Photobiomodulation as a cellular model of traditional Chinese medicine

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Yin-yang concepts of traditional Chinese medicine (TCM) for TCM objects such as whole body, five *zang*s or six *fu*s are widely used to discuss cellular processes. In this paper, the concept of the degree of difficulty (DD) of a process was put forward to redefine *yin* and *yang* and extend TCM *yin-yang* model to DD *yin-yang* model. It was shown that healthy cells are in DD *yin ping yang mi* so that there is no photobiomodulation, and there is photobiomodulation on non-healthy cells until the cells become healthy so that photobiomodulation can be called cellular rehabilitation.

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Photobiomodulation is an effect of low intensity monochromatic light or laser irradiation on biological systems, which stimulates or inhibits biological functions but does not result in irreducible damage. There are two kinds of pathways mediating cellular photobiomodulation[1] , one kind is specific, which is mediated by the resonant interaction of light with molecules such as cytochrome nitrosyl complexes of mitochondrial electron transfer chain, singlet oxygen, or endogenous photosensitizer such as hemoglobin and porphyrines, the other kind is non-specific, which is mediated by the non-resonant interaction of light with membrane proteins. The cytochrome c oxidase mediated pathway has been supported by many groups[2,3]. Since the light intensity is so low that the photodynamic effects of some specific pathways can not damage membrane or cell compartments, photobiomodulation should be dominantly mediated by the non-specific pathways[1]. The radiation from UVA (ultraviolet A 320–400 nm) to IRA (infrared A 700–1000 nm) has been classified into two kinds, the cold color (green, blue, violet or UVA) and the hot color (red, orange, yellow or IRA). It has been shown that the biological information model of photobiomodulation (BIMP) holds for the non-specific pathway[1,4]. There are two recent studies investigating cellular mechanisms of photobiomodulation using most advanced contemporary experimental techniques, cDNA microarray technology[5] and single cell confocal microscopy[6], which might open a new page in investigation of cellular mechanisms of photobiomodulation and the improvement of understanding of clinical usefulness of this therapeutic modality as Karu[7] has pointed out.

The role of processes or function in traditional Chinese medicine (TCM) is the same as the one of states or structure in modern sciences so that TCM might be called process medicine. As process philosophy becomes more popular and TCM becomes more important. *Yin-yang* is one of the basic models of TCM to establish a system of physiology, pathology, diagnosis and therapy of diseases[8]. It should be pointed out that the *yin-yang* model is only used to discuss TCM objects such as whole body, five *zang*s or six *fu*s. However, the *yin-yang* concept is widely used in the cellular level for modern sciences[9−13]. For example, Ou *et al.*[13] proposed that *yin-yang* balance is antioxidation-oxidation balance with *yin* representing anti-oxidation and *yang* as oxidation. At this point, the *yin-yang* model of TCM should be extended to discuss cellular processes. In this paper, TCM will be discussed from viewpoint of the process-specific time and cellular photobiomodulation.

The degree of difficulty (DD) of a process has been defined in terms of the process-specific time $t_{\rm p}$[4] so that the higher the DD of a process, the more difficult the process occurs

$$t_{\rm p}\downarrow,\ DD\uparrow. \tag{1}$$

As a typical example, we discuss the cellular signal transduction pathways. They can be classified into two classes, the one mediated by the G proteins, and the other one mediated by receptor-linked enzyme which is one of gualylate cyclase, tyrosine kinase and serine/threonine kinase and so on. The receptor of the former pathway strides membrane seven times. However, the receptor of the latter pathway strides membrane less than seven times. In terms of Eq. (1), we have

$$t_{\rm p}({\rm receptor-linkedenzyme}) > t_{\rm p}(G\ {\rm protein}). \tag{2}$$

