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Review

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Low-Intensity Visible and Near-Infrared Light-Induced Cell Signaling Pathways in the Skin: A Comprehensive Review

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Abstract

Objective: To describe current knowledge regarding established and putative cell signaling pathways involved in skin photobiomodulation.
Background: The skin is the largest and most accessible organ of the body. It is the first line of defense against the external environment, including solar radiation. Among solar rays, visible and infrared non-ionizing photons may reach human skin and trigger a cascade of non-thermal cell signaling pathways called photobiomodulation (PBM). The use of PBM using artificial light sources has been known for more than 50 years, but it has not yet been widely accepted due to uncertainty about the cellular mechanisms of action. However, much knowledge has been gained in this field in recent years, which will be summarized in this review.
Methods: An extensive literature review was performed using Medline, Embase, and Google Scholar as research databases to acquire relevant publications in this particular field.
Results: A comprehensive description of chromophores, primary and secondary effectors is provided in addition to a visual representation of known and putative cell signaling mechanisms involved in such complex light-skin interactions. Also, a summary of clinical indications of skin PBM, key light parameters, and promising skin applications (local and systemic) are mentioned.
Conclusions: In PBM, skin cells are the first to absorb photons, triggering specific cell-signaling pathways through primary and secondary effectors, leading to enhanced cell repair and survival, notably in hypoxic or stressed cells. A better understanding of the mechanisms of action will help us optimize known indications and discover new ones.

Keywords: photobiomodulation, low-level light therapy, phototherapy, light, skin, cytochrome C oxidase, mitochondria, ion channels, opsins, light therapy

Introduction

As for plants, the skin can absorb solar rays beyond ultraviolet radiation (UVR). Our ancestors knew that the sun could be harnessed to promote health. Romans, Greeks, Egyptians, and Babylonians all recognized that the sun had powerful curative properties. Around 400 B.C., Hippocrates promoted sunbathing and constructed a large solarium at his treatment center on the Greek island of Cos.[1] Today, we are still learning from the sun's ability to improve people's lives, notably at low intensity harmless visible and near-infrared (NIR) light wavelengths reaching the skin. Biomimicry can

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provide some clues by observing daily fluctuations in intensity and solar emission spectra.

Indeed, beneficial visible and infrared (IR) wavelengths are more prominent in the morning and late afternoon, conferring cutaneous preconditioning against harmful zenithal UVR at noon and skin repair, later in the day.[2] As a result of technological innovations like lasers and light-emitting diodes (LEDs), we can now imitate part of the solar emission spectra for therapeutic purposes. The use of low-intensity light in the visible and NIR spectra to treat humans and animals is called photobiomodulation (PBM).

Photosynthesis Versus PBM

Plant cells absorb visible light (i.e., 380–740 nm) through their chloroplasts to synthesize adenosine triphosphate (ATP), and ultimately carbohydrates,[3] a process called photosynthesis. Like plants, human cells also absorb the energy of light, and it is not only limited to UV. Recent studies have demonstrated the modulation of several cell signaling pathways following cell-absorption of visible and NIR.[4,5] Subsequently, this light-dependent modulation generally abrogates cellular imbalances caused by some physiological states, such as inflammation or hypoxia.

The skin is the largest organ of the body (with a surface of $2\,m^2$) and the first interface of living cells that is capable of absorbing light (photons) like the leaves of a tree. By natural ways, morning or late-afternoon sun rays provide these visible and IR wavelengths in higher proportion to the human body, especially skin cells.[2,6] Artificially, using low-intensity light via lasers or LEDs, this spectrum can be reproduced with more specificity and flexibility.

Light-tissue interactions are defined according to light intensity and exposure time (Fig. 1). Unlike destructive (thermal) light-based devices such as ablative lasers in photomedicine, low-intensity light therapy uses non-thermal photons. For a long time, it has been referred to as low-level laser therapy (LLLT), although it is now named PBM.[7] The term ''PBM'' is more descriptive since it implies using visible and NIR light (Fig. 2) to modulate a cellular response, thus helping cells to self-correct if necessary.

Many studies show its capacity to accelerate the healing process in acute healing disorders, like diabetic wounds.[8–12] Also, PBM can modulate acute and chronic inflammatory disorders by stabilizing cytokine signaling.[13–17] As a result, there are now many medical specialties using PBM, including dermatology, surgery, rheumatology, neurology, psychiatry, and ophthalmology (and the list is expanding).

Despite more than 50 years of research, thousands of peer-reviewed articles, and widespread use, PBM is still not mainstream medical therapy. One of the main reasons is the uncertainty about the mechanisms of action at the molecular and cellular levels.[18] This review intends to improve our understanding of the cell signaling pathways involved in the course of low-intensity light exposure, notably in the skin.

Several photon acceptors (i.e., chromophores) absorbing visible and NIR light have been identified in PBM. Well-documented chromophores and other PBM-related molecules will be discussed from a historical perspective, followed by a detailed review of the known effector molecules involved in putative cell signaling pathways.

Established Chromophores of PBM

Regardless of well-known skin chromophores like melanin, hemoglobin, and water targeted by high-energy light sources to achieve selective photothermolysis, low-intensity PBM aims at more discrete chromophores.[19]

Cytochrome C oxidase

Red and NIR light absorption largely centers around cytochrome C oxidase (CCO) as the primary chromophore in PBM, mainly unit IX of the electron transport chain located in the inner mitochondrial membrane. CCO is responsible for the final reduction of oxygen (O_2) to water using essential redox cofactors formerly generated through glycolysis and the tricarboxylic acid cycle.[20] CCO transmembrane enzyme activity may be inhibited by nitric oxide (NO), especially in hypoxic or damaged cells.

This inhibitory NO can be dissociated by photons of light (i.e., photodissociation) absorbed by CCO, containing two

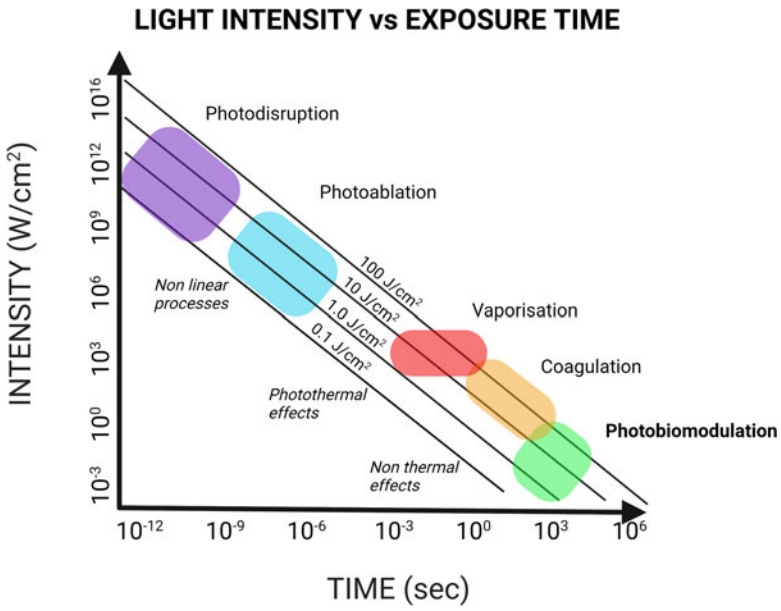

FIG. 1. Light-based device intensity versus exposure time and ensuing effects on tissues. This figure was designed on *Biorender*.

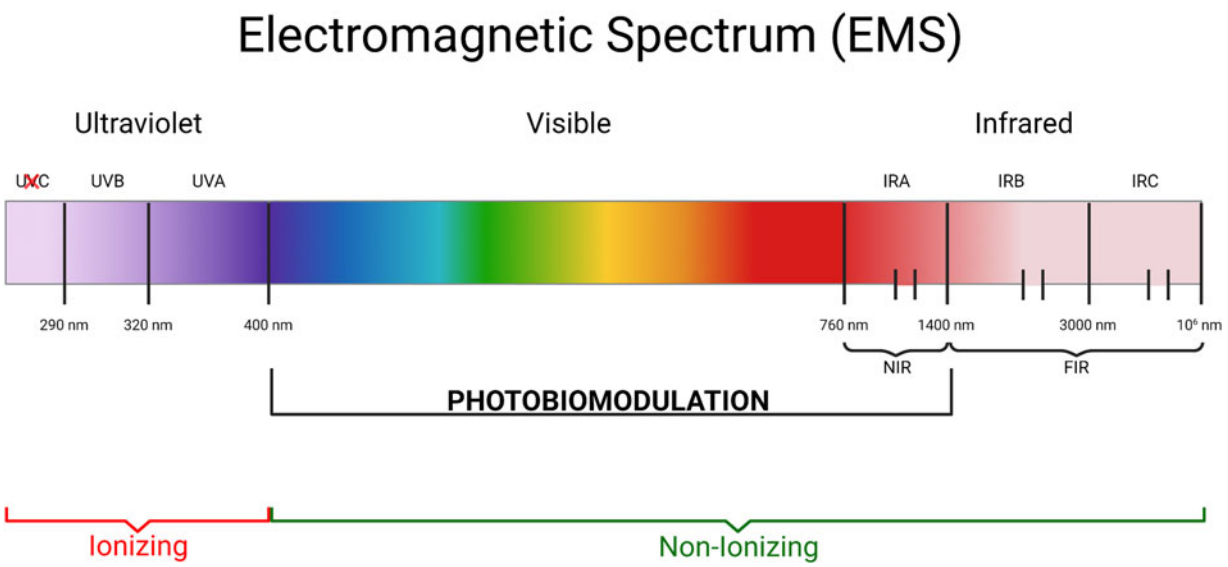

FIG. 2. As for the sun, PBM uses visible and NIR light to modulate a cellular response. It is worth mentioning that UVC is blocked by the ozone layer. FIR, far infrared; IRA, infrared A; IRB, infrared B; IRC, infrared C; NIR, near-infrared; PBM, photobiomodulation; UVA, ultraviolet A; UVB, ultraviolet B; UVC, ultraviolet C. This figure was created on *Biorender*.

heme (i.e., cytochrome a and cytochrome a3) and two copper centers (i.e., CuA and CuB) with different absorption spectra.[21] These absorption peaks are mainly in the red (600–700 nm) and NIR (760–940 nm) spectral bands for oxidized CCO. When NO is dissociated from the CCOs binuclear center (i.e., Cyt.a3 and CuB together), the inner mitochondrial membrane potential rises, more oxygen is consumed, more glucose is metabolized, and more ATP is produced through ATP synthase enzymes in the mitochondria.

