Surgery: Current Research
ISSN: 2161-1076
OPEN ACCESS Freely available online
Review Article

Photobiomodulation, Energy and Cancer: A Quantum Notion

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ABSTRACT

Photobiomodulation therapy is defined as the utilization of non-ionizing electromagnetic energy to trigger photochemical changes within cellular structures that are receptive to photons. At the cellular level, visible red and Near Infrared Light (NIR) energy are absorbed by mitochondria, which perform the function of producing cellular energy (ATP). Continuous energy supply is a necessary condition for life. Electromagnetic energy has the capacity to carry large bundles of information that may control and coordinate all chemical reactions in the cells. Disturbances in oxidative metabolism and coherence are a central issue in cancer development. Cancer can be perceived as an entropic cellular survival state that lacks differentiation information. This increase in ATP production may provide the needed energy to achieve negative entropy. Negative entropy may reestablish the necessary order, organization and compartmentalization for cellular redifferentiation. Photobiomodulation may help restore cellular homeostasis by inducing physiologically reparative activity for disease reversal in cancer and other degenerative diseases with minimal adverse side effects, and with potentially marked improvements in quality of life even in patients with advanced neoplasms.

Keywords: Photobiomodulation therapy; Photochemical changes; Cancer

INTRODUCTION

The use of light as a medical intervention has entered into the field of energy medicine. The term for this modality is Photobiomodulation. Photobiomodulation Therapy (PBMT) is the best technical term for Low Level Laser Therapy (LLLT) which is the use of monochromatic; low-fluence light to induce primarily non-thermal photochemical effects. It is basically a light therapy using lasers to improve tissue repair; reduce pain and inflammation wherever the beam is applied. It involves the delivery of light energy to modulate cellular mechanisms that often result in better health. Light is the most fundamental energy particle that is the source of life on earth. Photobiomodulation might be energy medicine Final Frontier. Pigmented substances that accept photons in living tissue are called Chromophores. When a photon within a specific wavelength strikes a matching chromophore; the energy of the photon is transferred to the chromophore. This causes series of biochemical reactions that result in changes within the cell or tissue. When these changes activate or improve cellular function it is called photobioactivation. It is a process very similar to the action of sunlight in plant photosynthesis. Also metals; cofactors; proteins [1] and water [2;3] are capable of chromophore activity. Bioelectromagnetics and photobiomodulation may provide the mechanisms needed to modify the malignant behavior of cancers [4;5].

Methodologically there are two basic techniques; Intravenous Laser Blood Irradiation (IVLBI) and Percutaneous Low Laser Therapy (PLLT). IVLBI was developed experimentally by Russian researchers; Meshalkin and Sergievskiy [6] and introduced into clinical practice in 1981. Originally the method was applied in the treatment of cardiovascular abnormalities. Intravenous Laser Blood Irradiation (IVLBI) has a wide range of actions; which include biostimulation; analgesia; antiallergic effects; immunomodulation; vasodilatation; antiarrhythmic; antihypoxic; spasmolytic; and anti-inflammatory effects [7-13].

IVLBI improves the rheological properties of blood; increasing its fluidity and activating transport functions. This is accompanied by increased oxygen levels; as well as decreased carbon dioxide partial pressures. The arteriovenous difference for oxygen is increased; which confirms a reduction in tissue hypoxia with a return to normal metabolism. Probably; the basis for activation of oxygen transport by IVLBI is through an effect on hemoglobin. The augmentation of oxygen levels improve tissue metabolism. In addition; laser irradiation activates ATP synthesis and energy formation in cells [8]. The application of IVLBI in cardiology has shown that the procedure has analgesic effects; which increase exercise tolerance for patients and prolong periods of remission. The mechanism might be through reduced platelet aggregation and activation of fibrinolysis and so increased peripheral blood flow and tissue oxygenation. The improvement seen in the microcirculation is also attributable to vasodilatation and changes

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Received: October 06; 2020; **Accepted:** March 05; 2021; **Published:** March 12; 2021

Citation: Gonzalez JM, Olalde J, Cintron K, Weber KH (2021) Photobiomodulation; Energy and Cancer: A Quantum Notion Surg: Curr Res 11:110.

in the physicochemical properties of erythrocytes. In particular there is a rise in their negative electric charge. In addition there is unblocking of capillaries and collaterals as well as normalization of the nervous excitability of smooth muscle in vascular walls [10].

