

# Lightening up Light Therapy: Activation of Retrograde Signaling Pathway by Photobiomodulation

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## Abstract

Photobiomodulation utilizes monochromatic (or quasimonochromatic) light in the electromagnetic region of 600~1000 nm for the treatment of soft tissues in a nondestructive and nonthermal mode. It is conceivable that photobiomodulation is based upon the ability of the light to alter cell metabolism as it is absorbed by general hemoproteins and cytochrome c oxidase (COX) in particular. Recently it has been suggested radiation of visible and infrared (IR) activates retrograde signaling pathway from mitochondria to nucleus. In this review, the role of COX in the photobiomodulation will be discussed. Further a possible role of water as a photo-receptor will be suggested.

**Key Words:** Photobiomodulation, Hemoprotein, Cytochrome c oxidase, Retrograde signaling, Water

## INTRODUCTION

A famous experiment carried out by Otto Warburg uncovered the enzyme responsible for the critical step of cellular respiration (Lane, 2006), which converts the energy conserved in foods to ATP the cell can use. The enzyme he identified is cytochrome oxidase (COX), which is a major player in cellular energy metabolism. To extract energy from exogenous molecules, the cells break down ingested glucose to more simple molecules *via* glycolysis process. Then, pyruvate, a C3 compound enters the energy-producing subcellular organelle, mitochondria through pyruvate transporter compartmentalized to mitochondrial outer membrane (Divakaruni *et al.*, 2013). The captured electrons from sugar compounds can produce ATP with the aid of oxygen. Cytochrome c oxidase controls the last step of this process, which commonly called oxidative phosphorylation (Lane, 2006; Karu, 2008).

The method that Warburg used to discover is rather intriguing since he has exploited two seemingly unrelated things; carbon monoxide (CO) and light (Lane, 2006). While CO can block cellular respiration by binding and inhibiting COX in place of oxygen, a flash of light can displace the gas molecule. Thus oxygen can bind to the enzyme again and utilize it to produce ATP (Fig. 1). Cells frequently use CO and nitric oxide (NO) to block cellular respiration (Moncada and Bolaños, 2006; Zuckerbraun *et al.*, 2007).

Both gas molecules are constantly synthesized in the body *via* enzymatic catalysis (Kim *et al.*, 2006). Interestingly evidences suggested that those enzymes (i.e., mitochondrial NO synthase, heme oxygenase-1) are also compartmentalized in the mitochondria (Slebos *et al.*, 2007; Zaobornyj and Ghafourifar, 2012). With regards to the existence of gas-producing enzyme in the specific organelles, Moncada (2006) has proposed the idea that slowing respiration by binding of NO instead of oxygen to COX is to divert oxygen elsewhere in cells and tissues. Thus, the strategy may prevent falling down of oxygen levels to a certain extent in the neighboring cells. In fact, it has been demonstrated that NO blocks respiration in endothelial cells, which helps to deliver oxygen to smooth muscle cells in the blood vessel.

Coincidentally, light has long been considered to augment wound healing (Mester *et al.*, 1971; Conlan *et al.*, 1996; Reddy *et al.*, 2001; Whelan *et al.*, 2003; Ells *et al.*, 2004). So far, however, the molecular basis for the therapeutic potential of light has only recently uncovered. At long wavelengths in the infrared (IR) spectrum region, photons may penetrate about several centimeters into the skin (Schindl *et al.*, 2000; Lane, 2006). More recently Dr. Karu (2008) suggested that near-IR radiation may modulate cellular respiration and retrograde signaling from mitochondria to nucleus. This opens new modalities of therapeutics by adopting light, photobiomodulation (PBM).

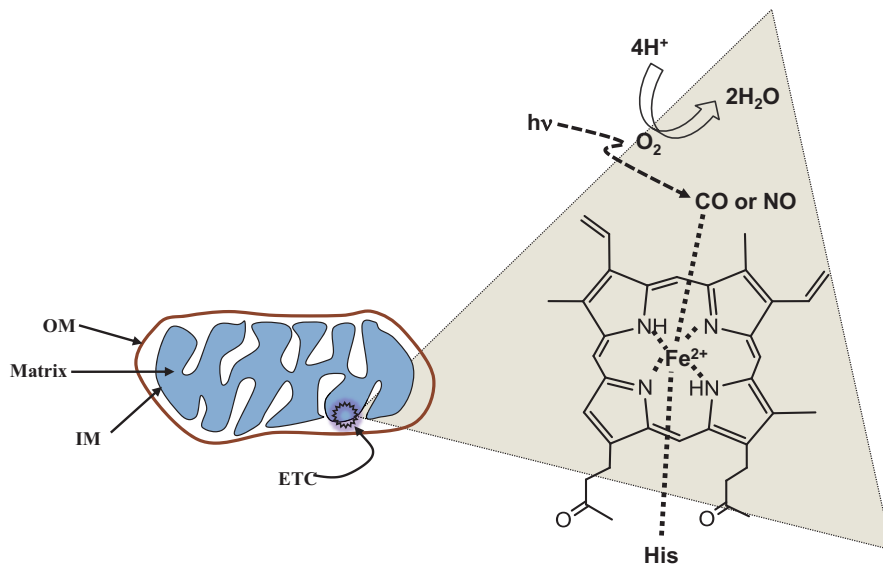
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Received Jul 9, 2014 Revised Jul 24, 2014 Accepted Jul 31, 2014  
Published online Nov 30, 2014

