Innovations with lasers could lead regenerative dentistry

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With this year, 2015, being designated as the year of light, the acknowledgment for the key role of light in multitudinous areas of our very existence and more specifically, in areas of human health are being widely promulgated. Many references to the beneficial effects of light and specifically sunlight are replete in the literature across ancient civilisations.

Notably, the ability of concentrated light radiation in the management of lupus vulgaris by Niels Lyborg Finsen received the Nobel Prize in Medicine and Physiology in 1903. The all-permeating nature of light and photonic electronics in our current society is readily evident such as the simplest supermarket laser scanners and optical communications to precision medical lasers and more recent laser weapon systems. This is also perhaps best highlighted by this year’s Nobel Prize in Physics to the inventors of the blue light emitting diodes (LEDs), a simple invention with profound impact on our current society.

Clinical laser application

Dentistry has historically been a leading clinical specialty in adoption of new technologies. Light has been a central part of the complex dental technology of evolving as key modality for treatment of tissue injuries and augmenting the beneficial effects of light. The use of lasers in dental applications is well-documented with a multitude of studies and clinical applications to dentin regeneration and hard tissue growth. The new field of photobiomodulation (PBM) and Photodynamic therapy with endogenous chromophores (PdT) has a broad spectrum of applications in dental and medical specialties.

First discoveries

Following the invention of this exciting new tool, early biological concerns focused around the safety of this new device with natural comparisons being drawn to ionizing forms of electromagnetic radiation. Among the early pioneering studies, Anderson and colleagues reported the peculiar phenomenon - high doses destroyed tissue in a precise and predictable manner but very low doses produced a startling improvement in wound healing and promoted hair growth. This was a surprising discovery on many accounts.

While high energy electromagnetic radiation, such as Gamma, X-rays and Ultraviolet, were able to achieve significant linear energy transfer generating biological damage (molecular acid strand breaks), the effects of visible (and later infra-red) lasers did not appear to fall within these routine biological responses (Fig. 1). With much excitement, these initial observations spurred many investigations for the use of low powered lasers and other light devices (including filter-based broad light sources and LEDs) in many clinical and laboratory studies.

Barriers in application

Unfortunately, a combination of the complexity of the early technology and a lack of understanding of its biological mechanisms has resulted in significant discrepancies in their reported therapeutic benefits. Hence, the lack of robust clinical efficacy has largely relegated the field to be side-lined as a pseudo-scientific and alternative medicine field. Current problems in the field from its basic terminology that prevents accurate indexing of the literature, to appropriate disease or biological response-specific clinical dose recommendations appear to be major barriers. Nonetheless, development of low power laser applications has also shown significant progress specifically in the areas of traumatic brain injury, post-traumatic stress disorders, reversal of methanol toxicity and wound healing. In more recent years, mechanistic insights into light-biological tissue interactions have contributed to our better understanding for the therapeutic applications of laser therapies.

Defining photobiomodulation

Our operational definition for Photobiomodulation (PBM) is a form of phototherapy that utilises non-ionising sources (including broad light, LEDs and Lasers) in the visible and infrared spectrum that result in therapeutic benefits such as alleviation of pain or inflammation, immunomodulation and promotion of wound healing and tissue regeneration. PBM is a non-thermal process involving photochemical and photothermal processes at varying power densities resulting in beneficial photobiological responses. Its clinical applications could be appended as PBM therapy.

Study 1: Activating TGF-β1

Based on prior reports, we began studies to establish the parameters of the near infrared laser to effectively promote seal wound healing at low doses (5 J/cm², 10 mW/cm², 5 minutes). We performed a thorough literature search to evaluate possible biological pathways involved in promoting wound healing. There appeared to be distinct correlations with the reported use of exogenous TGF-β1 and laser treatments in wound healing.

Based on these observations, we assessed the laser-treated healing response of oral tissues using laser-generated ROS activated TGF-β1 expression and noted increased expression immediately post treatment and at 14 days. The increase at 14 days correlated well with an increase in monocyte-macrophage influx, well-known cellular sources of TGF-1. We next looked into the increased early expression of active TGF-1 in these wounds. TGF-β1 is secreted as a latent growth factor complex which associated with a Latency Associated Peptide (LAP). The activation process involves dissociation of LAP from active TGF-β1 dimer that is well-documented with a wide range of physio-chemical modalities such as proteases, extreme pH, heat, ionizing radiation and immune binding among others. The early wound has been shown to contain latent TGF-β1 from degranulating platelets present in the early wounds.

