

Laser Technology in Medicine: Types, Mechanisms, and Applications With a Focus on Stem Cell Biology and Regenerative Medicine

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Abstract

Laser technology has profoundly restructured the biomedical field by providing selective, minimally invasive therapeutic interventions. Lasers with quantum electronics principles can generate coherent, monochromatic light with the potential to influence microorganisms. Recent data have confirmed the putative stimulatory and inhibitory role of laser irradiation on the regulation of different stem cell bioactivities and obtaining regenerative outcomes. The

potential effect of laser irradiation on stem cell differentiation capacity, paracrine activity, proliferation, dynamic growth, etc., has been proven using several *in vitro*, pre-clinical, and clinical studies. Therefore, laser technology can be used as a complementary and alternative approach in the control of cell therapy efficiency. Here, in this chapter, we aimed to illuminate laser applications through stem cell and regenerative biology. Remarkably, the advent of LLLT¹ as a non-thermal light-based technique with positive effects on different cell activities will be discussed. Data from the current chapter can help us in the translation of laser technology to the clinical setting with cutting-edge advances to improve stem cell-based therapy outcomes.

Keywords: Low-level Laser Irradiation, Stem Cells, Cell Therapy, Regenerative Medicine.

1. Introduction

Laser beams are emitted by photons via optical amplification based on the stimulated emission of electromagnetic radiation [1, 2]. Parameters like monochromaticity, coherence, and collimation are integral to laser irradiation [2]. Of note, an energy source excites electrons within a lasing medium and emits photons, stimulating the emission of more photons of identical phases and energy [3]. Hence, this phenomenon creates a focused, amplified beam of light capable of precise interaction with biological tissues. It is thought that absorption, reflection, scattering, and transmission are involved in laser-tissue interactions [4-6]. During the past decades, various laser types, including CO₂, argon, and Nd: YAG² lasers, have been fabricated for different therapeutic purposes (**Table 1**) [7-10]. Considering the unique features, such as fewer toxic effects, precision,

¹. Low-level laser therapy

². Neodymium-doped yttrium aluminum garnet

and biological effects on unicellular and multicellular creatures, the application of lasers has been extended in biomedicine [11-13]. These effects are generated via the physical properties of the lasing medium and the emission of photons with certain wavelengths, with the potential to penetrate deep layers inside the cells and interact directly with the signaling biomolecules or subcellular compartments [14, 15]. Therefore, the classification of lasers in biomedicine is done based on the active lasing medium and emission wavelength [4, 15-17]. For instance, a CO₂ laser produces an infrared radiation beam at a wavelength of 10600 nm, which can be absorbed by water in biological systems [18, 19]. This laser type can be used for the destruction and removal of soft tissues with high accuracy and less damage to the neighboring tissues. Therefore, it can be applied to the regulation of scar tissue and cutaneous tissue rejuvenation, alleviation of various vocal cord and pulmonary system pathologies, and removal of masses from the reproductive system with the necessity for LEEP¹. In dentistry, laser application is common in gingivectomy and periodontal interventions [20-22]. The CO₂ laser can incise the tissues and simultaneously stimulate the coagulation for the inhibition of intraoperative bleeding [20, 23]. In contrast, Er: YAG² laser functions at 2940 nm and primarily targets aqueous phases in the biological systems [24-28]. Compared to the CO₂ laser, the Er: YAG laser exhibits less thermal diffusion with less collateral damage [4, 29-33]. These features can contribute to fidelity and rapid post-operative healing [34, 35]. The Nd: YAG laser emitting at 1064 nm can penetrate deep tissues [36]. Due to the stimulation of coagulation and photo-thermolysis, this laser type is applicable for the inhibition of tumor cell growth and treatment of

¹. Loop electrosurgical excision procedure

². Erbium-doped yttrium aluminum garnet

cardiovascular disease [37, 38]. However, uncontrolled thermal stress can damage the surrounding tissues [39].