Acupuncture is an important component of traditional Chinese medicine. As such; it remains one of the oldest therapeutic approaches still in contemporary use. The term acupuncture refers to puncturing the skin using fine metal needles at various points on the body known as acupuncture points or acupoints. According to traditional theory; energy or qi flows along energy channels or meridians that run through the body; which; when disrupted or blocked; can be released by stimulating specific points along each channel [8]. Correction of the flow or energy balancing is perceived as necessary for ensuring maintenance or restoration of health. Acupuncture deals with the body's own energy. More recently; different methods of stimulating the acupoints have been introduced including acupressure (applying pressure at the points); electrical stimulation (electroacupuncture) and laser acupuncture (use of low-level laser therapy at points).

Laser acupuncture is defined as the stimulation of traditional acupuncture points with low-intensity; non-thermal laser irradiation. There are practical and methodical advantages to this procedure compared to needle acupuncture: application is free of pain; there is no risk of infection; application is simple and not time-consuming. Also there is an increase in energy input provided by the photonic nature of the laser. Laser acupuncture may provide the necessary energy to drive the system back to the physiological balance necessary to restore the healthy state. Nevertheless conventional acupuncture mainly corrects the energy imbalance. Laser acupuncture raises the possibility of providing more energy to the system.

Biophoton therapy: quantum photobiomodulation

Biophoton is the universal stimulation of photons in the cell. In short a biophoton is a photon (a light particle/wave) of non-thermal origin in the visible and ultraviolet spectrum emitted from a biological system; a plant; animal and human. Biophoton therapy is the application of light for healing purposes. The light; or photons; that are emitted by these units are absorbed by the skin's photoreceptors and then travel through the body's nervous system to the brain; where they help regulate what is referred to as our human bio-energy. By stimulating certain areas of the body with specific quantities of light; biophoton therapy can help reduce pain as well as aid in various healing processes throughout the body. The theory behind biophoton therapy is based on the work of Dr. Franz Morell [14] and has been expanded by the work of L.C. Vincent and F.A. Popp [15,16]; who theorized that light can affect the electromagnetic oscillation or waves of the body and regulate enzyme activity. The body's communication system seems to be a complex network of resonance vibration and frequency. There is evidence that light in your body is stored by and emitted from the DNA molecule [17]. The DNA inside each cell vibrates at a frequency of several billion hertz. The vibration is created through the coil-like contraction and extension of the DNA structure which occurs several billion times per second and every time it contracts; it forces out a biophoton or light particle. That photon contains information about the DNA molecule. One single biophoton can carry more than four megabytes of information and relays this information to other biophotons. All the photons that are emitted from the body communicate with each other in this highly structured light field. The information transfer on biophotons is bidirectional. Illness occurs when biophoton emissions are out of sync. The light emissions from cancer patients lack such rhythms and appeared scrambled; which suggests that cancer cells are no longer communicating properly. Biophotons represent; within the cell; an actual electromagnetic language for coding morphogenetic information that triggers enzymatic processes to develop the functional dynamics of life. In relation to cancer; it has been reported that rat hepatocytes exhibit spontaneous biophoton emission; but from hepatoma cells this was not detectable [18].

Continuous energy supply; a necessary condition for life; excites a state from thermodynamic equilibrium; in particular coherent electric polar vibrations depending on water ordering in the cell). Recently; based on studies by Pollack [19] and others on the Exclusion Zone (EZ); described as a fourth phase of water; the high-energy EZ water forms along hydrophilic surfaces (e.g.; tissue interfaces) in response to radiant energy [20]. Remarkably; EZ water can separate and store electrical charges and can release up to 70% of such charges when it is disturbed. It seems likely that the EZ might be targeted by laser photobiomodulation as an energy reservoir; which cells may use to fuel cellular work and trigger signaling pathways and gene expression modification to overcome injury-induced redox potentials. Laser photobiomodulation may trigger reparative and regenerative mechanisms that can lead to restoring homeostasis or physiological balance [21-23].

