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Regulation of cellular immunity by photo(chemo)therapy

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1. ABSTRACT

Phototherapy and photochemotherapy are important treatment regimens for inflammatory as well as malignant diseases in dermatology. Both treatment modalities have been developed already three decades ago and therefore profound knowledge exists on the use, efficacy, and long-term side effects. Since the development of new immunosuppressive medications, biologics, and changes in medical reimbursement policies, phototherapy is currently less frequently used compared to previous years to treat psoriasis or atopic dermatitis. However, cost-effectiveness analysis demonstrated the phototherapy can induce significantly therapeutic beneficial effects on a large number of inflammatory and malignant skin disorders at a low cost of treatment rate. Since many chronic skin disorders require rotational treatment regimens to decrease the development of (long-term) adverse events, phototherapy will play an important role in dermatology in future years. In the following the molecular as well as cellular mechanisms of phototherapy are described and discussed in light of the fact that photobiology is a very active field in biomedical research.

2. INTRODUCTION

Phototherapy is a major treatment modality in dermatology and has significantly influenced the treatment of a wide variety of immune mediated cutaneous diseases, such as psoriasis, vitiligo, atopic dermatitis or cutaneous T cell lymphoma. The goals of therapeutic photomedicine are the suppression of ongoing disease processes and, more importantly, the prevention, modulation or abrogation of pathogenic mechanisms causing skin diseases. More than 30 years have passed since the discovery that ultraviolet (UV) radiation can affect the immune system in several ways. One of the main effects of UV irradiation on keratinocytes is the induction of apoptosis, inhibition of antigen presentation and the expression of immunosuppressive cytokines. Beyond distinctive wave length ranges, UV radiation was also found to suppress immunity in an antigen-specific way, which might be mediated by so called UV-induced regulatory T cells. Those T cells, formerly known as suppressor T cells, play an important role in the negative regulation of cellular immune responses and the preventation of autoimmunity. The assumption of an UV-induced immunosuppressive

effect is based on the fact that the vast majority of UV-responsive skin disorders respond equally well to immunosuppressive drugs. Phototherapy includes a variety of different regimens including broad-band UVB, narrow-band UVB, UVA, UVA-1 and photochemotherapy (PUVA). In the following the molecular mechanisms of phototherapy are discussed in light of its immunomodulating effects.

3. PHOTO(CHEMO)THERAPY

3.1. UVB phototherapy

Broad-band UVB (290-320nm) is the most frequently used and, concerning its biologic effects, best understood phototherapeutic regimen for the treatment of psoriasis, atopic dermatitis and many other inflammatory skin disorders. Acute and chronic side effects imply skin burn and the risk of carcinogenesis. The observation that shorter wavelengths of UVB are responsible for the dermatitis inducing effects and the antipsoriatric effect was shown to be induced by longer wavelengths have led to the development of narrowband UVB therapy (311-313nm) (1-3) . Whether narrow-band UVB is less carcinogenic than broad-band UVB is still a matter of debate, because data investigating the carcinogenic risks of narrow-band UVB and broad-band UVB is limited in humans (4). In mice, however, narrow-band UVB induced more skin tumors compared to broad-band UVB (5).

The molecular mechanisms underlying the beneficial therapeutic effects of UVB are still not entirely clear. For long it was believed that UVB can only act in the epidermis due to its lower penetration in comparison to UVA. However, there is recent evidence that UVB can also lead to systemic immunosuppression possibly via release of soluble mediators such as interleukin (IL)-1alpha, IL-10, tumor necrosis factor alpha (TNF-alpha), and cis-urocanic acid from UVB-irradiated epidermis into the circulation (6, 7).

Concerning direct UVB effects, transformation of UV electromagnetic energy into chemical energy by absorption is the most critical photobiological event. The receptive molecules (chromophores) develop an excited state, allowing conformational changes or even re-formation of covalent bounds. Hence, these so called photoproducts reveal altered functionality. The immunomodulating effects of UVB irradiation are partly caused by these direct photoabsorbing effects implying DNA damage, formation of reactive oxygen species (ROS), membrane changes and isomerization of trans- urocanic acid to the cis-form.

