REVIEWS

Laser photobiomodulation as a potential multi-target anticancer therapy-review

Luis Santana-Blank, Rodríguez-Santana Elizabeth, Jesús A Santana-Rodríguez, Karin E Santana-Rodríguez, Heberto Reyes

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Correspondence: Luis Santana-Blank. Address: MUN 1262 Calle Las Flores con Guaraguao, C.C. Carabel PB Local 2 Puerto La Cruz, Anzoátegui, Venezuela. E-mail: luissantanablank@gmail.com

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Abstract

Background: Anticancer drugs directed at single specific molecular targets tend to induce transitory responses, followed by relapses. Laser photobiomodulation may offer the possibility of targeting multiple hallmarks of cancer by using fit-for-purpose electromagnetic (EM) energy aiming to restore homeostasis-homeokinesis.

Methods/Principal Findings: A literature search of English-language articles in five databases (Medline, ISI Web of Knowledge, Cochrane, Google Scholar, Scirus) was conducted using search terms relating to cancer (neoplasm, advanced cancer, palliative) in combination with photobiomodulation and/or low-level laser therapy (LLLT) in the period from January 1990 to January 2013. Controlled clinical trials with at least 1 year of follow up and minimum compliance of 90% were included. Clinical studies evaluating lymphedema, mucositis or pain were also included to illustrate post-LLLT responses to adverse effects of chemo-radiotherapy. *In vitro* and *in vivo* studies were considered as preliminary data for clinical trials. Retrieved articles suggest that photobiomodulation can modulate anti-tumor effects and reduce the adverse effects of chemo-radiotherapy. Results are discussed giving particular attention to two mechanistic proposals with potential anticancer applications, photo-infrared pulsed biomodulation (PIPBM) and water oscillator (WO).

Conclusions/Significance: Translational research with laser photobiomodulation as a multi-target (multi-hallmark) therapy in cancer and other complex diseases appears warranted.

Key words

Photobiomodulation, Low level laser therapy, Homeostasis/homeokinesis, Hallmark of cancer, Warburg effect, Water dynamics

1 Introduction

It has been proposed that the hallmarks of cancer consist of biological capabilities acquired during the multistep development of human tumors, which taken as principles, allow rationalizing the complexities of neoplastic disease [1-2] These hallmarks include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, activating invasion and metastasis, reprogramming energy metabolism and evading immune destruction. Myriad hallmark-targeting cancer drugs have aimed at single specific molecular targets,

with a view to minimizing nonspecific toxicity. However, "clinical responses have generally been transitory, being followed by almost-inevitable relapses" [1].

The acquisition of cancer hallmarks is intricately linked and made possible by the tumor microenvironment (TME). The TME has been described as consisting of cells, soluble factors, signaling molecules, extracellular matrix, and mechanical cues that can promote neoplastic transformation, support tumor growth and invasion, protect the tumor from host immunity, foster therapeutic resistance, and provide niches for dormant metastases to thrive [3]. Tissue microenvironments and peripheral systems that control cancer are, thus, increasingly viewed as keys to cancer development and future treatments [4]. Anticancer therapies should then no longer aim at single molecular targets to kill cancer cells, but at re-establishing normal tissue microenvironments by promoting homeostasis-homeokinesis [4-7].

A common thread linking these perspectives in oncology and the field of photobiomodulation may be the possibility of using fit-for-purpose electromagnetic (EM) energy to restore tissue homeostasis-homeokinesis for multi-target disease reversal, a micro-environment effect that comprises and extends the Warburg effect previously discussed [8] This review updates and expands this discussion based on recent clinical and preclinical results on the potential application of photobiomodulation in the treatment of solid tumors. In particular, it explores whether laser photobiomodulation may hold potential as a multi-target (multi-hallmark) therapy in cancer and other complex diseases [9-12].

