Possible Molecular Basis of Qi in Traditional Chinese Medicine

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Abstract
Qi is arguably one of the most multifaceted and complex terms in all of Chinese philosophy, religion, science and medicine. To appreciate what qi is in the traditional Chinese medicine (TCM) we begin with the etymology and examined the usage of this character qi in pre-Qin classics and TCM literature to trace how it evolved from its original meaning to becoming a more encompassing medical term, loaded with high information content. The character qi was originally associated with vapor, gas, and moist emanation. In TCM literatures the character qi is frequently used in a term called xueqi 血氣 ‘blood and qi’. Although we know a great detail about the biochemistry and physiology of blood, we still cannot precisely explain qi in TCM using modern biomedical language. Recent research has shown that acupuncture with needle twisting can elicit a signal transduction cascade termed mechanotransduction along the connective tissue to sensory neuron as well as intrinsic sensory afferents directly innervating connective tissue. This research prompted us to propose that the ‘qi’ in TCM is related to signal transduction molecules that exist in gas state and such molecules can be transmitted via blood vessels. Based on the current knowledge of signal transduction in biological systems and our understanding of the TCM literature, possible candidate for the ‘qi’ in TCM would be a group of small gaseous molecules, including nitric oxide (NO), that are known as gasotransmitters, major regulators in the nervous, immune, and cardiovascular systems.

1. The etymology of the character qi
Qi is one of the most complex and multifaceted terms in Chinese that defies translation. As the meaning of qi and many qi-associated compound words appear to be so diverse and nebulous, it is practically impossible to identify an English equivalent that matches the term qi in the TCM literatures. Thus, like the words yin and yang, the word qi is transliterated, but not translated into other languages. (1) To understand what is qi in TCM literatures, we begin with the etymology of this character and examine the path along which this character evolved into a ‘loaded’ word with high information content. Fig. 1 listed the earliest Chinese character of qi that appeared in oracle bone inscriptions (ca. 1300-1100 BCE), bronze vessels (ca. 1100-400 BCE), and bamboo strips (ca. 400-200 BCE). (2) In this figure, there are three basic forms for qi graph: 肺, 質, 饂. The first form for graph 肺 appeared in oracle bone inscriptions, with the three bars signifying three layers of vapor. Thus the root meaning of qi is "vapor, moist emanation." However, in the late Shang, qi was mostly used as a syssemanantograph, meaning ‘until, transmitting to,’ an extension of the meaning of vapor or moisture emanation. To differentiate “vapor” from “transmitting to,” the second form of qi graph 質 was introduced which appeared frequently in the bronze inscriptions. This form became the root component (radical) 氣 for constructing words that are related to gas or vapor. The third form of qi graph 饂 appeared at the time of the Warring States period. This graph consists of two components, one represents vapor, the other food utensil, with fire underneath. The modern equivalent of this third graph is xi 饂, meaning “rice, meal.” This graph actually represents an additional differentiation of the original graph qi. In the Analect, Confucius mentioned that he would not allow the meat
portion that he took to exceed the due proportion for the rice portion, even though there was abundant meat supply (肉雖多，不使勝食氣) (3), where the word qi 氣 actually referred to xi 餓. The reason why qi 氣 was also used to signify cooked rice probably related to the fact that rice cooking is accompanied with vapor; it may also be related to the notion that rice is as essential as breath in maintaining life.

Based on the etymological analysis we can trace the evolution of the graph qi 氣 as summarized in Fig. 2. The root meaning of qi 氣 was 'vapor, breath,' which led to the extended meanings include 'transmitting to, till' and 'cooked rice.' With regard to the use of qi 氣 (xi 餓) for "cooked rice," the graph on Chu bamboo slip suggested that the rice sign in the modern graph qi 氣 was mistakenly derived from a fire sign huo 火. Thus the graph qi 氣 was created by adding a food utensil sign shi 食 to qi 氣 to differentiate it from qi 氣, the vapor.

2. The appearance of qi 氣 in pre-Qin classics

To further understand how the evolution and expansion of the meaning of qi occurred throughout the history, we monitored the frequency of appearance of the character qi 氣 in the thirteen pre-Qin classics (Fig. 3A), and the fourteen Master Literatures (Fig. 3B). (4) The character qi 氣 was missing in the Shangshu (尚書 the Book of Documents), the Shijing (詩經 the Book of Odes), the Gongyang Zhuan 公羊傳 and the Guiliang Zhuan 故梁傳, two of the Three Commentaries on the Spring and Autumn Annals. The meaning of qi 氣 used in the rest of the thirteen Classics, which dated from 1200 to 600 BCE, was expanded by forming various compound words. For example, in the Lunyu 論語, the Analect of Confucius, the word qi 氣 was used in compound words such as pingqi 屏氣 (屏氣似不息者), ciqi 與氣 (泰伯：出謂氣，斯道迩矣), and xueqi 血氣 (李氏：少之時，血氣未定), meaning 'holding one’s breath,’ ‘words and tones,’ and ‘blood and sap or physical power,’ respectively. In addition, as noted above, qi 氣 was also used in the Analect and other classics to indicate (cooked) rice or meal. Thus, in these thirteen classics the word qi 氣 was used to refer to physical forms somewhat related to vapor or gas. However, it is interesting to note that this character appeared in the Liji 禮記 with an unusually high frequency, over 50 times.