Diode lasers made of semiconductors emitting at ranges between 630–980 nm are used in surgical processes and therapeutic purposes [39-41]. In recent years, several studies related to LLLT and/or PBM¹ have led to profound insights into the regulation of cells and tissue for regenerative purposes. For instance, the potency of LLLT in the control and modulation of mitochondrial function can alter the metabolic profile and dynamic growth of the irradiated cells [42-47]. It was suggested that LLLT can be applied to control the regenerative properties of stem cells via the oxidative phosphorylation capacity and control of mitochondria in the injured recipient cells [47]. It has been proposed that the restoration of mitochondrial function or replacement of dysfunctional mitochondria with healthy counterparts can help the cells resist bioenergetic stress [48, 49]. The application of these laser types has been extended to dental soft tissue surgery, wound healing, and pain treatment [50-52]. The direct application of a diode laser inside the vascular system makes it possible to alleviate several pathologies, such as varicose veins, etc. [53].

Gas-based argon laser emitting at the range of 488–514 nm with blue to green spectra is efficiently absorbed by natural pigments such as hemoglobin and melanin [54, 55]. This laser type has been applied to the treatment of several cutaneous tissue injuries, anomalies, diabetic retinopathies, and macro- and micro-vasculopathies [56, 57]. The existence of parallel light scattering patterns and precise sensitivity improves its application in the clinical system [58, 59]. Along with these lasers, excimer lasers emitting UV at 193–308 nm can damage the biomolecules and intermolecular bonds. Excimer lasers remove the

¹. Photobiomodulation

tissues by different mechanisms, such as photothermal, photomechanical, and photochemical properties [60]. In ophthalmology, excimer lasers are used for LASIK¹ and PRK², and treatment of chronic cutaneous tissue conditions such as psoriasis and vitiligo [61-63]. In line with these comments, excimer lasers are beneficial in cellular layer removal with submicron precision, with less invasion [61, 64].

Femtosecond lasers emitting NIR³ regions with short duration (about 10⁻¹⁵ seconds) help us in non-thermal ablation and ultrafine tissue dissection with minimal collateral injuries [65, 66]. Due to these properties, femtosecond lasers are suitable for LASIK flap creation, cataract modification, and neurosurgery [67, 68]. This laser type is eligible to exert subcellular changes with the potential to be used in molecular surgery [69-72]. A He-Ne⁴ laser emitting red light at 632.8 nm has been used extensively in LLLT [73, 74]. This laser has the potency to stimulate ATP production and induce the transcription of several genes related to oxidative phosphorylation, dynamic growth, and differentiation potential [41, 50, 75]. The low energy output increases this laser's safety with prominent effects at cellular levels without collateral tissue injury [76-79].

Thulium lasers with emitting wavelengths of 1940 nm are cutting-edge laser technology and can be suitably absorbed by the aqueous phase [80-82]. These features make the thallium laser appropriate for soft tissue manipulation and the treatment of conditions such as strains and sprains [83, 84]. Ho: YAG⁵ laser operating at 2100 nm is also absorbed by water, but is distinguished by its pulsed emission mode. Therefore, this laser type

¹. Laser-assisted in situ keratomileusis

². Photorefractive keratectomy

³. Near-infrared

⁴. Helium-Neon

⁵. Holmium-doped yttrium aluminum garnet

is suitable for lithotripsy and elimination of soft masses, especially in the urinary system [85]. Besides, some surgeons tend to use this laser in other tissues such as the gastrointestinal tract and spine for cutting, ablating, and clotting purposes [86, 87]. In fiber laser technology, rare-earth-doped optical fibers such as ytterbium are used to produce laser beams transmitted through flexible fiber-optic cables [88-90]. This technology enables efficient energy transmission using laser beams for accurate surgical purposes and soft tissue manipulations [90-93].

Along with these descriptions, the application of laser technologies has been extended to stem cell biology and regenerative medicine [94]. Data have confirmed that LLLT using diodes and He-Ne lasers is eligible to stimulate the dynamic growth of stem cells and bioactivities *in vitro* and *in vivo* via engaging several intracellular chromophores (**Figure 1**) [74, 95, 96].

