BIO-373

Genetics & Genomics

Extranuclear inheritance

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Extranuclear inheritance

- Transmission of genetic information to offspring through cytoplasm, not nucleus

- Varieties in extranuclear inheritance
  - **Organelle heredity**
    - Mitochondria or chloroplasts
  - **Infectious heredity**
    - Symbiotic or parasitic association with microorganism
    - Inherited phenotype due to microbe in host's cytoplasm
  - **Maternal effect**
    - Influence of nuclear gene products present in oocyte

Plan

1. Organelle heredity
2. Human mtDNA and mitochondrial diseases
3. Maternal effect and infectious heredity

1. Organelle heredity

Endosymbiotic theory

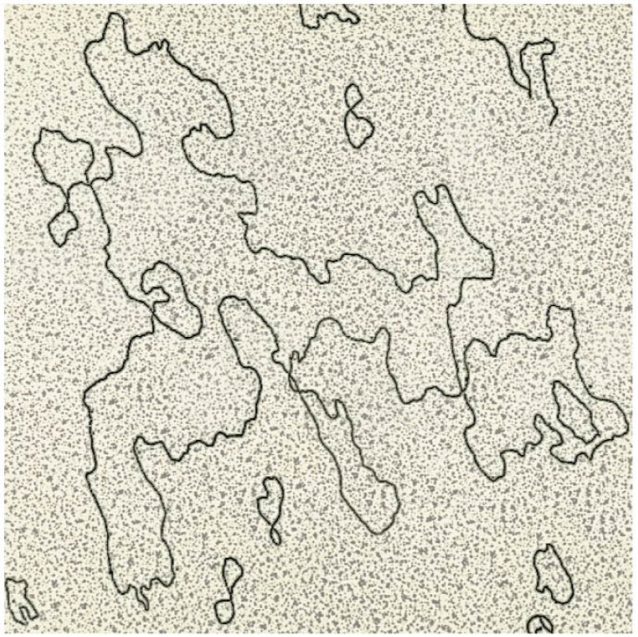
- **Mitochondria** and **chloroplasts** (organelles) arose independently 2 billion years ago from free-living bacteria

- **Main points of endosymbiotic theory**
  - Bacteria were engulfed by larger eukaryotic cells
  - Beneficial symbiotic relationship developed
  - Bacteria lost ability to function autonomously
  - Eukaryotic cells gained oxidative respiration / photosynthesis

DNA in chloroplasts and mitochondria

- DNA in mitochondria and chloroplasts (double-stranded circular DNA) is unlike DNA seen in the nucleus of eukaryotic cells

cpDNA



mtDNA

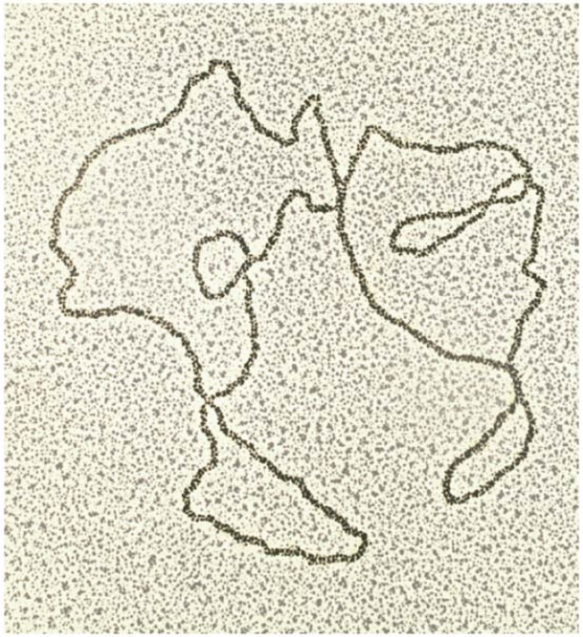


TABLE 9.1 **The Size of mtDNA in Different Organisms**

Organism	Size (kb)
Homo sapiens (human)	16.6
Mus musculus (mouse)	16.2
Xenopus laevis (frog)	18.4
Drosophila melanogaster (fruit fly)	18.4
Saccharomyces cerevisiae (yeast)	75.0
Pisum sativum (pea)	110.0
Arabidopsis thaliana (mustard plant)	367.0

mtDNA mutations

- **mtDNA is highly susceptible to mutations**
  - No structural protection from histones
  - mtDNA repair mechanism limited
  - High concentrations of reactive oxygen species (ROS) generated by cell respiration
    - ROS is toxic—damages organelle contents (proteins, lipids, mtDNA)

Chloroplast DNA variation

- ***Chlamydomonas*** **(unicellular alga)**
  - Excellent model system for studying organelle heredity
  - Has a single large chloroplast with 75 copies of circular double-stranded DNA
  - **Streptomycin resistance** has been shown to be encoded in cytosolic DNA (i.e. in chloroplast genome)
  - Studies by Ruth Sager (1954): differences in reciprocal crosses with susceptible strains ⇔ trait passed through female parent

