Discussion on the foundation of the theory of traditional Chinese medicine: a unique theoretical and clinical paradigm based on energy-phenotype relation

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JHH, XDD, and DDC conceived the idea, conducted the literature survey and drafted the manuscript; YXJ and XS contributed to the discussion. JHH, XDD, and DDC supervised the work and revised the manuscript. DDC and JHH designed and drew all the schematic diagrams, and all the authors read and approved the final submission.

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Abbreviations
TCM, traditional Chinese medicine; DNA, deoxyribonucleic acid.

Citation

Abstract
Traditional Chinese medicine (TCM) has been catching more and more attention due to its clinical efficacy, but the unique scientific basis of TCM compared to Western medicine has not been clarified. Here, we propose that Western medicine and TCM are two distinct medical paradigms. Western medicine is mostly based on material science, guided by reductionism, and the importance of energy is frequently underestimated while TCM is the opposite which is centered on energy and overlooking the material science. Energy plays a fundamental role in the origin and evolution of life, the creation and sexual reproduction of eukaryotes, sexual differentiation, aging, death, and other behaviors. Under the strain of evolution, life maximizes energy utilization efficiency by forming a multilevel network system with fractal characteristics, which explains the power-law scaling across species. Disease, aging, and death are all caused by an imbalance between free radical damage and repair in the process of energy generation. In the early stage, TCM expressed similar meanings with the following concepts: Yang Qi (Yang, a physiological term. In terms of function and form, Yang qi refers to function; In terms of zang-fu function, it refers to the qi of the six fu-organs; In terms of Yingwei qi, it refers to Wei Qi; In terms of the direction and nature of the movement, it is Yang Qi that is performed in the appearance, upward, hyperactive, enhanced, and light.), Essence Qi (Essence Qi source of vitality and an initial substance for the body.), and Tong (flowing, circulating, and penetrating). Understanding human physiology and pathology, and guiding treatment from the perspective of energy are the main aspects of TCM different from Western medicine. In brief, energy plays an essential role in clarifying the scientific principles of TCM.

Keywords: energy; phenotype; paradigm; traditional Chinese medicine
Background

Traditional Chinese medicine (TCM) is gaining popularity due to its clinical efficacy, but our understanding of its theoretical foundation still needs to be improved. We commonly assume that it is a medicine with a holistic perspective, a unique operating mode of the differentiation and treatment of syndromes, an emphasis on the interplay between nature and humans, and so on [1]. We believe these demonstrate the characteristics but do not point out the scientific foundations of TCM theory.

TCM is known for its apparent differences from modern Western medicine, which can be shown in concrete scenarios. Suppose a patient comes to the doctor with diarrhea. The first that occurs to the doctor of Western medicine will be pathogenic factors such as bacteria, viruses or parasites, etc. Further, he will consider the anatomical positions involved and the pathological nature. However, under the same circumstances, the TCM physician will check whether the condition is heat syndrome or cold syndrome, excess syndrome or deficiency syndrome. Such a mindset is completely different from that of Western medicine.

The concept of paradigm was laid out by the famous philosopher of science Thomas Samuel Kuhn in his masterpiece “The Structure Of Scientific Revolutions” [2]. Moreover, what does the so-called paradigm mean for medicine? It means that a primary principle or rule can be established that other rules must not conflict with, just as our social plans must not conflict with financial budgets. For example, if a tumor patient is diagnosed with Yang Qi (Yang, a physiological term. In terms of function and form, Yang qi refers to function; In terms of zang-fu function, it refers to the qi of the six fu-organs; In terms of Yingwei qi, it refers to Wei Qi; In terms of the direction and nature of the movement, it is Yang qi that is performed in the appearance, upward, hyperactive, enhanced and light.) deficiency syndrome in TCM, any herbs prescribed to him should not cause further damage to Yang Qi in the human body, even if this herb has been confirmed to have direct antitumor effects. If TCM does indeed have a different paradigm from Western medicine, is there some sort of scientific basis underlying this new paradigm? In general, all living organisms consist of two components: the genetic information system and the energy metabolism system. From the discovery of blood circulation, micro-organisms, and cells to the double helix structure of DNA and the central dogma, modern Western medicine steps into the age of molecular biology. So, modern Western medicine can be said to be a medical paradigm based on material science guided by reductionism. In this paradigm, the importance of the energy metabolism system has been underestimated. On the contrary, the energy metabolism system could play a dominant role in TCM. TCM is a medicine that establishes its own paradigm of thought and clinical paradigm based on energy. Here, we will show that the basis of TCM theory focuses primarily on the value of energy, the source and use of energy, and the diagnosis and treatment of energy disorders.

