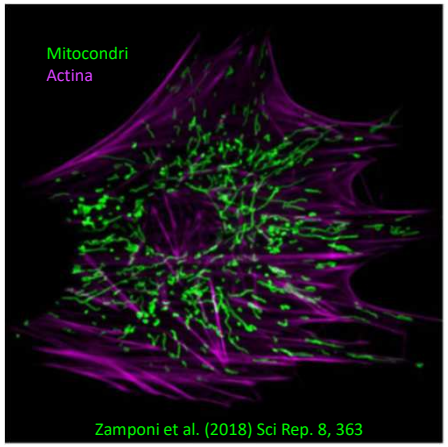
I mitocondri



I mitocondri

- Nel 1890 Altmann descrive i «bioblasti», strutture citoplasmatiche ubiquitarie che ricordano i batteri e conclude che si tratta di «organismi elementari» che vivono nelle cellule e svolgono funzioni vitali
- Nel 1898 Benda li chiama mitocondri dal greco «mitos» (filamento) e «chondros» (granulo) riferendosi all'aspetto di queste strutture durante la spermatogenesi

Altmann aveva ragione!

I mitocondri sono gli organelli dove avviene la **respirazione** e la **trasformazione dell'energia**, processi essenziali per la vita degli eucarioti

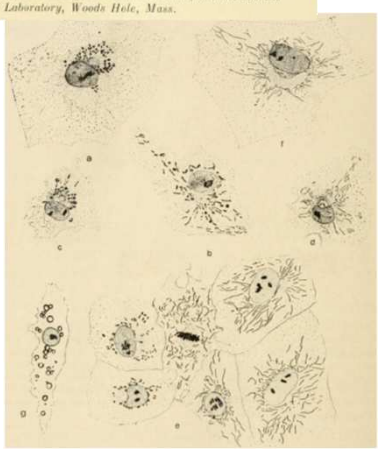
Con tutta probabilità derivano da antichi batteri che sono diventati degli endosimbionti con mutuo beneficio (Margulis, 1970). Hanno il loro DNA e si riproducono autonomamente.

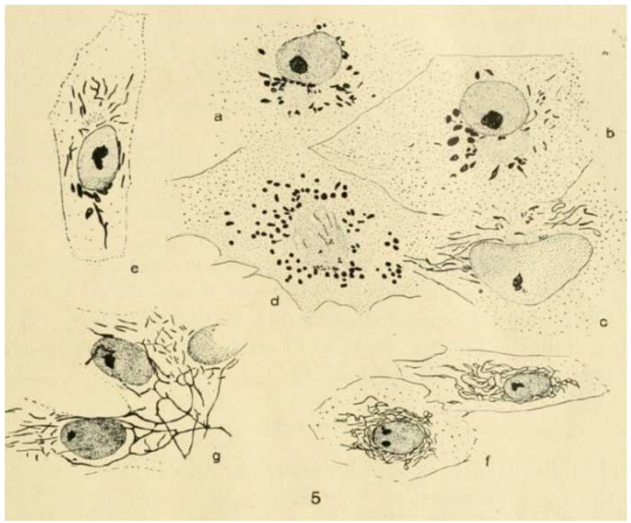
MITOCHONDRIA (AND OTHER CYTOPLASMIC STRUCTURES) IN TISSUE CULTURES

MARGARET REED LEWIS AND WARREN HARMON LEWIS[1]

From the Anatomical Laboratory, Johns Hopkins Medical School, and the Marine Biological Laboratory, Woods Hole, Mass.

The American journal of anatomy
Baltimore, MD. [s.n.], 1902-1991
https://www.biodiversitylibrary.org/bibliography/11165
v. 17 (1914-1915): https://www.biodiversitylibrary.org/item/43100
339-401





LETTER

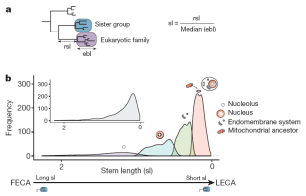
doi:10.1038/nature16941

Late acquisition of mitochondria by a host with chimaeric prokaryotic ancestry

Alexandros A. Pittis[1,2] & Toni Gabaldón[1,2,3]

The origin of eukaryotes stands as a major conundrum in biology[1]. Current evidence indicates that the last eukaryotic common ancestor already possessed many eukaryotic hallmarks, including a complex subcellular organization[1–5]. In addition, the lack of evolutionary intermediates challenges the elucidation of the relative order of emergence of eukaryotic traits. Mitochondria are ubiquitous organelles derived from an alphaproteobacterial endosymbiont[4]. Different hypotheses disagree on whether mitochondria were acquired early or late during eukaryogenesis[5]. Similarly, the nature and complexity of the receiving host are debated, with models ranging from a simple prokaryotic host to an already complex proto-eukaryote[1,3,6,7]. Most competing scenarios can be roughly grouped into either mito-early, which consider the driving force of eukaryogenesis to be mitochondrial endosymbiosis into a simple host, or mito-late, which postulate that a significant complexity predated mitochondrial endosymbiosis[5]. Here we provide evidence for late mitochondrial endosymbiosis. We use phylogenomics to directly test whether proto-mitochondrial proteins were acquired earlier or later than other proteins of the last eukaryotic common ancestor. We find that last eukaryotic common ancestor protein families of alphaproteobacterial ancestry and of mitochondrial localization show the shortest phylogenetic distances to their closest prokaryotic relatives, compared with proteins of different prokaryotic origin or cellular localization. Altogether, our results shed new light on a long-standing question and provide compelling support for the late acquisition of mitochondria into a host that already had a proteome of chimaeric phylogenetic origin. We argue that mitochondrial endosymbiosis was one of the ultimate steps in eukaryogenesis and that it provided the definitive selective advantage to mitochondria-bearing eukaryotes over less complex forms.

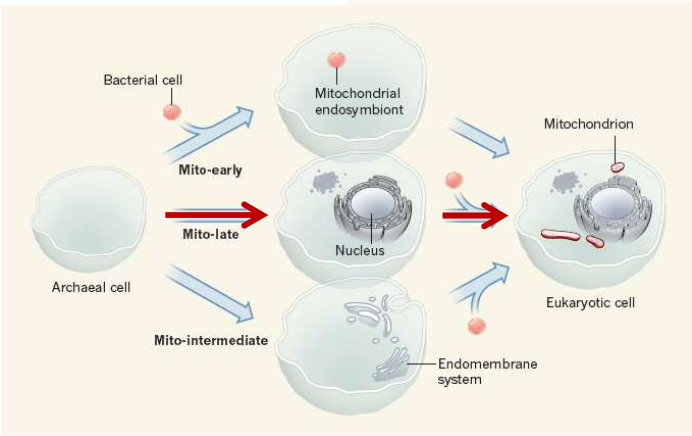
LECA family and connecting it to the last prokaryotic ancestor shared with its closest prokaryotic relatives (raw stem length; Fig. 1a). Branch lengths indicate the number of inferred substitutions per site, which reflect both divergence time and evolutionary rate. To disentangle time from rates, which may vary across families, we normalized the raw stem length by taking into account the median of the branch lengths within the LECA family (see Methods for further details). We used this measurement (hereafter referred to as stem length) as a proxy for the phylogenetic distance between a given LECA protein family and its last shared ancestor with prokaryotes. Competing mito-early and mito-late hypotheses naturally differ in their expectations of stem lengths for proteins of proto-mitochondrial origin compared with those of other putative origins. In a simple fusion model, with the proto-mitochondrion contributing most of the bacterial component, one would expect



Mitochondria in the second act

THIJS J. G. ETTEMA

3 MARCH 2016 | VOL 531 | NATURE | 39

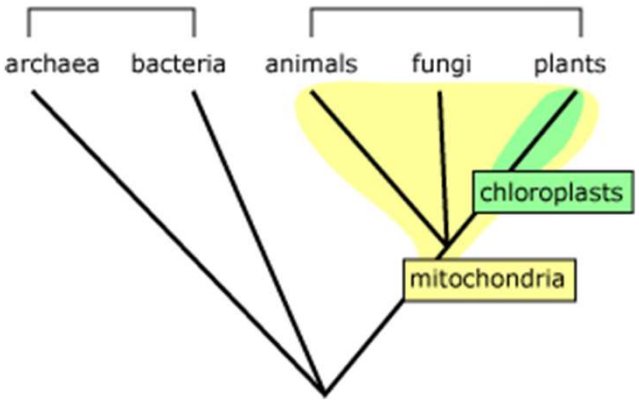


La catastrofe dell'ossigeno

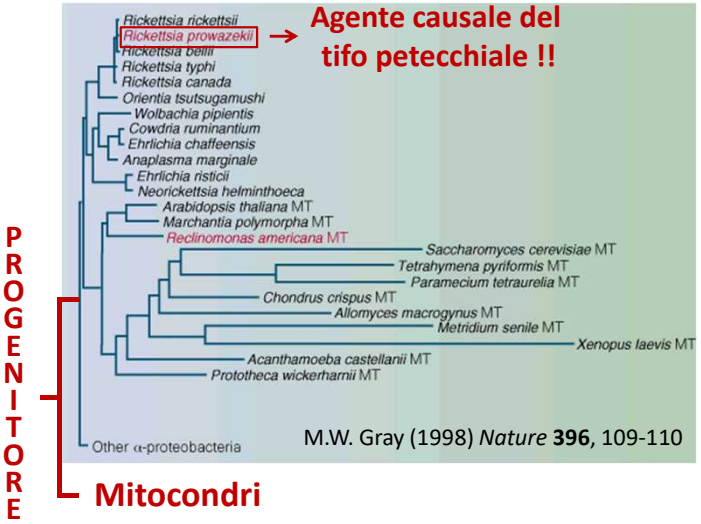
Circa 3.500 milioni di anni fa la comparsa dei cianobatteri, i primi organismi in grado di realizzare la fotosintesi che produce ossigeno, causò l'inizio della formazione di ossigeno molecolare libero (O_2) sulla terra.

