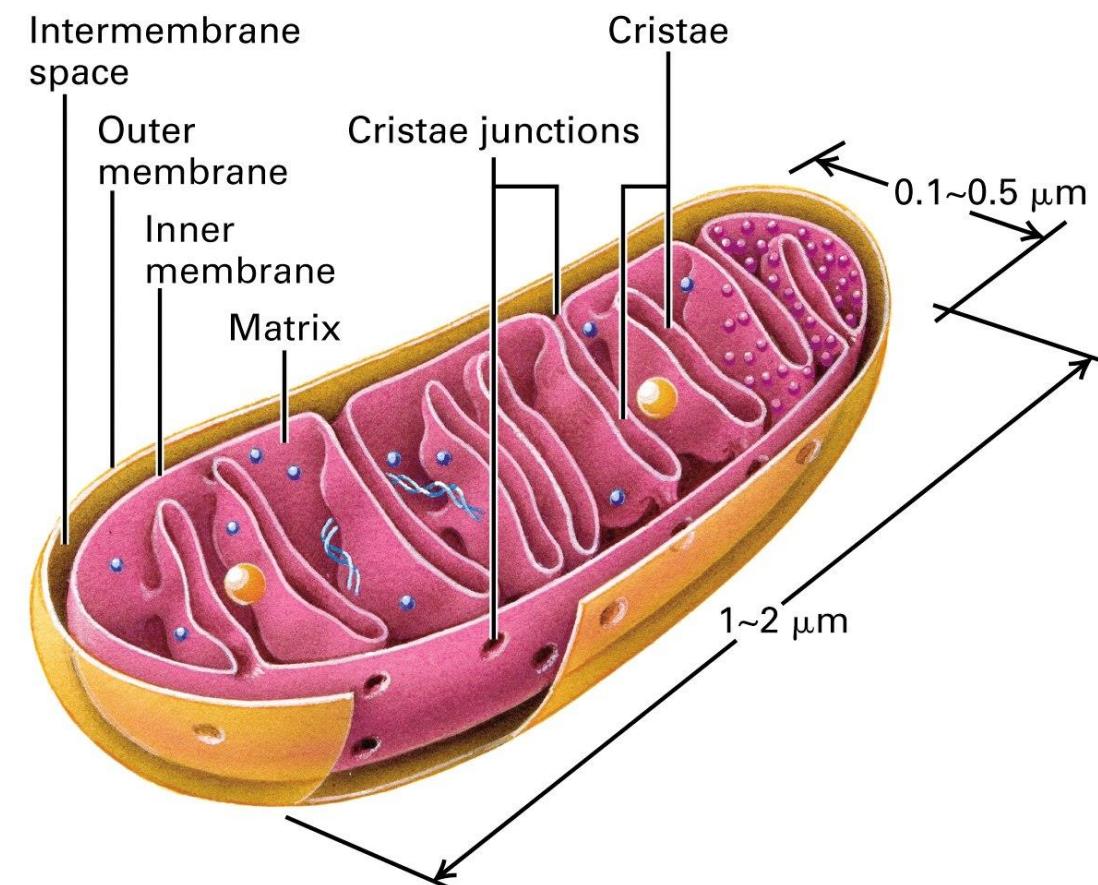


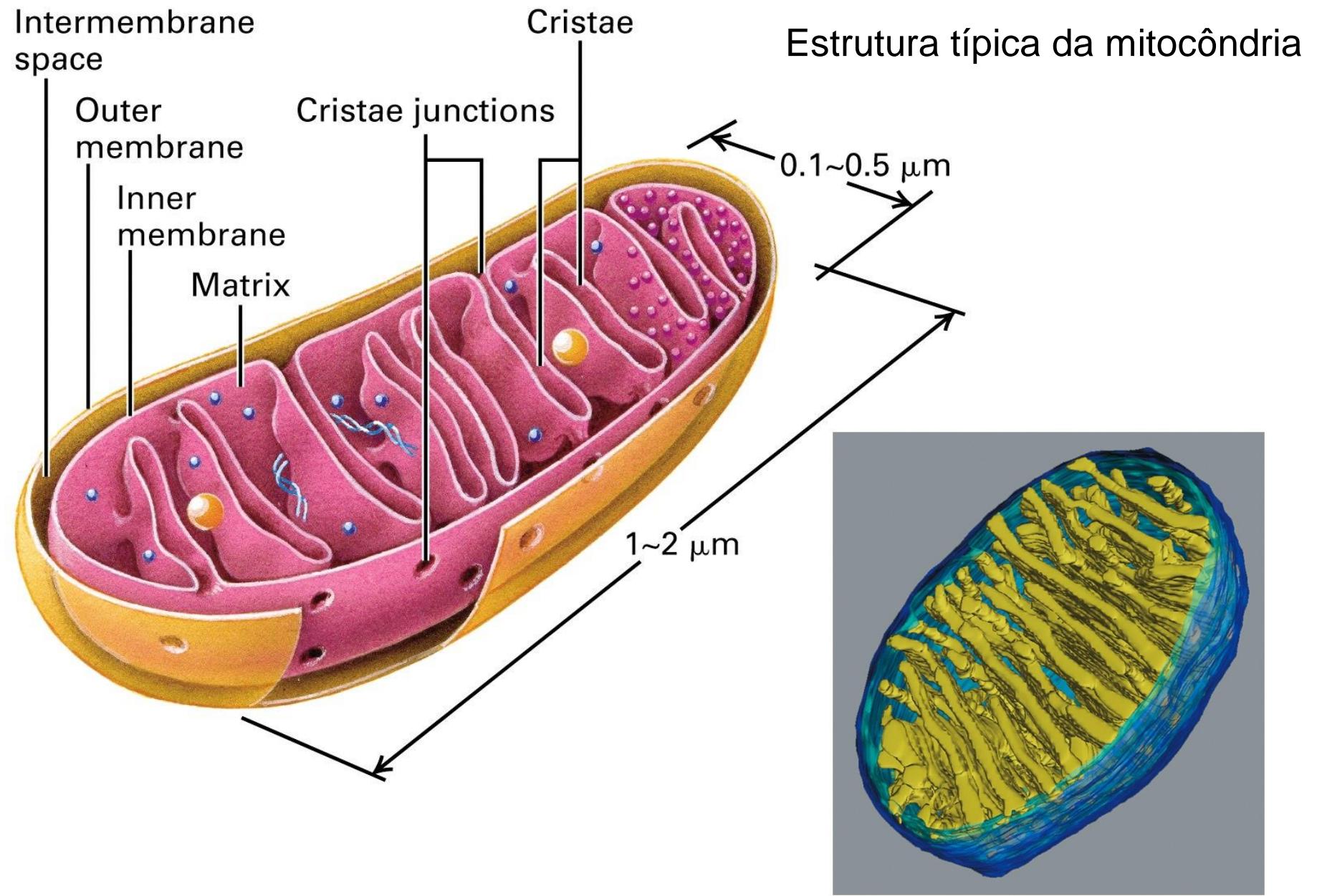
MITOCÔNDRIA

- . Estrutura
- . Função
- . Bioenergética Mitocondrial
- . Morte celular por apoptose

Mitocôndrias:

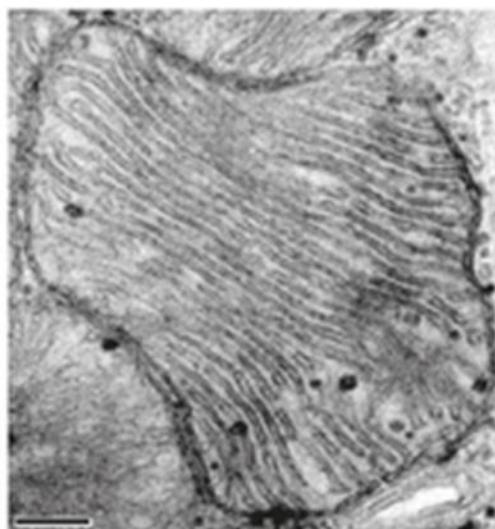
- . São organelos presentes em todas as células animais e vegetais.
- . Contém **DNA mitocondrial (mtDNA)** – várias cópias de uma **molécula circular** de DNA – que codifica algumas proteínas e componentes do seu sistema de síntese proteica, permitindo-lhes sintetizar algumas das suas proteínas, mas não todas.
- . São envolvidas por duas **membranas**, a **externa** e a **interna**, que definem 2 compartimentos: o **espaço intermembranar** e a **matriz mitocondrial**.
- . A **membrana interna** da mitocôndria possui invaginações que se projectam para o espaço interior – **cristas mitocondriais**. Estas cristas aumentam a área de superfície da membrana, e por isso a sua capacidade de produção de ATP.
- . A **matriz** contém a **maioria das proteínas** da mitocôndria, as enzimas envolvidas na oxidação do piruvato e ácidos gordos, as enzimas do ciclo de Krebs, o mtDNA, mRNA, tRNA, ribossomas e várias enzimas envolvidas na expressão genética.
- . Funcionam como “fábricas” de **produção de energia** da célula, através da produção de **ATP**.



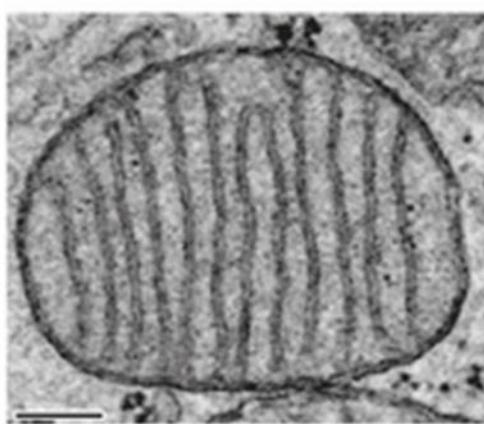


Algumas formas que as mitocôndrias podem assumir em diferentes tipos de células

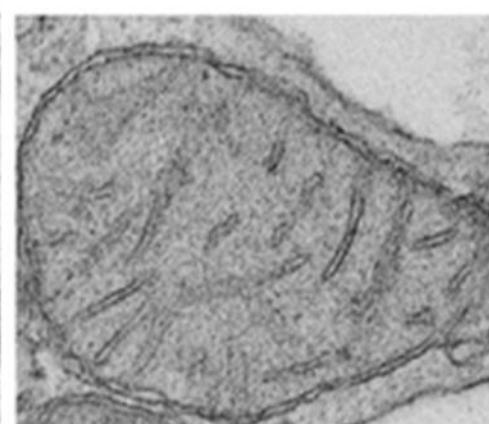
a



Heart



Brown fat



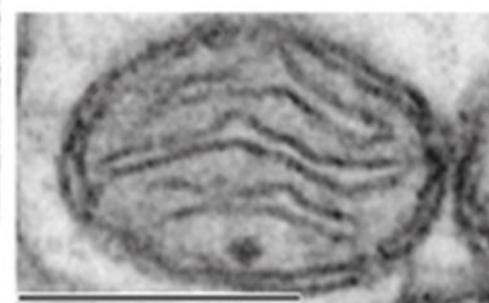
Liver



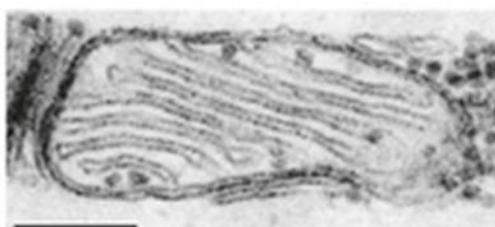
Pancreas



White fat



Brain



Skeletal muscle



Retina

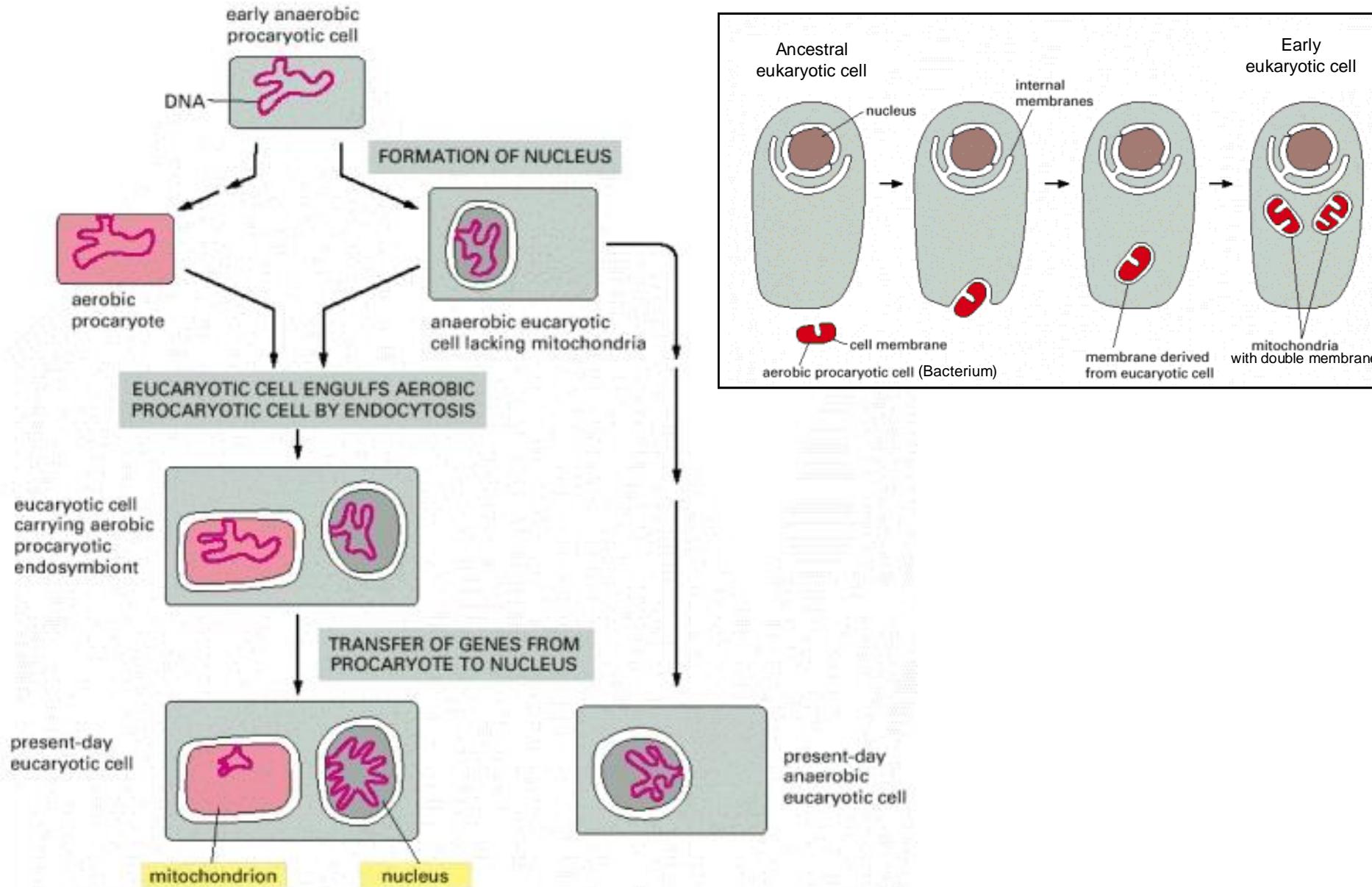


Peripheral nerve



Kidney

A origem endossimbiótica das mitocôndrias



A origem endossimbiótica das mitocôndrias

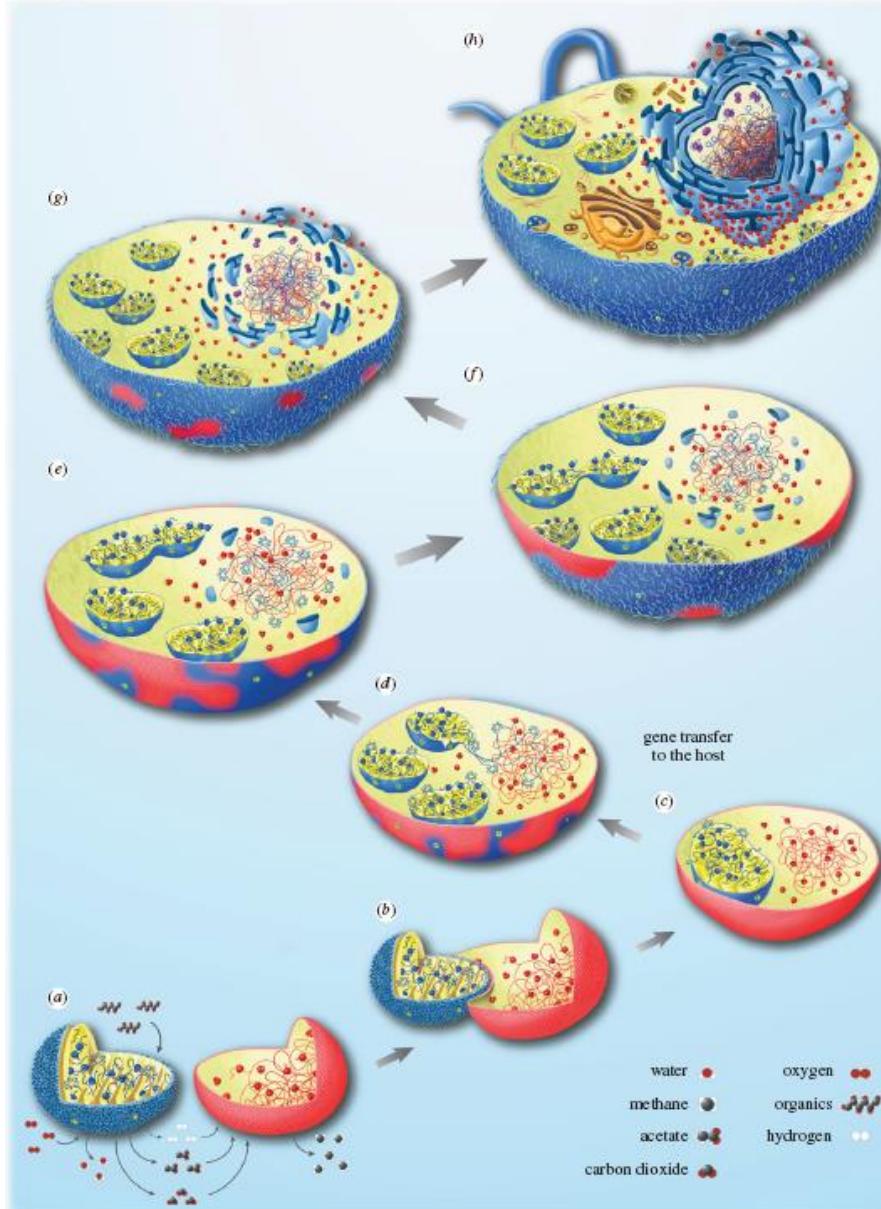
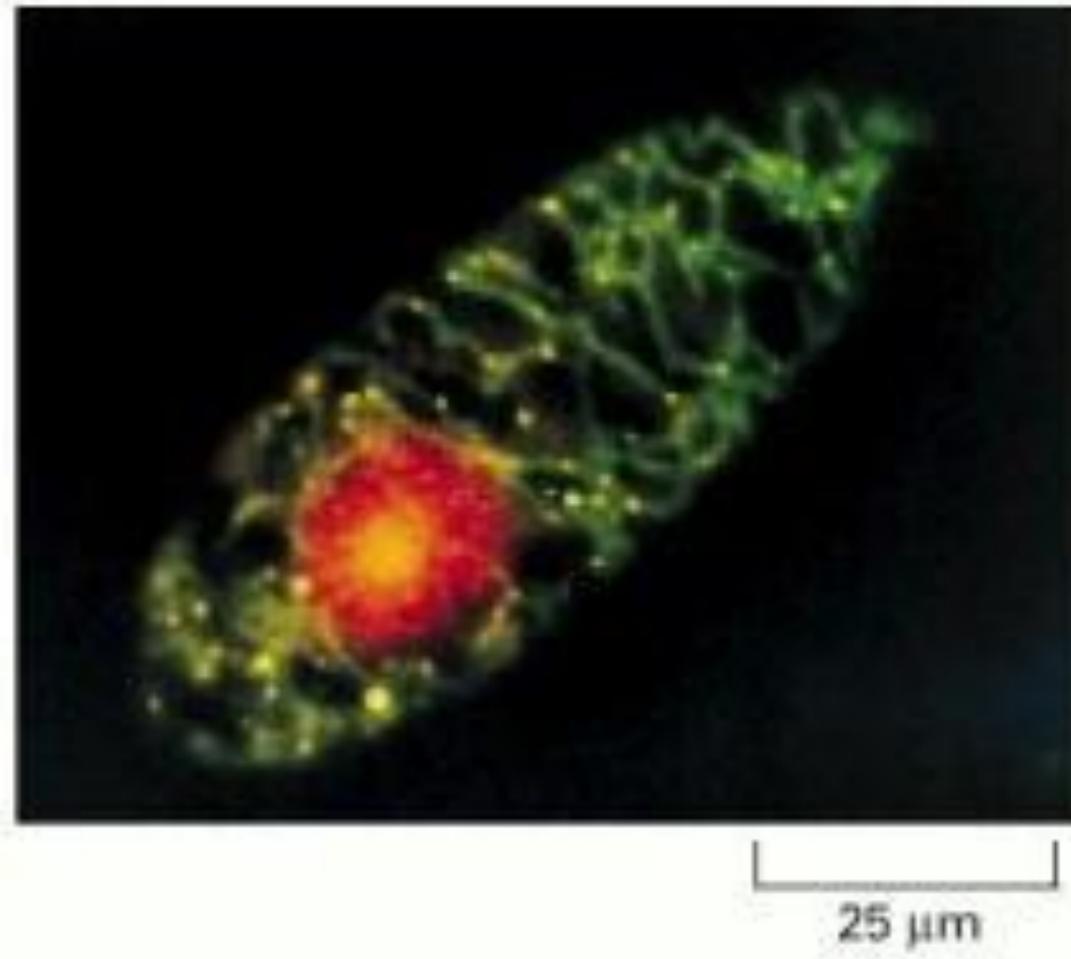


