



Mitochondria as the Essence of Yang Qi in the Human Body

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Abstract

The concept of Yang Qi in Traditional Chinese Medicine (TCM) has many similarities with mitochondria in modern medicine. Both are indispensable to human beings and closely related to life and death. This article discusses the similarities in various aspects between mitochondria and Yang Qi, including body temperature, aging, newborns, circadian rhythm, immunity, and meridian. It is well-known that Yang Qi is vital for human health. Interestingly, decreased mitochondrial function is thought to be key to the development of various diseases. Here, we further explain diseases induced by Yang Qi deficiency, such as cancer, chronic fatigue syndrome, sleep disorder, senile dementia, and metabolic diseases, from the perspective of mitochondrial function. We aim to establish similarities and connections between two important concepts, and hope our essay can stimulate further discussion and investigation on unifying important concepts in western medicine and alternative medicine, especially TCM, and provide unique holistic insights into understanding human health.

Keywords Mitochondria · Yang Qi · Diseases · TCM (Traditional Chinese Medicine)

Abbreviations

TCM	Traditional Chinese Medicine
mtDNA	Mitochondrial DNA
OXPPOS	Oxidative phosphorylation
nDNA	Nuclear DNA
TCA	Tricarboxylic acid
ETC	Electron transport chain
ATP	Adenosine triphosphate
ROS	Reactive oxygen species
UCP1	Uncoupling protein 1

MAPR	Mitochondrial ATP production rate
CFS	Chronic fatigue syndrome
A β	Beta-amyloid

Introduction

Mitochondria, as organelles in the cytoplasm, harbor their own genome called mitochondrial DNA (mtDNA), which contains 16,569 base pairs in humans. The mtDNA is a circular double-stranded molecule encoding 37 genes: 13 proteins, 22 transfer RNA, and 2 ribosomal RNA. These 13 proteins constitute the key subunits of the oxidative phosphorylation (OXPPOS) enzyme complexes I, III, IV, and V (Che et al. 2014; Filosto and Mancuso 2007; Kauppila et al. 2017). Human mtDNA is maternally inherited, as the paternal mtDNA is actively destroyed immediately after fertilization (Nunnari and Suomalainen 2012). Unlike nuclear DNA (nDNA), mtDNA is not protected by histones and does not recombine during meiosis. The mutation rate of mtDNA is about 10–100 times higher than that of nDNA (Filosto et al. 2011; Mancuso et al. 2007).

Mitochondria are vital to life. The major function of mitochondria is to generate large amounts of energy. As metabolic signaling centers, mitochondria can convert carbohydrates, proteins, and fat molecules into CO₂ and water using the tricarboxylic acid (TCA) cycle and electron transport

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chain (ETC), accompanied by the production of adenosine triphosphate (ATP). The coupling of substrate oxidation with ATP formation in mitochondria is called OXPHOS, which is essential for various tissues and organs (Johannsen and Ravussin 2009). The energy stored in ATP, which has been called the energy currency of cells and life, is used either directly or indirectly to drive all other cellular processes that require energy. In addition to energy production, mitochondria are of central importance for multiple cellular processes, such as apoptosis, β -oxidation of fatty acids, generation of cellular metabolites, reactive oxygen species (ROS) signaling, steroid synthesis, and Ca^{2+} homeostasis (Camello-Almaraz et al. 2006; Hamanaka and Chandel 2009; Kauppila et al. 2017; Le Bras et al. 2005; McBride et al. 2006; Murgia et al. 2009; Rossier 2006). Recently, it has been shown that mitochondria are also central regulators of epigenetics and immune responses (Banoth and Cassel 2018; Breda et al. 2019; Matilainen et al. 2017; Schell and Rutter 2017; Tatar and Sedivy 2016; Zhu et al. 2019).

Mitochondrial dysfunction is characterized by decreased ETC efficiency and reduced ATP synthesis, and is associated with a large proportion of human diseases, such as neurodegenerative disorders (e.g., Alzheimer's disease and Parkinson's disease), cardiovascular disorders, metabolic syndrome, cancer, obesity, and premature aging (Galluzzi et al. 2012; Holper et al. 2019; Leong et al. 2012; Nunnari and Suomalainen 2012; Schapira 2012). Various mitochondrial-related factors are associated with these diseases, including mtDNA deletion/mutation, ATP deficiency, increased production of ROS, mitochondrial permeability transition pore opening, apoptosis, Ca^{2+} deregulation, inflammation, and altered fusion/fission dynamics (Johannsen and Ravussin 2009; Lane et al. 2015; Murphy et al. 2016; Nunnari and Suomalainen 2012; Pacheu-Grau et al. 2018). For example, mtDNA mutations can cause severe damages to cellular energy conversion and tissue dysfunction, and mitochondrial diseases caused by mtDNA mutations include Leigh syndrome, Leber's hereditary optic neuropathy, MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes), MERRF (myoclonic epilepsy with ragged red fibers), diabetes, and deafness. These diseases can occur at any age and affect any organ system. Unfortunately, mitochondrial diseases induced by mtDNA mutations are currently difficult to treat.

