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Chapter 5

Immune System Modulation Produced by Ultraviolet Radiation

Eliana M. Cela, Mariela L. Paz, Juliana Leoni and Daniel H. González Maglio

Additional information is available at the end of the chapter

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Abstract

Exposure to ultraviolet radiation (UVr) contained in sunlight is a major cause of skin illness such as sunburn, aging and cancer. UVr triggers local effects on the skin, which involve local inflammation, tissue remodeling, regulatory cytokines release and migration of dendritic cells (DCs). However, these localized effects on the exposed area are not the only ones that take place after sun or UVr exposure. A less known effect of UVr is the modulation of systemic immunity, through the generation of specific regulatory cells. These cells are induced, at least in part, by skin-migrating tolerogenic DCs. Moreover, bone marrow cell precursors can also be biased to a tolerogenic or suppressor phenotype. The sunlight- or UVr-induced immune system modulation can cause skin disorders like skin cancer and cutaneous photosensitivity in Lupus, but it also may be useful to treat cutaneous pathologies such as psoriasis and vitiligo. Moreover, the systemic immunosuppressor effect of UVr exposure may also be useful to treat autoimmunity of internal organs. Finally, as an inducer of cutaneous inflammatory response, UV phototherapy may also be useful in the treatment of cutaneous infections. Overall, UVr has profound immunomodulatory capacity that can be beneficial or deleterious for human health.

Keywords: skin, sunlight, immunosuppression, cancer, autoimmunity

1. Introduction

Sunlight is essential for life on the Earth, since there will be no nourishment provision for all the earth life forms without it. In addition to its central role in the production of large macromolecules (carbohydrates) from carbon dioxide by photosynthetic organisms, it also plays an important role in promoting an adequate life environment through heat generation: our

planet's average temperature is around 15°C, comparing with 482°C in Venus and −63°C in Mars (the two nearest planets of our system). Unfortunately, global temperature is increasing during the last years due to global warming, a problem that exceeds the scope of this chapter. Sunlight is an electromagnetic field composed of radiations with different wavelengths, ranging from X-rays to infrared radiation. Some of these radiations are absorbed in the space and in our atmosphere. Due to this absorption, sunlight spectrum that reaches the Earth's surface is composed of ultraviolet (UV) radiation (280–400 nm), visible light (400–720 nm) and near infrared radiation (720–2500 nm). The UV-radiation at the Earth surface is subdivided into UVB (280–320 nm) and UVA (320–400 nm), which have different characteristics in their effects on biological systems.

But sunlight not only provides warmth and food to the planet but also to the human beings. The different radiations that constitute the sunlight have impacts on mammalian cells, particularly on skin cells, since these are the naturally exposed cells. These effects are multiple and include DNA damage [1], reactive oxygen species (ROS) production [2], mitochondrial alterations [3, 4], matrix metalloproteases expression [5] and complex immune system changes, which are discussed in detail in this chapter. Many of these effects are specifically mediated through UV radiation, but visible light and infrared radiation also mediate cellular alterations [6].

Human skin exposure to sunlight has a range of effects on health, both beneficial and detrimental and not only cutaneous but also systemic.

On the side of the beneficial effects, the bright side, it is very well known that sun exposure is required to provide adequate amounts of circulatory Vitamin D, since this vitamin level depends on a step of UVB-induced photoisomerization of 7-dehydrocholesterol to previtamin D_3 [7]. Sunlight has also been used to treat skin diseases. In ancient India and Egypt, there was a treatment for vitiligo that consisted of the consumption of an herbs extract and a subsequent exposure to the Sun, a treatment that is used in our days known as photodynamic therapy or photochemotherapy [8]. In 1901, Niels Ryberg Finsen published his work in which he treated Lupus vulgaris, a cutaneous infection caused by *Mycobacterium tuberculosis*, using an artificial source of ultraviolet light, during the years where the antibiotics were still undiscovered [9]. For his investigations, Finsen was awarded with the Nobel Prize in 1903, and he still remains as the only dermatologist in winning this prize, more than a century later. It is not surprising that sunlight has been employed as a treatment of different diseases. In 1903, the first hospital specialized in heliotherapy opened its doors in Switzerland. In that hospital patients with tuberculosis and rickets were treated with a precise schedule of sunbathing during several weeks [10]. Moreover, during the First World War, heliotherapy was used to treat ulcers and wounds in the absence of antibiotics.