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**Fig. 1.** Heme-iron axial ligands. Histidine in COX protein and CO or oxygen can be axial ligands. Lights can displace gas molecules with oxygen, which functions as an electron acceptor to make water. Electron transport chain (ETC) located to inner membrane of mitochondria.

### WHAT IS “PHOTOBIMODULATION”

Laser PBM, also called as low-energy laser therapy, manifests the utilization of monochromatic or quasimonochromatic low-level light to induce mainly non-thermal and non-invasive photochemical activities (Mester *et al.*, 1985; Schindl *et al.*, 2000; Desmet *et al.*, 2006). Some investigators are skeptical for this multidisciplinary field since they deeply believe electromagnetic light must ionize biological systems it affects. Or they thought of the light signals are so weak to induce significant biological effects (Karu, 2008).

However, it has been demonstrated that PBM could stimulate or inhibit a wide variety of cellular processes, thereby modulating cell functions (Mester *et al.*, 1985; Schindl *et al.*, 2000; Desmet *et al.*, 2006). Santana-Blank *et al.* (2013) recently reported a singular low-energy IR pulsed laser device with high-frequency ultrasound and near-IR radiation could successfully adopted to treat patients who suffered from advanced and progressive neoplasia. Morphological study revealed that the PBM triggers the selective activation of programmed cell death only in neoplastic cells, but not in peripheral tissues, which is further supported by the subsequent data obtained from Tanaka’s group (2010). Even intriguingly, magnetic resonance imaging data showed the alteration of water content in the tumor may act as an early diagnostic predictor of tumor response (Santana-Blank *et al.*, 2013).

Other investigations demonstrate that PBM can activate regenerative responses, alone or associated with stem cell therapy (Desmet *et al.*, 2006; Karu, 2008). Recent effects also focused on the dentistry (Carroll *et al.*, 2014), degenerative neuronal disorders (Wong-Riley *et al.*, 2005; Ying *et al.*, 2008; Quirk *et al.*, 2012), and metabolic syndromes (Reddy *et al.*, 2001). Therefore, the advent of PBM is likely to cover a wide spectrum of clinical applications. The finding that irradiation of external electromagnetic energy can increase and substitute for endogenous ATP production, provide a theoretic back-

ground to account for the potential of PBM.

### THERAPEUTIC POTENTIALS OF PBM

One of the most studied PBM would be an arena of wound healing. Low-density red laser light therapy was first introduced to accelerate wound healing in 1970’s (Mester *et al.*, 1971). The light therapy has been applied to a variety of pathological conditions such as wound healing and dermatologic, neurologic diseases (Desmet *et al.*, 2006). It further extended their boundary to blood disorders and musculoskeletal diseases and pain (Abergel *et al.*, 1984; Lee *et al.*, 1996; Wedlock *et al.*, 1996; Yaakobi *et al.*, 1996; Rochkind *et al.*, 2013). Red laser therapy was known to affect cellular processes without significant thermal effects.

Zhang *et al.* (2003) have reported that irradiation of red light (628 nm) resulted in expression shift of 111 genes in HS27 human fibroblasts. They also grouped those genes into 10 functional categories. Most genes seem to play roles in the cell proliferation and suppression of cell death. Besides, they also promote the production of extracellular matrix proteins, all of which are important factors in wound healing. Overall, these genes orchestrated a prolonged increase in mitochondrial ATP production and cellular stress resistance (Lane, 2006). Energy transduction and production of ATP is largely relied on electron transport chain in mitochondria. The protein complex in the chain has a lot of metal clusters including iron and copper. In most cases, the iron is incorporated in iron-sulfur cluster or heme cofactors found in electron transport chain.