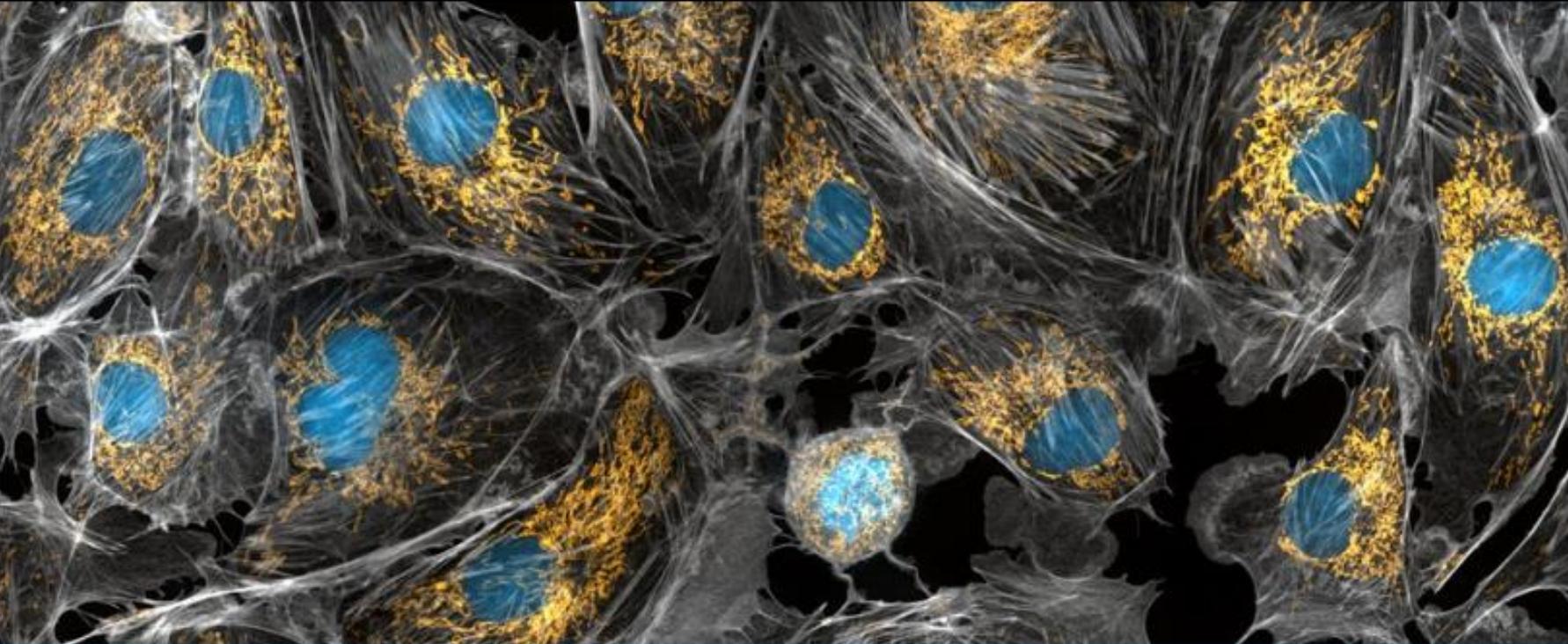
Figure 3. Mitochondrial origin in a prokaryotic host. (a-h) Illustrations for various stages depicting the transition of a H₂-dependent archaeal host (in red) and a facultatively anaerobic α-proteobacterium (in blue) to an eukaryote. See also [25,34,35] regarding this transition, and [116,117] regarding gene transfer from organelles to the nucleus.

Cite this article: Martin WF, Garg S, Zimorski V. 2015 Endosymbiotic theories for eukaryote origin. *Phil. Trans. R. Soc. B* **370**: 20140330.
<http://dx.doi.org/10.1098/rstb.2014.0330>



DNA mitocondrial e nuclear marcado com uma sonda fluorescente

This micrograph shows the distribution of the nuclear genome (*red*) and the multiple small mitochondrial genomes (*bright yellow* spots) in a *Euglena gracilis* cell. The DNA is stained with ethidium bromide, a fluorescent dye that emits red light. In addition, the mitochondrial matrix space is stained with a green fluorescent dye that reveals the mitochondria as a branched network extending throughout the cytosol. The superposition of the *green* matrix and the *red* DNA gives the mitochondrial genomes their *yellow* color.



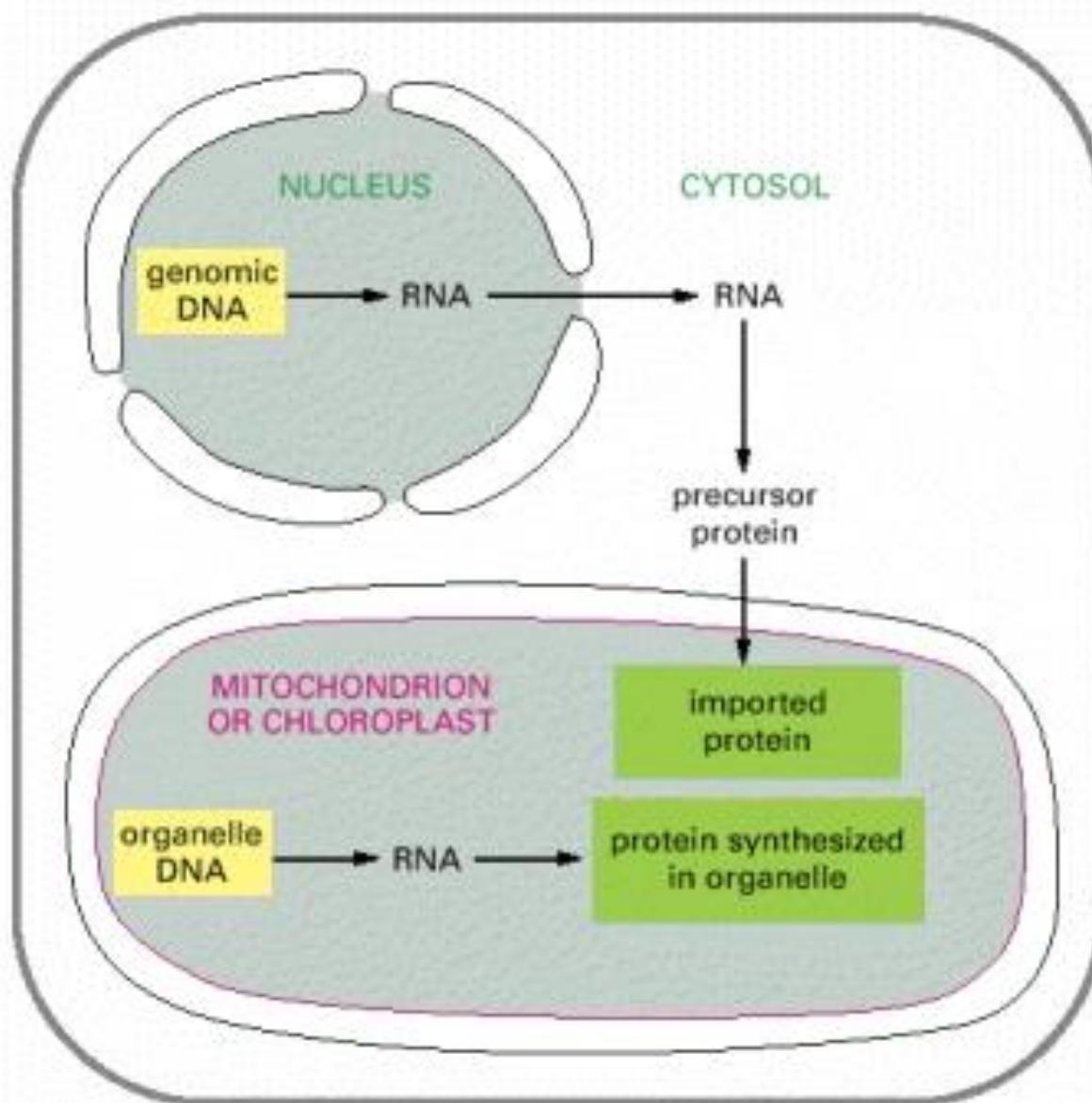
(Torsten Wittmann/University of California/NIGMS/CC BY 3.0)

HEALTH

Radical Findings Show Mitochondrial DNA Can Be Inherited From Dads

PETER DOCKRILL 27 NOV 2018

Not all DNA is the same, and science has long held that not all kinds of DNA are passed down from both your mother and your father. But it looks like the time has come to rewrite the textbooks.



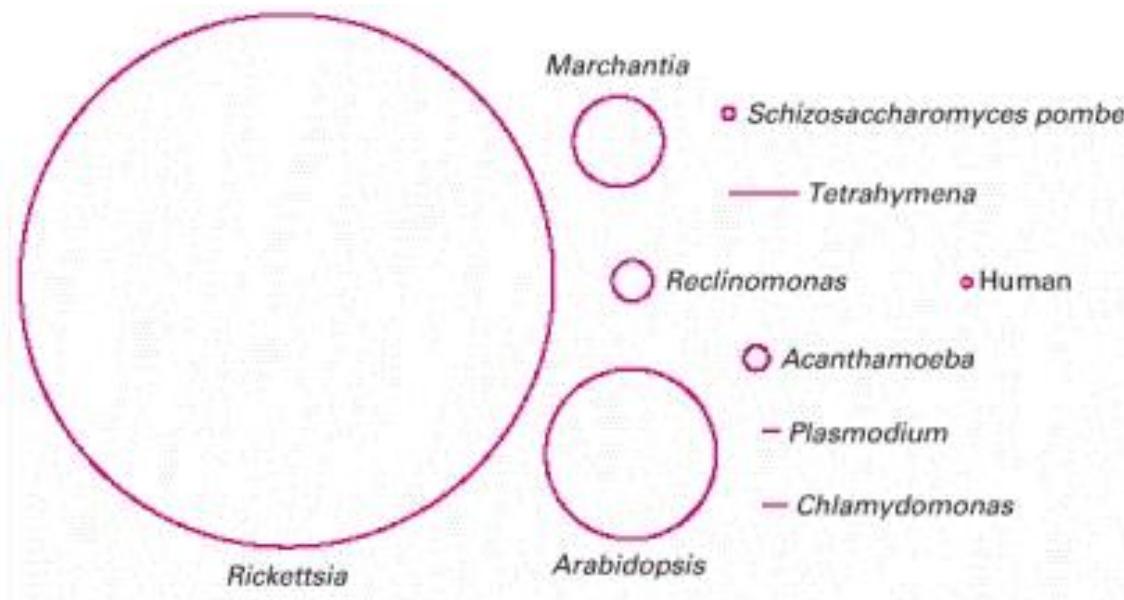
Produção de proteínas mitocondriais e de cloroplastos através de 2 sistemas genéticos

A maioria das proteínas destes organelos é codificada no **núcleo** e tem de ser importada a partir do **citosol**.

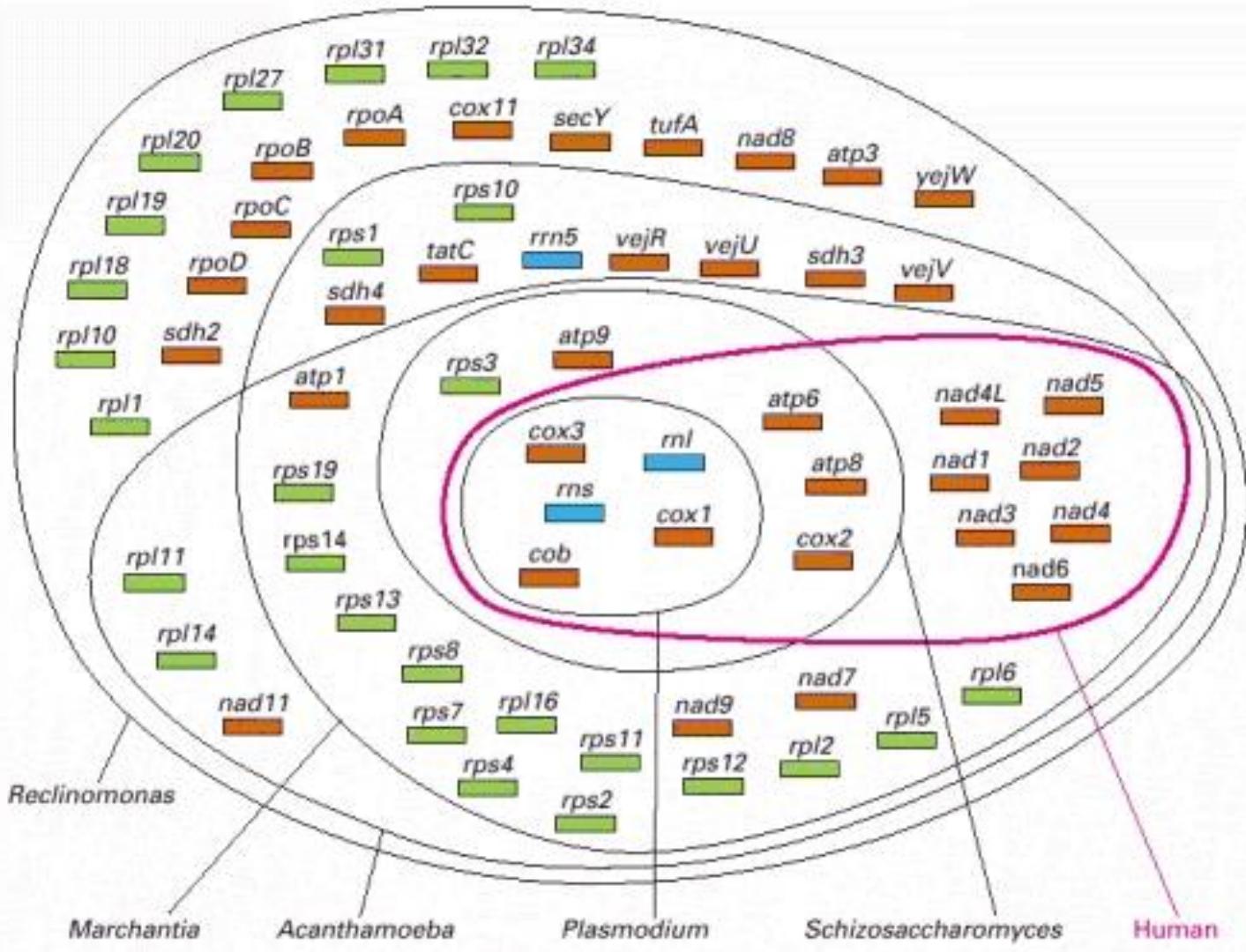
Table 14-2 Relative Amounts of Organelle DNA in Some Cells and Tissues

ORGANISM	TISSUE OR CELL TYPE	DNA MOLECULES PER ORGANELLE	ORGANELLES PER CELL	ORGANELLE DNA AS PERCENTAGE OF TOTAL CELLULAR DNA
MITOCHONDRIAL DNA				
Rat	liver	5–10	1000	1
Yeast*	vegetative	2–50	1–50	15
Frog	egg	5–10	10^7	99
CHLOROPLAST DNA				
<i>Chlamydomonas</i>	vegetative	80	1	7
Maize	leaves	20–40	20–40	15

* The large variation in the number and size of mitochondria per cell in yeasts is due to mitochondrial fusion and fission.

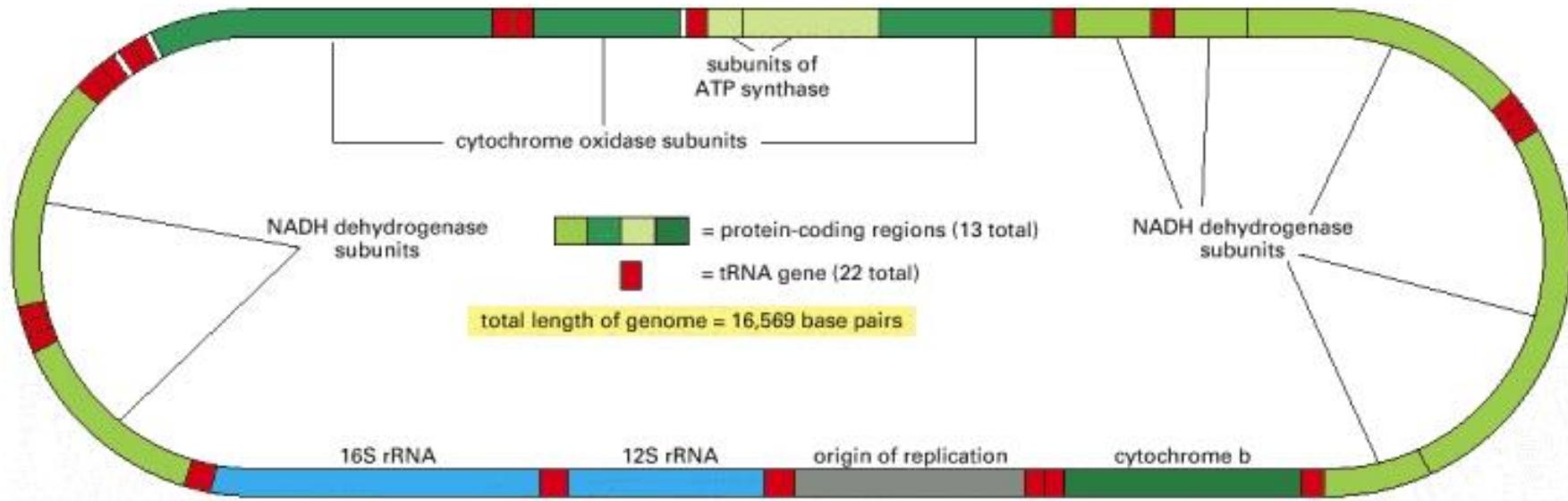


O **tamanho do genoma mitocondrial** não se correlaciona bem com o número de proteínas codificadas nele: enquanto o mtDNA humano codifica 13 proteínas, o mtDNA de *Arabidopsis*, que é 22 vezes maior, codifica apenas 32 proteínas, ou seja, apenas cerca de 2,5 o nº de proteínas codificado pelo mtDNA humano. O DNA adicional que é encontrado em *Arabidopsis*, *Marchantia* e outras mitocôndrias de plantas podem ser “junk DNA”. O DNA mitocondrial do protozoário *Reclinomonas americana* tem 97 genes, mais do que a mitocôndria de qualquer outro organismo analisado até agora.



Comparação dos genomas mitocondriais

Genomas mitocondriais menos complexos codificam subconjuntos de proteínas e rRNAs que são codificados pelos genomas mitocondriais maiores. Os cinco genes presentes em todos os genomas mitocondriais conhecidos codificam rRNAs (*rns* e *rnl*), citocromo b (*cob*), e duas subunidades da citocromo-oxidase (*cox1* e *cox3*).



