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Photobiomodulation of breast and cervical cancer stem cells using low-intensity laser irradiation

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Abstract

Breast and cervical cancers are dangerous threats with regard to the health of women. The two malignancies have reached the highest record in terms of cancer-related deaths among women worldwide. Despite the use of novel strategies with the aim to treat and cure advanced stages of cancer, post-therapeutic relapse believed to be caused by cancer stem cells is one of the challenges encountered during tumor therapy. Therefore, further attention should be paid to cancer stem cells when developing novel anti-tumor therapeutic approaches. Low-intensity laser irradiation is a form of phototherapy making use of visible light in the wavelength range of 630–905 nm. Low-intensity laser irradiation has shown remarkable results in a wide range of medical applications due to its biphasic dose and wavelength effect at a cellular level. Overall, this article focuses on the cellular responses of healthy and cancer cells after treatment with low-intensity laser irradiation alone or in combination with a photosensitizer as photodynamic therapy and the influence that various wavelengths and fluencies could have on the therapeutic outcome. Attention will be paid to the biomodulative effect of low-intensity laser irradiation on cancer stem cells.

Keywords

Stem cells; cancer stem cells; breast cancer; cervical cancer; low-intensity laser irradiation; photodynamic therapy

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Introduction

Breast cancer is presently the second most commonly diagnosed invasive cancer, after lung cancer, predominantly affecting woman and the leading cause of cancer-related deaths in women worldwide.[1] With approximately 1.7 million new cases diagnosed in 2012, breast cancer accounted for 12% of all cancer and 25% of cancer affecting women worldwide. Cervical cancer occupies the second and third position on the list of the most commonly diagnosed cancers in women and the leading cause of cancer-related death worldwide, respectively.[2] With nearly 527,600 new cases diagnosed in 2012, cervical cancer accounted for 7.9% of all cancer affecting women (Table 1).[2,3]

Post-therapeutic cancer recurrence is believed to be caused by cancer stem cells (CSCs).[4] Stem cells are embryonic or adult (somatic), undifferentiated cells that have the remarkable potential to differentiate into any cell type of the living organism.[5] CSCs and normal stem cells share phenotypic similarities, including the self-renewal, the differentiation, and the proliferation abilities.

The capacity of low-intensity laser irradiation (LILI) to enhance natural functions of the mitochondria such as the metabolic energy synthesis of adenosine triphosphate (ATP) and programmed cell death activation has been observed in both normal and cancer cells and has made LILI a novel approach in disorders whose treatment effectiveness relies on cellular biostimulation or bioinhibition. Light absorption is made possible by the chromophores (photoacceptors) located in the mitochondrial inner membrane.[6] The proliferative cellular response to LILI is believed to be the result of a change in the redox state of mitochondrial redox couples, which in turn regulates a number of signaling pathways and transcription factors that are involved in cell proliferation, growth, and motility.[7,8]

Breast cancer

Breast cancer is a life-threatening heterogeneous disease caused by multiple alterations of epithelial cells found in the milk-producing lobules and the milk ducts within breast tissues.[9] Based on their immunohistochemical (IHC) characteristics and their expression of protein receptors, breast cancers are classified clinically into four subtypes, namely, lumina A, lumina B, human epidermal growth factor receptor 2 (HER2), and triple-negative breast cancers (TNBC). They all require different therapeutic approaches and have different prognosis.[10]

The estrogen and progesterone receptor protein overexpression is observed in both the lumina A and B breast cancer subtypes, which represent 40% and 20% of all breast cancers, respectively.[11] Given their estrogen positive (ER+) and progesterone positive (PR+) status, both lumina A and B show favorable responses to the endocrine therapy using drugs such as tamoxifen, toremifene, and fulvestran, which decrease or stop the estrogen production in cancer cells, thus disrupting their growth.[12] The knowledge of the gene expression profile and protein synthesis turns out to be helpful in determining the behavior of a given cancer in order to decide on the suitable treatment. The deregulation and overexpression of the enhancer of zeste homolog 2 (EZH2) protein have been associated with CSC formation,

angiogenesis, progression, metastasis, epithelial–mesenchymal transition (EMT), drug resistance, and poor prognosis in breast and cervical cancer.[13]

