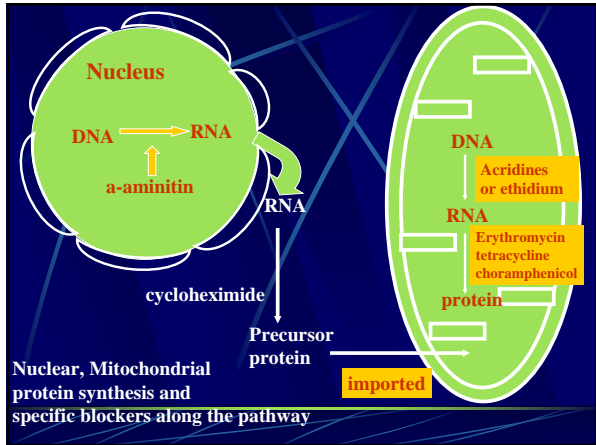


Mitochondria: genetics and transport

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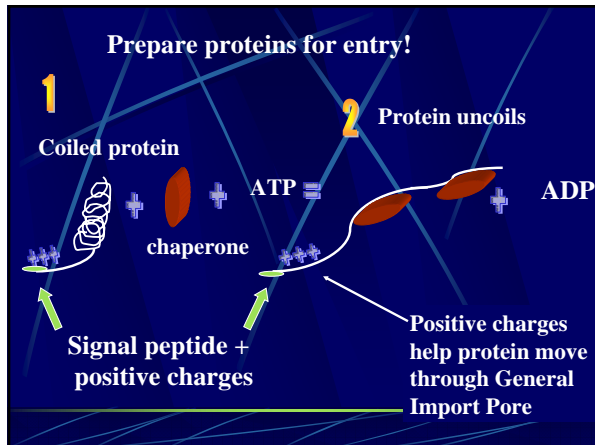


How do you get the protein through the outer membrane?

1. **First, protein must have a signal sequence that can be recognized.**
 - Specific Tom receptors recognize import proteins: Tom70, Tom22, and Tom20.
 - Different proteins bind to different Tom receptors.
2. **Second, it binds to a "chaperone" that uncoils it so it can get through the channel. (Hsp70)**
3. **Then it needs guidance (Tom guiding proteins 5, 6, and 7) through the General Import Pore (GIP)**

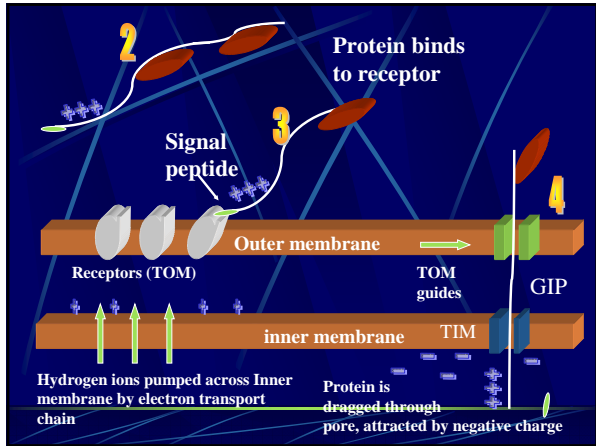
How do you get a protein into the inner membrane or matrix?

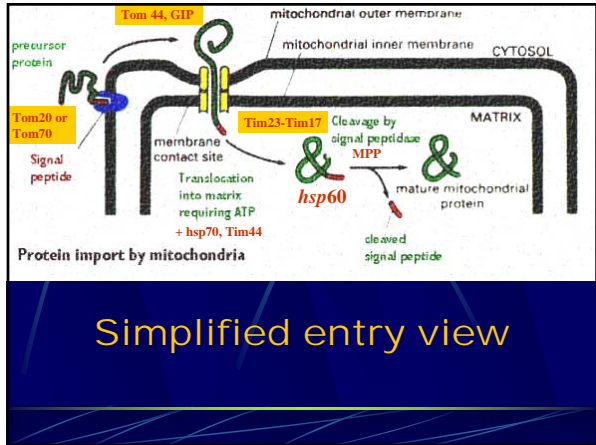
- Mitochondria can't make all of their own proteins. How do the remaining proteins and subunits get in?
- Both membranes contain complexes of receptor and translocator proteins that promote passage of membrane and matrix proteins.
 - Translocator Outer Membrane (Tom proteins)
 - Translocator Inner membrane proteins (TIM proteins)