Organização do genoma mitocondrial humano

O genoma contém 2 genes de rRNA, 22 genes de tRNA, e 13 sequências que codificam para proteínas

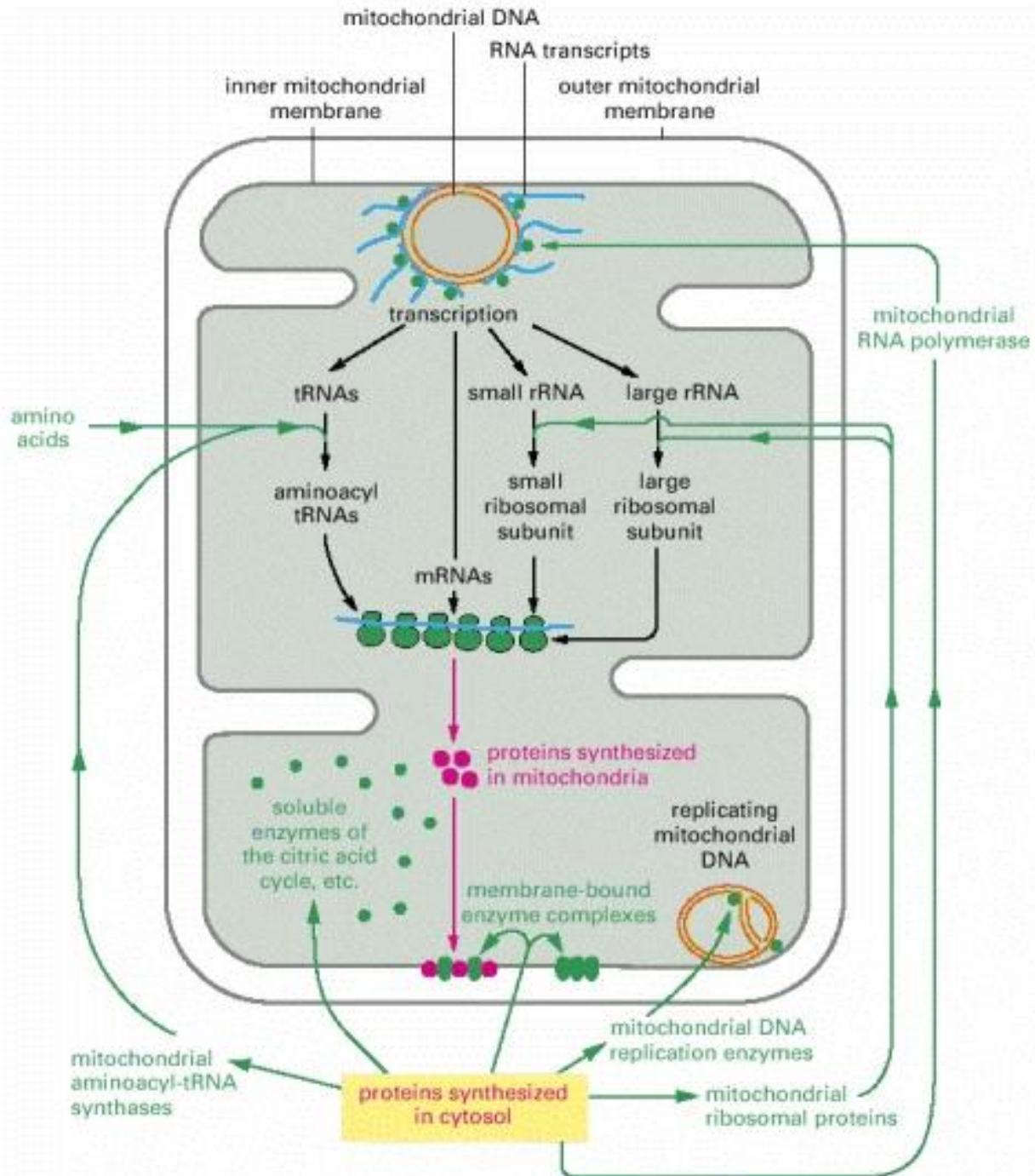
Table 14-3 Some Differences Between the “Universal” Code and Mitochondrial Genetic Codes*

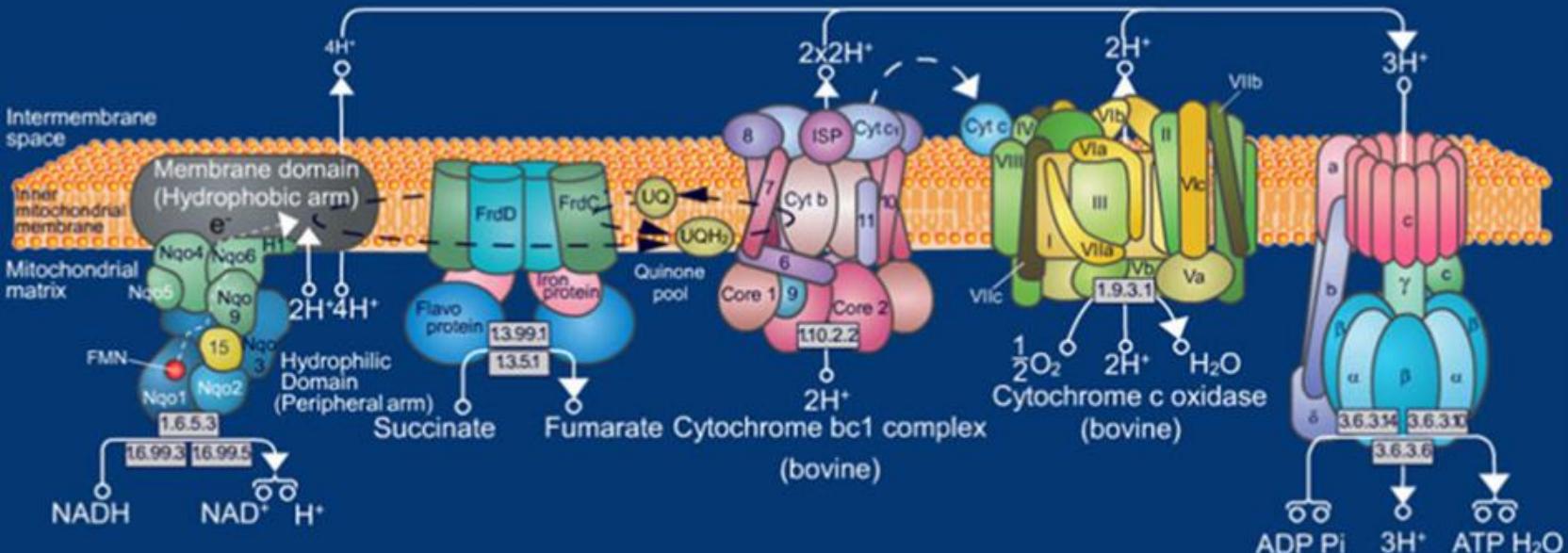
CODON	“UNIVERSAL” CODE	MITOCHONDRIAL CODES			
		MAMMALS	INVERTEBRATES	YEASTS	PLANTS
UGA	STOP	Trp	Trp	Trp	STOP
AUA	Ile	Met	Met	Met	Ile
CUA	Leu	Leu	Leu	Thr	Leu
AGA	Arg	STOP	Ser	Arg	Arg
AGG					

*Italics and color shading indicate that the code differs from the “Universal” code.

As origens do RNA e das proteínas mitocondriais

As proteínas codificadas no núcleo e importadas do citosol têm um papel importante na criação do sistema genético da mitocôndria, além de contribuirem para a maior parte das proteínas do organelo. Não está indicado no diagrama as proteínas adicionais codificadas pelo núcleo que regulam a expressão de genes mitocondriais individuais a nível pós-transcricional. A mitocôndria por si só contribui apenas com mRNA, rRNA e tRNA para o seu sistema genético.





	CI	CII	CIII	CV	CV
Total # of subunits	46	4	11	13	17
Mitochondrial Encoded	7	0	1	3	2
Nuclear	39	4	10	10	15

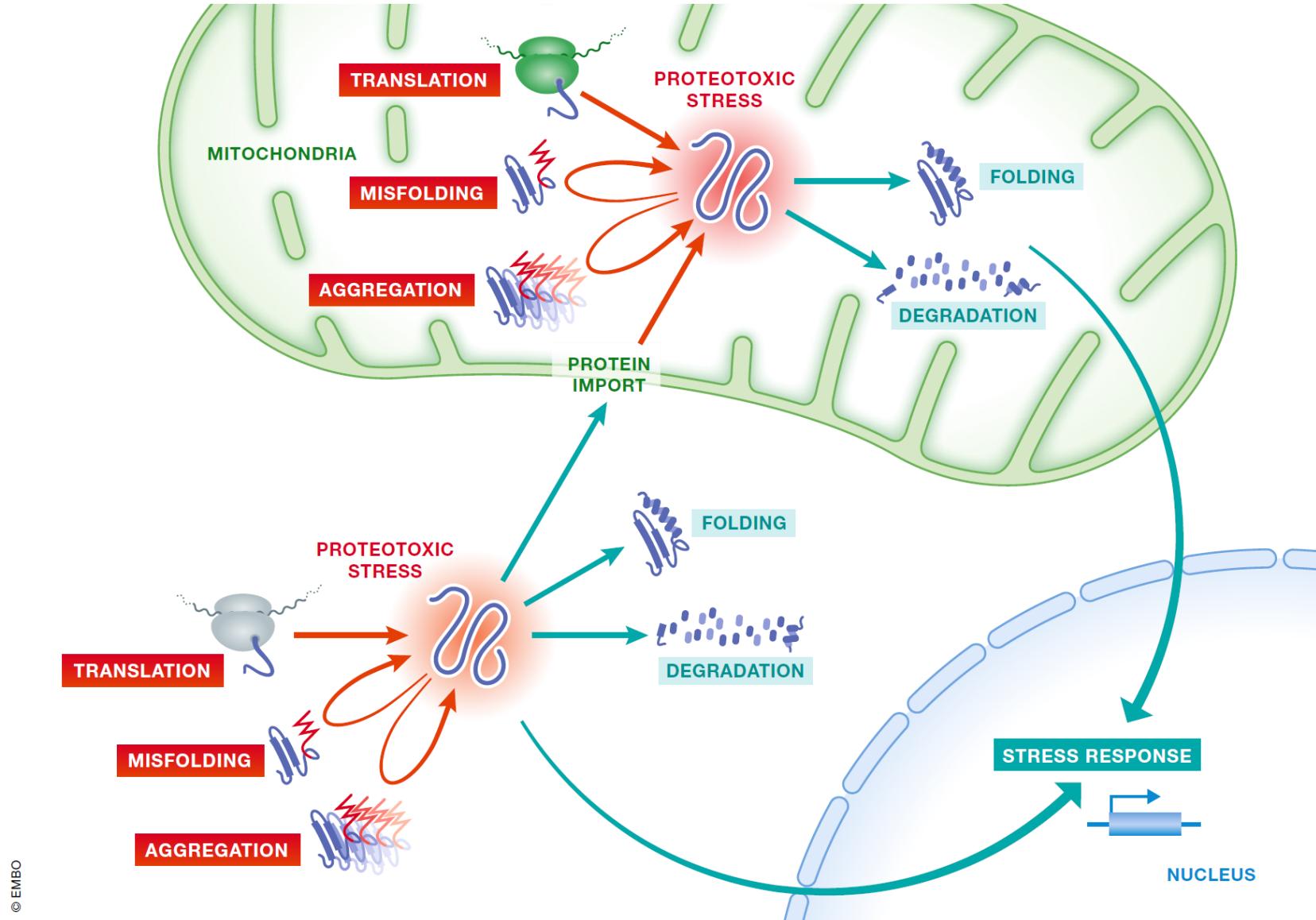
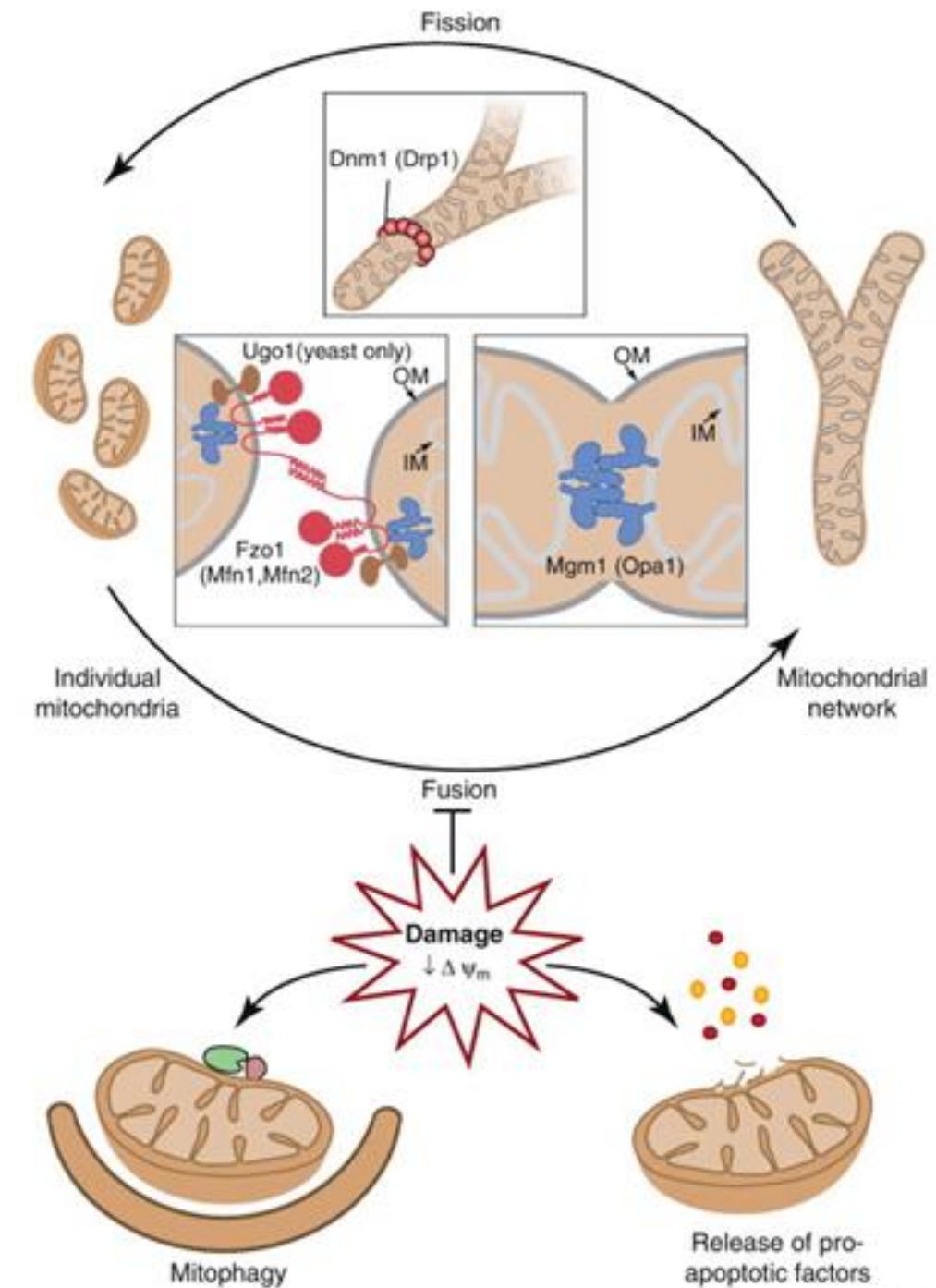
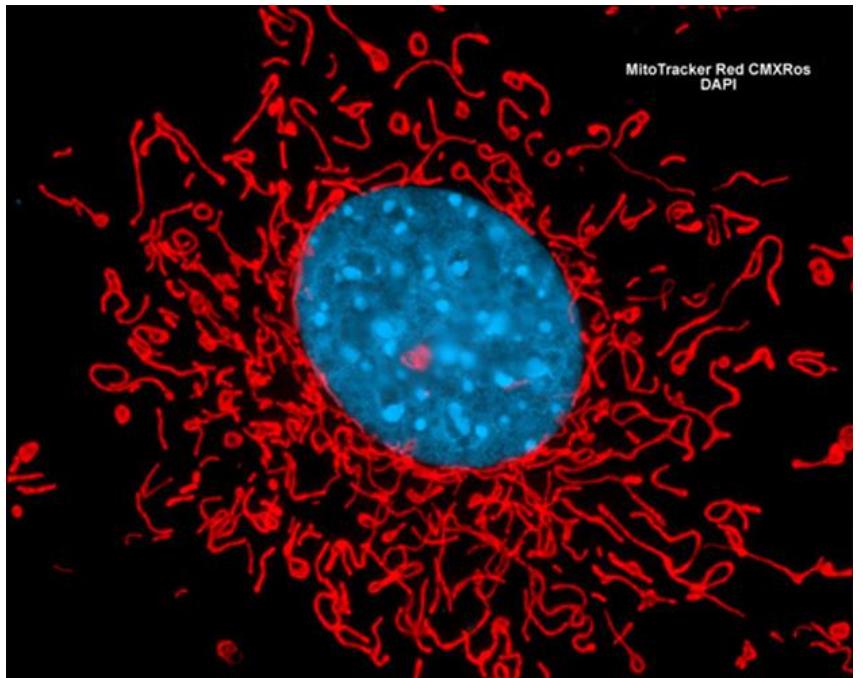
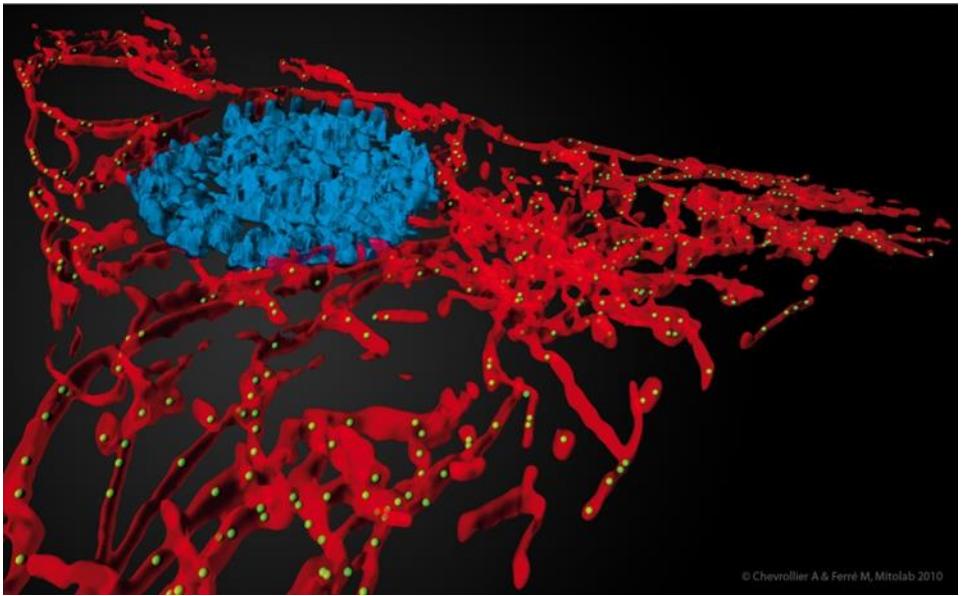


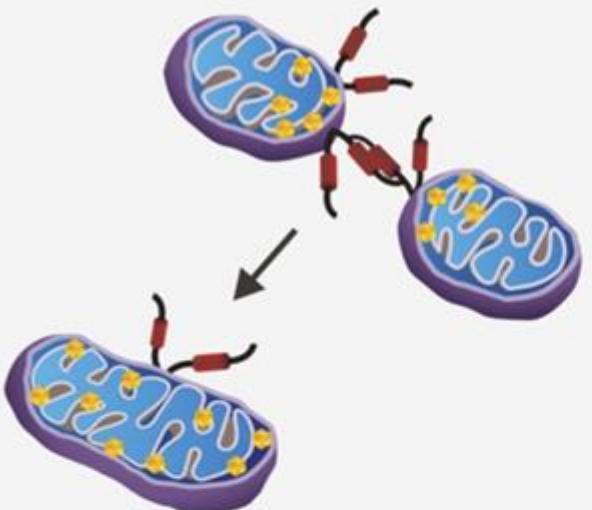
Figure 2. Flow through the proteostasis system.

The net in- and outflow of polypeptides in non-native conformation determines the state of the proteostasis system. Newly synthesized proteins exiting the ribosome as well as misfolded proteins constitute the major inflow, while organellar import of newly synthesized peptides (e.g., into the ER and mitochondria) and protein folding as well as proteolytic degradation represent the main outflow from the cytosolic proteostasis system.