Coherent light has the capacity to carry large bundles of information; information carried on coherent light may control and coordinate all chemical reactions in the cells. Laser therapy may stimulate a florescent effect *via* signalling processes to the mitochondria (which is the main cellular target of laser absorption); but also Laser Therapy may produce a resonance effect with the spontaneous production of bio-photons. Laser Therapy may develop a complex information and energy exchange activity with generation of bio-photons that may guide the functional organization of life. So laser therapy can generate photobiostimulation of florescent light and a coherent photo-biomodulation that may be relevant for cell differentiation. Laser light is generated on the principle of light amplification of stimulated emission of radiation. The laser beam is potent because it is highly coherent (all waves in phase); polarized (waves in which the vibrations occur in a single plane); focused and monochromatic (a single wavelength).

Photobiomodulation; energy and cancer: the frankenstein effect

Disturbances in oxidative metabolism and coherence are a central issue in cancer development. Cancer can be perceived as an entropic cellular survival state that lacks differentiation information. Oxidative metabolism may be impaired by mitochondrial dysfunction [24,25]. This can in turn lead to disturbance in water molecules' ordering; diminished power and coherence of the electromagnetic field.

In tumors with the reverse Warburg effect concomitant with mitochondrial dysfunction; cancer cells have low power [25,26]. Therapeutic strategies restoring mitochondrial function may trigger apoptosis and/or redifferentiation [27]. Also in tumor tissues with the reverse Warburg effect; Caveolin-1 levels should be restored and the transport of energy-rich metabolites that is interrupted to cancer cells.

In order to reestablish mitochondrial function; in addition to providing all the necessary mitochondrial function co- factors (Magnesium; lipoic acid; acetyl L Carnitine; B Complex; CoQ10; oxygen) in their proper form and dose there is a need

for mitochondrial electro molecular activation: when a photon is absorbed by a molecule; its electrons will change position between the orbits at the atomic level; resulting in high energy state known as Singlet state. This molecular excited singlet state behaves differently than the same molecule in its normal state and can cause Electron transfer to its neighbor molecule; resulting in tissue excitation. When this occurs in the mitochondria (via cytochrome oxidase c); the electron transport chain reaction is activated 10 times its normal rate; resulting in more ATP production. This can theoretically be achieved by the use of class 4 IV lasers. Once the mitochondrial cofactors are aligned the laser beam may provide the energetic burst to turn on the system again. This increase in ATP production may provide the needed energy to achieve negative entropy. Negative entropy may reestablish the necessary order; organization and compartmentalization for cellular redifferentiation. These ideas are a paradigm shift or quantum leap in the understanding and use of coherent; monochromatic light (laser) and its interaction with water (4th phase) and other relevant biological photo-acceptors capable of restoring the cellular balance or normal physiologic function.

Mitochondrial photobiomodulation: increasing ATP production

It is generally accepted that mitochondria are the initial site of light action in cells and cytochrome c oxidase (the terminal enzyme of the mitochondrial respiratory chain) is the main responsible molecule. Although other chromophores with similar activity seem to be present in mitochondria [28]. The excitation of the photoacceptor molecule sets in motion cellular energy metabolism through cascades of reactions called the retrograde mitochondrial signaling. Mixed-valence copper components of cytochrome c oxidase; are believed to act as the photoacceptors. ATP is not only an energy currency inside cells; but it is also a critical signaling molecule that allows cells and tissues throughout the body to communicate with one another [29]. ATP is believed to play a role as an important signaling molecule to many metabolic activities. It is known that even small changes in the ATP level can significantly alter cellular metabolism by a spiral of pleiotropic reactions. Increasing the amount of this energy may improve cellular metabolism; especially in suppressed or ill cells and provide the needed force to attain negative entropy to establish or maintain the necessary order; organization and compartmentalization characteristic of the healthy state [30].