However, there is also a dark side of sunlight exposure. It is also very well known that sunlight has the ability to promote skin cancer, both melanoma and non-melanoma ones [11]. This ability to induce malignant transformation of skin cells and their subsequent progression to form a tumor is based on its capacity to induce DNA damage and mutations to the exposed cells. This damage, described in 1958, consists of the formation of pyrimidine dimers, a covalent bond between adjacent DNA bases, being the thymidine dimers the most frequent lesions [1]. Even though mammalian cells have a specialized enzymatic machinery to detect

and correct DNA lesions, these mechanisms can be overwhelmed leading to DNA mutations. Damaged cells can arrest their growth in order to detect and correct DNA damage, being p53 a key regulator of the process. If the damage is too extensive to be repaired, apoptotic cell death is initiated, through the intrinsic pathway [12]. Besides nuclear damage, UV radiation also promotes mitochondrial alterations, leading to electron transport chain uncoupling, loosing of mitochondrial membrane polarization and increasing superoxide anion production [13, 14].

UV radiation effects on the biology of exposed cells are very well known, but it also has profound effects on immune system that may affect the local and systemic immune responses. These effects are studied in the field of photoimmunology and are presented in this chapter.

2. Ultraviolet radiation effects on skin immune system

As it was mentioned, sunlight has an important impact on human health. A vast majority of the effects initiated by sunlight are triggered by UV radiation, being UVB the most relevant in terms of induction of DNA damage and detrimental effects on immune system.

The UV-induced immune system alterations can be divided into direct effects and indirect effects. The first ones are produced on the exposed organs (most likely the skin, but also the eyes) by specific responses of UV-exposed cells, which have the ability to produce several molecular mediators and, in the case of dendritic cells, to migrate. The second ones are induced in distant organs, both primary and secondary lymphoid organs, by the skin-produced molecules and migrating cells.

2.1. Direct effects on cutaneous immune system

The energy contained in the UV radiation can be transferred to different molecules within skin cells. This energy transference can modify the target molecules, such as DNA, trans-urocanic acid (UCA) and L-tryptophan, leading to molecular changes and a downstream cascade of complex cellular responses.

Trans-UCA absorbs energy from UVB radiation and isomerizes to cis-UCA, which interacts with the serotonin receptor [15], activating gene transcription and promoting reactive oxygen species (ROS) production [16], which may act as intracellular second messengers activating different kinases such as Erk1/2 in UVB-exposed keratinocytes [17]. But not only ROS can activate cellular kinases. After UV exposure, many intracellular pathways are activated, including NF-κB and MAPK ones, leading to the transcription of many inflammation-related genes [18, 19].

As keratinocytes are the most abundant cell type in epidermis, around 95% of total cells, they are the most frequent target of UV radiation. This is particularly important considering that UVB radiation only reaches the epidermis, and UVA is the only one which can penetrate deeper into the skin to reach the dermis. For these reasons, keratinocytes are central players in the establishment of the UV-induced inflammatory response. These cells are able to sense and react to different stimuli (including UV radiation) by producing pro-inflammatory

cytokines (TNF-α, IL-1 α and IL-1β, IL-6, IL-18, INF-γ), chemokines (IL-8, CCL-20), growth factors (GM-CSF, VEGF-α) and antimicrobial peptides (α and β-defensins, cathelicidin, S100 proteins and ribonucleases). These molecules create an environment that promotes vasodilatation and an increase in vascular permeability, leading to edema formation and recruitment of different immune cells, such as neutrophils, macrophages and lymphocytes to the exposed area, reinforcing the inflammatory response. But keratinocytes are not the only cell type directly affected by UV radiation. Langerhans cells (LCs), the specific dendritic cell subtype present in the epidermis, are also affected. It has been very well described that after UV exposure, the epidermis is depleted of LCs [20], but it has also been established that in vitro UV-exposed LCs promotes defective T cell activation due to UV-induced LCs apoptosis and co-stimulatory molecules alterations [21, 22].

