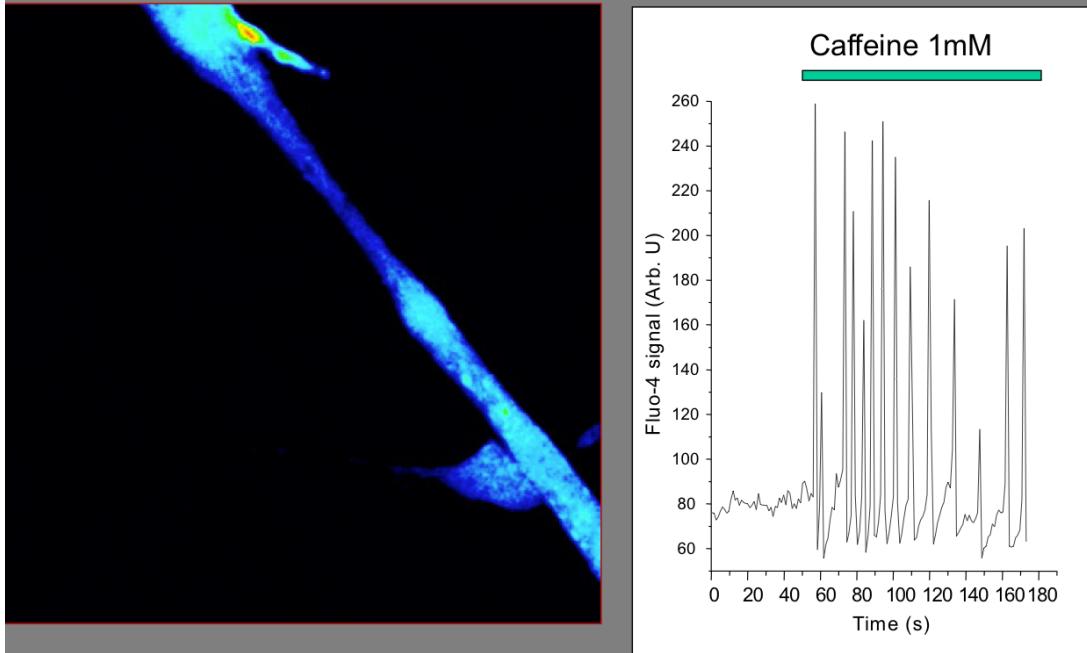


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- Biogenesis is enhanced by caffeine-induced Ca²⁺ (exercise, contraction)
 - caffeine promotes calcium transients (released by ER)
 - caffeine treated muscle showed stronger TMRM signal — upregulated no. of MT

In muscle, mitochondrial biogenesis is driven by changes in intracellular calcium – i.e. in activity.

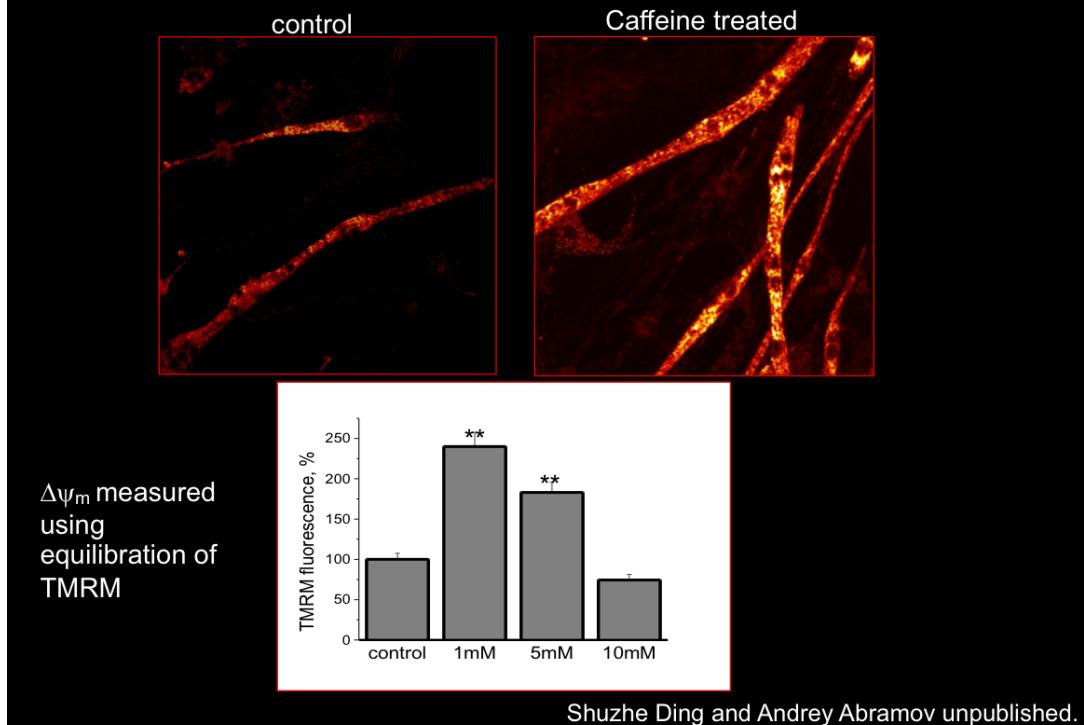
Long term treatment with caffeine at low doses causes regular calcium transients