Does Life Follow Some Macroscopic and Universal Laws?

The significance of energy on the origin, evolution, and development of life.

When we talk about energy, we usually think it's all about food or nutrition. Many bacteria, however, rely on hydrogen, hydrogen sulfide, and even minerals for survival [3]. Electrons from the donors are transferred to the electron acceptors. The energy released in the process converts into a proton gradient and is eventually stored in the molecules containing high-energy chemical bonds, such as ATP. This ability is a prerequisite for all living beings [4]. In addition to carbohydrates, hydrogen, hydrogen sulfide, ferrous ions, etc., can also provide electrons. Similarly, there are many other electron acceptors besides oxygen.

In recent decades, various studies have provided a possible picture of the origin of life. The surfaces of seabed rocks are rich in olivine-bearing iron ions. When the seawater penetrates the rock, the ferrous ions are oxidized, releasing heat and a large amount of hydrogen. Then the hydrogen-containing hydrothermal fluid moves upwards and forms the alkaline hydrothermal vents of the deep sea. In the above process, there are reducing electron-donating substances such as hydrogen, catalytically active substances such as iron sulfide, and special microporous structures that can concentrate reaction products. Moreover, proton gradients can also form on both sides of the microporous rock layers, resembling the mitochondrial inner membrane flanks. In this state, hydrogen donates electrons to carbon dioxide, resulting in the formation of simple organic carbonaceous small molecules and the formation of proton gradients. Ultimately, energy is conserved in high-energy phosphate bonds (acyl phosphates) that drive subsequent biochemical reactions, the generation of biological macromolecules, and the formation of the original cell structure, such as the cell membrane [5-9]. The energy mechanisms of electron transfer and proton motive force emerged in the pre-life stage and were inherited by all lives.

The cells of eukaryotes are much more complex than those of prokaryotes. This complexity may derive from the process by which the ancestors of eukaryotic cells acquired mitochondria through endosymbiosis, causing the average energy for each gene to increase by several orders of magnitude, allowing the synthesis of more proteins, increasing the size of the genome and forming more complex cell structures [10,11]. The appearance of mitochondria may have promoted sexual reproduction in eukaryotes[12]. It may also be based on evolutionary selection pressure on mitochondrial quality control, leading to the emergence of bisexual reproduction and mitochondrial uniparental inheritance in eukaryotes [13,14]. There was a very early view that sex determination may be related to metabolic rate, the most typical example being the relationship between sex development and temperature in some reptiles [15,16].

Why do living beings grow fast at birth, then gradually slow down, and finally stop? Energy is the answer given by some biologists. Energy can be divided into two parts: one is for sustaining the body's existence and the other is for growth. As body volume increases, the energy used to sustain the body's existence increases rapidly in proportion to the increase in volume. However, energy production is related only to the area of the inner mitochondrial membrane. As a result, the proportion of energy expended on growth gradually decreases, eventually leading to growth arrest [17]. The significance of energy to life is outlined in Figure 1.

Figure 1 The importance of energy for life. For living organisms, energy plays an important role in the origin, evolution, and development of life. For humans, energy also counts in aging, illness, and death.
Constraints on energy utilization.
In 1932, Max Kleiber proposed “Kleiber’s 3/4 power scaling law”: Metabolic rate scales as the 3/4 power of mass. If body weight increases by four orders of magnitude, its metabolic rate increases by only three orders of magnitude [18]. It was later found that this law applies to organisms spanning 27 orders of magnitude, from bacteria, fish, birds, and plants, to large mammals [19]. The integer multiple of quarter powers is perhaps the most consistent and systematic scaling law in life. For example, the heart rate of animals decreases by 1/4 of mass, the length of the aorta, genome size, and lifespan increase by 1/4, and the volume of white and gray matter in the brain increases by 5/4 powers [20].

The magic transspecies power scaling law is related to energy utilization. For energy and nutrients to reach every cell in the body, the organism has evolved into a multi-layered system with fractal properties. The small variation in cell size among different species determines the similarity in the size of network terminal units contacting the cells. That is why the diameter of the aorta of the blue whale is about ten times bigger than that of humans, but the thickness of the capillaries of both is similar. Natural selection exploits the mathematical properties of fractal networks to optimize energy distribution. Organisms operate in four dimensions instead of three, which explains why the power scaling law is always 1/4 and multiples [21,22]. Energy is limited, so the utilization of energy must be optimized in the process of evolution. The principle of optimization is that the energy consumption in the process of heart delivery should be minimized and energy utilization by peripheral tissues should be maximized, which is the constraint the organisms must obey.