2 Background

Shortly after the first working laser was built by T. Maiman in 1960, P. McGuff et al., at Tufts-New England Medical Center in Boston, reported the results of experiments performed with ruby laser applied directly on malignant tumors such as melanomas. They concluded, as cited by L. Hode that, laser energy has a selective effect on certain malignant tumors, resulting in their progressive regression and ultimate dissolution [13, 14]. In the same period, but half across the world at Semmelweis University in Hungary, E. Mester, as told by Hamblin, "wanted to test if laser radiation might cause cancer in mice [15]. He shaved the dorsal hair, divided them into two groups and gave a laser treatment with a low powered ruby laser (694 nm) to one group. They did not get cancer, and to his surprise the hair on the treated group grew back more quickly than the untreated group." These early experiences exemplify one of the main characteristics of light. Over the following decades, it has been found that light can stimulate or suppress (i.e., modulate) a growing list of genes, oncogenes, cellular proteins, cytokines, cytochrome oxidase (CcO), nitric oxide (NO), reactive oxygen species (ROS), as determined by signal parameters and cell characteristics [16, 17]. However, until recently, emphasis on the stimulatory potential of certain light parameters on *in vitro* tumor cells [18] and concern about the poor quality of some reports with low-powered lasers stifled investigations into possible anti-cancer applications. However, there is increasing evidence that low-energy lasers of certain characteristics may be able to control subtle, yet powerful mechanisms that could help resolve one of the most intractable problems in the treatment of cancer and other complex diseases: the modulation of apoptosis [2, 9].

3 Mechanistic foundations

Eighty years ago, O. Warburg found that most cancer cells tend to rely on anaerobic forms of energy generation such as glycolysis even in the presence of sufficient oxygen for mitochondrial phosphorylation, a phenomenon known as the Warburg effect [19].

Warburg further identified enzyme CcO as responsible for the last critical step of respiration in mitochondria. Healthy and diseased cells often use NO to block respiration by binding to CcO instead of oxygen as part of a complex signaling process [20]. Cancer requires this system to go awry. Signaling pathways implicated in proliferation, notably the phosphoinositide 3-kinase (PI3K) pathway, regulate metabolic pathways that incorporate nutrients into biomass [21]. Cancer-related mutations enable tumor cells to acquire and metabolize nutrients in a manner conductive to proliferation.

Remarkably, low-energy pulsed light can displace NO (freeing the site for oxygen to bind to CcO again), modulate inositol phosphate via water dynamics in cell membranes [22] and exert other striking effects [23].

Laser photobiomodulation, also known as low-level laser therapy (LLLT), consists of the use of red to near infrared (NIR) monochromatic or quasi-monochromatic laser light to induce primarily photochemical and photophysical effects. Photobiomodulation is a non-linear process that induces a biphasic response described by the Arndt-Schultz (A.S.) curve, which shows that weak stimuli can excite physiological activity while strong stimuli can inhibit it as documented by the concentration of ROS [24, 25]. Over the last decades, progress has been made toward unmasking primary and secondary mechanisms of photobiomodulation [26, 27].

Yet, despite a wealth of substantiated reports, controversy around photobiomodulation has remained in part because (a) experimental reproduction of effects has not always been observed, especially for some unsupported reports, and (b) due to theoretical objections that very small field magnitudes sometimes reported seem to be below allowed thermal noise (1/f). Indeed, a core problem concerning the therapeutic effects of low-energy light (as well as other weak EM signals) is the sensitivity of cells in relation to signal to noise ratios. For bio-effects to be positive, EM signals must fulfill target dielectric properties and induce sufficient voltage to be detectable above thermal noise [28]. Moreover, it is the combination of signal and receptor characteristics what determines biological outcome, which is usually optimal for only one set of conditions [28].