There seems to be a role of ATP as an information molecule. There is evidence of ATP as an extracellular neurotransmitter [31]. Moreover a tumor-killing effect of ATP has been described. ATP itself may be a potential cancer-fighting molecule. Rapaport [32] described the tumor killing effect of ATP in 1983. He demonstrated that the addition of exogenous ATP to pancreatic and colon cancer cells inhibited cell growth by causing cell cycle arrest in the S-phase. Further research has shown that ATP can inhibit growth in prostate; breast; colorectal; ovarian; and esophageal tumors as well as melanomas [33-39]. ATP signaling appears to act in part promoting tumor cell suicide and in part fostering differentiation; which slows tumor cell proliferation [38,39].

Another hypothesis is that the laser photons dissociate inhibitory nitric oxide from the enzyme; leading to an increase in electron transport; mitochondrial membrane potential and ATP production. Stem cells and progenitor cells appear to be particularly susceptible to photobiomodulation energy enhancement [40,41]. At the cellular level; visible red and near infrared light energy stimulates cells to generate more energy and undergo self-repair [42].

Monochromatic coherent chromotherapy: physiological actions of colors or wavelengths of lasers

LASER is short for Light Amplification by Stimulated Emission of Radiation. This light is generally a collimated beam of coherent (all the waves moving in lock-step) electromagnetic energy with a very pure color or narrow bandwidth. Intravenous Laser Therapy or intravascular blood irradiation involves the in vivo illumination of the blood by feeding low level laser light generated by a low power laser at a variety of wavelengths through a fiber optic inserted in a vascular channel; usually a vein in the forearm with a therapeutic effect circulated through the circulatory system [43]. The use of monochromatic laser-irradiation can produce calculated biological effects that are set off with defined wavelengths. It is a known fact that the cytochrome-C-oxidase-complex located at the mitochondrial respiratory chain is capable of absorbing in the red- and infrared range; and the NADH-complex as the first component is absorbing in the blue range. Another advantage of laser-light beside monochromasy is the coherence of the radiation which by means of particular order functions (in-phase-conformity of the waves) and possibly has specific biological effects.

By referring to colors; (colors in the visible range) they range from about 400nm-700nm. As for visible lasers; there are several types that emit in a variety of colors. The wavelength of laser sources defines its output color. Color is frequency within the visible spectrum of light; which composes a very small band of the total electromagnetic spectrum; from violet at 400 nm (higher energy photon) through red at 780 nm (lower energy photon). Beyond violet in increasingly shorter wavelengths; are ultraviolet light; x-rays; and gamma radiation which contain tremendous amounts of energy. In the opposite direction; infrared and radio waves are longer wavelengths beyond the red end; with relatively very little energy. Each color of the spectrum is composed of a band of frequencies. Therapeutic application of light to the body is accomplished by applying a single monochromatic wavelength within that band.

A blue laser is a laser that emits electromagnetic radiation with a wavelength between 360 nm and 480 nm. Blue laser Improves microcirculation by nitric oxide release (which also is very powerful at stimulating stem cells to work); strong anti-inflammatory and antibacterial effects; accelerates wound healing; supports pain relief; stimulates the immune system to be more active; and activates telomerase and biogenesis of mitochondria with maximum anti-aging effects. Irradiation with blue laser leads to increase of the release of Nitric Oxide (NO) from hemoglobin. Increased production of NO activates the telomerase and thus stopping shortening of telomeres; which has been associated with aging [44] also increases in NO can lower blood pressure [45]. Blue laser is known to act anti-inflammatory by reducing pro-inflammatory cytokines and contributory factors for a variety of conditions (NF-kB; CRP; IL2; IL6; TNF alpha; Leptin; chemokines etc.) [46]. Blue light is effective for treating infections by production of ROS; especially in combination with photosensitive substances like Curcumin or Riboflavin [47].

Red laser is good for relieving inflammation and inflammatory conditions. Its wavelength is 630 nm-680 nm and its power is 5 mW and below. In addition to reducing inflammation and healing time; red laser has an energizing effect (increased ATP production); strengthens the immune system; increases cell activity; regenerates damaged tissue structures and improves circulation [34]. It also has a positive influence on rheological properties of the blood

[48]. It diminishes the tendency of aggregation of thrombocytes and improves deformability of erythrocytes [49,50]. It activates phagocytic activity of macrophages [42,43]. It has a positive effect on the proliferation of lymphocytes and B-and T-cell subpopulations [39,44].It stimulates of interferon; interleukins and TNF-alpha [46; 51]. It develops giant mitochondria with activation of various metabolic pathways; increased production of ATP and normalization of cell membrane potential [47,48]. Blue laser produces analgesic; spasmolytic and sedative effects [52].