The other side of the coin.
Electrons are transferred in the respiratory chain through a series of redox centers and eventually taken up by acceptors such as oxygen for energy production. However, electron leakage and direct reaction with oxygen still occur, which is generally a sign of mitochondrial dysfunction. The increased free radicals oxidize the lipids of the mitochondrial membrane, resulting in the release of cytochrome c and the initiation of apoptosis to eliminate poor-quality mitochondria [23]. However, excessive free radical production can cause cumulative damage in the body, especially when the repair function is inadequate. For example, suppose the father’s nuclear genome does not match the mother’s mitochondrial genome. In that case, the distance between the redox centers can increase during the respiratory chain assembly, resulting in a sharp drop in electron flow velocity and electron leakage [24,25], contributing to infertility and age-related diseases [26]. In addition, various excessive stresses can also result in the extreme formation of free radicals, which lead to significant damage to biological macromolecules, resulting in decreased activity and function of tissue cells [27]. When the functions of most cells in the body or vital organs are so damaged that they can no longer sustain the lowest level of functioning of life, it means death. This is how evolution works. Evolution combines the favorable or unfavorable mechanisms for survival into one process, and only in this way can life thrive but be doomed to die.

Life in the eyes of physicists.
Energy and entropy are the concepts most familiar to physicists. The second law of thermodynamics states that the entropy of an isolated system increases in one direction. In the famous book What Is Life?, Erwin Schrödinger suggested that life feeds on negative entropy. However, there are various views on the meaning of entropy and the relationship between energy and entropy. Many studies have shown that the energy metabolism rate decreases as organisms age and entropy increases [28,29]. The meaning and measurement of entropy has always been a difficult problem in biology. Ilya R. Prigogine generalized the classical second law of thermodynamics and proposed that entropy also increases in an open system and the concept of a self-organizing dissipative system. The system maintains itself by absorbing and dissipating energy away from equilibrium. The human body is a typical dissipative system [30]. Obviously, in the eyes of physicists, everything is inescapable from energy.

Energy and Energy Distribution in TCM
Of course, there are no such terms as energy, mitochondria and free radicals in TCM, but TCM has grasped the importance of energy and established the method and treatment system for energy disorders.

Yang: the power source of life.
In ancient times, the Chinese had gotten used to observing natural phenomena, from which some deep insights emerged.

The sun meant everything in ancient times. It dominates the day and night rhythm, the annual rhythm, the climate change, and the growth of all things, and it represents energy and life. The sun played a significant role in the life of early humans. In the Xia Dynasty (2070–1600 B.C.E.) of China more than 3,000 years ago, Yang refers to where the sun shined. The place without sunlight was called Yin. For example, the side of the mountain facing the sun was the Yang side, and the dark side was the Yin side [31]. Thus, in this period, Yang had actual reference related to the sun, but Yin had no actual references. It was just a symbol of the absence of sunlight. The origin of the famous Five Elements Theory in TCM may derive from the observation of the seasonal movement of the sun [32]. In the ancient Chinese calendar, a year was divided into five seasons and ten months [33]. The seasons are determined by the movement of the sun. Therefore, we can say that the original Five Elements theory was another way to express Yang (Figure 2).

Later, both Yang and Yin deviated away from the original actual meaning and were developed into abstract concepts. At this time, Yang and Yin were in an equal state. The relationship between Yang and Yin evolved into a profound and unique philosophical model in ancient China [34]. The experience of the Five Elements theory is somewhat similar to that of the Yin-Yang theory. It gradually became abstract and finally evolved into a philosophical model demonstrating the universal link of mutual promotion and/or inhibition (Figure 2).

The importance of the sun is projected to the understanding of the human body by analogy. Yang resides in the human body and provides a power source for all life processes. Su Wen (475–221 B.C.E. unknown), the ancient book of Chinese medicine, the earliest classic of TCM, said that “Yang Qi to the body is like the sun to the earth. If the sun loses its brilliance or illuminating effect, all things on earth become inactive”. By this time, the concept of Yin hasn’t been attached to importance. It is possibly true that early culture and medicine may have placed more emphasis on Yang. For example, the earliest clinical book of TCM, Treatise On Febrile Diseases ancient book of Chinese medicine (200–210 C.E. Zhong-Jing Zhang), classified the disease into three-Yang syndrome and three-Yin syndrome. The former is the excess of Yang, while the latter is the deficiency of Yang to varying degrees.

