MITOCHONDRIE

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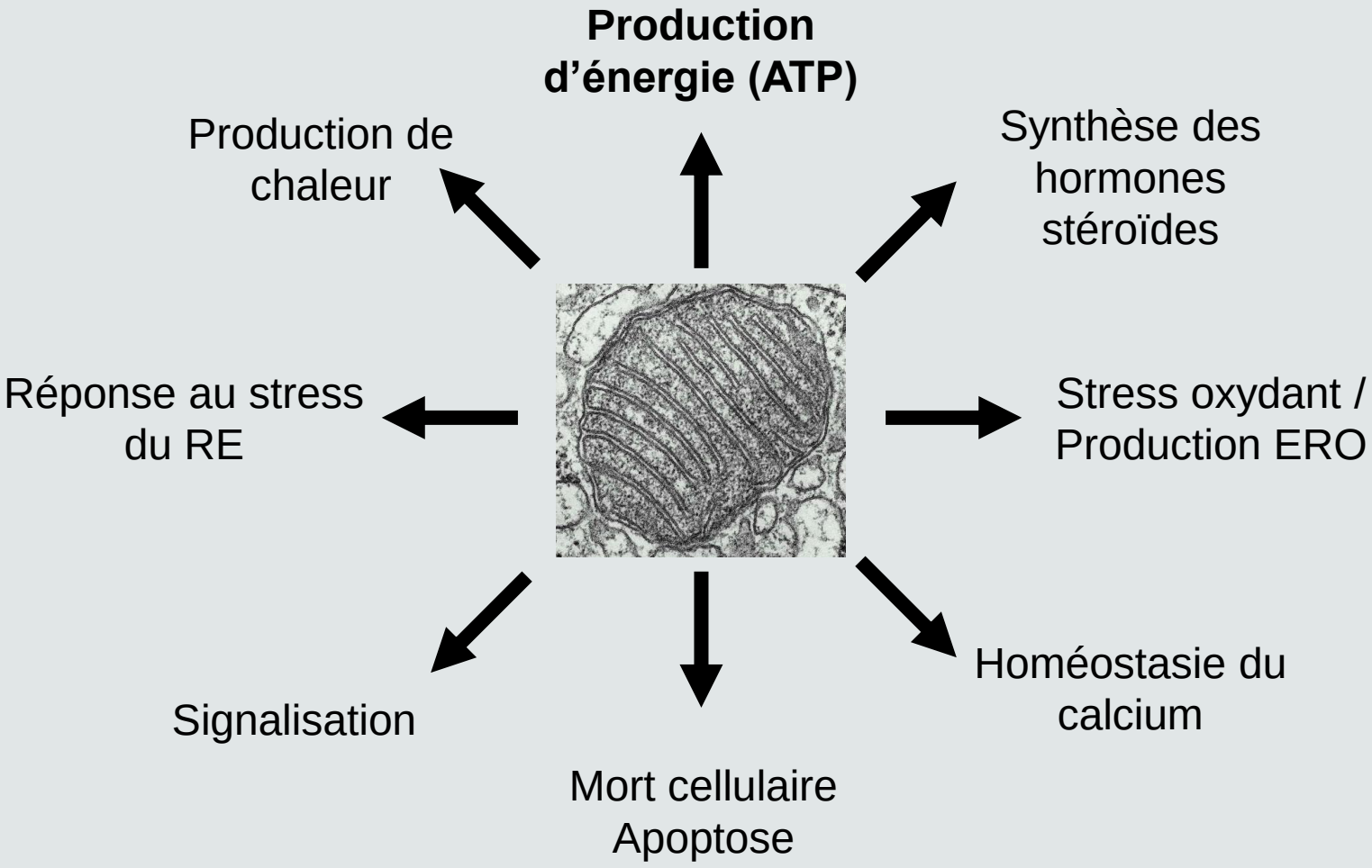
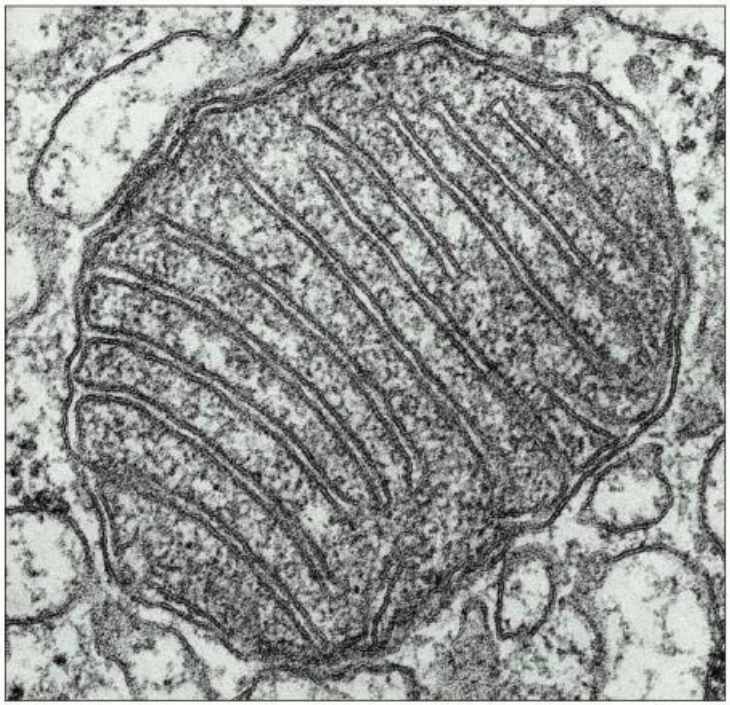
Rôles des mitochondries



Mitochondries : structure, organisation et dynamique

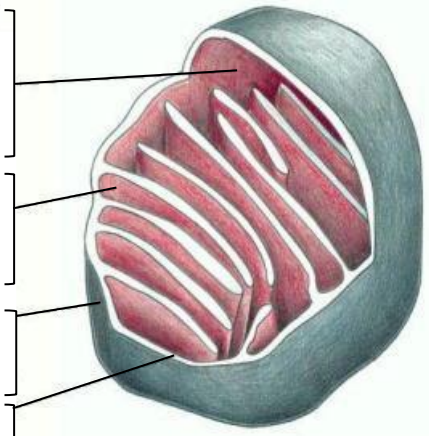


Matrice :
- Enzymes du métabolisme (cycle de Krebs, β-oxydation des acides gras…)
- ADN mitochondrial, ribosomes, ARNt mitochondriaux, protéines nécessaires à l'expression des gène mitochondriaux

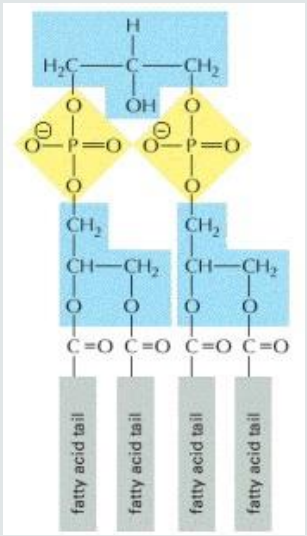
Membrane interne :
- Protéines de la chaine de transfert d 'électrons
- ATP synthase
- Protéines de transport

Membrane externe :
- Canaux (porines) : passage de molécules <5000 Da
- Enzymes (passage des lipides)

Espace intermembranaire :
- Enzymes



Cardiolipine
(bisphosphatidylglycérol)
Phospholipide spécifique de la membrane interne (20% des lipides totaux)



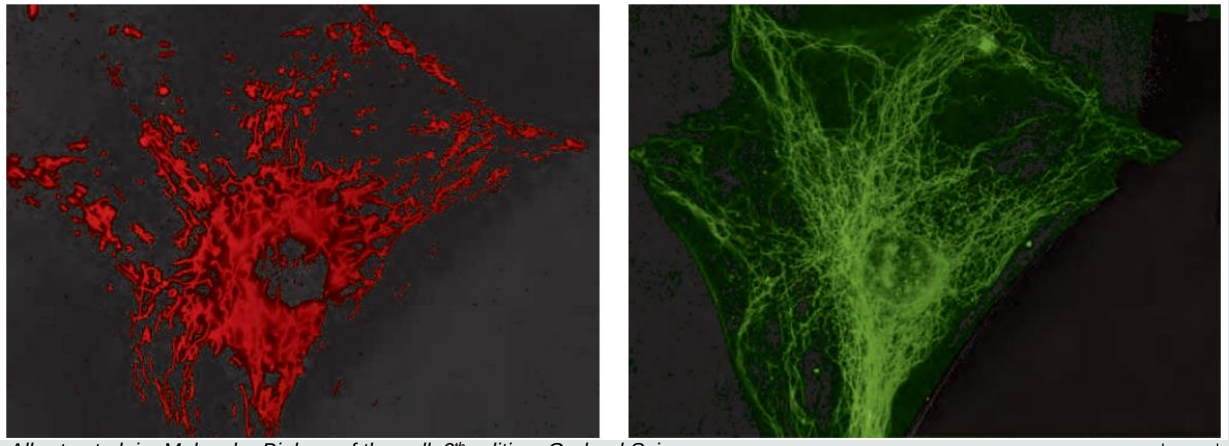
Hépatocytes (% des protéines totales)
- 67% dans la matrice
- 21% dans la membrane interne
- 6% dans la membrane externe
- 6% dans l'espace intermembranaire

Alberts et al. in Molecular Biology of the cell, 6th edition, Garland Science

Mitochondries : structure, organisation
Rôle du cytosquelette

Marquage de mitochondries
(rhodamine 123)

Marquage des microtubules

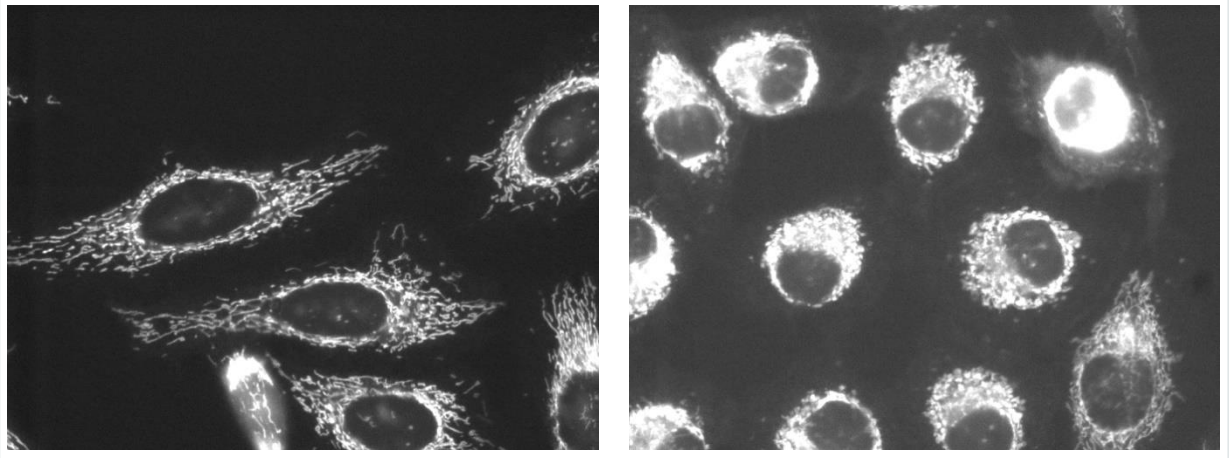


Alberts et al. in Molecular Biology of the cell, 6th edition, Garland Science

10 µm

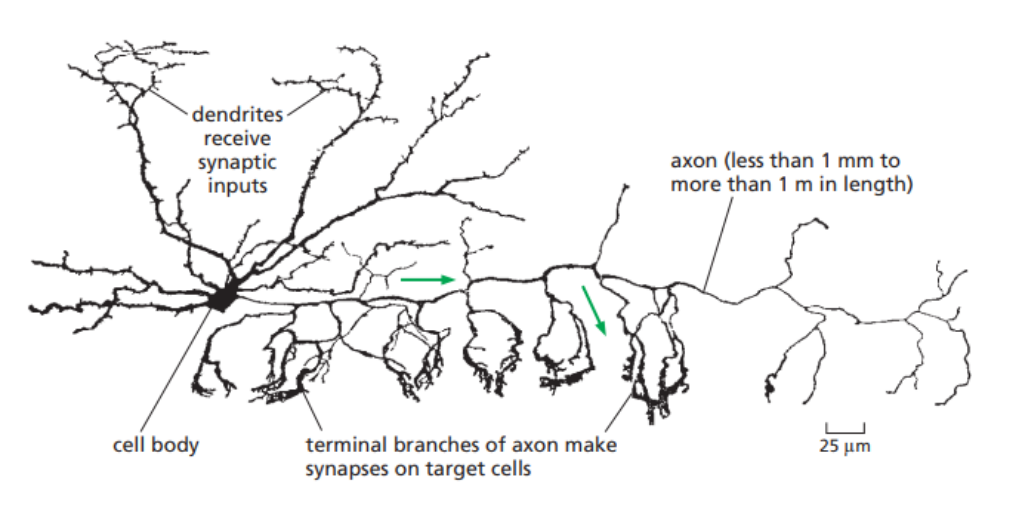
Contrôle

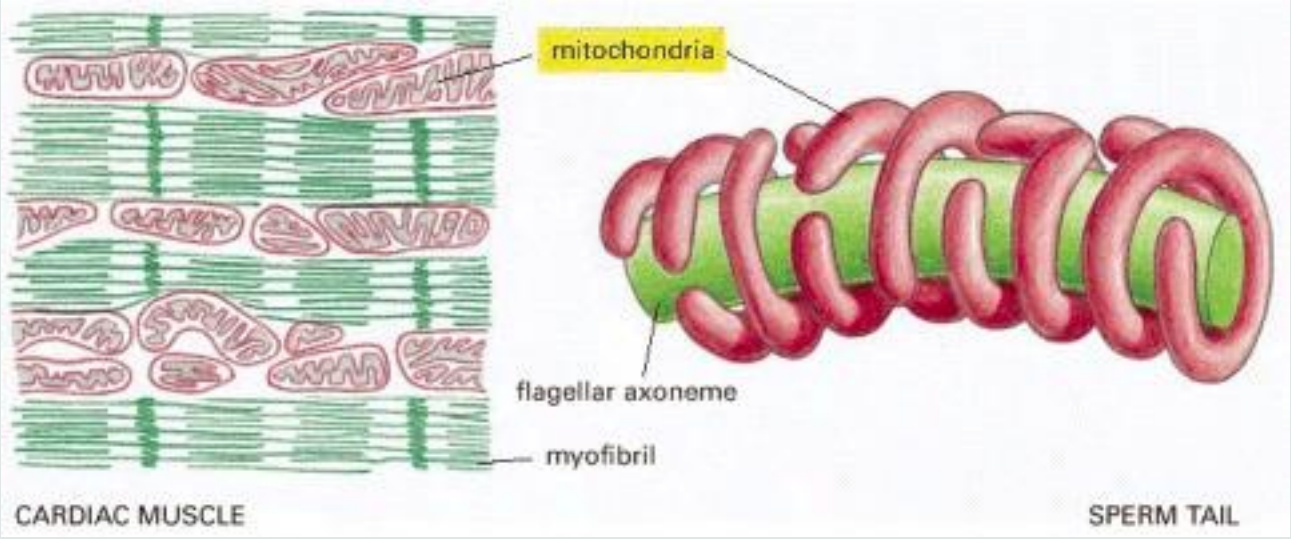
Inhibition de la kinésine



Marquage de mitochondries
(rhodamine 123)

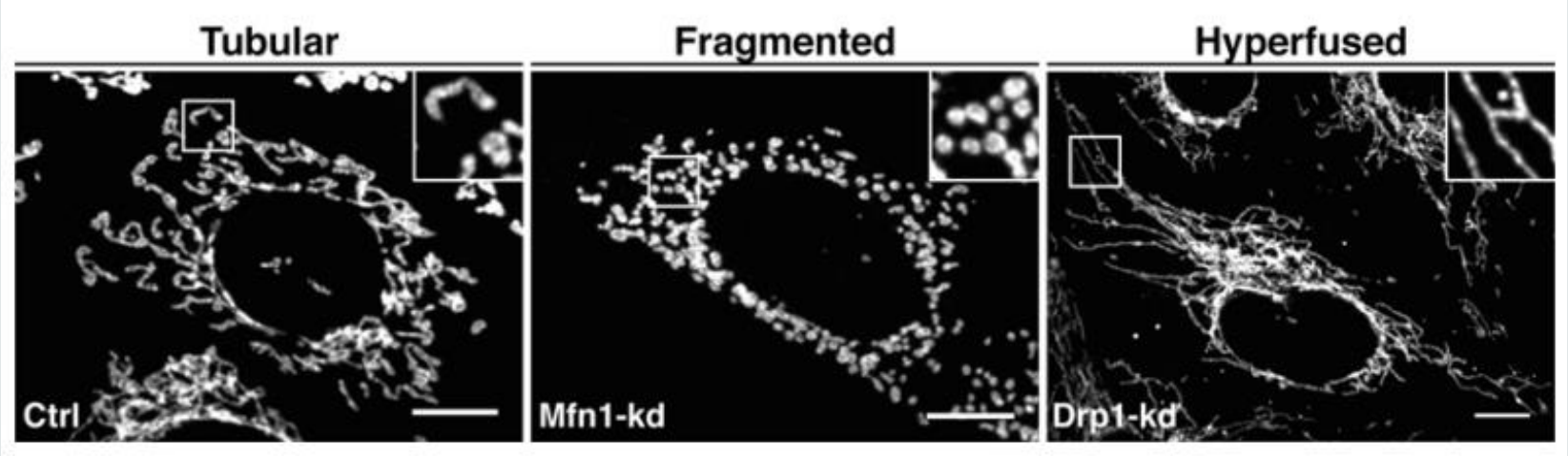
L'organisation du réseau de mitochondrie varie en fonction du type cellulaire



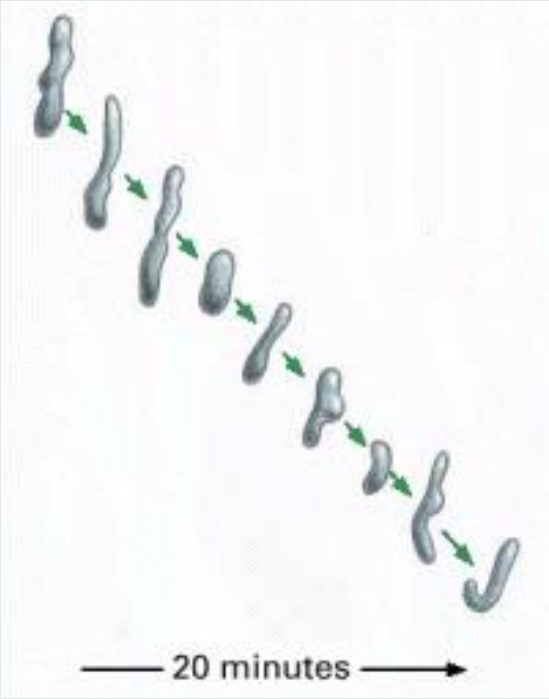


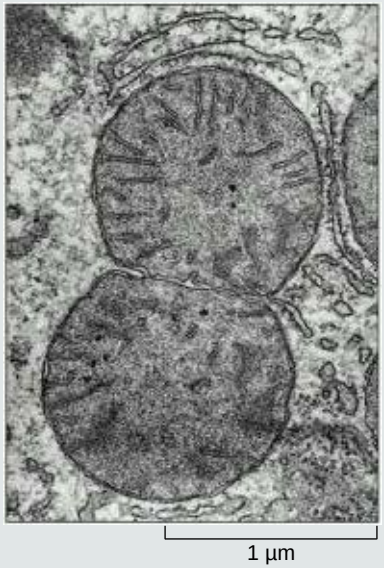
Alberts et al. in Molecular Biology of the cell, 6th edition, Garland Science