Further, CCOs binuclear center is known to absorb photons at 655 nm,[22] which often results in the upregulation of oxygen reduction, increasing the proton gradient that will eventually increase ATP synthesis. Hypothetically, when an NO molecule clogs up CCO in hypoxic or impaired cells, red light absorption may explain, in part, the photodissociation of the NO molecule from the CCOs binuclear center, releasing NO within cells. NIR irradiation appears to re-oxidize the newly reduced CuA, by cytochrome C, thereby recycling electrons anaerobically. Figure 3 summarizes the release of three known mitochondrial light-induced primary effectors.

Nevertheless, Quirk and Whelan have established that NIR has no significant effect on isolated CCO protein.[23] Further, Lima et al. reported two different cell lines lacking CCO that responded to 660 nm exposure with increased proliferation, ATP and citrate activity levels. They conclude that CCO is not solely required for its cell proliferating effects in PBM.[24] Therefore, PBM implies a more complex interaction between light and the living cell, other than just mitochondrial CCOs absorption alone.[18]

Opsins

Opsins (OPNs) have been recently described as meaningful chromophores in PBM. The eyes, as well as brain and skin, are important organs for sensing light via light-sensitive opsin receptors. Although visual phototransduction is well studied, less is known about how the skin ''sees'' light through opsins.

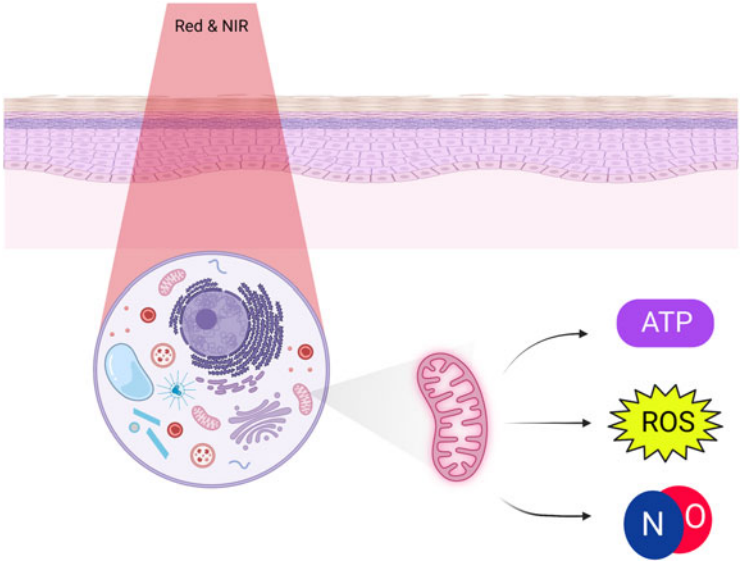

FIG. 3. Primary effectors released by mitochondrial CCO following red/NIR low-intensity light exposure. Note that in PBM, the release of ROS bursts is beneficial. ATP, adenosine triphosphate; CCO, cytochrome C oxidase; NIR, near-infrared; ROS, reactive oxygen species. This figure was sketched on *Biorender*.

Essentially, they are mostly absorbing photons in the blue/green spectrum and are made of receptors formed of seven transmembrane domains. In humans, the eye's main photoreceptors are visual OPNs, such as OPN1 and OPN2.

OPN1 is subdivided into three forms following their absorption spectra, such as OPN1-short wavelength (SW), OPN1-medium wavelength, and OPN1-long wavelength.[25] OPN1s are found in cones located in the fovea, and OPN2 (i.e., Rhodopsin) is found primarily in rods. In the human eye, OPN2 absorbs mostly cyan light (505 nm). These OPN receptors are also expressed in other organs, such as the skin. Recent studies have shown that OPN1-SW in the skin is activated by UVA-violet light in humans.

Humans also express non-visual OPNs, like OPN3 (i.e., Encephalopsin and panopsin), and OPN5 (i.e., Neuropsin) with absorption peaks that cover the UVA and blue/green spectra. For instance, OPN5 exhibits a peak at 380 nm.[26–28] Ozdeslik et al. have shown that OPN3 expressed in melanocytes absorbs light in the UVA spectrum mostly. Using spectrophotometric analysis and monitoring calcium influx, they observed an absorption peak at 360 nm.[29]

The OPNs are G protein-coupled receptors (GPCRs) that bind a chromophore (i.e., a ligand that changes in conformation following light absorption). Combined, they form a heterodimer named according to the opsin and its attached chromophore, such as rhodopsins (OPN2 and Retinal), melanopsins (i.e., OPN4 and Retinal), etc. In humans, the chromophore is a retinal molecule derived from vitamin A, which is the 11-cis-retinal.[30] Therefore, by combining different OPNs with it, cells sense light of different wavelengths.

Small molecular changes, where the chromophore binds to OPNs, are enough to modify its absorbance maxima. Retinal can be in either cis- or trans-conformation. Cis-retinal is bound to OPNs and keeps it in a close conformation. On light activation, retinal changes are observed in trans-conformation. Then, OPN releases its G-protein, tagged as α-subunit, which activates further different pathways. After light absorption, OPN must enhance the retinal's isomerization efficiency so that human cells can benefit from fully functioning light sensors.

Castellano-Pellicena et al. showed that OPN1-SW, OPN3, and OPN5 are all expressed within the epidermis of human facial and abdominal skin *in situ*. Their model for regenerating epithelium, as an *ex vivo* re-epithelialization, also increased OPN3 expression following blue light irradiation (i.e., 453 nm at 2 J/cm^2).[30]

Despite OPN2 high expression in mammalian skin, OPN3 was recently discovered with high expression in epidermal skin and melanocytes. The OPN3-mediated regulation of melanocyte pigmentation via MC1R uncovers how OPN3 can interact with another GPCR in a light-independent manner.[29,31]

A recent review on the effects of blue light concludes that despite inducing intriguing skin pigmentation (partly mediated by OPN3), blue light may provide a photoprotective effect against UV irradiation.[32]

The Hunt for New Chromophores

Light-sensitive ion channels

There is also another class of newly discovered light-gated ion channels. They are named transient receptor potential (TRP) channels. Light-mediated activation of TRP seems to explain some mechanisms of action related to PBM. The TRPs were originally discovered in *Drosophila* and used as the primary photoreceptor for their vision. They are selective calcium channels modulated by many different phosphoinositides (e.g., PIP_2, PIP_3, etc.).

Presently, there are seven subfamilies of TRPs, such as TRPC (Canonical), TRPV (Vanilloid), TRPM (Melastatin), TRPP (Polycystin), TRPML (Mucolipin), TRPA (Ankyrin), and TRPN (NOMPC—Mechanoreception).[33] The TRPs are stimulated by various stimuli, such as light, heat, cold, sound, chemical compounds, mechanical forces, hormones, neurotransmitters, and electrical stimuli.[34] It is worth mentioning that the 2021 Nobel prize in physiology demonstrated how signals responsible for temperature and pain sensation are transmitted by TRP channels, which activate across different temperature and pain ranges.[35]

Some studies have investigated the potential involvement of TRPs in the beneficial effects of PBM, notably TRPV1 and TRPV4. Yang et al. have shown that the intracellular concentration of calcium increases in mast cells after green light irradiation (i.e., 532 nm).[36] Such calcium influx promoted mast cells to release histamine through their calcium-dependent degranulation pathway, promoting favorable wound healing. They also stated that TRPV1 may be modulated in a power-dependent manner. However, they showed that blue and red lights were not able to activate TRPV1.[37]

Likewise, other groups have demonstrated that wavelengths considerably longer than the red wavelengths can trigger beneficial effects. Wavelengths such as 980 nm,[38,39] 1064 nm laser,[40] 1072 nm LED,[41] and even broadband IR light[42] have all been described as exhibiting PBM effects. Moreover, explicit changes in intracellular calcium concentrations are observed and likely explained by light-mediated opening of calcium ion channels, such as members of the TRP superfamily.[43]

TRPV1 was recently identified as the biological receptor for capsaicin (the active ingredient in hot chilli peppers).[44] Besides, longer mid-infrared (MIR) light (i.e., 2780 nm) was able to weaken TRPV1 activation in mice.[45] TRPV4 activation was also reduced after MIR irradiation.[45] Moreover, pulsed MIR light (i.e., 1875 nm) was able to evoke neuronal voltage variations, and TRPV4 was shown to be the main effector of this depolarization transient.[46]

Water as an active molecule

NIR water absorption appears to be a potential chromophore since it is abundant in biological tissues. A small increase in water's vibrational energy on a sensitive protein such as a heat-gated ion channel would be sufficient to disrupt the protein's tertiary structure, allowing modulation of the intracellular calcium level.[47] Pollack et al. demonstrated that water at specific cell sites is not like water behaving as an inert solvent, but it rather acts as an active molecule.[48]

Intracellular water is predominantly dynamic and has a predetermined structure that supports cellular processes. Also, since inert water is abundant in the dermis, a rise in temperature (inside-out heating) may occur following the absorption of photons by water,[2] mostly explaining the increased dermal temperature measured following irradiation in the NIR spectrum in particular above 980 nm.[2]

Other chromophores

Several light-sensitive chromophores are playing a minor role in PBM. For instance, flavins, cryptochromes, porphyrins, hemoglobin, and myoglobin have all been described.[5,49] However, their clinical significance remains to be proven experimentally.