Questo causò una grande estinzione di massa delle primitive forme di vita anaerobica a causa dell'effetto letale dell'ossigeno che si andava accumulando nell'atmosfera.

Questo evento è noto anche come **Crisi dell'Ossigeno** o **Grande Ossidazione,** ed avvenne circa 2.450 milioni di anni fa all'inizio del Sideriano, il primo periodo del Protozoico.



1.000.000.000 di anni fa ….



ARTICLE

doi:10.1038/nature14963

Endosymbiotic origin and differential loss of eukaryotic genes

Chuan Ku[1], Shijulal Nelson-Sathi[1], Mayo Roettger[1], Filipa L. Sousa[1], Peter J. Lockhart[2], David Bryant[3], Einat Hazkani-Covo[4], James O. McInerney[5,6], Giddy Landan[7] & William F. Martin[1,8]

Chloroplasts arose from cyanobacteria, mitochondria arose from proteobacteria. Both organelles have conserved their prokaryotic biochemistry, but their genomes are reduced, and most organelle proteins are encoded in the nucleus. Endosymbiotic theory posits that bacterial genes in eukaryotic genomes entered the eukaryotic lineage via organelle ancestors. It predicts episodic influx of prokaryotic genes into the eukaryotic lineage, with acquisition corresponding to endosymbiotic events. Eukaryotic genome sequences, however, increasingly implicate lateral gene transfer, both from prokaryotes to eukaryotes and among eukaryotes, as a source of gene content variation in eukaryotic genomes, which predicts continuous, lineage-specific acquisition of prokaryotic genes in divergent eukaryotic groups. Here we discriminate between these two alternatives by clustering and phylogenetic analysis of eukaryotic gene families having prokaryotic homologues. Our results indicate (1) that gene transfer from bacteria to eukaryotes is episodic, as revealed by gene distributions, and coincides with major evolutionary transitions at the origin of chloroplasts and mitochondria; (2) that gene inheritance in eukaryotes is vertical, as revealed by extensive topological comparison, sparse gene distributions stemming from differential loss; and (3) that continuous, lineage-specific lateral gene transfer, although it sometimes occurs, does not contribute to long-term gene content evolution in eukaryotic genomes.

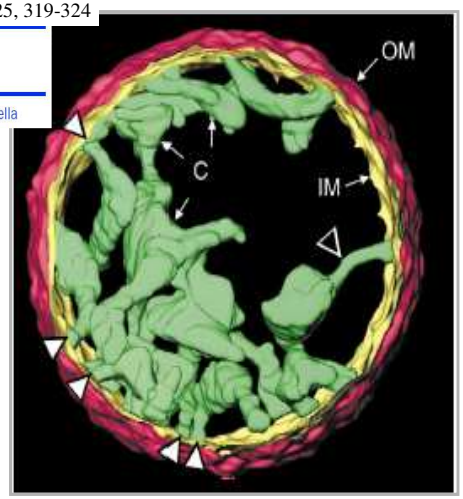
27 AUGUST 2015 | VOL 524 | NATURE | 427

Come sono fatti i mitocondri

Trends Biochem. Sci (2000) 25, 319-324

The internal structure of mitochondria

Terrence G. Frey and Carmen A. Mannella



Microsc Res Tech. 1994 Feb 15;27(3):198-219.

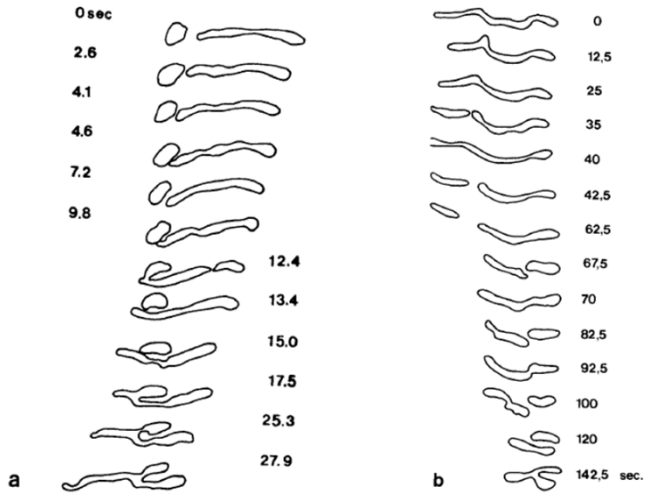
Dynamics of mitochondria in living cells: shape changes, dislocations, fusion, and fission of mitochondria.

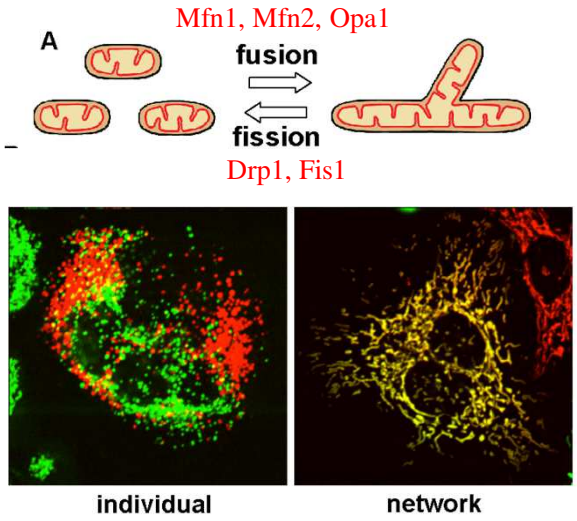
Bereiter-Hahn J[1], Vöth M.

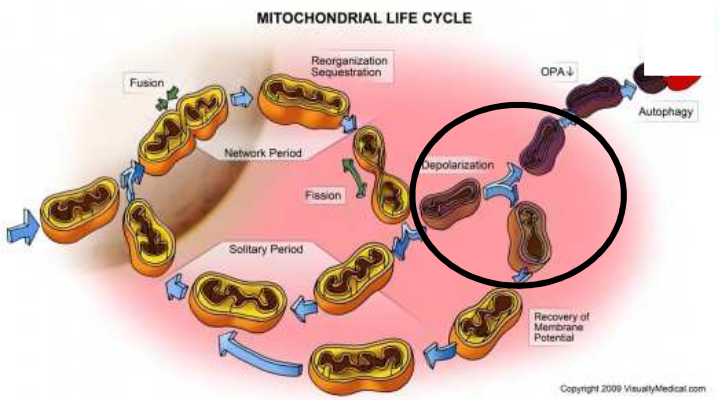
Author information

Abstract

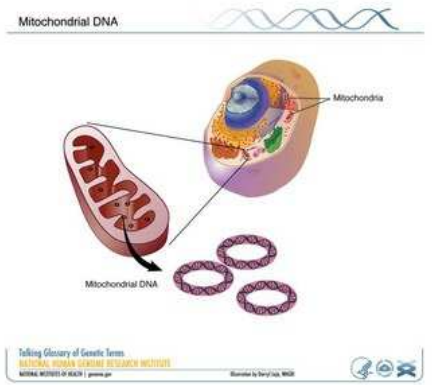
Mitochondria are semi-autonomous organelles which are endowed with the ability to change their shape (e.g., by elongation, shortening, branching, buckling, swelling) and their location inside a living cell. In addition they may fuse or divide. These dynamics are discussed. Dislocation of mitochondria may result from their interaction with elements of the cytoskeleton, with microtubules in particular, and from processes intrinsic to the mitochondria themselves. Morphological criteria and differences in the fate of some mitochondria argue for the presence of more than one mitochondrial population in some animal cells. Whether these reflect genetic differences remains obscure. Emphasis is laid on the methods for visualizing mitochondria in cells and following their behaviour. Fluorescence methods provide unique possibilities because of their high resolving power and because some of the mitochondria-specific fluorochromes can be used to reveal the membrane potential. Fusion and fission often occur in short time intervals within the same group of mitochondria. At sites of fusion of two mitochondria material of the inner membrane, the matrix compartment seems to accumulate. The original arrangement of the fusion partners is maintained for some minutes. Fission is a dynamic event which, like fusion, in most cases observed in vertebrate cell cultures is not a straight forward process but rather requires several "trials" until the division finally occurs. Regarding fusion and fission hitherto unpublished phase contrast micrographs, and electron micrographs have been included.



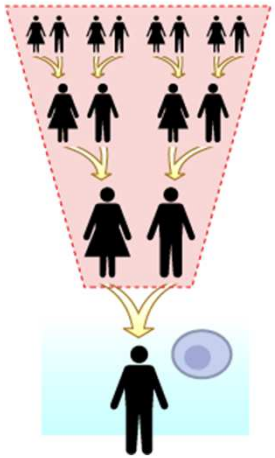




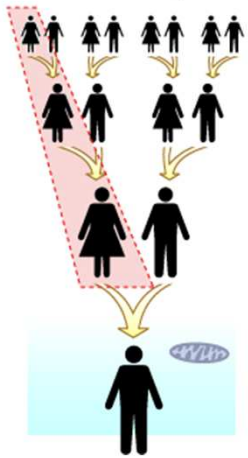
I mitocondri hanno un loro DNA



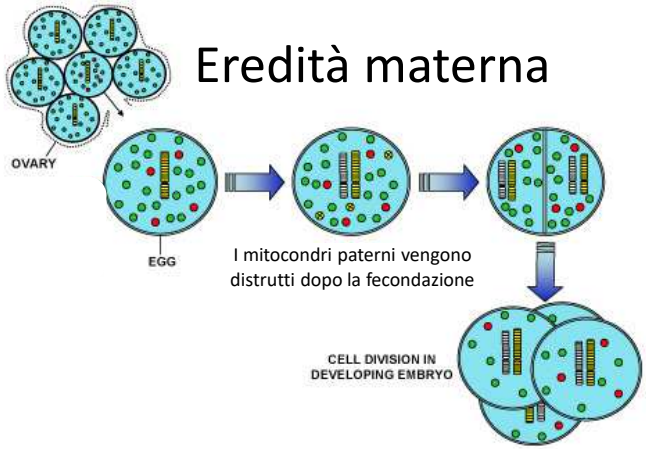
Il DNA nucleare viene da tutti i nostri antenati