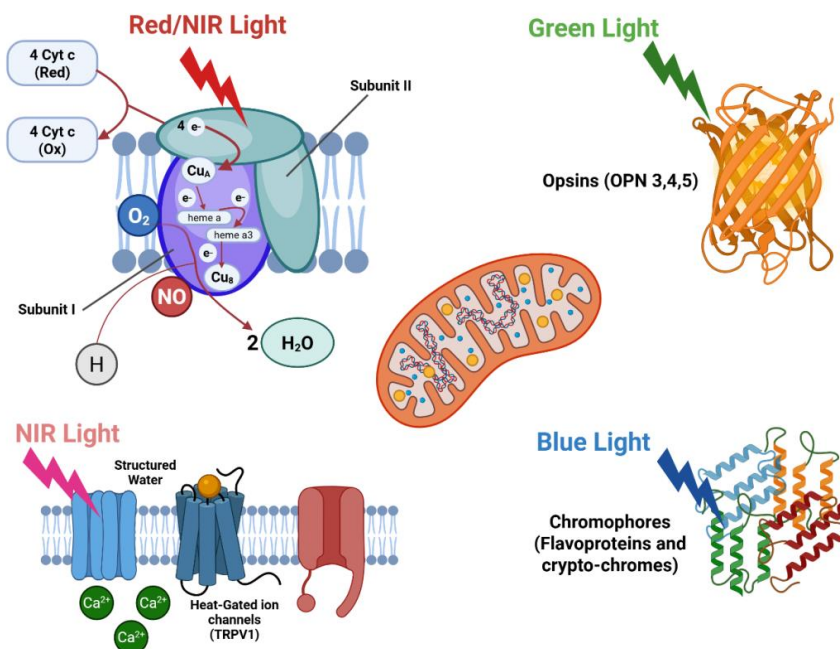


Figure 1. Mitochondrial Cytochrome c oxidase in the respiratory chain can absorb light at red and/or NIR wavelengths via heme and copper elements. NIR and blue wavelengths activate heat-gated TRP¹ ion channels by absorbing via structured water. Opsins mostly absorb blue and green wavelengths via cis-retinal. Blue wavelength via pterin is the most efficacious agent for the absorption of flavoproteins and cryptochromes. Created by Online BioRender software. 2025.

¹. Transient receptor potential channel

Table 2. Laser types and their medical applications

Laser Type	Wavelength (nm)	Active Medium	Primary Mechanism of Action	Medical Applications	Advantages
CO₂ Laser	10600	Gas (Carbon Dioxide)	Ablation, vaporization	Dermatology (scar revision, warts), ENT (vocal cord surgery), gynecology (LEEP), dentistry	High water absorption; precise tissue cutting
Er: YAG Laser	2940	Solid (Er: YAG crystal)	Ablation, minimal thermal damage	Dentistry, dermatology (resurfacing), orthopedics	Very high-water absorption; minimal collateral damage
Nd: YAG Laser	1064	Solid (Nd: YAG crystal)	Deep coagulation, photo-thermolysis	Oncology (tumor ablation), vascular lesions, urology (prostate surgery), ophthalmology	Deep tissue penetration; strong coagulative capacity
Diode Laser	630–980	Semiconductor	Photobiomodulation, coagulation	LLLT (wound healing, pain relief), dental surgery, varicose vein treatment	Portable, cost-effective, ideal for therapeutic use
Argon Laser	488–514	Gas (Argon)	Photocoagulation	Ophthalmology (retinal photocoagulation), dermatology (vascular lesions)	Specific for oxyhemoglobin; minimal scatter
Excimer Laser	193, 248, 308	Gas (XeCl)	Photoablation (UV range)	Ophthalmology (LASIK, PRK), dermatology (psoriasis, vitiligo)	The ultraviolet laser breaks molecular bonds precisely
Femtosecond Laser	~1030 (IR)	Solid (Yb-based)	Non-thermal ablation (optical breakdown)	LASIK flap creation, neurosurgery, nanosurgery	Ultra-short pulses; minimal thermal damage
Helium-Neon (He-Ne)	632.8	Gas (He and Ne mixture)	Photobiomodulation	Research, LLLT, ophthalmic diagnostics	Low energy; ideal for cellular stimulation
Thulium Laser	1940	Solid (Thulium-doped fiber)	Ablation, coagulation	Urology (BPH surgery), ENT	High absorption in water; adequate tissue resection
Holmium: YAG Laser	2100	Solid (Holmium-doped crystal)	Pulsed ablation	Urology (stone fragmentation), orthopedics, spinal surgery	Precise cutting; safe in wet environments
Fiber Laser	980–2000+	Optical Fiber Doped	Tunable, photothermal, PBM	Surgical cutting, tissue welding, and photothermal therapy	Flexible delivery; high beam quality

