Aging and metabolism in cardiovascular toxicities due to cancer therapies

Brian C. Jensen MD
University of North Carolina School of Medicine
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.
n = 6421 subjects (64% female) from 29 countries
8 days – 95 years old

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

Basal Energy Expenditure (BEE)
Indirect calorimetry (n=2008)
4 distinct age groups
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.
Aging impairs both mitochondrial quality and the systems for removal of damaged mitochondria (chiefly mitophagy).
The Mitochondrial Basis of Aging

Nuo Sun,1 Richard J. Youle,⁄2 and Toren Finkel1,⁄2

1Center for Molecular Medicine, National Heart, Lung and Blood Institute, NIH, Bethesda, MD 20892, USA
2Biochemistry Section, Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke, NIH, Bethesda, MD 20892, USA

*Correspondence: richard.youle@nih.gov (R.J.Y), finkel@nih.gov (T.F.)
http://dx.doi.org/10.1016/j.molcel.2016.01.028
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.
Mitochondrial Determinants of Doxorubicin-Induced Cardiomyopathy

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

Circulation Research, 2020;126:926–941.

Loss of contractile capacity
Mitochondrial Determinants of Doxorubicin-Induced Cardiomyopathy

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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!

bcjensen@med.unc.edu
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.