Mitochondries : structure, organisation et dynamique



L. Tilokani et al. Essays in Biochemistry (2018) 62 341–360



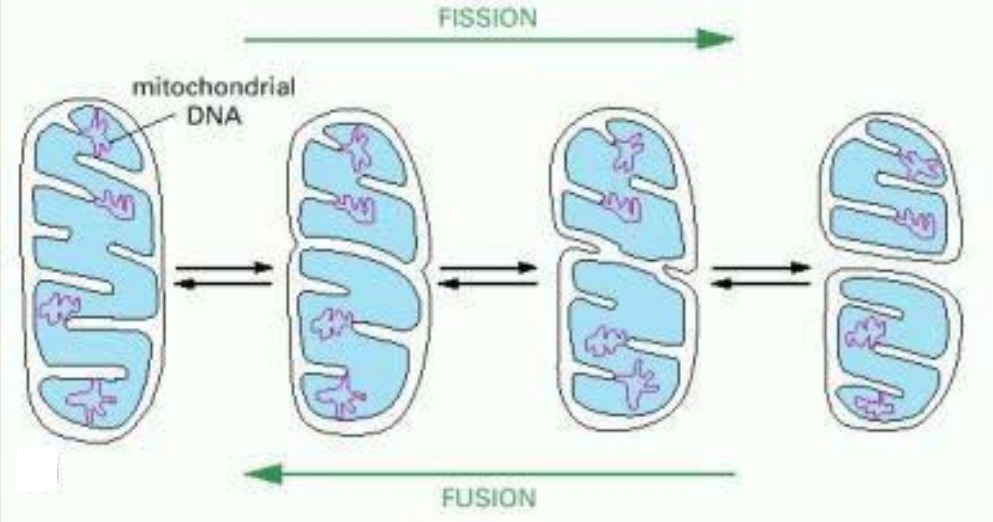


Les mitochondries forment un réseau très dynamique à l'intérieur de la cellule

Alberts et al. in Molecular Biology of the cell, 6th edition, Garland Science

Régulation de la balance fission/fusion

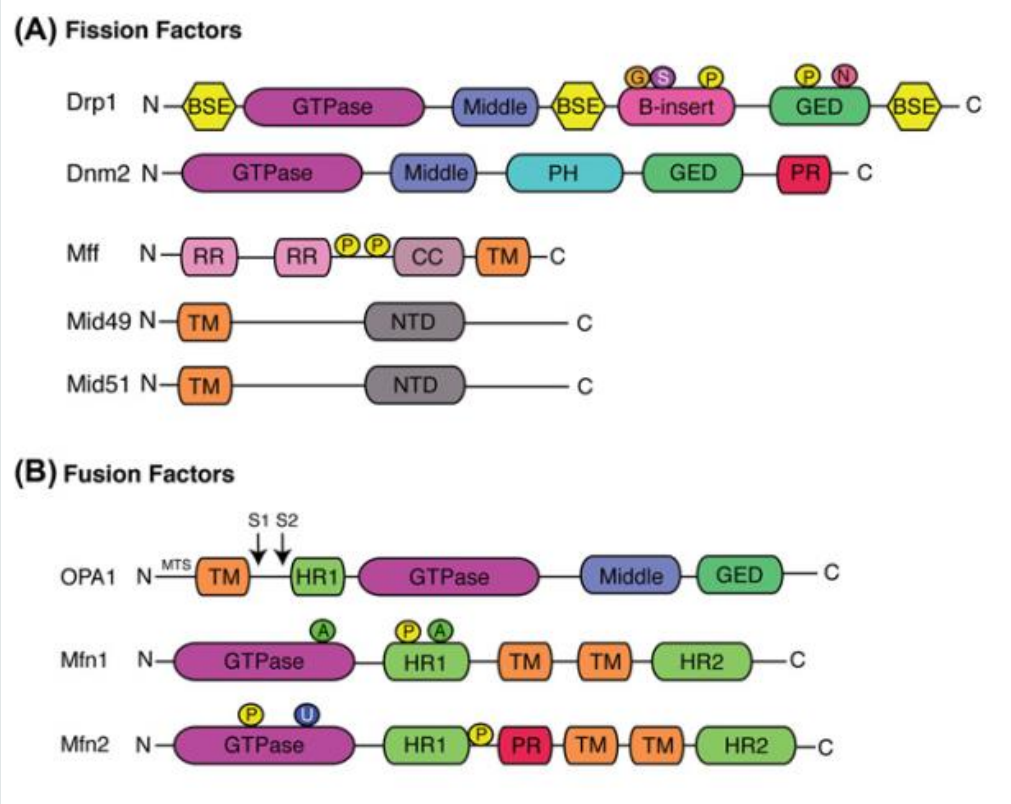
- Dysfonctionnement mitochondrial
- Stress cellulaire
- Mort cellulaire
- Augmentation du Calcium intracellulaire
- Dépolarisation de la membrane interne
- Transition G_2/M



Alberts et al. in Molecular Biology of the cell, 6th edition, Garland Science

- Adaptation aux besoins métaboliques de la cellule

Protéines impliquées dans la fission et la fusion des mitochondries



L. Tilokani et al. Essays in Biochemistry (2018) 62 341–360

Drp1 : dynamin related protein 1

Dnm2 : dynamin 2

OPA (optic atrophy) : fusion de la mb interne
Forme longue (L-OPA) et courte (S-OPA)

Mfn (mitofusins) : fusion de la mb externe

TM Domaine transmembranaire

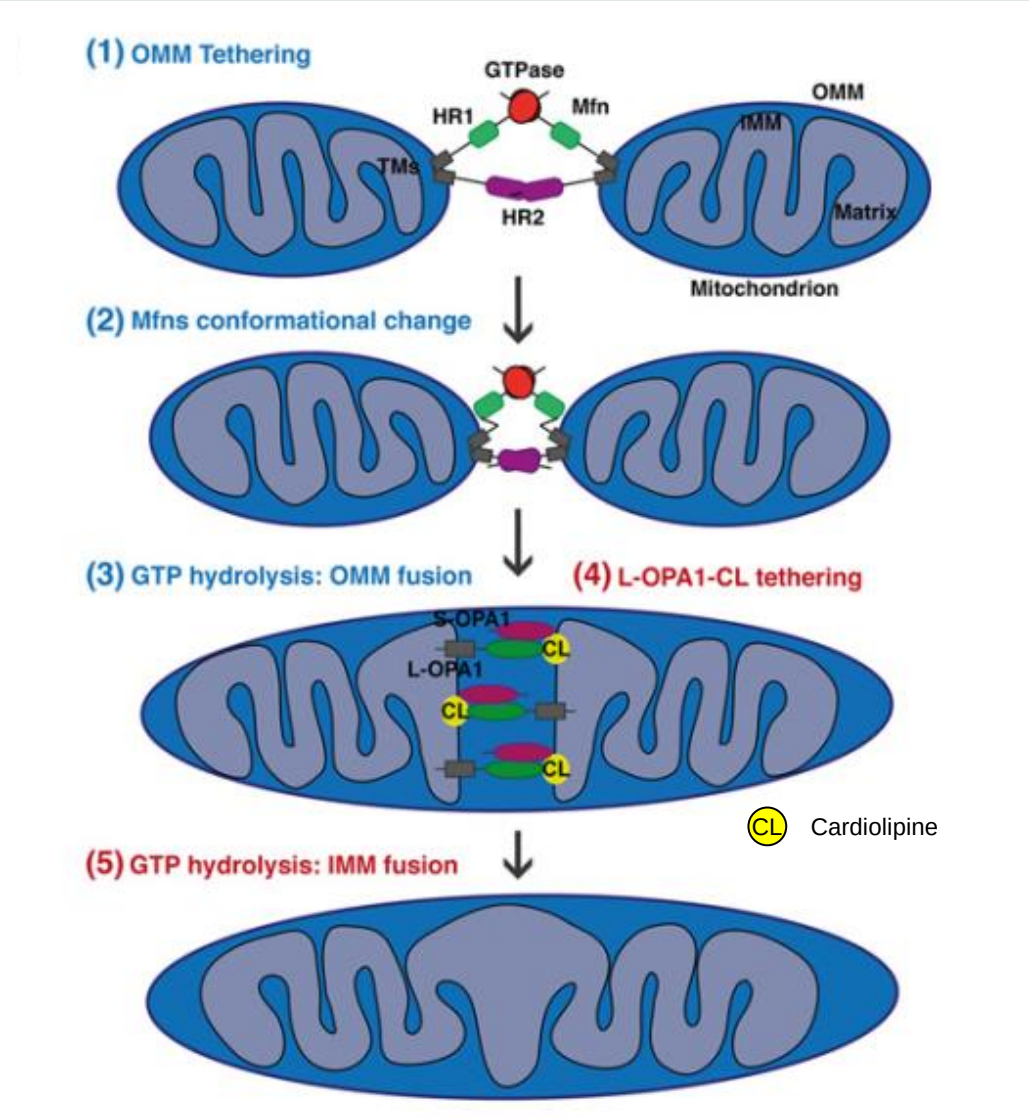
HR Heptad repeat

P Phosphorylation

A Acétylation

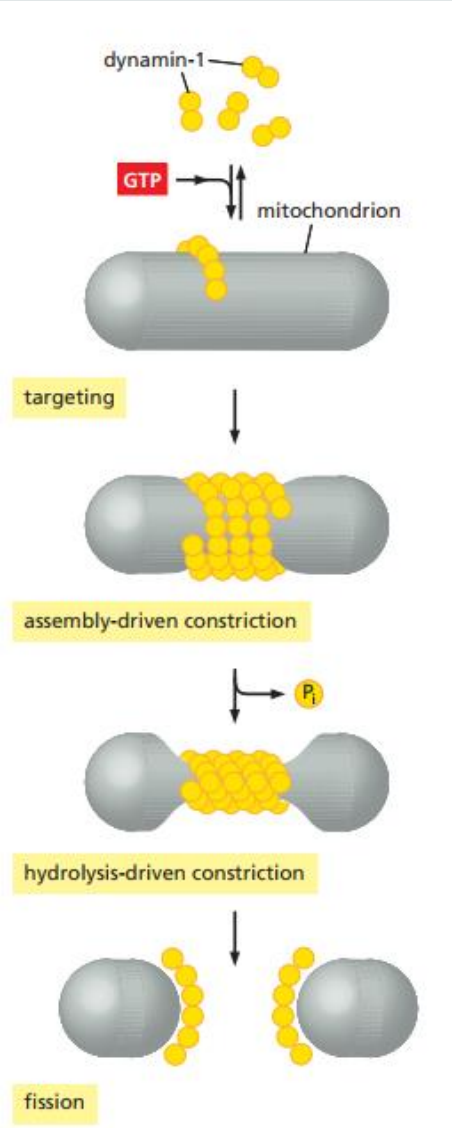
U Ubiquitination

Mécanisme de fusion



L. Tilokani et al. Essays in Biochemistry (2018) 62 341–360

Mécanisme de fission



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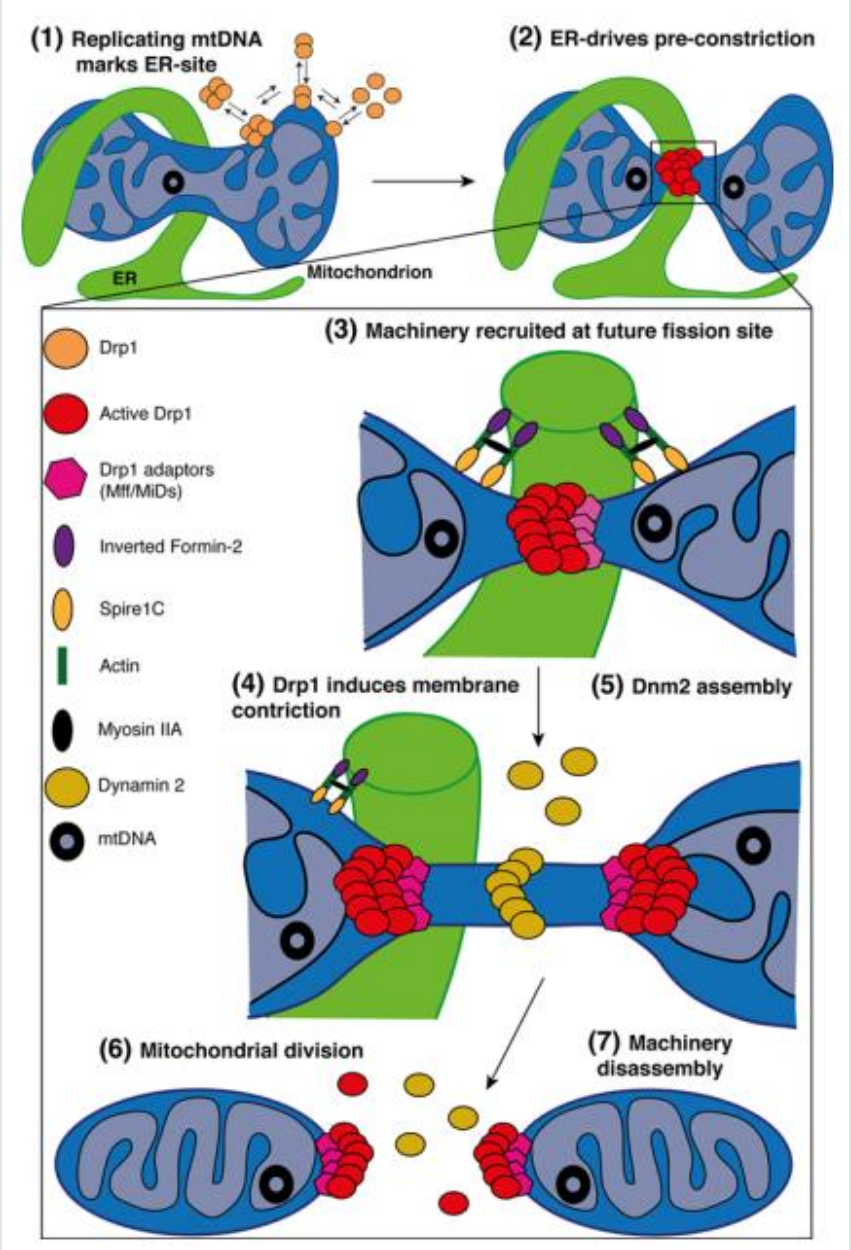

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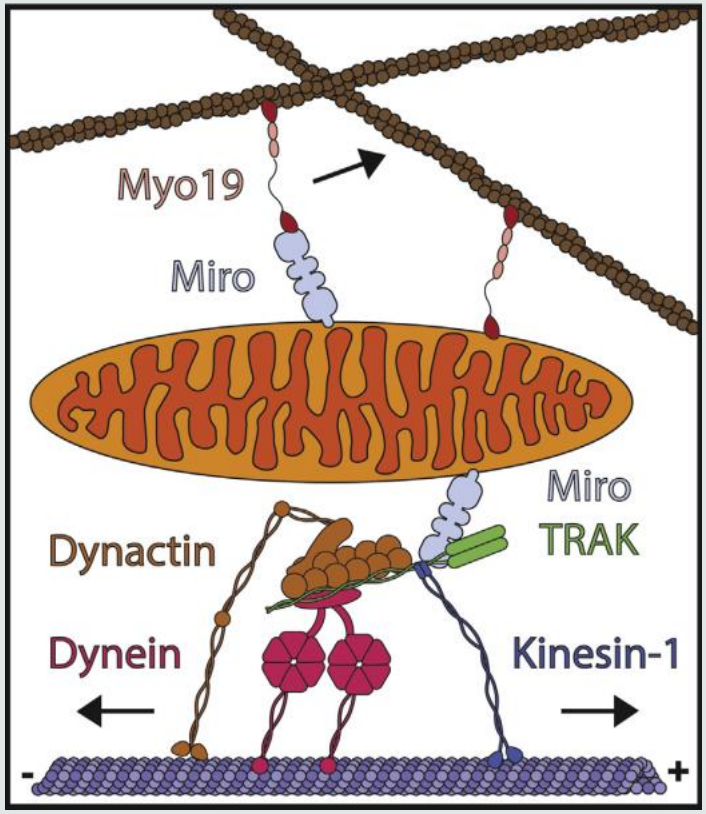
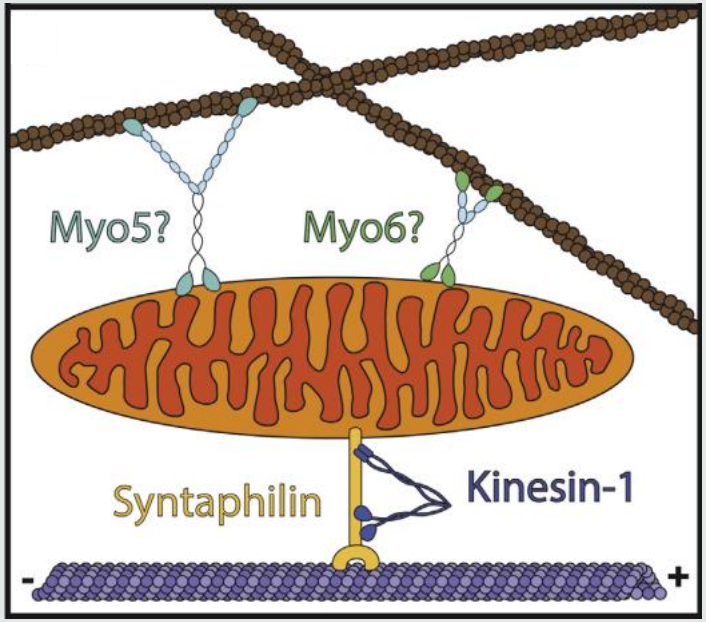
Organisation du réseau de mitochondries

Transport des mitochondries

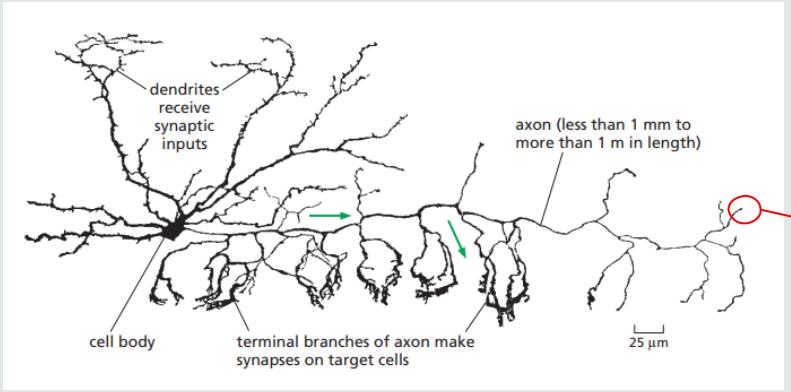


A. Fenton et al., Current Opinion in Cell Biology 2021, 68:28–36

Ancrage des mitochondries



A. Fenton et al., Current Opinion in Cell Biology 2021, 68:28–36



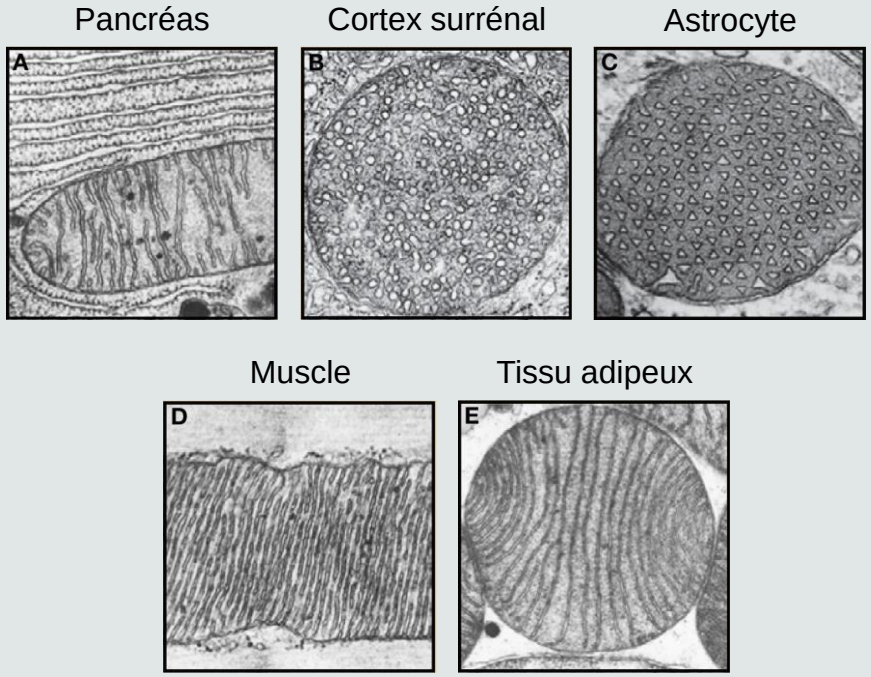
Alberts et al. in Molecular Biology of the cell, 6th edition, Garland Science

