

Mitochondria

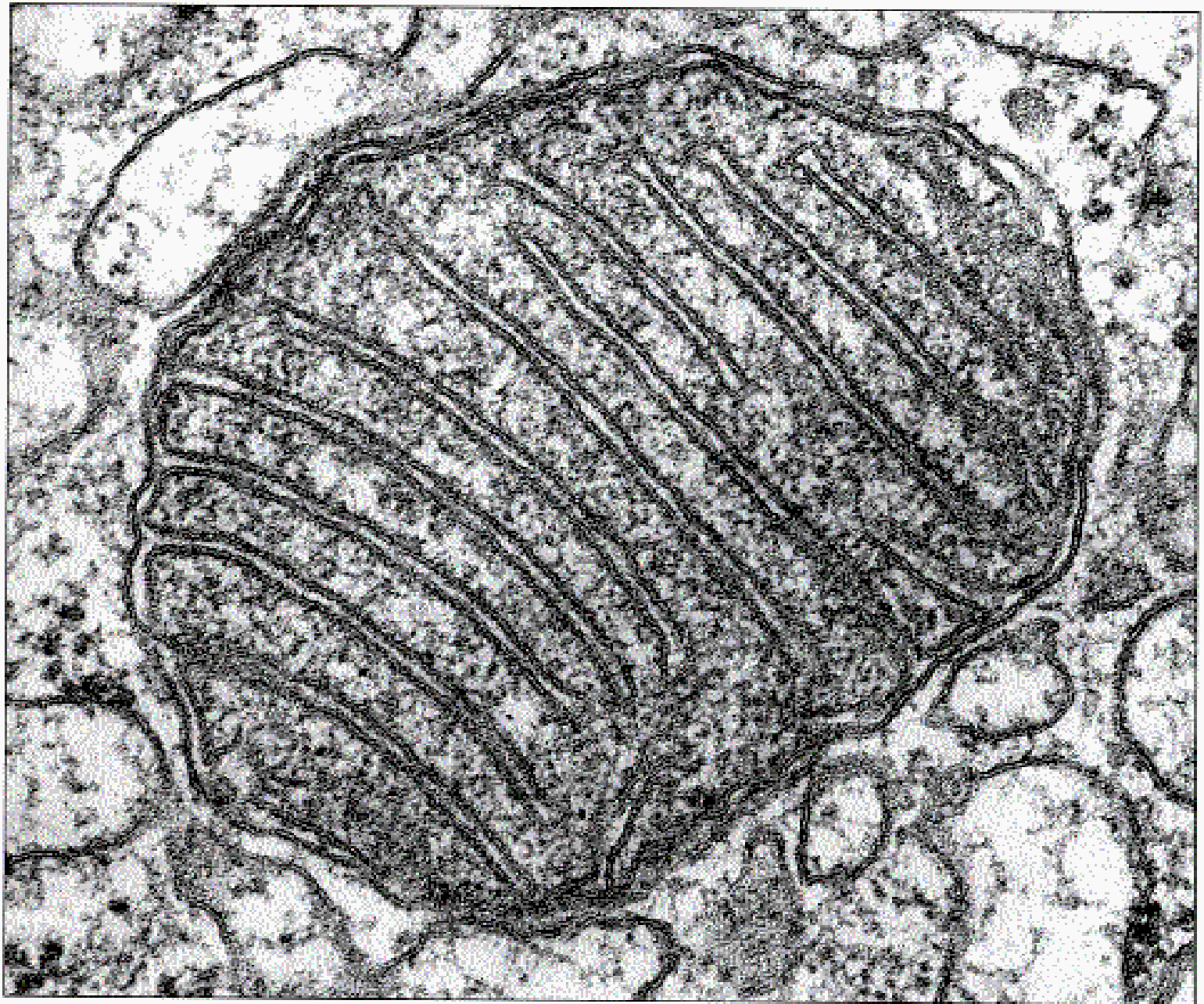
A cellular organelle probably of endosymbiotic origin that resides in the cytosol of most nucleated (eukaryotic) cells.

This organelle produces energy by oxidising organic acids and fats with oxygen by the process of **oxidative phosphorylation** and generates oxygen radicals (reactive oxygen species ROS) as a toxic by-product

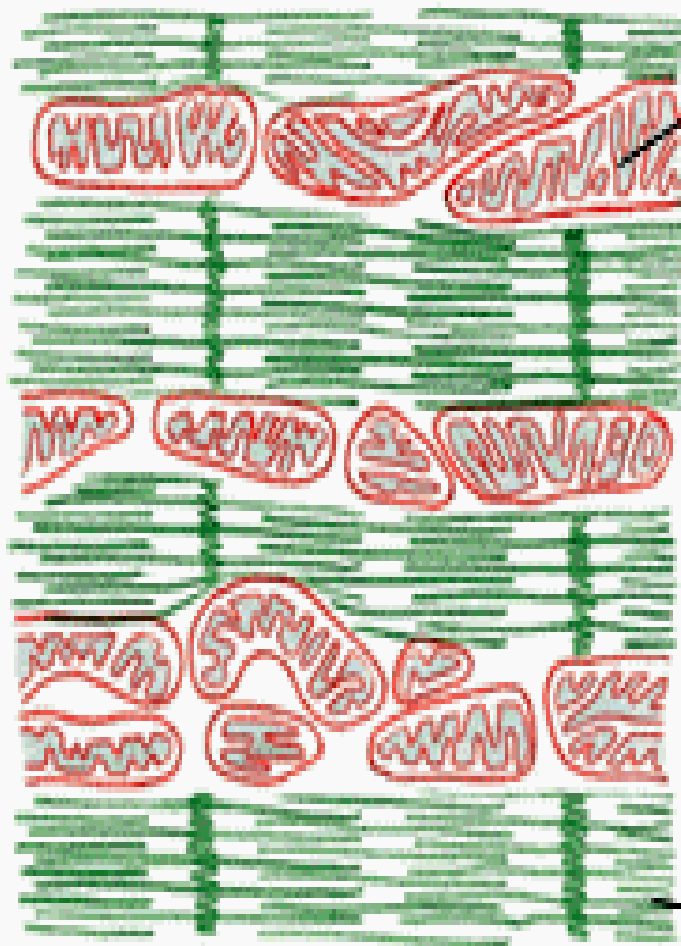
Modern Views of Mitochondrial Functions in Mammalian Cells

1. Act as the power plant of the cell to sustain life of the human and animals
2. Take a center stage in the studies of mechanisms of electron transport and oxidative phosphorylation
3. Major regulator of energy metabolism (via energy charge or phosphorylation potential).
4. Serve as an evolutionary link for higher organisms (conservation in the electron transport system and divergence in respiratory enzymes and mtDNA sequences).
5. A good model for the study of organelle biogenesis and inter-genomic communications between mitochondria and the nucleus

6. Play an important role in calcium homeostasis and calcium signaling of the cell
7. Permeability transition pore opening/closure in the mitochondrial membranes during the early phase of execution and regulation of cell death
8. Mitochondrial genetics and mtDNA mutations in neuromuscular diseases, aging and age-related diseases
9. Proteins involved in the initiation and propagation of apoptosis
10. Act as an arbitrator, executioner, and regulator of life and death of the cell
11. The most sensitive intracellular organelles in response to physiological and pathological signals and oxidative stress
12. It provides a unique system for the study of intracellular dynamics during different physiological and pathological conditions