Research on Traditional Chinese Medicine (TCM) is mostly recorded in ancient Chinese, and is quite different and difficult to understand from the perspective of western medicine, due to methodological limitations and publication biases (Cheuk et al. 2012; Feng et al. 2017; Yeung et al. 2009). TCM treatment of diseases focuses on a holistic approach, which is considered to be the typical characteristic and advantage of TCM (Tong et al. 2012; Zhang et al. 2010). For instance, TCM makes full use of its overall

body-regulating benefits in the treatment of complicated diseases, such as chronic fatigue syndrome, metabolic syndrome, anemia, and asthma. In ancient China, people believed that Qi is the most basic motive force for all living things and maintains their functional activities. Qi comes into being with new life, grows from young to old, and then descends from strong to weak, and finally, to death (Men and Guo 2010). In short, we can understand the essence of the word "Qi" as the driving force for all human activities.

A very significant assumption in TCM is that various kinds of diseases are caused by internal imbalances between Yin and Yang. If these Yin–Yang imbalances are corrected, the human body can return to a healthy state (Dashtdar et al. 2016; Yan 2018a, b). The ancient medical work *The Yellow Emperor's Inner Canon*, including two books *Su Wen* and *Ling Shu*, is one of the oldest medical textbooks in China. Yang is recorded as being as important as the sun, while Yin is recorded as being as important as water. Without the sun, there would be no living things on the earth. Without Yang, humans would not be able to survive. Whether a person is strong enough to ward off pathogenic factors is closely related to the abundance and function of Yang.

It is recorded in *The Yellow Emperor's Inner Canon* that Yang Qi is like the sun in nature. If Yang Qi runs abnormally, the life expectancy will be shortened. Yang Qi is a critical basic substance of the human body. The basic functions of Yang Qi include producing and transporting Qi, blood, and other body fluids, maintaining the human body temperature, generating and increasing energy, strengthening the immune system, preventing various diseases, reinforcing metabolism, and promoting circulation. Insufficiency of Yang Qi will bring about a variety of illnesses, such as fatigue, insomnia, menstrual cramps, headache, inability to lose weight, and even cancer. The leading causes of Yang Qi deficiency are social and environmental influences, improper living habits, diseases (such as asthma) and long-term use of antibiotics (Huo et al. 2020; Wang et al. 2016). More aspects of the essence and characteristics of Yang Qi need further investigation.

The Similarities Between Mitochondria and Yang Qi

According to the basic theory of TCM, Yang Qi is vital to life, and its deficiency is closely related to disease and death. In modern medicine, mitochondria are recognized as the central regulators of life, disease and death. For a long time, Yang Qi has always been considered as energy, and mitochondria can also serve as a representative of energy. From these perspectives, mitochondrial function could serve as a functional basis for discussing the role of Yang Qi in modern medicine. To explain TCM with modern medical

concepts and gain a deeper understanding of Yang Qi and mitochondria, this review discusses the similarities between mitochondria and Yang Qi in detail from six aspects, including body temperature, aging, newborns, circadian rhythm, immunity, and meridian (Table 1).

Body Temperature

Based on the theory of TCM, Yang deficiency is involved in the decline of the human body function and metabolic activities in various organs, including body temperature reduction. As recorded in *Su Wen* (one part of *The Yellow Emperor's Inner Canon*), when there is surplus Yang Qi, the human body will become hot, and when there is insufficient Yang Qi, the human body will be cold. Yang Qi deficiency is therefore characterized by a reduction in body temperature (Wu and Yan 2004). TCM holds that a decrease of Yang Qi (Yang insufficiency) will result in a phenomenon called Deficiency Cold Syndrome (such as feeling cold, fatigue and other symptoms), which is similar to Yang Deficiency Syndrome and should be treated by strengthening Yang. In a rat model of Yang deficiency, researchers observed severely impaired glucose and lipid metabolism, suggesting that a lack of Yang Qi is accompanied by insufficient energy supply (Zhao et al. 2013). In other animal models of Yang deficiency, the metabolism of metabolic energy molecules such as lactic acid and acetyl carnitine has been found to have varying degrees of impairment and/or abnormality (Huang et al. 2013; Lu et al. 2011; Tan et al. 2014).