Among the many biological effects of UVB radiation, induction of apoptotic cell death is one of the most intensively studied phenomena (8). UVB-induced apoptosis has been recognized as a complex process in which a variety of pathways appear to be involved. One of the major molecular triggers for UVB-induced apoptosis is UVB-induced DNA damage (cyclobutane pyrimidine dimers, (6–4) photoproducts). UV-induced DNA damage has been recognized as the major molecular trigger of UV-mediated immunosuppression, as reduction of DNA damage is associated with the release of immunosuppressive cytokines (7). Kulms *et al.* discussed that a reduction of DNA damage via application of the exogenic DNA repair enzyme (T4N5 endonuclease, photolyase) resulted most effectively in a decrease of apoptotic cell death (9-11). Accordingly, in DNA repair-deficient mice much lower doses of UVB radiation are required to induce the same number of apoptotic keratinocytes (sunburn cells) (12). Furthermore reactive oxygen species are crucially involved in UVB-induced cell death as addition of radical scavengers and antioxidants partially inhibits UV mediated apoptosis (9).

Additionally, the direct activation of death receptors by UVB contributes to UV-induced cell death by inducing receptor clustering without the need of the respective ligand (13, 14). Membrane bound death receptors such as CD95 (FAS), the TNF-receptor, and TRAIL receptors are characterized by an intracellular death domain. Upon interaction with their cognate ligands, these receptors trimerize and subsequently cluster, which results in the activation of the death domain, ultimately leading to the initiation of the apoptosis program. Evidence of a contribution of receptor clustering to UVB-induced apoptosis has been provided, since the prevention of death receptor clustering was associated with a partial reduction of UVB-mediated cell death (15). Each of these signaling pathways contributes in an essential and independent way to UVB-induced apoptosis since only the inhibition of all pathways results in complete blockade of UVB mediated cell death (9).

Apoptosis of T-lymphocytes has been postulated to be responsible for the therapeutic UVB effects in psoriasis, as T-lymphocytes have been recognized as one of the major pathogenic mechanisms in this disease. Ozawa *et al.* observed, that narrow-band UVB was superior in depleting T cells from the epidermis and dermis of psoriatic lesions than broad-band UVB. The primary mechanism of T cell depletion was UVB-induced apoptosis as proven by the terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labelling (TUNEL) of narrow-band UVB-exposed psoriatic skin specimens (16). As UVB-treated keratinocytes have been reported to up-regulate the death receptor ligand CD95L (17), it is possible that UVB-induced lesional T cell apoptosis is mediated indirectly by CD95L expression on neighbouring keratinocytes. However, apoptosis is also induced by UVB 311nm irradiation *in vitro* in isolated T cell populations cultured from psoriatic lesions, suggesting also a direct cytotoxic effect.

Urocanic acid (UCA) has been recognized as another chromophore in the epidermis to be involved in UV-induced immunosuppression (18). UCA is a metabolite of the essential amino acid histidine and accumulates in the epidermis because human and rodent keratinocytes lack the enzymes required for its catabolisation. UV radiation isomerizes *trans*-UCA to *cis*-UCA dose-dependently until a balanced photostationary state is reached. Removal of UCA by tape stripping of the epidermis prevents UV-induced suppression of contact hypersensitivitiy (CHS), indicating

that cis-UCA is involved in photoimmunosuppression (19). Intradermal injection of *cis*-UCA can impair the induction of contact hypersensitivity in a fashion similar to UVB irradiation. This effect seems to be dependent on the immunosuppressive cytokine TNF-alpha (20). Furthermore, cis-UCA is also able to inhibit the antigen- presenting function of Langerhans cells (21). This effect can be reversed by IL-12 (22). Due to its inhibitory properties cis-UCA was used as a topical immunosuppressant for the treatment of psoriatic plaques. A clear anti-psoriatic effect was detected which, however, was not superior to conventional anti-psoriatic treatment regimens (23). UVB-induced cis-UCA might also participate in the antiinflammatory effects of UVB phototherapy. In addition, injection of cis-UCA antibodies reduced the incidence of UV-induced skin tumours in a photocarcinogenesis model, suggesting a role of cis-UCA induced immunosupression in the generation of UV-induced skin cancer (22).