Shuzhe Ding and Andrey Abramov unpublished.

MT activity is linked to muscle contraction (?)

Mitochondrial membrane potential is increased in myotubes exposed to caffeine for 5 hours a day for 5 days.

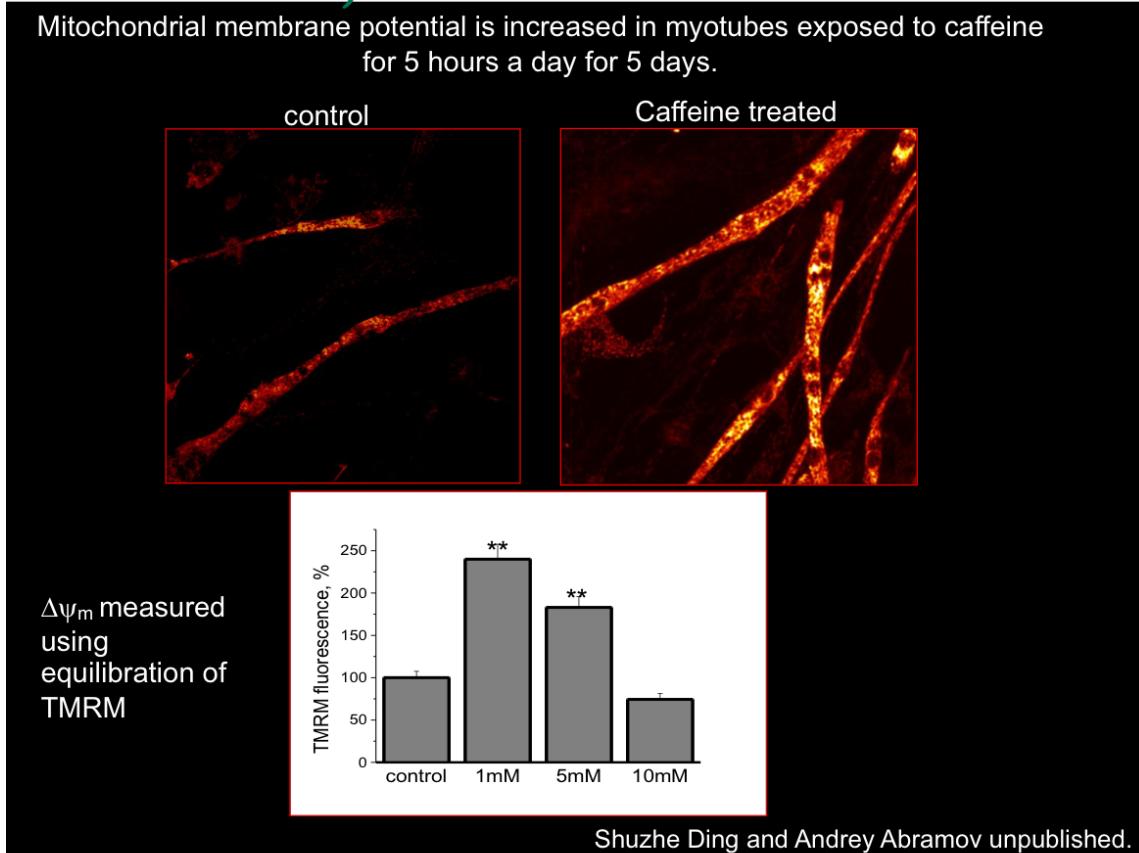


▼ Mitophagy

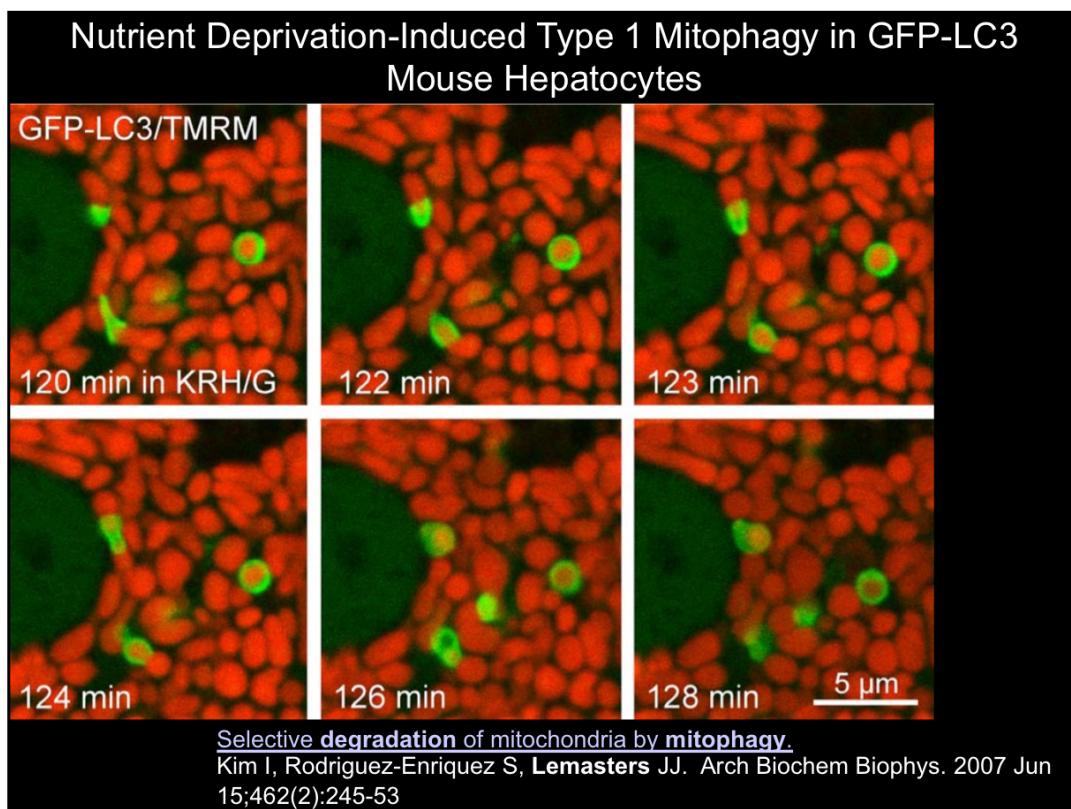
- radiates MT
 - label MT with TMRM
 - cells transfected with tagged LC3
 - seen RFP went dimmed and inclusion (autophagosome appeared)

MT activity is linked to muscle contraction ③

Mitochondrial membrane potential is increased in myotubes exposed to caffeine for 5 hours a day for 5 days.