Among the Master Literatures that we have examined, the word qi 氣 was used more frequently in the Zhuangzi 庄子, the Guanzi 管子, the Liezi 列子, and the Lushi Chunqiu 吕氏春秋 (Fig. 3b). All four are considered to be Daoism literatures, dated around the Warring States period (481–221 BCE), a period of explosion of competing schools of philosophical and political thoughts. It is quite clear that during this period the meaning of the word qi 氣 began to expand into the realm of metaphysics. For example, the Daoist philosopher Zhuangzi (369–286 BCE) wrote, "When the Great Clod [the Earth] exhales breath, it is called wind." (庄子齊物論 大塊噫氣，其名為風). The concept of breath gave rise to the meaning "vital spirit," that is, the life force of all creatures. Thus, the practice of yangqi 养氣 'nourishing the vital spirit' by means of diet, yogic exercises, and breath control, has become an important part of the Daoist quest. The following excerpts serve as examples to illustrate this kind of transition of qi 氣 from a physical arena for vapor or breath into a metaphysical and philosophical arena for more abstract ideas, like elemental forces, influences. (5)

The breath (qi 氣) of heaven is out of harmony; the breath (qi 氣) of
earth is bound up; the six elemental influences (six qi) do not act in concord; the four seasons do not observe their proper times. Now I wish to blend together the essential qualities of those six influences (six qi) in order to nourish all living things, how shall I go about it?

雲將曰：「天氣不合，地氣鬱結，六氣不調，四時不節。今我願合六氣之精，以育群生，為之奈何？」

Heaven and Earth are the greatest of all things that have form; the Yin and Yang are the greatest of all elemental forces (qi). 故天地者，形之大者也；陰陽者，氣之大者也。

This transition is understandable, for the Masters, although they did not know oxygen, they certainly would appreciate the essential nature of breath in maintaining life. It also seems natural for the Daoist Masters to extend the idea of essential nature of breath from human to nature. Thus, wind, cloud, mist, and anything vapor-like could be the breath of heaven, earth and nature. The frequent use of the word qi in the Daoism literatures suggests that the transition of qi from a physical term to a philosophical term was largely prompted by the development of Daoist thinking.

3. The transition of qi from a physical term to medical term

In light of the importance that Daoist literatures put on how to harmonize one’s life with nature, it is only natural that the philosophical term qi described in the Daoist literatures became the precursor of the medical term qi used in TCM. The transition, from a physical term to a philosophical term, and to a medical term, made qi not only an information-loaded word, but also a word sometimes clouded with many nebulous meanings. The original root meaning of qi as “vapor, steam, clouds, and mist,” is best illustrated in the Erh-ya 爾雅, the oldest surviving Chinese dictionary, dated to 3rd century BCE:

The elixir of sky comes down and does not dissipate on earth; it is called meng (brume, haze). The elixir of earth comes up and does not dissipate to sky; it is called wu (fog, mist, vapor). 天氣下，地不應曰雺；地氣發，天不應曰霧。（爾雅·釋天）(6)

This meaning was expanded to include ‘breath’, where the essential nature of breath to life and death has led to many discussions Isuch as the one cited below.

Life is the follower of death, and death is the predecessor of life; but who knows the Arranger (of this connexion between them)? The life is due to the collecting of the breath. When that is collected, there is life; when it is dispersed, there is death. Since death and life thus attend on each other, why should I account (either of) them an evil? 生也死之徒，死也生之始。孰知其紀！人之生，氣之聚也，聚則為生，散則為死。若死生為徒，吾又何患！《莊子·知北游》(7)

Why the breath is inhaled and exhaled? What is breath? Where does it go once it is inhaled? These questions then led to the development of theories to explain how and why breath is essential for maintaining life. Thereupon, it was natural that the word qi became a medical term to describe the functions of qi. That the Daoist’s view of the connection of qi (breath) to life has led to the development of theory of qi in TCM is vividly illustrated in the following excerpts cited from two Daoist literatures, the
Man and all living beings rely on qi to grow and mature. Nothing is more precious or important than the qi of human, for birth, growth, and development. 人與物類,皆禀一元之氣而得生成。生成長養,最尊最貴者莫過人之氣也。（《雲笈七簽》卷56 《元氣論》）