Notch signaling pathway appears to be involved in the tumorigenesis, angiogenesis, cancer cell growth, and resistance to the anti-estrogen therapy through its interaction with the estrogen pathway.[14]

Signaling pathway crosstalk plays a crucial role in the cellular responses to different changes that occur in their environment. Cancer cells misuse of this intercommunication causes harmful effects in the entire organism.[11] One of the signaling networks misuse is the crosstalk between Notch and the HER2 signaling pathway which has been associated with the development of breast cancer.[11,14] HER2 protein is a receptor found in healthy breast cells and is involved in the cellular proliferation, division, and repair. HER2 gene amplification could lead to the malignancy of healthy breast cells. This happens in nearly 10%–20% of cases and the breast cancer is said to be HER2-positive (Figure 1).[12]

Cervical cancer

Cervical cancer develops in the lower part of the female uterus called cervix. Malignant lesions of the cervix are caused by a synergy between infection by the human papilloma virus (HPV) and the genetic and epigenetic alterations of healthy stem cells.[15]

The mechanism behind cervical cancer development due to HPV infection is the disturbance of vital cellular pathways such as notch caused by the E6 and E7 viral oncoproteins, whose overexpression has been associated with cancer malignancy.[16] The gene expression profiling of cervical cancer cells has shown aberrant methylations of the CpG Island within the promoters of several tumor-suppressor genes including p53, which is normally involved in the positive regulation of apoptosis and negative regulation of cell growth and migration.[17] Currently, hysterectomy and radiation therapy are used to treat and cure cervical cancer at early stage.[18] However, due to the lack of regular screening, the cancer is already at a malignant stage at the time of diagnosis and the post-therapeutic results are far from optimal. At this stage, the recurrence rate usually stands at 50% within a year after therapy.[19]

Stem cells

Stem cells are embryonic or adult undifferentiated cells that differ from other cells by their capacity to renew themselves and to transit from the undifferentiated to the differentiated state under specific physiological or experimental conditions.[20] Regardless of their origins, all stem cells divide through mitosis and can either renew themselves and give rise to undifferentiated daughter cells or become organ specific and give rise to differentiated daughter cells.[21] Based on their potency, stem cells are classified as totipotent, pluripotent, and multipotent. Totipotent stem cells are either from the zygote, spore, or morula embryonic tissues and have the potential to give rise to an entire functional organism given their ability to differentiate into any type of adult and embryonic cells.[22] Pluripotent stem cells are also from the embryonic tissues but can only give rise to adult cells. Multipotent stem cells are from the adult tissues and can only differentiate into a limited range of cells.[22]

Adult differentiated cells can be genetically reprogrammed into “induced pluripotent stem cells (IPSCs)” by forcing the expression of certain genes under specific conditions.[23]

CSCs

CSCs are malignant cells believed to originate from genetically or epigenetically altered healthy stem cells. They represent a minority of undifferentiated side-population (SP) cells possessing stem-like properties among cancerous cells of a heterogenic malignant tumor.[20,24] In addition, CSCs also possess tumorigenic phenotypes including the multidrug resistance, expression of anti-apoptotic proteins, drug efflux pumps, clonal long-term repopulation capacity, uncontrolled proliferation, metastasis, and epithelial–mesenchymal plasticity.[25,26]

Intratumoral heterogeneity, which consists of the simultaneous presence of several types of cells within a single neoplasm, is one of the main features observed in cancer cell populations of the majority of solid and hematopoietic malignancies.[27] The different cell subpopulations are distinguished from each other by characteristics such as their morphology and surface antigen expression. Due to these variations, different responses to treatments are expected and consequently the choice of appropriate treatment is more challenging.[27]

CSCs are biomarker-defined cell populations that can be characterized and isolated from the tumor mass based on their specific cell surface biomarkers.[28] Among an entire breast tumor cell population, breast CSCs are the ones possessing the CD44+/CD24−/low phenotype, while in cervical cancer, CSCs are CD133+ cells.[28,29] These biomarkers have been associated with tumor growth and cancer cell aggregation given their involvement in cancer cell migration and matrix adhesion. The stemness properties in CSCs as well as in their healthy counterparts are believed to be maintained by the same signaling pathways, namely, the Notch, Hedgehog, and Wnt signaling pathways.[30] These pathways are involved in the regulation of vital stem cell properties such as the self-renewal, differentiation, and fate determination in embryonic and adult stem cells.[31] Considering their role at the cellular level, it is understood that their slightest perturbation could be at the origin of drastic changes in the organism.[30,32] Several signaling pathways involved in the regulation of normal functions in healthy stem cells appear to be altered in CSCs.[33]

