Aging and metabolism in cardiovascular toxicities due to cancer therapies

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October 18, 2021

Overarching hypothesis

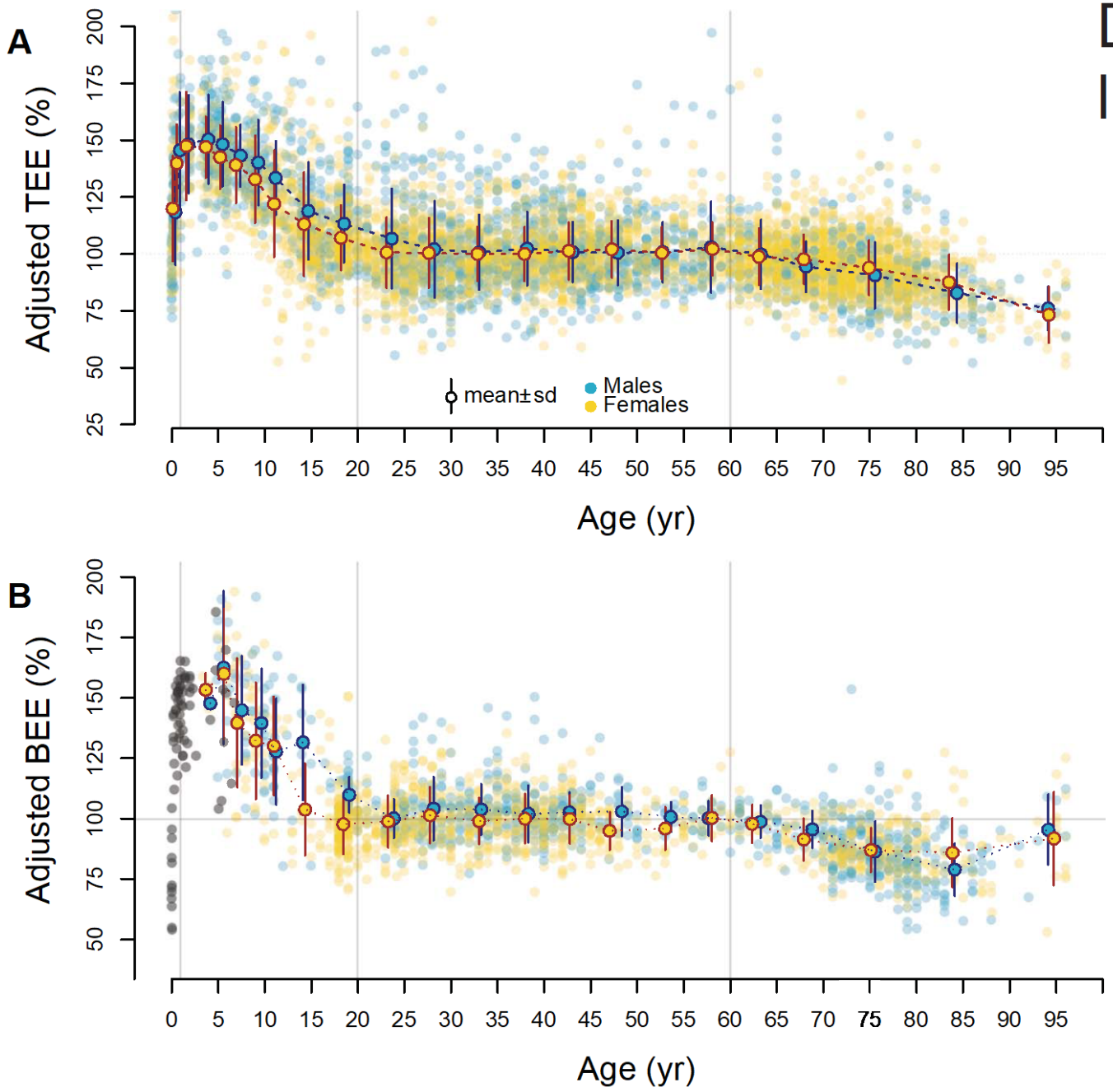
- Aging is characterized by a progressive decline in mitochondrial capacity across most tissues, including the heart and vasculature.

- Numerous cytotoxic and targeted cancer therapies induce mitochondrial injury

- Mitochondrial toxicity may represent a specific vulnerability to adverse cardiovascular effects from cancer therapies for aging patients.

METABOLISM

Daily energy expenditure through the human life course



Total Energy Expenditure (TEE)
Double isotope labeled water measurements
4 distinct age groups

n = 6421 subjects (64% female) from 29 countries
8 days – 95 years old

Basal Energy Expenditure (BEE)
Indirect calorimetry (n=2008)
4 distinct age groups

Pontzer et al. Science 373, 808-812 (2021)