In this three dimensional universe, change does not occur without dao, yuanqi follows the way, and thus everything grows and flourishes. In this universe, nothing is not born with dao. 六極之中,無道不能變化。元氣行道,以生萬物,天地大小,無不由道而生者也。《太平經》乙部 守一明法

Here, the frequent and tight coupling of the terms qi and dao, the namesake of Daoism, in Daoist literatures deserves further discussion. What is dao and what is precisely qi or yuanqi that follows the dao? Dao in Daoism generally refers to the Way, the template, the path, and the grand plan. (9) Careful reading of the relevant passages in the Daoist literatures, one is struck with the similarity in the relationship between dao and qi and that between DNA and signal transduction pathways. Just like dao is a grand plan, a template, DNA contains all the genetic information for producing a living being. Just like qi is to be circulated in order to execute the grand plan, signal transduction pathways in living organisms are essential for coordinating and regulating all biochemical events, which collectively constitute life. Thus, we propose that the term dao in the Daoist literatures is equivalent to genome when applied to living organisms, and the term qi is equivalent to agents involved in signal transduction pathways. In other words, the major functions of qi described in TCM literatures probably are related to signal transduction pathways in human body.

4. Qi in TCM Literature
There is no doubt that the Daoist philosophy greatly impacted the development of traditional Chinese medicine and the centrality of qi in TCM parallels the centrality of qi in Daoist literature. A general introduction about the functions of qi in human body has been succinctly summarized in a beginning paragraph of the Yimen Falü 醫門法律 written in 1658 CE:

Heaven accumulates qi, earth accumulates physical forms, human body relies on qi to develop the form. Only qi could help to develop physical form: when qi is collected, the physical form will exist; if qi is dissipated, the physical form will disappear. The influence of the qi on the form is indeed tremendous. However, with the body form, there are yingqi 营氣, weiqi 衛氣, zongqi 宗氣, qi of various organs, qi of jing 精 and luo 繫, they all differentiated to have different functions. To command and regulate all these qi’s so that they continue to circulate and function in every part of the body, it has to rely on the coordination and regulation of the Great Qi, which resides in the breast. 天積氣耳,地積形耳,人氣以成形耳。惟氣以成形,氣聚則形存,氣散則形亡。氣之關於形也,豈不巨哉? 然而身形之中,有營氣、有衛氣、有宗氣、有臟腑之氣、有經絡之氣,各為區分。其所以統攝營衛、臟腑、經絡,而令充周無間,環流不息,通體節節皆靈者,全賴胸中大氣,為之主持。《卷一·大氣論》

The paragraph begins by defining the relationship between qi 氣 and xing 形 `the
form’ with a tone closely resembles that described in the Daoist literatures. It states that qi is intimately related to the form (i.e. body form); once inside the body, qi can be differentiated into many kinds, including yingqi 精氣, weiqi 衛氣, zongqi 宗氣 etc. But, what are these different qi’s and why they can circulate, coordinate and regulate every part of the body? The Huangdi Neijing 黃帝內經 ‘Yellow Emperor's Inner Canon’ has employed two methods to define and describe qi in TCM: one is yiming min 以名命氣 ‘to name the qi based on its physiological functions, influence, or properties’; the other is yiwei min 以位命氣 ‘to name the qi based on its location in human body.’ Thus terms such as 元氣、精氣、宗氣、中氣、營氣、衛氣、正氣、邪氣、真氣、經氣、陽氣、陰氣、瘀氣 belong to the first group whereas terms such as 心氣、肺氣、胃氣、肝氣、腎氣、骨氣、脾氣、血脈之氣 belong to the second group. (11) It is fair to say that the development of the holistic theory of the qi-based TCM relies on the expansion of understanding of qi, both in terms of its function and its location in the body.

The Huangdi Neijing, compiled around the time of Warring States period, is considered to be the bible of TCM. In this bible and in all other TCM literatures, qi and the qi-related terms were extensively used to formulate theoretical basis for describing the physiological and pathological conditions and for developing diagnostic and treatment approaches. The use of the term qi in the Huangdi Neijing focuses on three areas:

(i) The relationship between qi and wu 物 ‘matter, material’. It states, “to clearly describe what is qi, one has to find the corresponding wu (matter), 善言氣者,必彰於物 (素問 氣交變大論). The term qi in TCM literatures is not an abstract concept, but should have some physical basis. Thus, although qi may not be visibly discernable, it could manifest via the wu, which it is associated with or it transforms.

(ii) The relationship between qi and life. It states that the fusion of qi from heaven and earth produces (human) life. 天地合氣, 命之曰人 (素問 寶命全形論). Qi in TCM is considered as an intimate and essential component of life.