Il DNA mitocondriale viene solo dalla linea materna

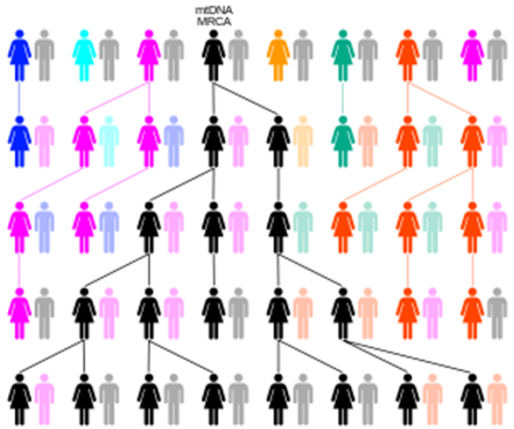


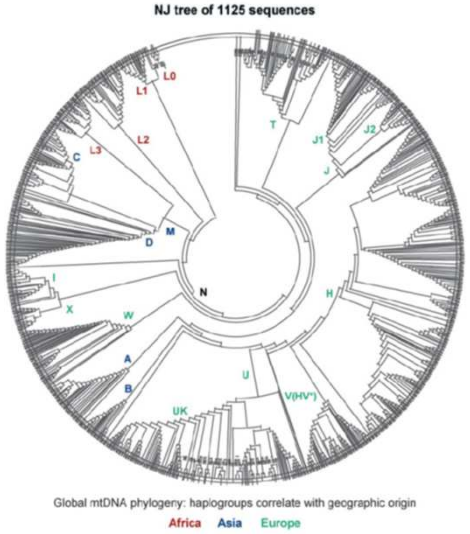
Eredità materna



«La Eva africana»

Attraverso la sequenza del DNA mitocondriale si è potuto stabilire che tutti gli uomini che vivono oggi sulla terra discendono da una madre che è vissuta in Africa fra 140.000 e 200.000 anni fa



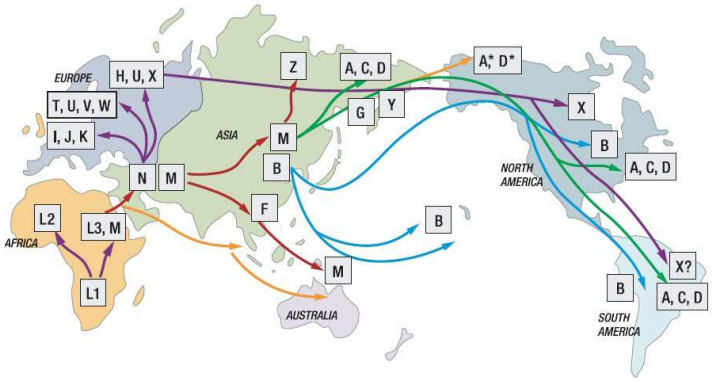


Global mtDNA phylogeny: haplogroups correlate with geographic origin

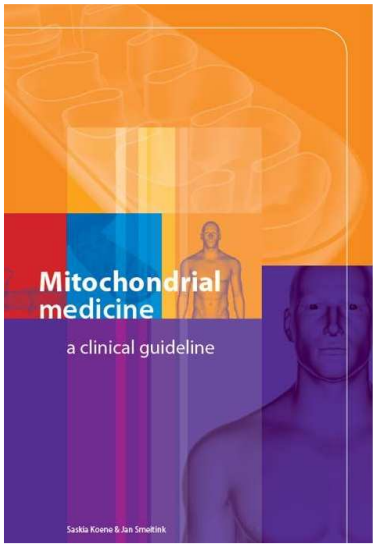
Africa Asia Europe

Phylogenic tree of human mtDNA coding sequence variants, demonstrating regional association of haplogroups. Haplogroups, groups of related haplotypes, are derived from a founding haplotype, harboring characteristic mtDNA sequence polymorphisms. Each haplogroup is designated by a letter with or without a subdividing letter. In this tree, the ticks around the perimeter of the circle represent the individual mtDNA sequences. The internal radial lines that connect the ticks represent the relative number of mtDNA nucleotide changes that separate one mtDNA sequence from another. The total number of mutational differences between two mtDNAs is related to the sum of the lengths of the radial lines necessary to trace a path from one mtDNA to the other. The mtDNA haplogroups have proven to be highly geographically associated. The African haplogroups are L0–L3. These cluster together on the deepest branches of the tree, demonstrating the African origin of the mtDNAs (131, 132). Only two mtDNAs, M and N, left Africa and colonized all of Eurasia. M gave rise to the Asian mtDNA lineages C and D as well as multiple others. N gave rise to the Asian mtDNA lineages A and B plus others; all of the European lineages I, U, Uk, V(HV*), H, J, J1, J2, and T; as well as the Eurasian mtDNA haplogroup X. Of all of the Eurasian mtDNAs, only representatives of haplogroups A, C, D, and X survived the Arctic to found the Native American populations. Haplogroup B joined these haplogroups in the Americas by a sub-Arctic route (135, 139, 140). Abbreviation: NJ, neighbor joining. Reprinted from the supplemental material of Reference 139.

Attraverso la sequenza del DNA mitocondriale si sono anche potute stabilire le migrazioni di *Homo sapiens* dall'Africa al resto del mondo



Secondo **Douglas C. Wallace** le varianti del DNA mitocondriale (che muta più rapidamente di quello nucleare) hanno avuto grande importanza nell'adattamento al **clima** e all'**altitudine**



C'è già chi ci guadagna ….

Why Do We Still Have a Maternally Inherited Mitochondrial DNA? Insights from Evolutionary Medicine

Douglas C. Wallace

Annu. Rev. Biochem. 2007. 76:781–821

The *Annual Review of Biochemistry* is online at biochem.annualreviews.org

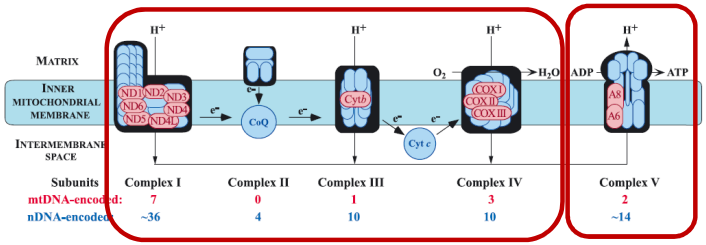
This article's doi:
10.1146/annurev.biochem.76.081205.150955

Abstract

The human cell is a symbiosis of two life forms, the nucleus-cytosol and the mitochondrion. The nucleus-cytosol emphasizes structure and its genes are Mendelian, whereas the mitochondrion specializes in energy and its mitochondrial DNA (mtDNA) genes are maternal. Mitochondria oxidize calories via oxidative phosphorylation (OXPHOS) to generate a mitochondrial inner membrane proton gradient (ΔP). ΔP then acts as a source of potential energy to produce ATP, generate heat, regulate reactive oxygen species (ROS), and control apoptosis, etc. Interspecific comparisons of mtDNAs have revealed that the mtDNA retains a core set of electron and proton carrier genes for the proton-translocating OXPHOS complexes I, III, IV, and V. Human mtDNA analysis has revealed these genes frequently contain region-specific adaptive polymorphisms. Therefore, the mtDNA with its energy controlling genes may have been retained to permit rapid adaptation to new environments.

- The **first hypothesis** is that the current mtDNA polypeptide genes became "frozen" in the mtDNAs because the mtDNA genetic codes diverged from that of the nDNA, thus rendering the mtDNA polypeptide genes uninterpretable by the nuclear-cytosolic system.
- The **second hypothesis** is that certain core mtDNA proteins have been retained to ensure that the OXPHOS complexes are only assembled in the mitochondrial inner membrane, either because the mtDNA proteins provide an essential scaffold for assembly of the complexes or because relocation of the OXPHOS complexes at inappropriate sites could generate ROS that would be destructive.
- The **third hypothesis** is that the retained mtDNA proteins are simply too hydrophobic to be translated in the cytosol and then to be appropriately incorporated in the mitochondrial inner membrane. Rather, they might be misdirected to another compartment such as the endoplasmic reticulum secretory apparatus.
- The **final hypothesis** argues that the remaining mtDNA-encoded polypeptides contain regions (mesohydrophic regions) that are too hydrophobic to be imported into the mitochondrion through the mitochondrial protein import machinery.