2. Laser-stem cell interaction and regenerative potential

Lasers such as LLLT have been extensively used because of their biological effects (**Table 2**) [97]. LLLT-exposed stem cells are prone to accelerate tissue healing via proliferation, differentiation, and migration capacities [98, 99]. At the cellular level, the laser-stem cell interaction is done via the absorption of laser beams (especially red or NIR wavelengths) by subcellular components that contribute to the activation of stem cells [100]. For instance, the entry of red laser beams can stimulate mitochondrial function and biogenesis [101, 102]. To be specific, the activation of the electron transport chain cytochrome c oxidase increases the function of mitochondria [44, 50]. In line with these statements, the local intensity of ATP¹ increases, which can help to proceed with several cellular functions [103]. Additionally, PBM² also facilitates the generation of ROS³. Excessive amounts of ROS can sensitize their host cells to oxidative stress and thereby cause injuries. However, normal levels of ROS can activate specific signaling pathways and metabolic activity [104, 105]. Of note, the regulation of specific effectors such as MAPK⁴ and PI3K⁵/Akt by laser irradiation can influence the gene expression and activity of several factors inside the stem cells. Some of these factors are directly or indirectly involved in the promotion of regeneration [50, 106]. It was suggested that LLLT-related ROS can promote stem cell maturation and differentiation into the different cell lineages [107]. Along with the increase of ROS, other factors such as HSPs⁶ are also activated, and these factors can increase the cell resistance against various insulting conditions [108]. Some studies have indicated that HSPs such as

¹. Adenosine triphosphate

². Photobiomodulation

³. Reactive oxygen species

⁴. Mitogen-activated protein kinase

⁵. Phosphoinositide 3-kinase/Akt

⁶. Heat shock proteins

HSP27 are involved in the maturation of NPCs¹ into the mature NeuN⁺ neuron [109]. LLLT has the potential to influence the angiocrine profile of stem cells by the release of VEGF², FGF³, TGF- β ⁴, etc., leading to the increase of local microvascular density and cell migration into remote sites (**Figure 2**) [75, 110, 111].

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1. Neural progenitor cells
 2. Vascular endothelial growth factor
 3. Fibroblast growth factor
 4. Transforming growth factor beta

Table 2. LLLT effects on stem cell types: parameters, mechanisms, and clinical potentials

Stem cell type	Wavelength range (nm)	Energy density (J/cm ²)	Mechanistic effects	Functional outcomes	Potential clinical applications
MSCs	630–850	0.5–5.0	ATP production via cytochrome c oxidase stimulation; reduction of oxidative stress; ERK/MAPK pathway activation	Proliferation, migration, and differentiation into osteoblasts, chondrocytes, and adipocytes	Bone/cartilage regeneration, spinal fusion, osteoarthritis treatment
NSCs	780–810	1.0–4.0	BDNF↑; ↑ mitochondrial biogenesis, Notch1/Hes1 signaling, and reduction of inflammation	Neuronal differentiation, neurogenesis; Neuronal survival	Traumatic brain injury recovery, spinal cord injury, AD, and PD therapies
HSCs	660–810	0.5–2.0	Expression of GATA-2, Nitric oxide modulation; ROS production within the physiological range	Engraftment efficiency, increase of colony-forming units, and cell survival in hypoxic conditions	Bone marrow transplantation, recovery from chemotherapy, and immune modulation
ADSCs	630–850	1.0–5.0	VEGF, HIF-1 α expression; activation of SDF-1/CXCR4 axis; increase of mitochondrial membrane potential, and reduction of apoptosis	Angiogenic potential, Endothelial and myogenic differentiation; Tissue repair capabilities	Wound healing, ischemic limb repair, facial aesthetics, soft tissue regeneration
iPSCs	780–830	0.5–3.0	Mitochondrial metabolism, stemness features (OCT4, SOX2), and telomerase activity	↑ Directed differentiation (preliminary); improved reprogramming efficiency (early studies)	Organ-on-chip systems, disease modeling, and autologous regenerative therapies
DPSCs	660–810	1.0–4.0	BMP-2, Runx2 expression, mineralization capacity, Neurite outgrowth; NGF release	↑ Odontogenic and neurogenic differentiation; ↑ Matrix deposition	Dental pulp regeneration, peripheral nerve repair, and craniofacial tissue engineering
EpSCs	635–670	1.0–3.0	KGF production, activation of Wnt/ β -catenin signaling; angiogenesis (ANGPT1, VEGF-A)	Proliferation, Epidermal repair, Epithelial barrier formation	Burn treatment, chronic ulcer healing, epidermal thinning disorders