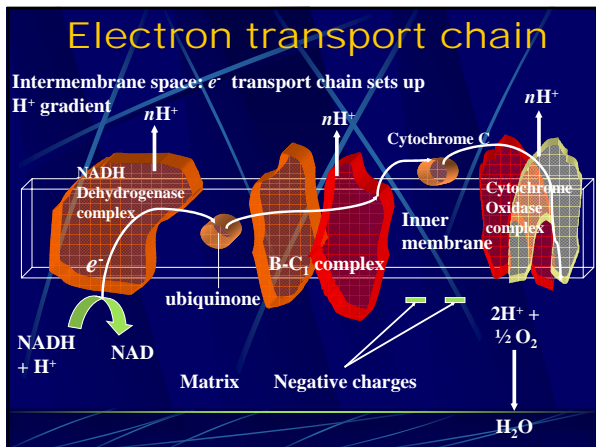


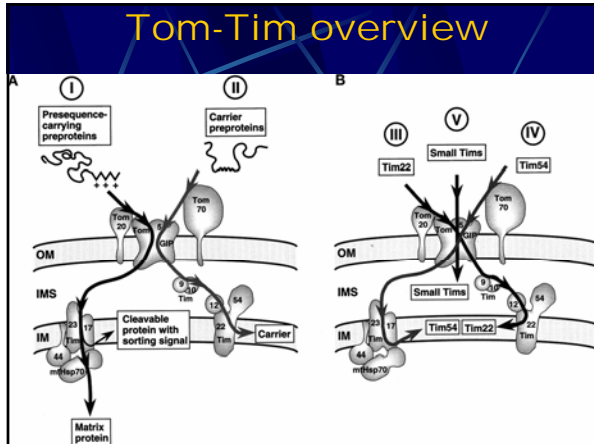
What makes the protein move through the pore?

- Mitochondria are pumping electrons from matrix!
 - This creates a net negative charge in the matrix.
 - Protein to be imported has a concentration of positive charges on the end that enters the pore.
 - The negative charges in the matrix “attract” the positive charges on the protein to be imported.









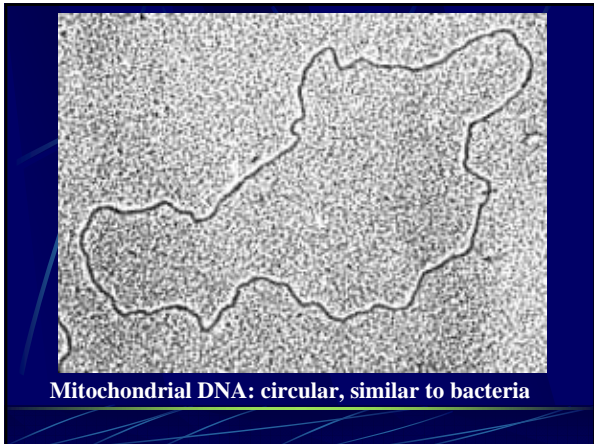
What happens to worn out mitochondria?

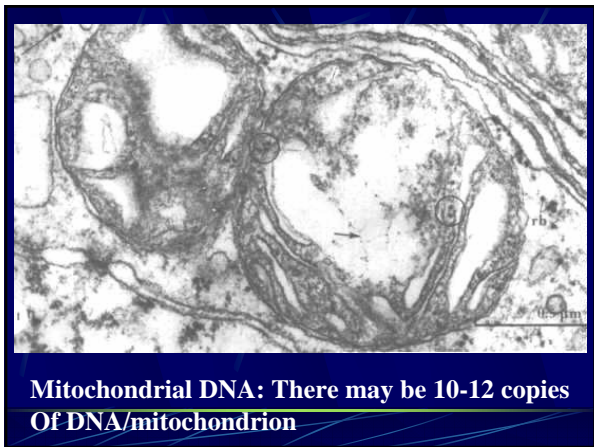
Mitochondrion in an autosome

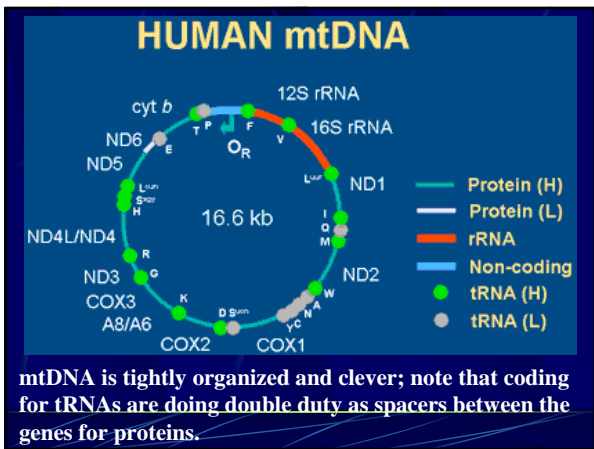
- RER wraps around mitochondrion
- Vesicles from Trans Golgi network bring acid hydrolases to autosome (on MPRs)
- Autosome digests mitochondrion

