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Immunomodulatory activity seen as a result of photobiomodulation therapy in stimulated primary human fibroblasts

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Highlights

- IL-1β upregulates cytokines in IL-1β-stimulated human periodontal ligament fibroblasts (hPDLFs).
- Photobiomodulation therapy mitigates pro-inflammatory responses mediated via IL-1β.
- 810 nm laser wavelength alone or in combinations with 980 nm regulates inflammatory responses in hPDLFs.
- Total dosage of 2–4 J/cm^2 shows promise in regulating inflammatory responses.

Abstract

Objective

Oral biofilms burden host responses by induction of inflammatory mediators, exacerbating periodontal inflammation. Photobiomodulation Therapy (PBMT) has been shown to decrease levels of pro-inflammatory cytokines and chemokines. However, optimal wavelengths and exposure doses have not been established. This study investigated the effects of PBMT on human periodontal ligament fibroblasts (hPDLFs) stimulated with inflammatory mediators (LPS, TNF-α, and IL-1β).

Methods

Cytotoxic effects of laser wavelengths 660 nm and 810 nm were assessed by measuring their effects on cellular dehydrogenase activity. The study was expanded to include 980 nm, 660 nm + 810 nm, and 810 nm + 980 nm. *P.g*. LPS, TNF-α, and/or IL-1β were added one hour before irradiation, then exposed to laser irradiation to determine the most appropriate stimulus. The levels of INF-γ, IL-6, IL-8, IL-17A/F, and MCP-1 production in stimulated hPDLFs were measured and analyzed.

Results

P.g. LPS was a poor stimulus for hPDLFs, while TNF-α and IL-1β significantly elevated the analytes. The 660 nm laser treatment induced pro-inflammatory cytokines when stimulated, while 810 nm exhibited significant suppression. IL-1β was the stimulus of choice and the 810 nm wavelength alone exhibited anti-inflammatory effects for all analytes except IL-8, while the 810 nm in combination with 660 nm and/or 980 nm exhibited effects similar to 810 nm alone.

Conclusions

The downregulation of inflammatory mediators by the combination or individual treatment with 810 nm wavelength shows promise for the management of periodontal inflammation. PBMT may lead to the development of a novel approach in the management of periodontal disease.

Introduction

Periodontitis (PD) is a chronic inflammatory disease affecting more than half a billion people worldwide with healthcare costs that exceed $14 billion in the U.S. alone (Brown, Johns, & Wall, 2002; Kassebaum et al., 2014). Oral pathogens like *Porphyromonas gingivalis* (P.g.) invade and colonize periodontal tissues resulting in bone destruction (Agace et al., 1993). In PD, the dysregulation and loss of homeostasis are due to activated host-induced responses that result in the upregulation of various cytokines and chemokines (Agace et al., 1993; Dickinson, Moffatt, & Hagerty, 2011; Jandinski, 1988; Jiang et al., 1996; Reinhardt, Masada, & Kaldahl, 1993; Stashenko, Dewhirst, Peros, Kent, & Ago, 1987; Tonetti, Imboden, & Lang, 1998; Tsai, Ho, & Chen, 1995; Yamazaki et al., 1994), resulting in alveolar bone resorption (Gemmell, Marshall, & Seymour, 1997). Conventional scaling and root planing is the gold standard (NIDCR NIoDaCR, 2013), but disease progression may require open flap or osseous surgery. Until now, non-invasive therapeutic options that reduce inflammation and restore periodontal health have been limited.

Photobiomodulation therapy (PBMT) has emerged as an approach to reduce inflammation by inducing anti-inflammatory effects to improve periodontal health. Lim, et al. demonstrated that the effects of laser treatment at 635 nm in fibroblasts resulted in a decrease of prostaglandin E2 (PGE2) production (Lim, Choi, & Kim, 2015). Their research also demonstrated the effects of lipopolysaccharide / endotoxin (LPS) induced human periodontal ligament cells (hPDLCs), in which 660 nm laser treatments downregulated Nuclear Factor – Kappa B (NF-κB) transcriptional activity and increased intracellular cyclic adenosine monophosphate (cAMP) to inhibit inflammation through the cAMP/NF-κB pathway (Lee et al., 2018). Moreover, light emitting diode (LED) irradiation also downregulates osteoclastogenesis by decreasing the production of reactive oxygen species (ROS) (Sohn, Ko, & Park, 2015), which may help manage bone loss in PD.

