Non-genetic, Exposure-related Mitochondrial Disease (“*Mitochondrial Toxicity*”)

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Mitochondrial Disease

- Multi-organ clinical presentation
- Metabolic phenotype
- Progressive

- Etiology
  - Genetic
  - Somatogenic/acquired (toxicity)

Mitochondrial Disease

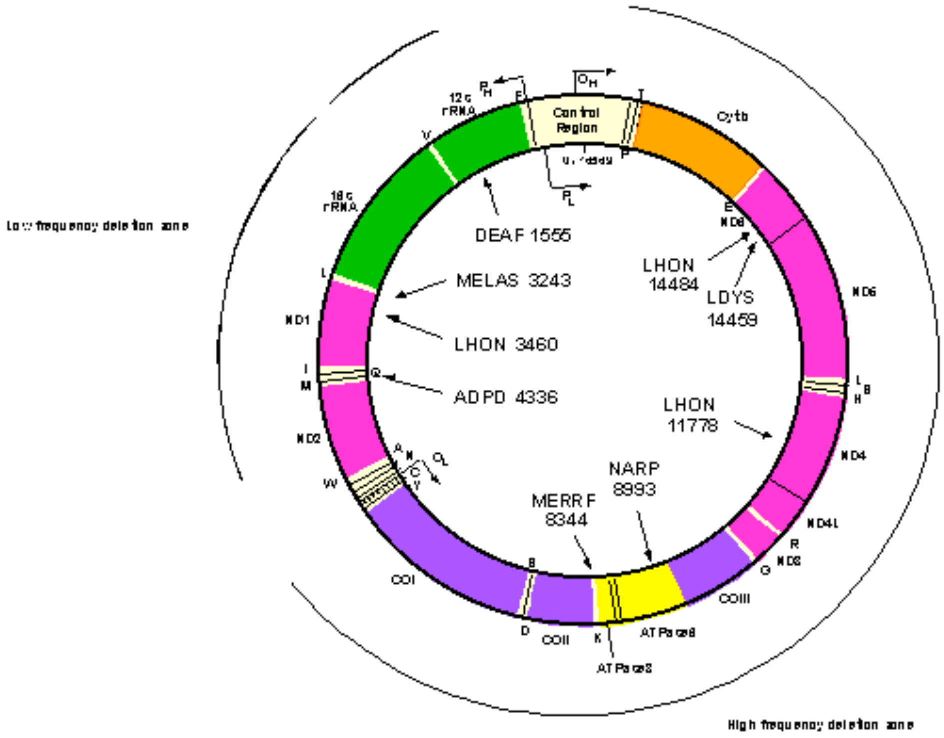
- Etiology

1.Genetic

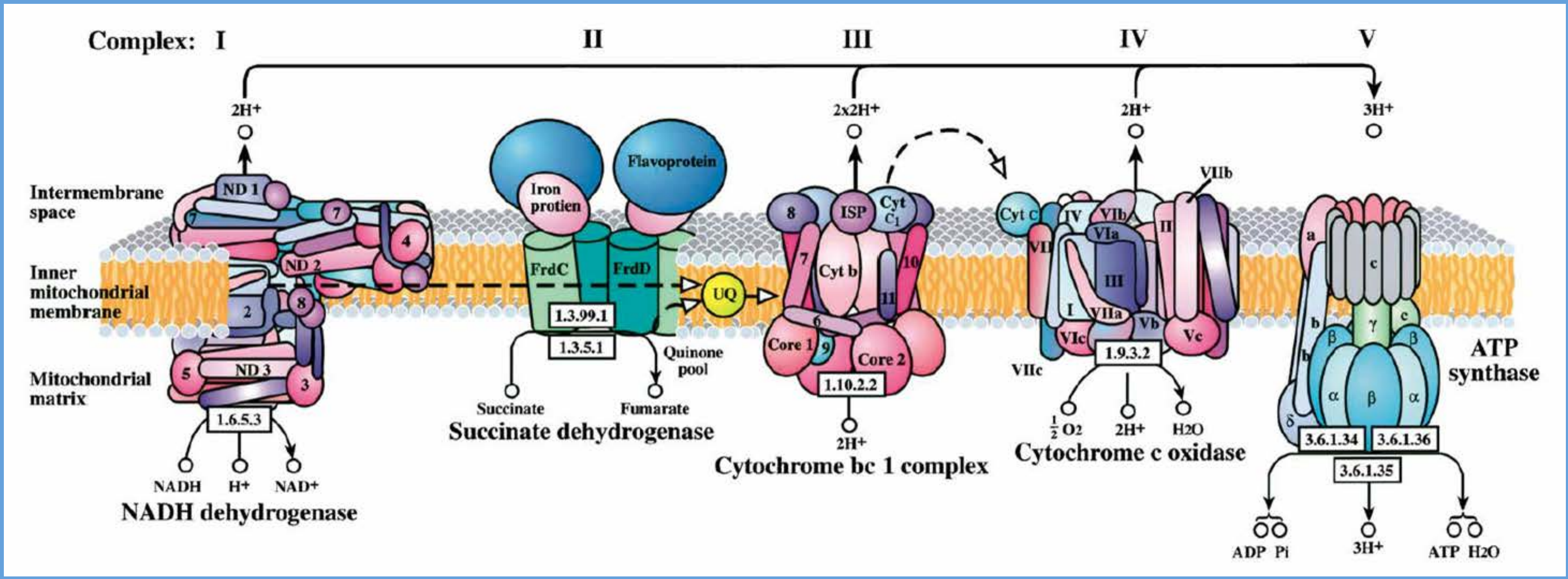
mutations to nuclear (nDNA) &/or mitochondrial DNA (mtDNA)

Heritable – X-chromosome

Mito Map



Mitochondrial Electron Transport Chain



nDNA	**35**	**4**	**10**	**10**	**12**
mtDNA	**7**	**0**	**1**	**3**	**2**

Genetic Mitochondria Disease Foundations

Mitochondrial Disease

- Etiology
  2. Somatogenic/acquired
  "Mitochondrial Toxicity"

  - Pharmaceutical
  - Environmental
  - Occupational

Mito Action Broadcasts
(drug-induced mitochondrial disease)

- May 1, 2009
  Dr. James Dykens, Pfizer Pharmaceuticals
  "Drug Toxicity and Pharmaceuticals"

- June 4, 2010
  Dr. Katherine Sims from Massachusetts General Hospital
  "Mitochondrial Toxicity"

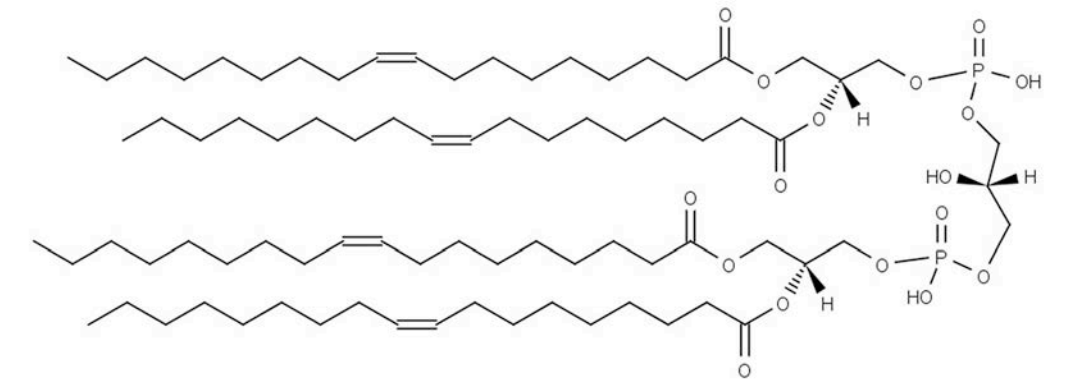
Multiple Targets for Drug-induced Mitochondrial Toxicity

(Wallace, K.B. Curr Med Chem. 2015 May 13)