Coincidentally, the metabolism of mitochondria-related energy molecules is also unbalanced or weakened in Yang Deficiency Syndrome patients (Huang et al. 2012). It is well-known that a basic function of mitochondria is to generate heat and maintain body temperature. The source of body heat is mitochondrial uncoupling, which is mediated by uncoupling proteins (UCPs) (Brand 1990; Busiello et al. 2015; Ricquier and Bouillaud 2000). Uncoupling protein 1 (UCP1) has been found to be involved in cold adaptation in human evolutionary history (Nishimura et al. 2017). It can be speculated that when human ancestors migrated from Africa to different cold environments, UCP1 underwent

adaptive evolution, which means that cold exposure induces UCP1 expression, resulting in more heat production in mitochondria. Similarly, cold acclimation causes many temperate-zone fish species to increase either their mitochondrial density in muscle, or the activity of mitochondrial enzymes, thereby enhancing their mitochondrial oxidative capacity to generate more heat (Guderley and Johnston 1996; Sanger 1993). It is not surprising that the mitochondrial dysfunction may lead to some abnormalities in the regulation of thermogenesis (Bertholet and Kirichok 2021; Enerback et al. 1997; Quiros et al. 2012; Rango et al. 2014). If mitochondrial metabolic function is impaired (e.g., mitochondria cannot efficiently convert sugar and oxygen into energy), it is likely to result in insufficient heat production, just like Yang Qi deficiency, which tends to make people feel cold. In short, the function of Yang Qi and mitochondria is the same in terms of maintaining body temperature.

Aging

The *Su Wen* recorded that Yang Qi is related to birth, growth, maturity, aging, and death, and it is of great significance to the life cycle of human beings. Yang Qi exhaustion is the primary cause of aging. In *Ling Shu* (another part of *The Yellow Emperor's Inner Canon*), it is pointed out that when people reach the age of forty, there is insufficient Yang Qi, leading to a dramatic increase in loss of life and physical damage every day. That means a person's life is a process of Yang Qi decay. TCM theory holds that Yang Qi deficiency is a major factor in aging and the main cause of geriatric diseases. Therefore, some Qi-invigorating Chinese herbal medicines (such as Schisandrin B) are often used to alleviate age-related diseases (Leong et al. 2012).

Notably, mitochondrial dysfunction (e.g., associated with the age-related accumulation of mtDNA mutations and mtDNA copy number decline) is thought to be a significant factor in age-related diseases (Chistiakov et al. 2014; Lane et al. 2015; Mengel-From et al. 2014; Ngo et al. 2013; Srivastava 2017; Sun et al. 2016; Wallace 1992a, 2008). Long-term Schisandrin B treatment can mitigate age-related impairment of mitochondrial function (Ko et al. 2008).

Table 1 The table summarizes the understanding of each of the six main concepts from the point of view of Yang Qi (left) and mitochondria (right)

Six aspects	Yang Qi	Mitochondria
Body temperature	Yang Qi deficiency → body temperature reduction	Mitochondria maintaining body temperature
Aging	Yang Qi exhaustion → aging and geriatric diseases	Mitochondrial dysfunction in age-related diseases
Newborns	Insufficient Yang Qi → poor oocyte quality	Mitochondrial defects linked to poor eggs
Circadian rhythm	Rhythm of Yang Qi → human biological clock	Mitochondria related to the circadian rhythm
Immunity	Lack of Yang Qi → immune reduction and pathogenicity	Mitochondria regulating human immunity
Meridian	Yang Qi circulation → in meridians	Mitochondria shuttling and transferring between cells

Similar to Yang Qi, mitochondrial function decays with age, resulting in a decreased efficiency of OXPHOS. The mitochondrial ATP production rate (MAPR) per gram of human muscle, which uses substrates to provide electrons primarily to either complex I or complex II, decreases with age by approximately 8% per decade (~5% decline per decade after normalizing MAPR per milligram of mitochondrial protein) (Johannsen and Ravussin 2009; Short et al. 2005). Age-related progressive impairment of mitochondrial complex I and complex IV activity has been found in primate cerebral cortices (Bowling et al. 1993). Age-associated decline in mitochondrial function plays an important role in cellular senescence, especially in the myocardium, which may be linked to the accumulation of mtDNA oxidative damage (Takasawa et al. 1993). mtDNA mutations have been found to accumulate with age in multiple tissues, causing respiratory chain function to decline dramatically (Larsson 2010). As the amount of mutant mtDNA increases, cellular energy drops below the minimum output required for normal cellular and tissue function, leading to decreased organ function and an aging phenotype (Wallace 1992b, a). In homozygous POLG mutant mice, mitochondrial mutations rapidly accumulate and an accelerated aging phenotype is exhibited (Kujoth et al. 2005; Trifunovic et al. 2004). It has been reported that age-related muscle mitochondrial dysfunction is associated with reduced mtDNA content in the elderly (Short et al. 2005). Aging phenotypes such as skin wrinkles and hair loss have been observed in mtDNA-depleted mice (Singh et al. 2018). Unsurprisingly, a decrease in mtDNA copy number with age has been also observed in other studies (Barazzoni et al. 2000; Cree et al. 2008).

