A Proteomics Study on Cardiac Ischemia: Understanding the Age Related Mitochondrial Dysfunction in the Subsarcolemmal and Interfibrillar Mitochondrial Subpopulations

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Abstract

Mitochondrial dysfunction is the hallmark of numerous diseases including cardiac ischemia, Alzheimer's disease, Parkinson's disease, liver disease, cancer, diabetes, and Lou Gehrig's disease. This is primarily due to the aging defects caused by the mitochondria and the production of Reactive Oxygen Species (ROS). Currently, there is limited research analyzing the whole mitochondrion to demonstrate differences in older and younger patients. The objective of this review is to analyze collected mitochondrial proteomic data to detect the proteomic divergence within the aged heart relative to the younger heart. Specifically, understanding the key differences between the Subsarcolemmal mitochondria (SSM) and the interfibrillar mitochondria (IFM) was investigated. This review focused on proteomic data achieved from the mouse model using LC-MS/MS data. Proteomics satisfies this exigence by enabling accurate, system-wide quantitative analysis of protein supply. In addition, cutting-edge proteomics methods reveal how proteins perform their functions in convoluted interaction networks where minute alterations that occur can be detected from early pathological states. The proteomic differences in the SSM and IFM reveal evidence for decreases in the rate of oxidative phosphorylation and inactivity in the AMPK pathways which reduces the yield of ATP molecules. Metformin treatment was seen to increase ATP yield making it a potential mitigator of cardiac injury. A further genetic experiment could be conducted to trace genes that might be unexpressed or overexpressed in the mitochondrial genome. Reversing the effects of mitochondrial aging can increase lifespans and decrease the likelihood of diseases to occur at old age.

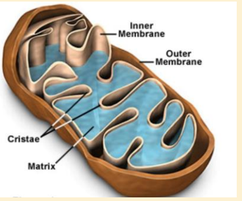
Introduction

There is a rising worry for the field of medicine that treating symptoms over the root cause of a complication will never provide potent cures for diseases

Aging is the hallmark characteristic that causes bodily issues. Reversing the biochemistry of aging can prevent convoluted medical problems

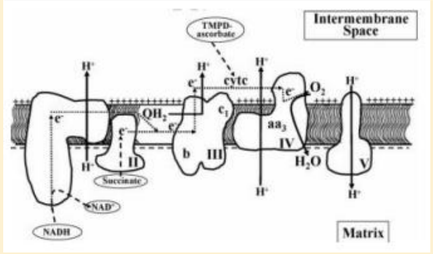
Various Theories have been created (i.e. Wear and Tear, Programmed Death, Telomeres, and Mitochondria)

Mitochondrial Free Radical Theory of Aging has the most evidence and literature to support it. In addition, mitochondrial aging has been seen in the skin, retina, and myelin sheath



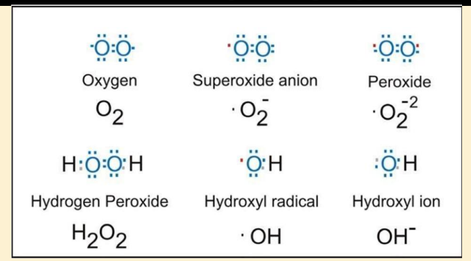
The mitochondrion is a double membrane- bound organelle where the outer membrane encapsulates the inner membrane sheltering the matrix region. The outer membrane is lined with protein channels called porins to allow integral proteins to enter the mitochondria through facilitated diffusion. The inner membrane contains the electron transport chains (ETC) and invaginates into the matrix as cristae to increase the surface area for the ETC to conceive the maximum amount of energy molecules possible.

Mitochondrial Free Radical Theory of Aging & Cardiac ischemia

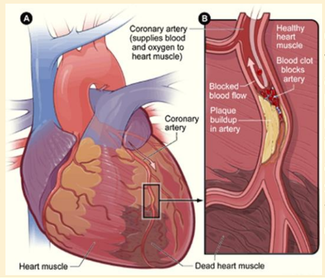


The ETC depends on two main electron carriers: FADH2 and NADH. When NADH is oxidized to release electrons that fuel the ETC, the following reaction occurs:
NAD⟶NAD+ + H+ + 2e-

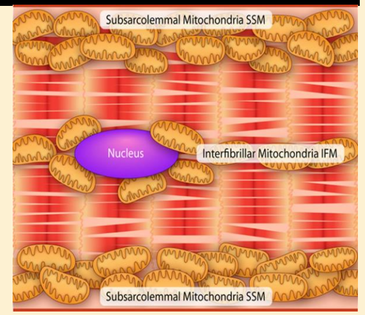
As the 2e- travels down the ETC proteins, they release energy used to pump protons across the cristae. The protons then travel down ATP synthase to fuel the formation of ATP molecules. After the electrons have reached Complex IV, they are reduced to form molecular oxygen, in a reaction that ultimately forms the byproduct of cellular respiration, water.
2e- +H+ +1.5O2 ⟶H2O



Sporadically, oxygen does not reduce completely producing toxic oxygen molecules that cause a multitude of issues such as oxidative stress, mitophagy, cell death, and cell damage.