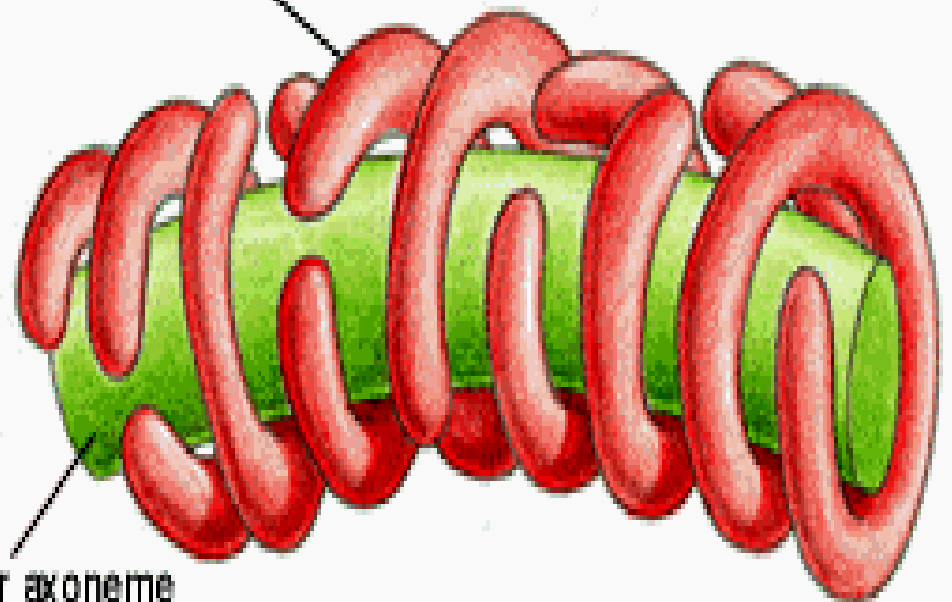


100 nm



CARDIAC MUSCLE

mitochondria



flagellar axoneme

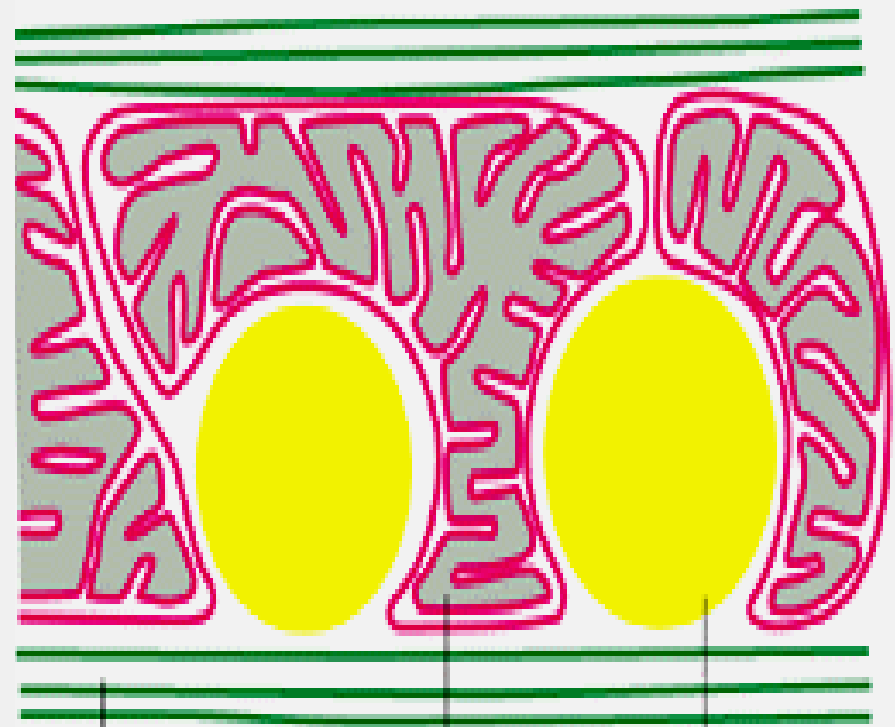
myofibril

SPERM TAIL



(A)

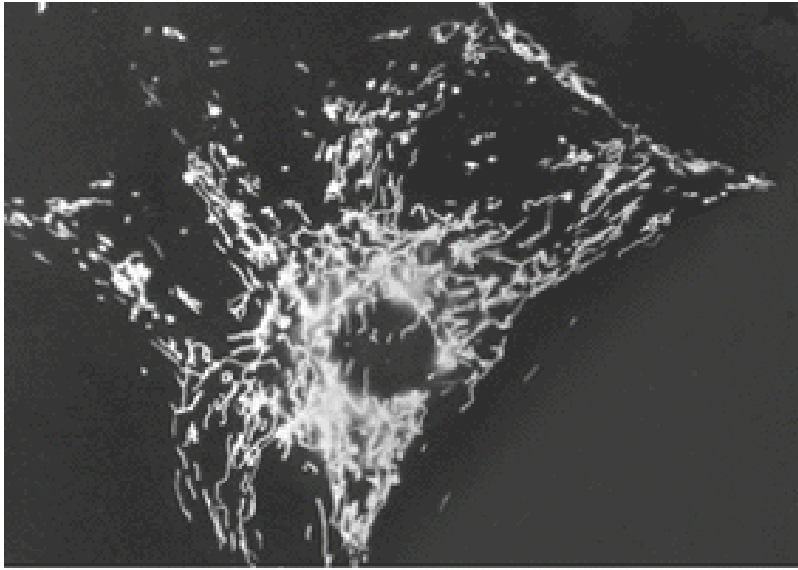
1 μm



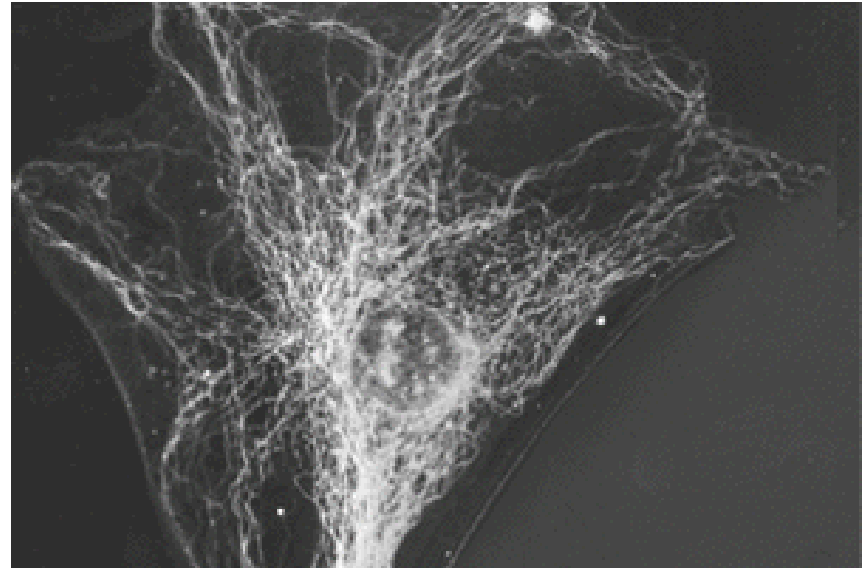
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mitochondrion

fat droplet



(A)

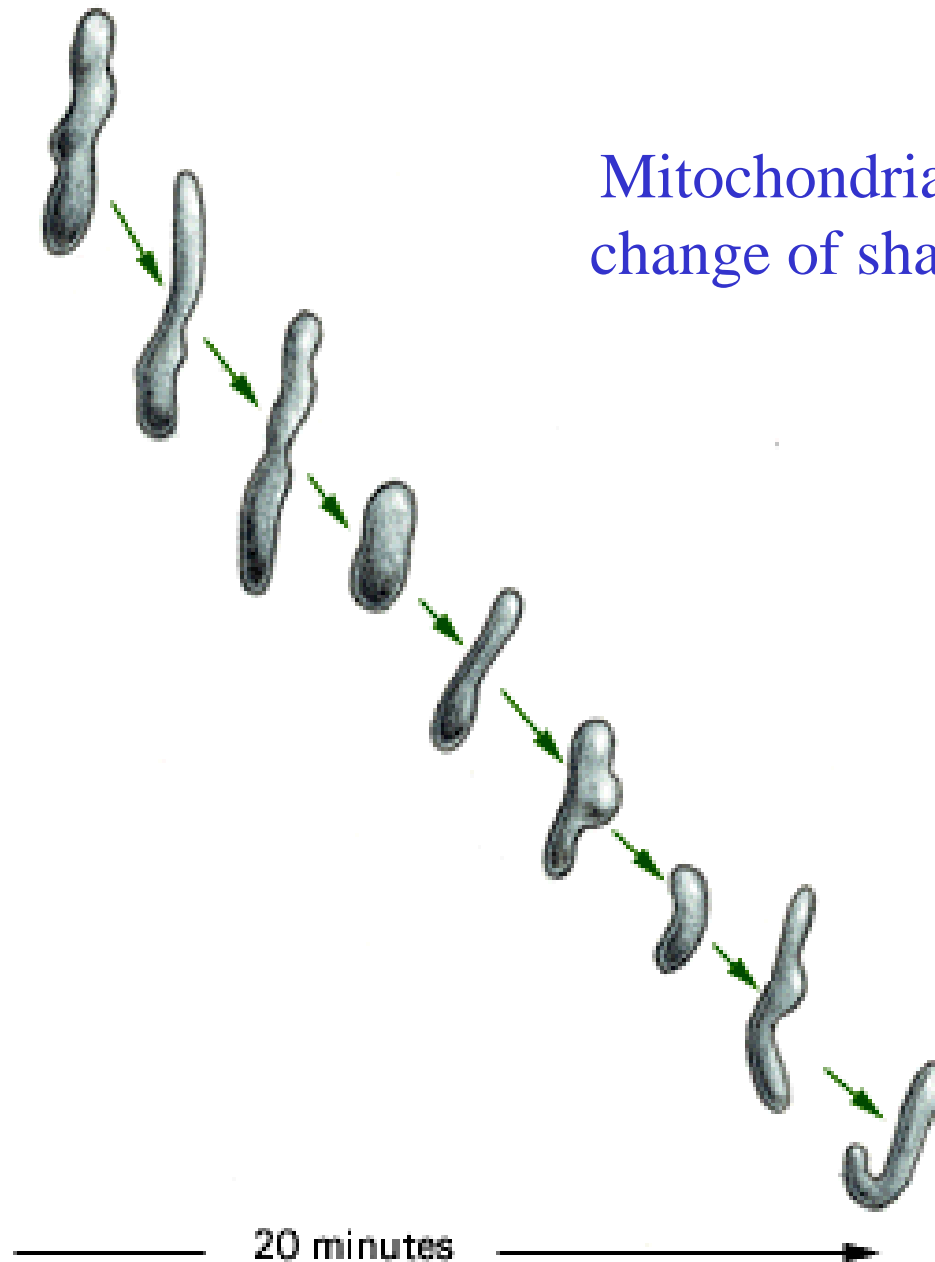


(B)

10 μm

Figure 14-4. Relationship between mitochondria and microtubules. (A) Light micrograph of chains of elongated mitochondria in a living mammalian cell in culture. The cell was stained with a vital fluorescent dye (rhodamine 123) that specifically labels mitochondria. (B) Immunofluorescence micrograph of the same cell stained (after fixation) with fluorescent antibodies that bind to microtubules. Note that the mitochondria tend to be aligned along microtubules. (Courtesy of Lan Bo Chen.)

