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INVITED REVIEW

Beyond ultraviolet radiation: Immune system modulation through skin exposure to visible light and infrared radiation

Nicolas Garimano[1] | **Taís Aguayo Frías**[2,3] | **Daniel H. González Maglio**[2,3]

[1]Instituto Nacional de Parasitología "Dr. Mario Fatala Chaben", Administración Nacional de Laboratorios e Institutos de Salud, Buenos Aires, Argentina

[2]Universidad de Buenos Aires, Facultad de Farmacia y Bioquímica, Cátedra de Inmunología, Buenos Aires, Argentina

[3]CONICET – Universidad de Buenos Aires, Instituto de Estudios de la Inmunidad Humoral (IDEHU), Buenos Aires, Argentina

Correspondence
Daniel H. González Maglio, Cátedra de Inmunología-IDEHU, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Junín 956, 4th floor, C1113AAD, Buenos Aires, Argentina.
Email: danielgm@ffyb.uba.ar; danielgonzalezmaglio@gmail.com

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Abstract

Sunlight profoundly affects skin health when it is exposed. After acute exposure, a robust inflammatory response is initiated locally. Moreover, chronic exposures lead to carcinogenesis and photoaging. Local and systemic immunosuppression is also triggered after skin irradiation, affecting adaptive immune responses. These effects are mainly produced by the ultraviolet radiation contained in sunlight and were extensively described and reviewed. However, using UV filters during sunbathing and outdoor activities may allow visible light (VL) wavelengths and infrared radiation (IRR) to reach skin cells. Additionally, the employment of therapeutic VL and IR-emitting lasers and LED devices is increasing for various skin conditions. This literature review aims to present current knowledge on the effects of VL and IRR modulating the skin and systemic immune system. These modulations impact healthy skin and can modify immune responses to diverse stimuli in various cell types. According to the wavelength and the dose, VL and IRR increase the production of reactive oxygen species and promote faster wound healing. Moreover, they modulate inflammatory mediators, such as several cytokines and prostaglandins. However, skin exposure to VL can also affect adaptive immune responses. The study of VL and IRR effects on immunity would promote new uses for phototherapy and may establish the need for new strategies in photoprotection.

KEYWORDS
inflammation, infrared radiation, photobiomodulation, phototherapy, visible light

INTRODUCTION

Since its beginning around 3.7 billion years ago, life on Earth directly depends on sunlight. Photochemical reactions that transform the sun's radiation-contained energy into biochemical molecules, triggering cellular responses, are present in an enormous variety of organisms. Human beings are not an exception; cells exposed to sun

Abbreviations: AMP, antimicrobial peptide; AP-1, activator protein-1; CCL, chemokine (C-C motif) ligand; COX-2, ciclooxygenase-2; CXCL, C-X-C motif chemokine; DC, dendritic cell; hBD, human beta defensin; IFN, interferon; IL, interleukin; IRR, infrared radiation; LPS, lipopolysaccharide; MMP, matrix metalloproteinase; NF-κB, nuclear factor kappa B; NHEK, normal human epidermal keratinocytes; NK, natural killer; PGE_2, prostaglandin E_2; ROS, reactive oxygen species; TGF-β, transforming growth factor beta; TLR, toll-like receptor; TNF-α, tumor necrosis factor alpha; UV, ultraviolet; VEGF, vascular endothelial growth factor; VL, visible light.

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radiation exhibit changes depending on the photoreceptor or photoacceptor molecules and the wavelength of the incident radiation.

The degree of skin exposure to sunlight depends on various factors, such as the year's season, geographical location, working conditions, and personal preferences. Human behavior regarding sun exposure has changed during the last centuries, especially after the mid-XXth century, when sun tanning started to be seen as a desirable effect in some cultures. Skin cancer development has increased since then due to sunlight's direct and indirect effects on exposed and unexposed cells. These carcinogenic effects are mainly triggered by the ultraviolet (UV) radiation in the sunlight, making UV-induced DNA mutations a hallmark of skin cancer. Cellular DNA, particularly adjacent pyrimidines, acts as a photoacceptor molecule for UVB radiation, leading to a crosslink between the adjacent bases with consequent replication errors and mutations. One of the radiation's most important indirect effects is related to alterations in the immune response directed against the mutated cells. A transient systemic immunosuppressive state is generated after skin exposure to UV radiation, negatively affecting immune attack to tumoral cells. Reactive oxygen species (ROS) production, extracellular matrix alteration, and local inflammation are other effects induced by UV radiation (both UVB and UVA).

Due to these genetic, oxidative, and immunological deleterious effects of UV radiation, various sun protectors, which include UVB and UVA filters, were developed and are commercially available. However, most of these products do not block visible light (VL) and infrared radiation (IRR), allowing them to reach skin cells effectively. Moreover, the VL/UV ratio is higher during the early morning and late afternoon hours, when it is more likely and safe to perform outdoor activities during the summer. Artificial VL and IRR are also increasing their use in clinical environments, employing different wavelengths and phototherapy devices (both laser and LED), as VL has shown the potential to treat several skin conditions. At the same time, IRR is being tested as a vaccine adjuvant due to its immunomodulatory activity. Finally, the increasing time humans spend in front of electronic devices, such as cellphones, computers, and tablets, represents new exposures of the skin to VL.