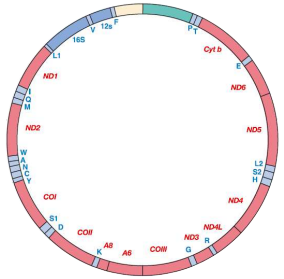
I complessi respiratori e la ATP sintetasi dei mitocondri



S. DiMauro / Biochimica et Biophysica Acta 1658 (2004) 80–88

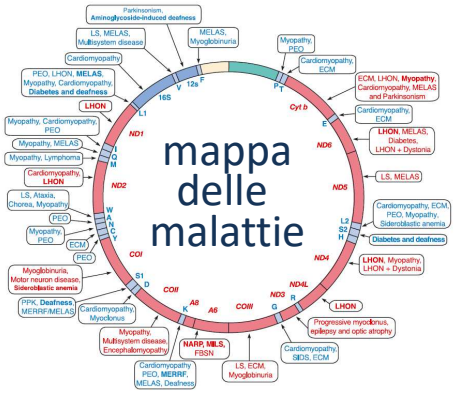
Il genoma mitocondriale umano

DNA a doppio filamento di 16,569 kb che codifica 37 geni:
2 per rRNA, 22 per tRNA, 13 strutturali
(11 subunità della catena respiratoria; 2 subunità della ATP sintetasi)



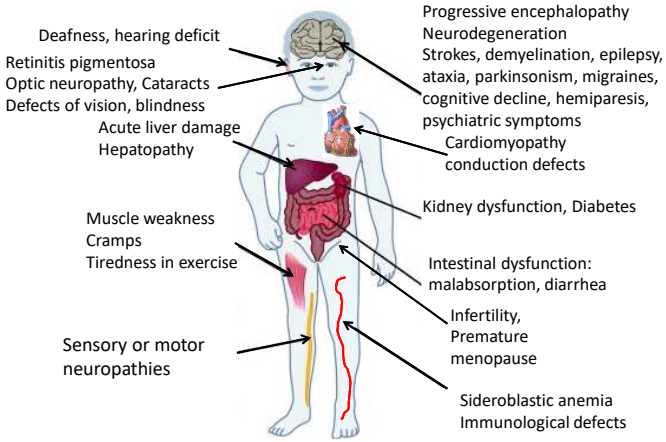
S. DiMauro / Biochimica et Biophysica Acta 1658 (2004) 80–88

Il genoma mitocondriale umano

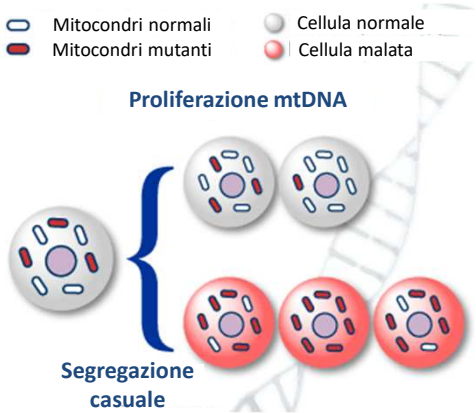


S. DiMauro / Biochimica et Biophysica Acta 1658 (2004) 80–88

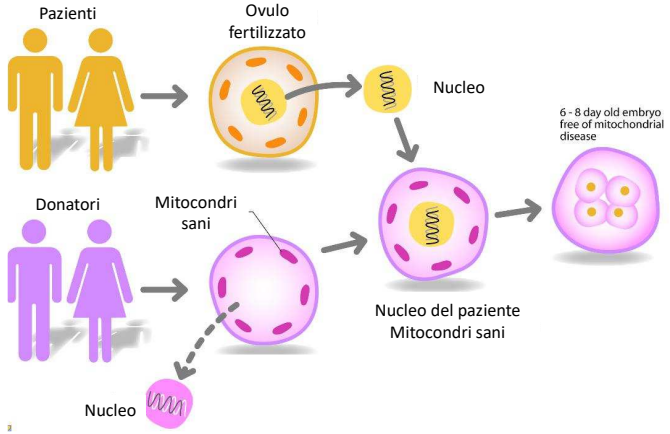
Mitochondrial disorders: exceptional variability cannot be explained only by ATP deficiency



Eteroplasmia e l'effetto soglia



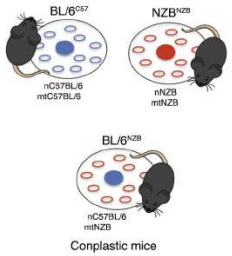
Trasferimento del nucleo in embrioni umani



LETTER 28 JULY 2016 | VOL 535 | NATURE | 561
doi:10.1038/nature18618

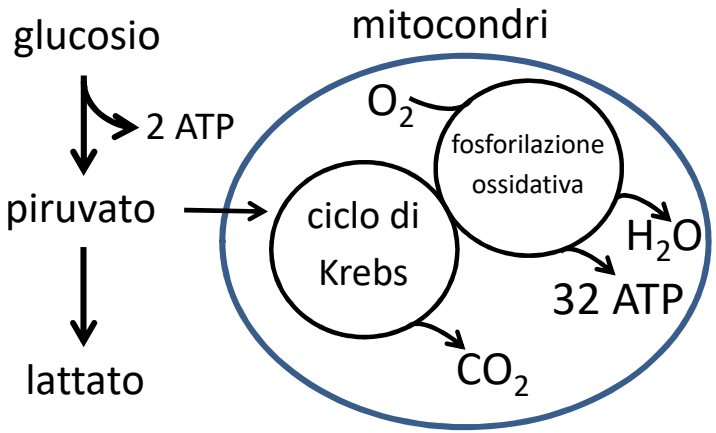
Mitochondrial and nuclear DNA matching shapes metabolism and healthy ageing

Ana Latorre-Pellicer[1,2], Raquel Moreno-Loshuertos[3], Ana Victoria Lechuga-Vieco[1,4], Fátima Sánchez-Cabo[1], Carlos Torroja[1], Rebeca Acín-Pérez[1], Enrique Calvo[1], Esther Aix[1], Andrés González-Guerra[1], Angela Logan[5], María Luisa Bernad-Miana[6], Eduardo Romanos[6], Raquel Cruz[2], Sara Cogliati[1], Beatriz Sobrino[7], Ángel Carracedo[2,7,8], Acisclo Pérez-Martos[3], Patricio Fernández-Silva[3], Jesús Ruíz-Cabello[1,4,9], Michael P. Murphy[5], Ignacio Flores[1], Jesús Vázquez[1] & José Antonio Enríquez[1,3]



Human mitochondrial DNA (mtDNA) shows extensive within-population sequence variability[1]. Many studies suggest that mtDNA variants may be associated with ageing or diseases[2–4], although mechanistic evidence at the molecular level is lacking[5,6]. Mitochondrial replacement has the potential to prevent transmission of disease-causing oocyte mtDNA. However, extension of this technology requires a comprehensive understanding of the physiological relevance of mtDNA sequence variability and its match with the nuclear-encoded mitochondrial genes. Studies in conplastic animals[7–9] allow comparison of individuals with the same nuclear genome but different mtDNA variants, and have provided both supporting and refuting evidence that mtDNA variation influences organismal physiology. However, most of these studies did not confirm the conplastic status, focused on younger animals, and did not investigate the full range of physiological and phenotypic variability likely to be influenced by mitochondria. Here we systematically characterized conplastic mice throughout their lifespan using transcriptomic, proteomic, metabolomic, biochemical, physiological and phenotyping studies. We show that mtDNA haplotype profoundly influences mitochondrial proteostasis and reactive oxygen species generation, insulin signalling, obesity, and ageing parameters including telomere shortening and mitochondrial dysfunction, resulting in profound differences in health longevity between conplastic strains.

A cosa servono i mitocondri?

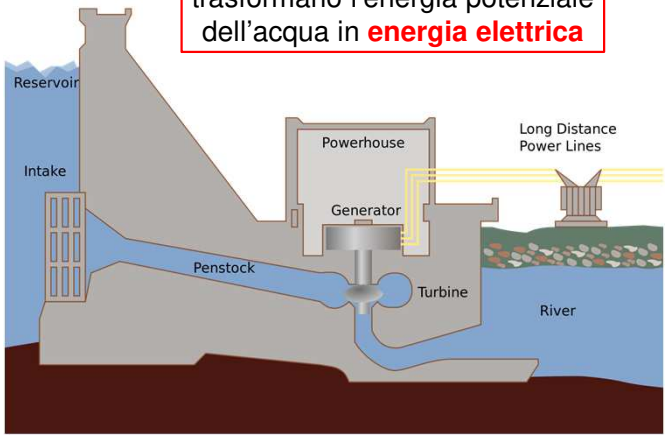


Le malattie mitocondriali

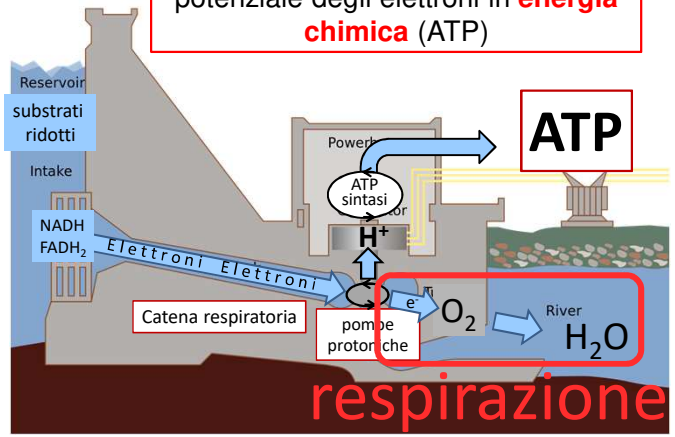
1. Causate da lesioni a carico di **geni mitocondriali** (trasmissione **materna**)
2. Causate da lesioni a carico di **geni nucleari** che codificano proteine mitocondriali (trasmissione **mendeliana**)

Malattie a **patogenesi** mitocondriale

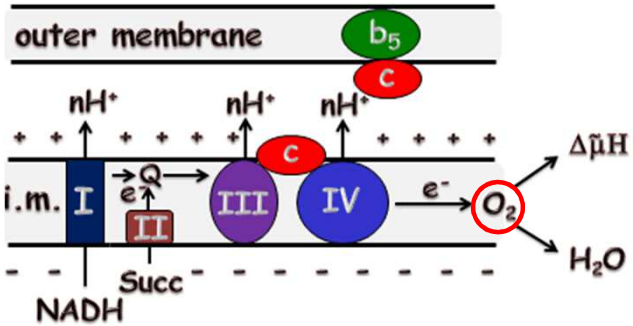
Le centrali idroelettriche trasformano l'energia potenziale dell'acqua in **energia elettrica**

