Photomedicine and Laser Surgery

Blue Laser Irradiation Generates Intracellular Reactive Oxygen Species in Various Types of Cells

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ABSTRACT

Objective: The purpose of this study was to measure intracellular reactive oxygen species (ROS) production after laser irradiation in various types of cells. ***Background data:*** ROS are considered to be the key secondary messengers produced by low-level laser therapy (LLLT). Although various mechanisms for the effects of LLLT have been proposed, and intracellular ROS were indicated as the one of the key factors, direct measurement of intracellular ROS of several types of cells after different wavelength lasers irradiation has not been reported. ***Materials and methods:*** Various types of cells were used in this study: mouse preadipocytes (3T3-L1), prechondrocytes (ATDC5), myoblasts (C2C12), mesenchymal stromal cells (KUSA-A1), lung cancer cells (LLC), insulinoma cells (MIN6), fibroblasts (NIH-3T3), human cervix adenocarcinoma cells (HeLa), macrophages differentiated from lymphocytes (THP-1) after treatment with phorbol ester, and rat basophilic leukemia cells (RBL-2H3). Cells were irradiated with a blue laser (wavelength: 405 nm), a red laser (wavelength: 664 nm) or a near infrared laser (wavelength: 808 nm) at 100 mW/cm^2 for 60 or 120 sec. Intracellular ROS levels were measured by fluorometric assay using the intracellular ROS probe, CM-H_2DCFDA in a flow cytometer. ***Results***: After a blue laser irradiation, intracellular ROS levels were increased in all types of cells. In contrast, intracellular ROS generation was not observed after irradiation

with a red laser or near-infrared laser. ***Conclusions:*** Potential sources of intracellular ROS were excited by blue laser irradiation, resulting in ROS production within cells. Although the low-level intracellular ROS should be generated after a red or a near-infrared laser irradiation, the only high level intracellular ROS were detected by the ROS probe used in this study. As ROS are considered to be key secondary messengers, the specific functional regulation of cells by laser irradiation will be studied in a future study.

Introduction

Cell signaling molecules can be generated in response to external treatments such as low-level laser therapy (LLLT). The key secondary messengers produced by LLLT are reaction oxygen species (ROS).[1] Various mechanisms for the effects of LLLT have been proposed, including ligand-free dimerization and activation of specific receptors that absorb laser energy, leading to their autophosphorylation and downstream effects,[2] or, alternatively, activation of calcium channels resulting in increased intracellular calcium concentration and cell proliferation.[3–9] The photon energy by laser may be absorbed by mitochondrial respiratory chain components, resulting in increased levels of ROS, adenosine triphosphate (ATP), and/or cyclic adenosine monophosphate (AMP) and initiating a signalling cascade that promotes cellular proliferation and cytoprotection.[2,10–16] Following increased synthesis of ATP and protein synthesis after LLLT, expression of growth factors and cytokines increases and ultimately leads to various functional changes in the cell.[17,18] Recent studies have also shown that light irradiation can alter cellular homeostasis parameters such as pH_i, the redox state of the cell, and expression of redox-sensitive factors such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), which can, in turn, lead to a variety of functional changes.[2,19–21] We have previously demonstrated that irradiation with a blue laser (405 nm) enhances osteogenesis and chondrogenesis and suppresses adipogenesis in mouse stromal cells or precursor cells.[22–24] We also examined the possible mechanisms underlying this effect, investigating the possibility that intracellular photoreceptors or second messengers, such as ROS, were playing key roles in differentiation.