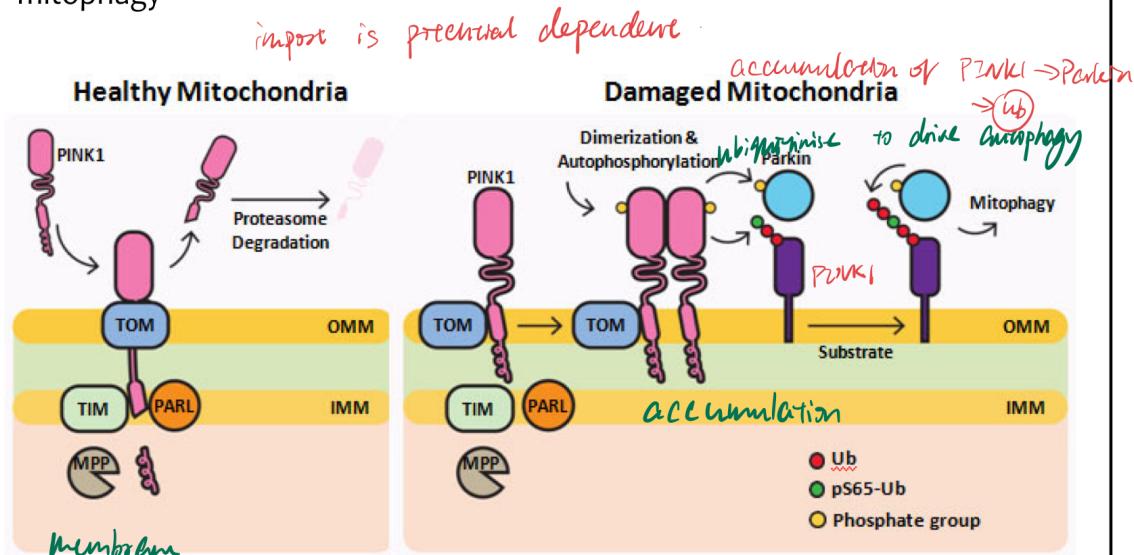
Shuzhe Ding and Andrey Abramov unpublished.



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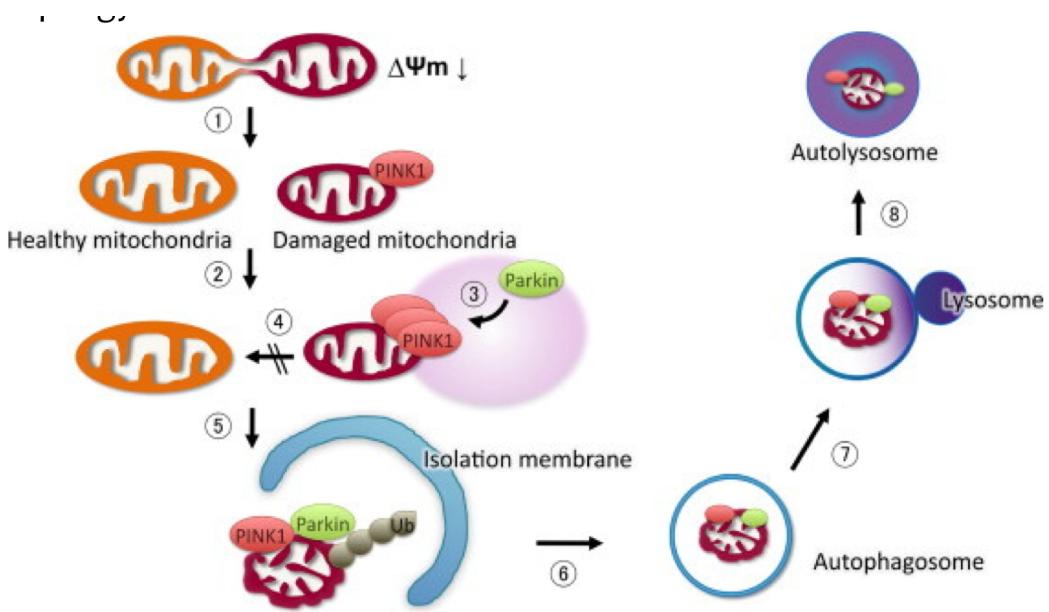
- The Mitophagy Flag is PINK1 (associated with Parkinson's Disease)