Abbreviations: Adipose-Derived Stem Cells: ADSCs; Angiotensin-converting enzyme 1: ACE1; Brain-derived neurotrophic factor: BDNF; Dental Pulp Stem Cells: DPSCs; Epidermal Stem Cells: EpSCs; Hematopoietic Stem Cells: HSCs; Induced pluripotent stem cells: iPSCs; Keratinocyte growth factor: KGF; Mesenchymal Stem Cells: MSCs; Nerve growth factor: NGF; Neural Stem Cells: NSCs

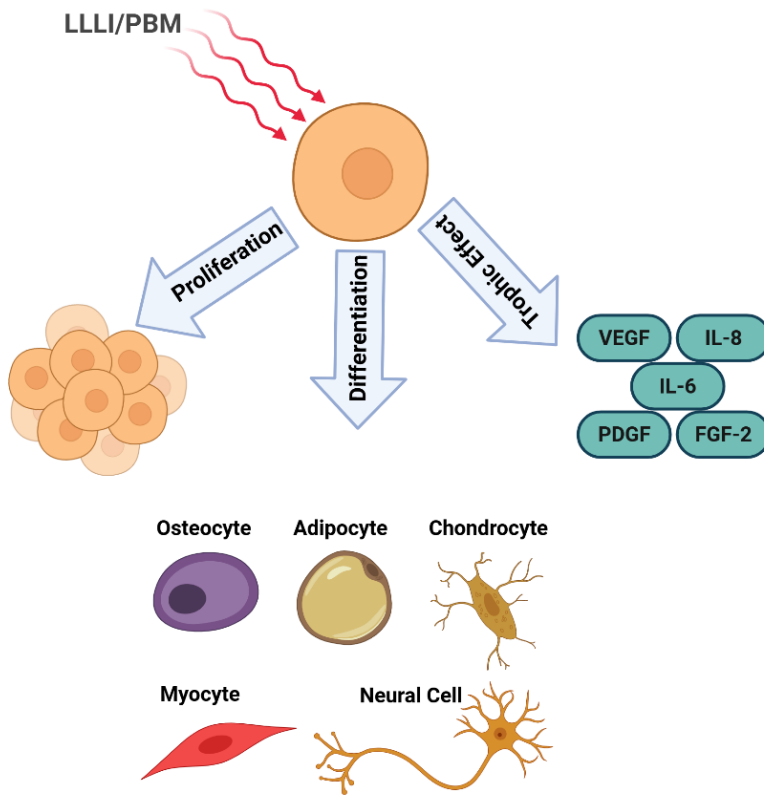


Figure 2. The potential impact of PBM¹ on stem cells. Created by Online BioRender software. 2025

By the regulation of LLLT intensity and irradiation time, it is possible to control the stemness feature of stem cells. For instance, it was suggested that LLLT can control the expression of Oct-4, Sox-2, and Nanog, which are involved in the maintenance of stemness features and self-renewal [112, 113]. These factors belong to regulatory networks with the potential to preserve stem cell phenotypes and undifferentiated status in iPSCs² and

¹. Photobiomodulation

². Induced pluripotent stem cells

ESCs¹ [114]. Thus, the regulation of gene expression enables us to control the stem cell bioactivity and behavior after transplantation into the target sites [115, 116]. The release of the abovementioned cytokines along with PDGF² is also important in the remodeling of ECM³ [117, 118]. The production and release of such growth factors in LLLT-treated stem cells can contribute to the stimulation of angiogenesis and *de novo* blood formation, resulting in the synthesis and production of collagen and other ECM components [119, 120]. These features are critical in the healing and regeneration of ischemic/hypoxic tissues. Of note, laser irradiation cannot only improve stem cell bioactivity but also increase the homing and recruitment of these cells in the target tissues. Numerous studies have shown that LLLT treatment dramatically increases CPCs⁴ and MSC⁵ recruitment, promoting tissue regeneration and functional recovery [114, 121]. Despite these advantages, it is thought that the right therapeutic effects of LLLT in human and animal medicine are closely related to the standardization of PBM parameters like wavelength, intensity, duration, and pulse mode [41]. Among various laser types, red and NIR wavelengths ranging from 600 to 1000 nm seem effective in biological systems because of penetration properties and further interaction with subcellular components such as mitochondria (**Figure 3**) [122-124]. Taken together, laser-tissue interaction is thought to be a relatively non-invasive modality in the alleviation and therapy of several pathological conditions [125, 126].

