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Letter to the Editor

Photobiomodulation Therapy: Communicating with Stem Cells for Regeneration?

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To the Editor:

NEVER HAS THERE been a more exciting time in the human race when the quest for knowledge has been expanded outward to the farthest universe, as well as inward to subatomic scales. It is likely not a mere coincidence that the ultimate frontier extending across all these vast scales happens to be light—a still mysterious but omnipresent form of physical energy whose impact on biological systems is still being uncovered.[1] The use of photonics in medicine has already changed our healthcare system dramatically from electronic access to data to better illumination fields, digital cytology and pathology, endoscopy, and precision surgery with lasers.[2] As in the clinical realm, biophotonics applications are leading research studies with innovations in optical imaging, optogenetics, molecular analyses, as well as surgical and nonsurgical applications.[3]

In other fields, the tremendous progress in our understanding of the human genome has paved the way for precision-medicine initiatives to harness this information for diagnoses and therapy.[4] Many of these breakthroughs have been made possible by the use of induced pluripotent stem cell technologies. These studies have demonstrated differentiated (lineage committed) cells, either morphologically or functionally, are in a stable but potentially reversible state.[5] There have been major concerns on the promiscuity of the process of lineage reversibility (epigenetic memory) and this remains an area of intense investigation.[6] Nonetheless, the ability of a few genes or small molecules to strikingly manipulate these stem-like states has prompted exploration of clinical applicability of these technologies for regenerative medicine.

A Biophysical Approach to Directing Differentiation: A Question of Communication?

The major premise of directed differentiation is based on the essential fact that every cell in our body is equipped with the complete genetic information that is essentially fully manipulatable. A stem cell or, a little less so, a progenitor cell offers the most primed state in a cell's potential for regenerative applications. It is, essentially, a blank permissive state receptive to signals that could direct its behavior and functions (Fig. 1). Regulatory cues such as small molecules (drugs), biological (miRNA, shRNA, and transcription factors), or biophysical agents (light, ionizing radiation, ultrasound, and radiofrequency) would all be potential regulatory modalities mediating biological communication. In this context, the use of low dose biophotonics therapy termed photobiomodulation (PBM) therapy, previously called low level light/laser therapy, would represent such a biophysical cell communication cue capable of modulating stem cell behavior.[7] The PBM-induced biological changes could affect stem cell bioenergetics, metabolism, signal transduction pathways, epigenetic modulators, or gene expression to evoke therapeutic benefits.

Sadly, since the inception of the PBM field, there has been persistent skepticism on the biological efficacy of this treatment modality. The inherent disbelief that such low doses (approximating routine ambient light irradiant energy) can evoke any substantive (nonthermal) biological response appears to be rather misplaced. It is indeed normal light irradiances that enable vitamin-D metabolism in skin or modulate the vision-enabling retinal pigment, rhodopsin.[8] It is also prudent to point out that biological reactions are predominantly either biochemical or biophysical (conformational) changes. Therefore, the use of PBM treatments not only offers a reasonable biophysical modality to modulate biological molecules therapeutically, but it may also be inherently harnessing naturally occurring photoreceptive biomolecules playing key roles in physiological homeostasis processes.

Evidence for the Use of PBM Therapy with Stem Cells

The major purpose of this special issue is to provide a collated overview of the progress and increasing excitement for the use of PBM therapy with stem cells for regenerative applications. The ethical controversies surrounding embryonic stem cells aside, a key fact remains that most tissues in the adult human have a potent pool of resident stem and progenitor cells. These cells play a pivotal role in routine physiological turnover during tissue–organ maintenance as well as contribute to repair after injury. This special issue including comprehensive, state-of-the-art reviews as well as primary research articles highlights the role of stem cells in various niches that have been noted to be responsiveness to PBM treatments. Three articles in this issue focus on fibroses in heart and kidney or damage to knee joint in animal models, where PBM therapy in combination with stem cells

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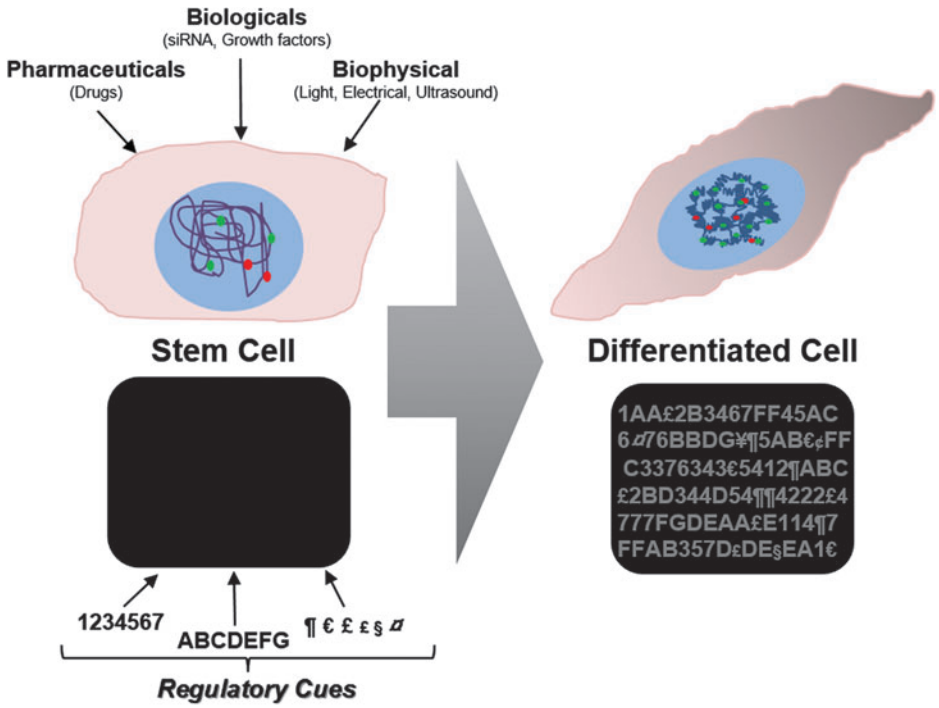

