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Why is Qi-Invigorating Therapy in Chinese Medicine Suitable for Mitochondrial Diseases? A Bioenergetic Perspective

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Additional information is available at the end of the chapter

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Abstract

The central player in bioenergetics is the mitochondrion. Bioenergetic dysfunction is emerging as a cornerstone for understanding the pathophysiology of mitochondrial diseases. Accompanying the depth of mitochondrial research and the rapid development of mitochondrial medicine, however, is rapid amplification of the number of mitochondrial diseases; mitochondrial dysfunction would undermine the function of cells, tissues, and organs, thereby causing cancer, diabetes, obesity, strokes, cardiovascular diseases, neurodegenerative diseases, and ageing, etc. Currently, there are no effective treatments; Western medicine is in crisis when it comes to mitochondrial diseases.

According to traditional Chinese medicine (TCM) theory, all kinds of diseases are born from Qi: Qi refers to the most basic motive force and maintains life's functional activities. Both life and death of humans depends on Qi. Qi always underpins the basic theory of TCM and acts as its cornerstone. Qi has been used as a healing technique in China for 4000 years. The author proposes a scientific hypothesis that "Qi" is "bioenergy", that Qi-deficiency can lead to bioenergetic dysfunction, which can be improved by Qi-invigoration, and demonstrates that Qi-invigoration was achieved through improved mitochondrial bioenergetics. Qi-deficiency is the common cause of mitochondrial diseases and Qi-invigoration is the basic principle for treatment of Qi-deficiency; therefore, Qi-invigorating therapy for mitochondrial diseases is logical. This chapter will focus on the role of mitochondrial bioenergetics in the aetiology and progression of several mitochondrial diseases and explore the potential therapeutic benefits of improving mitochondrial bioenergetics in mitigating the disease processes

by Qi-invigorating therapy. It will also provide a comprehensive overview of why Qi-invigorating therapy in TCM is suitable for mitochondrial diseases from a bioenergetics perspective, try to find its underlying mechanism, and to propose a novel way of thinking and provide scientific evidence in guiding Qi-invigorating therapy for the prevention and treatment of mitochondrial diseases.

The chapter will give an overview of some potential breakthroughs and the many challenges remaining in pursuit of the first effective treatment for mitochondrial disease by Qi-invigorating therapy. There seems to be light at the end of the tunnel; efforts to develop effective drugs should be devoted to the design of Qi-invigorating prescriptions that work in synergy to protect the mitochondria. It is hoped that the next few years will see a further convergence of Qi-invigorating therapy with mitochondrial bioenergetics, which will provide a comprehensive view of mechanisms on mitochondrial diseases. It seems likely that we are on the right track to acquiring this understanding, and that it will involve mechanisms rich with ideas from both the modern bioenergetics and the old Qi-invigorating therapy in TCM on mitochondrial diseases and how to counteract them.

Keywords: Qi-invigorating therapy, mitochondrial diseases, bioenergetics, mitochondria, energy metabolism

1. Introduction

As we all know, traditional Chinese medicine (TCM) is the summary of Chinese people's experiences in fighting diseases for thousands of years. Its theoretical system contains the essence of Chinese classical philosophy, embodies the Chinese people's own culture and profound speculative dialectical relationship between man and nature, and has made a great contribution to the healthcare of the Chinese people and the prosperity of the Chinese nation. TCM is also a unique treasure of the world's medical knowledge, and contributed to world civilization via the Silk Road and other external communication channels from very early on.

With the changes of the concept of people's health and the transformations of medical models in recent years, TCM pays more attention to the "preventive treatment of disease" and follows the "overall theory, system theory". It has ushered in a new development, not only having a significant effect on many common diseases but also plays an important role in the prevention and treatment of major incurable diseases and emerging infectious diseases, providing a source of knowledge and technology, and research and development ideas, for the development of a modern pharmaceutical industry and health services, and the evolution of medical science.

In the development of medical and health services with Chinese characteristics, the Chinese government has adhered to the policy of juxtaposing Chinese and Western medicines. The practice proves that the two medical systems have complementary advantages, promote each other. Both systems have salient features and advantages for China's medical and health

protection, and not only provide a unique impetus for the development of Chinese medical science, but also play an increasingly significant role for the realization of a healthy China. TCM is a treasure, this ancient wisdom should be respected and applied to the modern medical system; it will provide more choice and a wider field of vision for modern medicine at the two cognitive crossroads of East and West.

The mitochondria, whose main function is the production of the energy substance adenosine triphosphate (ATP), and are the hub and core of all life's activities, have been recognized as a cellular "Achilles heel". Interest in the roles that mitochondria play in human health and disease have grown markedly over the past two decades. Mitochondria lie at the heart of systemic metabolic regulation, they regulate the life and death of cells by manipulating several factors, including bioenergetics, mitochondrial permeability transition (MPT), and mitochondrial redox status. They are usually regarded as specialized organelles for cellular respiration and oxidative phosphorylation (OXPHOS). A lack of cellular energy, excessive free radical production, and dysregulated apoptosis are found alone or in combination in most human diseases, including neurodegenerative diseases, strokes, cardiovascular disorders, ischemia/reperfusion, and cancer [1].

Mitochondrial dysfunction has severe cellular consequences and is linked to ageing and mitochondrial diseases in humans. Since the discovery of the first case of mitochondrial disease in 1962 [2], the depth and development of mitochondrial research and medicine has increased rapidly, as has the number of mitochondria-related diseases; mitochondrial dysfunction would undermine the function of cells, tissues, and organs, thereby causing cancer, diabetes, obesity, strokes, cardiovascular diseases, age-related diseases, neurodegenerative diseases, and ageing, etc. Mitochondria have become a new target for the treatment of diseases, and mitochondrial dysfunction was listed as one of the nine hallmarks of ageing in the journal *Cell* in 2013 [3]. Therefore, mitochondrial protection is an important mechanism for the treatment of mitochondrial diseases.

Currently there are no highly effective mitochondrial disease treatments. Though related symptoms, such as seizures or attention problems can be managed with various medications, the mitochondrial disease itself is unchanged. As scientists have learned more about mitochondria's role in health and in disease, research suggests that mitochondrial function may be the unifying theme — the Holy Grail of medicine, perhaps — of understanding a spectrum of diseases, conditions, and why we grow old. Mitochondrial research across different disease disciplines will help all of us access treatments, and ultimately cures, much faster.

Continually increasing resources are being expended to combat mitochondrial diseases. Yet the causes of these diseases remain a mystery, while their incidence and morbidity either remain constant or are increasing. Huge investments in biomedical research in recent years have resulted in some striking accomplishments, but have failed to reveal the anticipated causes for the diseases. Western medicine is in crisis [4].

1.1. Mendelian paradigm of genetics and mitochondrial diseases

Western biomedical science has stood on two philosophical pillars: the anatomical paradigm of medicine and the Mendelian paradigm of genetics. The Mendelian paradigm of genetics

argues that genetic traits are transmitted across generations according to the laws of Gregor Mendel. However, Mendelian genetics is specific for nuclear DNA (nDNA) genes and have been powerful predictors of medical relationships for the past century, but fails to direct us toward answers for mitochondrial diseases. Since mitochondrial DNA (mtDNA) encodes genes for proteins of energy metabolism, human diseases affect many organs that could originate from systemic energy metabolism defects and could result from mutations in mtDNA [4]. The classical Mendelian genetic perspective has failed to explain the aetiology of mitochondrial diseases, because they are primarily systemic bioenergetic diseases, and the most important energy genes are located in mtDNA [5].

1.2. mtDNA and mitochondrial bioenergetics

In many animal species, mtDNA is a circular intron-free genome consisting of 14,000–17,000 base pairs (16,569 in humans), although in some species it is much larger, noncircular, and contains introns [6–7]. It is typically maternally inherited and present in multiple copies within each cell; the mtDNAs are grouped in DNA-protein complexes referred to as nucleoids [8–9] that are anchored to the inner mitochondrial membrane. Most somatic cells in mammals have 10^3 – 10^4 mtDNAs [10], but this number varies significantly by cell type and developmental stage [11].

Mitochondria are at the centre of bioenergetics and generate about 90% of cellular energy, regulate cellular redox status, and produce reactive oxygen species (ROS). The mitochondrial genome consists of thousands of copies of mtDNA, plus between 1,000 and 2,000 nDNA genes. mtDNA codes for 13 OXPHOS polypeptides, the 22 tRNAs, and the 12S and 16S rRNAs. mtDNA polypeptides encompass seven of OXPHOS complex I (ND1, ND2, ND3, ND4, ND4L, ND5, and ND6), one of complex III (cytochrome b), three of complex IV (COI, COII, and COIII), and two of complex V (ATPase6 and ATPase8). Consequently, mitochondrial biology and genetics become excellent candidates for expanding the anatomical and Mendelian paradigms to address the complexities of age-related diseases, ageing, and cancer [12], and life involves the interplay between structure and energy [4].

Both variation in the mtDNA and nDNA-coded mitochondrial genes sequences can perturb mitochondrial bioenergetics and result in disease. Since different tissues depend on mitochondrial energy to different extents, partial systemic energy deficiency can result in tissue-specific symptoms. Tissues with high energy demands include the brain, heart, muscles, kidneys, and the endocrine system: the organs commonly affected in metabolic and degenerative diseases [5]. A decline in energy is common in ageing, and the restoration of mitochondrial bioenergetics may offer a common approach for the treatment of numerous age-associated diseases [13].

The basic role of mitochondria in sustaining the normal cellular function has made dysfunction of this organelle a central feature of numerous diseases in any organ system at any stage of life [14–15]. “Mitochondrial medicine” has emerged as an active field of research. However, the mystery remains as to how tissue or cell type specificity occurs, and how a systemic disorder of one mitochondrial complex can cause a selective disease phenotype while leaving other tissues intact. It is believed that many of the mitochondrial diseases might actually be an

expression of progressive organ system failure due to disruption of specific aspects of mitochondrial function. Even though dysfunctional mitochondria appear to be a common underlying problem for all these diseases, they each exhibit unique triggers and symptoms.

1.3. Mitochondrial dynamics and bioenergetics

Mitochondria are highly dynamic organelles that show constant movement, fusion, and fission [16–17]. The role of mitochondrial dynamics is enabling content mixing of mitochondrial matrix and membranous components between mitochondria [18]. Disruption of mitochondrial dynamics causes a series of diseases, including neurodegenerative disease, cardiovascular disease [19], and even cancer [20]. Benard et al. describe the fundamental mechanisms by which mammalian cells regulate energy production, and put emphasis on the importance of mitochondrial dynamics for the regulation of bioenergetics. In addition, most neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and Hereditary Spastic Paraplegia are associated with defects in mitochondrial dynamics and bioenergetics [21]. Therefore, to unravel the fundamental mechanisms by which mitochondrial form interacts with mitochondrial function could permit us to increase our basic knowledge on the regulation of energy metabolism and to decipher the pathophysiology of a group of rare neuronal diseases.

