Molecular Disease Mechanisms

Lecture 6: Cancer and Mitochondria

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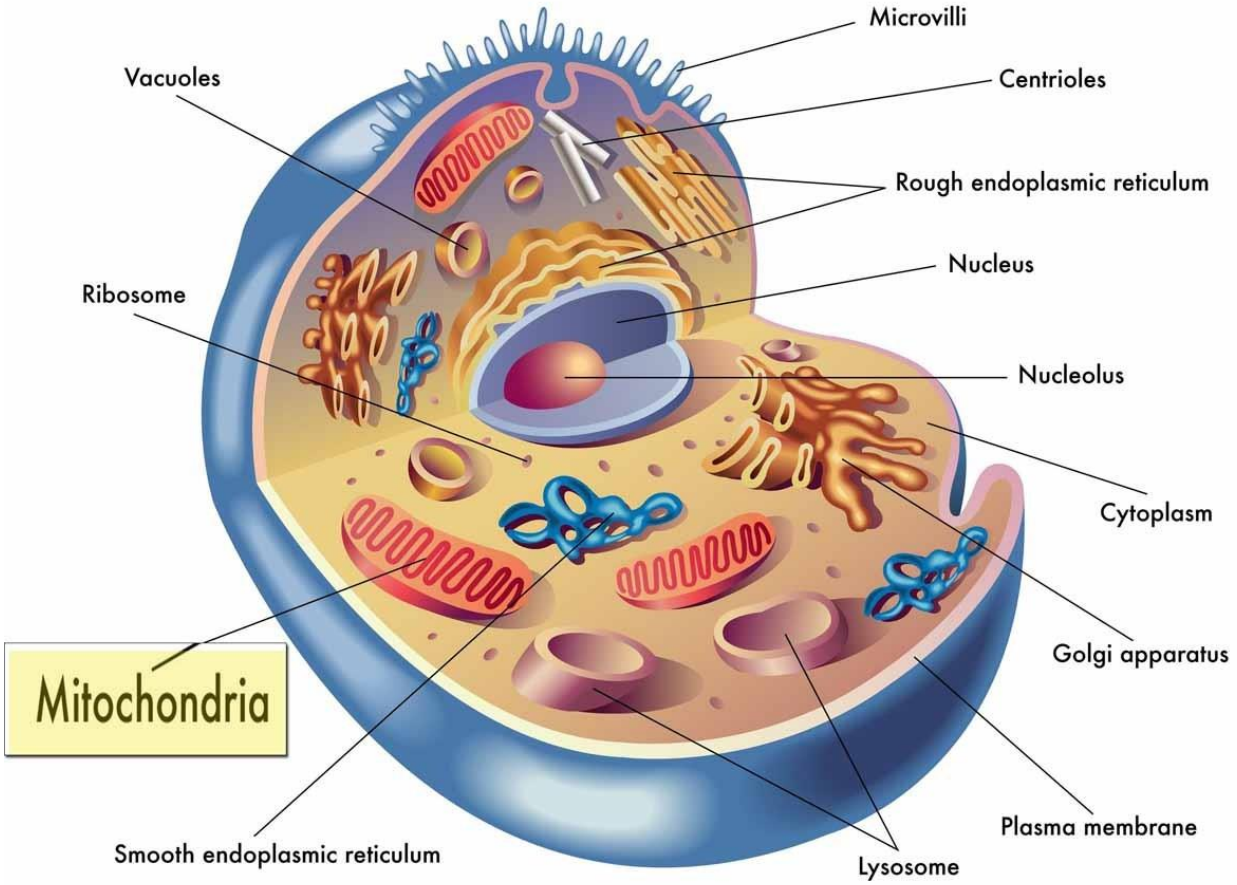
Lecture 6, Part 1

CANCER AND MITOCHONDRIA

After this lecture you will be able to:

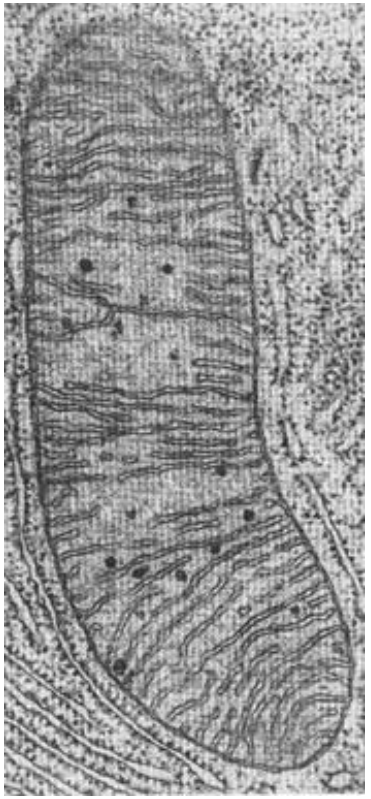
1. Understand mitochondrial anatomy and function
2. Aspects of mitochondrial dysregulation in cancer

Mitochondria – The Power House



Mitochondria Anatomy

- Size of bacteria
  - (0.5 µm diameter and 1.0 µm length)
- Smooth outer membrane, folded inner membrane
  - (# invaginations = cristae)
- Proteins for:
  - OXPHOS = bound to inner membrane
  - TCA = within inner membrane space