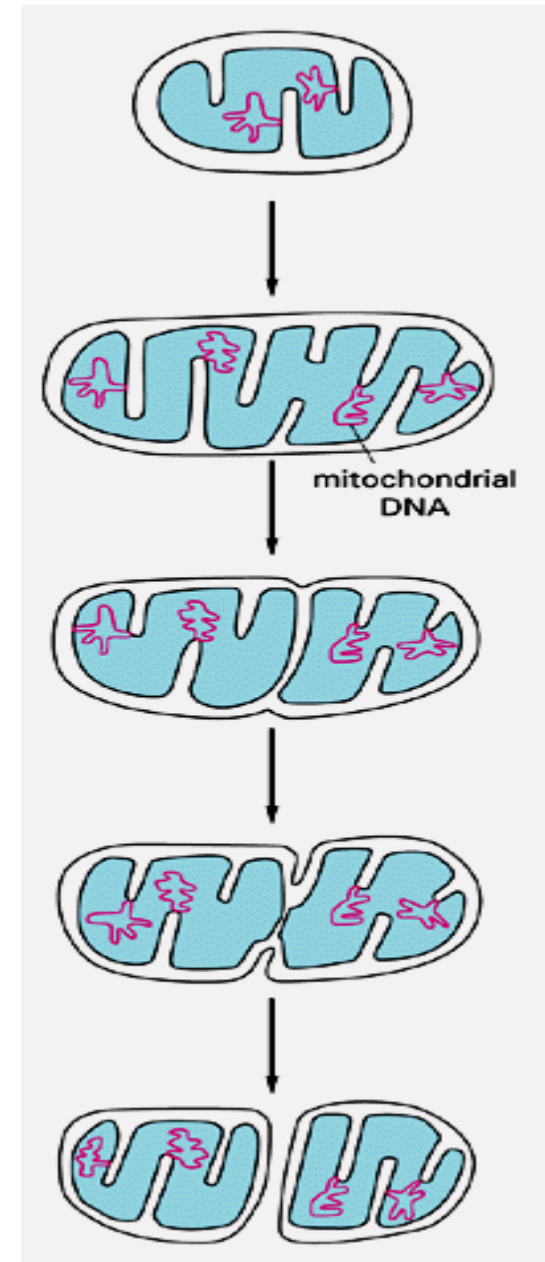
Mitochondrial plasticity: rapid
change of shapes in living cells



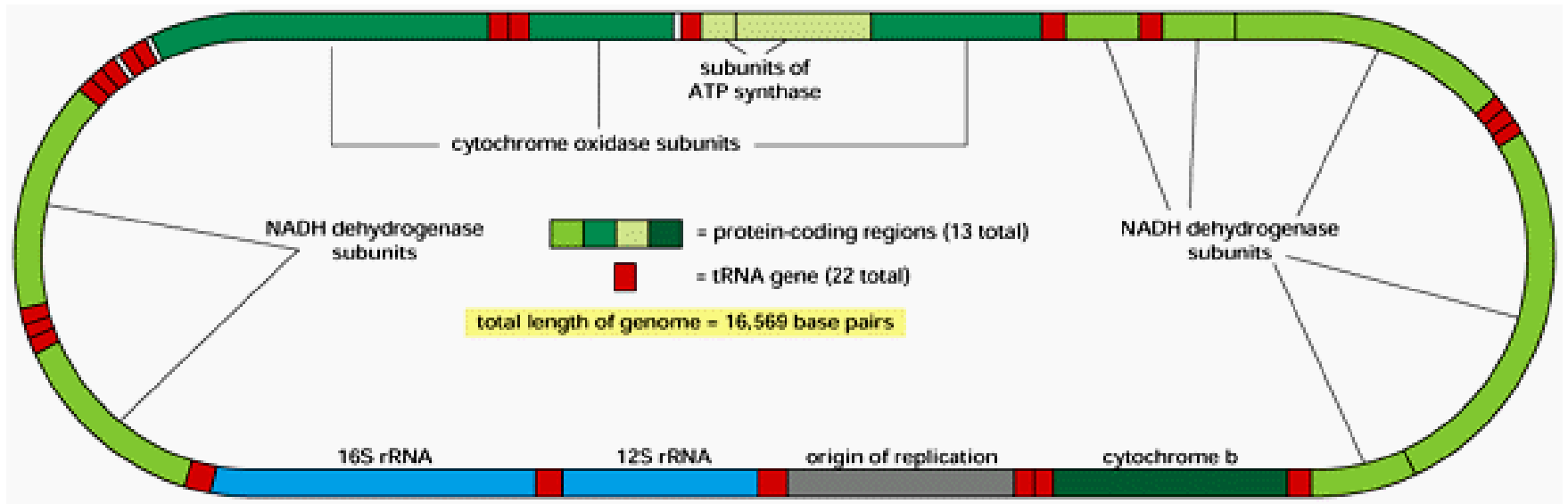
Number of Mitochondria per cell

- Most somatic cells 100-10,000
- Lymphocyte 1000
- Oocytes 100,000
- Sperm
hundred few
- No mitochondria in red cells and some terminally differentiated skin cells

Mitochondrial biogenesis



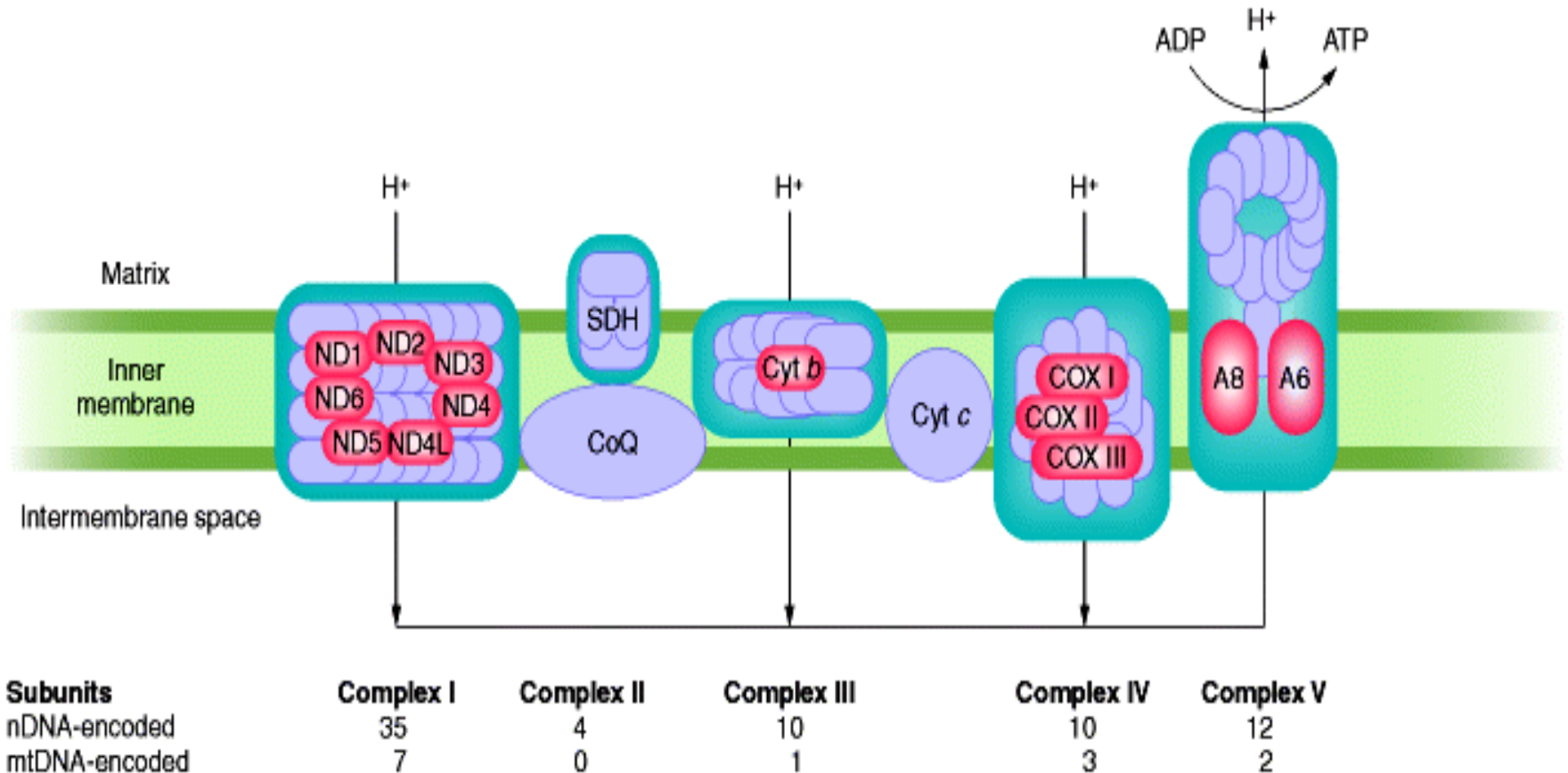
Mitochondrial genome

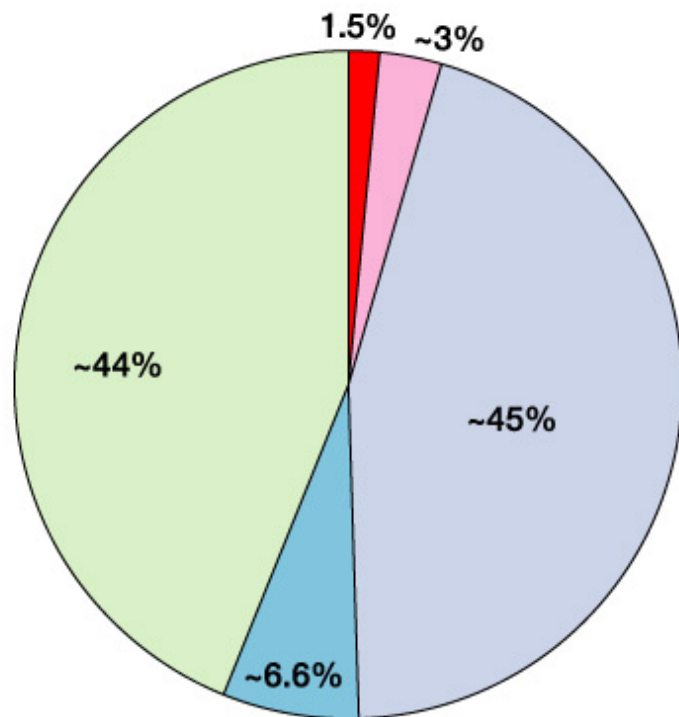


- 22 tRNA genes
- 13 polypeptide-encoding gene (for respiratory chain)
- 2 ribosomal RNA genes

