patients with panic attacks, depression and anxiety disorders. Its wavelength is 593.5nm. It has strong anti-depressive effects (especially in combination with Hypericin from St. John's Wort Plant) and positive influence on the general mood [52-56]. It also Improves Serotonin and Vitamin-D production [53]. Yellow laser additionally stimulates the mitochondrial respiratory chain at complex III cytochromes [54, 55].

Green laser increases the production of ATP in the irradiated mitochondria [52, 23]. It also improves oxygen carrying ability of blood cells, improves blood flow, helps reduce blood pressure, and increases nitric oxide [56, 57]. Its wavelength is 532nm.

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 [58]. It has shown that ultraviolet blood irradiation can strengthen the immune system and improve overall health [59-61].

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

Chromophores Responsible for Photobiomodulation

Cytochrome c oxidase in mitochondria

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 [62, 63] was the first to suggest activity, and this observation was confirmed by Wong-Riley [64]. 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 photo dissociation of inhibitory nitric oxide (NO) [65]. 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 [66]. 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, are 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 photo isomerization 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 occurs 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 [67].

A possible alternative chromophore is water molecules whose absorption spectrum has peaks at 980 nm, and also at most wavelengths longer than 1200 nm [68]. 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 [69]. This charge separation (equivalent to localized pH changes) could affect the conformation of proteins [70]. 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 [71]. Water provides efficient pathways for charge storage, separation, and subsequent release [19]. Santana [72] 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. In general, physiological rhythms (orderly, organized, compartmentalized frequencies and vibrations needed for effective communication) may be reactivated and synchronized through water, CO2, 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 [20, 73]. 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 [73].

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 [74]. 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 [75]. 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 [76]. 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 (Photobiomodulation as a metabolic differentiation energetic reprogrammer).

In the sixties, McGuff [77, 78] performed experiments with ruby laser applied directly on malignant melanomas. They reported a progressive regression and ultimate dissolution of the tumors. 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 [79]. A phase I trial in patients with advanced neoplasia's 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 [80]. Antitumor activity was observed in 88.23% of patients with 10 years of follow-up [80].

Photobiomodulation, Cancer as a metabolic disease and the Bioenergetic 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 [81-83]. 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 [82] showed in a mouse model of melanoma that PBM using three different protocols (660 nm, 50 mW/cm2, 3 J/cm2; 800 or 970 nm, 200 mW/cm2, 6 J/cm2, 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. Yet another mechanistic possibility is an increased in apoptosis of already damaged cells and

mitochondria [84], which also provide an anticancer, antitumoral effect [85, 86].

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 pyrophosphates 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, Intravenous Vitamin C, a low carbohydrate diet (Paleo, Keto), hyperbaric oxygen, umbilical cord exosomes and mitochondrial correction may be the future of non- toxic effective cancer therapy constituting a new emerging paradigm.

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