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Photodermatoses and Skin Cancer

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1. Introduction

Photodermatoses are a group of skin diseases caused or exacerbated by light. Their classification is traditionally based on the cause of the disorder and on the pathology of cutaneous response. **Polymorphic light eruption (PLE)** is the commonest photosensitive disorder affecting up to 20% of the population, characterized by an intermittent eruption of non scarring pruritic erythematous papules, vesicles or plaques that develop on ultraviolet (UV) radiation (UVR)-exposed skin (Stratigos et al., 2002). The course of the disease is mainly chronic. The disease is multifactorial: a genetic susceptibility has been identified as well as environmental components. The spectrum of radiation that induces PLE is most commonly UVA and/or UVB wavelengths and, rarely, visible light. Epstein first hypothesized, over 60 years ago, that PLE was an immune-mediated disease. He postulated that PLE was a delayed-type hypersensitivity reaction (DTHR) to UVR induced cutaneous antigens (Epstein, 1986). Only during the past 20 years have studies emerged that support this theory. It is hypothesized that the DTHR associated with PLE is secondary to a partial failure of UVR-induced immunosuppression in patients with PLE. Multiple studies highlighted the greater role of Langerhans cells (LCs) in the sensitization phase and therefore suggested that LC dysfunction may be the underlying cause of PLE. In fact, in patients with PLE, LCs persist in the epidermis after intermittent UVB exposure whereas, in normal subjects, LCs disappear from the epidermis. In contrast, neutrophil infiltration in the skin after UVB exposure is significantly decreased in patients with PLE. Less neutrophilic infiltration may lead to impaired local production of cytokines such as interleukin (IL)-4 and IL-10. Altering the local skin milieu after UVR exposure eventually leads to activation of the skin immune response instead of suppression (Cooper et al., 1992). These observations would lead one to suppose that failure of immunosuppression following UVR exposure might give an advantage with regard to recognition of UV-induced tumour antigens and more effective elimination of such antigenic cells by the immune system. UVR-induced **skin cancer (SC)** is the most prevalent form of human neoplasm. It is well known that UVB (280–320 nm) and UVA (320-400 nm) radiation can induce DNA damage leading to melanoma or non melanoma SC by provoking mutations and immunosuppressive effects. The molecular changes induced by UV generate multiple consequent or concomitant mechanisms: DNA damage with thymidine dimer formation, urocanic acid (UCA) isomerization from trans-UCA to cis-UCA, depletion of some protective cytokines such as IL-1, IL-12 and interferon-γ (IFN-γ), or the increase of tumour necrosis factor-α (TNF-α), IL-6, IL-10 and IL-15, resulting

in the immunosuppressed skin milieu that permits and maintains the proliferation of mutated cellular clones (Kamiya, 2003). It would seem that the skin performs a 'balancing act' between adequate elimination of early cancerous cells and suppression of abnormal reactions against UV-exposed cells that may suffer transient aberrations. PLE appears to be associated with an 'imbalance' between UV-induced proinflammatory and UV-induced suppressive immunoreaction. From previous experiences, a reduced incidence of SC has been shown in patients with PLE compared with gender- and age-matched controls (Lembo et al., 2008). In support of the findings of this study, other studies indicated that either LC subtypes or tumour-derived cytokines play a crucial role in UV-induced skin tumours, determining LC depletion, attraction and immunoprotective function. Whereas there is considerable circumstantial evidence that disruption in the density and function of these cells, during the early stages of UVR-induced carcinogenesis, may be important for enabling developing neoplasms to escape immune destruction, the role of the large number of these cells found infiltrating developed skin tumours, remains unclear. Our aim was to provide an overview of UVR effects, photodermatoses and skin cancer, their epidemiology, incidence and the relationship of UVR-induced imbalance between immunosuppression or immunoactivation in PLE with relative skin cancer risk

2. Ultraviolet radiation

Sunlight is a continuous spectrum of electromagnetic radiation that is divided into three major spectrums of wavelength: ultraviolet, visible and infrared. The UV range is the most significant spectrum of sunlight that causes photoaging and skin cancer. UVR is subdivided into: ultraviolet A [UVA (320–400 nm)], ultraviolet B [UVB (280–320 nm)] and ultraviolet C [UVC (100–280 nm)]. UVA represent the 90–99% of the solar UVR energy that reaches the earth's surface; it is not filtered by the stratospheric ozone layer in the atmosphere and has long wavelength and low energy so it can penetrate deeper into the skin. Once considered harmless, but now believed to be harmful, in case of excessive and long-term exposure, causes skin aging and induces immediate and persistent pigmentation (tanning). In the recent years a carcinogenic role for UVA has also been proved. Only approximately 1–10% of UVB reaches the earth's surface because it is filtered by the stratospheric ozone layer in the atmosphere; it has short wavelength and high energy so it can penetrate the upper layers of the epidermis. UVB is responsible for sunburns, tanning, wrinkling, photoaging and skin cancer. UVC is filtered by the stratospheric ozone layer in the atmosphere before reaching earth; the major artificial sources are germicidal lamps. UVC burns the skin and causes skin cancer. Ultraviolet radiation that reaches the earth's surface can increase or decrease based on a variety of factors. One factor is the ozone layer, which forms a thin shield in the stratospheric atmosphere, protecting life on earth from the sun's UV rays; this layer absorbs all UVC radiation, most UVB radiation and very little UVA radiation. Since the mid 1980s, scientists began to be concerned that the ozone layer was being depleted. The reason for thinning of the stratospheric ozone is resulting from the release of ozone-depleting substances and chemicals (chlorofluorocarbons) that are released from industry and motor vehicle into the atmosphere. An approximate 1% decrease in ozone levels corresponds to a 1–2% increase in the mortality caused by melanoma (World Health Organization, 2009). Likewise, a 10% decrease in the ozone levels will cause 300,000 new non-melanoma and 4500 new melanoma skin cancer cases moreover, multiple factors such as time of the day, time of the year, latitude and altitude, determine UVR levels reaching earth's surface.

Depletion of the ozone layer results in increased UVR, (especially UVB) reaching the earth's surface. UVB is directly absorbed by DNA and causes structural DNA damage. UVA causes indirect DNA damage through the formation of reactive oxygen species, which create breaks in DNA. These events lead to mutations and then to skin cancer (Brenner et al., 2008). The sun exerts its highest peak between 10 AM to 4 PM. During this time, the sun's rays have the least distance to travel through the atmosphere and UVB levels are at their highest. In the early morning and late afternoon, the sun's rays pass through the atmosphere at an angle and their intensity is greatly reduced. The sun's angle varies with the seasons, causing the intensity of UV rays to change. UV intensity tends to be the highest during the summer season. Environmental factors that increase the amount of UVR exposure to humans include latitudes closer to the equator. At higher latitudes the sun is lower in the sky, so UV rays must travel a greater distance through ozone-rich portions of the atmosphere and in turn, less UVR is emitted. Hence, living closer to the equator increases UV exposure, thus increasing the incidence of skin cancers. For every 1000 meters increase in elevation, the UVR intensity increases by 10–12%. UV levels also depend on cloud cover; thus, there are lower UV levels at higher cloud cover densities. In the summer, the sun is higher in the sky, and less ultraviolet radiation is absorbed during its passage through the atmosphere. Fog, haze, clouds and pollutants can reduce ultraviolet levels by 10–90%. Snow, sand and metal can reflect up to 90% of ultraviolet radiation. Sea water can reflect up to 15%, whereas little reflection occurs on still water (e.g., a pool). Shade alone reduces solar UVR by 50–95%. The amount of protection varies considerably between different shades settings, with a beach umbrella showing the least and dense foliage the most protection. The best technique for reducing ultraviolet exposure is to avoid the sun, especially in the middle of the day (Lautenschlager et al., 2007) . There is accumulating evidence that UVR in physiological doses exerts multiple effects on the immune system: such as inducing immune system but suppressing the adaptive one. Both effects may be beneficial, protecting from microbial infections on the one hand and toning down allergic and autoimmune reactions on the other hand; but these effects on the immune system are also responsible of the dangerous effects of UVR such as photodermatoses and skin cancer.

