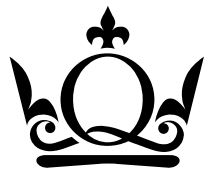
Cell Biology and Developmental Genetics

Lectures by

John F. Allen

School of Biological and Chemical Sciences, Queen Mary, University of London

jfallen.org



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Slides and supplementary information:

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Lectures in Cell Biology and Developmental Genetics

Presentation files and further information.

1. Endosymbiosis and the origin of bioenergetic organelles. Some history (Acrobat, .pdf file)
2. Endosymbiosis and the origin of bioenergetic organelles. A modern view (Acrobat, .pdf file)
3. Mitochondria as we know them and don't know them (Acrobat, .pdf file)
4. Why do chloroplasts and mitochondria have genomes? (Acrobat, .pdf file)
5. Co-location for Redox Regulation (Acrobat, .pdf file)
6. Mitochondria, ageing, and sex - energy versus fidelity (Acrobat, .pdf file

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Course web page

Cell Biology and Developmental Genetics web page

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Links and further reading

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- Transcriptional control of photosynthesis genes: the evolutionarily conserved regulatory mechanism in plastid genome function. Puthiyaveetil S, Ibrahim IM, Jurić S, Jeličić B, Tomašić A, Fulgosi H, Allen JF (2010). Genome Biology and Evolution. Advance Access published online November 11, 2010. doi:10.1093/gbe/evq073
- Lane N, Martin W. (2010) The energetics of genome complexity. Nature 467, 929-934.
- Energy transduction anchors genes in organelles. 2005 paper by Allen et al. (.pdf file).
- Mitochondria as we don't know them. 2002 paper by Tielens et al. (.pdf file)
- The hydrogen hypothesis for the first eukaryote. 1998 paper by Martin and Müller. (.pdf file).
- On the origins of cells. 2003 paper by Martin and Russell (.pdf file)
- Origin of Life - The Movie! 2010 animation devised and narrated by William Martin, Heinrich-Heine-Universitaet, Duesseldorf.
- Lane N, Allen JF, Martin W (2010) How did LUCA make a living? Chemiosmosis in the origin of life. Bioessays 32: 271-280.
- Why have organelles retained genomes? Race et al., Trends in Genetics 1999. (pdf file).
- The function of genomes in bioenergetic organelles. 2003 paper by John F. Allen. (.pdf file).
- Co-location for Redox Regulation - CoRR. Web page by John F. Allen
- Why do we still have a maternally inherited mitochondrial DNA? Insights from evolutionary medicine. 2007 Annual Review by Douglas C. Wallace (.pdf file).
- A mitochondrial model for premature ageing of somatically cloned mammals. 1999 paper by Allen J. F. and Allen C. A. (.pdf file).
- Separate sexes and the mitochondrial theory of ageing. 1996 paper by John F. Allen. (.pdf file).
- Power for life. Book review. (.pdf file).
- Chloroplasts and mitochondria: functional genomics and evolution • Meeting • Book review (.pdf file) • Editorial introduction (.pdf file)
- Mitochondrion Reconstructed by Electron Tomography web site by T. G. Frey of San Diego State University.

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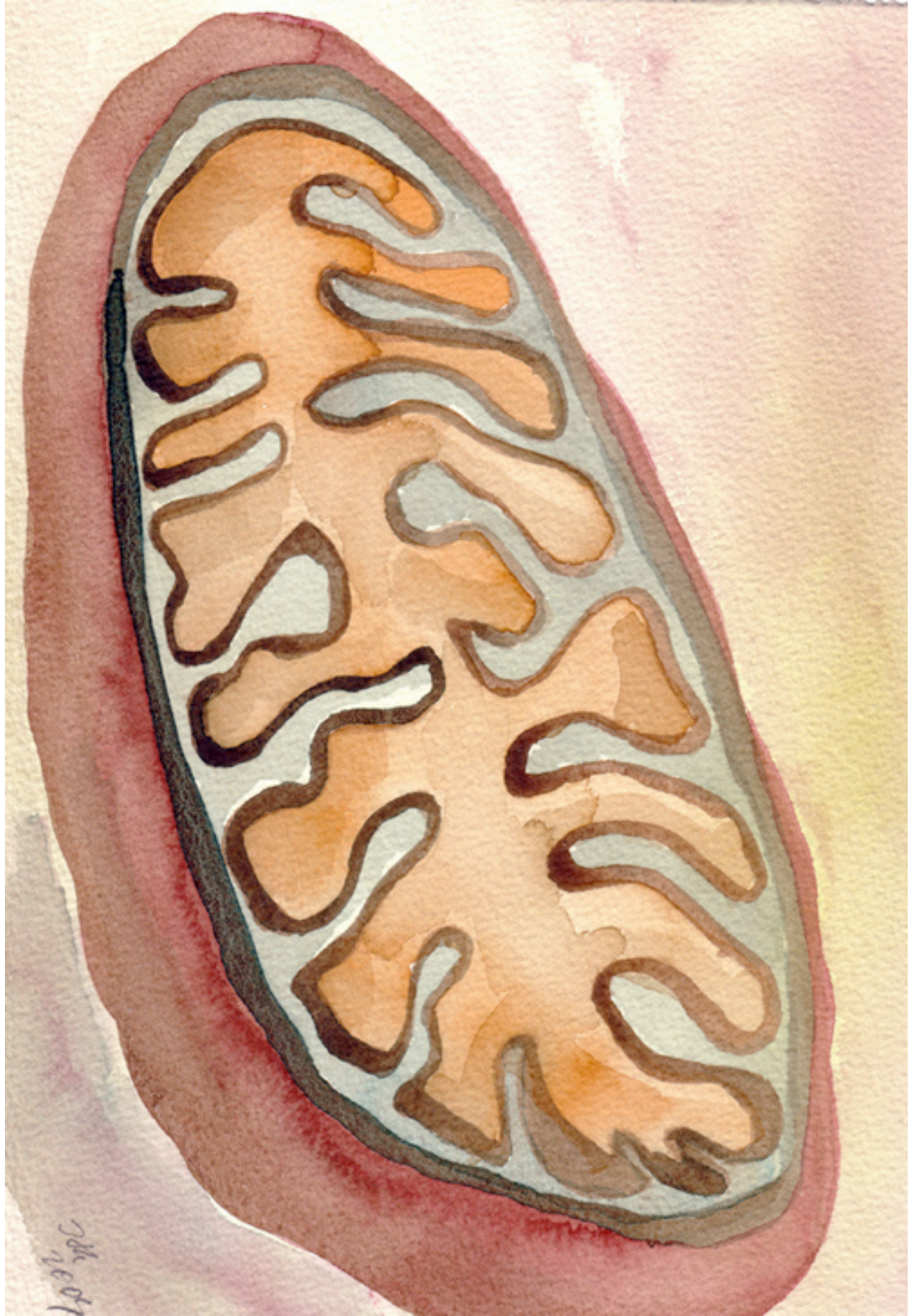
Mitochondria, ageing, and sex – energy versus fidelity

Lecture 6

Mitochondria, ageing, and sex – energy versus fidelity



Why mitochondria have genomes

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Problem: Why are there genes in mitochondria?

