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# Hormonal Therapies and Mitochondrial Demands

## A New Era of Women's Care

**Presenter:**
**Dr Leah Hechtman,**
Naturopathic Women's Health Specialist

**Host: Assunta Hamilton,**
Naturopath &
DFH Health Educator

# Your Host | Assunta Hamilton, Naturopath

Assunta is a Health Educator for Designs for Health, bringing extensive experience as a paramedic and naturopath with a strong foundation in both clinical practice and practitioner education.

She holds an Advanced Diploma in Naturopathy and a Diploma in Paramedical Science. Throughout her career, Assunta has supported individuals and practitioners alike – combining scientific insight, traditional wisdom, and a broad understanding to deliver truly holistic care.

Passionate about whole-person health, Assunta is dedicated to empowering others through education and compassionate support.

# Your Presenter | Dr Leah Hechtman

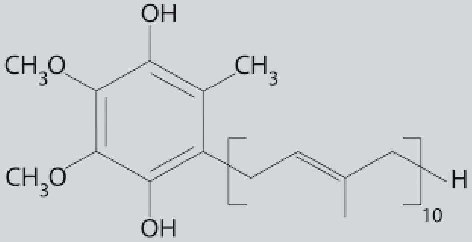
**Dr Leah Hechtman PhD**
**MSciMed (RHHG), BHSc (Naturopathy), ND, FNHAA**

Dr Leah Hechtman (PhD) is a globally renowned naturopathic clinician who specialises in fertility, pregnancy, and comprehensive reproductive health.

In addition to her clinical expertise, she is an active researcher, a published author, and a dedicated educator. She works in close coordination with each patient's healthcare team, often involving general practitioners and specialists, bridging gaps between different disciplines and theories to foster holistic and collaborative outcomes in both clinical practice and research.

# Hormonal Therapies and Mitochondrial Demands

## A New Era of Women's Care



# Disclosures

- Author, Elsevier Publishers
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- Director, The Natural Health and Fertility Centre
- Executive, NHAA Sexual and Reproductive Health SIG
- Lecturer – Various
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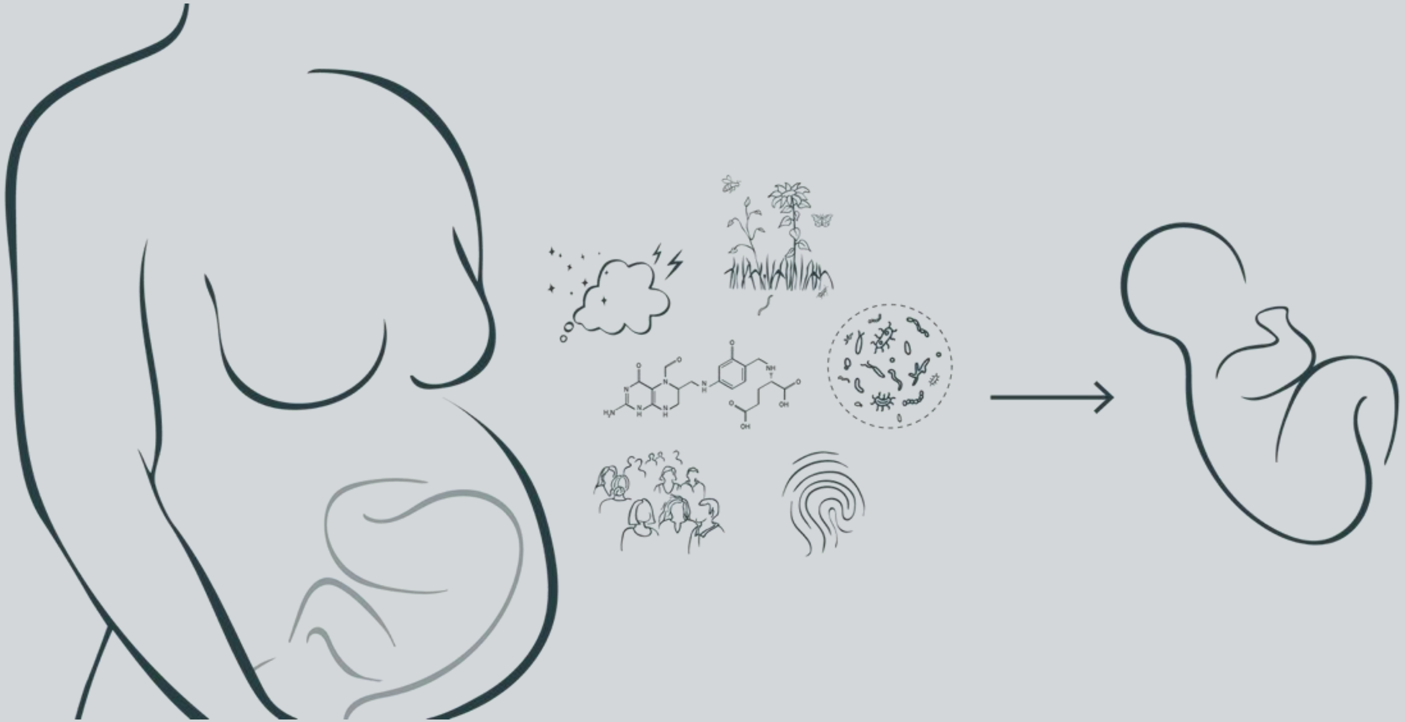
# The hallmarks of a woman's life

- in utero
- infancy, toddler
- childhood
- puberty
- reproductive years
- pregnancy, breastfeeding
- peri-menopause
- post menopause

