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Ideas in Scientific Research on Human Health and Heart Care Raised from the Electron Leak Pathways of Mitochondrial Respiratory Chain

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Abstract

Respiratory chain is a group of redox enzymes located in the inner membrane of mitochondria. Mitochondria are the cellular "power house" to produce ATP through the way of electron transfer of the respiratory chain. In our lab, it is established that the production of ATP is always combined with the ROS (Reactive Oxygen Species) generation through the electron leak pathways. The confirmation of electron leak pathways of respiratory chain reveals that the efficiency of ATP production in mitochondria is strongly affected by the electron leakage of the respiratory chain-the more the electrons leaked the less the ATP produced. How the electron leak pathways related to aging and age-related degenerative disease is a new investigative field of health and longevity. As the substrates of the respiratory chain (O₂ and nutrients) are delivered by heart pumping, the respiratory chain can be considered as the molecular hearts or a life-engine, the human body can be considered as an aggregate of huge numbers of molecular hearts or life-engines. With this in mind some ideas about human health and heart care are presented here for discussion.

Keywords: Respiratory chain; Molecular heart; Life-engine; Dissipative structure; Health; Longevity

Introduction

Four electron leak pathways of mitochondrial respiratory chain established in our laboratory

Ten years ago, we reported the experimental result showing that the ATP production in mitochondria through electron transfer of the respiratory chain is always combined with the generation of O_2^{-} and H_2O_2 in two electron leak pathways mediated by the cytochrome C [1-3]. Based on the involvement of the metabolic route of

 $O_2 \rightarrow O_2 \rightarrow H_2O_2 \rightarrow H_2O$ in the two electron leak pathways, a radical metabolism of O_2 in mitochondria was defined by four electron leak pathways shown as in the red part of the (Figure 1) [4].

Two of the cytochrome c mediated pathways of \mathbb{O} and ② we reported in 2003 of JBC, play a role of reducing the level of O_2^{-1} and H_2O_2 in mitochondria [1]. The pathway of $(O2-. + H+ \rightarrow HOO)$ is introduced based on the report of Bielski (J. Biol. Chem. 258: 4759-4761,1983). It is reported that the reaction of HOO• with the double allyl hydrogen atom of the unsaturated fatty acid is a heat release reaction (10 kcal/mol). Therefore, this pathway is probably in some way related to maintaining the body temperature. The pathway of $(O_2)^{-1}$ + NO>ONOO) is probably in some way related to maintaining the body temperature. The pathway of $(O_2^- + NO \rightarrow ONOO^-)$ is introduced based on the NO generation in mitochondria. The ONOO could pass through the membrane when it combines with H+, but we do not know if the cross-membrane long distance move has happened or what is the physiological role it plays. The H₂O₂ as a product of electron leakage of the respiratory chain has more pathological significance as H₂O₂ has a longer life-span and can be spread across membranes. Animal models show that the level of the electron leakage of the mitochondrial respiratory chain is always higher when animal in pathological condition [5-9].

The finding of electron leak pathways of the respiratory chain reveals that the mitochondrial oxygen consumption is divided into two parts: Consistent with Mitchell's theory the oxygen consumed in ATP production is KCN-inhibitory, while the oxygen consumed in the ROS generation is KCN-insensible and represents part of the electron leakage.



Figure 1: The dark cycles are the enzymes involved in ATP synthesis of mitochondria. Green color arrows show the way of electron transfer in the respiratory chain. Yellow color shows the Mitchell's theory on the coupling mechanism of respiratory chain and ATPase. The red colored part shows the four electron leak pathways established in our lab. As the involvement of reductive route($O_2 \rightarrow O_2^{-} \rightarrow H_2O_2 \rightarrow H_2O$), the electron leakage is defined as the radical metabolism partner to ATP production. Oxygen consumed in the electron leakage is not used in ATP production but spent in the generation of reactive oxygen species (ROS) such as O_2^{-} H_2O_2 HO-and ONOO-.