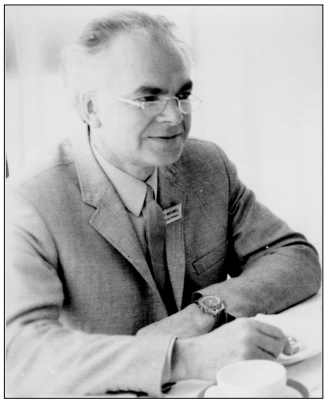


I mitocondri trasformano l'energia potenziale degli elettroni in **energia chimica** (ATP)



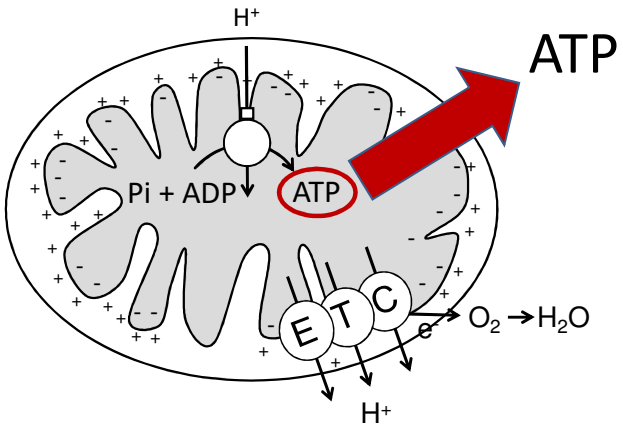
La catena respiratoria e la formazione del gradiente protonico

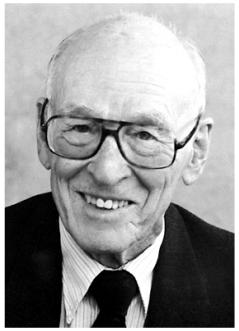




Peter Mitchell
(1920-1992)
Nobel Prize
for Chemistry
- 1978 -

Meccanismo di conservazione dell'energia





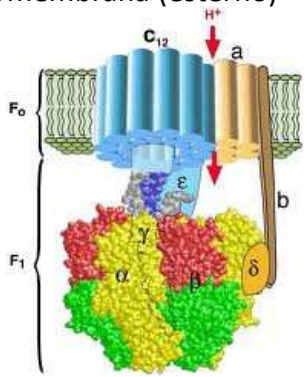
Paul D Boyer
(1918)

Sir John Walker
(1941)

Nobel Prize for Chemistry
- 1997 -

La ATP sintetasi dei mitocondri - l'enzima della vita

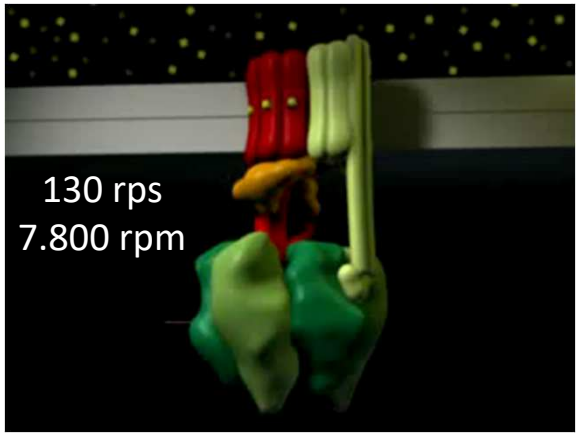
Spazio intermembrana (esterno)



Matrice
(interno)

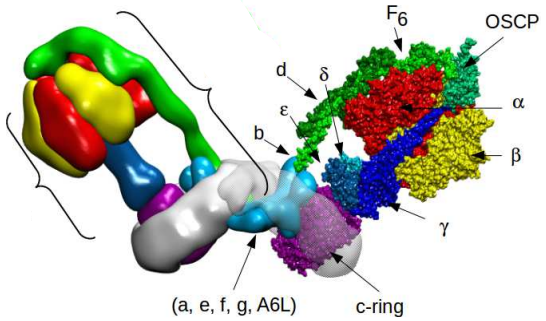
http://www.dnatube.com/video/104/ATP-synthase-structure-and-mechanism

http://www.youtube.com/watch?v=J8lhPt6V-yM



Arrangement of subunits in intact mammalian mitochondrial ATP synthase determined by cryo-EM

Lindsay A. Baker[a,b], Ian N. Watt[c], Michael J. Runswick[c], John E. Walker[c], and John L. Rubinstein[a,b,d,1]



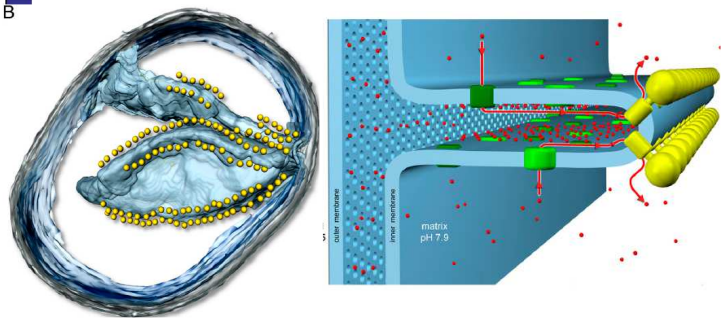
PNAS | July 17, 2012 | vol. 109 | no. 29 | 11675–11680

Macromolecular organization of ATP synthase and complex I in whole mitochondria 2011

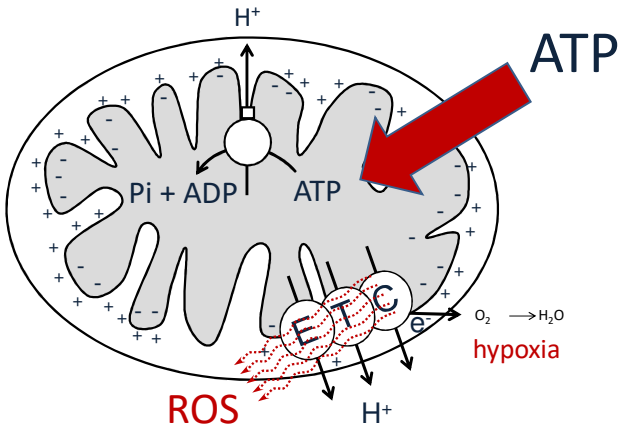
Karen M. Davies[a,1], Mike Strauss[a,1], Bertram Daum[a,1], Jan H. Kief[b], Heinz D. Osiewacz[c], Adriana Rycovska[d], Volker Zickermann[e], and Werner Kühlbrandt[a,2]

[a]Department of Structural Biology, Max Planck Institute of Biophysics, Max-von-Laue Strasse 3, 60438 Frankfurt am Main, Germany; [b]Mitochondrial Biology, Medical School, Goethe University Frankfurt am Main, Theodor-Stern-Kai 7, 60590 Frankfurt am Main, Germany, and Mitochondrial Biology, Frankfurt Institute for Molecular Life Sciences, Max-von-Laue-Strasse 9, 60438 Frankfurt am Main, Germany; [c]Molecular Developmental Biology, Goethe University, Max-von-Laue-Strasse 9, Germany, and Deutsche Forschungsgemeinschaft Cluster of Excellence Frankfurt "Macromolecular Complexes", 60438 Frankfurt, Germany; [d]Department of Molecular Membrane Biology, Max Planck Institute of Biophysics, Max-von-Laue Strasse 3, 60438 Frankfurt am Main, Germany; and [e]Medical Faculty, Molecular Bioenergetics, Goethe University, Theodor-Stern-Kai 7, 60590 Frankfurt am Main, Germany

Edited by Richard Henderson, Medical Research Council Laboratory of Molecular Biology, Cambridge, United Kingdom, and approved July 1, 2011 (received for review March 7, 2011)



Mechanism of energy dissipation

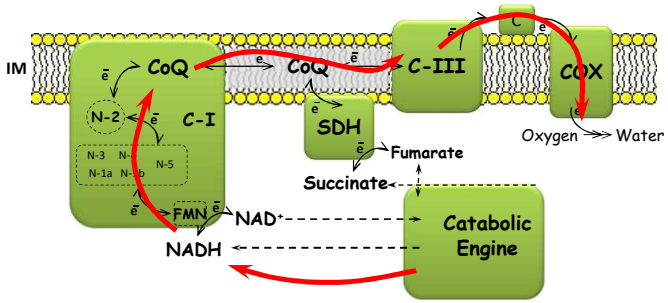


Mitocondri e ROS

Courtesy of Dr. Anatoly Starkov
Weill Cornell Medical College
1300 York Avenue
New York, NY

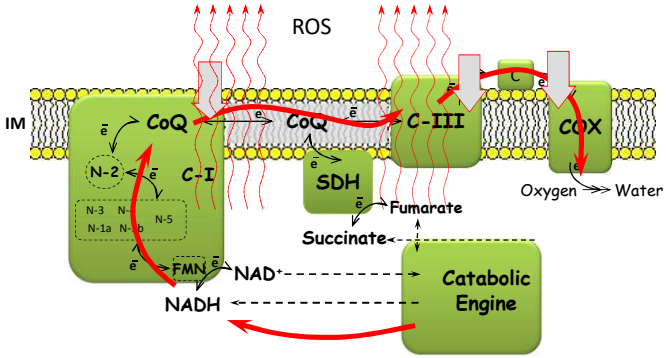
Starkov, AA (2008) The Role of Mitochondria in Reactive Oxygen Species Metabolism and Signaling, *Ann NY Acad Sci* **1147**, 37-52

Forward electron transfer (F.E.T.):
NADH (CoQ) → Oxygen



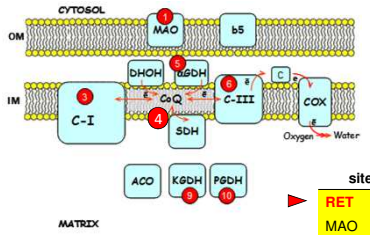
Starkov 2008

Forward electron transfer (F.E.T.):
NADH (CoQ) → Oxygen



Starkov 2008

ROS production capacity of major sites



all numbers are for mouse brain non-synaptic mitochondria

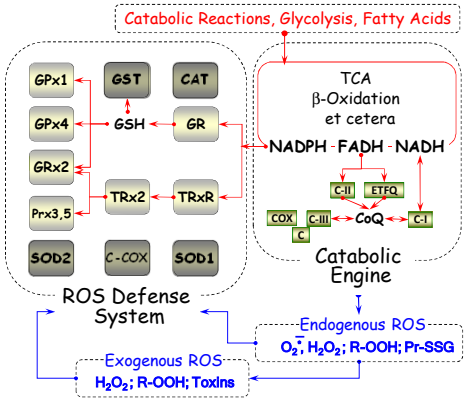
site	H_2O_2, nmol/min/mg	notes
RET	1.2-3.0	Succinate 3 4
MAO	0.7-1.5	Kynurenin 1
αGDH	0.2-0.5	α-Glycerophosphate 5
CI+matrix	0.1-0.3	Rotenone 3 9 10
KGDHC	0.1 - 0.3	α-Ketoglutarate 9
FET	0.06-0.2	NAD+ substrates
CIII	0 - 0.2	Antimycin 6
SDH	0	Succinate

RET – reverse electron transfer;
FET – forward electron transfer;
αGDH – α–glycerophosphate dehydrogenase;
KDGHC – α–ketoglutarate dehydrogenase complex;
SDH – succinate dehydrogenase;
C1 – Complex I of the respiratory chain;
CIII – Complex III of the respiratory chain;
MAO – monoamine oxidase.

