REVIEWS

Solid tumors and photobiomodulation: A novel approach to induce physiologically reparative homeostasis/homeokinesis-review

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Abstract

It has been argued that loss of homeostasis is what, in essence, allows cancer cells to divide and invade tissues. Hence, novel anticancer therapies should aim not only at killing cancer cells, but at reestablishing homeostasis/homeokinesis. This systematic literature review presents and discusses existing data on the potential application of photobiomodulation in the treatment of solid tumors. Based on assessed results, it is proposed that by supplying external electromagnetic energy within parameters fit to power ATP generation/signaling and regulate biological systems, photobiomodulation may help restore homeostasis/homeokinesis-reestablishing physiological rhythms and 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.

Key words

Photobiomodulation, Cancer, Homeostasis/Homeokinesis, Regenerative medicine, Tissue micro-environment, Exclusion zone, Clinical trial, Water dynamics

1 Introduction

For over two decades, cancer has been considered a "complex" disease. Complex diseases are typically characterized by being multifactorial; that is, they are caused by a combination of genetic, environmental, and lifestyle factors, many of which have not been identified [1]. Nonetheless, cancer is still viewed by many, predominantly, as a multistep genetic disorder [2]. Disruption of specific oncogenes has been seen as the unique hallmark of cancer, giving rise to the "oncogene-addiction" hypothesis of tumorigenesis [3]. New studies, however, support a much broader interpretation of the underlying causes and potential treatments of cancer. For instance, the discovery of enzymatic roles in glycolysis and oxidative respiration are leading to modern versions of the Warburg effect. Findings suggest that cancer cells are driven to metabolic changes to repel reactive oxygen species (ROS) and prevent oxidative damage [4-7]. For example, inhibition of pyruvate kinase M2 by ROS contributes to the cellular antioxidant response [6]. Hence, the expression of low-activity isoforms of pyruvate kinase and other enzymes [7] may be an evolutionarily-preserved mechanism to promote cellular redox homeostasis.

Homeostasis is the process by which a "stable" environment is maintained within an organism. Multiple dynamic equilibrium adjustment and regulation mechanisms make homeostasis possible; thus, homeokinesis is often a preferable term. Homeokinesis has been defined as "the ability of an organism functioning in a variable external environment to maintain a highly organized internal environment while fluctuating within acceptable limits [in a semiconductor-like operating range] by dissipating energy in a far-from-equilibrium state". According to Que et al., this definition of homeokinesis has several implications. "First, it states that variations in the internal environment are normal and result from energy consumption. It implies that lack of variation and excessive variation are abnormal. It indicates that failure to utilize and dissipate external energy sources will result in breakdown of homeokinesis, and it suggests that this might also occur with excessive energy utilization and dissipation." [8-9]

In a paradigm-changing editorial, Prendergast recently argued that disorders in the tissue microenvironment and the peripheral systems that control cancer might increasingly be viewed as primary rather than secondary factors in the root nature of cancer. This constitutes "a crucial and radical distinction from prevailing thought, since it implies that cancer may be a symptom of an underlying clinical disorder, rather than the root problem itself that needs to be addressed" [10-11]. Consequently, since loss of homeostasis is what allows cancer cells to divide and invade other tissues [10-12], new anticancer therapies should no longer aim at simply killing cancer cells but at reestablishing homeostasis–an idea which may lead to novel treatment approaches [13-14].