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*Redox reactions are chemical reaction in which an electron is transferred from one molecule to another - the basis of biological energy conversion.

Why Do We Still Have a Maternally Inherited Mitochondrial DNA? Insights from Evolutionary Medicine

Douglas C. Wallace

Center for Molecular and Mitochondrial Medicine and Genetics, Departments of Biological Chemistry, Ecology and Evolutionary Biology, and Pediatrics, University of California, Irvine, California 92697-3940; email: dwallace@uci.edu

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10.1146/annurev.biochem.76.081205.150955

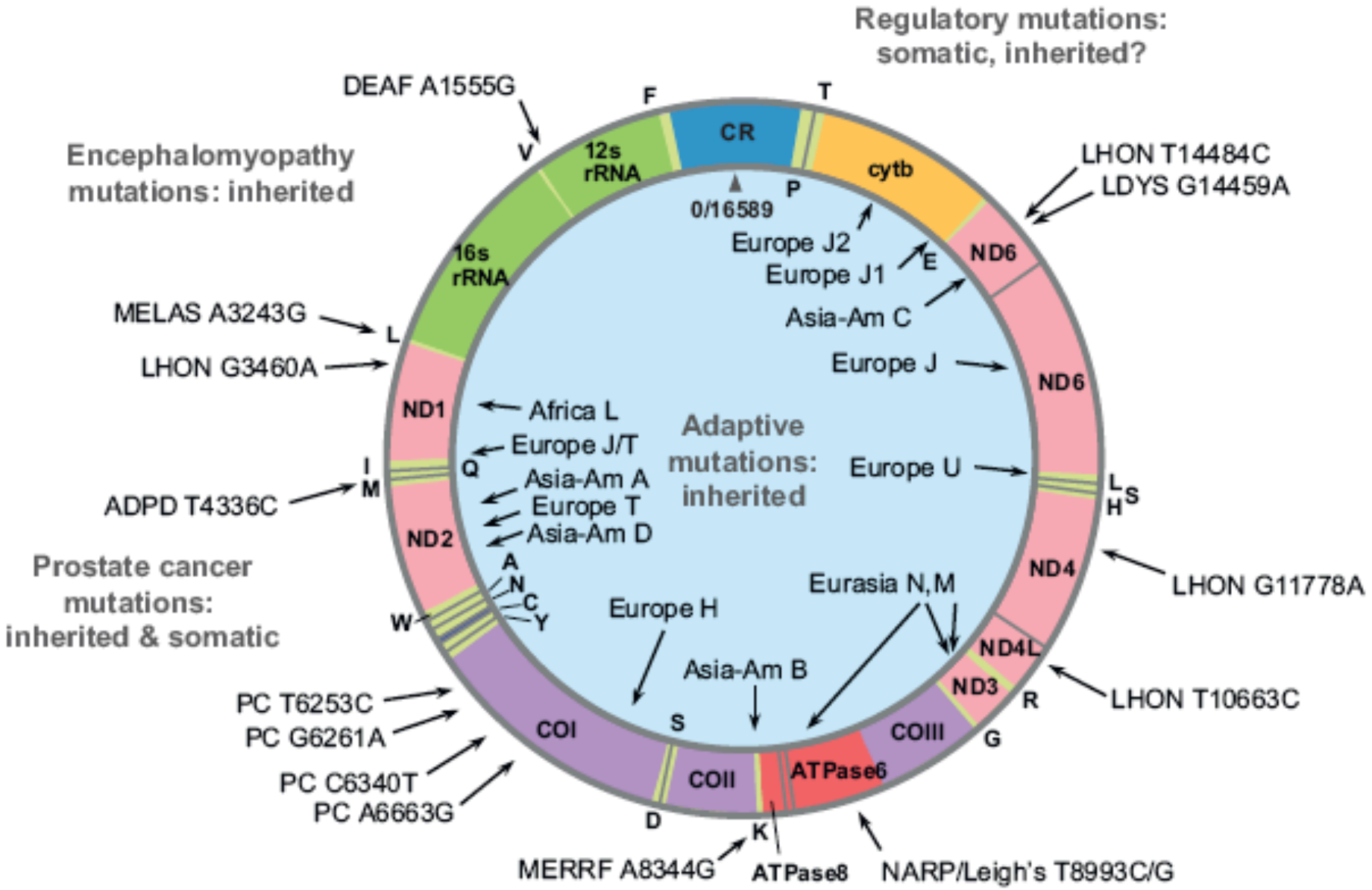
0066-4154/07/0707-0781$20.00

Key Words

adaptation, genomic evolution, mitochondrial disease, mtDNA, oxidative phosphorylation, proton-translocating OXPHOS complexes

Abstract

The human cell is a symbiosis of two life forms, the nucleus-cytosol and the mitochondrion. The nucleus-cytosol emphasizes structure and its genes are Mendelian, whereas the mitochondrion specializes in energy and its mitochondrial DNA (mtDNA) genes are maternal. Mitochondria oxidize calories via oxidative phosphorylation (OXPHOS) to generate a mitochondrial inner membrane proton gradient (ΔP). ΔP then acts as a source of potential energy to produce ATP, generate heat, regulate reactive oxygen species (ROS), and control apoptosis, etc. Interspecific comparisons of mtDNAs have revealed that the mtDNA retains a core set of electron and proton carrier genes for the proton-translocating OXPHOS complexes I, III, IV, and V. Human mtDNA analysis has revealed these genes frequently contain region-specific adaptive polymorphisms. Therefore, the mtDNA with its energy controlling genes may have been retained to permit rapid adaptation to new environments.



The mitochondrial genome:
mtDNA = 37 genes
Extracellular plasmids (chromosomes) ~ 1500 genes