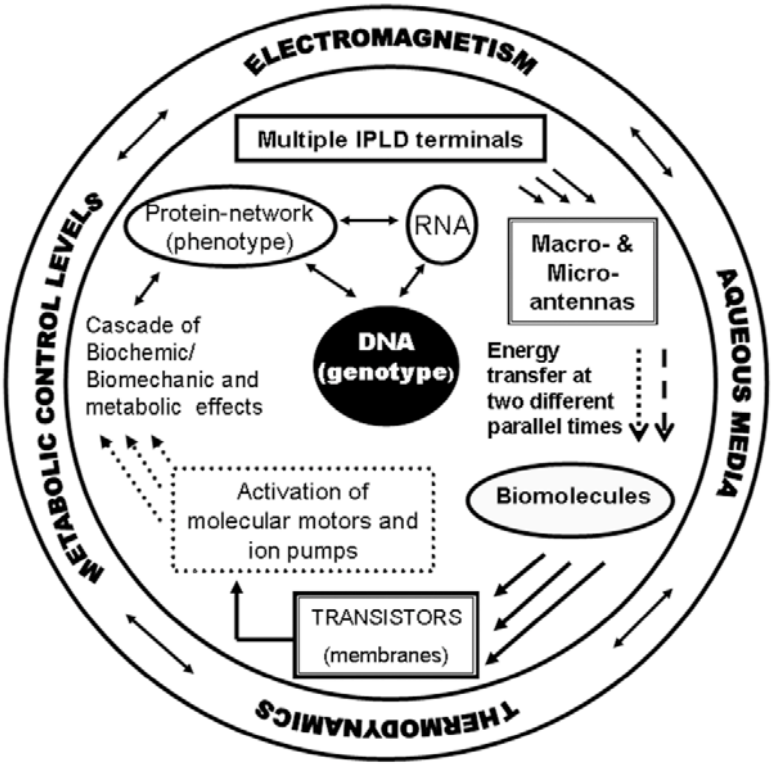

Figure 1. Simplified diagram of upstream components of the PIPBM mechanism.
Outer ring: Electromagnetic energy is transmitted through aqueous media to target tissues in accordance with the second law of thermodynamics to induce deterministic as well as non-fully deterministic effects, which are regulated by metabolic control levels. Inner circle: Energy from multiple IPLD terminals is captured by micro- (e.g., H_2O and CO_2) and macro- (e.g., vascular system) antennas. Energy is transported to biopolymers at two different times by water and biological liquid crystals (LCs) in the cell's lipid bilayer. As LCs, cellular membranes are particularly sensitive to pulsed electromagnetic fields (PEMFs) and behave as transistors that transmit energy to molecular motors and ion pumps causing a cascade of biochemical, biomechanical, and metabolic effects. On the other hand, the enhanced structuring of water in the solvation shell of molecules by the IPLD favors the physiologic activity of network proteins. This effect is reinforced by the activation of open-state dynamics, which induces changes in DNA translation and replication that are consistent with reported reductions in chromosomal aberrations. Arrows signal the flow of IPLD energy. [Ref 31. ©Mary Ann Liebert, Inc., 2005].

In addition, it has become apparent that, while NIR photo-biological effects have been ascribed primarily to light absorption by CcO and to the liberation of a number of reactive species, including ROS, NO, and H_2O_2, other photo-acceptors may be at play [29]. In that respect, a role for water as an oscillator in photobiomodulation has further been proposed and documented [30]. Previously, the cellular and molecular bases of an original mechanism for non-invasive, selective, long-range, energy supplementation termed Photo-Infrared Pulsed Bio-Modulation (PIPBM) were presented (Figure 1) [31]. PIPBM complements the classic LLLT photo-biological hypothesis (known to follow primarily ATP-

dependent pathways) and documents novel ATP-dependent and ATP-independent pathways for external energy supplementation through a proposed water oscillator (WO) [30], which can be photo-induced by absorption of NIR light or adsorption of red light [30, 31].Water dynamics are postulated to provide a separate pathway for light absorption and transportation, complementing and facilitating CcO energy transfer for increased efficiency in ATP production.

ATP is a key signaling molecule connected to the P1 and P2 family of specific receptors, of growing importance in cancer and other complex diseases [32-34]. In addition, ATP in of itself may be a potential cancer-fighting tool. Rapaport [34-41] first described the tumor killing effect of ATP in 1983. Since then, research has shown that ATP can inhibit growth in prostate, breast, colorectal, ovarian, and esophageal tumors as well as melanomas. ATP signaling appears to act in part promoting tumor cell suicide and in part fostering differentiation, which slows tumor cell proliferation [41, 42]. Thus, increased ATP production through PIPBM [31] and WO [30] water-driven pathway, along with the classic LLLT energy transfer mechanism, may hold significant potential for the treatment of tumors in accord the clinical studies described below.