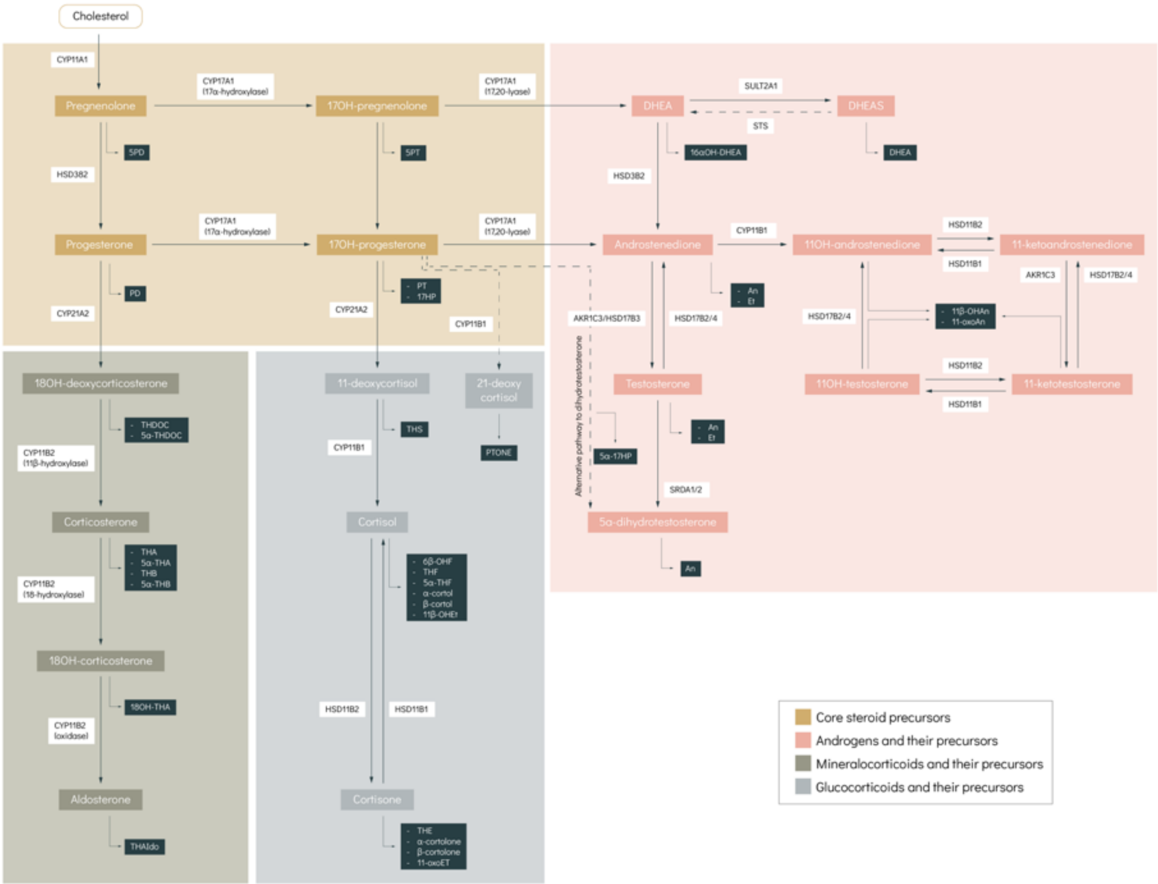
# Trigenerational wisdom



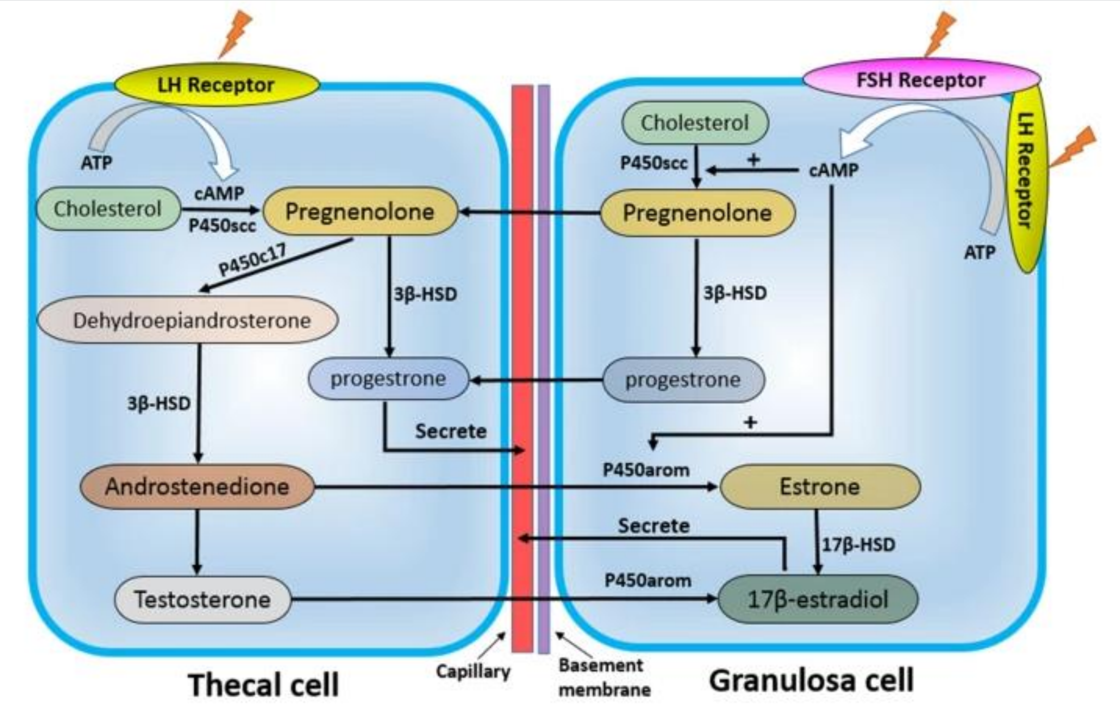
# What makes a woman a woman?