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The pathological significance of electron leakage of mitochondrial respiratory chain

It is obvious that the ATP production in mitochondria through the electron transfer of the respiratory chain is KCN inhibitory, whereas the generation of O_2^{-} and H_2O_2 through the electron leak pathways is KCN insensible. Then the KCN sensitivity can be a signature to report the level of the electron leakage of the respiratory chain. With this in mind, some animal models were examined and findings indicate that the level of the electron leakage of the mitochondrial respiratory chain is always higher when the animal is in a pathological condition as shown in the following figures (Figures 2-6).

The damaging effect of ROS is well established as the reason for causing aging and diseases. The following observations give the idea of how protecting ROS damage by controlling the electron leak pathways of the respiratory chain. The synthesized compound (3-nitro-N-methyl amine) has proven to be a weak inhibitor (less than half inhibition) of complex I and II by decreasing the electron transfer rate. The protective effect of 3-nitro-N-methyl amine on the ischemia reperfusion observed in animal model indicates that the explosive generation of ROS from the electron leak of the respiratory chain plays a key role in reperfusion damage [8]. The neuron toxic MPTP causes more electron leak of complex I. A strong



Figure 2: Injection T_s with 0.5 mg/g per day to five groups of mouse and each group have 5 mice and killed after injection. Mix 5 livers and prepare mitochondria to test the state 4 respiration in different concentration of KCN. Result shows that the KCN sensitivity is decreased with increasing T_s injected. $\circ-\circ$: one day injection; x-x: two days injection; $\blacktriangle-\bigstar$: five days injection; $\leftarrow\bullet$: control (no injection).



Figure 3: The KCN sensitivity is lower in the tumor growing mouse. 5 mice are injected with H22 and the liver mitochondria prepared after 8 days growing of ascites tumor. $\circ - \circ :$ injected group ; $\bullet - \bullet :$ control group.



Figure 4: The cyanide insensitive respiration of mouse liver mitochondria is increasing monthly from 1-5 months growing. Older than 5 months mouse the cyanide insensitive respiration keep in high level and the RCR ratio decrease can be observed after 9 months growing. (P< 0.05).



Figure 5 : A group of female mice injected with oxytocin. The cyanide resistant respiration of liver mitochondria was measured at, 2, 4 and 6 hours after the injection (each measurement take 5 mouse liver). Result shows that the KCN-insensitive respiration is remarkably higher than control at 1 hour after injection, and it is decreased hour by hour, after 6 hours it turn back to normal.



mediated by cytochrome c proved in our lab. It suggests the appearance of the detoxify event in the early stage of oxygen. The highly evolved respiratory chain, shown in (3), has a big change in the direction of the electron transfer in complex II. The experimental evidence is performed in the purified complex II [10]. The normal electron transfer of complex II is from succinate to cytochrome b_{560} ; once the oxygen in the reaction medium is replaced by argon, the electron transfer changed from cytochrome b_{560} to succinate.

ROS scavenger (Salvianic acid A extracted from Chinese herb) shows the protective effect on the MPTP-induced damage in SH-SY5Y cells [5-7]. This result further indicates the pathological role of the electron leakage of the respiratory chain in the neurodegenerative diseases [9,10].

Evolution of mitochondrial respiratory chain

In answering why the respiratory chain has the electron leak pathways in addition to the ATP production, we published a paper that reported the electron leak pathways were the evolutional event of life fighting against oxygen toxicity shown as in (Figure 6) [10].

It is well known that in the early stage of the earth there was no oxygen in the atmosphere. Reduced atmosphere was beneficial for the accumulation of the organic molecules, and the concentrated organic chemicals in the ocean incubated the forms of original life. The later appearance of oxygen let the original life face serious damage of oxygen toxicity. Survivors had to develop the ability to fight oxygen toxicity. The respiratory chain is the evolved event of the living organisms to defend against oxygen toxicity. The cytochrome c mediated two electron leak pathways proven in our lab reflects the early stage of detoxification [10]. Facing the strong power of oxygen toxicity, the evolved life selected the way from generation to generation to fight oxygen toxicity for survival. Then we can think of aging as the history of one generation of living body fighting oxygen toxicity and the longevity as the stronger detoxifying ability with less toxic damages. The warning is today's earth has not only oxygen toxicity, more industrial pollution makes it complicated for the research of health and longevity.