Three Strategic Effectors of PBM: ATP, Reactive Oxygen Species, and NO

Adenosine triphosphate

Recent studies have demonstrated that PBM can increase cellular ATP synthesis via mitochondrial respiratory chain enzymatic reaction (i.e., oxidative respiration). As mentioned earlier, CCO is the best-known targeted chromophore in PBM, especially with an absorption peak of 650–660 and 840–860 nm in its oxidized state.[22] Ferraresi et al. showed that red (630 nm) and NIR (850 nm) light delivered at a dose of 2.5 J/cm^2 [50] increases the mitochondrial membrane potential (MtMP) in muscle cells. MtMP and ATP showed an excellent correlation ($r = 89$), reaching peak levels 6 h after light exposure.

The same group established a significant increase in ATP and mitochondrial metabolism (i.e., oxidative stress) in mice. They irradiated mice with red (630 nm) and NIR (850 nm) at 7.2 J/cm^2 and observed a 10-fold increase in ATP concentration compared to controls, doubling their muscle performance.[51]

Zhu et al. tested the implication of PBM in the prevention of myocardial ischemic reperfusion injury. They irradiated isolated rat hearts with red light (660 nm) and observed an increase in cardiac functionality along with a rise in NO and ATP availability 18 h post-injury.[52]

In addition, it has been clearly shown that *in vitro* ATP and mitochondrial membrane potential show a biphasic dose response to low-intensity light exposure in PBM with a dose-dependent therapeutic window.[53]

Hormetic dose response is a biphasic dose/concentration response characterized by a low dose stimulation and a high dose inhibition. It is commonly reported in PBM wound-healing models.[54,55] Using lower fluences of visible or NIR light can have stimulatory effects in wound-healing closure,[56] whereas higher fluences can be beneficial by inhibiting cell growth and proliferation in skin fibrosis using red light.[57]

Reactive oxygen species

Reactive oxygen species (ROS) have had a bad reputation for years because of their reactive nature and potential cellular toxicity. However, PBM is now known to produce beneficial bursts of mitochondrial ROS. Wang et al. demonstrated this assumption using mouse embryonic fibroblasts irradiated at 810 nm.[58] These PBM-related ROS bursts were abrogated by antioxidants, thereby confirming the effect of NIR on these cells.

Many studies have shown the beneficial impact of ROS at low levels and their harmful effect at high levels. Rupel et al. have demonstrated PBMs effect on redox homeostasis intracellularly.[59] They showed that various wavelengths differentially modulate ROS production in neutrophil polymorphonuclear granulocytes and keratinocytes. For instance, 660 nm increased ROS production in cell lines irradiated either before or after the application of an oxidative stimulus. In contrast, 970 nm wielded moderate redox reactions both *in vivo* and *in vitro*. Finally, the most substantial reduction of ROS production was triggered by 800 nm alone or the combination of the former three wavelengths (660, 800, and 970 nm).

On the other hand, Heo et al. observed a reduction of ROS production using 660 nm in hippocampal cell lines and mouse

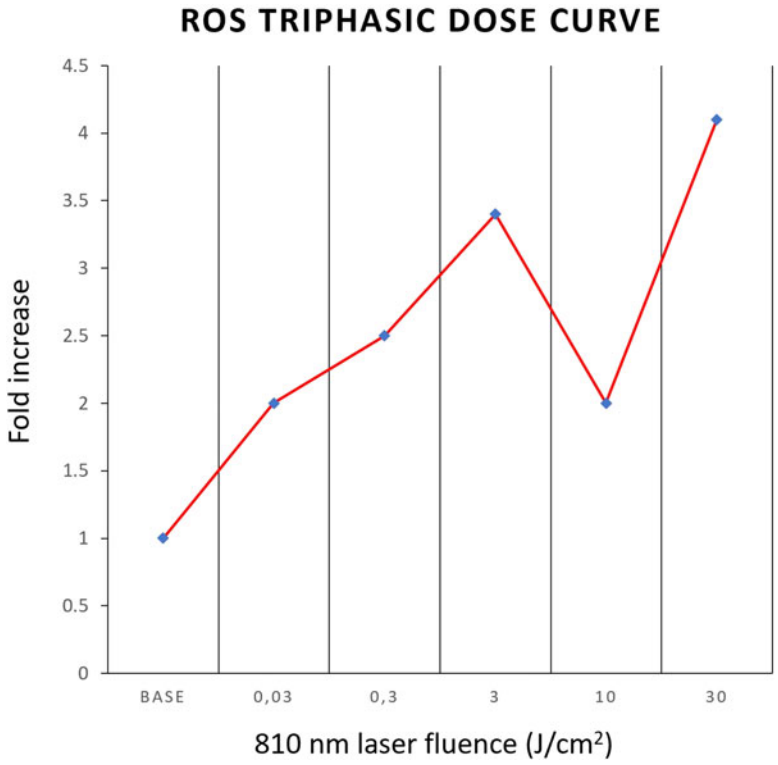

FIG. 4. Mean expression levels of ROS (measured by MitoSox red fluorescence) in primary mouse cortical neurons treated with various fluences of 810-laser delivered at 25 mW/cm^2 over times varying from 1.2 to 1200 sec. Adapted from Huang et al.[53]

organotypic hippocampal tissues subjected to oxidative stress by hydrogen peroxide.[60] Hence, PBM modulates ROS production up and down to establish redox homeostasis. Yun and Finkel have discussed the beneficial impacts that low levels of mitochondrial ROS production have on human cells by selectively activating many useful signaling pathways, thereby initiating a cascade of favorable cellular events.

They named this beneficial control mitohormesis.[61] Typically, when the MtMP is altered either upward or downward, ROS production is increased intracellularly. This alteration is often seen in many cellular impairments, such as excitotoxicity, inhibition of oxidative phosphorylation, inflammation, etc. As such, when MtMP is abnormally low, light absorption by CCO increases MtMP, thereby re-establishing a normal potential.[62,63] This abrogates the overproduction of cellular ROS.

Despite *in vitro* ATP and mitochondrial membrane potential showing biphasic dose-response patterns in PBM, mitochondrial ROS exhibit a unique triphasic dose-response with two distinct peaks (Fig. 4) at least in primary mouse cortical neurons.[53]

Nitric oxide

Several nitrogen-containing compounds, notably NO, can behave as key effector molecules in PBM. In 2006, Lane proposed that CCO could be inhibited by NO in hypoxic or stressed cells and that the inhibitory NO could be photodissociated from the heme or copper centers after light exposure.[21] It later proved to be rather difficult to confirm.[24] Nevertheless, even if this attractive hypothesis would apply, the amount of photodissociated NO would be negligible.

However, a huge amount of NO-derived compounds are readily available in the skin. For instance, UVA light exposure may release skin NO stores via a process called photolysis.[64] PBM may also release NO with non-ionizing photons in the visible/NIR spectrum,[65] presumably via enzymatic pathways.

NO, a small free radical, is an important cellular signaling molecule involved in many physiological processes throughout the body.[66] It has been shown to protect certain cell types from damage caused by UV light exposure.[67,68] In the skin, NO is involved in the proliferation and differentiation of keratinocytes,[69] wound healing,[70,71] as well as skin inflammation and immune reactions,[72,73] among other functions. NO is part of a nitrogen oxide species cycle, including nitrate (NO_3^-), nitrite (NO_2^-), and various other nitrogen-containing compounds from endogenous and exogenous sources.

These cycle components are readily interconverted. Therefore, nitrite and nitrate can be considered a stable pool of potential NO bioactivity in the body.[73] PBM is believed to increase NO release in the skin via NO synthase (NOS)-dependent (enzymatic) and NOS-independent (non-enzymatic) conversion to NO from different nitrogen-containing compounds throughout the skin (Fig. 5).