mitophagy



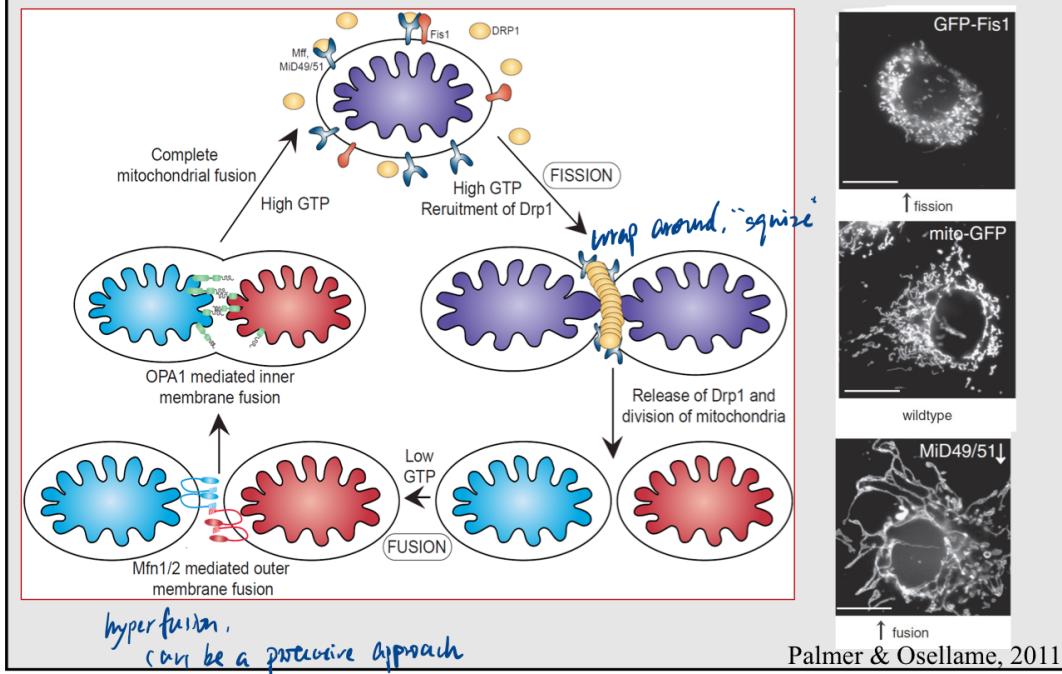
www.biologics.com

- Normally: the PINK1 imported to MT (via TOM and TIM) will be degraded by PARL and then dissociate from MT
- This is dependent on the MT potential
- When the MT potential is damaged: PINK1 degradation is impaired — PINK1 accumulation — dimerisation & autophosphorylation — activate by Parkin — polyubiquitination → Mitophagy