Photosynthesis is dependent on the absorption of photon energies from the visible and near-visible spectrum. Subsequent photoexcitation is tightly linked to biomolecular electron transport, which in essence involves the oxidation and reduction of biomolecules within the chain. This electron transport is used to create the proton-motive force, and thus generates energy to be used for the regulation of transcriptional factors. This electron transport also influences the reduction and oxidation of biomolecules associated with the electron transport chain (i.e., the production of associated ROS). In this way, visible and near-visible light provide the energy for the production of high-energy molecules and influences the reduction/oxidation (redox) state of the cell. ROS play an important role in many biological systems. ROS formation is closely related to the body's response to infection, ischemia–reperfusion, and heavy metal and ethanol toxicity, as well as to many other conditions.[25,26] It is also believed to play important roles in normal cell signaling events.[27,28]

LLLT research has revealed that specific wavelengths of light in the visible and near-visible spectrum (at the correct dose, intensity, and pulse frequency) can induce a variety of cellular effects in some nonphotosynthetic cells.[29–38] Our understanding of such effects will help determine the clinical utility of low-intensity lasers. Interestingly, these cellular effects appear to share some mechanisms with the specialized processes of photosynthesis. In this study, we tested the hypothesis that increased ROS production is associated with exposure to visible light. Our findings provide insight on the production of intracellular ROS in response to irradiation of cells with light of different wavelengths.

Materials and Methods

We used a range of cell types in this study: mouse preadipocytes (3T3-L1), prechondrocytes (ATDC5), myoblasts (C2C12), mesenchymal stromal cells (KUSA-A1), lung cancer cells (LLC), insulinoma cells (MIN6, kindly provided by Professor Jun-ichi Miyazaki, Osaka University, Japan) fibroblasts (NIH-3T3), human cervix adenocarcinoma cells (HeLa), macrophages differentiated from lymphocytes (THP-1) after treatment with phorbol ester, and rat basophilic leukemia cells (RBL-2H3). Each cell line was cultured in Dulbecco's Modified Eagle's Medium (DMEM) or RPMI 1640 medium (Sigma-Aldrich, Inc. MO) containing 10% fetal calf serum (FCS, Biowest, France), 100 units/mL penicillin, and 0.1 mg/mL streptomycin (Sigma-Aldrich, Inc., MO) at 37°C in a 5% CO_2 atmosphere.

Intracellular ROS levels were measured by fluorometric assay using an intracellular ROS probe, CM-H_2DCFDA (Molecular Probes, Inc., OR). Fluorescence was observed only when ROS was reacted with CM-H_2DCFDA inside cells. Cells were trypsinized, suspended in culture medium (1×10^5 cells/mL), and incubated with 8.65 μM CM-H_2DCFDA in culture medium for 30 min in the dark. After cells were washed with

phosphate-buffered saline and switched to FCS-free medium, they were laser-irradiated and collected in microcentrifuge tubes. For laser irradiation, cells were suspended (1×10^5 cells/0.1 mL in each well) in a Black with Clear Bottom 96-well Microtest™ Optilux™ Plate (BD Bioscience Inc., CA). The irradiated area in each well was 28.3 mm^2. Cells were irradiated with a blue laser (VLM 500®, Sumitomo Electric Industries, Ltd., Japan, adjustable power [1–500 mW] at 405 nm wavelength, continuous wave), a red laser (JENOPTIK unique-mode GmbH, Germany, adjustable power [<1 W] at 664 nm wavelength, continuous wave) or a near-infrared laser (Seiko Electric Co., Ltd, Japan, adjustable power [<1.4 W] at 808 nm wavelength, continuous wave) at 100 mW/cm^2 for 60 or 120 sec via a fiber attached to the bottom of the culture plate in the dark. Laser irradiation was applied at a uniform power density to whole cells cultured in the well because the laser beam was spread and only the non-Gaussian beam was selected and collimated. The optimization of these laser irradiation conditions is described in our previous reports.[22–24] The optical instrument, with a temperature control and an automated stage for positioning, was purchased from Sigma Koki Co., Ltd., Japan,[22–24, 39–42] and its diagram is shown in supplementary Fig. 1 (see online supplementary material at http://www.liebertonline.com). The temperature of the culture medium was controlled, and did not change during laser irradiation. Immediately after laser irradiation, the cells were analyzed by flow cytometer (Cell Lab Quanta SC, Beckman Coulter K.K., Japan) and $>1\times10^4$ cells were analyzed in each group. The representative data from each experiment performed in triplicate were shown.