2.1 UVR effects

Solar UVR makes up just 5% of the electromagnetic spectrum that reaches the earth's surface. Three spectral regions have been designated based on their biological effects. Terrestrial UVR consists of 3– 6% UVB and 94– 97% UVA. Negligible amounts of UVC reach the earth's surface due to the filtering capacity of the ozone layer (Diffey, 2002). UVR is a potent environmental carcinogen and is largely responsible for the development of the most common cancer worldwide: skin cancer. The steady increases in melanoma and non-melanoma skin cancer cases, contrast with the recent downward incidence for all other cancers (excluding lung cancer in women). The increases in skin cancer are largely attributed to recreational sun exposure (including tanning beds) practiced by the population. Concern that further increases in skin cancer incidence may result due to ozone depletion, may be tempered by positive global efforts to reduce ozone-depleting substances in the atmosphere (Jemal et al., 2007). The genetic mechanisms by which UVR transforms and promotes various skin cancers have been under intense investigation for decades, and much progress has been made in identifying genes that contribute to the oncogenic process in the development of melanoma, squamous cell carcinoma (SSC) and basal cell carcinoma

(BCC). However, in addition to generating genetic mutations, UVR actively suppresses the normal processes of immune surveillance responsible for eliminating mutant cells, and permits tumor growth. UVR is highly mutagenic but is only partially absorbed by the outer stratum corneum of the epidermis Depending on melanin content UVR can penetrate into the deeper layers of the epidermis, where induces DNA damage and apoptosis in epidermal cells, including those in the germinative basal layer. The cellular decision, to initiate either the cellular repair processes or undergo apoptosis, has evolved to balance the acute need to maintain skin barrier function with the long-term risk of retaining precancerous cells. Langerhans cells are positioned suprabasally, where they may sense UV damage directly, or indirectly through recognition of apoptotic vesicles and soluble mediators derived from surrounding keratinocytes. Apoptotic bodies will contain UV-induced altered proteins (enzymes, proteins that regulate cells proliferation and apoptosis process) that may be presented to the immune system as foreign. The observation that UVR induces immune tolerance to skin-associated antigens suggests that this photodamage response has evolved to preserve the skin barrier by protecting it from autoimmune attack. LC involvement in this process is not clear and controversial. In order to ameliorate the world-wide burden of UVR related pathologies such as sunburn, aging, autoimmunity, immune suppression and skin cancer, it is imperative that we gain a better understanding of the mechanisms of UVA and UVB induced photodamage and how they relate to the molecular and immunologic nature of photodamage responses.

2.1.1 The link between UV-induced inflammation and carcinogenesis

UV augments blood flow and infiltration by blood leukocytes, such as macrophages and neutrophils into the skin, observed clinically as inflammation. Increased production of NO and prostaglandins contribute to these events. UVR-induced lipid peroxidation increases production of prostaglandins (PG), including PGE2, which, in turn, cause inflammation in the skin. PGE-2 is produced from arachidonic acid by the inducible form of cyclooxygenase (COX), COX-2. This is thought to be due to UV increasing phospholipase activity, thus enhancing arachidonic acid availability for PG production. Dietary supplementation with fish oils has been shown to reduce UV-induced inflammation in humans, probably due to a reduction in UV-induced PGE-2 production. Other UV-induced mediators, such as tumour necrosis factor and interleukin 1 also contribute to UV-induced inflammation. The inflammatory cells, infiltrating UV exposed skin, produce ROS that further drive damage to lipids, proteins and DNA. Thus, UV-induced oxidative damage to lipids, and activation of NO synthase (Warren, 1994) initiates a cascade of events resulting in inflammation, which causes further reactive oxygen stress in the skin. As ROS produced by inflammatory cells is linked to gene mutations, it seems to be a reasonable hypothesis that UV-induced inflammation results in genetic damage, which contributes to photocarcinogenesis. There is a large amount of literature supporting a role for inflammation in driving tumour progression, and anti-inflammatory drugs have been shown to reduce the incidence of cancer (Balkwill & Mantovani, 2001). A number of animal models have shown that inhibition of COX-2 helps prevent skin cancer: Celecoxib, a COX-2 inhibitor, decreases macrophages and neutrophils infiltration into skin tumours; Indomethacin, which inhibits both COX-1 and 2, reduces photocarcinogenesis in mice. The cancer protective effect of COX-2 inhibition may be due to prevention of inflammation: it has been suggested, in fact, that this may enhance apoptosis of UV damaged keratinocytes as PGE2 signalling is

required for growth of skin tumour cells (Thompson et al., 2001). UV-induced infiltration of the skin by granulocytes and macrophages has been shown to enhance the growth of a UV-induced regressor skin tumour. UV-induced regressor skin tumours grow for about 1–2 weeks after transplantation into syngeneic mice before being rejected by the immune system, so that they decrease in size after this time. In these studies, a single inflammatory dose of UVR caused infiltration of the skin by CD11b+, Gr-1+, CD45+, MHC Class II+ cells, which were likely to be macrophages and or granulocytes (Thompson et al., 2001). Time courses demonstrated an enhancement of tumour growth only when these cells were present at high numbers in the skin: therefore UV-induced inflammatory cells promoted skin tumour growth. Other studies have shown that UV radiation induces infiltration of neutrophils and macrophages into the skin of mice and humans. As UV-induced inflammatory cells produce hydrogen peroxide and NO, it is likely that ROS produced by these inflammatory cells contribute to skin tumour development at least in part by enhancing gene mutation, but they may also suppress immunity. Moreover, it has also been suggested that inflammatory cytokine induction of iNOS results in increased NO production which inhibits DNA repair, thus promoting carcinogenesis. Both of these are likely to contribute to skin cancer formation.

2.1.2 UV-induced oxidative damage and gene mutation

There is little direct evidence for oxidative damage to DNA making a substantial contribution to photocarcinogenesis.

The formation of micronuclei is an indication of chromosomal rearrangement or genetic instability. UVA-induced micronucleus formation in cultured HaCaT cells was reduced by treatment with catalase, suggesting a role for hydrogen peroxide in this form of UVA-induced genetic damage (Phillipson et al., 2002). UVB absorbed by two adjacent cytosine (C) residues in DNA causes the formation of cyclobutane pyrimidine dimers (CPD), which result in GC to AT mutations. These only occur in response to UVB and can be regarded as fingerprints for UVB; UVA-induced CPD formation is orders of magnitude less frequent. In contrast, UVA indirectly induces the fingerprint mutations AT to CG at high frequency, but these rarely result from UVB or other mutagens. Reactive oxygen and nitrogen species can cause many different types of gene mutations, but guanine is the most sensitive of the DNA bases to oxidation, as it has the lowest oxidation potential. Hence, G to T, G to C and G to A mutations at sites other than dipyrimidines are frequently caused by ROS (Kamiya, 2003). However, ROS cannot be assigned to be the mutagen as confidently in these cases as UVB and UVA can be identified when the fingerprints mentioned above are observed. UVA itself can cause oxidation of guanine indirectly via ROS production, or the ROS can come from other sources such as inflammatory cells. However, in combination with UVA-induced fingerprints to account for the role of UVA, mutations at guanine sites can give an indication of the likely extent to which DNA is mutated in response to ROS from sources other than UVA, such as inflammatory cells. In a recent study, different regions of about 20 keratinocytes from human solar keratosis (SK) and SCC were microdissected to analyse the p53 gene for mutations. Using the criteria described above, the mutations could be grouped into those most likely caused by ROS, UVB or UVA. When the cause of the mutations could not be unambiguously identified they were grouped as "other", but some of these could have been due to ROS, UVB or UVA. About one-third of the mutations in SK were caused by sunlight with an equal number resulting from UVA and UVB. ROS caused a slightly

larger number of mutations than UV, showing that ROS make a significant contribution to the mutational burden in these benign pre-malignant lesions. When comparing SK to SCC, it was found that SCC contained an increase in mutational burden of 14 ROS, 5 other, 4 UVB, but 0 UVA-induced mutations (Agar et al., 2004). Thus, ROS appear to be responsible for the majority of the increase in mutations as SK progress into SCC. UV does not appear to be the major mutagen driving SK progression towards SCC, as there was little difference in UVB and UVA fingerprints between these lesions. Therefore, the increase in ROS induced mutations probably did not result from UVA-induced ROS. This data appear to indicate that the mixture of UVA and UVB in sunlight is largely responsible for the mutations that lead to SK, but the main factor that then drives these benign lesions to progress to malignancy is ROS. The cause of a large number of the mutations could not be identified, and therefore some caution is required in interpreting this data. These mutations could have been caused by UVB, UVA or ROS, but were not identifiable as such, or they may have resulted from a yet unknown event. It has been reported that patients with SK have reduced plasma antioxidant defence (Vural et al., 1999), which may contribute to oxidation induced gene damage in SK. Most SK do not develop into SCC and often spontaneously regress. However, an inflammatory response, developing for unknown reasons in a small subset of SK appears to be associated with progression towards malignant SCC. The major mutagen driving SK progression to SCC appears to be ROS, rather than sunlight, suggesting that reactive oxygen and nitrogen species from inflammatory cells is responsible for progression of SK into SCC. While UVA can cause gene mutations indirectly, via reactive oxygen mediated processes, the absence of a large increase in UVB-induced gene mutations as SK progress towards SCC suggests that little of the ROS-mediated damage driving progression of SK to SCC arose from sunlight.