Near infrared light is in the range of 700 nm-1400 nm on the electromagnetic spectrum and has wavelengths that are longer than those of visible light. Near-infrared laser is proposed for three main purposes: to promote wound healing; tissue repair; and the prevention of tissue death; to relieve inflammation and edema because of injuries or chronic diseases; and to be used as an analgesic. It is proposed as a treatment for serious neurological conditions such as traumatic brain injury; stroke; spinal cord injury; and degenerative central nervous system disease [53]. Near-infrared laser regenerates deeper structures such as tendons; bones and cartilage; orthopedic and musculoskeletal problems [54].

Yellow light lasers are commonly used in hospitals and have good effects on viral infections; multiple sclerosis; and helps patients with panic attacks; depression and anxiety disorders. Its wavelength is 593.5 nm. It has strong anti-depressive effects (especially in combination with Hypericin from St. Johns Wort Plant) and positive influence on the general mood [55-59]. It also Improves Serotonin and Vitamin-D production [60]. Yellow laser additionally stimulates the mitochondrial respiratory chain at complex III cytochromes [61,62].

Green laser increases the production of ATP in the irradiated mitochondria [59,60]. It also improves oxygen carrying ability of blood cells; improves blood flow; helps reduce blood pressure; and increases nitric oxide [63; 64]. Its wavelength is 532 nm.

Ultraviolet laser light is currently used superficially to sanitize things and for certain skin disorders. Ultraviolet laser is antimicrobial; it activates the immune system; increases oxygen absorption; increases the body's ability to make vitamin D; helps with detoxification; etc. (UV treatment of blood also known as Ultraviolet Blood Irradiation (UBI) was developed in the United States. It improves oxygen affinity; increases attraction of oxygen to hemoglobin; Improves ability to carry more oxygen; decreases lactic acid [65]. It has shown that ultraviolet blood irradiation can strengthen the immune system and improve overall health [66-68].

The laser lights are administered intravenously and individually for about 10 minutes each.

Chromophores responsible for photobiomodulation

Cytochrome C Oxidase (CCO) is unit IV in the mitochondrial electron transport chain. It transfers one electron (from each of four cytochrome c molecules); to a single oxygen molecule; producing two molecules of water. At the same time the four protons required are translocated across the mitochondrial membrane; producing a proton gradient that the ATP synthase enzyme needs to synthesize ATP.

Karu [69,70] was the first to suggest activity; and this observation was confirmed by Wong-Riley et al. [71]. The postulation of CCO as the main target of PBM supports the wide use of red/NIR wavelengths as these longer wavelengths have much deeper tissue penetration than blue or green light. The most popular theory to explain why photon absorption by CCO leads to increase of enzyme activity; increased oxygen consumption; and increased ATP production is based on photodissociation of inhibitory Nitric Oxide (NO) [72]. Since NO is non-covalently bound to the heme and Cu centers and competitively blocks oxygen at a ratio of 1:10; a relatively low energy photon can kick out the NO and allow increase respiration to take place [73]. Nevertheless other probable chromophores molecules should be present in the Electron Transport System; good candidates are Coenzyme Q10; Cytochrome b and Cytochrome a.

Photoreceptors: light gated ion channels and opsins

More recently it has become apparent that another class of photoreceptors is involved in transducing cellular signals; particularly responding to blue and green light. Three photoreceptors have been proposed to be members of the family of light-sensitive G-protein coupled receptors known as Opsins (OPN). Opsins function by photoisomerization of a cis-retinal co-factor leading to a conformational change in the protein. The most well-known opsin is rhodopsin; which is responsible for mediating vision in the rod and cone photoreceptor cells in the mammalian retina. There are other members of the opsin family; which are expressed in many other tissues of the body including the brain. One of the best-defined signaling events that occur after light activation of opsins; is the opening of light-gated ion channels such as members of the transient receptor potential family of calcium channels.

