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Pathogenic mechanisms of polymorphic light eruption

Alexandra Gruber-Wackernagel,[1] Scott N. Byrne,[2] Peter Wolf[1]

[1]Research Unit for Photodermatology, Department of Dermatology, Medical University of Graz, Auenbruggerplatz 8, A-8036 Austria,[2]Department of Dermatology, Blackburn Building, D06, University of Sydney, Sydney, 2006 Australia,[1]Research Unit for Photodermatology, Department of Dermatology, Medical University of Graz, Auenbruggerplatz 8, A-8036 Austria

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1. ABSTRACT

Polymorphic light eruption (PLE) is a photodermatosis (i.e. "sun allergy") with a high prevalence, particularly among young women in temperate climates. It is characterized through itchy skin lesions of variable morphology, occurring in spring or early summer on sun exposed body sites. As yet the exact etiology and pathogenesis of PLE are unknown although a resistance to ultraviolet (UV)-radiation-induced immunosuppression (i.e. a physiologic phenomenon in normal healthy subjects) and a subsequent delayed type hypersensitivity (DTH) response to a UV-modified skin antigen (i.e. neo-antigen) has been suggested as a key factor in the disease. This article reviews the cellular and molecular disturbances associated with and most likely playing a role in pathogenesis of the disease.

2. INTRODUCTION AND CLINICAL ASPECTS

Polymorphic light eruption (PLE; "i.e., sun allergy") is the most common form of photodermatosis, with a prevalence of up to 10 to 20% in young women of the North American and European populations (1-4). Similar to lupus erythematosus (LE), a systemic autoimmune disease, PLE has a female preponderance and its mean onset in the second to third decade of life (5-8); however, symptoms may also begin in early childhood or late adulthood (5, 9-11). Although women are affected much more often (by a factor of approximately 4) (7, 8), men also do develop the condition in significant numbers (9). As the name of the condition implies, itchy non-scarring skin lesions of variable morphology appear several hours or even days after sun exposure on sun exposed skin sites, but not less than 30 minutes, and

subside in 7-10 days if further exposure is avoided (4, 7, 10-13). PLE lesions usually appear in spring or early summer (4, 10). Several morphological variants of PLE have been described, including papular, papulovesicular, plaque-type, erythema multiforme (EM)-like and insect bite-(strophulus) like forms (4, 6, 7, 9-11, 14). Despite the different morphology among different individuals, in general lesions are usually monomorphic in the same individual (4, 6). Jansen and Karvonen followed 114 PLE patients for 7 years and 76% reported consistent lesion morphology during the follow up period (15). The affected body sites are sun-exposed areas, particularly those that are normally covered during the winter such as the upper chest, the neck and the extensor aspects of the arms (6). The face and the hands of PLE patients are typically spared, presumably because these sites often receive daily sun exposure and thus undergo continuous natural hardening (16). Indeed, many individuals experience a hardening effect with prolonged sun exposure, occurring after repetitive exposures to UV radiation (10, 17). This means that, as summer progresses, skin lesions are less likely to occur, or may be less severe than they were in early spring allowing prolonged sun exposure. PLE is chronic in nature and in most affected subjects the disease has a persistent course with a slow tendency to amelioration (15, 18).

PLE has a wide geographic distribution and is seen much more frequently in temperate than tropical areas near the equator (1-4, 19). This difference is unlikely to be due to cultural, dietary or ethnic factors because the incidence rate of PLE in the UK, for instance, is approximately 15% compared with less than 5% in Australia, a difference that most likely can be attributed to the different amounts of UV in these geographical regions (3). The observation that PLE increases in prevalence and severity towards higher northern latitudes, where the relative differences in UVB between summer and winter are bigger may also indicate the importance of UV adaptation. Loss of adaptation of the skin to UV radiation (UVB) during winter, making the patients sun-sensitive in spring, is of paramount importance in the disease (20).

3. PHOTOBIOLOGIC WAVEBAND ASPECTS

The UV waveband action spectrum inducing PLE appears to be quite broad. In general, laboratory studies revealed that most PLE patients are sensitive to UVA, but lesions can also be induced with UVB alone, and some patients are sensitive to both waveband ranges (5, 6, 21-26). The observation that most PLE patients exhibit a sensitivity to sunlight through window glass (6, 27), along with the lack of protection from pure UVB absorbing sunscreens in the majority of PLE patients (28) substantiate the role of UVA in triggering the eruption. The importance of UVA is also supported by the fact that in PLE patients sunburn is not mandatory for provoking the manifestation of the disease. Additionally, the higher incidence of PLE in subjects living in temperate areas compared with tropical regions, may relate to the higher proportion of UVA compared to UVB rays during the spring and autumn in the former areas (3).