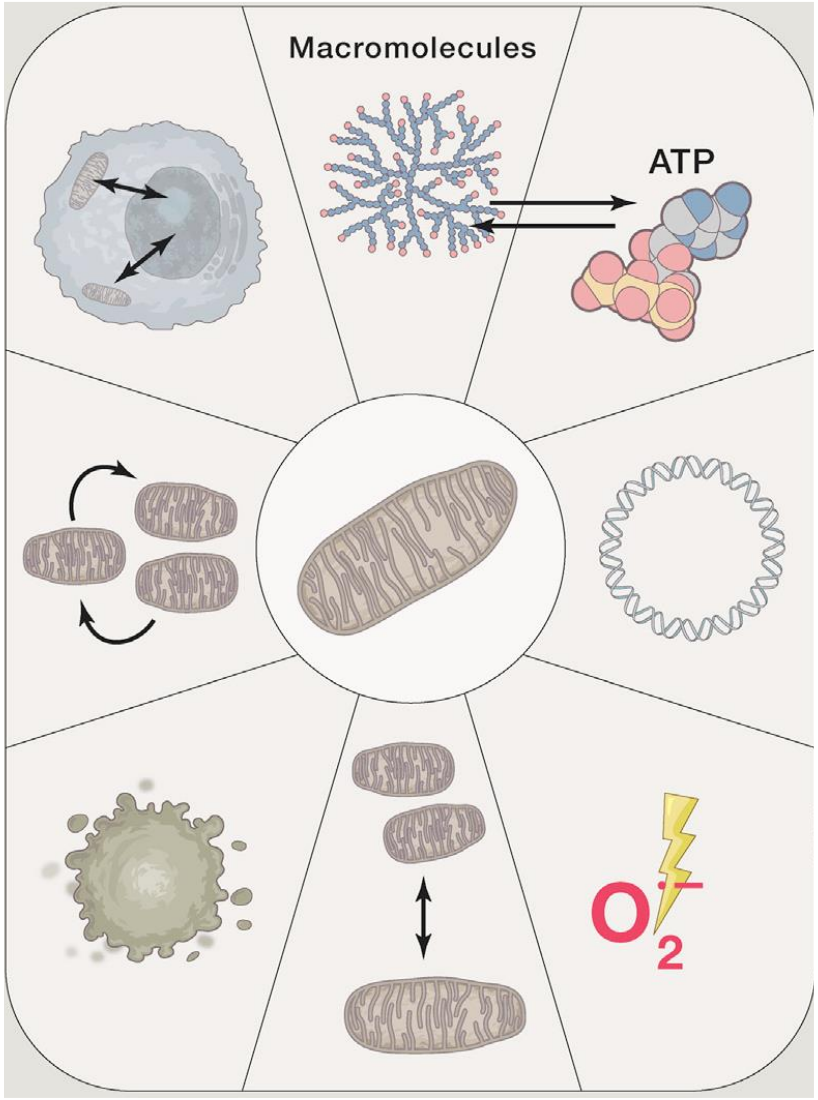


Mitochondria and Cancer

Nuclear-Mitochondria Crosstalk (PolG mutations)