Pathogenic mutations in genes essentials for mitochondrial fusion and fission have complicated the mechanisms of these diseases [22]. Thus, the mitochondrial network organization is a new parameter for physiopathological analyses of mitochondrial diseases [21]. The possible interaction between mitochondrial dynamics and energy production could offer an opportunity for the discovery of drugs that target mitochondrial fusion or fission with a stimulatory effect on energy metabolism, to the benefit of patients suffering from mitochondrial diseases [23–24].

1.4. Qi-invigoration and mitochondrial bioenergetics improvement

In TCM, “Qi” is expressed as the basic material that constitutes the body, maintains human life activities, and is its basic driving force. Qi, as the master of the brain, regulates Yin-Yang and five elements, tonifies the five vital organs of the human body, and keep the six hollow viscera unobstructed, and is in charge of chemical and biological transformation and defences, Qi dominate the whole vital activities. Qi is the centre in TCM from basic theory to clinical practice. According to TCM, “Qi is the root of the human”; “All the diseases originate from Qi”; “Both life and death depend on Qi, if Qi gets together, it will result to the birth; if Qi is strong, then the human body is healthy; if Qi is waning, the body will be weak; if Qi is disordered, the human will be sick; if Qi is depleted, the human will die”. This shows that Qi is closely related to health, disease, and life.

Qi can make the human body work in an orderly fashion by promoting a variety of physiological activities; “Qi-deficiency” will lead to a decline of physiological functions. As one part of a central medical classic *The Yellow Emperor's Inner Canon*, ‘Plain Questions’ pointed out that consumption of the vital essence Qi leads to deficiency, ‘Miraculous Pivot’ says that Qi-

deficiency in the heart, liver, spleen, lung, or kidneys becomes worse with increasing age, and ultimately all five internal organs of the body become deficient, spirit and Qi leave the body, and eventually the human will die. The basic idea of TCM to prevent and cure diseases is strengthening vital Qi to eliminate pathogenic factors. Strengthening vital Qi can improve body's resistance to disease, in order to eliminate weakness syndromes, ward off illnesses, and be physically strong. On the understanding of the aetiology, TCM theory emphasizes the cause of disease — “vital Qi-deficiency”, especially.

Due to the fact that both Qi and bioenergy are at the centre of life activity, the author suggests that Qi and bioenergy are closely related, and proposes a scientific hypothesis that “Qi” is “bioenergy” [25]; that Qi-deficiency can lead to mitochondrial energy metabolism obstacles, which can be improved by Qi-invigoration; and demonstrates that Qi-invigoration can be achieved through improved mitochondrial bioenergetics [26]. Qi-deficiency is the common cause of a variety of diseases (including mitochondrial diseases) and Qi-invigoration is the basic principle for the treatment of Qi-deficiency. Doctors of TCM usually compose prescriptions made up of Qi-invigorating herbal medicines (QIHM) for Qi-deficiency, and have accumulated abundant clinical experience for a long time. QIHM is a group of herbal medicines which can invigorate Qi and treat syndromes of Qi-deficiency.

1.5. The central premise of the chapter

This chapter will examine the role of mitochondrial bioenergetics in the aetiology and progression of several mitochondrial diseases and explore potential therapeutic benefits of improving mitochondrial bioenergetics in mitigating the disease processes by Qi-invigorating therapy. The chapter aims to provide a comprehensive overview of why Qi-invigorating therapy in TCM is suitable for mitochondrial diseases from a bioenergetic perspective, try to find its underlying mechanism, and provide a novel way of thinking and scientific evidence in guiding Qi-invigorating therapy for the prevention and treatment of mitochondrial diseases.

2. Mitochondrial bioenergetics dysfunction and diseases

2.1. A Primer on mitochondrial bioenergetics

The standard model of mammalian cellular bioenergetics is based on the pioneering work of Krebs and Mitchell over half a century ago [27]. In 1961, Peter Mitchell published a unique hypothesis regarding cellular bioenergetic conservation, to elucidate the role of mitochondria in energy generation — Mitchell theory, namely the chemiosmotic theory of OXPHOS, is one of the most fascinating discoveries in the history of science. ATP synthase was driven to produce ATP by the transmembrane proton gradient induced when electrons transfer along a series of respiratory enzyme complexes in the mitochondrial inner membrane, an insight for which Mitchell was awarded the Nobel Prize in Chemistry in 1978 [28]. Studies on bioenergetics have occupied an important position in the life sciences, the generation mechanism of ATP (the most important energy molecule in life activity) was elucidated by an academic of the National Academy of Sciences — Boyer — who proposed binding change and rotational

catalysis mechanism of ATP synthase, and won the 1997 Nobel Prize in Chemistry. Products of the Krebs cycle, such as nicotinamide adenine dinucleotide (NADH) and succinate, are the obligatory factors that drive mitochondrial electron transport and maintain OXPHOS and ATP production (Figure 2) [27]. Mitochondrial bioenergetic processes are central to the production of cellular energy, and a decrease in the expression or activity of enzyme complexes responsible for these processes can result in an energy deficit that correlates with many metabolic diseases and ageing [29].

An increase in the slippage of complex I and III of the electron transport chain (ETC) [30–32] can lead to overproduction of ROS, which can further damage the mtDNA and create a vicious feed-forward loop of energetic decline. The consequence of such an energetic decline is potentially grave, which might be manifested as either the normal progression of ageing, or as the onset of major diseases such as diabetes, AD, PD, and cancer [33–34]. Interest in the roles that mitochondria play in health and disease has grown markedly over the past two decades [35]. Mitochondria are involved both in male and female germ-line formation, which may also be affected by sexual antagonism of mitochondrial-nuclear gene interaction. Mitochondrial energy metabolism is also involved in tissue and organism differentiation. The mitochondrial bioenergetics system should be recognized as a candidate key driver of speciation events, at least in animals [36].

Cardiolipin is a unique phospholipid which is almost exclusively located in the inner mitochondrial membrane, where it is biosynthesized. Cardiolipin plays the functional role in several reactions and processes involved in mitochondrial bioenergetics [37]. Cardiolipin contains unsaturated fatty acyl chains which are readily oxidizable targets. Peroxidation of cardiolipin is now considered an important event in mitochondrial dysfunction in cellular pathophysiology and also an early step in apoptotic cell death. Abnormalities in cardiolipin content, fatty acyl chain composition, and remodelling appear to be, at least in part, responsible for mitochondrial dysfunction associated with several pathophysiological situations, including hypo- and hyperthyroid states, heart ischemia/reperfusion, heart failure, diabetes, Barth syndrome, as well as ageing and age-related cardiovascular and neurodegenerative disorders. Pharmacological strategies designed to prevent cardiolipin oxidation may open new perspectives for treatment of these disorders [37].

High-fat feeding is associated with reduced whole body respiration and, over sufficient duration, results in reduced mitochondrial respiration and ATP production. High-fat feeding also results in more ROS per unit respiration and per unit ATP being produced. The impaired high-fat-induced bioenergetics is, in part, mitigated by partial substitution of n-3 fatty acids in the diet [38]. Most of the beneficial effects of melatonin in a number of physiopathological situations, which may depend on its effect on mitochondrial bioenergetics, involve mitochondrial dysfunction as a primary cause of disease [39].

2.2. Mitochondrial bioenergetic dysfunction

Bioenergetic dysfunction is emerging as a cornerstone for understanding the pathophysiology of cardiovascular disease, diabetes, cancer, and neurodegeneration. A substantial bioenergetic reserve capacity of cells is a prospective index of ‘healthy’ mitochondrial populations, which appears to be essential for cell survival under conditions of pathological stress [40].

It has long been known that mitochondria show a diminished functional activity when isolated from a broad range of tissues subjected to pathological stress. Well-established examples are alcohol-dependent hepatotoxicity, cardiac ischemia/reperfusion, and neurodegenerative diseases [41–43]. In all of these cases, a role for reactive oxygen or nitrogen species (ROS/RNS) in causing mitochondrial dysfunction has been proposed. Typically, mitochondrial damage is defined as a relative decrease in respiratory parameters, such as a change in oxygen consumption in the presence of substrates and ADP (state 3 respiration), in the presence of substrates alone (state 4), or the ratio of these parameters (i.e., respiratory control ratio (RCR)). Other parameters include decreased activity of specific enzymes, deletions in mtDNA, and increases in oxidative markers such as protein oxidation. The challenge with these data is in integrating them into an overall model of cellular and tissue bioenergetic function. It is becoming apparent that mitochondria under pathological stress exhibit multiple defects that overall can be viewed as a decrease in mitochondrial quality [43–44].

An existing mitochondrial population is examined that was subjected to pathological stress with the formation of reactive oxygen, nitrogen, and lipid species (ROS/RNS/RLS). This oxidative stress damages mtDNA, impairing the ability of the organelle to replace damaged electron transport proteins and decreasing bioenergetic reserve capacity; the resulting increased mitochondrial ROS then oxidatively damage previously unmodified mitochondria. The damaged mitochondria are turned over by a mitophagic mechanism that then suppresses this vicious cycle. The mitochondrial population is now renewed through mitochondrial biogenesis. The bioenergetic reserve capacity is essential for resistance to oxidative stress and supplying ATP demand. Once the bioenergetic reserve is depleted, bioenergetic failure occurs and the cell is programmed for cell death [40].

A unique feature of the molecular machinery controlling cellular bioenergetics is that the proteins necessary for electron transport and OXPHOS are encoded by both nuclear and mitochondrial genomes. An emerging concept in the energetics field is that the reserve capacity can be used as an index of mitochondrial health [45–47]. It appears that a higher bioenergetic reserve capacity results in a greater ability to withstand oxidative stress [40].

The mitochondrial genome encompasses in the order of one to two thousand nDNA genes and thousands of copies of the mtDNA. Hence, a large number of mitochondrial gene targets can mutate and have significant effects on cellular bioenergetics. Given that a human has in the order of 10^{17} mitochondrial capacitors, this is a great deal of potential energy, the vital force that animates our life. When breathing stops, the membrane potential collapses, energy transduction ceases, and death ensues [48–51]. However, there is a clear need to determine whether the contribution of mitochondrial dysfunction to different age-related diseases is explained by a cellular bioenergetic deficiency or by changes in mitochondrial ROS production affecting oxidative damage and signalling [52].