Dynamique mitochondriale et pathologies

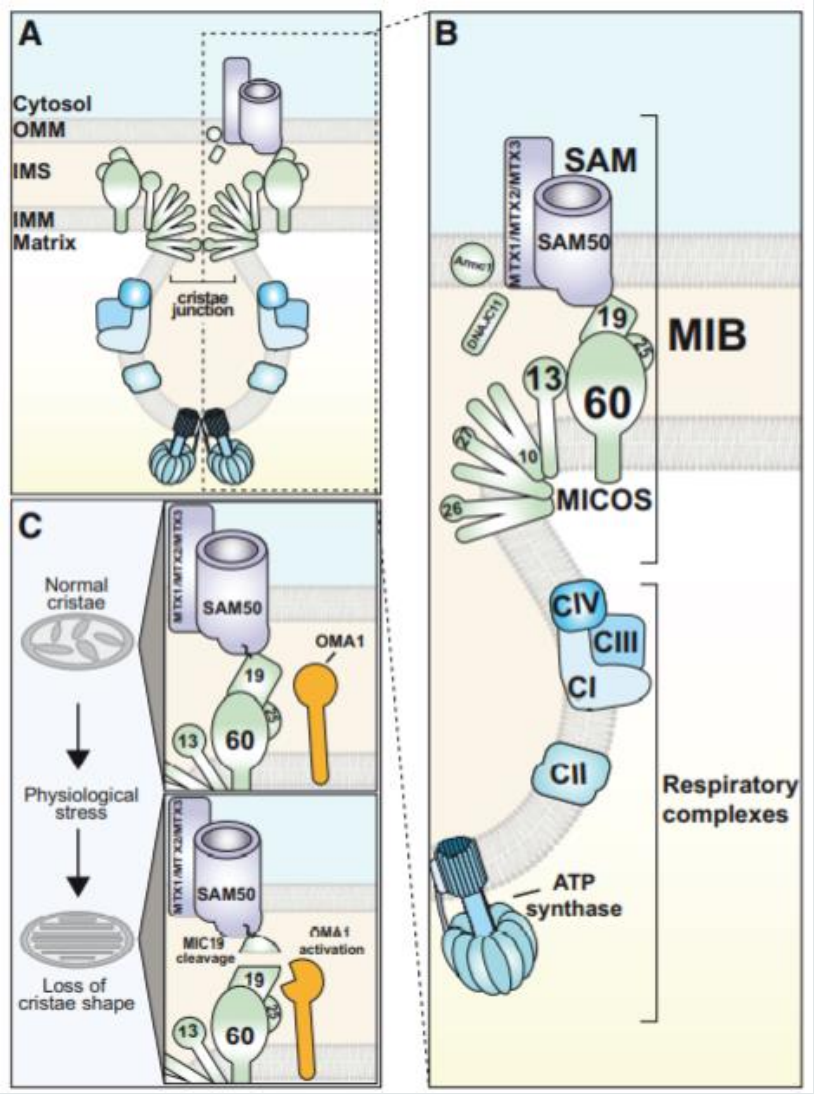
Gene	OMIM	Inheritance	Disease	Symptoms
MFN2	608507	AD	Charcot–Marie–Tooth disease type 2A	Distal limb muscle weakness and atrophy, axonal degeneration/regeneration, areflexia, distal sensory loss (pain and temperature more frequent) with or without: (a) CNS involvement (cognitive decline, spasticity, encephalopathy), (b) optic atrophy, (c) hearing loss and (d) vocal cord paresis
		AR	Charcot–Marie–Tooth disease type 2A	
		AD	Hereditary motor and sensory neuropathy VIA	
OPA1	605290	AD	Optic atrophy 1	Progressive loss of visual acuity, temporal optic nerve pallor, central scotoma with or without: (a) CNS (ataxia, spasticity, hearing loss) and (b) PNS (axonal sensorineural polyneuropathy) symptoms. Early-onset optic atrophy accompanied by neurologic features, including ataxia, pyramidal signs, spasticity and mental retardation
		AD	Optic atrophy plus syndrome	
		AR	Behr syndrome	
MFF	614785	AR	Encephalopathy	Seizures, dysphagia, optic and peripheral neuropathy, developmental delay, microcephaly, cerebellar atrophy and basal ganglia lesions
DNM2	602378	AD	Centronuclear myopathy 1	Slowly progressive muscle weakness.
		AD	Charcot–Marie–Tooth disease, axonal type 2M	Distal limb muscle weakness and atrophy and sensory impairment, areflexia +/-neutropenia.
		AD	Charcot–Marie–Tooth disease, dominant intermediate B	
		AR	Lethal congenital contracture syndrome 5	Polyhydramnios, decreased foetal movements, intracranial bleeding, retinal haemorrhage, joint contractures and respiratory insufficiency
INF2	610982	AD	Charcot–Marie–Tooth disease type E	Distal limb muscle weakness and atrophy and sensory impairment, areflexia, sensorineural hearing loss and foot drop
		AD	Focal segmental glomerulosclerosis	Proteinuria and renal failure

L. Tilokani et al. Essays in Biochemistry (2018) 62 341–360

L’organisation interne des mitochondries varie selon les types cellulaires



W. Neupert et al., Cell, 2012, 149, 27

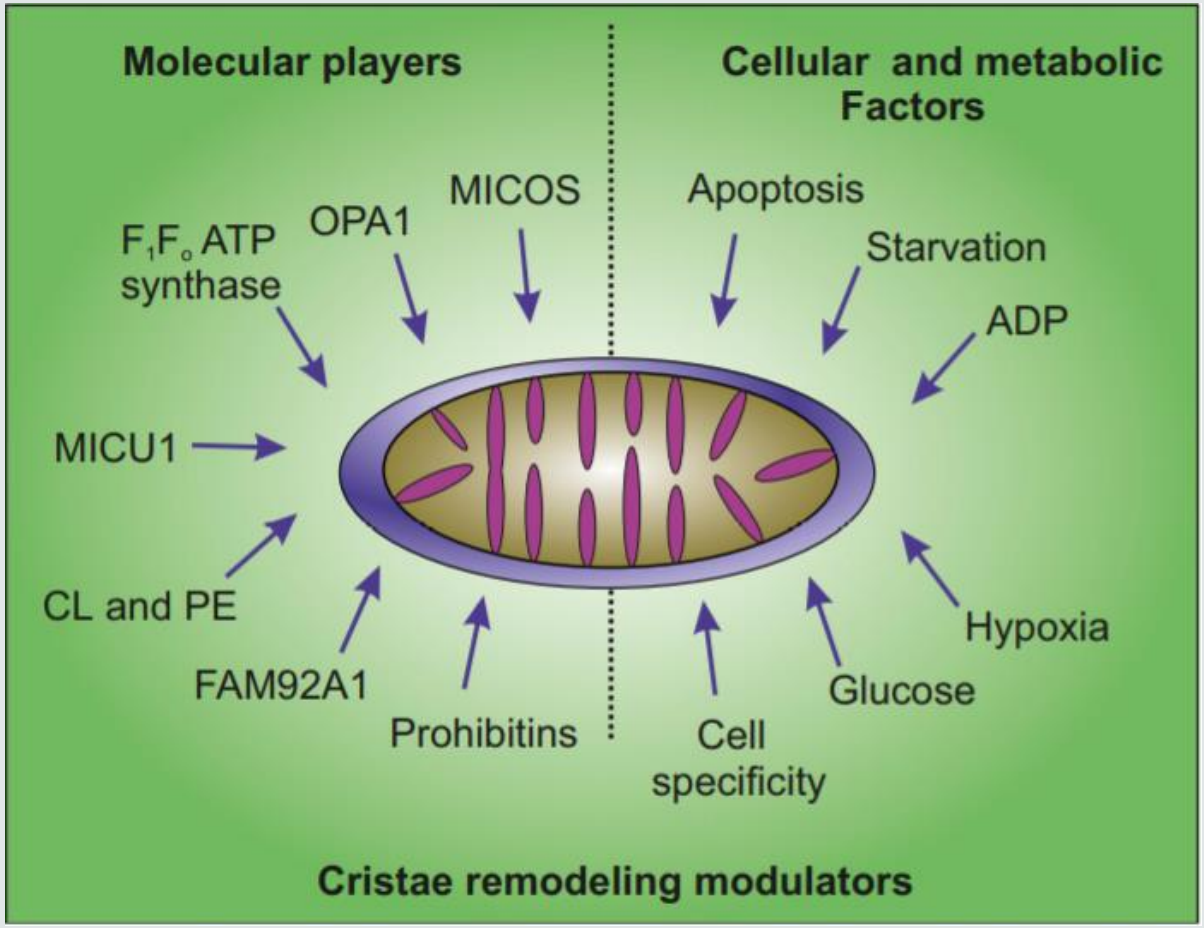


M. Eramo et al., J. Biochem. 2020;167(3):243–255

MICOS: mitochondrial contact site and cristae organizing system

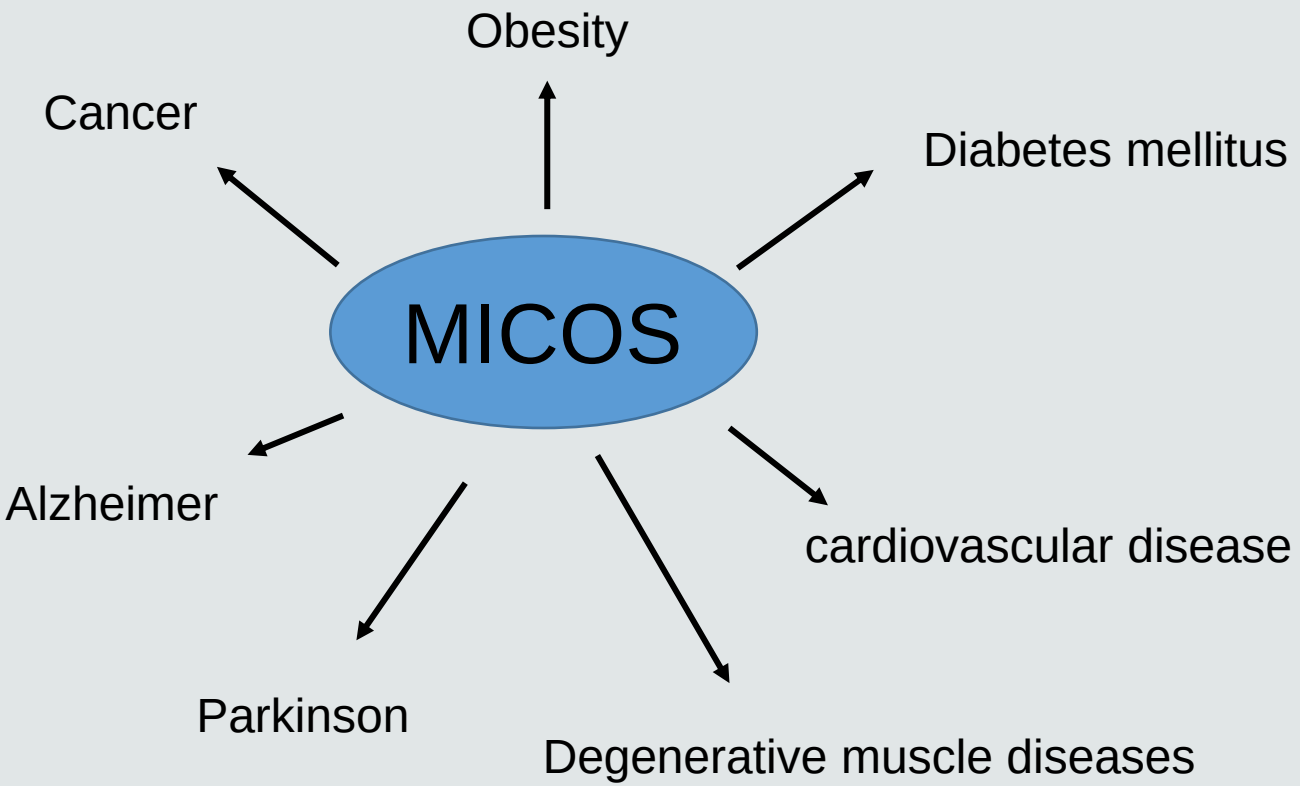
MIB: mitochondrial intermembrane space bridging complex