Biphasic dose and wavelength-related cellular response to LILI treatment

LILI, also known as photobiomodulation, is a non-thermal and non-toxic phototherapy that uses coherent monochromatic low-intensity light, usually corresponding to the visible red (400–720 nm) and the near-infrared (NIR; 700–1000 nm) range of the light spectrum to induce photobiological processes at the cellular level.[34] The clinical use of LILI has so far shown no side effects in patients, making it a promising therapeutic approach in a wide range of clinical applications.[8]

In the past decades, the medical application of LILI has been focused on its non-invasive biostimulatory effect. LILI has been used in wound healing, stimulation of the immune system, swelling reduction, and acute/chronic pain relief.[35,36] Since the introduction of laser

in cancer therapy, the use of LILI has mostly been focused on the reduction of acute and chronic symptoms caused by the cancer condition itself or the cancer treatment.[37] Further attention should be turned to the possible bioinhibitory effect of LILI used alone at specific wavelengths and fluencies or in the form of photodynamic therapy (PDT) as a potential therapeutic tool for CSC eradication.[8]

The biomodulative effects of LILI vary from cellular proliferation to the programmed cell death. LILI is said to have a biphasic dose and wavelength-dependent effect.[7] Either effect can be beneficial for therapeutic purposes. The biostimulatory effect is believed to be linked to the increased ATP production, and the bioinhibitory effect has been linked to the oxidative stress due to the reactive oxygen species (ROS) overload.[38] The following are some concrete examples of research reports supporting the biphasic dose effect hypothesis of LILI in non-cancerous and cancer cells. Research results supporting the biostimulatory effect of LILI were observed in human adipose–derived stem cells (hADSCs) where a statistically significant increase in cell proliferation could be seen 48 h post-irradiation when using 5 J/cm^2 at a wavelength of 636 nm.[39] In a study on diabetic induced human skin fibroblast cells (WS1), an increase in the cellular proliferation and viability was observed when cells were treated with a wavelength of 830 nm and fluencies of 5, 10, and 15 J/cm^2, whereas no significant change could be seen when using wavelength of 680 nm and the same fluencies.[40] This confirms the wavelength dependency of cellular bio-activation due to LILI. The dose dependency was observed in neoplastic cells (EMT-6 and RIF-1) when wavelength of 632.8 nm and fluence of 180 mJ/cm^2 promoted cell growth, while fluencies ranging from 400 to 600 mJ/cm^2 induced growth inhibition.[35]

Effect of LILI on CSCs and mechanism of action

As normal cells and CSCs share similarities in their mitochondrial content, the chromophores located in the inner membrane of CSCs are expected to play a photoacceptor role as the ones found in normal cell. As previously mentioned, the photobiological effect of LILI highly depends on the cell properties and light parameters. This could be seen in a study on lung cancer that aimed to evaluate the photo stimulatory effect of low and high fluences of LILI on lung CSCs isolated from the A549 cell line which has been demonstrated to have a chemo and multidrug resistance phenotype.[3,41] One of the outcomes of this study confirmed that unlike non-cancer cells that undergo apoptosis through ROS overproduction after exposure to high dose of light, CSCs on the contrary have the capacity to self-renew after being exposed to the same laboratory condition.[41] When using low fluencies ranging from 5 to 10 J/cm^2 at 600 and 800 nm, a statistically significant increase in both viability and proliferation was observed in CSCs. Unexpectedly, the same biostimulatory effect could be observed after exposure to higher fluence of 20 J/cm^2.[41] However, a statistically significant decrease in viability and proliferation going hand to hand with an increase in apoptosis could be seen upon exposure to 40 J/cm^2.[3] The outcome of this study supports that the biostimulatory and bioinhibitory effect of LILI relies on the fluence and wavelength of light. This is in agreement with the “The Arndt-Schultz Law” which basically states that weak stimuli (referring to the irradiation time or dose of light) increase physiologic activity, medium stimuli inhibit activity, and very strong stimuli stop activity.[42]

Although the exact mechanism behind the bioinhibitory effect of high-fluence LILI is unclear, the possibility of the excessive production of harmful ROS such as singlet oxygen and hydroxyl radicals should be considered. It is proposed that prolonged exposure to laser light at a certain wavelength can prompt the mitochondria to produce excess ROS that escape the control of the antioxidant defence mechanism of CSCs.