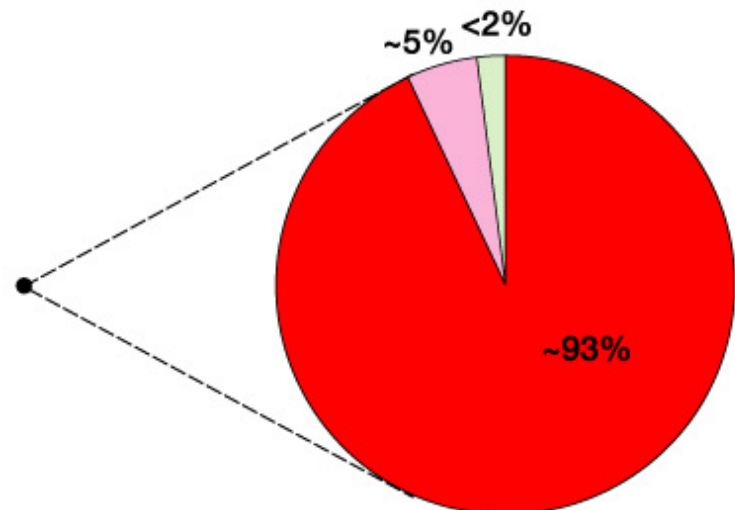
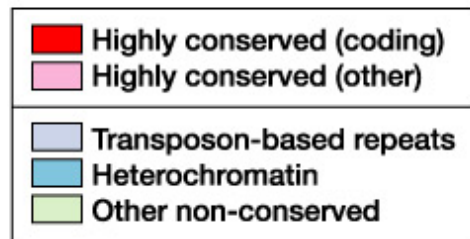
Two-way Communication and Coordination between Two Genomes

Coordinated Expression of Proteins by Genes in Both Nuclear and the Mitochondrial Genome





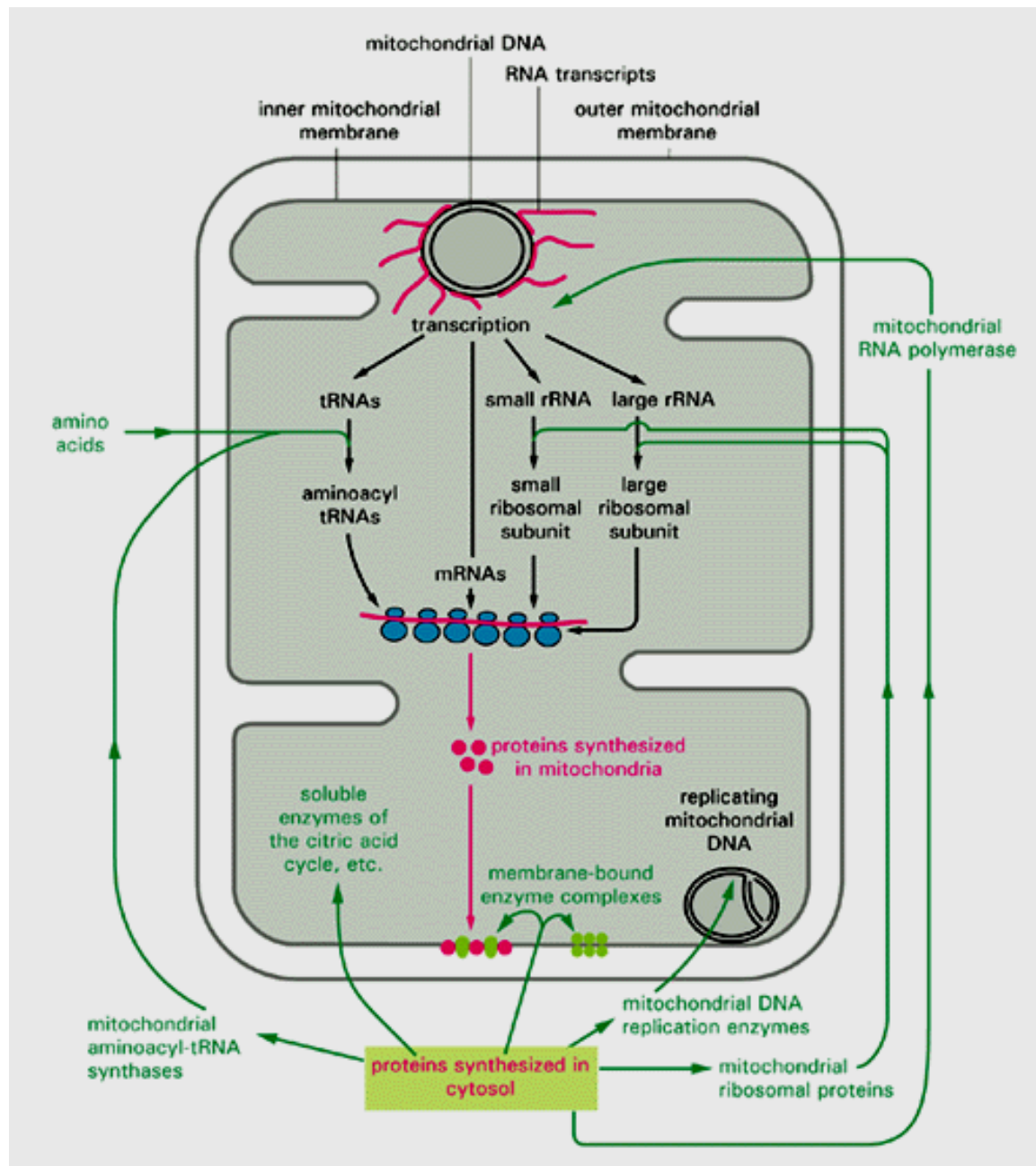
Nuclear genome
 (24 linear double-stranded DNA molecules – 3200 Mb; ~30 000 genes)



Mitochondrial genome
 (1 circular double-stranded DNA 16.6 kb; 37 genes)

The human nuclear and mitochondrial genomes

	Nuclear Genome	Mitochondrial Genome
Size	3200 Mb	16.6 kb
No. of different DNA molecules	23 (in XX cells) or 24 (in XY cells); all linear	One circular DNA molecule
Total no. of DNA molecules per cell	46 in diploid cells, but varies according to ploidy	Often several thousands (but variable)
Associated protein	Several classes of histone & nonhistone protein	Largely free of protein
No. of genes	~ 30 000 ~35-000	37
Gene density	~ 1/100 kb	1/0.45 kb



“Mitochondrial Diseases” = Respiratory Chain Disorders

- More than 40 known types
- Mitochondrial disease is a difficult disorder to identify because it can take many forms, and range from mild to severe
- The problems it causes may begin at birth or not occur until later in adult life.
- It is estimated that mitochondrial disease affects between 40,000 and 70,000 Americans, occurring in one in 2,500 to 4,000 births.

Modes of inheritance of RC defects

- Maternal - mtDNA point mutations & duplications
- Sporadic - mtDNA single deletions
- Autosomal Recessive - subunit genes, SURF1, etc
- Autosomal Dominant - multiple mtDNA deletions
- X-linked - DDP1, ABC7, (Barth syndrome)
- Complex - LHON

- In most diagnoses, we don't know!

The clinical features of mitochondrial disease 1:

“Classical” presentation

- MELAS (Mitochondrial Encephalomyopathy with Lactic Acidosis and Stroke-like episodes)
- MERRF (Myoclonic Epilepsy with Ragged Red Fibres)
- Leber Hereditary Optic Neuropathy (LHON)
- External Ophthalmoplegia
 - Kearns-Sayre syndrome
 - Chronic progressive external ophthalmoplegia
- NARP (Neurogenic weakness Ataxia with Retinitis Pigmentosa)

Clinical Features of Mitochondrial disease 2: Features suggestive of mitochondrial illness but not classical syndrome

Neuromuscular

- External ophthalmoplegia
- Ptosis
- Deafness
- Neuropathy
- Migraine
- Seizures
- Encephalomyopathy
- Dementia
- Ataxia
- Stroke-Like episodes
- Spastic paraparesis
- Neuropathy
- Pigmentary retinopathy
- Optic atrophy
- Dystonia

