

4th International Conference on Clinical & Experimental Cardiology

April 14-16, 2014 Hilton San Antonio Airport, TX, USA

Four electron leak pathways of mitochondrial respiratory chain and their physiological functions

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It was proved in our lab that the ATP production in mitochondria by the way of electron transfer of respiratory chain is always combined with the generation of O_2^- and H_2O_2 through the electron leak pathways. There are four electron leak pathways in the mitochondrial respiratory chain. Two of the cytochrome c mediated pathways play as a protective role by the way of down regulating the level of O_2^- and H_2O_2 in mitochondria. The third pathway is $O_2^- + H^+ \rightarrow HOO$. It is a way in somehow related to maintain body temperature because the reaction of HOO with the double allyl hydrogen atom of the unsaturated fatty acid is a heat producing reaction. How the third pathway related with obesity is unknown. The fourth pathway is $O_2^- + NO \rightarrow ONOO^-$. The $ONOO^-$ could pass through the membrane when it combines with H^+ . Therefore the fourth pathway could make O_2^- and NO transportation long-distance pass through membranes. The physiological roles of the four electron leak pathways are not well known yet but the level of electron leakage is always higher when animal in pathological condition or diseases and aging. The H_2O_2 as a product of electron leakage of respiratory chain may be more pathological significance as it has longer life-span to spread across membranes and it can be changed to more dangerous HO when in the presence of iron.

- 1. Evidence for the pathological significance of electron leakage of respiratory chain:** A weak inhibitor (3-nitro-N-methyl amine) of complex I and II could decrease the electron leak of respiratory chain and also decrease the damage of ischemia reperfusion. This result proved that the explosive generation of ROS by the electron leakage of respiratory chain plays a key role in the damage of ischemia reperfusion. A strong radical scavenger (Salvianic acid A) decreases the generation of ROS in mitochondria and also protect the MPP⁺- induced damage in SH-SY5Y cells. This result indicates the pathological role of electron leakage of respiratory chain in disease.
- 2. The mitochondrial ROS play an important role in health and longevity:** The ROS generated in the electron leak pathways of respiratory chain can be a dangerous factor causing oxidative damager and aging, but more important is that the ROS in mitochondria play as the signals to stimulate anti-oxidative function and the ability of damage repairing. The later is the theoretical base of human health and longevity. Pay attention to the physiological role of different pathways of respiratory chain is a new field of bioenergetics.
- 3. The physiological role of O_2^- and NO in mitochondria:** The fourth pathway of $O_2^- + NO \rightarrow ONOO^-$ indicates that the balance between O_2^- and NO in mitochondria has an important role in controlling the rate of ATP production in different physiological conditions. It is well known that the NO can be bind to the oxygen reactive center of complex IV to reduce ATP production of mitochondria. Whereas the O_2^- can release the bond NO to increase the ATP production of mitochondria. The ratio of O_2^- and NO in mitochondria is an important factor to regulate ATP production of mitochondria.
- 4. The role of O_2^- in the functional migration of cytochrome c:** The functional role of cytochrome c is depending on its location in the mitochondria. It is producing ATP in the respiratory chain. It is a scavenger to dispose of O_2^- and H_2O_2 in the space of mitochondrial membranes. It is a factor to stimulate cell apoptosis in cytosol out of mitochondria. A functional migration of cytochrome c during the life span of cell is performed following aging. The O_2^- generated in the electron leakage of respiratory chain plays a key role in driving cytochrome c migrating.
- 5. Clinical use of coenzyme Q in cardiology diseases:** A side effect of oral coenzyme Q is lead to stomach uncomfortable. To overcome this side effect a combined use of coenzyme Q with antioxidant was suggested based on the electron leakage of mitochondrial respiratory chain. A mixture of coenzyme Q with vitamin E and selenium is good for health and longevity according to the leaked electrons can fall in different locations of mitochondria.

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