NO has been shown to protect certain cell types from damage caused by UV light exposure. Weller et al.[67] demonstrated the *in vitro* and *in vivo* suppression of UVB-induced apoptosis in human keratinocytes by increasing the NO concentration in their samples. The NO donor S-nitroso-*N*-acetyl-penicillamine, which was added right after UVB irradiation, resulted in a complete abrogation of

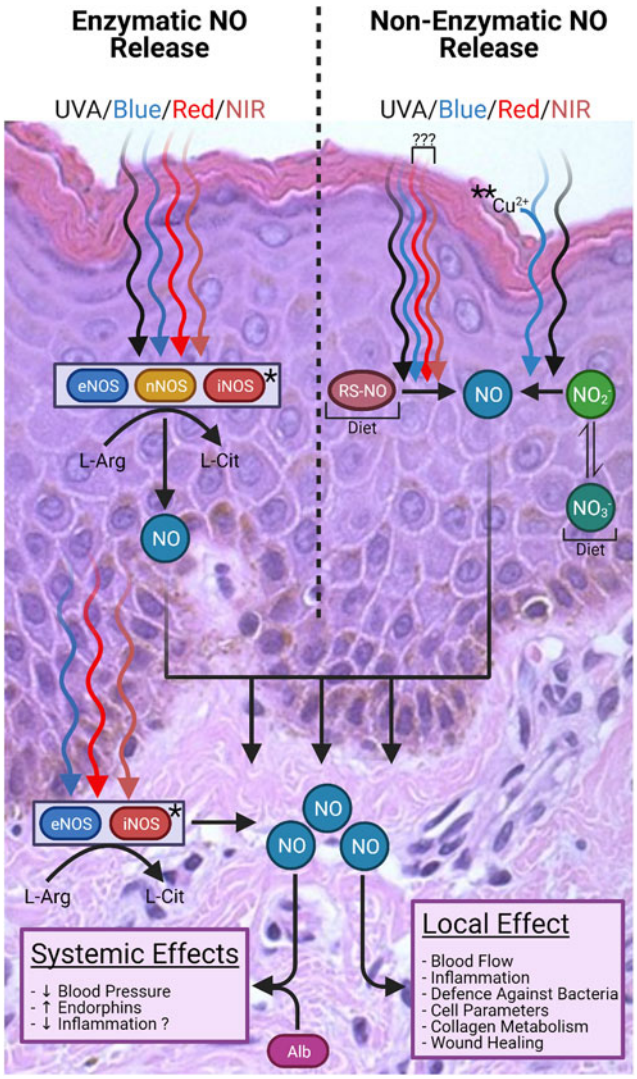

FIG. 5. Summary of proposed NO metabolism in the skin with enzymatic and non-enzymatic (photolytic) pathways occurring concomitantly, leading to local and systemic effects. The epidermal activity of NOS enzymes mainly involves eNOS and nNOS. Whereas dermal NOS activities essentially concern eNOS alone, except for mast cells that slightly express nNOS. *In specific conditions, iNOS activation is induced in both epidermal and dermal cells, but it is not constantly expressed compared to nNOS and eNOS. **Blue light-induced photodecompositon of nitrite is most likely taking place only at the surface of the skin (i.e., stratum corneum), where there is free copper and a relatively high concentration of nitrite. Alb is proposed as a transporter of very potent NO radicals throughout the body for systemic effects. Red and NIR-related photodecomposition of RS-NOs has not been proven yet but is plausible. Note that nitroso compound (NO_3^-, NO_2^-, and RS-NO) interactions can occur in the following skin cells: keratinocytes, melanocytes, fibroblasts, Langerhans cells, endothelial cells, immunocompetent cells, and smooth muscle cells. Alb, albumin; eNOS, endothelial nitric oxide synthase; iNOS, inducible nitric oxide synthase; L-Arg, L-arginine; L-Cit, L-citrulline; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; NO_2^-, nitrite; NO_3^-, nitrate; RS-NO, S-nitrosothiols; Temp., temperature. Adapted from Barolet et al.[65]

cell apoptosis. Moreover, they showed via their positive control that cell apoptosis could also be induced by the NO synthase (NOS) inhibitor NG-nitro-L-arginine methyl ester (L-NAME), showing the importance of NO signaling in cell regulation.

In another study, the NO donor S-nitroso-cysteine, when added during or after UVA exposure, protected rat endothelial cells from apoptosis and necrosis by limiting lipid peroxidation, which is considered a crucial step in cell destruction.[68] Also, NO was involved in the inflammatory response to UVB irradiation of *in vivo* rat skin. Indeed, Lee's group showed that lipid peroxidation decreased with the intensity of the NO response.[74] Despite established UVR and blue light photolytic release of NO in the skin,[75,76] light exposure in the red/NIR spectrum is a promising alternative using safe non-ionizing photons.[77,78] The authors published an extensive review on this topic recently.[65]

Cutaneous NO stores are significant, particularly in the epidermis, where it modulates local cytomodulatory effects and presumably many remote systemic effects like lowering blood pressure.[79]

PBM visual overview. Figures 6–8 provide a visual representation of tentative cell signaling mechanisms involved in PBM:

- Fig. 6. General overview
- Fig. 7. ROS-mediated cell signaling
- Fig. 8. ATP and NO and light-sensitive receptors and ion channels

(Please note that some light-cell interactions illustrated in Figs. 6–8 are putative signaling pathways not yet confirmed).

Secondary Effectors

Calcium

As mentioned earlier, calcium (Ca^{2+}) influx is often observed following PBM irradiation. TRPV and many other PBM-dependent proteins, such as cyclic nucleotide-gated channels (CNGC), may explain this Ca^{2+} increment from extracellular stores. However, PBM-related Ca^{2+} increase is sometimes generated by intracellular supply, such as the mitochondria or endoplasmic reticulum.[80] Typically, PBM leads to an upsurge in intracellular Ca^{2+} levels. Macedo et al. showed this intracellular Ca^{2+} increment in mouse muscle cells following LLLT (PBM) using fluorescent probes.[81] Since PBM modulates calcium-derived signaling on stressful cells, cellular equilibrium may be re-established.

Nowadays, upstream pathways related to Ca^{2+} are abundant and well-documented. The most important ones known to play beneficial effects in PBM are; Calmodulin, protein kinase C (PKC), Ca^{2+}/Calmodulin dependent kinase II (CamKII), and Calcineurin (Fig. 8).[82]

Cyclic adenosine monophosphate

Intracellular adenosine-3′,5′-cyclic-monophosphate (cAMP) increases following exposure to visible and NIR wavelengths. de Lima et al. showed that 660 nm light decreases inflammation by inhibiting tumor necrosis factor (TNF) in mice lungs.[83] They hypothesized that this anti-inflammatory effect was secondary to a rise in cAMP levels in lung epithelial cells. Like prostaglandin E2, lipid-derived molecule elevates cAMP levels; thus, PBM could non-enzymatically increase cAMP levels.

Initially, the cAMP upsurge was thought to occur via an increase in ATP synthesis. Recent studies found no correlation between the rising level of these two adenosine-based molecules. Hence, PBM must exert an indirect effect on adenylyl cyclase to generate such high levels of cAMP.[84–86] The exact mechanism of action is still unknown.

cAMP is well identified as a protein kinase A (PKA) activator (Fig. 8). Two molecules of cAMP bind PKA, which dimerizes and phosphorylates cAMP-response element binding protein (CREB). Phosphorylated CREB is then active and translocates to the nucleus. It binds to cis-regulatory element on DNA, resulting in several genes' transcription upstream to numerous cellular pathways.[87] Among them, many have anti-inflammatory effects.

Further, cAMP is also known to bind CNGC, letting ions circulate once opened.[88] Other receptor proteins can be directly activated by cAMP, like exchange protein activated by cAMP.[89] Again, these upsurges of intracellular calcium and receptor proteins' activation may explain part of the anti-inflammatory effects of PBM.

Akt (protein kinase B)

Akt is a major kinase affected by PBM. So far, several studies have shown the capacity of low-level light to upregulate Akt, ultimately leading to the activation of different transcription factors (TFs) (Fig. 7). PBM seems to increase levels of Akt through the phosphorylation of serine 473 (S473).[90,91] Active Akt (i.e., pAkt-Ser473) is upstream to many signaling pathways, notably (i) inhibiting glycogen synthase kinase 3β (GSK3β) and (ii) upregulating the mammalian target of rapamycin (mTOR) activation. The former kinase is phosphorylated by Akt on its serine 9 (Ser9), where its N-terminus can now bind its catalytic domain.[92]

Active GSK3β stabilizes Bax translocation to mitochondria, known as a massive apoptosis cell signal. Hence, by stabilizing β-catenin translocation to the nucleus and inhibiting Bax translocation to mitochondria, GSK3β inhibition can have various pro-survival effects on human cells. On the other hand, PBM-related activation of Akt can lead to mTOR stabilization, which is implicated in cell growth, cell proliferation, cell motility, protein synthesis, autophagy, and transcription.

Recent studies have found that PBM-related mTOR activation increases cyclin D1, which is a major signaling protein involved in cell proliferation. Gomes Henriques et al. showed this post-irradiation cyclin D1 increase in a squamous carcinoma cell line (SCC25).[93] Consequently, since PBM stimulates cell proliferation, it is crucial to keep in mind that it may hypothetically stimulate cancer invasion and dysplasia in some instances.