In this study, we examined the anti-inflammatory effects of PBMT on hPDLFs in reducing cytokine production after a pro-inflammatory stimulus. These fibroblasts behave similarly to immune cells and can amplify inflammatory responses when stimulated (Jonsson, Nebel, Bratthall, & Nilsson, 2011). The cytokine interleukin-6 (IL-6) is upregulated in PD as compared to gingivitis, while increased levels of interferon-gamma (IFN-γ) in gingival crevicular fluid (GCF) samples have been detected in chronic

periodontal lesions (Dutzan, Vernal, & Hernandez, 2009). Additionally, the roles of IL-1β and TNF-α are well established in PD and are involved in tissue destruction and alveolar bone resorption in various cell types (Gemmell et al., 1997; Ozaki, Hanazawa, & Takeshita, 1996). IL-8 increases in the majority of periodontal sites exhibiting PD (Emingil, Atilla, & Hüseyinov, 2004). Meanwhile, monocyte chemoattractant protein 1 (MCP-1) contributes to bone resorption via mobilization and regulation of monocytes (Emingil et al., 2004), and Interleukin-17 (IL-17) functions to increase host immunological response to periodontal pathogens (Behfarnia, Birang, Andalib, & Asadi, 2010) and is elevated in patients with PD (Dutzan, Gamonal, Silva, Sanz, & Vernal, 2009; Honda, Aoki, & Takahashi, 2008; Johnson, Wood, & Serio, 2004; Zhao et al., 2011). These cytokines and chemokines are clinically relevant biomarkers which is why we focus on them in this study.

We have previously observed that increased interleukin-6 (IL-6) and MCP-1 in hPDLFs, stimulated with interleukin-1 beta (IL-1β), present the most robust response when compared to other stimuli (Abidi et al., 2018). To further validate these findings, we have included *Porphyromonas gingivalis* lipopolysaccharide (*P.g.* LPS), IL-1β, and tumor necrosis factor-alpha (TNF-α), since this cell line stemmed from a different donor than our previous work. We hypothesize that the cytokines and chemokines involved in significant upregulation in PD will be reduced.

The anti-inflammatory effects of red wavelengths between 635 nm to 660 nm has been well-established (Albertini, Villaverde, & Aimbire, 2007; Fabre, Navarro, & Oltramari-Navarro, 2015; Gupta, Dai, & Hamblin, 2014; Lim, Lee, & Kim, 2007). Our comparative study includes irradiation at 660 nm, 810 nm, 980 nm, 660 nm + 810 nm, and 810 nm + 980 nm, to observe anti-inflammatory effects on broader levels. To our knowledge, IL-1β-stimulated hPDLFs have not been studied to this extent with PBMT. This study also aims to find whether other PBMT wavelengths and combinations provide more effectiveness to regulate periodontal inflammation and reduce inflammatory cascades.

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Section snippets

Cell culture of primary human periodontal ligament fibroblasts

Primary human periodontal ligament fibroblasts (hPDLFs) were used in this study (CC-7049, Lonza, Walkersville, MD, USA). Cells were cultured in the manufacturer's recommended stromal cell basal medium (SCBM, CC-3204) with 5% fetal bovine serum (FBS) and SingleQuot Kit Supplements & Growth Factors (SCGM, CC-4181). The cells were sourced from healthy individuals who were negative for HIV-I, Hepatitis B, and Hepatitis C. Furthermore, these fibroblasts were validated via pan-cytokeratin staining by …

Evaluation of the effects of P.g. LPS, IL-1β, and TNF-α on hPDLFs response rates

The stimulation of inflammatory responses on hPDLFs is well characterized by *P.g.* LPS, IL-1β, or TNF-α due to their key roles in inflammation. We first measured their responses in hPDLFs, which resulted in no cytotoxic effects at the given concentrations (Honda et al., 2008) (*P.g.* LPS [1 μg/mL], IL-1β [1 ng/mL], and TNF-α [10 ng/mL]). In alignment with our previous study, we used IL-6 and MCP-1 as pro-inflammatory markers strongly associated with inflammation and PD (Abidi et al., 2018; Gupta…

Discussion

Chronic inflammation is a significant contributing factor in the progression of PD and currently, there is no consistently effective non-invasive adjunctive therapy to reduce it. There is current promise in research showing enhanced epithelization and wound healing after gingival procedures (Ozcelik, Cenk Haytac, Kunin, & Seydaoglu, 2008) and bone repair (Guzzardella, Torricelli, Nicoli-Aldini, & Giardino, 2003) using bio-stimulatory effects of PBMT to influence several types of cells. A…

Main text

This study was conducted in accordance with the Helsinki Declaration of 1975, as revised

in 2013, using human periodontal ligament fibroblasts, hence informed consent was not required. Approval by the human subject's ethics board of The University of Tennessee Health Science Center was not required, as the fibroblasts were acquired from Lonza, who obtained informed consent from their donors before distribution.…

Declaration of Competing Interest

The authors report no declarations of interest.…

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