Essence Qi: source of vitality and an initial substance for the body.
Ancient Chinese people found that all visible things generally went through the cycle of growth, prosperity, and death and seemed to result from aggregation and scattering by some fine, pure and tiny things. In primitive religious activities, such as praying to heaven, they found that their communication with heaven might require some subtle medium, which they believed existed but was invisible. The characteristics of the medium were like that of the fog on the mountain and the clouds in the sky, which is real, subtle, but ethereal. This is the earliest thought sprout of the idea of Qi [35]. At the same time, Chinese ancestors were still thinking about another important question: did such diverse things have a single source? In the ideological history of the pre-Qin Dynasty (1636–1912 C.E.), soil and water were considered the origin of all things [36]. However, since it was difficult to explain the origin of everything by a concrete object, more abstract ideas, such as Essence, have gradually been developed. With the combination of all the above ways of thinking, a new theory has emerged that explains the origin, survival, death, and vitality of
things, namely the theory of Essence Qi (Figure 2).

Figure 2 The TCM theory derived from Yang and the origin of Essence Qi theory. (A) Initially, due to sun-worship, yang was predominate and yin represented the absence of yang, and then gradually evolved into the theory of yin and yang. According to the movement of the sun, people divided a year into five seasons (33) which is where the theory of the five elements and five internal organs comes from. (B) Endowing the cloud and mist the meaning of communicating with gods, the concept of primitive Qi was born. Soil and water had been put forward as the origin of all things (36), and the concept of essence developed. With the combination of all kinds of thinking sprouts above, a new theory that explains the origin, survival, death, and vitality of things has emerged, namely the theory of Essence Qi.

In TCM theory, Essence Qi mainly contains two meanings. First, it can fill the whole body and give it vitality. Secondly, Essence is the initial substance that sustains the human body and can also be some regenerative potential hidden in the body. Essence and Qi both can rise and decline. For example, The Yellow Emperor's Canon Of Internal Medicine (475–221 B.C.E., unknown), the ancient book of Chinese medicine, believes that Essence Qi dominates the human life cycle and describes in detail the changes in Essence Qi from birth to death. It develops gradually after birth, peaks in the prime of life, and then gradually decays. Regarding the first meaning of Essence Qi, which somewhat overlaps with the meaning of Yang, Yang Qi is also suggested to express the meaning of life force, vitality, etc.

Tong (flowing, circulating and penetrating): requirements for energy distribution in TCM.

In an economic system, keeping people and things circulating is the condition for the system's regular operation. TCM has long before recognized the importance of Tong for health. For example, The Synopsis Of The Golden Chamber ancient book of Chinese medicine (200–210 C.E., Zhong-Jing Zhang), puts forward “If five organ original Qi being unobstructed (Tong's) status, and people are fit.” It emphasizes that Tong is a necessary condition for maintaining health.

Ye Tianshi (1667–1745 C.E.), a famous doctor in the Qing Dynasty, developed a new idea of collateral disease theory. Under physiological conditions, collaterals are the final unit of nutrient distribution. Under pathological conditions, a chronic illness damages the collaterals. A prolonged illness impairs the collaterals and leads to the stagnation of Qi and blood (37). The theory of collateral disease embodies the requirement of the principle of Tong that Qi and blood should reach the ultimate and most subtle places of the body. Although TCM does not know what fractal is and its mathematical properties, it has nevertheless accurately grasped the idea that energy distribution should reach each end unit.

Abnormality and recanalization of Tong are essential for diagnosis and treatment in TCM. Tong does more than just promote blood circulation and clear blood congestion. In a broad sense, it also includes calming the liver, promoting qi, resolving phlegm, dispersing knots, dredging collaterals, laxatives, sweating, and diuresis (38).

Energy-phenotype relationship in TCM.

The technology of antiquity could not support ancient medicine to take the path of materials science. They neither knew that there were deoxyribonucleic acid (DNA) molecules in the human body nor did they have the technical means to detect DNA and its abnormalities. However, it is much better possible to identify the energy state and energy distribution. An energy-phenotype relation system was established in TCM by phenotype and a combination of phenotypes.