L’organisation interne des mitochondries dépend de nombreux facteurs

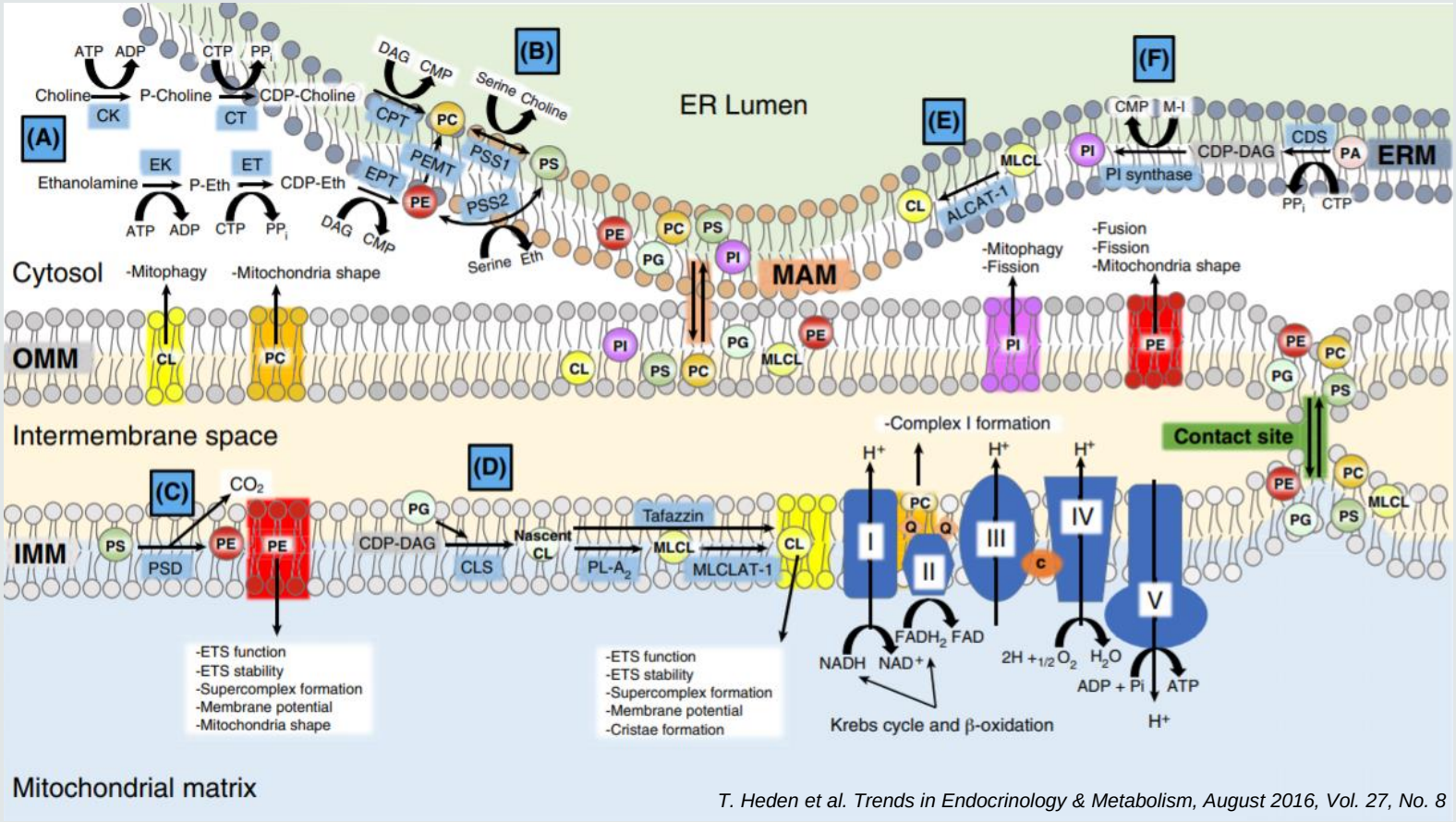


A. Kondadi et al., Trends in Cell Biology, 2020

Organisation des crètes et pathologies



Synthèse des phospholipides mitochondriaux



T. Heden et al. Trends in Endocrinology & Metabolism, August 2016, Vol. 27, No. 8

Muscle squelettique

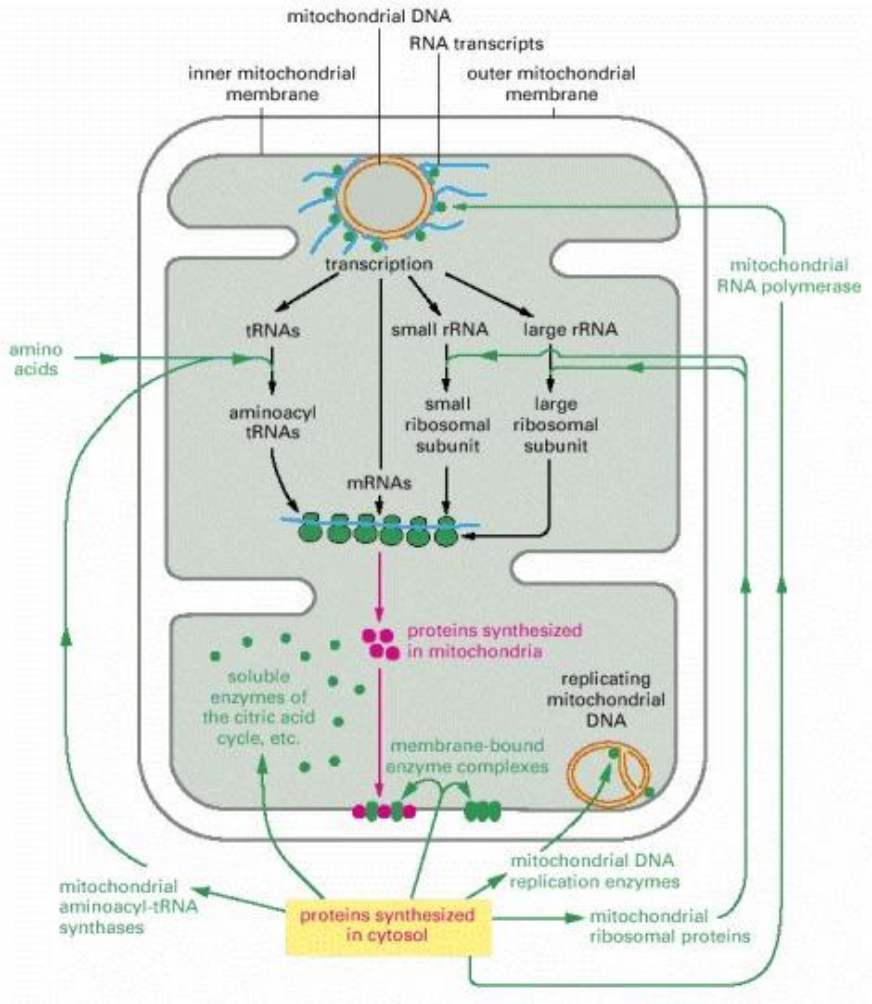
PC (40%), PI (7%) : **RE**

CL (15%) : **Mito**

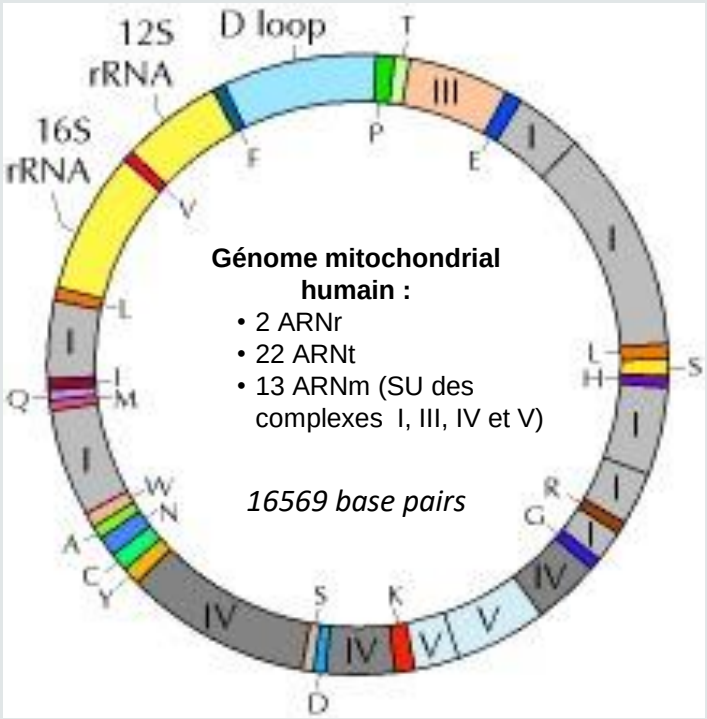
PE (30%) : **RE + <u>Mito</u>**

Abbreviations: ALCAT-1, acyl-CoA: lysocardiolipin acyltransferase-1; c, cytochrome c; CDS, CDP-DAG synthase; CK, cholinekinase; CL, cardiolipin; CLS, cardiolipin synthase; CPT, CDP-choline phosphotransferase; CT, CTP:phosphocholine cytidylyltransferase; DAG, diacylglycerol; Eth,ethanolamine; EK, ethanolamine kinase; ER, endoplasmic reticulum, ERM, ER membrane; EPT, CDP-ethanolamine phosphotransferase; ET, CTP:phosphoethanolamine cytidylyltransferase; ETS, electron transport system; IMM, inner mitochondrial membrane; MAM, mitochondrial associated membrane; M-I, myo-inositol; MLCLAT-1, monolysocardiolipin acyltransferase-1; OMM, outer mitochondrial membrane; PA, phosphatidic acid; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PEMT, phosphatidylethanolamine N-methyltransferase; PG, phosphatidylglycerol; PI, phosphatidylinositol; PL-A2, phospholipase-A2; PS, phosphatidylserine; PSD, phosphatidylserine decarboxylase; PSS1/2, phosphatidylserine synthase 1/2; Q, coenzyme Q10

Synthèse des protéines mitochondriales



Alberts et al. in Molecular Biology of the cell, 4th edition, Garland Science



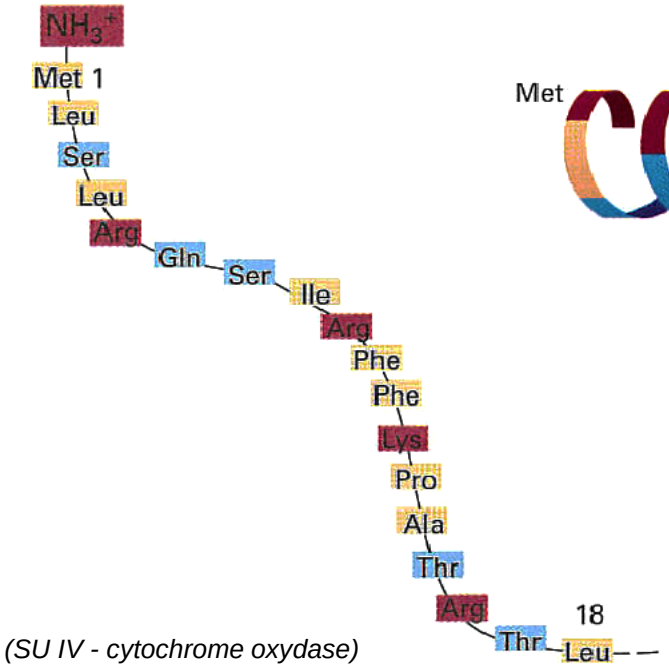
Codon	Universal code	Human mitochondrial code
UGA	STOP	Trp
AGA	Arg	STOP
AGG	Arg	STOP
AUA	Ile	Met

The Cell: A Molecular Approach. 2nd edition. Cooper GM. Sunderland (MA): Sinauer Associates; 2000.

Import des protéines synthétisées dans le cytosol

Matériel nécessaire

Séquence signal d'import mitochondrial

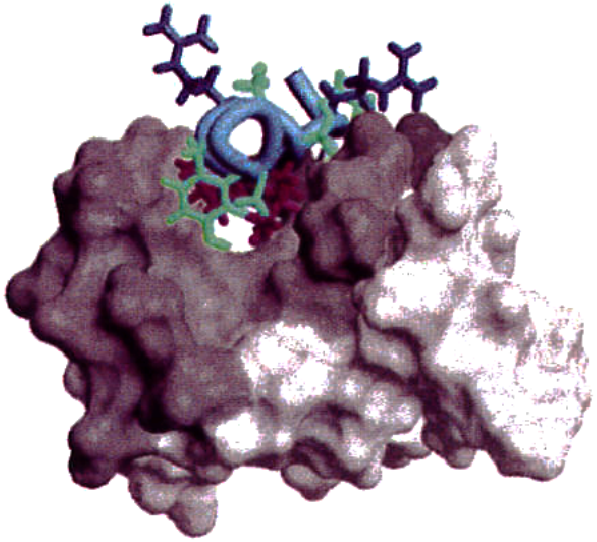


(SU IV - cytochrome oxydase)

Hélicie α

AA chargés +

AA hydrophobes



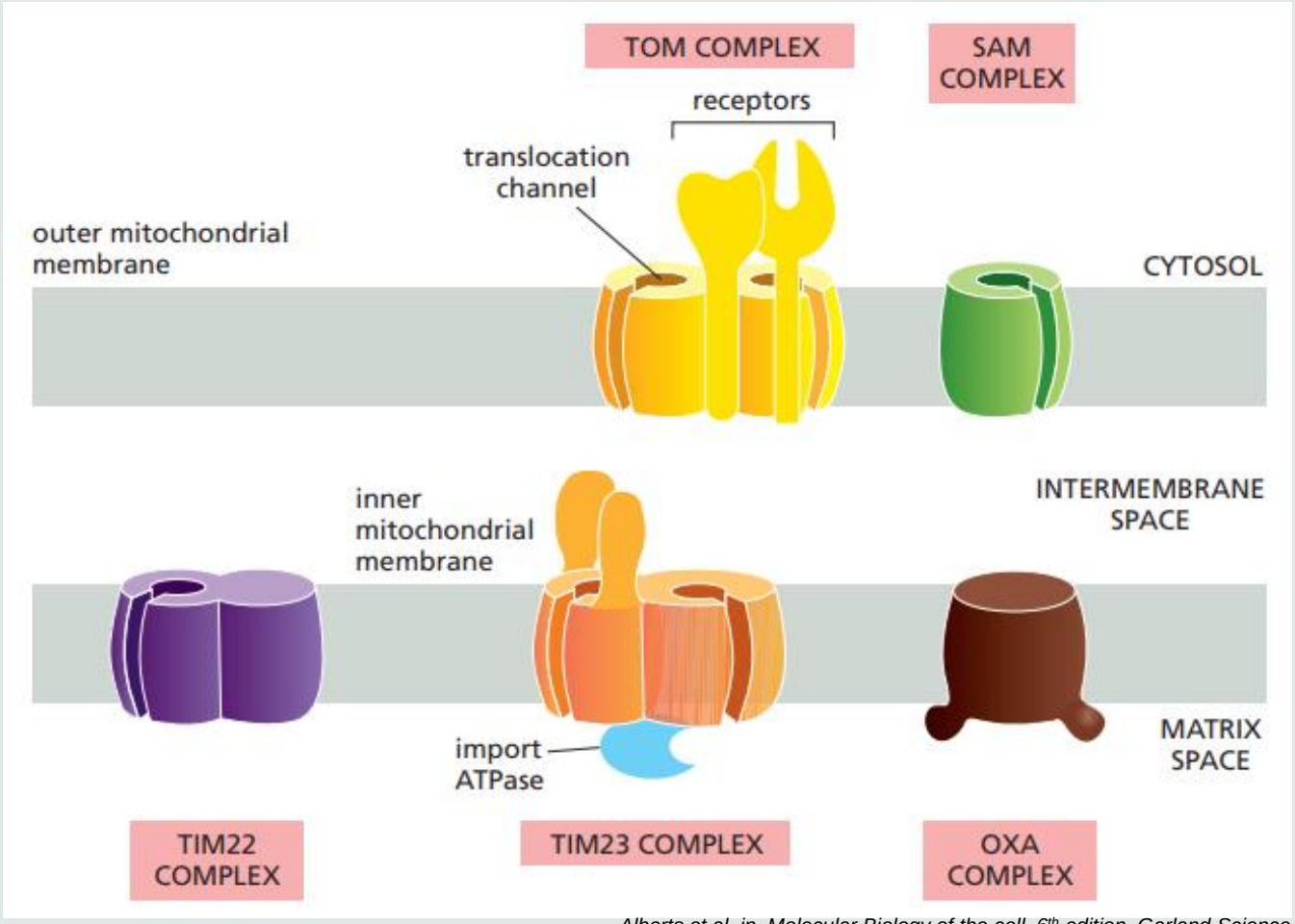
(Alcohol dehydrogénase + importreceptor)

Alberts et al. in Molecular Biology of the cell, 6th edition, Garland Science

Import des protéines synthétisées dans le cytosol

Matériel nécessaire

Transporteurs membranaires



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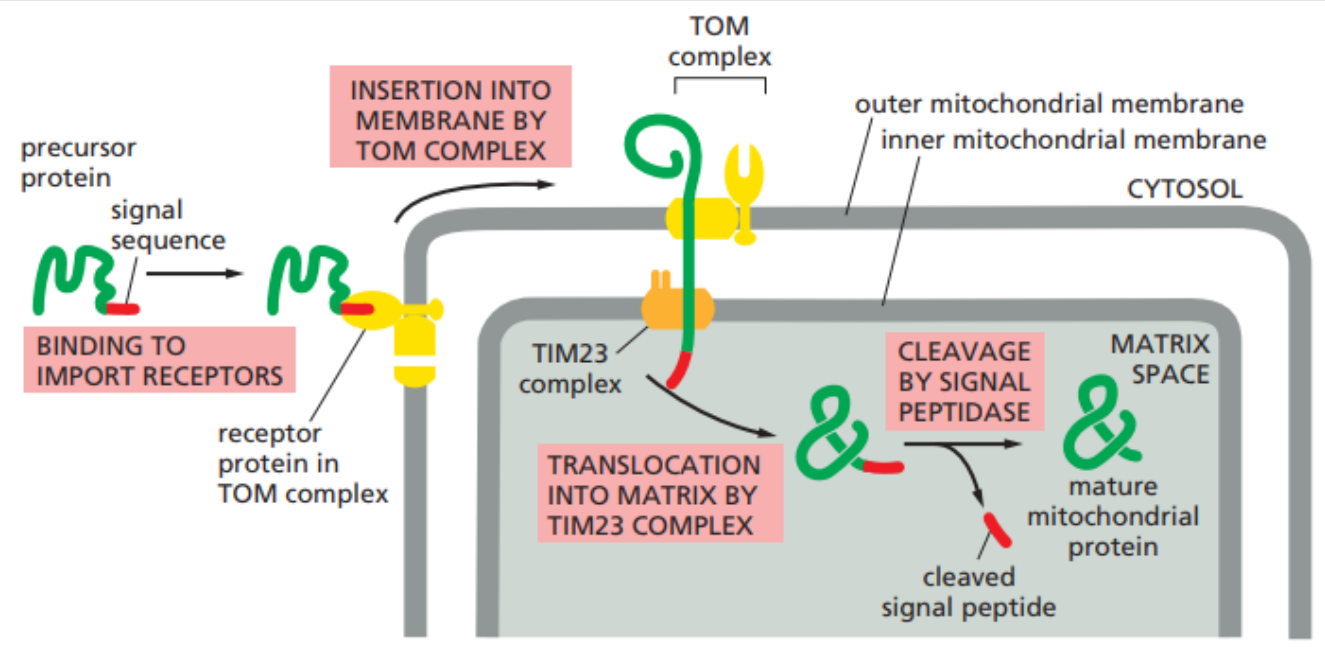
Import des protéines synthétisées dans le cytosol

Schéma général



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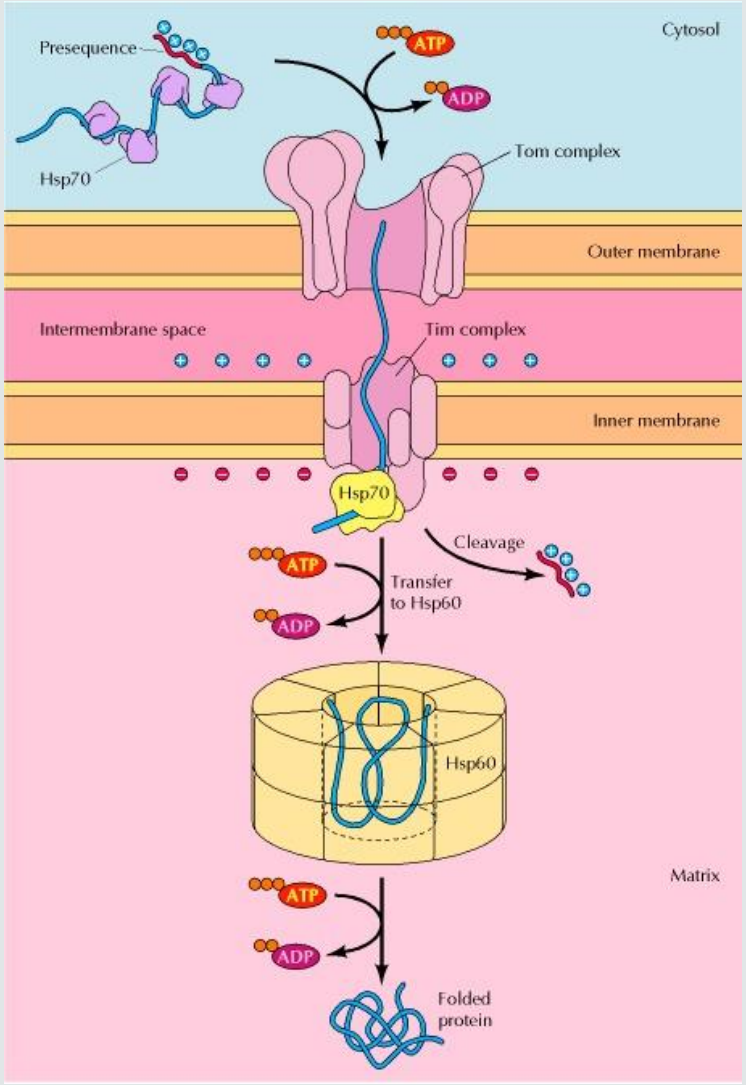
Import des protéines synthétisées dans le cytosol

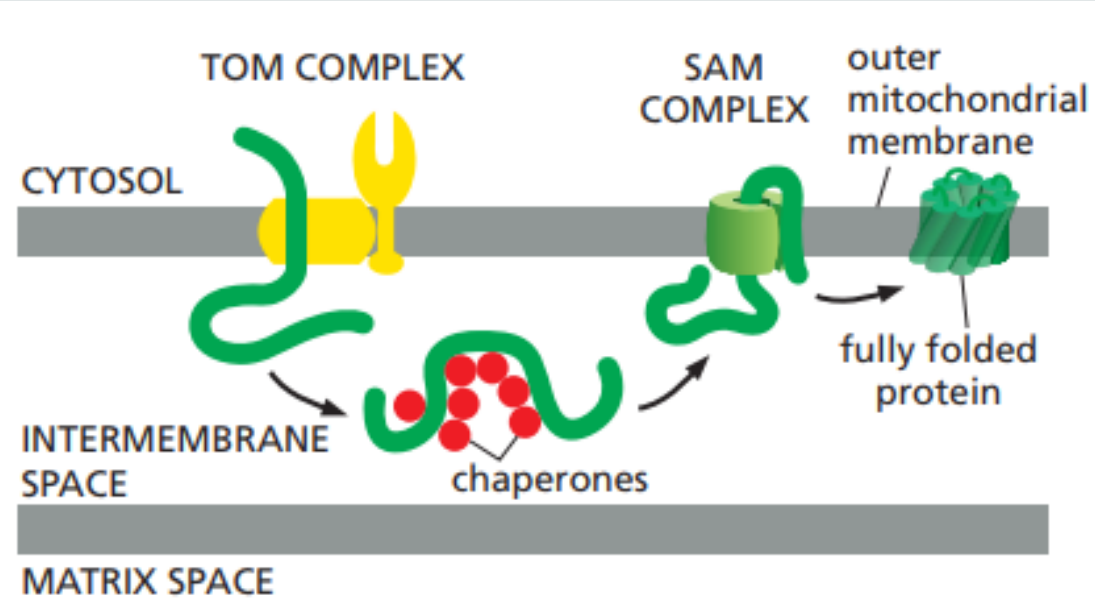
Hydrolyse d'ATP et gradient de protons



The Cell: A Molecular Approach. 2nd edition. Cooper GM. Sunderland (MA): Sinauer Associates; 2000.