2.3. Bioenergetics and disease

2.3.1. mtDNA mutation and mitochondrial heteroplasmy

The mitochondrial genome encompasses both mtDNA and nDNA genes and the assembly and function of mitochondrial OXPHOS requires the cooperation of both genomes. Hence, the

interaction of the Mendelian and non-Mendelian mitochondrial genes generates a “complex genetics” that nicely explains many of the hereditary anomalies of many “common” clinical problems. Moreover, the central importance of energy metabolism for health provides a direct explanation of the pathophysiology of many diseases [53]. The frequency of mtDNA diseases is indeed high, currently estimated as having an incidence of 1.65/10,000 [54]. Moreover, mtDNA mutations have been linked to a broad spectrum of clinical problems affecting the central nervous system, the heart and cardiovascular system, the musculoskeletal system, and the renal and endocrine systems — many of the same systems that are affected by ageing and the age-related diseases. The appearance of a new mtDNA mutation in a cell results in an intracellular mosaic of mutant and normal mtDNAs, a state known as heteroplasmy. Identical twins derived from the same heteroplasmic egg can have different mtDNA genotypes and different clinical phenotypes and manifestations [4].

Rodell et al. present the contrasting view that the effects of mitochondrial heteroplasmy, in a broader sense, are not limited to a decline from a healthy norm, leading to unhealthy ageing and disease, but may also serve as the fabric of positive adaptive responses, at the genetic and epigenetic levels, to challenging bioenergetic events. The roles of mitochondrial biogenesis and dynamic fission and fusion mechanisms are vital to the maintenance of healthy mitochondrial populations, and impairment of the respective mechanisms is implicated in many age-related diseases [55]. Recently, Jose et al. reviewed the adaptive biology of mitoplasticity as a protective mechanism against ageing, diabetes, cancer, and neurodegenerative diseases, which Rodell et al. extend to the specific and directed promotion of healthy ageing [55–56].

Ageing is associated with decreasing bioenergetic capacity, as mitochondria increasingly become unable to meet the respiratory energy demands of cells [57]. Free radicals increasingly damage mtDNA with age, leading to an age-dependent state of variable heteroplasmy in individual cells, with detrimental effects on the bioenergetic capacity of the tissue [58]. Studies of mtDNA mutator mice show that increased accumulation of damaged mtDNA exacerbates the heteroplasmic conversion, with rapid onset of unstable health as the hallmark of ageing and the onset of age-related diseases. Such heteroplasmic variation can be described as the consequence of an age-dependent lack of selection [59].

2.3.2. Bioenergetic deficiency for mitochondrial diseases

The role of mitochondria in mitochondrial diseases aroused people’s concern due to the central role of mitochondria in producing chemical energy (ATP) to meet cellular requirements. Old mitochondria appear morphologically altered and functionally produce more ROS and less ATP. Mitochondrial bioenergetic processes are central to the production of cellular energy, and energetic deficit correlates with many metabolic diseases and ageing. As the mutant mtDNAs accumulate, they progressively erode the individual cell’s energetic capacity. Ultimately, cellular energetics drops below the threshold necessary for normal cellular and tissue function, and leads to a decline in organ function, tissue failure, and an ageing phenotype [12,60].

While mitochondrial defects are systemic, the clinical manifestations are often organ specific. This is because different organs and tissues have different needs and roles in energy homeo-

stasis. Certain tissues require high levels of mitochondrial ATP, such as the central nervous system, the heart, and the muscles. These organs are preferentially affected as mitochondrial energy production declines. Other tissues store energy in fat. The liver is an energy homeostatic tissue, maintaining the serum glucose level within acceptable limits [49].

Mitochondrial disease or dysfunction (a cellular energy deficiency problem) is at the root of all these diseases. It is generally accepted that minimizing mitochondrial dysfunction is of central importance in maintaining cellular and body's fitness and also in counteracting mitochondrial diseases. The chapter may hold an important key to understanding mitochondrial disease (i.e., the body cannot make enough energy, or ATP). Mitochondrial diseases primarily affect the brain, heart, and muscle tissues at varying levels of severity. Almost all cells in the body have mitochondria, which are tiny "power plants" that produce the body's essential energy. When someone has mitochondrial disease, their power plants do not work properly and some functions in the body (e.g., muscles and neurological pathways) do not work normally. The body can have a power failure similar to a "brown out" or a "black out".

Mitochondria are highly dynamic organelles which play a central role in cellular homeostasis. Mitochondrial dysfunction leads to life-threatening disorders and accelerates the ageing process. A common denominator of these lifespan-modulating interventions seems to be defined by their ability to impact on cellular energy metabolism and stress response [61].

Alterations in mitochondrial structure and function, nDNA, and/or mtDNA mutations can impair OXPHOS, which in turn can reduce energy production, alter the cellular redox state, increase ROS production, deregulate Ca^{2+} homeostasis, and ultimately activate the mitochondrial permeability transition pore (MPTP), leading to apoptosis. The consequences of OXPHOS perturbation result in decline of mitochondrial function, and energy output declines, which accounts for ageing, degenerative diseases, metabolic deregulation, endocrine dysfunction, and symptoms such as diabetes, obesity, and cardiovascular disease. As inflammatory response initiates, this will contribute to autoimmune diseases. Finally, cancer cells must manage energy resources to permit rapid replication [5] (Figure 1).

The milder mtDNA variants can also affect caloric metabolism and result in metabolic diseases, such as diabetes and obesity, and degenerative diseases, such as psychiatric disorders, Parkinson's disease (PD), and Alzheimer's disease (AD). The more severe mtDNA mutations, like MERRF (myoclonus epilepsy with ragged red fibres) and MELAS (myopathy, encephalopathy, lactic acidosis, stroke-like episodes), cause progressive multisystem diseases, frequently resulting in premature death. The most severe mtDNA mutations can lead to lethal childhood diseases, such as Leigh syndrome [62].

While mtDNA mutations have permitted humans to adapt to stable regional environmental energetic differences, many energy resources and demands fluctuate cyclically, for example, seasonal changes in temperature and food supply. As these mitochondrial bioenergetic parameters fluctuate with the environment, they drive posttranslational modification of the proteins of the epigenome and the signal transduction pathways. In this way, the expression of nDNA-coded bioenergetic genes is coupled to environmental changes through mitochondrial energy flux [63–64]. This new bioenergetic perspective not only provides a framework

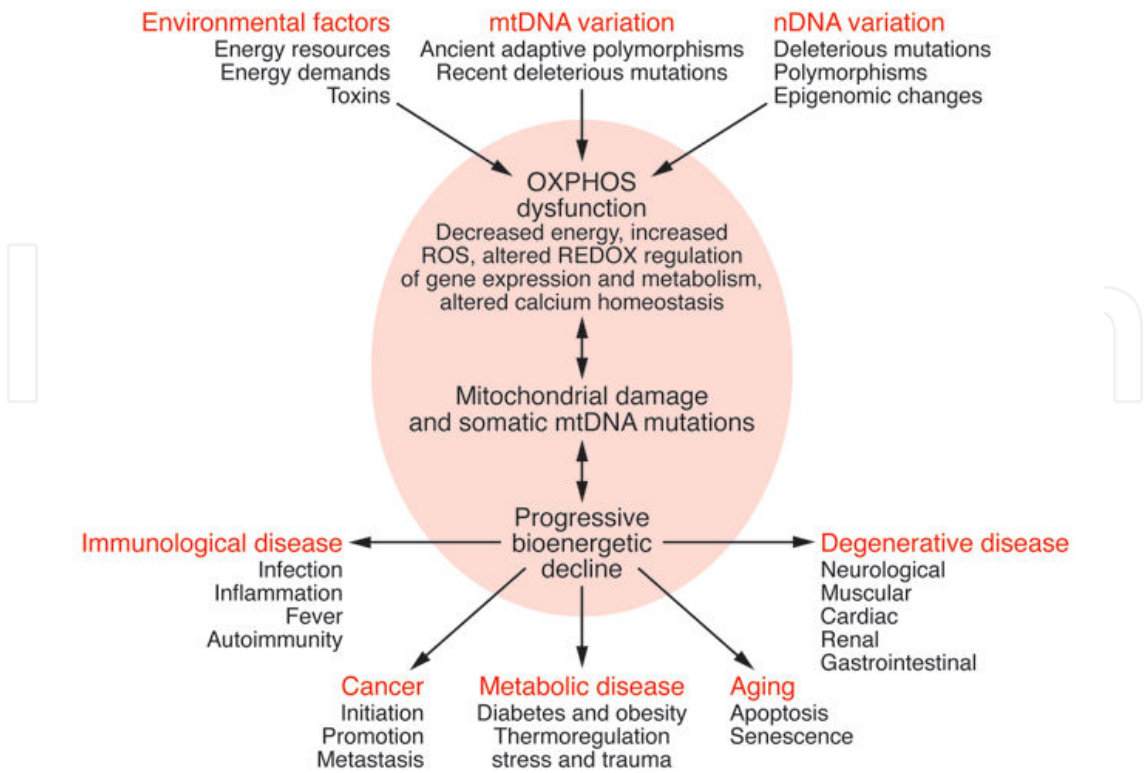


Figure 1. Bioenergetic paradigm for metabolic and degenerative diseases, cancer, and ageing. Figure adapted from reference [5].

within which the genetics and pathophysiology of “complex” diseases, such as PD, AD, autism spectrum disorders (ASDs), and psychiatric disorders [5] can be re-evaluated, it also provides a coherent theory for the aetiology of the “complex” metabolic and degenerative diseases, suggesting powerful new approaches for their presymptomatic diagnoses, reliable prognosis, and effective treatment and prevention.

3. Mitochondrial diseases

Enormous strides have recently been made in our understanding of the biology and pathobiology of mitochondria. Many diseases have been identified as having been caused by mitochondrial dysfunction, and many pharmaceuticals have been identified as previously unrecognized mitochondrial toxicants. Meyer et al. reviewed the importance of mitochondrial function and maintenance for health based on the genetics of mitochondrial diseases and the toxicities resulting from pharmaceutical exposure [11]. There are, however, currently no pharmaceutical cures for any mitochondrial disease [65].