Another systemic mechanism of *cis*-UCA showed the induction of interleukin (IL)-10 in activated CD4+ T cells (24). Since IL-10 is associated with regulatory T cell function, we speculate that these effects might mediate cis-UCA-induced immunomodulation. Only recently, the binding of *cis*-UCA to serotonin (5-HT) receptors has been demonstrated to be involved in mediating UV induced immunosupression upstream to IL-10. 5-HT_{2A} blockade by antiserotonin antibodies or by treating mice with 5-HT_{2A} antagonists resulted in a loss of UV- and *cis*-UCA mediated immunosupression. These results might bear some significant therapeutic capacity in light of the fact that a variety of approved drugs affect serotonin-metabolism (25).

Besides the direct immunomodulating effects of UVB exposure on immunocompetent T cells, UVB irradiation is also known to modulate immune responses via the release of a variety of cytokines (26). Keratinocytes are a rich source for a number of soluble mediators including immunostimulatory as well as pro-inflammatory cytokines such as IL-1 alpha, IL-6, IL-8, TNF-alpha (27) and IL-18, which has been recently discovered to affect photoimmunosupression by reducing UV irradiation-induced DNA damage (28). UV radiation can stimulate the secretion of immunosuppressive mediators since intravenous injection of supernatants obtained from UV-exposed keratinocytes into naive mice prevented epicutaneous hapten sensitisation (29). Accordingly, UV-induced keratinocyte-derived immunosuppressive mediators may get into the circulation and inhibit immune reactions at areas not directly exposed to UV radiation, explaining the phenomenon of UV induced systemic immunosuppression.

The major soluble player involved in systemic UV induced immunosuppression appears to be IL-10. IL-10 is a T helper cell type 2 (Th2) cytokine and abrogates the production of T helper cell type 1 (Th1) cytokines such as interferon-gamma (IFN-gamma) and IL-2. Moreover, IL-10 suppresses proinflammatory cytokine production and the antigen presenting capacity of macrophages and dendritic cells (30). UVB-induced IL-10 production by murine keratinocytes or macrophages and by keratinocytes in human skin, shifts the immune response from a Th1 to a Th2 type. This might explain why Th1-mediated cellular immune reactions are impaired by UV radiation. According to the predominant expression of IL-2 and IFN-gamma in skin lesions, psoriasis is regarded as a Th1-driven disease. Interestingly, a relative deficiency in IL-10 expression was detected in psoriatic skin compared with other inflammatory skin disorders and IL-10 expression was found to be up-regulated secondary to anti-psoriatic treatment protocols, indicating that IL-10 might be a key cytokine in psoriasis (31, 32). Experimental systemic application of IL-10 in psoriatic patients induced significant anti-psoriatic effects (33). These findings suggest that UV-induced expression of IL-10 may additionally contribute to the beneficial effects of UVB phototherapy in psoriasis. Other soluble mediators involved in UV-induced immunosuppression besides IL-10 are TNF-alpha (34), IL-4, prostaglandin E2 (35), calcitonin gene related peptide (CGRP) (36), alpha-melanocyte stimulating hormone (alpha-MSH) (37), and platelet activating factor (PAF) (38). PAF is a potent phospholipid mediator, which recently has been identified as an UVB radiation-induced pathway, whereas IL-10 has been demonstrated to be the downstream cytokine to be involved in immunosupression but not in inflammation. Considering the beneficial and detrimental effects of UV radiation, the discrimination of these downstream pathways could imply great therapeutic potential (38). Recent findings in mice indicate that IL-10 is furthermore critically involved in the protection against UV-induced tumor development (39). IL-10 production can be reversed by the release of IL-12, a typical pro-inflammatory Th1 cytokine.