The ROS generated in the electron leak pathways of the respiratory chain can be a dangerous factor in the human body for causing oxidative damager and then leading to disease or aging, but more important is that the ROS in mitochondria plays as the signals to stimulate anti-oxidative function and strengthen the ability of repairing on the damage. The latter is the theoretical base of health and longevity. Then the physiological role of different electron leak pathways of the mitochondrial respiratory chain would be more important for the investigation of health and longevity [11].

The role of ubiquinone in heart care

Ubiquinone is the linkage of cytochrome c with complex I and II in the defence against oxygen toxicity. Both ubiquinone and cytochrome c performed key role in saving life from the disaster of oxygen toxicity in the early stage of life evolution. In this consideration, the role of ubiquinone in health care is definite [10]. \boldsymbol{Q}_{10} has been purified and used in heart care clinically in the 1960's. The problem is that a side effect on stomach appears when more dose of Q₁₀ is taken orally. The finding of electron leakage of the respiratory chain revealed that the ROS generated in the electron leak pathways is the reason for causing the side effect. The electrons leaked into the inside of the inner membrane of mitochondria let the mitochondrial DNA in higher rate of ROS risk. whereas the electrons leaked to the outside of the inter membrane let the cytochrome c in dilemma of scavenge ROS and transfer electrons [10]. In the following (Figure 7) a cocktail of Q_{10} is suggested for the clinical use. The Vitamin E as a scavenger can decrease the ROS damage on the local absorptive cells (patent: ZL 2000 00102763.8). The Selenium is necessary for the activity of GSH-px which protect mitochondrial DNA from ROS damage (patent: ZL 2009 1 0085018.5).

The Thermodynamic Principle of Health and Longevity: A Theory from the Electron Leak Pathways of **Mitochondrial Respiratory Chain**

The discovery of the electron leak pathways of the mitochondrial respiratory chain inspires us to investigate human health with a new insight of bioenergetics. Respiratory chain has been investigated as a group of redox enzyme. In view of biophysics the respiratory chain can be considered as a thermodynamic machine.

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Respiratory chain functions as the molecular life-engine

The discovery of the electron leak pathways gives the respiratory chain a new functional view as molecular life-engine. Engine is an energy converter producing driving force by burning oil. The respiratory chain as the molecular life-engine is producing ATP by burning food. The ATP production through the electron transfer of the respiratory chain can be thought of as life-engine doing the "real work". The ROS generation through the electron leak pathways can be thought of as doing the "idol work". Doing idol work is the reason for causing engine aging. The oxidative damage of ROS causes the cell disruption and body aging is similar as engine doing idol work. However, a significant difference of life-engine than non-life-engine is that the ROS generated in mitochondria also plays as the signal to stimulate the power of antioxidative function and to strengthen the ability of damage repairing. This is more important for the scientific research of health and longevity.

The vitality of human body can be thought of as an aggregate of huge amount life-engines. The normal operation of life-engines makes the human body in a healthy state. The damage of life-engine causes the human body to age and infect with diseases. Therefore we can explore the principles of health and longevity in the concept of thermodynamics.

The human body can be described as the thermodynamic dissipative structure

Entropy is the thermodynamic term to describe the orderliness; the increase of entropy means more chaotic, while the decrease of entropy means more orderly. The Nobel Prize winner Ilya Prigogine introduced a concept of dissipative structure in 1977; it is a thermodynamic theory to describe the organizing process of material from its chaos disorder. Two conditions must be satisfied for the organization: one is supplying energy to generate negative entropy continually; another is exchanging material to regenerate the structure from time to time. Once the condition is not satisfied the dissipative structure would lose orderliness and be destroyed. The theory of dissipative structure is far more valuable than its thermodynamic use; it provides a new idea for studying highly complicated system. The characteristic of dissipative structure is coincident with the metabolism of living organisms, so that all the living organisms can be described as dissipative structure. A variety of organisms can be thought of as the various states of dissipative structure in the living world.

