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Letter to the Editor

Photoimmunotherapy: A Novel Field with Overlapping Light Treatment Approaches

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THE USE OF LIGHT AS a therapeutic modality is often met with some skepticism. Despite its all-pervasive nature in our daily lives, there are several evidences for the ability of the human body to perceive and utilize the physical form of electromagnetic radiation energy that light represents. Two key examples are the ability of sunlight to promote vitamin D metabolism (ultraviolet-B, UV-B 300 nm) and visible light (400–700 nm) enabling vision. The therapeutic use of light can simply be termed *phototherapy*. There are multiple iterations of these light-based treatments that has led to several biophotonics-focused centers dedicated to harnessing their immense potential.[1] However, a lack of unified terminology is leading to much confusion, and often a lack of its optimal clinical use. The current use of surgical lasers is not conventionally considered within the spectrum of light-based treatments, but is included here in an attempt to outline the breadth of spectrum of biological responses. Also, the precise categorization of current blue light phototherapy for neonatal jaundice, Psoralen UV-A (PUVA) or narrow band UV-B (NB UV-B) for dermatological disorders, as well as extracorporeal UV plasmapheresis appears to remain unspecified despite their routine clinical use. Although there remain some well-placed concerns with the use of UV applications, its therapeutic potential remains to be fully explored.

This communication outlines a simple nomenclature for therapeutic light treatments based primarily on the presence (or absence) of heat generation followed by the nature of the incited photobiological response (Fig. 1). The generation of heat by light treatments to extreme temperatures (>100°C) results in photoablation (photoevaporation or photodestruction), moderate temperatures (45°C–65°C) results in photocoagulation, while lower temperatures (>45°C) result in vasodilation.[2–4] These effects could be collectively categorized as *photothermal* phototherapy. These effects are primarily attributed to direct energy transfer through absorption of photonics energy via a wavelength-specific tissue chromophore. Rapid transfer of the physical photonic energy results in destruction of the biological target. As a potential consequence of the rapid photothermal response, generation of photomechanical (photoacoustic) effects can disrupt tissues focally and have been utilized for both targeted disruption and diagnostic imaging.[5]

In contrast to these thermal light–biological tissue interaction processes, light treatments in the non-thermal regimen (<45°C) can be utilized therapeutically. These treatments can be broadly categorized as *photodynamic therapy* (PDT) and *photobiomodulation* (PBM) therapy.[6] A major difference between these two types of non-thermal low-dose light treatments is that the final outcome of PDT is destruction of its biological target. PBM, on the other hand, results in evoking a modulatory, inhibition, or stimulation, but never a destructive response. Our laboratory recently demonstrated a role for Activating Transcription Factor-4 (ATF-4) in orchestrating the photoresponsive cell damage pathway that can enable distinguishing these disparate responses.[7] Classically, PDT has been performed with exogenous dyes and targets either tumor-PDT (tPDT) or antimicrobial-PDT (aPDT) for disinfection. In contrast, absorption of light by endogenous chromophores such as bilirubin and melanin also results in an eventual destructive biological response. These would be best categorized as endogenous-PDT (ePDT). Other examples of these are the previously referenced blue light phototherapy, PUVA therapy, and NB UV-B treatments and extracorporeal plasmapheresis for psoriasis, eczema, or graft versus host disease.

The use of low-dose non-thermal light for PBM therapy elicits either inhibiting or stimulating specific biological responses. PBM includes the therapeutic use of low-dose light to either inhibit pain, alleviate inflammation, or aberrant (self, auto) immune responses, and to stimulate tissue healing, regeneration, and immune surveillance (e.g., antitumor). Our current understanding of PBM therapy has focused on three discrete cellular compartments namely the mitochondria (Cytochrome C Oxidase), cell membrane (photosensitive transporters and receptors), and extracellular milieu [latent Transforming Growth Factor-β (TGF-β) activation].[8] The use of light treatments for repigmentation in vitiligo is based on the ability of UV to induce αMSH in melanocytes inducing melanin.[9] The use of sunlight stimulators and bright light therapy for mood elevation and circadian rhythm disorders are similar examples. This could be all arguably categorized as PBM processes.

Photoimmunotherapy: a new opportunity from confluence of several current treatments

The photobiological destruction, either directly through photothermal or photodynamic action, would be expected to generate a host immune response. However, the inherent destructive nature would presumptively generate sub-optimal

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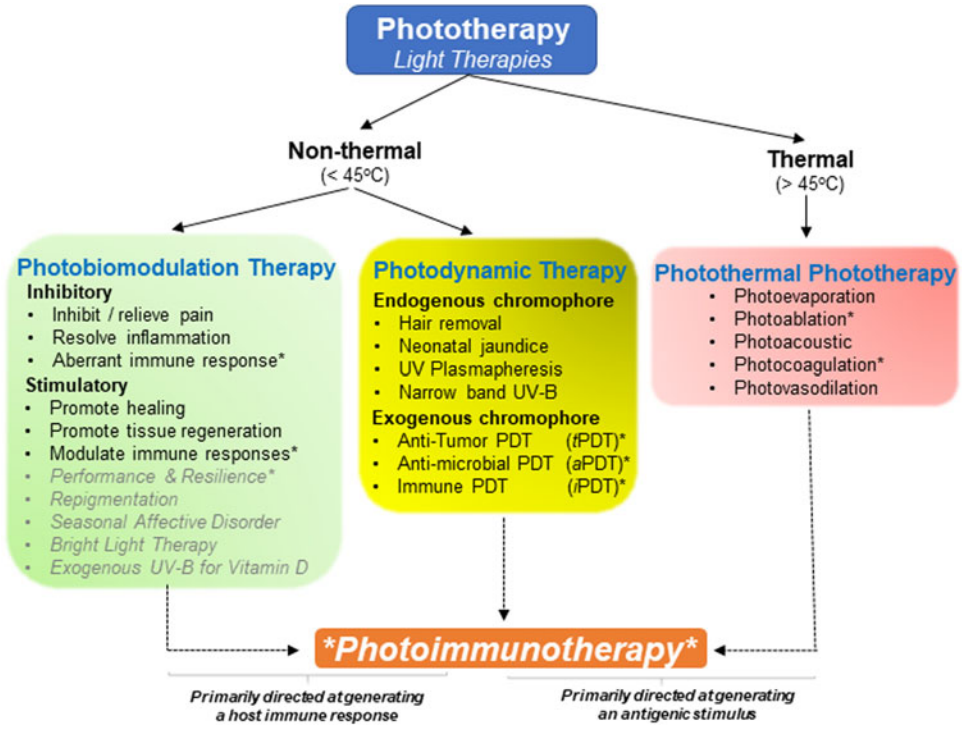