(iii) The relationship of qi and medical practice. The extensive discussion in various chapters of the Huangdi Neijing centers on how to apply the core idea of qi to present a holistic view of human body, from mental, cognitive state to physiology, and how to apply such an understanding to develop approaches for preventive strategy, diagnosis, prognosis, and clinical treatment, either with medicine or with physical therapy including acupuncture.

The following are samples of relevant excerpts from the Huangdi Neijing, which provide a glimpse of the core concept of qi used as a medical term in TCM. (12)

Covered by heaven and carried by the earth, all the myriad beings have come to existence. None has a nobler position than man. Man comes to life through the qi of heaven and earth; he matures in accordance with the laws of the four seasons. 天覆地載,萬物悉備,莫貴於人,人以天地之氣生,四時之法成。《素問 寶命全形論》

Hence, the [moving] influences [between the kidneys] constitute a person’s root and foundation. 氣者,人之根本也 (《難經·八難》)

Heaven feeds man with the five qi’s; the earth feeds man with the five flavors. The five qi’s enter through the nose and are stored in the heart and in the lung. They cause the five complexions to be clear
above, and the tones and voices can manifest themselves. The five flavors enter through the mouth and are stored in the intestines and in the stomach. When the flavors have a place where they are stored, this serves to nourish the five qi’s. When the qi’s are generated in harmony and when the body liquids complete each other, then the spirit will be alive by itself.

天食人以五氣，地食人以五味，五氣入鼻，藏於心肺，上使五色修明，音聲能彰；五味入口，藏於腸胃，味有所藏，以養五氣，氣和而生，津液相成，神乃自生。《素問·六節臟象論》。

Flavor turns to physical appearance. Physical appearance turns to qi. Qi turns to essence. Essence turns to transformation. Essence is nourished by qi. Physical appearance is nourished by flavor. Transformations generate essence. Qi generates physical appearance. Flavor harms physical appearance. Qi harms essence. Essence turns into qi. 《素問·陰陽應像大論》

Qi cannot be without moving, like the flow of water, like the cycling of sun and moon. Hence the yin vessels enrich zang 藏, yang vessels enrich fu 腑, like a circle without the end, without knowing how to count, continue to cycle. The flowing qi inside nourishes the organs, outside fill the interstice structures. 《靈樞·脈度》

I know that the hundred diseases are generated by the qi. When one is angry, then the qi rises. When one is joyous, then the qi relaxes. When one is sad, then the qi dissipates. When one is in fear, then the qi moves down. In case of cold the qi collects; in case of heat, the qi flows out. When one is exhausted, then the qi is wasted. When one is pensive, then the qi lumps together. These nine qi’s are not identical. Which diseases generate [these states]? 《素問·舉痛論》

Hence, if one carefully balances the five flavors, the bones are upright, and the sinews are soft. As a result, qi and blood flow, and the interstice structures are closed. If such [a state has been reached], the bones and the qi will be firm. If the Way is carefully observed as the law [demands], the mandate of heaven will last long. 《素問·生氣通天論》

Proper qi resides inside, evil qi cannot interfere; while evil qi accumulate, [proper] qi must be depleted. 《素問·刺法論》

Start from that which has surplus and know what is insufficient. Measure the circumstances above and below. This will [enable one] to arrive at a proper [diagnosis of the] circumstances of the vessels. Therefore, when the physical appearance is weak and the qi is
depleted, [the patient will] die. When the qi of the physical appearance has a surplus, while the qi in the vessels is insufficient, [the patient will] die. When the qi in the vessels has a surplus, while the qi of the physical appearance is insufficient, [the patient will] survive.  

The fact is, for nourishing the spirit, one must know whether the physical appearance is fat or lean and whether the camp and the guard [qi], the blood and the qi, abound or are weak. Blood and qi, [they are] the spirit of man; it is essential to nourish them carefully.”

**5. What constitutes a candidate molecular of Qi?**

In light of the key role of qi in developing the theoretical foundation and practice of TCM, and the notion that qi is not an abstract concept, an important issue to be addressed is whether there is a physiological and molecular equivalent of qi in modern biomedical science. In other words, is it possible that there are physiological molecules in human body, which behave like qi as described in TCM? Based on the description and discussion of qi in the *Huangdi Neijing* and other TCM literatures, we propose that for some of the qi's described in TCM literatures the possible molecular candidates for qi should possess some, if not all, of the following properties:

1. It is likely to be a gaseous molecule under physiological conditions. (e.g. oxygen and nitrogen in the breath).
2. It can circulate in the body, probably moving or diffusing along blood vessel or some jingluo conduit (e.g. gas molecules that can dissolve in blood plasma or bind to hemoglobin).
3. It probably can reside in various organs of the body. (e.g. it accumulates in microvascular capillary at different organs).
4. It can be generated in the body from other biological molecules, like nutrients. (e.g. food substances, herbal medicine can affect the levels of qi).
5. It can be regulated in the body with biochemical and physical means.
6. It may serve as a signaling molecule to direct biological messages to target sites.
7. It has significant and possibly essential biological functions

In living organisms signal transduction pathways are involved in transducing all kinds of regulatory signals. Many small molecules such as cAMP, cGMP, Ca^{2+}, IP3 etc. function as second messengers in modulating these pathways. To execute the grand plan of life, from cell division to cell death, living organism relies on sophisticated and complicated signal transduction network to coordinate, to regulate and to execute. In light of the almost essential role of qi in maintaining life and well-being, qi-equivalent molecules are likely to be involved in signal transduction pathways. We therefore propose that these qi-equivalent molecules would play roles as messengers, regulators, and modulators in human body.

Among the biological molecules involved in signal transduction, there is a class of compounds termed 'gasotransmitters', a term coined in 2002 to describe some gaseous molecules such as nitric oxide that have been identified in human body serving as signal transduction molecules. (13) For a gas molecule to be qualified as a
gasotransmitter, it will have to meet all of the following criteria: (i) It is a small molecule of gas; (ii) It is freely permeable to membranes. As such, its effects do not rely on the cognate membrane receptors. It can have endocrine, paracrine, and autocrine effects. In their endocrine mode of action, for example, gasotransmitters can enter the blood stream; be carried to remote targets by scavengers and released there, and modulate functions of remote target cells; (iii) It is endogenously and enzymatically generated and its production is regulated; (iv) It has well defined and specific functions at physiologically relevant concentrations. Thus, manipulating the endogenous levels of this gas evokes specific physiological changes; (v) Its exogenously applied counterpart can mimic the functions of this endogenous gas; (vi) Its cellular effects may or may not be mediated by second messengers, but should have specific cellular and molecular targets. (13)

It is truly amazing that the criteria for gasotransmitters fit so closely to the properties listed above for the putative qi-equivalent molecules. Could qi-equivalent molecules be one or more of these gasotransmitters? To determine this possibility, we will first examine the functions of gasotransmitters such as nitric oxide in human body.

6. Just say NO
Nitric oxide (nitrogen oxide, nitrogen monoxide) has a chemical formula NO. This simple small molecule has long been known as a by-product of combustion of substances such as fossil fuels in the air. NO is also known to be generated naturally during lightening in thunderstorms. It is therefore quite a surprise that it was proclaimed to be the “Molecule of the Year” in 1992 by Science Magazine. (14) Three scientists, Robert Furchgott, Ferid Murad, and Louis Ignarro won Nobel Prize in 1998 for their discoveries concerning “the nitric oxide as a signaling molecule in the cardiovascular system.” (15) It turns out that despite being a very simple molecule, NO is an important biological regulator and is a critical component in the fields of neuroscience, physiology, and immunology. Furchgott’s research during 80’s demonstrated that endothelial cells produce some signal molecule, which he termed endothelium-derived relaxing factor (EDRF), that makes vascular smooth muscle cells relax. Murad found that nitroglycerin (nitrates) release nitric oxide, which relaxes smooth muscle cells, resulting in vasodilation. Finally Ignarro, through a series of analyses, concluded that EDRF was identical to nitric oxide. Subsequently, NO has been shown to be functioning as an important cellular signaling molecule involved in many physiological and pathological processes, from cardiovascular modulation, vasodilation, neuronal transmission, penile erection, immunomodulation to stem cell differentiation and proliferation. Soon, it became clear that the unique biological (signaling) and physical (gaseous) nature of NO may also be shared by some other small molecules and therefore a term ‘gasotransmitter’ was coined. (13)