We observed low power laser treatments were capable of activating the latent TGF-β1 complex. To further pursue this observation mechanistically, we noted that near infra-red laser was capable of generating reactive oxygen species (ROS). This highly reactive, transient chemical intermediate was sensed by a key metalloproteinase on the latent TGF-β1 complex that resulted in a change in its conformation, resulting in its activation.

Study 2: Dentin regeneration

Having noted the effects of low power lasers on promoting oral mucosal wound healing in the prior study, we extended our clinical applications to dentin regeneration where TGF-β1 has been shown to play a pivotal role in dentin physiology. We noted the ability of low power lasers to promote dentin regeneration using human dental stem cells. To validate these observations, recently generated iPSC-dentinogenic cells (MDPC-23) cells grown in a polymeric scaffold, simulating a 3-D niche were treated with low power lasers. Laser treatments were able to induce dentin differentiation as evident by increased dentin-specific gene expression and mineralisation. To confirm the role of TGF-β1 in vivo, transgenic mice (utilising a Dentin Sialophosphoprotein specific transgene) were generated. Experiments in these mice did not demonstrate any significant dentin induction following laser treatment validating the critical role of TGF-β1 in mediating its effects.

Previous studies have shown the therapeutic benefits of supplementing exogenous (recombinant) TGF-β for reparative
dentin, this study suggests that the use of low power lasers can activate endogenous latent TGF-β1 present naturally in the pulp-dentin complex to drive differentiation of resident dental stem cells (Fig. 2). Thus, this therapy can utilise the inherent reparative and regenerative responses naturally present in native tissues.

Clinical Applications of Laser-Dentin induction

These observations have potential implications where dentin would need to be therapeutically generated. The two directly relevant clinical scenarios are for pulp capping following deep carious lesions and for dentin desensitisation. In the former case, removal of decayed or damaged tooth structure approximating the pulp (close to or clear exposure) that require the use of pulp capping agents (such as Calcium hydroxide) could be potentially replaced with low power laser treatments.

In the second scenario, the use of low power laser treatments on exposed dentinal tubules could potentially generate an intrinsic dentin barrier that would relieve tooth sensitivity. This would be more effective than our current approach to extrinsically occlude exposed tubules modes.

The two major limitations of the current study were that we noted calcifications interspersed throughout the pulp chamber, spatially distinct from the laser-biological tissue interface. We believe this is perhaps a combination of the inherent near-infrared laser wavelength that readily permeates throughout biological tissue as well as the soluble nature of the activated molecules. This could be potentially addressed by better optical focusing techniques and use of specific reagents that absorb the radiant energy and spatially restrict the biological interphase.

A second limitation in this study was the observation that laser-generated dentin was a tertiary or reparative form that lacks pristine tubular structure. It appears that additional cues both biophysical (architecture) and biochemical (soluble, organizational), are likely necessary to promote morphodifferentiation of the newly induced dentin.

In attempts to further explore these molecular mechanisms, we have more recently extended developed a polymeric scaffold system with precise morphogen fields. Using this model, we were able to extend our observations with dental stem cells and laser-activated TGF-β1 mediated dentin differentiation to mesenchymal stem cells suggesting this approach could have significant potential with other stem cell types as well.

Conclusion

Both ROS and TGF-β1 are central biological mediators in a wide range of biological responses. The ability to selectively activate them in a spatiotemporally defined manner in vivo using low power lasers provides a significant clinical tool for various therapeutic interventions.

Questions on precise wavelengths, clinical protocol (delivery and dose ranges) and context of the pathophysiological response are all critical issues that need to be explored rigorously to enable further effective clinical translation of this therapy.

Further, the ability to effectively move this therapy into mainstream clinical dentistry will require more basic research, development of robust clinical standards and education at various levels (basic dental training and continued education) (Fig. 3).

In the current era of personalized medicine and strategies to utilise sophisticated technologies and pharmaceuticals to individualise health care, the significant promise of lasers in clinical dentistry may indeed be the leading, pivotal technology thatushers in the new era of regenerative dentistry.

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