Researchers studied that near IR therapy protects from methanol poisoning (Eells *et al.*, 2003), which can injure the retina and optic nerve. A metabolic toxicant of methanol, formic acid binds and inhibits COX activity. In this animal model, irradiation of near IR restores the function of retina. *Retinitis pigmentosa* was shown to be attenuated by near IR photo-

**Table 1.** Representatives of hemoproteins and their function, location

Hemoprotein	Function	Subcellular localization
Succinate dehydrogenase	Electron transport (complex II)	Mitochondria inner membrane (IM)
Cytochrome bc1 complex	Electron transport (complex III)	Mitochondria IM
Cytochrome c	Electron transport	Intermembrane space
COX	Electron transport (complex IV)	Mitochondria IM
Cyp11A1	Steroid biosynthesis	Mitochondria matrix
Hemoglobin	Gas-binding	Cytosol
Myoglobin	Gas-binding	Cytosol
Neuroglobin	Gas-binding	Cytosol
Cytoglobin	Gas-binding	Cytosol
NOS	NO signaling	Cytosol, membrane
Soluble guanylyl cyclase	NO and calcium signaling	Cytosol
Hap1	Transcription factor	Nucleus
Bach1	Transcription factor	Cytosol/nucleus
Rev-erba	Transcription factor	Nuclear
DGCR8	miRNA processing	Nuclear
mPer2	Circadian rhythm	Cytosol/nuclear
Cytochrome b5	Electron carrier	Cytosol
P450 cytochromes	Xenobiotics metabolism	ER* membrane, cytosol
Prostaglandin synthase	Signaling (COX-1, COX-2)	ER
myeloperoxidase	Microbicide	Lysosome-like azurophil granule
Catalase	Antioxidant	peroxisome
Thyroperoxidase	Thyroid hormone synthesis	Plasma membrane
Ferric reductase	Iron transport	Plasma membrane
Lactoperoxidase	Microbicide	Secreted
Ligninase	Nutrient breakdown	Secreted
Heme-containing chloroperoxidase	Haloperoxidase	Secreted
Peroxidasin	Extracellular matrix synthesis	Secreted
HRG-3	Heme mobilization	Secreted

Korolnek, T. and Hamza I. (2014) Like iron in the blood of the people: the requirement for heme trafficking in iron metabolism. *Front. Pharmacol.* **5**, 126 (modified). \*ER: endoplasmic reticulum.

therapy *via* inhibiting apoptosis in retinal cells.

## HEMOPROTEINS

Heme cofactors are found in many proteins (Kim *et al.*, 2006; Munro *et al.*, 2009; Lee *et al.*, 2013). Hemoproteins play various roles in oxygen transport, energy transduction, gene regulation, *de novo* steroid and lipid biosynthesis, cellular signaling and gene expression (Table 1). Diverse physiological functions performed by hemoproteins make heme as one of the most versatile of protein cofactors (Munro *et al.*, 2009).

A wide variety of heme axial ligands are known (Munro *et al.*, 2009). These ligands are very important for the modulation of heme iron reduction potential; thereby the capability of the cytochromes to take parts in the redox reactions. Ligands to heme iron can be removed or replaced by other ligands during catalytic cycles of certain hemoproteins to carry out their functions (i. e., light replace NO with oxygen). Thus, alteration of the protein environment, along with the changes in axial ligands to the heme iron resulted in considerable variations in heme iron reduction potential and in the activity of hemoproteins. So far, there is a wealth of structural data available for hemoproteins depending on their redox states and ligand-bound forms.

Probably hemes are the most easily identifiable cofactors since their conjugated porphyrin structures give rise to electronic transitions in the visible region and strong red color (Munro *et al.*, 2009). The factors for determining the absorption spectra for heme proteins are unique, for example, redox state, the nature of the ligands to the heme iron, and the heme iron spin-state. Characteristic feature of the absorption spectra for heme proteins are shown in Table 2. The spectra for various hemoproteins are ranging from visible to near IR or IR region at 800-2,500 nm (Munro *et al.*, 2009).