Chemical Targeting to Mitochondria

Drugs & chemicals are not distributed equally throughout the cell

- Cardiolipin

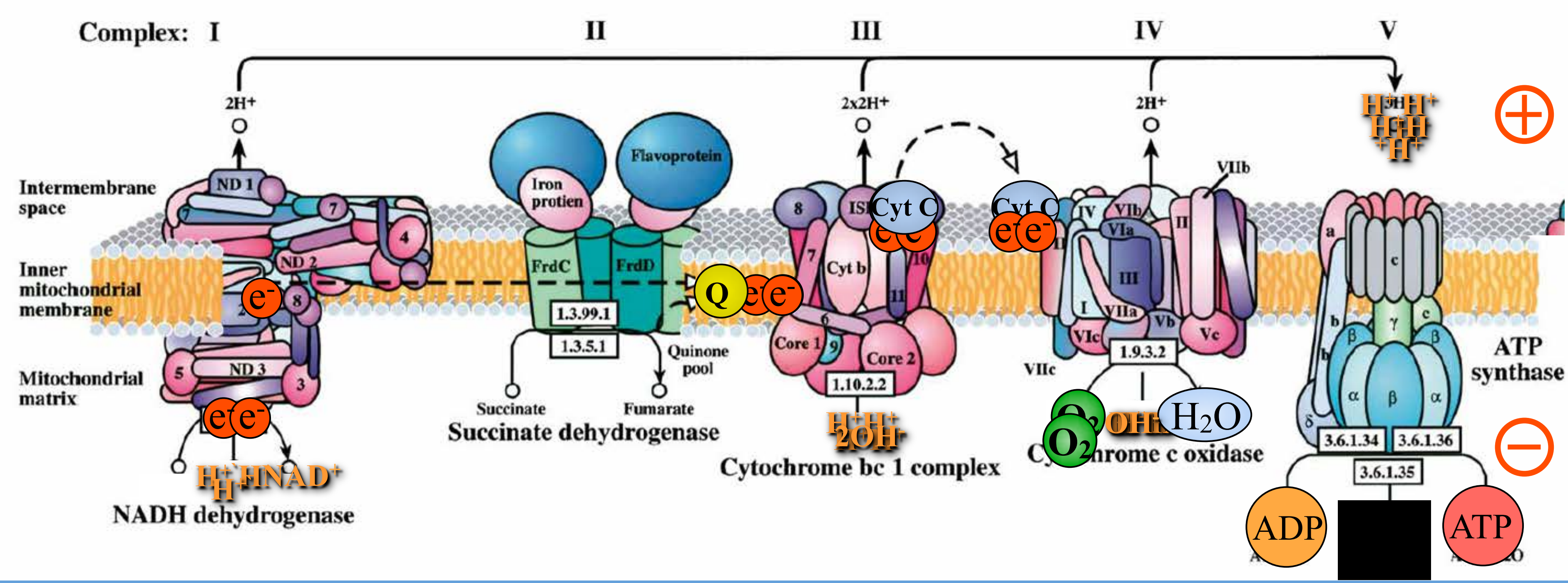


Cardiolipin
1',3'-Bis-[1,2-di-(9Z-octadecenoyl)-sn-glycero-3-phospho]-sn-glycerol

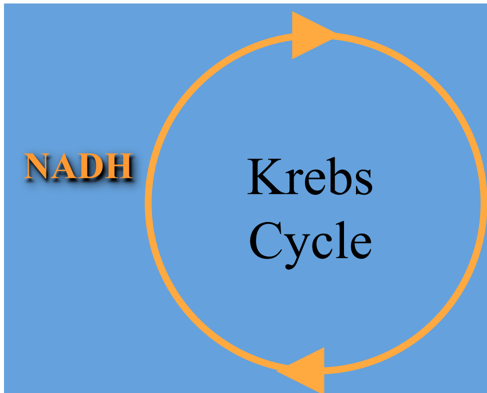
http://figshare.com/articles/_Structure_of_Cardiolipin_/658399

- Electrical membrane potential

Mitochondrial Electron Transport Chain

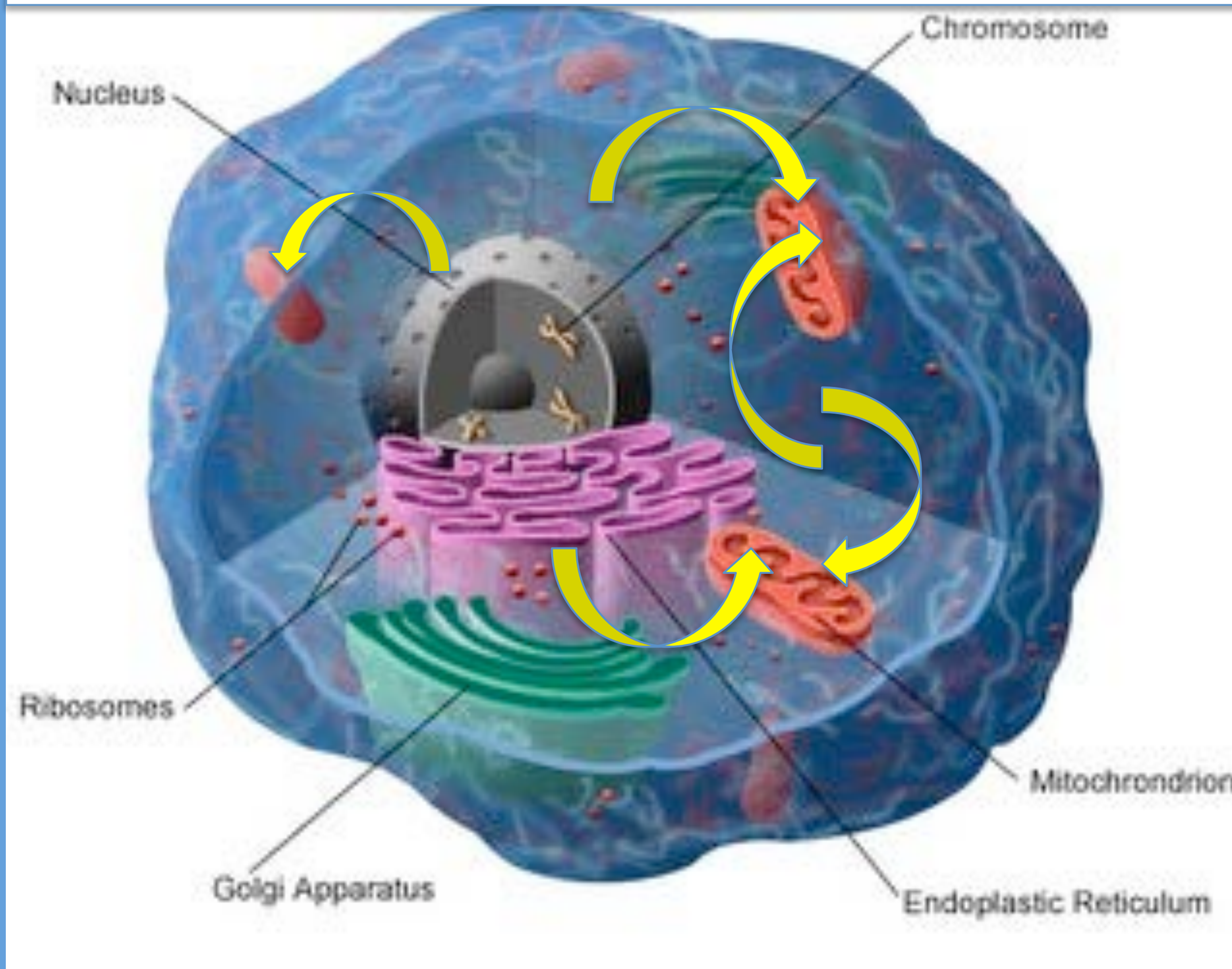


Modified from: Peter S. Rabinwitch after Mandavilli et al, Mutation Research 509 (2002) 127–151



Transmembrane potentials:
~ 1 pH unit alkaline matrix
~ 180 mV negative matrix

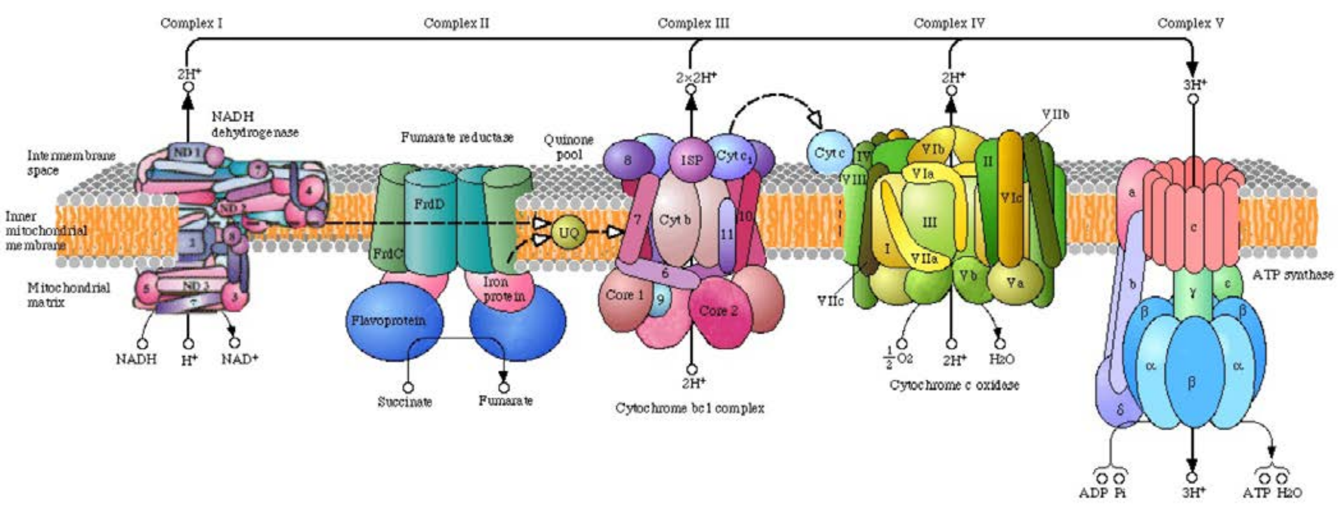
Positively charged chemicals are drawn from the cell contents into and accumulate in mitochondria