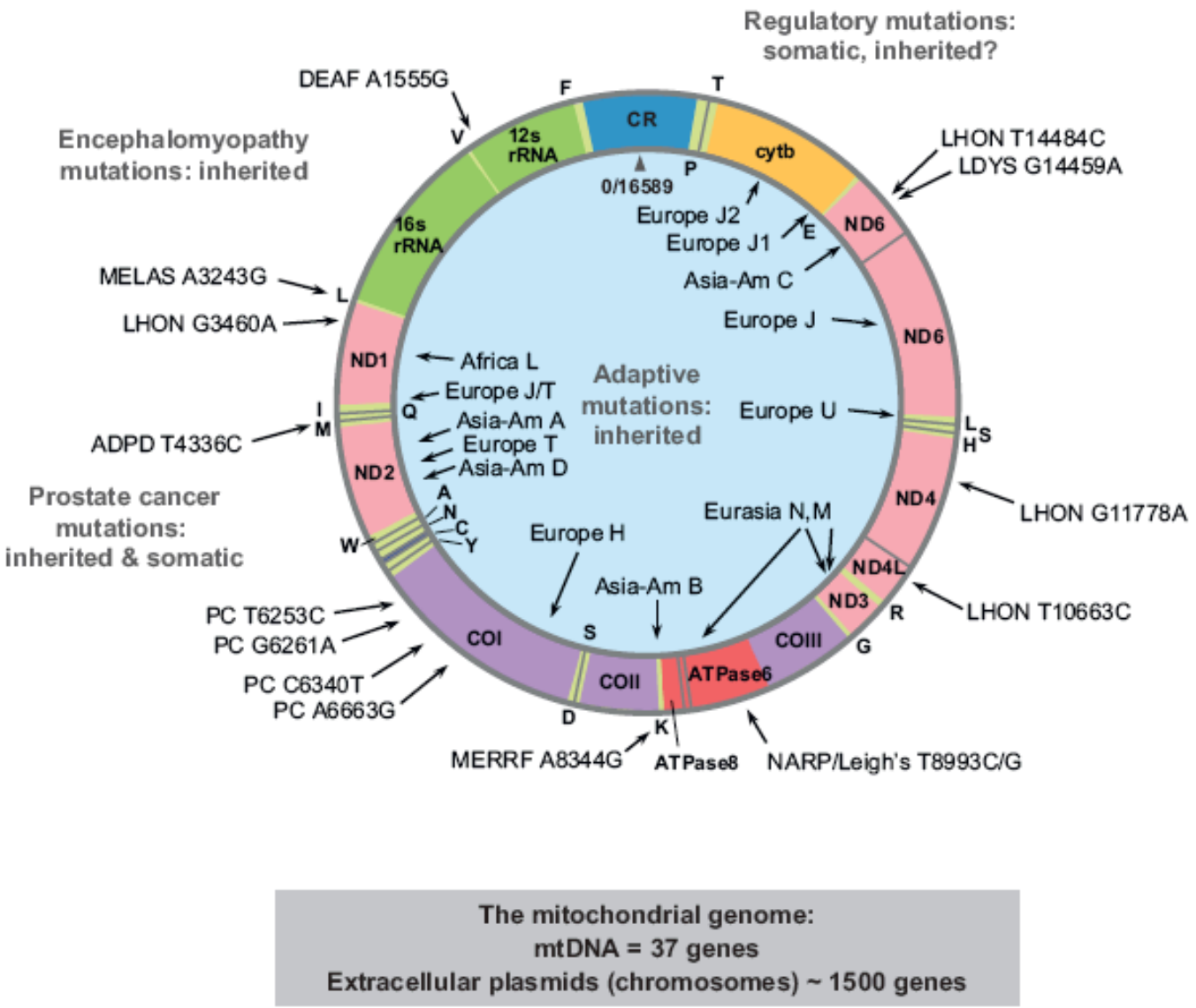


Figure 2

The human mtDNA map. The human mtDNA encompasses three classes of clinically relevant mutations: recent maternally inherited disease-causing mutations, examples of which are shown on the outside of the circular map; ancient geographically correlated and frequently adaptive polymorphic variants, examples presented inside the circle; and somatic mutations that accumulate with age in postmitotic tissues and provide the aging clock. Letters around the outside perimeter indicate cognate amino acids of the tRNA genes. Letters within the ring represent the proteins encoded by the gene sector, all of which are integral membrane components of the proton-translocating complexes of OXPHOS. The polypeptides, corresponding gene, and complexes are ND1-4, -4L, -5, and -6 (*nad1-4, -4l, -5*, and *-6* gene) of complex I; cytb or cytochrome *b* (*cob* gene) of complex III; COI-III (*cox1–3* genes) of complex IV; and ATP6 and ATP8 (*atp6* and *atp8* genes) of complex V.

The mitochondrial theory of ageing

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"Errors" in electron transfer - transfers to the "wrong" electron acceptor - occur at fixed frequency.

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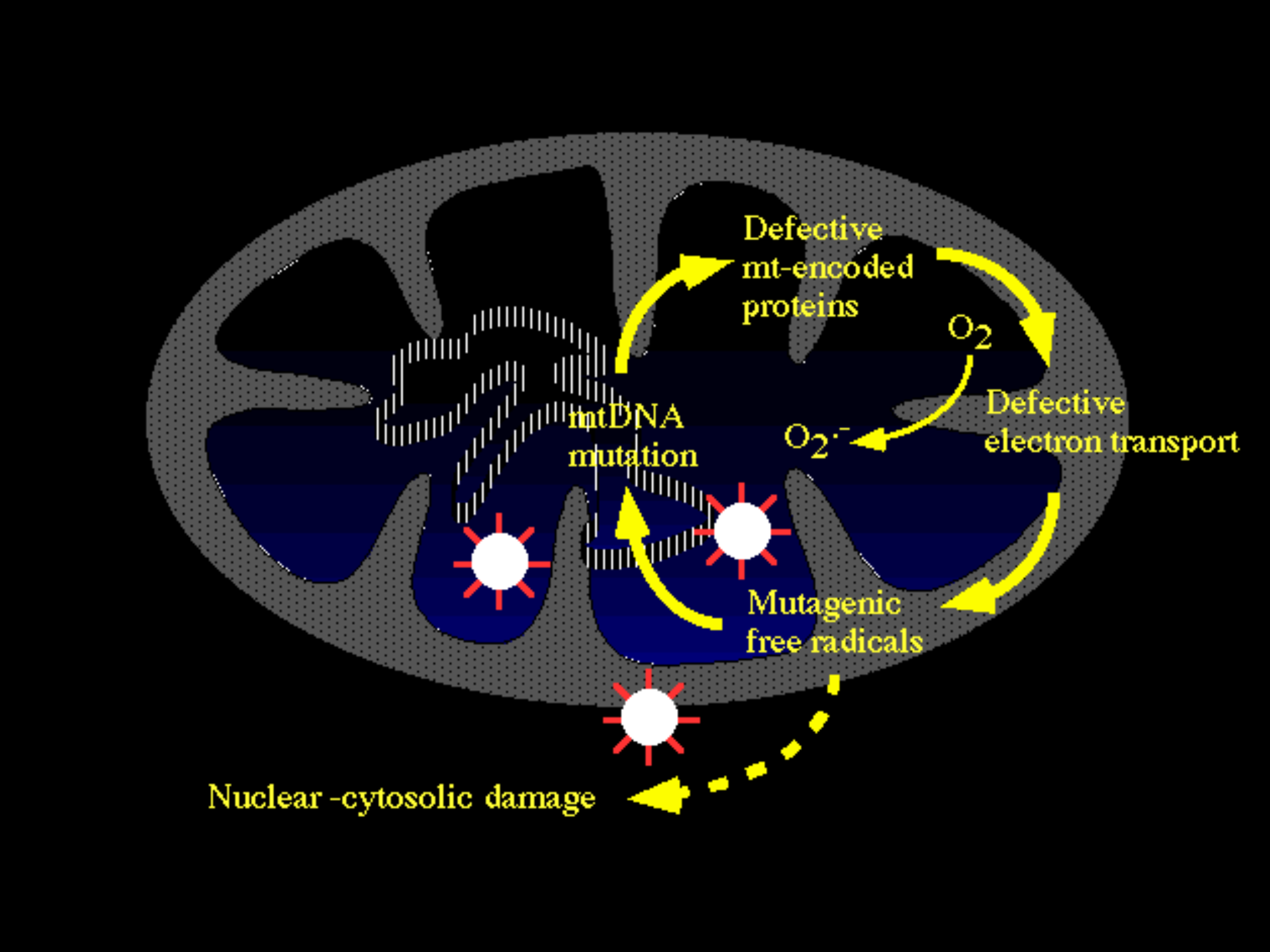
The products of these reactions damage mitochondrial genes, which then produce defective proteins, which then make more "errors" in electron transfer....damaging more genes, making more defective proteins....and so on.