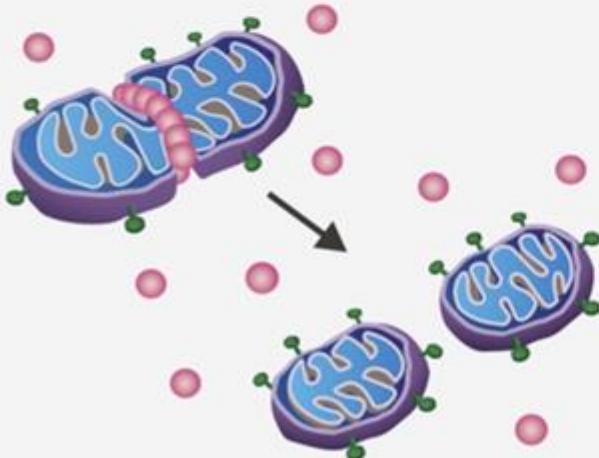
Redes mitocondriais: equilíbrio entre fissão e fusão



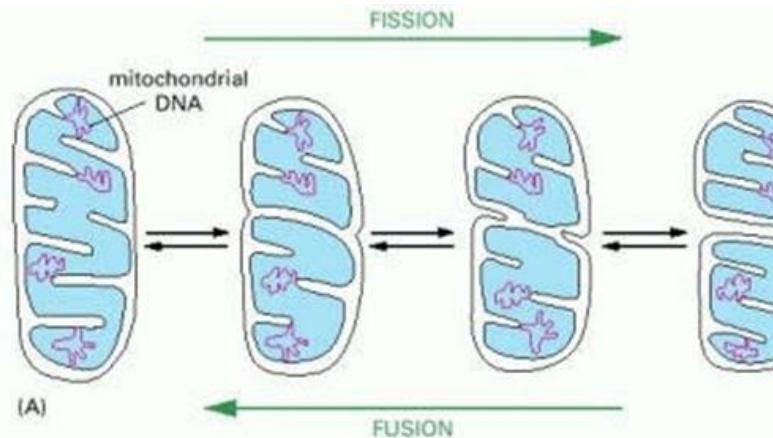
Ciclos de fissão e fusão mitocondrial



fusion



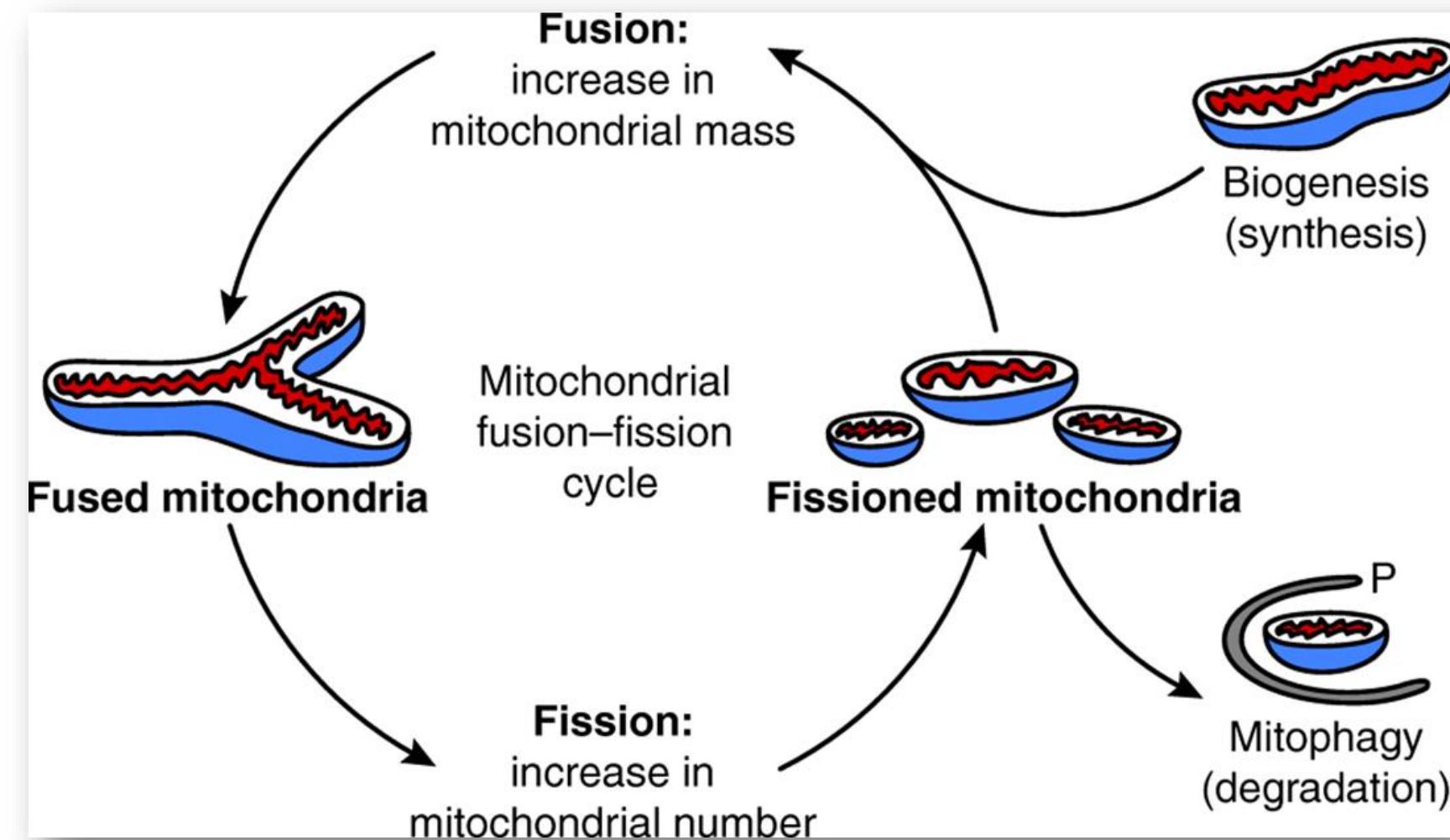
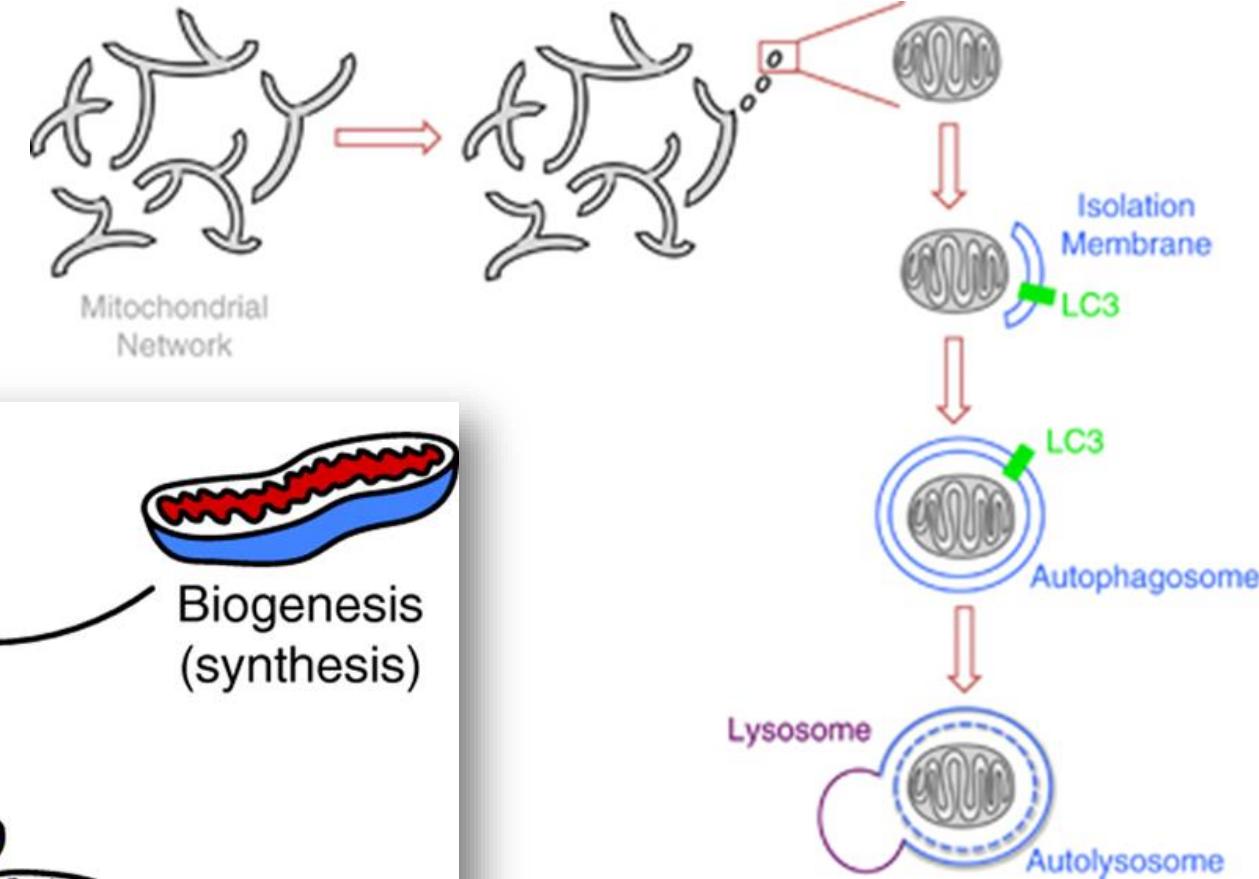
fission



Os processos de **fusão** e **fissão** envolvem ambas as membranas mitocondriais, a **externa** e a **interna**. Durante a fusão e a fissão, a compartmentalização quer da matriz como do espaço intermembranar são mantidos. A **maquinaria** envolvida na fusão membranar da membrana interna e externa pensa-se que seja diferente. Conceptualmente, o processo de fissão assemelha-se ao da **divisão celular** bacteriana. Esta via tem sido postulada a partir de imagens estáticas (TEM), tais como o mostrado em (B).

Ciclos de fissão e fusão e disfunção mitocondrial

Envolvimento da autofagia (mitofagia)



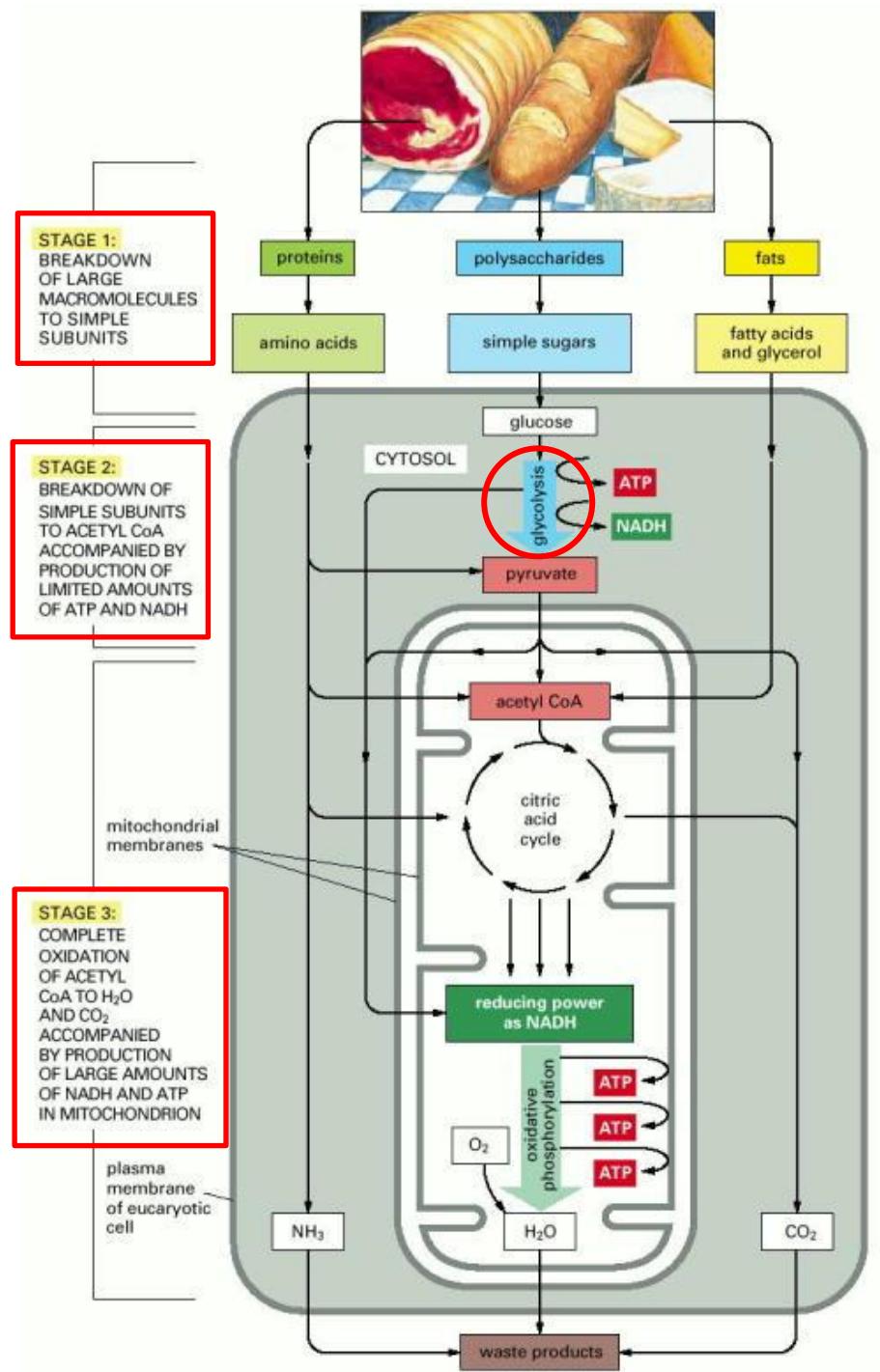
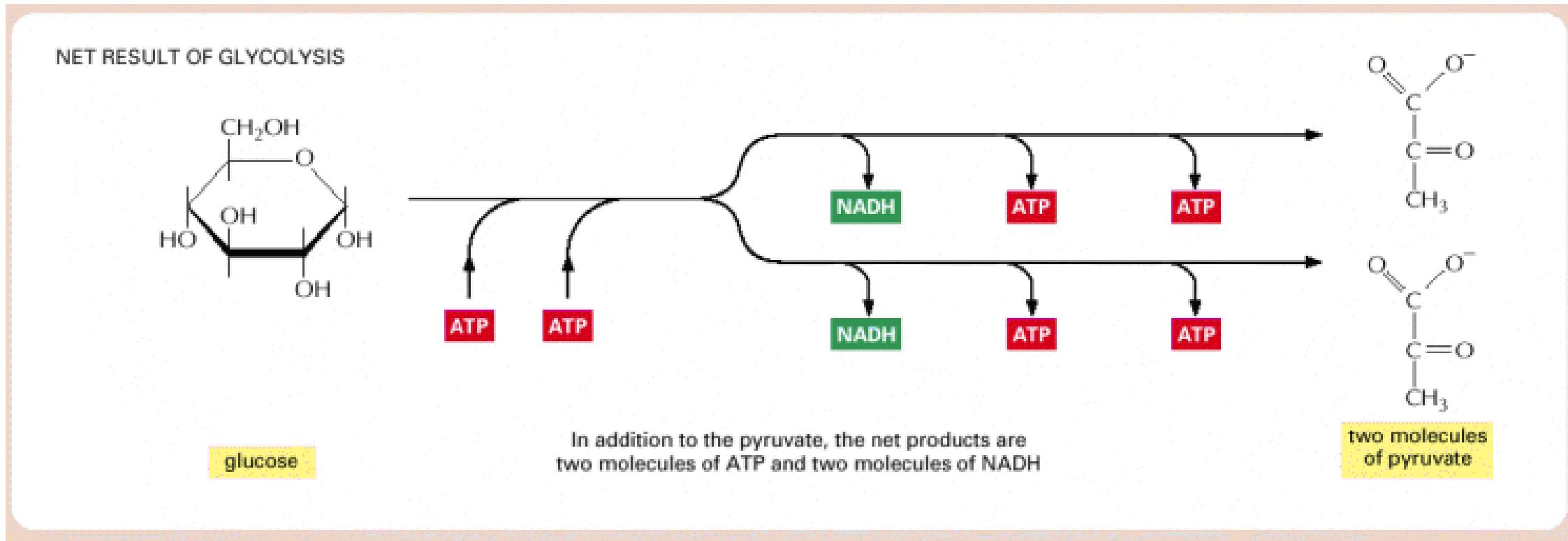


Diagrama simplificado das três etapas do metabolismo celular em células animais. Esta série de reacções produz ATP, que é então utilizado para desencadear reacções biossintéticas e outros processos celulares que requerem energia. A fase 1 ocorre fora das células. A fase 2 ocorre principalmente no citosol, excepto o passo final de conversão de piruvato em acetil-CoA, que ocorre nas mitocôndrias. A fase 3 ocorre nas mitocôndrias.

Glicólise: Resultado energético



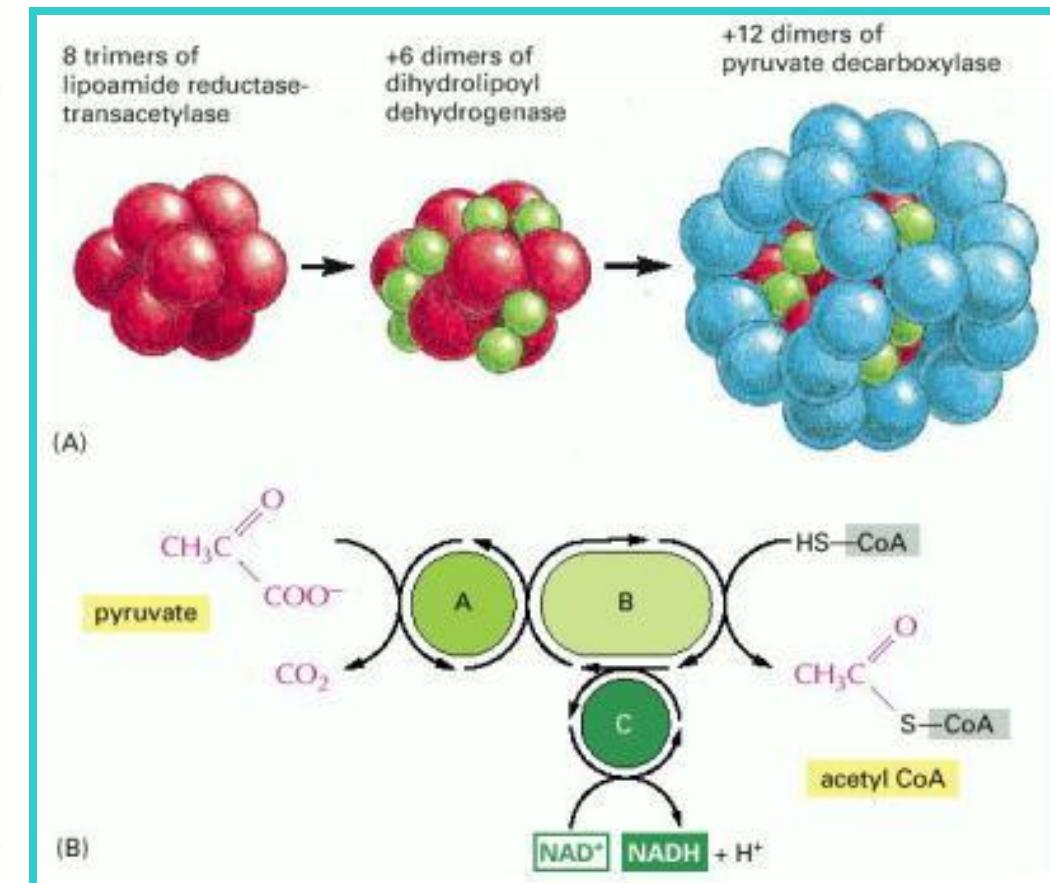
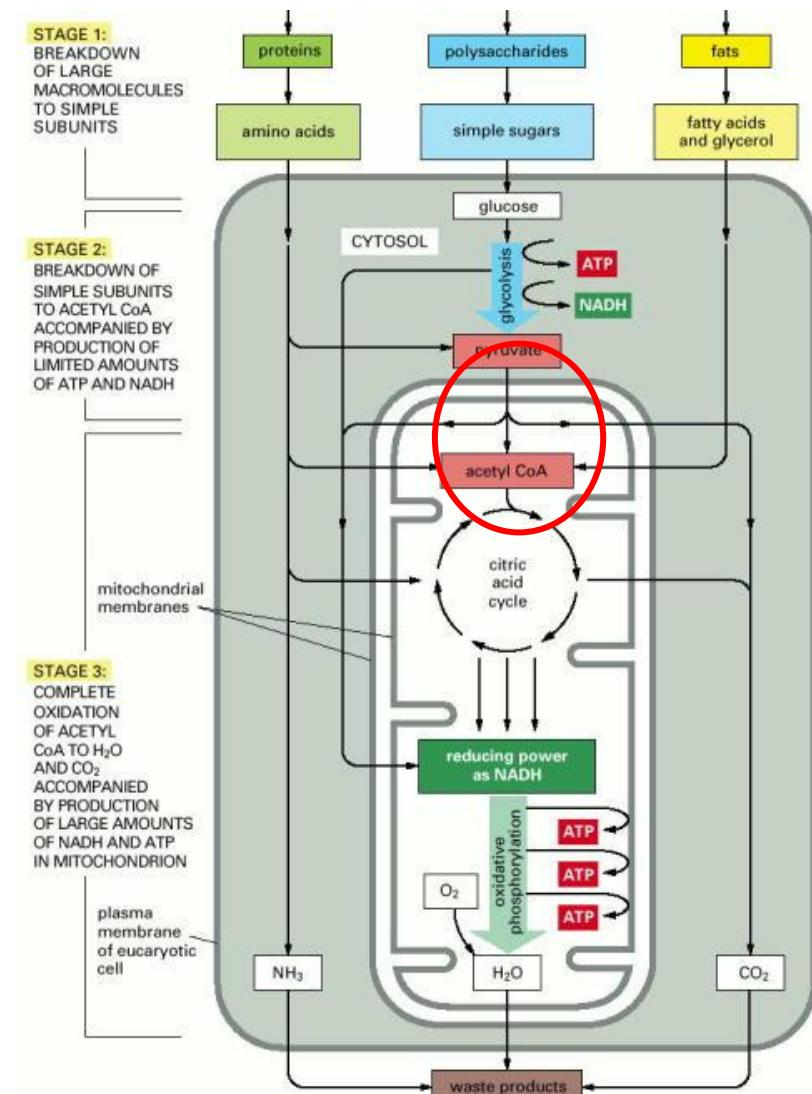
Glicólise:

Quebra de uma molécula de glucose, com produção final de 2 moléculas de piruvato, 2 moléculas de ATP e 2 moléculas de NADH

Os passos 6 e 7 não requerem O₂.

Em ambientes aeróbios, o **piruvato** formado na glicólise é rapidamente **descarboxilado** por um conjunto de 3 enzimas mitocondriais: **complexo piruvato desidrogenase**.