# Mitochondria and steroidgenesis

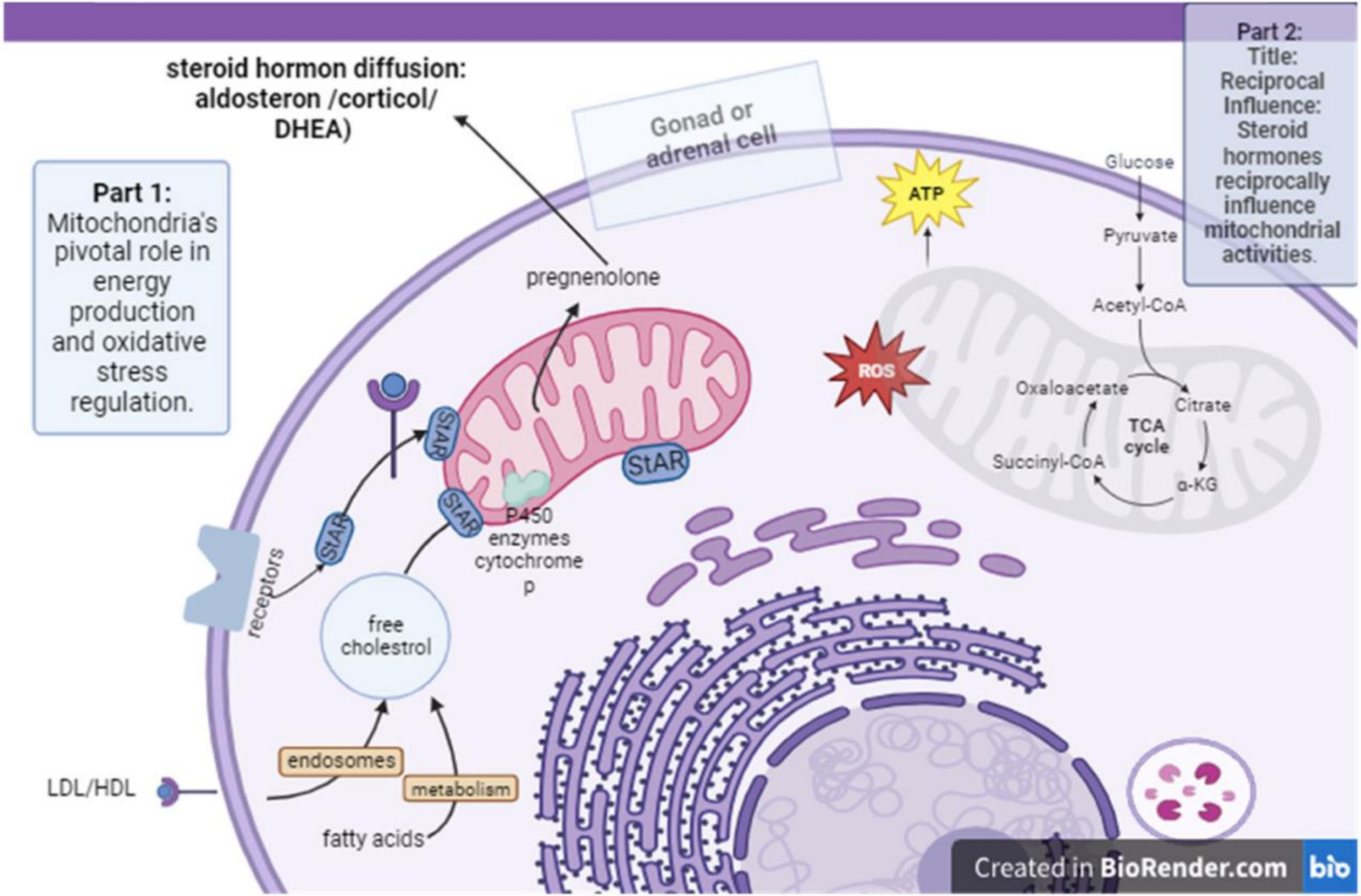
# Steroidgenesis



# Two-cell, two-gonadotropin hypothesis




Xiao et al., 2023



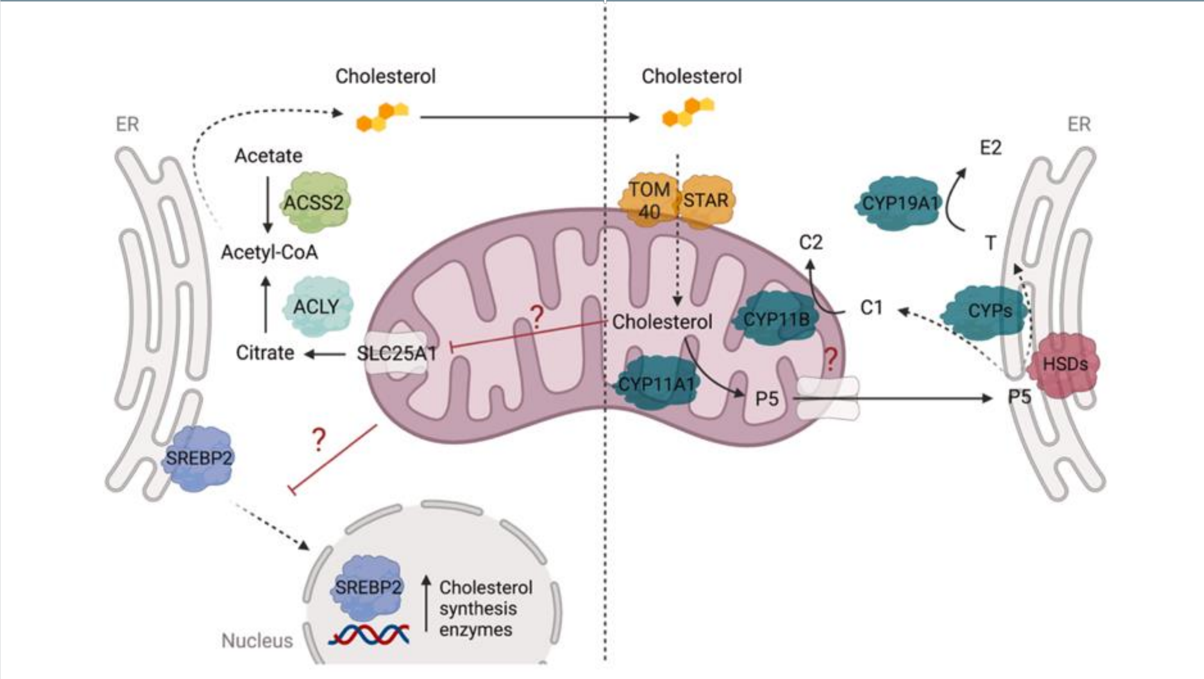


Al-Suhaimi et al., 2024

Mitochondria produce and export citrate which is the main cholesterol precursor

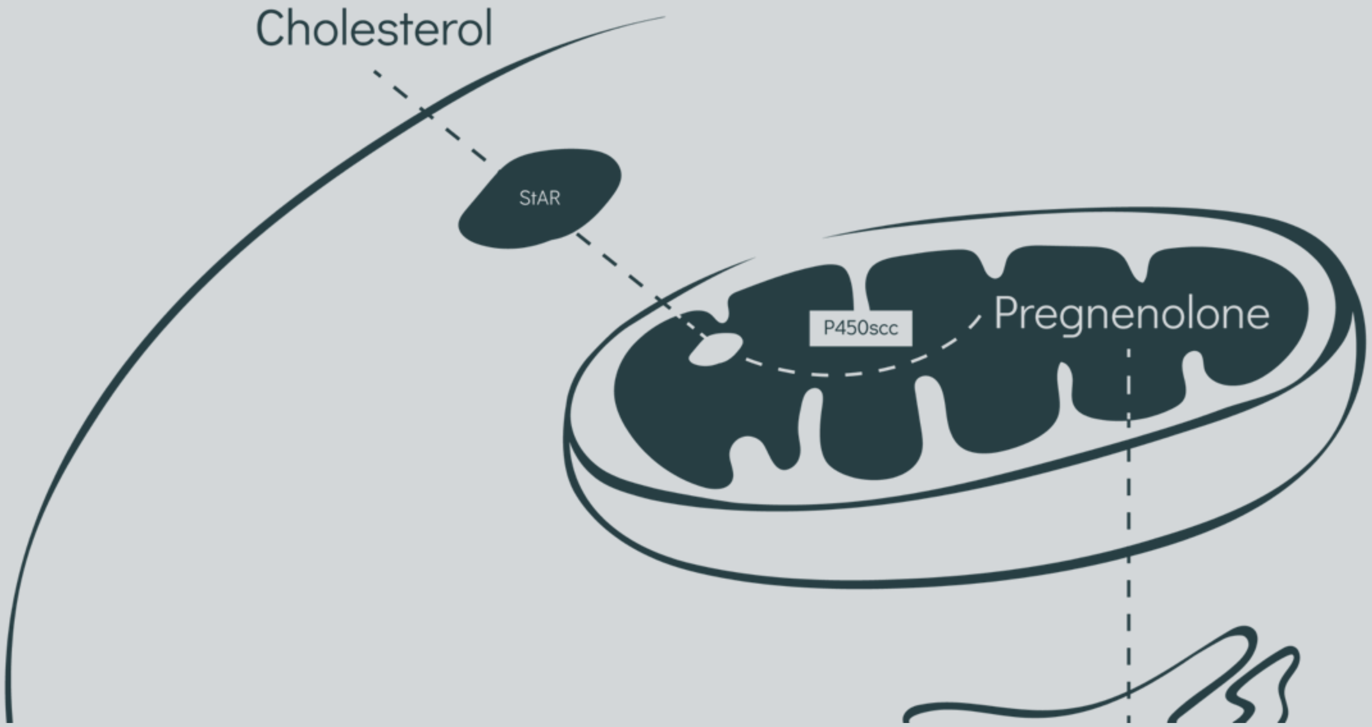
Melchinger & Garcia, 2023

| Cholesterol synthesis | Steroid hormone synthesis |
| --- | --- |

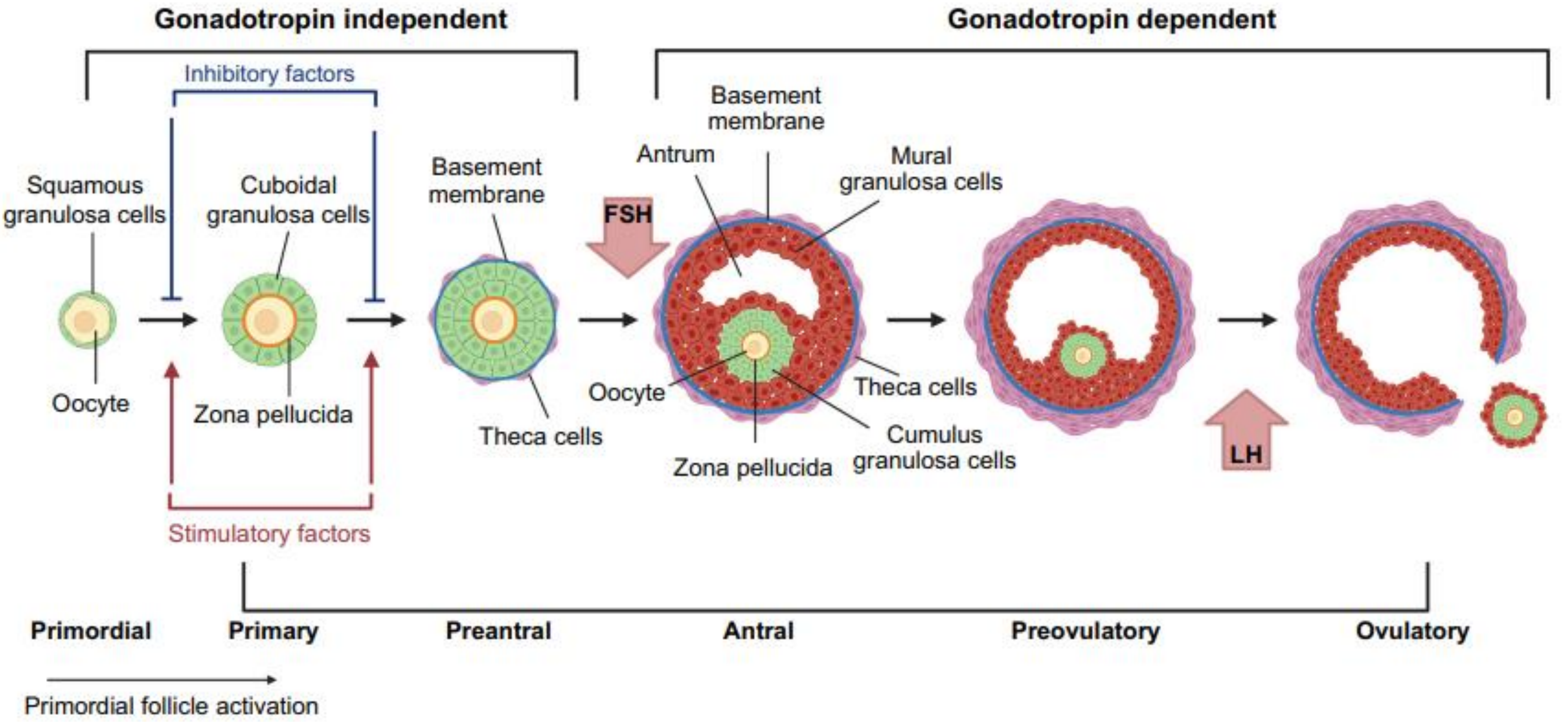



Pregnenolone (P5); 11-Deoxycortisol (C1); Cortisol (C2); Testosterone (T); and Estradiol (E2).

(Melchinger & Garcia, 2023


Cholesterol
StAR
P450scc
Pregnenolone

# What about the oocyte?




Telfer et al., 2023

Oocytes house approximately 100,000 mitochondria compared with about 1000-2500 mitochondria in other human cells

# Estimated number of mitochondria per cell from various mammalian cell types.

| Cell type | Number of mitochondria per cell[a] | Refs |
|---|---|---|
| Cardiomyocytes | 3000–8000 | [9,10,15] |
| Hepatocytes | 1000–1700 | [6,11,12] |
| Skeletal muscle | 120–160 | [13] |
| Fibroblasts | 200–350 | [13] |
| Neurons[b] | $\sim 2 \times 10^6$ | [18] |
| Macrophages | 100–700 | [13] |
| Erythrocytes | 0 | [19] |
| Platelets | 4–10 | [20–22] |
| Spermatozoa | 50–75 | [23,24] |
| Mature oocyte | $10^5$ | [25–27] |
| Female germ cells (excluding mature oocytes)[c] | $10 \rightarrow 5000$ | [28,29] |