¹. Embryonic stem cells

². Platelet-derived growth factor

³. Extracellular matrix

⁴. Cardiac progenitor cells

⁵. Mesenchymal stem cell

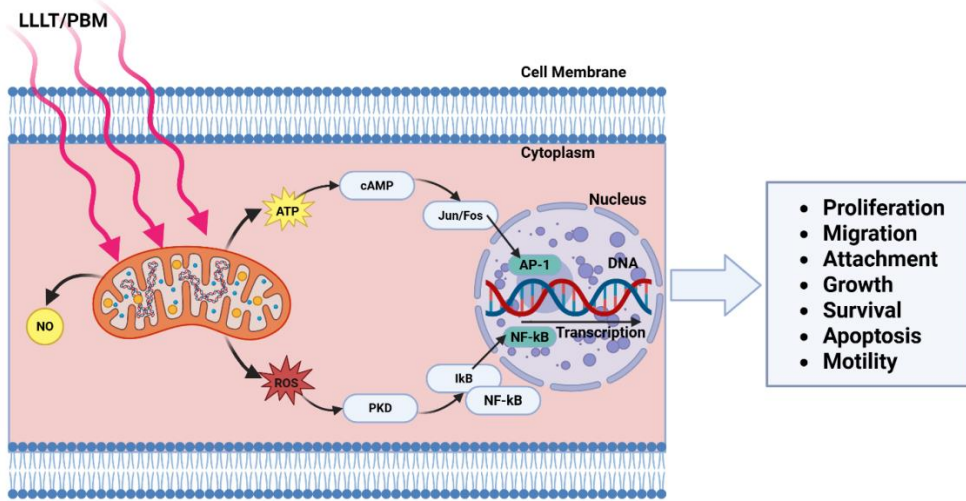


Figure 3. The LLLT-induced cellular signaling pathways are shown schematically. Chromophores in mitochondria absorb light, which increases respiration and ATP synthesis as well as the creation of signaling chemicals, including NO and ROS. Created by Online BioRender software. 2025

3. Clinical applications of laser technology in stem cell-based regenerative medicine

Recent data have confirmed the eligibility of LLLT for enhancing stem cell function and bioactivity in the target sites [112, 127-129]. Here, we focused on the recent works related to laser technology in stem cell-based treatments. As mentioned above, LLLT can boost the dynamic growth and function of MSCs and iPSCs [128, 130]. This strategy has been applied in the induction of osteogenesis, articular and joint regeneration, and wound healing via the control of stem cell bioactivity [128, 131]. Such effects can also be documented in other cell types, like stem cells. For example, LLLT promotes the healing process by regulating the proliferation of various cell types such as fibroblasts, keratinocytes, ECs¹, and lymphocytes [132]. Based on research conducted by our group, LLLT can modulate different signaling