Desta reacção forma-se: CO₂, 1 NADH e acetil CoA



Glicólise
(catabolismo de açucares)

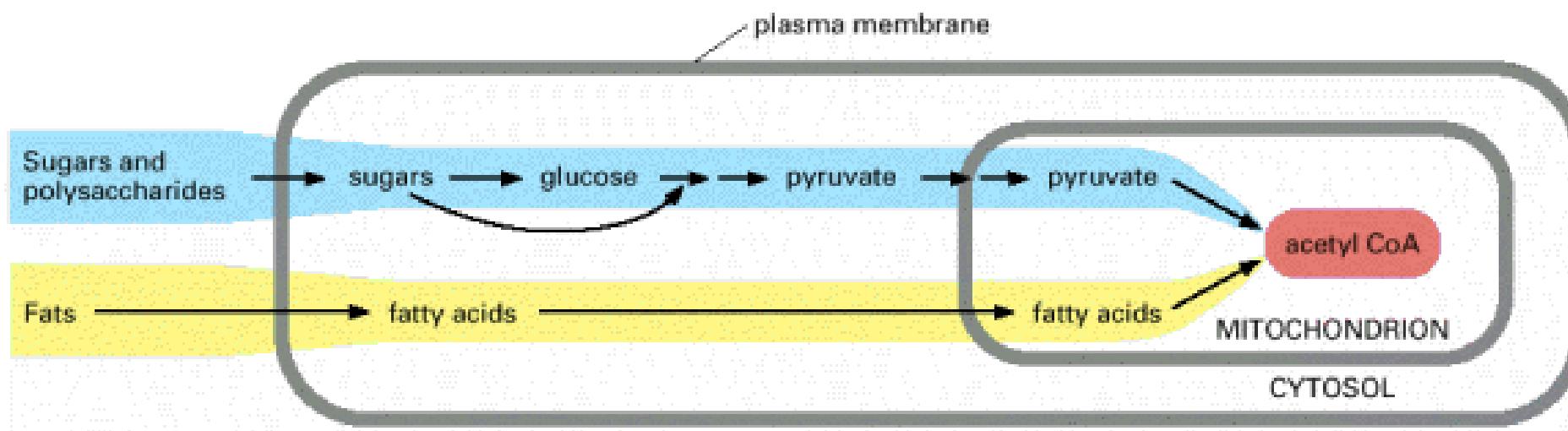
Catabolismo de ác. gordos

Energia sob forma de Acetyl CoA

Ciclo ácido cítrico*

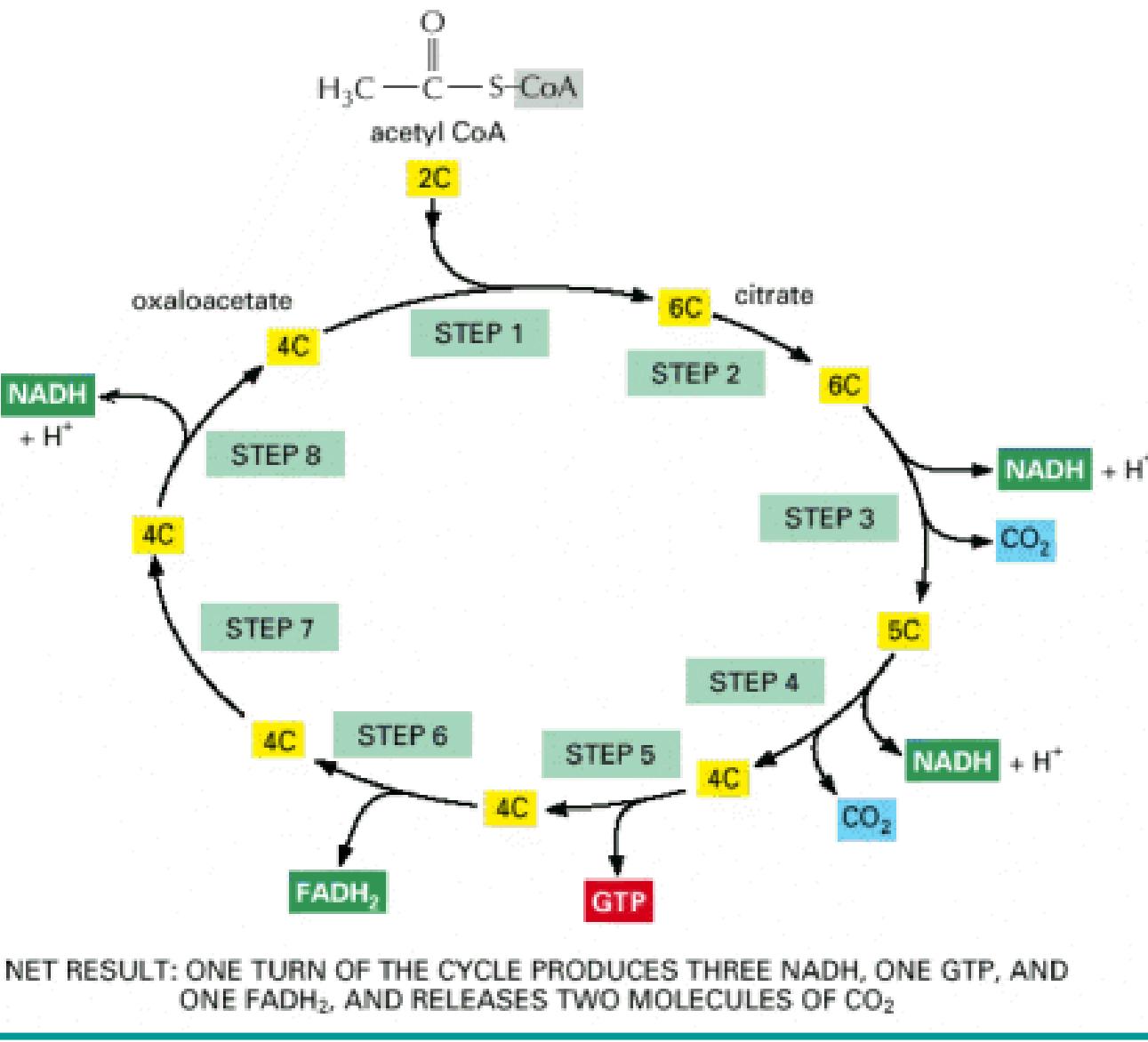
CO₂

H₂O



*Metabolismo energético principal dos organismos aeróbios – **Mitocôndria** (local da célula onde é produzida a maior parte do ATP)

Ciclo do ácido cítrico ou ciclo de Krebs



Simple overview of the citric acid cycle. The reaction of acetyl CoA with oxaloacetate starts the cycle by producing citrate (citric acid). In each turn of the cycle, two molecules of CO₂ are produced as waste products, plus three molecules of NADH, one molecule of GTP, and one molecule of FADH₂. The number of carbon atoms in each intermediate is shown in a yellow box.

The Nobel Prize in Physiology or Medicine 1953



Hans Adolf Krebs
Prize share: 1/2



Fritz Albert
Lipmann
Prize share: 1/2

The Nobel Prize in Physiology or Medicine 1953 was divided equally between Hans Adolf Krebs "*for his discovery of the citric acid cycle*" and Fritz Albert Lipmann "*for his discovery of co-enzyme A and its importance for intermediary metabolism*".

Nature rejects Krebs's paper, 1937

Telegraphic Address:
PHUSIS, LESQUARE, LONDON
Telephone Number:
WHITEHALL 8831.



Editorial and Publishing Offices:
MACMILLAN & CO., LTD.,
ST. MARTIN'S STREET,
LONDON, W.C.2.

RAG.AH/N.

14th June 1937.

The Editor of NATURE presents his compliments to
Mr. H. A. Krebs and regrets that as he has
already sufficient letters to fill the correspondence
columns of NATURE for seven or eight weeks, it is
undesirable to accept further letters at the present
time on account of the delay which must occur in their
publication.

If Mr. Krebs does not mind such delay,
the Editor is prepared to keep the letter until the
congestion is relieved in the hope of making use of it.

He returns it now, however, in case Mr. Krebs
prefers to submit it for early publication to another
periodical.

É no último passo na degradação de uma “molécula energética” (açúcar ou gordura) que a maior parte da energia química é libertada.

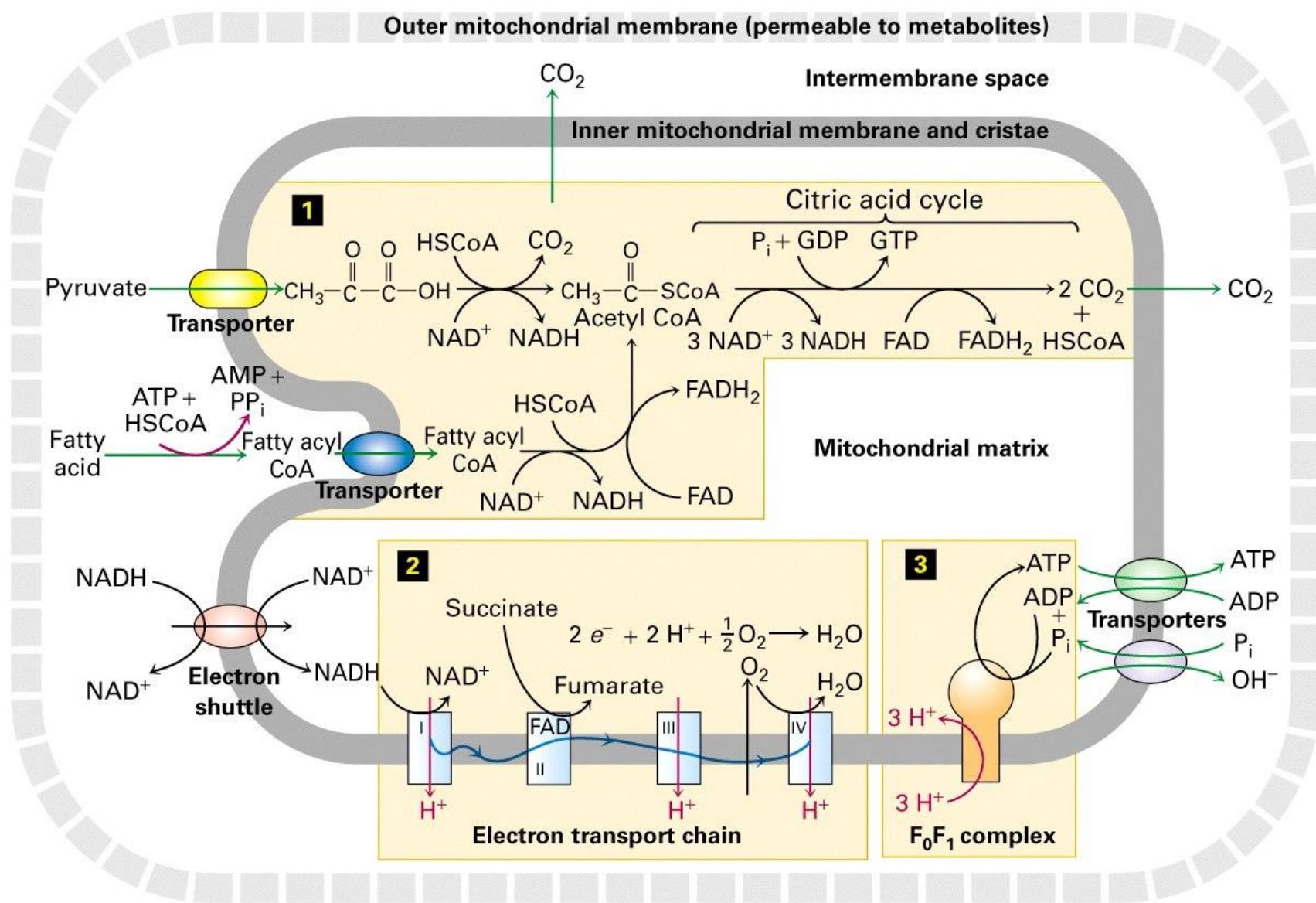
No processo final, os transportadores de electrões **NADH** e **FADH₂** transferem os electrões que ganharam na oxidação de outras moléculas para a **cadeia transportadora de electrões**.

À medida que os **electrões** passam ao longo de uma cadeia de aceitadores de electrões e de moléculas dadoras, vão passando para níveis energéticos cada vez menores.

Neste processo gera-se um gradiente de **H⁺** - fonte de energia para outras reacções, tais como a formação de **ATP** pela fosforilação do **ADP**.

No final da série de transferência de electrões, os electrões passam para moléculas de **O₂** (gás) que difundem para a mitocôndria, combinando-se simultaneamente com **H⁺** e gerando moléculas de **H₂O**.

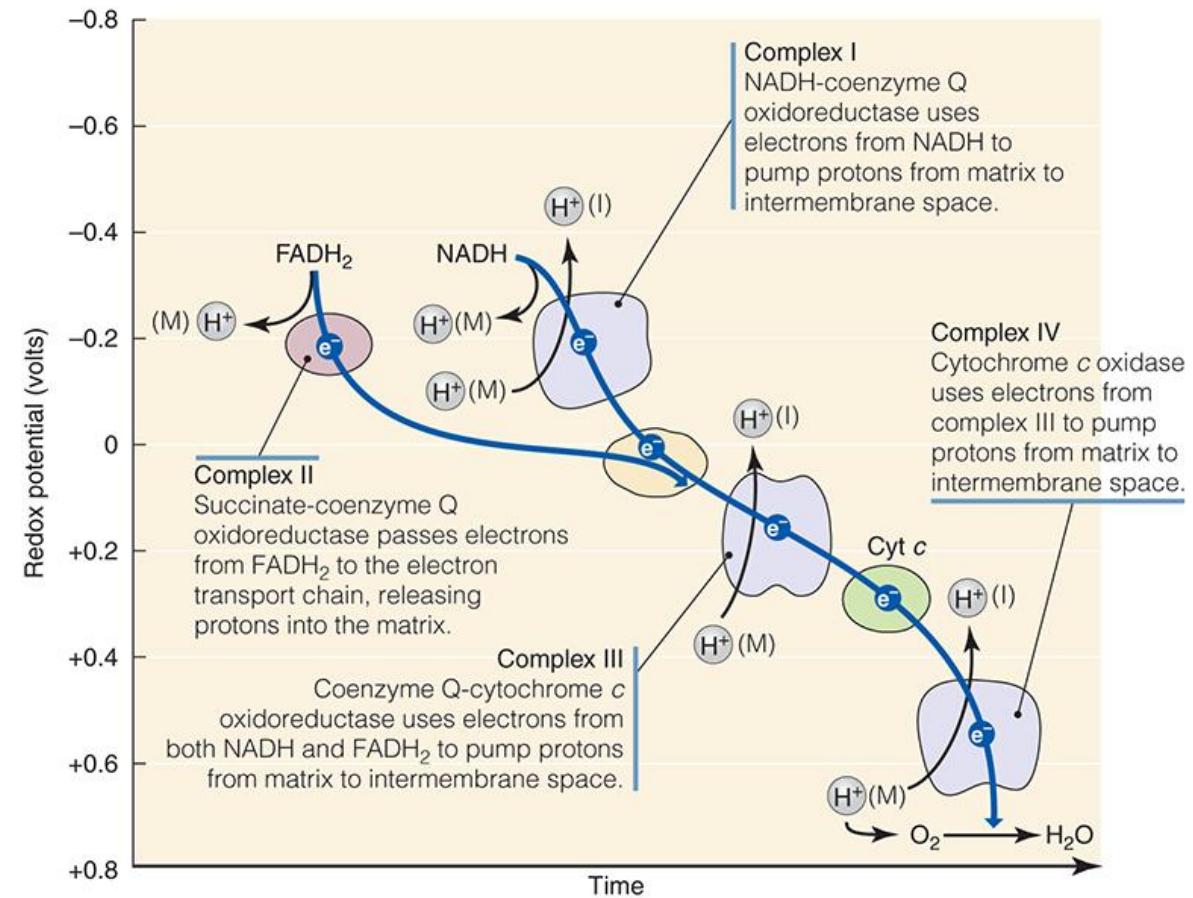
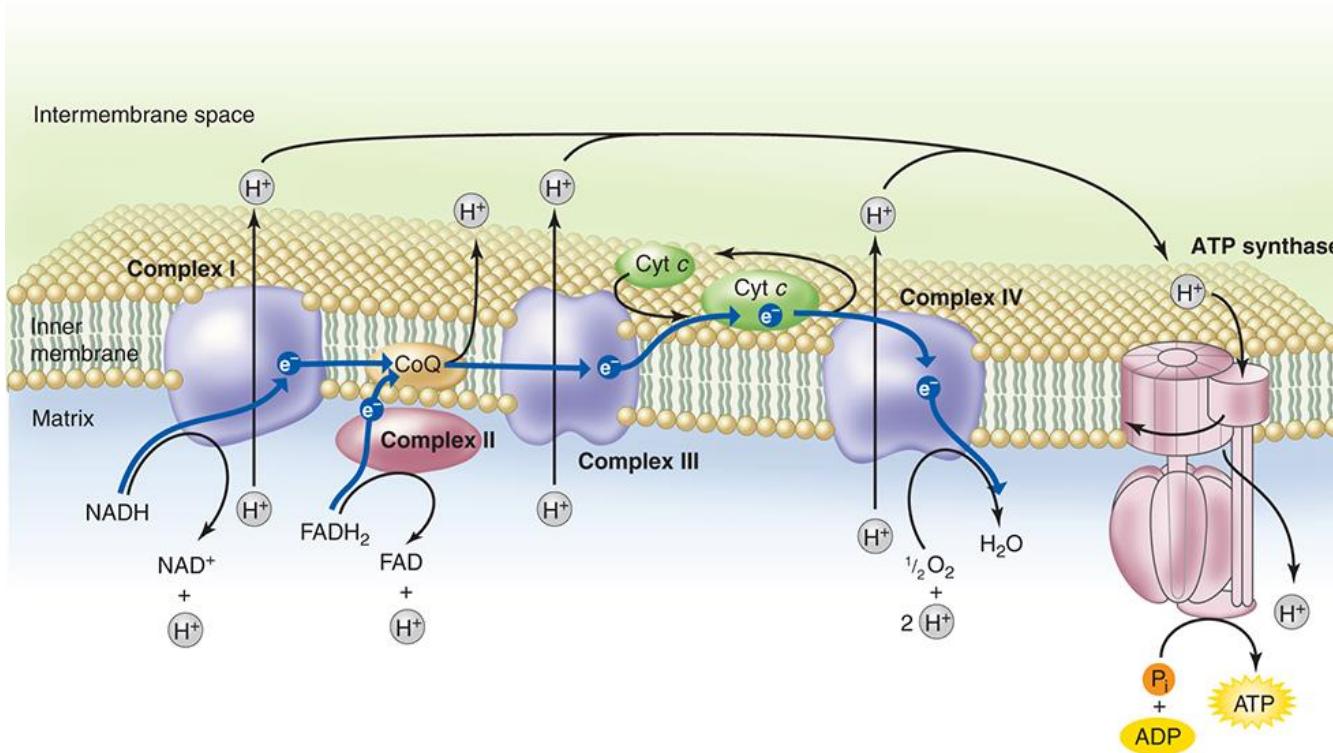
Os electrões atingem o nível de energia mais baixo, e consequentemente toda a energia disponível foi extraída pela oxidação das “moléculas energéticas” – **Fosforilação oxidativa**.