In the context of photobiology IL-12 has been described to be able to prevent the suppression of contact hypersensitivity by UV, to prevent the development of regulatory T cells and even to break UV-induced tolerance by a yet unknown mechanism (7). The inhibition of UV-induced immunosuppression by IL-12 may be due to its recently described capacity to reduce DNA damage via induction of DNA repair mechanisms (40), as the preventive effect of IL-12 is not observed in DNA repair-deficient mice (41), these findings suggest, additional and independent factors in the regulation of immunotolerance have to be considered. UV-induced DNA damage appears to be also an important trigger for the induction of UV-induced regulatory T cells, as Langerhans cells containing DNA damage in the regional lymph nodes draining UV-exposed skin induced development of regulatory T cells. On the other hand IL-12 was able to prevent UV induced DNA damage in UV exposed Langerhans cells so that UV-induced regulatory T cells were not activated (42). In support of these results, it was shown that in DNA repair-deficient mice IL-12 failed to prevent the development of UV-induced regulatory T cells. In light of the fact that immature dendritic cells can induce regulatory T cells (43), these findings may have identified another way to induce regulatory T cells, via the presentation of antigens by UV-damaged cutaneous dendritic cells.

UVB-induced immunosuppression affects the immune system in a rather specific than general fashion

(41, 43, 44). To this end, contact hypersensitivity is a leading paradigm in photoimmunology. In one of the pivotal experiments it was observed that topical application of contact allergens (haptens) onto UV-exposed skin did not result in sensitization. In addition, hapten-specific tolerance developed, because the very same animals could not be sensitized against the same hapten at a later time point, although other immune reactions were not suppressed (45). This unresponsiveness could be adoptively transferred, because injection of splenocytes and lymph node cells obtained from UV-tolerized mice into naive mice inhibited the sensitization against the respective hapten in the recipients (46). Accordingly, it has been suggested that UV-induced tolerance is mediated via the induction of hapten-specific T suppressor cells, nowadays called UV- induced regulatory T cells (47). Several types of UV-induced regulatory T cells have been described (47, 48). The currently best characterized regulatory T cells are involved in the UV low-dose suppression of hapten-mediated delayed type hypersensitivity. They belong to the CD4+CD25+ subtype of regulatory T cells (49), express the negative regulatory molecule CTLA-4 (50), and bind the c-type lectin dectin-2 (51). In addition, they secrete upon stimulation IL-10 upon hapten-specific stimulation and may use the apoptosis-related FAS/FAS-ligand system to confer immunoregulation (50, 52).

Since regulatory T cells can perform their initial immunomodulating activity in an antigen-specific manner, which is expected to be of great therapeutic value by potentially avoiding general unspecific immunosuppression. Therapeutic administration, however, could only be promising if these cells not only prevent sensitization but also inhibit the elicitation in already sensitized hosts, as the aim is not only to prevent but to treat overt diseases. UV-regulatory T cells, however, exert suppressive activity in mice only when injected i.v. into naive but not into sensitized mice. This implied that they inhibit only the afferent but not the efferent limb of CHS. This led to the final conclusion that UV regulatory T cells are not active in the presence of T effector cells and thus are inferior to T effector cells (53). This observation gave rise to the speculation that UV-induced regulatory T cells only act in naive and not in sensitized hosts and thus that their therapeutic potential may be limited because they could only prevent but not cure already manifested immune- mediated diseases (54). However, UV-induced regulatory T cells are also able to suppress the induction and the elicitation of CHS via the release of high amounts of IL-10 (55, 56).

The inability of regulatory T cells to migrate into the skin is determined by their unique expression pattern of homing receptors. FACS analysis revealed that UV-induced regulatory T cells express the lymph node homing receptor CD62L (L-selectin) (49), but not the ligands for the skin homing receptors E- and P-selectin (57). Because of the capacity of bystander suppression, speculations exist about the therapeutic potential of regulatory T cells that could be generated in response to antigens known to be present in the target organ that are not necessarily the precise antigen that drives the pathogenic response (58). However, these findings suggest that this strategy might be only successful if the regulatory T cells home to the target organs. Recent studies show that the migratory behavior can be reprogrammed by tissue-specific dendritic cells such as Langerhans cells and may have input on strategies trying to use regulatory T cells not only for the prevention but also for the treatment of ongoing immune-mediated diseases (59).