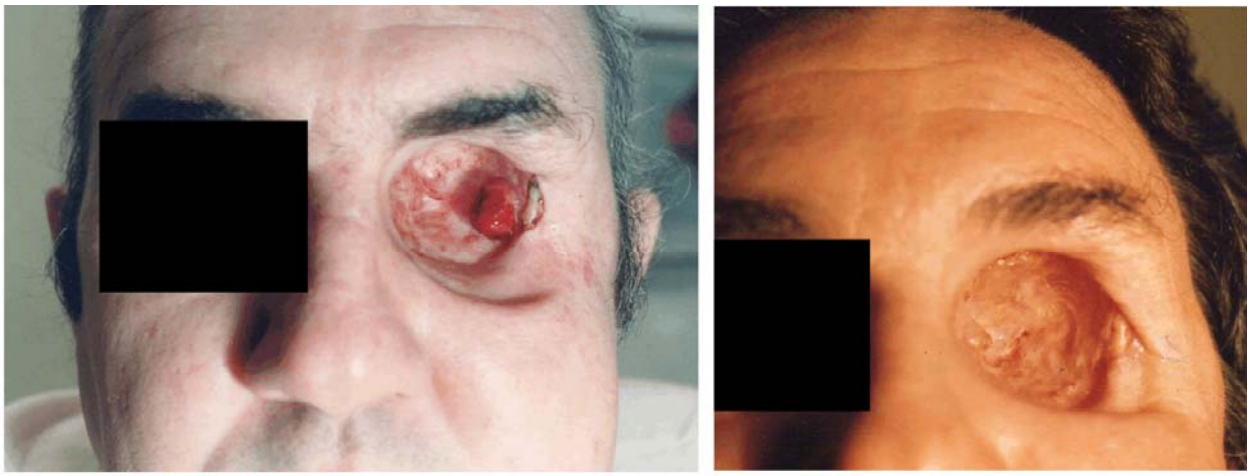

Figure 2. Pictures of a 45 year old patient with malignant papillary meningioma.
(a) Pre-IPLD treatment image shows metastasis on outer section of the left supra-orbital region and highly recurrent intra-orbital metastasis on the zygomatic region and greater sphenoid wing of the left lateral orbital wall. (b) After IPLD-treatment and local metastectomies recurrence ceased. Note wound healing effect on tissue covering previously exposed orbital margin of the zygomatic bone, and change in hair color and volume.

In solid tumors, ATP and its P- and A-type receptors jointly with inositol pyrophosphates (which regulate ATP concentration by controlling GCR1 factor) have primordial roles. Photobiomodulation may 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 [30, 43-48]. Among other reasons, this is important as AMPK activity opposes tumor development, and its loss has been shown to foster tumor progression in part by regulating cellular metabolic pathways that support cell growth and proliferation [49].

Research supports that CcO is a key photo-acceptor of red and NIR light [50, 51] in accord with reports of increased electron transfer in purified CcO, higher mitochondrial respiration and ATP synthesis in isolated mitochondria [52] and up-regulation of CcO activity in cultured neuronal cells following LLLT [53]. Increased ATP levels and electrical charge across the mitochondrial membrane have been found to be followed by a concerted shift in the activity of more than 110 genes [54, 55]. LLLT may also stimulate the upregulation of genes coding for subunits of enzymes involved in complexes I and IV and ATP synthase [56].

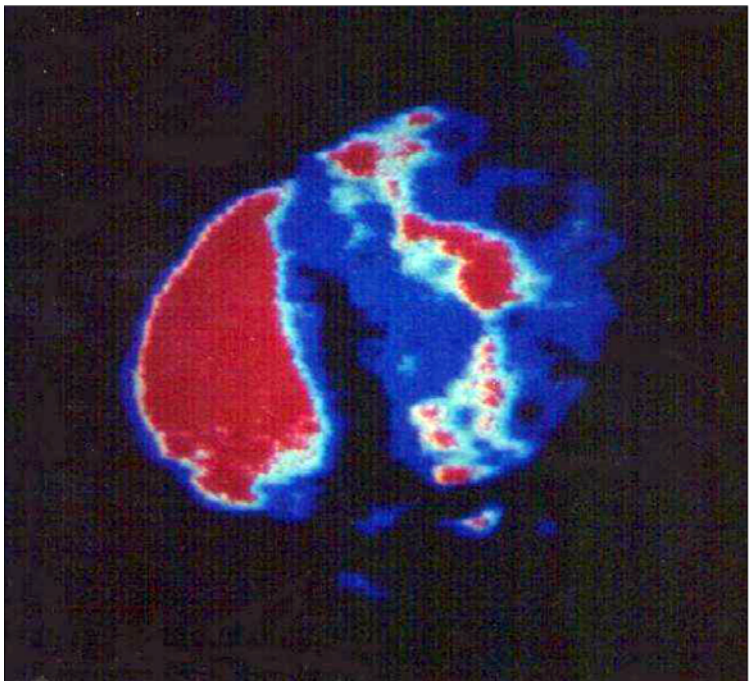

Figure 3. Raw microdensitometry image post IPLD treatment of cheek metastasis of patient with malignant papillary meningioma.
Red tones relate to regions with high water content resulting from photo-induced cellular death. Blue shades correspond to active tumor areas. Wide divide partially separating the image of the tumor is in agreement with described loss of cellular adhesion suggesting microscopic effects of anoikis. Case 1 of Figure 4 shows the corresponding Microdensitometry of T2-weighted MRI.