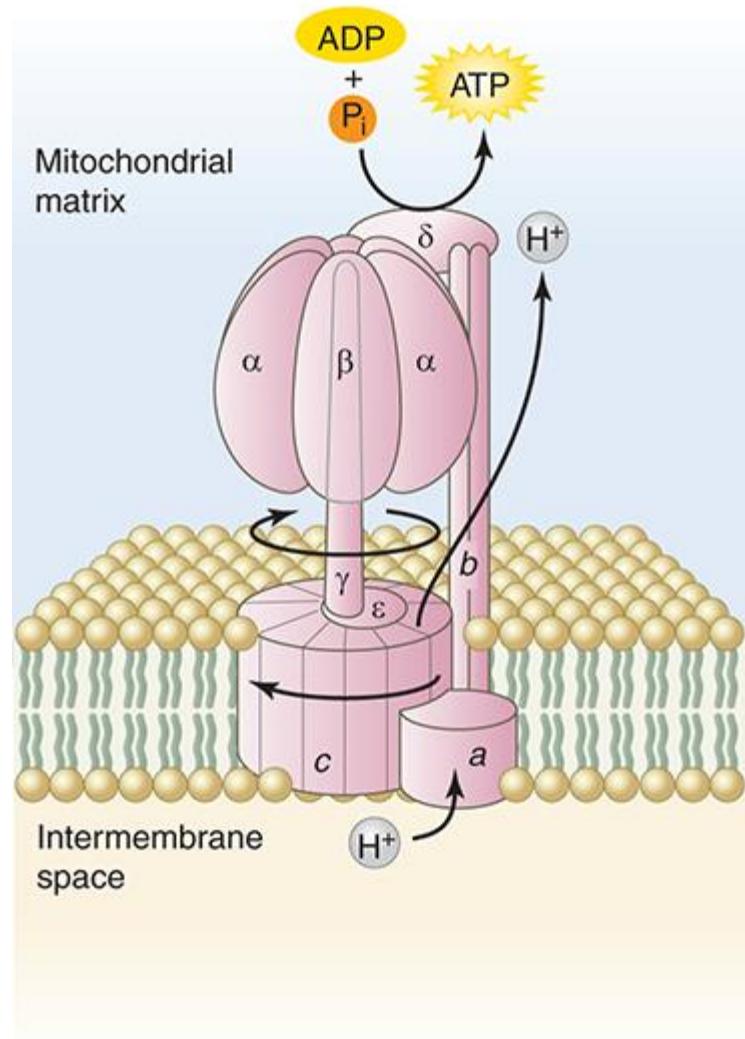
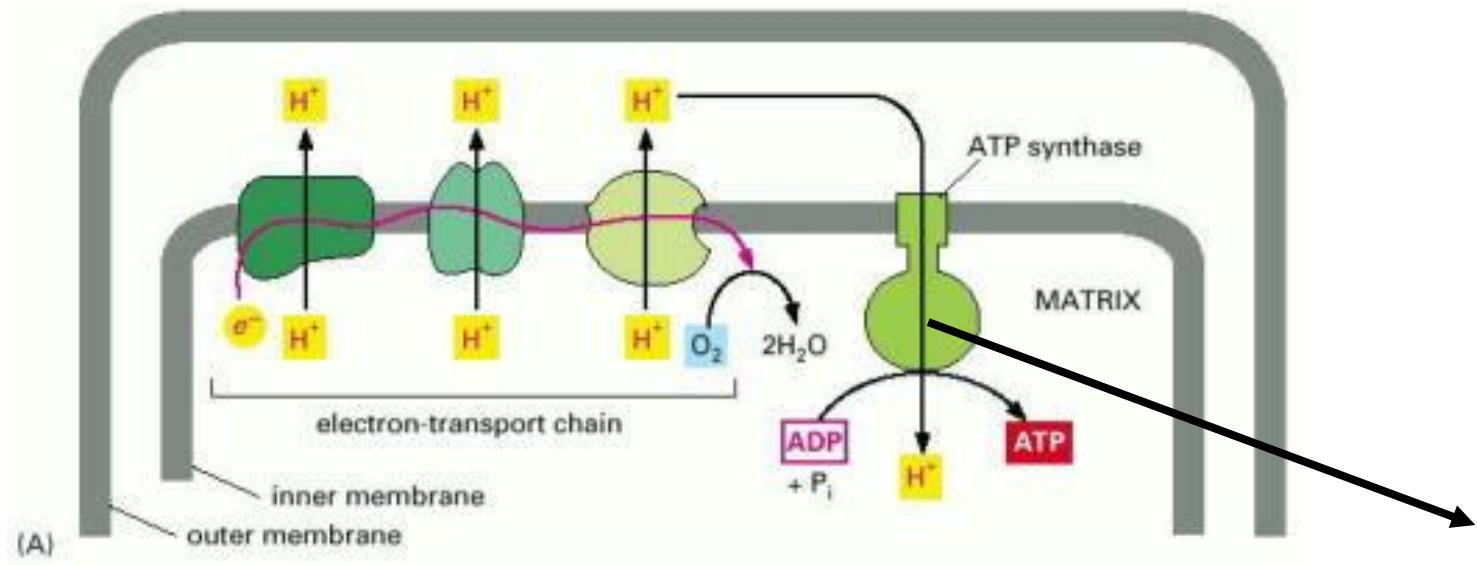
1 Pyruvate dehydrogenase, citric acid cycle, and fatty acid metabolism

2 Electron transport from NADH and FADH₂ to oxygen; generation of proton-motive force

3 ATP synthesis by F₀F₁ using proton-motive force

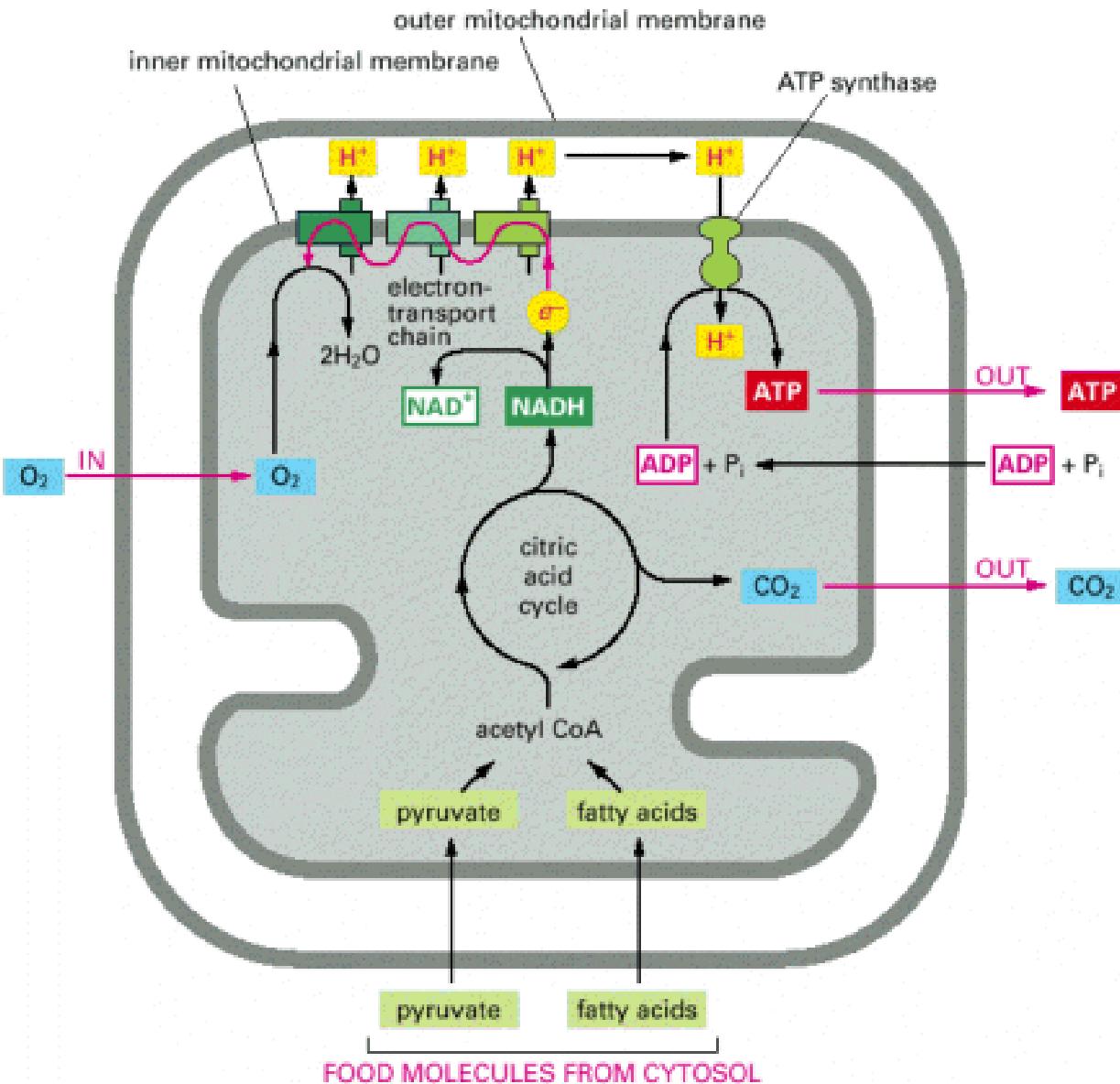


The redox potential of reactants indicates the energy level of the electrons moving through the mitochondrial electron transport chain



Mecanismo geral da fosforilação oxidativa. (A) À medida que os electrões de alta energia passam ao longo da cadeia de transporte de electrões, uma parte da energia libertada é utilizada para accionar os três complexos de enzimas respiratórias que bombeiam H^+ para fora da matriz. O gradiente electroquímico de protões resultante através da membrana interna acciona a entrada de H^+ de volta através da ATP sintase, um complexo proteico transmembranar que utiliza a energia do fluxo de H^+ para sintetizar ATP a partir de ADP e Pi na matriz.

Resumo do metabolismo e geração de energia na mitocôndria



A summary of energy-generating metabolism in mitochondria. Pyruvate and fatty acids enter the mitochondrion (bottom) and are broken down to acetyl CoA. The acetyl CoA is then metabolized by the citric acid cycle, which reduces NAD⁺ to NADH (and FAD to FADH₂, not shown). In the process of oxidative phosphorylation, high-energy electrons from NADH (and FADH₂) are then passed along the electron-transport chain in the inner membrane to oxygen (O₂). This electron transport generates a proton gradient across the inner membrane, which is used to drive the production of ATP by ATP synthase. The NADH generated by glycolysis in the cytosol also passes electrons to the respiratory chain (not shown). Since NADH cannot pass across the inner mitochondrial membrane, the electron transfer from cytosolic NADH must be accomplished indirectly by means of one of several "shuttle" systems that transport another reduced compound into the mitochondrion; after being oxidized, this compound is returned to the cytosol, where it is reduced by NADH again.

TABLE 8-1 Net Result of the Glycolytic Pathway and the Citric Acid Cycle

Reaction	CO ₂ Molecules Produced	NAD ⁺ Molecules Reduced to NADH	FAD Molecules Reduced to FADH ₂
1 glucose molecule to 2 pyruvate molecules	0	2	0
2 pyruvates to 2 acetyl CoA molecules	2	2	0
2 acetyl CoA to 4 CO ₂ molecules	4	6	2
Total	6	10	2

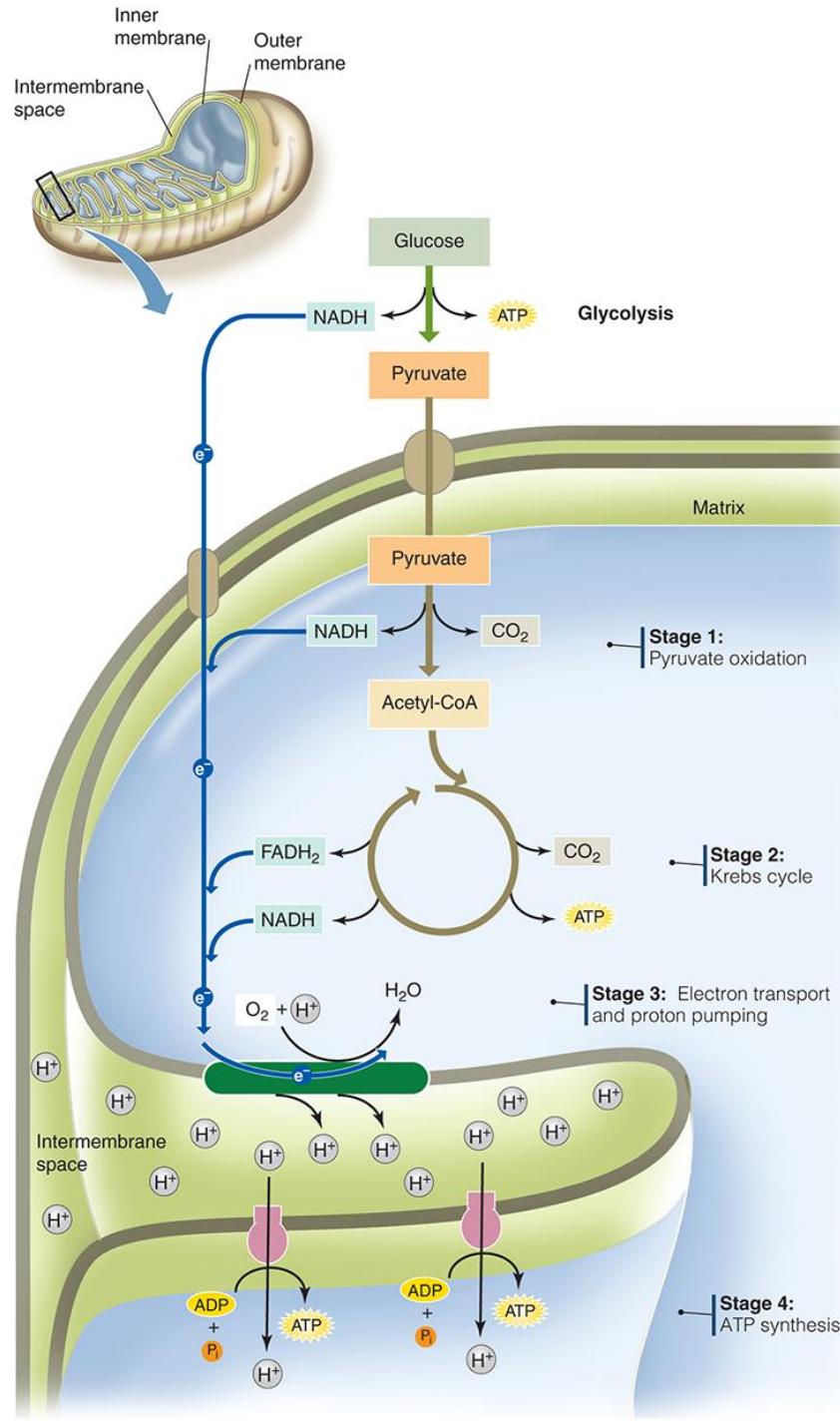
1 NADH → 3 ATP*
1 FADH₂ → 2 ATP
1 GTP → 1 ATP

2 ATP (Glicólise)
2 GTP (Ciclo Krebs)
10 NADH
2 FADH₂

TOTAL:

38 (36*) ATP

* Os 2 NADH produzidos na glicólise podem gerar apenas 2 ATP cada devido ao transporte do citosol para a mitocôndria



An overview of oxidative respiration



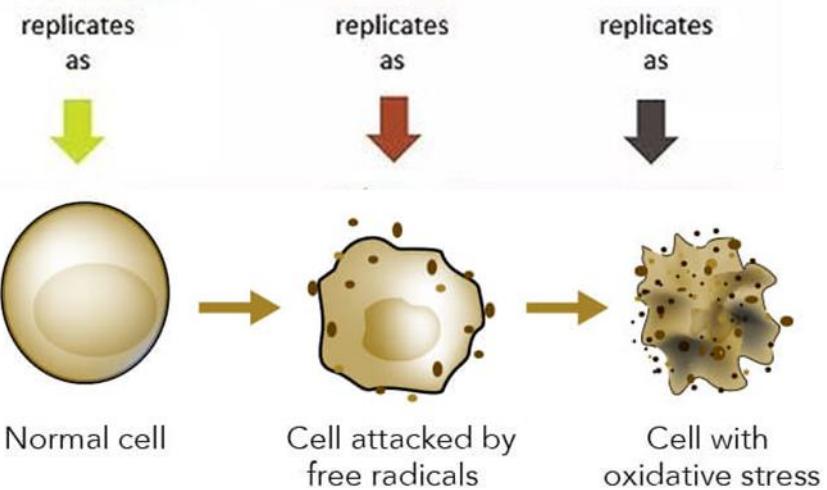
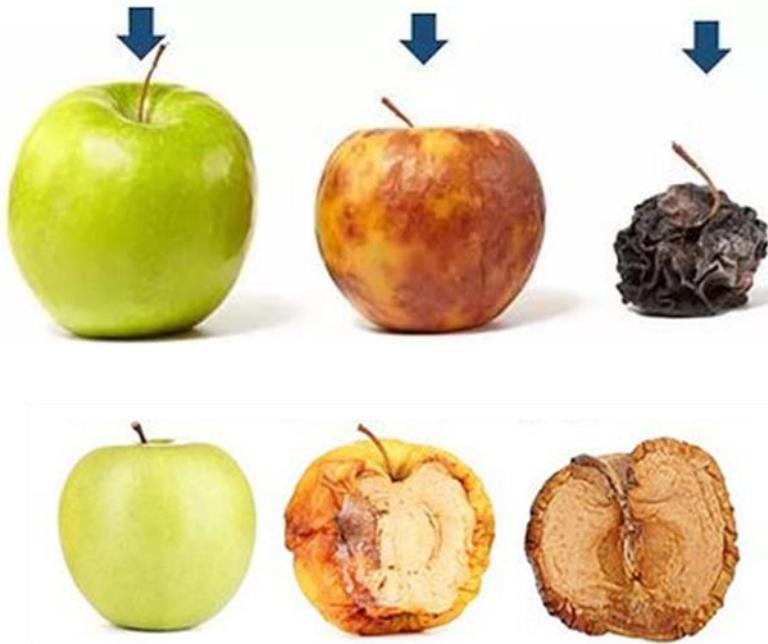
Examples of oxidation

Oxidative stress

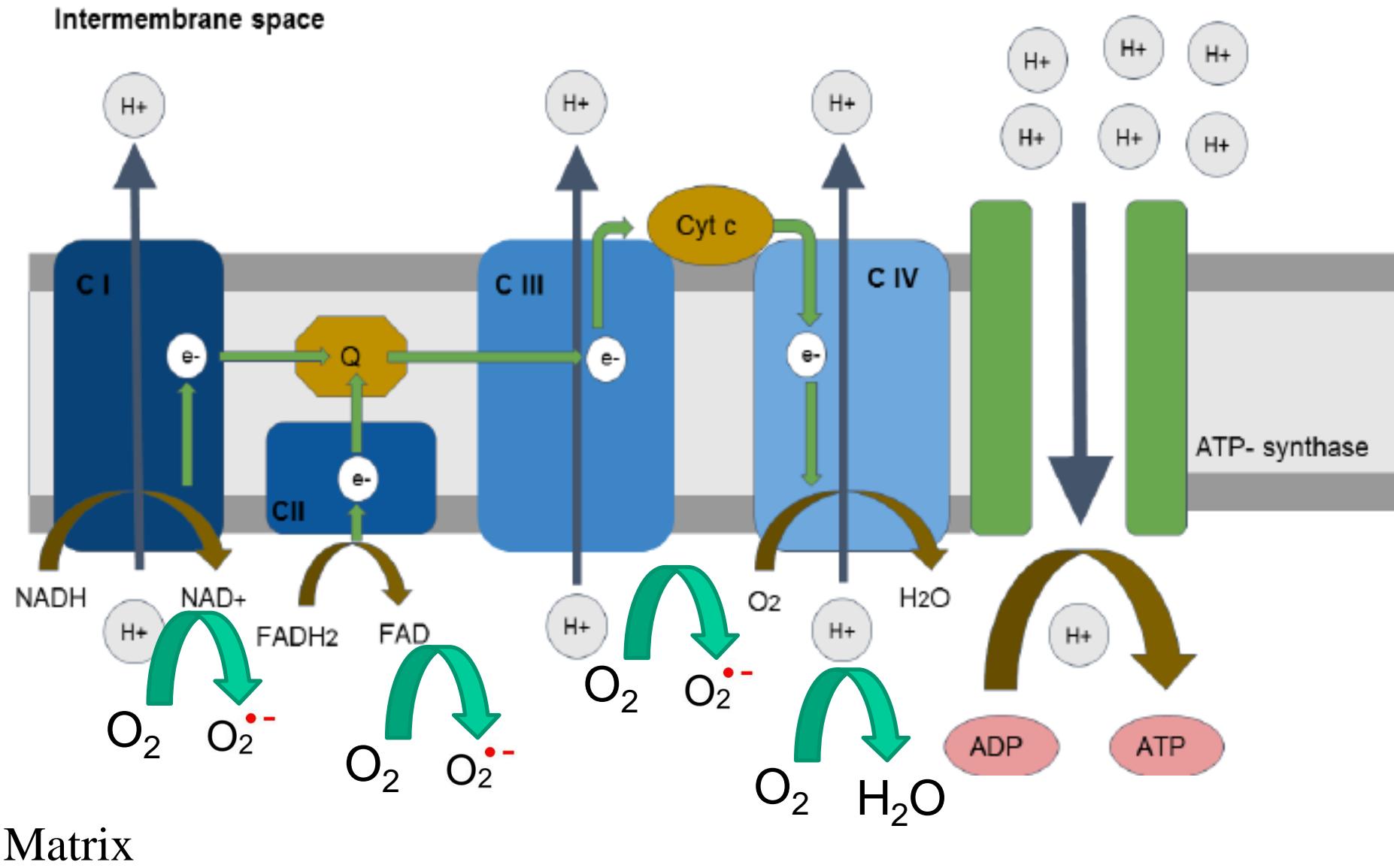
Imbalance between the production of free radicals and the ability of the cells/body to detoxify their harmful effects through neutralization by endogenous antioxidant mechanisms.

Oxidative stress accelerates aging and disease.