Import des protéines synthétisées dans le cytosol

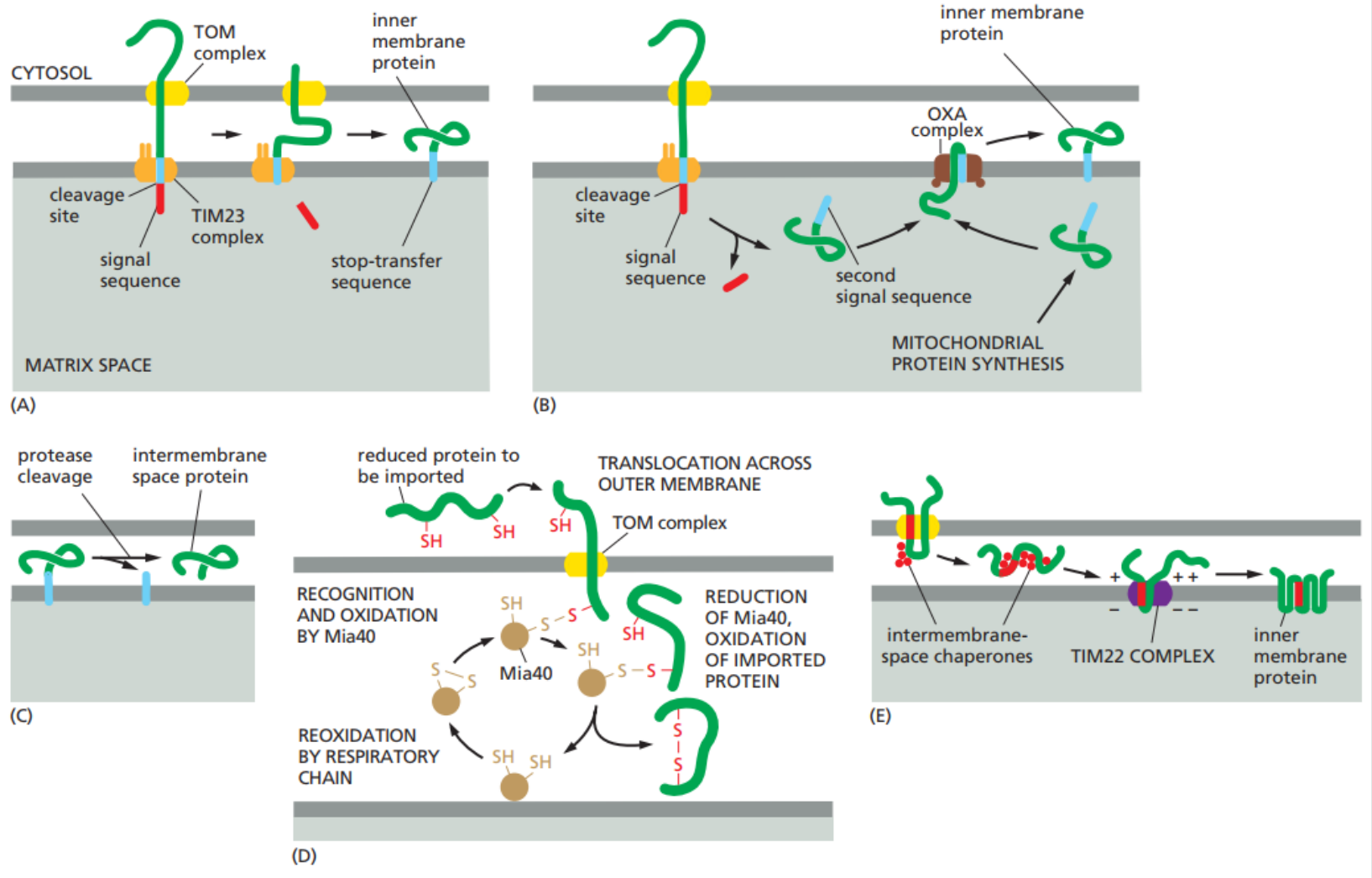
Protéines de la membrane externe



Alberts et al. in Molecular Biology of the cell, 6th edition, Garland Science

Import des protéines synthétisées dans le cytosol

Protéines de la membrane interne ou de l'espace intermembranaire



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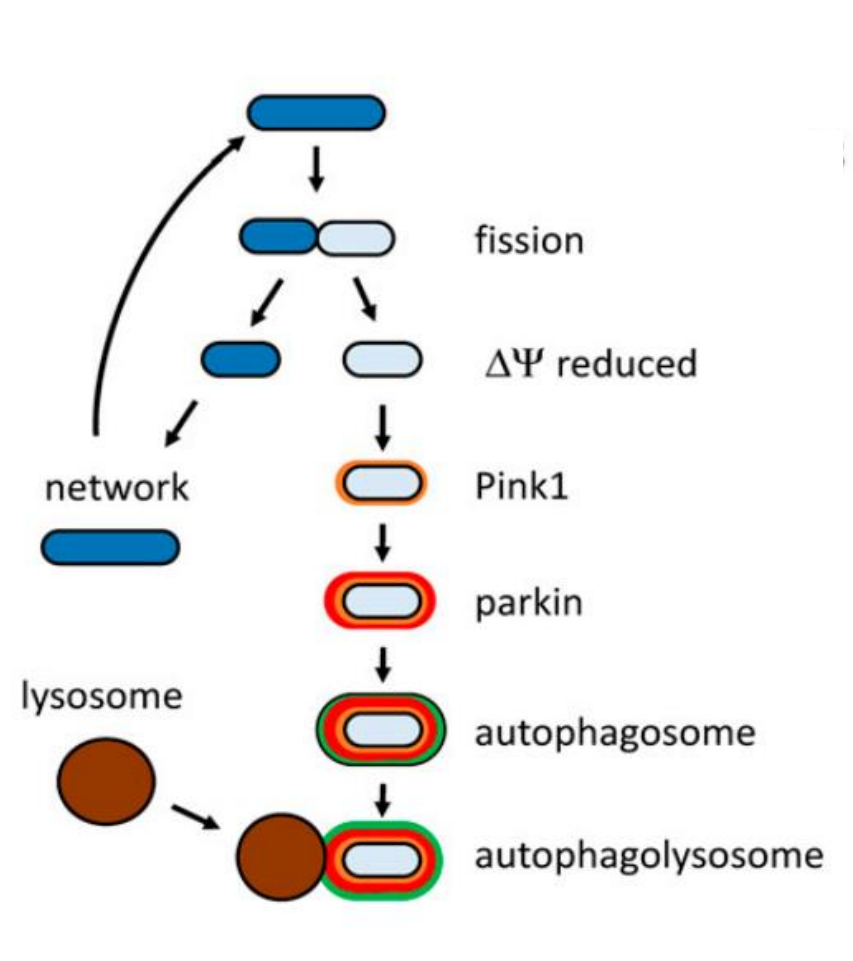
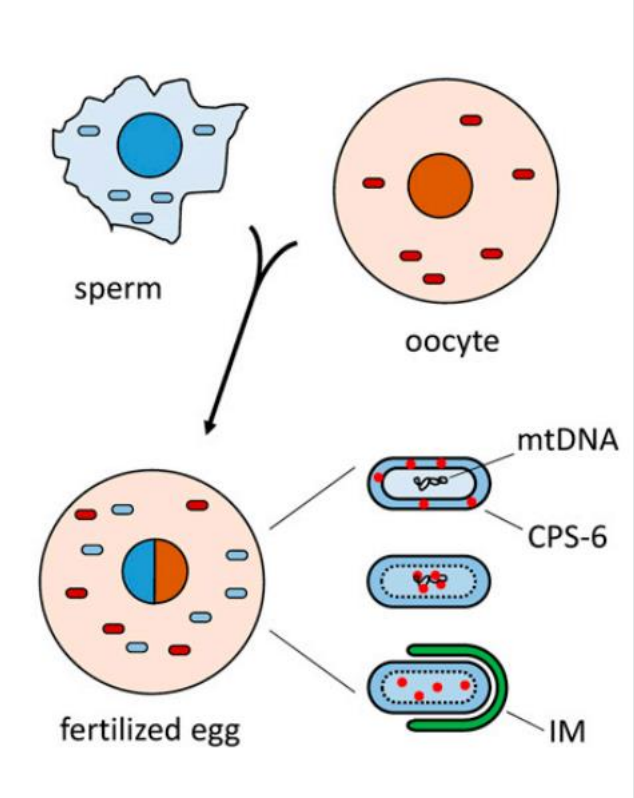
Elimination des mitochondries : mitophagie



Van Der Bliek A.M. et al. Genetics, Vol. 207, 843–871

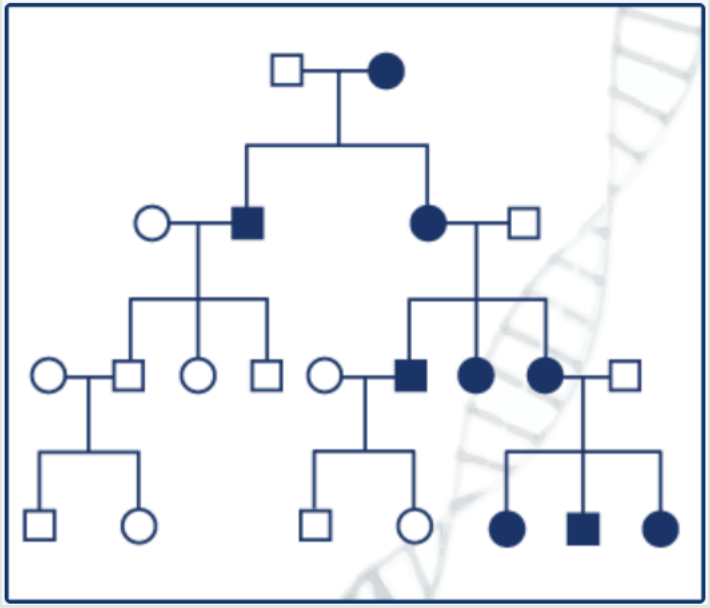
Autre rôle de la mitophagie

Elimination of mitochondries paternelles lors de la fécondation



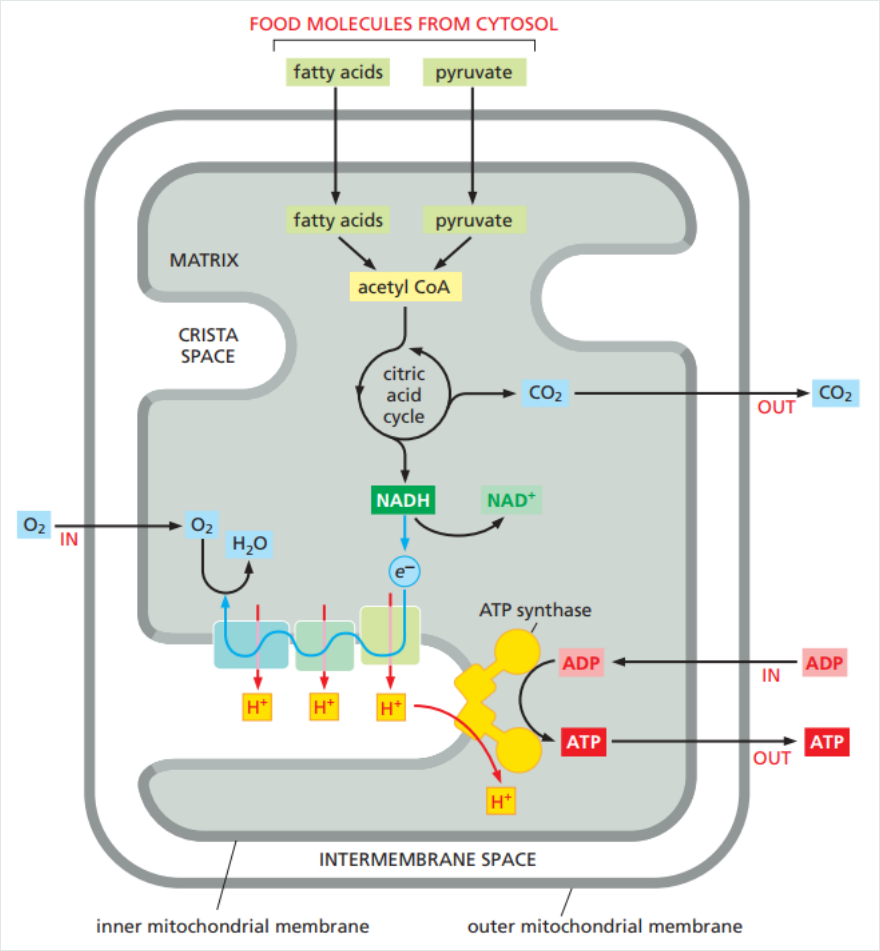
Van Der Bliek A.M. et al. Genetics, Vol. 207, 843–871

Conséquence sur la transmission des pathologies dues à une mutation de l'ADN mitochondrial



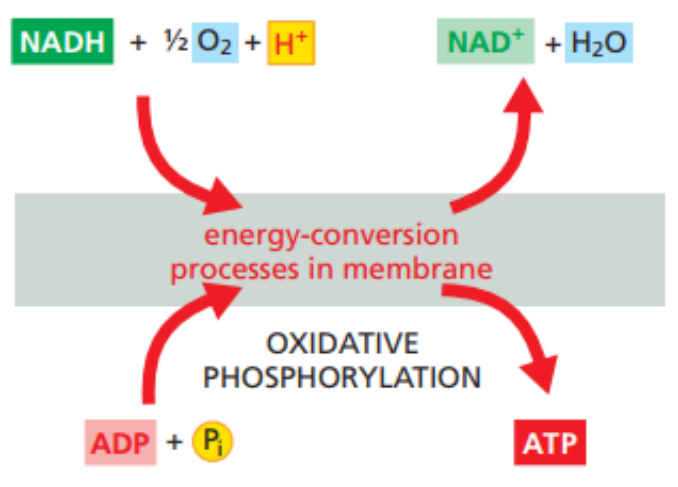
Métabolisme énergétique dans la mitochondrie

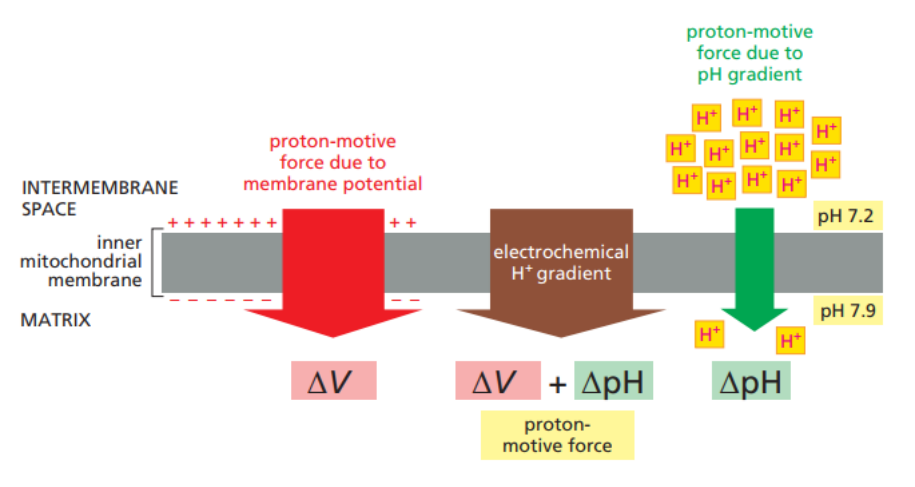
Schéma général



Alberts et al. in Molecular Biology of the cell, 6th edition, Garland Science

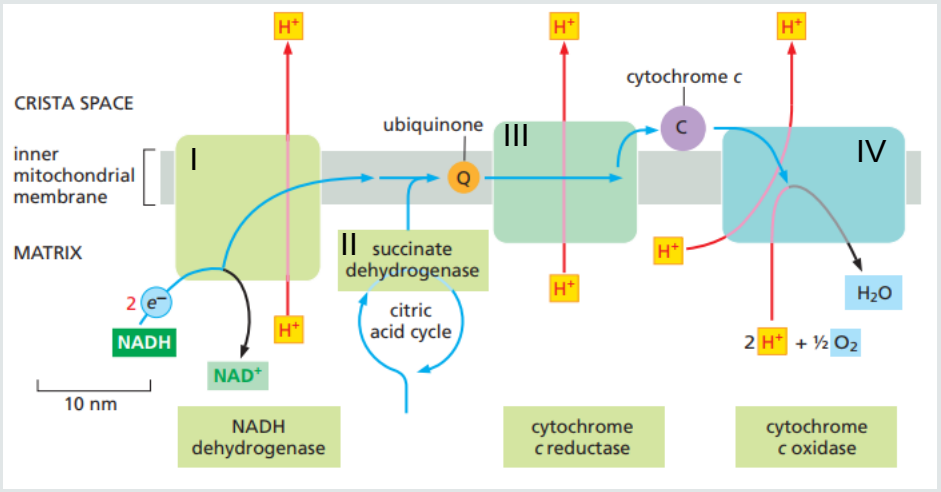
Gradient électrochimique de protons
Conversion d'énergie

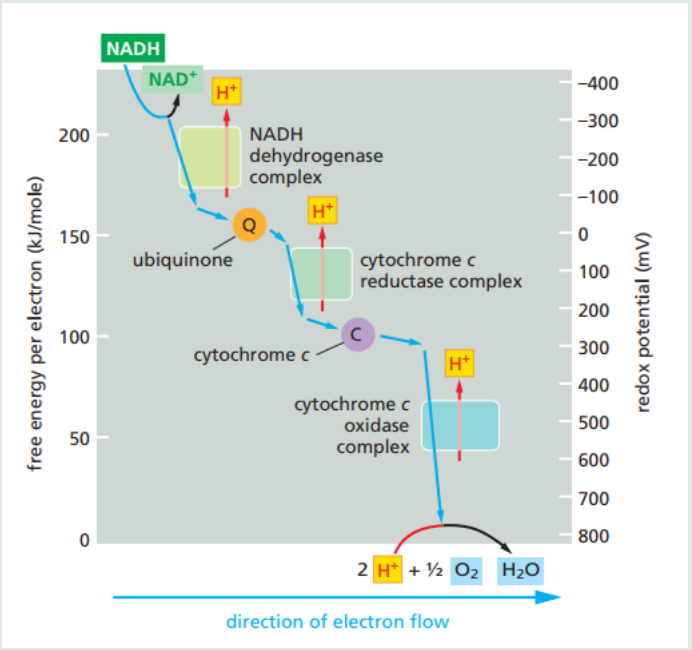


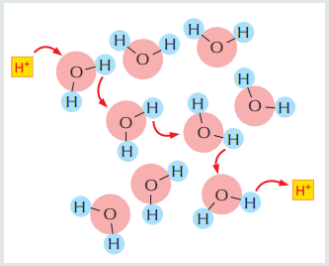


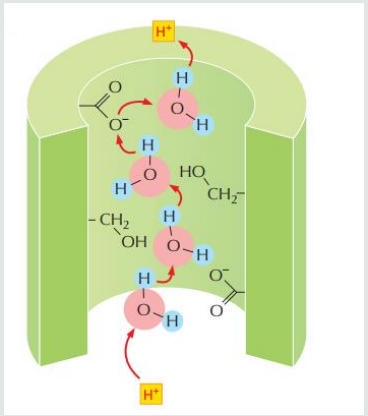
Alberts et al. in Molecular Biology of the cell, 6th edition, Garland Science