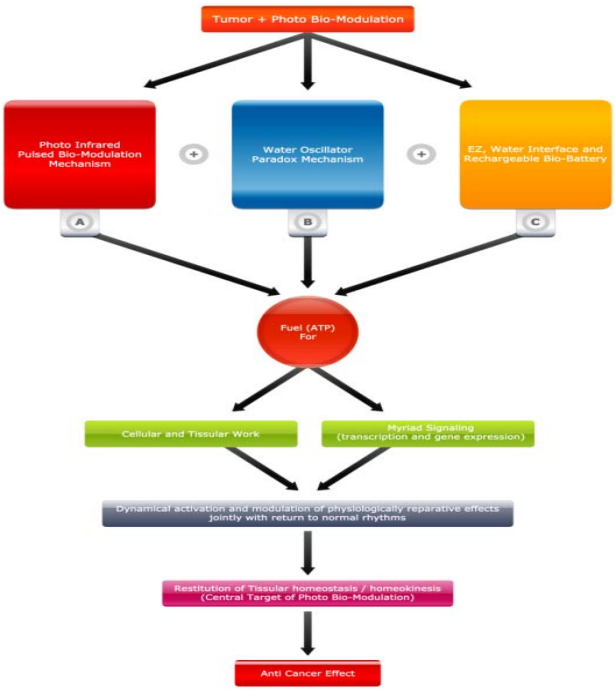


Figure 1. Concurrence of proposed mechanisms and anticancer effects aimed at inducing homeostasis/homeokinesis.

Together, (A) the photo-infrared pulsed biomodulation (PIPBM), (B) Water Oscillator and (C) Exclusion Zone (EZ) mechanisms are proposed to power and regulate metabolic energy pathways for ATP production and signaling. This leads to the activation and modulation of physiologically reparative effects that tend to reestablish normal rhythms, restitute homeostasis/homekinesis and trigger anticancer effects.

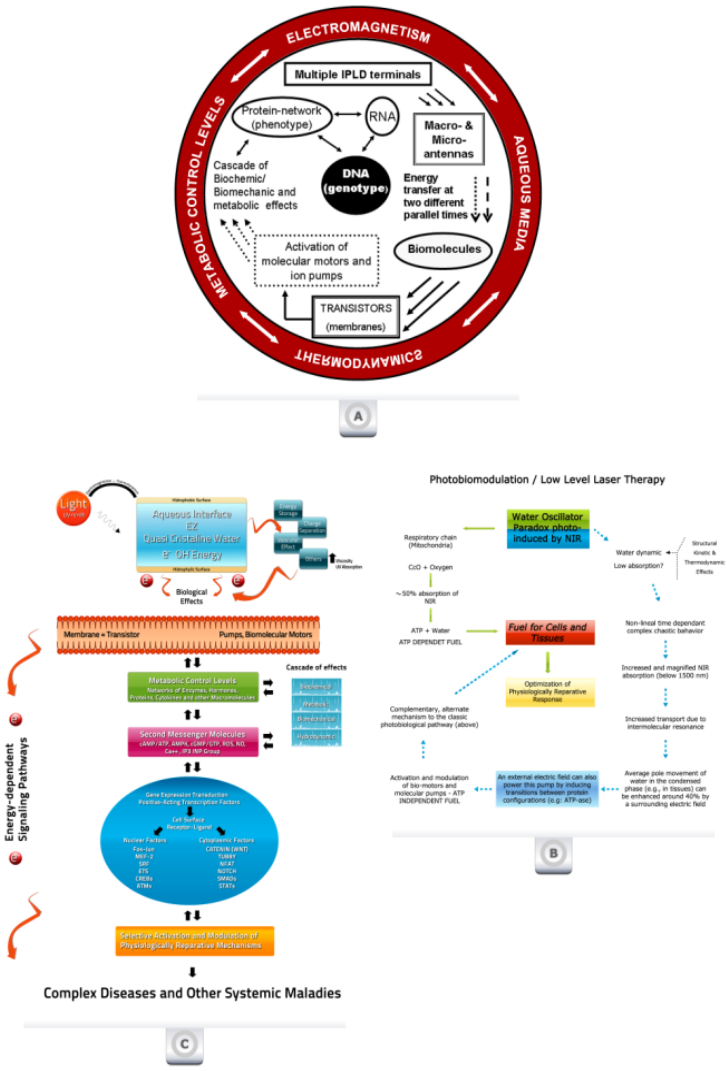
As will be detailed, the human body is a complex, energy-dependent, thermodynamically-open electrochemical system immersed in primarily aqueous media, where there is a fine evolutionary balance between robustness and fragility. It is precisely because of these characteristics that external light energy supplementation may become a major conduit for therapeutic effects. Laser photobiomodulation, also known as low-level laser therapy (LLLT), may help restitute tissue homeostasis-homeokinesis through micro-environment effects that comprise and extend beyond the Warburg effect previously discussed [15]. Recently, Karu [16] and Lanzafame [17] have stressed experimental and clinical results supporting the potential anticancer effects of photobiomodulation. New data have further confirmed that, under certain parameters, photobiomodulation may indeed be safe for use in cancer patients, despite decades of controversy [18-19]. This systematic