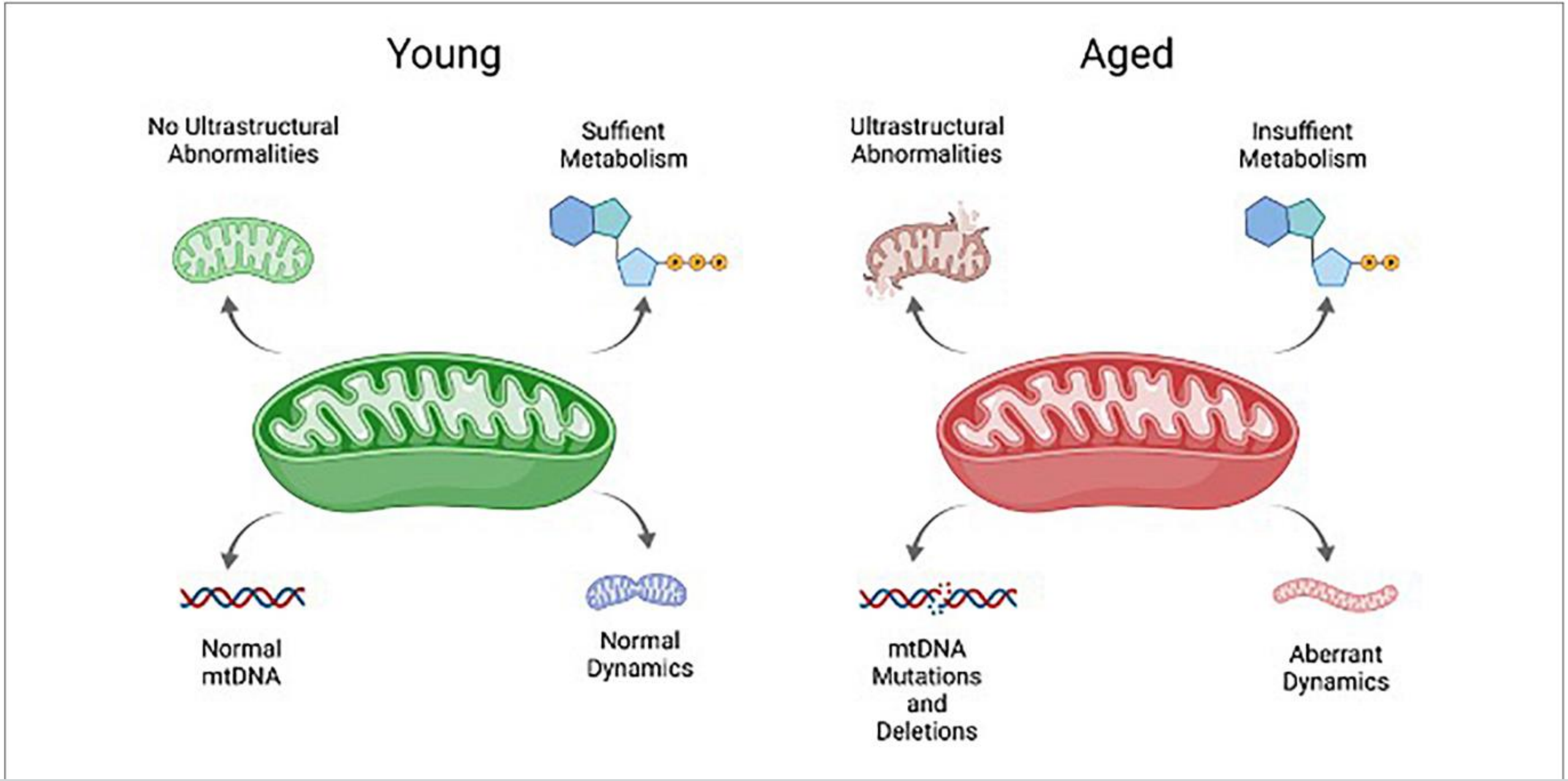


Moura 2025

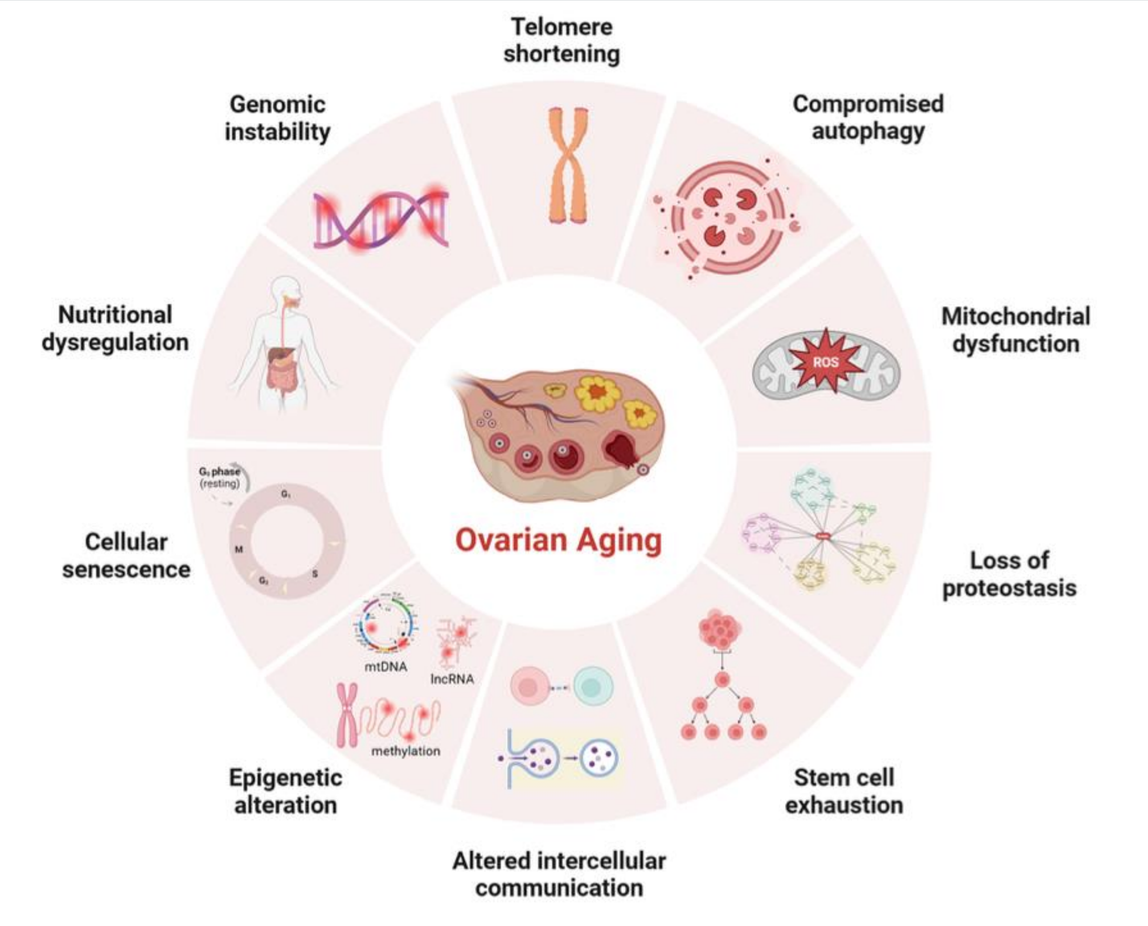
Mitochondria = energy supply centre within oocytes

CoQ10 acts as cofactor for ATP production

Ubiquinol deficiency linked to hormone loss, infertility and poor embryonic development




Alberico & Woods, 2022


Telomere shortening
Compromised autophagy
Mitochondrial dysfunction
ROS
Loss of proteostasis
Stem cell exhaustion
Altered intercellular communication
Epigenetic alteration
mtDNA
lncRNA
methylation
Cellular senescence
Nutritional dysregulation
Genomic instability
Ovarian Aging

Ju et al., 2024

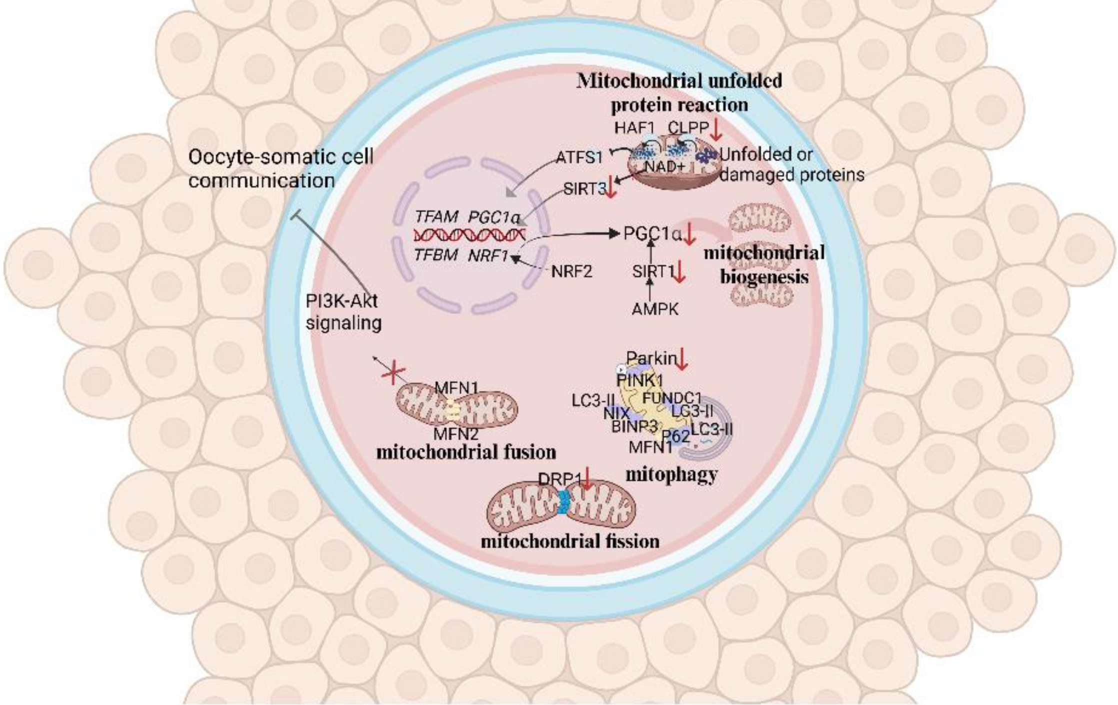
# Mitochondria and women's health

# What makes a healthy oocyte?

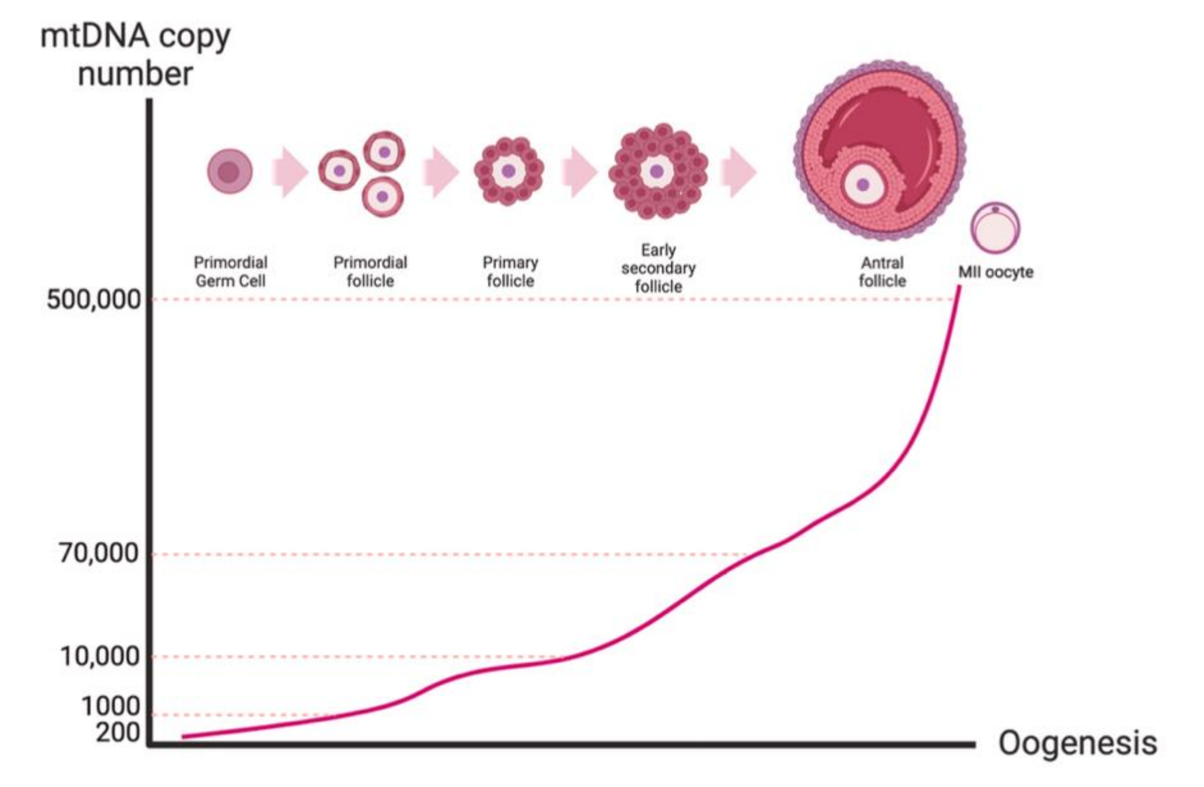
- Mitochondrial function.
- Granulosa cell mitochondria – maintains the antioxidant system to protect oocytes from oxidative stress.