Organelle dynamics

Apoptosis



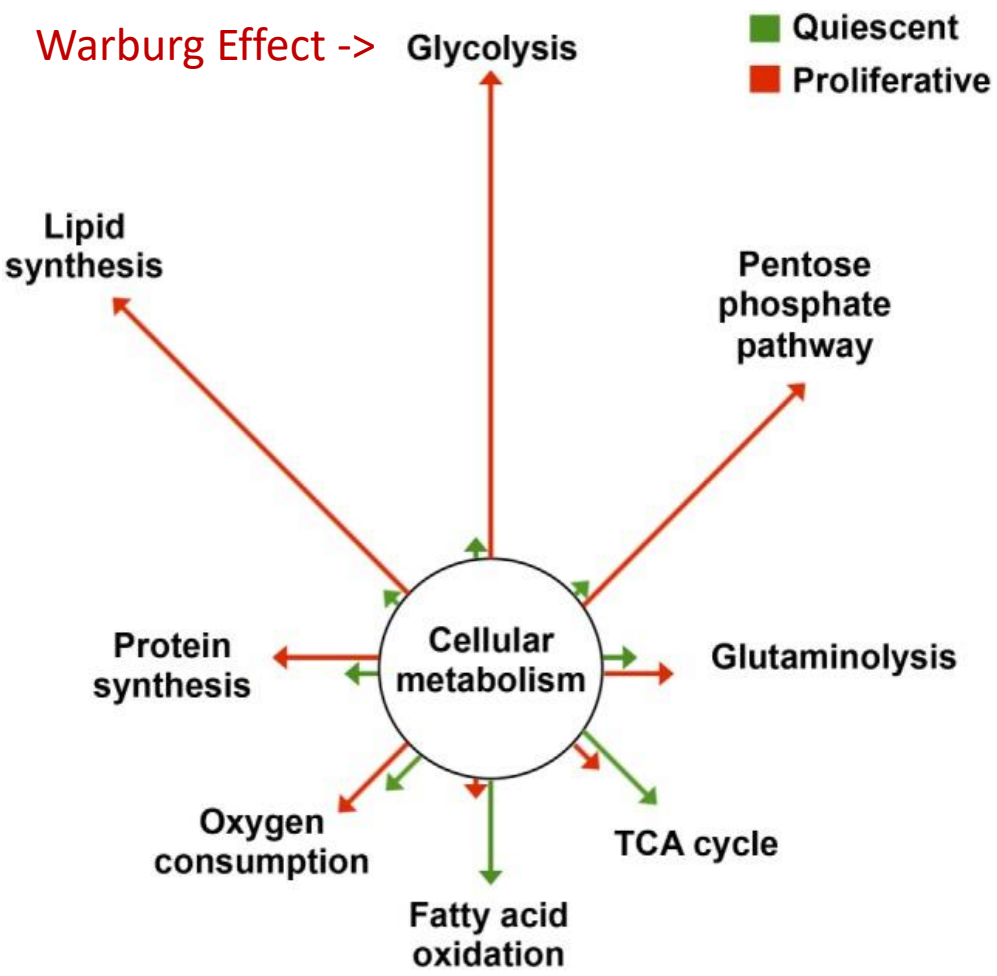
Metabolic reprogramming

mtDNA genome

Reactive oxygen species

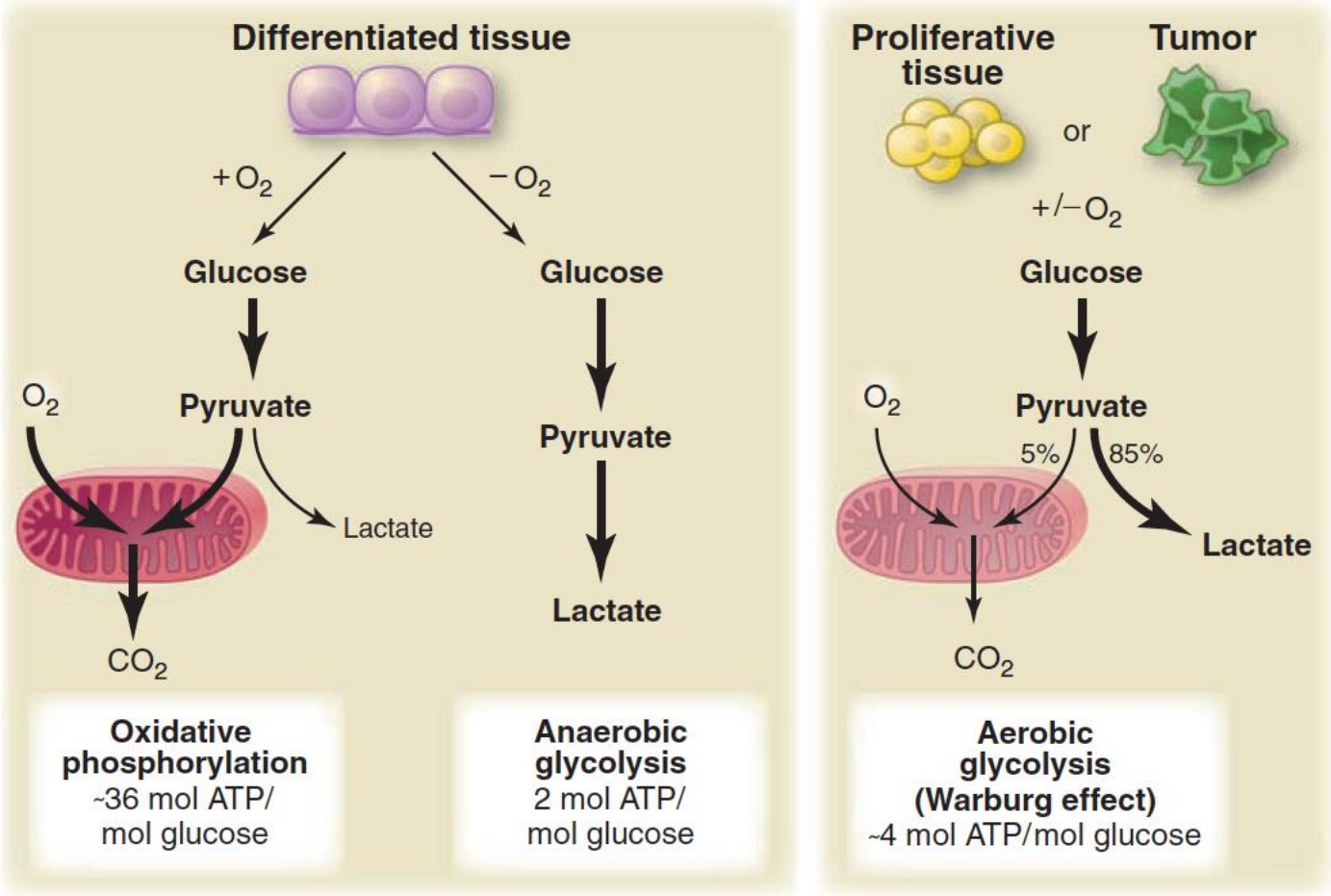