In the pathway mediated by $G_{\rm s}$, $G_{\rm i}$ or $G_{\rm q}$ protein, the migration of the α subunit is the key elementary process that is of the shortest process-specific time. As molecular mass ($\alpha_{\rm s}$) > molecular mass ($\alpha_{\rm q}$) > molecular mass ($\alpha_{\rm i}$), from Eq. (1) we have

$$t_{\rm p}(G_{\rm i}) > t_{\rm p}(G_{\rm q}) > t_{\rm p}(G_{\rm s}). \tag{3}$$

As the signal transduction pathways have been classified into two kinds, pathway 1 which is $G_{\rm s}$ protein mediated pathway: cAMP↑(cyclic adenosine 3', 5' - monophosphate), and pathway 2 which is $G_{\rm i}$ protein mediated pathway, $G_{\rm q}$ protein mediated pathway, or one of receptor-linked enzyme: cAMP↓ according to BIMP, from Eqs. (2) and (3) we have

$$t_{\rm p}({\rm pathway\ 2}) > t_{\rm p}({\rm pathway1}). \tag{4}$$

After comparative research with TCM *yin-yang* model[8], we redefine *yin* and *yang* in terms of DD: the process of low DD is defined to be *yang* and the process of high DD is defined to be *yin* for the two nonlinearly coupled processes of a system, which is called DD *yin-yang* model.

According to DD *yin-yang* model, we have cellular *yin* and *yang* from Eq. 4 since the protein kinases of two kinds of pathways might phosphorylate the same protein bands and the transcription factor *yin-yang* 1 might work:

$$\text{pathway 1 belongs to } yin, \text{ and}$$
$$\text{pathway 2 belongs to } yang. \tag{5}$$

According to time parallel principle, the change of the process-specific times of two weakly nonlinearly coupled processes is parallel[4]:

$$t_1 \uparrow,\ t_2 \uparrow. \tag{6}$$

This is in agreement with TCM *yin-yang* parallel principle for TCM objects[8] according to DD *yin-yang* model so that it is called DD *yin-yang* parallel principle: the *yin* process of one system is related with the *yin* process of the other system and the *yang* process of one system is related with the *yang* process of the other system between the processes of two weakly nonlinearly coupled systems, which is in agreement with the experimental results of Ou *et al.*[13] and Ko *et al.*[14]. As Ou *et al.*[13] have stated, the *yin*-tonic traditional Chinese herbs have, on average, about six times more antioxidant activity (*yin*) and polyphenolic contents than the *yang*-tonic herbs. As Ko *et al.*[14] have pointed out, although *yang*-tonic herbs tend to boost body function possibly through enhancing the mitochondrial oxidative processes (*yang*), the *yin* property (i.e. antioxidant potential) of these herbs can also play a role in safeguarding mitochondrial adenosine 5'–triphosphate (ATP) generation, and the pharmacological basis of '*yang*-invigoration' by Chinese tonic herbs might be due primarily to the enhancement of mitochondrial ATP generation.

Yin and *yang* are antagonistic, but they will transform into each other under some condition[8], which can be extended to other systems such as cells according to DD *yin-yang* model so that it is called DD *Yin-Yang* inter-transformation. This holds for BIMP. The *yin* and *yang* of laser irradiation or monochromatic light depend on its dose. At dose 1, the lowest dose for photobiomodulation, we have the *yin-yang* of light since the peak wavelength of resonant absorption is shorter than the one of UVA (320–400 nm):

$$\text{hot color belongs to } yin, \text{ and}$$
$$\text{cold color belongs to } yang. \tag{7}$$

We then have BIMP1 from Eqs. (5) and (7) and DD *yin-yang* parallel principle:

$$\text{hot color activates pathway 1,}$$
$$\text{cold color activates pathway 2.} \tag{8}$$

If the dose is at dose 2 which is larger than the threshold of dose 1, the *yin-yang* properties of laser irradiation or monochromatic light will transform into each other according to DD *Yin-Yang* inter-transformation so that we have

$$\text{hot color belongs to } yang, \text{ and}$$
$$\text{cold color belongs to } yin. \tag{9}$$