▼ Fission & Fusion

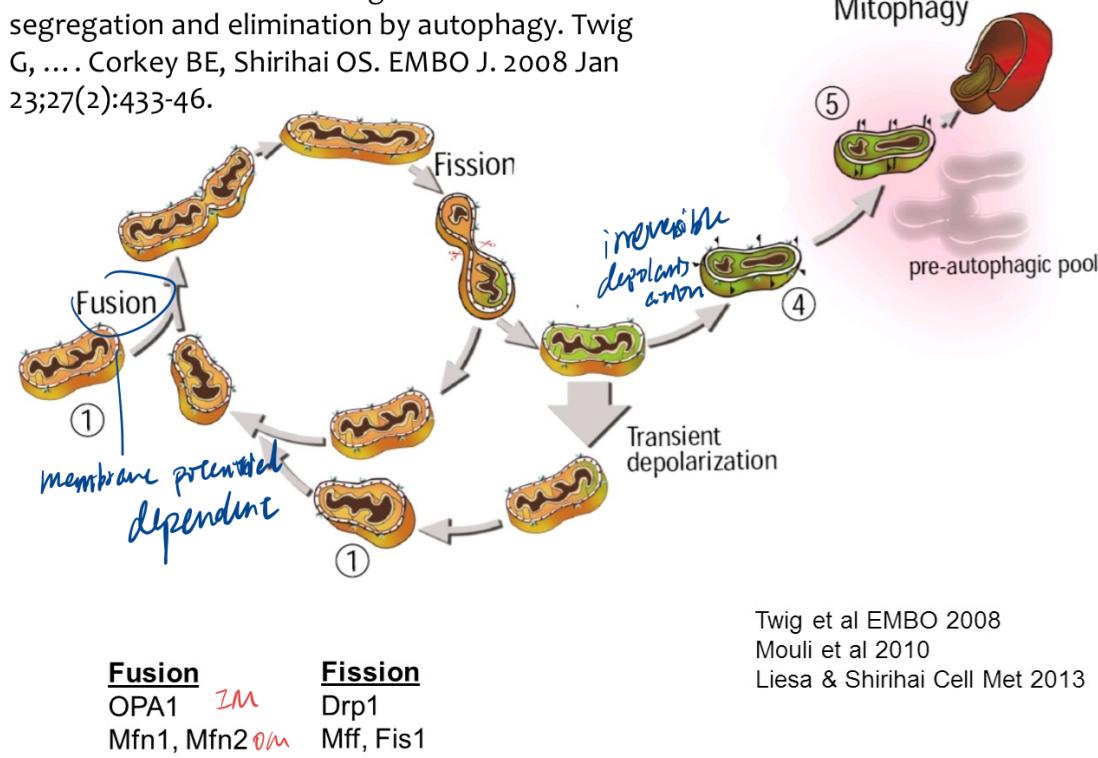
Mitochondrial Morphology



- There is equilibrium between fusion and fission under healthy condition — this can be broken under certain process
- Fusion occurs during low GTP — can be a protective mechanism
 - **dependent on MT membrane potential**
 - Kiss and run
 - exchange the proteins
- Fission can fragmentise MT which can then drive Mitophagy

The Mitochondria Life Cycle

Fission and selective fusion govern mitochondrial segregation and elimination by autophagy. Twig G, Corkey BE, Shirihi OS. EMBO J. 2008 Jan 23;27(2):433-46.