literature review presents and discusses existing clinical and experimental results on the potential application of photobiomodulation in the treatment of solid tumors. Based upon assessed results, it is proposed that by supplying external electromagnetic (EM) energy within parameters fit to power adenosine triphosphate (ATP) generation/signaling and regulate biological systems, photobiomodulation may help restore homeostasis/homeokinesis–reestablishing physiological rhythms and 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 [20-21] (Figure 1).

2 Photobiomodulation background

Photobiomodulation is a form of energy supplementation that employs monochromatic and quasi-monochromatic light to induce photochemical mechanisms. Relevant effects are primarily non-thermal in standard protocols (overall temperature increase ≤ 0.01℃) [22], and were initially documented inside a spectral window (~ 600-1000 nm) that now spans from the visible blue (~400 nm) to mid-infrared (MIR ~3200 nm).

Figure 2. Composite diagram of proposed mechanisms.



(**A**) Photo-infrared pulsed biomodulation (PIPBM) (Ref.29). Outer ring: energy is transmitted through aqueous media to target tissues according to the second law of thermodynamics, inducing deterministic and non-fully deterministic effects regulated by metabolic control levels. Inner circle: energy is captured by micro- and macro-antennas. It is transported to biopolymers in two different times by water and liquid crystals (LCs). As LCs, membranes are sensitive to pulsed EMFs and transmit energy to molecular motors and ion pumps, causing a cascade of biochemical, biomechanical and metabolic effects. Also, enhanced water structuring in solvation shells favors physiologic network protein activity. This is reinforced by open-state dynamics, which induce changes in DNA transcription and replication consistent with reported reductions in chromosomal aberrations. Arrows show energy flow. (**B**). Water Oscillator (Ref.13). Left: Classic photobiomodulation mechanism. Right: ATP-independent pathway explains how external EMFs can power biomolecular pumps and motors by inducing transitions between protein configurations through the activation and modulation of the water oscillation pathway. (**C**) The exclusion zone (EZ) as a rechargeable bio-battery capable of storing charge and powering cellular work and signaling pathways in the presence of injury-induced redox potentials caused by complex diseases (Ref.14). Top left: UV, V and IR light energize EZ water. Top right: energy regulates effects via vascular- and membrane-related pathways. Mid-center: as biotransistors, membranes are capable of signal detection, switching and amplification. Center-right: when injury potentials arise, EZ water can donate electrons, triggering a cascade of biochemical, metabolic, biomechanical, and hydrodynamic effects. Lower center: effects are modulated by metabolic control levels comprising networks of enzymes, hormones, proteins, cytokines, etc. Below: second messengers and surface receptor ligands lead to gene expression and transduction through energy-dependent nuclear and cytoplasmic transcription factors. Bottom: light selectively activates and modulates physiologically reparative mechanisms. Copyright Mary Ann Liebert, Inc.