$str^R\ mt^+ \times str^S\ mt^-$

↓

1/2 mt^+	1/2 mt^-
all str^R	

$str^S\ mt^+ \times str^R\ mt^-$

↓

1/2 mt^+	1/2 mt^-
all str^S	

2. Human mtDNA and mitochondrial diseases

mtDNA in humans

- **Human mtDNA**
  - Double-stranded DNA, 16,569 base pairs
  - 5-10 copies per mitochondrion
  - Coding for 2 rRNA, 22 tRNA and 13 proteins required for aerobic cellular respiration

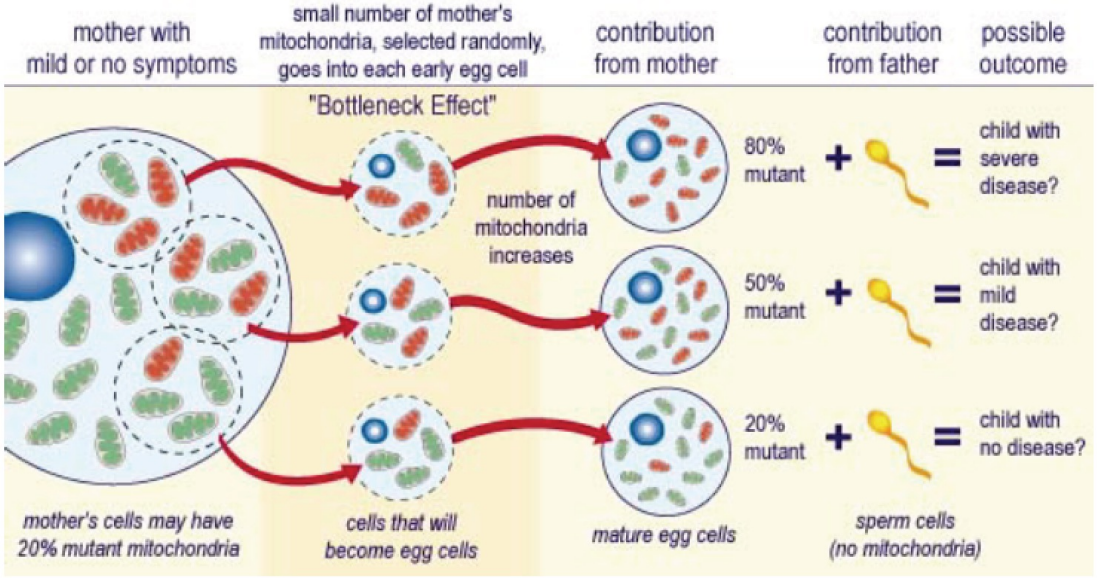
	Total	Mito	Nucléaire
Complexe I	43	7	36
Complexe II	4		4
Complexe III	11	1	10
Complexe IV	13	3	10
Complexe V	16	2	14
	87	13	74

mtDNA human disorders

- **Criteria for human disorder to be attributed to mtDNA**
  - Maternal inheritance pattern
  - Disorder reflects a deficiency in the bioenergetic function of organelle
  - Mutation in one or more mitochondrial gene

Heteroplasmy

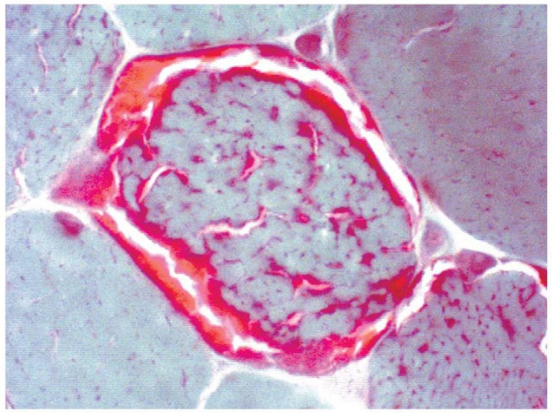
- If mutation are present in a subset of mitochondria present in the zygote, they will be found at various levels in adult cells
- This “mixture” of normal and abnormal organelles is called **heteroplasmy**
- Very variable clinical presentation, hard to do genetic counseling



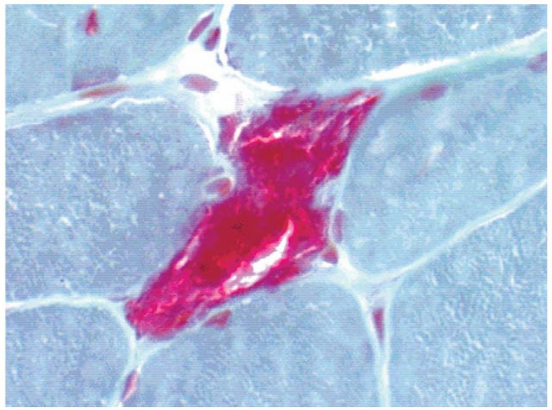
Example of human disease: MERRF

- **Myoclonic epilepsy and ragged-red fiber disease**
  - Pattern of inheritance consistent with maternal transmission
  - Ataxia (lack of muscular coordination), deafness, dementia, epilepsia
  - “Ragged-red” skeletal muscle fibers: red color results from proliferation of abnormal mitochondria
  - Due to a mutation in the *MT-TK* mitochondrial gene, which encodes a transfer RNA for Lysine - $tRNA^{LYS}$