CellPress

The Mitochondrial Basis of Aging

Molecular Cell
Review

Nuo Sun,[1] Richard J. Youle,[2,*] and Toren Finkel[1,*]
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[2]Biochemistry Section, Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke, NIH, Bethesda, MD 20892, USA
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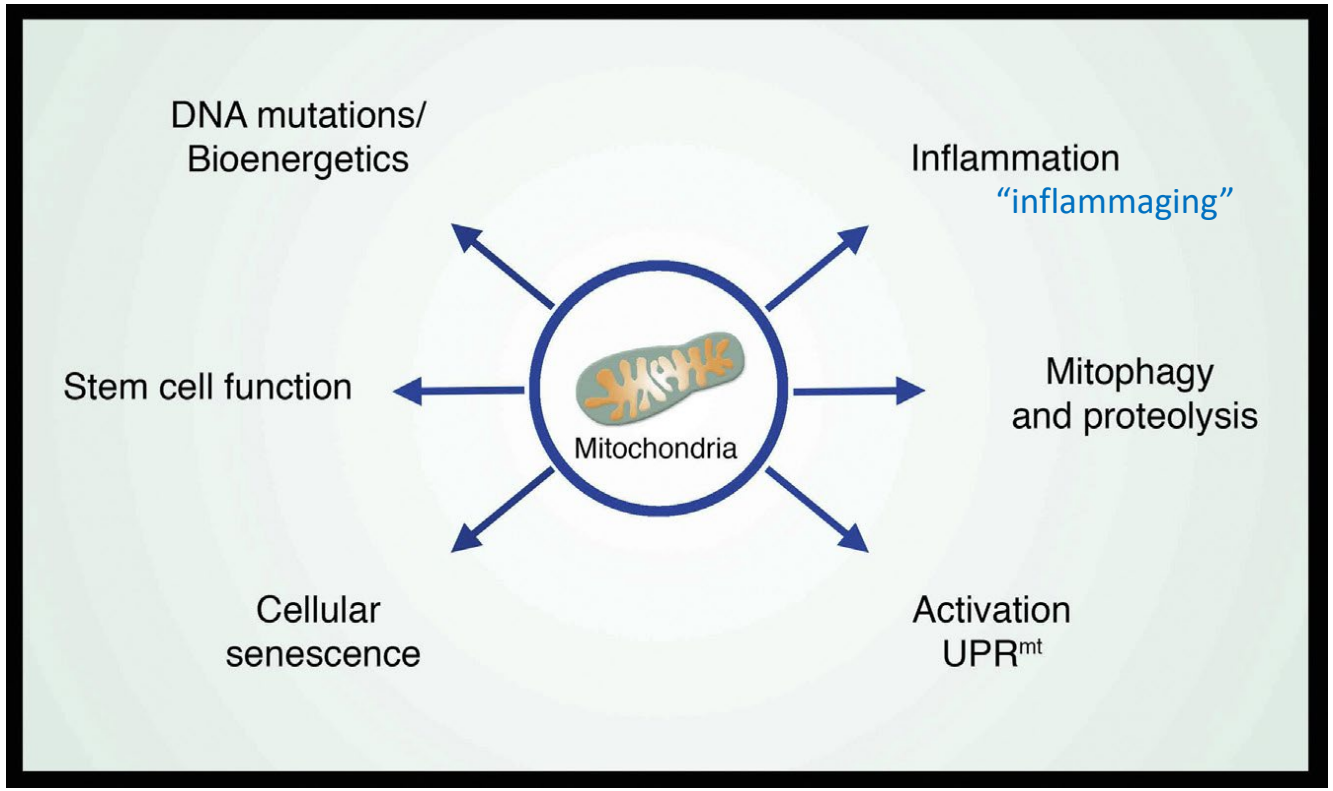
http://dx.doi.org/10.1016/j.molcel.2016.01.028



Hypothesis: Declines in multiple aspects of mitochondrial function, mediated by mitochondrial DNA mutations and impaired clearance of defective mitochondria, constitute a major basis of aging.