4. TREATMENT

The selection of the appropriate PLE treatment requires knowledge of the individual clinical course of the disease and depends on the frequency, duration and severity of the disease and the degree of lifestyle affection (29, 30). As PLE often causes problems during leisure-time activities and holidays, resulting in a substantial loss of quality of life, prophylaxis is an important therapeutic approach (29). Mild cases respond well to basic photoprotective measures such as avoiding sun exposure, the use of broad-spectrum sunscreens with high UVA protection capacity, and protective clothing (29). Topical corticosteroids and occasionally oral antihistamines reduce the inflammation, alleviate itch and can shorten the duration of the eruption (4, 10, 30). In patients with occasional bouts of the disease, oral steroids can be used to suppress PLE (31, 32). Other treatment options particularly in cases with severe symptoms include the administration of azathioprine (33), anti-malarials (6, 34, 35), or thalidomide (6).

Most PLE patients benefit from prophylactic treatment with phototherapy or photochemotherapy (hardening) to alleviate discomfort and lifestyle restrictions during the summer months or vacation periods in areas with high intensity sun exposure. As phototherapy modality, broad-band UVB (290-320nm), narrow-band UVB (311nm), broad-band UVA or psoralen plus UVA (PUVA) photochemotherapy is effective in PLE (5, 13, 22, 36-39). Photo(chemo)therapy stimulates the naturally occurring phenomenon of hardening and aims to induce photoadaptation with small, carefully regulated doses of UV radiation without inducing the manifestation of the disease. The mechanisms underlying this hardening effect are unknown but may be the result of increased melanization in the skin, thickening of the stratum corneum or immunological changes induced by UV radiation (12, 40, 41). Watanabe *et al* (42) reported that photo-hardening might be due to UV-induced immunosuppression, a theory supported by the down regulation of cell adhesion molecules and partially due to removal of un-identified endogenous antigens which cause a DTH reaction.

5. GENETIC FACTORS

The exact pathogenesis of PLE remains unclear but genetic factors seem to play a role. Epstein reported that PLE is particularly prevalent in the North American, Latin American Indian and the Finnish populations and that in these populations there appears to be a genetic (dominant) predisposition to develop the disorder (11). PLE patients with a family history of photosensitivity are described, ranging from 15% to 56% (1, 3, 17, 41, 43-46). Several authors have speculated that PLE is inherited as an autosomal dominant gene with reduced penetrance (6, 13, 16, 17, 43).

Two studies have investigated the genetics of PLE in greater detail, and the results of these studies suggest that a polygenic model can explain PLE inheritance (45, 46). These twin studies and genetic

modelling have established a clear genetic influence (45, 46). Millard *et al* (46) examined 420 pairs of adult female twins (119 monozygotic and 301 dizygotic twins) to assess the question of PLE inheritability. The prevalence of PLE, assessed by a quantitative genetic model, was 21% and 18% in monozygotic and dizygotic twins, respectively. The probandwise concordance for PLE was higher in monozygotic (0.72) than in dizygotic twin pairs (0.30), indicating a strong genetic effect. In addition, a family history of PLE in first-degree relatives was present in 12% of affected twins, compared with 4% in unaffected twins, providing evidence of a familial clustering. The data substantiate the possibility of a genetic susceptibility to PLE and demonstrate that the disease is multifactorial, comprising both genetic and unique environmental components. The authors estimated that the heritability of PLE is 84 to 87%, and that both a polygenic model of inheritance and a dominant single gene model could explain these data. Mc Gregor *et al* (45) used segregation analysis to assess the inheritability of photosensitivity in 420 individuals of PLE and actinic prurigo ascertained families. Across the pedigrees of 23 PLE probands a 21% prevalence of photosensitivity among the first-degree relatives of the probands was observed. The expression of PLE in genetically susceptible individuals was determined in large part by a polygenic model of inheritance, with an important additional environmental component, possibly exposure to sunlight. No evidence for a dominant single gene model was observed, but the authors caution that the small number and size of the PLE pedigrees analyzed limited the power to detect major single gene effects.

6. PATHOPHYSIOLOGY

6.1. Neo-antigens

The UVB radiation (290-320nm) is a potent activator of photochemical reactions and has the required energy to modify cellular organic molecules such as proteins and DNA (47, 48). Exposure to UVB can therefore create new or altered skin antigens that the immune system may recognize as foreign. While these neo-antigens have the potential to provoke (auto)-immune reactivity, at the same time the immunosuppressive properties of UV radiation may ensure that this adverse reaction does not occur in normal subjects (49-51) (Figure 1). For instance, epidermal cells derived from the skin of PLE patients and exposed to UV radiation are able to stimulate autologous peripheral blood mononuclear cells, suggesting indeed that a sensitization against autologous UV light modified skin antigens does occur in PLE (52).