It has been described that VL and IRR can promote ROS generation and wound healing, with different effectivity, according to the wavelength used. For example, Denda and colleagues described that white and green light did not affect the epidermal recovery after disruption by tape stripping. In contrast, red light delayed it, whereas blue light increased re-epithelization.[1] Additionally, IRR has shown positive effects on wound healing in rat and mouse skin abrasion models, promoting transforming growth factor-beta (TGF-β) and matrix metalloproteinases 1 (MMP-1) production and collagen accumulation.[2–4] Recently, the intracellular pathways triggered by blue light have been reviewed.[5]

There is a need to understand the possible effects of these different skin exposures to non-UV radiation on the immune system, both in healthy and pathological conditions. This literature review was performed by searching the terms “visible light” or “infrared radiation” and “skin” or “keratinocyte” or “fibroblast” in PubMed and Google Scholar and selecting those articles that include descriptions of immunological outcomes. The review summarizes the effects of visible light and IRR on skin immunity, considering different wavelengths and doses. The study of VL and IRR effects on immunity may promote new uses for phototherapy and establish the need for new strategies in photoprotection.

DIRECT EFFECTS OF RADIATION ON HEALTHY SKIN

As the introduction mentions, UV radiation induces changes in exposed healthy cells. Irradiated cells increase the production of several inflammatory molecules, such as interleukin (IL)-6, tumor necrosis factor-alpha (TNF-α), cyclooxygenase-2, and MMPs. The transcription of these molecules is mediated by particular factors, such as NF-κB and AP-1, both activated by UV radiation. As UV can only penetrate the skin up to the dermis (UVB can only reach the epidermis, whereas UVA can penetrate deeper into the dermis), it mainly affects keratinocytes and fibroblasts. However, according to the radiation dose and the time post-irradiation evaluated, exposed cells can also secrete anti-inflammatory or modulatory molecules, such as IL-10, prostaglandin E2, and TGF-β. Some of these well-known effects produced by sunlight through the UV component can also be produced by VL and IRR. These effects are presented in the following sections and summarized in Figure 1.

Direct effects in vitro using cell culture models

Keratinocytes, the most abundant cell type in the epidermis, are a direct sunlight target. There are two principal in vitro models of these cells: normal human epidermal keratinocytes (NHEK), a primary cell culture isolated from healthy human donors, and HaCaT cells, an immortalized, non-tumorigenic cell line derived from basal keratinocytes (exposed initially to high calcium and temperature culture conditions).[6]

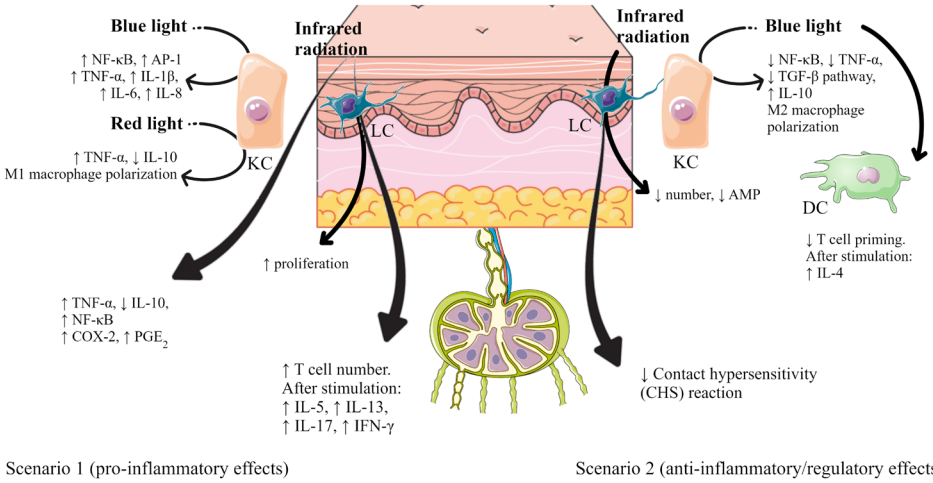

FIGURE 1 Summary of the effects produced by VL and IRR on healthy skin, skin cells and associated immune tissues. Two contradictory scenarios are presented, showing both pro- and anti-inflammatory effects. DC, Dendritic cell; KC, Keratinocyte; LC, Langerhans' cell.

Keratinocyte exposure to VL affects cellular functions. Exposure of NHEK to doses between 100 and 200 J/cm^2 of a 410 nm radiation source induces, beyond ROS production and consequent DNA damage, the secretion of inflammatory mediators: TNF-α, IL-1β, IL-6, and IL-8.[7] Yoo and colleagues also observed this pro-inflammatory effect of blue light in HaCaT cells exposed to lower doses of similar radiation (between 4 and 15 J/cm^2 of a 470–480 nm radiation lamp). They also observed an increase in ROS production but also reported NF-κB and AP-1 activation, as well as the consequent TNF-α release after exposure.[8] However, there is some contradictory evidence about blue light's pro-inflammatory role. HaCaT cells exposed to 41.4 J/cm^2 of a 453 nm blue light source were prepared for a gene expression analysis by Becker and colleagues. They observed the down-regulation of genes in the pro-inflammatory NF-κB and TNF-α signaling pathways, as well as in the TGF-β fibrosis pathway. These results suggest a regulatory role for blue light, decreasing both inflammation and fibrosis in normal cells.[9] In line with this evidence, NHEK exposed to 30 J/cm^2 of violet or blue light (410 and 457 nm, respectively) decrease their transcription of the antimicrobial peptides (AMP) human β-defensin (hBD)-1,-2, and-3, LL-37, and S100A7. Moreover, a slight down-regulation in NF-κB expression can also be seen in the western blots of violet light-exposed cells.[10] The authors also reported alterations in response to TLR ligands due to exposure to violet and blue light, described in section 2.1 of this article. However, other VL sources (530, 590, and 660 nm) did not affect the AMP production or NF-κB expression. Finally, it has been recently reported that blue light (450 nm) and red light (630 nm) showed opposite effects on the inflammatory response of mouse keratinocytes. Consistent with previously described effects, blue light (80 mJ/cm^2) exerted an anti-inflammatory profile in keratinocytes, characterized by decreased TNF-α and increased IL-10 production, with concomitant induction of M2 profile macrophage differentiation (treated with blue light-irradiated keratinocyte supernatant). Interestingly, red light (80 mJ/cm^2) presented exactly the opposite effect: a pro-inflammatory profile increasing TNF-α and decreasing IL-10 production and inducing M1 macrophage profile through stimulation with irradiated-keratinocyte supernatant.[11] This pro-inflammatory effect of red light was also observed by Sun and colleagues, exposing HaCaT cells to an LED light source (625 nm). They showed an increase in NF-κB activation, COX-2 expression, and PGE_2 production by exposure to red light.[12]

