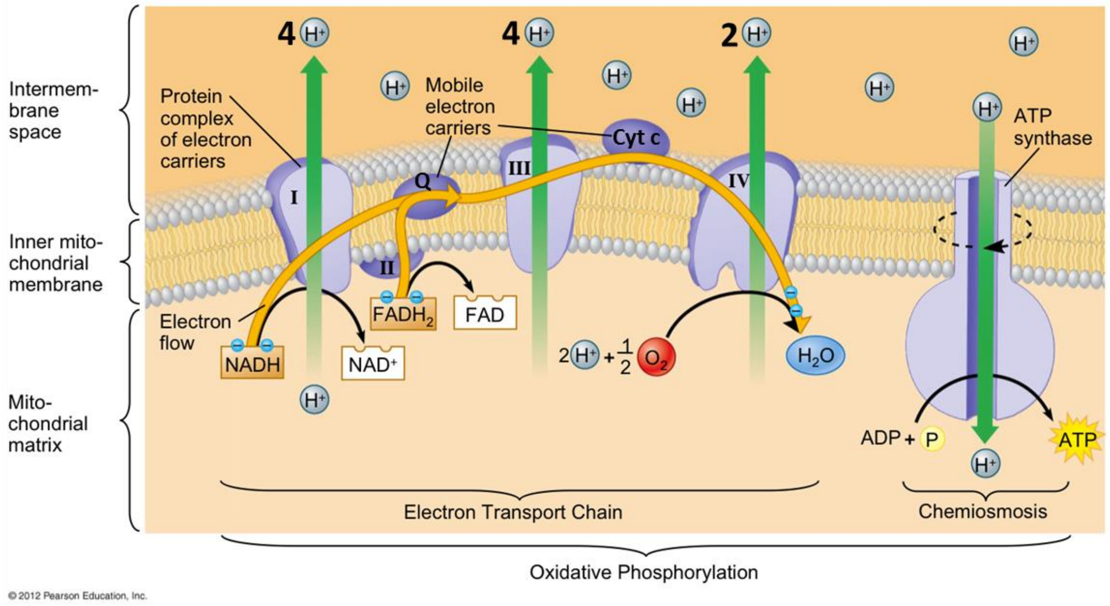
Megacomplexes



Electron flow through the respirasome

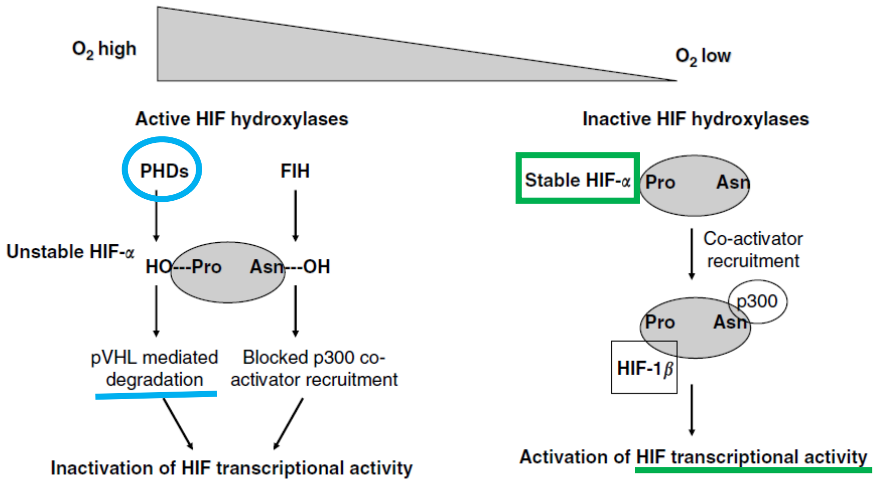


Schematic of electron flow through the tight respirasome. Image from Letts et al. (2016), *Nature*.



- Substrate channelling
- ROS production

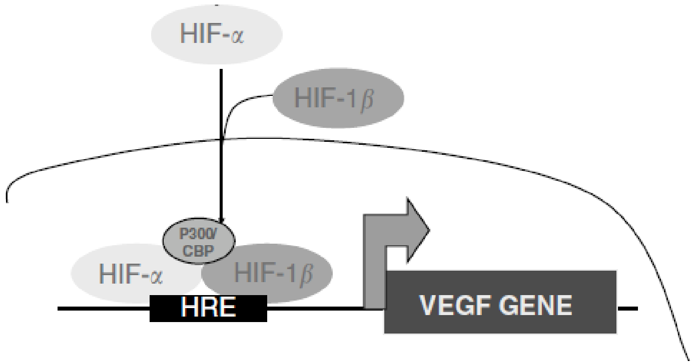
Hypoxic activation of HIF and mitochondria



PHDs
prolyl hydroxylate enzymes

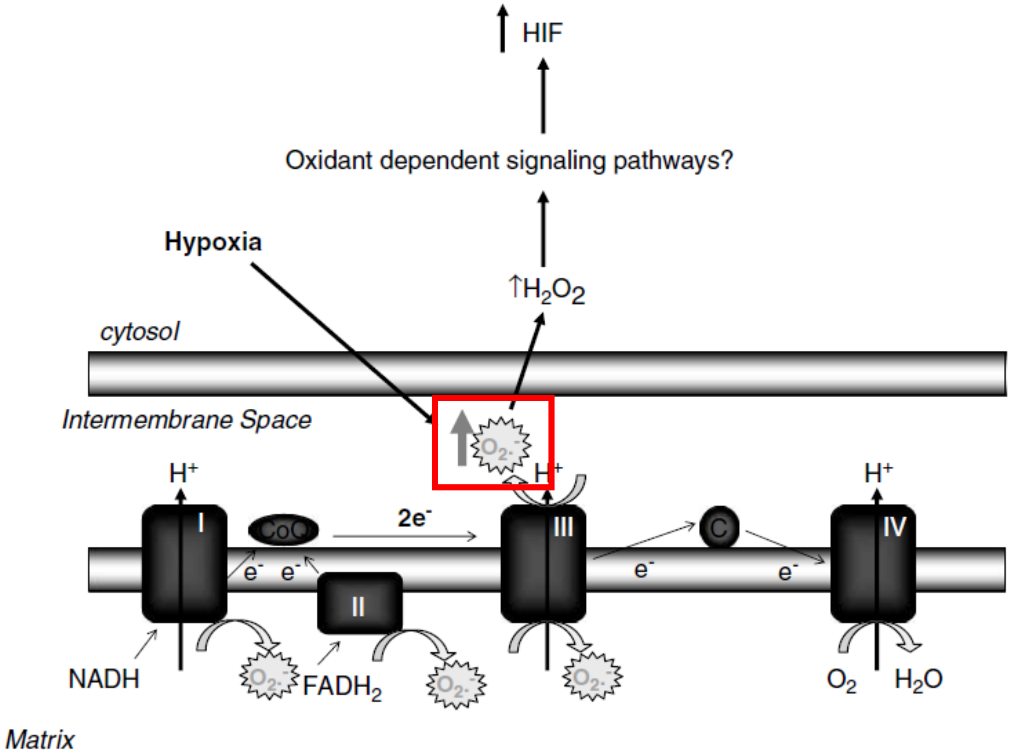
FIH
factor-inhibiting HIF

pVHL
von Hippel–Lindau protein



1) **Oxygen consumption model**

2) **Mitochondrial ROS generation model**



All images from Klimova, T. and Chandel, NS. (2008), *Cell Death and Differentiation*.

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- Grazie per l'attenzione -