Defective
mt-encoded
proteins
O_2
Defective
electron transport
mtDNA
mutation
$O_2^{\cdot -}$
Mutagenic
free radicals
Nuclear -cytosolic damage

Even without the Mitochondrial Theory of Ageing….

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The mitochondrion is the worst imaginable place in the cell to keep genes.

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The mitochondrion is the worst imaginable place in the cell to keep genes.

Whatever the reason for the persistence of mitochondrial genomes, it had better be a good one.

Separate sexes as mitochondrial division of labour (“labor” - U.S.)

Why there are two sexes

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Problem: Mitochondrial Ageing predicts that offspring should inherit their mothers' acquired state of accumulated damage, but they evidently do not. Babies are not born at the physical age of their mothers.

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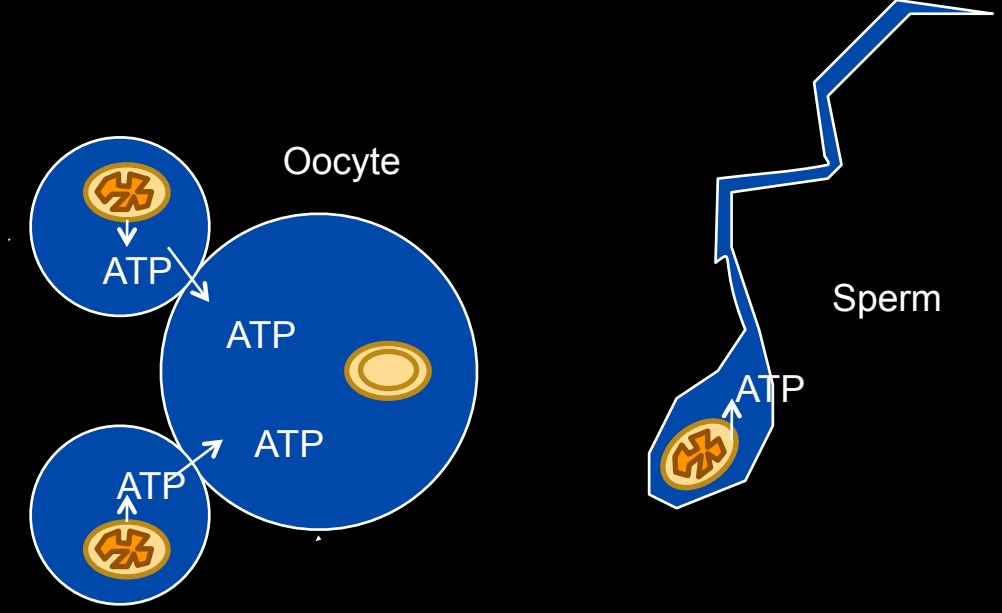
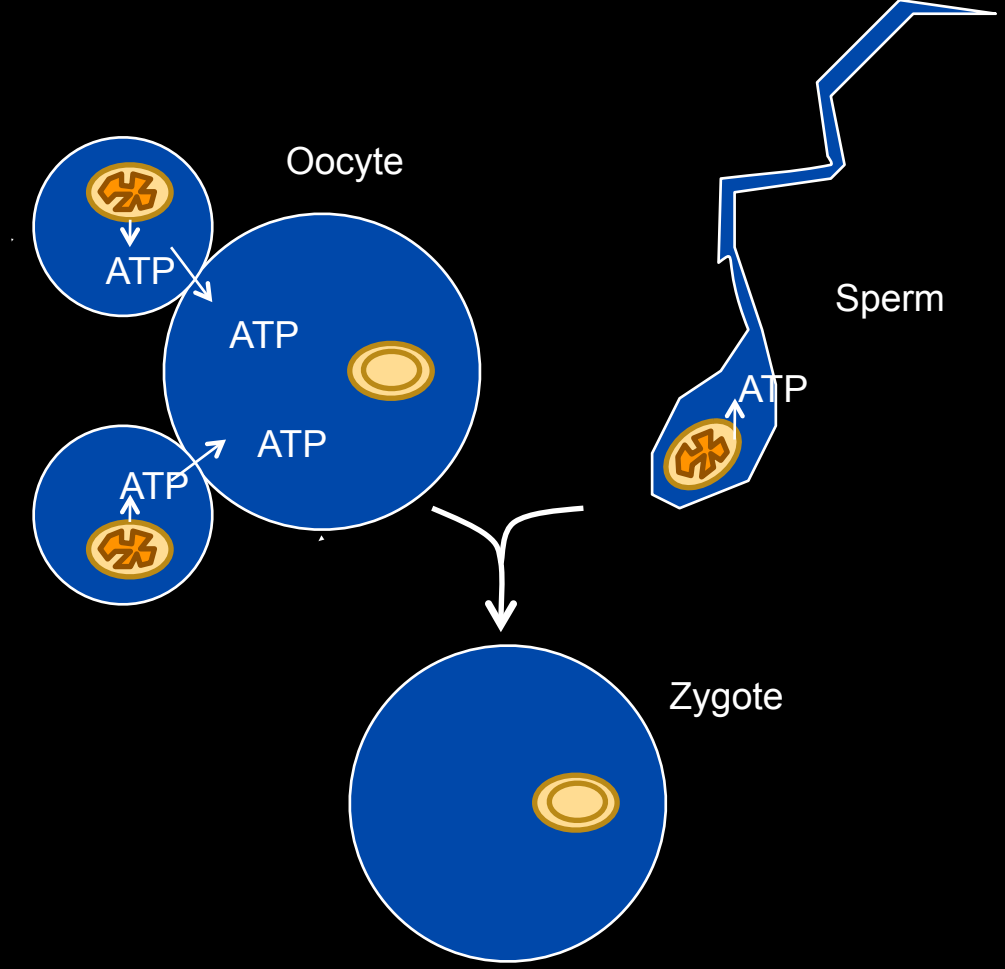
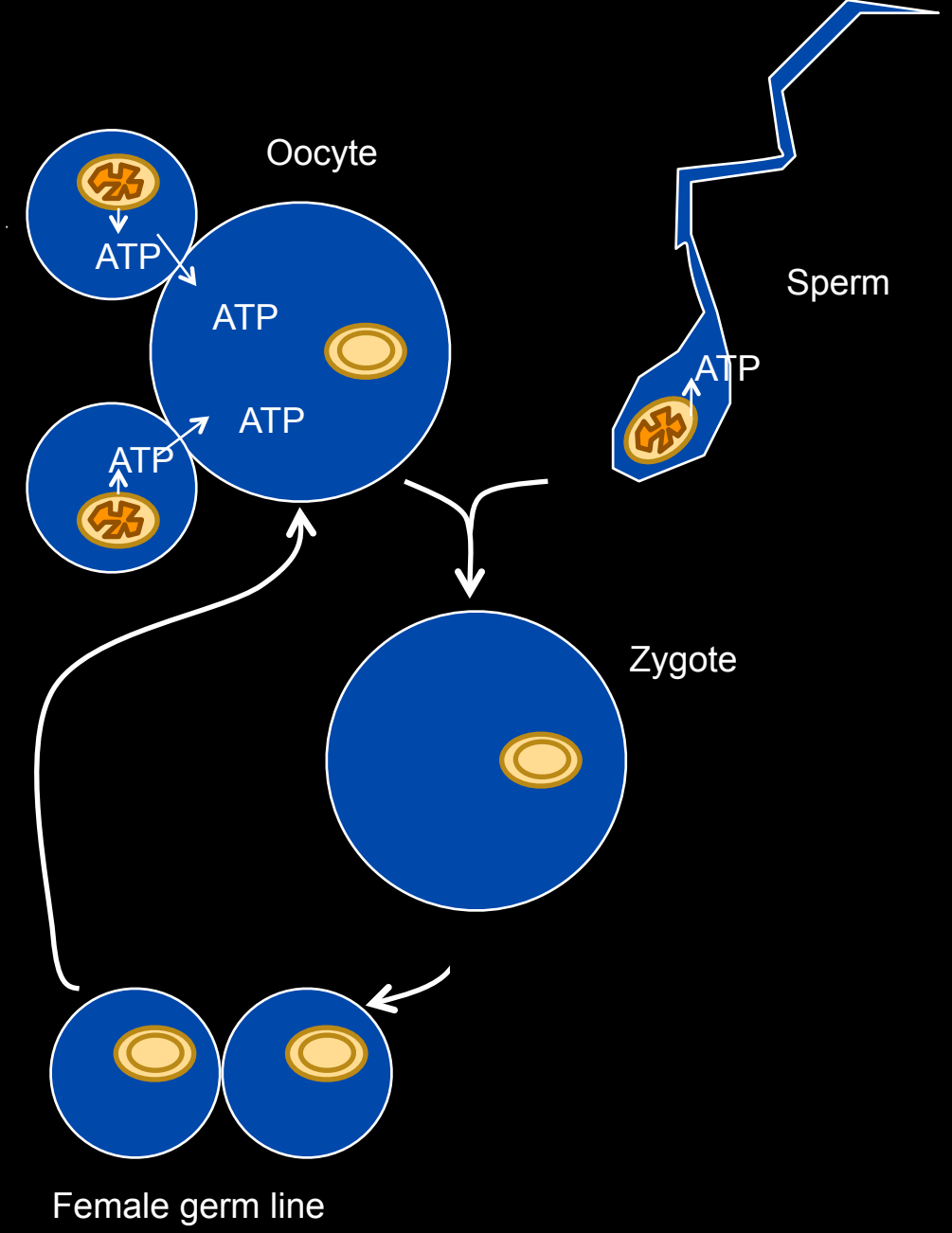
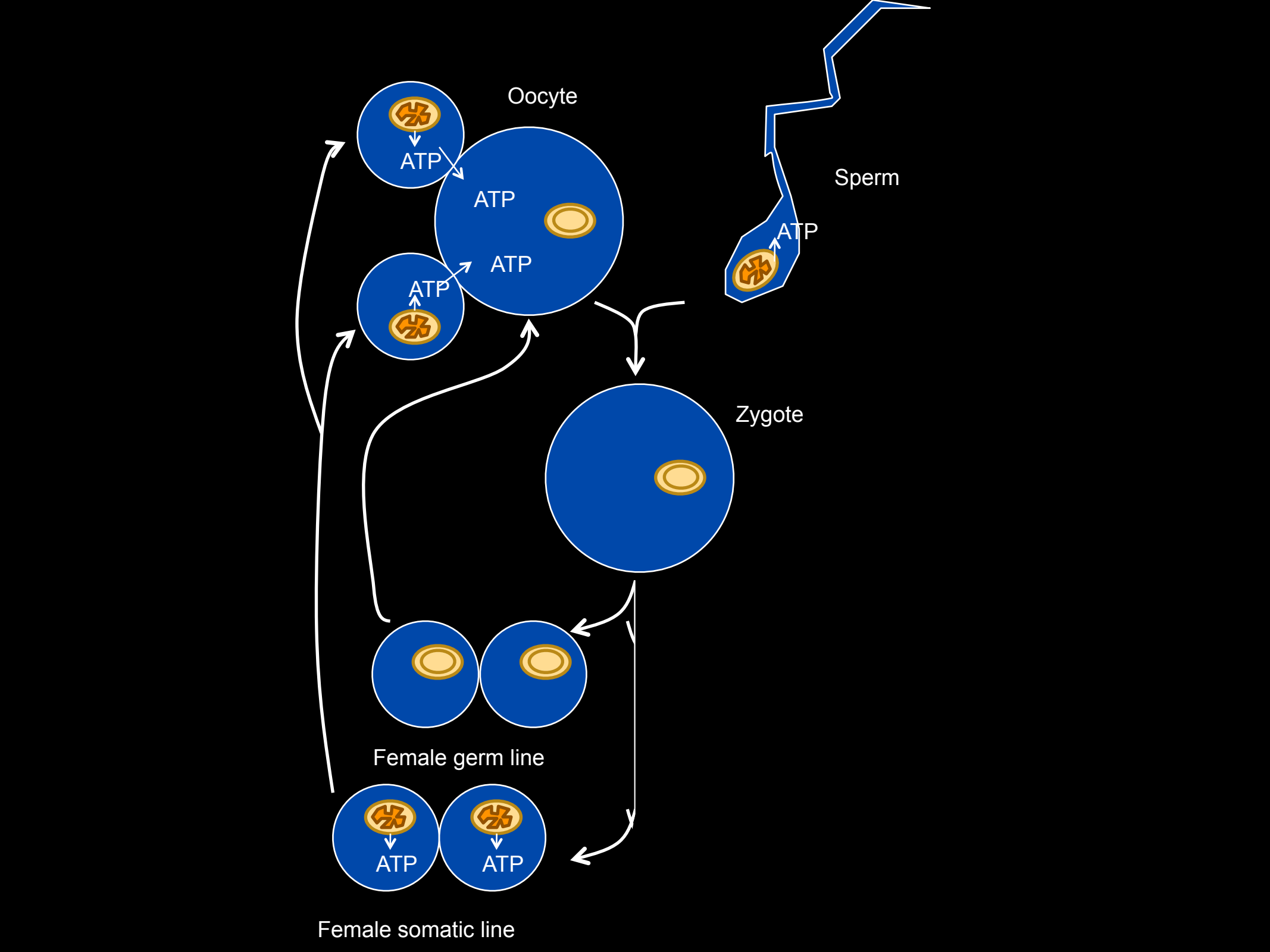
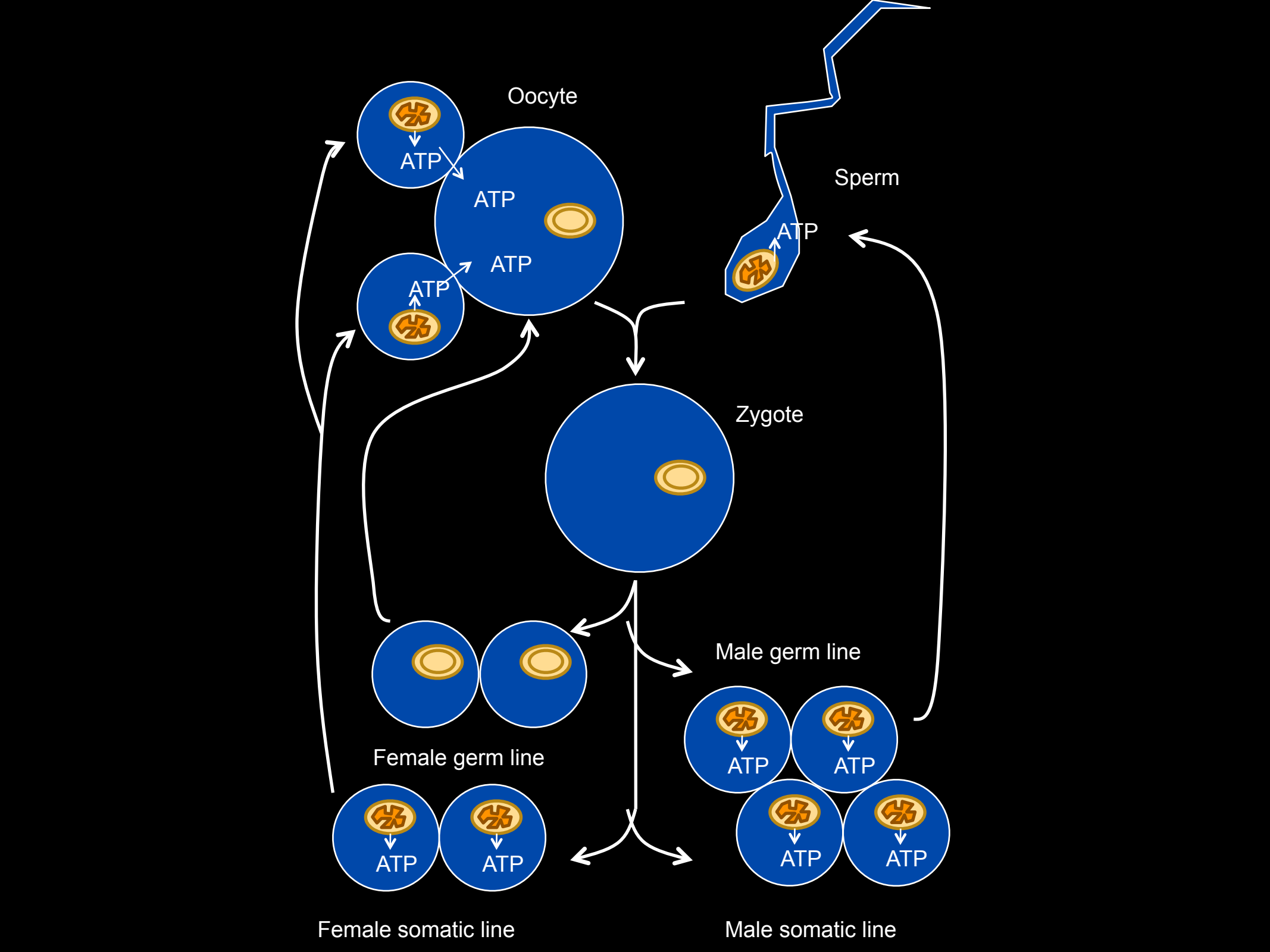
And they can never be both.