Acids & bases

Image modified from: http://www.westernspring.co.uk/how-small-genetic-differences-give-racial-diversity/

Pharmaceutical Inhibitors of Mitochondrial Electron Transport

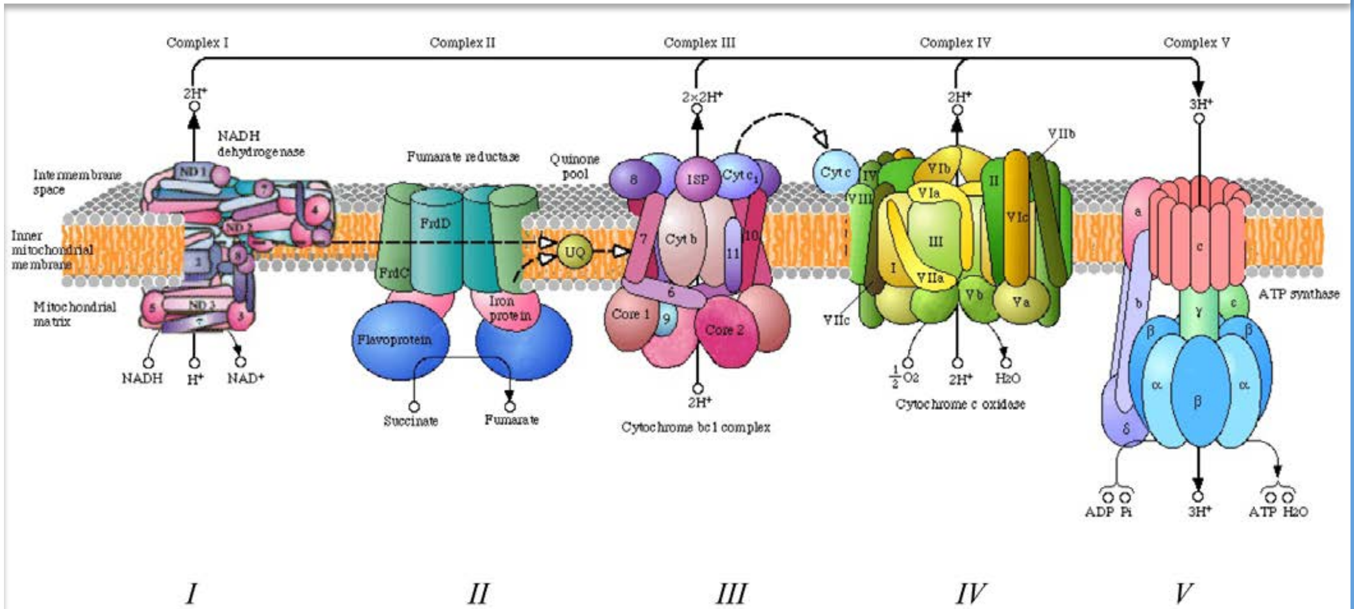


I	II	III	IV	V
Amytal Haloperidol Chlorpromazine Fluphenazine Risperidone Clozapine Nefazodone Clofibrate, Fenofibrate, Ciprofibrate Troglitazone, Rosiglitazone, Pioglitazone Metformin, Phenformin, Buformin, Metformin Bupivacaine, Lidocaine, Halothane, Flutamide, Dantroline Phenytoin	Cyclophosphamide Ketoconazole Hydrazine Isoniazid	Acetaminophen Isoflurane Sevoflurane Propofol	Cephaloridine Cefazolin Cefalotin Tamoxifen	Oligomycin Propofol

Pharmaceutical Uncouplers of Mitochondrial Respiration:

Amphetamines, doxorubicin, Flufenamic acid, Diflunisal, Tolfenamic acid, Mefenamic acid, Diclofenac, Indomethacin, Naproxen, Nimuesulide