Fig. 4 provide a general overview of the action of NO, which shows that the binding of acetylcholine to its receptor elicits a sequence of events that lead to the stimulation of NO synthase, the key enzyme for the biosynthesis of NO, converts arginine to citrulline and NO. The release of NO in vascular endothelial cells causes the relaxation of the vascular smooth muscle (vasodilator) in blood vessels via its own receptor. (16) As a powerful vasodilator with a short half-life of a few seconds in the blood, low levels of nitric oxide production are important in protecting organs such as the liver from ischemic damage. Long-known pharmaceuticals for cardiovascular diseases such as nitroglycerine and amyl nitrite are active since they are precursors of nitric oxide.
As illustrated below, the extraordinary complexity of regulating the nitric oxide system further underscores the importance, the ubiquity, and the essential nature of NO. There are at least three different NOS enzymes in the NOS family: nNOS, eNOS, and iNOS. NOS is the most regulated enzyme in human body; it utilizes five co-factors and can be regulated by a wide range of biological molecules such as Ca\(^{2+}\), calmodulin, tetrahydrobiopterin, cytokines, and phosphorylation (cAMP-PK, cGMP-PK, PKC). (17) The complexity of NO system as revealed by the NOS regulation is further illustrated by the byproducts from the action of NOS. NO catalysis yields superoxide when NOS is uncoupled by oxidation of tetrahydrobiopterin (BH4) to dihydrobiopterin (BH2). Reduction of BH2 to BH4 is catalyzed by dihydrofolate reductase (DHFR). NO-dependent activation of the soluble isoform of guanylate cyclase (sGC) leads to accumulation of cGMP. Formation of nitrosothiol (RSNO) adducts yields adducts that have distinct biochemical properties. NO can interact with [Fe-S] centers in mitochondria and elsewhere, and can lead to formation of methemoglobin (MetHb) through its interaction with ferrous (Fe\(^{2+}\)) heme. NOS-derived NO can inhibit mitochondrial respiration. Superoxide not only is formed by uncoupled NOS but also may arise from oxidative metabolism in mitochondria. NADPH oxidases (NOX), xanthine oxidoreductases (XO), and other oxidases also lead to the formation of ROS in cardiovascular tissues. Superoxide can undergo rapid dismutation to form hydrogen peroxide (H\(_2\)O\(_2\)), a stable ROS that plays key roles in cellular signaling. H\(_2\)O\(_2\) promotes activation of eNOS through Akt dependent phosphorylation, as noted by the green arrows. H\(_2\)O\(_2\) leads to activation of the AMP-activated protein kinase (AMPK), a process that depends on specific AMPK kinases, including the calcium/calmodulin-dependent protein kinase- (CaMKK). eNOS tonically inhibits endogenous H\(_2\)O\(_2\) formation in endothelial cells. The complex interplay of reactive nitrogen and ROS modulates both physiological and pathophysiological responses in cardiovascular tissues.

More interestingly, it has been shown that hemoglobin, besides shuttling oxygen to tissues and retrieving carbon dioxide, also delivers NO. The link of NO to hemoglobin allows blood vessels to expand or contract, depending on how much of the molecule is present. The NO binds to cysteine, an amino acid in hemoglobin, to form a molecule called an S-nitrosothiol. When the red blood cells arrive at the capillaries, they release oxygen and the S-nitrosothiols. The NO in the S-nitrosothiols dilates blood vessels and thus allows oxygen to better reach tissues. (18) In addition, NO binds to transcription factors and enzymes that regulate proteins in invading pathogens and in cancer and other abnormal cells. As a key signaling molecule nitric oxide controls blood pressure and nerve impulses. Yet, when concentrations of NO are too high, it is toxic to cells. Thus, when the body is under attack from microorganisms, for instance, mammalian immune cells called macrophages produce NO, which attacks critical metabolic enzymes and other proteins in the pathogens, serving as a first line of defense against the invasion. (19)

The jingluo conduits (channels and collaterals) described in TCM literatures are most likely vascular structures related to blood vessels, lymphatic systems and interstice structures. According to TCM there are twelve regular conduits in which qi flows from one visceral organ (zang- or fu-organ) to another in sequential manner. The intimate relationship between the flow of blood and qi was described in TCM as qixing xuexing 氣行血行 ‘where qi goes, blood will flow’. Such a description can be fittingly illustrated by the relationship of a vasodilator NO and blood flow. As the first known gasotransmitter, NO is ubiquitous, highly regulated, transported by blood vessel, diffusible in and out of the tissues, organs, and interstice structures, positioned in
many signal transduction pathways, and connected with many physiological activities. Indeed, it seems that NO does fulfill some of the functions of qi as described in TCM, particularly, its role in regulating blood flow.

7. Say YES to NO
Research over the past two decades has firmly established the role of NO as an omnipresent gasotransmitter, essential not only in cardiovascular system, but also in almost every aspect of mammalian physiology, from neuronal to immune system. Since the features of gasotransmitters are almost identical to the criteria listed for qi candidate molecules, it is highly likely that NO could be one of the qi-equivalent molecules described in TCM. One approach to test this possibility is to examine whether any TCM treatment can cause changes in NO at certain body sites. Acupuncture is one of the most common therapeutical practices in TCM. Acupuncture is based upon the theory of the circulation of qi along jingluo network. According to the TCM literatures, qi tends to collect and travel along jingluo conduits and permeates in every part of the body. It is therefore quite feasible to examine whether some of the effects of acupuncture could involve or mediated by NO?