Regarding the human body as a physical object, its energy consumption can be divided into three parts (39): one is required for maintaining basal metabolism, the other for external mechanical activities, and the third for maintaining body temperature and heat dissipation. The most basic syndrome type of TCM is considering energy expenditure in these aspects. As shown in Figure 3, excess heat syndrome may increase the patient’s basal metabolism and external activities, manifesting as restlessness, loud voice, excessive movement, forceful action, strong pulse, blushing, etc. Heat production will also increase, manifesting as fear of heat, sweating, thirst and other symptoms. In contrast, under Yang Qi deficiency syndrome or cold deficiency syndrome, the patient’s basic metabolism and external activities are reduced, manifesting as a lack of Qi, laziness, weakness, slow pulse, mental distress, etc. Meanwhile, heat production is reduced, manifesting as lukewarm hands and feet, fear of cold, etc. Deficiency heat syndrome may be the middle of transitioning from excess heat syndrome to Yang Qi deficiency syndrome.

When the most basic syndrome types and disease sites of TCM are linked, a very complex system for assessing local and/or systemic energy status arises, such as Lung Warmth syndrome, Spleen-Kidney Yang deficiency syndrome, etc. That is, by phenotype and/or combination of phenotypes, TCM can easily identify energy's state, distribution, and development in different circumstances.

Figure 3 The system of energy-phenotype established in TCM. Description of the most basic syndrome type of TCM from the perspective of energy.

Discussion on the Energy-Based Medical Paradigm and TCM.

Yang, Essence Qi, and Tong are the theoretical concepts of TCM and contain some ancient Chinese ideas about human health. From a philosophy of science point of view, TCM is a world different from modern Western medicine. However, there are some projections between them. The meaning of Yang suggests the importance of energy. Note, however, that we cannot directly regard the Yang Qi of TCM as the mitochondria of modern medicine since the factors and processes of energy regulation are very complex. Neuroendocrine, physicochemical, and microbial factors can cause abnormal energy regulation. The principle of Tong shows the requirement for energy utilization. The Essence Qi can refer to something with regenerative ability, and the attenuation of the Essence is related to the debilitation of the life vigor caused by the accumulation of damage, which fails to be repaired promptly in the process of energy production in the body. A brief projection between TCM and modern Western medicine is shown in Figure 4.
Some experimental studies also strongly support the connection between TCM theory and energy. The function of Yang Qi is closely related to the function of mitochondria, including the regulation and maintenance of body temperature, age-related changes, neonatal diseases, circadian rhythms, immune responses, and flow channels [40]. Previous research showed that patients who used glucocorticoids could be diagnosed as “Yin deficiency and fire prosperous” in the early stage, and long-term use of glucocorticoids changes the syndrome type to “Yang deficiency” or “Yin and Yang deficiency” [41,42]. We observed that short-term application of glucocorticoids significantly increased resting energy metabolism rate, while long-term application of glucocorticoids decreased it. We believe that resting energy metabolism rate changes can describe the transition from kidney-Yin deficiency to kidney-Yang deficiency [43]. Warming-Yang medicines Fu zi (Aconiti lateralis radix praeparata) and its components [44], Ganjiang (Zingiberis rhizoma) and its components promoted mitochondrial production or activity [45]; In contrast, heat-clearing medicines such as Zhimu (Rhizome anemarrhena) and its components could cause the mitochondrial membrane potential to drop rapidly, causing mitochondrial autophagy or apoptosis [46,47]. It has also been reported that berberine, a component of Huanglian (Coptidis rhizoma), can inhibit the activity of respiratory chain complex I [48].

The therapeutic importance of energy may have been underestimated for a long time. Given that life can arise under the action of a continuous flow of energy, is using energy as a guide to repairing damage in the body a particularly unimaginable means? For example, instead of struggling with the pro-inflammatory cells by scrambling to find targeted anti-inflammatory molecules, perhaps imploding them by inhibiting the energy of these cells would be a better substitute. Herbs like Zhimu (Anemarrhenae Rhizoma), the composition of the Baihu decoction, have a rapid and powerful effect on the mitochondria [46,47].

By reviewing the importance of energy and the most fundamental theories of TCM, we concluded that TCM established a theoretical and practical paradigm focused on energy which is quite different from Western medicine. And that is why TCM can survive tenaciously in modern society as traditional medicine. Now, TCM is capturing more and more attention, and studying TCM from the energy perspective could be an important way to reveal its mysteries.

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Conclusion


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