The diseases described above are unambiguously caused by mitochondrial dysfunction. There are also many very common diseases for which there is strong correlative evidence suggesting that mitochondrial dysfunction is at least partially causative [50]. These are frequently diseases of old age or energy homeostasis and include neurodegenerative diseases such as PD and AD

[42], many cancers [34,66], diabetes, metabolic syndrome, cardiovascular disease [67], and others [68]. Considerable effort is currently devoted to investigate whether these relationships are causal. There is experimental evidence demonstrating that defective mtDNA replication and repair can accelerate organismal ageing [52].

The existence of so many mitochondrial diseases illustrates the critical importance of mitochondria for health. Why did it take us so long to realize that many diseases are in fact mitochondrial diseases? Part of the answer is surely that they are very complicated, although they often target tissues with high energy use, and there is significant variability in their presentation. Some mtDNA mutations result in single-tissue diseases, others affect a wide spectrum of tissues, and others affect different tissues in different patients, with varying ages of onset [69]. However, the absence of fundamental knowledge about the biology and genetics of the mitochondrion limited a deeper understanding of the inheritance and pathophysiology of mitochondrial diseases.

3.1. Classic mitochondrial disorders

Classic mitochondrial disorders result from mutations in mtDNA or nuclear genes that disrupt mitochondrial respiratory function. These diseases typically have brain and skeletal muscle manifestations, and therefore they are often referred to as mitochondrial encephalomyopathies. Based on the tissues typically affected in mtDNA diseases, it is generally thought that tissues such as brain, skeletal muscle, heart muscle, and endocrine glands are particularly dependent on respiratory function and have a lower bioenergetic threshold [70].

Leber's hereditary optical neuropathy (LHON) and mitochondrial myopathies were in 1988 the first diseases demonstrated to be caused by mtDNA mutations [71–72]. There are now more than 200 such diseases, including MELAS, MERRF, and many others [73]. Importantly, cellular dysfunction and clinical disease do not occur until a threshold proportion of mtDNAs carrying mutations (heteroplasmy) is reached [74–75]. Together, these diseases affect at least 1/10,000 people clinically [76], establishing mtDNA mutations as a major cause of disease.

Most patients with mtDNA diseases caused by deletions that cross two or more gene boundaries (intergenic mutation) generally do not reproduce. Therefore, most intergenic mutations arise *de novo*, resulting in sporadic disease [71]. Common presentations of this class of diseases include chronic progressive external ophthalmoplegia (CPEO) and the Kearns-Sayre syndrome (KSS) [77]. In contrast, most maternally inherited mtDNA diseases are the result of mutations confined within the gene commonly involving one or few base changes (intragenic mutations). Examples of this latter class of mtDNA mutations include LHON [72], MERRF syndrome [78–79], and neurogenic muscle weakness, ataxia, retinitis pigmentosum (NARP), and Leigh syndrome [80]. Over 200 pathogenic mtDNA base substitution mutations associated with a broad spectrum of clinical phenotypes have been identified, including encephalomyopathy, mitochondrial myopathy, exercise intolerance, gastrointestinal syndromes, dystonia, diabetes, deafness, cardiomyopathy, AD, and PD, etc [81].

In addition to recent deleterious mutations and ancient adaptive mtDNA variants, somatic mtDNA mutations play an important role in human health. Moreover, somatic mtDNA

intergenic and intragenic mutation levels are elevated in the organs of patients with degenerative diseases. The accumulation of somatic mtDNA mutations causes an age-related decline in mitochondrial function, thus exacerbating partial inborn defects in mitochondrial function leading to the delayed onset and progression course of age-related diseases [53]. Experimental results from mtDNA mutator mice suggest that mtDNA mutations in somatic stem cells may drive progeroid phenotypes without increasing oxidative stress, thus indicating that mtDNA mutations that lead to a bioenergetic deficiency may drive the ageing process [52]. Thus, somatic mtDNA mutations provide the ageing clock. Large-scale deletions in some cell types can attain a threshold to directly affect OXPHOS. Single-cell studies have shown that deletions can occur in ~32 to 80% of mtDNA molecules in *substantia nigra* neurons of brains from patients with PD [82].

Since most mitochondrial proteins are nuclear encoded, it is not surprising that mutations in many nuclear genes also cause mitochondrial diseases. For example, mutations in DNA polymerase γ — the only mtDNA polymerase and thus responsible for all mtDNA replication and repair — cause a wide range of mitochondrial diseases including progressive external ophthalmoplegia, and Leigh's syndrome, among others [83]. Friedreich's ataxia is caused by mutations in the gene encoding frataxin which is involved in iron-sulphur cluster assembly [84]. Diseases caused by mtDNA and nDNA mutations are estimated to collectively have an incidence of ~1/4000 individuals [85–86].

These and related studies will permit determination of exactly how important the mitochondrial and mtDNAs are in determining the complex physiology and inheritance of the common “complex” metabolic and degenerative diseases that demand much of the healthcare resources in both developing and developed countries.

3.2. Mitochondria and cardiovascular diseases

Cardiovascular disease remains the commonest form of mortality and morbidity in the Western world. There remains an urgency to identify and translate therapies to reduce the effects of this disease and its associated co-morbidities. Vascular smooth muscle cells are the primary source of extracellular matrix and collagen, and it has been suggested that loss of viability and vitality of these cells contributes to plaque vulnerability and rupture. It is the loss of ATP that may ultimately be more detrimental. Finding alternative sources of ATP synthesis by energetic reconfiguration may also provide a vital link in delaying the kinetics of plaque rupture [87].

Excitation–contraction coupling in cardiac myocytes consumes vast amounts of ATP that need to be replenished by OXPHOS. During a single heartbeat, ~2% of the cellular ATP is consumed, and the whole ATP pool of cardiac myocytes is turned over within one minute. To orchestrate OXPHOS in response to constantly changing workloads of the heart, constant availability of ATP must be secured [88].

A large body of work has shown that endothelial dysfunction contributes to the pathogenesis of cardiovascular disease, and considerable effort has been put into defining operative mechanisms. Recent work has emphasized the importance of mitochondria for

endothelial function. Although they have long been recognized for their role in bioenergetics, mitochondria participate in a host of other cellular processes. It is now recognized that endothelial mitochondria play a prominent role in signalling cellular responses to environmental cues. An important mode of mitochondrial signalling is the regulated production of ROS. Blood markers of mitochondrial dysfunction, such as mtDNA damage and mitochondrial oxygen consumption in circulating leukocytes or platelets, may facilitate studies of systemic abnormalities of mitochondrial function and their relation to cardiovascular disease [89]. The presented studies suggest that mitochondria-directed therapies have potential for the prevention and management of cardiovascular disease, in part by improving mitochondrial function in the endothelium.

3.3. Mitochondria and metabolic diseases

Metabolic syndrome is a growing epidemic in the United States and worldwide. Currently, approximately 34% of the US population are living with this diagnosis [90–91] and it is expected that this number will continue to increase. One of the hallmarks of metabolic syndrome is central obesity, an increase in visceral white adipose tissue (WAT) around the midsection. Central obesity not only contributes to metabolic syndrome but also increases individual risk for type 2 diabetes mellitus (T2DM) and cardiovascular disease [92].

3.3.1. Obesity

An excess consumption of high-calorie foods appears to be one of the key factors in the epidemic of obesity [93], which increases the risk for developing diseases with a bioenergetic component [94]. As described above, these include cardiovascular disease [95], hepatotoxicity, and neurodegenerative diseases. While a high caloric intake can be offset by exercise (for example, the gold medallist Michael Phelps remains lean despite consuming up to ~12,000 calories per day), increasing evidence suggests that physical activity, on average, is declining [95]. This has led to heightened efforts to promote increased energy utilization and to better understand how altered intermediary metabolism, perturbations in cellular bioenergetics, and genetic differences contribute to the risk for becoming obese and insulin resistant [40].

Obesity is a primary risk factor for numerous metabolic diseases including metabolic syndrome, T2DM, cardiovascular disease, and cancer. Although classically viewed as a storage organ, the field of white adipose tissue biology is expanding to include the consideration of the tissue as an endocrine organ and major contributor to overall metabolism. Given its role in energy production, the mitochondrion has long been a focus of study in metabolic dysfunction, and a link between the organelle and white adipose tissue function is likely [90]. Physical exercise is a promising strategy to counteract liver mitochondrial damage [96–98]. Exercise is considered a non-pharmacological tool against several lifestyle disorders in which mitochondrial dysfunction is involved. Both exercise types (voluntary physical activity and endurance training) counteracted oxygen consumption (RCR, P/O ratio, and FCCP-uncoupling state) impairments and improved mitochondrial membrane potential ($\Delta\psi_m$) (lag-phase). In conclusion, exercise prevented or reversed the bioenergetic impairment induced by non-

alcoholic steatohepatitis, and both prevents and mitigates non-alcoholic steatohepatitis-induced liver mitochondrial structural and bioenergetic impairments [96].

Mitochondria lie at the heart of systemic metabolic regulation. They act as end-point regulators of metabolic rate and affect thermogenesis primarily by increasing proton leak. In brown fat, the relatively high expression of uncoupling protein 1 (UCP1) allows re-entry of protons into the mitochondrial matrix without generating ATP. This uncoupling therefore generates an increase in substrate utilization and ETC turnover, as well as energy in the form of heat [99]. Despite the low amounts of brown fat in humans, as little as 50g of brown fat has been estimated to be capable of utilizing up to 20% of basal caloric needs [100]. This suggests that decreasing mitochondrial efficiency is an attractive therapeutic option for obesity [40].

3.3.2. *Diabetes Mellitus (DM)*

DM is a common degenerative disease and one of the leading causes of morbidity and mortality in developed countries. DM is a heterogeneous disease, affecting nearly every organ in the body. It has a common phenotype of impaired glucose tolerance and can be divided in type 1 (T1DM) and type 2 (T2DM). T1DM occurs mainly in childhood and puberty and is characterized by an absolute insulin deficiency, requiring daily insulin replacement therapy. T2DM usually develops in adults over the age of 40, accounts for 90–95% of all DM cases and is characterized by insulin resistance and/or inadequate compensatory insulin secretion response [101–102].

DM has become a worldwide epidemic with a substantial social and economic burden [103]. The prevalence of this disorder is rising dramatically; an estimated 370 million people worldwide will be suffering from diabetes in 2030 [104]. Among the wide range of chronic complications associated with diabetes, brain degenerative events, cognitive deterioration, and dementia have assumed pivotal importance in the last few decades [105]. In particular, diabetes is considered to be a major risk factor for the development of AD and PD [106–107]. Mitochondria take centre stage in the brain since neurons have a limited glycolytic capacity, making them highly dependent on aerobic OXPHOS to fulfil their energetic requirements [108].