Chemical Inhibitors of Mitochondrial Electron Transport



Rotenone

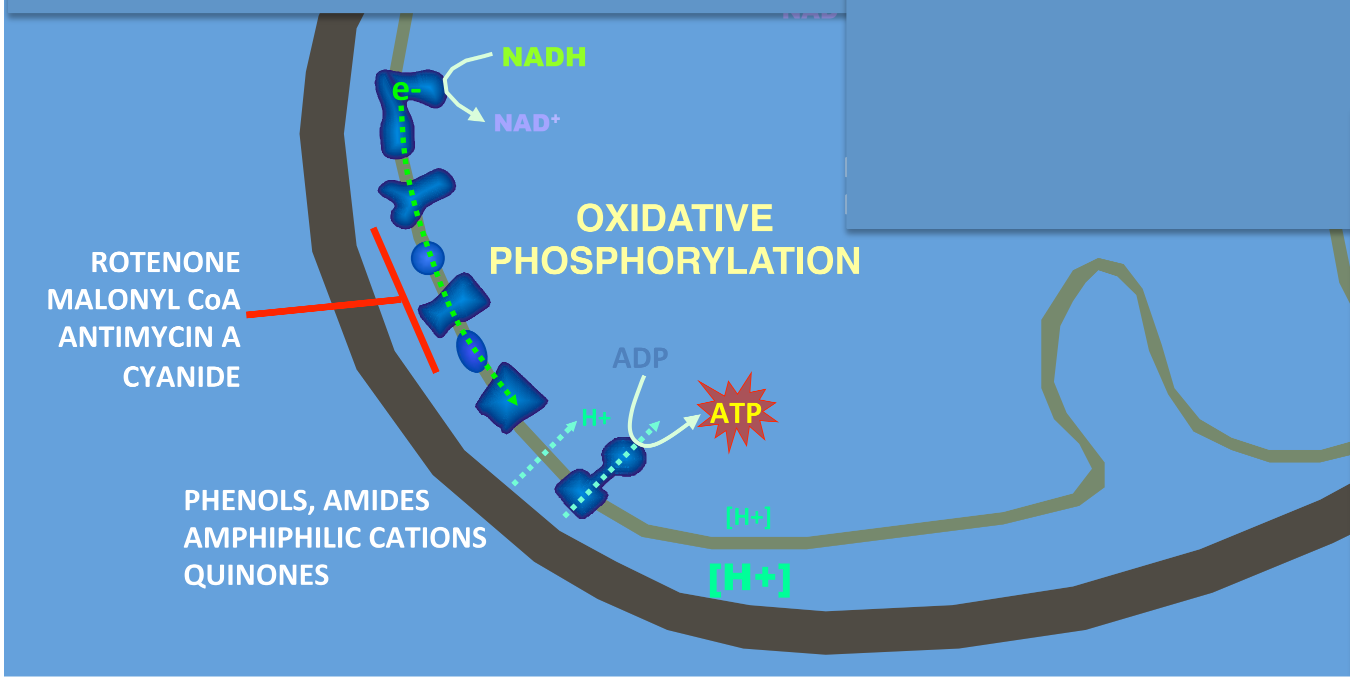
Menadione
Benzoquinone

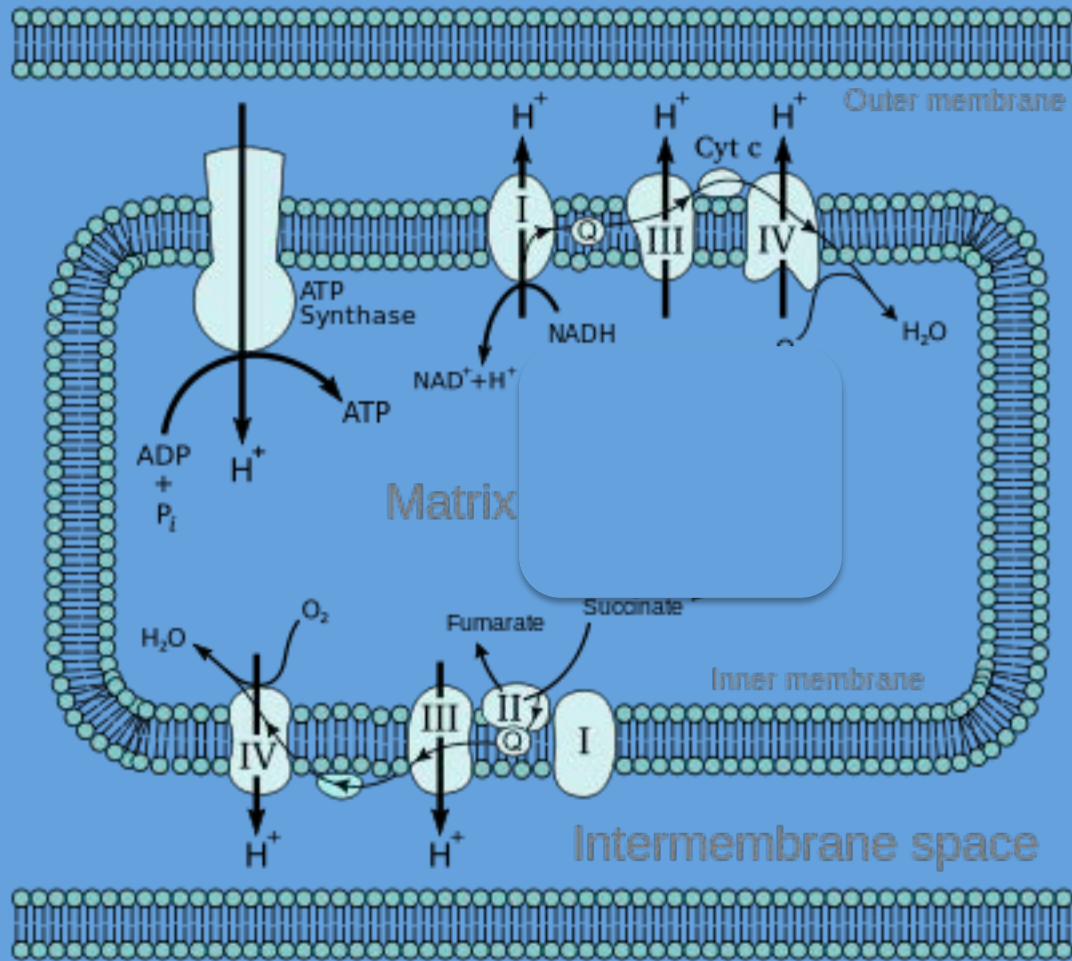
Cyanide
CO
H_2S

Chemical Uncouplers of Mitochondrial Respiration
- Pentachlorophenol
- Heavy metals: Pb^{2+}, As^{2+}, Cd^{2+}, Hg^{2+}
- Paraquat
- perfluorosulfonamide

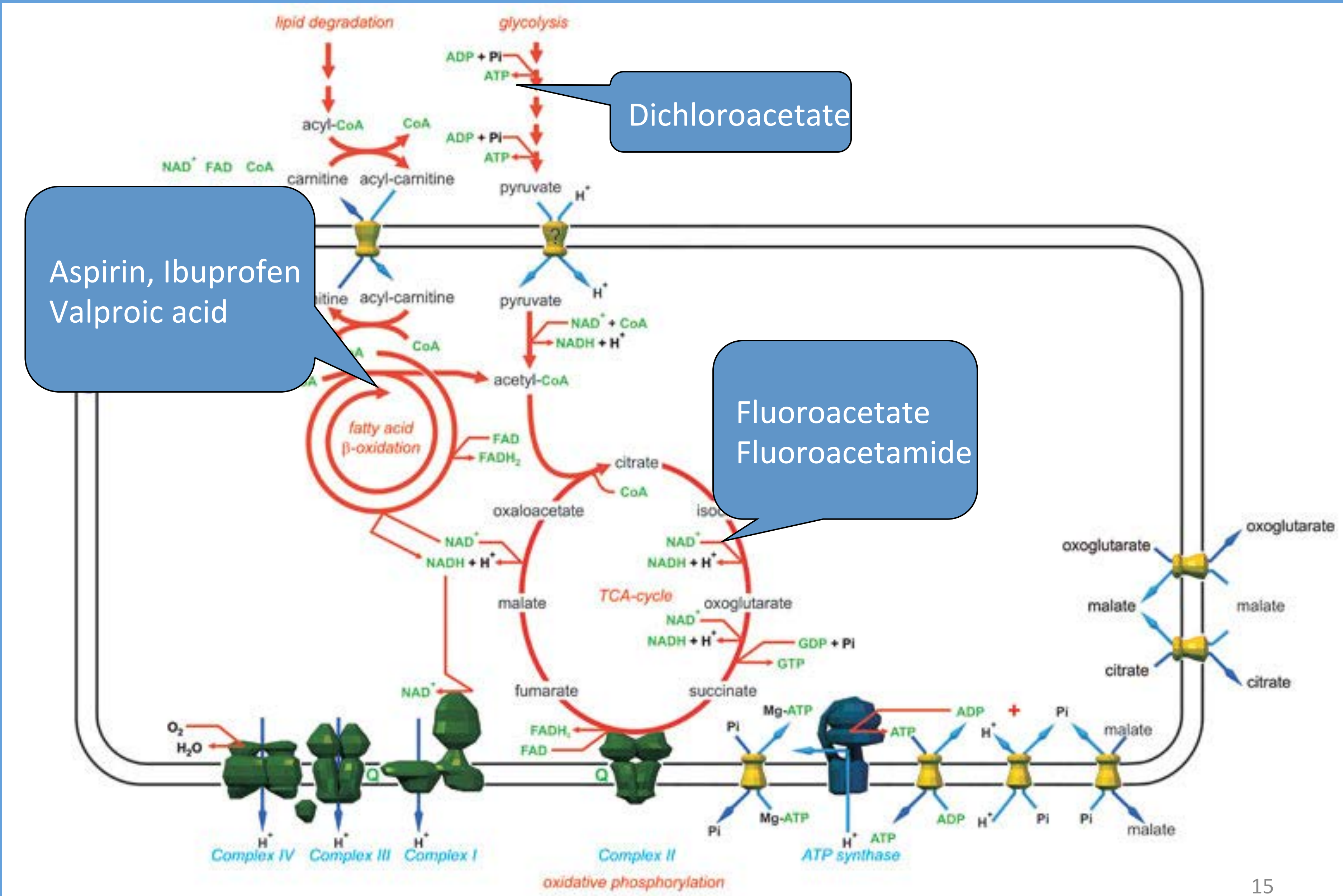
The Bigger Picture of "Mitochondrial Toxicity"