Newborns

According to TCM theory, Yang Qi gets revitalized in every generation at birth, and a lack of Yang Qi in newborns causes various diseases. What is the underlying mechanism of these observed phenomena? It is speculated that the reason for Yang Qi deficiency at birth may be that the mother's Yang Qi is insufficient, which makes the embryos susceptible to the pathological cold during pregnancy. TCM theory believes that excessive body fat is associated with Yang Qi deficiency. Obese mothers' eggs are of poor quality, because obesity can impair the development of oocytes and even fertilized embryos (Igosheva et al. 2010; Minge et al. 2008; Shah et al. 2011). These suggest a potential correlation between Yang Qi deficiency and poor oocyte quality.

Perhaps it is also possible to try to explain these phenomena from the perspective of mitochondria. Eggs from obese mothers have been reported to have mitochondrial defects, resulting in offspring with fewer normal mitochondria than controls (Wu et al. 2015). This is similar to Yang Qi insufficiency. It has been found that mitochondria are selected in

nurse cells, and “good” mitochondria (with very few mtDNA mutations and excellent functional activity) are preserved and injected into the egg (Cox and Spradling 2006; Frederick and Shaw 2007). In addition, the researchers have discovered that “bad” mitochondria are cleared away and “good” mitochondria are retained during egg development (Bilinski et al. 2017). If any of these processes go wrong or are incomplete, it can lead to neonatal illness. A recent work has revealed a key driver of mtDNA-purifying selection in the female germline, a process by which mitochondrial fragmentation drives the selective removal of deleterious mtDNA in the germline (Lieber et al. 2019).

Circadian Rhythm

On the basis of TCM theory, it is possible to use Yin and Yang to explain the effect of day–night alternation on the physiological status of the humans body. As described in *Su Wen*, Yang Qi is dominant in the daytime, which starts to emerge at dawn, grows and prospers at noon, and declines and weakens at night. When Yang Qi is exuberant, a status of excitement and activity prevails, enabling humans to study and work energetically and efficiently during the day. In the evening, Yin Qi begins to appear and prosper while Yang Qi is hidden, which restrains and rejects the excitement and active status of the human body and makes people fall asleep. As Yang Qi emerges at dawn and grows, people will gradually wake up. Hence, it is not difficult to understand that the human biological clock (biorhythm) may actually reflect the workings of the rhythm of Yang Qi.

Similar to the biological rhythm of Yang Qi, a relationship between mitochondria and the circadian rhythm has been observed. Some mitochondrial inhibitors (e.g., uncouplers and azide) can cause large phase shifts in biological rhythms. Mitochondria may play a role in circadian clock rhythm mechanisms, either through their influence on biosynthetic pathways or their contribution to determining ionic gradients (Brody 1992). Given that mitochondria are central to metabolism and potentially regulate the transcriptome, additional mechanisms may link mitochondria to circadian rhythms (Sardon Puig et al. 2018). In fact, mitochondria have their own rhythms. Recent studies have indicated that changes in mitochondrial morphology (e.g., shape and size, fusion and fission), mitochondrial respiration, generation of new mitochondria, and mitochondrial-dependent ROS production are all related to a viable circadian clock (de Goede et al. 2018; Manella and Asher 2016). Whole blood mtDNA copy numbers display a fluctuating daily rhythm, due to fluctuations in the ratio of white blood cells and platelet content (Wang et al. 2020). Mitochondria have also been shown to have circadian rhythms in the degree of interconnectivity, or the number of physical connections that mitochondria have with each other (Schmitt et al. 2018). Furthermore,

fluctuations in mitochondrial function have been found in whole-body energy expenditure, demonstrating a day-night rhythm in the oxidative capacity of human skeletal muscle (van Moorsel et al. 2016).

Immunity

In TCM theory, the human body has the ability to resist pathological factors, which is given by Yang Qi. The spirit consumes most Yang Qi, and once the loss of Yang Qi is extensive, it will cause diseases. *Ling Shu* records that most diseases remain stable during the daytime, but are aggravated at night, which is associated with the exhausted status of Yang Qi. When Yang Qi dominates in the daytime, the number and activity of pathological factors are reduced. When Yang Qi is insufficient at night, pathological factors may become rampant and active, making the disease worse. These indicate that the disease status changes with the total amount of Yang Qi, and Yang Qi is closely related to immunity.