Mitochondrial dysfunction is at the centre of many metabolic disorders, such as obesity and T2DM. It is widely believed that these disorders can be avoided by regular exercise and restricted food intake [109–110]. Imbalanced energy homeostasis is characteristic of obese and T2DM patients. Interestingly, metabolic inflexibility can already be observed in pre-diabetic individuals suffering from insulin resistance [111], limiting the ability to switch from fatty acid breakdown to fat storage after a meal, and vice versa [112]. Diverse mitochondrial parameters vary between insulin-resistant and insulin-sensitive subjects, such as mitochondrial number, structure, and function. This suggests that mitochondrial dysfunction might contribute to metabolic inflexibility and insulin resistance [113].

Chronic overnutrition and physical inactivity are major risk factors for insulin resistance and T2DM. Recent research indicates that overnutrition generates an increase in hydrogen peroxide (H₂O₂) emission from mitochondria, ultimately decreasing insulin sensitivity. Fisher-

Wellman et al. review the principles of mitochondrial bioenergetics and redox systems' biology, and offer new insight into how H_2O_2 emission may be linked via redox biology to the aetiology of insulin resistance [28]. This concept is consistent with the principles of cellular energetics and suggests that, in the absence of lifestyle (e.g., exercise) and/or dietary (e.g., caloric restriction) interventions designed to restore metabolic balance, pharmacological strategies must be devised [28].

More importantly, the dynamic behaviour was impaired in high-fat diet-induced (HFD) obese mice, accompanied with disturbed mitochondrial respiratory function and decreased ATP content in skeletal muscle. Altogether, mitochondria are dynamic organelles *in vivo* in skeletal muscle, and are essential in maintaining mitochondrial respiration and bioenergetics. It appears that mitochondrial dynamics and bioenergetics in diabetic skeletal muscle are impaired [16]. Dysfunctional mitochondrial bioenergetics and oxidative stress exist in T1DM [114].

Disruption of mitochondrial function is also implicated in the aetiology of the disease. For example, mitochondria of T2DM patients have reduced ETC capacities [115]. The ability of pancreatic β -cells to regulate blood glucose levels rely on mitochondrial ATP generation. Mitochondrial dysfunction or reduced mitochondrial number could impair the insulin-signalling cascade. Excess mitochondrial ROS in β -cells inhibits OXPHOS, leading to a decrease in ATP for glucokinase and the low ATP/ADP ratio will result in inactivated K_{ATP} channels and impaired insulin secretion [15]. A decline in ATP generation affects the glycolysis ratio, decreasing glucose, fructose, and several amino acids' utilization [116–117], leading to severe energetic impairment. Therefore, improving mitochondrial respiratory activity seems to be a metabolic adjustment to circumvent injury in hepatocytes. It seems plausible that similar decreases in ATP/ADP ratio occur in streptozotocin-treated rats, and the enhanced activity of the respiratory chain of diabetic rats can be a consequence of these decreased ratios [101].

Pre-diabetes, a risk factor for type 2 diabetes development, leads to metabolic changes at a testicular level. Every year, about 5–10% of the individuals with pre-diabetes become diabetic [118], and population habits may increase these rates. Adenylate energy charge was decreased in pre-diabetic rats, as were ATP and ADP levels. Conversely, AMP levels were increased, evidencing a decreased ATP/AMP ratio. Testicular mitochondrial function was compromised by inhibiting the PGC-1 α /Sirt3 axis and the mtDNA copy number, decreasing respiratory capacity, and increasing oxidative stress in pre-diabetes [119].

3.4. OXPHOS disorders

OXPHOS disorders can be classified genetically according to whether the primary defect is in the nuclear or mitochondrial genome, as well as by the pathway primarily affected. There remains a considerable lack of understanding of the pathogenic mechanisms involved in clinical symptoms and the deterioration. The central role of OXPHOS in metabolism suggests that many features are related to abnormal metabolic consequences of the defects.

In addition, OXPHOS defects can be tissue specific, due to the variable metabolic thresholds for the different OXPHOS enzyme complexes in each tissue [120]. Tissue specificity may limit

the systemic effect of metabolic changes while still inducing marked abnormalities within the affected tissue. There are, however, likely to be many contributing factors including tissue-specific expression of nuclear OXPHOS genes, different metabolic needs of a tissue (for example, burst activity seen in some neurons versus cells with predominantly continuous biosynthetic functions), and tissue-dependent segregation of heteroplasmy [121].

The treatment of patients with OXPHOS disease remains very limited, but counteracting the most damaging metabolic changes may be beneficial in some patients, and is the mainstay of treatment at present. An inability of mitochondria to supply sufficient ATP to meet cellular needs is often assumed to be the primary effect of mitochondrial disease mutations [122].

3.5. Mitochondria and neurodegenerative diseases

The neurodegenerative diseases are a key health issue because they are profoundly debilitating [123]. In the past decade, the genetic causes underlying many familial neurodegenerative disorders, such as Huntington's disease (HD), Parkinson's disease (PD), Alzheimer's disease (AD), dominant optic atrophy, Friedreich ataxia, amyotrophic lateral sclerosis, and Leber's hereditary optic atrophy have been elucidated. However, the common pathogenic mechanisms of neuronal death are still largely unknown. Mitochondrial dysfunction has emerged as a potential 'lowest common denominator' linking these disorders [124]. Oxidative damage to mitochondrial membranes, enzymes, and the ETC components, culminate in impaired mitochondrial ATP production and facilitated MPTP opening [125]. Mitochondria play multiple roles in the maintenance of neuronal function under physiological and pathological conditions [126].

Brain function is almost totally dependent on a continuous supply of glucose and oxygen. Although the brain represents only 2% of the body weight, it receives 15% of the cardiac output, and consumes 20% of total body oxygen and 25% of total body glucose [127]. A high aerobic capacity of the brain is required for the mitochondria to generate sufficient ATP to maintain and restore ion gradients across the enormous area of plasma membrane, to maintain the compartmentation of neurotransmitters, and to drive exocytotic and endocytotic synaptic vesicle cycling [126]. Given the brain's high energy requirements, any decline in brain respiratory chain enzyme complexes' activity with ageing could have a significant impact on brain function, as well as on the aetiology and progression of age-associated neurodegenerative disorders [128–130].

An aged brain has a decreased capacity to produce ATP by OXPHOS and this becomes limiting under physiological conditions in aged individuals. The impairment of brain mitochondrial function in ageing is mainly due to decreased electron transfer rates in complex I and IV [131]. Previous results have shown an impairment of complex I activity in brain mitochondria of aged rats which was ascribed, in part, to oxidation of cardiolipin [132]. The age-associated alterations to brain mitochondrial cardiolipin were prevented by treatment of aged rats with melatonin [133]. It is reasonable to assume that melatonin's ability to prevent the age-related alterations of mitochondrial bioenergetic parameters in rat brains, could be ascribed (in addition to other factors) to its protective effect against cardiolipin peroxidation. Thus, the effect of long-term administration of melatonin against the age-dependent mitochondrial

oxidative damage could be accompanied by an improvement of mitochondrial bioenergetics and brain function, and therefore to health in general [128].

Deficiency in complex IV activity may be a crucial factor in the aetiology, progression, and prevalence of several neurodegenerative diseases associated with ageing, in particular AD. The results may prove useful in elucidating the molecular mechanisms underlying mitochondrial dysfunction associated with the brain's ageing process, and may have implications in the aetiopathology of age-associated neurodegenerative disorders, and in the development of potential treatment strategies. Melatonin treatment may represent a valid therapeutic strategy for combating brain ageing process and age-related neurodegenerative disorders, in which complex IV deficiency and oxidation/depletion of cardiolipin could play a critical role [128].

In recent years, the field of neurometabolism has been greatly amplified by the recognition that bioenergetic dysregulation may be a critical pathophysiological factor in diseases of the nervous system [130]. Indeed, there is increasing appreciation for the concept of energy failure — principally from mitochondrial dysfunction — as a key mechanism resulting in neuronal death seen in neurodegenerative diseases [134].

Previous studies have suggested that mitochondrial dysfunction plays a central role in the pathogenesis of neurodegenerative disorders, including AD [135]. Alzheimer's pathology is accompanied by a decrease in expression and activity of enzymes involved in mitochondrial bioenergetics, which would be expected to lead to compromised ETC complex activity and reduced ATP synthesis [136]. Mitochondrial bioenergetic deficit precedes Alzheimer's pathology; in addition to the lowered mitochondrial bioenergetic capacity, impairment of OXPHOS is associated with increased free radical production and the resultant oxidative damage. Overproduction of ROS and higher oxidative stress is characteristic of brains from AD [137]. Mitochondria and brain bioenergetics are increasingly thought to play an important role in AD [138]. In summary, mitochondrial dysfunction and deficits in bioenergetics occur early in pathogenesis and precede the development of observable plaque formation of AD. Mitochondrial dysfunction provides a plausible mechanistic rationale for the hypometabolism in the brain that precedes AD diagnosis and suggests therapeutic targets for prevention of AD. Further, the age of reproductive senescence markedly exacerbated mitochondrial and bioenergetic dysfunction, which is coincident with marked increases in AD pathology. In addition, one consequence of oxidative damage to mtDNA may be impairment of mitochondrial respiratory capacity. Mitochondrial DNA damage is associated with reduced mitochondrial bioenergetics in Huntington's disease. HD cells may be more dependent on glycolysis than respiration to compensate for ATP production [139]. A number of studies have identified mitochondrial abnormalities within neuronal cell bodies in progressive multiple sclerosis, leading to a deficiency of mitochondrial respiratory chain complexes or enzymes [140].

3.6. Mitochondria and cancer

Cancer cells exhibit large varieties of metabolic changes which are associated with alterations in mitochondrial structure, dynamics, and function. Mitochondria can regulate tumour growth through modulation of the TCA cycle and OXPHOS, and are also crucial in controlling redox

homeostasis in the cell, inducing them to be either resistant or sensitive to apoptosis. All these reasons locate mitochondria on centre stage in understanding the molecular basis of tumour growth [141]. A change in cellular bioenergetics is one of the key hallmarks of cancer. The Nobel prize-winning German physician and scientist, Otto Warburg, discovered that mitochondria in cancer cells do not efficiently generate energy; that almost all neoplastic cells demonstrate enhanced uptake and utilization of glucose for glycolysis to generate ATP. While increased glycolytic flux may provide some benefit to cancer cells by increasing ATP production, recent studies suggest that it is advantageous mainly because it generates chemical “building blocks” required for the anabolic processes that must occur prior to cell division [142]. The most glycolytic tumour cells were found to be most resistant to therapy, and most aggressive in metastasis [143–144].