Besides keratinocytes and LCs, dermal cells also play an important role in the UV-induced cutaneous inflammation. Dermal fibroblasts, mast cells, macrophages and dermal dendritic cells can be stimulated both directly by UV radiation (mainly UVA, since UVB does not reach the dermis) and indirectly by epidermal produced soluble mediators [23–27]. As a consequence of repetitive acute exposures to UV radiation, there is a degeneration of skin cells, a destruction of collagen fibers and blood vessels, which, in turn, leads to premature aging, photodermatoses and actinic keratosis. These alterations are consequence of the production of ROS by exposed keratinocytes and fibroblast and the increased production of metalloproteases, which finally ends in the extracellular matrix degradation.

Besides the abovementioned pro-inflammatory mediators, when the skin is exposed to UV radiation, keratinocytes and other immune cells, such as mast cells, neutrophils and monocytes, also produce regulatory soluble mediators such as IL-10, IL-4, prostaglandin E_2 (PGE_2) and platelet-activating factor (PAF). PAF induces the expression of cyclooxygenase-2 (COX-2, the inducible form of the COX enzyme), which is necessary to produce PGE_2. At the same time, cis-UCA induces keratinocyte's production of neuropeptides that stimulates mast cells to release histamine, which, in turn, induces the production of PGE_2 leading to a retro alimentation system. PGE_2 induces the production of IL-4 by lymphocytes and monocytes, potentiating the release of IL-10 by keratinocytes. In this way, all the described mechanisms converge in the production of IL-10.

UV-induced cutaneous inflammation can be controlled by specific regulation of the immune system. It has been recently described that both epidermal LCs and apoptotic keratinocytes are essential for the correct control of UV-induced cutaneous inflammation, through the phagocytosis of apoptotic keratinocytes by LCs [28].

2.2. Systemic effects on immune responses

As it was mentioned in the introduction, skin cancer development is one of the major health problems associated with UV exposure. This carcinogenic effect was first demonstrated in a mice model by Dr. George Marshall Finley in 1928 [29]. More than four decades later, Dr. Margaret Kripke observed that UV-induced skin carcinomas were highly immunogenic and were rejected once transplanted on naïve mice [30]. Dr. Kripke realized that there must had been something else than mutagenic effects on UV-radiation, and she proved that this

extra effect was a marked systemic immunosuppression that impeded the immune system to attack the tumor [31, 32]. Since Dr. Kripke pioneering work, photoimmunologists from all over the world have elucidated many mechanisms involved in UV-induced systemic immunosuppression [33].

One of the most employed models to study this specific suppression of immune responses is the contact hypersensitivity reaction (CHS) to different molecules (the most commonly used are oxazolone and dinitrofluorobenzene). The reaction consists of a first contact between the antigen and the skin, named sensitization, where specific T cell activation takes place in draining lymph nodes, and a second contact in the ear skin of sensitized animals, named challenge. After the challenge, a specific T cell-driven inflammatory response is established and can be measured as the increase in ear thickness. Using CHS reaction, it was demonstrated that several immune cells are involved in the UV-induced immunosuppression:

- The DCs that migrate from the skin to lymph nodes to present antigens to T cells expose a tolerogenic phenotype after UV irradiation. This leads to the promotion of T cell differentiation to a regulatory phenotype. The exact role of LCs in this process is controversial, since it was demonstrated that these cells are not essential to establish the UV-induced immunosuppression [27, 34], but it was also observed in other experiments that LCs are required to produce the phenomena [35]. These events were demonstrated applying the sensitizer onto the irradiated skin.
- During T cell activation by tolerogenic DCs in skin draining lymph nodes, a differentiation to regulatory T cells (Tregs) is produced [36]. These Tregs are antigen specific and may transfer the immunosuppressive estate when injected to naïve mice. Moreover, these Tregs can modulate new immature DCs to turn them into tolerogenic, reinforcing the suppression on the immune response [37].
- Skin mast cells can also migrate to the lymph nodes after irradiation. This migration is essential to establish the immunosuppression [38], and these mast cells are necessary for the generation of regulatory B cells (Bregs), which are other important regulators of the immune response that are involved in the cutaneous response after UV exposure [39].
- Regulatory B cells, as well as Tregs, can modulate DCs' induction of immunity [40], favoring a vicious circle of specific immunosuppression that is set up after skin exposure to UV radiation.

The abovementioned cells produce their effects by sensing and releasing soluble mediators. A pivotal cytokine involved in this suppression is IL-10, since its blockade by specific antibodies [41, 42] or using knock-out mice [43] leads to normal immune responses even after UV exposure. This cytokine is produced by many cells, described earlier in this chapter, such as keratinocytes [44], DCs [45], Tregs, mast cells [46] and Bregs. Vitamin D, whose synthesis in the skin is dependent on UV exposure, also plays an important role as a soluble mediator of UV-induced immunosuppression. This vitamin induces a tolerogenic phenotype on DCs in vitro [47] and can mimic the effect of the radiation in vivo [48]. Another important soluble mediator with systemic effects which is produced in the skin after UV exposure is

prostaglandin E_2. This eicosanoid is a main product of cyclooxygenase-2 (COX-2), which is up-regulated in irradiated skin and whose drug-mediated blockade decreases the UV-induced immunosuppression [18]. Other soluble mediators have been implicated specifically in UVA-induced suppression such as the alternative complement component factor B [49] and serotonin [50]. Platelet-activating factor, TNF-α, IL-4 and histamine also play a role in that process.

Besides its effects on mature T and B cells during their activation in skin draining lymph nodes, UV radiation can also modulate the differentiation of immune cells in primary lymphoid organs. In particular, bone marrow cells are affected in UV-exposed animals. DCs (CD11c + cells) differentiated in vitro from the bone marrow of UV-exposed animals were less competent than the control cells (differentiated from non-exposed animals). The defective bone marrow precursor phenotype can be restored by treating the exposed animals with a COX-2 inhibitor, demonstrating the role of PGE_2 in affecting bone marrow cells [51].

2.3. Other indirect effects on immune system

The effects of microbiota on immune system has been vastly described and is a topic of growing interest during the last years. Even though the most important efforts are directed to study and to explain the interaction of immune system with gut microbiota, this is not the only important microenvironment that may affect the human health. Skin microbiome is indeed an important stimulus for cutaneous immunity. It is composed of a complex group of microorganisms, including bacteria, virus and fungus, which has their particular equilibrium. A disbalance in the commensal microbial community may impact on skin health, as is the case of *Staphylococcus aureus* role in atopic dermatitis [52]. It is not the aim of this chapter to discuss in detail the role of skin microbiome in health and disease, but what is certain is that it can modulate the skin immune system.

Skin exposure to the Sun and UV radiation not only impact skin cells, but also may affect microorganisms living on the skin surface. The effect of the radiation on the microorganisms depends on the type of microbe, its life cycle (spores tend to be more resistant that other forms) and the location (microbes can penetrate deep into the skin appendages). However, UV radiation can definitely affect skin microbiota, leading to different interactions with both adaptive and innate immunity [53]. The exact role of UV radiation on skin microbiome and its effects on immune system need to be studied in detail during the next years, in order to elucidate their implications in skin diseases.