REVIEW SERIES: MITOCHONDRIAL DYSFUNCTION IN DISEASE
Series Editor: Michael Sack

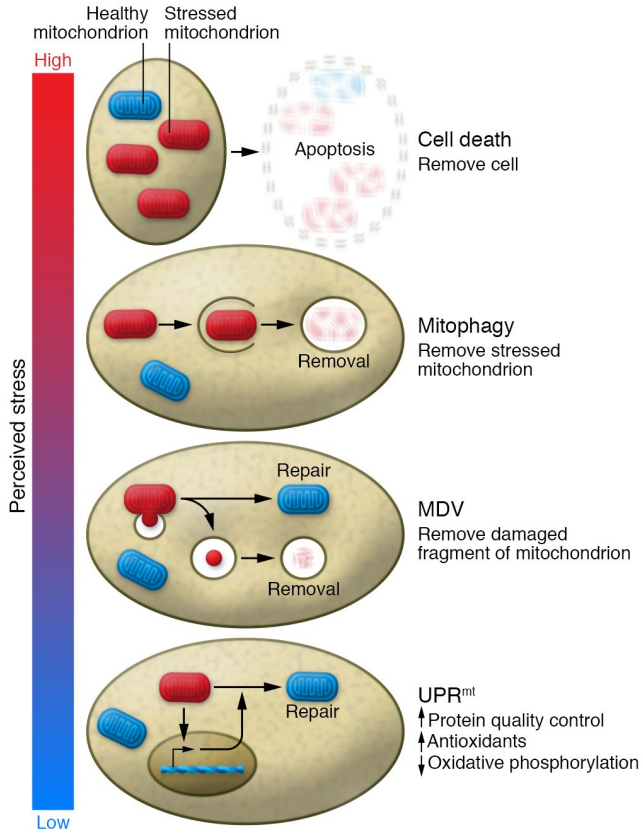
The Journal of Clinical Investigation

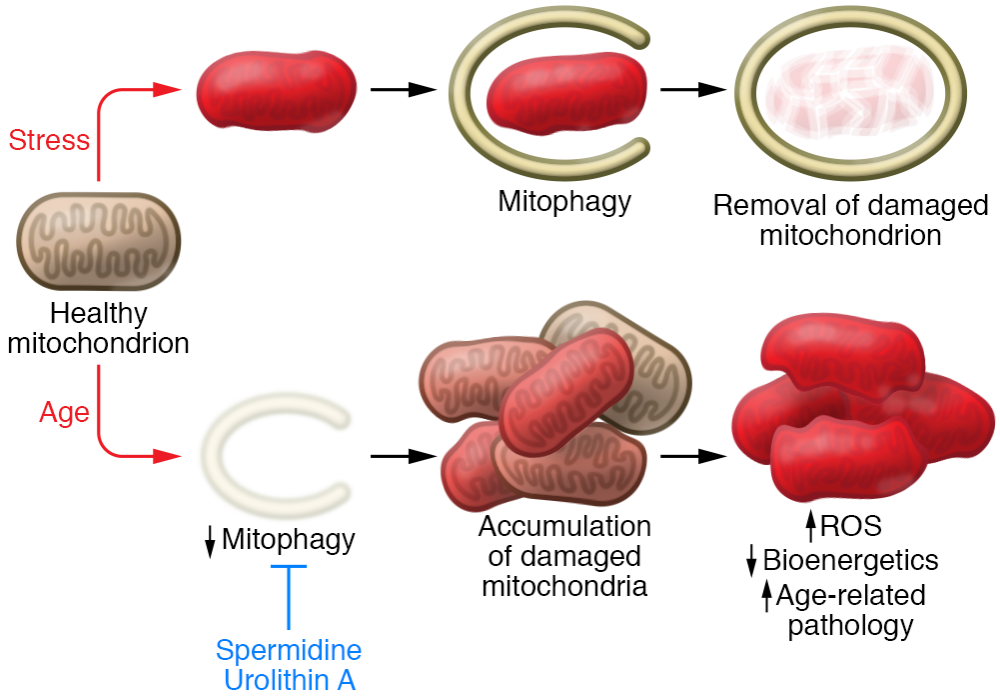
The role of mitochondria in aging

Ji Yong Jang,[1] Arnon Blum,[2] Jie Liu,[1] and Toren Finkel[1]

jci.org Volume 128 Number 9 September 2018

[1]Aging Institute, University of Pittsburgh and University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA. [2]Baruch Padeh Medical Center, Bar-Ilan University, Ramat Gan, Israel.





Aging impairs both mitochondrial quality and the systems for removal of damaged mitochondria (chiefly mitophagy)

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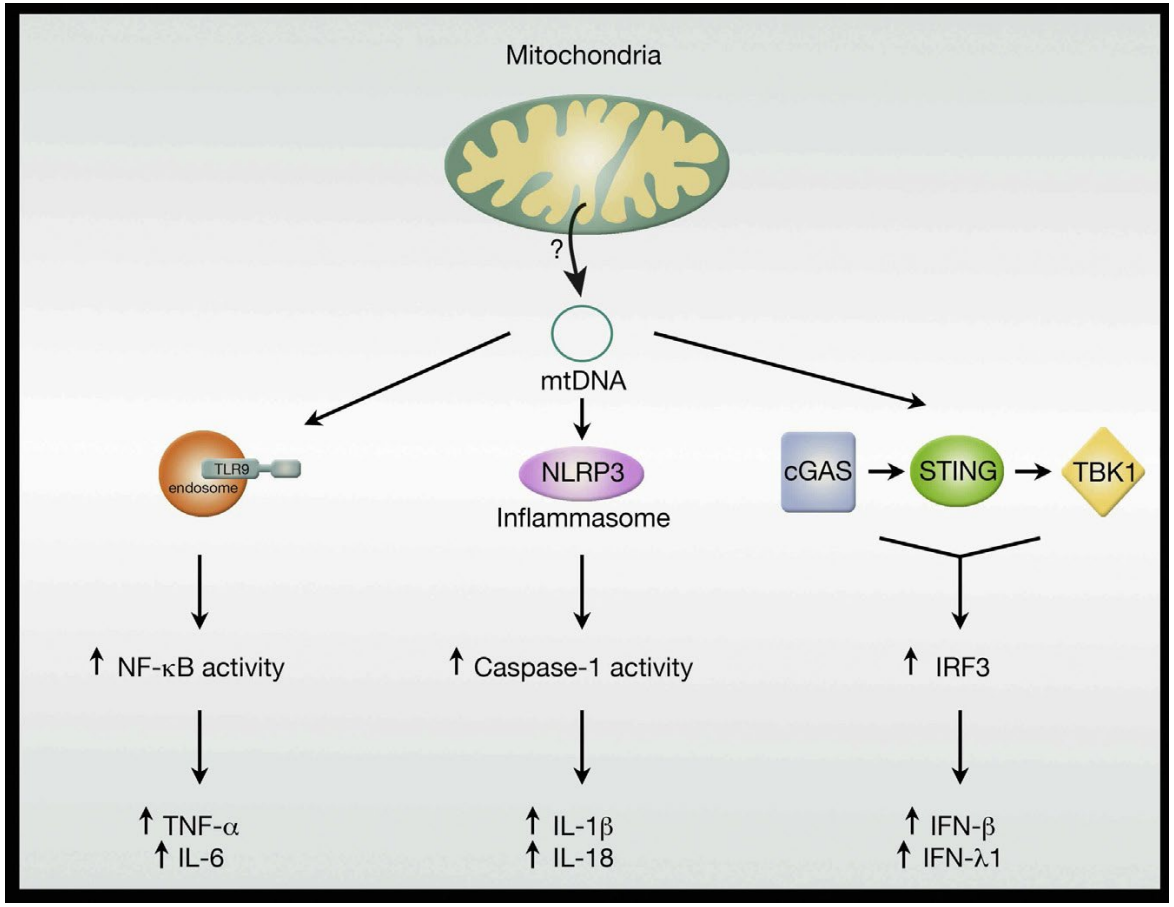