Cardiac
HCOM
Heart Block

Endocrine
Diabetes Mellitus
Hypogonadism
Infertility

GIT
Dysphagia
Vomiting
Pseudo-obstruction
Pancreatic failure
Liver failure

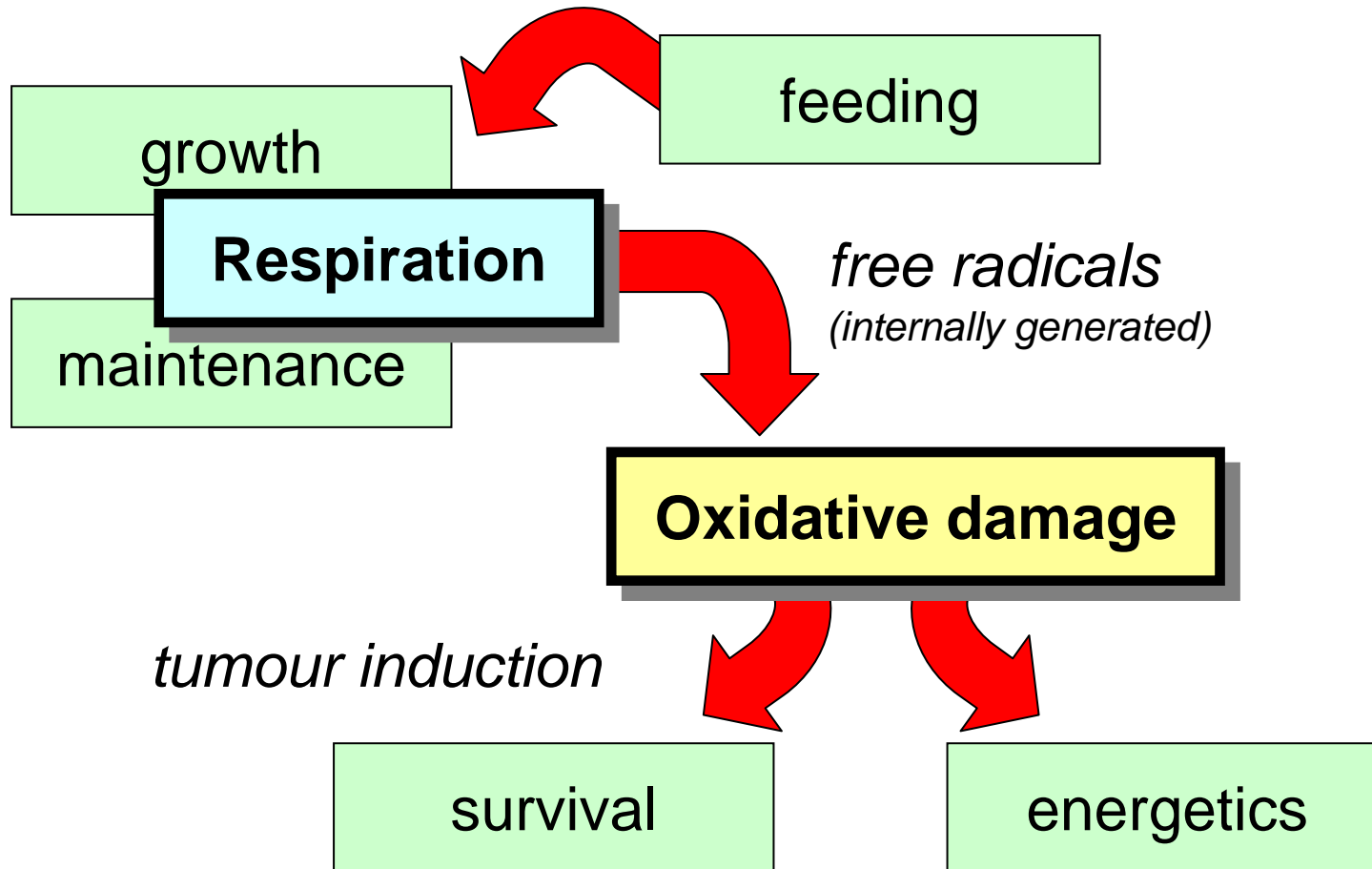
Haematological
Sideroblastic anaemia
Pancytopenia

Psychiatric
Depression
Psychosis

Dermatological
Lipomatosis

Renal
Aminoaciduria
Tubule dysfunction
Fanconi syndrome

Intracellular reactive oxygen species



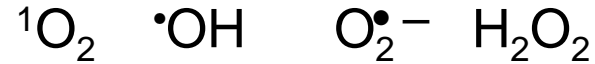
Major sources of Reactive Oxygen Species (ROS)

- Mitochondria (Electron Transport Chain)
- Peroxisomal β -oxidation system
- Xanthine and glucose oxidases
- Cyclooxygenases
- Plasmamembrane-localized NAD(P)H oxidoreductase complex

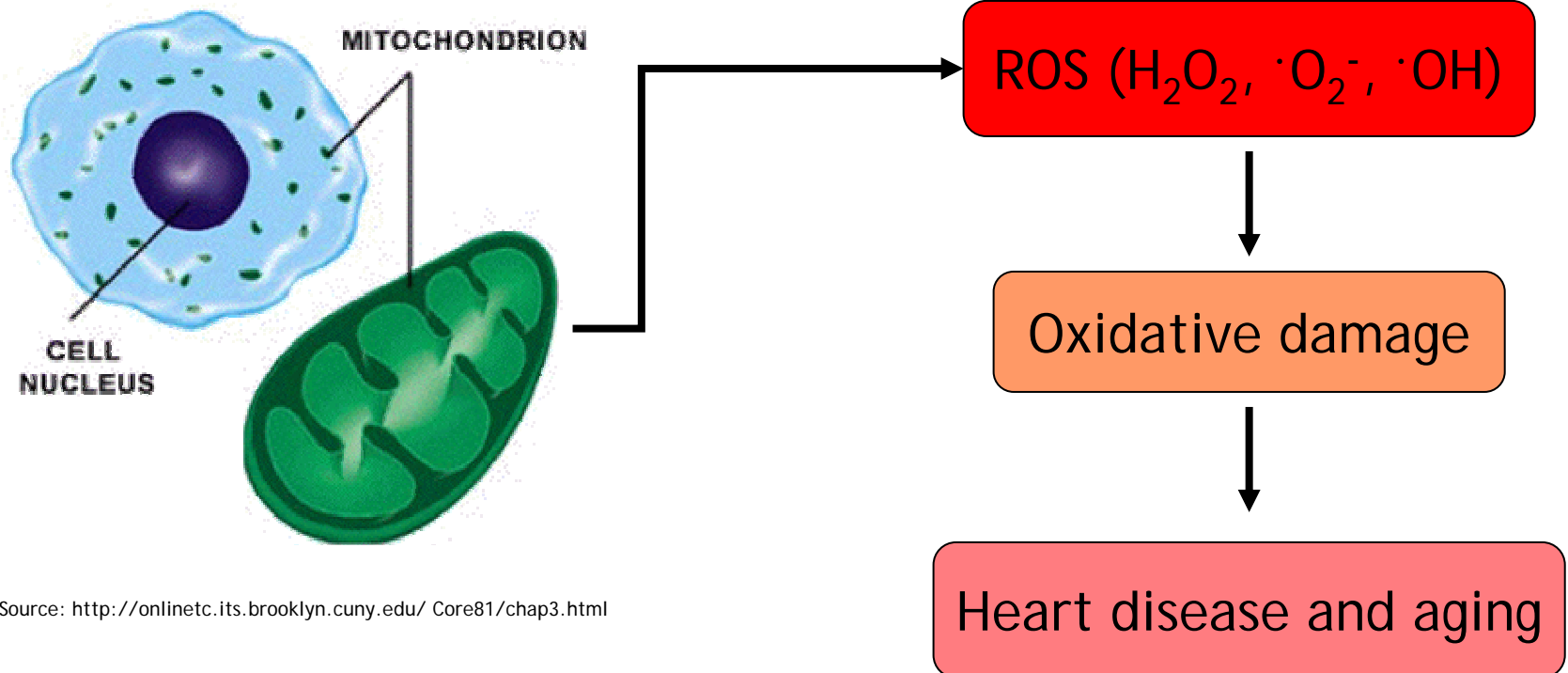
Mitochondria and ROS

Reactive oxygen species (ROS): hydroxyl radical, superoxide, hydrogen peroxide
Reactive nitrogen species (RNS)

Reactive Oxygen Species (ROS)

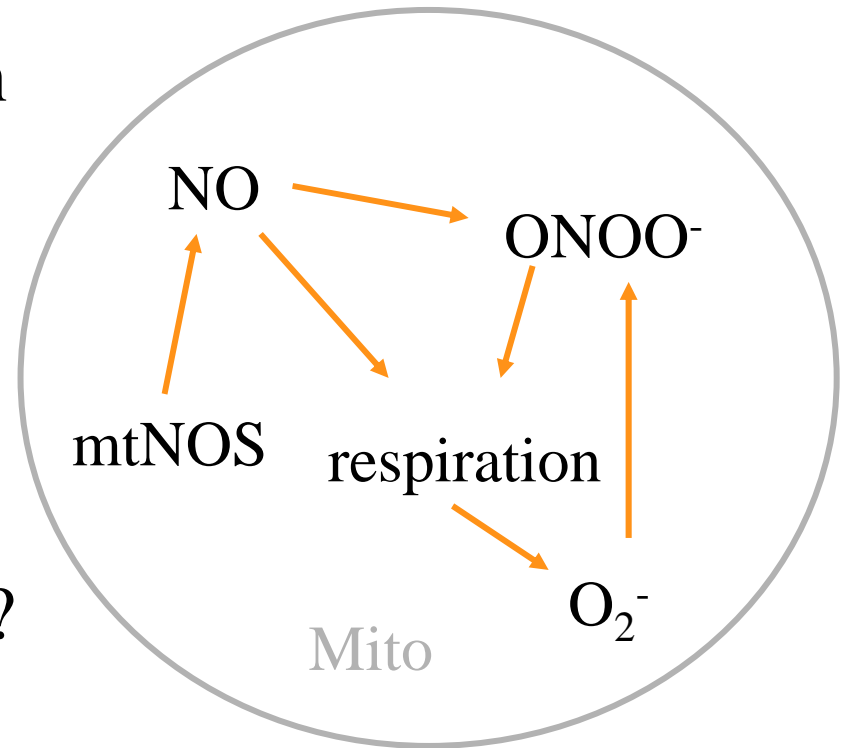


Reactive Nitrogen Species (RNS)

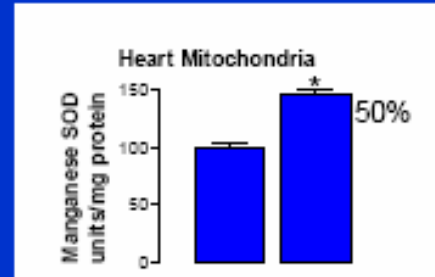
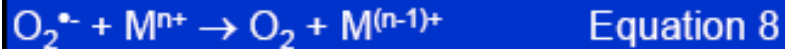
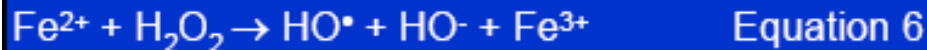


NO in mitochondria?