A possible photoantigen candidate is heat shock protein 65 (HSP65), which given its importance in autoimmune processes such as LE has been implicated in PLE lesions (53). Mc Fadden *et al* (54) studied the expression of 65kD HSP (HSP65) immunoreactivity in skin biopsies from experimentally induced PLE lesions to investigate its possible role as a photo-induced antigen responsible for precipitating the manifestation of the disease. Increased HSP expression was detectable in epidermal keratinocytes and endothelial cells of dermal blood vessels from 1 h post-irradiation, and in dermal dendritic cells from 5 h sustained through to 6 days. In normal subjects there was no increase in HSP65 labelling.

One other possible photo-target is herpes simplex virus (HSV) because erythema multiforme (EM), a frequently recurring (muco)cutaneous syndrome often caused by HSV infection shares some similarities with PLE (55, 56). Both diseases are suspected to have an etiology involving cell-mediated (auto)immune reactivity, but while this reactivity in EM manifests itself against pertinent antigens like HSV, the PLE antigen remains unidentified. Reports of PLE patients, who became totally free of PLE symptoms while taking the anti-viral substance acyclovir (57), and of cases in which episodes of PLE were followed by recurrent EM (58), led us to search for the presence of HSV DNA in PLE skin lesions as a potential allergen in UV-exposed PLE skin. However, in contrast to EM lesions (10 of 31; 32%) we did not detect by PCR and Southern blot hybridization HSV DNA in any PLE skin sample, contradicting the hypothesis that a direct immune response to HSV antigens in the skin is involved in the pathogenesis of PLE (59).

6.2. Immune system

6.2.1. General immunological aspects

The skin infiltrate of PLE is composed mainly of activated Ia+ (HLA+) CD4+ cells resembling the histopathologic characteristics of DTH reactions (60). Moncada *et al* (61) characterized the dermal cell infiltrate and found a predominance of T helper (Th) cells and cells expressing high levels of Ia antigens, suggesting that an abnormal immune response is responsible for the tissue damage in PLE (61). This was later supported by the immunohistochemical studies of Norris *et al* (62) who observed that UVB exposure of PLE skin resulted in an initial influx of CD4+ T lymphocytes up to 72h in early lesions, followed by CD8+ T cells in established lesions, consistent with a cellular mediated immune reactivity underlying the pathogenesis of PLE. The predominantly lymphocytic perivascular cellular infiltration was associated with increased numbers of dermal macrophages and both dermal and epidermal Langerhans cells (LCs) within 5h of UV exposure. These features support the early hypothesis in 1942 by Epstein that PLE represents a DTH response to photo-induced antigens (63). The suggested immune response, responsible for the tissue alteration (64, 65) is also supported by the therapeutic response of PLE to immunosuppressive drugs (9). A critical factor in the pathogenesis of PLE is the effect of UV light on skin components (66). It was hypothesized that in genetically predisposed subjects UV light induces a modification of certain skin molecules that renders them immunogenic. Supporting this hypothesis is the observation that cultured epidermal cells from PLE patients are capable of stimulating autologous peripheral blood mononuclear cells after exposure to high doses of UVA or UVB, suggesting that an immune sensitization against autologous UV light-modified skin antigens occurs in PLE (52).

An immunological basis for the pathogenesis of PLE is further supported by the findings of Norris *et al* (67, 68), who compared the expression of endothelial leukocyte

adhesion molecule-1 (ELAM-1), intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) in UVB-induced erythema with delayed hypersensitivity. The expression of ELAM-1 was more prolonged and both VCAM-1 and ICAM-1 were induced in response to intra-cutaneous tuberculin-purified protein derivative (PPD) compared to UVB. Norris *et al* later extended their immunohistologic analysis of UV-induced PLE lesions (62) to correlate the expression of adhesion molecules ELAM-1, ICAM-1 and VCAM-1 to the presence of leucocytes during the evolution of this condition (68). The pattern of adhesion molecule expression was similar to that seen in normal skin during a DTH reaction, supporting an immunological basis for PLE. Additionally, Norris *et al* studied neutrophil tissue infiltration in developing PLE lesions and demonstrated neutrophil migration into the dermis beginning at 5h with maximal infiltration occurring from 24h onwards (68), similar to that observed in DTH responses (67). These results provide additional understanding of the immunologic basis of PLE and add further support to the concept that PLE is not simply an aberrant reaction to UV exposure (68). The findings are consistent with the hypothesis that PLE consists of a type IV hypersensitivity reaction to endogenous antigens induced by UV exposure, although the nature of the antigens remains obscure.