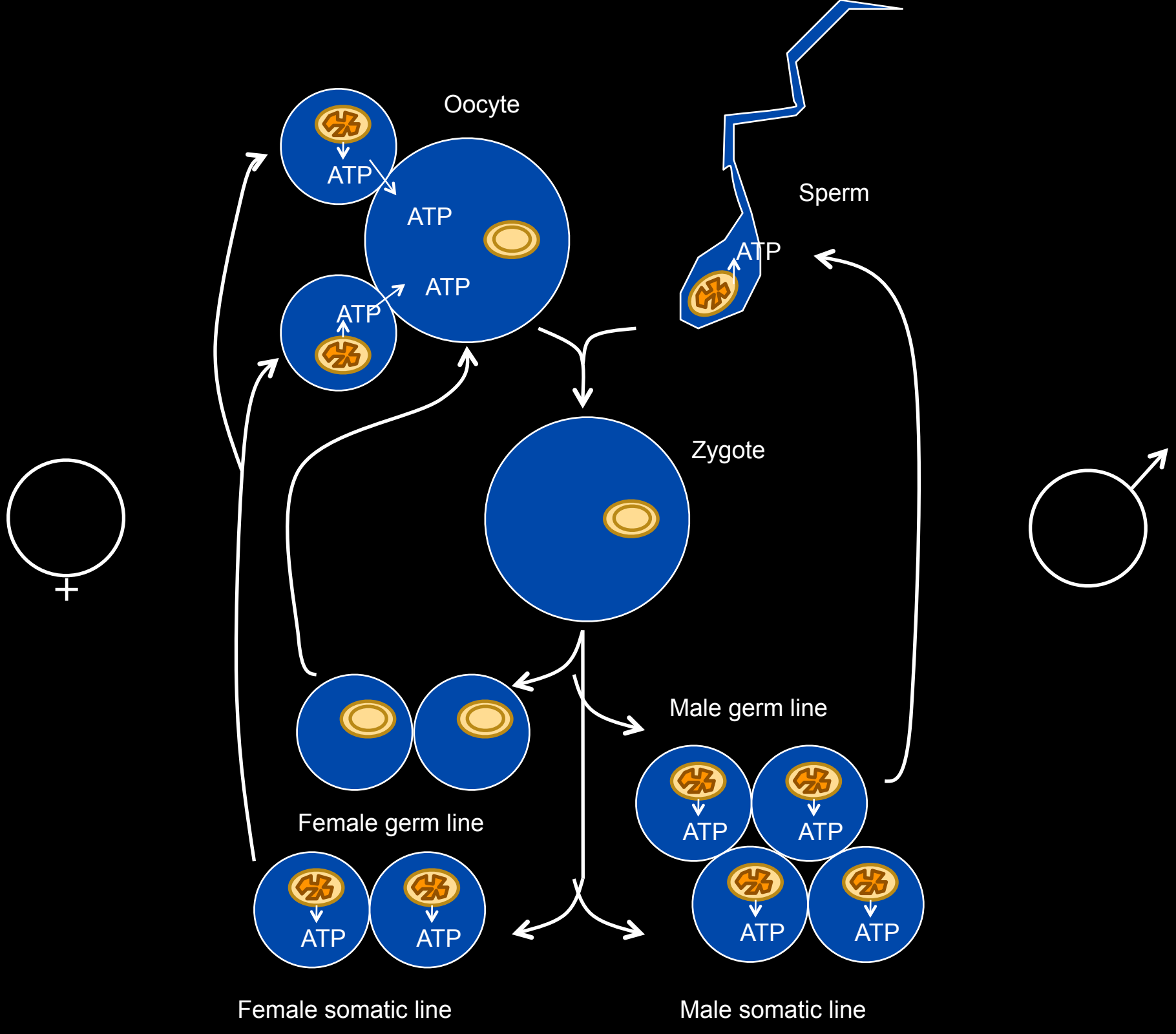

Oocyte
ATP
ATP
ATP
ATP
Sperm
ATP


Oocyte
ATP
ATP
ATP
ATP
Sperm
ATP
Zygote


Oocyte
ATP
ATP
ATP
ATP
Sperm
ATP
Zygote
Female germ line


Oocyte
ATP
ATP
ATP
ATP
Sperm
ATP
Zygote
Female germ line
ATP
ATP
Female somatic line