As light-induced apoptosis requires the involvement of the mitochondrial respiratory chain, the shift in cell redox potential (increased oxidation) induced by high-fluence LILI treatment on CSCs could be a trigger for apoptosis through an oxidative stress.[7] The presence of free radical outside the mitochondria as a consequence of the oxidative stress causes the formation of BH123 aggregate facilitating the release of cytochrome c from the intermembrane to the cytoplasm, which acts as a signal for the activation of the initiator caspase (caspase 9) which in turn activates the executioner caspase (caspase 3) and eventually leads to programmed cell death (Figure 2).[43]

Effect of high-fluence LILI on the immune system

It is well known that cancer cells in general have a weakening effect on the innate and adaptive immune system of the host organism. Unlike the majority of conventional cancer therapies like chemotherapy and radiation therapy which are toxic to the bone narrow and tend to further weaken the immune system, phototherapy on the contrary has been proven to strengthen immunity through the activation of tumor-specific cytotoxic T-cells.[44,45]

While the immune stimulatory effects of PDT have been extensively studied, we cannot say the same for high-fluence LILI. As PDT and high-fluence LILI share similarities in their outcome which is the activation of apoptosis through excessive ROS production, it is suggested that LILI could have immune stimulatory effects as a consequence of the traumatic insult to the tumor mass and the microenvironment in which they live. Just like in PDT, an inflammatory reaction could raise from the above traumatic insult following high-fluence LILI treatment.[44] As a reminder, an excessive ROS production results in an irreversible damage of the disorganized blood vessel networks that make up the tumor vasculature causing a lethal drop in the nutrient and oxygen supply.[46] This shut down of the tumor angiogenic switch which is usually continuously on may constitute a great advancement in challenges encounter during tumor therapy.[47,48]

PDT

The development of drugs that would only be toxic toward a targeted biomarker-defined cancer cell population is one of the objectives pursued by scientists. PDT, which associates low-intensity light with a photosensitizer (PS), has proved its effectiveness in numerous cancer therapies and approaches in vitro and in vivo.[49] The mechanism of action behind the effectiveness of PDT is the oxidative stress overload caused by the photo-active PS which is first excited into an unstable singlet state quickly followed by its relaxation into a more stable triplet state.[8]

For the photochemical process to occur, the wavelength of the light must correspond to the absorption spectra of the PS.[8] Light absorption by tissue is directly proportional to the

increase in the wavelength from the red to the deep red region of the electromagnetic spectrum.[50] PSs with absorption peaks between 600 and 800 nm are the most efficient and provide sufficient energy to convert oxygen molecules into their excited singlet state. Shortly after being injected to the cancer location, the PS is absorbed by cancer cells and some healthy surrounding cells. Afterward, only cancer cells have retained the PS and the visible light can be applied to the cancer cells site.[37] The application of PDT in cancer treatment has only been approved for a limited number of cancer types (mostly localized cancers).[37] Currently, Porfimer is one of the most commonly used PSs in the treatment of cancers such as the non-small-cell lung cancer, cancer of the esophagus, and Barrett's esophagus with dysplasia (pre-cancer).[37] Further researches aiming the application of PDT in a wider range of cancer types including breast and cervical cancers and the production of appropriate PSs are being conducted.

PDT treatment of CSCs

Studies are being carried out to evaluate the effect of PDT on CSCs and to find appropriate photosensitizer that could be used for various types of cancer. A 5-aminolevulinic acid (5-ALA)–mediated PDT study (ALA-PDT) done on head and neck cancer–derived cancer stem cells (HNC-CSCs) using wavelengths of 635 ± 5 nm revealed a significant decrease in the aldehyde dehydrogenase 1 (ALDH1) activity, mammosphere formation, and CD44 biomarker expression in HNC-CSCs.[51] This set of results show that ALA-PDT affects the stemness of HNC-CSCs by disturbing their self-renewal capacity. In a study done on HT29 cell line from colorectal cancer, after CSC isolation based on their expression of the CD133 biomarker, the effect of PDT on both CD133+ and CD133− cells using protoporphyrin IX (PpIX) as PS and a light-emitting diode (LED) laser of 632 nm using fluencies of 2 and 5 J/cm^2 was evaluated.[49] Measurement of cell viability showed 80% of cell death in CD133− cells when using 2 J/cm^2. The same outcome was obtained in CD133+ when using 5 J/cm^2. One could conclude that although PpIX-mediated PDT has shown effectiveness in CD133+ CSCs eradication, higher fluence is required compared to CD133− cells.[49] This confirms that CSCs show more resistance than the differentiated cancer cells.[49]