Altered metabolism was among the first cancer biomarkers [145]. Nevertheless, the notion that glycolysis is a universal feature of aggressive tumour growth, and that OXPHOS is counter-productive to tumorigenesis still pervades the literature [146]. There is accumulating evidence that mitochondrial metabolism plays an essential role in tumour cell proliferation. Growing tumours alter their metabolic profiles to meet the bioenergetic and biosynthetic demands of increased cell growth and proliferation [147–149].

Warburg proposed that cancer could originate from the sole inhibition of respiration in human cells, but are the mitochondria of cancer cells dysfunctional? Different studies have indicated that OXPHOS is capable of synthesizing ATP in cancer cells, albeit with a low efficiency [150]. To survive under conditions of glucose limitation, tumour cells use OXPHOS to derive energy from the amino-acids, glutamine, and serine. This process (glutaminolysis) has been demonstrated to occur in multiple types of cancer cells [142,151–153]. Deregulated energetics is a hallmark of malignancy, but metabolic heterogeneity among individual tumours is unknown. A study by Caro et al. [154] demonstrates that a subset of lymphomas is defined by reliance on mitochondrial energy generation and is selectively killed when this pathway is impaired.

Collectively, these studies illustrate how differences in mitochondrial economy, bioenergetic reserve capacity, and autophagy regulate health and disease. It is now also becoming clear that physiological processes such as cell differentiation are associated with profound changes in cellular bioenergetics, including reserve capacity [155]. The challenge for us is to continue to strive to understand more fully how bioenergetics regulates cell and tissue function. Certainly, this would place us in the best position to develop better and more targeted therapies [40].

Numerous studies on cancer cell bioenergetics evidence a large variability in the relative contribution of glycolysis and OXPHOS to cellular ATP production. The corresponding differences in the capacities for glycolysis and OXPHOS demonstrate that there is a cancer-specific metabolic remodelling caused by a combination of genetic and environmental factors. The dogma that cancer cells use solely glycolysis is no longer valid; as such, a detailed bioenergetic characterization of each type of tumour must be performed in order to develop adequate treatments. The growing interest in the mitochondrion in cancer research could lead to the development of adapted metabolic therapies that might also serve to treat mitochondrial diseases [151].

The differences in mitochondrial function between normal cells and cancer cells may offer a unique potential for the design of anticancer agents that deliver mitochondrial targeting drugs to selectively kill cancer cells. The journal *Science* revealed that bioenergetics was the core of malignant transformation of tumour [156], and abnormal energy metabolism was concluded as one of the 10 most notable features of cancer cells by the journal *Cell* [157] — bioenergetics dysfunction is becoming the cornerstone for understanding the pathophysiology of mitochondrial diseases [40]. Here, we summarize the metabolic changes of cancer cells.

In cancer cells, anabolism is enhanced, both glucose and glutamine are important carbon sources which are metabolized for the generation of energy, and anabolic precursors, heavily consumed by cancer cells, are early precursors of non-essential amino acids. This process predominates in cancer cells rendering glutamine an essential amino acid and the source of tricarboxylic acid (TCA) cycle-derived anabolic metabolites. Mitochondrial dysfunction may lead to the activation of HIF-1, therefore triggering the hypoxia pathway in the tumourigenic process. The inability of mitochondria to provide enough ATP for cell survival under hypoxic conditions, results in up-regulation of the glycolytic pathway. This occurs by induction of HIF-1, which not only stimulates key steps of glycolysis but also suppresses mitochondrial respiration in cancer cells, therefore, modulating the reciprocal relationship between glycolysis and OXPHOS. The switch between glycolysis and OXPHOS is controlled by the relative activities of pyruvate dehydrogenase (PDH) and lactate dehydrogenase (LDH). HIF-1 inactivates PDH through pyruvate dehydrogenase kinase 1 (PDK1) induction, resulting in suppression of the Krebs cycle and mitochondrial respiration. In addition, HIF-1 stimulates the expression of lactate dehydrogenase A, which facilitates the conversion of pyruvate to lactate. As a result, mitochondrial contribution to ATP synthesis declines, although the mitochondria might remain functionally intact [158] (Figure 2).

Glucose is mostly phosphorylated by hexokinase II (HKII) in cancer cells, which is up-regulated as its gene promoter sensitive to typical tumour markers such as HIF-1 and has easy access to ATP being more strictly bound to the mitochondria. HKII plays a pivotal role in bioenergetic metabolism, phosphorylates glucose using ATP synthesized by OXPHOS, and releases the product ADP in close proximity of the ANT to favour ATP re-synthesis within the matrix. Its product, Glucose-6-P, is only in part oxidized to pyruvate. This, in turn, is mostly reduced to lactate being both LDH and PDK1 up-regulated. A significant part of Glucose-6-P is used to synthesize nucleotides that also require amino acids and glutamine. Glutaminolysis (breaking down glutamine into α -ketoglutarate (α -KG)) generates malate which, through the malic enzyme, will give rise to NADPH that can be used to fuel lipid biosynthesis, and oxaloacetate (OAA), which will generate citrate, which is necessary for lipid biosynthesis. Citrate in part is diverted from the TCA cycle to the cytosol, where it is a substrate of citrate lyase, which supplies acetyl-CoA for lipid and phospholipid synthesis that also requires NADPH. The reprogramming of mitochondrial metabolism in many cancer cells comprises reduced pyruvate oxidation by PDH followed by the TCA cycle, and increased anaplerotic feeding of the same cycle, mostly from glutamine. This also increases the free fatty acids' uptake, therefore β -oxidation is pushed to produce acetyl-CoA. In cancer cells, many signals can converge on the mitochondrion to decrease the mitochondria permeability transition

(MPT), with consequent enhancement of apoptosis resistance. ROS can enhance Bcl-2 and may induce mtDNA mutations. As indicated, ROS in many cancer cells are over produced. Interestingly, studies have also shown that the $\Delta\psi_m$ is approximately 60 mV higher in carcinomas as compared to their normal controls, which also contribute to the increased ROS [158] (Figure 2).

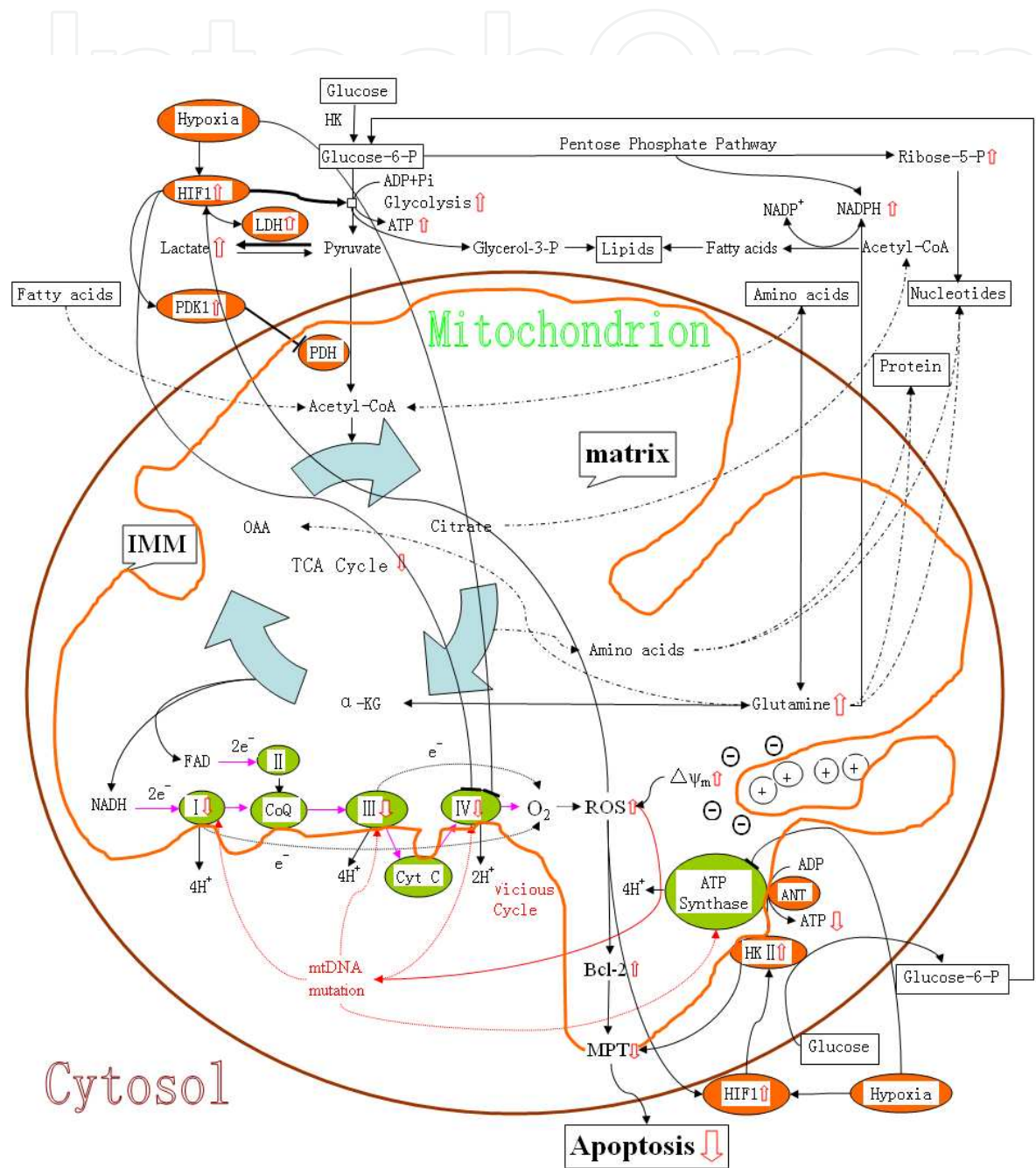


Figure 2. Schematic illustration of metabolic reprogramming frequently occurring in cancer cells, compared with mitochondrial metabolism in normal cells. Cancer cells showed increased glycolysis, pentose phosphate pathway, glutamine consumed, anabolism, $\Delta\psi_m$, and ROS generation, and reduced TCA cycle flux, respiratory complex activities, MPT, and apoptosis.