- *Substrate delivery*
- *Molecular organization*

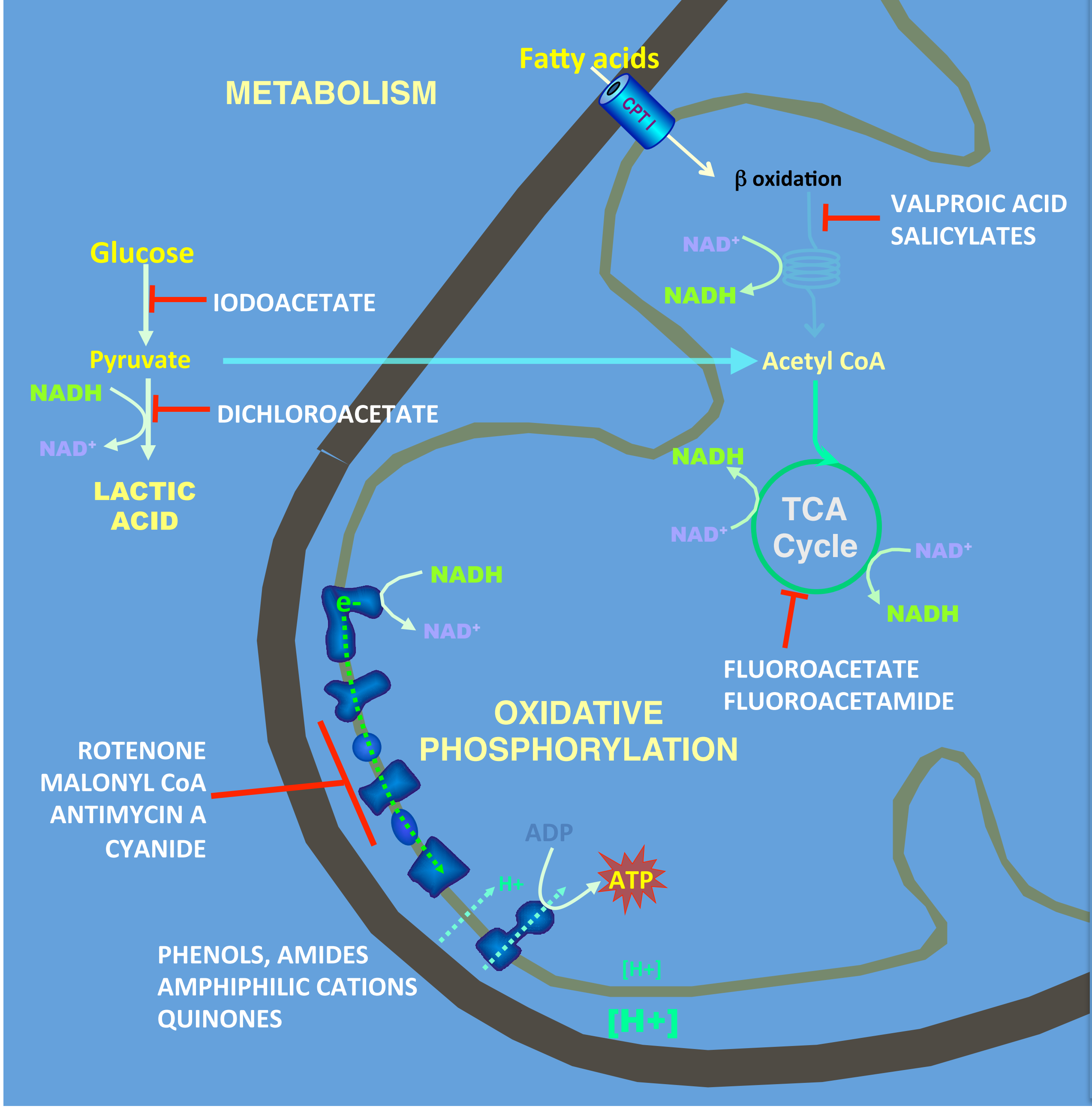




https://en.wikipedia.org/wiki/Electron_transport_chain


Dichloroacetate
Aspirin, Ibuprofen
Valproic acid
Fluoroacetate
Fluoroacetamide
lipid degradation
glycolysis
acyl-CoA
CoA
carnitine
acyl-carnitine
pyruvate
acetyl-CoA
fatty acid β-oxidation
citrate
oxaloacetate
malate
fumarate
succinate
oxoglutarate
TCA-cycle
Complex IV
Complex III
Complex I
Complex II
ATP synthase
oxidative phosphorylation