Additionally, mitochondria can also regulate human immunity. Mitochondria are closely related to cell apoptosis/death, and some viral proteins and bacterial effectors manipulate cell death and/or host cell survival pathways by targeting mitochondria. Mitochondria are the central platform of human immunity, as mitochondrial signaling appears to be necessary to mount an immune response to a variety of intruders in both innate and adaptive settings (Weinberg et al. 2015). The mitochondria-associated viral sensor (MAVS) provides a pivotal link between mitochondrial function and immune signaling, as it plays an essential role in antiviral immunity (Arnoult et al. 2011). Interestingly, mtDNA has been reported to have a crucial role in immune responses and inflammatory pathology (West and Shadel 2017). mtDNA can be released as a powerful and highly potent inflammatory trigger and is observed outside of blood cells in various pathologies (Boudreau et al. 2014). Even in normal human plasma, there are very short mtDNA fragments (Zhang et al. 2016). The deletion of mtDNA leads to defects in inflammasome activation (Zhong et al. 2016). It is worth noting that there are abundant common features shared between mtDNA and bacterial genomes (mitochondria are thought to be descendants of the *Alphaproteobacterium* species), so extracellular mtDNA has the potential to elicit immune reactions and generate proinflammatory signals (Marques et al. 2012; Oka et al. 2012). Some studies have found that mitochondria increase mtDNA secretion under stressful conditions, and this long-term stress can eventually lead to various diseases. One example is that mtDNA levels are significantly elevated in patients with granulomatosis with polyangiitis compared to controls (Surmiak et al. 2015). Electro acupuncture can improve the anti-fatigue capacity of aging rats with Yang-deficiency,

which may be related to its effects on reducing the oxygen consumption and increasing the respiratory control rate of liver mitochondria (Wang et al. 2013).

Meridian

As described in TCM, there is a low hydraulic resistance channel system called the meridian, which is an inborn body fluid circulation system with the characteristic of an energy network throughout the whole body. These meridians connect each organ and spread over the surface of the entire body, perfectly integrating the inside with the outside of the body (Wang et al. 2010; Zhang et al. 2015). *The Yellow Emperor's Inner Canon* states that the function of meridians is to transport Qi-blood and circulate Yin-Yang to nourish the body. Therefore, Yang Qi circulates in the meridians to provide health and vitality to various tissues and organs. As long as Yang Qi circulates freely and smoothly through meridians, the organs can work in harmony and the body will stay healthy. However, when Yang Qi in the meridians is blocked, disrupted, or unbalanced, it will cause symptoms of the disease. Scientists have discovered the structure and distribution of an unrecognized interstitium in human tissues, and described it as a “new organ” (Benias et al. 2018). In terms of features, the “new organ” and the meridian are alike. Recently, it has been reported that Chinese researchers have clearly observed a continuous fluorescent signal which migrates along the human meridian for the first time (Li et al. 2021).

To date, many studies have confirmed that mitochondria can shuttle and transfer between cells. Neurons have been observed to release damaged mitochondria and transfer them into astrocytes for disposal and recycling (Davis et al. 2014), while astrocytes in turn release healthy and functional mitochondria into neurons for survival signal amplification (Hayakawa et al. 2016). Additionally, mitochondrial transfer from bone marrow-derived stromal cells to pulmonary alveoli protects against acute lung injury (Sinha et al. 2016). Mitochondria have been found to circulate through the blood to various tissues and organs following an intravenous injection, which can be used to treat some diseases, such as fatty liver and Parkinson's disease (Fu et al. 2017; Shi et al. 2017). Therefore, if mitochondrial transfer is blocked or destroyed, diseases will occur. From this point of view, mitochondria and Yang Qi are similar. However, it is still unclear whether mitochondria have any pattern of distribution or movement outside cells, and whether they can constitute a circulatory system or network similar to meridians. We know that mitochondria are able to shuttle among cells, but we do not know whether mitochondria are distributed and move along the meridian. We wonder whether mitochondria will be used to explain the thermal radiation and photomagnetic properties of meridians in the future.

Yang Qi Deficiency-Related Diseases and Mitochondria

As stated in TCM, if the human body maintains a healthy status, both Yin and Yang should be in dynamic balance. Otherwise, the human body will be later attacked by diseases. Coincidentally, *The Yellow Emperor's Inner Canon* records that if vital Qi prospers in the body, the pathological factors are always restricted. In fact, Yang Qi, as a kind of vital Qi, plays a crucial role in human health. It is a major force in the body and helps to resist pathological factors, and prevents and cures diseases. In our opinion, there are many similarities between mitochondria and Yang Qi. For instance, it seems that the biological process of invigorating Qi by herbal medicines is closely related to mitochondrial pathways. The biological functions of mitochondria are consistent with the basic pharmacological effects of these Qi-invigorating herbal medicines, such as regulating apoptosis, clearing ROS, activating the immune system, fighting fatigue, and improving the exercise capacity (Li et al. 2015). TCM holds that Yang Qi deficiency in the heart is the root cause of chronic heart failure. Similarly, modern medicine has found that mitochondrial dysfunction can cause heart failure. Here, we attempt to explain Yang Qi decay-induced diseases from the perspective of mitochondria, including mtDNA mutations, reduced ETC efficiency, ROS production, impaired ATP generation, and other mitochondrial dysfunctions.