Using immunogenic skin tumors that would normally be rejected by naïve recipients, Fisher and Kripke pioneered in the seventies the field of photoimmunology and demonstrated that exposure to UV radiation prior to tumor inoculation would cause tumors to grow progressively (69). They concluded that UV radiation had immunosuppressive properties, inhibiting the host anti-tumor response. This UV-induced immunosuppression mimics what occurs in transplant patients on immunosuppressive chemotherapy (70). In addition to the suppression of anti-tumor immune responses, UV radiation also inhibits cell-mediated immune reactions generated during allergic contact dermatitis (49, 51). In normal human subjects the ability of contact allergens to generate strong T cell mediated immune responses is significantly suppressed by UV radiation (71-74). In addition to this failure to mount a primary immune response, immunological tolerance develops. This is observed when individuals treated in this way cannot be re-sensitized against the same hapten even when topically applied at a later time point. Furthermore, this UV-induced tolerance is hapten specific, as the sensitization against another non-related hapten is not affected. In the meantime we know that the UV-induced suppression of the ability of contact allergens to generate T cell-mediated responses in normal subjects (49) involves the release of cytokines, particularly tumor necrosis factor (TNF)-alpha, interleukin (IL)-4 and IL-10, the appearance of a HLA-DR+/CD11b+/CD1a- macrophage subset and the migration of LCs out of the epidermis (75) (Figure 1). Additionally mast cells are required for UV-induced immunosuppression as mast cell deficient mice are resistant to the effects of UVB (76). UVB exposure induces a recruitment of mast cells into irradiated skin sites, followed by migration of these cells to the draining lymph nodes, required for the activation of regulatory cells (77, 78). When this migration is blocked, UV-induced immunosuppression is prevented (77).

In addition to the dynamics in migration of these different cell populations, UVB radiation causes a temporal change in the cutaneous cytokine micromilieu, and the microenvironment becomes favorable to the development of type 2 helper (Th2) cell like immune responses (79) (Figure 1). Moreover, neuropeptides in the skin including calcitonin gene related peptide (CGRP) and substance P are significantly upregulated in UVB-exposed skin and play a significant role in UV-induced immunosuppression (80, 81). While UV-induced immunosuppression is often thought of as an obstacle to an effective anti-tumor immune response, there are many conceivable situations including induction and/or preservation of allograft tolerance (82), treatment of the autoimmune disease psoriasis, and the use of photopheresis to control graft versus host disease (83) where photo(chemo)therapy-induced immunosuppression can be beneficial.

6.2.2. Immune function in PLE

There is the hypothesis that PLE results from a failure of UVB-induced immunosuppression allowing a DTH reaction to UV induced neo-antigens (44, 62, 68, 84) (Figure 1). The delayed reaction time to UV radiation in PLE resembles that observed in immune responses mediated by CD4+ cells (85). This delay between sun exposure and manifestation of the PLE rash led Epstein to first suggest in 1942 that PLE might be due to a DTH response to autologous cutaneous antigens generated by UV radiation (63). It is hypothesized that the production of these antigens occurs in all people, but that in PLE there is a critical failure of UV-induced immunosuppression. However, a DTH response takes many hours (usually 48h) to develop (86) and so this hypothesis fails to explain the immediate photo-sensitive reaction displayed by PLE patients (i.e. lesions that appear in less than 1hr of UV exposure). This rather implies that PLE may be not directly related to a DTH reaction to neo-antigens (50).

Supporting the link between susceptibility to UV-induced immunosuppression and PLE incidence is the fact that PLE patients demonstrate a functional resistance to UV-induced immunosuppression, favoring a DTH response to potential UV-induced neo-antigens under certain circumstances (87, 88). The work by van de Pas *et al* (87) revealed that there was a narrow UV-dose window for this resistance to immunosuppression, with a significant difference found between groups irradiated with 1 minimal erythema dose (MED) of solar simulated UV radiation, but not those exposed to 0.6 or 2 MED. Contact hypersensitivity (CHS) responses of unirradiated skin of PLE patients were identical to healthy controls. The highest UV radiation dose used in this study (2 MED) was highly immunosuppressive in both PLE patients and controls, leading to almost complete immunosuppression by more than 90% in magnitude (87). This might explain why PLE lesions are often provoked by exposure to low doses of UV radiation but rarely by severe sunburn. Van de Pas *et al* further noted the possibility that PLE patients were less immunosuppressed after 1 MED exposure