Besides keratinocytes and fibroblasts, normal skin presents specialized phagocytes. These include macrophages and dendritic cells, presented mainly in the dermis but also in the epidermis (Langerhans' cells). These phagocytic and immune cells are also naturally exposed to VL. However, THP-1 macrophages irradiated with 45 J/cm^2 using an odontologic Quartz-Tungsten-Halogen lamp (range 400–500 nm) did not change the amount of TNF-α or IL-8 secreted to the culture medium.[13] On the other hand, the priming capacity of dendritic cells (DC) is affected by blue light. Immature monocyte-derived DC exposed to 7.5 and 15 J/cm^2 (400–450 nm) were deficient in activated isolated T lymphocytes since responder cells proliferated less than in the control conditions. Moreover, supernatants from these co-cultures exhibited increased levels of IL-4 dependent on the irradiation dose, showing an allergic-biased T-cell response.[14] In line with these observations, a co-culture

of keratinocytes and macrophages (THP-1 cells) exposed to red light (605–660 nm, 1 J/cm^2) also increased their production of IL-4.[15]

Finally, and less extrapolable to physiological conditions, the exposure of peripheral blood mononuclear cells to blue light (400–450 nm, 28.9 J/cm^2) induced an increase in IFN-γ production without affecting IL-6 or TNF-α production.[16] These results, however, may have a future impact in the field of extracorporeal photopheresis, considering its ability to bias responses toward a Th1 profile.

Regarding IRR, as far as we could find in our search, there are no direct effects on cytokines or other immune mediators' secretion. However, exposure of immune cells to this radiation may impact their function. Neutrophils isolated from healthy volunteers and exposed to IRR before Zymozan stimulation (830 nm, continuous wave, 9.5 and 19 J/cm^2) decreased their ROS production levels. The anti-oxidative effect was more significant in neutrophils isolated from smoker patients. This effect may alter the antimicrobial capacity of the neutrophils. However, CD11b and CD16, markers of neutrophil phagocytic activity, were not affected by IRR.[17]

Analyzing another innate immune cell, eosinophils, it was observed that these cells (isolated from healthy and allergic patients) showed signs of degranulation after their in vitro exposure to IR irradiation (890 nm, 12–14 J/cm^2). The effect is triggered via calcium channel-dependent mechanisms.[18]

Finally, in cultured bone-marrow mast cells and keratinocytes, the irradiation with a continuous wave near-IR laser (1064 nm, 300 J/cm^2) induced an increment in ROS production in vitro, the opposite of the results observed in neutrophils.[19]

Direct effects in vivo on animal models

Normal mouse skin is affected by VL exposure. Deng et al. showed that the immune microenvironment in healthy skin of BALB/c mice is affected by blue (450 nm) and red (630 nm) light in opposite ways. Whereas blue light increased M2 macrophage levels and anti-inflammatory IL-10 and decreased TNF-α production, red light promoted the accumulation of M1 macrophages with higher production of TNF-α and lower levels of IL-10.[11] These results are consistent with the in vitro results obtained by the same group, as well as the anti-inflammatory role of blue light and the pro-inflammatory effect of red light.

On the other hand, some reports explore the effects of IRR on healthy skin using animal models. Piazena and colleagues evaluated the capacity of water-filtered IR-A radiation and heat to modify inflammation and ROS production on an ex vivo bovine udder model. No differences were found between the IR-exposed and control skin samples, but convectively heated (45°C) skin showed increased free-radical production.[20] In another study, IRR (700–1000 nm, 90 J/cm^2) and heat were independently administered to C57BL/6 mice to assess their impact on several immunological parameters. IRR, but not heat alone, managed to increase draining lymph node cells total account as well as anti-CD3-dependent proliferation. Upon CD3 activation, these cells displayed an increased IL-5, IL-13, IL-17, and IFN-γ production, without affecting IL-10. These effects occurred under both IRR and heat treatment, highlighting the importance of IRR upon Th1/Th2 but not regulatory adaptive immune responses. Moreover, both heat and IRR promoted epidermal Langerhans cell proliferation and dendrite formation.[21] Finally, it has been reported that wide spectrum IRR (700–1000 nm, 30 or 60 J/cm^2) and its accompanying heat cause a decrease in Langerhans' cells number in the epidermis of healthy mice reversibly. Moreover, the contact hypersensitivity response to dinitro-fluorobenzene, a way of measuring T-cell-mediated immune responses, was also significantly reduced after irradiation.[22]