- Reversibly inhibits respiration (complex IV)
- Reacts with superoxide to form ONOO^-
- Irreversibly inhibits respiration (complex II-III)
- Is there a mitochondrial NOS?



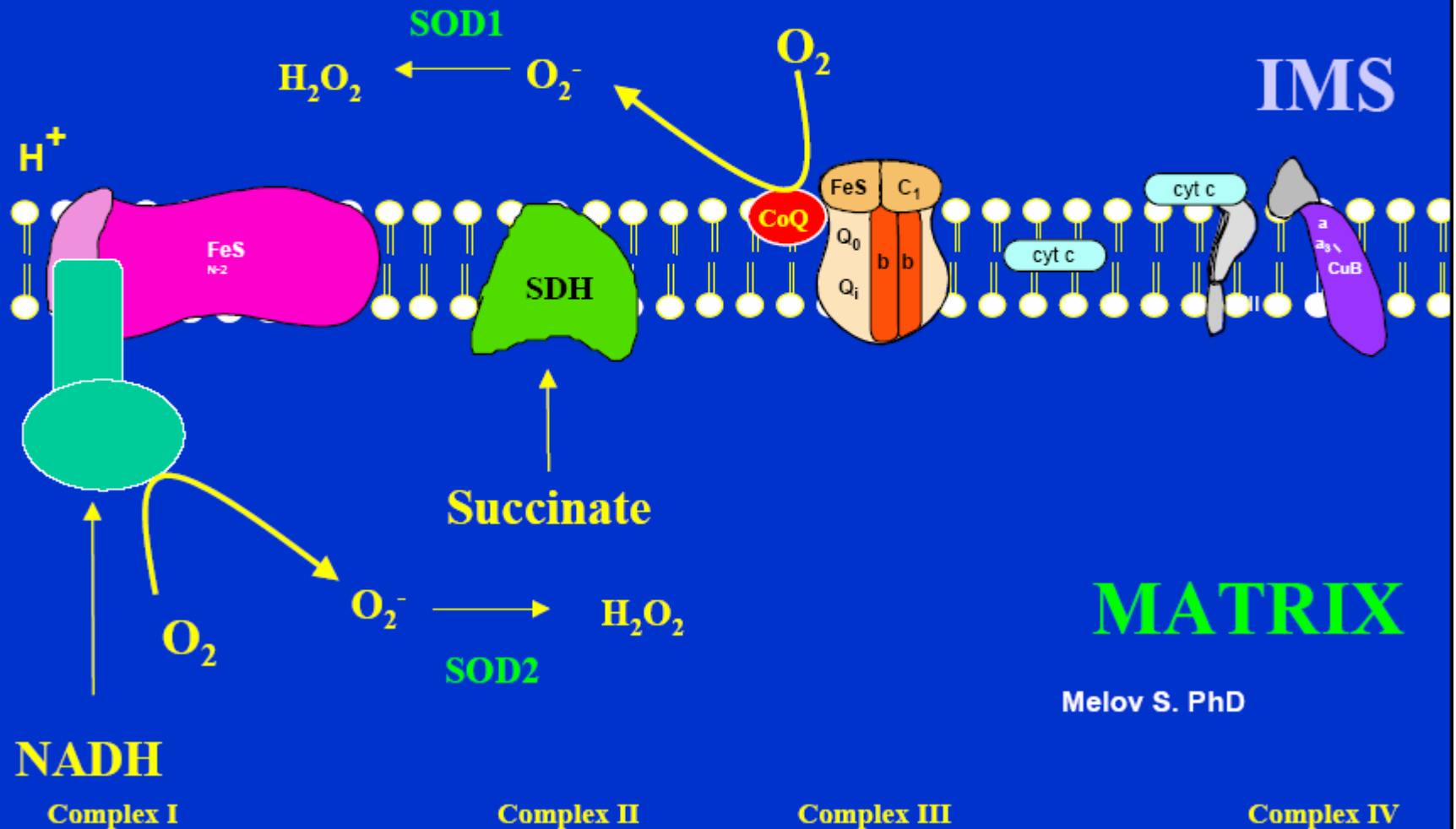
“Radical” Reactions



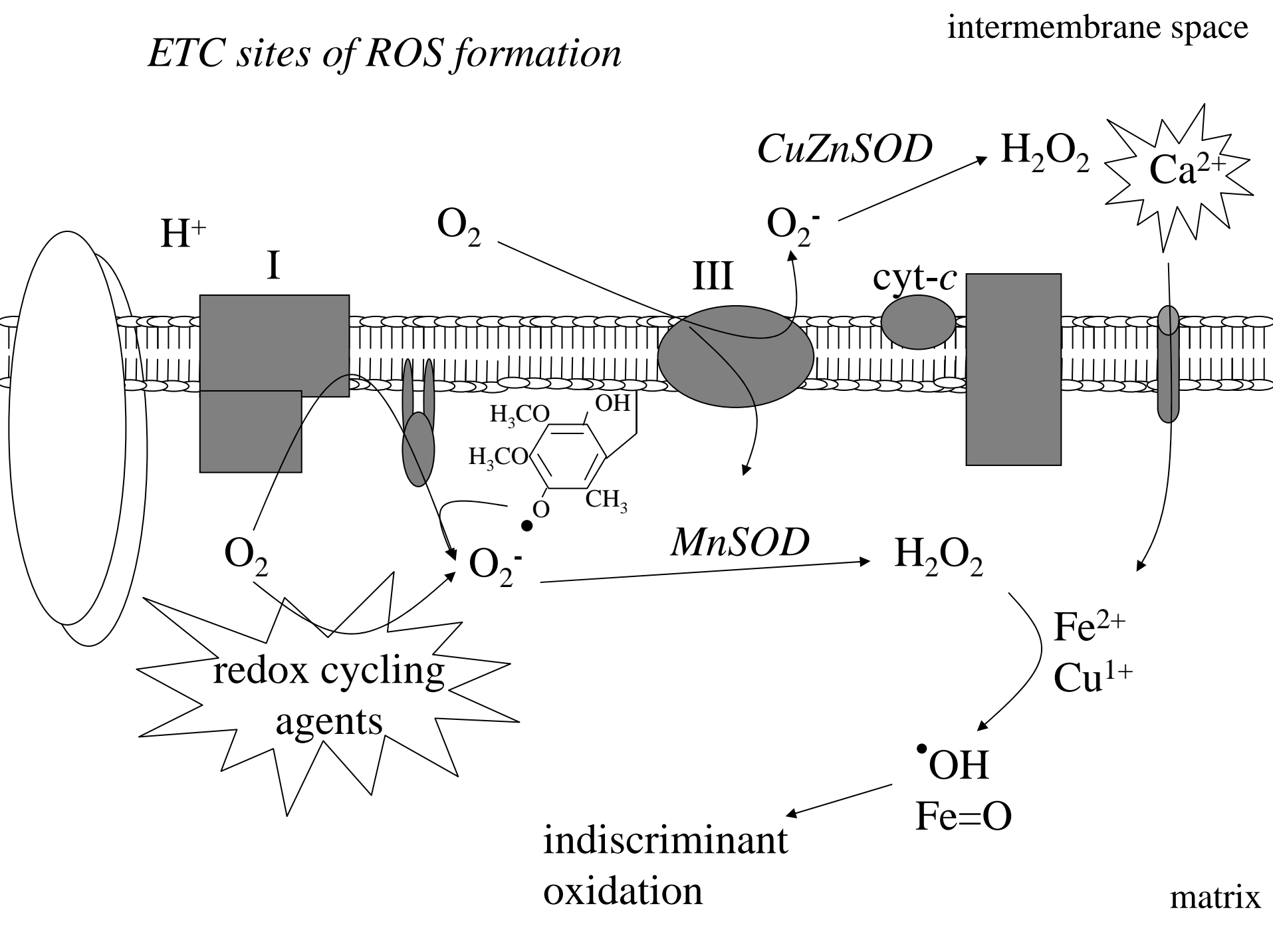
Primary antioxidants metabolizing ROS