3. Role of UVradiation exposure and immune system modulation on skin diseases

As it was mentioned earlier in this chapter, the most important effect of UV radiation on human health is the induction of skin cancer and the establishment of an immunosuppressive environment which allows the growth of the tumors. However, skin cells malignant transformation is not the only affection produced by UV radiation on the skin. Photosensitivity in Lupus erythematosus is also produced by UV exposure. Moreover, skin infections may be favored by skin UV irradiation. The mechanisms of these skin malignancies are discussed in the following sections.

3.1. UV-induced immune effects implicated with skin cancer development

The skin exposure to sunlight, as well as to artificial sources of UV radiation, is the main etiological factor in basal cell carcinoma, squamous cell carcinoma, cutaneous malignant melanoma, actinic keratosis and melanocytic nevi [11]. The mutagenic role of UV radiation was already mentioned, but it is important to mention the most common mutated genes in skin cancer. Even though the mutagenic effect is directed to DNA sites with adjacent pyrimidines, there are some target genes more frequently affected, as is the case of p53. The protein codified by this gene is crucial in the regulation of cell cycle, favoring cell arrest in order to allow enzymatic machinery, another important protective factor, to repair the UV-induced DNA damage. More than 60% of aggressive basal cell carcinoma was found to have mutations on p53 gene [54]. These mutations were also found in normal sun-exposed skin of skin cancer patients [55]. The importance of cellular DNA repair machinery can be seen in patients with xeroderma pigmentosum. These patients present an autosomal recessive deficiency of DNA repair enzymes, developing basal cell carcinoma and other skin cancers at a very young age [56]. These patients are highly susceptible to sunlight, and they need, in some cases, to completely avoid sun exposure, being known as "children of the moon" [57].

Besides cell biology affections produced by UV radiation, this carcinogen promotes systemic immunosuppression. The relevance of the immune system alterations in skin cancer can be weighted through different experimental data:

- As it was mentioned, IL-10 is a pivotal cytokine in UV-induced suppression, which is secreted by several cell types after skin irradiation. In IL-10 knock-out mice, it has been reported the absence of skin tumors after chronic UV irradiation, besides the mutagenic effect of the radiation [58]. Moreover, in human studies, it has been demonstrated that the presence of a polymorphism in the IL-10 promoter that leads to a deficient transcription of the gene is inversely correlated with the development of skin cancer in UV-exposed skin areas [59].
- Prostaglandin E2 is also a very important molecule implicated in the UV-induced skin carcinogenesis. The pharmacological blockade of its production, by oral or topical administration of the drugs, along chronic irradiation protocols in mice, lead to a decrease in the number and size of the tumors [60, 61]. The selective inhibition of the inducible isoform of the enzyme cyclooxygenase (COX-2) by drugs, like Celecoxib, as well as with nonselective drugs (COX-1 and COX-2 inhibitors), like indomethacin or naproxen, both show the same antitumoral effect [62]. However, even though the number of tumors is decreased by these treatments, there is still a high frequency of mice with at least one tumor. The role of COX-2 in UV-induced skin tumors is described in detail in [18], but it is important to mention that plenty of natural compounds derived from plants are effective in decreasing the expression or the activity of this enzyme.
- The relevance of IL-12 to the immune response against UV-induced tumors was reported by Meeran et al. [63]. They observed that the animals which were deficient in this cytokine were more sensitive to the UV-induced carcinogenesis, developing a greater number of tumors and also generating them in a shorter period of chronic irradiation.

But the modulation of the immune system to allow transformed cells to growth is not the only effect of UV radiation. It has been recently reported that UV promotes angiogenesis and metastasis of melanoma, once this tumor is developed [64]. Using a genetically engineered mice model, Bald et al. demonstrated that, once the tumor is established, the chronic exposure to UV radiation lead to the release of DAMPs (damage associated molecular patterns) from keratinocytes, promoting an TLR-4-dependent inflammatory response. This inflammation recruits neutrophils and promotes vascular activation, allowing melanoma cells to invade blood vessels and to migrate to distant organs, like the lungs.