La chaine respiratoire mitochondriale









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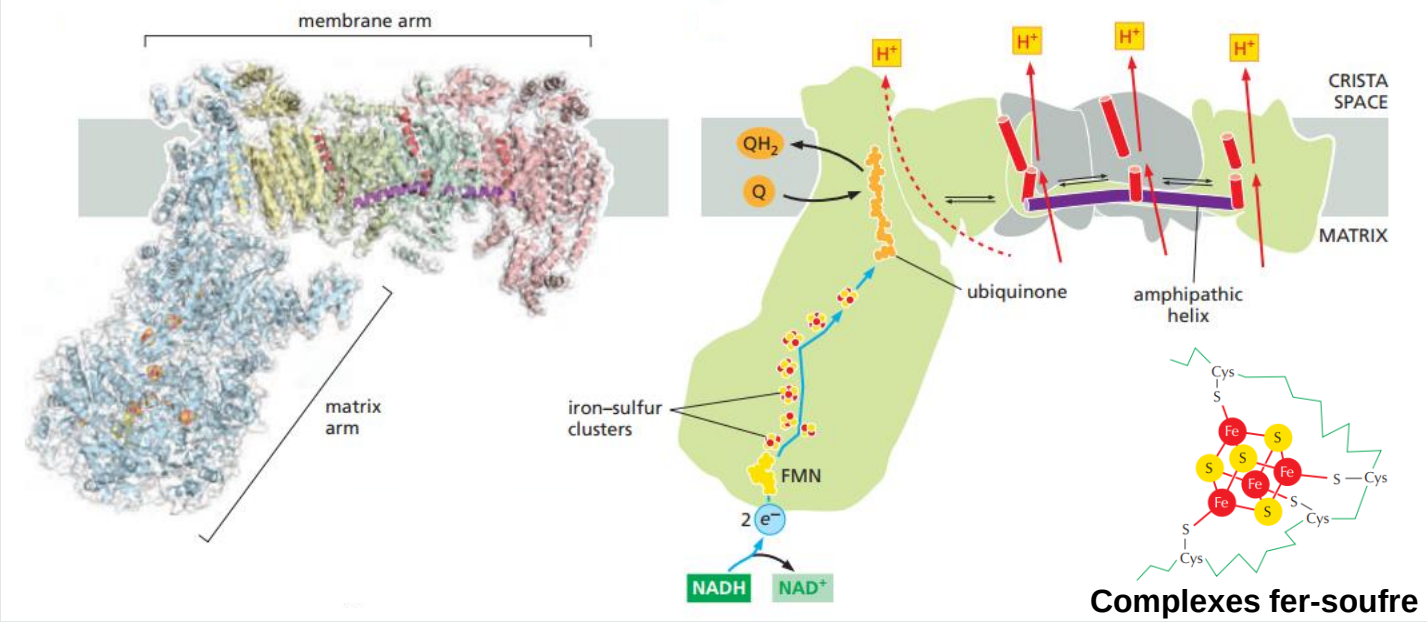
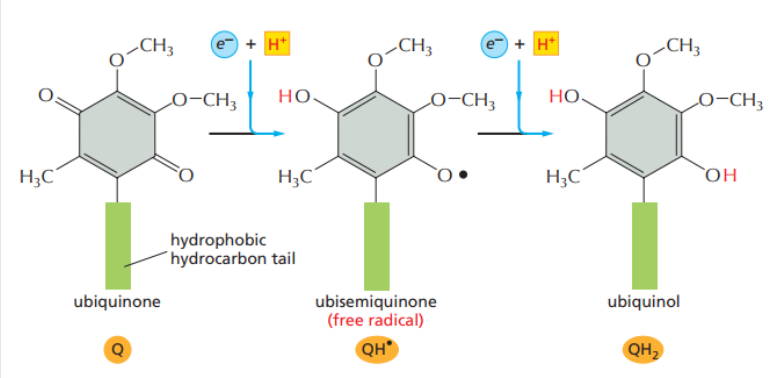
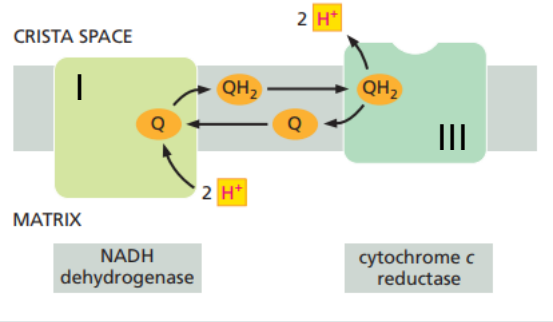
NADH déshydrogénase (complexe I)







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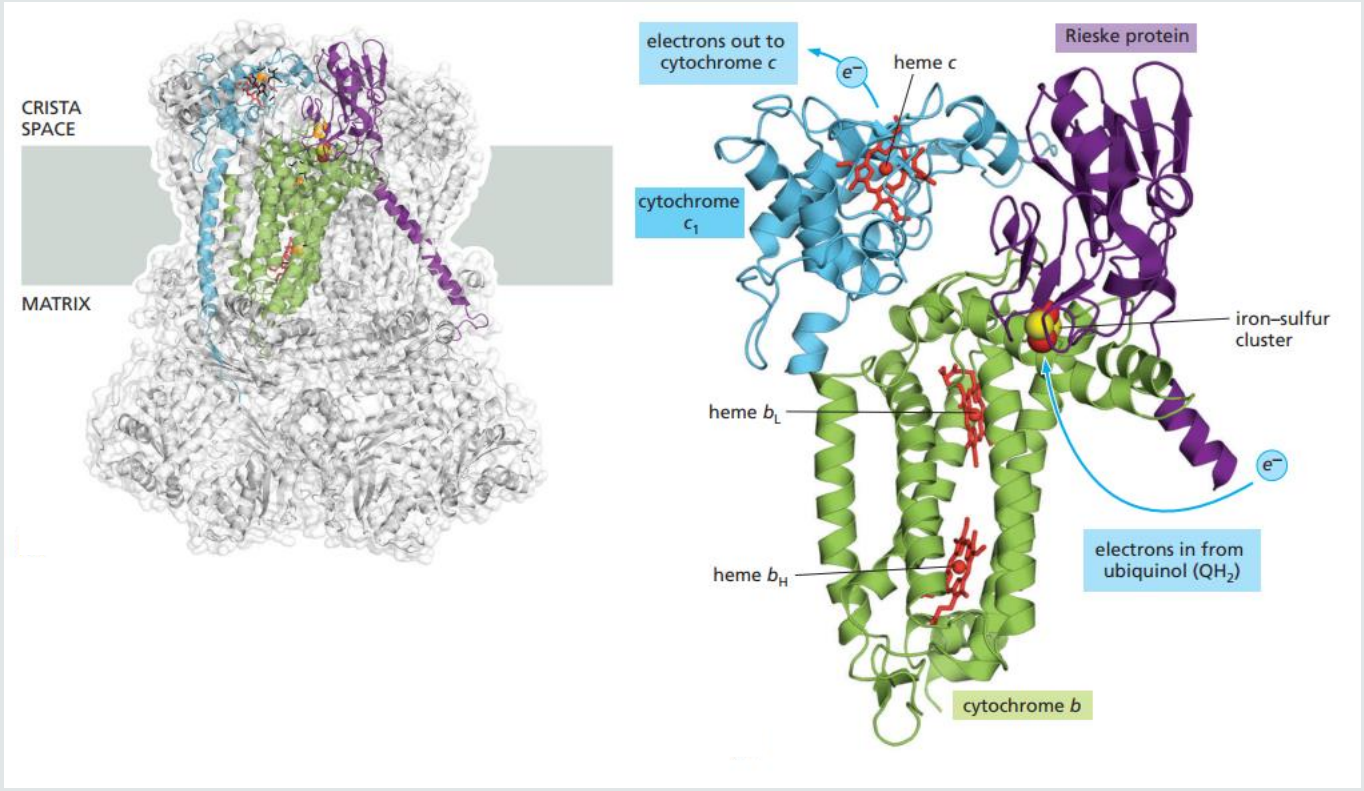
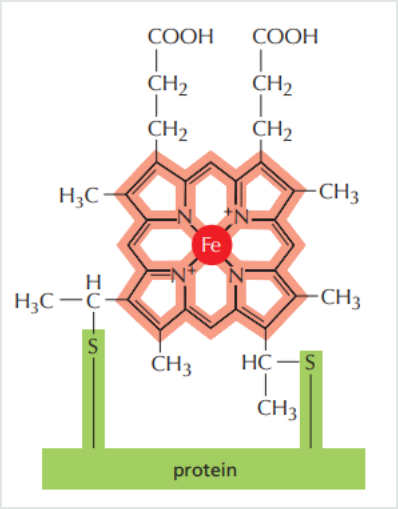
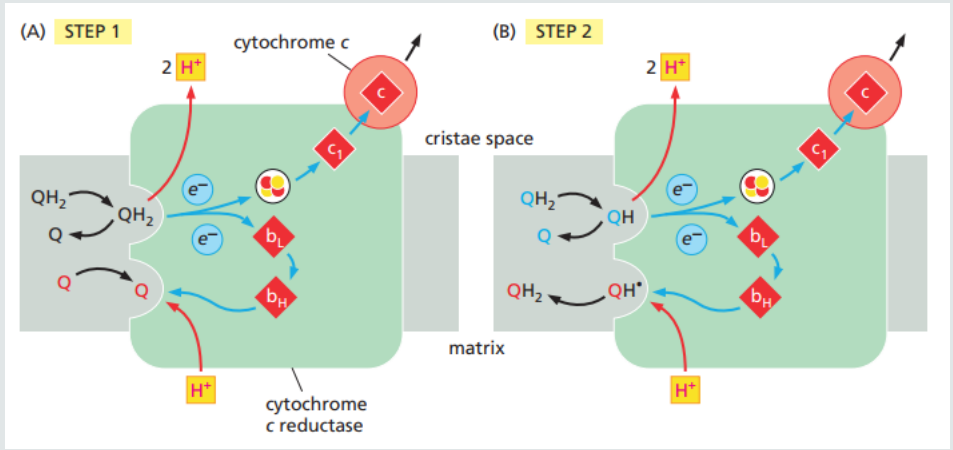
Cytochrome c réductase (complexe III)





Hème (cytochrome c)



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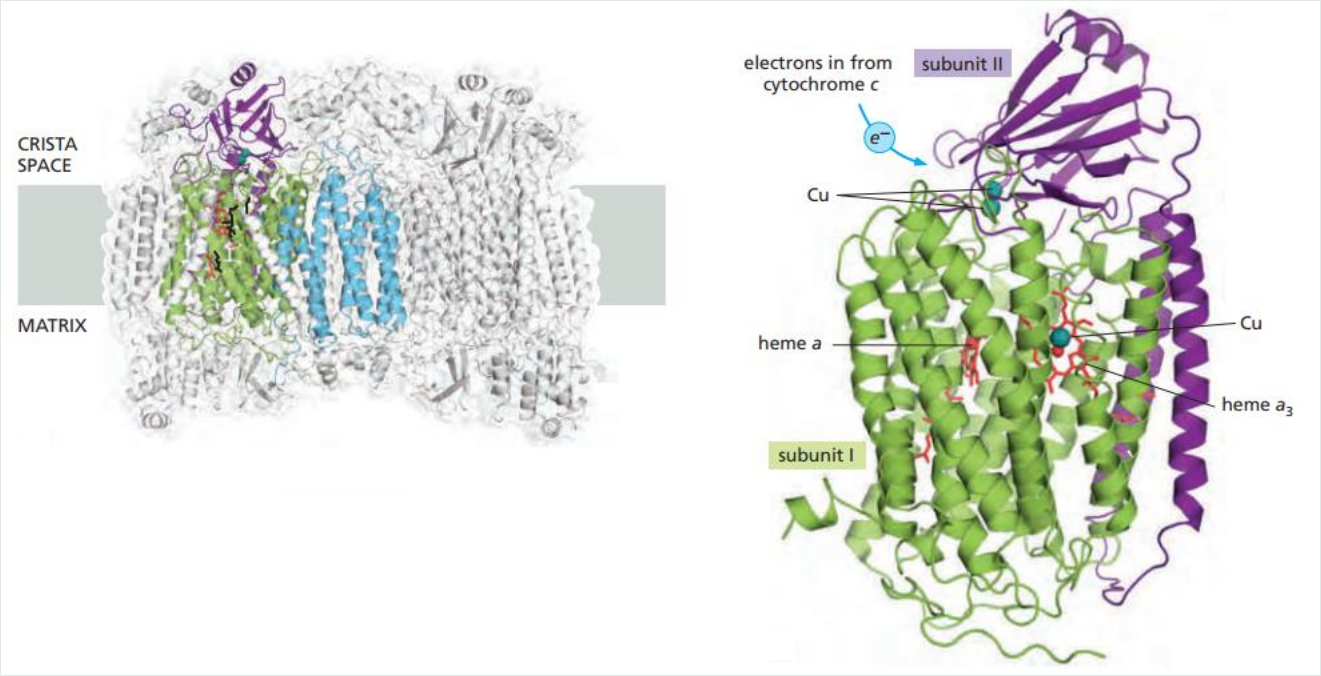
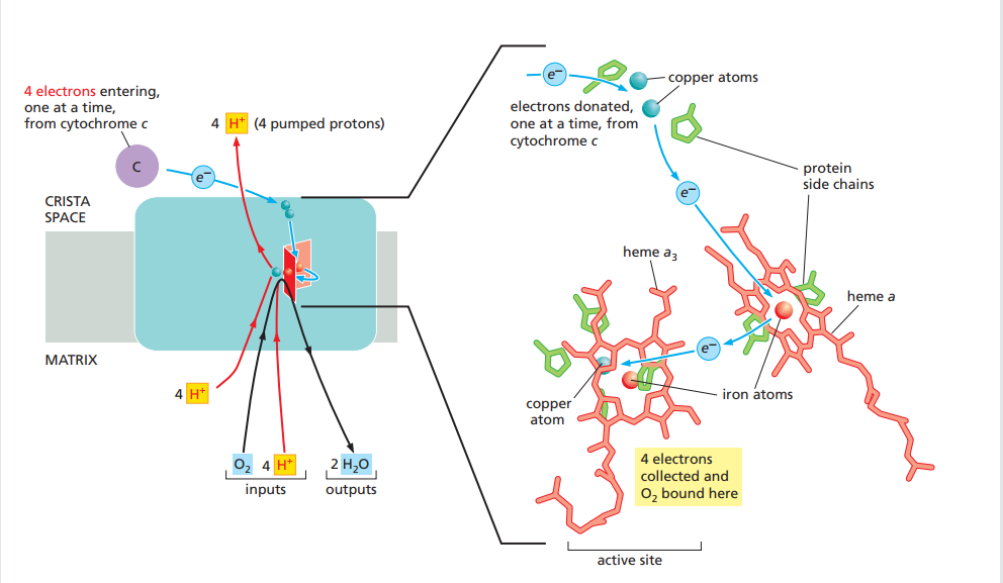
Cytochrome c oxydase (complexe IV)





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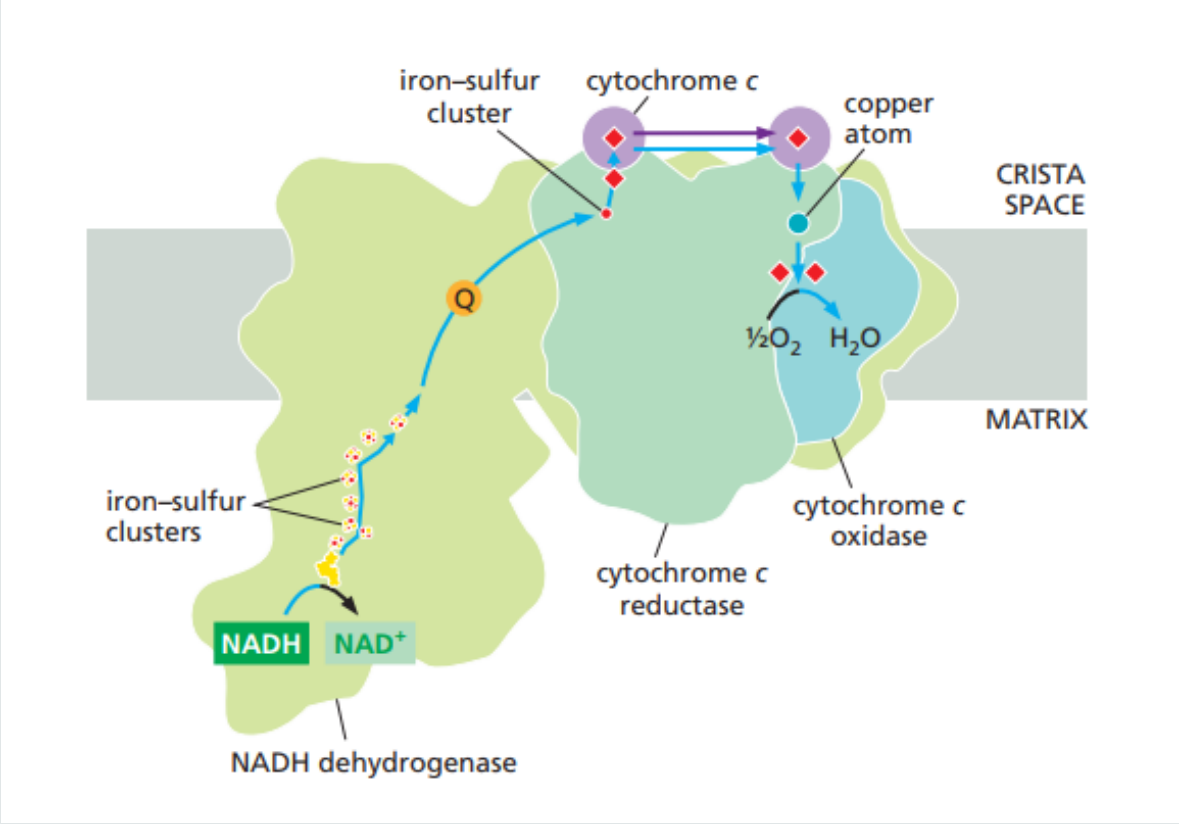
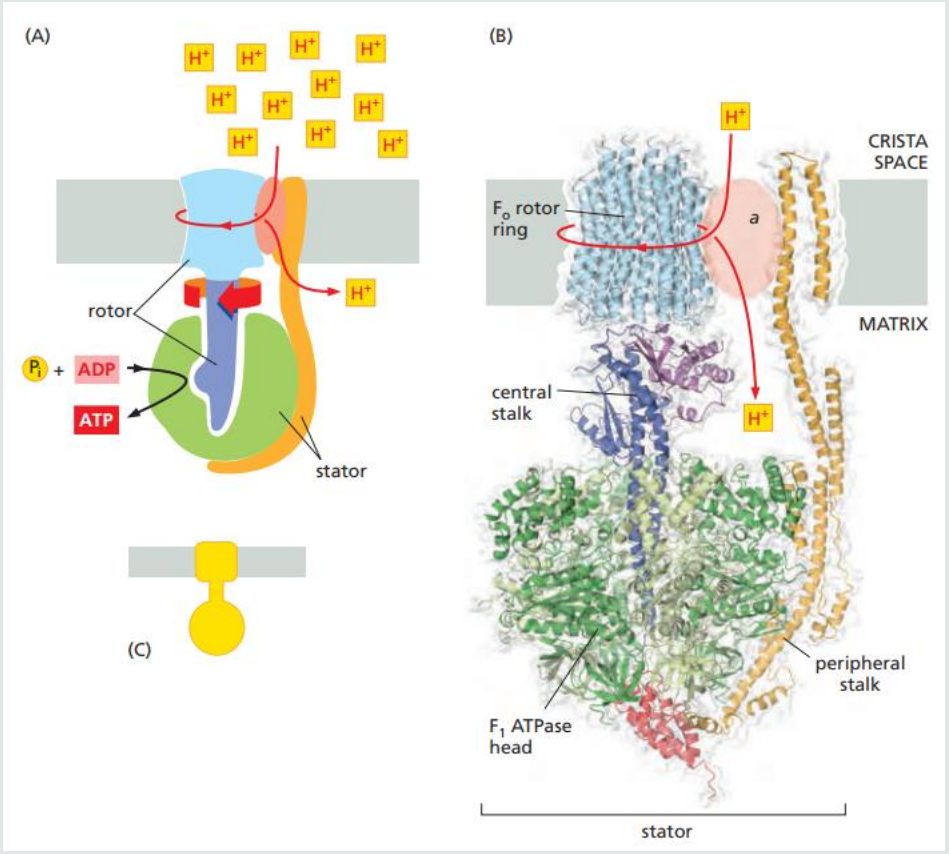
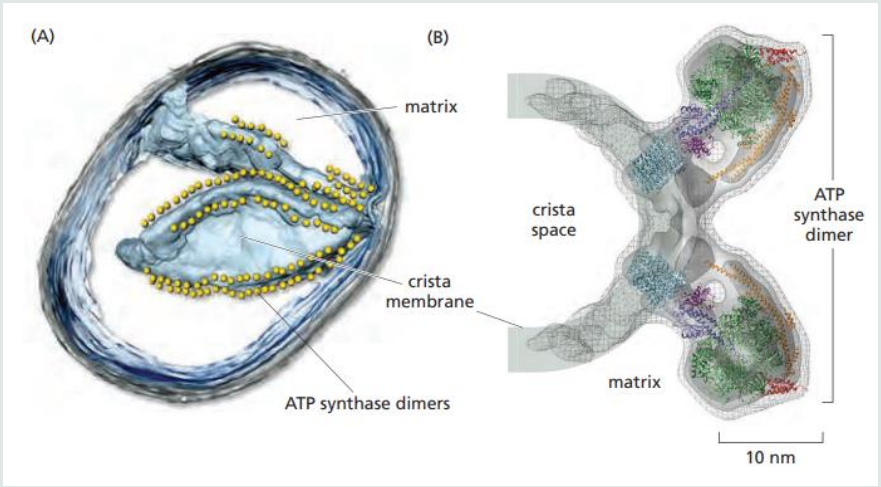
Les sous-unités de la chaine respiratoire forment des supercomplexes dans la membrane mitochondriale interne