Mitochondria and Cancer. Cell. 2016

Metabolic Reprogramming



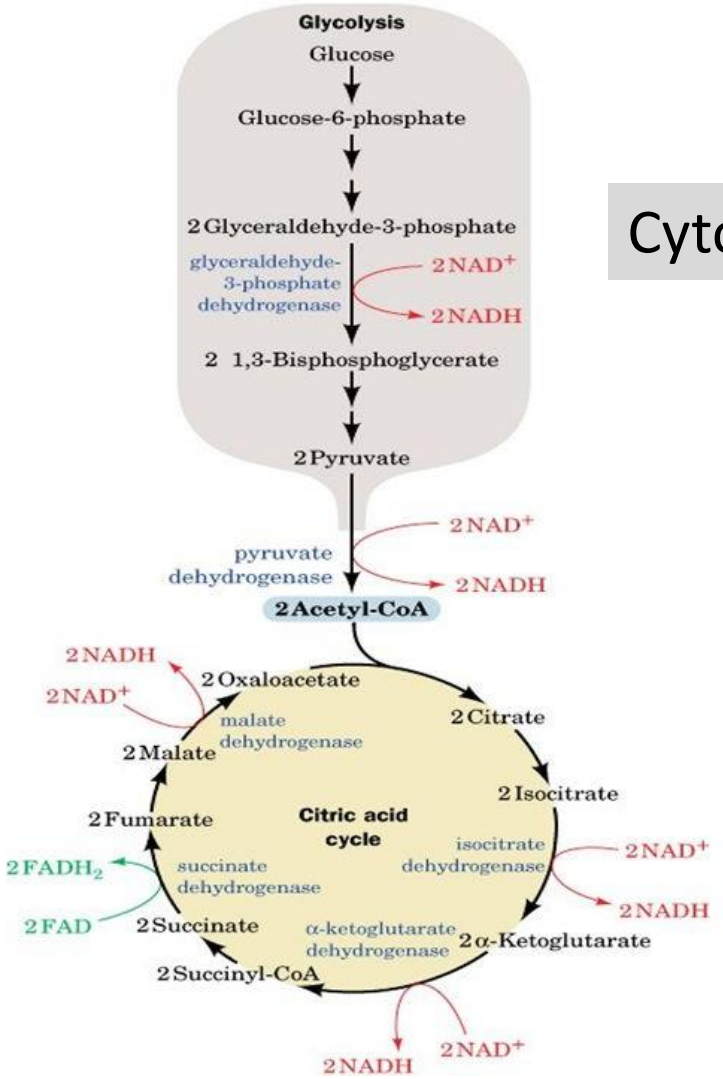
The Role of Mitochondrial H+-ATP Synthase in Cancer. 2018. Frontiers