Protein kinase C

PKC is widely known to be modulated by calcium influx,[94] which is also triggered by PBM. Recent studies have shown the direct impact of PBM on this kinase.[95,96] PKC is known to activate many TFs that autoregulate human cells. Moreover, it activates Nicotinamide adenine dinucleotide

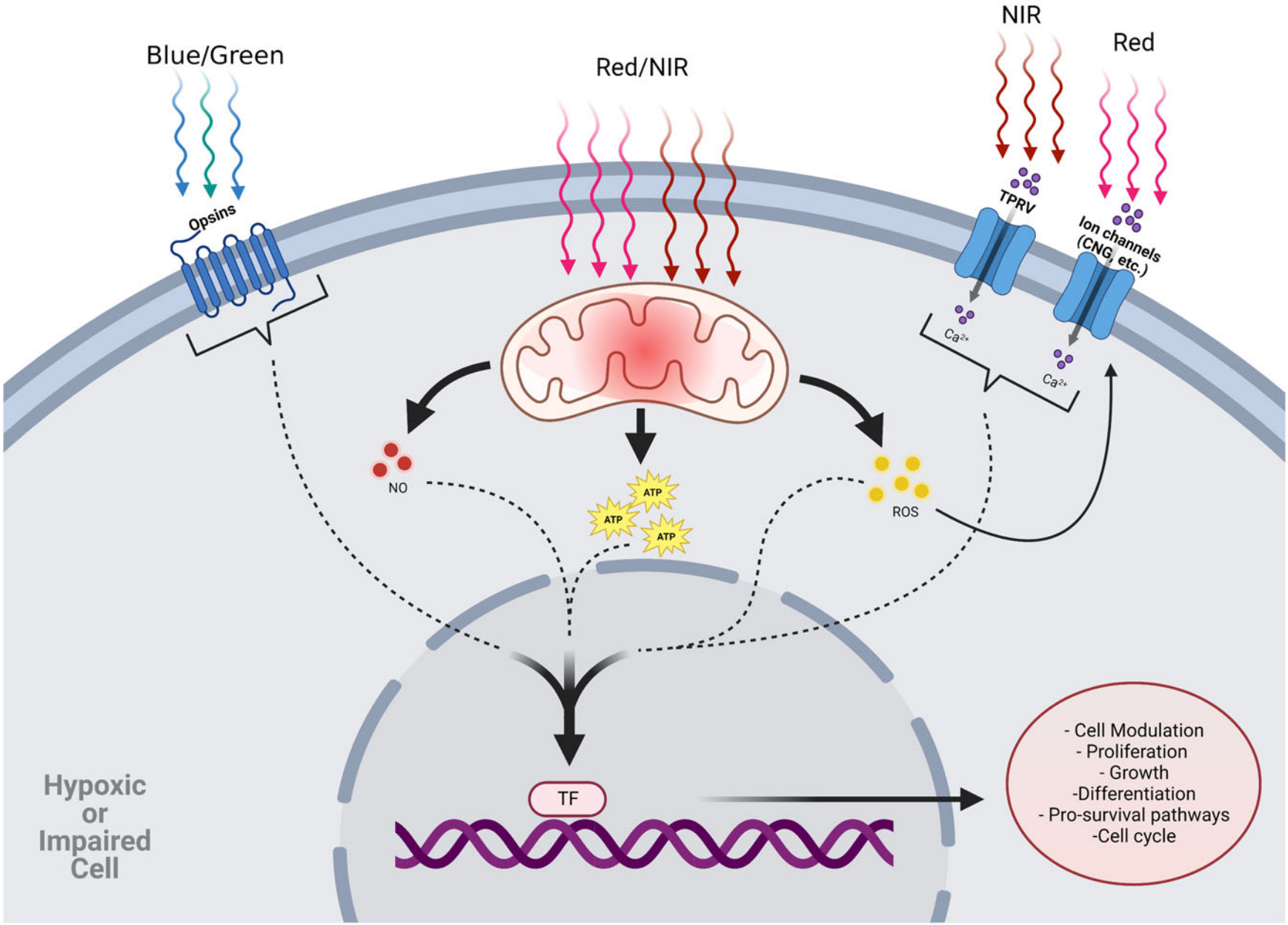

FIG. 6. Chromophores involved in PBM include mitochondrial CCO, membrane receptors such as opsins and light-sensitive ion channels. Apart from the three main effectors (ATP, ROS, and NO) generated from the mitochondria as shown here, the resulting triggered signaling mediators and TFs are detailed in the figures below (i.e., Figs. 7 and 8). Figure 7 illustrates the pathways related to ROS whereas Fig. 8 shows the pathways activated by ATP, NO, as well as other receptors and channels. ATP, adenosine triphosphate; CNG, cyclic nucleotide-gated ion channel; NIR, near-infrared; TF, transcription factor; TRPV, transient receptor potential cation channel subfamily V. This figure was sketched on *Biorender*.

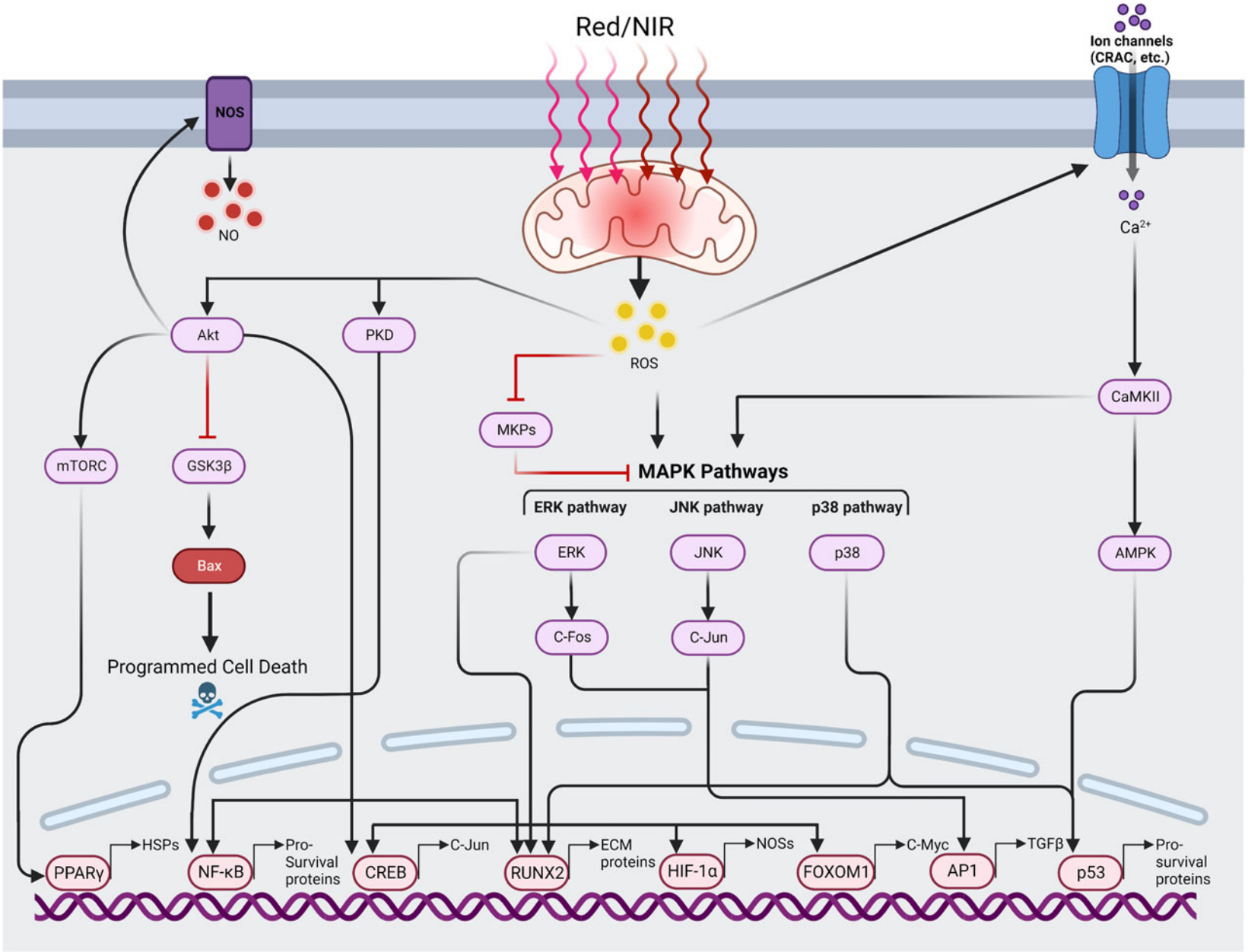

FIG. 7. Visual summary of light-induced ROS-mediated cell signaling in PBM (redox-sensitive signal transduction pathways). On red and NIR stimulation, bursts of ROS are released from the mitochondria, thereby activating many signaling pathways and inhibiting others. Akt (PKB), Ak strain transforming (protein kinase B); AMPK, AMP-activated protein kinase; AP-1, activator protein 1; Bax, BCL2-associated X protein; CaMKII, calmodulin kinase II; cAMP, cyclic adenosine monophosphate; CRAC, calcium release activated channel; CREB, cAMP-response element binding protein; ECM proteins, extracellular matrix related proteins; ERK, extracellular signal-regulated kinase; FOXM1, forkhead box protein M1; GSK3β, glycogen synthase kinase 3β; HIF-1α, hypoxia-inducible factor 1-alpha; HSP, heat shock protein; JNK, jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MKP, MAP kinase phosphatase; mTORC, mammalian target of rapamycin complex; NF-κB, nuclear factor kappa B; p38, p38 MAPK; p53, tumor suppressor protein p53; PKD, protein kinase D; PPARγ, peroxisome proliferator-activated receptor gamma; RUNX2, runt-related transcription factor 2; TGFβ, transforming growth factor β. Figure 6 was created on *Biorender*.