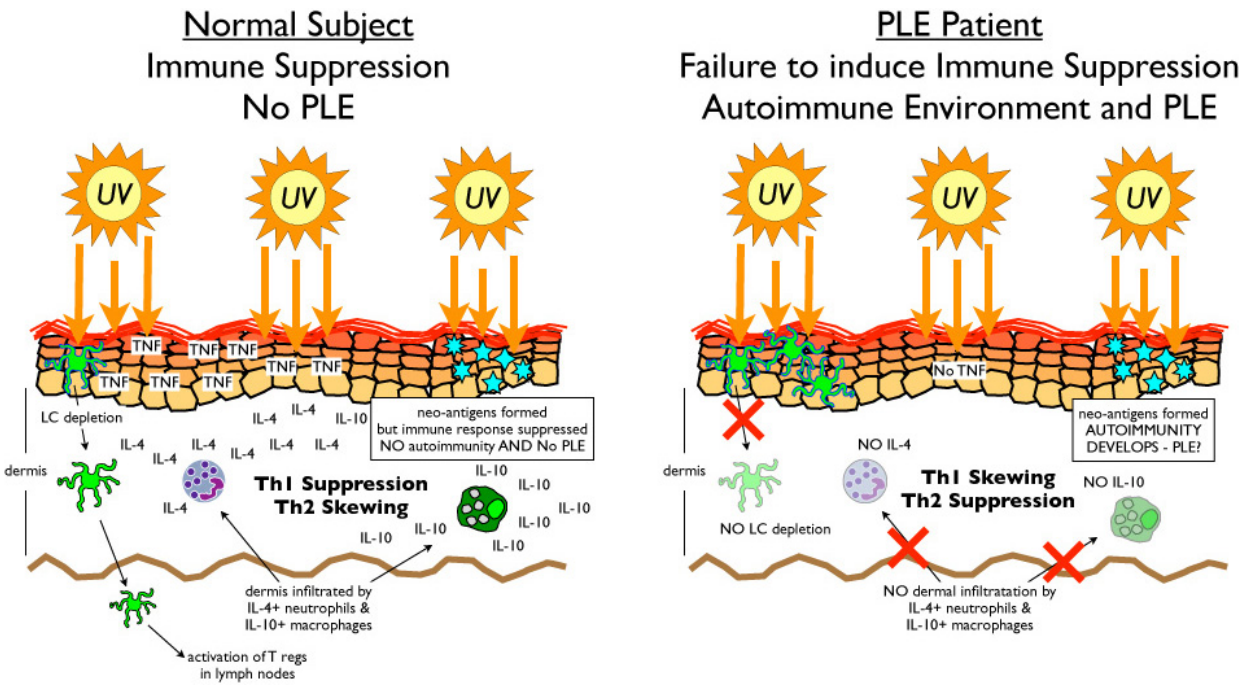

Figure 1. The schematic diagram highlights the potential pathogenic resistance to UV-induced immunosuppression in patients with PLE. It is hypothesized that exposure to UV radiation leads to the continuous formation of neo-antigens in the skin. In patients with PLE, a failure of UV-induced immunosuppression may favor the occurrence of autoimmunogenic skin rashes. In normal subjects, simultaneous UV-induced immunosuppression may prevent autoimmunity, and, therefore, the formation of skin rashes upon UVexposure.

possibly because in their study the physical dose of UV radiation required to induce erythema in PLE patients was slightly lower than that in controls. The dose response for immunosuppression is quite steep between 0.6 and 1 MED, so a small difference in physical dose may have confounded the results. To that end, and in contrast to the findings of van de Pas *et al,* we have found that the MED values of PLE patients did not differ significantly from those of normal subjects (5). Further studies are required to illuminate these differences and pathways.

6.2.3. Altered cell migration patterns in PLE

In healthy individuals, LCs disappear from the epidermis after UVB irradiation (51, 79, 89-91). IL-1beta, TNF-alpha, and IL-18 release can modulate LC migration out of the skin (92-98). Koelgen *et al* (99) investigated which of the two most likely mechanisms for LC disappearence, apoptosis or migration, is responsible for UVB induced LC depletion in healthy individuals (99). Their results suggested that in human healthy skin UVB-induced LC depletion is mainly caused by migration and not by apoptosis. Concurrently with the depletion of CD1a+ LCs after UV exposure, CD36+CD11+CD1- macrophage like cells expand in the dermis and infiltrate the epidermis (100). CD11b+ macrophage-like cells, including both macrophages and neutrophils, play an important role in the induction of tolerance and suppression of DTH after UVB irradiation (49, 101, 102). The CD11b+ macrophages, infiltrating the dermis and epidermis after UVB exposure were found to be potent producers of the immunosuppressive cytokine IL-10 (102, 103). Neutrophils expressing CD15 and CD11b, also migrate into human skin after UV irradiation (67, 104-107). In addition to other cells, including T cells, mast cells and NK cells, neutrophils are able to produce IL-4 (104, 108, 109). These cell migration patterns have important consequences for immunosuppression and current theory suggests that the migration of cells upon UV exposure in PLE skin differs from that in the skin of healthy individuals (Figure 1).