Review on Warburg Effect



Alterations in glucose utilization

Electron transfer sites forming NADH and $FADH_2$



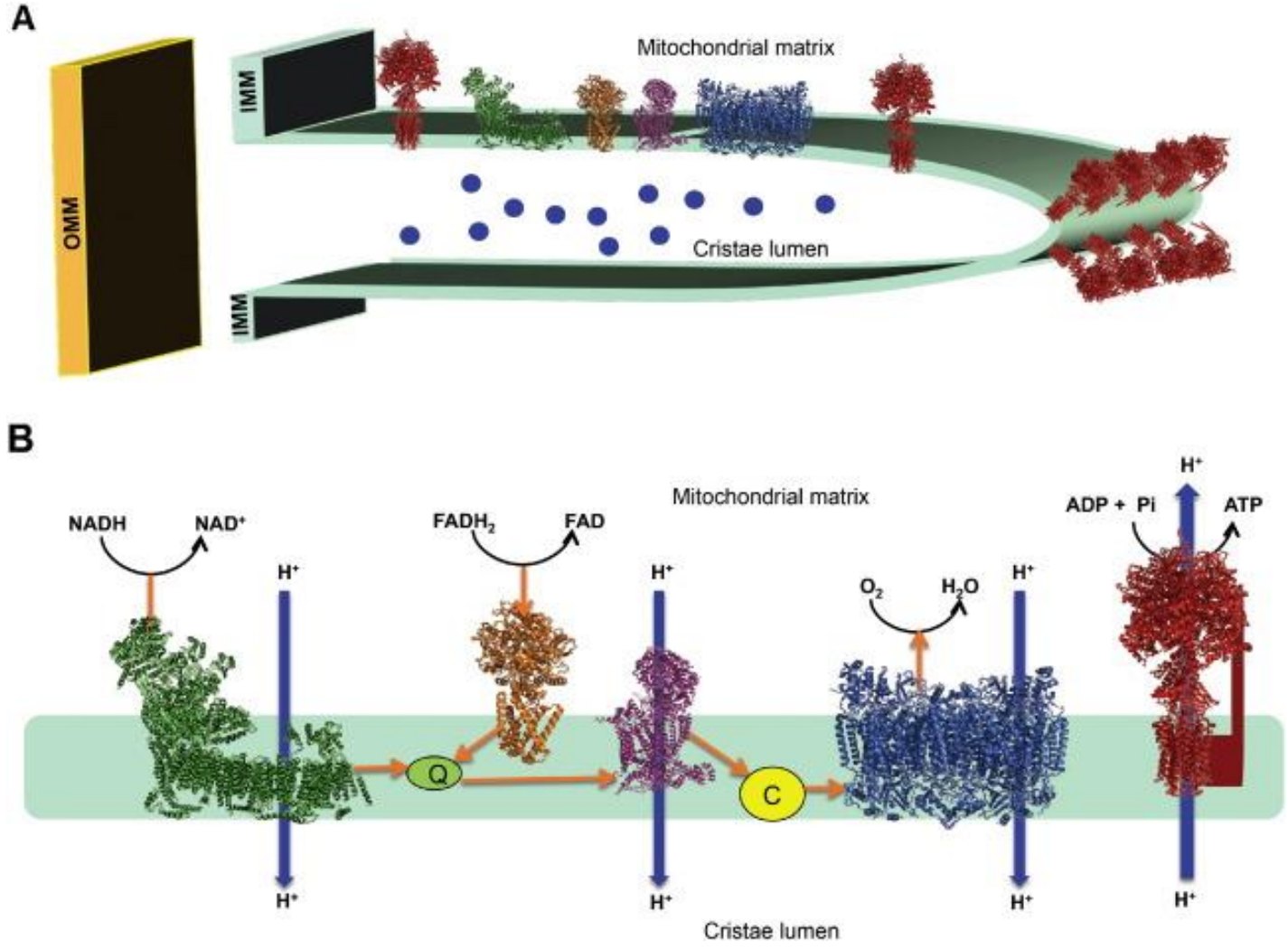
Cytosol

Matrix of Mitochondria (inner membrane space <50% water with high [protein] for TCA cycle)

Oxidative phosphorylation - OXP

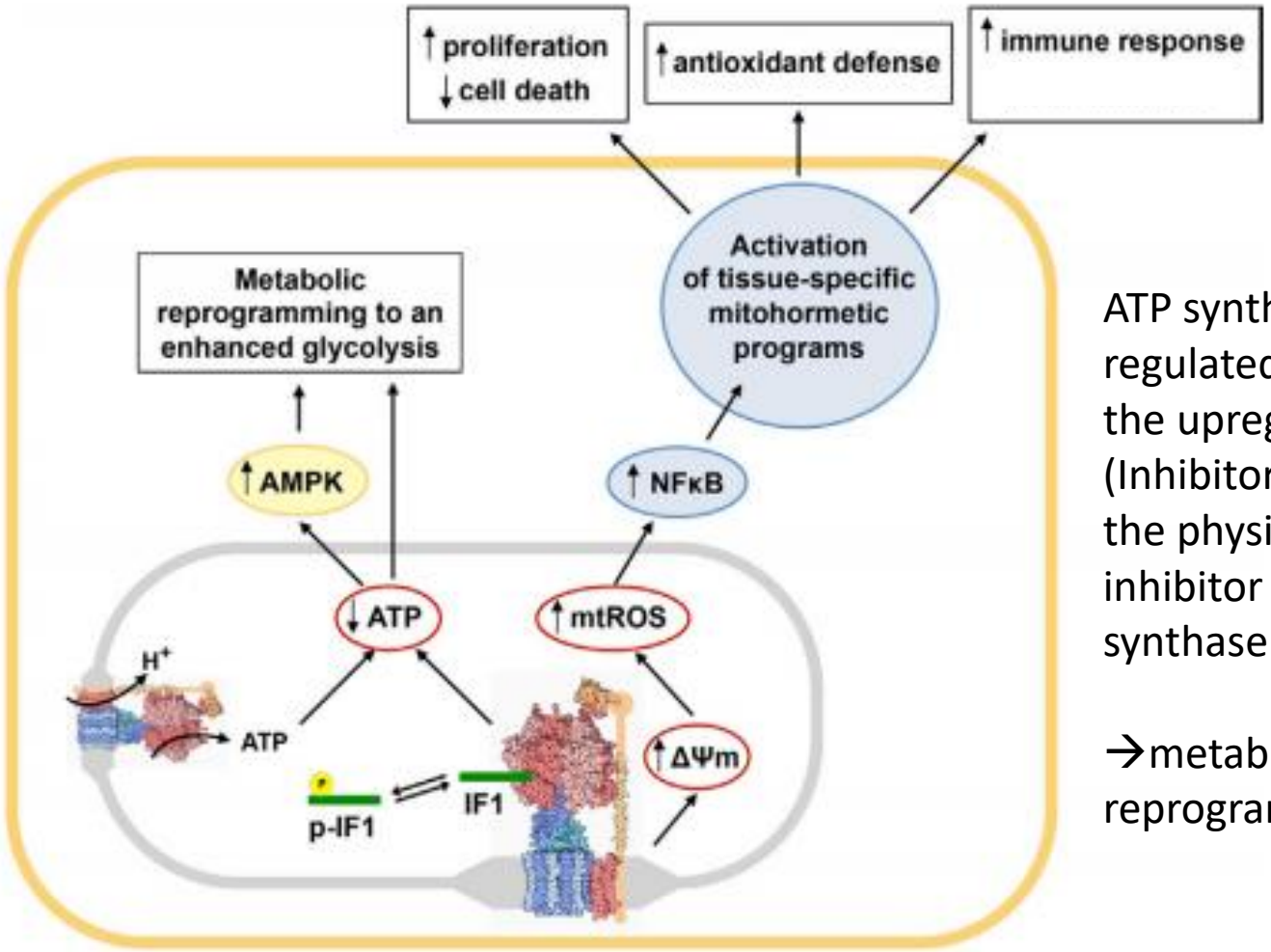
- Metabolic pathway that enzymes oxidize nutrients to release energy used to make ATP
- Takes place in the mitochondrial matrix
- Electron transport chain: free energy of electron transfer from NADH and $FADH_2$ to O_2 through protein bound redox centers coupled to ATP synthesis.
  - 4 enzyme complexes and ATP synthase