¹. Endothelial cells

pathways inside the ECs, leading to the regulation of cell paracrine activity via the release of Exos¹ [133]. These data indicated that the LLLT can influence both cell growth and secretome production (**Figure 4**) [110]. It has been found that such mechanisms exist in stem cells as well [110]. Based on the frequency and irradiation time, laser treatment has helped increase the osteoarticular and adipogenesis capacity of MSCs [134]. Via the activation/inhibition of certain signaling pathways, LLLT can exert its therapeutic effects. For instance, LLLT helps NSCs² make new neurons and protect existing neurons via the regulation of the Notch signaling system [135]. To be specific, the appropriate irradiation protocol has benefits to treat several neurological illnesses like PD³ and AD⁴ [102, 136-138]. LLLT treatment can increase the migration of endogenous and exogenous stem cells toward the injured sites in a cytokine gradient manner [16]. Besides, laser irradiation is thought of as an innovative modality to promote neurogenesis via increasing neural plasticity and reducing oxidative stress inside the brain parenchyma [139-141]. The local increase of chemotactic factors post-LLLT, i.e., VEGF, SDF-1 α ⁵, and other factors, can orchestrate the homing of stem cells [142]. VEGF can stimulate the formation of blood vessels while SDF-1 α recruits several cell types, which are important for the angiogenesis and healing of injured tissues [143-145]. In MI⁶ patients exposed to LLLT, the rate of recruited stem cells in the infarcted myocardium was stimulated. Likewise, laser irradiation can speed up the homing of stem cells in individuals with bone tissue fractures [146, 147]. It has been thought that MSC-to-osteoblast differentiation is stimulated in the presence of LLLT [148]. Several pre-clinical

1. Exosomes

2. Neural stem cells

3. Parkinson's disease

4. Alzheimer's disease

5. Stromal cell-derived fact

6. Myocardial infarction

and clinical studies have proved the induction of osteogenesis and bone mineral deposition after the LLLT [149]. In addition to osteogenesis properties, LLLT can also improve chondrocyte differentiation of MSCs in patients suffering from osteoarthritis and joint injuries [150]. LLLT can lower scar formation in MI patients by improving CPC differentiation into mature and functional cardiomyocytes, leading to restoration of myocardium function [151-153].

Despite the advantages related to the application of lasers in human regenerative medicine, the lack of standard laser irradiation protocols is the main problematic issue. Therefore, it is suggested to use calibrated therapeutic irradiation regimes with precise power intensity, frequency, etc. Although some early and preclinical studies have shown promising results, more randomized controlled studies must be conducted to prove these results and look into the possible adverse effects of long-term LLLT radiation.

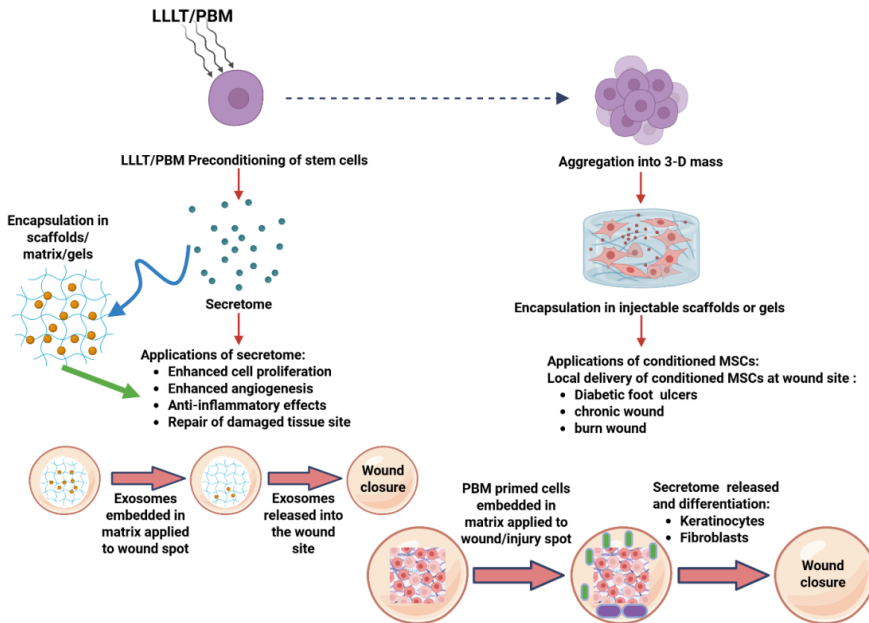


Figure 4. Potential pathways of LLLI/PBM-stimulated stem cells' secretome production. Created by Online BioRender software. 2025.

4. Conclusions

Using certain types of LLLT, it is possible that the intracellular signaling pathways of stem cells can be modulated, which accelerates their regenerative potential following several pathologies. Due to the existence of intricate molecular mechanisms inside the stem cells and involvement of diverse effectors, several studies should be done to find the beneficial impact of LLLT on stem cell regulation and differentiation into the target cell lineages. By developing sophisticated PBM systems, human medicine will witness splendid progress in laser-based therapies.

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