Human body is a very complicated and highly organized orderly system. If using the thermodynamic dissipative structure to describe the organization of the human body, then the orderliness can be used as a measure on the health of the human body. Pregnancy can be thought of as the constructive process of the dissipative structure under the control of gene regulation. The inborn orderliness can be thought as the health capital inherited from the parents. The inborn orderliness is different from person to person and it is not the pink of perfection. The shortage of the inborn orderliness is the weak point of the dissipative structure; it comes from the defection of parent's genes. The defect is always well covered during embryonic development, and not well covered defection is the children born with congenital genetic diseases.

Key role of the respiratory chain in human health and longevity

The huge numbers of life-engine are the key for the human body to exchange energy and material with the surround. They play an important role in the maintenance of the dissipative structure of the human body. Once life-engine becomes damaged or aged, the highly ordered human body would go down to disorder, that is aging and diseases. Then we can define health and longevity in terms of thermodynamics: the health is the maintenance of the inherent orderliness; the longevity is the history of human body fighting against damaging factors for the maintenance of the inherent orderliness.

The Ideology of Chinese Medicine is in Agreement with the Thermodynamic Principle of Health and Longevity

Chinese medicine stresses the integrity of human body and emphasizes the unity of the human body with the environment. This point of view is coincident with the property of the dissipative structure continual exchange energy and material with the surrounding. Put the thermodynamic interpretation on the principles of Chinese medicine would help people better understand Chinese medicine scientifically.

Jing Luois the concept of Chinese medicine to describe the integrity of human body

JING_LUO(经络) is the word to describe the cellular orderliness of the human body. Pregnancy is the constructive process of the human body as the dissipative structure, in which the fetus is growing up from one fertilized cell to million billion highly ordered organisms under the control of genes. The orderliness of the million billion cells is constructed as the family tree in human body. The network mechanism of cellular communication and recognition in the family tree is the JING LUO(经络). It makes the countless cells of the human body in one functional unity.

JING LUO (经络) exists only in the multicellular organisms. The number of cells in the primary multicellular organism, such as the protozoan, is a fixed number in each generation. The law of cell constancy indicates that the number of cells (or nuclei) in the whole body or parts of a multicellular animal in the life cycle is maintained. This cellular law indicates the existence of JING LUO (经络); the cells in multicellular organisms are not accumulated randomly but in a definite orderliness of the dissipative structure of their own.

The Chinese medicine believe that the smooth communication of JING LUO (经络) is the base of health. Acupuncture, cupping, massage, moxibustion and so on are the skills of the Chinese medicine to smooth the communication of JING LUO (经络). QI GONG (气功) is the way of self-exercise for getting through the communication of JING LUO (经络).

Qi_xue (气血) is the concept of Chinese medicine to describe the unity of the human body with the environment

The continued exchange of materials with the surround is the property of dissipative structure; it keeps the orderliness of the structure in regenerating at all times. This property of dissipative structure is the same of the metabolism. Western medicine searches the detailed biochemical reactions of the metabolism and design chemicals to correct the abnormal reactions in patients.

Chinese medicine use the word QI_Xue (气血) to describe the metabolism of the human body and use the word of Yin-Yang (阴阳) to judge the deviation of patients from their normal metabolic state. The balance of Yin-Yang (阴阳) is necessary for the healthy state. The Chinese doctor has the knowledge of Yin-Yang (阴阳) properties of foods (or herbs) and uses the combination of them (prescription) to redress the Yin-Yang (阴阳) balance of the patients. The respiratory chain is indeed a Yin-Yang element. If the ROS generation in the electron leak pathways is considered as Yin (阴) and the ATP production in the electron transfer as Yang (阳), then the human body can be thought as an aggregate of huge numbers of Yin-Yang elements. Chinese medicine is the holistic medicine of Yin-Yang.

The exchange of materials with the surround is performed by the internal organs. To describe the functional unity of different internal organs Chinese medicine developed a theory of \bigstar (wood), \pounds (fire), \pm (earth), \pm (gold), \bigstar (water) as shown in (Figure 8). Each organ can be thought of as a fraction of the Yin-Yang element aggregation.