Electron transport chain



The Role of Mitochondrial H+-ATP Synthase in Cancer. 2018. Front. Oncol.

ATP Synthase and Cancer

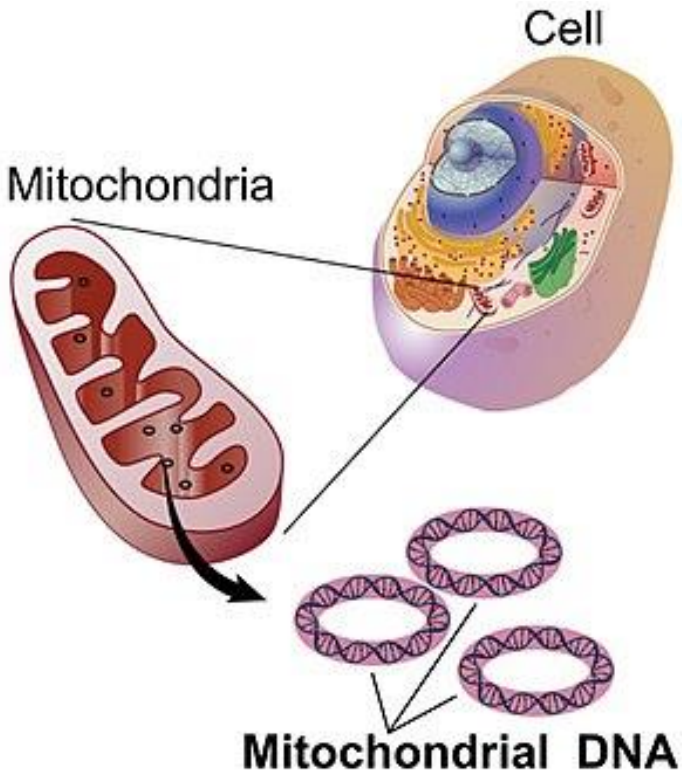


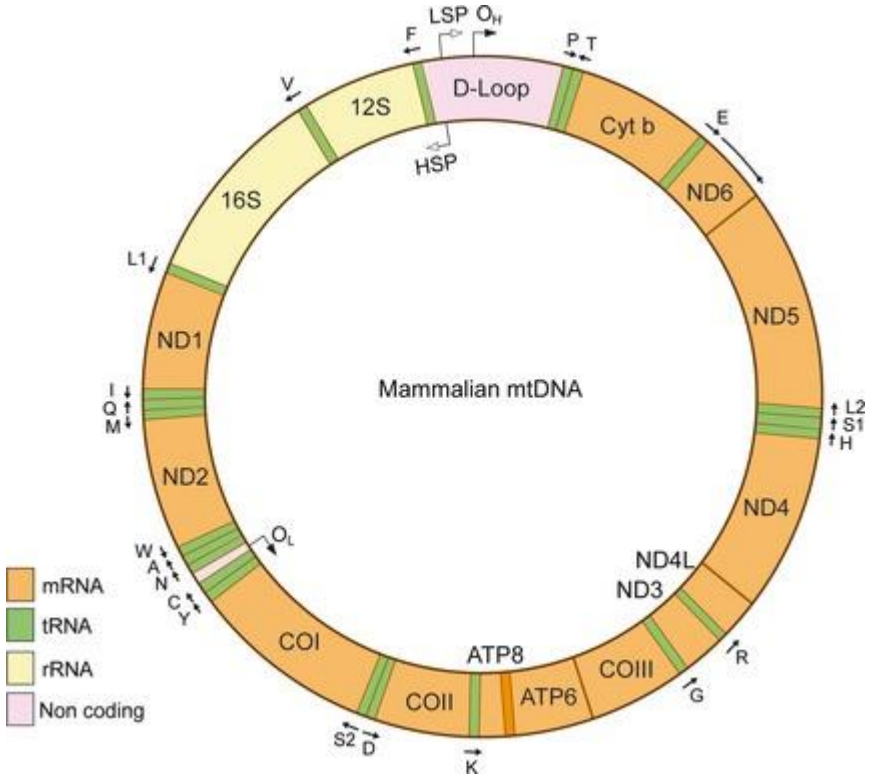
ATP synthase is down regulated in cancer via the upregulation of IF1 (Inhibitor Factor 1) - the physiological inhibitor of ATP synthase

→metabolic reprogramming

The Role of Mitochondrial H+-ATP Synthase in Cancer. 2018. Front. Oncol.

