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Guest Editorial

Emerging Applications of Photobiomodulation Therapy: The Interaction Between Metabolomics and the Microbiome

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After attending the SPIE meeting in San Francisco in February, I was reflecting on the many great advances in medical imaging, including the use of nanolanterns to greatly magnify the autofluorescence of signal transduction pathways within the cell, and the monitoring of ultraweak photons to map oxidative stress within cells,[1] both of which give an instant snapshot of metabolites and signaling profiles *in situ*. These advances allow us to study mechanisms of therapy in a detail greater than ever before. Combined with an ability to follow genetic and epigenetic changes, the possibility exists for an unprecedented understanding of how treatments can be formulated to suit individuals as a precision-based medicine approach.

There is an increasing awareness of the need for effective and affordable nonpharmaceutical treatments, especially for the treatment of the diseases of aging and other diseases that involve neuroinflammation, including musculoskeletal pain, inflammatory arthritis, cardiovascular disease, muscle fatigue, comorbid diseases of cancer management (lymphoedema, oral mucositis), and other autoimmune inflammatory pain conditions.

Photobiomodulation therapy (PBMt), the use of nonthermal light in the treatment of health conditions,[2] has been shown to be effective in many of these conditions, such as chronic neck pain (as recommended by the Bone and Joint Taskforce[3] guidelines) and wounds including oral mucositis (NICE guidelines, www.nice.org.uk/guidance/ipg615). PBMt appears to be poised to become an effective evidence-based solution to many of the problems facing world health, including diseases of aging. Indeed, in many diseases previously thought of as intractable, PBMt has shown promise as a treatment or preventive measure: effects of aging such as loss of muscle strength and balance, and diseases such as Parkinson's disease (PD), Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis.

I would like to introduce an exciting area of mechanism and treatment, involving the neuroprotective abscopal effect of PBM,[4] with particular emphasis on the treatment of PD: work being carried out in laboratories at Sydney University, Australian Catholic University in Sydney, and the Australasian Research Institute in Sydney. The mechanisms of action of PBM has been extensively studied for the past 40 years and the advances in knowledge of the photoreceptors involved, the cell signaling that transfers the light signal to mechanical, molecular, and chemical responses, the proteomic (protein interactome), genetic regulation[5] (transcriptome), and modulation of metabolites and triggered small molecules, all continue to increase our understanding and fuel increasing number of translational trials into an expanding range of diseases.

Metabolomics is the study of the metabolites within the cell and the organism, which is critical to an understanding of the mechanisms of PBM action. Although a great deal is already known about the effect of light on the electron transport chain, specifically cytochrome c oxidase, and the downstream effects of this, we have turned our attention to the cell membrane to seek further insights into the effects of PBM at a cellular level.

In a previous editorial by Santana-Blank and Rodriguez-Santana, the importance of circadian rhythms and oscillatory rhythms to PBMt was described. The effect of PBM on the mechanotransductive process within the cell, including the effect on metabolites, is crucial in determining signaling profiles, altering phenotypic expression (such as the ability of light to act as an allosteric switch and modify macrophage phenotype from M1 to M2[2]) and can also affect post-translational modification of proteins by small molecules, including by tyrosination, by methylation, by phosphorylation, by nitrosylation, and most particularly by SUMOylation.[6] These modifications can involve entire body events, exemplified by global SUMOylation in which the addition of a SUMO molecule across many proteins results in context-driven modification of signaling pathways.[6] As well as SUMOylation marrying short- and long-term reaction to environmental stress and stimuli, it has recently been shown to be instrumental in dictating circadian clock protein function and inherent circadian rhythms.[7] Many small molecules and proteins that are influenced by PBM, including the metabolites NAD^+, CREB, and α-MSH,[8] demonstrate circadian rhythms[9] and many receptors associated with PBM also influence circadian rhythms and, in the case of glutamate, are especially affected by aging. Response to light and circadian rhythms can be up to 20 times decreased in both humans and animal models as a result of aging.[10] The decrease in sleep, in the circadian rhythms of organs, and many other effects of aging have great potential to be treated by PBM.