Chromophores: flavins and flavoproteins

There is another family of biological chromophores called cryptochromes. These proteins have some sequence similarity to photolyases ; which are blue light responsive enzymes that repair DNA damage in bacteria caused by UV exposure. Cryptochromes rely on a Flavin (flavin adenine dinucleotide; FAD) or a pterin (5,10-methenyltetrahydrofolic acid) to actually absorb the light (again usually blue or green). Recent evidence has emerged that mammalian cryptochromes are important in regulation of the circadian clock.

Water as a chromophore

Water represents about 70% by mass of an adult human body. In addition; high-order organisms; including humans; can be represented as complex electrochemical (semiconducting) systems that comprise a vast array of energy-sensitive materials and machinery; such as ion pumps; molecular motors (e.g.; ATP synthase); transistors-capacitors (e.g.; cell membrane); liquid crystals (e.g.; membrane structure) and rechargeable electrolytic biological batteries (e.g.; hydrophilic interface in cells/tissues;).

Szent-Gyorgyi postulated that water was at the core of energy transfer in biological systems (i.e.; quantum biology); and that that explained how energy from biomolecules could be translated into free energy for cells [74].

A possible alternative chromophore is water molecules whose absorption spectrum has peaks at 980 nm; and also at most wavelengths longer than 1200 nm [75]. Moreover; water is by the far the most prevalent molecule in biological tissue. At present the proposed mechanism involves selective absorption of IR photons by structured water layers (also known as interfacial water or water clusters) at power levels that are insufficient to cause any detectable bulk-heating of the tissue. A small increase in vibrational energy by a water cluster formed in or on a sensitive protein such

as a heat-gated ion channel; could be sufficient to perturb the tertiary protein structure thus opening the channel and allowing modulation of intracellular calcium levels. Pollack has shown that interfacial water can undergo charge separation when it absorbs visible or NIR light [76]. This charge separation (equivalent to localized pH changes) could affect the conformation of proteins [77]. It has also been suggested that PBM could reduce the viscosity of interfacial water within the mitochondria; and allow the ATP synthase; which rotates as a nanomotor to turn faster [78]. Water provides efficient pathways for charge storage; separation; and subsequent release [19]. Santana et al. proposes that light water interactions offer a potent; alternate and complementary pathway to activate or modulate tumor suppression and/or proto-oncogenic expression through energy transfer via water and CO2 in multi-fractal regimes; leading to the coupling of spatiotemporal oscillators [79]. In general; physiological rythms (orderly; organized; compartmentalized frequencies and vibrations needed for effective communication) may be reactivated and synchronized through water; CO_2; and membrane receptors by selective; noninvasive; long-range; external energy supplementation by light in the presence of the necessary cofactors. Light-induced vibrations act as Hamiltonian dynamic systems; which exhibit complex nonlinear; time-dependent chaotic behavior that strongly enhances molecular interaction. Moreover; the human body can be in resonance while energy is transferred among different modes or trajectories; magnifying energy absorption and transport due to its multi-fractal architecture [80,81]. Hydrophilic interfaces; including the exclusion zone; has been shown to be able to separate and store charges; thus acting as a potential energy reservoir. Such charges may later fuel intracellular electron (OH^-) transfer and proton (H^+) movement in the bulk's aqueous flow for cell signaling [81].

Water's permittivity is generally high; therefore; radiant energy can penetrate and be absorbed by tissues. One example is the Exclusion Zone (EZ) described by Pollack [19]. High-energy EZ water forms along hydrophilic surfaces (e.g. tissue interfaces) in response to radiant energy. EZ water can separate and store electrical charges; and can release up to 70% of such charges when it is perturbed; such as by injury-induced redox potentials [82]. In this manner supplied energy can power and modulate cellular work and signaling pathways; even when the metabolic energy pathway has been compromised; steering cells toward or away from programmed cell death [83]. EZ water may; thus; act as an electrolytic bio-battery; which can efficiently and selectively transfer energy to sites expressing redox injury potentials; as found in cancer and other degenerative diseases; triggering reparative and regenerative mechanisms that can lead to restoring homeostasis and ultimately; health [84]. An important aspect in understanding and controlling the biophysics and biochemistry of higher-order organisms might be ingrained in their dual aqueous and energy-dependent nature.