Chinese medicine divides the internal organs into WU_ZANG (五 脏) and LIU_FU (六腑). WU_ZANG (五脏) are the heart, liver, spleen, lung and kidney. LIU_FU (六腑) are the stomach, gall, bladder, small intestine, large intestine. They are arranged into five domains according to their physiological functions as shown in (Figure 8). Five domains interact with each other in a way of promotion and restriction. The balance of Yin-Yang of the internal organs is the normal physiological state. The harmony and adaptation of the five domains is necessary for the healthy state. The art of the Chinese medicine is regulating the functions of the five domains with the treatment of prescription as shown in (Figure 9).

Call for Attention to the Chinese Medicine

The fact is that the ROS generated in the electron leak pathways of the mitochondrial respiratory chain have two opposite effects on



Figure 8: Functional unity of internal organs based on the theoretical principle of Yin and Yang.



the human body: the negative effect of ROS is causing the oxidative damage on the order of human body, that induces disease and aging; the positive effect of ROS is playing as the signal to stimulate the antioxidative function and strengthen the ability of damage repairing, that is a reconstructive process of the order of dissipative structure of the human body.

The question is: What makes the judgment telling ROS to play as a positive role or a negative role? How the judgment is made?

Answer to this question is not an easy task because the judgment depends on a process of mutual communication of both the mitochondrial DNA and the chromosome DNA. The complexity of the mutual communication in both DNA system is much more complicated than the chromosome DNA alone (see: Douglas C. Wallace: Mitochondria as "chi". http://www.genetics.org/ content/179/2/727. short). Douglas C. Wallace is right as he pointed out the necessity of introducing the ideology of "chi" of the Asian herbal medicine for the development of scientific research of medicine. Douglas C. Wallace said "chi" is the same as above mentioned QI (\leq), and it is the word to describe the vitality of human body in Chinese medicine.

The exploration of cytological knowledge is the motive power for developing medical science. The increased knowledge on the molecule biology presented the basic principles for medical research. The Western medicine is developed based on those principles in the experimental verification of animal model. The Western medicine developed pharmaceutical chemicals and various physical equipments to find out the focal lesion and then remove it by chemicals or surgery. It is obvious that the Western medicine is precise and accurate, but facing to the complexity of the human body it has the limitation in rely on the improvement of investigative technology. The complexity of the human body not only comes from the mutual communication between the mitochondrial DNA and the chromosome DNA, but also comes from the highly developed brain. In fact the human body has two brains; the inborn brain and the educated brain. The inborn brain like a computer fixed with only operation software, whereas the educated brain is equipped with different utility software. The desires of the inborn brain come from the physiological needs, whereas the desires of the educated brain come from social competition. The educated brain is the identification of the human body from animal, and it is different from person to person depending on their level of education and their different civilization. The Chinese medicine believes that most of the diseases come from the stress of the educated brain on the inborn brain or the indulgence in bad habits. This complexity cannot be reflected in the animal model.

The Chinese medicine jumps over the complexity, treating the human body as a dark box and investigating diseases in a way of signal input–output relationship. The signal input is the plan of the treatment, such as the herbs prescription or acupuncture etc. The signal output is the representations of diseases in the surface of the human body, such as the representation in tongue, the pulse manifestation and so on. During 5,000 years' accumulation of direct observations on the curative effect in huge numbers of patients, the Chinese medicine developed a systematic theory and therapeutic methods. The knowledge accumulated in the direct observations on the patients is a precious wealth of medicine recorded in the ancient Chinese medical books.

Western medicine is precise, accurate, and deep into the structure and function of the biological molecules, whereas the Chinese medicine pays more attention to the energy and the communication of the different parts in the entirety of human body. The ideologies of the Chinese medicine and western medicine are different but they are complementary in the final goal when dealing with the patients. Scientists should pay more attention to the Chinese medicines and develop a new medicine by combining the advantages of both the western medicine and the Chinese medicine.

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