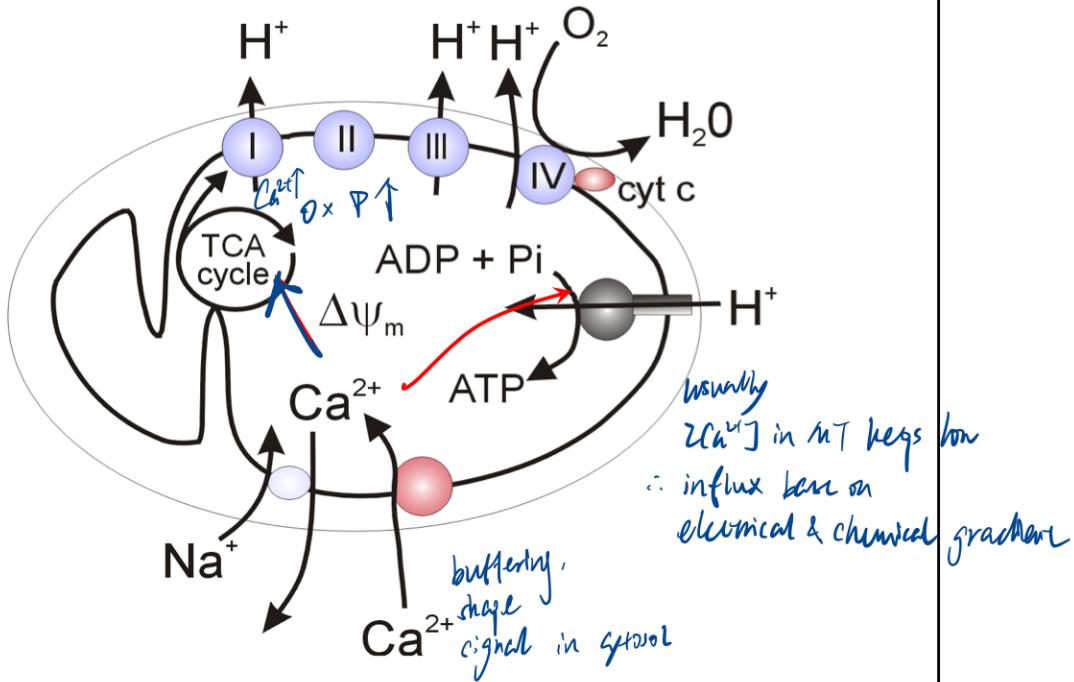


MT and Calcium signaling

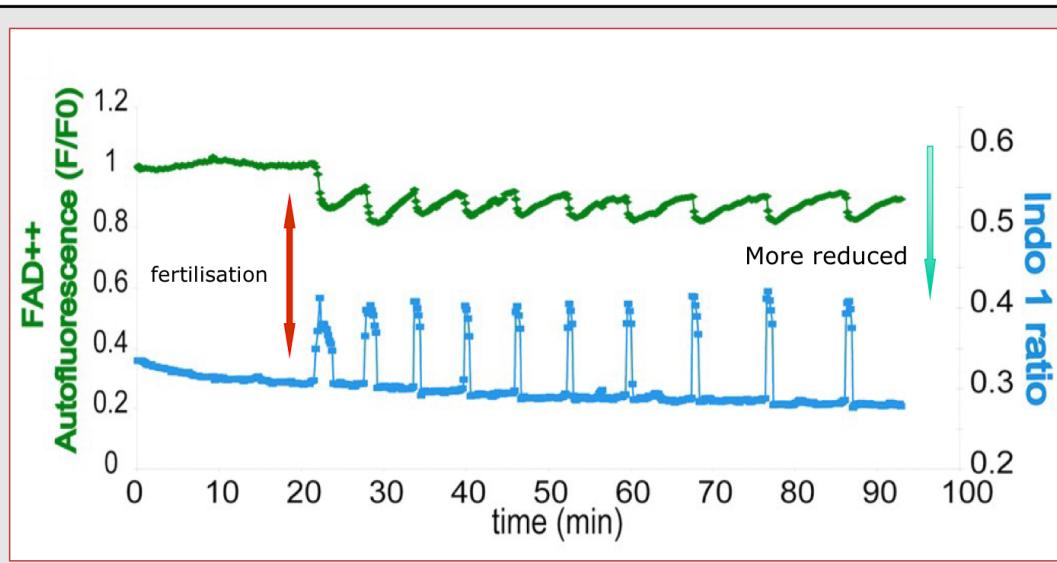
- Ca²⁺ in MT matrix upregulates the rate limiting enzymes of the turnover TCA cycle

M_T has huge capacity to taking up Ca²⁺