3.2. UVA phototherapy

Monotherapy with UVA is currently almost exclusively performed with long-wave UVA-1 (340–400 nm) irradiation. One of the major differences between UVA-1 and UVB or UVA/UVB irradiation is the fact that UVA-1 radiation penetrates deeper into the skin and thus therapeutic UVA-1 doses are able to reach the dermis as well as dermal vessels. The rationale for using UVA-1 was the assumption to reduce the adverse effects induced by shorter wavelengths UV. With the development of high output UVA-1 irradiation devices rather high doses of UVA-1 can be delivered in a reasonable period of time (60). Initially, these high output UVA-1 irradiation phototherapy was first used for the treatment of patients with acute, severe exacerbation of atopic dermatitis (61). Further *in vivo* studies revealed that T cell depletion was preceded by the induction of apoptosis in skin-infiltrating T cells and it is therefore now generally accepted that induction of T cell apoptosis is one basic mechanism of action of UVA-1 phototherapy (62). UVA-1-induced immediate apoptosis (0–4 h) is probably related to cellular membrane damage with a time-dependent loss of plasma membrane integrity, whereas DNA damage, such as the formation of pyrimidine dimers, most likely initiates UVB- and UVC induced delayed apoptosis (>20 h) (63, 64). *In vitro*, UVA-1 radiation was shown to induce apoptosis in CD4+ cells by a mechanism that was initiated through the generation of singlet oxygen and subsequently involved the FAS/FASL (CD95/ CD95L) pathway (62).

Since the detection of a T cell depleting mechanism, the indication spectrum of UVA-1 has been gradually extended and now includes other T cell mediated skin diseases (65, 66) Accordingly, UVA-1 phototherapy has been introduced in the treatment of patients with early-stage cutaneous T cell lymphoma (67, 68). It remains to be determined whether the same remission periods can be achieved as with PUVA, which still is the gold standard for this disease. One of the mechanisms explaining the efficacy of UVA-1 phototherapy in cutaneous T cell lymphoma might be a higher sensitivity of malignant T cells to UVA-1 irradiation compared with non-malignant T cells. Caspases represent a molecular sensor for the susceptibility of T cells toward UVA-1 radiation/ singlet oxygen-induced apoptosis. IFN-gamma significantly enhanced UVA-1 irradiation induced T cell apotosis via elevation of caspase levels and, therefore, might in combination increase the efficacy of UVA-1 phototherapy (69). In skin specimens of patients with atopic dermatitis it was recently shown that a functional subset of regulatory T cells was below detection level. Therefore, efficient down-modulation of allergen-driven

immune activation might be impaired, indicating defective immunoregualtion in this skin disorder (70).

Besides its effects on skin infiltrating T cells, UVA-1 irradiation is also able to activate dermal fibroblasts to synthesize the collagen degrading enzyme collagenase I a member of the matrix metalloproteinase family (MMPs) (71, 72). Phototherapy in particular UVA-1 has been shown to improve sclerosing skin conditions including localized scleroderma and sclerosing cutaneous graft-vs.-host disease (73). Ultramicroscopic analysis of skin specimens of patients with systemic sclerosis revealed that UVA-1 treatment decreased the diameter of the broad collagen fibrils, mainly in the upper reticular layer (74). Sclerotic skin plaques appear to result from increased production of type I and type III collagen secondary to a malfunction of dermal fibroblasts in their ability to express the enzyme collagenase. Accordingly, UVA-1 treatment softened sclerotic plaques and complete clearance was even reported in several patients (75, 76). Cutaneous ultrasound imaging showed a significant decrease in lesional skin thickness after UVA-1 exposure. Biopsies taken from lesional skin before and after light treatment demonstrated a strong up-regulation of collagenase I after irradiation, suggesting that indeed UVA-1 therapy was able to induce enzyme expression *in vivo* (77). Additionally, these skin specimens showed loosening of collagen bundles after phototherapy, which provides indirect evidence for functional collagenase activity in irradiated sclerodermic skin plaques.