ATP synthase et phosphorylation oxydative





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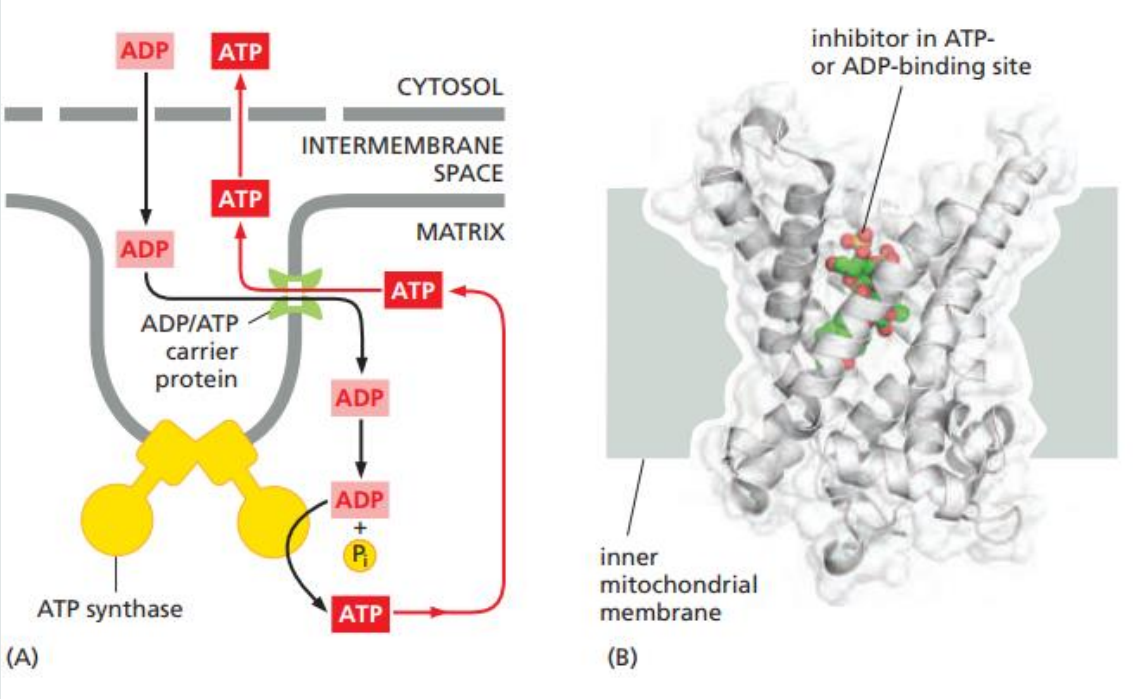
Transporteurs ATP/ADP



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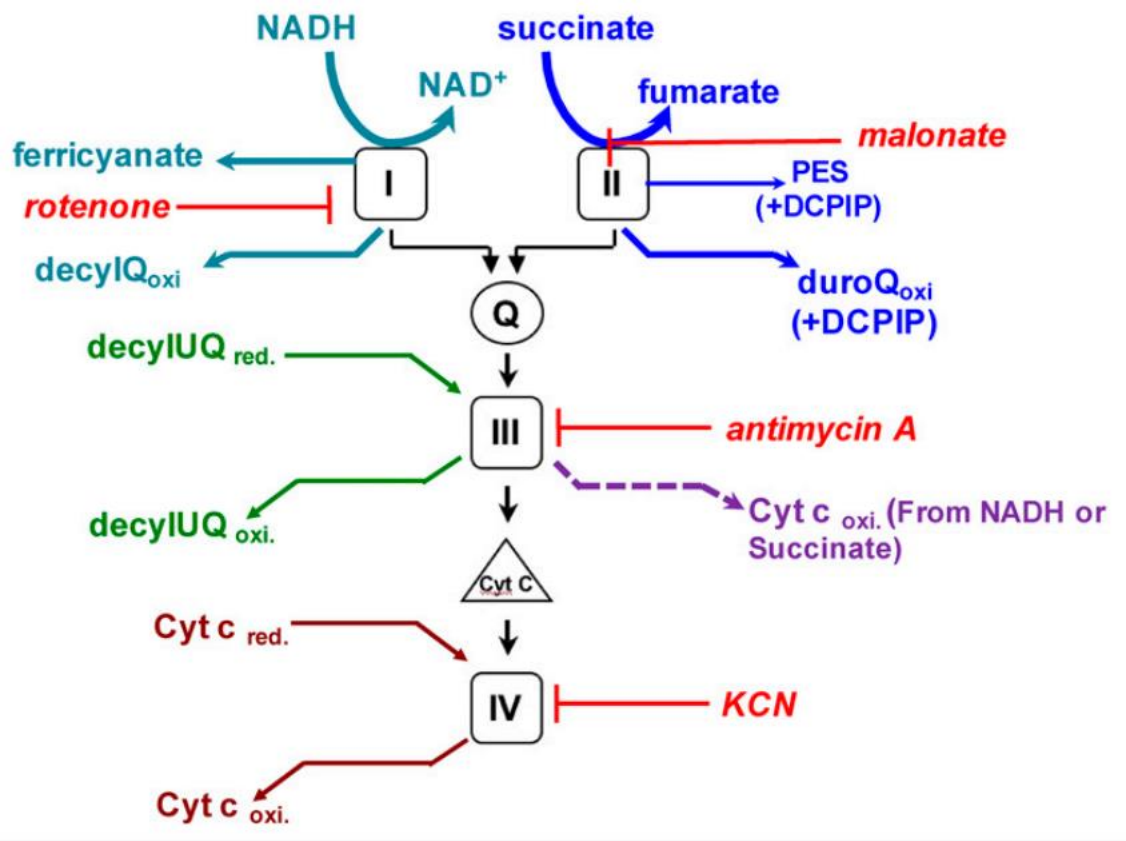
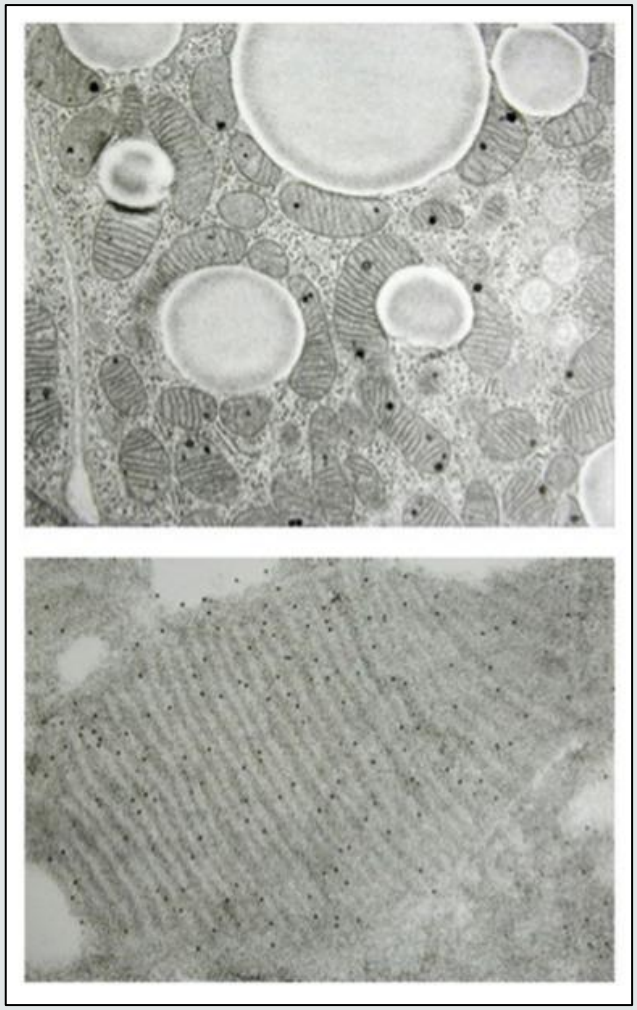
Inhibiteurs de la chaine respiratoire

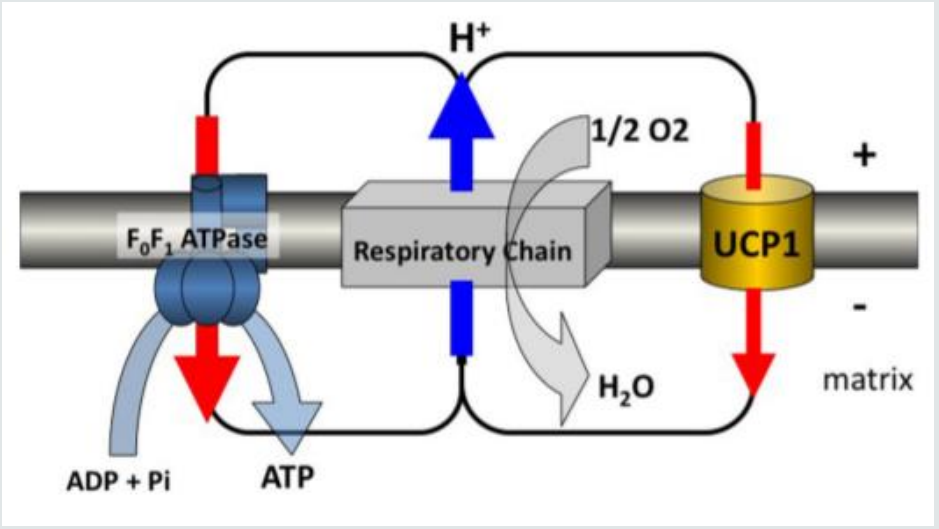


La chaine respiratoire peut participer à la thermorégulation

Tissu adipeux brun

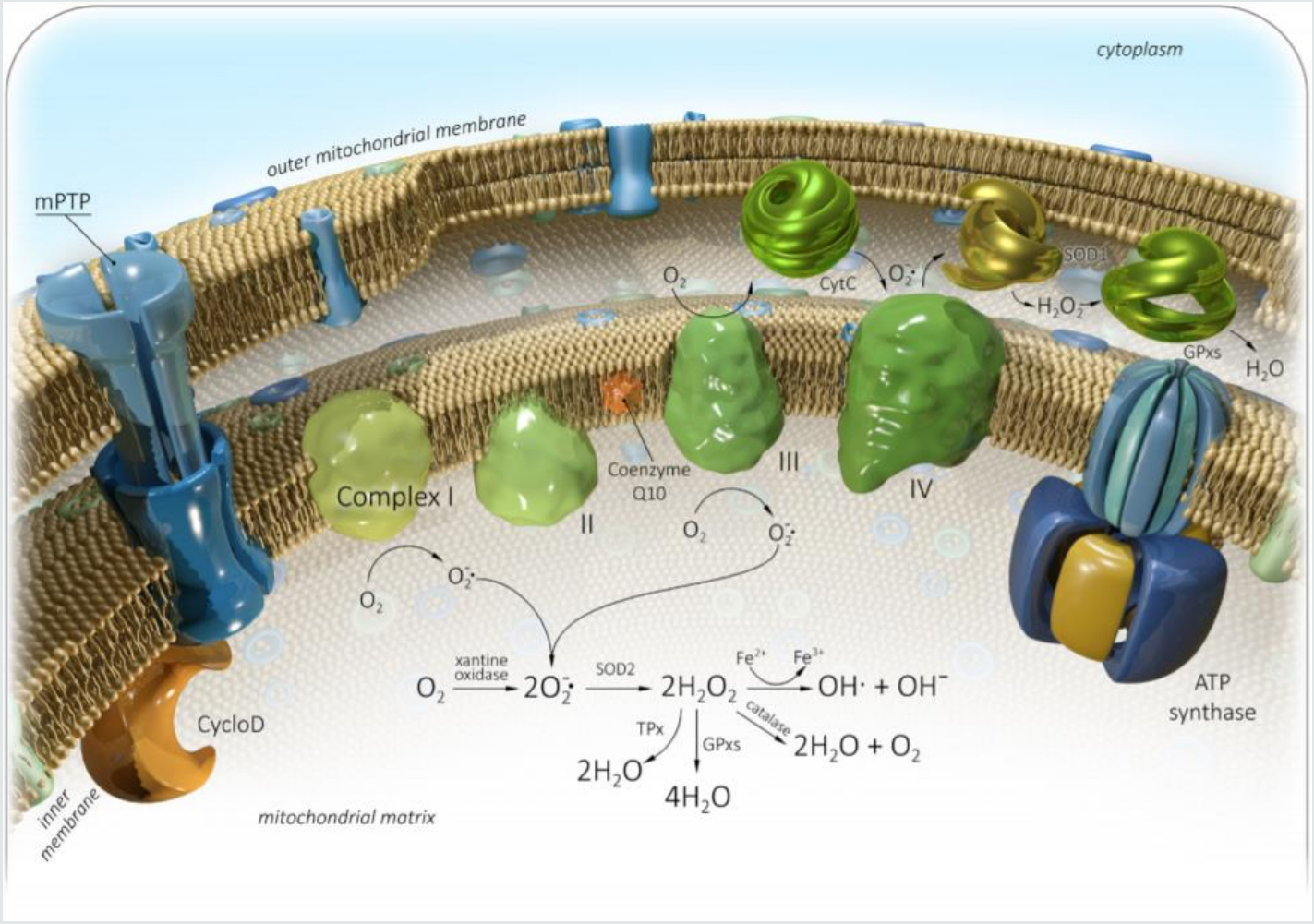


Marquage UCP1



Libération de chaleur

Génération d'espèces réactives de l'oxygène par la chaine respiratoire



A. Kudryavtseva et al., 2016, Oncotarget, Vol. 7, No. 29

Formation et détoxification des ERO

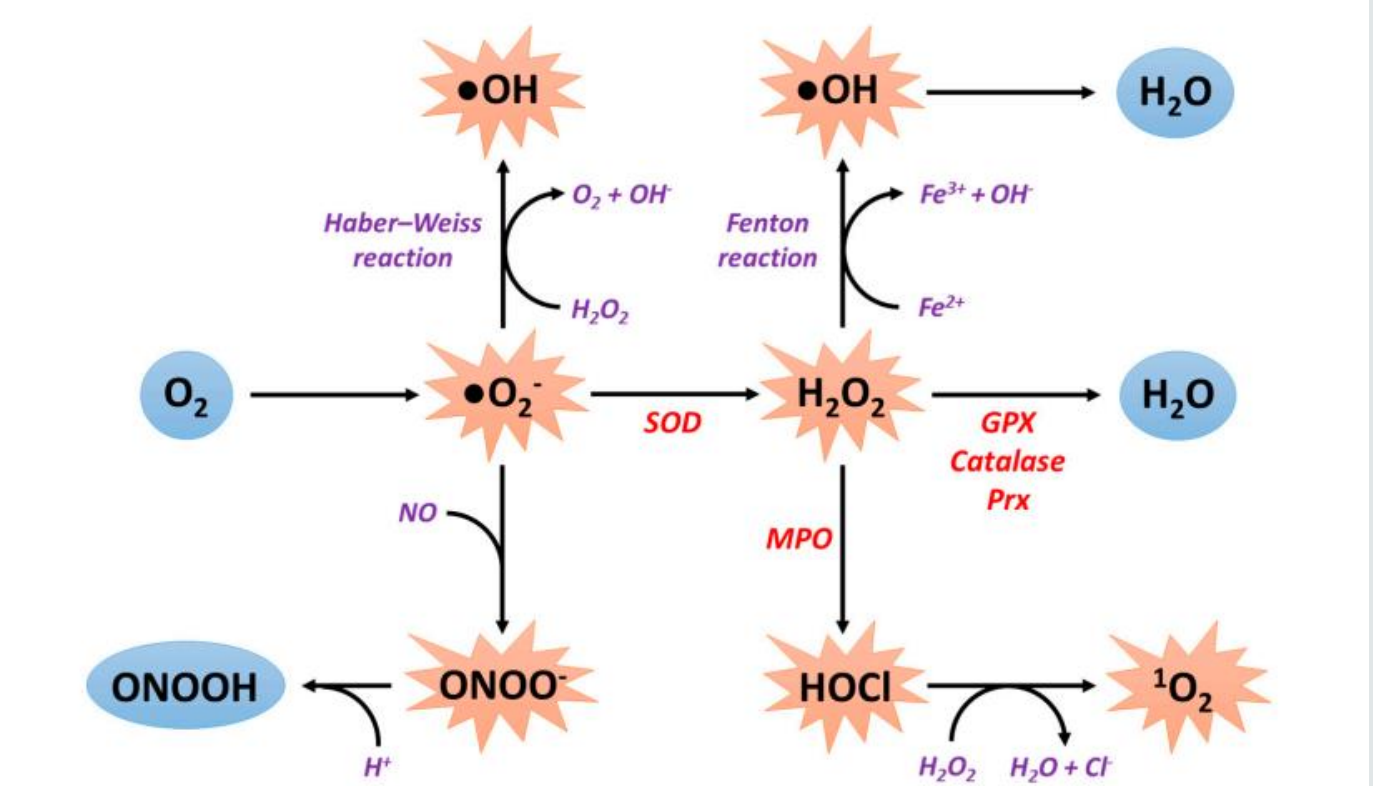


Figure 1. ROS formation and detoxification. $^1O_2$: singlet oxygen; Cl^-: chloride ion; Fe^{2+}: iron (II) ion; Fe^{3+}: iron (III) ion; GPX: glutathione peroxidase; H^+: proton; H_2O: water; H_2O_2: hydrogen peroxide; HOCl: hypochlorous acid; MPO: myeloperoxidases; NO: nitric oxide; O_2: dioxygen; $\bullet O_2^-$: superoxide anion; •OH: hydroxyl radical; ONOO-: peroxynitrite; ONOOH: peroxynitrous acid; Prx: peroxiredoxins; SOD: superoxide dismutases.