3.2. Role of UV exposure on cutaneous photosensitivity in systemic lupus erythematosus patients

Lupus (word that means wolf in Latin) is a widely known autoimmune disease, since Hippocrates times [65]. Its name was due to the characteristic destructive injuries that resemble the bites of the animal. One of SLE patients' main symptoms is a cutaneous rush on the face, butterfly-shaped, due to skin exposure to the Sun.

The immune mechanism involved in this symptom is supposed to be mediated by specific autoantibodies directed against nuclear proteins, Ro/SS-A 52, Ro/SS-A 60 and La/SS-B [66]. During the apoptotic cell death of irradiated keratinocytes, the nuclear antigens are relocated to the cellular membrane and exposed to the immune system [67, 68]. This exposure of nuclear antigens is supposed to be involved in two different processes:

- The induction of the specific autoantibodies, which involves the recognition of the apoptotic bodies, with the nuclear antigens exposed on their membranes, by specific B cells. This recognition promotes the production and release of the specific autoantibodies anti-Ro/SS-A and anti-La/SS-B, a common laboratory finding in these patients.
- Once the autoantibodies are produced, they can reach the irradiated skin, recognize the apoptotic cells that expose the antigens on their surface and lead to an attack to the apoptotic bodies by complement factors. This can ultimately produce the lysis of apoptotic cells, releasing their cellular content to the extracellular space. The release of the cellular content produces a strong inflammatory reaction where, in a normal condition, there will be no inflammation.

However, this theory does not explain why patients with other pathologies who are also positive for anti-Ro/SS-A and anti-La/SS-B autoantibodies, such as Sjögren's syndrome patients, do not show cutaneous photosensitivity. This controversy is still present in the bibliography [69], and the molecular mechanism underlying the butterfly-shaped rush is still unknown.

3.3. Other skin conditions

As skin exposure to UV radiation affects DCs function, T and B cell activation, macrophage phagocytic activity and other immune mechanisms, it is expected to find alterations in responses against pathogens, including virus, bacteria, parasites and fungus [70]. In different

infectious diseases in mice models, it has been described the alteration of T cell function by exposing the animals to UV light before or after the infectious challenge [71]. It has been recently published that different procedures of irradiation, which include a single high UV dose and repetitive low UV doses, differentially affect the evolution of a *Staphylococcus aureus* cutaneous infection [72]. However, in humans, this effect is more elusive. There are just a few infections, mainly viral infections that have been observed to be affected by exposure to UV radiation.

4. Immune system modulation by UV radiation as a therapy

Due to the profound effects that UV radiation promotes on exposed cells and on local and systemic immune system, the use of this radiation for human therapy is widely spread. Besides all the knowledge on the molecular effects of UV radiation described earlier, the first therapeutic use of this radiation was Finsen's work, mentioned in the introduction of this chapter, where he treated Lupus vulgaris using a carbon arc lamp, more than a century ago [73]. Currently, UV phototherapy is mainly employed in different dermatological disorders, including psoriasis, vitiligo, atopic dermatitis and cutaneous T cell lymphomas [74]. However, the usage of phototherapy has also been proposed to treat different systemic conditions like autoimmune diseases. Phototherapy procedures include exposure to broad-band UVB (BB-UVB), narrow-band UVB (NB-UVB) and psoralen + UVA (PUVA), but the analysis of their differences exceeds the purpose of this chapter [75].