Oocyte
ATP
ATP
ATP
ATP
Sperm
ATP
Zygote
Male germ line
Female germ line
ATP
ATP
ATP
ATP
ATP
ATP
Female somatic line
Male somatic line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ATP
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Predictions:

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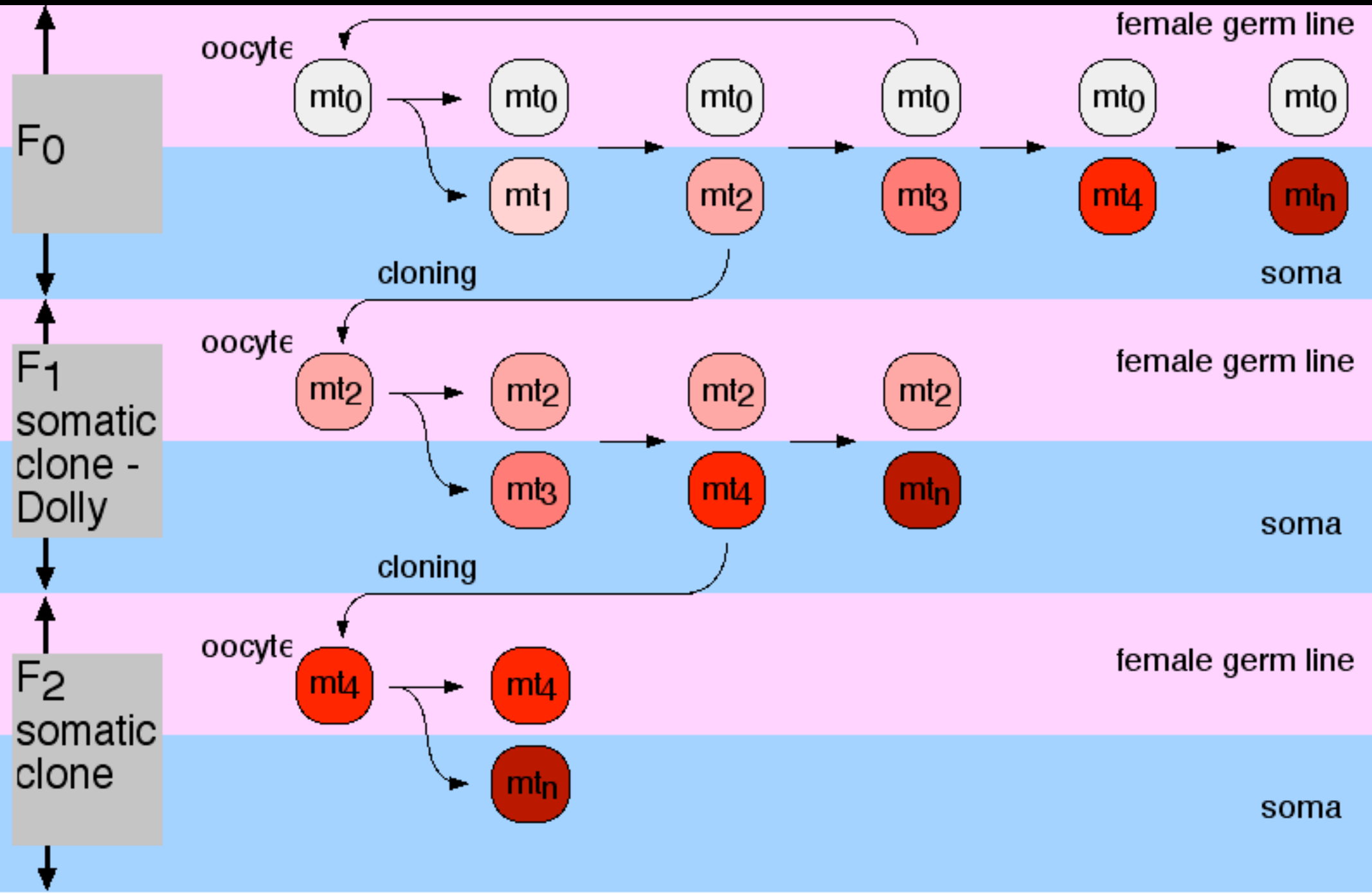
– Experimental predictions…



Allen JF, and Allen CA. IUBMB Life 48: 369-372, 1999

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Dolly, the Finn Dorset ewe, the first mammal to be cloned from an adult cell. Finn Dorset sheep normally live to 11 or 12 years. Dolly had been suffering from lung cancer and died of a drug overdose on 14th February 2003, aged 5. Dolly is survived by three or four of her six lambs.

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Obituary: Dolly the Sheep
http://www.nature.com/nsu/030210/030210-15.html

TIMESONLINE

From The Times

August 27, 2009

DNA swap could cure inherited diseases

(Oregon National Primate Research Center at OHSU)

The first two monkeys to be born were twins called Mito and Tracker, after a dye called MitoTracker used in the experiment

Mark Henderson, Science Editor

The prospect of a human baby with three biological parents has moved closer after scientists created monkeys using a technique that one day could stop children from inheriting severe genetic diseases.

The birth of four healthy macaque monkeys in the US offers the strongest evidence yet that DNA can be transplanted safely from one egg to another to correct genetic defects that damage health.

The successful experiment in a close human relative suggests that it should be possible within a few years to use the method to help women who carry genetic disorders to avoid passing them to their children.

It should allow scientists to replace faulty “cellular batteries” called mitochondria, which affect about 1 in 6,500 births. While most mitochondria defects have mild effects, some can trigger severe brain, heart, muscle and liver conditions, as well as cancer, diabetes, blindness and deafness.

The technique is controversial, however, because the children it creates would inherit genetic material from three parents. The mother and father would contribute most of their child’s DNA but a small amount would come from a second woman donating healthy mitochondria.

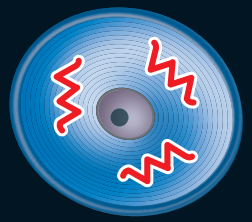
Such children would be the first produced by germline genetic engineering, in which genes introduced by artificial means would be passed to successive generations.