(a)



(b)



Example of human disease: LHON

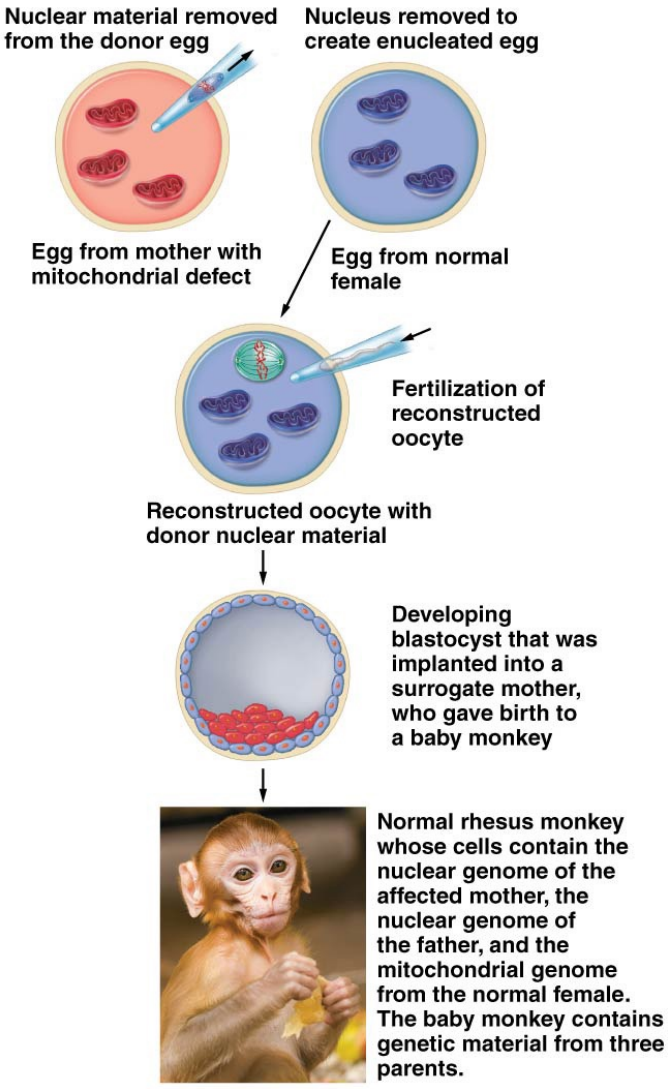
- **Leber's hereditary optic neuropathy**
  - Pattern of inheritance consistent with maternal transmission
  - Bilateral blindness with rapid progression, age 20-30
  - Various mutations affecting oxidative phosphorylation
  - Most often sporadic (no familial history)

Mitochondria, health and aging

- **Mitochondrial dysfunction implicated in most human diseases**
  - Anemia
  - Type II diabetes
  - Infertility
  - Neurodegenerative diseases
- Likely due to the progressive accumulation of somatic mutations, leading to a loss of mitochondrial function

Prevention of mtDNA disorders?

- 1 in 5000 humans have mtDNA-based disease or are at risk for developing one
  - Can be detected by genetic testing
  - New therapies can prevent transmission of mtDNA mutations to offspring
  - **Mitochondrial swapping in oocytes**



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日本語要約

Mitochondrial replacement in human oocytes carrying pathogenic mitochondrial DNA mutations

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NATURE | NEWS

‘Three-parent baby’ claim raises hopes — and ethical concerns

Questions surround report of baby created using controversial mitochondrial-replacement technique.

3. Maternal effect and infectious heredity

Maternal effect

- Offspring's phenotype is under control of nuclear gene products present in egg
- Nuclear genes of female gamete transcribed; genetic products accumulate in egg's cytoplasm
- Products distributed among newly formed cells, influencing patterns/traits established early in development

Maternal effect in snail

- ***Lymnaea peregra***
  - Maternal effect on shell coiling
  - Example of maternal effect on permanent rather than transitory phenotype
  - Coiling pattern of progeny snails determined by genotype of parent producing egg, regardless of phenotype of parent

Infectious heredity

- Results from the presence in eukaryotic cytoplasm of a micro-organism or a particle
- Most often symbiotic
- Example: CO_2 sensitivity in *Drosophila*, dependent on the presence of a *sigma* virus