Direct effects observed in humans in clinical trials

To the best of our knowledge, no clinical trials or papers studied the direct effects of VL on healthy human skin immune components. In comparison, there is vast evidence in clinical trials of the role of photobiomodulation in wound healing or even in modulating systemic immune responses, reviewed in.[23]

The effects of a combination of visible and IRR, both polarized and non-polarized (400–3400 nm, 95% polarization, 12 J/cm^2), on the humoral immunity of a group of volunteers was evaluated.[24] After a single exposure or 10 consecutive days of irradiation, IgM and IgA serum levels increased within normal levels. However, a normalizing effect (decreasing immunoglobulin) was also noted on subjects with initially high IgM levels. Moreover, all patients' immune complex levels decreased, with a more pronounced effect on those with initially high levels.

In another study, healthy patients were irradiated with an IRR (830 nm, 66 J/cm^2) and/or red-light LED lamp (633 nm, 126 J/cm^2), and distinct immunological parameters were measured in irradiated skin biopsies. IL-1β and TNF-α transcription levels were increased irrespective of the type of radiation used, while IL-6 levels remained unchanged.[25]

MODULATION OF SKIN RESPONSES TO NOXIOUS STIMULI

The skin immune system comprises epidermal and dermal cells that recognize and respond to different noxious stimuli. For example, keratinocytes or dermal macrophages are capable of recognizing microbial components and secreting cytokines as a consequence. Environmental factors, such as pollutants or trauma, also trigger specific immune responses in the skin. This section summarizes evidence of the ability of VL and IRR to modulate these skin immune responses to different stimuli (Figure 2). This manuscript focuses on immune responses; consequently, we decided to exclude photobiomodulation results in wound healing unrelated to skin immunity. Moreover, these results have been reviewed before.[23,26]

Modulation of skin responses in vitro using cell culture models

Keratinocytes can respond to different TLR (toll-like receptors) ligands, triggering local inflammatory responses. High doses of blue light (410 nm, 30 J/cm^2) are able to decrease the immune response of normal human keratinocytes induced by poli:IC, decreasing activation and translocation of NF-kB and transcription of human β-defensins 1, 2, and 3.[10]

Skin dendritic cells are critical mediators of immunity and respond to TLR ligands, cytokines, and many other stimuli. Immature dendritic cells exposed in vitro to blue light (400–500 nm, 2.5, 5, 10, and 15 J/cm^2) increased their expression of surface CD83 and CD86 (activation markers). However, they reduced the secretion of pro-inflammatory IL-6 and TNF-α upon LPS stimulation, showing the modulatory capacity of VL irradiation.[27]

The effects of VL and IRR were studied using a model of dermal trauma. To this aim, human skin fibroblasts were wounded and subjected to helium–neon (632.8 nm, orange/red light), diode (830 nm IR), and Nd:YAG (1064 nm, IR) laser irradiation. Exposures were performed on days 1 and 4 after wounding, using doses of radiation of 5 or 16 J/cm^2. In this model, wounded cells exposed to 16 J/cm^2 of the 632.8 nm laser showed higher IL-6 production levels when compared with unirradiated wounded cells. Moreover, IL-6 production was also stimulated when wounded cells were irradiated with 5 J/cm^2 of the 1064 nm laser, compared with normally irradiated and wounded unirradiated cells. No differences between normal or wounded irradiated cells were found when comparing wavelengths.[28]