6.2.4. Differential expression of cytokines in PLE

To establish whether UVB exposure induces aberrant cytokine expression in the non-diseaseed skin of patients with PLE, Koelgen *et al* (110) compared the expression of UVB-induced cytokines in the skin of normal individuals with that from PLE patients. Their results showed that the skin of PLE patients contains lower levels of cytokines related to LC migration (IL-1, IL-18 and TNF-alpha). No differences were observed in the expression of Th1 related cytokines (IL-12, IFN gamma and IL-6), while there were fewer cells expressing the Th2-biasing cytokine, IL-4, in the epidermis of PLE patients 24h after irradiation (110). The results from concurrent immunohistochemical staining for neutrophils (elastase+), mast cells (tryptase+) and macrophages (CD36+) showed that after UV exposure, TNF-alpha, IL-4 and, to a lesser extent IL-10 was predominantly expressed by neutrophils, suggesting that the differences between healthy and PLE subjects might be attributable to the differences in cytokine secretion by neutrophils. Koelgen and colleagues concluded that the

reduced expression of neutrophil-derived TNF-alpha, IL-4 and IL-10 in UVB-irradiated PLE skin is responsible for both reduced LC migration and a failure to suppress Th1 responses in these patients (Figure 1).

In contrast to this study, we found no difference in cell migration or cytokine gene expression (mRNA levels of TNF-alpha, IL-1 beta, IL-10 and IL-12) between PLE patients and healthy controls. Furthermore, whereas Koelgen *et al* observed a persistence of epidermal LCs 48h and 72h after UV exposure in PLE skin, we found that the migration levels of CD1a+ LC did not significantly differ between PLE patients and healthy control subjects (111). There may be several explanations for the apparent differences in the results of these two studies including spectra (narrowband UVB in the Koelgen study vs solar simulated UV in our study), dose (6 MED vs 1, 2 and 3 MED) and kinetics (48-72h vs 6-24h). Nevertheless, our two studies both highlight the complexity of PLE pathogenesis and hint to further study into the immunological mechanisms of the disease**.**

6.2.5. Role of neutrophils in PLE

A role for neutrophils in UVB-induced skin pathology was supported by a study of Teunissen *et al* (104), who showed that UVB radiation induces a transient appearance of IL-4^+ neutrophils in normal human skin, and that these cells contribute to the enhanced development of Th2 cells in UVB-irradiated skin. This UV-induced IL-4 was of sufficient quantity to be measured in suction blister fluid obtained from UV-irradiated skin, although the cellular origin could not be determined (104). The authors could not exclude the possibility that IL-4 in the blister fluid originated from other cutaneous cells, for instance from mast cells, which are known to degranulate upon UVB irradiation (112). In addition to IL-4, an induction or increase in the levels of TNF-alpha, IL-6, and IL-8 was detected in the suction-blister fluid of UVB-exposed skin (104). Additionally it was shown that the presence of neutrophils affects T cell responses in primary T cell cultures derived from UVB-exposed skin. Dermal cell cultures from UVB-exposed skin, in contrast to unexposed skin, induced a predominant Th2 cell response that was abolished by removing the CD15+ neutrophils from the co-culture. The results by Teunissen *et al* suggest that the presence of neutrophils and IL 4, a strong Th2-polarizing cytokine (113), in UVB-exposed skin favor the development of Th2 cell responses in this tissue, while Th1 cell responses are concomitantly inhibited. This is relevant because IL-4 is known to be involved in UV-induced suppression of both DTH (114) and CHS (115).

IL-10 is an immunosuppressive cytokine that acts via inhibiting antigen presentation to Th1 cells (116) and is induced in normal skin upon UVB irradiation (102, 103, 117, 118). IL-10 counteracts IL-12 activity and inhibits the activation of Th1 cells allowing for the activation of Th2 cells (119). Piskin *et al* (107) reported that neutrophils infiltrating UVB-irradiated normal human skin display high IL-10 expression, although it is generally believed that IL-10 is predominantly expressed by CD11b+ HLA-DR+ macrophages that infiltrate the UVB-exposed skin (102, 103). However, since neutrophils invade UVB-exposed skin and, like macrophages, express CD11b and HLA-DR (104), Piskin *et al* sought to determine whether neutrophils represent another source of IL-10. As expected IL-10 could be detected in CD11b+ HLA-DR+ CD36+ macrophages in both the epidermis and dermis of UVB-exposed skin. Surprisingly, however, the majority of the abundant IL-10 expression was found in CD11b+ HLA-DR+ elastase+ neutrophils.