Chemical-induced Mitochondrionopathies



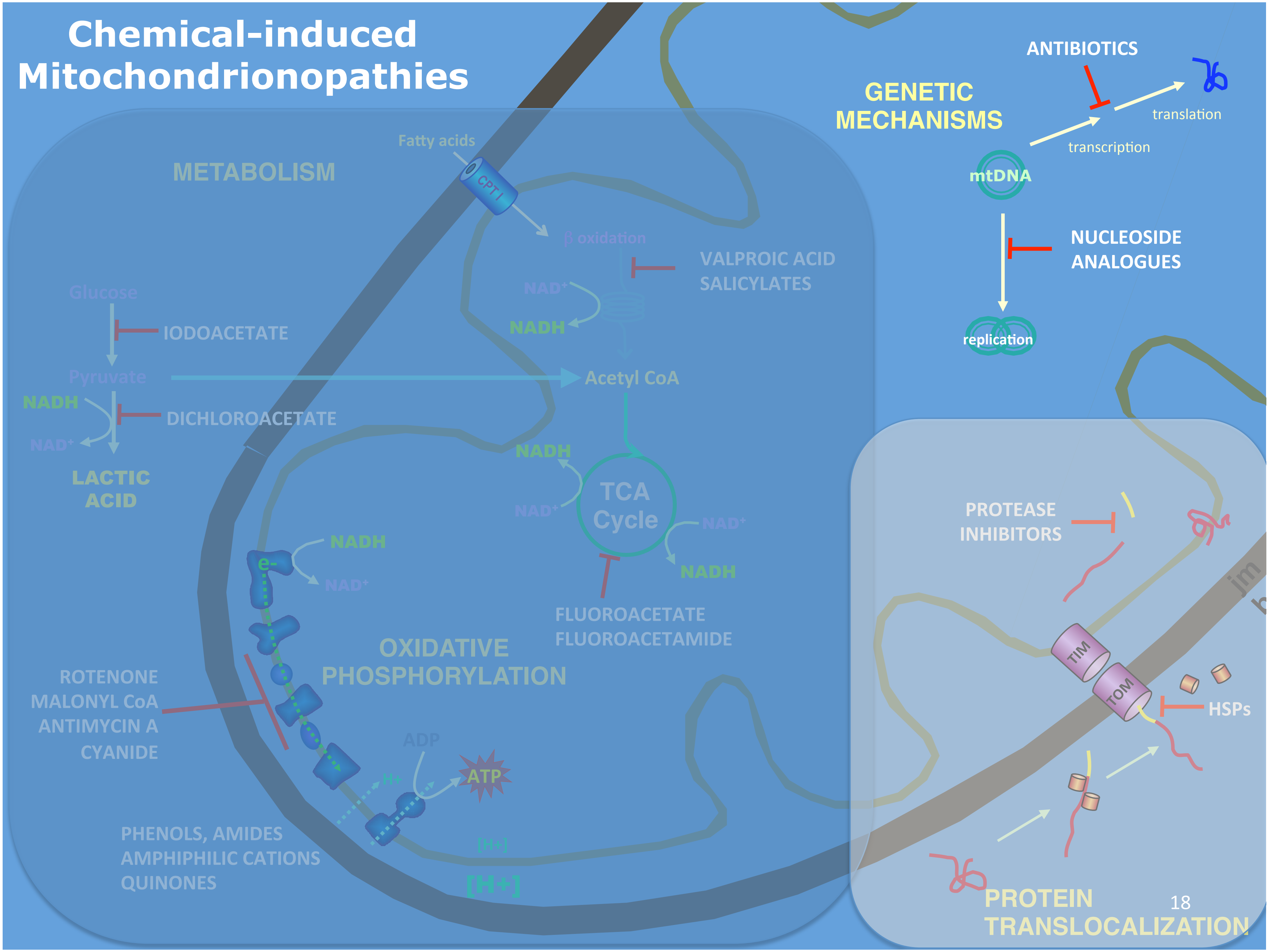
Summary update

Molecular Targets for Mitochondrial Toxicity

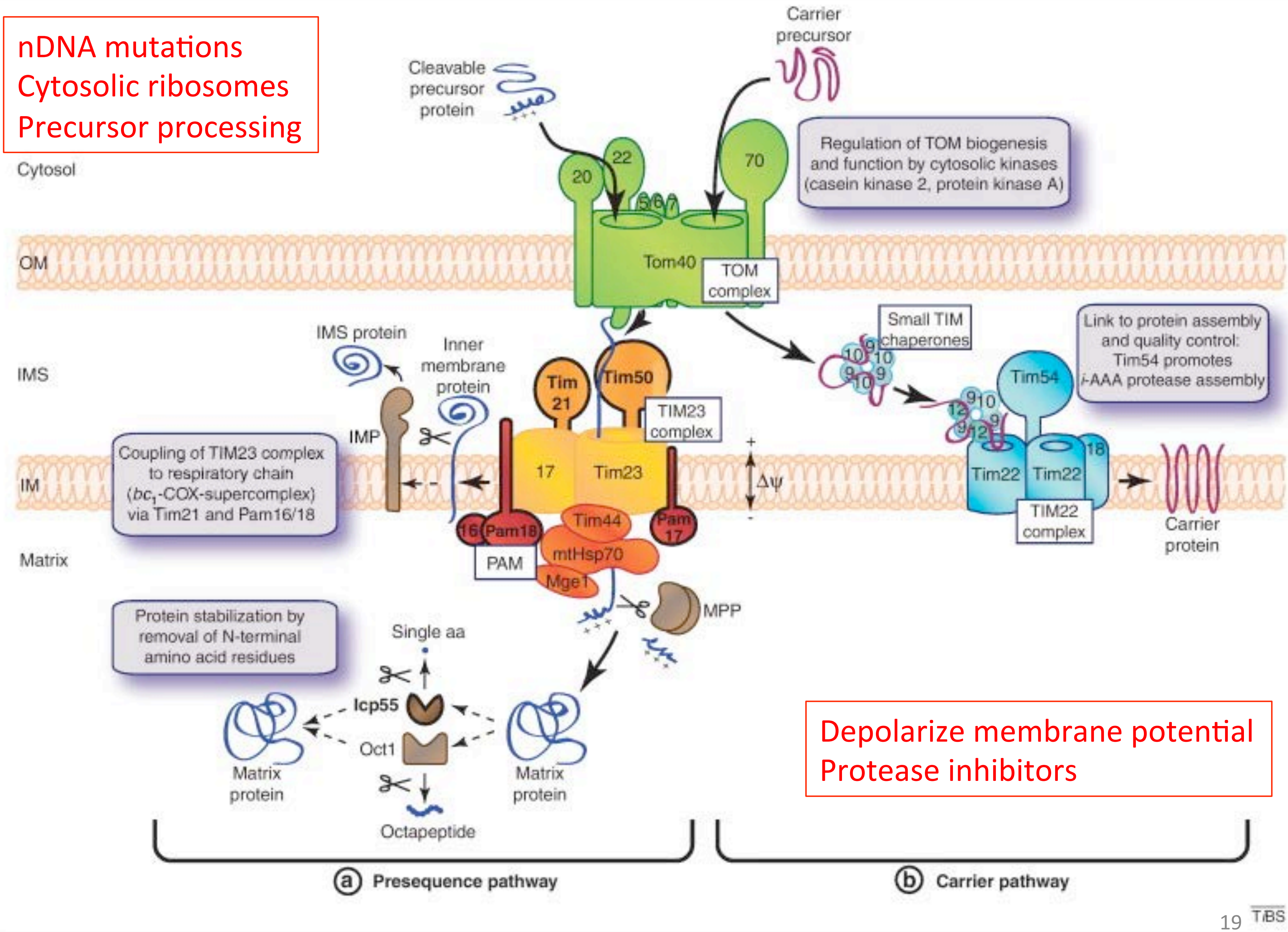
From the mitochondrial or nuclear genome to protein incorporated into the mitochondrial structure

- Gene translation
- Protein synthesis
- Protein translocation and assembly

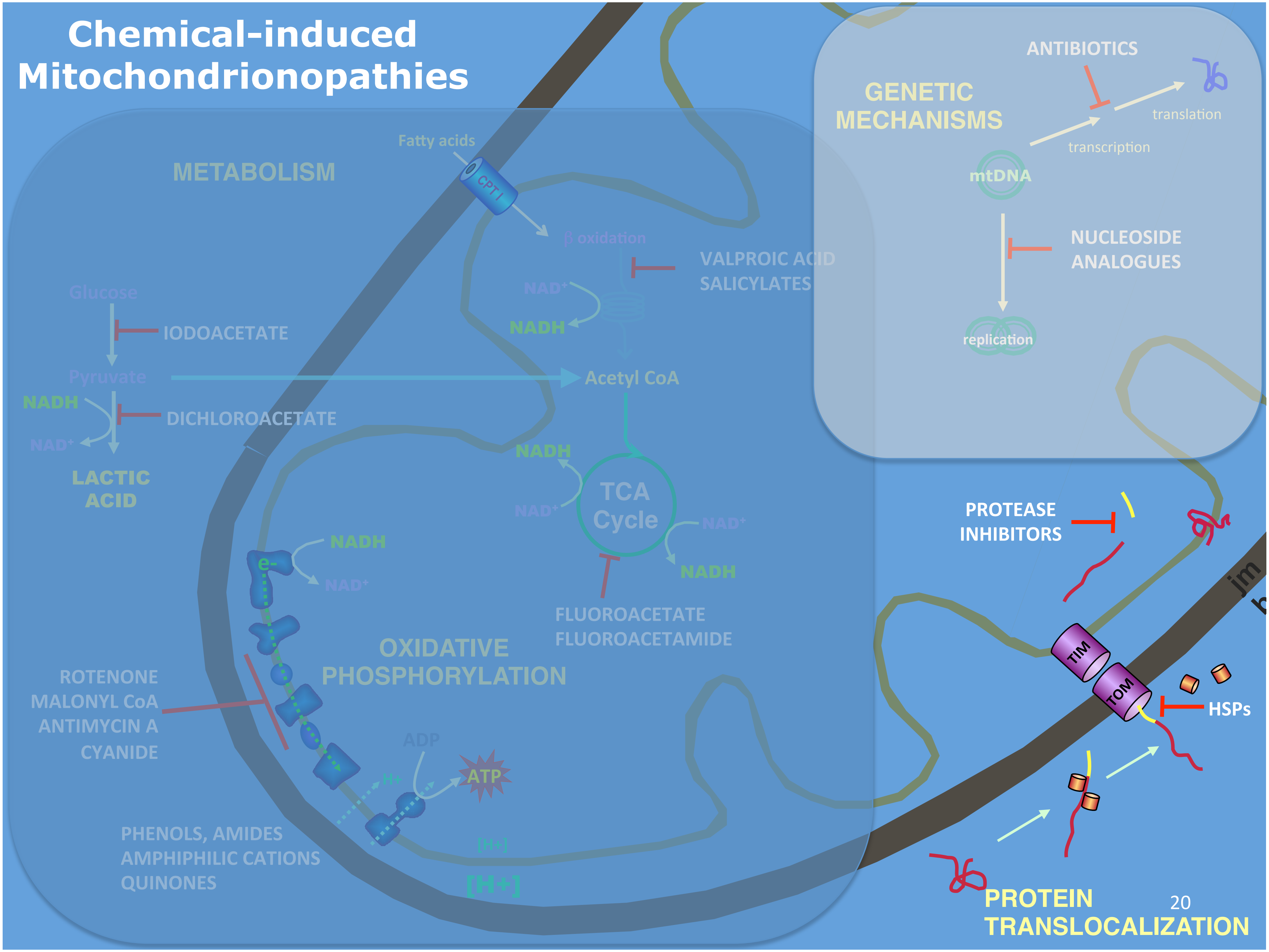
Chemical-induced Mitochondrionopathies



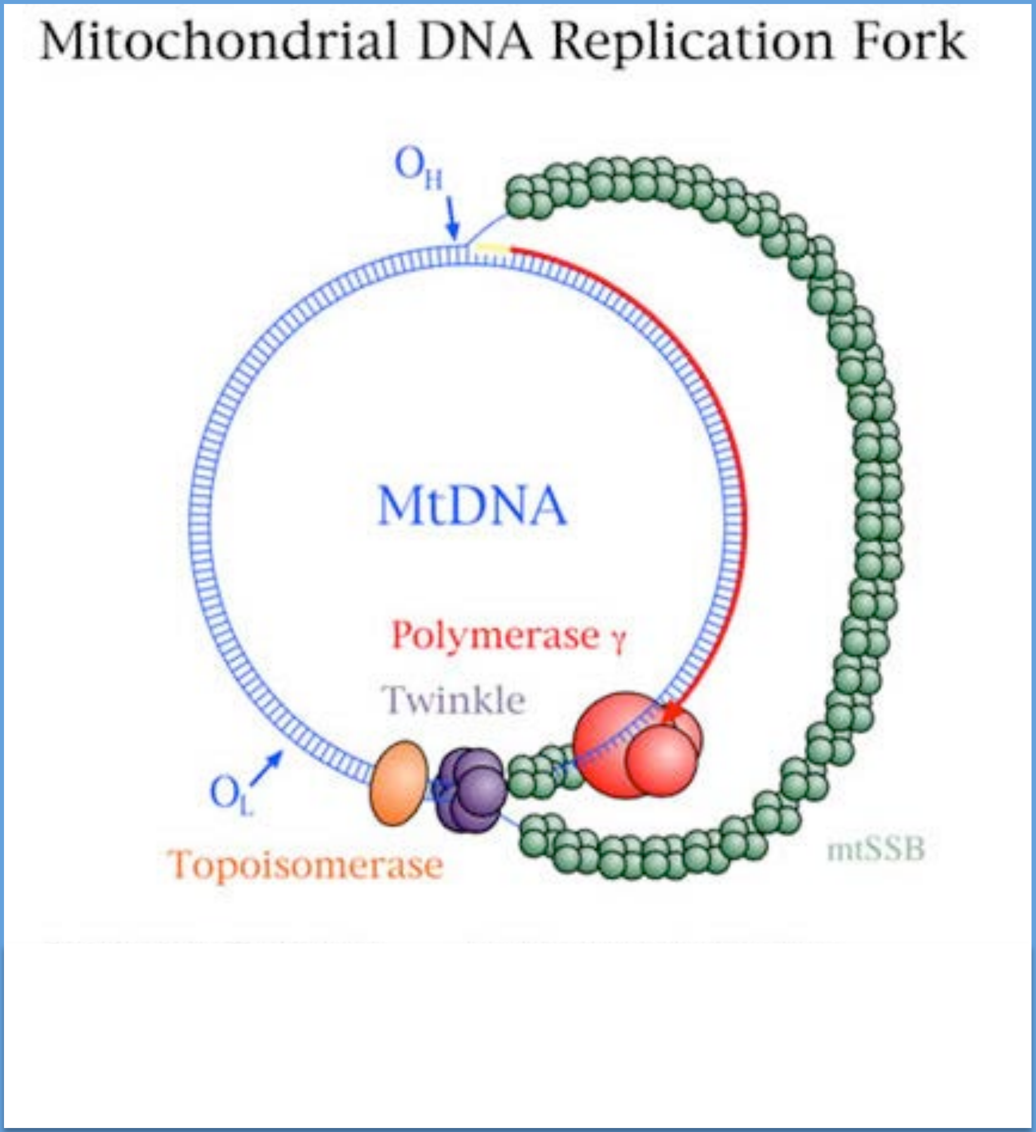
nDNA mutations
Cytosolic ribosomes
Precursor processing