More than 80% of acupuncture points, or acupoints, in the arm are located along connective-tissue planes. (20) Connective tissue is an integral part of musculoskeletal system, which surrounds nerves, blood vessels, and lymphatics. Langevin and co-workers showed that a twisted acupuncture needle creates a localized stretch by gripping the underlying connective tissue and such stretch could transmit the mechanical signal to sensory nerves as well as intrinsic sensory afferents directly innervating connective tissue. (20, 21) To demonstrate that acupuncture indeed can trigger mechanotransduction, namely, transform the mechanical signal into cellular responses, including gene expression, they have demonstrated that in response to stretching, fibroblasts changed shape, followed by the stretching-sensitive activation of the focal-adhesion complex, and hence Rho signaling pathway. They reported an increased production of ATP and its release into extracellular space (21). The work is significant in that it demonstrates that physical force can be converted into biochemical signalings, which then lead to physiological responses. It certainly would be of interest to further examine whether such mechanotransduction may involves NO and/or other gassotransmitters. Several recent studies have offered encouraging preliminary results.

According to the jingluo theory (i.e. meridian theory) of TCM, there are discrete acupoints that punctuate the itinerary of the conduits. Manipulating these points through transdermic needling can change the flux of qi. As NO is a vasodilator for facilitating blood flow, one wonders whether the change of qi flux may have anything to do with NO level. Indeed, Ma has attempted to determine the NO content and NOS activity at the meridian sites. He found that the NO contents and nNOS expression are consistently higher in the skin acupoints/meridians associated with low electric resistance. The source of the enhanced NO in the acupoints/meridians appears to be generated from multiple resources including neuronal NOergic system. His study provided the first evidence that NO might be associated with acupoint/meridian functions including low electric resistance. (22) Another study demonstrated more directly that acupuncture actually led to the increase NO and local circulation, just like what qi would do. They have quantitatively shown that acupuncture manipulation increases the NO level in treated regions (by 2.8±1.5 mol/L at 5 min and 2.5±1.4 mol/L at 60 min after acupuncture.) and thereby increases local circulation. (23) These two studies provided evidence suggesting that
The gasotransmitter nitric oxide induced by needle twisting at the acupoints may perform some of the functions of qi as described in the TCM literatures.

8. Don’t Just say NO
Carbon monoxide and hydrogen sulfide (H_2S) have been identified as two additional gasotransmitters that function as physiological mediators in the cardiovascular, immune and nervous systems (24). The roles of H_2S in the cardiovascular system include reduction of vascular tone, inhibition of leukocyte adherence to the vessel wall, cardioprotection, inhibition of apoptosis and stimulation of angiogenesis. In addition, H_2S exerts antioxidant effects and downregulates pro-inflammatory signal transduction processes in cells challenged with pro-inflammatory stimuli. The pharmacological effects of H_2S (similar to the other gasotransmitters) follow a characteristic bell-shaped curve: whilst low, physiological concentrations of H_2S are cytoprotective, high concentrations of H_2S can be detrimental. Carbon monoxide binds to hemoglobin more strongly than oxygen and was thought to be highly toxic. However, recently evidence indicating that at low concentrations, it can function as physiological gasotransmitter. (25) Fig. 5 summarizes the synthesis, targets, and substrates of these three gasotransmitters (26). It is worth noting that the gasotransmitter CO in the body is actually derived from blood hemoglobin. (25)

Since the terms of qi in TCM are so multi-faceted, it is possible that a single gasotransmitter such as NO could not cover all the functions ascribed to qi. Nevertheless, the possible link between acupuncture and NO provide strong rationale for further investigating possible involvement of not only NO, but also other gasotransmitters, including H_2S and CO, in the action of qi in TCM.

9. Conclusion
The philosophy and the approaches of TCM are different from that of western medicine, one is holistic and synthetic whereas the other is compartmental and analytical. One can argue that it is futile to look for the molecular identity of qi because the holistic qi in TCM has nothing to do with the modern science, which stemmed from the western tradition. This argument neglects the fact that despite the differences, both TCM and western medicine deal with physiology of human body. If a TCM treatment is effective, it must have a physiological basis to be effective and as such, the effect must be mediated by certain biochemical processes that involve biological molecules. In other words, the concept and practice described in TCM should and can be reasonably explained in the light of modern molecular biomedical science.