Photobiomodulation has made significant progress toward dispelling skepticism caused by early methodological deficiencies and unsubstantiated results [23]. Rigorous studies have found significant stimulatory and inhibitory phenomena that follow a biphasic dose response (Arndt-Schulz (AS) curve) [24-27]. Action mechanisms, as discussed by Karu, include "changes in the redox properties of the respiratory chain components following photoexcitation of their electronic states, generation of singlet oxygen, localized transient heating of absorbing chromophores, and increased superoxide anion production with a subsequent increase in the concentration of the product of its dismutation, H_2O_2. A cascade of reactions connected with alteration in cellular homeostasis parameters (pHi, [Cai], cAMP, Eh, [ATP] and some others) is considered as a photosignal transduction and amplification chain in a cell (secondary mechanisms)" [28]. While this sequence of events has gained wide acceptance, from a biological standpoint, the activation and modulation of ATP generation appears to be the center and starting point of what may be called the "classic" photobiomodulation pathway. Novel action mechanisms related to absorption and adsorption of pulsed infrared (IR) and red light by bulk and confined water have also been described and documented [13-14, 29-31] (Figure 2).

3 Methods

Search strategy: Citations were evaluated in two phases. In phase 1, two reviewers (JAS-R/KES-R) screened all the titles and abstracts and identified potentially relevant articles. In phase 2, the full papers of identified studies were assessed independently by the other two reviewers (LS-B/ER-S) using the inclusion/exclusion criteria defined. Search terms related to anti-cancer effects, solid tumors, photobiomodulation, LLLT, and low-energy laser were input into Pubmed/Medline, ISI Web of Knowledge, Cochrane Library, Google Scholar, Scirus. Search terms and the number of citations returned for each search are presented in Table 1.

Table 1. Search terms and results returned. Period: January, 1990 – August, 2012

Search terms	Consulted Databases				
	Pubmed/ Medline	**ISI Web of Knowledge,**	**Cochrane Library**	**Google Scholar**	**Scirus**
Photobiomodulation	89	290	1	1270	400
LLLT	2931	984	3	12100	2499
Low-power laser	348	5697	1	10900	3023
Photobiomodulation AND Cancer	4	15	0	405	92
LLLT AND Cancer	325	48	0	1530	301
Photobiomodulation AND Solid tumors	0	0	0	59	4
LLLT AND Solid tumors	29	0	0	270	33
Anti-cancer effects AND Photobiomodulation	0	0	0	10	9
Anti-cancer effects AND LLLT	0	0	0	77	20

Inclusion and exclusion criteria: Clinical and experimental papers published in the English language between January, 1990 and August 2012 were reviewed. Clinical reports of anticancer effects were based on clinical, imagining, histological, immune, and laboratory results. Compliance of applicable ethical standards was deemed an inclusion requirement. Articles related to the induction by light of proliferative effects (e.g., in a manner consistent with the stimulatory portion of the A-S [24] curve) and/or to palliative care (e.g. mucositis, lymphedema), about which a significant

body of literature exists, were excluded. Studies combining other agents/therapies (e.g. chemotherapy, radiotherapy) were also excluded.

4 Clinical & experimental results

Clinical and experimental results meeting defined criteria are described in this section.

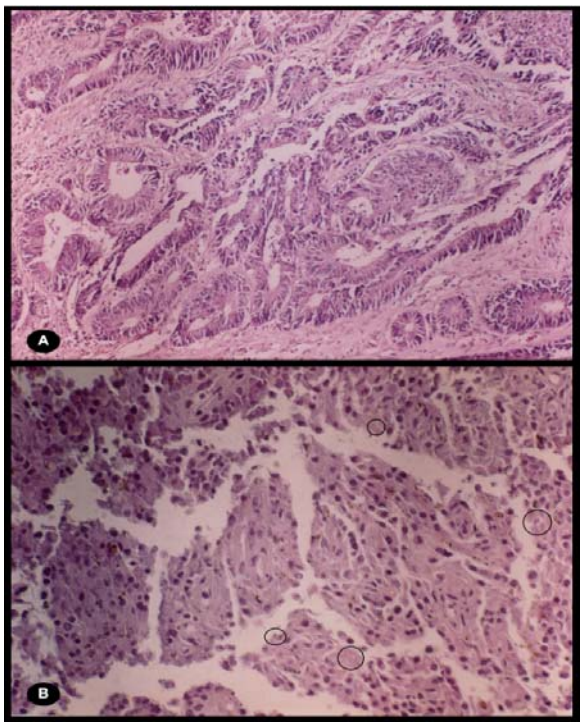


Figure 3. Specimens from advanced-cancer patient (Colon ADC) during the phase I trial of IPLD.