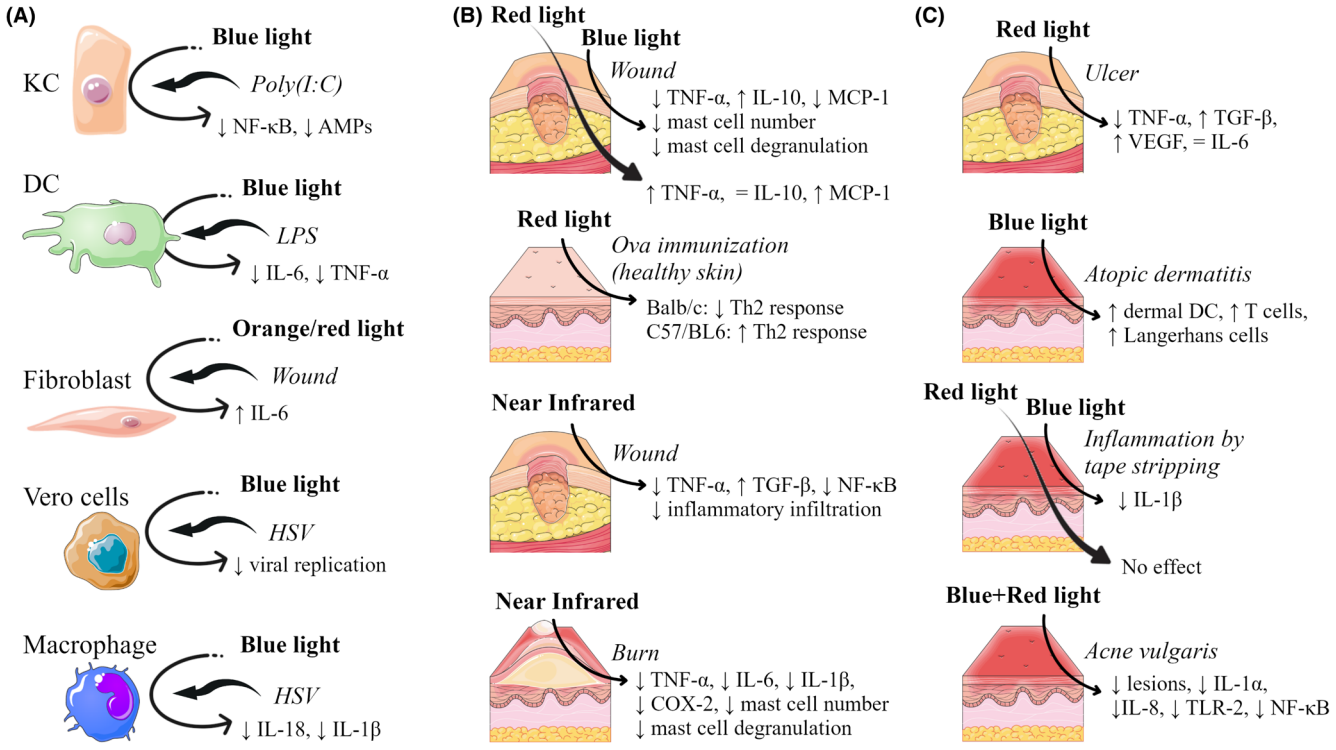

FIGURE 2 Summary of modulatory effects of VL and IRR on the response of skin cells to different noxious or pathological stimuli. (A) Evidence observed in vitro on different skin models. (B) Results obtained in animal models of healthy or altered skin. (C) Observations performed in clinical trials with human volunteers in different skin inflammatory situations. DC, Dendritic cell; HSV, Herpes simplex virus; KC, Keratinocyte; LPS, Lipopolysaccharide (TLR-4 ligand); Ova, Ovalbumin; Poly(I:C), Polyinosinic:Polycytidylic acid (TLR-3 ligand).

Interestingly, a natural challenge, such as a viral infection, can be modulated by exposure of infected cells to VL. Vero cells infected with herpes simplex virus type 1 and exposed to a high dose (10 J/cm^2) of blue light showed an inhibition in viral replication, which may be considered an option to control the infection. However, macrophages (THP-1) infected with the same virus and exposed to the same radiation produced less pro-inflammatory IL-18 and IL-1β, suggesting a deficient infection control.[29]

Modulation of skin responses in vivo on animal models

As they demonstrated in vitro, Deng et al. also evaluated the modulation of inflammatory response in an animal wound healing model. Blue light decreased TNF-α production compared with control unirradiated wounded skin, but red light induced higher levels of this cytokine. However, the production of the anti-inflammatory IL-10 was highly increased by blue light and not affected by red light. According to this anti-inflammatory role, blue light promoted a decreased production of MCP-1, a macrophage attractant chemokine, while red light increased its production.[11]

Blue light also enhanced wound healing in mice, using a dose of 20.6 J/cm^2 of a 410–430 nm lamp. Magni et al.[30] also observed no differences in the inflammatory infiltrate of the wound but an increase in mast cell number and degranulation in blue light-exposed animals.

According to the previously mentioned pro-inflammatory role of red light, this radiation source was employed to study its modulatory capacity on the adaptive immune response against a protein applied by the epicutaneous route. Balb/c and C57/BL6 mice were exposed to low-energy red light (633 nm, doses of 4.8 J/cm^2) and then challenged epicutaneously with ovalbumin. The two strains present different types of Th responses, so modulation varied accordingly. Th2 immune response in Balb/c was abrogated in red-light-exposed animals, whereas this profile of T-cell response was increased in C57/BL6.[31] These results may justify the use of red phototherapy for allergic patients but not for healthy individuals.

Regarding IRR, it was shown that irradiation with pulsed or continuous wave low-level NIR laser at 810 nm contributed to wound healing via anti-inflammatory effects in an immunocompromised dermal-wounded rat model. In this study, IRR-exposed rats showed decreased inflammatory infiltrate, TNF-α, and NF-kβ expression at the dermal wound site, while TGF-β2, a potent anti-inflammatory mediator, was up-regulated.[32,33]

In the same direction, low-level laser IRR with an 890 nm diode laser was administered to rats in a third-degree burn model, which compromised both the dermis and epidermis of the experimental animals. In this model, IRR decreased mast-cell populations at burned sites, which were also incapable of degranulating. These effects were observed locally and at distant skin sites during the healing process. In a similar model, third-degree burn-wounded rats were irradiated with a pulsed wave (810 nm, 24 J/cm^2) or LED (808 nm, 24 J/cm^2) laser, showing a higher wound contraction and lower pro-inflammatory cytokine production (TNF-α, IL-6, IL-1β, and COX-2) at the burn site when exposed to the source of radiation.[34]

Taken together, this evidence outlines IRR's anti-inflammatory and wound-healing effects in animal models presenting diverse skin lesions.