E. Dubois-Deruy et al., Antioxidants 2020, 9, 864

Production de différentes ERO

Reactive oxygen species	Intracellular sources	Compartment
Hydroxyl radical (OH•)	Proton-catalyzed decomposition of peroxynitrite Fenton reaction Haber-Weiss reaction Decomposition of ozone (O3) Beckman-Radi-Freeman pathway	Mitochondria Cytosol Endoplasmic reticulum Lysosome
Hydrogen peroxide (H2O2)	Superoxide dismutase (SOD)-mediated reaction NADPH oxidase-mediated reaction Cytochrome P450-mediated reaction Xanthine oxidase (XO)-mediated reaction Monoamine oxidases (MAO)-mediated reaction Peroxisomal fatty acid oxidation Flavin adenine dinucleotide (FAD)-mediated reaction Antibody-catalyzed water (H2O) oxidation Electron-transfer flavoprotein pathway	Mitochondria Cytosol Peroxisomes Plasma membrane Endosomes Endoplasmic reticulum Lysosome Nucleus
Superoxide anion (O2•−)	Fenton reaction NADH/NADPH oxidase (NOX)-mediated reaction Xanthine oxidase (XO)-mediated reaction Lipoxygenase pathway Cyclooxygenase pathway Cytochrome P450 monooxygenase reaction Mitochondrial oxidative phosphorylation Electron-transfer flavoprotein reaction Hemoglobin auto-oxidation (within erytrocyte) Nitric oxide synthases (NOS)-mediated reaction	Mitochondria Cytosol Plasma membrane Peroxisomes Nucleus Endoplasmic reticulum
Hydroxyl ion (OH-)	Fenton reaction Haber-Weiss reaction Hydroperoxide (ROOH) decomposition	Mitochondria Cytosol Endoplasmic reticulum Lysosome

A. Kudryavtseva et al., 2016, Oncotarget, Vol. 7, No. 29

Rôles physiologique du stress oxydant

Production ↑ Elimination

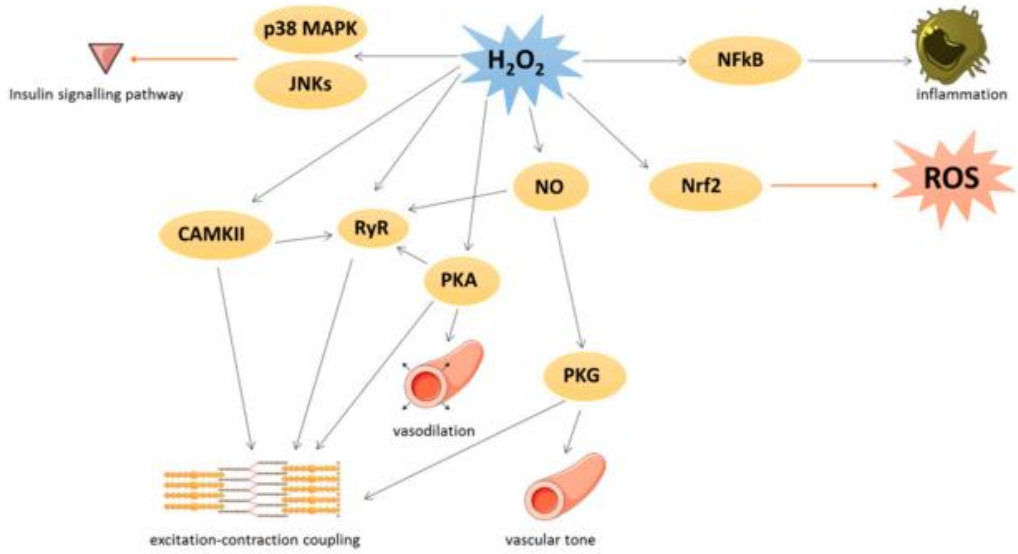


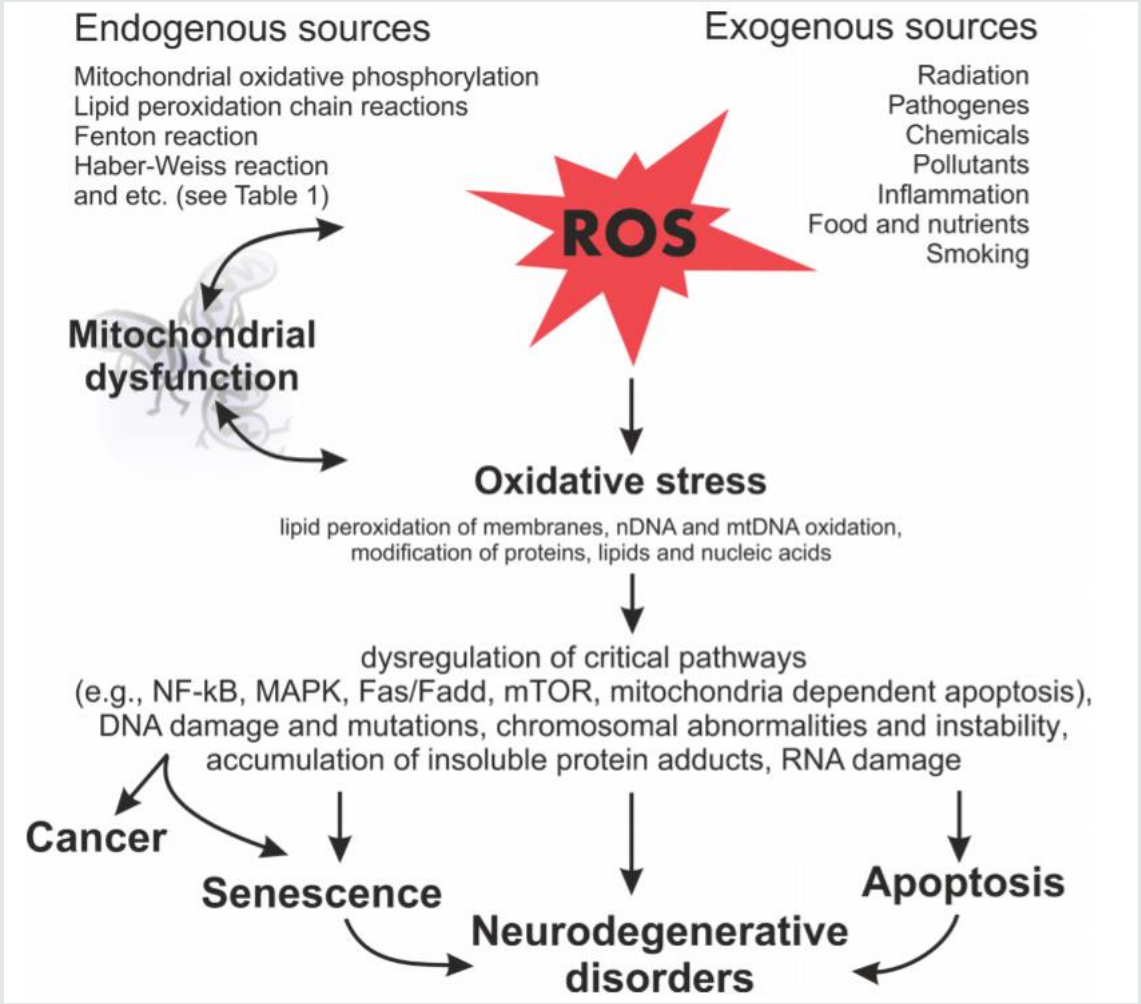
Figure 3. Physiological roles of oxidative stress in cardiovascular tissues. Black arrow represents activation and red arrow represents inhibition. p38 MAPK: p38 mitogen-activated protein kinase; JNK: c-Jun N-terminal kinase; H_2O_2: hydrogen peroxide; NFκB: nuclear factor-kappa beta; CAMKII: Ca/calmodulin-dependent kinase II; RyR: ryanodine receptor; PKA: cAMP-induced protein kinase A; NO: nitric oxide; PKG: protein kinase G; Nrf2: nuclear factor erythroid 2-related factor 2.

E. Dubois-Deruy et al., Antioxidants 2020, 9, 864

Effets délétères des ERO sur la cellule et conséquences pathologiques

Production

Elimination



A. Kudryavtseva et al., 2016, Oncotarget, Vol. 7, No. 29

Effets délétères des ERO sur la cellule et conséquences pathologiques

Elimination

Production

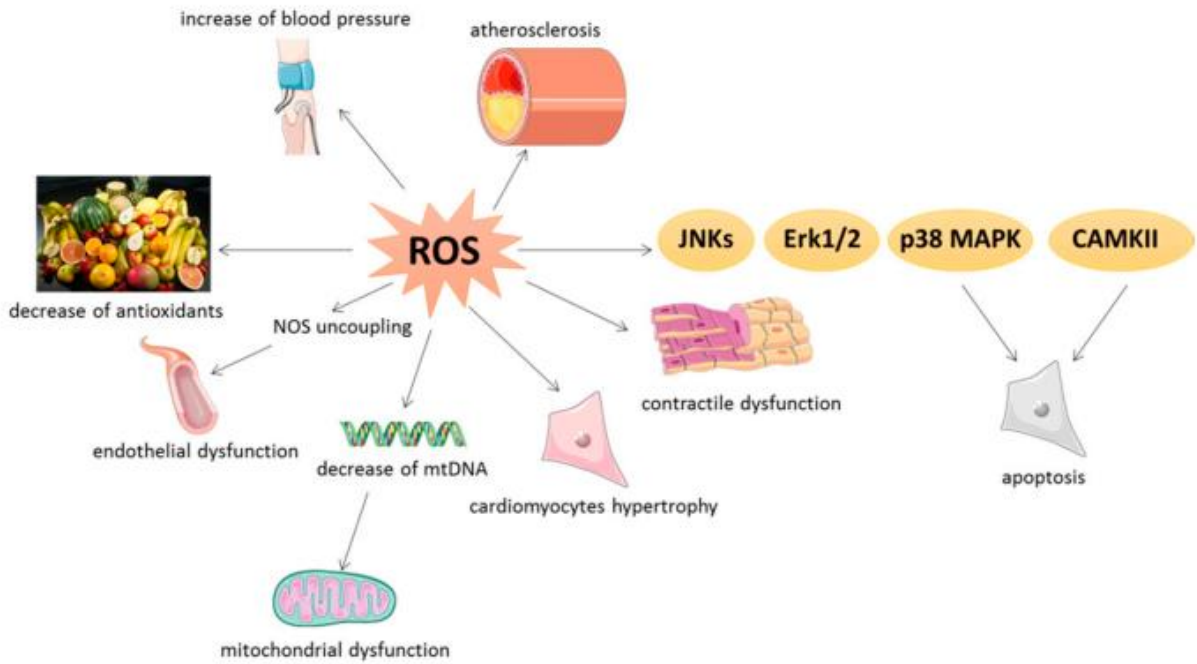
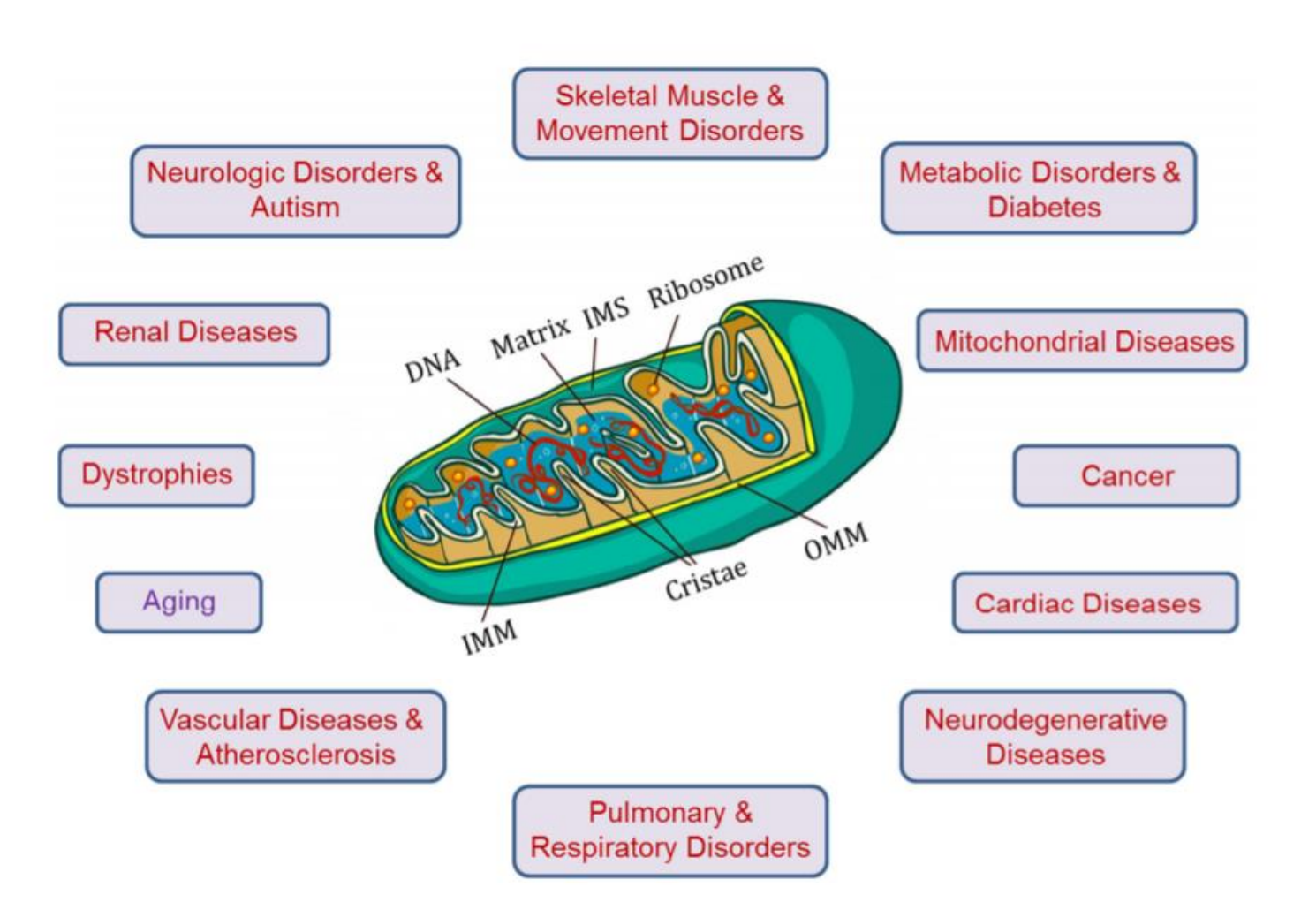


Figure 4. Pathological roles of oxidative stress in cardiovascular tissues. ROS: reactive oxygen species; NOS: nitric oxide synthase; mtDNA: mitochondrial DNA; JNK: c-Jun N-terminal kinase; Erk1/2: Extracellular signal-regulated kinases; p38 MAPK: p38 mitogen-activated protein kinase; CAMKII: Ca/calmodulin-dependent kinase II.

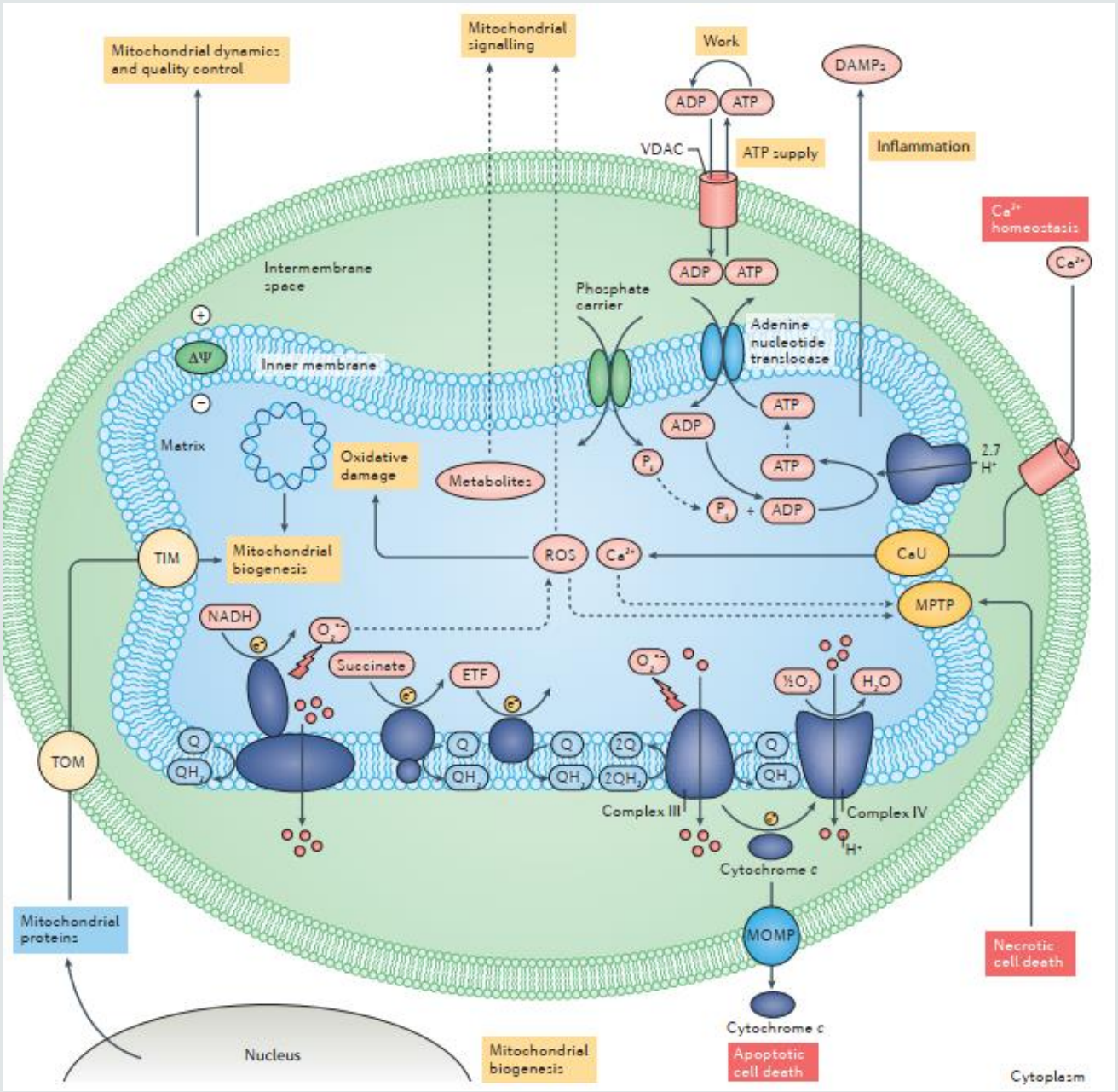
E. Dubois-Deruy et al., Antioxidants 2020, 9, 864

Mitochondries et pathologies humaines



Sabzali Javadov et al., Cells 2020, *9*, 1177

Cibles thérapeutiques potentiels



M. Murphy and R. Hartley, Nature review Drug Discovery, 2018, 17,865

Agents thérapeutiques ciblant les mitochondries

Agent	Mode of action	Disease and/or effect	Trial and/or animal model
Protection			
Cyclosporin A	Block MPTP	Heart attack	CIRCUS phase III
			CYCLE phase II
CoQ_{10}	Antioxidant	Heart failure	Q-SYMBIO phase II
MitoQ	Mitochondria-targeted antioxidant	Parkinson disease	PROTECT phase II
		Chronic kidney disease	Mitochondrial oxidative stress and vascular health in chronic kidney disease phase IV
		Hepatitis C	Phase II
MTP-131 (Bendavia/ SS31)	Unknown	Heart attack	EMBRACE STEMI phase II
		Skeletal muscle mitochondrial dysfunction in the elderly	MOTION phase II
Biogenesis			
AICAR	Activates AMPK, which then acts on PGC1α	Oxidative phosphorylation defect	Mouse model of myopathy
Dynamics			
Mdivi1	DRP1	Slowed mitochondrial fission	Mouse model of excitotoxicity
Quality control			
Urolithin A	Enhanced mitophagy	Muscle function	Mouse models of ageing-associated skeletal muscle decline
Signalling			
NMN	Increase NAD^+ pools	Activate mitochondrial unfolded protein response	Mouse model of fatty liver disease
		Enhance multiple NAD^+	Mouse model of Alzheimer disease

AICAR, 5-aminoimidazole-4-carboxamide ribonucleotide; AMPK, AMP-activated protein kinase; CoQ10, coenzyme Q10; DRP1, dynamin-related protein 1; Mdivi1, mitochondrial division inhibitor 1; MPTP, mitochondrial permeability transition pore; NMN, nicotinamide mononucleotide; PGC1α, peroxisome proliferatoractivated receptor-γ co-activator 1α.

M. Murphy and R. Hartley, Nature review Drug Discovery, 2018, 17,865