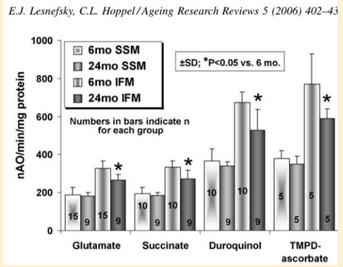


Cardiac Ischemia occurs when fatty plaque clogs arteries and stops normal blood flow leading to heart muscle death. To fix the issue, stenting procedures are carried out and the sudden resume of blood flow causes reperfusion damage to nearby tissue

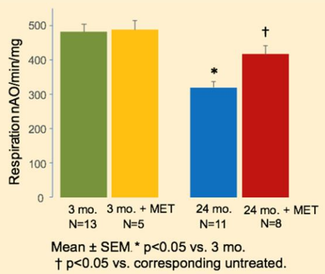


The heart muscle uniquely houses two distinct subpopulations of mitochondria known as the subsarcolemmal mitochondria (SSM) and the Interfibrillar mitochondria (IFM). They both differ in their biochemical properties and relative location. Studies analyzing how both subpopulations react with age and cardiac ischemia will be the primary lens in this review.

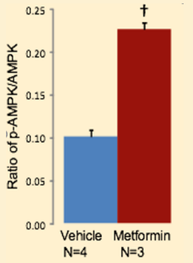
Results & Data Analysis



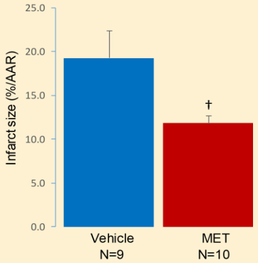
Age related decrease in oxidative phosphorylation was present in the IFM and not the SSM. Therefore, the IFM mitochondria yield much less ATP molecules than the SSM through age.



Metformin, a common drug for diabetes improved respiration rates in the aged mice. Therefore, metformin could be a potential protein drug that could mitigate the effects of age related OXPHOS damage.



Metformin treatment increased AMPK pathways which are crucial for harnessing ATP molecules



Metformin decreased cardiac injury in the aged mice from cardiac ischemia and reperfusion. The heart muscle was relatively similar to the younger mouse heart despite being form a 24 month mouse.

Implications

ENZYMATIC STUDY-ANALYZE REACTION RATES OF EACH PROTEIN OF THE MITOCHONDRIA-SSM & IFM

GENETIC STUDY-ANALYSIS OF GENES RESPONSIBLE FOR PROTEINS

GENETIC ENGINEERING-CHANGE PROTEOMIC CONCENTRATIONS EARLY TO AVOID PROBLEM

REVERSAL OF INTERVAL CLOCK

Conclusion

There are significant differences in how the SSM and IFM mitochondrial subpopulations react to cardiac ischemia and age related changes. The IFM mitochondria are less resistant to damage through age than the SSM. In addition, metformin treatment proved to mitigate the damage of the IFM mitochondria and reduce cardiac injury through age. Metformin treatment also yields more ATP molecules in the aged mouse than aged mice without metformin treatment. Future experiments analyzing the whole proteomic structure of the mitochondria would be extremely beneficial in tracing the exact age-related disparity between the SSM and IFM. Then, results could show concentration increases and decreases through age which could them be adjusted through drugs to increase longevity and prevent painful deaths.

Acknowledgements

- I would like to sincerely thank Dr. Edward Lesnefsky and Dr. Qun Chen for their mentorship and guidance throughout my research process. I appreciate their willingness to provide me proteomic data that I could analyze for my review
- I would like to thank Dr. Michelle Whitehurst-Cook for being the program sponsor and helping me realize I can be an actor and a doctor at the same time ☺
- I truly appreciate the help the MSIP Co-Directors Yumna Rahman, Polina Bukina, and Martina Abuphilipous provided in editing my work