Mitochondria Genome

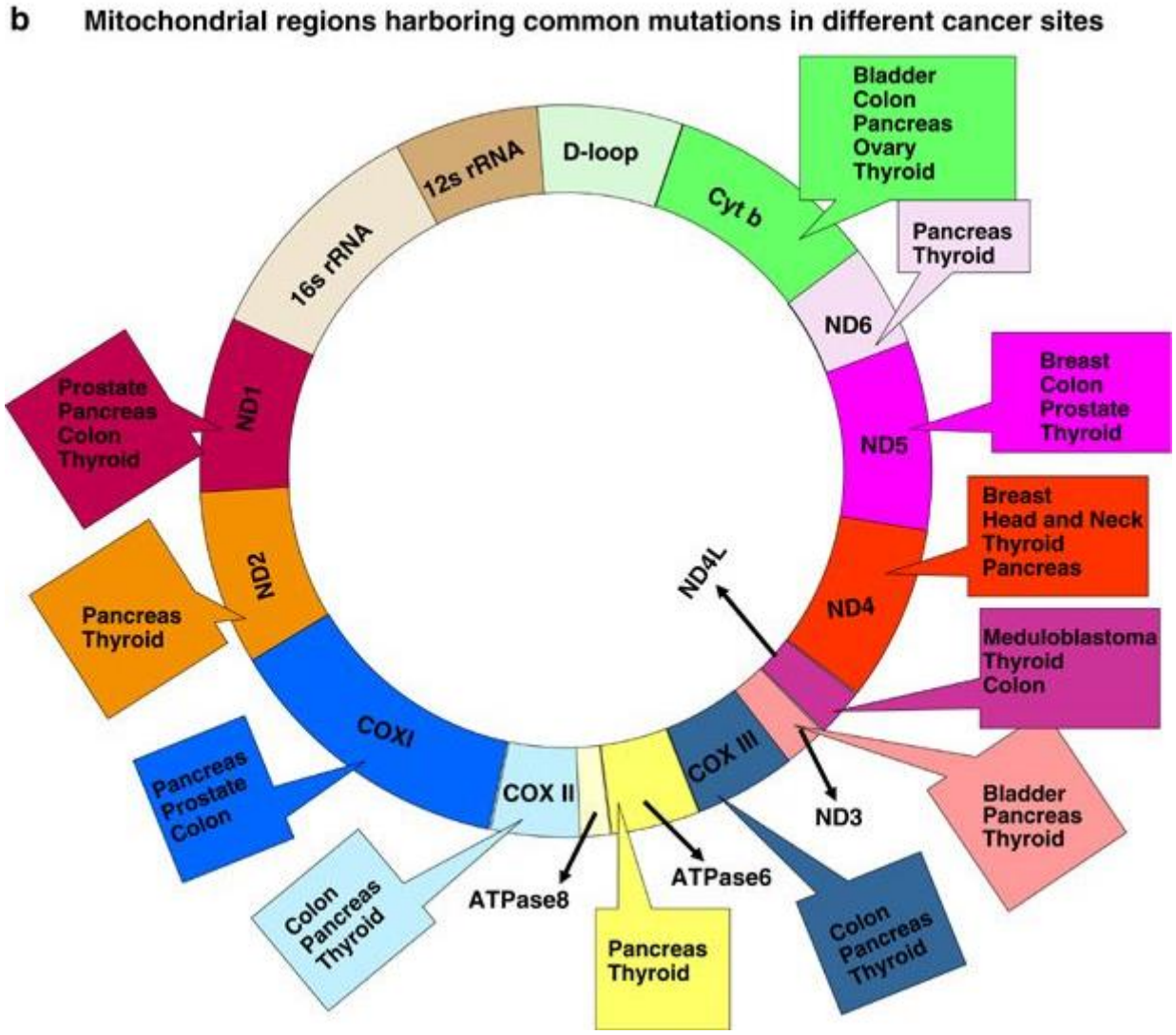




mtDNA vs nDNA

mtDNA	nDNA
ds circular	ds linear
Single chromosome	Several chromosomes
16,569 bp -37 proteins	3.3 billion bp -30,000 proteins
No histones	Histone packing
No introns (non coding)	Many introns
Cell cycle independent replication	S-phase replication
Maternal inheritance	Maternal and Paternal Inheritance (Recombination events)

mtDNA mutations and cancer



Mitochondrial DNA mutations in human cancer. 2006. Oncogene

mtDNA mutations and cancer

Several mtDNA mutations have been identified in various types of human cancer.