2.1.3 UV-induced immunosuppression

Ultraviolet radiation not only causes DNA damage but also is a potent immunosuppressive agent. This was demonstrated in a series of elegant experiments carried out by Kripke (Fisher & Kripke, 1977). In syngeneic mice, UVR-induced skin cancers were transplanted into mice which were either irradiated with UVB or not irradiated. In those mice irradiated with UVB the tumours continued to grow, whereas those not irradiated were able to reject the transplanted tumours. The induced immunosuppression was also transferable by lymphocytes from irradiated mice (unable to reject the tumours) injected into non irradiated mice. It is known that UVR-induced immunosuppression is a complex process (Figure 1). *UVR action* spectrum for induction of CPDs is now known to be identical to that of Tumour necrosis factor alpha which in turn is induced by Interleukin-1. Direct immunosuppression locally in the skin comes about when UVB directly impacts on Langerhans cells. LCs: dendritic cells critical for the presention of antigens to the immune system, very sensitive even to UVR minimal dose. In a series of human experiments, solar simulated radiation whether, given as a single minimal erythema dose, or over ten times the time period, but with irradiance at 10% of the dose, or over 10 days at one tenth of MED, the outcome was the same: LCs numbers were depleted (Figure 1). The ability to do this appears to be genetic, and, in those individuals who fail to deplete LCs when initially exposed to antigen in the setting of UV exposure, PLE occurs. This ability to resist UV-induced depletion appears to be protective against skin cancer development. This hypothesis is supported by an epidemiological study of the prevalence of polymorphic light eruption in those who have

skin cancer, despite apparently equivalent UVR exposure, the prevalence of PLE appeared reduced (Lembo et al., 2008). Kripke's experiments in mice suggest that SCCs are highly antigenic, thus mechanisms whereby antigen is recognised are relevant in the process of preventing UVR initiated skin cancers (Timares et al., 2008). Mutated cells carrying highly relevant p53 mutations are well described. Such clones of mutated cells are found in chronically UVR exposed skin. If the immune system is functioning, such mutant cells may be policed by antigen presenting cells and T memory cells and progression to skin cancers can be stopped. CPD are linked with the suppression of T memory cells thus UVR reduces immune surveillance by this mechanism. Therefore when immune regulation is perturbed, such as with ongoing sun-exposure, chronic lymphatic leukaemia or with long term systemic immuno-suppression, failure of immune regulation leads to progression of these clones to actinic keratoses and frankly invasive squamous cell carcinomas. Nucleotide excision repair is a very important protective response against skin cancer. Pyrimidine dimer formation in DNA initiates the tanning response in UV-irradiated mice. DNA repair results in fragments of DNA being excised from the DNA molecule, these tiny oligomers have been shown to directly cause immunoprotective effects when applied to the skin (Arad et al., 2006). A further UVR immunosuppressive effect is the isomerisation of a chemical component of the stratum corneum.: urocanic acid normally exists in its trans-isoform but with irradiation by UVB is transformed to its cis-isomer which is a powerful systemic immunosuppressant (Figure 1). The action spectrum for the induction of this process appears to be in the UVB range. There is evidence to suggest that cis-urocanic acid's ability to suppress contact hypersensitivity is mediated via TNF-α (McLoone et al., 2005). UV-irradiated urocanic acid is also able to suppress delayed hypersensitivity reactions to herpes simplex in mice (Ross et al., 1986). The complexity of UV-induced immunosuppression is compounded by the ability of UVR to modulate four main families of growth factors: epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), and insulin receptor (IR), and in addition primary cytokines each of which has immunosuppressive effects. Apart from TNF-α, the interleukin family have wide ranging effects often interdependent. UV induces IL-1, IL-6, IL-10 amongst others. IL-10 is considered very important as a mediator of systemic immunosuppression (Ghoreihi & Dutz, 2006): tolerance induction by immunisation through UVR irradiated skin is transferable through CD4+CD25+ T regulatory cells and is dependant on IL-10 produced by the host. The mechanisms underlying UVR-induced tolerance therefore are complex and constantly being refined. UVR also induces platelet-derived growth factor (PDGF) thought to be pivotal both in UVB-induced immunosuppression and also the immunosuppression induced by PUVA. UVB activates receptors for the primary cytokines interleukin-1 and tumor necrosis factor-α and the death receptor Fas. UV also induces melanin stimulating hormone (MSH) locally, from keratinocytes; such paracrine secretion plays a critical role in local cell regulation from an immunosuppressive and proinflammatory point of view. The receptor for pigment regulation within melanocytes: melanocortin receptor (MCR) is also regulated by UVR (Figure 1). While increasing doses of UVB were found to cause increasing levels of immunosuppression, only a narrow range of UVA or solar-simulated UV suppressed the immune system. Doses of about 1.8 J/cm2 solar-simulated UV (0.5 minimum erythema dose [MED]) delivered for three consecutive days, but not twice this dose-suppressed immunity to an antigen delivered to un-irradiated skin (induction of systemic immunosuppression). The *UVA component* of this, 1.68 J/cm2, was also

immunosuppressive, but twice this dose was not. It appears that while this low dose of UVA damages the immune system, higher doses can actually protect the immune system from UVB effects . UVA has also been reported to be as effective as solar-simulated UV at suppressing the reactivation of secondary immunity in mice (Moyal & Fourtanier, 2001). It, therefore, appears that different doses of UVA can affect immunity in quite different ways, presumably because UVA has complex dose effects on unknown molecular events. Doses of UVA within the range used some studies have been shown to produce ROS in human skin, and these ROS can be inhibited with reactive oxygen quenchers (Ou-Yanh, 2004). As increasing doses of UVA cause higher levels of ROS in the skin. It is likely that ROS are involved in UVA-induced immunosuppression. High dose UVA, which reverses UVB-induced immunosuppression has been shown to mediate this effect via production of the antioxidant heme oxygenase enzyme. Thus, it seems probable that low doses of UVA initiate ROS production, which suppress skin immunity. In contrast, higher does of UVA stimulate production of protective antioxidant enzymes, thus reversing the suppressive effects of ROS and UVB. There has been some experimentation that supports the above hypothesis that UVA causes immunosuppression via a ROS-dependent mechanism, but considerably more work is required to definitively answer this issue and determine the steps involved. Other mediators may also be involved in UVA modulation of immunity, such as PGE2. It has been suggested that a cascade of events, initiated by UV-induced PGE2 production in the skin, in turn induces production of IL-4 and IL-10, which cause systemic immunosuppression (Figure 1). As increase PGE2 is a downstream event of lipids oxidative damage, the important role of UV-induced oxidative damage in photoimmunosuppression is highlighted. PGE2 has also been implicated in immunosuppression during chemical carcinogenesis in the skin (Andrews et al., 1991). More recently it has been shown that oxidized lipids, such as phosphatidylcholine, are recognized by the platelet activating factor receptor able to trigger immunosuppression (Walterscheid et al., 2002). The practical and visible consequences of these immunological perturbations are those of carcinogenesis, photoallergic reactions and infections. *Latent viral infection* can be triggered or enhanced by UVR. The action spectrum for induction or activation of Herpes Simplex and/or Varicella Zoster virus seems to be in the UVB range. A new viral infection linked with UVR is the recently described *Merkel cell polyoma virus* (Paulson et al., 2009) and *Human papilloma virus (HPV)*. HPV is ubiquitous in human skin, it is thought that the skin is colonised shortly after birth. More than 100 different virus subtypes are described and divided into mucosal and non-mucosal types. Different subtypes are associated with different clinical pictures. Up to recently, it was assumed that cutaneous sub-types did not interfere with apoptosis, as is the case for high risk subtypes, in which the E6 protein functions as a block in the apoptotic pathway interfering with the tumour suppressor gene p53. The consequence for those carrying high risk mucosal HPV may be anogenital squamous cell carcinoma. The role of human papilloma virus in carcinogenesis is well established in cervical cancer, in which persistent carriage of high risk viral types 16, 18, 31 and 33 are incontrovertibly implicated in cancer pathogenesis. In keratinised skin, until recently, the story was less clear other than in the rare syndrome epidermodysplasia verruciformis (EV), where medium risk oncogenic type 5, 7 and 12 HPV interact with UVR to induce cancer. High risk HPV types 16 and 18 on keratinised skin are found rarely in periungual warts. Something important is supposed to occur in transitional areas: keratinised skin-mucosal epithelium or keratinised skin-nail. HPV favours anogenital areas,

