02.02.09
Lecture 8 - Mitochondria
Mitochondria perform 2 functions within the cell

1. They are the primary sites for ATP synthesis in the cell

2. They have a key role in apoptosis - programmed cell death
Mitochondria are actively transported along microtubules in some cells
Mitochondria are anchored near sites of high ATP consumption in other cells.
Mitochondria have a very plastic shape in living cells
Mitochondria dynamics
Relative contributions of nuclear and mitochondrial genes to protein composition

- Nuclear genes on nuclear DNA
- Over 600 mitochondrial proteins synthesized in cytoplasm
- Import into mitochondria
- Mitochondrial genes on mitochondrial DNA
  - 13 mitochondrial membrane proteins
  - 22 tRNAs
  - 2 rRNAs

Mitochondria are organized into 4 distinct compartments.
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Compartments of a mitochondrion compared with a bacterium
Mitochondria are organized into 4 distinct compartments

- **Outer membrane:**
  - Perforated with large channels (porins) that allow entry of molecules < 5000 kD
  - Enzymes involved in mitochondrial lipid synthesis
Mitochondria are organized into 4 distinct compartments

- Intermembrane space:
- Enzymes that use newly-made ATP to phosphorylate other nucleotides
- Compartment into which H+ is pumped
Mitochondria are organized into 4 distinct compartments

- Inner membrane:
  - Folded into **cristae** to maximize surface area
  - Proteins that carry out redox reactions of the electron transport chain
  - Proteins that synthesize ATP
  - Transport proteins that move molecules into and out of the matrix
Mitochondria are organized into 4 distinct compartments

- **Matrix:**
  - Internal space containing enzymes for Krebs cycle
  - Contains mitochondrial DNA, special ribosomes, tRNAs, and enzymes required for gene expression
Mitochondria catalyze a major conversion of energy by oxidative phosphorylation.
Mitochondria use pyruvate or fatty acids to make energy

Pyruvate from sugars, fatty acids from fats
High energy electrons are generated via the citric acid (Krebs) cycle
Protons are pumped across the inner mitochondrial membrane
The electron transport chain consists of 3 enzyme complexes.
The electrochemical gradient of H+ across the inner membrane has 2 components:
The proton gradient drives ATP synthesis
ATP synthase is a protein complex embedded in the inner mitochondrial membrane.
ATP synthase acts as a rotary motor

(A) ATP SYNTHESIS

(B) ATP HYDROLYSIS
ATP synthase acts as a rotary motor
ATP synthase is a motor

- Motor complex attached to glass and bound to fluorescent actin filament
- ATP added and the complex is imaged by fluorescent microscopy
- Actin filament is spun like a propeller
The proton gradient also drives coupled transport
Defect in mitochondrial function is the cause for numerous inherited diseases

Problems Associated with Mitochondrial Cytopathies, 1 in 4000 children per year

**Brain**
Developmental delays, mental retardation, dementia, seizures, neuro-psychiatric disturbances, atypical cerebral palsy, migraines, strokes

**Nerves**
Weakness (which may be intermittent), neuropathic pain, absent reflexes, gastrointestinal problem (gastroesophageal reflux, delayed gastric emptying, constipation, pseudo-obstruction), fainting, absent or excessive sweating resulting in temperature regulation problems

**Muscles**
Weakness, hypotonia, cramping, muscle pain

**Kidneys**
Proximal renal tubular wasting resulting in loss of protein, magnesium, phosphorous, calcium and other electrolytes

**Heart**
Cardiac conduction defects (heart blocks), cardiomyopathy

**Liver**
Hypoglycemia (low blood sugar), liver failure

**Eyes**
Visual loss and blindness

**Ears**
Hearing loss and deafness

**Pancreas**
Diabetes and exocrine pancreatic failure (inability to make digestive enzymes)

**Systemic**
Failure to gain weight, short stature, fatigue, respiratory problems including intermittent air hunger