Modulation of skin responses observed in humans in clinical trials

The use of VL or IRR to treat different skin conditions has increased during the last decades. Light sources include broad-spectrum lamps, pulsed lasers, and LED; employed with varying irradiation doses and schedules. Many human trials have studied these photobiomodulation treatments, showing promising results in pathologies' indexes and wound healing, as reviewed previously.[35]

One of those trials that studied local skin immune mediators is mentioned to validate the previously described anti-inflammatory effects of VL. Ruh and colleagues studied patients with pressure ulcers (grade III and IV) in a trial, exposing wounded areas to low-level laser therapy (660 nm, 12 exposures on consecutive days to 2 J/cm^2). Skin samples obtained before and after the treatment were analyzed using qPCR. A significant decrease in pro-inflammatory TNF-α was found, with no changes in IL-6 and increases in anti-inflammatory TGF-β. Moreover, higher levels of VEGF were also observed after treatment. Global anti-inflammatory modulation after treatment is correlated with better ulcer healing.[36]

In another study, a cohort of atopic dermatitis patients was fully exposed to a blue light lamp (66% of emission within the 400–500 nm range, 5 cycles of exposure to 28.9 J/cm^2). Modifications in innate and adaptive immunity were observed on the skin, with an increase in dermal dendritic and T-cell numbers and a rise in Langerhans' cells in the epidermis of irradiated patients (opposite to the effect caused by UV radiation). These cellular modifications correlated with a clinical improvement of skin lesions.[37]

In a group of articles by Falcone and colleagues, the ability of VL to promote skin barrier recovery after a

TABLE 1 Effects produced by VL and IRR on systemic alterations of the immune system in different pathologies.

Disease	Model	Radiation source	Effect
Arthritis	Synoviocyte stimulated with IL-1β	Visible light + Infrared radiation	↓ IL-8, ↓ CCL5
Arthritis	Mouse immunized with collagen	Red light	↓ Articular inflammation, ↓ NF-κB, ↓ NLRP3 activation
Peritonitis	Mouse injected with LPS i.p.	Infrared radiation	↓ IL-6 and TNF-α production (PBMCs), ↓ IL-6 and TNF-α levels (serum), ↓ leukocyte and neutrophil number (peritoneal cavity)
Breast cancer	Mouse injected with EMT6 cell line	Infrared radiation	↓ Tregs, ↑ activated DC number, ↑ tumor infiltrating CD8 T cell.
Arthritis	Rats immunized with collagen	Infrared radiation	↓ inflammation, ↓ specific serum IgG, ↓ IL-17, ↓ PGE_2, ↓ NO, ↑ IL-10, ↑ TGF-β
Knee inflammation	Rats injected with carrageenan	Infrared radiation	↓ leukocyte counts, ↓ neutrophil number, ↓ MPO activity, ↑ mononuclear cells, ↓ PGE_2, ↓ IL-1β, ↓ IL-6
Vaccination	Mouse vaccinated with Influenza virus	Infrared radiation	↑ specific IgG, ↑ DC migration
Healthy subjects	Human volunteers	Visible light + infrared radiation	↓ TNF-α, ↓ IL-6, ↓ IFN-γ, ↑ IL-10, ↑ TGF-β (serum)
Breast cancer	Volunteers after mastectomy	Visible light + infrared radiation	Prevention of immunological alterations
Lymphedema fibrosis	Human volunteers	Far-infrared radiation	↓ IL-18, ↓ TGF-β

tape-stripping and histamine iontophoresis aggression was examined. Red light (656 nm, single exposure to 3.6 or 30 J/cm^2) did not affect immunological mediators, even though it reduced redness after the histamine challenge (3.6 J/cm^2).[38] However, a decrease in IL-1α was observed in volunteers exposed to blue light (430–470 nm, 18 J/cm^2, pulsed or continuous).[39]

In a trial on mild-to-moderate acne vulgaris patients treated with blue light plus red light LED phototherapy, patients were exposed to 0.91 J/cm^2 of blue light (429 nm) and 1.22 J/cm^2 of red light (660 nm) twice a day for 4 weeks. After treatment, inflammatory and non-inflammatory cutaneous lesions decreased in irradiated patients. Moreover, a decrease in the production of the pro-inflammatory mediators IL-1α, IL-8, TLR-2, and NF-κB was observed, highlighting the anti-inflammatory capacity of this co-administered treatment.[40]

CONDITIONING OF SYSTEMIC IMMUNE RESPONSES BY SKIN IRRADIATION

It is very well known that exposure to sunlight modulates systemic immune responses. Skin resident cells and soluble mediators produced in the skin as a consequence of sunlight exposure migrate to distant organs, affecting immune responses triggered there. The role of UV radiation in this systemic immune modulation has been widely reviewed. Still, the effects of non-UV radiation on systemic immune response remain more elusive.[41]

This section summarizes evidence of systemic immune modulation induced by exposure to VL and IRR in vitro, in animal models, and in human trials (Table 1).

Conditioning of immune responses in vitro using cell culture models

Evaluating systemic effects employing in vitro models is complex and can only be achieved through supernatant transfer. To the best of our knowledge, no publications are using this approach. However, it has been published that a synoviocyte cell line (MH7A), cells that resemble rheumatoid fibroblasts, is sensitive to direct exposure to polarized VL-IRR (600–1600 nm, 3.8 J/cm^2). Cells were stimulated with a low dose of inflammatory cytokine IL-1β and then irradiated with the polarized light. Irradiation significantly decreased IL-8 and CCL5 (RANTES) production, chemokines responsible for neutrophil (IL-8) and eosinophil, monocyte, and lymphocyte (CCL5) recruitment.[42]

Conditioning of immune responses in vivo or ex vivo on animal and animal tissue models