4.1. Phototherapy effects in psoriasis

Psoriasis is a chronic inflammatory skin disease. It is characterized by cutaneous lesions, produced by hyperproliferation of keratinocytes under the control of T cells. In the pathogenesis of the disease, different inflammatory cytokines are involved, like TNF-α and IL-17. UVB phototherapy has been widely used for psoriasis treatment during decades, evolving from BB-UVB to NB-UVB. The role of phototherapy in these patients can be inferred from the abovementioned molecular mechanisms induced by UV radiation. Basically, it promotes several changes in the affected skin, including the direct effect on keratinocytes preventing their proliferation and indirect effects on immune system. The T cell activity is unbalanced by UV radiation, increasing IL-4 production that affects Th-17 and Th-1 profiles, both implicated in the perpetuation of the inflammatory state in the patients. In this way, UV phototherapy produces a decrease in the production of IFNγ, TNFα, IL-17 and IL-22 and an increment in IL-10 secretion. Moreover, an augmented migration of Tregs to the irradiated psoriatic skin has been observed, which may also contribute to control this disease [76].

UVB phototherapy must be rationally employed, since the chronic exposure to this treatment may increase the risk of skin cancer development. Patients under this therapy may have to replace it by any other available therapy, such as topical and systemic drugs or blocking antibodies, after a prolonged period of use.

4.2. Phototherapy in vitiligo

Vitiligo is an autoimmune disease characterized by the absence of melanin in particular zones of the skin, which remains unpigmented. This lack of pigmentation is due to deficient activity of melanocytes, the epidermal cells with the ability and the enzymatic machinery to synthesize this pigment [77].

Phototherapy in vitiligo promotes two main cellular effects such as the activation of melanocytes and the promotion of Tregs. The first effect is directly related to the lack of pigmentation, and melanocytes are sensitive to UV radiation as a signal that induces melanin synthesis. In this way, UV phototherapy directly promotes the melanin synthesis. The second effect is associated to the main topic of this chapter, the modulation of the immune system by UV radiation. The mechanisms are the same that have been discussed in this chapter, but the goal is to induce immunological tolerance once it has been lost [78, 79]. The exact antigens that trigger vitiligo are unknown, but the mechanisms that lead to suppression of immunity after UV irradiation seem to be effective to counteract this cutaneous autoimmune disease.

4.3. Experimental phototherapy for cutaneous infections

As it was mentioned, UV irradiation may promote several changes in skin and systemic immune system. These changes are dependent on the dose and the periodicity of the exposure, and include local inflammation, activation of innate immune response, generation of tolerogenic DCs and Tregs [80]. Many of these changes can positively impact on the progression of cutaneous infections produced by different types of pathogens.

The parasite from the genus *Leishmania*, an endemic pathogen in some South American, African and Asian countries, promotes characteristic cutaneous lesions on infected individuals. Using mice models, it has been demonstrated that the exposure of animals to low dose UVB radiation (exposures on 4 consecutive days) prior to the challenge with *Leishmania amazonensis* promastigotes protects the animals against the cutaneous lesions. Moreover, UV-exposed animals presented higher levels of serum IFN-γ and TNF-α, compared to nonirradiated control infected mice [81]. These results demonstrate that cutaneous leishmaniasis can be modulated by UV radiation. However, the exposure to the radiation was performed prior to the parasite challenge, and the results cannot be extrapolated to a treatment for infected individuals. It is worth to notice that there is a research vacancy on experimental phototherapy for cutaneous leishmaniasis, but there are a few reports that have demonstrated the effectiveness of this treatment in mice models, which received UV or sunlight irradiation prior to the infection as well as during the long-term observation of the lesions. In the works of Giannini and Hoseinipoor et al., it can be observed that irradiated animals can recover from the infection faster than nonirradiated control animals [82, 83].

As UV radiation, especially UVC, present a direct bactericidal effect, it was directly used for the treatment of a cutaneous infection caused by antibiotic-resistant bacteria. The case reported by Aleem et al. shows the use of an UVC germicidal lamp to treat a poly-microbial burn wound infection. The infection was caused by *Staphylococcus aureus*, *Klebsiella pneumoniae*

and *Pseudomonas aeruginosa*, and the antibiotic therapy was unsuccessful. The physicians decided then to use UVC phototherapy and, finally, the 9-year-old patient recovered from the infection [84]. The success obtained with this treatment may be due to a direct germicidal effect or by immune system modulation. More studies need to be performed to clarify this point and to allow the establishment of new treatments for cutaneous infections produced by antibiotic-resistant bacteria.