Via the production of these immunosuppressive cytokines, neutrophils may contribute to the development of a Th2 milieu, supporting an immunosuppressive microenvironment in UVB-exposed skin (104, 107, 120). The prominent role of IL-10 has been clearly demonstrated in UVB irradiated mice in which blocking of IL-10 resulted in the abolishment of not only UVB-induced immunosuppression (121) but also photocarcinogenesis (122). In IL-4 gene knockout mice the DTH response is not suppressed by UVB exposure (114) and injection of blocking anti-IL-4 abolishes UVB-induced immunosuppression (123), indicating that IL-4 plays an important role in the development of this immunosuppression.

Immunohistochemical studies by Schornagel *et al* (124) clearly demonstrated a significantly impaired neutrophilic infiltration into the skin of PLE patients compared with healthy controls after UVB irradiation. Neutrophils migrate to the skin shortly after UV exposure by binding to adhesion molecules expressed on the dermal endothelium (125). Because ICAM-1 and E-selectin on endothelial cells is critical to this migration, they compared the relative expression of these adhesion molecules. The immunohistochemical results showed that in both PLE patients and healthy controls ICAM-1 and E-selectin expression increased at 6h after UVB irradiation (124). Morevoer, neutrophil chemotactic responses to IL-8 and CD5a was similar in PLE patients and healthy controls. Thus, it is not entirely clear whether the failure of neutrophils to infiltrate PLE skin after UV-irradiation is due to local and/or not systemic pathogenic mechanisms.

In light of the fact that neutrophils produce a variety of immunosuppressive cytokines (IL-4 and IL-10) and can regulate immune reactions (104, 107, 120), it has been suggested that the oberserved decreased neutrophil infiltration after UVB irradiation of PLE skin leads to an impaired local production of IL-4 and IL-10, thereby altering the local skin cytokine milieu after UVB irradiation, resulting in activation of the skin immune response rather than suppression (Figure 1). Restoring normal immune cell migration may explain the beneficial effects of phototherapy in PLE patients. Koelgen *et al* (91) found that in a particularly sun sensitive PLE patient, successful hardening therapy increased the migration of LCs from the epidermis 48h after 6 MED overexposure. Similarily, studies by Janssens *et al* (126) showed that before hardening therapy, epidermal LC depletion and neutrophil influx at 48h after 6MED was impaired in UVB-provocable PLE patients compared with healthy controls. Phototherapy significantly improved UV-induced cell

migratory responses in these patients restoring both the capacity of UV-induced LC depletion and neutrophil infiltration into the skin.

6.3. Sex hormones

Another aspect of PLE that requires further investigation is the disproportionate incidence observed in females. This is interesting because it was recently found that compared to males, females are resistant to the immunosuppressive effects of UV radiation (74). Moreover, an earlier study by Widyarini *et al* (127) leads us to hypothesize that this sex difference may be due to protection from UV-induced immunosuppression afforded to females via signaling through the estrogen receptor. Interestingly, however, the role of oral hormonal contraceptives has been discussed controversially (128, 129). There does not seem to be a straightforward relationship between their use and the manifestation of PLE.

6.4. Relation to lupus erythematosus

Photosensitivity is one of the pathognomonic features of LE and in some cases the sun-related skin rash in lupus is virtually indistinguishable from PLE (130-133). The presence of antinuclear anibodies (ANA) in lupus patients was one of the early criteria used to distinguish PLE from lupus; however, several studies have demonstrated that PLE patients may have elevated ANA titers in the absence of other apparent lupus symptoms (5, 15, 18, 134, 135).

It has been suggested that PLE and LE may share a common pathogenesis (133-135). While progression of PLE to LE has been proposed, long term follow up studies of PLE subjects have not shown an increased risk of transition to LE (15, 18) although PLE lesions may precede the development of LE (132). The reported high prevalence of PLE in LE patients, together with the clustering of PLE among first degree relatives of subacute cutaneous lupus erythematosus (SCLE) and chronic cutaneous (discoid) lupus erythematosus (CCLE/DLE) subjects, suggests a shared pathogenic basis for PLE and cutaneous LE (132, 133). Millard *et al* (136) examined the relative risk (RR) attributable to the presence of PLE, together with the effect of the major histocompatibility complex (MHC) in the development of cutaneous LE. They found that PLE and the HLA DRB1 0301 extended haploptye are independent risk factors for cutaneous LE. An association was observed between PLE and cutaneous LE, but not between PLE and any HLA allele. It was estimated, for the general population, that the RR of developing SCLE given the presence of PLE, DRB1*0301 and both PLE and DRB1*0301 is 3.37, 5.45 and 12.03, respectively. For CCLE/DLE, equivalent RRs are 3.11, 2.15 and 6.94. These data imply the involvement of both PLE and HLA DRB1*0301 in the development of SCLE and CCLE/DLE.