An additional piece of the PBM mechanism jigsaw that I would like to explore is the influence of the microbiome on

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the body. The microbiome is the sum of the collective genomes of the commensal microbiota that live within us all (gut, oral, urogenital, etc.). The sum of the interaction between the genomic responses of our cells and the genomic actions of the microbiota is labeled the holobiome. The interactions between the microbial and the host metabolites are called the holobiont. There is increasing evidence for the influence of the microbiome on a diverse range of diseases. There is ample evidence of a gut–brain axis, where changes in the gut microbiome are strongly correlated with a number of neurological conditions and diseases, such as fear and risk-taking behaviors, cognition, schizophrenia, depression, and neurological diseases such as PD and AD.

The microbiome also has a direct influence on metabolic diseases and cardiovascular disease (summarized by Bicknell et al.[11]). Although the definition of metabolomics expressly excludes the microbiome as a factor, the mechanism of PBMt action should take this important component of the body into account, given the demonstrated influence of the microbiome on an individual's health and diseases and the two-way communication between the microbiome and the body. Many of the diseases that are known to be directly influenced by the microbiome are also modulated by PBMt.

In our laboratories, we have shown that PBMt, delivered as laser light (660 and 808 nm), is able to change the microbiome in a mouse model. In particular, one species of bacterium (*Allobaculum*) was shown to increase as a proportion of the microbiota when infrared laser was administered regularly over a 14-day period. This particular bacterium is strongly associated with a healthy microbiome in the mouse and can be increased with other treatments that target the microbiome, such as the diabetic drug, metformin (reviewed by Bicknell et al.[11]).

Interestingly, Blivet et al.[12] have demonstrated that a reduction of Alzheimer's symptoms occurs in a mouse model, using a combination of laser and LED wavelengths and a static magnetic field, when both the head and abdomen are treated, but not when either is treated alone. The authors suggest that the microbiome may play a role in this treatment.

The delay in the response of the microbiome to PBMt suggests that the primary effect is to the metabolomics of the body, which then communicates with the microbiome. This healthy microbiome can, in turn, have a beneficial feedback to the body. One way that the microbiome can communicate with the metabolome is by the production of identical metabolites or metabolite mimics, including α-MSH[13] (an antioxidant), tryptophan (a precursor to serotonin and melatonin), and other kynurenine pathway metabolites. These metabolites can influence behaviors such as visceral pain, cognitive function, social behaviors, depression, and potential diseases such as PD.[14,15]

The metabolomic and microbiome effects could account for the delayed, abscopal, and preconditioning aspects of PBMt,[2] such as the neuroprotection against PD seen when the abdomen is irradiated.[4] PBM influences the metabolomics of cytokine expression,[2] especially IG-γ and the kynurenine pathway, and, crucially, α-MSH and its resultant cytokine inhibitory melanocortin pathway. Interestingly, the microbiome also influences these pathways, through release of identical metabolites or mimicking molecules.[13] Preconditioning with PBMt does not have an immediate effect on healthy cells in experimental models but does change metabolomic factors that will influence the immune response and immune memory.[16]

The consideration of PBMt as an influence of the metabolomic as well as the genomic, proteomic, and microbiome influences is an important concept in the understanding of responsiveness/unresponsiveness to treatment and the effective dose prescription for individualized precision medicine. The extension of PBMt from its well-documented use in pain management, wound repair, lymphoedema, and preconditioning for exercise and surgery, to its increasing use as a treatment for neurodegenerative disease, will require an expanded knowledge of these metabolic processes. PBMt is successful as a treatment since it targets specific sites, as opposed to drug therapy that can affect many (often unwanted) sites. PBMt at the correct effective wavelength, energy density, and frequency can be effectively used in an individual way to promote homeostatic mechanisms within the body. Knowledge of individual response to light, through genomics, epigenetics, and the microbiome, as well as environmental parameters, is essential to this process.

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