lips nose and also UV-irradiated skin. Plane warts are almost inevitably found on the dorsum of the hands and the face, sites of maximal UV dose. Immunosuppression caused by UVR in irradiated areas leads to skin exquisitely suited to the proliferation of HPV; with the defences down, immune surveillance at a minimum, it is no surprise therefore that warts or dysplastic lesions, depending on HPV type, will flourish in these circumstances (O' Connor, 2001). Recently mechanistic evidence has emerged implicating medium risk HPV in the aetiology of non-melanoma skin cancer, particularly squamous cell carcinomas, specially in immunosuppressed individuals. Mutated cells normally are shifted to the apoptotic pathway, but HPV has the ability to abrogate the proapoptotic BAK signalling via the E6 protein, leading to damaged cell survival (Leverrier et al., 2007). One of the difficulties when discussing immunosuppression is the absence of a good and standardized measure of immunosuppression. Most studies have measured effects of UVR on abrogating delayed hypersensitivity responses. In the context of contact dermatitis the immunosuppression-immunosurveillance state can be clinically evident through patch testing before and after UVR exposure. There is no good marker which reliably determines immunosuppression: the only epidemiological marker is circulating CD4 count.
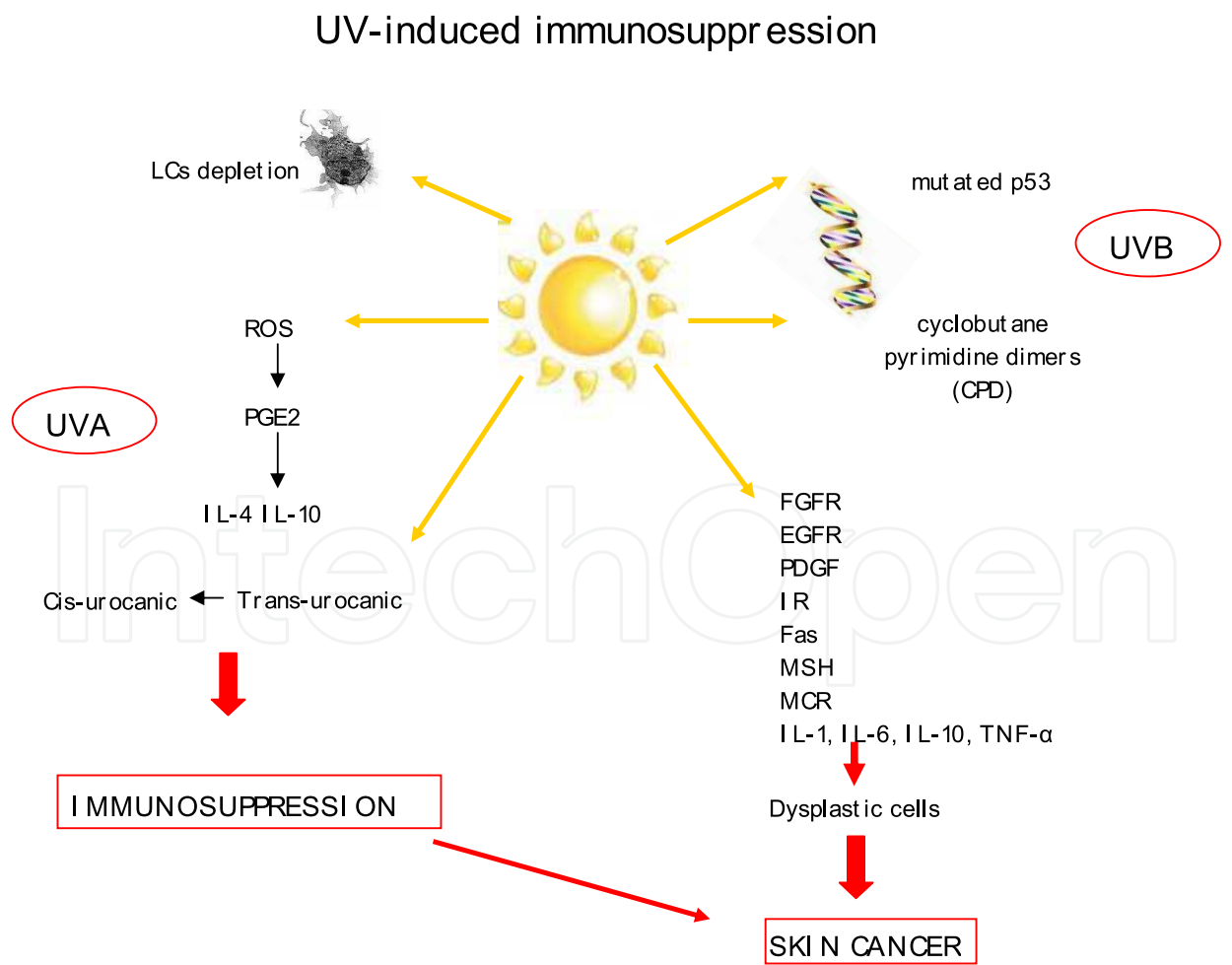

Fig. 1. UV-induced immunosuppression.

3. Photosensitive disorders

Photosensitive disorders occur when human skin reacts abnormally to UVR or visible light (Murphy et al., 2001). Normal human skin produces a range of responses designed to protect man from adverse effects of UVR. The normal response is determined by skin colour, which is in part genetically determined, and skin thickness, which is influenced by adaptive responses to UVR (Murphy et al., 1991). The presence, extent and thickness of hair determine photoprotection. Age, pigment adaptation, body site and also antiinflammatory agents influence responsiveness to UVR. Classification of the photodermatoses traditionally is based on the cause of the disorder, where known, and on the pathology of cutaneous response (Table 1). Observation of the clinical patterns of skin reactivity and the timing of the response helps the investigator to classify disorders as many photodermatoses are of unknown cause. Photosensitive disorders may be broadly classified as primarily UVR induced such disorders include the idiopathic (some of which may perhaps now be better described as autoimmune) photodermatoses: Polymorphic light eruption, Juvenile spring eruption, Actinic prurigo (AP), Solar urticaria (SU), Hydroa vacciniforme, Chronic actinic dermatitis (CAD), Brachioradial pruritus, Actinic folliculitis. Phototoxic diseases are caused by external agents either systemic, or topically applied, which predictably lower the threshold for abnormal UVR responses. Photoallergic disorders occur idiosyncratically and may not be predicted, they are less common than phototoxic reactions and are determined by either delayed hypersensitivity responses or, more rarely, immediate hypersensitive reactions IgE mediated. Diseases that are characteristically *photosensitive*, but with other manifestations, include: xeroderma pigmentosum (XP), trichothiodystrophy (TTD), the Rothmund–Thompson syndrome and the cutaneous porphyries. *Photoaggravated* diseases are numerous: Lupus erythematosus (LE), Dermatomyositis, Psoriasis, Rosacea, Lichen Planus, Autoimmune bullous disease; these disorders occur independently of environmental UVR exposure, but may be worsened by exposure to UV. History and physical examination are most important aspects in the diagnosis of the photodermatoses. Most photodermatoses are manifest by cutaneous response to the sun at a lower dose to that which might be expected. The responses may be summarized either as inappropriate redness of the skin occurring immediately or as a delayed response. Immediate erythema occurring minutes after UVR exposure may be caused by SU, drugs, chemicals such as tar or creosote. Erythropoietic protoporphyria or rarely porphyria cutanea tarda may exhibit immediate erythema and urticaria, these latter responses are observed during formal testing with UVR and visible light more than with ambient daylight. Immediate erythema may, rarely be caused by contact allergens such as sunscreens. The morphology of responses is very variable and polymorphic: maculopapular eruptions occurring after UV are, most frequently, expression of PLE. However, similar reactions may also occur with LE, AP, erythema multiforme and drug eruptions. *Urticaria* case occurs in response to UV in SU, rarely as a response to drugs and in case of porphyria (erythropoietic protopophyria (EPP). *Eczema,* as a late reaction to UVR, occurs in CAD, in photosensitive atopic eczema and in AIDS where patients at a young age may develop photosensitive eczema (Wong & Khoo, 2003). In drug-induced photosensitivity, eczema also may be the consequence of agents such as thiazides. *Lichenoid responses* also may occur in response to many drugs including thiazides (Johnston, 2002). *Bullous reaction* to UVR and visible light can represent the clinical

picture of Hydroa vacciniforme (HV), a rare childhood disorder, mainly induced by UVA. Umbilicated blisters occur on the face and other exposed areas. Blistering, most frequently on the backs of the hands, can be seen also in cutaneous porphyrias. Drugs such as frusemide, nalidixic acid and amino-quinolones do not infrequently produce blistering in sunlight. Pseudo-porphyria is also recognized as a reaction to numerous agents. This disorder may occur not only with drugs, but also to sunbed over-exposure, and in those who sunbathe excessively with poor sun protection, with excessive UVA exposure. Endogenous porphyrins may be the relevant chromophore in the absence of a relevant drug (Murphy, 1989). *Telangiectasia* may be the endpoint of photosensitivity in some situations. ACE inhibitors lead to photodistributed telangiectasia in patients, especially in renal transplant patients. *Phototoxic burning* represents an immediate discomfort of the skin on exposure to UVR or visible light in the absence of visible signs. This may also occur with drugs, topical agents such as tar or porphyria, especially in patient attended with EPP, or in treatment with photodynamic therapy (PDT) using amino-laevulinic acid or its esters that are metabolized to protoporphyrin IX. Phototoxic burning with PDT is particularly a problem with renal transplant patients where interactions may occur with the many photoactive drugs being taken. *Hyperpigmentation* also occurs as a response to photosensitivity, this may represent post-inflammatory hyperpigmentation, or interaction of UV/visible light with hormonally induced pigmentation as in melasma. In dark skin, photosensitivity may be primarily observable as hyperpigmentation. All dermatologists will be aware of the ability of PUVA to pigment skin. Lichen planus may be photoaggravated; clinically this may look like hyperpigmentation, but histology shows a lichenoid infiltrate. *Hypopigmentation* may be seen in CAD, and this seems to be post-inflammatory hypopigmentation. In some patients, as post-inflammatory reaction because of the Koebner phenomenon, vitiligo occurs. Vitiligo is made worse by sun exposure in some patients. Prurigo lesions, in the absence of obvious primary lesions are seen in AP, excoriations are maximally seen in UV-exposed areas but sun-protected sites also may be affected possibly as autosensitization. *Photo-onycholysis* may occur as an idiopathic phenomenon, but may be caused by some drugs, particularly tetracyclines, psoralens or it may occur in porphyria. It is infrequent because of the protective nature of the nail itself: thick keratin is very photoprotective. *Photorecall* reactions may also occur. Perhaps, 5-fluorouracil given systemically is the most frequent cause of this reaction. Patients undergoing chemotherapy with this agent may develop florid redness and burning and even erosion of photodamaged skin even though they may not have been outdoors for weeks. Presumably the reaction is similar to that of topical Efudix that selectively kills cells with the most UV-induced damage. *Pruritus* may be the sole manifestation of photosensitivity. Immediate pruritus suggests SU, and it rarely occurs in the absence of erythema and urticaria. *Pruritus* occurring within hours with the same time course as PLE has been described sine eruptione. Itching can occur 1–2 weeks after sunburn probably representing the reaction of sensitive skin to desquamation, soothed by emollients. *Dysaesthesia* occurring after intense UV exposure may persist for weeks; threshold responses are normal, and brachioradial pruritus appears to be neuralgia secondary to UVR damage to the skin. Many disorders develop *photoadaptation*; thus, the patient and clinician may be misled by the fact that the face is unaffected, but sites only occasionally exposed to the sun are worst affected. Photodermatoses may occasionally be highly localized and the nature of the disorder can be elucidated only by testing. Formal