(**A**) Pre-IPLD treatment (Microscopic view/40×). (**B**) Post-IPLD treatment (Microscopic view /40×): monotonic image of lymphomatous aspect showing cracked pattern caused by decreased inter-cellular adhesion. Circles show anoikis.

Clinical studies show strong preliminary evidence of anticancer response [17, 20, 32-34]. A phase I trial in patients with advanced neoplasias demonstrated that a first treatment approach using an infrared pulsed laser device (IPLD) [35] was safe for clinical use and improved Karnofsky Performance Status (KPS) and Spitzer Quality of Life Index (QLI) [20]. Antitumor activity was observed in 88.23% of patients with a 10-year of follow-up and 96% compliance of the treatment prescribed [20]. In the same series, early-signs of anticancer activity were found through a microdensitometry analysis of T2-weighted MRIs, which showed increased water content in tumor heterogeneities preceding tumor-volume reduction caused by selective tumor cell death and resulting therapeutic anticancer effects [33, 36]. Structural, kinetic, and thermodynamic implications of such changes in water dynamics have been analyzed at the tissue, cell, and interstitial levels [33]. A tumor characterization algorithm showed displacement of treated tumors away from the described malignancy relaxation rate window caused by increased water diffusion secondary to selective photo-induced cellular death [36]. In agreement with these results, selective activation of apoptosis and necrosis [32] and photo-induced cytomorphologic modifications (i.e., reduced size, increased roundness, increased vacuoles, loss of cellular adhesion, cracking of tumor tissue architecture, anoikis) were found in neoplastic cells and tissues, but not in peripheral cells and normal tissues [32]. Figure 3 illustrates the activation of anoikis, a form of apoptosis induced by interactions between the cell and the surrounding extracellular matrix. Anoikis is involved in variety of tissue homeostatic, developmental and oncogenic processes [37]. Finally, photo-activation of CD25+ in all patients, and photo-activation and modulation of TNF-α, soluble IL-2 receptor (sIL-2R) and CD4+ CD45 RA+ were documented [34]. IL-2 has been associated with homeostatic balance between the regulatory and conventional CD4+ T cell compartments during peripheral T cell

reconstitution in cancer [12]. As a side note, it must be stressed that other clinical results have been reported, notably in Russia and Eastern Europe [38]. However, given that study parameters are not available in English, they could not be evaluated.

Identified experimental [26, 39-44] studies further confirm that photobiomodulation can modulate antitumor effects. Tanaka et al. evaluated the non-thermal effects of IR radiation on cancer cells and found that IR light, independent of thermal energy, can kill cancer cells [45]. Basic and experimental research reported by Lane [39], Moncada and Erusalimsky [46], and Burnstock [47] have emphasized the ability of light to release nitric oxide (NO) from cytochrome c oxidase (CcO) as a way to modulate apoptosis in cancer and degenerative diseases. A comparative study on the metabolic response of non-confluent and confluent human malignant brain cancer cells to He-Ne laser exposure found confirmation of laser-enhanced cellular H_2O_2 production and a laser-induced bystander effect, suggesting an important role for light-enhanced cellular H_2O_2 generation to yield local and distant photobiomodulation effects [48], in accord with research by Wentworth et al. [42] and with the interpretation of the above-cited clinical results [13, 20]. Wang et al. [43] have showed that low-power laser irradiation may induce apoptosis of human lung adenocarcinoma cells [49]. The effects of laser irradiation on the proliferation of human breast carcinoma, melanoma, and immortalized mammary epithelial cells have also been studied [50]. Lastly, a recent study of the safety of red light phototherapy of tissues harboring cancer found that LLLT within studied parameters may be safe even when malignant lesions are present [18].