An et al., 2024

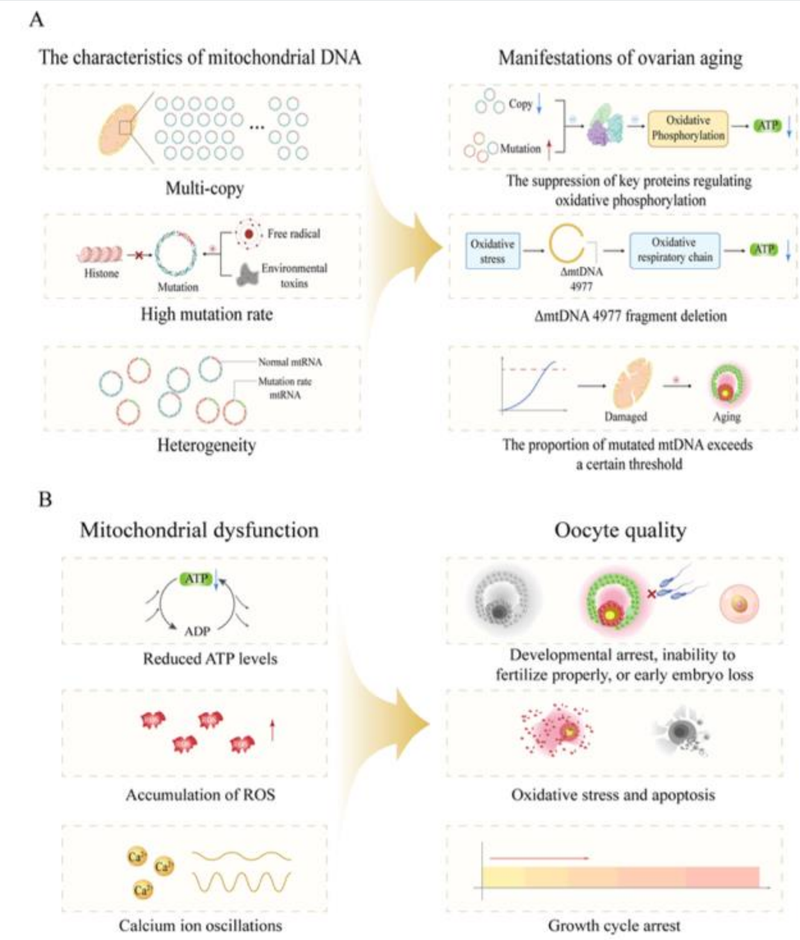
# Mitochondrial quality monitoring and ovarian aging