The Journal of Clinical Investigation

The role of mitochondria in aging

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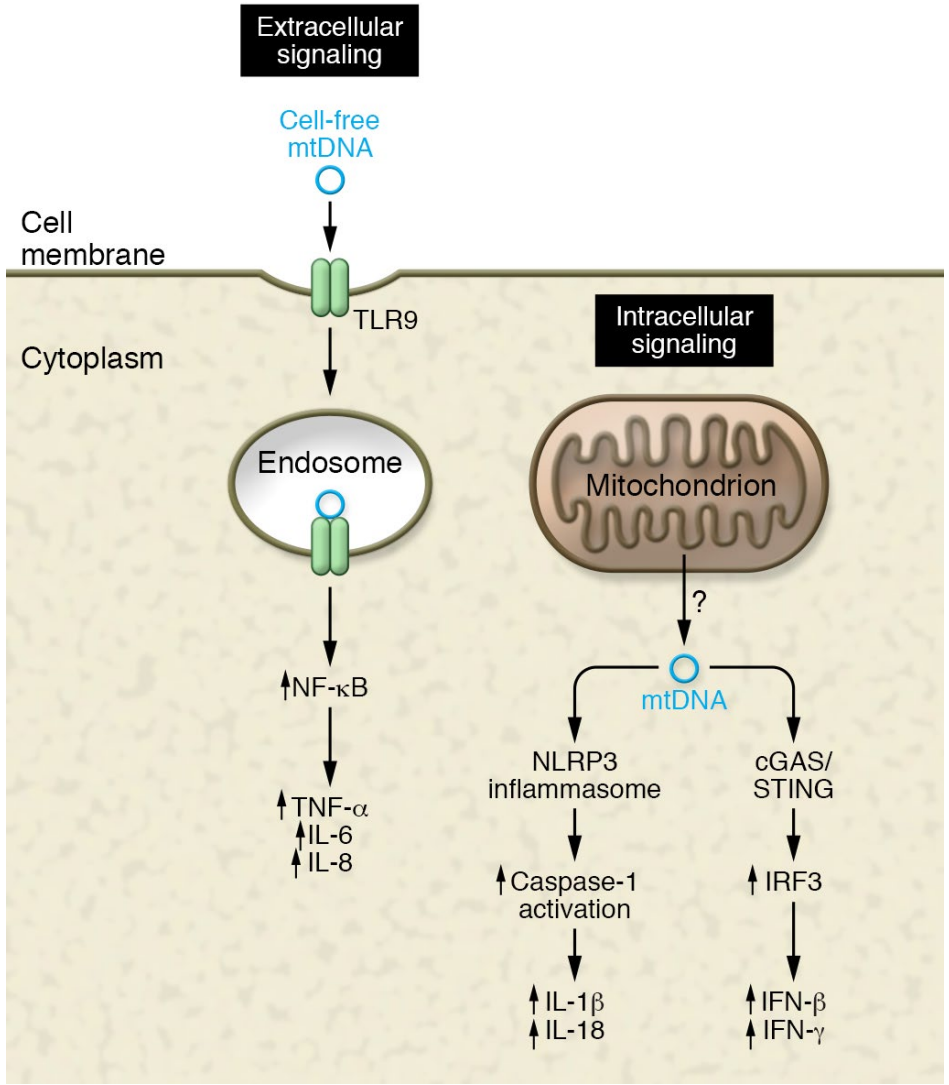
JCI