5 Discussion

Clinical and experimental reports suggest immense potential for photobiomodulation in the treatment of cancer and other complex diseases. Anticancer effects may be possible because photobiomodulation can employ the characteristics of biological systems to activate (in a physiological, selective, irreversible, local and distant manner) tumor targets to promote the comprehensive restoration of homeostasis/homeokinesis, with minimal, if any, adverse effect. Below are some characteristics of higher-order biological systems through which the photo-induced activation and modulation of homeostasis/homeokinesis may be able to determine the difference between health and disease (life or death). For each biochemical, metabolic, biomechanic and/or hydrodynamic effect, applicable molecular pathways and metabolic network levels are proposed. Light (EM) energy supplementation is characterized by its wide range of potential interactions. Given the scope and focus of this paper, concepts are summarized, sacrificing non-essentials. System traits of interest are as follows:

a. Complexity

b. Energy dependence

c. Electrochemical nature

d. Thermodynamic openness (dissipative)

e. Preeminence of aqueous media

f. Robustness/Fragility

a. Complexity: The human body comprises multiple networks. These include metabolic and signaling pathways, neural connections, genes (genome), and proteins (proteome). Networks exhibit regular, irregular and chaotic physiological rhythms within a temporal range that goes from micro-scales at the boundary of recordable physical observation (e.g., resonant inter-molecular transfer of vibrational energy in water, important in stabilizing biological systems coupled to hydrogen bond networks) to meso- and macro-scales lasting seconds, minutes, hours, and more [51]. Alterations of

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physiological rhythms are often associated with disease [52]. External signals may help re-establish altered rhythms because oscillatory states can act as carrier signals for temporal coding, and pulsating signals have transduction functions. In practice, the re-establishment of most physiological rhythms is very complex, in part because such oscillations exhibit nonlinear dynamics that originate from the combined influence of a fluctuating environment and the noise inherent to biological systems. Still, energy at low, physiologically-useful, levels—whether in EM or mechanical form—may interact with and power physiologic rhythms if the signal can satisfy system requirements [51]. The signal parameters, the signal-to-noise ratio and the characteristics of the receptor determine the biological outcome, which is usually optimal for only one set of conditions. Interestingly, Barbault et al. have proposed that cancer-related frequencies appear to be tumor-specific, and treatment with tumor-specific frequencies (rhythms) may be feasible, well tolerated and biologically efficient in patients with advanced cancer [53]. The latter is consistent with cited clinical results in advanced cancer patients treated with the IPLD with more than 10 years of follow-up [20].

b. Energy-dependence: Cellular work and signaling require large amounts of energy derived mainly from ATP, cyclic adensine monophosphte (cAMP) and cyclic guanosine monophosphate (cGMP). For the average adult, physiological processes lead to a daily turnover of 40 kg of ATP [54]. Yet, in addition to providing fuel, ATP is a key signaling molecule connected to the P2 and P1 family of specific receptors of growing importance in cancer and other complex diseases [55-56]. In solid tumors, ATP and its P- and A- receptors together with inositol pyrophosphates P7-P8 (which regulate ATP concentration by controlling GCR1 glycolytic transcription factor) have primordial roles. Moreover, ATP may be, in of itself, a cancer-fighting tool. Rapaport was the first to describe its tumor-killing effect [57-58]. Since then, research has shown that ATP can inhibit growth in several tumors, including prostate, breast, colorectal, ovarian, esophageal and melanomas among others. ATP acts by promoting tumor cell suicide and by fostering differentiation, which slows tumor cell proliferation [43, 59-63]. AMP-activated protein-kinase (AMPK) further responds to reduced energy charge (decreased ATP and increased AMP) [64] and plays a key role regulating growth and reprogramming metabolism [65].