testing is essential to make a definite diagnosis of CAD. In the absence of abnormal tests, the diagnosis cannot be made. Most patients have abnormal threshold responses to UVR with the same action spectrum as the human erythema spectrum, suggesting that the chromophore for CAD is DNA. A minority of patients exhibit UVA photosensitivity, but this is more commonly the pattern of drug-induced photosensitivity and thus drugs should be excluded in such cases. PLE and juvenile spring eruption usually exhibit normal light tests; 30% of PLE patients demonstrate abnormal responses, either to UVB, UVA or both, and very rarely PLE may be induced by visible light. AP is more often UVA-induced with about 70% of patients showing abnormal reactions. HV is also usually UVA sensitive. SU patients usually produce immediate responses with erythema and urticaria to the eliciting wavelengths. The action spectrum of SU is usually UVA, often UVB and visible light. In individual patients, the action spectrum may broaden, and in some patients, the disorder may spontaneously clear (Beattie, 2001). A solar simulator is a xenon arc lamp fitted with filters such that the output of the lamp reproduces terrestrial sunlight. The intensity of the lamp is much higher so photodermatoses may be reproduced in the laboratory, confirming diagnosis and proving photosensitivity if a patient has normal monochromator tests. Depending on the population tested, 100% of patients with CAD have abnormal responses. Seventy per cent of patients with PLE have reproducible PLE as do AP and HV. SU is almost always reproduced, but occasional patients only react to natural sunlight. Different schedules are used to provoke photodermatoses (van de Pas et al., 2004). Large areas of 4x4 cm^2 or more, need to be used, on body sites where the rash normally occurs. Thirty per cent of patients react with one exposure, repeating the irradiation twice more increases the yield to 70%. This is useful to prove a rash is UV-induced in the absence of other pointers. All patients with exposed surface eczema should be patch and photopatch tested. Photoallergic contact dermatitis is uncommon (Darvay et al., 2001). Review of the relevant allergens for photopatch testing shows that virtually all positive photopatch tests in recent years are because of sunscreen ingredients. Previous photoallergens such as 6-methyl coumarin, musk ambrette and related molecules have been discontinued by the perfume industry in Europe because of previous relatively frequent sensitization. Tetrachlorosalicylanilide also is no longer encountered; thus, it is no longer relevant to test with these agents. Testing perfume ingredients, plant materials and drugs such as promethazine, chlorpromazine and non steroidal anti-inflammatory drugs leads to such a number of false-positive phototoxic reactions that it is better to omit these agents. In the rare true allergic reaction it is important to use a low concentration of the allergen and administer no more than 5 J/cm2 UVA or even 1–2 J/cm2. The crescendo pattern of test reaction, with most intense picture observed the second reading, compared with the first, distinguishes allergy from phototoxic reactions that fade after the time of the first reading. Some patients may need testing to their own products, but if a new agent is being assessed, it is essential to test a control panel of 20 subjects to this agent to exclude false-positive results. Investigation of the photodermatoses offers a considerable amount of information not otherwise available. Some patients are surprisingly photosensitive when formally tested. Clinical impressions may be completely overturned. Formal testing conclusively proves the diagnosis of photosensitivity if the tests are abnormal. Photosensitive individuals may, however, have normal light tests. Photoprovocation using a solar simulator is helpful to demonstrate that the disorder is UV-induced.

Idiopathic photodermatoses	Photoallergic contact dermatitis/photoxic contact sensitivity Drug induced (photoxic/photoallergic)	Genophotodermatoses	Photoaggravated disease	Disease aggravated or precipitated by UVR-induced immunosuppression
Polymorphic light eruption	Antibiotics	Xeroderma pigmentosum	Lupus erythematosus	Herpes simplex infection
Juvenile spring eruption	Diuretics	Trichothiodystrophy	Dermatomyositis	Viral exanthemata
Actinic prurigo	Antipsychotics	Bloom's syndrome	Eczema	Plane wart
Solar urticaria	Sedatives	Cutaneous porphyries	Psoriasis	Skin cancers
Hydroa vacciniforme	Antihypertensive agents	Kindler-Weary syndrome	Rosacea	
Chronic actinic dermatitis	Non-steroid anti-inflammatory drugs	Smith-Lemli-Opitz syndrome	Lichen planus	
Brachioradial pruritus	Antidiabetic-agents		Autoimmune bullous diseases	
Actinic folliculitis	Lipid-lowering agents		Vitiligo	
	Protease inhibitors		Vitamin B6, niacin deficiency	

Table 1. Classification of photodermatoses

3.1 Polymorphous light eruption

Polymorphic light eruption (PLE) is the most common of the idiopathic photodermatoses. It is an acquired disorder characterized by an intermittent, transient, delayed response, 30 minutes to several hours after UV light exposure. The cutaneous response has been described as nonscarring, pruritic, erythematous papules, vesicles, or plaques on light-exposed skin. Other presentations include vesiculobullous, hemorrhagic, erythema multiforme-like, and strophulus-like (insect bite) appearances. In the absence of additional UV exposure, the eruptions resolve in hours to as long as 2 weeks, leaving completely normal skin. PLE is the most common photosensitivity. It affects females two to three times more often than males and onset is typically in the first three decades of life. The incidence is estimated at 10% in the United States, 21% in Sweden, 15% in the United Kingdom, and 5% in Australia. All racial skin types have been documented as being affected in the medical literature, however, it most commonly occurs in fair-skinned individuals of Fitzpatrick skin types I–IV. PLE has been widely reported, but it occurs most frequently in temperate

climates and is least prevalent in subtropical and tropical areas. Episodes of PLE usually occur in the spring and occasionally in the fall. Patients are usually less susceptible during the summer and winter. This prevalence during the spring and fall, as well as the predilection for temperate climates, may be explained by the greater proportion of UVA to UVB light in these settings. It is possible that the higher proportion of UVB to UVA during the summer months may inadvertently reduce UVA exposure because of earlier sunburning and, therefore, reduce susceptibility through a UVB-induced alteration in immunologic reactivity. Although classified as an acquired idiopathic photodermatoses, familial clustering is suggestive of a genetic etiology. A recent study examined 119 monozygotic twin pairs and 301 dizygotic twin pairs, revealing an incidence of 21% among the monozygotic twins and 18% in dizygotic twins. The study also demonstrated that PLE was present in one or more first-degree relatives (excluding the co-twin) in 12% of affected twin pairs compared with 4% of relatives in unaffected twin pairs, thus providing statistically significant evidence of familial clustering (p< 0.0001) (Milliard et al., 2000). Ultimately a combination of genetic and environmental factors is probably responsible for expression of PLE. PLE has been considered, for long as a possible, delayed-type hypersensitivity (DTH) response to an endogenous, cutaneous UV-induced antigen, because of the hours or days delay between sun exposure and manifestation of symptoms, and the histological appearance of lesional skin. Firm evidence, however, has been lacking and the responsible allergen has not been identified. UV irradiation may convert a potential precursor in the skin to an antigen that causes a DTH reaction, resulting in the clinical appearance of the disease. The nature of this hypothetical precursor or antigen, however, remains obscure. More recently, timed biopsies following irradiation with artificial light sources, with doses below the MED, have shown perivascular infiltrates of mainly CD41 T lymphocytes within a few hours and CD81 cells within days; an increased number of dermal and epidermal Langerhans cells and dermal macrophages has also been observed, suggesting the DTH pattern seen in allergic contact dermatitis and the tuberculin reactions. In addition, E-selectin, vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), identified on keratinocytes above areas of dermal leukocyte infiltration, are also expressed as in other DTH responses. UV-induced immunosuppression is a consistent finding in normal skin and it was hypothesized that this process may protect the skin from UV-induced photoallergens. Thus, susceptibility of individuals to PLE could arise from a failure of normal UV-induced immunosuppression. Kolgen et al. reported that the skin of PLE patients was less susceptible to UVB-induced migration of CD11 Langerhans cells. Following a six MED dose of UVB, there was a significant failure of LC to migrate from the epidermis of PLE as compared with normal subjects. They also found a significant reduction in UVB-induced infiltration by CD11b1 macrophage-like cells in PLE compared with healthy skin, which was considered to represent an important finding in view of the prominent role of these cells in the secretion of the immunosuppressive cytokine IL-10. It was thus postulated that the pathologic defect underlying PLE might be a failure of normal photoimmunosuppression. If this is the case, the balance of UV-induced suppression and UV-induced provocation would be altered, allowing sunlight exposure to provoke PLE eruption. More recently, Kolgen et al. assessed whether there are abnormalities of UV-induced secretion of TNF-α and interleukin-1b, cytokines known to be important in affecting LC migration. Secondly, they examined the effects of UV on secretion of T-helper cell type 2 (TH2) cytokines IL-4 and IL-10, which mediate immunosuppression. They concluded that the reduced expression of TNF-α, IL-4, and IL-10 in the UVB irradiated skin