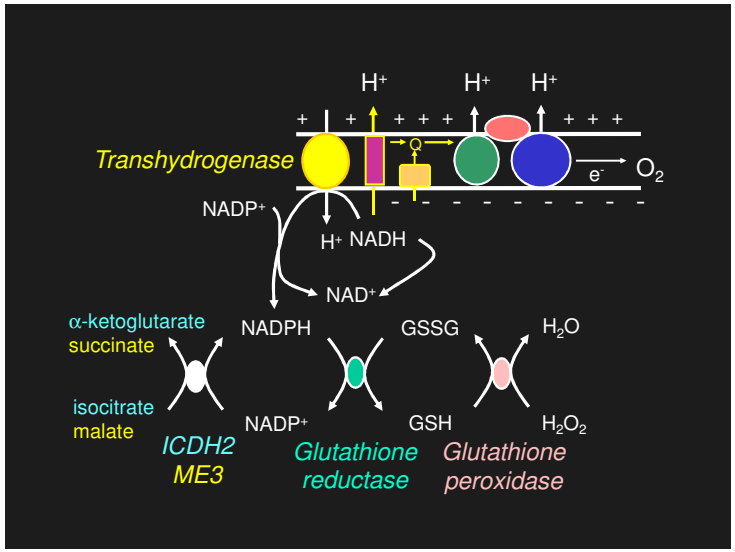
● sites on the diagram that are involved in ROS generation.

Starkov 2008, modified

Mitochondria are high-capacity ROS-scavenging organelles



GPx1 – glutathione peroxidase 1; GPx4 –glutathione peroxidase 4; GRx2 – glutaredoxin 2; Prx3,5 – peroxiredoxins 3 and 5; SOD2 – MnFe superoxide dismutase; GST – glutathione-S-transferase; GSH – reduced glutathione; TRx2 – thioredoxin 2; c-COX – cytochrome c + cytochrome c oxidase; CAT – catalase; GR – glutathione reductase; TRxR – thioredoxin reductase; SOD1 – CuZn superoxide dismutase.



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Vol. 269, No. 48, Issue of December 2, pp. 30553–30560, 1994
Printed in U.S.A.

Different Prooxidant Levels Stimulate Growth, Trigger Apoptosis, or Produce Necrosis of Insulin-secreting RINm5F Cells

THE ROLE OF INTRACELLULAR POLYAMINES*

(Received for publication, June 30, 1994, and in revised form, September 9, 1994)

Jeanette M. Dypbukt, Maria Ankarcrona, Mark Burkitt, Åke Sjöholm, Kerstin Ström, Sten Orrenius, and Pierluigi Nicotera‡

From the Institute of Environmental Medicine, Division of Toxicology, Karolinska Institute, Box 210, S-171 77, Stockholm, Sweden

Neuron, Vol. 15, 961–973, October, 1995, Copyright © 1995 by Cell Press

Glutamate-Induced Neuronal Death: A Succession of Necrosis or Apoptosis Depending on Mitochondrial Function

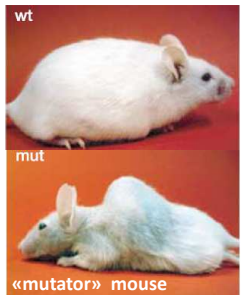
Maria Ankarcrona,* Jeannette M. Dypbukt,* Emanuela Bonfoco,* Boris Zhivotovsky,* Sten Orrenius,* Stuart A. Lipton,† and Pierluigi Nicotera*‡

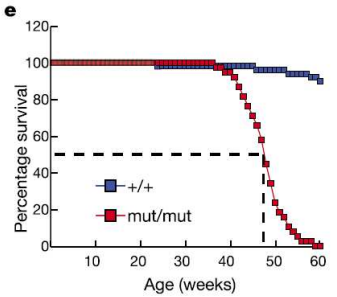
Mitochondrial ROS and aging: An open question

Premature ageing in mice expressing defective mitochondrial DNA polymerase

Nature (2004) 429, 417-423

Aleksandra Trifunovic[1,2], Anna Wredenberg[1,2], Maria Falkenberg[1], Johannes N. Spelbrink[3], Anja T. Rovio[3], Carl E. Bruder[4], Mohammad Bohlooly-Y[1], Sebastian Gidlöf[1,2], Anders Oldfors[5], Rolf Wibom[6], Jan Törnell[1], Howard T. Jacobs[3] & Nils-Göran Larsson[1,2]



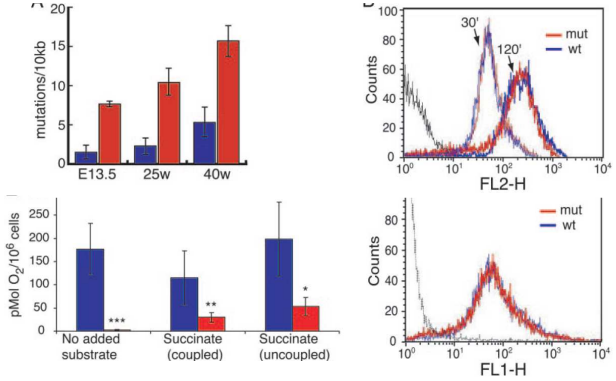


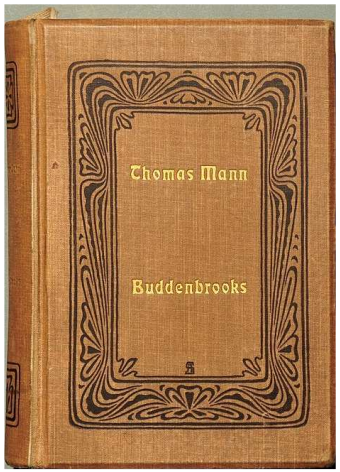
PNAS | December 13, 2005 | vol. 102 | no. 50 | 17993–17998

Somatic mtDNA mutations cause aging phenotypes without affecting reactive oxygen species production

Aleksandra Trifunovic*, Anna Hansson*, Anna Wredenberg*, Anja T. Rovio†, Eric Dufour*, Ivan Khvorostov*, Johannes N. Spelbrink†, Rolf Wibom*, Howard T. Jacobs†, and Nils-Göran Larsson*‡

*Department of Laboratory Medicine, Karolinska Institute, S-141 86 Stockholm, Sweden; and †Institute of Medical Technology and Tampere University Hospital, FI-33014 University of Tampere, Finland





Parte decima

9

Per un dente… Il senatore Buddenbrook era morto per un dente, si diceva in città. Ma, perbacco, non si muore certo per questo! Aveva avuto dei dolori, il signor Brecht gli aveva spezzato la corona e poi era semplicemente svenuto per strada. Si era mai sentito niente di simile?…

7

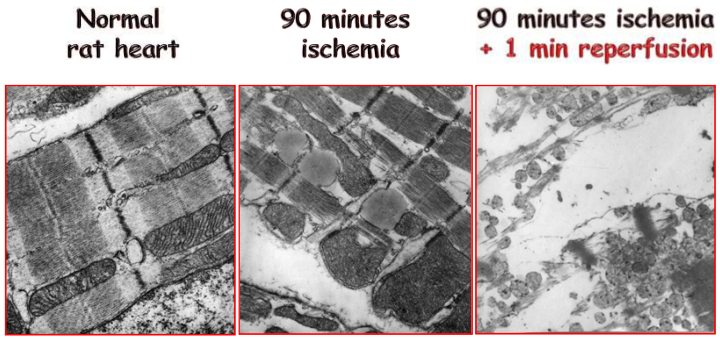
«Dove ti fa male?»
«Qui sotto a sinistra… Un molare… Ovviamente è cariato… È insopportabile…»
….
Era un dolore selvaggio, bruciante e tormentoso, **una sofferenza maligna** che da un molare guasto si era **diffusa a tutto il lato sinistro della mandibola**. L'infiammazione la percuoteva con martelletti ardenti …

8

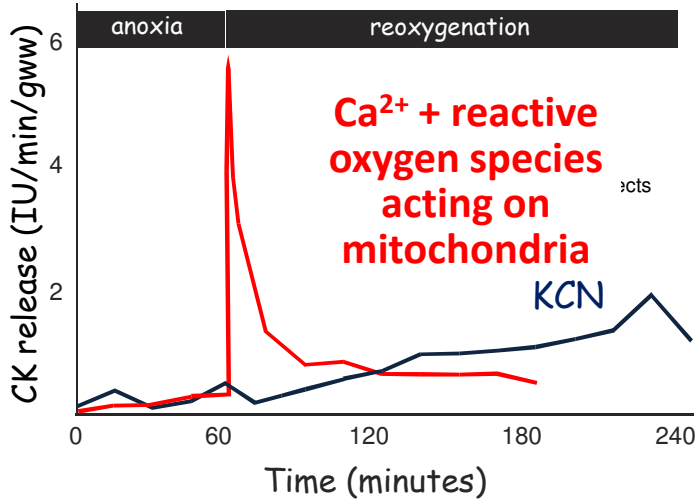
E poi nel silenzio non si udì più nulla se non il gorgoglio agonizzante di Thomas Buddenbrook.