Cancer

In the logic of TCM, cancer is mainly caused by an imbalance between Yin and Yang, in which the body's Yang Qi is constantly attenuating and Yin Qi always dominates. Some exogenous pathogenic factors (e.g., toxins and viruses) contribute to cancer, but these factors can only induce cancer when an imbalance of the body's Yin-Yang occurs. If Yang Qi is insufficient for a long time, it will lead to energy dysfunction. Researchers have found that energy function disorders are closely related to cancer. Warburg first described the metabolic phenomenon (Warburg effect) whereby cancer cells predominantly produce their energy by glycolysis with a concomitant suppression of mitochondrial metabolic activities (Warburg 1956). Thus, scientists have proposed that defects in mitochondrial functions are crucial for malignant cells. Remarkably, mtDNA mutations are thought to be associated with tumorigenesis and progression and are observed in a variety of cancers, including ovarian, thyroid, liver, lung, colon, gastric, brain, bladder, and breast cancers (Desler and Rasmussen 2012; Lee and Wei 2009; Lu

et al. 2009). In cancer cells, mtDNA defects accumulate continuously, resulting in deficient mitochondrial respiration and ATP generation. The identification of deleterious mtDNA mutations in cancer tissues has confirmed the correlation between pathogenic mutations and neoplastic transformation (Horton et al. 1996; Lorenc et al. 2003). Usually, mtDNA mutations in cancer cells inhibit OXPHOS, increase ROS, stimulate neoplastic transformation to adapt to changes in the bioenergetic environment, and promote tumor cell proliferation (Brandon et al. 2006; Wallace 2012). For example, a termination mutation of COI located on mtDNA has been found to be a homogenous mutant in tumor cells, but the COI is homogenous wild-type in adjacent normal tissue (Petros et al. 2005). This termination mutation enhances tumorigenesis by increasing ROS production, whereas normal mtDNA can suppress tumorigenesis. In addition, it has been reported that mitochondrial decay may be associated with genomic instability, which is prone to carcinogenesis (Leong et al. 2012). *Astragalus polysaccharides*, an herb used in TCM to invigorate Qi, may protect against cancer by protecting mitochondria and enhancing their functions (Li et al. 2012). Taken together, abnormalities in both mitochondria and Yang Qi are associated with cancers, and we propose that mtDNA mutations and mitochondrial dysfunction are equivalent to a decline and deficiency in Yang Qi.

Chronic Fatigue Syndrome (CFS)

According to TCM theory, Yang Qi is the basic driving force through which the human body can maintain biological activities. The deficiency of Yang Qi is accompanied by a high incidence of fatigue syndrome, which cannot be alleviated, even after bed rest (Yiu and Qiu 2005). In TCM, CFS is described as a Yang Qi deficiency-induced fatigue syndrome, and there are many kinds of traditional crude Chinese drugs for improving and treating symptoms of CFS, especially those with beneficial effects on invigorating Yang Qi (Chen et al. 2010). Western medicine emphasizes how to alleviate the symptoms of CFS, while TCM provides a permanent and holistic cure for chronic fatigue illness through herbal medicines, acupuncture, and moxibustion combined with a psychological approach (Guo 2007). Interestingly, some clinical evidence has shown that CFS is related to mitochondrial dysfunction. A significant correlation between the degree of mitochondrial dysfunction and the severity of CFS has been found (Myhill et al. 2009). Various forms of mitochondrial dysfunction, such as lowered ATP production, decreased membrane potential, and impaired oxidative phosphorylation, may play a key role in CFS symptoms and partially explain the metabolic abnormalities observed in CFS (Morris and Maes 2014). One report has shown

an unusual pattern of mitochondrial DNA deletions in the skeletal muscle of an adult human with CFS (Zhang et al. 1995). A subsequent study also showed that the frequency of mtDNA variants correlates with symptoms in CFS (Billing-Ross et al. 2016). The structural integrity of mitochondria in the skeletal muscle is destroyed, which may be the reason for the decreased energy level in CFS patients (Plioplys and Plioplys 1995). Furthermore, changes in gene expression induced by CFS indicate unusual expression patterns of mitochondrial-related genes, as well as reduced mitochondrial metabolic processes (Pietrangelo et al. 2009). Therefore, Yang Qi-invigorating herbs, with the ability to enhance mitochondrial function and regulation, may be useful for CFS treatment (Leong et al. 2015).