4. Qi-deficiency and mitochondrial diseases

Under normal circumstances, the body is under conditions in which the viscera are coordinated, Qi and blood are in harmony, and it is in a state of equilibrium known as “both Yin and Yang in equilibrium”. If this balance is broken, the “Yin and Yang in imbalance” appears; this weakens the body’s responses against disease, and the disease will later attack. Just like the Inner Canon of the Yellow Emperor says: “If the vital Qi exists in your body, the pathogenic factors won’t disturb you”. “If the various pathogenic factors attack the body together, Qi deficiency must occur”. “wind, rain, hot or cold, will not lead to Qi deficiency alone, only the pathogenic factor won’t hurt the human”, these indicate the important role of the vital Qi in the fight against pathogenic factors. The so-called “vital Qi” refers to the body’s primordial Qi, necessary to the body’s normal functioning and ability to stay healthy; “pathogenic factors” refers to various contributing factors in illnesses. The body’s vital Qi is the root cause, the pathogenic factors that cause mitochondrial diseases are symptoms.

Since Qi-deficiency is the inherent basis of mitochondrial diseases, Qi-invigorating herbal medicines and prescriptions (QIHMP), therefore, can prevent the occurrence of mitochondrial diseases according to TCM theory. Qi-invigorating herbal medicines (QIHM) are a class of herbs that can tonify the viscera and Qi of the human body, improve Qi-deficiency syndromes, enhance the body’s function, improve disease resistance, have the effects of tonifying five internal organs, calming the mind, regenerating muscles, aiding resistance to cold and heat, and anti-ageing. Commonly-used QIHM include ginseng, astragalus, Codonopsis, Atractylodes, American ginseng, Chinese yam, liquorice, jujube etc., all rich in polysaccharides, which provides the material basis for improving Qi-deficiency syndrome and energy metabolism.

Studies have shown that all QIHM have the effects of improving exercise capacity, anti-fatigue, anti-oxidation, anti-hypoxia, anti-ageing, scavenging ROS, anti-apoptosis, improving immune function, and other benefits. The common regular pharmacological effects of these QIHM are closely related to the mitochondrial function; it is reasonable to assume that all QIHM invigorate Qi through the mitochondrial pathway, which provide evidence for Qi-invigorating therapy used for mitochondrial diseases.

Still, the number of therapeutic approaches for mitochondrial diseases is severely limited in Western medicine. How might we jump-start the search for treating the diseases? One promising approach might be TCM. If mitochondrial dysfunction is as important a factor in the diseases as proposed in this essay, then Qi-invigorating therapy should be as likely to target mitochondrial energetic function. If so, we might be able to modulate mitochondrial function by screening traditional Chinese therapies. These could then be applied to treating the mitochondrial diseases. If this strategy proves successful, then it may have been prescient that a major concept in the parlance of TCM is “Qi”, which we propose that “Qi” is “bioenergy” [25].

According to TCM theory, all kinds of diseases and ailments are born from Qi; Qi refers to a kind of refined nutritive substance that constitutes the human body, and is the most basic motive force, maintaining life’s functional activities. Qi is fundamental to our body; both life and death of humans depends on Qi. Qi is often described in the West as energy, or vital energy.

Therefore, life's activities depend on Qi. Qi underpins the basic theory of TCM and acts as its cornerstone. Qi has been used as a healing technique in China for 4000 years. Chinese people from all walks of life seek relief through a rebalancing of their Qi for ailments, from colds to cancer. From the Chinese perspective, Qi is the origin of true strength and power as well as genuine health — body, mind, and soul. In order to have good health you must have sufficient Qi. If there is not enough Qi (Qi-deficiency), one or more organs can become imbalanced and develop energy function disorders. Impaired mitochondrial ATP formation may be the key characteristic of Qi-deficiency.

The author found that Qi-deficiency led to a marked fall in cellular ATP, and a rise in cellular AMP. Qi-deficiency is the common cause of mitochondrial diseases and can lead to mitochondrial bioenergetics dysfunction, and Qi-invigoration is the basic principle for treatment of Qi-deficiency [26]. As ATP, an energy-rich biomolecule, is universally used for energizing cellular activities, the “Qi-invigorating” action may be mediated by the enhancement of mitochondrial ATP generation. In this regard, our previous studies show that all four widely used QIHM (including ginseng, astragalus root, pilose asiabell root, and white atractylodes rhizome) can increase ATP levels of liver cells *in vivo*. The concept of “Qi” in TCM is closely related to bioenergy in modern medicine; we propose a hypothesis that Qi is bioenergy according to both the ancient concept of Qi and modern bioenergetics [25]. Based on our findings, Qi-invigorating representative prescription Sijunzi decoction [26] and QIHM can enhance the mitochondrial ATP generation capacity, and they have a good effect in the treatment of Qi-deficiency syndrome. It is plausible that mitochondrial diseases involve an improvement of cellular energy status which can be accomplished by Qi-invigoration. We believed that the up-regulation of cellular activities by “Qi-invigoration” in Chinese medicine requires an increased supply of ATP, which is in turn largely supported by mitochondrial OXPHOS. Qi-invigorating prescriptions and herbal medicines have a good effect in improving energy metabolism. Mitochondrial diseases are a result of a decline in “Qi” (Qi-deficiency), and lead to deterioration in functions; therefore, Qi-invigorating therapy for mitochondrial diseases is logical.

5. Qi-invigorating therapy and prevention and treatment of mitochondrial diseases

“Qi theory” in Chinese medicine is profound. Investigation into the scientific connotations of the concept “Qi” and the mechanism of Qi-invigorating herbal medicines and prescriptions (QIHMP) by modern science over the past decade, have become a key point for the modernization of TCM.

“Qi” is closely related to “bioenergy”, both “Qi” in TCM and “bioenergy” in the life sciences have played an important role. Qi-deficiency can lead to energy metabolism dysfunction, which is a common feature of mitochondrial diseases in turn, and this confirmed that Qi-deficiency is the basis of the incidence of mitochondrial diseases; Qi-invigoration is the basic principle for treating Qi-deficiency, Qi-invigoration is also able to improve mitochondrial bioenergetics. Logically, therefore, Qi-invigoration can prevent mitochondrial diseases. TCM

usually interpret the properties of herbal medicines with Qi, and has become one characteristic of treating diseases, this can be understood as “regulating Qi by Qi”.

Therefore, the broad and profound TCM Qi theory and the most recent research of mitochondrial diseases were integrated, the mechanism of Qi-invigorating therapy for mitochondrial diseases was clarified from the perspective of improving mitochondrial bioenergetics, and a novel perspective and new hope were provided for the prevention and treatment of mitochondrial diseases with original academic ideas.

QIHMP have a positive effect in improving the energy metabolism; for example, the Qi-invigorating representative prescriptions Sijunzi Decoction (SD) was able to improve mitochondrial function by enhancing cellular bioenergetics and had the pharmaceutical activities of mitochondrial protection [26]. *Panax ginseng* is one of the most popular QIHM and has been used to promote health, vitality, and longevity in China for millennia. *Panax ginseng* invigorates Qi by improving energy metabolism and boosting energy levels in different body parts to delay ageing [159]. QIHMP can help in boosting the level of vital energy in the body. The studies provide scientific evidence for the mechanism of Qi-invigoration in TCM, which is achieved by improving mitochondrial energy metabolism. As deficiency of Qi is thought to be the cause of mitochondrial diseases in TCM, this property is especially important for using Qi-invigorating therapy to counteract mitochondrial diseases.

The central therapeutic action of QIHMP is their ability to preserve Qi. One direction that scientists have recently explored is the mitochondrial dysfunction theory. *Astragalus membranaceus* is the most popular Qi-invigorating herbal medicine in TCM, is often used in formulas for Qi-deficiency characterized by limb weakness, fatigue, lack of appetite, and dizziness. *Astragalus polysaccharides* (APS), an important bioactive component of *Astragalus membranaceus*, have been applied in the prevention and treatment of cancer in TCM. APS can ameliorate vacuolar degeneration of mitochondria and fragmentation of mitochondrial cristae of hepatocytes in insulin-resistant mice, which indicates the mitochondrial dysfunction and the protective effect of APS [160]. Our preliminary studies indicate that APS can protect mitochondria by scavenging ROS, inhibiting lipid peroxidation and mitochondrial swelling, and increasing the activities of antioxidant enzymes [161]. We proposed that APS perhaps ultimately ameliorate mitochondrial dysfunction by improving energy metabolism; this may be the hypothetical anticancer and cancer-preventive mechanism of APS.

In the book *Cancer — Cares, Treatments and Preventions*, we demonstrate that APS play a role in cancer prevention by improving mitochondrial energy metabolism. We also discovered accidentally that APS could increase the levels of ATP and total adenylate pool (TAP) in hypoxic liver cells, reduce AMP levels, increase ATP/ADP, ATP/AMP ratios and adenylate energy charge (AEC) (i.e., increase cellular bioenergetics), and feedback inhibit OXPHOS by reducing the liver mitochondrial respiratory control rate (RCR), respiratory states 3, and P/O ratio, to regulate energy generation. We found that hypoxia leads to a marked fall in cellular ATP and ADP, and a rise in cellular AMP. Cellular ATP levels are closely linked to mitochondrial function, which is regulated perhaps by AEC. APS stimulated an increased output of ATP and can further decrease state 3 respiration, RCR, and P/O ratio of liver mitochondria compared to a normal group — we consider that this is the result of feedback inhibition by

improving mitochondrial energy metabolism and the bioenergetic level [156]. The mitochondrial energy state can retro-regulate the nuclear-encoded energy genes. The changes in mitochondrial respiratory chain activity are followed by changes in “energy-state messengers” which include ROS (such as the diffusive H_2O_2), mitochondrial and cytosolic calcium, NADH/NAD⁺, ATP/ADP, GTP, AMP, cyclic AMP (cAMP), $\Delta\psi_m$, and ΔpH [162]. APS was able to improve mitochondrial function by enhancing cellular bioenergetics and had the pharmaceutical activities of mitochondrial protection by scavenging ROS, inhibiting lipid peroxidation, and increasing the activities of antioxidant enzymes. The study provides scientific evidence for the pathophysiological mechanism of mitochondrial diseases, which is achieved by improving mitochondrial bioenergetics.