Oscar Mondadori, 2012, traduzione di Silvia Bortoli

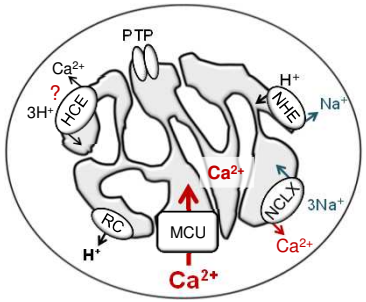
Mitocondri e infarto cardiaco



R.B. Jennings and Coworkers



1. Calcio
2. Specie reattive dell'ossigeno



RC, Respiratory Chain
MCU, Mitochondrial Calcium Uniporter
NCLX, Na-Ca Exchanger
NHE, Na-H Exchanger
HCE, Putative H-Ca Exchanger
PTP, Permeability Transition Pore

Vol 467|16 September 2010|doi:10.1038/nature09358 nature

291

***MICU1* encodes a mitochondrial EF hand protein required for Ca^{2+} uptake**

Fabiana Perocchi[1], Vishal M. Gohil[1], Hany S. Girgis[1], X. Robert Bao[1], Janet E. McCombs[2], Amy E. Palmer[2] & Vamsi K. Mootha[1]

336 | NATURE | VOL 476 | 18 AUGUST 2011

A forty-kilodalton protein of the inner membrane is the mitochondrial calcium uniporter

Diego De Stefani[1,2*], Anna Raffaello[1,2*], Enrico Teardo[3], Ildikó Szabò[3] & Rosario Rizzuto[1,2]

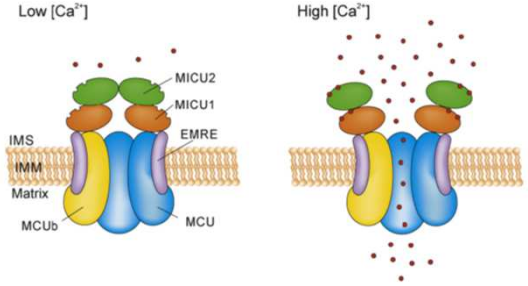
18 AUGUST 2011 | VOL 476 | NATURE | 341

Integrative genomics identifies MCU as an essential component of the mitochondrial calcium uniporter

Joshua M. Baughman[1,2*], Fabiana Perocchi[1,2*], Hany S. Girgis[1,2], Molly Plovanich[1,2], Casey A. Belcher-Timme[1,2], Yasemin Sancak[1,2], X. Robert Bao[1,2], Laura Strittmatter[1,2], Olga Goldberger[1,2], Roman L. Bogorad[3], Victor Koteliansky[4] & Vamsi K. Mootha[1,2]

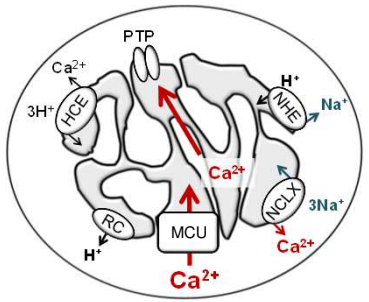
Molecular structure and pathophysiological roles of the Mitochondrial Calcium Uniporter☆

Cristina Mammucari [a,*], Anna Raffaello [a,*], Denis Vecellio Reane [a], Rosario Rizzuto [a,b,**]



The MCU complex is a multicomponent structure conferring a sophisticated control to mitochondrial Ca^{2+} transport through the channel

Biochimica et Biophysica Acta 1863 (2016) 2457–2464



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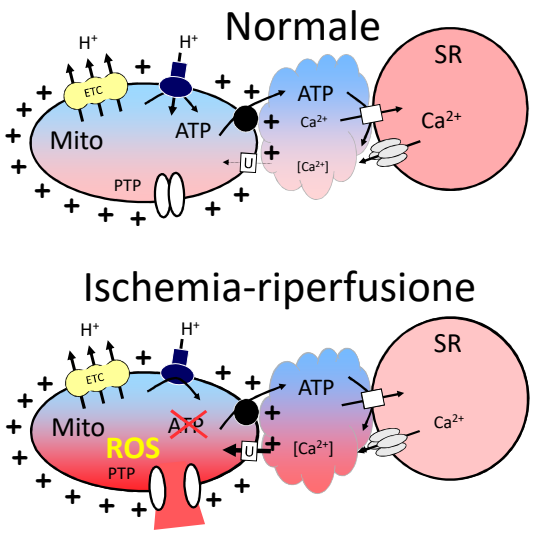
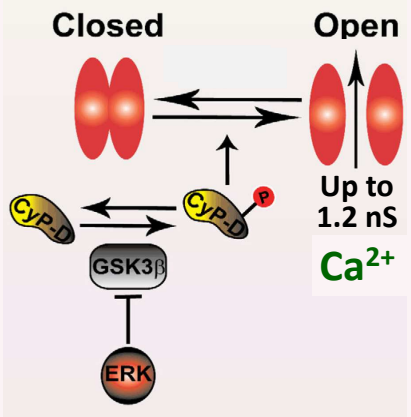
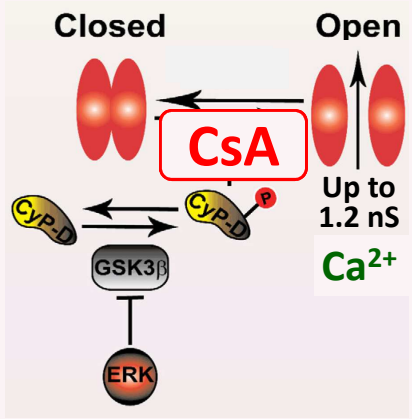


The permeability transition pore (PTP)



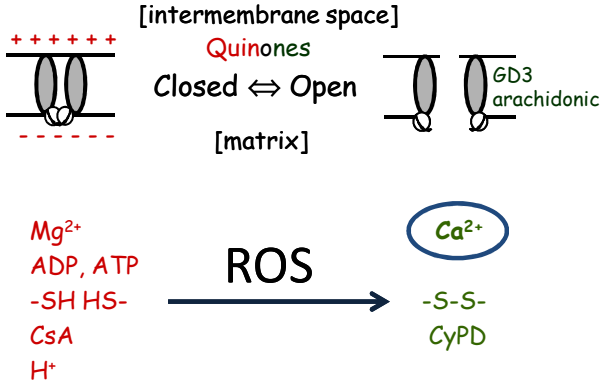
Rasola and Bernardi (2011) *Cell Calcium* 50, 222-233

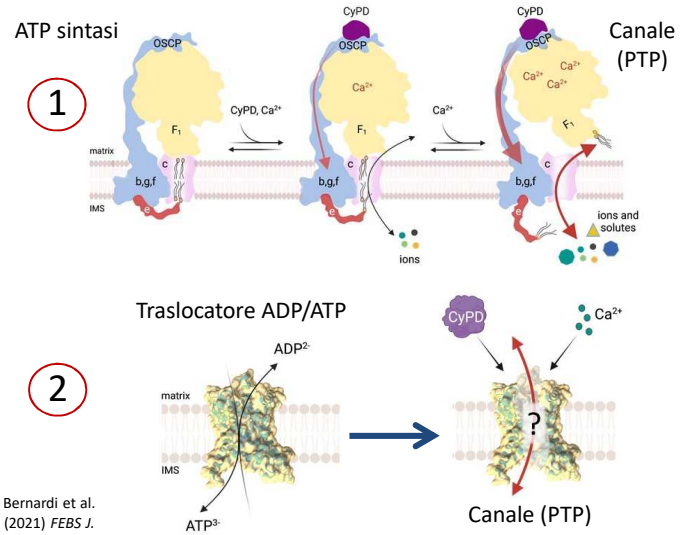
The permeability transition pore (PTP)



Rasola and Bernardi (2011) *Cell Calcium* 50, 222-233

The Permeability Transition Pore





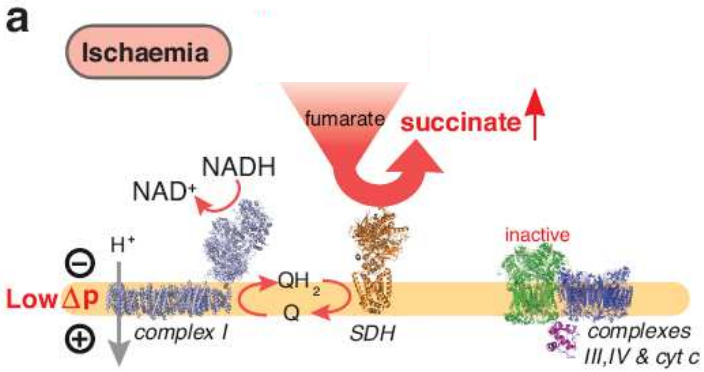
Bernardi et al. (2021) *FEBS J.*

1. Calcio
2. Specie reattive dell'ossigeno

Nature (2014) 515, 431-435

Ischaemic accumulation of succinate controls reperfusion injury through mitochondrial ROS