of patients with PLE appears largely attributable to a lack of neutrophils and it is indicative of reduced Langerhans cell migration and reduced TH2 skewing. Impairment of these mechanisms essential for UVB-induced immunosuppression may be important in the pathogenesis of PLE (Kolgen, 2004). Palmer and Friedmann performed functional studies examining DTH responses in PLE and concluded that induction of sensitization by 2,4-dinitrochlorobenzene (DNCB) is less suppressed by UV in patients with PLE compared with healthy controls. Beyond this, van de Pas et al. recently showed a reduction in UV-induced suppression of DTH response to DNCB in PLE, such that these patients are less easily sensitized to DNCB than in healthy subjects. Also Schornagel et al. suggested a role for neutrophils in the pathogenesis of PLE, by showing a relative reduction in UVB-induced infiltration with neutrophils. It is conceivable that abnormalities in both neutrophil and mononuclear cell activity could be implicated in the pathogenesis of PLE. However, the most recent findings on the effect of solar-simulated radiation on the elicitation phase of contact hypersensitivity revealed no significant difference between controls and patients with PLE. These results contrasted with previous findings of the same group that had indicated a resistance to UV-induced suppression of sensitization to DNCB in PLE. This difference may reflect the greater importance of Langerhans cells in the sensitization phase, and is consistent with the hypothesis that PLE arises from impaired suppression of Langerhans cell activation or migration (Palmer, 2005). The reason for the occurrence of PLE appears likely to be genetic with a significant environmental component, with 70% of the population perhaps having a tendency to the condition but not all expressing it because of poor penetrance. However, the culprit gene has not been identified yet. This genetically determined factor, which leads to the putative immune recognition of an autologous cutaneous antigen generated by UV radiation in PLE, but not normal subjects, although the antigen is presumably expressed in all individuals. The inducing UV absorbers and antigens in PLE have not been characterized; tough has been suggested a form of heatshock protein. A variety of such antigens within and between patients, however, seems more likely. In addition, the induction of lesions by a UVA sun bed in the non-tanning sacral pressure area further suggests that the UV–chromophore interaction in at least some patients may be oxygen independent. Determination of the action spectrum of PLE by experimental reproduction of skin lesions using artificial radiation sources has led to conflicting results. A lack of response, often to adequate doses of artificially produced UV radiation, by patients who react readily to just suberythemogenic doses of natural sunlight may be attributed to a number of variables. These include the size of the UV irradiation site and its location, the irradiation of small, normally unaffected areas perhaps not eliciting sufficient immunologic stimulus to activate the response, but also to the UV spectrum, irradiation dose, dose rate, and degree of cutaneous immunologic tolerance, which may be increased by any recent prior exposure. Moreover, there is a lack of universally accepted, standardized phototest protocols under revision of board of experts. The complex interrelationships between factors such as these, have clearly contributed significantly to the conflicting nature of reports concerning the most effective wavelengths for PLE induction. In most series, UVA has been more effective than UVB. Thus, in one of these studies, following exposures of buttock skin to UVA or UVB daily for 4–8 days, the action spectrum was in the UVA range in 56%, UVB in 17%, and both in 27%. In another study 68% of reaction were triggered by UVA, 8% by UVB, and 10% by both wavelengths. This apparent diversity in action spectrum of PLE is possibly the result of different UV-provoked inducing antigens, and perhaps also of different cutaneous levels for these antigens. Variation in the proportions of UVA and UVB

present in terrestrial sunlight may also explain certain clinical characteristics of PLE. Thus, the greater proportion of UVA to UVB in temperate climate zones, and during the spring and fall months, might be expected to contribute to a higher incidence of PLE in temperate, rather than tropical regions, with greater susceptibility to the condition in spring and occasionally autumn, rather than summer in most patients. Moreover, the higher proportion of UVB to UVA in summer sunlight also probably inhibits PLE development through a predominantly UVB-induced cutaneous immunosuppressive mechanism. Older generation sunscreens without substantial UVA protection, encouraged to stay much longer in the sun, thereby receiving a much higher UVA dose than without UVB protection, did not provide adequate protection against provocation of PLE. Clinical features of PLE are characterized by lesions that, generally, develop symmetrically and affect only some sun-exposed areas of the skin, often those that are normally covered in winter, such as the V area of the chest, the external aspects of the arms and forearms and lower anterior aspect of the neck. Occasionally, the face can be involved. Symptoms are worse in spring and early summer. The eruption typically begins each spring or early summer, on sunny vacations, or after recreational tanning use, often moderating with continuing exposure. Also outdoor activities in winter may induce the rash, and it may also occur by exposure through window glass (Hampton, 2004), which is penetrated by UVA such as light cotton clothing. The eruption develops after minutes to hours or sometimes days of sun exposure and lasts for one to several days or occasionally weeks, particularly with continuing exposure. Skin eruption, however, often fades or ceases as summer or the vacation proceeds ('hardening process'). A PLE severity index (PLESI) has been proposed to produce a simple, valid, and reproducible method to assess the severity of the disease (Palmer, 2004). In the absence of further exposure, lesions gradually subside completely, without scarring over a few days, occasionally over a week or two. In a given patient, the eruption tends always to affect the same skin sites. Associated systemic symptoms are quite rare: chills, headache, fever, and nausea have been reported but may have been the consequence of accompanying sunburn.This condition may last life-long but gradually improves over years in many patients: over 7 years, 64 of a series of 114 patients (57%) reported steadily diminishing sun sensitivity, including 12 (11%) that totally cleared. PLE has many morphologic variants, as indicated by the name. Lesions vary widely between patients, but are generally pruritic, grouped, erythematous or skin-colored papules of varying size, not infrequently coalescing into large, smooth or rough-surfaced plaques, sometimes resembling subacute cutaneous lupus erythematosus. Vesicles, bullae, and papulovesicles, as well as confluent edematous swelling (particularly of the face), are also possible, while rarely erythema or pruritus alone (PLE sine eruptione) may occur. Insect bite-like, and erythema multiforme-like variants have also been described. A particular variant in African Americans occurs as 'pinpoint' variant. In addition, the helices of the ears may be primarily affected often with vesicles, particularly in boys. This form of PLE was previously termed 'juvenile spring eruption'. The papular form, of either large or small separate or confluent lesions, generally tending to be in clusters, is the most common, followed by the papulovesicular and plaque variants; the others are rare. The eczematous form probably does not exist, representing rather chronic actinic dermatitis instead. A final morphologic variant, a small papular form generally sparing the face and occurring after several days of exposure on vacations has been designated as benign summer light eruption in Europe. Hematoxylin and eosin staining of PLE reveals superficial and deep dermal inflammatory cell infiltrate. While the infiltrate is predominantly perivascular, there is sometimes a heavy interstitial infiltrate of lymphocytes

in the upper dermis, in those variants characterized by prominent subepidermal edema. The upper dermis frequently exhibits edema, particularly in plaque-like lesions. Epidermal changes, if present, are variable and range from mild spongiosis to acanthosis. A study performed to explore the immunohistopathology of photoinduced cutaneous lesions in LE patients revealed some important differences between these lesions and the cutaneous lesions seen in PLE patients. Of 22 person enrolled in this study, 16 patients had LE and 6 PLE. The study explored both cellular infiltrate and deposition of immunoreactants in the epidermis and dermis of lesions. The biopsies that were taken from two patient groups were examined for multiple classes of cellular infiltrates using standardized markers. The biopsies were screened for CD3+, CD4+, CD8+, M718+, CD15+, CD1+, CD22+ cells, and lue7 cellular marker. Specific attention was paid to the perivascular and dermoepidermal interface. Summation of the cellular populations from these samples revealed two significant differences. The first observation noted was the high prevalence of M718 cells at the dermoepidermal interface in LE patients, suggestive of active migration of M718+ monocytes toward the epidermis. The other significant difference was the increased CD1+ cell population seen throughout the entire dermis of PLE patients. The findings seen in the biopsies agree with past studies conducted on PLE patients. Current data suggests that this increased population of CD1+ cells represents the epidermal Langerhans cell population that is migrating toward the area's lymph nodes to present their antigen and elicit a type IV immune reaction. To examine if there were any significant findings related to immunoreactant deposition, the biopsies were tested for IgA, IgG, IgM, and C3c at the basal membrane zone. Results from past studies have revealed little or no presence of immunoglobulin at the basal membrane zone in patients with PLE. In summary, these results did not allow any positive significant conclusions to be drawn about diagnostic significance or pathologic etiology of PLE related to LE. Microscopic analysis of skin tissue is mostly not necessary, but can be helpful where there is diagnostic difficulty. The diagnosis of PLE is made principally on clinical grounds based on the typical morphology of the eruption. Although the diagnosis is mainly clinical, provocative phototesting may be valuable in winter if no lesions are present, to confirm the diagnosis. The best way to do this is by using repetitive irradiations on the V area of the neck or forearms for 1-4 consecutive days. This can be done with high-intensity monochromatic UVA and UVB sources or with a solar simulator. The doses needed are not necessarily erythemal. Readings are made immediately and up to 72 h after the last irradiation. As mentioned above, abnormal reactions can be provoked in more than 60% of patients. In most studies more patients reacted to UVA than to UVB. In case of positive UVA or UVB test, the reaction does not necessarily correlate to PLE clinical features and not significant relationship with clinical disease severity has been showed (Janssens et al., 2007). There are no diagnostic laboratory tests available for PLE. Laboratory examinations are usually performed to exclude other dermatoses, such as photosensitive lupus erythematosus or erythropoietic protoporphyria. Subacute cutaneous lupus erythematosus, which is generally not itchy as PLE, must be excluded in some patients by determining antinuclear, Ro (SSA) and La (SSB) antibody titers. Persistent plaque-type PLE must also be differentiated from Jessner–Kanof's lymphocytic infiltration of the skin, while the photo-exacerbation of dermatoses such as atopic and seborrhoeic eczema may occur in susceptible subjects with the same time course as for PLE, but with differing and characteristic morphology. PLE treatment has to be subdivided into therapy for the acute exacerbation and prophylactic therapy before expected sun exposure. The mild disease of many patients is satisfactorily controlled by the