The systemic effects of VL irradiation may differ from the local ones described before. Ryu and colleagues described the effects of exposing an animal collagen-induced arthritis model to red light on the articular and systemic inflammation. Daily exposure to 24 J/cm2 (610 nm LED) during 2 weeks reduced articular inflammation by decreasing NF-kB nuclear translocation and NLRP3-dependent inflammasome activation. Moreover, exposure to VL also reduced serum levels of inflammatory cytokines TNF-α, IL-6, IL-1β, and IL-17, as well as anti-inflammatory IL-10 and TGF-β.[43]

A mouse model of LPS-induced peritonitis was employed to analyze the effects of skin exposure to far IR on this inflammatory model.[44] The animals were injected i.p. with LPS (100 ug/kg) and exposed to the light source (>3000 nm) at a distance of 25 cm in 4 periods of 15 minutes for 2 hours, and blood samples were obtained for qPCR (PBMCs) and ELISA (serum). Unfortunately, the radiation dose was not included in the publication, but we estimated it at 12–15 J/cm^2. Far IR significantly reduced pro-inflammatory cytokines IL-6 and TNF-α transcription in PBMCs. Moreover, it also inhibited the early rise in serum IL-6 and TNF-α levels compared with control mice. These results show a general systemic anti-inflammatory effect of Far IR irradiation.[44]

In a similar model, mice were subjected to LPS-induced peritonitis and posteriorly exposed to IRR (GaAs diode laser, 904 nm, 3, 7.5, and 15 J/cm^2). In this study, total leukocyte and neutrophil counts in the peritoneal cavity were decreased by IRR treatment, regardless of radiant fluence.[45]

In a more recent study, the effects of IRR-induced hyperthermia on mouse mammary carcinoma (tumors induced with the injection of the EMT6 cell line) were reported. In this model, the tumors and the surrounding skin were irradiated intermittently with a water-filtered IR halogen lamp (820 nm peak) to maintain a temperature of 43°C on three consecutive days. Different immune-related parameters were assessed 10, 14, and 21 days after treatment. The tumor-draining lymph nodes analysis showed that activated dendritic cells (CD11c+, CD80^{high}, and CD86^{high}) were found in higher numbers in irradiated mice. Moreover, CD8+ T cells infiltrated in significantly higher numbers in tumors of irradiated mice, while Tregs (CD4+, CD25+, FoxP3+) significantly decreased after irradiation. Interestingly, no significant differences were found in intratumoral cytokine expression (IL-10, IL-2, TNF-α, or IFN-γ).[46] The pro-inflammatory effects observed may be due only to the hyperthermia induced on the tumors, but systemic effects triggered on the skin by the light source cannot be ruled out.

IRR has also shown anti-inflammatory effects in a collagen-induced arthritis model in rats. In this model, arthritis was induced via intradermal injection of collagen type II in rats housed with an IR-emitting ceramic bedding for 5 days before the immunization procedure (full spectrum IRR, peaking at 9300 nm, with an hourly dose of 1 J/cm^2). Under this irradiation treatment, rats showed significantly less inflammation, lower serum levels of specific IgG antibodies, and lower IL-17 production in supernatants of inflamed tissue cultures. Additionally, IR cage bedding reduced the migration of innate CD11b+ cells into draining lymph nodes. Still, it enhanced its phagocytic capacity, accompanied by reduced CCL19 and CCL21 production at the lymph nodes. When examining the production of pro- and anti-inflammatory cytokines in inflamed tissue cultures, PGE_2 and NO levels were lower, while IL-10 and TGF-β were higher in the IR-treated rats. Similarly, IRR exerted an anti-inflammatory effect in carrageenan-induced paw inflammation.[47]

In a similar model, Wistar rats were subjected to carrageenan-induced knee inflammation and then exposed to IRR (810 nm, 50–500 J/cm^2). When analyzing articular washes, it was found that lower doses of IRR induced early drops (3 h) in total leukocyte count, while higher doses led to a delayed (6 h) drop in counts. Moreover, all doses of IRR induced decreases in neutrophil and myeloperoxidase activity and increments in mononuclear cell counts 6 h after irradiation. Regarding pro-inflammatory cytokines, a decreased level of PGE_2, IL-1β, and IL-6 was observed only when irradiation fluence was high, reflecting a potent anti-inflammatory effect of IRR.[48]

The influence of IRR radiation on the efficacy of vaccination was evaluated both in animal models and in clinical trials. In previous research, C57BL/6 mice were irradiated with a continuous wave near-IR laser (1064 nm, 300 J/cm^2) before intra-dermal influenza vaccination at the same site. In this model, increased production of ROS, specific IgG response, non-inflammatory chemokine production, and dendritic cells' migration to the draining lymph node were observed in irradiated mice, leading to a higher survival rate after the viral challenge. These vaccine-adjuvant effects of IRR were dependent on the presence and activation of mast and dendritic cells and ROS generation.[19] These results show that IRR can also be a potent immune stimulator of innate and adaptive immune responses.

Conditioning of immune observed in human tissue or clinical trials

Using sunscreens implies the blockade of UVB and UVA radiation and the allowance of VL and IRR to impact the skin. Zhevago and colleagues evaluated the effects

of polychromatic radiation (480–3400 nm) on the modulation of systemic immune mediators of healthy volunteers.[49] Both gender volunteers, ranging from 18 to 65 years old ($n = 43$), were exposed daily for 5 days to a polarized light that includes VL and IRR, at a dose of 12 J/cm^2 and on a surface of 15 cm^2 of healthy skin at the sacral area (usually sun unexposed skin). Nineteen healthy volunteers were included as a placebo group, blocking the lamp with an opaque filter but maintaining the same experimental procedure. Three peripheral blood samples were obtained at 0.5 and 24 h after the first irradiation and 24 h after the fifth exposure to analyze cytokine levels and PBMC responses in vitro. A global anti-inflammatory response was observed, with decreased levels of TNF-α, IL-6, and IFN-γ, increased production of anti-inflammatory IL-10 and TGF-ß, and no effects on IL-1, IL-2, IFN-α, and IL-4.