FIG. 1. Outline of directed differentiation strategies in regenerative medicine. The upper left image depicts a stem cell amenable to extrinsic manipulation by a range of regulatory cues that result in reprogramming of their genomes to initiate a differentiated, morphological, and/or functional state as shown in the upper right image. The images in the bottom represent the manipulatable, empty blackboard (black slate) that can be programmed with various regulatory (numbers, alphabets, and symbols) cues that communicate with the stem cell to direct its differentiation to a functional, differentiated state (filled-in black slate).

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was noted to reduce damaged tissues and improve tissue remodeling–regeneration. Interestingly, the three investigators take distinct approaches for the combinatorial treatments. In the first study, O'Connor et al. injected exogenous mesenchymal stem cells (MSCs) into circulation before PBM treatment locally to the site of surgically induced renal damage.[9] In the second study, Blatt et al. demonstrate mobilization of bone marrow stem cells with PBM treatment into circulation by treating long bones (tibia or iliac) directly after cardiac injury.[10] In the third study, Fekrazad et al. place scaffolds with seeded bone marrow-derived mesenchymal stem cells locally into osteochondral defects in rabbit knee followed by PBM treatment.[11] All three studies have noted the ability of PBM treatments to synergize with the therapeutic benefits of stem cells in alleviating pain and inflammation as well as promoting tissue healing in these distinct ailments. Along with these primary research articles, three reviews by Zhang and Liu (cardiac), Marques et al. (dental), and Fekrazad et al. (MSCs) summarize prior studies outlining the most effective PBM treatment parameters on these stem cells.[12–14]

In other studies, investigators examined the effects of PBM treatment on surgical wounds after bariatric surgery. Ojea et al. noted decreased pain and inflammation along with reduced scarring in the PBM-treated surgical wounds.[15] In another study, the mechanistic basis of improved skin or mucosal wound healing was examined by assessing changes in colony-forming units (CFUs) that is used as a functional assay for epithelial stem cells.[16] Khan and Arany observed that skin and mucosal keratinocytes have increased CFUs after PBM treatment that would contribute to wound closure (reepithelization). In another study, Myula and Abrahamse note the paracrine interactions of stem cells and smooth muscles in coculture models treated with PBM.[17] Besides these highlighted studies, there is growing pieces of evidence for the presence of stem cell niches at discrete anatomical sites that appear to be amenable to PBM treatments such as in the skeletal muscle and lung among many others.[18] Striking clinical successes of PBM therapy in a wide range of disease pathologies such as neuropsychology (e.g., traumatic brain injury (Concussions), Alzheimer's and Parkinson's diseases, multiple sclerosis, post-traumatic stress disorders, and depression among others), ophthalmology (e.g., dry acute macular degeneration and diabetic retinopathy), and dermatology (e.g., facial rejuvenation and hair growth) suggest that there may be a common regenerative mechanism being harnessed, indicating putative roles for stem–progenitor cells at these locations.[19,20]

Clinical Delivery and Safety of PBM Therapy with Stem Cells

The two major areas of PBM research have focused on clinical validation and laboratory mechanisms. Although the latter has focused on molecular pathways in biological systems, the major advancement in clinical delivery has emphasized standardizing and reporting PBM device parameters.[8] One study in this issue addresses one of the major PBM delivery issues, which is the light beam profile. Benedicenti et al. describe a flat top beam profile that enabled uniform dose delivery to the treatment samples, noting prominent changes in the mitochondrial electron transport activity and cell metabolism. They summarize their findings by suggesting that perhaps some of the discrepancies in clinical outcomes with PBM are due to the Gaussian beam profile of many current clinical biophotonics devices.

An interesting article in this issue attempts to address effects of PBM treatments on cancer stem cells. There is little evidence that nonionizing radiation wavelengths used for PBM therapy have any appreciable potential for malignant transformation. A recent article outlined the mechanisms of near-infrared (NIR) laser phototoxicity and

demonstrated the lack of any mutagenic or transformative potential.[21] Nonetheless, there remain few concerns on how the stimulatory effects of PBM noted in normal cells may potentially influence pretransformed or cancer stem cells. Crous and Abrahamse assess effects of dose-dependent PBM treatments on lung cancer stem cells and speculate on its clinical safety concerns.[22] Their technical assessment of cell viability and proliferation deserves careful scrutiny and could be interpreted contrarily. Nonetheless, this work raises fascinating avenues to examine biological responses in normal and malignant stem cell tissues, especially the nature of cellular (epigenetic) memory, to PBM treatments.

In summary, this special issue on PBM therapy and stem cells attempts to present some of the recent exciting progress in this area. The field of regenerative medicine appears to be poised at practically harnessing the tremendous advances we have made with stem, cell-molecular, and developmental biology. Indeed, the premise of directing differentiation appears to present the next formidable challenge in clinical translation of stem cell biology to regenerative medicine. Besides conventional pharmaceutical, biological, and biomaterial approaches maintain center stage in these attempts, biophysical modalities such as PBM therapy could add an additional approach to the clinical translational regenerative armamentarium.

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Author Disclosure Statement

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