Sleep Disorder

Sleep is a consequence of the balance and interaction of Yin–Yang in the body, and insomnia is the result of a vicious cycle of “daytime low-spirit” and “nighttime hyperarousal state” (Park et al. 2008; Wen et al. 2016). As recorded in *Ling Shu*, when Yang Qi is extremely scarce and Yin Qi is abundant and predominant, one falls asleep. On the contrary, if Yang Qi is prosperous and dominant, then one is awake. TCM holds that once the interplay of Yin–Yang is out of balance, insomnia will occur, mainly due to less Yin Qi but more Yang Qi at night. Acupuncture, which is often used to treat insomnia in TCM, is considered to be beneficial in restoring regular sleep–wake cycles, by regulating and restoring the natural rhythm of Yin–Yang (Wen et al. 2016). We can also see that mitochondria are related to sleep disorders. The unique occurrence of sleep–waking dysrhythmia in a family of diabetes mellitus patients is associated with a mitochondrial mutation (Suzuki et al. 1997). Scientists have identified 54 patients with a proven or suspected primary mitochondrial disorder who have been evaluated for sleep disturbances, and have proposed that sleep pathology may be an under-reported complication of primary mitochondrial diseases (Ramezani and Stacpoole 2014). Not surprisingly, people with mitochondrial diseases are particularly affected by sleep deprivation, because they have difficulty with oxygen consumption and energy production. Another study has shown that the expression of the key components of mitochondrial function and protein synthesis pathways is severely impaired, in parallel with neuron loss in the mediodorsal thalamus at terminal stages of fatal familial insomnia (Frau-Mendez et al. 2017). Unfortunately, we still do not know the direction of causality, whether mitochondrial damage comes first, or subsequent neurodegeneration (Glatzel and Sepulveda-Falla 2017).

Senile Dementia

There are records in TCM that with the increase of age, especially after the age of 50, decreased physical functions induced by Yang Qi deficiency may cause a series of adverse symptoms, such as speech disturbances, audiovisual instability, and forgetfulness. This is consistent with the symptoms of senile dementia described in modern medicine. Further theoretical investigation indicates that when Yang Qi is insufficient for a long time, its basic functions cannot be performed properly, which leads to a lack of motivation to produce and transport Qi, blood, and other body fluids, possibly resulting in accumulation and stasis of phlegm and blood in the brain, eventually causing senile dementia. Therefore, it is not surprising that Yang Qi-invigorating herbal medicines and acupuncture can alleviate the symptoms of senile dementia. In modern medicine, it has been shown that mitochondrial dysfunction plays a critical role in senile dementia (Tobore 2019). Diverse mitochondrial abnormalities have been detected in the brain and even throughout the body of patients with senile dementia. These abnormalities of mitochondria related to metabolism and energy deficiency include mtDNA mutations, defective mitochondrial enzymes, decreased ETC function, altered mitochondrial morphology, autophagy, fission–fusion dynamics, and biogenesis (Baloyannis 2006; Gibson et al. 1998; Selfridge et al. 2013; Yan et al. 2013). It is widely accepted that beta-amyloid (A β) is involved in the pathogenesis of senile dementia. In the “mitochondrial cascade hypothesis”, the deposition of A β is a downstream effect of evolving mitochondrial dysfunction (Swerdlow 2011; Swerdlow et al. 2014; Swerdlow and Khan 2004). Indeed, drug-induced cellular mitochondrial damage has been shown to enhance A β formation (Leuner et al. 2012). Excessive production of A β and similar symptoms of senile dementia are also observed in mice with mitochondrial dysfunction (Leuner et al. 2012). Of particular note is that as age increases, more mutations are accumulated in mtDNA, which makes mitochondrial function decline in the elderly and potentially causes senile dementia. It is no exaggeration to say that mtDNA can be considered as the molecular basis for senile dementia (Chakravorty et al. 2019; Oliver and Reddy 2019). Thus, mitochondria in the brain can be thought of as a primary target in the development of treatment strategies for senile dementia (Aliev et al. 2009). In summary, we speculate that “phlegm and blood stasis in the brain” in TCM is equivalent to “A β deposition” in modern medicine; TCM holds that Yang Qi deficiency is the cause of senile dementia, while modern medicine suggests that it may be caused by mitochondrial dysfunction.