3.3. Photochemotherapy

The combination of 8-methoxypsoralen (8-MOP) and long-wave ultraviolet radiation (UV-A), which is commonly referred to as photochemotherapy or PUVA is known to affect the immune system (78) and provides beneficial effects in disorders such as cutaneous T cell lymphoma (CTCL) as well as psoriasis (79).The mechanism underlying the therapeutic effects of the combination of psoralens plus UVA is much less understood compared with that of UVA or UVB treatment. Since PUVA is most effective in hyperproliferative skin disorders it is generally assumed that UVA-induced DNA–psoralen photoadducts impair cell replication, ultimately leading to inhibition of cell proliferation. In fact, inhibition of cell proliferation is observed at psoralen concentrations and UVA doses that do not affect T cell viability (80). Different oxygen-independent and oxygen-dependent mechanisms have been related to PUVA cytotoxicity (81). On the one hand, the photosensitizer reacts directly with cellular components (i.e. nucleic acids and lipids), as psoralen has been shown to bind covalently to and cross-link DNA (82). On the other hand, the generation of radical oxygen species or singlet oxygen is likely to cause a rapid alteration of metabolic processes and cellular structures. Higher doses of combined psoralen/ UVA therapy caused irreversible cell damage, resulting in both apoptosis and necrosis, whereas sole application of even higher psoralen doses did not have the potential to induce apoptosis (83-85). Induction of cell death of lymphocytes may be responsible for the antinflammatory effects of PUVA and for the beneficial therapeutic effects on lymphoproliferative diseases, such as cutaneous T cell lymphoma.

Upon UVA irradiation, psoralen photoproducts (POPs) are generated, which are likely to contribute to PUVA cytotoxicity (86). POP were reported to elicit a wide variety of effects, such as oxidation of proteins as well as unsaturated lipids and modulation of the immunologic response and inhibition of the tumor-growth in an experimental murine model of human CTCL (87).

Furthermore, PUVA-induced apoptosis involves mitochondrial dysfunction caused by opening of the permeability transition pore (PTP), a high-conductance channel located in the inner mitochondrial membrane. PTP channel modulation is regulated by several factors including cyclosporin A, a high affinity inhibitor of calcineurin signalling (88, 89). A recent study revealed PTPs to be the missing link between POP generation and apoptosis induction (90). PUVA has been shown to induce apoptosis in mouse epidermal cells by a mechanism that involves p53 and FAS/FASL interactions (91). Additionally, PUVA has been shown to induce apoptosis of human microvascular endothelial cells *in vitro*, suggesting a possible mechanism of photochemotherapy in the treatment of angiogenesis-related diseases such as psoriasis (92).

Kripke *et al.* (93) were among the first to report that PUVA suppressed the induction of contact hypersensitivity responses in a systemic fashion. This suppression was associated with the development of regulatory T cells preventing the induction, but not the elicitation, of contact hypersensitivity in recipient mice. Hence this effect is similar to the effect induced by shorter wavelength UV radiation. It was furthermore reported that also photochemotherapy is associated with the induction of splenic regulatory T cells, which were able to suppress immune responses in normal recipients upon adoptive transfer (94).

Intercellular adhesion molecule 1 (ICAM-1) is a surface molecule that plays an important role during inflammatory and immune responses (95). Accordingly, in inflammatory skin lesions, expression of ICAM-1 was found to be upregulated, particularly on keratinocytes within inflamed skin (96). Concerning the influence of PUVA on ICAM-1 expression the results are currently inconsistent. On the one hand, epidermal ICAM-1 expression has been shown to be downregulated after multiple PUVA therapy sessions (96, 97), On the other hand, Lüftl *et al.* (80) observed that PUVA did not affect ICAM-1 expression. Since PUVA is quite effective in treating inflammatory dermatoses, Neuner *et al.* (98) studied the effect of PUVA on the release of the proinflammatory cytokines, such as IL-1, IL-6, IL-8, and TNF-alpha. Peripheral blood mononuclear cells (PBMCs) obtained from humans were incubated with 8-MOP and exposed to UVA. This treatment resulted in a significant reduction of IL-1, IL-6, IL-8, and TNF-alpha levels in the PBMC supernatants (98). PBMCs were obtained from psoriatics undergoing oral photochemotherapy before the beginning and after completion of treatment. The PBMCs collected after PUVA spontaneously produced significantly less IL-6 and IL-8 in comparison to the respective samples