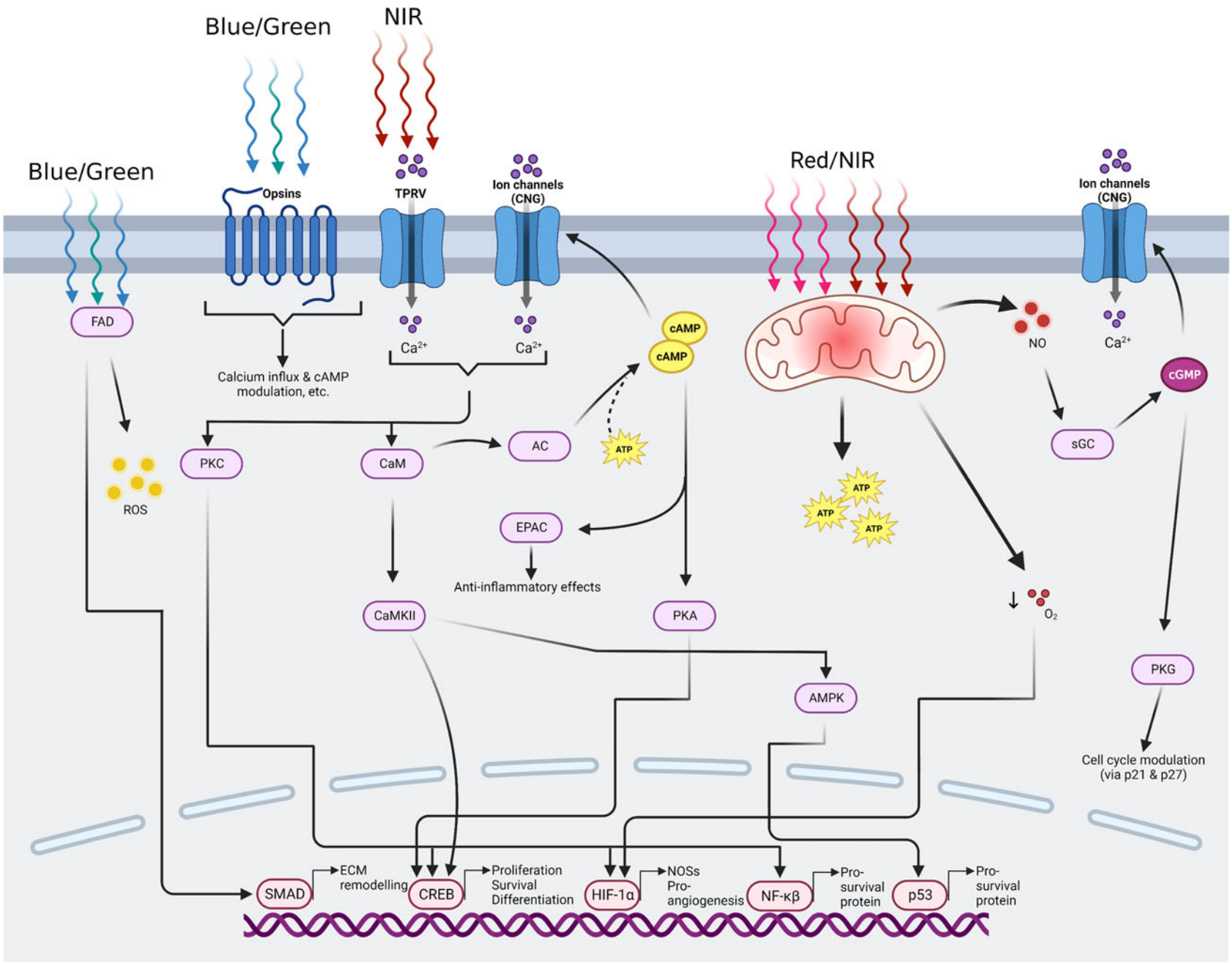

FIG. 8. Summary of other light-induced signaling pathways majorly related to ATP and NO. Following light absorption, ATP and NO are released by the mitochondria, indirectly diminishing intracellular O_2 content. Light-sensitive receptors and ion channels involvement are also represented in this figure. AC, adenylate cyclase; CaM, calmodulin; cGMP, cyclic guanosine monophosphate; EPAC, exchange proteins activated directly by cAMP; FAD, flavoprotein; O_2, oxygen; PKA, protein kinase A; PKC, protein kinase C; PKG, protein kinase G; sGC, soluble guanylate cyclase; SMAD, small mothers against decapentaplegic. This figure was sketched on *Biorender*.

phosphate oxidase (NOX) by phosphorylating its *p47-phox* subunit at Ser303, Ser304, and Ser328.[97] NOX is an enzyme complex that produces superoxide anion and ROS using NADPH as a reducing agent.

It is worth mentioning that NOX can be activated through other kinases stimulated by PBM, such as mitogen-activated protein kinases (MAPK), cAMP-dependent kinases (e.g., PKA), and protein kinase B (PKB). The increased production of ROS may further activate other cellular signaling pathways, as shown in Figs. 7 and 8.

MAPK pathways

The MAPK pathways are serine-threonine protein kinases that have a major impact on signal transduction from the cell membrane to the nucleus. It has been demonstrated that these pathways are activated by PBM.[98–100] The MAPKs consist of growth factor-regulated extracellular signal-regulated kinases (ERKs), c-jun N-terminal kinases (JNKs), and p38 MAPKs (Fig. 7). JNKs and p38 MAPKs are stress-activated MAPKs, like ROS-activated kinases.[101]

The MAPK pathways are part of a three-kinase signaling cascade composed of upstream MAPK kinase kinase (MAP3K), MAPK kinase (MAP2K), and downstream MAPK. The PBM-related ROS are known to activate MAPK pathways upstream via the oxidative modification of amino acids found on RTK and MAP3K intracellular domains.[102] Further, Choi et al. showed that ROS-induced oxidative stress sustains the activation of MAPK pathways via a mechanism that inhibits MAP kinase phosphatases (MKPs), especially MKP-1.[103]

Hence, PBM-related ROS modulation directly activates the MAPK pathways and may neutralize their inhibitors to sustain their activation indirectly. CaMKII is also known to upregulate MAPK activation. Hence, further investigation is needed to establish a direct relation between CaMKII and MAPK pathways independently of ROS-related activation, such as non-canonical PBM pathways.

AMP-activated protein kinase

The PBM also regulates AMP-activated protein kinase (AMPK) activation. PBM-related Ca^{2+} influx leads to CaMKII upregulation, which, in turn, activates AMPK. Guo et al. showed this AMPK induction using red light at 635 nm in diet-induced diabetic mice.[104] AMPK acts as an ''energy sensor'' and constitutes an important regulator of cellular metabolism. AMPK activities are mostly related to processes that inhibit ATP consumption. AMPK is also capable of modulating mitochondrial biogenesis via phosphorylation of the epigenetic factors DNMT1, RBBP7, and HAT1.

These activations increase the expression of proteins implicated in mitochondrial biogenesis, such as Pparg coactivator 1 alpha (PGC-1α), mitochondrial transcription factor A (TFAM), and uncoupling proteins 2 and 3 (UCP2 and UCP3).[105] Lastly, AMPK can also activate tumor suppressor p53 by phosphorylating its Ser15.[106] This may, in part, explain the modulation of p53 in PBM.

Protein kinase D

Protein kinase D (PKD) is another kinase modulated by PBM.[107] Like PKB and MAPK pathways, PBM-related activation of PKD is mediated through ROS production (Fig. 7). Also, a recent review mentioned that PKC is implicated in PKD activation by phosphorylating its Ser738 and 742.[108] Intrinsically, mitochondria-generated ROS added to PKC activation through PBM leads to PKD activation.[109]

TFs Activated by PBM

PBM often leads to the direct or indirect activation of many TFs.

Nuclear factor-kappa B (NF-κB) is an inflammatory regulator that is characterized as a pro-survival TF. It has intracellular redox sensory functions. When the ROS level rises, NF-κB is activated and translocated to the nucleus. A negative feedback loop regulates NF-κB. Inhibitor of nuclear factor kappa B (IκB) binds and sequesters NF-κB.

Since PBM has shown the capacity to generate bursts of ROS, low-level light itself can activate this pro-survival TF to decrease cell death, and increase cell proliferation and cell migration, thereby restoring normal cellular behaviour, notably in impaired cells (Fig. 7). PKD is known to phosphorylate IκB, leading to its degradation, which in turn leads to NF-κB activation.[108] Chen et al. have shown this NF-κB activation post-PBM using mouse embryonic fibroblasts.[110]

Activator protein 1 (AP-1) is a TF that regulates gene expression in response to a variety of stimuli. It controls mainly cell differentiation, proliferation, and apoptosis.[111] The structure of AP-1 is a heterodimer composed of proteins belonging to c-Fos and c-Jun families. It may be triggered by ROS and cAMP signaling pathways following light irradiation (PBM), through MAPK pathways and CREB, respectively.[112,113] AP-1 is involved in skin physiology, notably in tissue regeneration.[114]

Receptor activator of nuclear factor kappa-B ligand (RANKL) is a TF part of the TNF superfamily. Moreover, it is an apoptosis regulator protein that can bind the RANK receptor and control proliferation, such as regulating DNA-binding protein inhibitor ID-4, DNA-binding protein inhibitor ID-2, and Cyclin D1 levels.[115]

Hypoxia-inducible factor 1-alpha (HIF-1α) is involved in the cellular response to hypoxia. This TF is stable at low levels of O_2 and inversely unstable at high levels of O_2. At a high level of O_2, prolyl hydroxylase enzymes are activated and tagged HIFs for degradation.[116] HIF-1α is well known to be involved in the expression of vascular endothelial growth factor (VEGF), vascular endothelial growth factor receptor (VEGFR), glucose transporter 1, and phosphoglycerate kinase.[117] There are two possible relations between light and HIF-1α.

