## Discussion

### *Nitric Oxide*

NO has been the most widely studied signaling molecule for more than a decade. It regulates blood pressure, contributes to the immune responses, controls neurotransmission and participates in cell differentiation and in many more physiological functions [8].

Nitric oxide (NO) the diffusible, signaling gas, is synthesized by 3 nitric oxide synthase isoforms (NOS): a neuronal (nNOS), inducible (iNOS) [9], or endothelial NO synthetase (eNOS) [10,11]. Using BH4 (tetrahydrobiopterin) [12] as a cofactor, these enzymes convert arginine to citruline and NO. The levels of NOS are altered by a variety of pathophysiological conditions such as hypertension, hypercholesterolemia, aging, cigarette smoking, diabetes, heart failure and under physical activity [13] and dementia [14].

NOS were also shown to be associated with a plethora of more than 20 proteins that affect the activity and spatial organization of NO synthesis within the cell. Some of these interactions may have functions beyond NO formation [15].

NO is such a crucial entity that the mammalian genome encodes three NOS genes with partially overlapping function that may compensate for each other if one of them is not functioning. For example, the essentiality and flexibility of the NO system allows nNOS enzyme to compensate for eNOS, in mutant mice lacking eNOS [16,17]. Recently NOS was shown to be essential for development (in Drosophila) by taking advantage of the fact that, unlike those of mammals, the genome of the fruit fly has only one NOS gene and is thus more amenable to mutagenesis [18].

### *Qi, meridians and acupuncture*

The idea of qi is fundamental to Chinese medical thinking. Qi is involved with all biological functions and circulates throughout meridians reaching the entire human body [19,20]. The goal of acupuncture as well as other Eastern medicinal methods (herbs, massage, Qigong) is to ensure the unobstructed flow of qi. When qi is strengthened or balanced, it can improve health and ward off or slow the progression of disease. Chinese medicine considers sickness or pain, a result of the qi blockage or unbalanced qi energy in the body [2]. Like NO, qi is essential for life, as Guanzi said [21] in 5$^{th}$ century BCE, "When there is qi, there is life".

Much information has accumulated regarding the physiological effects of acupuncture. In 1998, a NIH panel concluded that acupuncture is an effective technique for relieving nausea and vomiting and an effective agent for relieving pain [22]. Needling of acupuncture points has subjective (needle sensation) and objective (e.g., serum cortisol increase or Ca(2+) oscillations) effects [23,24]. Acupuncture increases blood flow [25] and acupuncture points have high electrical conductance [26,27]. A relationship between acupuncture points and meridians to connective tissue planes [28] and perivascular space [29] has also been suggested. Possible mechanisms of acupuncture have been reviewed [30] and data are available at the site of the National Center for Complementary and Alternative medicine [NCCAM] [31]. They include conduction of electromagnetic signals, activation of opioid systems or changes in brain chemistry, sensation and involuntary body functions.

This article does not deal with the physiological effects of qi manipulation but rather with the nature of qi flow along the meridians. The hypothesis is that the transmission of qi is based on an intercellular communication system and that nitric oxide (NO) is a prime candidate to be a signaling molecule in the meridian system.

### *Information and signals*

Information links increase the ability to handle complexity and thus, control mechanisms in the body can be regarded as information processing. This was proposed by H. R. Maturana & F. Varela in the concept of Autopoiesis, the process by which systems organize themselves out of disorder, forming a responsive, self-maintaining network characteristic of life [32]. Autopoiesis is parallel to the concept of qi, streaming along the meridians' net, regulating our well being.

It is expected that the qi type signal molecule in the body, will be an essential entity and probably a gas so that it can spread as well as dissipate very quickly to allow following information to be transferred. Furthermore, the dual nature of NO [33,34], being either beneficial or detrimental, is parallel to the dual nature of qi [19] and fits the basic character of a signal. Signals can not always be beneficial, in that "cost" must be associated with them to ensure their "integrity", e.g., those who wish to transmit information about their richness, are likely to exhibit it by expensive jewels or costly cars, signals which are hazardous to poor people who can't afford them [35,36]. With biochemical signals, such integrity can be attained by variety of costly characters, see for example cAMP and Ca2+ [37] or Glutamate and GABA [38]. One of such characters may be the toxicity of a molecule like NO which demands very cautious and strict handling. NO differs from other neurotransmitters in that its levels are regulated solely by synthesis, rather than by storage, release or targeted degradation. NO is impossible to live without, short lived, highly diffusible and toxic [39] and is thus an excellent