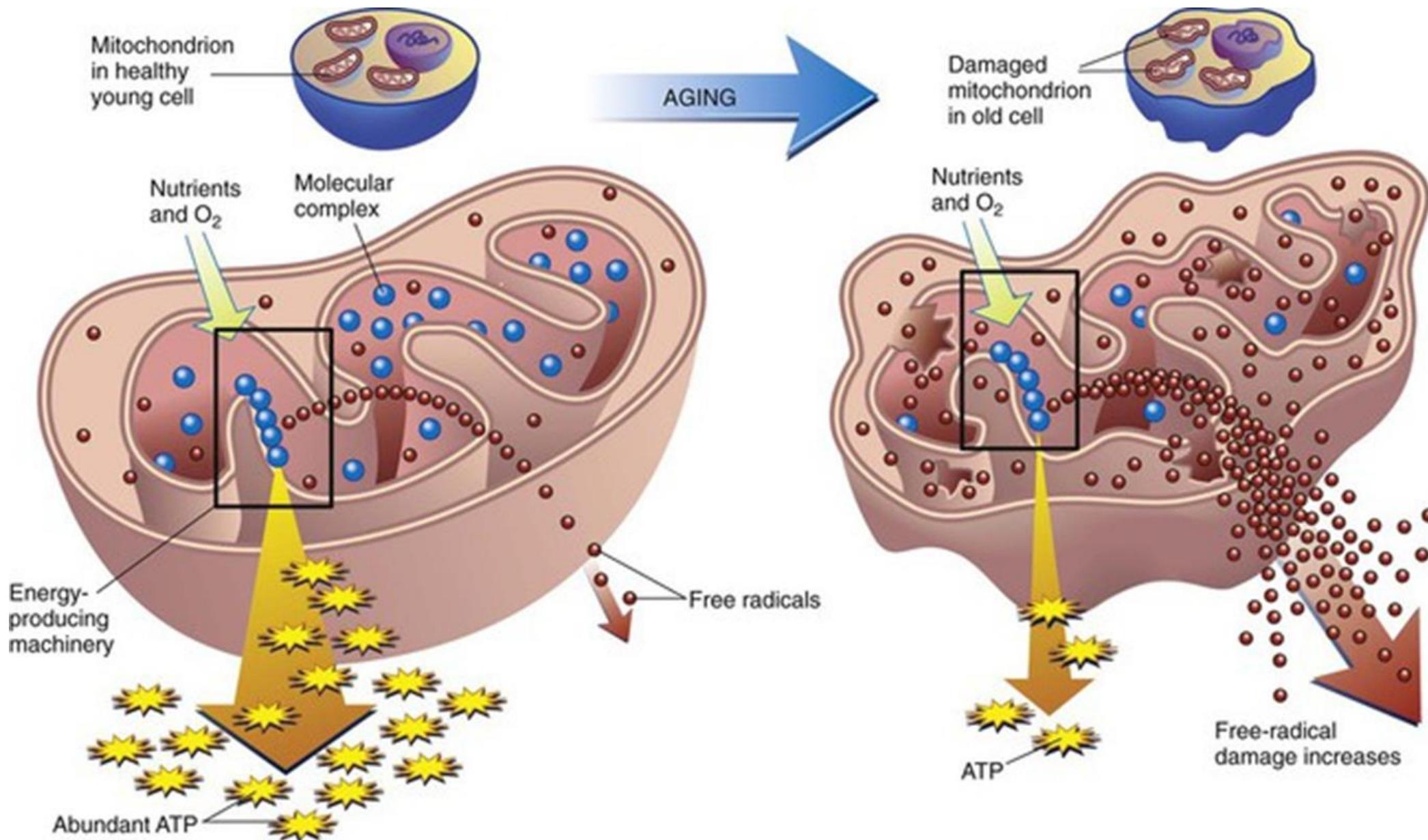
Stages of oxidative stress

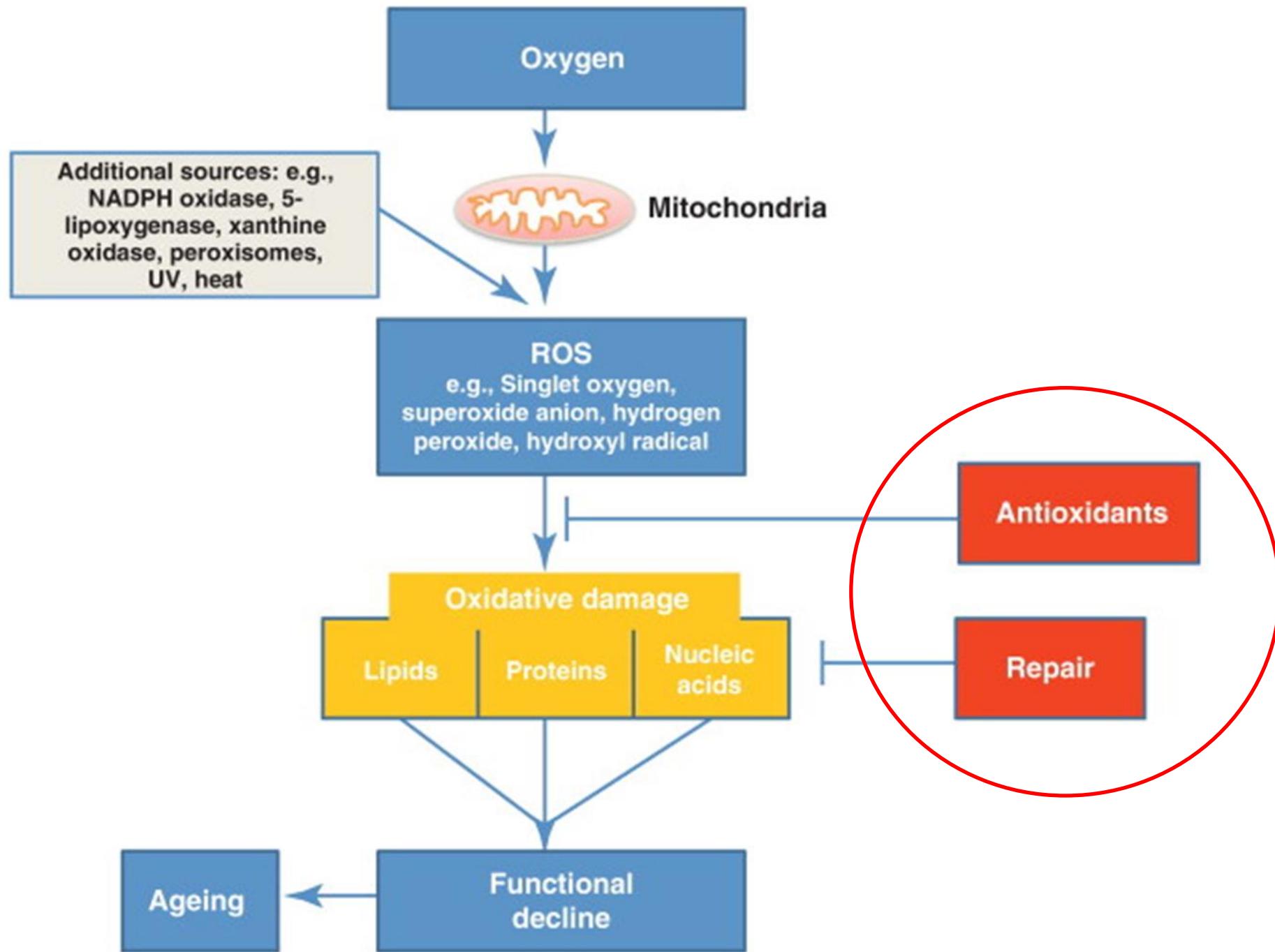


Generation of ROS - Mitochondria

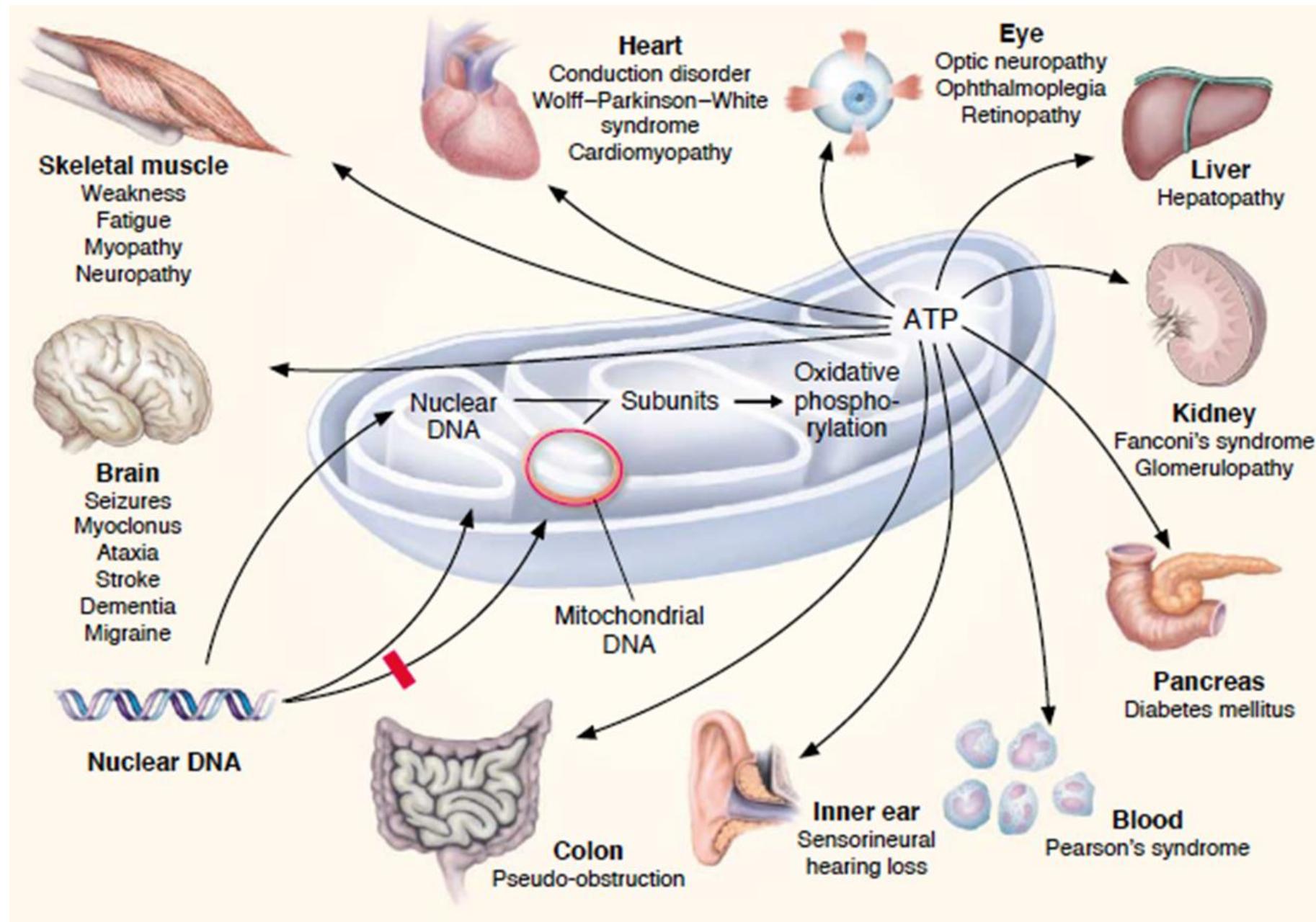


Aging and Generation of ROS

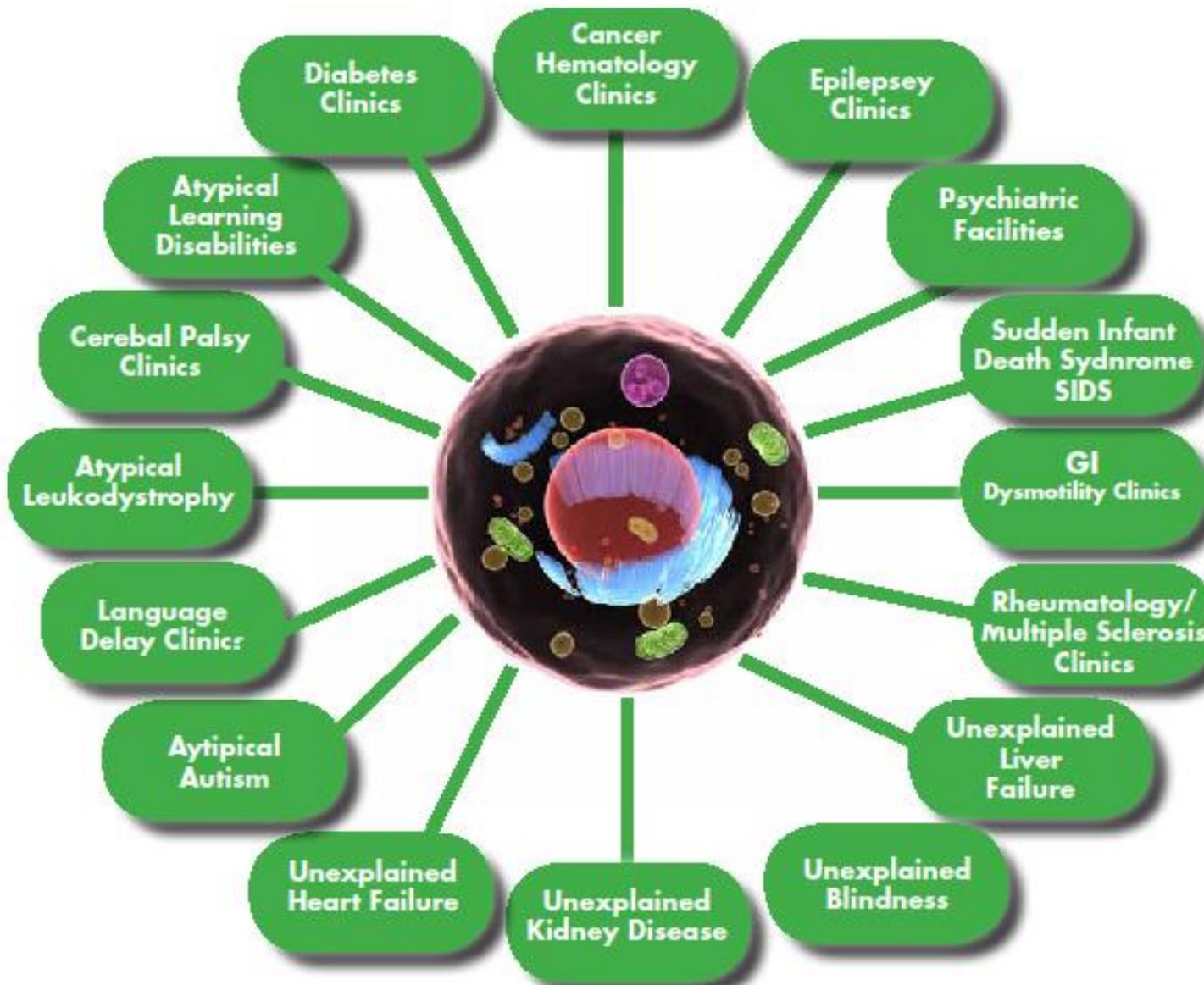




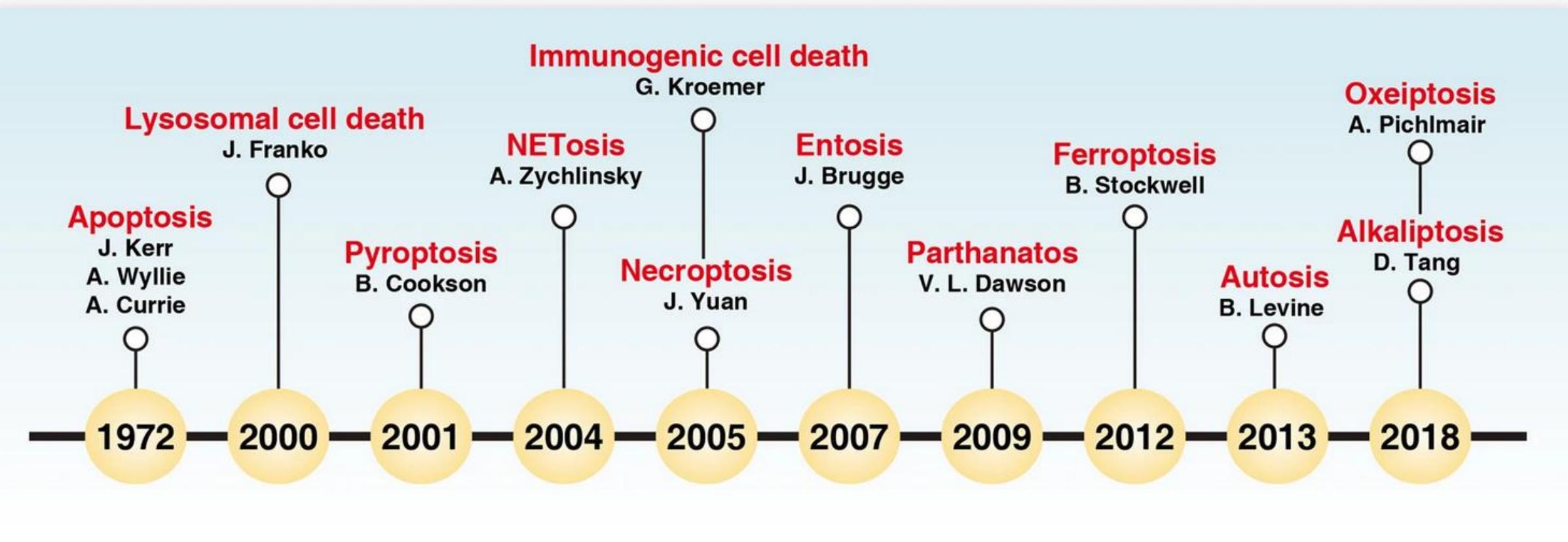
Disfunção mitocondrial e doença



Where does Mitochondrial Disease Hide?



Cell Death Discoveries timeline



APOPTOSIS

NETOSIS

PYROPTOSIS

FERROPTOSIS

MPT-RN

ENTOSIS

AUTOPHAGY

NECROPTOSIS

PARTHANATOS

...

Apoptose

Prémio Nobel 2002



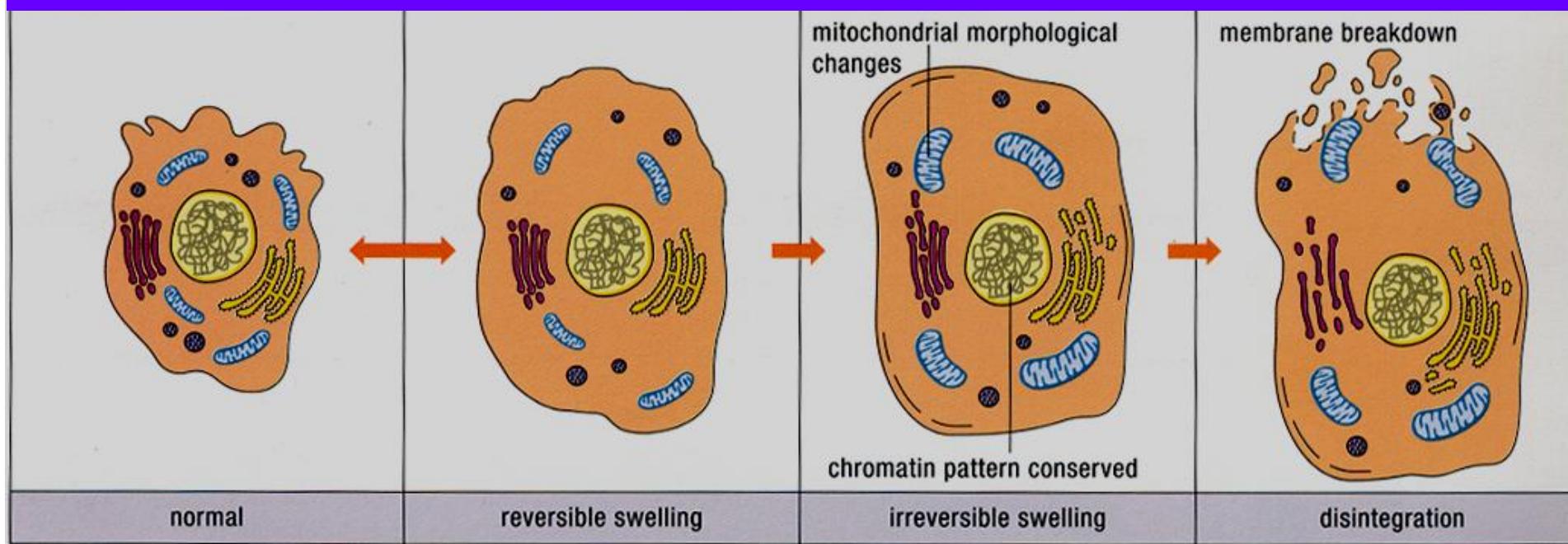
Sydney Brenner

H. Robert Horvitz

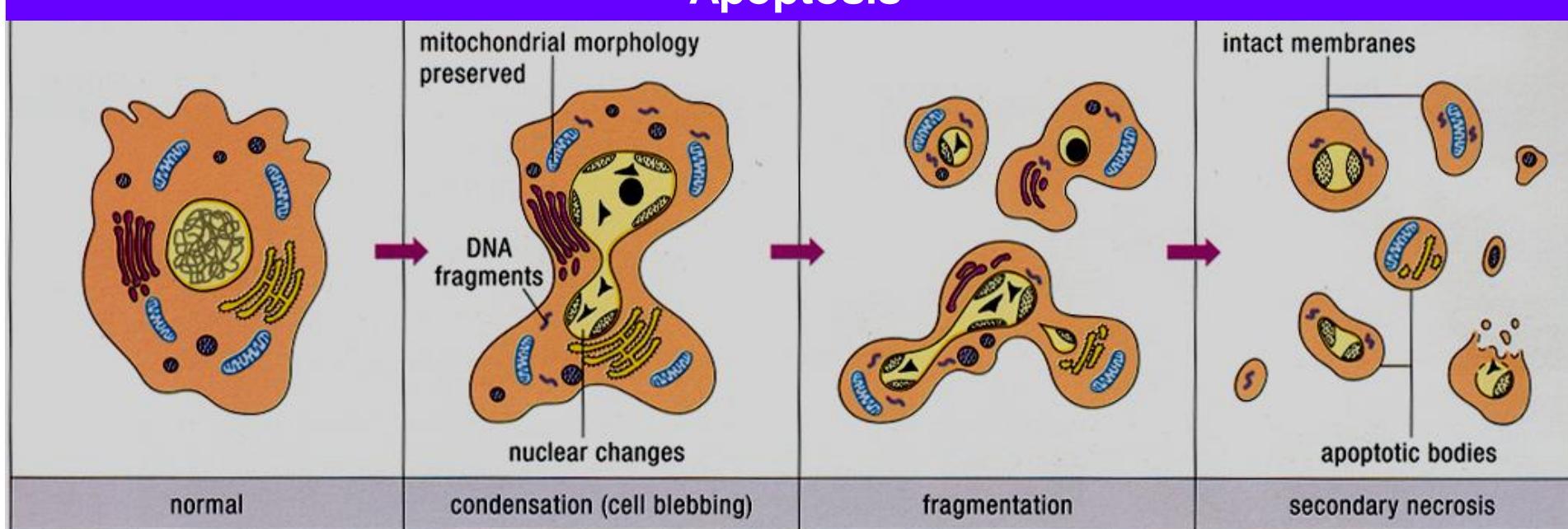
John E. Sulston

“For their discoveries concerning the genetic regulation of organ development and programmed cell death (PCD)”