The first is via the activation of the MAPK/PI3K/AKT pathway, resulting in HIF-1α activation. The other is possibly through CCO upregulation, inducing small depletion of intracellular O_2 which will activate HIF-1α.[118] HIF-1α can also be harmful to cells if overexpressed, which is often observed in inflammatory and highly hypoxic environments. In this respect, PBM may regulate the overexpression of HIF-1α. Hsieh et al. have demonstrated PBM modulation in animals with chronic constrictive injury using immunoassay analysis. They showed a reduction of HIF-1α activity in these impaired tissues.[119]

Tumor protein p53 is known as the guardian of the genome. p53 has a transcriptional activity that upregulates the

expression of various DNA-repairing proteins.[120] p53 activation is often stimulated by omnipresent cellular stressors, such as UV light irradiation, causing thymine dimerization and genomic instability.[121] This TF is known to either stop the cell cycle progression at G1/S transition or trigger cell death (i.e., apoptosis).[122] Its capacity to arrest the cell cycle is mediated via the cyclin-dependent kinase (CDK) inhibitor 1 (p21), a protein that binds directly to cyclin-CDK complexes.[122,123]

p21 binding inhibits normal CDK activities, stopping cell cycle progression and allowing other p53-related proteins to repair damaged DNA. PBM is known as an MAPK activator, thereby explaining part of p53 activation.[124] Frank et al. have shown this p53-PBM activation using broadband IR spectrum (700–2000 nm) to activate p53-deficient SaOs cells and normal human dermal fibroblast (NHDF).[125] They showed that p53-deficient SaOs cells are not protected from UVB cytotoxicity by PBM preconditioning, suggesting that the preconditioning effect of PBM is p53-dependent. Moreover, NHDF exposed to broadband IR 700–2000 nm showed a p53 protein accumulation.

The investigators also observed a p53 stabilization and activation by the phosphorylation of Ser20 and Ser15, respectively. p53 accumulation correlated with increased expression of p21, suggesting that broadband PBM irradiation stimulates p53 transcriptional activity.

Further, they observed that the ratio between Bax and Bcl2/Bcl-xL proteins was rather pro-apoptotic immediately after IR exposure switching to an anti-apoptotic ratio 24 h post-IR irradiation, implying a delayed protective effect modulated by the IR spectrum. The authors hypothesized that this IR-related protective effect might be associated with the IR modulation of p53, which is known to regulate Bax transcription.[125,126] Future studies should investigate the effect of monochromatic NIR on the p53 axis.

Forkhead box protein M1 (FOXM1) is also triggered via PBM. Supposedly, this activation may be via the MAPK/ERK pathway. Ling et al. have demonstrated the capacity of 630 nm to upregulate extracellular signal-regulated kinase (ERK)/FOXM1 transcriptional activity in UVB-induced senescent mouse embryonic fibroblasts (NH3T3).[127] FOXM1 activation resulted in upregulated c-Myc expression, thus inhibiting p21 expression. p21 is a CDK inhibitor known to inhibit cyclin-CDK2, -CDK1, and -CKD4/6 complexes, regulating cell cycle progression of G1 to S phase.[123]

Therefore, 630 nm treated fibroblasts quit their senescent state to resume a normal cell cycle. Alone, FOXM1 is a TF regulator of the cell cycle by regulating its normal transition and its progression to the mitotic division. Hence, PBM activation of ERK/FOXM1 may open a new therapeutic tool for cell protection against molecular stressors, such as ionizing irradiation.

Cytokines, Growth Factors, and Many More Signaling Molecules

Inflammatory cytokines, whether pro- or anti-, are often mediated by PBM. Numerous studies have shown PBMs potential effects on cytokines level, such as TNF, many interleukins, histamine, transforming growth factor β (TGF-β), prostaglandins, and eicosanoids.[5,128–130] de Freitas and Hamblin describe the anti-inflammatory effects of PBM, and further in the absence of inflammation the release of pro-inflammatory cytokines promoting tissue remodeling and beneficial cell functions.[118]

TGF-β is a vital growth factor (GF) that stimulates collagen production and other extracellular proteins. It is known to mediate the cellular expression of extracellular matrix (ECM) and inhibits its degradation by neutralizing matrix metalloproteinases (MMPs). TGF-β is highly expressed in the initial stages of inflammation. It maintains ECM to assist leukocytes' migration and newly formed cells toward the injured site. PBM is capable of stimulating TGF-β expression (Fig. 7). Keskiner et al. demonstrated this PBM effect by analyzing palatal wound fluid (PWF) from patients who underwent free gingival graft surgery.[131]

PBM treatments at 1064 nm were performed every 24 h for four consecutive days post-surgery. PWF was collected at day 7 and 12. They observed significant increases in TGF-β on day 7 and 12 in the PBM group compared with the sham group.[131] TGF-β mediates wound healing mostly through the intracellular Suppressor of Mothers against Decapentaplegic pathway. Prior research showed that TGF-β1 was responsible for fibrotic scarring and scarless healing was due to TGF-β3.[132] Recent studies have shown that it is far more complex and that TGF-β modulation also depends on PBM treatment parameters.

Fekrazad et al. found a decrease in TGF-β1 levels at late stages in healing when a combination of wavelengths was used.[9] A recent study by Krassovka et al. describes the effect of blue light on TGF-β1 signaling in human fibroblasts. They found that repeated blue light irradiation (80 J/cm^2) significantly reduced TGF-β1-induced myofibrogenesis. They postulate that the downregulation of catalase and photoreduction of flavoprotein induce intracellular oxidative stress, leading to less myofibrogenesis.[133]

Fibroblast growth factors (FGFs), such as FGFs 1–10, play crucial roles in wound healing. These GFs are mainly acting not only on endothelial cells, melanocytes, and fibroblasts proliferation but also as chemoattractants. In terms of wound healing, FGFs are known to optimize granulation tissue formation and promote re-epithelization. Keratinocyte growth factor (KGF) is similarly implicated in wound healing.

It is released by fibroblasts and has a paracrine effect on keratinocytes. KGF is known to increase the migration and proliferation of keratinocytes and melanocytes, maintaining epithelial equilibrium. Hence, these skin GFs are essential to orchestrate healthy wound healing. Recent studies showed that PBM is capable of increasing FGFs, especially FGFs 1 and 2 (acidic [a]FGF and basic [b]FGF), and KGF expression in skin cells.[10,134] Maldaner et al. showed increases in FGF1 and KGF levels by using PBM to treat *in vitro* senescent-induced human foreskin fibroblasts (HFF-1). They used red light at 660 nm and observed increases in aFGF, KGF, and interleukin-10 (i.e., anti-inflammatory cytokine) expression.[135]

VEGF is an important GF implicated in angiogenesis. It acts cooperatively with HIF-1α on blood vessel formation. In hypoxic environments or wounded areas, visible and/or NIR exposures are often followed by the sprout of new blood vessels around the treatment area.[129,136] Kawano et al. showed that PBM is also able to increase VEFG production in human granulosa cells. Also, they

demonstrated that PBM increases the MAPK signaling pathway, therefore explaining the upstream effector of this amplified VEGF expression.[99]

Moreover, Góralczyk et al. observed lower levels of soluble VEGF receptors (sVEGFR-1/-2) post-PBM compared with sham groups by analyzing the supernatant of human umbilical vein endothelial cell (HUVEC).[137] They also remarked more proliferation from these HUVECs compared with the control. These sVEGFRs compete with membrane-bound VEGFRs for VEGF binding, which ultimately inhibits endothelial cell proliferation, thus neutralizing angiogenesis. Hence, they have hypothesized that the higher VEGF expression and lower VEGFRs concentrations may explain these pro-angiogenesis characteristics observed post-PBM.[137]

Heat shock proteins (HSPs) are often activated by PBM, especially by using wavelengths in the IR spectrum. So far, the ones broadly known to be modulated by PBM are HSP-27 and HSP-70.[138,139] HSPs are important proteins activated by heat or other cellular pathways, which help cells to adapt to many cellular stressors.[140] They have chaperone activity by assisting the cell with proper protein foldings. Also, most HSPs have anti-apoptotic activities, such as inhibiting apoptosome formation, and regulating cell development and differentiation. They also act as signaling molecules and activate other effector proteins, like proteasomes.[140]

IR penetration generates vibrating movement of water molecules by increasing their electron energy levels, inside and outside cells, at frequencies around 60,000–150,000 MHz,[141] generating heat. These IR-induced increased energy levels are dissipated in the form of heat.[141] The ensuing cell-temperature increase may activate some HSPs. Frank et al. showed this HSP modulation using broadband IR 700–2000 nm spectrum on stressed human dermal fibroblasts.[126] They demonstrated that IR was capable of activating HSP-27, thus preventing apoptosome assembly in UVB-treated fibroblasts.

Relevance of PBM in Skin Applications

In terms of tissue repair, wound healing is accelerated by PBM (Fig. 9). Cutaneous wounds,[142] erosive mucositis in oncology,[143] leg ulcers,[11] as well as burns and radiodermatitis[144] all benefit from PBM treatment. Widely used to accelerate healing after aggressive aesthetic treatments, PBM reduces inflammation following treatments like skin resurfacing, vascular and benign pigmented lesions, or chemical peels.[145]

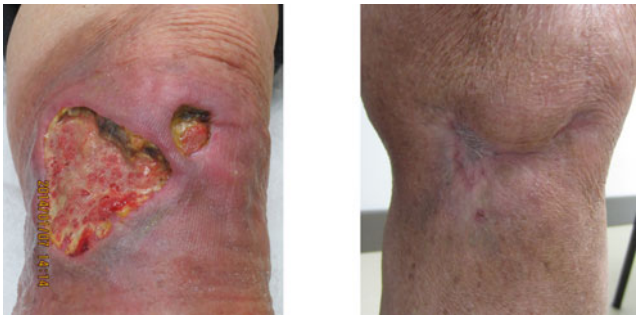

FIG. 9. Wound-healing closure by PBM at 660 nm (Lumiphase®). This 68-year-old female patient was inoperable (i.e., surgical closure or skin graft) due to congestive heart failure. Three weekly treatments for 16 weeks (4 J/cm^2, 50 mW/cm^2) were successful to heal this deep post-traumatic ulcer.