Photobiomodulation and cancer: the mechanistic perspectives

In the sixties; McGuff et al. performed experiments with ruby laser applied directly on malignant melanomas. They reported a progressive regression and ultimate dissolution of the tumors [85,86]. Warburg found that malignant cells rely on anaerobic glycolysis for energy even in the presence of sufficient oxygen for mitochondrial phosphorylation; a phenomenon known as the Warburg effect [87]. A phase I trial in patients with advanced neoplasias demonstrated that the infrared pulsed laser device (904 nm infrared laser; pulsed at 3 MHz) studied was safe for clinical use and improved performance status and quality of life [88]. Antitumor activity was observed in 88.23% of patients with 10 years of follow-up [88].

Photobiomodulation; cancer as a metabolic disease and the bioenergetics theory of carcinogenesis

These considerations are related to the Warburg effect; by which the cancer cells change their metabolism to carry out aerobic glycolysis instead of oxidative phosphorylation. This phenomenon occurs due to mitochondrial dysfunction. The consequences of the Warburg effect are that malignant cells and normal cells may behave very differently in response to PBM. In cancer cells; where Adenosine Triphosphate (ATP) supply is quite limited; the ATP boost given by PBM may allow the cancer cells to respond to pro-apoptotic cytotoxic stimuli with more efficiently executed cell death (apoptosis) programs; which are heavily energy dependent (i.e.; require a lot of ATP). In contrast; in normal healthy cells that have an adequate supply of ATP; the effect of PBM may produce a burst of Reactive Oxygen Species (ROS) that could induce protective mechanisms either by producing important signaling molecules or neutralizing other reactive oxygen species. This activity may reduce the damaging effects of cancer therapy on healthy tissue. Although this physiological favorable scenario remains a hypothesis at present; there are some published articles that suggest that it could indeed be the case in some anticancer strategies. Moreover; it has been reported that the addition of low dose ATP to cancer cell lines inhibited their growth [89-91]. In theory; PBM increases cell death in cancer cells in response to either cytotoxic stimuli or necessary informational feedback. The third mechanism; by which PBM could be beneficial to cancer patients; is its possible role in stimulation of the immune system. Ottaviani et al. [90]; showed in a mouse model of melanoma that PBM using three different protocols (660 nm; 50 mW/cm^2; 3 J/cm^2; 800 or 970 nm; 200 mW/cm^2; 6 J/cm^2; once a day for 4 days) could all reduce tumor growth and increase the recruitment of immune cells. PBM also reduced the number of highly angiogenic macrophages within the tumor mass and promoted vessel normalization; which is another strategy to control tumor progression.

CONCLUSION

Photobiomodulation may offer the possibility of targeting multiple hallmarks of cancer and other degenerative diseases using electromagnetic (light) energy to restore physiologically reparative and regenerative mechanisms that can help reestablish homeostasis. Photobiomodulation may help restore cellular homeostasis by inducing physiologically reparative activity for disease reversal in cancer and other degenerative diseases with minimal adverse side effects; and with potentially marked improvements in quality of life even in patients with advanced neoplasms. Of major importance to achieve this is the activation and modulation of mitochondrial oxidative energy pathways. Photobiomodulation has the potential to activate and modulate the production of ATP; GTP; AMPK and inositol pirophosphates P7-P8; not only through the respiratory chain but also through absorption and transportation of IR light by water. A major goal for laser photobiomodulation in cancer is to control apoptosis (programmed cellular death) and differentiation; thus providing another cancer therapy tool . Laser-based technologies can be significantly less expensive than most cancer drug protocols. It is conceivable that a protocol combining therapies such as photobiomodulation; IV Vitamin C; a low carbohydrate diet (Paleo); hyperbaric oxygen and mitochondrial correction may be the future of non- toxic effective cancer therapy

constituting a new emerging paradigm.

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