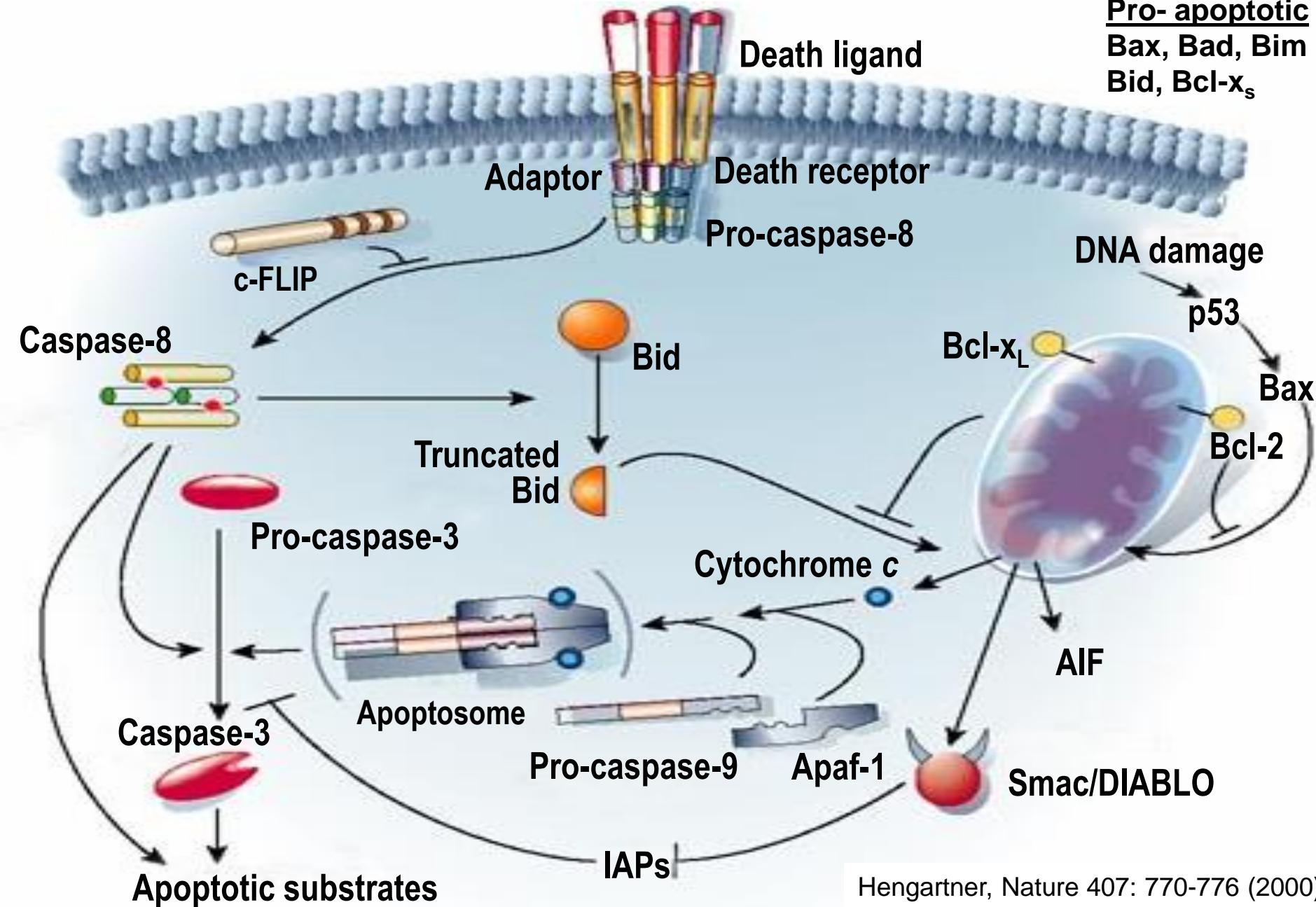
Necrosis



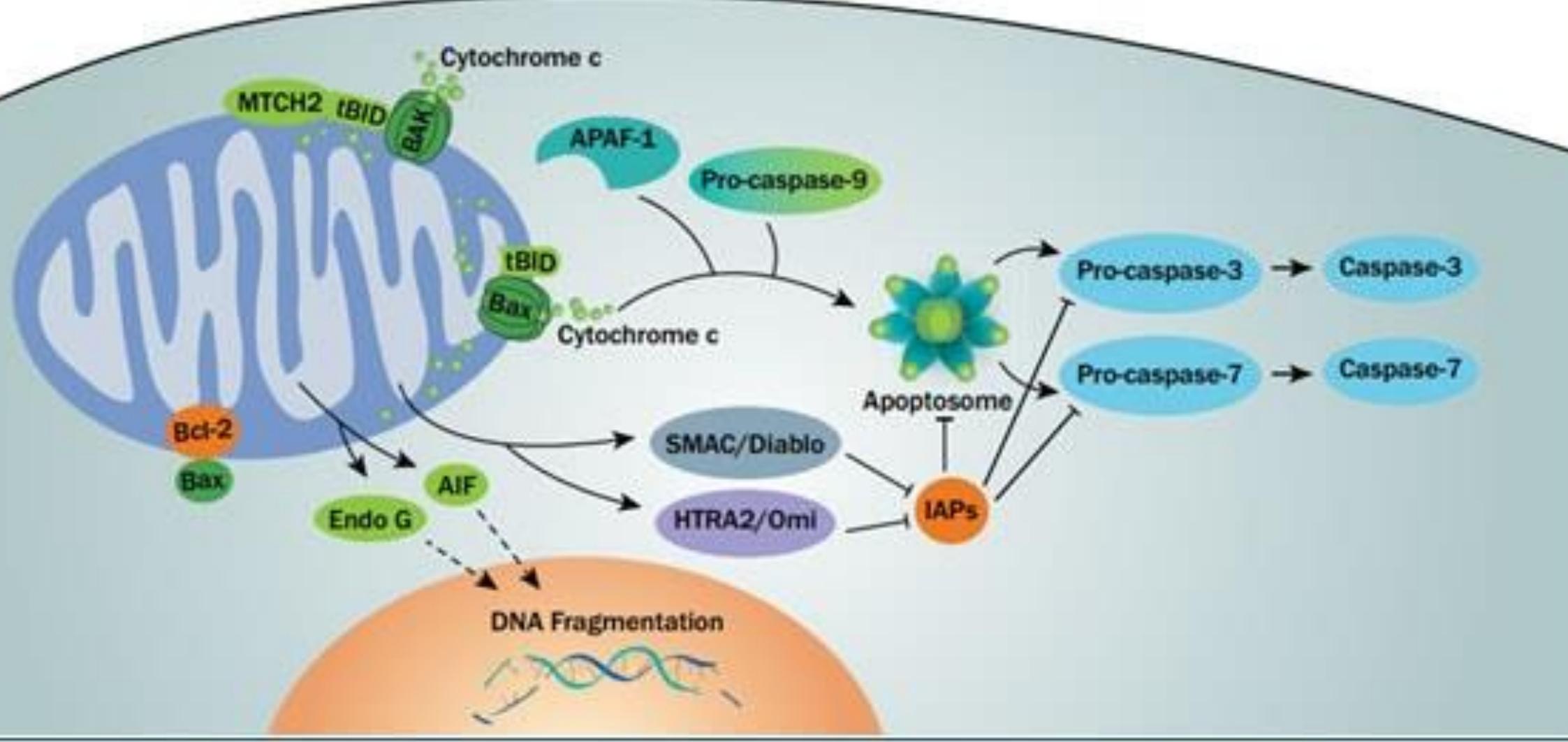
Apoptosis

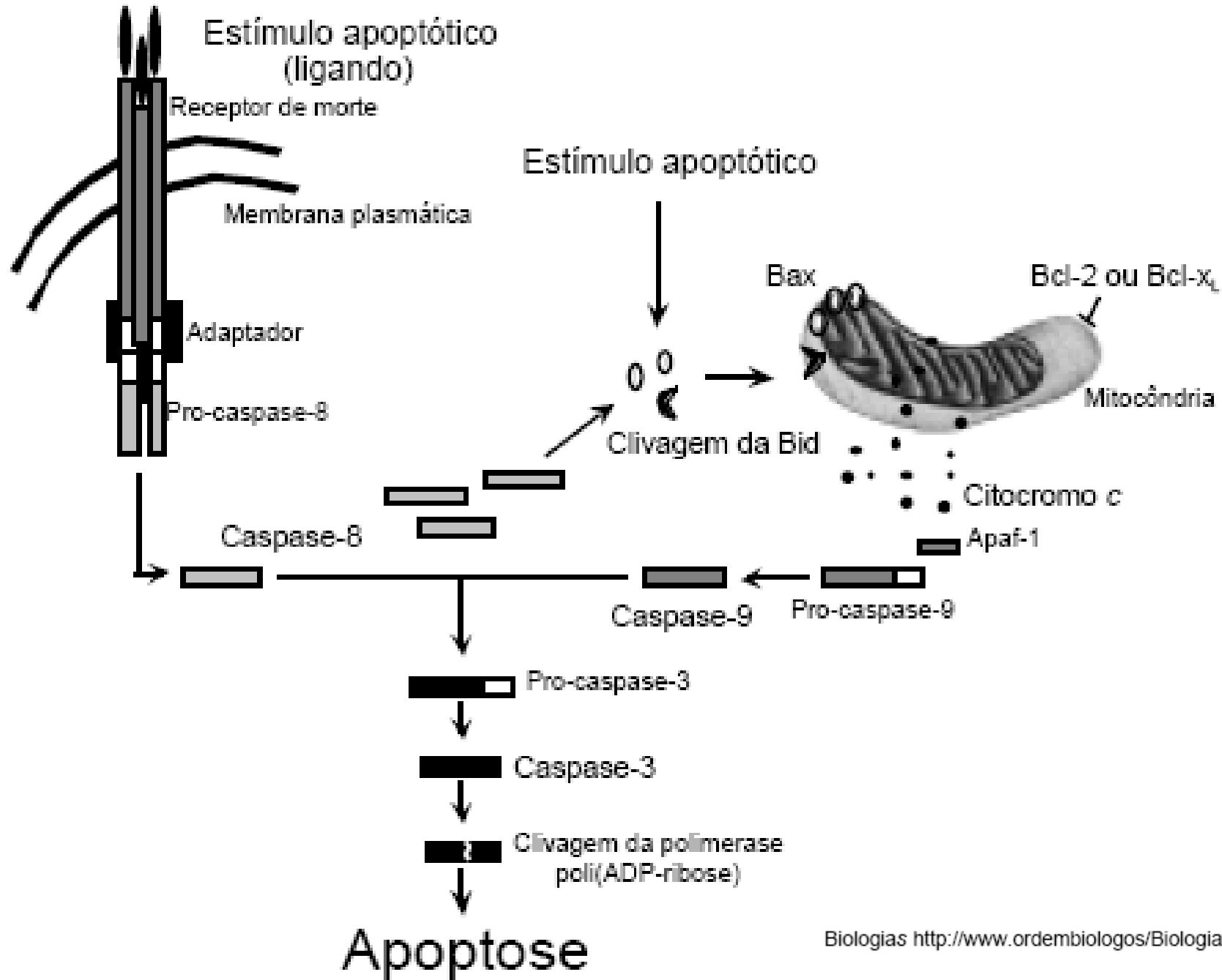


VIAS APOPTÓTICAS



Hengartner, Nature 407: 770-776 (2000)

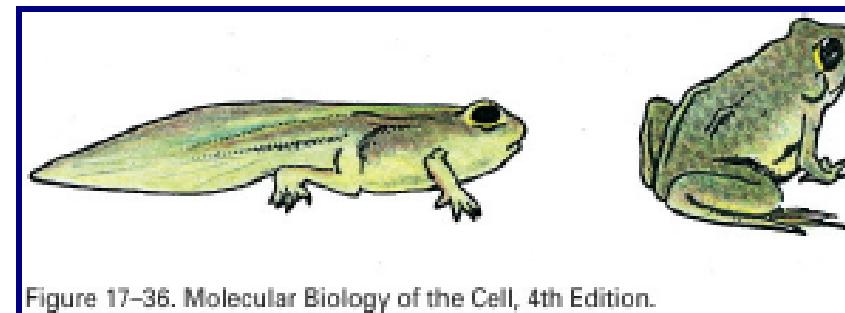
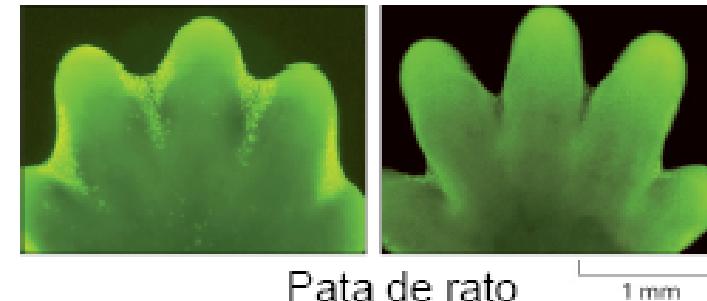
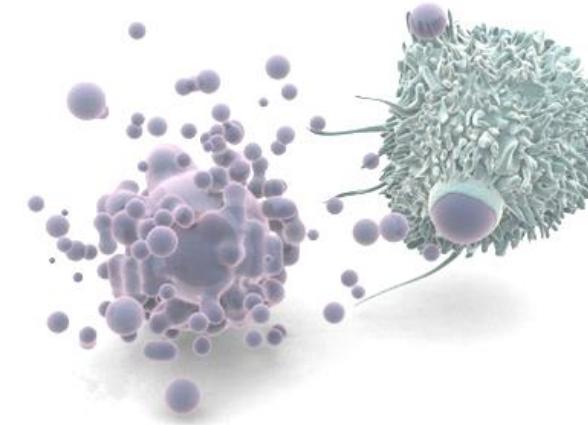




Apoptose

Importância biológica da apoptose

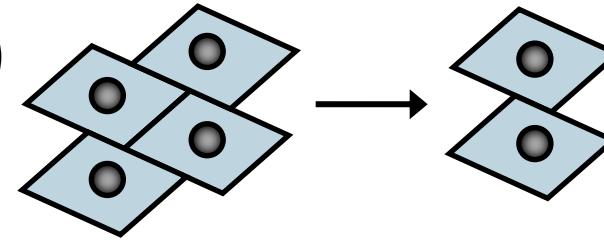
- Células extra
- Células obsoleta
- Homeostasia celular
- Células infectadas por vírus
- Células potencialmente perigosas
 - Células com danos irreparáveis no DNA
 - Células que determinam autoimunidade



DISFUNÇÃO DA APOTOSE

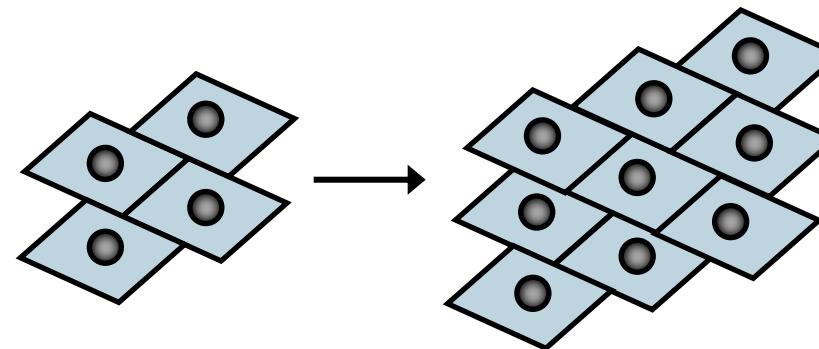
Apoptose excessiva

- Neurodegenerescênci
- Danos na isquémia-reperfusão (AVC)
- Falência cardíaca
- Trauma
- Infecções bacterianas e virais
- Rejeição de enxertos (transplantes)

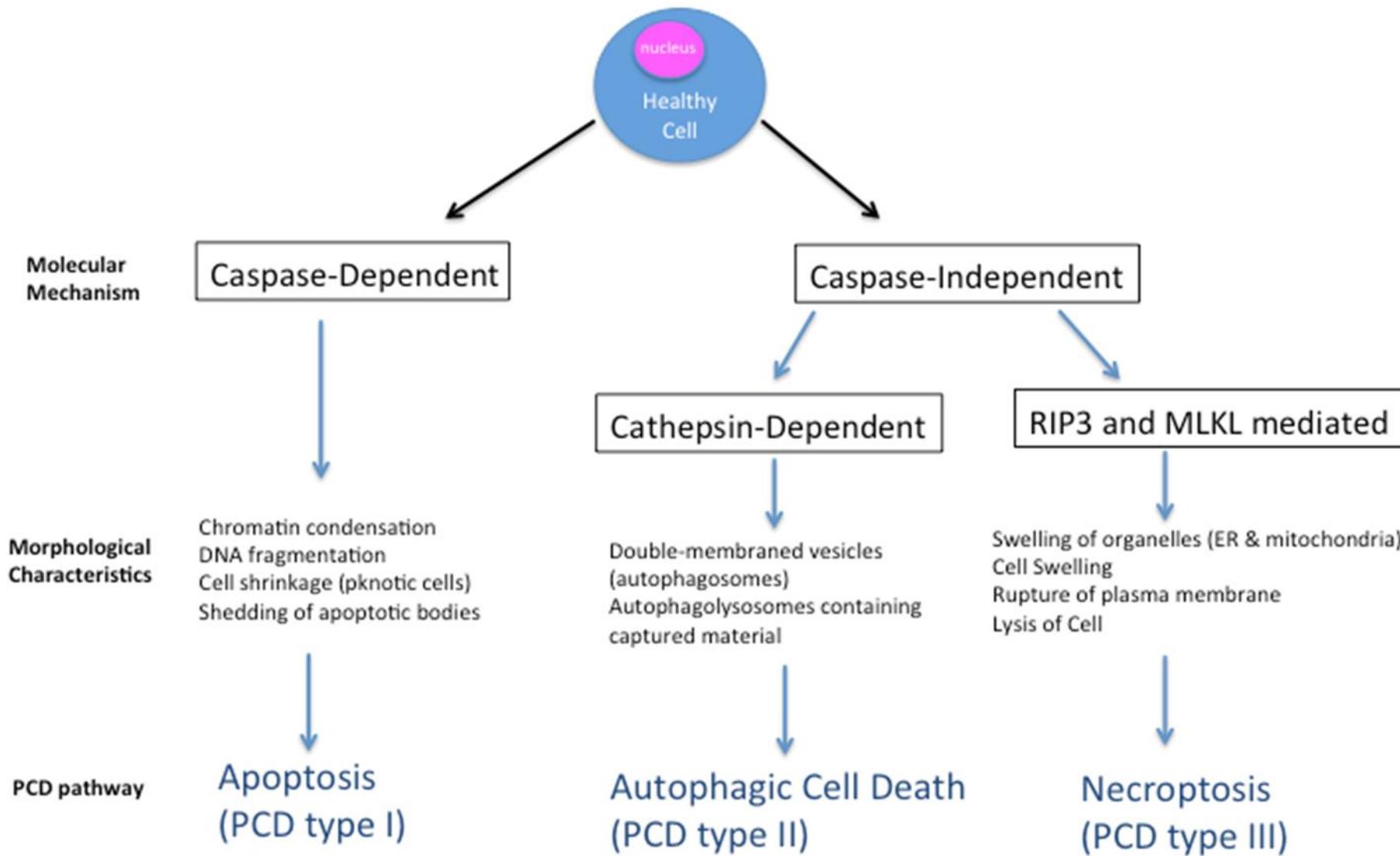


Apoptose insuficiente

- Tumores
- Doenças autoimunes
- Infecções persistentes



Comparison of PCD Pathways



Mitocôndrias

Mitocôndria:

<https://www.youtube.com/watch?v=vnw76pfiteQ>

<https://www.youtube.com/watch?v=c4JsEBI9u6I>

<https://www.youtube.com/watch?v=vkYEYjintqU>

<https://www.youtube.com/watch?v=39HTpUG1MwQ>

Teoria endossimbiótica:

<https://www.youtube.com/watch?v=-FQmAnmLZtE>

DNA mitocondrial:

https://www.youtube.com/watch?v=6lts-50Y_vs

Mitocôndria e apoptose:

<https://www.youtube.com/watch?v=kbXYL6IDv-U>

<https://www.youtube.com/watch?v=SyvOPXeg4ig>

<https://www.youtube.com/watch?v=-vmtK-bAC5E>

<https://www.youtube.com/watch?v=03usjXU5Cgk>

Necroptose:

<https://www.youtube.com/watch?v=-hXFb6GvEL4&list=UUDCg5AAslixldHh5D7Nu6-g>