4.4. Experimental phototherapy for autoimmune diseases

As it was mentioned earlier, skin exposure to UV radiation leads to an important systemic immunosuppression. The influence of this tolerogenic effect on an internal organ autoimmune disease was deeply studied by Dr. Scott Byrne's group using a mice model of multiple sclerosis (MS), the experimental autoimmune encephalitis (EAE). They showed that exposing the animals to UV radiation prior to the antigenic challenge, and also during the evolution of the disease, it was possible to decrease the severity of the EAE, including the demyelination process [85]. This effect was dependent on B cells, since the protection against the pathology can be obtained by transferring B cells from irradiated animals to naïve mice. Moreover, pharmacological depletion of B cell abolished the UV-mediated protection against EAE.

Being aware of these effects on mice, it seems promising to treat MS patients using phototherapy. Dr. Prue Hart faced this challenge, and set a clinical trial to treat patients suffering clinically isolated syndrome, who have a high susceptibility to develop MS [86]. The results of this clinical trial may open a new era on the treatment of autoimmune diseases using cutaneous phototherapy.

4.5. Extracorporeal blood irradiation

Skin exposure to UV radiation is not the only therapeutic procedure that employs artificial sources of this radiation. There are two procedures based on the extraction of blood from the patients and its subsequent exposure to a source of UV radiation: extracorporeal photopheresis (ECP) and ultraviolet blood irradiation (UBI). These two procedures base their efficacy on the modulation of the immune system. However, while ECP promotes a downregulation of immune effector mechanisms, UBI produces the opposite effect.

ECP consists of blood extraction, buffy coat separation, its subsequent mixture with a sensitizer (psoralens) and an exposure to a UVA source. The irradiated white blood cells are then reinfused to the patient. This procedure has shown to be not only effective but also safe, and it has mainly mild and transient side effects. It was first described to treat cutaneous T cell lymphoma and chronic graft versus host disease, but it can also be employed in different autoimmune pathologies such as scleroderma, multiple sclerosis, Type 1 diabetes mellitus, rheumatoid arthritis or Crohn's disease [87]. Its mechanism of action is not completely understood, but it has been shown that the PUVA treatment produces the apoptosis of exposed cells, which are phagocyted by DCs once they are reinfused. These DCs acquire a tolerogenic phenotype, promoting the generation of regulatory T cells that ultimately lead to the control of the pathologic T cells [88].

On the other hand, UBI is an old and almost forgotten technique, whose use was extensive in the 1940s and 1950s. Similarly to ECP, it consists of blood extraction with citrate (around 5–7% of total blood) and its subsequent irradiation using UVC or UVB radiation, without any cellular separation. It was employed to treat many infectious diseases such as septicemia, tuberculosis and pneumonia, and other pathologies like arthritis and asthma [89]. The exact mechanisms of action are not fully understood, but it is known that an activation of antigen presenting cells is produced during the procedure. Even though this treatment has almost been abandoned, it may be a therapeutic option against multi-resistant bacterial infections.

5. Conclusions

Skin exposure to sunlight, specifically to UV radiation, triggers very well-known mechanisms that may ultimately promote a profound modulation of the immune system, including both innate and adaptive immunity. This modulation of the immunological response leads to a defective control of tumor cells and pathogens. Moreover, as it affects systemic immunity, it can also alter the response to vaccines. On the other hand, the knowledge of these detrimental effects has led to multiple options to treat immune-based pathologies. In this way, the potentiality of cutaneous and systemic immunomodulation by different types of phototherapy is yet far to be completely explored.

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Conflict of interest

The authors have no financial conflict of interest.

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