We propose here that if qi in TCM has a physical basis for its physiological effects, then this qi must be related to some signal transduction small molecules that exist in gas state at room temperature and atmospheric pressure. Moreover, such molecules are likely capable to be transported via blood vessels or other channels. Careful reading of the vast TCM literatures on the nature of qi and qi-associated terms, one is struck with the close similarities between qi and gasotransmitters described in modern biomedical science. Currently scientists have identified three gasotransmitters in human body (Fig. 5). The gasotransmitter NO is essential in maintaining the healthy state of cardiovascular, immune, nervous system and has diverse functions. Two other gasotransmitters, i.e. CO and H_2S, have been recently recognized to be important in human physiology and pathology. Strikingly, two of the gasotransmitters, NO and CO, can bind and thus be transported by hemoglobin in red blood cells. More strikingly, recent studies demonstrate good correlation of NO and NOS activity with acupuncture manipulation, a seasoned TCM practice. Therefore, based on the diverse and versatile functions of gasotransmitters, and
their ubiquitous distribution in human body, particularly at the acupoints along the meridian, it is highly possible that the various qi's discussed in TCM literatures have a molecular basis in one or more of these gasotransmitters. With the development of controllable gasotransmitter donor molecules that can generate NO, H₂S, and/or CO in situ (27), possible link between qi and gasotransmitters can be further tested with pharmacological means.

10. References

(1) The difficulty to find an English equivalent of qi has long been recognized. See discussions in (i) Li Zhaoguo and Li Xiaohong (1999) Yi guwen yingyu fangyi jiqiao (Techniques on English translation of ancient Chinese medical literatures), Shanghai Zhongyi Daxue Publisher. 李照國、李肅紅 《醫古文英語翻譯技巧》 上海中醫藥大學出版社 1999. (ii) Kong Y C Huangdi Neijing A synopsis with comments 內經知要譯詁 The Chinese University Press.

(2) The graphs of qi as revealed in oracle bone inscriptions (Shang Dynasty, ~1300 BCE), bronze inscriptions (Zhou Dynasty, ~1100 BCE), and bamboo and silk slips (Chu, ~300 BCE). Data extracted from http://xiaoxue.iis.sinica.edu.tw/.


(4) The frequency of the appearance of the graph qi in the thirteen pre-Qin classics and the fourteen Master Literatures were determined by analyzing data gather by using the search engine in Hanquan 寒泉 http://210.69.170.100/s25/

(5) The Zhuangzi, Outer Chapters 外篇, Chapter of Zaiyu 在宥 - Letting Be, and Exercising Forbearance. see http://ctext.org/zhuangzi/letting-be-and-exercising-forbearance Miscellaneous Chapters, Chapter of Ze-yang (則陽- Ze-yang), see http://ctext.org/zhuangzi/ze-yang

(6) Er-Ya 烏雅, Chapter of Shi-tian 釋天 Interpreting Heaven. The translation is mine.


(8) (i) Yunji Qiqian 雲笈七签 compiled by Zhang Junfang 張君房 around 1017-1021. vol. 56 On yuanqi and Preface 諸家氣法部一, 元氣輪並序. (ii) Taipingjing 太平經 Part II 乙部 On Shouyiming 守一明法.


(10) Yimen Falü vol. 1, On Grand Qi 醫門法律, 卷一・大氣論. The translation is mine. See http://ctext.org/wiki.pl?if=en&chapter=374344

(11) The notion of 'yiming mingqi' can be found in the Huangdi Neijing, Suwen, Zhizhenyao Dalun (Chapter 74) 內經·素問·至真要大論. The term 'yiwei mingqi' is not
in the *Huangdi Neijing*. Instead, the term ‘*yiqi mingchu*’ 以氣命處 was used. Also see discussion in *An Annotated Translation of Huang Di’s Inner Classic – Basic Questions*, (Paul U. Unschuld and Hermann Tessenow in Collaboration with Zheng Jinsheng, University of California Press, 2011) vol. 2, p. 588.

(12) The translation of these excerpts was based on Unshuld and co-workers. For details, see Unschuld, P.U. Tessenow, H and Zheng, J. *Huangdi neijing suwen, An Annotated Translation of Huang Di’s Inner Classic – Basic Questions*. University of California Press, 2011

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(14) Culotta, E. and Koshland, D.E. Science NO news is good news. 258, 1862-1865, 192


(27) For example, see Wang, P.G.; Cai, T.B. and Taniguchi, N. (eds.) Nitric oxide Donors. For Pharmacological and Biological Applications. Wiley-VCH Verlag GmbH, 2005.
Fig. 1. The etymology of the graph qi: The graph qi in oracle bone inscriptions, bronze inscriptions and bamboo slips.

Fig. 2. The etymology of the graph qi: The genealogy and differentiation of the graph qi.
Fig. 3. (A) The frequency of appearance of the graph qi in the thirteen pre-Qin classics. (B) The frequency of appearance of the graph qi in the fourteen pre-Qin Master Literatures.
Fig. 4. Schematic diagram on the regulation, biosynthesis and function of nitric oxide (NO).

Fig. 5. Schematic Diagram on the source, biosynthesis, and potential targets of the three gasotransmitters, NO, H₂S, and CO.