The Mitchell theory has been unable to explain this phenomenon; in recent years, studies have shown that the Mitchell theory has limitations for OXPHOS in eukaryotic cells. The Mitchell theory implies the proton motive force (Δp) across the inner mitochondrial membrane as the energy-rich intermediate of OXPHOS. Δp is composed mainly of an electrical ($\Delta\psi_m$) and a chemical part (ΔpH) and generated by the respiratory chain complexes I, III and IV. The free energy of electron transport of the mitochondrial proton pumps is sufficient to create a Δp of 240 mV, most of which (>80%) represents the mitochondrial membrane potential ($\Delta\psi_m$) and a smaller part ΔpH . The passive proton permeability of biological membranes or the basal proton leak increases exponentially at $\Delta\psi_m$ values above 130 mV. At $\Delta\psi_m$ values above 140 mV, the formation of reactive oxygen species (ROS) increases exponentially. The rate of F_0F_1 -ATP synthase is saturated and maximal at $\Delta\psi_m$ values of about 120 mV. Thus $\Delta\psi_m$ values above 140 mV are not required for maximal rates of ATP synthesis. Instead at high $\Delta\psi_m$ values, the efficiency of OXPHOS decreases due to increased basal proton leak of biological membranes. In addition, part of oxygen will be converted into harmful ROS. From both an economic and health point of view, multicellular organisms require a mechanism that does not rely on the Mitchell theory, while maintaining the $\Delta\psi_m$ at reasonably low levels (120–140 mV), thereby optimizing the efficiency of OXPHOS and can suppress the occurrence of mitochondrial diseases. Surprisingly, the German scientist Kadenbach et al. propose a new mechanism that does not rely on the Mitchell theory, in which high ATP/ADP ratio feedback inhibits CcO (complex IV), and maintains a low $\Delta\psi_m$ value, thereby preventing ROS generation and maintaining high efficiency of OXPHOS — the mechanism represents the new extension of Mitchell theory, known as the “The second mechanism of respiratory control” [163].

According to recent studies, the authors propose that QIHMP, such as *Panax ginseng*, *Astragalus membranaceus*, and the Sijunzi Decoction can improve mitochondrial bioenergetics, while higher levels of bioenergy will feedback inhibit OXPHOS. These studies enriched Kadenbach’s “New extension of the Mitchell Theory” through multiple bioenergetic parameters; this not only provides the strongest evidence for the contention that “The second mechanism of respiratory control represents new extension of the Mitchell Theory for OXPHOS”, but also proposes how to improve bioenergetic levels of cells by QIHMP intervention. A theoretical basis and novel ideas were provided for the research and development of new drugs for mitochondrial diseases, using mitochondrial bioenergetics as a target. Therefore, the authors propose that improving mitochondrial energy metabolism and bioenergetic levels are the

possible biological mechanisms to prevent and treat mitochondrial diseases. Based on the current research on mitochondrial protection and improvement of energy metabolism by QIHMP, we prove that QIHMP act by improving the bioenergetic state, and have activities of making the body more energetic and dynamic. Qi-invigoration is achieved through the mitochondrial energy metabolic pathway. This provides a scientific basis to clarify why Qi-invigorating therapy in Chinese medicine is suitable for treating mitochondrial diseases from a mitochondrial bioenergetic perspective.

QIHMP have a unique advantage in the process of counteracting mitochondrial diseases; intervention can be performed by multi-level, multi-channel, and multi-target methods, focusing on increasing the vital Qi of our body, helping to improve symptoms and signs, to improve the life quality of patients, and prolong survival. This is one of the characteristics of TCM for the prevention and treatment of mitochondrial diseases, and Qi-invigorating therapy plays an important role in the comprehensive treatment of mitochondrial diseases. Qi-invigorating prescriptions (QIP), the combination of commonly used QIHM, are used for the treatment of Qi-deficiency under the guidance of Qi-invigorating therapy. If doctors can focus on pathogenesis features of Qi-deficiency at the different levels of the main symptom, accompanying symptoms, deteriorated case syndromes, and synergize with Chinese herbal medicines, such as warming Yang, nourishing Yin, calming the nerves, reducing phlegm, invigorating the circulation of blood, astringing, clearing heat medicines, and others, based on benefiting Qi and complementing deficiency, so that the monarch and ministerial drugs synergize in an orderly fashion, just match the symptoms, then QIP can be widely used in a variety of clinical disorders.

In summary, mitochondria are responsible for the generation of cellular energy and are believed to play a central role in ageing and mitochondrial diseases. *In vivo* experiments have shown that almost all QIHM could promote mitochondrial ATP generation in various types of tissue including the brain. We propose in this chapter that Qi-invigorating therapy can be used for the prevention and treatment of mitochondrial diseases for the first time in the world, and that good medical effects may thereby be attained.

6. Conclusion and perspectives

This chapter has focused on the growing body of evidence that mitochondria, although the major source of ATP, are also intimately involved in the aetiology of numerous human pathologies. Therefore, effective prevention and treatments for mitochondrial diseases has become a pressing issue. It is evident that Qi-invigorating therapy will furnish a greater efficacy and selectivity for these diseases, but will lead to fewer undesirable side effects. It has been over 50 years since the first description of a patient with a mitochondrial disease [2]; with the rapid development in mitochondrial medicine, mitochondrial disease research focused on unravelling the aetiology of mitochondrial dysfunction for the first 30 years. Currently, the most important focus is on providing a preventive method or cure for these devastating diseases.

A rational way to combat mitochondrial dysfunction is to correct the bioenergetic alterations seen at the cellular level. This approach is theoretically applicable in all mitochondrial diseases. Many research groups around the world have established ways to manipulate mitochondrial pathology in cellular models. Now is the time to test these therapies *in vivo*. Despite the apparent lack of therapy, the confirmation of a mitochondrial disease is important to prevent secondary mitochondrial dysfunction as seen in malnutrition or deconditioning. This chapter gives an overview of some potential breakthroughs and the hopes in pursuit of the first effective prevention and treatment for mitochondrial diseases by Qi-invigorating therapy. There seems to be light at the end of the tunnel, although currently it is difficult to predict when such treatment will become available. The primary cause of most mitochondrial diseases is a multifaceted aetiology; hence, efforts to develop effective drugs should be devoted to the design of Qi-invigorating prescriptions that work in synergy to protect the mitochondria.

TCM will provide new philosophical thinking and selective application for modern medicine. TCM is full of ancient Chinese wisdom and philosophical speculation, it advocates “preventive treatment of disease”, and Chinese Preventive Medicine benefits a lot from it. Chinese medicine views the human body as a whole, focusing on the adjustment of inner balance, pays more attention to patients than to the diseases, and the systemic therapy was used for more than 2,000 years.

Developmental ideas of traditional Chinese medical philosophy and modern Western medicine are converging. The current health concepts and medical models are profoundly changed; from the perspective of developmental trends, Western medicine also began to pay attention to the disease prevention, self-care, individualized treatment and environmental influence on the disease, transition from disease-centred to patient-centred, which match the concept “disease prevention is the primacy”, “man is an integral part of nature”, and is consistent with the essential characteristics of “overall concept” and “treatment based on syndrome differentiation” in TCM for thousands of years. Chinese medicine believes that the health of people is interrelated with nature and is under its dominance, that people should preserve harmony with nature, that the human body is a systemic whole, that the relationship between the main viscera can be described by the five elements theory, and that health depends on the balance of Yin and Yang. TCM guides doctors in the prevention and treatment of disease through the system’s theory.

However, not all clinical questions can be explained by TCM’s theory; the new concepts and breakthroughs of modern Western medicine are sometimes difficult to integrate into the theoretical framework of TCM. Therefore, there is an urgent need to achieve exchanges and a convergence between the two systems, to translate the theory of TCM into the language of modern life sciences.

Qi theory is the core of the basic theory in TCM, the concept of “Qi” is complex and messy, the connotation of Qi is colourful, the extension of Qi is unlimited, and Qi has become an enigma of Chinese medicine. Since there is no concept of “Qi” in modern medicine, it is the biggest difference between Chinese and Western medicine, which leads to obstacles for the mutual communication between the two medical systems. The essence of Qi is extremely important and is an unavoidable major scientific problem to the modern development of TCM.

So the nature of “Qi” should become the key scientific issue to be resolved first. This chapter may provide a breakthrough point to reveal the essence of Qi in TCM, and to achieve further genuine integration with Western medicine.

It is not easy to do this, but it is very important for the entrance of TCM into the international academic community, and then to endow it with vitality in the future. The purpose of both Chinese and Western medicine is to maximize health protection; we should gradually break through the barriers between Chinese and Western medicine, and give full play to their respective advantages. On the one hand we want to make full use of new theoretical ideas and methods, new technologies, and multi-disciplinary cross-penetration of modern Western medicine, accelerating innovation of traditional medicine theory and technology. On the other hand, we should give full play to the characteristics and advantages of traditional medicine in the concepts of life, health, the medical model, and other aspects, provide more treatment ideas, and methods and means for modern Western medicine. The material basis and mechanism of Chinese materia medica are clarified on the basis of efficacy.

We think it is possible to build a modern medical system which fuses the advantages of both Chinese and Western medicine. This system will be inclusive and eclectic, not rest on its laurels; both based on history and look to the future; and will be superior to TCM, and possibly also superior to current Western medicine. If the challenges are shared, the challenges will be divided; if the results are shared, the results will be doubled.

With respect to the sacred cause (the maintenance and promotion of human health), let us have a broader vision, more multi-dimensional thinking, and an open mind. We believe that the convergence of traditional Chinese medicine and modern Western medicine will not only help us to achieve better health outcomes and benefit humans’ well-being than are possible with the simple application of either one, but also that it will be possible to open a door leading to a wider world for us in the near future, promoting the development of the health industry.

“Qi is the root of human”, Qi is the centre of TCM from basic theory to clinical practice, Qi theory is the core of the basic theory of TCM, Qi is also an enigma of Chinese medicine. The essence of “Qi” is the key scientific issue needing to be resolved first; “Qi essence, the mechanism of Qi-invigoration and Qi-invigorating therapy for the prevention and treatment of mitochondrial diseases” have been systematically studied by us in the past 20 years and had led to a series of original academic achievements. This has important scientific significance for Chinese medicine theory and its practical application. These studies may help us to find a breakthrough point to reveal the essence of Qi in TCM, in order to achieve genuine integration with Western medicine and lead the development of Western medicine. We proposed the original creative academic ideas that “Qi” and bioenergy are closely related, demonstrated that the mechanism of Qi-invigorating action was implemented by improving mitochondrial energy metabolism, and proposed a new scientific hypothesis for the prevention and treatment of mitochondrial diseases by improving mitochondrial bioenergetics with Qi-invigorating therapy.

It is hoped that the next few years will see a further convergence of Qi-invigorating therapy with mitochondrial bioenergetics function, which will provide a comprehensive view of

mechanisms on mitochondrial diseases. It seems likely that we are on the right track to acquire this understanding, and that it will involve mechanisms rich in novel modern medical sciences and old Qi ideas in TCM about mitochondrial diseases and how to counteract them. New perspectives, new ideas, and new hopes were proposed for mitochondrial diseases.

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