The same group employed the evaluated source of light and dose of radiation (480–3400 nm, 12 J/cm^2) in a clinical trial to study the effects of light on breast cancer patients subjected to mastectomy in Russia. They demonstrated that this broad-band radiation prevents the postoperative count decrease of monocytes, NK, CD3+, CD4+, activated T lymphocytes, IgA levels, and impaired intracellular digestion of bacteria by neutrophils. Also, the irradiation treatment elicited a faster normalization of serum leukocytosis and activation of cytotoxic CD8+ cells while reducing the elevated concentration of immune complexes, IL-6, and IFN-γ found in mastectomized patients.[50] These results highlight the immune modulatory ability of VL and IRR, potentiating some mediators and decreasing others.

IRR was also employed to modulate autoimmune and allergic diseases. The use of IRR to stimulate IgA production and decrease immune complexes was suggested several times as a therapeutic or preventive strategy for acute mucosal diseases in respiratory or digestive organs.[51–53]

Exposure to far-infrared radiation thermotherapy (6000–14,000 nm wavelength, 42°C) was tested in patients suffering from lymphedema fibrosis. The treatment was performed 5 days a week for 4 weeks, obtaining 20 sessions. In this study, and according to the modulatory ability of radiation, IL-18 and TGF-β1, which are cytokines strongly associated with fibrosis, decreased in lymphedema tissue fluid after irradiation.[54]

Finally, and in the same line as the previously described work in mice,[19] IRR (continuous wave diode laser, 1064 nm, 300 J/cm^2) may positively modulate immune responses. Consequently, it was tested on human volunteers as a candidate vaccine adjuvant. In this work, a portion of the lower back of healthy subjects was irradiated, and a local skin biopsy was performed 4 hours after irradiation. Biopsies from irradiated sites showed significantly less dermal, but not epidermal, Langerhans cell count (CD1a+), which also had distinct diminished dendritic processes. Also, CD11c+ dermal dendritic cells were found in lower numbers in the irradiated dermis, demonstrating potentially increased APC migration to the draining lymph nodes. To this potential dendritic cell migration, some tendencies in chemokine production may be added. The authors reported non-statistically significant increments in gene expression of desirable pro-adjuvant chemokines, such as CXCL13, CCL17, and CCL20 in situ, showing promising perspectives of IRR as a vaccine adjuvant.[55]

CONCLUDING REMARKS

No doubts remain about the biological effects of the non-UV portion of the solar spectrum on human health. The direct effects on the skin cells have been described and reviewed previously, and there is enough evidence to demonstrate that those effects are not limited to the production of ROS. Modulation of the immune system mechanisms can be effectively achieved by exposing the skin to VL and IRR. However, the exact modulation depends on the source of radiation as well as the dose employed. For example, IRR promotes systemic anti-inflammatory effects on rats exposed to an 810 nm source of light with a dose of 500 J/cm^2[48] but induces an opposite effect, increasing skin inflammatory mediators in mice and human volunteers exposed to a 1064 nm source of light with a dose of 300 J/cm^2.[55] Besides the wavelength's impact, different radiation doses present different (and sometimes contradictory) effects, as previously observed for UV radiation.[56,57]

Evidence of activation or inhibition of innate or adaptive immunity has been presented in this article. Moreover, local and systemic modulation of immunity may be observed. The final effects depend not only on the radiation itself (wavelength and dose) but also on the exposed patient's precondition. Exposing normal, healthy skin to sunlight may increase the production of some inflammatory mediators, contributing to skin damage in highly exposed persons who used to sun-protect themselves adequately because sunscreens cannot block VL and IRR. However, according to experimental designs in animal and in vitro models, the doses needed to achieve that level of damage are difficult to obtain under natural conditions. They are more related to artificial sources of radiation than to natural exposure.[58]

Finally, regarding human radiation therapy, a long road has been traveled since Arnold Rikli's heliotherapy.[59] However, many cellular and molecular changes in immune responses due to skin exposure to radiation have been described during the last decades. In this article, a description of those effects produced by VL and IRR was

made, and different study models were described. Those therapies that may have initiated being empirical and based on the patient's progression have started to find their molecular explanations. Understanding these mechanisms may allow phototherapy and photobiomodulation to become a therapeutic option for skin and internal diseases, including allergic, autoimmune, infectious, and tumoral diseases. The spectrum of modulation of immune responses presented, from stimulating local inflammation to suppressing systemic adaptive immunity, reinforces the possibilities of different treatments using the same equipment but varying doses or irradiation schedules. In this way, an institution equipped with UV, Blue, Red, and Infrared phototherapy lamps can offer alternative therapies for a wide spectrum of patients and even to healthy individuals.

As the different types of phototherapies impact different targets than the commonly used drugs (such as immunosuppressants for autoimmunity, chemotherapies for cancer, antibiotics for infections, etc.), they must be considered not only as alternative therapies but also as adjuvant ones.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ORCID

Nicolas Garimano https://orcid.org/0000-0003-4646-1155
Daniel H. González Maglio https://orcid.org/0000-0002-3150-7475

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