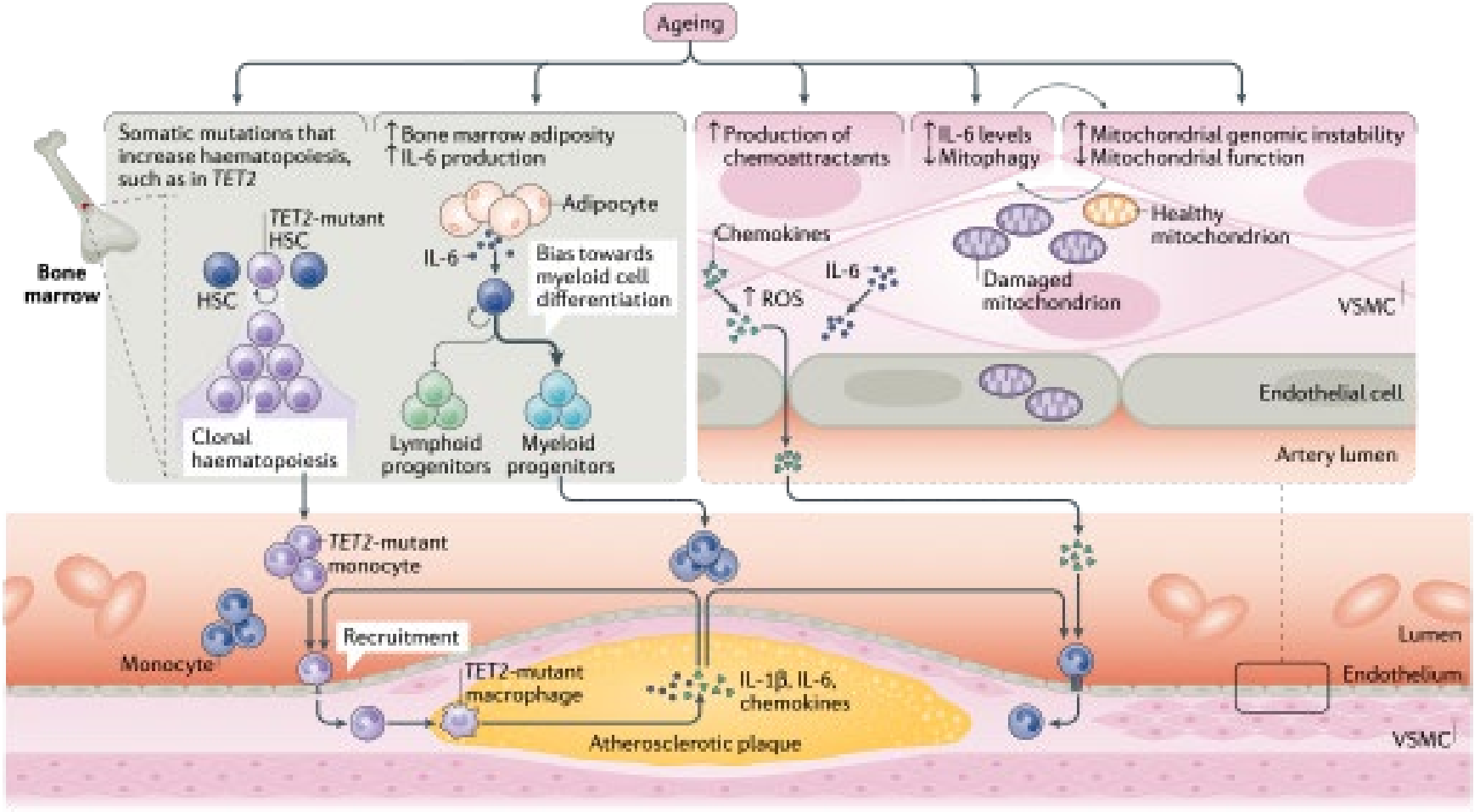
[1]Aging Institute, University of Pittsburgh and University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA. [2]Baruch Padeh Medical Center, Bar-Ilan University, Ramat Gan, Israel.

Conflict of interest: The authors have declared that no conflict of interest exists.
Reference information: *J Clin Invest*. 2018;128(9):3662–3670.
https://doi.org/10.1172/JCI120843



Persistent mitochondrial injury leads to release of mitochondrial DNA (mtDNA) that activates inflammatory signaling pathways (serving as a Damage Associated Molecular Pattern—DAMP)

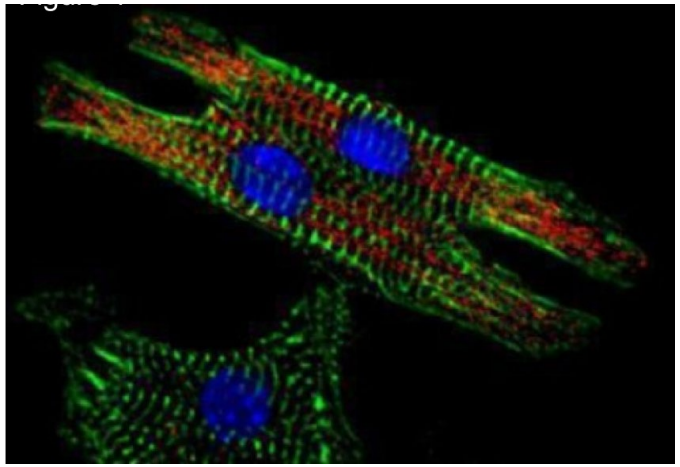
“Inflammaging” induced by mitochondrial defects contributes to atherosclerosis in aging