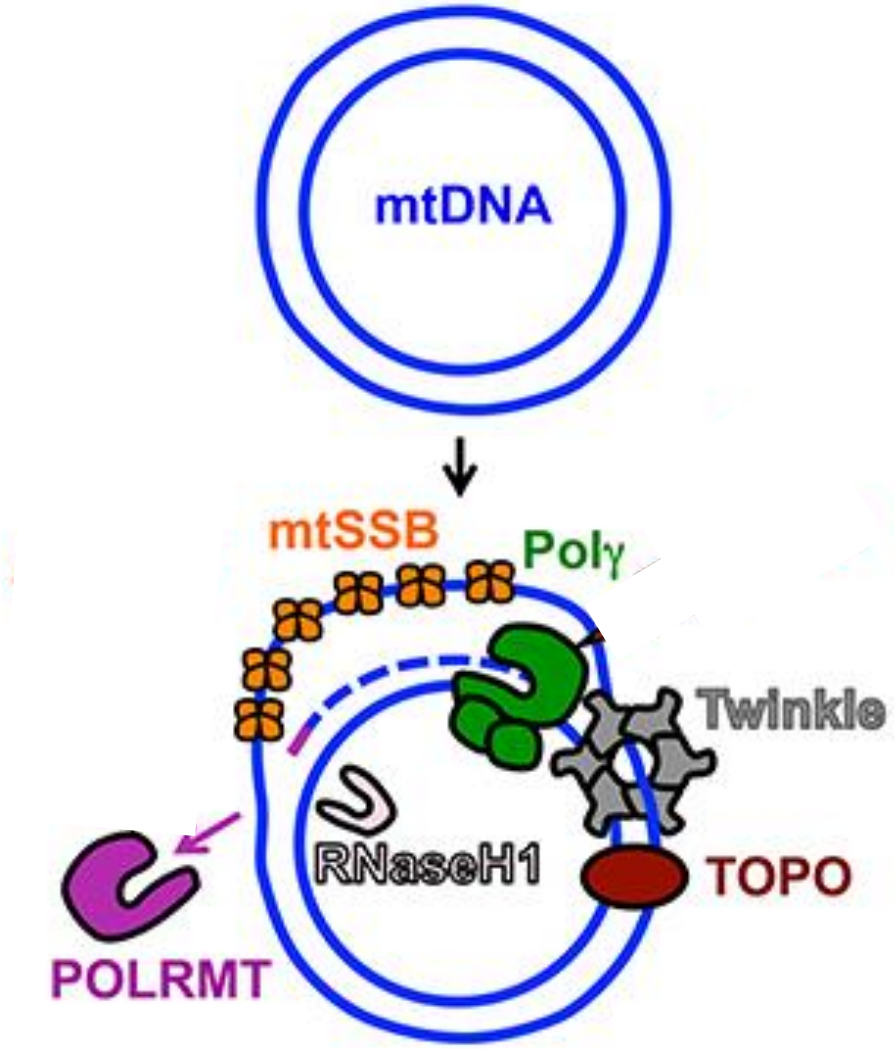
Mutations have been found to be present in both the non-coding region and coding regions of the mtDNA.

Table 4 Mutations in complex V

Region	*Nucleotide change*	*Nucleotide position*	*Cancer type*	*Amino acid change*	*Ref number*
ATPase6	T-C	8996	Pancreatic	MET-THR	Jones *et al.* (2001)
ATPase6	T-G	9070	Pancreatic	SER-ALA	Jones *et al.* (2001)
ATPase6	A-G	8701	Thyroid	THR-ALA	Maximo *et al.* (2002)
ATPase6	T-C	9137	Thyroid	ILE-THR	Maximo *et al.* (2002)
ATPase6	A-G	8716	Thyroid	LYS-GLU	Maximo *et al.* (2002)

Mitochondrial DNA mutations in human cancer. 2006. Oncogene

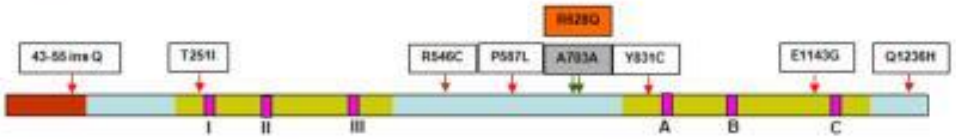
mtDNA replication: DNA Pol Gamma



Mutations in mitochondrial DNA polymerase γ promote breast tumorigenesis

Keshav K. Singh,[1,*] Vanniarajan Ayyasamy,[1] Kjerstin M. Owens,[1] Manika Sapru Koul,[2] and Marija Vujcic[1]

Arrows indicate PolG disease associated mutations



Mutant(R628Q)	HGWGYLVPGRQDNL
Homo sapiens	HGWGYLVPGRRDNL
Pan troglodytes	HGWGYLVPGRRDNL
Macaca mulatta	HGWGYLVPGRRDNL
Equus caballus	HGWGYLVPGRRDNL
Mus musculus	HGWGYLVPGRRDNL
Canis familiaris	HGWGYLVPGRRDNL
Rattus norvegicus	HGWGYLVPGRRDNL

Breast tumors contained mutations in mtDNA. Mutations in POLG are known to cause mutations in mtDNA.

The mtDNA mutator mice that harbor the mutation in the exonuclease domain (that abolishes the POLG proof reading activity) show a marked reduction in lifespan due to the increased rate of mtDNA mutation

It is possible that mtDNA mutations do not initiate tumorigenesis, i.e., transform normal cells, but rather are involved in the promoting tumorigenesis.

Take home message: POLG gene mutations in human cancer suggest a role for POLG in human tumorigenesis.

J Human Genet, 2009.

Concluding remarks on cancer