Targeted photodynamic nanotherapy

The selectivity in the systemic drug delivery and the delivery of hydrophobic PSs such as porphyrin and phthalocyanine derivatives are challenging.[52] The use of nanoparticles (NPs) in the systemic delivery of PS is in constant evolution. Mostly, biodegradable polymers such as polylactide (PLA) and polyglycolide (PGA) and carbon nanotubes with strong absorption in the NIR such as the single-walled nanotubes (SWNTs) are used as nanocarriers.[52,53] The PSs are encapsulated in NPs attached to a ligand or antibody that have affinity with specific CSC surface markers.[54] The PS interaction with the NP can either be hydrophobic or electrostatic.[52] NPs are also involved in drug loading and drug release into CSCs, charge transfer, and free radical formation. This novel technique has been proven to enhance the cytotoxic effect of PDT in CSCs. A study on MCF-7 breast CSCs using methylene blue (MB) as PS investigated and compared the cytotoxic effect of MB when used alone and when encapsulated in dioctyl sulfosuccinate sodium salt NP (MB NP). CSCs self-renewal was investigated by assessing the mammosphere formation ability of CSCs after both MB

and MB NP mediated PDT. When compared to the untreated control, colony formation on soft agar gel decreased to 8% with MB used alone and 1% with MB NPs. This indicated that nanoencapsulation of the PS enhances its cytotoxic effect.[55]

Conclusion

Considering the life-threatening status of breast and cervical cancers, there is an urgent need to develop appropriate therapeutic approaches to cure these malignancies. Over the last years, overwhelming evidence has confirmed the involvement of CSCs in driving cancer in most human affecting malignancies including breast and cervical cancers. The post-therapeutic recurrence observed in malignant cancers has pushed scientists to find alternative therapies to eradicate CSCs. In the quest for effective treatments, it has been discovered that treatment with LILI alone or as PDT could be a potential therapeutic tool, given its ability to trigger apoptotic cell death. Unlike chemotherapy, PDT offers a better post-therapeutic life quality without any known side effects. LILI and PDT could be used as adjuvant therapy to chemotherapy, radiotherapy, and surgery.[32] It is worth to consider that LILI treatment might have a bioinhibitory effect on breast and cervical CSCs. Presently, the number of studies in breast and cervical cancer treatment using LILI alone or as PDT is limited; hence, there is a need to increase the number of studies on that subject.