It has also been shown to be effective in treating dyspigmentation.[146,147] In hyperpigmentation, melanin synthesis is inhibited with NIR light. In addition, PBM has shown benefits in the treatment of acne,[148] and the prevention/treatment of hypertrophic scars.[149] It has shown promise in skin rejuvenation,[150] the treatment of alopecia,[151] cellulite,[152] as well as other skin diseases like scleroderma and eyelid inflammatory diseases.[153,153a]

It has been commonly said that when using PBM, it is all in the parameters. Indeed, the choice of specific light delivery parameters maximizes the therapeutic response with wavelength, total fluence, and irradiance being of particular importance (Table 1). Hence, beyond the green thumb skills of successful clinicians, more science is needed to standardize treatment parameters. This will certainly improve along with a better understanding of the mechanisms of action.

Future Directions

Promising skin applications are worth mentioning in PBM. They can be subdivided into local and systemic applications.

Local

Although PBM has been used for numerous inflammatory processes in the skin, rosacea has been recently studied. In a rosacea mouse model, Wu et al. demonstrated that PBM decreased erythema scores and inflammatory cell infiltration (downregulation of S100A9, p65, CD31), and it attenuated the dysregulation of immune cell infiltration.[154]

In skin oncologic applications, new protocols have been proposed regarding oral mucositis (OM) and radiodermatitis. Numerous articles have been published recently on these topics.[155–161] The consensus outlines evidence and prescribed PBM treatments for prophylactic and therapeutic use in supportive care for cancer patients.[161] For example, in OM, recommended light parameters may vary according to light delivery (intraoral vs. transcutaneous) and new guidelines are revised periodically.

A recent clinical trial on scleroderma patients treated every week for 2 months showed that application of blue light (400–430 nm, 120 mW/cm^2, 7.2 J/cm^2) in addition to debridement produced faster healing of skin ulcers with complete healing in 41.6% of patients.[162]

Several studies have shown the potential of high fluence red light (320–640 J/cm^2) to improve skin fibrosis by reducing fibroblast proliferation, collagen deposition, and migration.[163–166] Transcriptional changes leading to antifibrotic cellular responses such as an increase in MMP-1 have been reported regarding this potential scar treatment modality.[167]

In regenerative medicine, the self-assembled skin substitute (SASS) is a method where intact human skin is grown *in vitro* from primary skin cells (i.e., fibroblasts and keratinocytes), avoiding the use of synthetic or heterologous material[168–171] and where cells grow their own ECM. SASS is now used to graft severely burnt victims[168] when the

Table 1. Description of Photobiomodulation Irradiation Parameters

Irradiation parameter	*Measurement unit*	*Description*
Wavelength	nm	Most important parameter: determines chromophore absorption & depth of penetration.
Irradiance	mW/cm^2	More important than fluence (law of reciprocity): determines the cellular activation threshold.
Pulsation	Frequency (Hz), Duration (sec), Duty cycle (%), Sequence (sec)	Pulsing seems superior to CW mode.
Irradiation time	Sec	Minimal irradiation time most likely ≥2 min.
Fluence	$Joule/cm^2$	Classically set at 4 $Joules/cm^2$, this parameter may be unreliable considering it assumes a reciprocity relationship with irradiance and time.
Treatment interval	Hours, days, weeks, or months	Different time intervals may result in different outcomes, although 48 h is the most widely used. It may be modified according to specific clinical applications.
Coherence	Coherence length depends on spectral bandwidth	Once believed to play an important role in PBM. Ultimately, LEDs and lasers have similar effects in skin.
Polarisation	Linear polarized or circular polarized	In highly scattering media like the skin, light will lose its polarity. This property is then not frequently considered regarding the effects of PBM.

CW, continuous wave; LED, light-emitting diode; PBM, photobiomodulation.

surface area available for harvesting autografts is insufficient. However, grafted SASS does not express skin pigmentation. Consequently, newly grafted patients need to stay away from daylight exposure, to avoid photodamage leading to potential skin cancers.

The goal is therefore to implement a safer way to pigment SASS, like modulating melanocytes with low-intensity non-ionizing visible light. Further, pigmenting SASS may help discover other mechanisms of melanogenesis and their secretomes within the skin. Hence, pigment stimulation or inhibition could benefit greatly patients exhibiting skin pigmentation disorders like vitiligo, melasma, and post-inflammatory hyperpigmentation.

Systemic

The skin is also the interface for light-induced NO release, especially after large surface exposure leading to systemic hemodynamic effects.[79] NO stored in a pool of compounds is easily converted to N, via photolytic or enzymatic effects, after skin exposure to UVA/blue light. The innovation is that

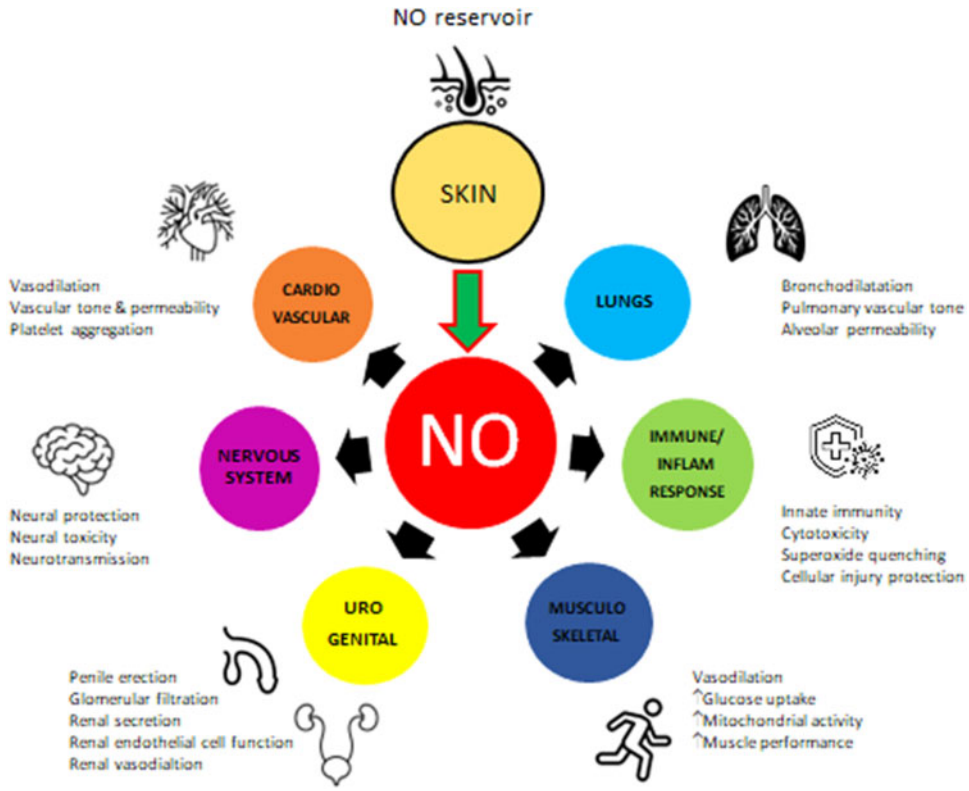

FIG. 10. Potential systemic light-induced NO release therapeutic applications to distant organs (adapted from Barolet et al.[65]).

beyond these wavelengths in the red and near IR spectra, NO can also be released from the skin.[65,78] Following large surface skin exposure via LED beds, NO could induce multiple site-specific effects on remote organs (Fig. 10), including the potential modulation of inflammation in distant unexposed areas.[65] The future is bright.

Conclusions

Among important chromophores of PBM, CCO, with absorption peaks in the red and near IR wavelengths and opsins absorbing blue and green wavelengths, are well described. Other light-sensitive receptors and ion channels are also involved to a lesser extent. PBM can activate cell signaling processes via primary and secondary effectors. The mitochondrial release of three main effectors (i.e., ATP, ROS, and NO) leads to enhanced cell repair and survival, particularly in hypoxic or stressed cells. Likewise, the resulting modulation of specific cell signaling pathways via TFs, GFs, and cytokines, becomes more comprehensible. Hopefully, we provided an overview and more clarity on such complex light-tissue interactions.

The skin is not only the largest organ of the body but also its interface to the outside world. The promising role of PBM in skin applications will further expand as we better understand the full spectrum of intracellular local and distant events resulting from this light-tissue interaction.

By analogy, it has been said that laser (and LEDs) is to light what music is to sound. Accordingly, using low-intensity light in PBM translates into listening to Vivaldi's four seasons, both having soothing effects on human well-being.

The art of taming low-intensity photons continues. Future research will continue to untangle their local and systemic effects on human health.

Authors' Contributions

A.B.: Conceptualization (lead), Writing—Original draft (lead), Writing—Review and editing (lead), Visualization (lead), and Graphic arts and Illustrations (lead). A.M.V.: Writing—Review and editing (equal). A.J.: Writing—Review and editing (equal). I.L.: Writing—Review and editing (equal). D.B.: Conceptualization (lead), Writing—Original draft (lead), Writing—Review and editing (supporting), Visualization (supporting), and Supervision (lead).

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