Results and Discussion

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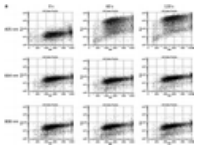
After blue laser irradiation, the intracellular ROS levels were increased in many types of cells (Fig. 1a–j). The observed percentages of intracellular ROS produced by each cell line after blue laser irradiation are summarized in Table 1. In contrast, intracellular ROS generation was not detected after irradiation with a red or a near-infrared laser by using the intracellular probe used in this study, CM-H_2DCFDA. Flavins have previously been found to be responsible for a blue light induction of free radical reactions in cell medium.[43] The chemistry of photosensitization of biomolecules by riboflavin has been studied extensively and found to be complex.[44] Eichler et al. reported that light-induced free radical formation sensitized by flavins may play a significant role in interactions between blue light and tissue.[45] However, they discovered that red light-induced ROS were also detected by using a more sensitive reagent.[46] Although a low level of ROS should be generated after a red laser or a near-infrared laser irradiation, these ROS were not detected by the intracellular probe used in this study, CM-H_2DCFDA.



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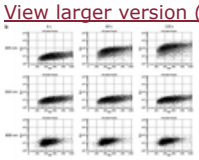

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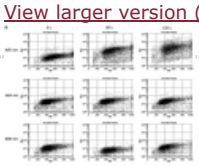

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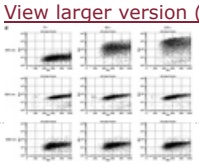

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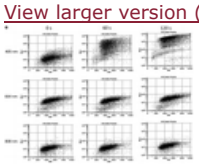

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FIG. 1. Several cell types were subjected to laser (wavelength: 405, 664 or 808 nm) irradiation for 0, 60, or 120 sec: **(a)** mouse preadipocytes (3T3-L1), **(b)** prechondrocytes (ATDC5), **(c)** myoblasts (C2C12), **(d)** mesenchymal stromal cells (KUSA-A1), **(e)** lung cancer cells (LLC), **(f)** insulinoma cells (MIN6), **(g)** fibroblasts (NIH-3T3), **(h)** human cervix adenocarcinoma cells (HeLa), **(i)** macrophages differentiated from lymphocytes (THP-1) after treatment with phorbol ester, and **(j)** rat basophilic leukemia cells (RBL-2H3). Following irradiation, intracellular ROS levels were measured by flow cytometer. The y-axis indicates the fluorescent intensity of the ROS indicator, CM-H_2DCFDA. The x-axis indicates the electronic volume (EV), which reflects cell size.

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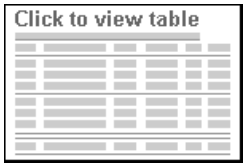
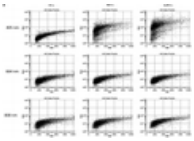