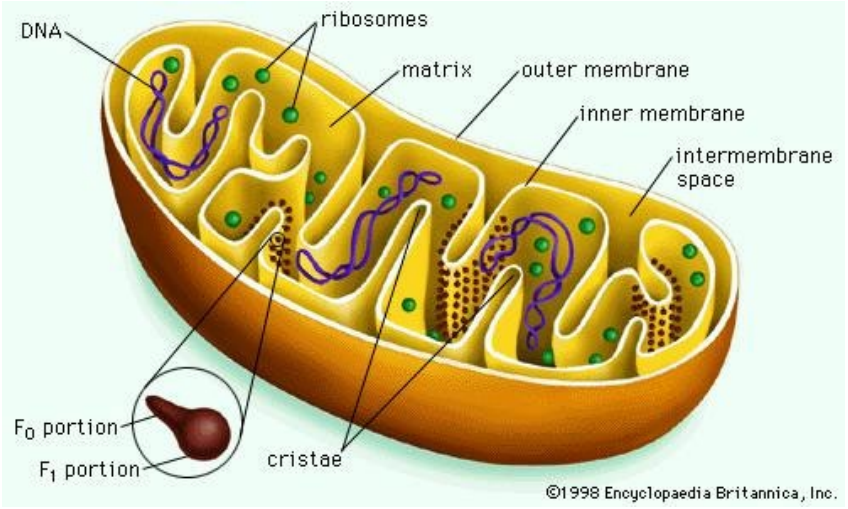


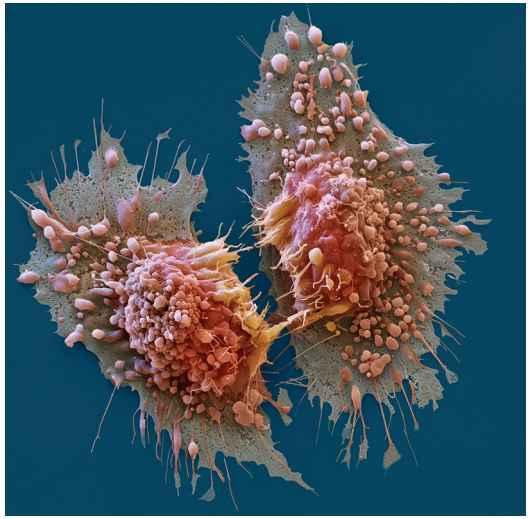
Nat Rev Cardiol Jan 2021, Vol 18

The heart is highly reliant on optimal mitochondrial function

- Mitochondria constitute roughly 1/3 of cardiomyocytes by volume
- The heart consumes 6 kg of ATP per day, the highest energy requirement for any organ
- Cardiomyocytes rely on fatty acid oxidation to fuel oxidative phosphorylation; cancer cells are more flexible metabolically
- Aging compromises the metabolic resilience of the heart







The high energy requirement and limited metabolic repertoire in cardiomyocytes may represent a specific vulnerability for cancer therapy cardiotoxicity

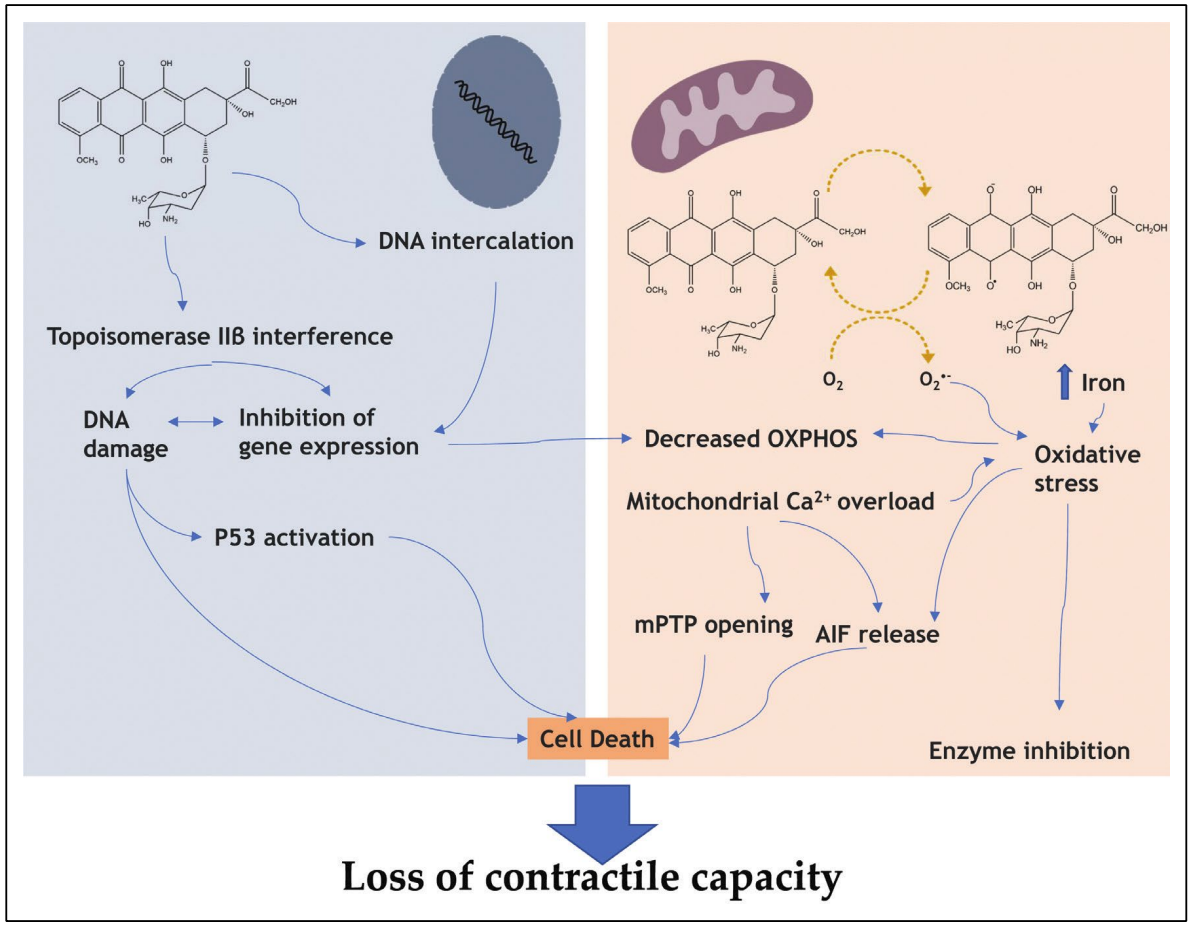
Circulation Research

REVIEW

Mitochondrial Determinants of Doxorubicin-Induced Cardiomyopathy

Kendall B. Wallace, Vilma A. Sardão, Paulo J. Oliveira

Circulation Research. 2020;126:926–941.