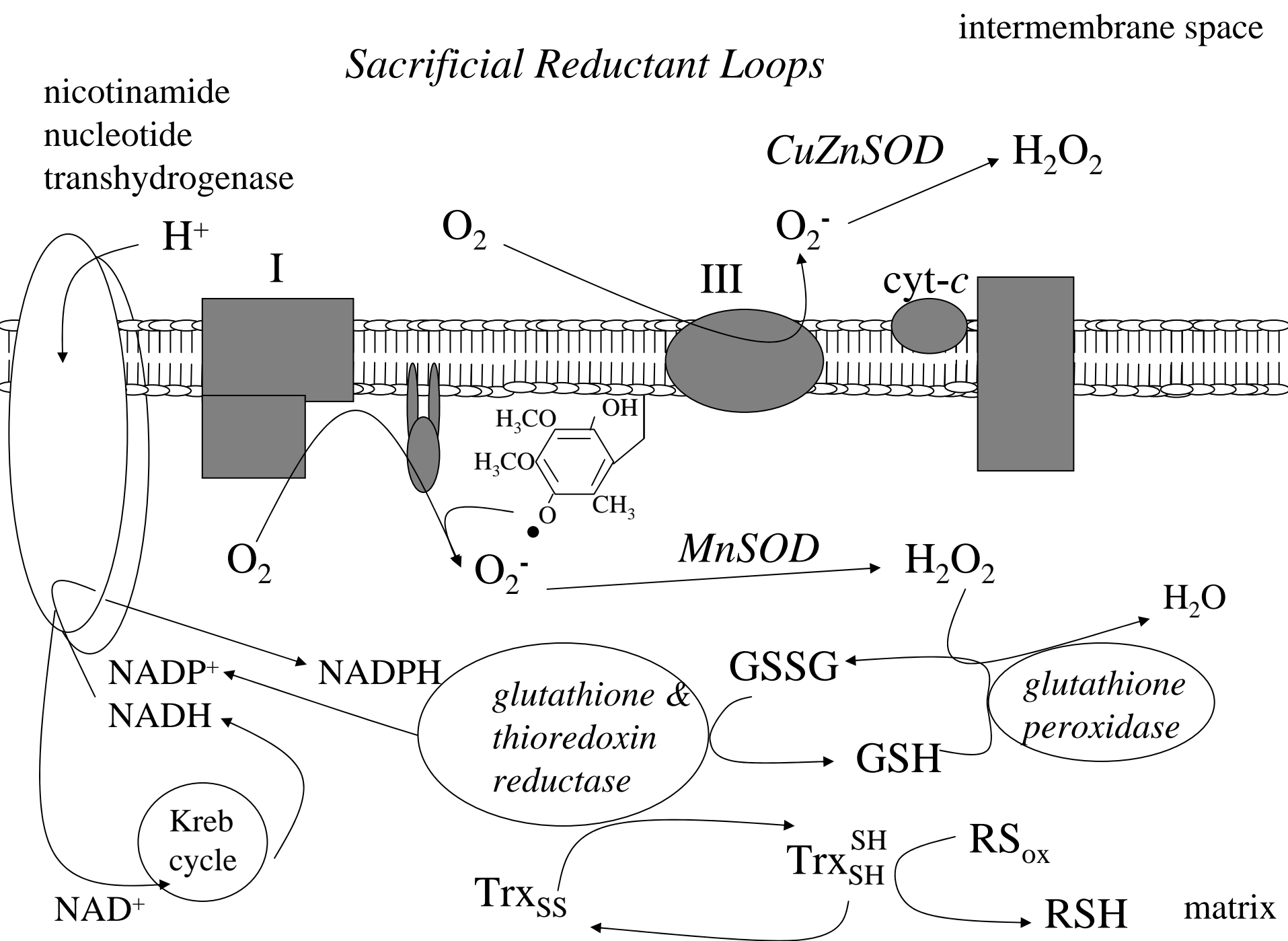
- Glutathione (GSH) and related enzymes (peroxidases, reductases, S-transferases, and efflux pumps)
- Thioredoxin and Peroxiredoxin families
- Catalase
- Superoxide dismutases (SODs)

Reactive Oxygen species and the Respiratory Chain

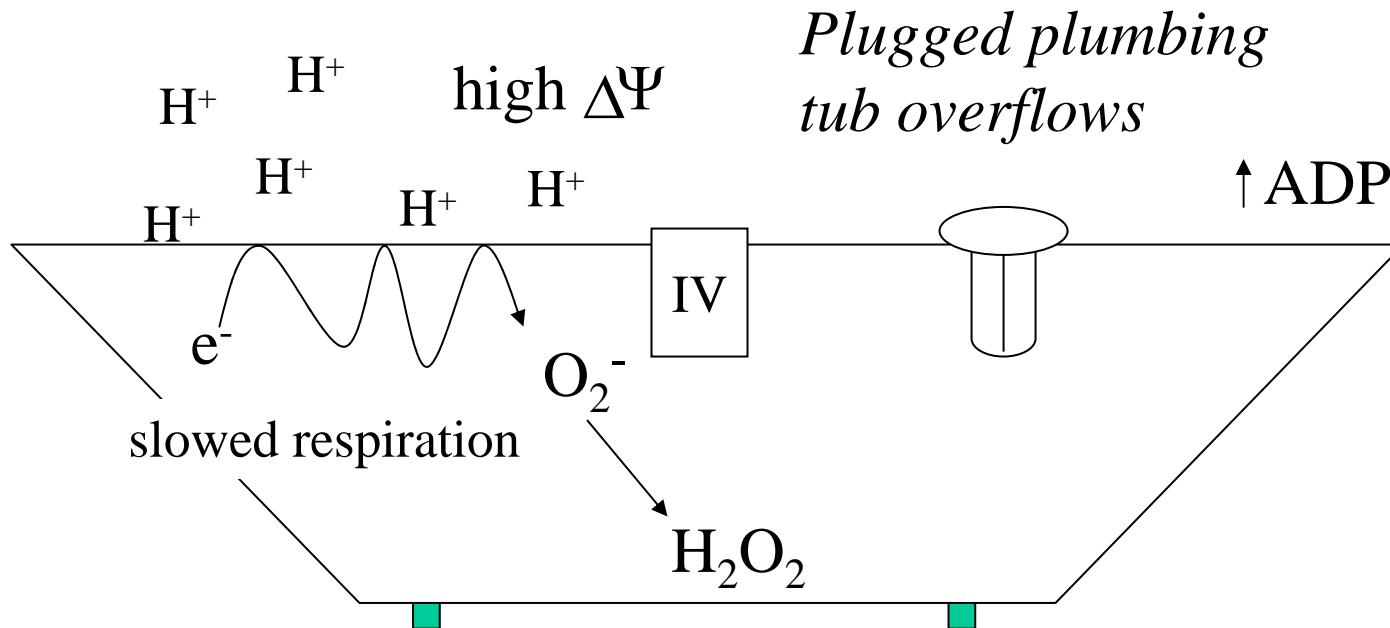
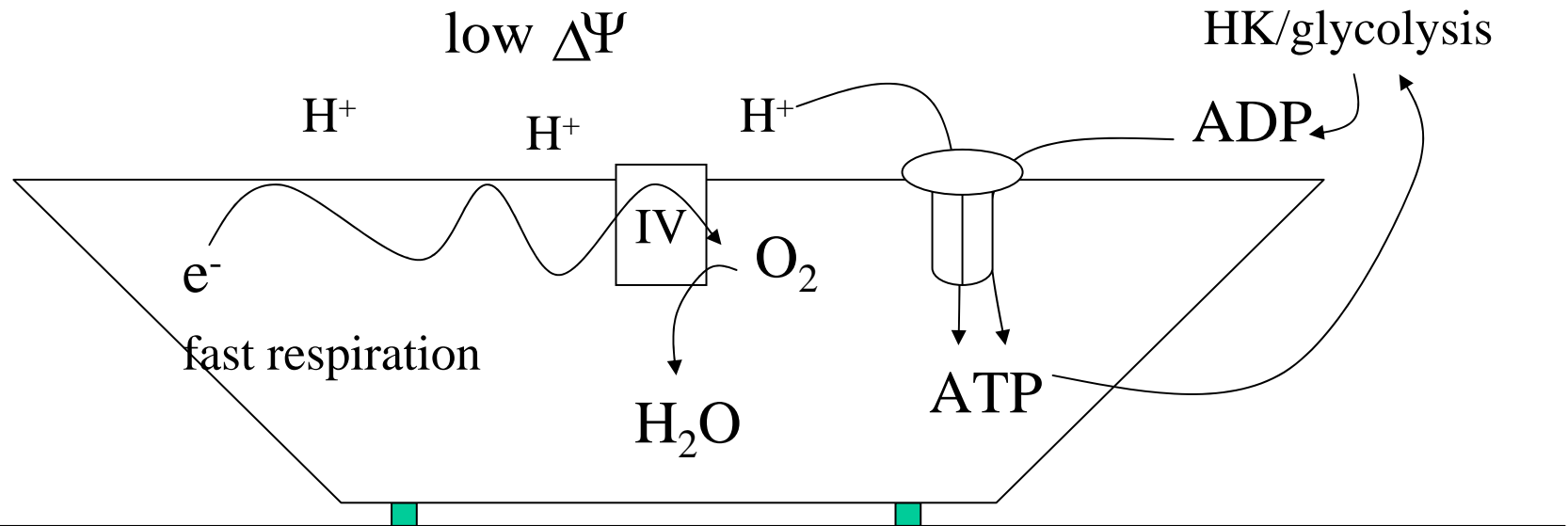