Photobiomodulation may activate and modulate the production of ATP [13-14, 16, 31], AMPK [66-69], and inositol pirophosphates P7-P8 [70- 71], not only through the classic respiratory chain pathway, but also by the absorption and transportation of IR light by water through novel mechanisms. This suggests a pathway back to tissue homeostasis/homeokinesis through the reestablishment by light energy of physiologic rhythms and the enactment of physiologically reparative mechanisms in cancer and other complex diseases [31, 70-71]. Citing its capacity to modulate ATP signaling, which can promote tumor cell suicide in a manner consistent with cited clinical results [20, 32- 34], Karu has proposed considering the use of photobiomodulation to treat tumors [16]. Yet, external EM energy supplementation, including photobiomodulation[20], can complement or substitute metabolic energy and activate and modulate local and/or distant effects under paradigms that go past this extensively-documented concept and into the idea of physiologically reparative effects in solid tumors and other complex diseases [13-14,20,29] . Experimental and clinical studies demonstrate that water can absorb, transport, and respond to light, substituting and enhancing metabolic energy generation in a manner that favors and complements the widely-accepted classic mechanism of photobiomodulation, but several orders of magnitude faster and more comprehensively [13-14,29].

c. Electrochemical nature: Within biological systems, reciprocal relationships between electrical energy and chemical reactions are established. As part of them, redox processes occur. Examples include ATP synthesis or conversely hydrolysis of ATP to generate electrical impulses (e.g., in neurons or muscles). Adequate energy modulation can, thus, have profound effects. On the cell surface, light can activate classic EM processes related to membrane diffusion mechanisms, and also control phenomena recently described by Goldenberg et al., at cellular and biophysical interfaces. This is important because "the interface of cell biology and biophysics has established a new paradigm in protein targeting and function in which the electrostatic charge at the surface of a biological membrane has emerged as a key determinant of signaling protein localization and activity" [72-74]. According to the same authors, "electrostatic phenomena are also likely determinants of various cell functions: membrane surface charge can target GTPase, compartmentalize signaling platforms, and provide specificity to signaling cascades. Many of these processes converge uniquely upon cancer biology;

a large proportion of the proteins affected by surface charge, as well as several responsible for establishing surface charge, have previously been identified as tumor surface charge, and have been identified as tumor suppressors or oncogenes" [75]. Examples of this include PTEN [75-76], among others.

d. Thermodynamic openness (non-equilibrium theory, chaos): The free-energy product of cellular work is guided by the second law of thermodynamics. Yet, the efficiency of cellular and tissue work does not properly fit with this classic law. Nobel Prize laureate (1968) Lars Onsager [77] and others have formulated the theory of non-equilibrium thermodynamics and have showed that, while the second law continues to hold [78], when certain conditions are not met, the theory breaks down. One type of failure occurs "when the system is so small that the chaotic jumble of molecular motions dictates its behavior and causes the system's properties to vary wildly over short distances" [78-81]. Still, even when molecules may be maximally disordered (chaos), the overall system can be symmetrical and orderly because these processes are connected by the reciprocity relation formulated by Onsager [82-83]. At the macroscopic level, irreversibility arises when particles are considered en masse. These ideas are essential to understand how order appears from chaos in biological systems and how light may crucially impact the activation and modulation of homeostasis/homeokinesis associated to physiologically reparative effects in cancer and other complex diseases.

e. Preeminence of aqueous media: Water represents nearly 70% of body mass. It comprises bulk water, confined water and the important biological interface [52], which is marked by thermal and quantum fluctuations [51]. Bases for water-mediated photobiomodulation have been documented [13-14, 29]. Figures 2 (A, B, C) illustrates in a simplified manner the mechanisms proposed. Most recently, and in tune with Pollack and others [84-88] who have made extensive contributions to the understanding of the cell's water interface and exclusion zone (EZ), it has been proposed that the quasi-crystalline EZ [87] may be selectively targeted in photobiomodulation as an efficient energy reservoir that cells may use to expeditiously fuel cellular work, triggering signaling pathways and gene expression in the presence of injury-induced redox potentials [14].