Edward T. Chouchani[1,2,*], Victoria R. Pell[2,*], Edoardo Gaude[3], Dunja Aksentijević[4], Stephanie Y. Sundier[5], Ellen L. Robb[1], Angela Logan[1], Sergiy M. Nadtochiy[7], Emily N. J. Ord[8], Anthony C. Smith[1], Filmon Eyassu[1], Rachel Shirley[8], Chou-Hui Hu[2], Anna J. Dare[1], Andrew M. James[1], Sebastian Rogatti[1], Richard C. Hartley[9], Simon Eaton[10], Ana S.H. Costa[3], Paul S. Brookes[7], Sean M. Davidson[6], Michael R. Duchen[5], Kourosh Saeb-Parsy[11], Michael J. Shattock[4], Alan J. Robinson[1], Lorraine M. Work[8], Christian Frezza[3], Thomas Krieg[2] & Michael P. Murphy[1]

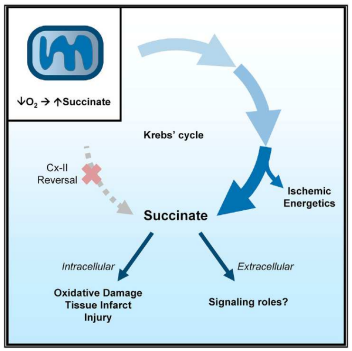


Chouchani et al (2014) Nature, modificata

Cell Reports 23, 2617–2628, May 29, 2018 © 2018 The Authors. 2617

Accumulation of Succinate in Cardiac Ischemia Primarily Occurs via Canonical Krebs Cycle Activity

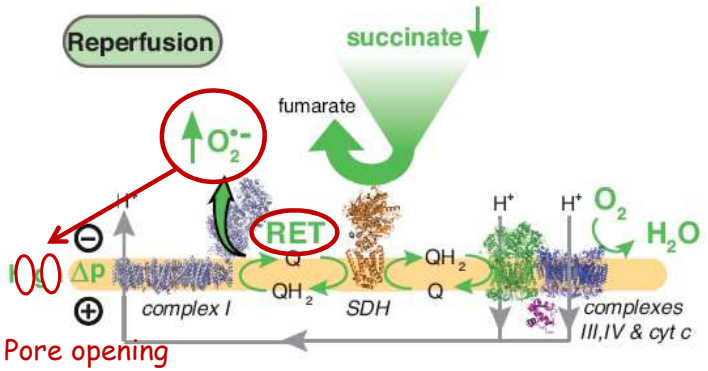
Jimmy Zhang,[1] Yves T. Wang,[2] James H. Miller,[2] Mary M. Day,[2] Joshua C. Munger,[3] and Paul S. Brookes[1,2,4,*]



Canonical Krebs cycle, rather than complex II reversal, generates ischemic succinate

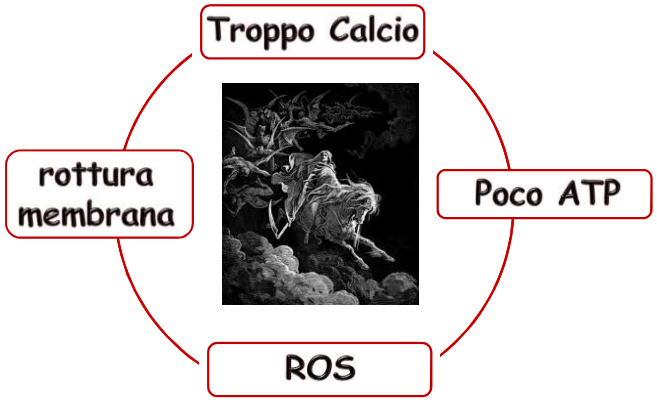
Ischemic succinate accumulation may improve ischemic energetics

At reperfusion, succinate is primarily washed out rather than oxidized



Chouchani et al (2014) Nature

Il circolo vizioso della morte cellulare



ChemPubSoc Europe
DOI: 10.1002/cmdc.201500284
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Very Important Paper
(2015) 10, 1655-1671

Discovery, Synthesis, and Optimization of Diarylisoxazole-3-carboxamides as Potent Inhibitors of the Mitochondrial Permeability Transition Pore

Sudeshna Roy,[a] Justina Šileikytė,[b] Marco Schiavone,[b] Benjamin Neuenswander,[a] Francesco Argenton,[c] Jeffrey Aubé,[a] Michael P. Hedrick,[d] Thomas D. Y. Chung,[d] Michael A. Forte,*[e] Paolo Bernardi,*[b] and Frank J. Schoenen*[a]

ChemPubSoc Europe
DOI: 10.1002/cmdc.201500545
CHEMMEDCHEM Communications
(2016) 11, 283-288

N-Phenylbenzamides as Potent Inhibitors of the Mitochondrial Permeability Transition Pore

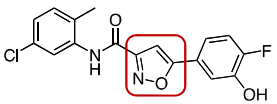
Sudeshna Roy*,*[a] Justina Šileikytė*,[b] Benjamin Neuenswander,[a] Michael P. Hedrick,[d] Thomas D. Y. Chung,[e] Jeffrey Aubé,[a] Frank J. Schoenen,*[a] Michael A. Forte,*[c] and Paolo Bernardi*[b]

ChemPubSoc Europe
(2019) 14, 1771-1782
DOI: 10.1002/cmdc.201900376
CHEMMEDCHEM Full Papers

Second-Generation Inhibitors of the Mitochondrial Permeability Transition Pore with Improved Plasma Stability

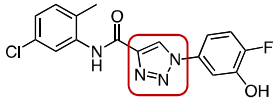
Justina Šileikytė*,[a] Jordan Devereaux*,[b] Jelle de Jong,[d] Marco Schiavone,[d] Kristen Jones,[a] Aaron Nilsen,[b] Paolo Bernardi,[d] Michael Forte,[a] and Michael S. Cohen*[c]

Excessive mitochondrial matrix Ca^{2+} and oxidative stress leads to the opening of a high-conductance channel of the inner mitochondrial membrane referred to as the mitochondrial permeability transition pore (mtPTP). Because mtPTP opening can lead to cell death under diverse pathophysiological conditions, inhibitors of mtPTP are potential therapeutics for various human diseases. High throughput screening efforts led to the identification of a 3-carboxamide-5-phenol-isoxazole compounds as mtPTP inhibitors. While they showed nanomolar potency against mtPTP, they exhibited poor plasma stability, precluding their use in in vivo studies. Herein, we describe a series of structurally related analogues in which the core isoxazole was replaced with a triazole, which resulted in an improvement in plasma stability. These analogues were readily generated using the copper-catalyzed "click chemistry". One analogue, *N*-(5-chloro-2-methylphenyl)-1-(4-fluoro-3-hydroxyphenyl)-1*H*-1,2,3-triazole-4-carboxamide (**TR001**), was efficacious in a zebrafish model of muscular dystrophy that results from mtPTP dysfunction whereas the isoxazole isostere had minimal effect.



Compound 63

$t_{1/2}$ in mouse plasma **21 min**



Compound TR001

$t_{1/2}$ in mouse plasma **990 min**

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A novel class of cardioprotective small-molecule PTP inhibitors

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Ischemia/reperfusion (I/R) injury is mediated in large part by opening of the mitochondrial permeability transition pore (PTP). Consequently, inhibitors of the PTP hold great promise for the treatment of a variety of cardiovascular disorders. At present, PTP inhibition is obtained only through the use of drugs (e.g. cyclosporine A, CsA) targeting cyclophilin D (CyPD) which is a key modulator, but not a structural component of the PTP. This limitation might explain controversial findings in clinical studies. Therefore, we investigated the protective effects against I/R injury of small-molecule inhibitors of the PTP (63 and TR002) that do not target CyPD. Both compounds exhibited a dose-dependent inhibition of PTP opening in isolated mitochondria and were more potent than CsA. Notably, PTP inhibition was observed also in mitochondria devoid of CyPD. Compounds 63 and TR002 prevented PTP opening and mitochondrial depolarization induced by Ca^{2+} overload and by reactive oxygen species in neonatal rat ventricular myocytes (NRVMs). Remarkably, both compounds prevented cell death, contractile dysfunction and sarcomeric derangement induced by anoxia/reoxygenation injury in NRVMs at sub-micromolar concentrations, and were more potent than CsA. Cardioprotection was observed also in adult mouse ventricular myocytes and human iPSc-derived cardiomyocytes, as well as *ex vivo* in perfused hearts. Thus, this study demonstrates that 63 and TR002 represent novel cardioprotective agents that inhibit PTP opening independent of CyPD targeting.

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Fondation Leducq Transatlantic Network of Excellence Targeting Mitochondria to Treat Heart Disease

Elizabeth Murphy, Paolo Bernardi, Michael Cohen, Fabio Di Lisa, Michael Forte, Jeffery D. Molkentin, Michel Ovize

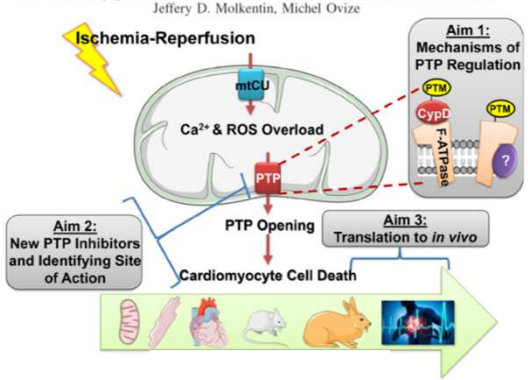

Figure. Multipronged approach of the Leducq Network targeting mitochondria to treat heart disease. The Network has 3 main aims: (1) to define the mechanisms that regulate permeability transition pore (PTP) opening, including posttranslational modification (PTM) and identification of novel PTP protein targets; (2) to refine the collection of PTP inhibitors and define their site of action, using newly developed chemistry approaches; and (3) to translate these findings to the clinic through testing in human cells and biopsies and relevant in vivo models. CypD indicates cyclophilin D; mtCU, mitochondrial calcium uniporter; and ROS, reactive oxygen species.