How the technique works

Mitochondria are structures found within most cells, often described as “cellular power plants” because they generate much of the cells’ energy

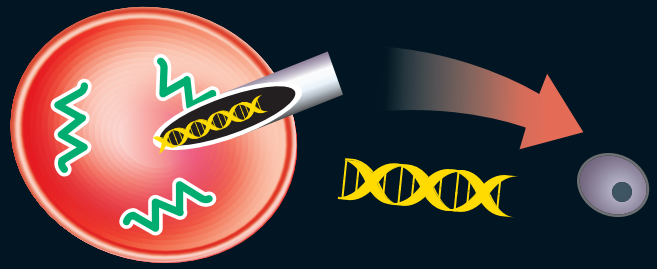
Transplant in monkeys

Egg with mitochondrial deficiency



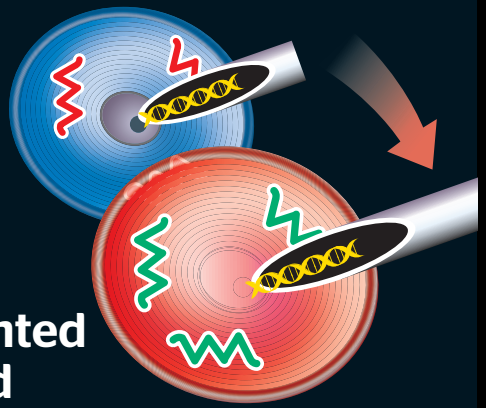
Egg with healthy mitochondria

1



Chromosomes removed from the healthy egg and discarded

2 Chromosomes removed from egg with mitochondrial defects and transplanted into emptied healthy egg



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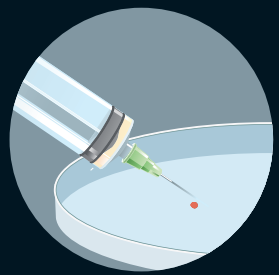

Egg with transplanted chromosomes and healthy mitochondria is fertilised by sperm

4 Embryo placed into a female monkey surrogate mother and healthy baby monkey is produced

Summary

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–but are predicted to exist also in female germ lines as protected genetic templates, incapable of energy conversion, and from which all other mitochondria derive

Coda. Two views of mitochondria
View 1

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John Burn (Newcastle Institute of Clinical Genetics).
Quoted in *The Times*, 9th September 2005

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Mitochondria:

– *"…are not part of the genetic material that we consider makes us as human beings."*

"My belief is that what we are doing is changing a battery that doesn't work for one that does….Changing the mitochondria won't affect the important DNA."

Coda. Two views of mitochondria
View 2

Coda. Two views of mitochondria
View 2

Nick Lane. *Power, Sex, Suicide. Mitochondria and the Meaning of Life.* Oxford University Press. Publication: 27th October 2005.

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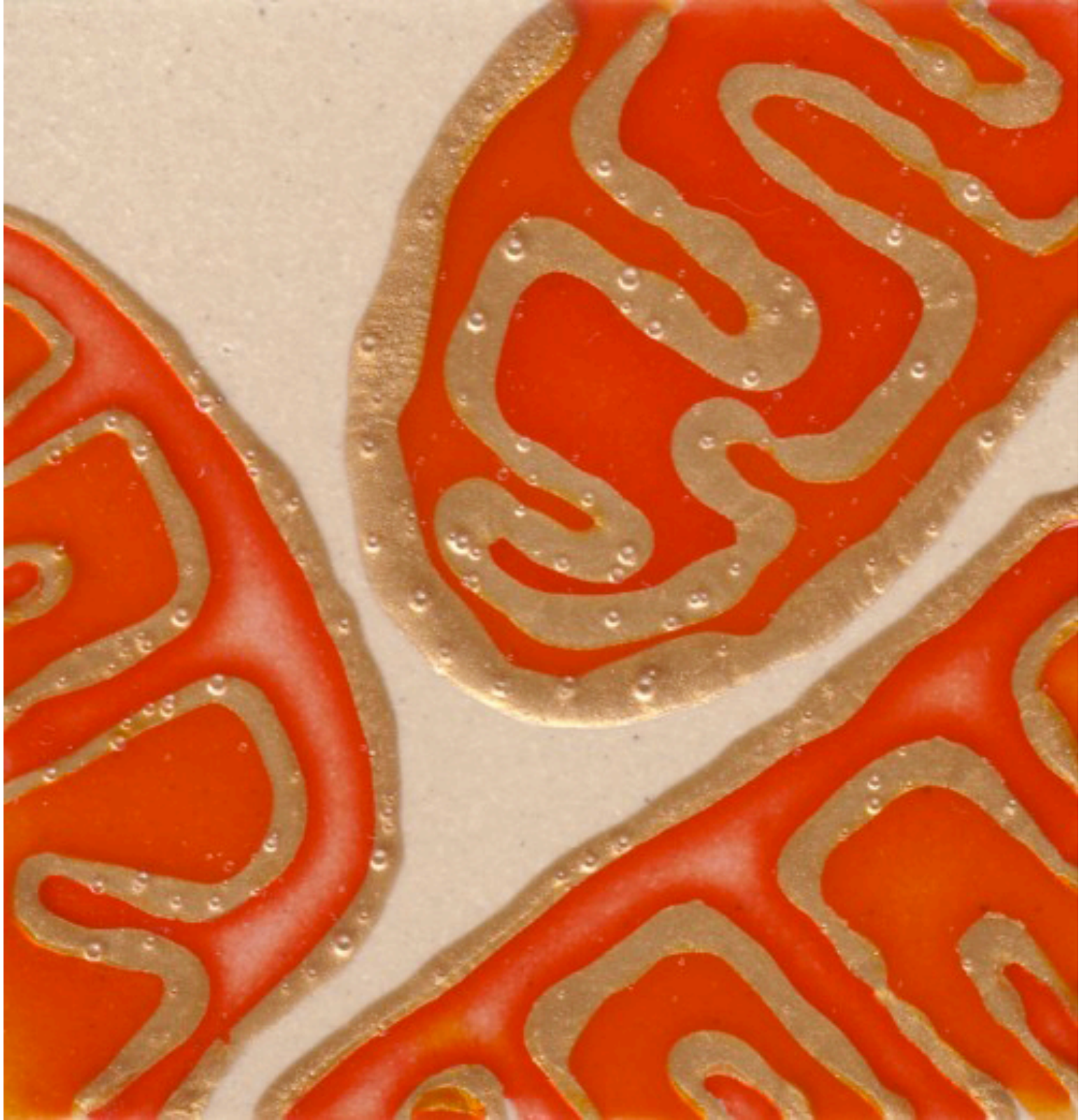
Mitochondria:

– "…give striking new insights into why we are here at all, whether we are alone in the universe, why we have our sense of individuality, why we should make love, where we trace our ancestral roots, why we must age and die—in short, into the meaning of life."



Reading

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Lane, N. Power, sex, suicide: Mitochondria and the meaning of life. OUP, Oxford 2005. Review Allen JF (2005) Nature 437: 1235-1236.

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