obtained before therapy. Similar suppression of IL-1-beta and TNF-alpha by *in vivo* PUVA was observed in lipopolysaccharide (LPS)-stimulated PBMCs. The presented data demonstrate that PUVA both *in vitro* and *in vivo* suppressed production of the proinflammatory cytokines IL-1-beta, IL-6, IL-8, and TNF-alpha by PBMCs (98). Based on these findings the authors suggested that the inhibitory effects on cytokine expression could contribute to the antiinflammatory activity of PUVA. Recently PAF and PAF like molecules have been identified to be involved in the pathophysiologic effects of PUVA. Comparable to the UVB induced effects, IL-10 is also in PUVA part of the PAF- triggered cytokine cascade implying future therapeutical prospects (99).

In addition to oral PUVA, photochemotherapy can be also applied extracorporally. Extracorporal photophoresis is another example of therapeutically induced immunosuppression by an UV regimen. After having utilized photopheresis almost exclusively in the treatment of lymphoma patients, since its development, it is increasingly evident, that photopheresis is highly effective in the treatment of autoimmune diseases, transplant rejection, and graft-versus-host disease (100). Extracorporeal photopheresis is a pheresis treatment whereby the approximately $5x10^9$ leukocytes are extracorporally treated with 8-MOP and UVA light, and immediately returned to the patient in a closed-loop, patient-connected system. This therapy induces apoptosis of potentially inflammatory or malignant T cells. An experimental murine model for photopheresis gave evidence that photopheresis might induce antigen-specific regulatory T cells (101). Regulatory T cells generated by this method express CD4 and CD25, as demonstrated by depletion transfer studies. Future investigations have to show whether these types of regulatory T cells are also induced in humans undergoing extracorporal photopheresis.

4. SUMMARY AND PERSPECTIVES

Within the last decades a significant increase of knowledge has been achieved in the field of photoimmunology. As the result of various experimental studies, the mechanisms underlying UV-mediated beneficial and harmful effects are now much better understood in detail. UV-mediated immunosuppression and photocarcinogenesis are based on a highly complex crosstalk involving (among others) effects of chromophores, DNA-mutations, apoptosis, IL-10, *cis*-UCA, and regulatory T cells. Although many events contributing to the complexity of UV-induced immunoregulation have been unraveled, the results have not only answered questions but also led to new ones. To this end a new emerging field of photobiology is the research on the complexity of human skin color development and its role in vitamine D metabolism, skin infections, inflammation, and photocarcinogenesis. The advances made in photoimmunology could open future prospects not only for the treatment of dermatoses with immunological mechanisms but also for the prevention of UV-induced skin cancer.

5. ACKNOWLEDGMENTS

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Abbreviations: 5-HT: serotonin; 8-MOP: 8-methoxypsoralen alpha-MSH: alpha-melanocyte stimulating hormone; CD: clusters of differentiation; CGRP: calcitonin gene related peptide; CHS: contact hypersensitivitiy; CTCL: cutaneous T cell lymphoma; DNA: deoxyribonucleic acid; i.v:: intravenous; ICAM: intercellular adhesion molecule; IFN: interferon; IL: interleukin; L: ligand; LPS: lipopolysaccharide; MMP: matrix metalloproteinase family; PAF: platelet activating factor; PBMC: peripheral blood mononuclear cells; POP: psoralen photoproduct; PTP: permeability transition pore; ROS: reactive oxygen species; Th: T helper cell; TNF: tumor necrosis factor; TUNEL: terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labelling; UCA: urocanic acid; UV: ultraviolet

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