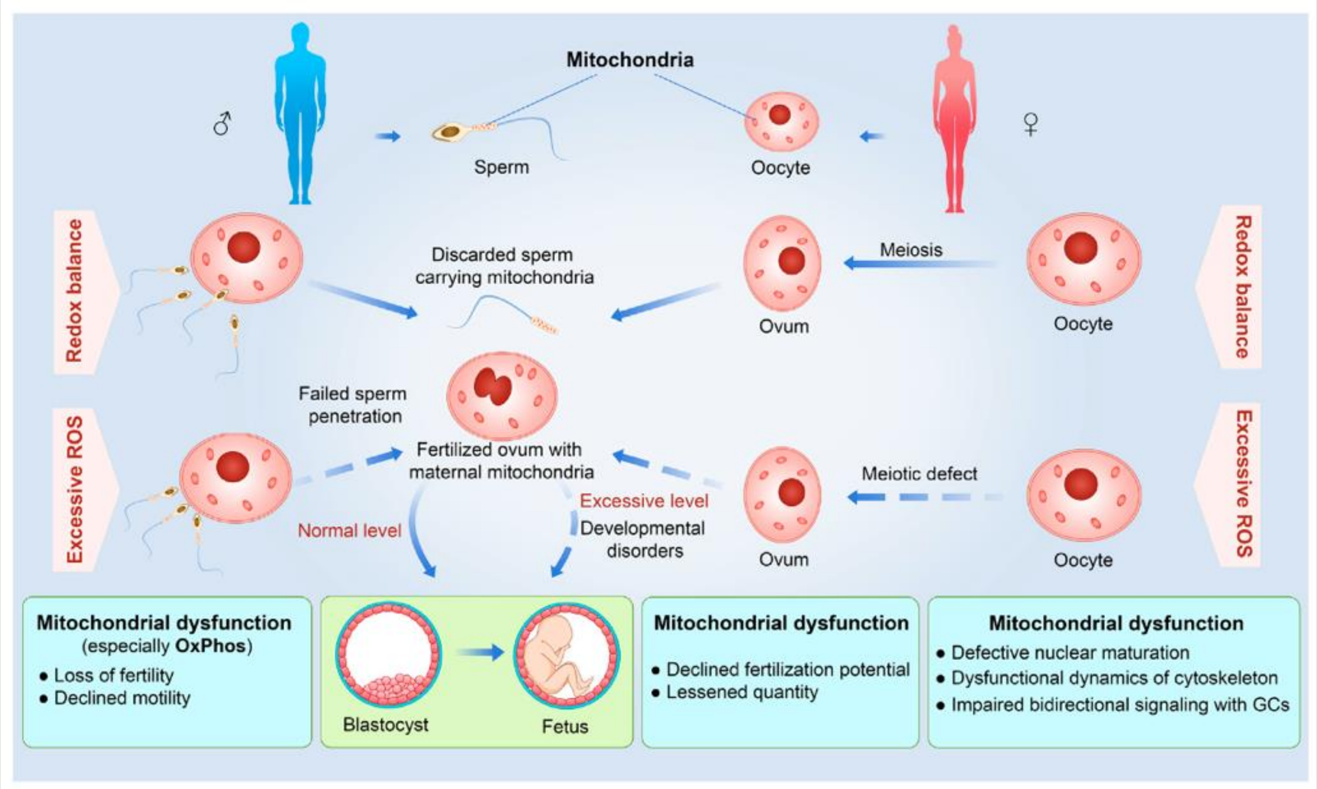

Ju et al., 2024



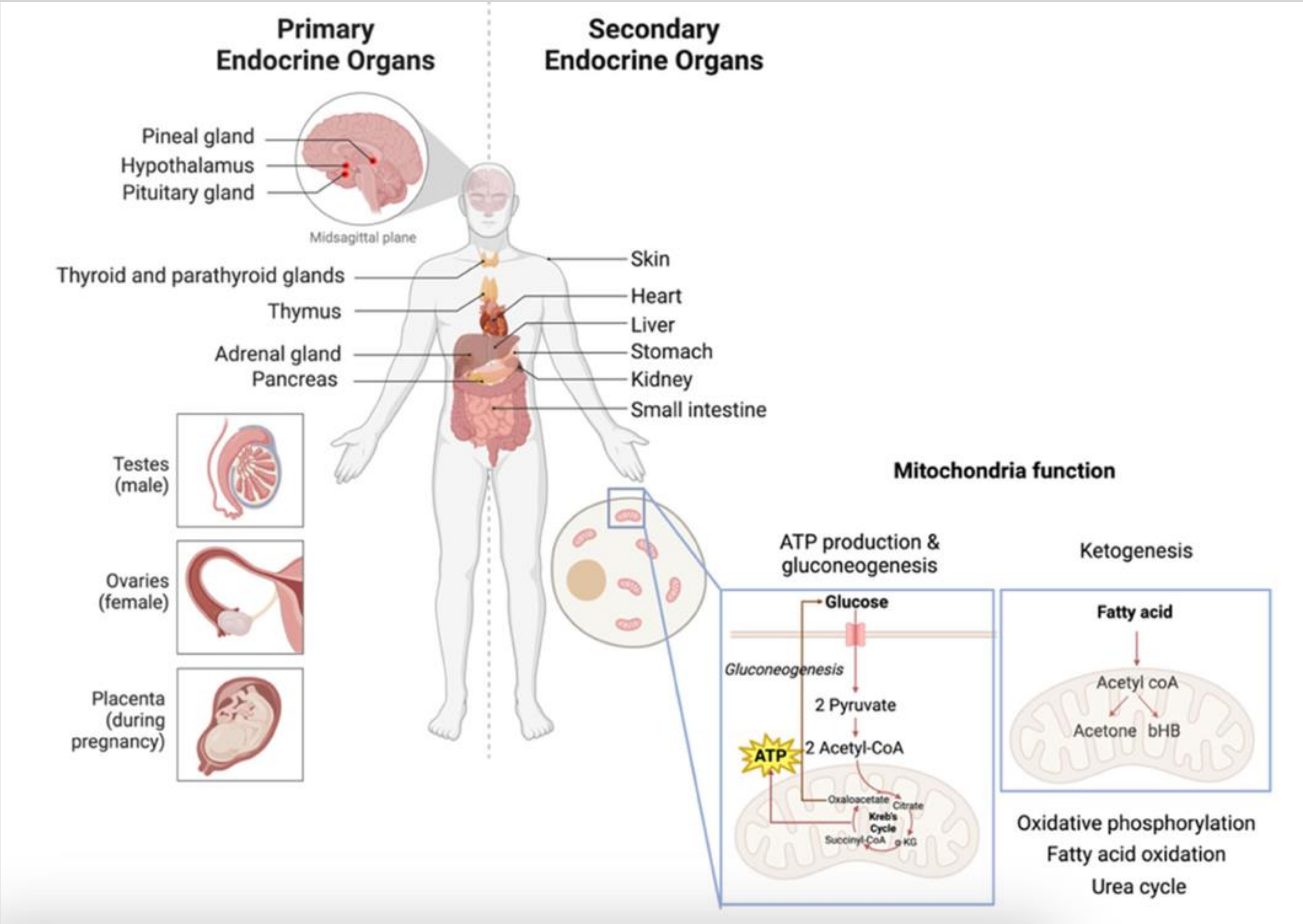

Yildirim & Seli, 2024




Zhang et al., 2025




Song et al., 2024




Al-Suhaimi et al., 2024

The humble mitochondria shouldn't be so humble…

| Function | Physiology |
| --- | --- |
| Signaling Organelles | Retrograde, Metabolite, Reactive Oxygen Species (ROS), and Calcium Signaling |
| Aerobic Respiration | Citric Acid Cycle (Mitochondrial Matrix), Electron Transfer and ATP production (inner mitochondrial membrane) |
| Ion Regulation | Calcium Signaling and Electrochemical Gradient (inner mitochondrial membrane) |
| Haemostasis | Platelet Activation |
| Cell Growth | ATP Supply, Metabolic Intermediates |
| Redox Stress Management | Reactive Oxygen Species (ROS) Production, Antioxidant Defense |
| Apoptosis | Cytochrome c Release, Mitochondrial Permeability Transition Pore (MPTP) |
| Metabolism | ATP production, Nutrient Breakdown Pathways, Biosynthesis Precursors |
| Stress Management | Mitophagy, Mitochondrial Biogenesis |
| Immune Responses | Inflammasome Activation, Metabolic Shift, Autophagy and Mitophagy |

Al-Suhaimi et al., 2024

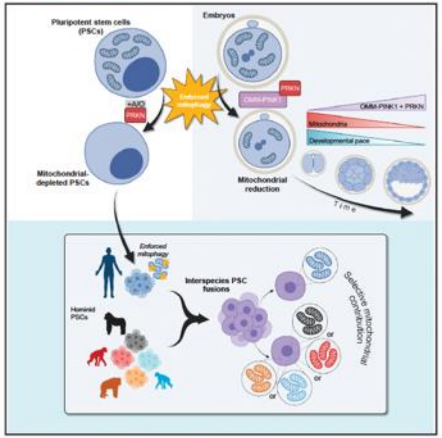
# Some newer findings for the roles of the mitochondria

Cell

Resource

# Unraveling mitochondrial influence on mammalian pluripotency via enforced mitophagy

## Graphical abstract





## Authors

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## In brief


Enforced mitophagy enables efficient mitochondrial depletion in pluripotent stem cells and embryos, allowing the creation of human-ape fusion PSCs with defined mitochondrial origins, which reveal critical mitochondrial contributions to pluripotency and early development.


## Highlights

- Enforced mitophagy enables mitochondrial depletion in pluripotent stem cells (PSCs)
- Interspecies human-ape composite PSCs are featured with selective mtDNA contribution
- Human-ape composite PSCs with species-specific mtDNA present subtle phenotypes
- Reducing mitochondrial abundance slows pre-implantation development


Schmitz et al., 2025, Cell *188*, 4773–4789



https://doi.org/10.1016/j.cell.2025.05.020


CellPress

nature communications

Article

https://doi.org/10.1038/s41467-025-59427-5

# Mitochondrial membrane hyperpolarization modulates nuclear DNA methylation and gene expression through phospholipid remodeling

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Check for updates

Mateus Prates Mori[1], Oswaldo A. Lozoya[2], Ashley M. Brooks[3], Carl D. Bortner[4], Cristina A. Nadalutti[1], Birgitta Ryback[5], Brittany P. Rickard[6], Marta Overchuk[7], Imran Rizvi[7,8], Tatiana Rogasevskaia[9], Kai Ting Huang[10], Prottoy Hasan[10], György Hajnóczky[10] & Janine H. Santos[1]

Maintenance of the mitochondrial inner membrane potential (ΔΨm) is critical for many aspects of mitochondrial function. While ΔΨm loss and its consequences are well studied, little is known about the effects of mitochondrial hyperpolarization. In this study, we used cells deleted of *ATP5IF1* (IF1), a natural inhibitor of the hydrolytic activity of the ATP synthase, as a genetic model of increased resting ΔΨm. We found that the nuclear DNA hypermethylates when the ΔΨm is chronically high, regulating the transcription of mitochondrial, carbohydrate and lipid genes. These effects can be reversed by decreasing the ΔΨm and recapitulated in wild-type (WT) cells exposed to environmental chemicals that cause hyperpolarization. Surprisingly, phospholipid changes, but not redox or metabolic alterations, linked the ΔΨm to the epigenome. Sorted hyperpolarized WT and ovarian cancer cells naturally depleted of IF1 also showed phospholipid remodeling, indicating this as an adaptation to mitochondrial hyperpolarization. These data provide a new framework for how mitochondria can impact epigenetics and cellular biology to influence health outcomes, including through chemical exposures and in disease states.

CellPress
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Immunity

Review

# Mitochondria reactive oxygen species signaling in immune responses

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https://doi.org/10.1016/j.immuni.2025.07.012

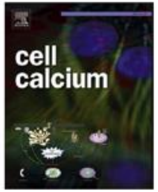
## SUMMARY

Mitochondria are key regulators of immune cell function, going beyond their traditional role in ATP and metabolite production to support anabolic processes and act as hubs for intracellular signaling. A key aspect of this signaling function is the production of mitochondrial reactive oxygen species (mtROS), which act as critical second messengers in both adaptive and innate immune regulation. Immune cells maintain an optimal concentration of mtROS to maintain physiological responses, and excessive or lack of mtROS production contributes to chronic inflammation, autoimmunity, and cancer. Here, we review the molecular mechanisms controlling mtROS production and detoxification, their role in shaping macrophage and T cell fate and function, and their implications for disease pathogenesis.