In addition, the above-referred PIPBM and WO mechanism may support ATP-independent effects over ion pumps, molecular motors, and the chemical response rate of biomolecules such as nucleic acids and proteins. Indeed, it has been found that pulsed light can substitute ATP to power cellular work by modulating Brownian motion [30, 42]. Among other reasons, this is significant because cancer and many neurodegenerative diseases share age-related and metabolic disorder–dependent damage of cellular energy and transport processes that are mostly caused by ROS stress. Theoretical [57-59], experimental [60, 61] and clinical [8-12] studies further suggest that PIPBM and WO may enhance physiologically reparative processes in a noninvasive, non-toxic, systemic, and selective manner through the activation and modulation of chaotic dynamics in water. These in turn lead to local and long-distance (systemic) effects with many potential applications in medicine.

4 Method

Literature search

Five databases (Medline, ISI Web of Knowledge, Cochrane, Google Scholar, and Scirus) were searched, from January 1990 to January 2013, using terms relating to cancer (neoplasm, advanced cancer, palliative) in combination with photobiomodulation and/or LLLT. Controlled clinical trials with at least 1 year of follow up and a minimum 90% compliance were included. Clinical studies evaluating lymphedema, mucositis or pain were also obtained to illustrate post-LLLT responses to adverse effects of chemo-radiotherapy. *In vitro* and *in vivo* studies were considered as preliminary data for clinical trials. Non-English publications were excluded because of the difficulty in obtaining, assessing and comparing them against other retrieved studies.

5 Results

5.1 Clinical results

Clinical data from a controlled human trial have been reported with a first approach at PIPBM using an infrared pulsed laser device (IPLD) [62] (904 nm pulsed at 3 MHz with 35 mW of power) using a 10 mm spot size (top-hat), under a

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one-dose, one-procedure design (field intensity / power density, 4.5×10^4 mW/cm^2), radiant exposure was fractionated and treatment administered during daytime. A phase I trial in patients with advanced neoplasias demonstrated that the IPLD was safe for clinical use and improved performance status and quality of life [9]. Antitumor activity was observed in 88.23% of patients with a 10-year follow-up (Figure 2) [9]. T2-weighted MRIs showed increased water content in tumor heterogeneities preceding tumor-volume reduction and therapeutic anticancer effects [9, 11]. Figure 3 is an example of high water content resulting from photo-induced cellular death in a sample raw-microdensitometry image. Figure 4 depicts the corresponding microdensitometric analysis of T2-weighted MRIs, indicative of early anti-cancer response, which precedes the reduction of tumor volume. Structural, kinetic, and thermodynamic implications of these changes in water dynamics have been analyzed at the tissue, cell, and interstitial levels [11]. In addition, a tumor characterization algorithm showed displacement of treated tumors within a described malignancy relaxation rate window (Figure 5) [63, 64]. Figure 6 shows the sequential histological analysis of tissue samples from a colon ADC (TNM IV) patient in the phase I trial. Significant selective photo-activation of apoptosis, anoikis and necrosis and cytomorphologic modifications, such as reduced size, increased roundness and increased vacuoles, were found in neoplastic cells, but not in peripheral tissues [6, 10].