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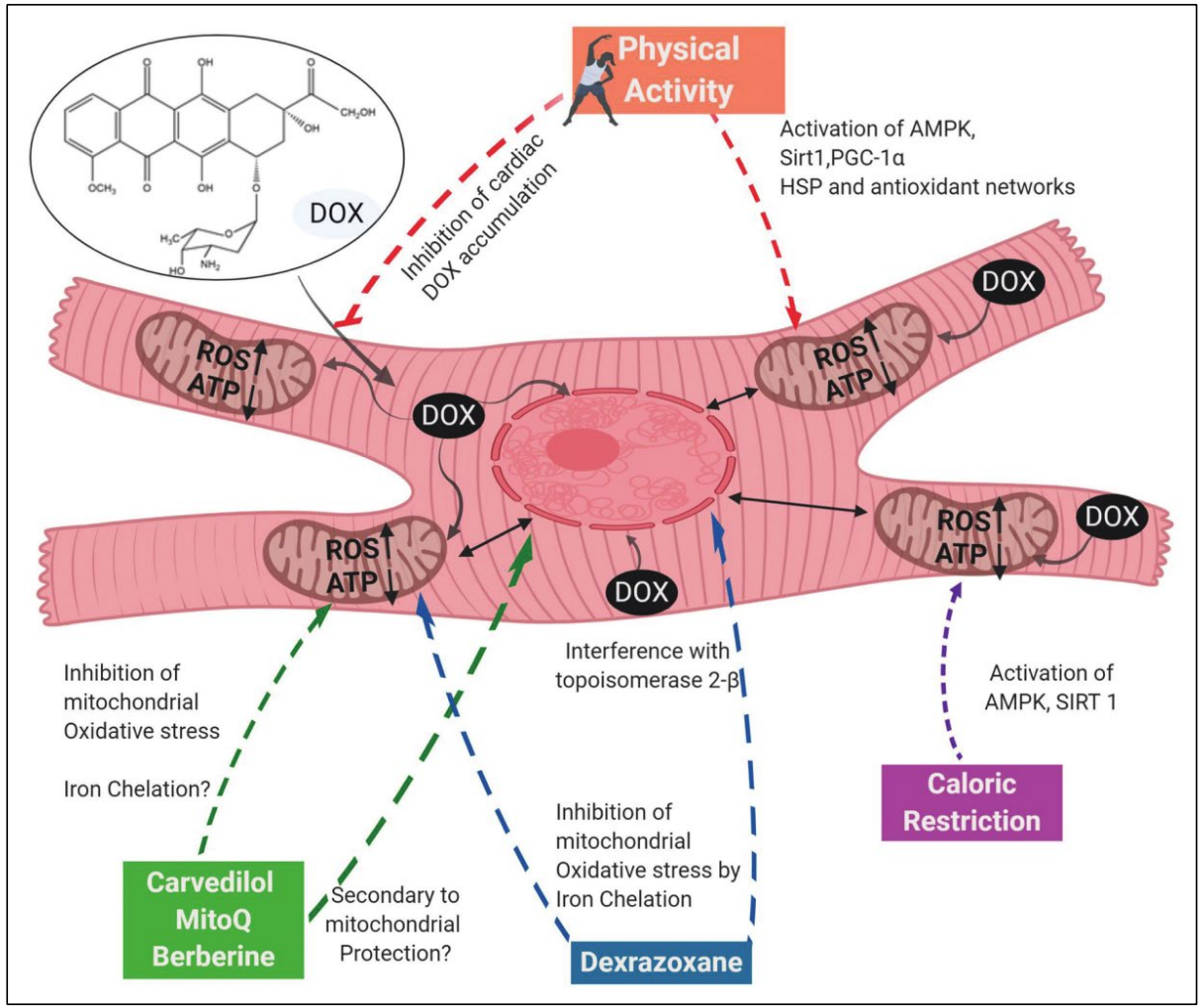
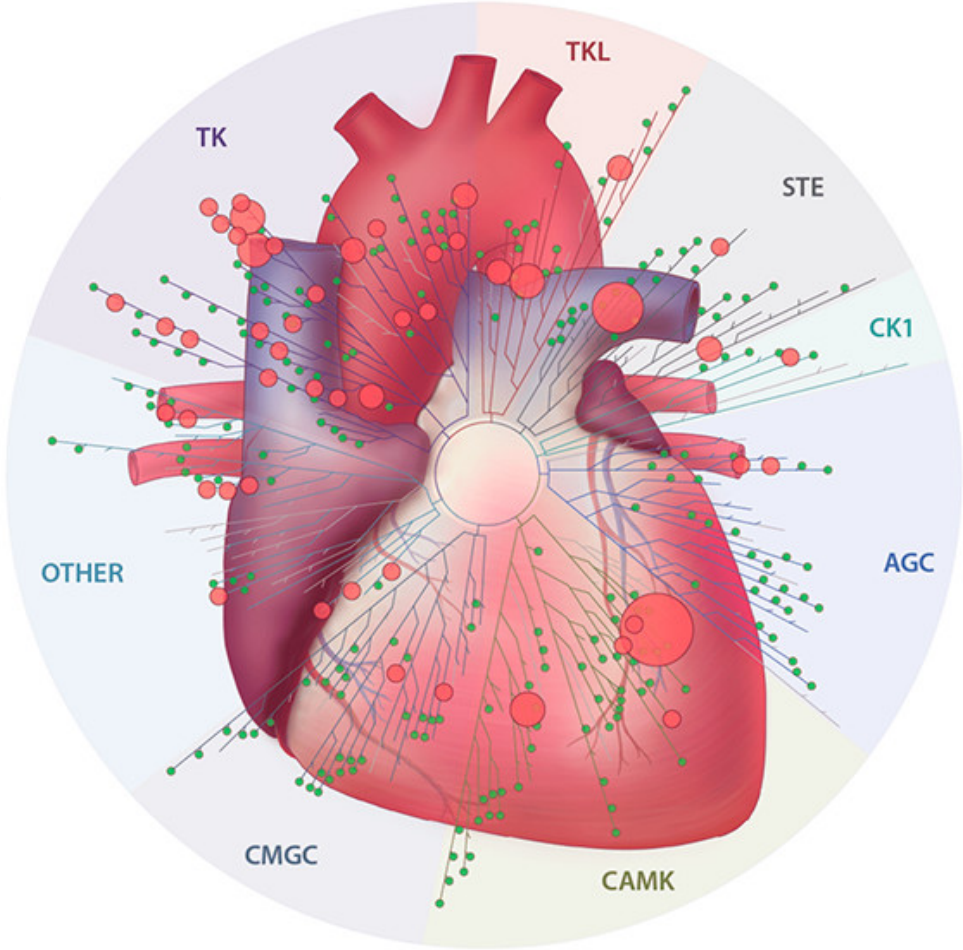