moderation of sun exposure at times of high UV intensity, use of protective clothing, and the regular application of broad-spectrum sunscreens with high-protection factors including UVA filters. A combination of sunscreens with antioxidants was reported to be more effective than sunscreen alone, but this awaits further confirmation (Patel et al., 2000). Patients with fully developed disease require topical corticosteroids, in some cases in the form of wet dressings, for several days. More severe attacks may be treated effectively with a short course of systemic (oral or injection) corticosteroids (Patel et al., 2000). Because PLE will subside spontaneously and is not a life-threatening condition, all possible risks of therapy should be carefully considered. Many patients will agree to undergo some sort of preventive measures. Prophylactic treatment consists of several approaches. The mildly affected majority of patients will prevent their PLE, to significant degree, by control or avoidance of sunlight exposure and by using a topical high-factor broad-spectrum sunscreen. For others, gradual sun exposure in spring effects browning and thickening of the skin (so called hardening), which often helps to avoid PLE. Severely affected subjects, suffering frequent attacks throughout the summer may require courses of prophylactic phototherapy or photochemotherapy in the early spring before the expected sun exposure. At a first glance it appears somewhat bizarre to use light treatment to prevent a condition that is caused by light, and the mechanisms by which UVB and PUVA induce tolerance to sunlight are not completely understood. Pigmentation and thickening of the stratum corneum may be important factors for the protective effect, and UVB, high-dose UVA, and PUVA are efficient triggers of both. Although these local effects may provide some barrier against photosensitivity, they probably do not suffice to explain the degree of protection induced in many patients. Thus, other mechanisms may be involved, as photodermatoses do occur in dark-skinned subjects (Kontos et al., 2002). It is therefore now generally accepted that UVA, UVB, and PUVA therapy exert a variety of immunomodulatory effects on human skin and that this is of critical importance for the therapeutic efficacy of phototherapy. Janssens et al.. showed that UVB hardening significantly normalizes UV-induced cell migratory responses of Langerhans cells and neutrophils in patients with PLE. PUVA is a very effective preventive treatment. In approximately 70% of patients with this condition, a 3–4-week course of PUVA, 3 times a week, suffices to suppress the disease upon subsequent exposure to sunlight. The initial exposure and dose increments should be performed according to the guidelines outlined for psoriasis. PUVA induces pigmentation rapidly and intensively at relatively low suberythemogenic UVA doses that usually remain well below the threshold doses for eliciting PLE. About 10% of the patients develop typical lesions during the initial phase of PUVA. Interruption of treatment or reduction in the UVA dose is rarely required in such cases. Usually, brief symptomatic treatment with topical corticosteroids suffices. PUVA therapy protects only temporarily, and regularly repeated sun exposures are subsequently required to maintain protection. However, a considerable number of patients remain protected for 2–3 months, even after pigmentation has faded. The use of narrow-band 312 nm UVB phototherapy has become increasingly popular, being simpler to administer, perhaps safer than PUVA and of comparable efficacy. Also exposure of prophylactic UVB may sometimes trigger the eruption, particularly in severely affected subjects, necessitating occasionally concurrent systemic corticosteroid therapy. Commercial 'sun beds' are not recommended because they are most likely to provoke PLE rash. Patients who only develop their disorder during infrequent vacations, also generally have good result from preventive oral corticosteroids course. Other therapies, that are quite often listed in textbooks, are of uncertain efficacy. Such remedies include antimalarials, long been

advocated, b-carotene, and nicotinamide, likewise probably only moderately effective are 0-3 polyunsaturated fatty acids (Murphy et al., 1987) (38). The efficacy of Escherichia coli filtration (Colibiogen) awaits further confirmation. Also systemic antioxidants were unable in reducing the severity of the disease (Eberlein-konig et al., 2000). The use of immunosuppressants should certainly be restricted to some rare severe disabling cases (Shipley, 2001). Recently, the photoprotective activity of oral polypodium leucotomos extract was shown to exert significant improvement in PLE patients (Caccialanza et al., 2007).

4. UV-induced skin cancers

Lifestyle changes during the past five decades, with increased sunlight exposure because of outdoor activities and worsening sunbathing habits, often result in skin cancers (SCs). Among Caucasians, intense early sunburns and blistering sunburns are closely associated with the development of melanoma. As a result of chronic UV exposure: skin aging, wrinkles, uneven skin pigmentation, loss of skin elasticity and a disturbance of skin barrier functions are nowadays well recognized. These changes in the skin that superimpose the alterations of chronological aging refer to photoaging. The development of squamous cell carcinomas, SCCs and BCCs, and malignant melanoma is often associated with painful sunburns. In fact, more than 1 severe sunburn in childhood is associated with a 2-fold increase in melanoma risk (Ma et al., 2007). Chronic exposure to UVR is known as the most important risk factor for the development of actinic keratoses (precursors of SCC). Exposure to UVR during childhood and adolescence plays a role in the future development of skin cancer. It was noted that in the US, most people receive 22.73% of their lifetime exposure to the sun by 18 years of age. This meant that during childhood (1–18 years of age), most people received approximately one-fifth of their total sun exposure. The total amount of sun received over the years, and overexposure resulting in sunburns are associated with skin cancers. The epidemiology implicating UV exposure as a cause of melanoma is further supported by biological evidence that damage caused by UVR, particularly damage to DNA, plays a central role in the development of melanoma. The relative risk of skin cancer is three times as high among people born in areas that receive high amounts of UVR than those who move to those areas in adulthood. Likewise, outdoor workers have a higher risk than indoor workers (Glanz et al., 2007). The aforementioned citations conclude that there is a dose-related relationship between sunlight exposure and the incidence of skin cancer. For the development of BCC and melanoma, intermittent intense exposures appear to carry a higher risk than lower level chronic exposures, even if the total UV dose is the same. By contrast, the risk for SCC is strongly associated with chronic UV exposure but not with intermittent exposure. Taken together, epidemiologic studies and experimental studies indicate that intermittent intense and chronic exposures to solar UVR are the primary cause of non melanoma skin cancer (NMSCs) and melanoma. Indeed photo-carcinogenesis plays a pivotal role in skin cancer occurrence in the general population and not only in high risk group such as patients affected by Gorlin's syndrome or Xeroderma pigmentosum. Other agents, relevant in the past such as arsenic are now extremely rare as population exposure manly ceased in the 1960s. Ionizing radiation is an ongoing cause of skin cancer, but overall ultraviolet radiation accounts for more than 90% of skin cancers. Ultraviolet radiation is a complete carcinogen which means that, on its own, it has the ability to cause skin cancer without the need for other factors, although other co-carcinogens may have an expediting

effect on skin cancers leading to earlier onset or increasing SC number. Initiation of skin cancer comes about by DNA absorption of UVR, specific wavelengths which are similar to the ones able to induce erythema. Such absorbed photons lead to CPDs, which in case are not removed, they lead to errors in the transcribed DNA strand. The DNA repair mechanism is complex and comprises a series of enzymatically controlled steps whereby the DNA double helix is uncoiled, the cross-linked thymine dimer usually is repaired and DNA is reconstituted. DNA repair is an error–prone process and mutated genes may be retained. More than thirty different enzymatic steps contribute to the process of DNA repair involving nucleotide excision repair (NER), a specific response to the damage caused by absorption of UVR in human skin. Use of topically applied liposomal enzyme T4 endonuclease V which specifically removes CPDs in a clinical trial on xeroderma pigmentosum led to fewer basal cell carcinomas and actinic keratoses indicating the relevance of these lesions to carcinogenesis. Aging skin is less efficient at removing CPDs; this together with the accumulation of UV-induced DNA damage augments carcinogenesis. Though UVB is most efficient at inducing CPDs, UVA also induces these lesions participating in the carcinogenic UVR effect. As defence mechanism, apoptosis should help prevent SC. Cells carrying too much in the way of damaged DNA for easy repair, or accurate NER, are instructed, by complex cell signalling pathways caspase mediated, to self distruct: the so called programmed cell death. Damaged cells escaping repair or apoptosis proliferate and skin cancer arise. The genome guardian p53 has a key role in this process. Ultraviolet radiation induces p53 and it leads to p21 synthesis, able to stop the cell cycle in S1, enabling DNA repair to take place. MDM2 protein is also induced and serves as a mechanism for shutting off p53, and enabling its degradation via the ubiquitination pathway. The time course for these UVR-induced molecular events has been elucidated in vivo in human skin; further studies measured the time for apoptosis induction after 3 repeated MED exposures. Later, in the time course of the sunburn response the protein Bax is induced which leads to apoptosis and safe elimination of damaged cells. Skin cancer is the most common type of cancer in light skinned populations around the world. Skin cancers are mainly divided into melanoma, and non-melanoma skin cancers (NMSCs), the latter including basal and squamous cell carcinomas. Melanoma is responsible for most of the cancer related mortalities, and NMSCs are typically described as having a more benign course with locally aggressive features. Nevertheless, they represent ''the most common type'' of cancer in humans and they can result in significant disfigurement, leading to adverse physical and psychological consequences (Suarez, 2007). It is estimated that 2–3 million cases of NMSCs occur worldwide each year. The incidence varies with very high rates in the Caucasian populations. For incidence, the overall upward trend observed in most parts of Europe, Canada, USA and Australia shows an average increase between 3% and 8% a year (Rhee et al., 2007). The incidence of NMSCs is over 1.3 million cases each year in the U.S.; in fact, this incidence rate is expected to double in the next 30 years (Rhee et al., 2007). Approximately 30% of all newly diagnosed cancers in the U.S. are BCC, making it the most commonly diagnosed cancer in this country (Rittiè et al., 2007). BCC, which accounts for 80–85% of all NMSCs, rarely metastasizes to other organs. It is the most common malignancy in white people. Its worldwide incidence is increasing by up to 10% with highest rates in elderly men and increasing incidence in young women. Although mortality is low, this malignancy causes considerable morbidity and places a huge burden on worldwide healthcare systems. SCC, which accounts for 15–20% of all NMSCs, is more likely to invade other tissues and can cause death. As a result of the benign nature of NMSC