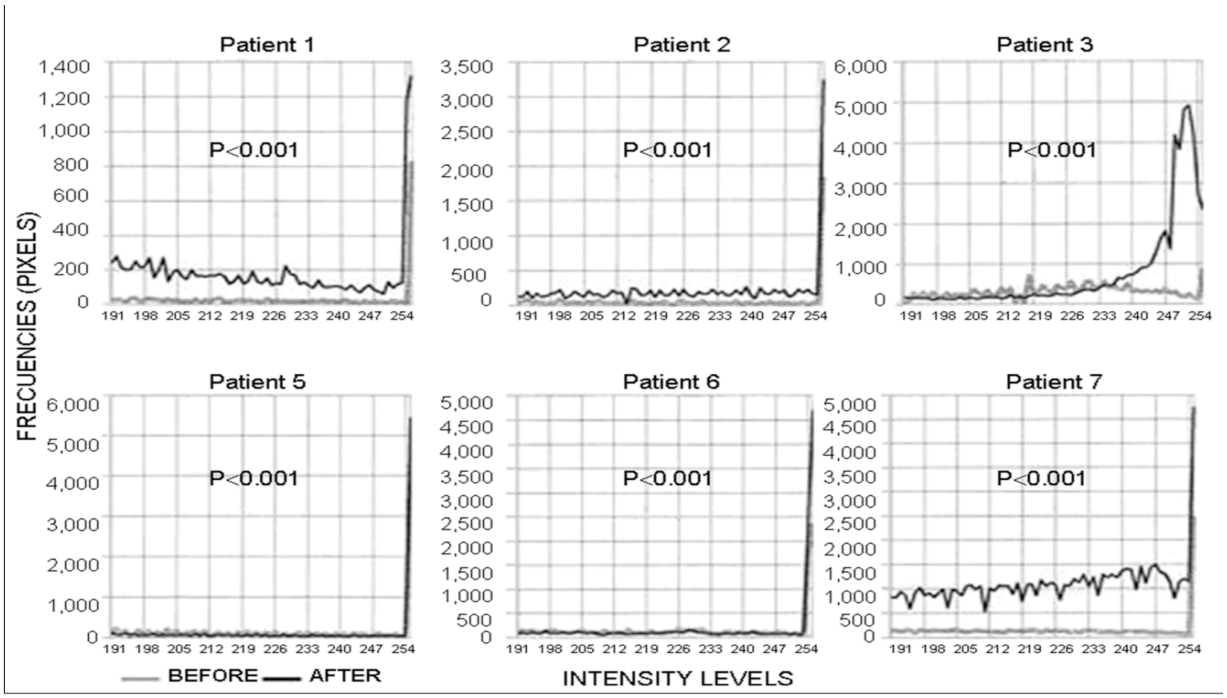

Figure 4. Microdensitometry of T2-weighted MRIs. Curves show early evidence of IPLD-induced anti-cancer response in the form of a significant increase in the water content of tumor heterogeneities before measurable reduction in tumor volume after IPLD-photo-induced tumor cell death. Significant post-treatment values for six patients, with intensity levels ranging from 191 to 255, are shown [For details, see Ref. 11].

Monitoring further showed activation of CD25$^+$ cells in both surviving and deceased patients, and modulation (initial increase and later decrease) of CD4 CD45 RA$^+$, TNF-α, and soluble IL-2 receptor (sIL-2R) in surviving patients [12] - in agreement with subsequent reports [65]. As recently argued, to be effective, cancer immunotherapy must co-activate CD4$^+$ T cells, suggesting that future immunotherapy trials should aim at activating CD4$^+$ T helper cells in an antigen-specific manner [66]. IL-2 has also been associated with homeostatic balance between the regulatory and conventional CD4$^+$ T cell compartments during peripheral T cell reconstitution in cancer [67]. In addition, studies suggest pro-tumorigenic roles for

immune cell subsets linked to cancer-associated inflammation. Thus, if such cells could be reprogrammed, as suggested by the above photobiomodulation results, it may be possible to counteract chronic, cancer-promoting, inflammation [68].