FIG. 1. An outline of various light-based treatments categorized on the basis of their ability to induce a nonthermal versus thermal response and eventual biological outcome. PDT, photodynamic therapy; UV-B, ultraviolet-B. The italicized topics are proposed new inclusions.

antigenic determinants and hence would appear to be an inefficient approach in itself. A more recent advance in this field utilizes photoactivated targets such as CD47, EGFR, HER2, PSMA, and CD25 among others that induce a specific form of immunogenic cell death in tumor cells that has been termed *photoimmunotherapy*.[10] As the basic mechanism here is directed at developing an antigenic immune stimulus, rather than developing a host immune response, this treatment is best categorized as a variant of classical PDT, perhaps as immuno-PDT (iPDT).

The use of near-infrared–mediated hyperthermia to increase efficacy of antitumor treatments has been noted to increase local perfusion as well as improve immune reactivity.[11] This has also been termed *photoimmunotherapy*. These scenarios appear to utilize photothermal and, perhaps PBM (nitric oxide generation), non-thermal vasodilation at the tissue level to reduce hypoxia that improves ionizing radiation-induced tumor cytotoxicity or improved tumor access to chemo- or immunotherapeutic agents.[12] At the cellular level, tumor hyperthermia appears to induce a potent heat shock response that activates antigen-presenting cells to modulated immune cell trafficking.[11] The latter effects would be akin to those reported following PBM treatments. Further, the use of UV treatments, especially UV-A and NB UV-B, has been noted to entail immunomodulation.[13] As previously noted, these appear to be largely directed at destruction of the aberrant immune infiltrations and could be considered within the spectrum photoimmunotherapy. The utility of PBM in therapeutic modulation of the immune system has been observed in several studies.[14,15] There have been several reports on the ability of PBM treatments to shore up the immune system as potent vaccine adjuvants.[16,17] In a recent study from our laboratory, we have noted an antimicrobial peptide, Human beta Defensin 2 (HBD2), is secreted as a bystander PBM response to enhance the antimicrobial host response with the use of surgical or PDT-based light treatments.[18]

In purview of these referenced evidences, it would seem prudent to categorize *photoimmunotherapy* as a novel application that modulates the immune responses. This appears to be capable of being accomplished by multiple discrete light treatment approaches including photothermal destruction, nonspecific or directed photodynamic responses, and PBM therapy. The former approaches are primarily directed at generation of antigenic stimuli that indirectly stimulate the host immune surveillance responses (Fig. 1). However, PBM treatments are capable of direct modulation of the host immune mechanisms.

Implications and Future Directions

Far from being a mere cerebral exercise, the proposed new nomenclature based on the biological response can have a profound impact on the regulatory, policy, and clinical decision-making processes. The significance of these distinctive approaches will enable development of more rigorous clinical protocols as well as focused research investigations. Moreover, these individual light–biological responses offer a robust mechanistic rationale for their combinatorial utilization such as destruction of microbial or tumor cells followed by stimulation of host immune responses. The urgent need for categorization of light therapeutic is perhaps best highlighted by the recent acceptance of PBM treatments as standard clinical practice guidelines for oncotherapy-associated oral mucositis.[19] There appears to be much confusion among policy making on device regulation as well as reimbursements, despite the highest level of clinical evidence for safety and efficacy of this treatment that can benefit patients right now. The current Coronavirus disease 2019 pandemic is another example where the use of several light-based treatments are being proposed. These necessitates careful attention to specify biological targets and evoked responses for optimal safety and efficacy.

There are also several parallel developments that deserve mention in these discussions. A routine use of nocturnal light filters on electronic devices such as smartphones and computers has led to a concept of *light hygiene*.[20] On the flipside, there are several exciting developments on the use of sunlight-simulating indoor lighting for seasonal affective disorders and circadian rhythm disorders that have been noted to have direct health benefits.[21] These observations appear to emphasize the potential role of specific wavelengths and dose as a natural *light supplement*. These discussions on precise light dosimetry have raised several tantalizing debates on its use as an active phototherapeutic agent or *light as a drug*. These concepts would significantly benefit from a focus on the precise biological targets that elicit photobiological responses. Fascinatingly, these appear to further strengthen the observations that several mammalian photobiological responses are inherently nonlinear such as olfaction and enzyme catalysis that have been termed *quantum biology*.[22] In summary, a key role for light in human health is clearly evident. Our ability to harness these therapeutically via more fundamental research and well-designed, rationalized clinical studies is poised to truly revolutionize health care.

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