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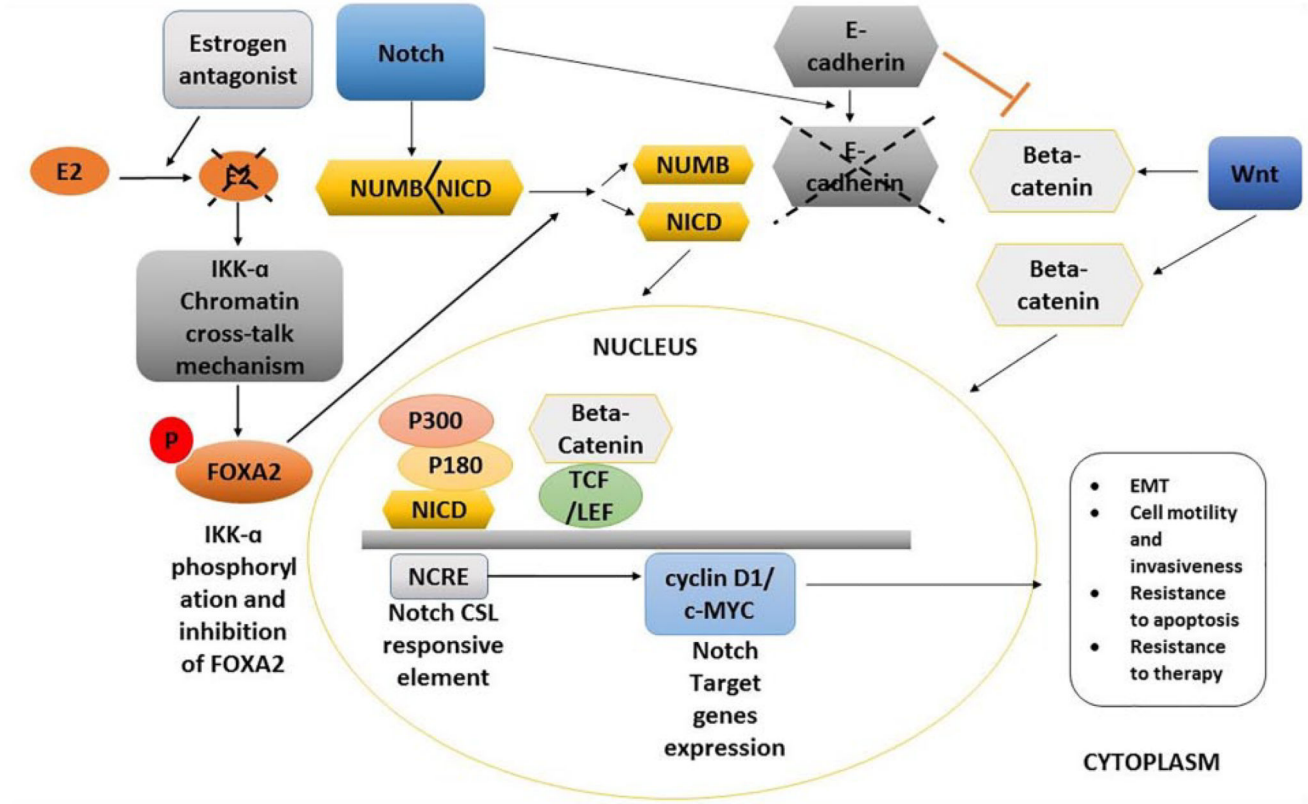

Figure 1.

Proposed mechanism of the influence of Notch and Wnt pathways in the oncogenesis and stemness maintenance of breast cancer cells in the absence of estrogen. Following the estrogen inhibition by estrogen antagonist drugs, Notch pathway activation induces the expression of estrogen-responsive genes via the IKK-α cooperative chromatin recruitment of Notch-CSL-MAML1 transcriptional complex (NTC). NTC promotes the recruitment of transcriptional co-activator proteins such as p180 and p300 on the estrogen-responsive gene promoters resulting in the expression of the downstream Notch target genes including cyclin D1 and c-MYC, both involved in tumor formation, rapid progression, aggressiveness, and poor prognosis. E-cadherin inhibition as a consequence of Notch activation induces the accumulation of free β-catenin (β-catenin) proteins in the cytoplasm followed by their entry in the nucleus facilitated by Wnt pathway. Inside the nucleus, β-catenin binds to the TCF/LEF protein and acts as a transcriptional co-activator of the Wnt target gene c-MYC whose upregulation has been associated with the acquisition of mesenchymal characteristics by epithelial cells also known as the EMT.