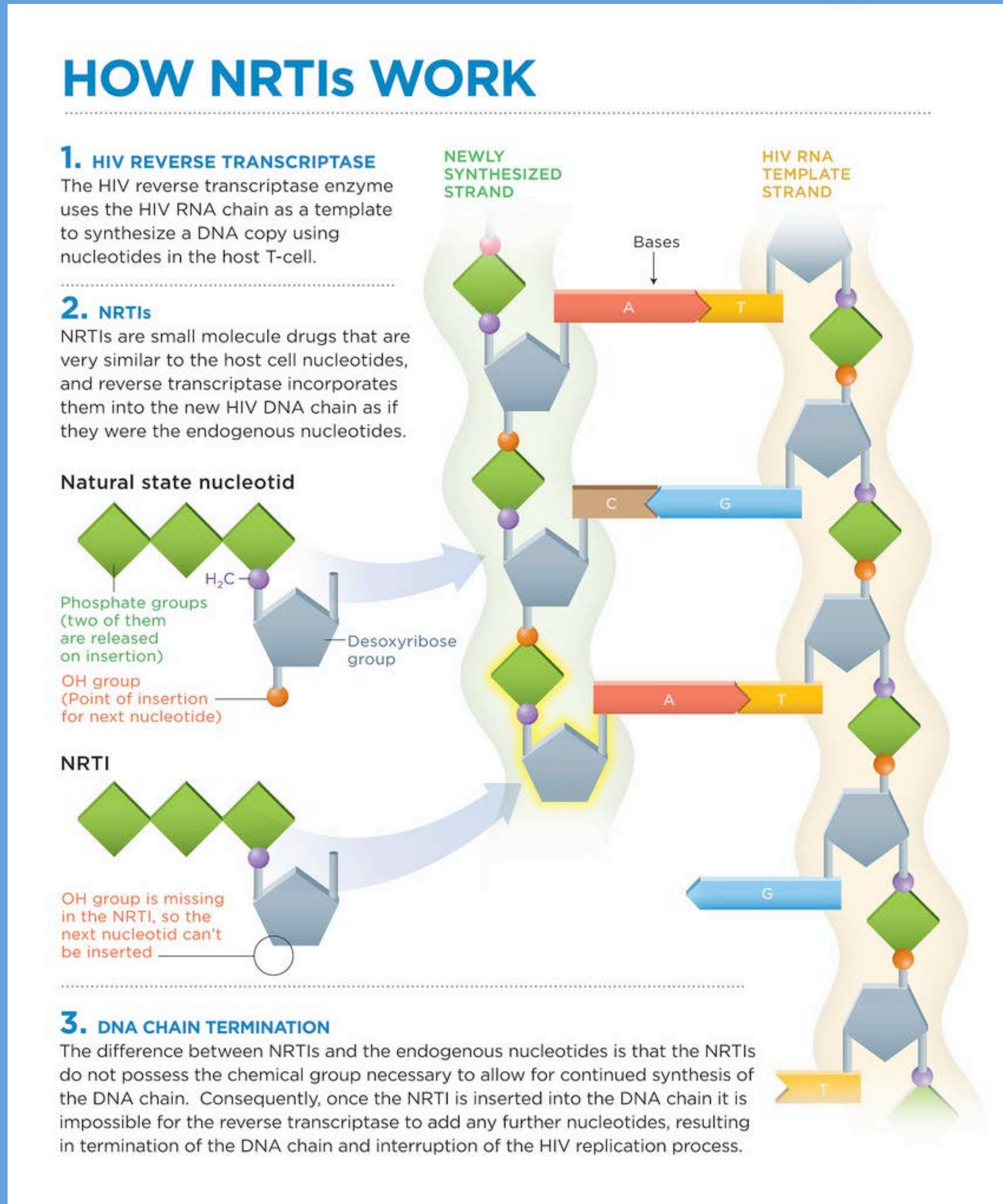


Depolarize membrane potential
Protease inhibitors


Chemical-induced
Mitochondrionopathies
METABOLISM
Fatty acids
CPT I
β oxidation
VALPROIC ACID
SALICYLATES
NAD+
NADH
Glucose
IODOACETATE
Pyruvate
Acetyl CoA
NADH
DICHLOROACETATE
NAD+
LACTIC ACID
NADH
NAD+
TCA Cycle
NAD+
NADH
FLUOROACETATE
FLUOROACETAMIDE
e-
NADH
NAD+
OXIDATIVE PHOSPHORYLATION
ROTENONE
MALONYL CoA
ANTIMYCIN A
CYANIDE
ADP
H+
ATP
[H+]
[H+]
PHENOLS, AMIDES
AMPHIPHILIC CATIONS
QUINONES
GENETIC MECHANISMS
ANTIBIOTICS
translation
transcription
mtDNA
NUCLEOSIDE ANALOGUES
replication
PROTEASE INHIBITORS
TIM
TOM
HSPs
PROTEIN TRANSLOCALIZATION