ETC sites of ROS formation

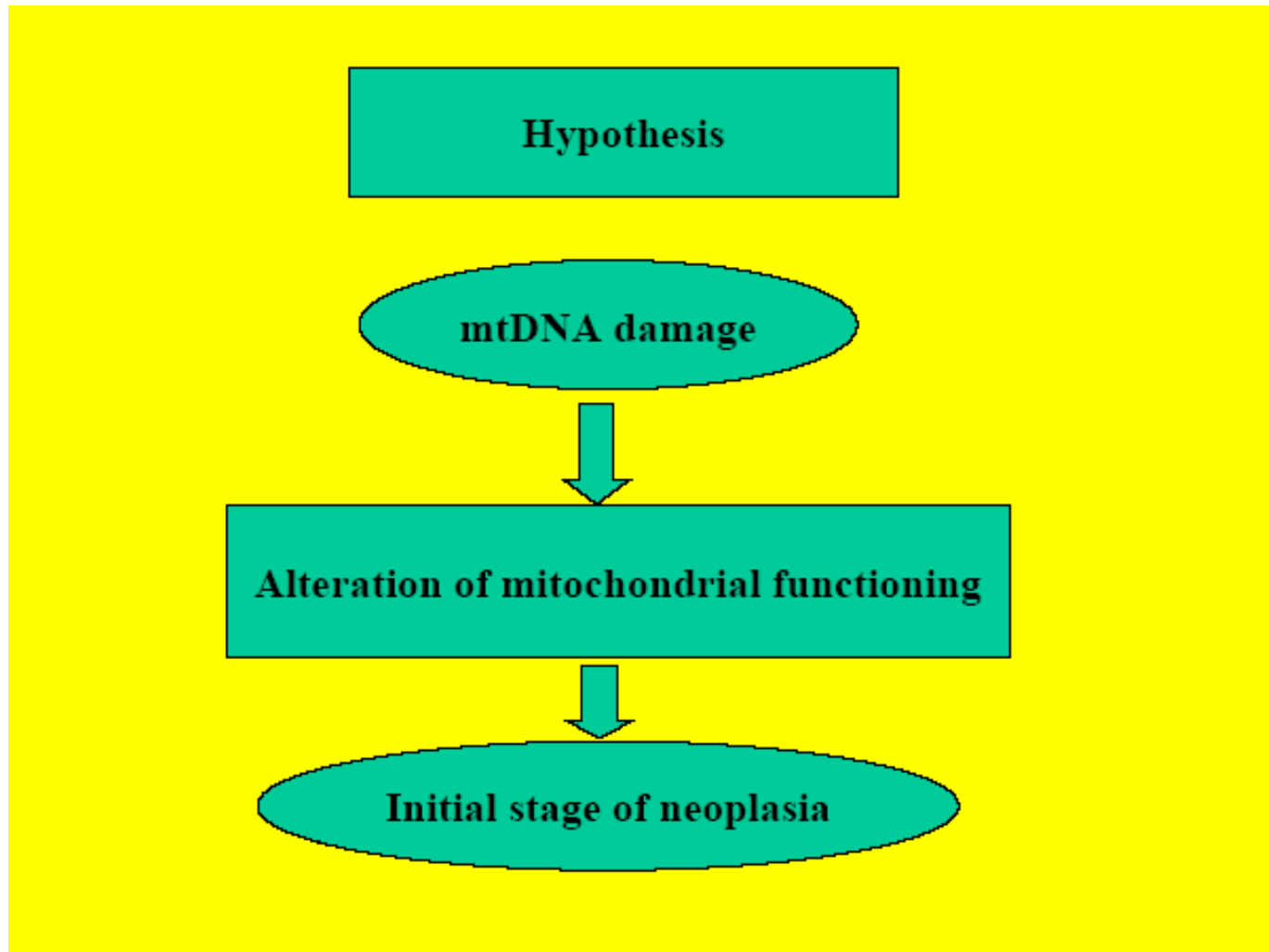




ETC ROS formation and the bathtub



mtDNA damage



mtDNA

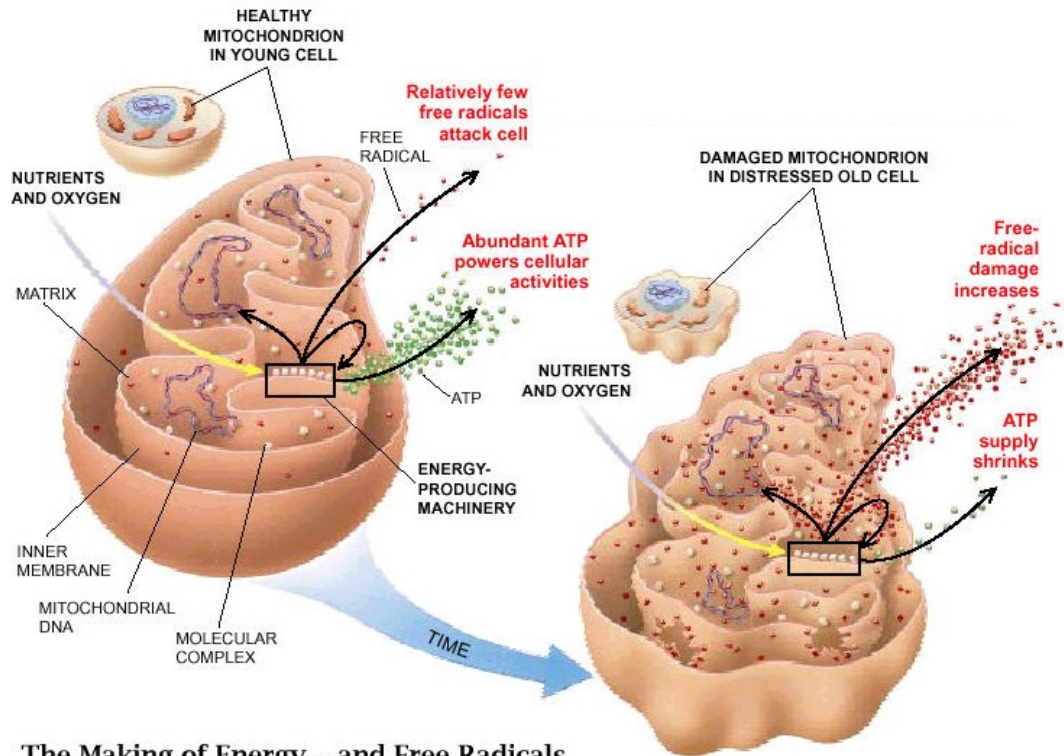
- **Lack of protective histones**
- **Limited capacity for repair (DNA polymerase γ)**
- **Lack of introns (>> probability that a mutation will be detrimental)**

mtDNA: an attractive target for pathological damage

- **Proximity of mtDNA to the site of ROS generation**
- **Mitochondrial genome is highly sensitive to genotoxic agents**

Amplification mechanisms

1) Affected mitochondria produce more ROS



The Making of Energy...and Free Radicals

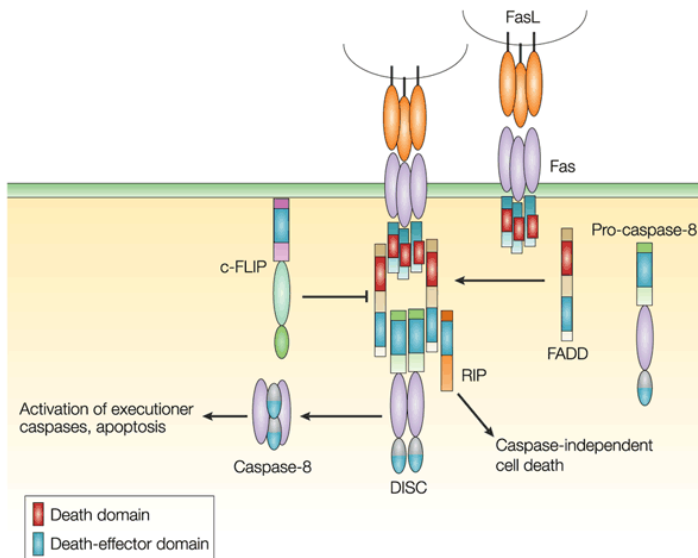
Weindruch R 1996 Caloric restriction and aging. *Scientific American* **231**, 46-52.

2) Affected mitochondria grow and degrade at different rates

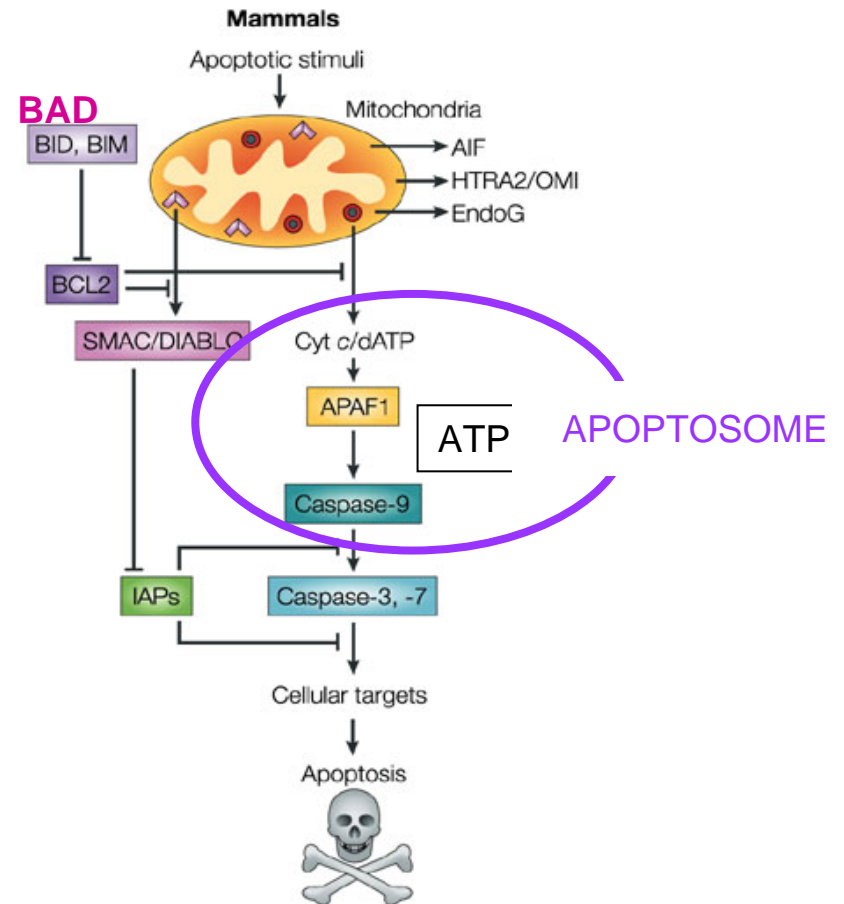
- **Kowald A 2001** The mitochondrial theory of aging, *Biological Signals & Receptors* **10**, 162-175.
- **Kowald A & Kirkwood TBL 2000** Accumulation of defective mitochondria through delayed degradation of damaged organelles and its possible role in the aging of post-mitotic cells. *Journal of Theoretical Biology* **202**, 145-160.

Cancer: evade apoptosis

- Fas/TNFA extrinsic pathway for apoptosis
- Mitochondrial intrinsic pathway
- Both pathways have caspases in common
- Ironically, oncogenes can also induce apoptosis



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Growth & death signal