Plasmacytoid Dendritic Cells (pDCs) are identical to the natural type I interferon (IFN)-producing cells (137), a rare CD4+/major histocompatibility complex (MHC) II+ population that is capable of synthesizing extremely high amounts of type I IFN upon viral infection (138). In addition to their classical antiviral and antiproliferative effects, type I IFNs like IFN-alpha also perform several prominent immunoregulatory functions, including the promotion of antigen-activated Th1 cell survival and differentiation, the development of autoantibodies, and, thus, the promotion of autoimmunity (139-141). Farkas *et al* (142) reported that pDCs accumulate in CCLE and systemic LE skin lesions and that their density correlates well with the high number IFN alpha/beta-inducible protein MxA+ cells (a surrogate marker for INF-alpha/beta in such lesions). Increased levels of IFN-alpha/beta is often found in LE patients and correlates with disease activity and severity. In light of these findings, we investigated whether pDCs populate the skin of UV-exposed PLE patients (143). Microscopic examination of the immunohistochemically stained sections confirmed the presence of CD68+/CD123+ pDCs in most specimens obtained from LE (10/11 [91%]) but not at all in those obtained from PLE patients. The absence of pDCs in PLE skin lesions did not support the hypothesis that these cells in conjunction with an increased production of IFN-alpha, play an immunomodulating role in PLE.

Concerning the suggested shared pathogenesis with LE, other investigators additionally found that UV-irradiated (with 6 MED), uninvolved skin of photosensitive LE patients did not exhibit the same pathologic trafficking of LCs and neutrophils as described for PLE patients. A gradual decrease of epidermal LCs and a gradual increase of epidermal neutrophils and macrophages were observed at several timepoints after six MED irradiation equally in both LE patients and controls (144). In light of all these studies it would seem that PLE is not generally predictive of LE. Indeed, there is increasing evidence supporting the idea that these two diseases may follow separate and distinct pathoetiological paths.

7. CONCLUSIONS AND PERSPECTIVES

In conclusion, clinical and experimental evidence supports the hypothesis of an aberrant cellular immune response in UV-exposed PLE skin, suggesting the presence of a UV-induced neo-antigen together with a failure of UV-induced immunosuppression. As yet, the presence of a possible photo-neo-antigen has not been confirmed but a resistance to UV-induced immunosuppression has been found in PLE patients. Considering the high prevalence of PLE, together with its increasing incidence, associated discomfort and life style restrictions, future studies are required to establish new therapeutic and/or preventive strategies. One such strategy may build on liposomes containing DNA repair enzymes (145-149). Indeed, a recent experimental study from our laboratory has revealed that DNA damage is a potential trigger of PLE, and that increasing DNA repair by topical application of liposomes containing specific DNA repair enzymes may afford protection from the induction of PLE symptoms (150). In an experimental set-up, the external administration of an after sun lotion with liposomes containing a combination of DNA repair enzymes (photolyase from *Anacystis nidulans* and endonucleases from *Micrococcus luteus* lysate)

significantly diminished PLE symptoms in human volunteers upon photoprovocation with artificial solar simulated UV radiation. While the exact mechanism, by which improving DNA repair may prevent PLE lesions remains to be determined, one possibility is that the enhanced removal of UV-induced DNA photoproducts may eliminate the initial antigenic trigger for an immune response in the UV-exposed skin of PLE patients. It furthermore remains to be investigated in more detail why patients with PLE are incapable to respond upon UV exposure with sufficient neutrophil infiltration of the skin (104, 124), possibly associated with a failure of immunosuppression (87, 88). One possibility is that there are biochemical abnormalities of the arachidonic acid and prostaglandin metabolism (151-153).

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Abbreviations: ANA: antinuclear antibodies; CCLE/DLE: chronic cutaneous (discoid) lupus erythmatosus; CHS: contact hypersensitivity; DTH: delayed type hypersensitivity; ELAM-1: endothelial cell adhesion molecule-1; EM: erythema multiforme; HSP65: heat shock protein 65; HSV: herpes simplex virus; ICAM-1: intercellular adhesion molecule-1; IFN: interferon; IL: interleukin; LC: Langerhans cell; LE: lupus erythematosus; MED: minimal erythema dose; MHC: major histocompatibility complex; pDC: plasmacytoid dendritic cell; PLE: polymorphic light eruption; RR: relative risk; Th: T helper; Th2: type 2 helper ; Th1: type 1 helper; TNF-alpha: tumor necrosis factor-alpha; UV: ultraviolet; VCAM-1: vascular cell adhesion molecule-1

Key Words: Polymorphic Light Eruption, UV radiation, UV-induced immunosuppression, UV resistance, neutrophil, Review

Send correspondence to: Peter Wolf, Department of Dermatology, Medical University of Graz, Auenbruggerplatz 8; A-8036 Austria, Tel: 43-316-385-2371, Fax: 43-316-385-2466, E-mail: peter.wolf@meduni-graz.at