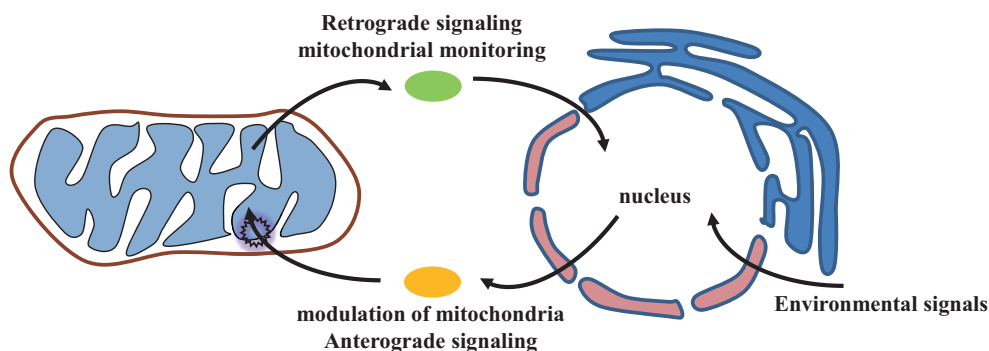
## CYTOCHROME C OXIDASE

Oxidative phosphorylation take place in mitochondria composed of four complex (Wong-Riley *et al.*, 2001; Lane, 2006; Karu, 2008). Among them, cytochrome c oxidase (1.9.3.1, COX) is a component of complex IV with metal clusters containing iron and copper. COX is a large transmembrane protein complex found in bacteria and the mitochondria of eukaryotes. It is the last enzyme in the respiratory electron transport chain of mitochondria, receives an electron from each of four cytochrome c molecules, and transfers the electrons to an oxygen molecule, forming 2 moles of water (Fig. 1). Since most of the oxygen consumption in cells are catalyzed by the heme-

**Table 2.** Principal UV/Vis characteristics of some hemoproteins

Enzyme	Status	Absorption wavelength (nm)
Bovine COX	Fully oxidized	425, 597
	Fully reduced	444, 604
	Compound A (CO)	588-590 (+CO), 608-612 (-CO)
Horseradish peroxidase	Ferric	402-404, 495-500
	Ferrous	437, 556-560
Yeast cytochrome c peroxidase	Ferric	408, 507, 647
	Ferrous	438, 560

Rich, P. R. and Iwaki, M. (2007) A comparison of catalytic site intermediates of cytochrome c oxidase and peroxidases. *Biochemistry* (Moscow) **72**, 1047-1055 (modified).



**Fig. 2.** Integration of intracellular mitochondrial function rely on both anterograde and retrograde signaling pathway. The anterograde signaling system transduces signals from environments (external and/or internal) to nucleus, activating genomic program to adjust mitochondrial functioning. The retrograde signaling system monitors the function of mitochondria and transduce signals back to the nucleus. Studies on cytoplasmic transducers are actively pursued. See text for details.

copper oxidases, their uniqueness in the cellular respiration and energy supply is essential for aerobic organisms. COX catalyzes the reduction of oxygen to water and utilizes the free energy of the redox reaction for proton pumping across the membrane, establishing the electrochemical proton gradient that drives ATP production.

The rationale of retrograde signaling from mitochondria is based upon 2 observations. First, PBM (300-860 nm) can increase in DNA synthesis rate in cultured cells. However, the nucleus does not have chromophores absorbing light in this range of spectrum. Second, cumulating data by this time clearly shown that the photoacceptors are localized to the respiratory chain of mitochondria (Karu, 2008). Therefore it would be reasonable to propose the existence of cellular signaling pathway originated from this organelle. Experimental data also support retrograde signaling can be mediated *via* mitochondrial membrane potential (MMP), reactive oxygen species (ROS), changes in calcium flow, NO binding to COX (Fig. 1). Impairment of mitochondrial functioning routinely generates signaling mediators described above, which may determine the fate of this organelle. Rapidly growing cells prefer cell death instead of fixing the damaged mitochondria. In contrast, quiescent cells such as neuron try to recover the injured mitochondria by retrograde signaling pathway (Fig. 2). Therefore, it would be a survival strategy adopted by cells or organisms to maintain homeostasis of the quintessential sub-

cellular organelle, mitochondria. In line with this notion, Park *et al.* (2013) reported that repeated thermal therapy by far-IR irradiation improves vascular functions *via* acute activation of endothelial NO synthase (NOS). The increase of eNOS was accompanied by an increase in intracellular calcium levels. Therefore, they suggested a possible involvement of temperature-sensitive calcium channel, transient receptors potential vanilloid (TRPV) ion channel at the plasma membrane as a photoacceptor. They did not discuss the involvement of retrograde signaling pathway in this setting, it might be possible that NO acts as a mediator for the signaling pathway.

As described above, the analysis of the PBM action on DNA and RNA synthesis rate at the wavelength range 330-860 nm helped conclude that in fact COX acts as a photoacceptor (Karu, 2008). The band peaks of light for the activation of DNA synthesis were identified by analogy with metal-ligand absorption spectra, which span through visible, near IR ranges. This conclusion goes also well with Warburg's old experimental data (Lane, 2006).