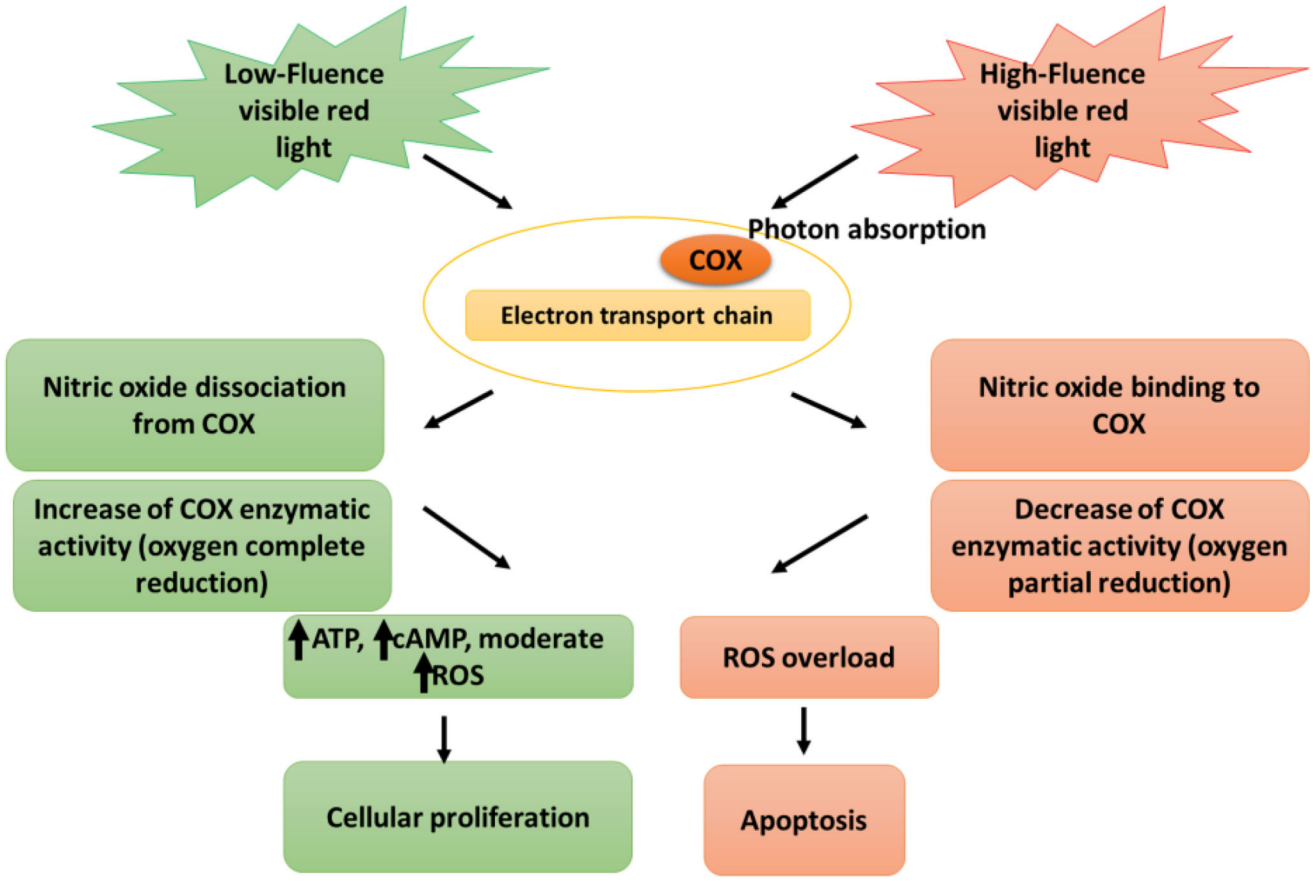

Figure 2.

Proposed mechanism of the biphasic dose effect of LILI treatment on CSCs. Light photon from laser is absorbed by the cytochrome c oxidase (COX) of the respiratory chain. The energy of photons donated by low-fluence visible red light is sufficient to dissociate nitric oxide (NO) from COX and enhance the COX reduction capacity which eventually leads to CSC proliferation through ATP, cAMP, and moderate ROS production. By contrast, the energy of photons donated by high-fluence visible red light is sufficient to decrease the COX reduction capacity leading to the massive conversion of dioxygen into ROS which prompts the programmed cell death. High level of ROS within the inner membrane of the mitochondria serves as signal for the opening of the mitochondrial permeability which triggers caspase-3 activation leading to the release of COX in the outer membrane which in turn serves as signal for the activation of pro-apoptotic enzymes.

Table 1

Comparison of breast and cervical cancer statistical analysis.

	Breast cancer	Cervical cancer
Incidence	1,700,000	527,600
Incidence rate (%)	12	7.9
Incidence rate in female (%)	25	7.9
Rank	2	7
Mortality	521,900	265,700
Mortality rate (%)	6.4	3.2
Mortality rate in female (%)	14.7	7.5
5-year prevalence rate (%)	19.2	4.8
5-year prevalence rate in female (%)	36.3	9
Estimated incidence in 2016 in the US	246,660	12,990
Estimated incidence rate in 2016 in the US (%)	14.6	0.8
Estimated mortality in 2016 in the US	40,450	4120
Estimated mortality rate in 2016 in the US (%)	6.8	0.7