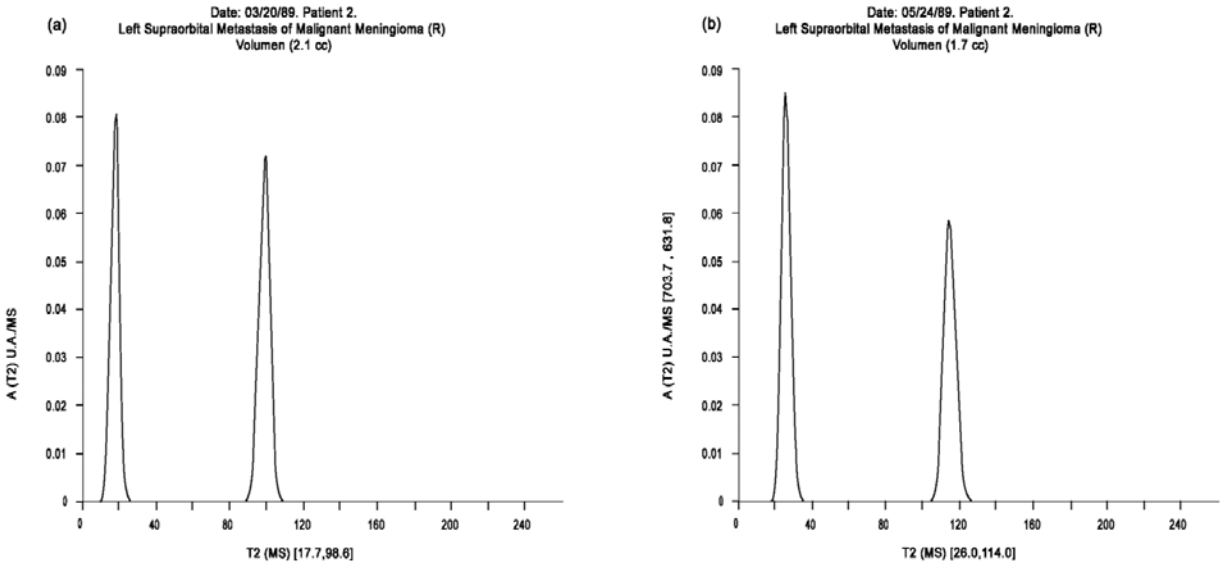

Figure 5. Results of an algorithm for tumor characterization by analysis of transversal relaxation rate distribution. Curves show the evolution over two months of a recurrent left supra-orbital metastasis of a patient with malignant papillary meningioma [Patient 2, in Ref. 9]. (a) The second curve from the left shows mean weighted T2 times inside the proposed neoplastic window (90 to 120 T2 ms). (b) The second curve from the left remains in the aforementioned window, but shows a notable rightward shift toward longer T2 values. The first curve on both graphs shows a lack of major changes in the water diffusion of the solvation shell of biopolymers and macromolecules outside the malignancy window (short times). A sharp shift in the curves inside the malignant window can be observed, indicating increased water diffusion associated to higher cell death as a result of IPLD treatment (longer times). Over the period, tumor volume decreased from 2.1cc to 1.7cc (~20%). [Images courtesy of Rafael Martin PhD. School of Physics, Faculty of Science, Universidad Central de Venezuela]

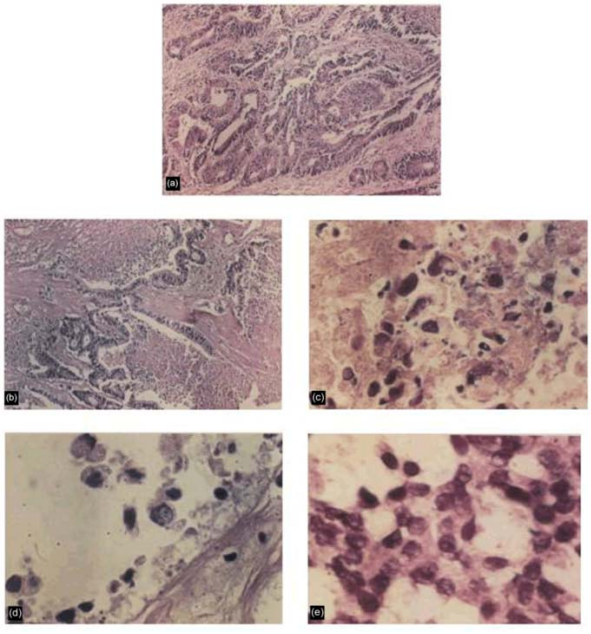

Figure 6. Sequential analysis of tissue samples from Colon ADC patient in phase I trial. (a) Microscopic view (40×) of sample at Time 0 (pre-IPLD treatment). (b) & (c) Microscopic views (40× and 100×, respectively) of surgical specimens at Time I (2 months of IPLD treatment). Increased apoptosis and necrosis, reduced cell size, and changes in the shape of neoplastic cells and tumor architecture can be observed; a more cracked pattern caused by decreased inter-cellular adhesion is noticeable. (d) & (e) Microscopic views (100×) of tissue sample at Time II (6 months of IPLD treatment). Neoplastic cells are smaller and rounder, there is rupture of the nucleus and cytoplasm, and cytoplasmatic and nuclear vacuoles are visible.

As an important side note, it must be noted that clinical experiences have been reported in Russia and Easter Europe [69, 70] but given they appear in non-English language papers, they could not be evaluated and included in this review.

5.2 Pre-Clinical results

The above clinical results are in agreement with independent reports from groups in Russia [50, 71], United Kingdom [21, 72], China [73, 74], Japan [75], United States and elsewhere [9, 76-79], supporting the premise that low-energy lasers can modulate antitumor effects, in contrast with long-held views [80]. For instance, Karu [50] has proposed reconsidering the use of LLLT to treat tumors, citing its capacity to modulate ATP signaling, which can promote tumor cell suicide as discussed above and in a manner consistent with above clinical results [8-12]. On the other hand, basic and experimental investigations reported by Lane [72], Moncada [21] (Warburg effect) and Burnstock [81] (ATP signaling), emphasize the ability of light to release NO from CcO as a way to modulate apoptosis in cancer and degenerative diseases. ATP signaling related to purinergic receptor-mediated effects in high-grade bladder cancer has also been documented [82].