### RETROGRADE SIGNALING FROM MITOCHONDRIA: THE FUNCTION OF CELLULAR RESPIRATION

Mitochondria are the central organelle for diverse cellular functions as an integrator of signals originated from outside or

inside of the cells (Lee *et al.*, 2013). Many reports proposed that extramitochondrial factors which control the nuclear gene expression for mitochondrial proteins and their biogenesis (Fig. 2). A major cellular communication includes the transduction of extracellular signal to nucleus (Karu, 2008). However, other pathway of cellular communication from mitochondria to the nucleus is known as a mitochondrial retrograde signaling pathway. It is, therefore, not surprising that mitochondria are once free-living organisms accidentally residing in eukaryotic common ancestors. The most investigated retrograde signaling pathway is performed using budding yeasts *Saccharomyces cerevisiae*. Later, the signaling pathway of mitochondria-nucleus crosstalk is also described in mammalian cells, including myocytes and tumor cells (Karu, 2008).

Recently Karu (2008) provides a summary for the mitochondrial retrograde signaling which operates in the irradiated cells. As described above, the retrograde signaling is associated with mitochondrial membrane potential, ROS and calcium mobilization. In some cases biological gases are involved in the signaling pathway by binding to heme center of a certain hemoproteins in general, COX in particular. Mitochondria have their own gas-synthesizing enzymes, mtNOS and heme oxygenase-1 (Slebos *et al.*, 2007; Zaobornyj and Ghafourifar, 2012). The enzymatic activity is localized to the mitochondrial inner membrane where the electron transport chain resides and operates. Binding of the gas molecules produced by PBM to COX hemoprotein can divert the fate of oxygen into ROS formation (Moncada and Bolaños, 2006; Zuckerbraun *et al.*, 2007). Under the condition of metabolic demand, COX hardly has more than 20% of the total control over ATP production in cells, implying that the gas-mediated changes in oxygen consumption can occur without a significant decline of ATP synthesis (Karu, 2008). Thus a window exists at which low level of gas molecules can regulate mitochondrial ROS production without ATP loss. But the spatio-temporal regulation of gas producing enzyme by PBM is not known.

Retrograde signaling pathway transduces the signal via regulation of redox sensitive transcription factors, nuclear factor (NF)- $\kappa$ B or AP-1 (Karu, 2008). In some tumors, reduced production of ATP also linked to the activation of NF- $\kappa$ B via generation of ROS (Chen *et al.*, 2014). Besides, retrograde signaling pathway contributes for the maintenance of mitochondrial homeostasis by controlling fusion-fission events (Karu, 2008).

## WATER: A NOVEL PLAYER?

The IR absorption spectrum of water was known as early as 1950's (Curcio and Petty, 1951). With advances in new technology the absorption spectra of water was more clearly demonstrated (Santana-Blank *et al.*, 2013). However most of the studies were carried out using ordinary liquid water. Recently, experimental evidences show that the intracellular water structure is not the same as that of ordinary bulk water. As mentioned above, the structured water, also termed exclusion zone (EZ) water, is formed at the interface of most hydrophilic surfaces (polymers or biological molecules). This feature of EZ is a solute-free area, extending hundreds of micrometers (Pollack, 2013). Very recently, Pollack (2013) summarized and noted the exclusion zone (EZ), defined as a fourth phase of water. Based upon this water state, a few investigators hy-

pothesize that EZ might be a target of PBM as an energy sinker, which cells may use this to fuel cellular processes (from page 2).

In biological milieu, intracellular proteins may serve as a surface for water structuring. Interestingly, it has been reported that PBM can increase potential energy in the EZ water, which in turn, acts as an energy reservoir. The reserved energy, then, can selectively supply energy demands in cells (Pollack, 2013).

The behavior of cells is one of the current topics in cell biology. Water contents in tumor cells may different from those found in normal cells (Pollack, 2013). Cellular aging and neurodegenerative diseases are at least in part attributed to the impairment of water handling in cells or organisms (Pollack, 2013). If PBM can modulate the behavior of water in some ways, it would affect the integrity of biological molecules including DNA and proteins. It warrants further investigations.

## CONCLUSION

PBM including near IR irradiation therapy starts its journey to cell biology and medicine. The molecular target of PBM might be a variety of hemoproteins, but COX was the only target to be investigated actively. In addition, the targets of the PBM may be a simple molecule, water. Two-thirds by volume, 99% by number are water in mammalian cells. But water research is in its embryo state, slowing the better understanding of cell biology.

## ACKNOWLEDGMENTS

The work was supported by National Research Foundation, Korea 2011-0024407.

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