We then have BIMP 2 from Eqs. (5) and (9) and DD *yin-yang* parallel principle:

$$\text{cold color activates pathway 1,}$$
$$\text{hot color activates pathway 2.} \tag{10}$$

Generally, we have Eq. (10) according to DD *yin-yang* inter-transformation if the dose is at dose $2n$ ($n = 1, 2, 3, \ldots$) which is larger than the threshold of dose $2n-1$ if it does not damage membrane or cell compartments such as mitochondria, lysosomes, endoplasmic reticulum so that Eq. (10) is called BIMP $2n$, and we have Eq. (8) according to DD *Yin-Yang* inter-transformation if the dose is at dose $2n+1$ ($n = 1, 2, 3, \cdots$) which is larger than the threshold of dose $2n$ if it does not damage membrane or cell compartments so that Eq. (8) is called BIMP $2n+1$. BIMP n ($n = 1, 2, 3, \cdots$) has been supported by its successful applications at the cellular level, animal model level and clinic level[1,4], which supports our DD *yin-yang* model.

Yin and *yang* are antagonistic. Yova *et al.*[15] have shown that the effects of low intensity He-Ne laser irradiation at dose 2 and adrenalin on red blood cell deformability are antagonistic. Adrenalin can elevate the intracellular cAMP level, which belongs to *yin*. However, low intensity He-Ne laser irradiation can lower the intracellular cAMP level according to BIMP2, which belongs to *yang*. The observed result is due to the *yin-yang* antagonism. One has the same results when the HeLa cells were simultaneously irradiated with narrow-band red light at dose 2 and a wide-band cold light at dose 2[2]. In this cases, the red light belongs to *yang*, and the cold light belongs to *yin* according to BIMP 2, and the DNA synthesis rate of HeLa cells simultaneously irradiated with narrow-band red light at dose 2 and a wide-band cold light at dose 2 was near to the control level due to the *yin-yang* antagonism.

Karu[2] has studied the stimulation of DNA synthesis in HeLa cells after consecutive irradiation with blue and red light at dose 2, and she found, the sequence 633 nm followed by 404 nm had no effect on DNA synthesis, but the sequence 404 nm followed by 633 nm stimulated it. DNA synthesis mediated by pathway 2 in HeLa cells belongs to *yang* according to Eq. 5, and the stimulation of DNA synthesis in HeLa cells is to reinforce *yang*. Karu's results[2] show that the sequence reinforcing *yang* followed by replenishing *yin* can not reinforce *yang* due to the *yin-yang* antagonism, only the sequence replenishing *yin* followed by reinforcing *yang* can reinforce *yang* due to *yin-yang* interdependence.

There are two kinds of modern viewpoints on *yin ping yang mi* of TCM *yin-yang* model, *yin-yang* balance[8] and homeostasis in which both *yin* and *yang* work in optimum[16]. Whether there is photobiomodulation depends on the initial state of a cell or tissue. According to Karu's theory[2], there is no photobiomodulation on the cells which redox potential is so that the cells normally functions; the lower the redox potential of cells comparing with the normal redox potential, the stronger the photobiomodulation. As Tunér *et al.*[17] have summarized, the light energy is thought to reap the greatest benefit where it is most needed. In other words, a healthy cell is in homeostasis so that there is no photobiomodulation,

and there is photobiomodulation on a non-healthy cell until the cell is healthy so that photobiomodulation can be called cellular rehabilitation which has been discussed by King *et al.*[18]. At this point, our research supports Zhu's viewpoint on *yin ping yang mi*[16].

The objects of TCM are whole body, five *zang*s or six *fu*s. It can be extended to cells in view of our successful discussion. Cells are extensively and deeply studied in modern life science. Cellular TCM might be a discipline to bridge a gap between TCM and modern life sciences. As cellular model is a popular approach to study life science, cellular TCM suggests that TCM rules might hold for life science, which might become a new discipline of modern sciences. Of course, the further research should be done.

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