Calcium in the matrix upregulates the rate limiting enzymes of the TCA cycle...



- Ca²⁺ can upregulate TCA cycle
 - cause NADH / FADH₂ into a more reduced state

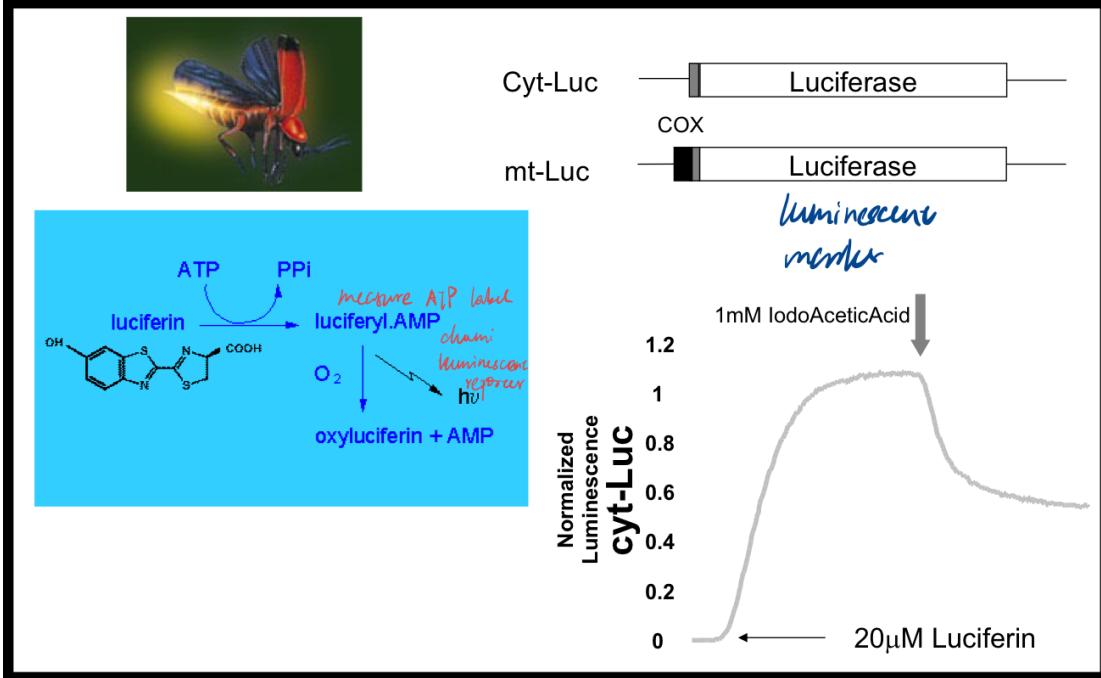


Calcium oscillations are a key trigger to early development in the oocyte.