Other antineoplastic agents with mitochondrial (and cardiovascular) toxicities

Kinase Inhibitors
Bevacizumab
Dasatinib
Imatinib
Lenvatinib
Regorafinib
Sorafenib
Sunitinib
Trametinib



Others
Cisplatin
Trastuzumab
Mitoxantrone
Imatinib

DOI: (10.1021/acs.chemrestox.9b00387)

Challenges and Opportunities

- Preclinical assessment for cardiovascular toxicities should include mitochondrial profiling

- Therapeutic strategies for cancer therapy associated toxicity should incorporate mitochondrial protection

THANKS!

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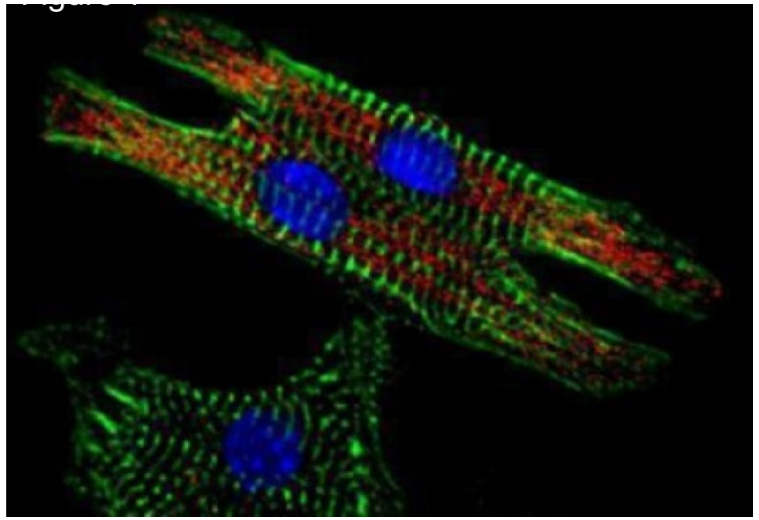
Contrasting cardiomyocytes and cancer

Cardiomyocytes

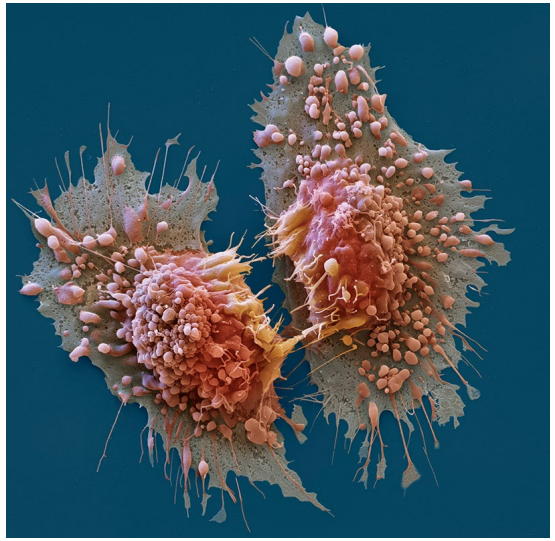


Terminally differentiated

Very limited regeneration

Energy derived from fatty acids

Cancer cells



Undifferentiated

Nearly limitless replication

Energy derived from glucose and glutamine

The differences between cardiomyocytes and cancer cells suggest the possibility that we could develop truly targeted and “cardiosafe” cancer drugs.