Contents lists available at ScienceDirect

Cell Calcium

journal homepage: www.elsevier.com/locate/ceca




Commentary

# Calcium acts as a critical determinant of mitochondria-nuclear networking driven retrograde signaling

Kriti Ahuja, Rajender K. Motiani *

*Laboratory of Calciomics and Systemic Pathophysiology (LCSP), Regional Centre for Biotechnology (RCB), Faridabad, Delhi-NCR, India*

A R T I C L E I N F O

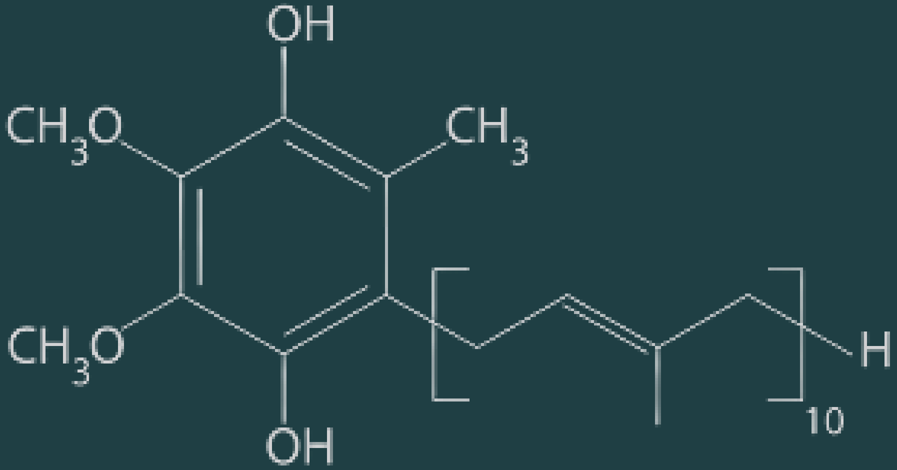
*Keywords*
Mitochondrial calcium signaling
Nuclear transcription
Calcium sensitive transcription factors
Retrograde signaling

A B S T R A C T

Mitochondria are robust signaling organelle that regulate a variety of cellular functions. One of the key mechanisms that drive mitochondrial signaling is inter-organelle crosstalk. Mitochondria communicates with other organelles primarily via exchange of calcium ($Ca^{2+}$), reactive oxygen species (ROS) and lipids across organelle membranes. Mitochondria has its own genome but a majority of mitochondrial proteins are encoded by nuclear genome. Therefore, several mitochondrial functions are controlled by nucleus via anterograde signaling. However, the role of mitochondria in driving expression of genes encoded by nuclear genome has recently gained attention. Recent studies from independent groups have demonstrated a critical role for mitochondrial $Ca^{2+}$signaling in stimulating nuclear gene expression. These studies report that inhibition of mitochondrial $Ca^{2+}$uptake through silencing of Mitochondrial $Ca^{2+}$Uniporter (MCU) leads to $Ca^{2+}$oscillations in the cytosol. The rise in cytosolic $Ca^{2+}$ results in activation of $Ca^{2+}$ sensitive transcription factors such as NFATs and NF-κB. These transcription factors consequently induce expression of their target genes in the nuclear genome. It is important to highlight that these groups used different cell types and elegantly presented a phenomenon that is conserved across various systems. Notably, mitochondrial $Ca^{2+}$ signaling mediated transcriptional regulation controls diverse cellular functions ranging from B-cell activation, melanogenesis and aging associated inflammation. Future studies on this signaling module would result in better understanding of this axis in human pathophysiology and could lead to development of novel therapeutic strategies.

For mitochondria to achieve all this it needs…

# Ubiquinol




As women age oocytes, become increasingly susceptible to oxidative stress, mitochondrial dysfunction



Derbyshire, 2025

Ubiquinol makes up approximately 95% of all CoQ10 circulating in the body



Derbyshire, 2025

# Our beloved Ubiquinol has some new achievements

- Endogenous synthesis of CoQ10 requires tyrosine participation and eight vitamins, thus is a complex process affected by status of other micronutrients.
- In humans at least 10 genes are required for Ubiquinol biosynthesis and mutations in any of these may impact on CoQ10 status and result in deficits.
- Secondary CoQ10 deficiencies are more common than primary deficiencies and result from causes other than defects in its biosynthesis. Depletion of CoQ10 levels can result from defective variants in genes unrelated to CoQ10 biosynthesis, the effects of ageing, exercise, prescription-type medications, availability of lipoprotein bloodstream carriers, and various illnesses.



Derbyshire, 2025, Staiano et al., 2023, Fernández-Ayala DJM, 2014

# Ubiquinol makes hormones reset

- Several RCTs recruiting women with PCOS have shown that 200 mg/d CoQ10 can improve hormone profiles (namely reductions in testosterone) and the chances of ovulation induction.



Derbyshire, 2025

# HRT and COC diminishes Ubiquinol

- HRT reduces blood levels of Ubiquinol.
- COC reduces blood levels of Ubiquinol.
  - Low Ubiquinol = under functioning mitochondria = ageing

Mantle & Hargreaves, 2023

# Further research

- In a study of CoQ10 supplementation in women undergoing IVF treatment (200 mg for 60 days before and throughout the IVF cycle), coenzyme Q10 supplementation was positively correlated with several in vitro fertilization outcomes



Li, Yang, & Liu, 2024

# Further research

- A pilot study indicated that in women aged <36 years, Ubiquinol (150 mg/d) was associated with a significant improvement in menstrual "Control"; in women >36 years, it was associated with significant improvement in premenstrual and menstrual "Control" and premenstrual "Negative affect".



Kinoshita, Maruyama, Katakami, & Sakiyama, 2025

# Further research

- In a meta-analysis of antioxidants used in women with ovarian aging during IVF, CoQ10 tended to be more effective than melatonin, myo-inositol, and vitamins.
- Subgroup analysis on CoQ10 indicated that 30 mg/d for 3 mo before the controlled ovarian stimulation cycle was the optimal regimen, and women with diminished ovarian reserve were the most appropriate population to benefit from CoQ10 treatment, especially those aged <35 y.



Shang, Song, He, & Wu, 2024

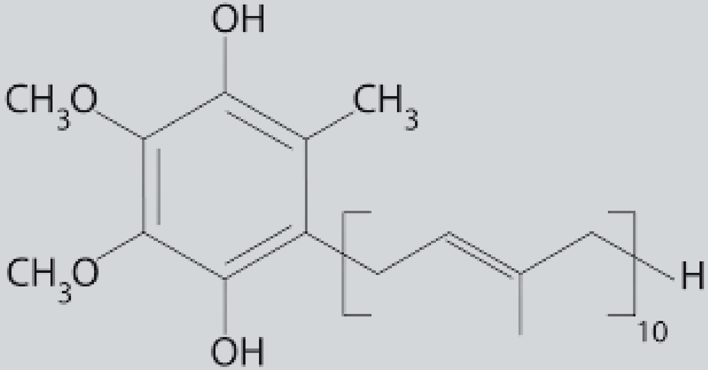
# Further research

- Improved pregnancy rate when combining CoQ10 and Omega 3 fatty acids for infertility patients.

Ozdemir et al 2019

| Classification | Drug | Mechanism |
|---|---|---|
| Improve mitochondrial energy metabolism | Ubiquinol, vitamin E, vitamin C, astaxanthin, L-carnitine, melatonin, quercetin, resveratrol, metformin, ginsenoside Rb1 | Reduce superoxide radicals and scavenge hydrogen peroxide |
| | Ginsenoside Rb1 | Akt-FOXO1 interaction |
| | Metformin | Regulation of calcium ion homeostasis |
| | $NAD^+$ nucleoside | Promotes TCA cycle |
| Coordinate mitochondrial quality control | Ginsenoside Rg1, Ubiquinol | SIRT1 or PGC1α activator |
| | Melatonin, metformin | AMPK activator |
| | Resveratrol, Ubiquinol | Upregulate Parkin-induced mitochondrial autophagy |
| | $NAD^+$ nucleoside | Mitochondrial autophagy enhancers |
| Regulating mitochondrial apoptosis pathway | Metformin | Inhibit release of BAD and caspase |
| | Resveratrol | Inhibition of caspase 3 and BAX, upregulation of BCL2 |

# 2 humble ingredients create the essence of who we are



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