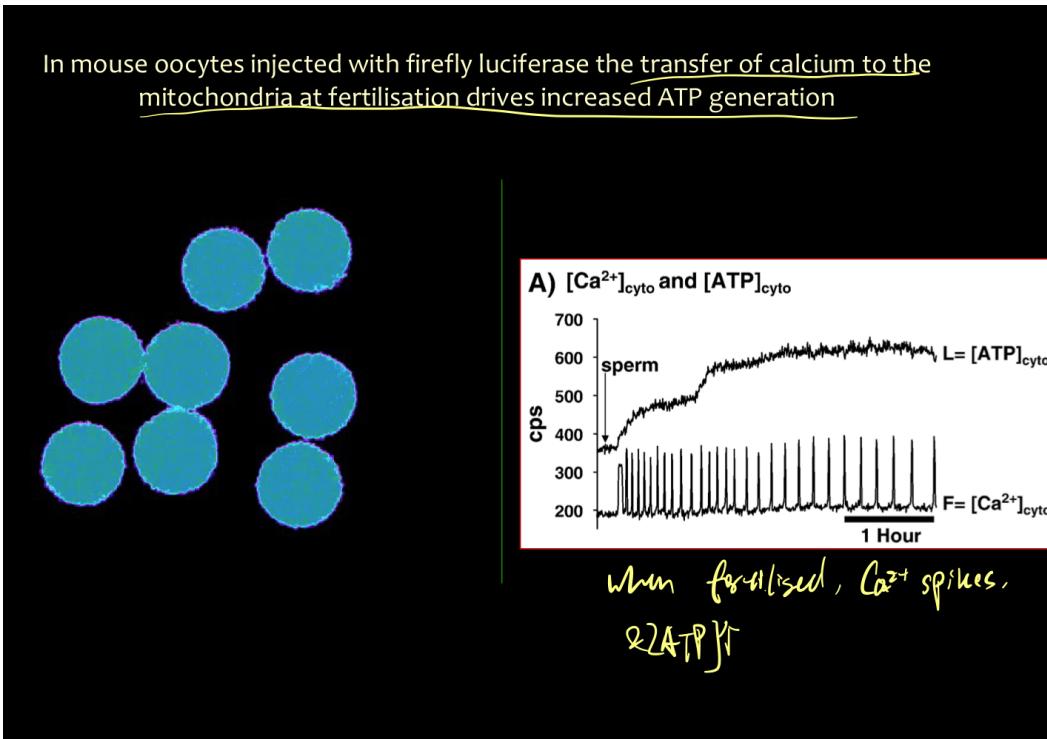
Each calcium signal promotes a more reduced state of NADH or FADH₂ (shown here) as the TCA cycle is stimulated.

- Ca²⁺ can upregulate ATP synthesis
 - The chemical luminescence by **luciferase** is proportional to **ATP level**
 - The increased Ca²⁺ level increased luciferin luminescence (ATP production)

Firefly luciferase is used to measure ATP – luminescence is ATP dependent.



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- Conclusion: Changes in work that require ATP are usually associated with a rise in Ca²⁺; the **transmission of calcium into MT matches energy supply with demand**
- Ca²⁺ in MT usually is kept low; Ca²⁺ can be removed by Na⁺/Ca²⁺ exchanger (**NCLX**)
- Ca²⁺ is transported into MT matrix via uniporter — protein complex
 - MCU: inner membrane transmembrane protein: probably forming tetrameric channels
 - MICU1 & MICU2: sensitive to Ca²⁺; regulate the opening / closure of the channel
 - EMRE: scaffolding
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