In addition, a comparative study on the metabolic response of non-confluent and confluent human malignant brain cancer cells to He-Ne laser exposure found evidence of laser-enhanced cellular H_2O_2 production and laser-induced bystander effect, suggesting an important role for light-enhanced cellular H_2O_2 generation to yield photo-bio-modulatory effects locally and at a distance [31] in accord with research by Wentworth, et al. [83] and with the interpretation of the above clinical results [9]. LLLT has been also found to activate and modulate NF-kB via generation of ROS. Thus, LLLT may not only enhance mitochondrial respiration, but activate the redox-sensitive transcription factor NF-kB by modulating ROS as signaling molecules [84].

Recent studies suggest a role of NF-kB in colorectal cancer (CRC) etiology [85] and a physiologic role of NF-kB in protecting cells from apoptosis can help explain the pathologic activation of NF-kB in multiple human cancers [86]. Wang, et al. [75] have showed that low-power laser irradiation may induce apoptosis of human lung adenocarcinoma cells (ASTC-a-1). Dong-Liang, Timon Liu and Hua reported that a diode 808 nm GaAlAs continuous wave laser has an inhibitory effect on the proliferation of human hepatoma cells line HepG2 and J-5 [87, 88]. In addition, Sommer, et al. proposed the use of laser photobiomodulation to promote the uptake of chemotherapeutic agents in cancer cells, given an observed transmembrane convection mechanism that exploits the effect of moderately intense red laser light on the density and viscosity of nanoscopic interfacial water layers (IWL) in the cell- forcing cancer cells to uptake high doses of cytostatic drugs in a short time [89].

In agreement with the modulating properties of light, evidence also suggests that certain light parameters may cause tumor cells to proliferate. For instance, Pinheiro, et al. reported that irradiation with 670-nm laser light applied at doses between 0.04 and 4.8 10(4) Jm(-2) could significantly increase proliferation of laryngeal cancer cells [90]. Similarly, Frigo, et al. argued that LLLT Irradiation should be avoided over melanomas, as the combination of high irradiance (2.5 W/cm^2) and high dose (1,050 J/cm^2) significantly increases melanoma tumor growth *in vivo* [91].

6 Palliative care

Studies suggest that LLLT may be effective in reducing lymphedema in a clinically meaningful way for some women including a potential decrease in fibrosis, stimulation of macrophages and the immune system, and have a possible role in encouraging lymphangiogenesis [92, 93]. LLLT was effective in reducing grade 3 or 4 oral mucositis and in reducing radiotherapy interruptions in these head and neck cancer patients treated with concurrent chemo-radiation (CRT), which may translate into improved CRT efficacy and tolerance [94-96].The most important benefit for Nes and Posso was considered to be the value for the patients of better and quicker treatment with a drastic reduction in painful mucositis [97]. It has also been argued that LLLT may be given for pain and other symptoms relief during the terminal stages of the illness with the consent of both the patient and consultant involved [98], and it is expected that LLLT will soon become part of routine oral supportive care in cancer [99]

7 Conclusion

The results discussed suggest that, by supplying external EM energy within parameters fit to power and modulate biological systems, photobiomodulation may help restore homeostasis-homeokinesis, inducing physiologically reparative effects for disease reversal in cancer and other complex diseases with minimal, if any, adverse effects, and with potentially marked improvements in quality of life - even in patients with advanced neoplasms. A major conduit for such effects must lie in the activation and modulation of central physiological energy pathways and ATP-independent energy mechanisms. As discussed, photobiomodulation may 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 [6, 30, 100]. This suggests a pathway back to tissue homeostasis-homeokinesis through the reestablishment and the enactment of physiologically reparative mechanisms in cancer and other complex diseases. More incontrovertible evidence from pre-clinical studies as well as randomized controlled clinical trials and greater understanding of light-matter interactions should lead to translational progress. Together these should allow photobiomodulation to make the final leap from the lab to the patients' bedside as a potentially safe and effective multi-target anticancer therapy, potentially amenable for use with other therapies or as a stand-alone approach.

Competing interests

The author(s) declare that they have no competing interests.

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