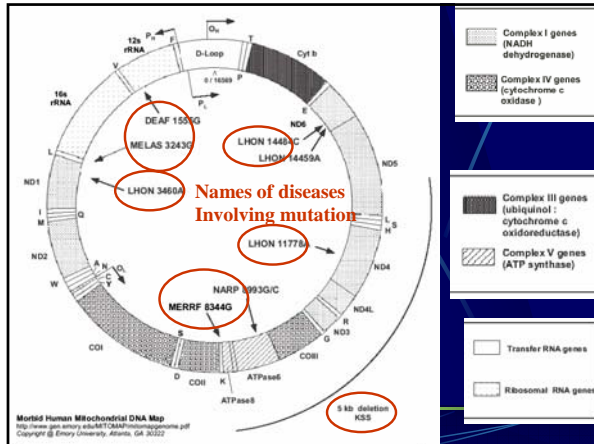
What can mitochondrial DNA encode?

- Human mtDNA is 16,569 bp
- Encodes a number of mitochondrial proteins
 - Subunits 1, 2, and 3 of cytochrome oxidase
 - Subunits 6, 8,9 of the F₀ ATPase
 - Apocytochrome b subunit of CoQH2-Cytochrome C reductase
 - Seven NADH-CoQ reductase subunits









Mitochondrial Inheritance

- 🌍 99.99% of mtDNA is maternal
- 🌍 100 mitochondria in sperm + 100,000 in egg. Most of sperm tail does not get in.
- 🌍 Eventually sperm mitochondria are deleted or diluted out.
- 🌍 Thus, any mutations in mitochondrial DNA are inherited from the mother.

Maternal inheritance

Hae II restriction enzyme polymorphism in mitochondrial DNA (16.4kb)

Three siblings inherited disease (I); Male did not pass it on; two females did; Severity varied. Note that children from third female patient did not reproduce. How can you get this variability?

Background...

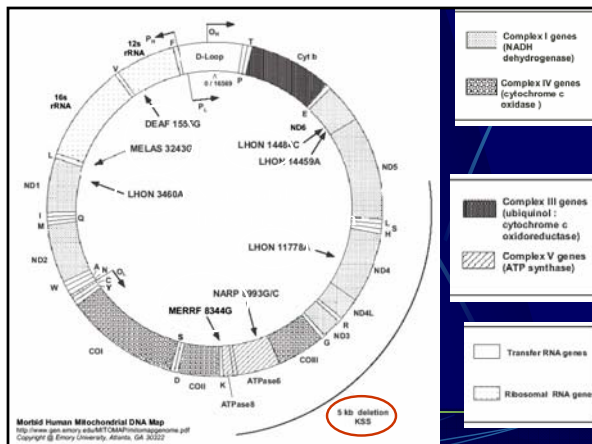
- mtDNA may affect different tissues unequally
- Those tissues requiring the most ATP (like muscle) are affected most profoundly.
- Accumulation of mutant mtDNAs may increase in a tissue (seen by biopsy)
 - Mitochondria replicate even faster as ATP drops.
 - Decreased after muscle damage and repair. Why?
 - Satellite cells used for muscle replacement contained low mutant mtDNA.

Poulton, J and Marchington DR, *Reproduction* 121: 751-755 (2002)

D-loop mutations in Mitochondrial DNA...

- mtDNA replication begins with synthesis of RNA primer
 - Light strand promoter is on the displacement loop (D-loop) of mtDNA
 - Primer is cleaved at "conserved sequence blocks (CSB)" by RNase.
 - DNA is then polymerized by mtDNA polymerase gamma
 - D-Loop is the main cis-regulatory region of the mtDNA.
- What happens if it is mutated?

Barthelemy, C Oglar de Baulny, A Lombes *Human Genetics* 110: 470 (2002)



Mutations and deletions in MT DNA cause a variety of diseases, including diabetes, hearing loss, muscle weakness, blindness.

It has also been implicated in aging and related diseases, such as Alzheimer's Disease (AD), Parkinson's Disease (PD), neurosensory hearing loss.

A type of mutation in tRNAs can cause mitochondrial myopathy and ragged red (muscle) fibers (RRF), and, when the percentage of mutant is high, myoclonic epilepsy.

How would you differentiate?

- Disease due to Mitochondrial gene mutation for cytochrome oxidase?
- D-Loop mutation?
- Disease due to mutation of nuclear gene?

How does mitochondrial architecture dictate function?

- Architecture of inner membrane complexes allow electron flow and functioning of ATP synthase.
- Architecture of Inner membrane sets up charges that attract entry of matrix and Inner membrane proteins.

How does mitochondrial architecture determine function?

- Matrix contains DNA, RNA, ribosomes which encode and translate the code for key proteins.
- Outer membrane architecture recognizes mitochondrial proteins and translocates them to appropriate space/membrane
- Inner membrane architecture continues translocation of proteins to matrix or Inner membrane.