f. Robustness/Fragility: Robustness is a fundamental and ubiquitous feature of complex evolvable systems [89]. As argued by Radman, errors and infidelity, even wastefulness, can cause individual failure, but they are also a source of innovation and robustness, ensuring the perpetuation of life [90]. Biological systems accept small perturbations to allow for the adaptability needed to evolve. Olson et al. have focused on one important mechanism underpinning tumor robustness and degeneracy: the cellular heterogeneity that is a hallmark of most solid tumors. They argue that stochastic noise, as a component of the critical signal-to-noise ratio, is an underlying perturbation of the microenvironment energy of tumor heterogeneity and, particularly, degeneracy [91]. Impairment of these elements prevents adequate metabolic energy supply, curtailing cellular work and health. While a full elucidation of the principles underlying such phenomena remains an elusive and important challenge [92], it might be inferred that external EM (light) energy supplementation with proper signal characteristics could become the foundation for safe new therapeutic strategies aimed at reestablishing tissue homeostasis/homeokinesis to defeat the adaptable cancer phenotype, particularly given that the path from the genotype to the phenotype is energy-dependent [18, 93].

6 Challenges and concurrent approaches

Two main challenges for the approach described in this review are determining optimal treatment-dosage parameters and ascertaining the underlying mechanisms for potential applications in oncology [94]. The former implies thorough dosimetry and signal optimization efforts, which might eventually lead to further applications in medicine [51]. The later requires overcoming technical difficulties involved in obtaining direct data from light-photoacceptor interactions and ensuing reactions that occur at or beyond the resolution limit of most currently-available research tools [14]. Still, there seem to be reason for cautious optimism on both fronts. Firstly, significant work as already been done in determining, at the very least, the safety parameters needed for additional trials. Secondly, the pace of technical progress in femto- and now atto-science has been breathtakingly fast and shows no sign of slowing down.

It must also be mentioned that there are several concurrent approaches, which do not fall within the scope of this review but may prove fruitful. These include the study of modulated EM fields for the treatment of cancer [94] and laser-activated thermal bystander effects [95]. Non-EM methods to affect tumor micro-environments are also under investigation [96]. In accord with Prendergast [10-11], Sonnenschein and Soto [97] have proposed that "the differences between normal and cancerous states are identifiable at the tissue level of biological organization, and therefore, the search for identification of a cancer cell should be abandoned" [97]. These views are leading to refocused efforts to target the metabolic dependencies of cancer cells as a selective anticancer strategy [98]. In the same vein, Wellen and Thompson suggest that it "is becoming increasingly clear that cellular signaling and metabolism are not just separate entities but rather are tightly linked" [99]. It has thus been argued that since genetic events in cancer activate signaling pathways that alter cell (energy) metabolism, metabolic energy pathways may hold potential as new cancer therapies. All of these EM and non-EM based approaches signal a growing appreciation of the importance of both the tissue micro-environment and of weak EM interactions in cancer research.

7 Conclusions

The results of this literature review suggest that properly tailored external EM (light) energy may be able to substitute and/or complement metabolic energy pathways and activate signaling pathways conducive to the restoration of homeostasis/homeokinesis. Such effects could modulate and power extensive cell signaling networks, which lie behind the structure and functioning of metabolic control levels. Though not a panacea, this approach would represent a potentially universal method for the therapeutic modulation, alone or with other therapies, of reparative physiologic processes capable of promoting positive clinical results and improving quality of life with minimal, if any, adverse effects. The later may be particularly important given that, in the case of metastatic cancer, it has been proposed that a treatment can be recommended even without an improvement in survival if it can improve quality of life [100]. What is more, because of their basic bioenergetic roots, applications may extend to multiple complex diseases, some of which have few or no currently viable effective treatment alternatives [13-14, 31]. Given the existing and growing body of knowledge based upon sound experimental and clinical results, the start of translational efforts aimed at converting these ideas into part of the scientific therapeutic arsenal appears imminent.

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