Metabolic Diseases

Obesity is widespread in today's society, and obese people exhibit metabolic abnormalities and have a great risk of suffering from various metabolic diseases (e.g., hypertension, dyslipidemia, and diabetes). As discussed in TCM, nine out of ten obese people suffer from Yang deficiency. TCM holds that Yang Qi, as the foundation of life, has the function of warming the whole body and maintaining the normal function of organs. If Yang Qi is insufficient, the physiological function of the human body will be reduced and the metabolism will slow down. At the same time, the body's fat metabolism process will also slow down. That is to say, there will be abnormal metabolism, which leads to fat accumulation in the body. Consequently, obesity caused by Yang Qi deficiency will occur. Usually, babies look chubby because the level of Yang Qi is still low in the ascendant stage, and middle-aged people are likely to gain weight because the level of Yang Qi is beginning to fall. In addition, the main cause of "thin-thirst syndrome" (xiao-ke) in TCM is due to an imbalance between Yin and Yang, which subsequently leads to metabolic disorders. This may correspond to diabetes in modern medicine. Coincidentally, mitochondria in modern medicine are at the core of fat metabolism (Hittelman et al. 1969; Kunau et al. 1995; Novak et al. 1974). Mitochondrial beta-oxidation is the principal pathway of fatty acid oxidation, reducing excess accumulation of fat and producing energy for organisms. Abnormal mitochondrial function leads to fatty acid oxidation defects and lipid accumulation, and some factors (e.g., adipocyte transcription factors, adipokines, and growth factors) link mitochondrial dysfunction to obesity (Bournat and Brown 2010). Scientists have shown that mitochondrial dysfunction is closely related to age-dependent fat accumulation (Lopez-Lluch 2017). Obesity is thought to be associated with a decreased expression of mtDNA and reduced levels of proteins involved in oxidative phosphorylation (Patti and Corvera 2010; Vernochet and Kahn 2012). It has been reported that obesity and type 2 diabetes patients have defects in the subsarcolemmal mitochondria, which show a significant decrease in ETC activity (Ritov et al. 2005). Furthermore, a link between mitochondria and type 2 diabetes has been confirmed in some other studies (Cho et al. 2017; Choo et al. 2006; Szendroedi et al. 2011). Hence, mitochondria play an important role in metabolic processes, and Yang Qi-related metabolic diseases may be explained by mitochondrial dysfunction.

Conclusion and Prospects

The theory of Yang Qi is a crucial academic thought in *The Yellow Emperor's Inner Canon* and has been highly valued in TCM for a long time. Unfortunately, as far as we know,

there is currently no direct and effective method to accurately measure Yang Qi. One of the key issues that have hampered the integration of TCM into Western medicine and research is the measurement problem. TCM can judge whether a person lacks Yang Qi through the four diagnostic methods of inspection, listening and smelling, asking, and palpation. However, it is difficult to do this in modern medicine, which is a major barrier to integrating Oriental and Western scientific approaches.

From a traditional point of view, Yang Qi represents "material energy" or "energy flow". Yang Qi runs through the meridians and spreads throughout the body to maintain human life activities. It is the root of human growth, development, and reproduction. Coincidentally, mitochondria also represent energy and are closely related to life. Without mitochondria, humans cannot survive. In this paper, we propose a new perspective that mitochondria may be the essence of Yang Qi in the human body. First, mitochondria and Yang Qi display various similar aspects. We have conducted a detailed analysis of six of these aspects, including the regulation and maintenance of body temperature, changes with age, neonatal diseases, circadian rhythms, immune responses, and flow channels. Secondly, we have attempted to find out the association between Yang Qi deficiency-related diseases (cancer, CFS, sleep disorder, senile dementia, and metabolic diseases) and mitochondria, and explain these diseases from a mitochondrial perspective. In addition, there are some clinically common diseases of insufficient Yang Qi, such as hypothyroidism, decline in sexual function, increased nocturia, and edema. However, due to limited amounts of current research, it is not clear whether mitochondrial dysfunction can be used to explain the cause and development of these diseases.

Our analysis has linked TCM with modern mitochondrial medicine and can help in establishing Yang Qi in TCM as an important functional perspective of modern medicine. Moreover, some concepts in TCM can also be used to guide mitochondrial research. Much experimental evidence has suggested that a number of Chinese herbal medicines that increase Yang Qi can also enhance mitochondrial function. Conversely, we do not know whether drugs (e.g., nicotinamide nucleotides, nicotinamide mononucleotide, and coenzyme Q₁₀) that enhance mitochondrial activity can also increase Yang Qi. Chinese medicine holds that a class of foods that improve Yang Qi can help treat diseases caused by Yang Qi deficiency, but can they also contribute to the treatment of mitochondria-related diseases in modern medicine? It would be interesting to discover more evidence in support of mitochondria as the essence of Yang Qi in the human body.

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Declarations

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