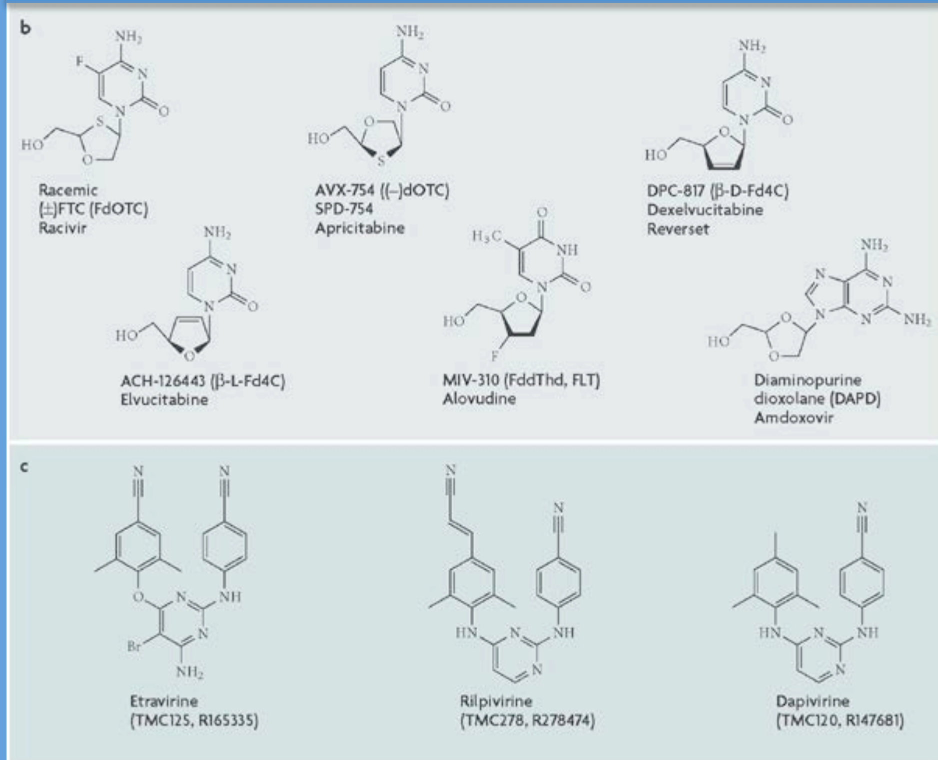
mtDNA replication and translation





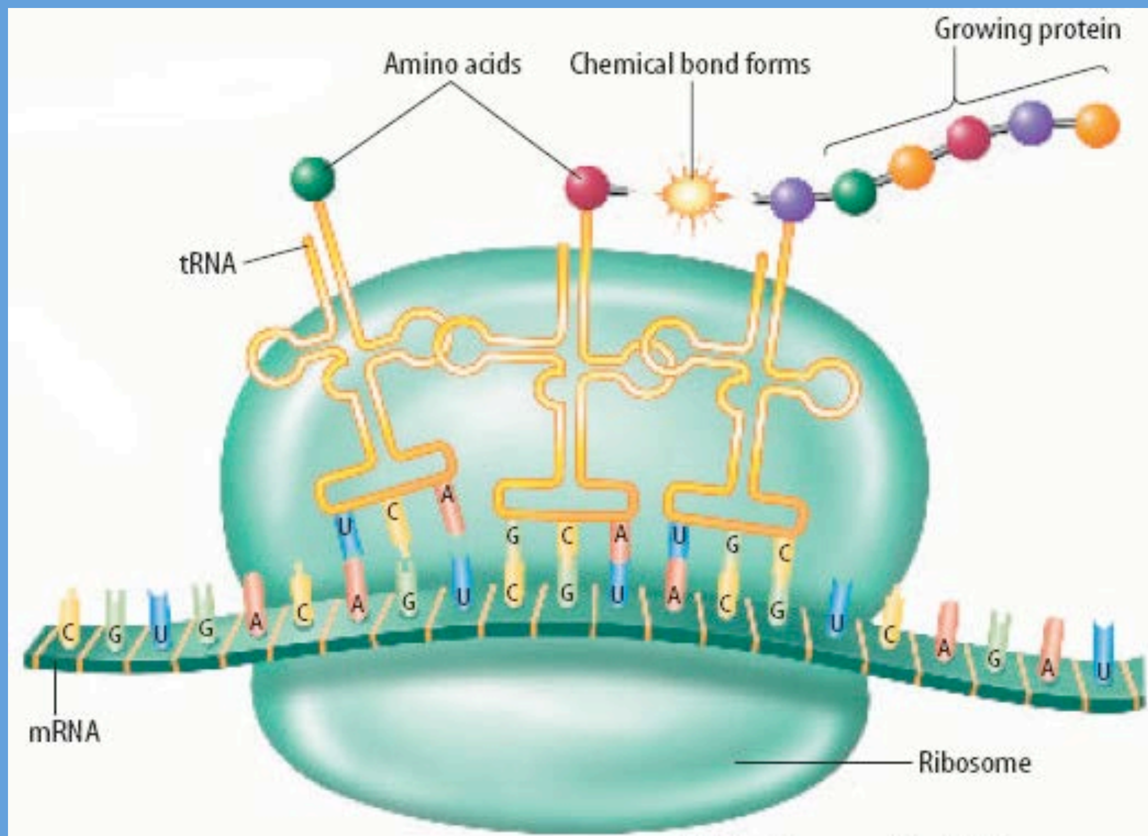
https://www.flickr.com/photos/5winfographics/9034866105

Examples of NRTIs



Nature Reviews | Drug Discovery

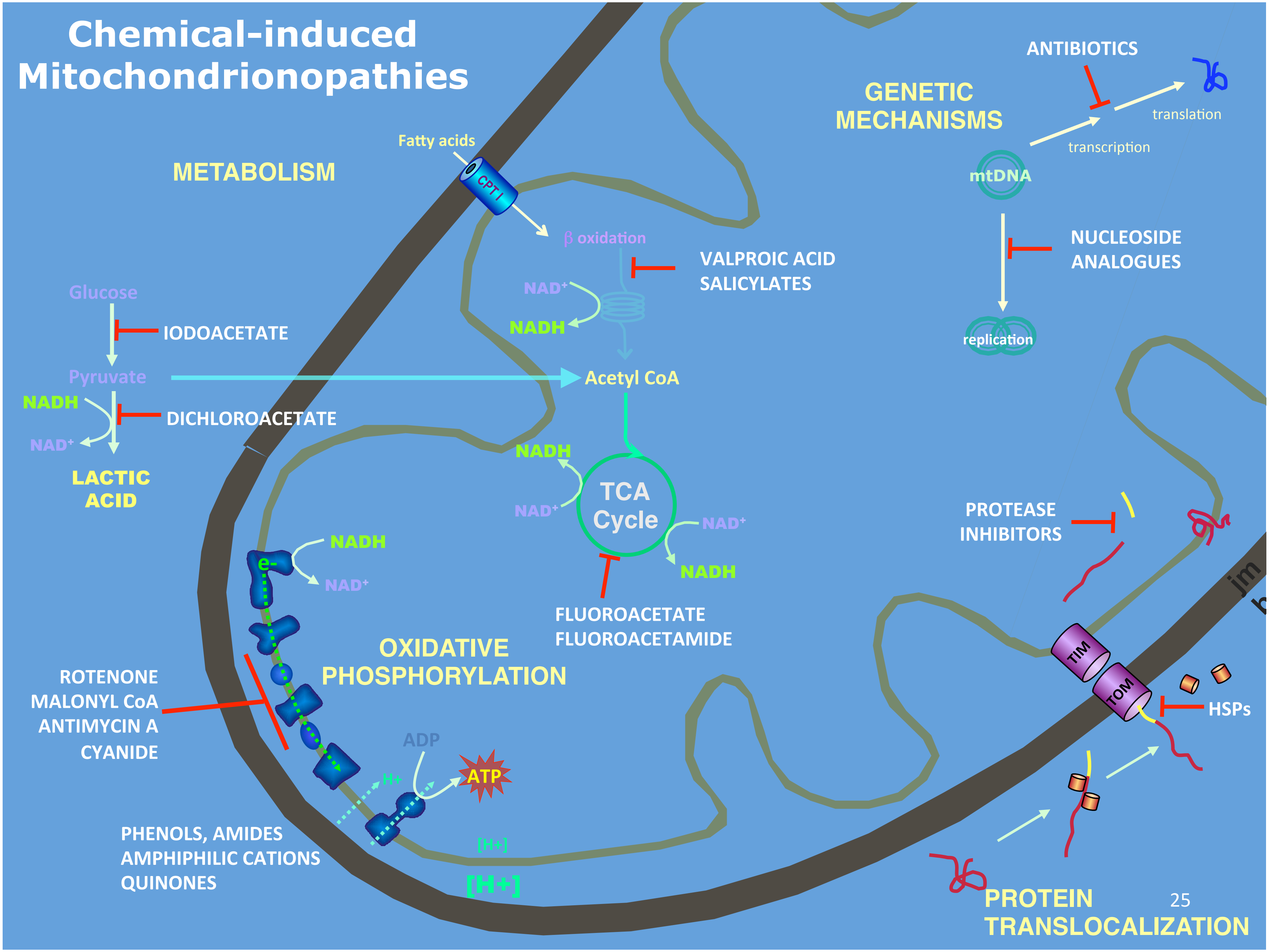
Mitochondrial Protein Synthesis Inhibitors



At the ribosome, the RNA's message is translated into a specific protein.

http://www.hvatinn.is/frodleiksmolar/hvad-er-rna/

Antibiotics
- Chloramphenicol
- Tetracycline
- Linezolid



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IODOACETATE
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translation
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mtDNA
NUCLEOSIDE ANALOGUES
replication
PROTEASE INHIBITORS
TIM
TOM
HSPs
PROTEIN TRANSLOCALIZATION

Other "uncharacterized" Environmental Mitochondrial Toxicities

- Cigarette smoke
- Air pollution, particulates
- Poly aromatic hydrocarbons (PAHs)
- Herbicides 2,4-dichlorophenoxyacetic acid (2,4-D), dinoseb
- mtDNA genotoxicants, mutagens
- etc.

Reports of demonstrated mitochondrial toxicity represent a “hazard” that may or may not be a “real” risk under normal or intended exposure conditions.

“hazard” versus

“risk”

Extended Readings

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Mitochondrial Disease v. Mitochondrial Toxicity

Genetic v. Environmental

Thank you