TABLE 1. THE OBSERVED PERCENTAGES OF INTRACELLULAR RD: PRODUCED BY EACH CELL LINE AFTER BLUE LASER IRRADIATION

Cellular production of ROS after laser irradiation may occur from both enzymatic and nonenzymatic sources. Any electron-transferring protein or enzymatic system can generate ROS via electron transfer reactions. In mitochondria, the unintended generation of ROS accounts for 1–2% of total O_2 consumption under reducing conditions.[47] Because of high concentrations of mitochondrial superoxide dismutase (SOD), the intramitochondrial concentrations of O_2^- are maintained at very low steady-state levels.[48] Therefore, unlike H_2O_2, which is capable of diffusing across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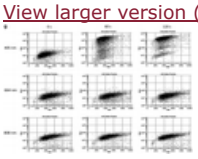
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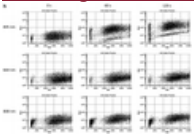
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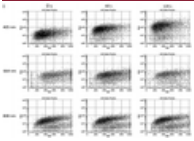
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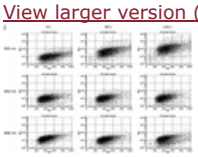
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the mitochondrial membrane into the cytoplasm,[49] mitochondria-generated O_2^- is unlikely to escape into the cytoplasm. The potential for mitochondrial ROS to mediate cell signaling has gained significant attention in recent years, particularly with regard to the regulation of apoptosis.[50–55] There is evidence to suggest that tumor necrosis factor (TNF)-α and interleukin (IL)-1–induced apoptosis may involve mitochondria-derived ROS.[56–58] It has also been suggested that the mitochondria may function as an "O_2 sensor" to mediate hypoxia-induced gene transcription[59,60] and red to near-infrared lasers were thought to be absorbed by mitochondrial respiratory chain components, resulting in the increase of ROS.[1,2,4,21] However, in our results, intracellular ROS were detected only after a blue laser irradiation to cells. As an intracellular ROS probe used in this study was distributed only in the cytoplasm, ROS generated in the mitochondria might not have been detected in this study even if red to near-infrared laser irradiation induced ROS generation in the mitochondria.

In addition to intracellular membrane-associated oxidases, soluble enzymes such as xanthine oxidase, aldehyde oxidase, flavoprotein dehydrogenase, and tryptophan dioxygenase can generate ROS during catalytic cycling.[47] Our studies also suggested that cryptochrome, a flavoprotein, is excited by blue laser irradiation, and that homeostasis is regulated by the expression of cryptochrome after such irradiation.[22,23] The most extensively studied of these cryptochromes is the O_2^--generating xanthine oxidase, which can be formed from xanthine dehydrogenase after tissue exposure to hypoxia.[61,62] Xanthine oxidase is widely used to generate O_2^-*in vitro* to study the effect of ROS on diverse cellular processes; however, no studies have revealed a direct physiological role for endogenous xanthine oxidase in cell signaling. Autooxidation of small molecules such as dopamine, epinephrine, flavins, and hydroquinones can be an important source of intracellular ROS production.[47] In most cases, the direct product of such autooxidation reactions is O_2^-. Although there is no known role for autooxidation of small molecules in growth factor and/or cytokine signaling, such reactions may induce oxidative stress and alter the overall cellular redox state.

Although a large number of signaling pathways appear to be regulated by ROS, the signaling molecules targeted by ROS are less clear. There is growing evidence, however, that redox regulation might occur at multiple levels in the signaling pathways from receptor to nucleus. Receptor kinases and phosphatases themselves may be targets of oxidative stress. Growth factor receptors are most commonly activated by ligand-induced dimerization or oligomerization concomitant with autophosphorylation of cytoplasmic kinase domains.[63] Ligand-independent clustering and activation of receptors in response to ultraviolet (UV) light have also been rigorously demonstrated,[64,65] and these effects appear to be mediated by ROS.[66,67] Exogenous H_2O_2 has been shown to induce tyrosine phosphorylation and activation of the platelet-derived growth factor (PDGF)-α, PDGF-β, and epidermal growth factor (EGF) receptors.[68–70] Lysophatidic acid–induced activation of the EGF receptor appears to be mediated by formation of ROS.[71] However, to our knowledge, no studies have demonstrated the ability of endogenous, growth factor–stimulated ROS to regulate their own or other receptors' activation. On the other hand, H_2O_2 production in response to EGF has been shown to require a functional EGF receptor kinase domain,[72] suggesting that growth factor–induced ROS may function downstream from EGF receptor activation. This does not exclude the possibility that, under certain pathological conditions associated with oxidative stress, ROS generated after laser irradiation may directly activate cell surface receptors. Because most growth factors and cytokines appear to generate ROS at or near the plasma membrane, phospholipid metabolites are potentially important targets for redox signaling.

In this report, we demonstrated that intracellular ROS are generated in response to LLLT. Although this is beyond the scope of the present study, the specific functional regulation of cells by laser irradiation will be studied in our future study because ROS are considered to be key secondary messengers in cells.

Acknowledgment

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Author Disclosure Statement

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No competing financial interests exist.

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