characteristics, some patients may remain unregistered and undiagnosed, leading to an under-representation of the number of cases. Moreover, as NMSCs have localized symptoms and primarily manifest in older individuals, they may remain undiagnosed. BCC and SCC are usually found in sun exposed areas, especially the head and neck regions. They are both positively related to the amount of UVR received and inversely proportional to the degree of skin pigmentation in the population. Women have higher occurrences than men for both types of cancers on the legs, consistent with greater sun exposure at this site. In 2006, a study reported that the ratio of BCC to SCC is 4 : 1 for the head and neck (Gloster & Neal, 2006). The probability of getting SCC is less than getting BCC; however, SCC carries a > 10-fold higher risk of metastasis and mortality. It is estimated that 132,000 new cases of melanoma occur worldwide each year. Incidence rates are at least 16 times greater in Caucasians than African Americans and 10 times greater than Hispanics. The WHO also estimates that as many as 65,161 people a year worldwide die from malignant skin cancer, approximately 48,000 of whom are registered. Melanoma represents only about 3% of all skin cancers in the U.S., but it accounts for about 75% of all skin cancer deaths. The American Academy of Dermatology (AAD) in 2009, reported about 121,840 new melanoma cases in the U.S. with 8650 deaths (1 death every hour). This mortality value is remarkably high considering the fact that melanoma is nearly always curable in its early stages; however, this high number can be attributed to the late diagnosis of the disease in which the cancer spreads to other parts of the body. Over the last three decades, the incidence and mortality rates of melanoma have increased in the U.S. In particular, of all neoplasms, approximately 20–30% of skin cancers are diagnosed in Caucasians, 2–4% are in Asians and 1–2% are in blacks and Asian Indians. In 2006, of all skin cancers, melanoma represented 1–8% in blacks, 10–15% in Asian Indians and 19% in Japanese. Moreover, even though skin cancers are not as prevalent in individuals with darker skin, they can have more morbidity and fatalities as they may go undiagnosed for a while. Melanoma most often appears on the trunk of men and the lower legs of women, although it can be found on the head, neck, or elsewhere. As the incidence of skin cancer is increasing at an alarming rate, it is one of the greatest threats to public health.

5. PLE and skin cancer: Is one protective against the other?

For everything said so far, it would seem that the skin performs a 'balancing act' between adequate elimination of early cancerous cells and suppression of abnormal reactions against UV-exposed cells that may suffer transient aberrations. PLE appears to be associated with an 'imbalance' between UV-induced proinflammatory and UV-induced suppressive immunoreaction. 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, favouring a DTH response to potential UV-induced neo-antigens under certain circumstances (Palmer, 2004). High UV radiation dose (2 MED) resulted highly immunosuppressive in both, PLE patients and controls, leading to almost complete immune suppression by 93%. This might explain why PLE lesions are often provoked by exposure to low doses of UV radiation but rarely by severe sunburn PLE patients MED values do not differ significantly from those of normal subjects, although in some study it results lower. Further studies are required to fully elucidate these pathways. Another aspect of PLE that requires further investigation is the disproportionate incidence observed in females compared with males. Notably, it has been

found that females are probably due to a more resistant to the immunosuppressive effects of UV radiation. Moreover, the results of a study by Widyarini et al. suggest that the sex difference in PLE may be due to protection from UV-induced immunosuppression afforded to females via signalling through the oestrogen receptor (Widyarini et al., 2006). Indeed, female hormone 17b-oestradiol may prevent UVR-induced suppression of the CHS response caused by the release of immunosuppressive cytokines (e.g. IL-10) from keratinocytes (Hiramoto et al., 2004). This might explain why PLE is more common in females than in males and why the risk decreases in women after the menopause. Because of these gender differences in UV-susceptibility together with the higher incidence of skin cancer in males, future studies must address the question of whether resistance to UV-induced immunosuppression lowers the skin cancer risk in PLE patients. Yoshikawa et al. compared normal healthy population versus NMSC patients. Using a protocol that achieved virtually complete depletion of epidermal LCs from UV irradiated skin, they found that approximately 60% of healthy volunteers developed a vigorous CHS to a given dose of DNCB painted on the UV-irradiated test site. These individuals were designated UVB-resistant, and were distinguished from other individuals who were designated UVB susceptible, by their failure to develop CHS. They then discovered that more than 90% of skin cancer patients exposed to UVB and DNCB failed to develop CHS, i.e. were UVB-susceptible. In subsequent experiments, epicutaneous application of the same dose of DNCB to unirradiated skin of UVB-susceptible individuals revealed a further distinction between normal persons and skin cancer patients. Approximately 45% of the latter (and none of the former) remained unresponsive, implying that they had been rendered immunologically tolerant. Because the incidence of UVB-susceptibility was significantly higher in skin cancer patients, and as specific unresponsiveness could be demonstrated only in these patients, it was proposed that UVB-susceptibility might be a risk factor for the development of skin cancer. Indeed, if patients with PLE have a general increased resistance to UV-induced immunosuppression, this may make them more resistant to UV carcinogenesis. In an earlier case–control study (Wolf et al., 1998), using a questionnaire for phenotypic markers and sunlight-related factors and habits, it was observed that UV-induced skin rashes indicative of PLE, were recalled by 12% (22/183) of melanoma patients compared with 18% (57/315) of healthy control subjects. Although not statistically significant, these results suggest that PLE-susceptible patients, possibly being more resistant to UV-induced immunosuppression, may have a lower melanoma risk. This hypothesis is supported by the results of a recent study by Lembo et al. who investigated the link between PLE and skin cancer prevalence. They performed two prospective case–control studies analysing a group comprising 214 patients with SC and 210 gender-and aged-matched controls (study A), and a group comprising 100 patients with PLE and 155 gender- and aged matched controls (study B). Skin type and cumulative exposure to UVR were documented. Three sun exposure levels, depending on lifestyle, were identified in different sections of the questionnaire designed for the survay, investigating work (in/outdoors) and free time (in/outdoors) activities. Their results showed that the prevalence of (histologically confirmed) SC in the PLE group was 4%; the prevalence of SC in the PLE matched control group was 7.1%, which is similar to the National Cancer Registry of Ireland figure of 6% prevalence of SC in the general population, with a cumulative risk of 12.5% by the 8th decade. These studies show that there is a reduced incidence of SC in patients with PLE compared with gender- and age-matched controls. There is less evidence of a reduced incidence of PLE in patients with SC compared with controls: the study size was too small to determine this and only a trend was observed.

One study of patients with melanoma showed sensitivity of LCs to the effects of solar-simulated radiation compared with controls. There has been much speculation as to the role of LCs in the induction of anti-tumour immunity. Whereas there is considerable circumstantial evidence that disruption in the density and function of these cells during the early stages of UVR-induced carcinogenesis may be important for enabling developing neoplasms to escape immune destruction, the role of the large number of LC infiltrating developed skin tumours is less clear. Interestingly, people "costumes and fashion" are not influenced by photoallergy or photoinduced SC. It might be expected that people change their behaviour in the sun after being affected by either SC or PLE. Surprisingly, as shown in multiple surveys, most subjects with a history of SC were not inclined to use regular sunscreen (Moloney et al., 2005). Awareness about sun exposure and SC risk does not necessarily influence patients' sun protection behaviour. Although people are aware of the risks of sunbathing, they continue to expose themselves to the sun without taking precautions, in accordance with the long-established habits of 'sun holidays' and sunbathing and the social belief that tanned skin is more aesthetically pleasing. Similarly, although patients with PLE might be expected to avoid the sun, many continued to go for sunny holidays despite their skin eruption. PLE patients recall more sun exposure than controls and in many cases have equivalent sun exposure to patients with SC.
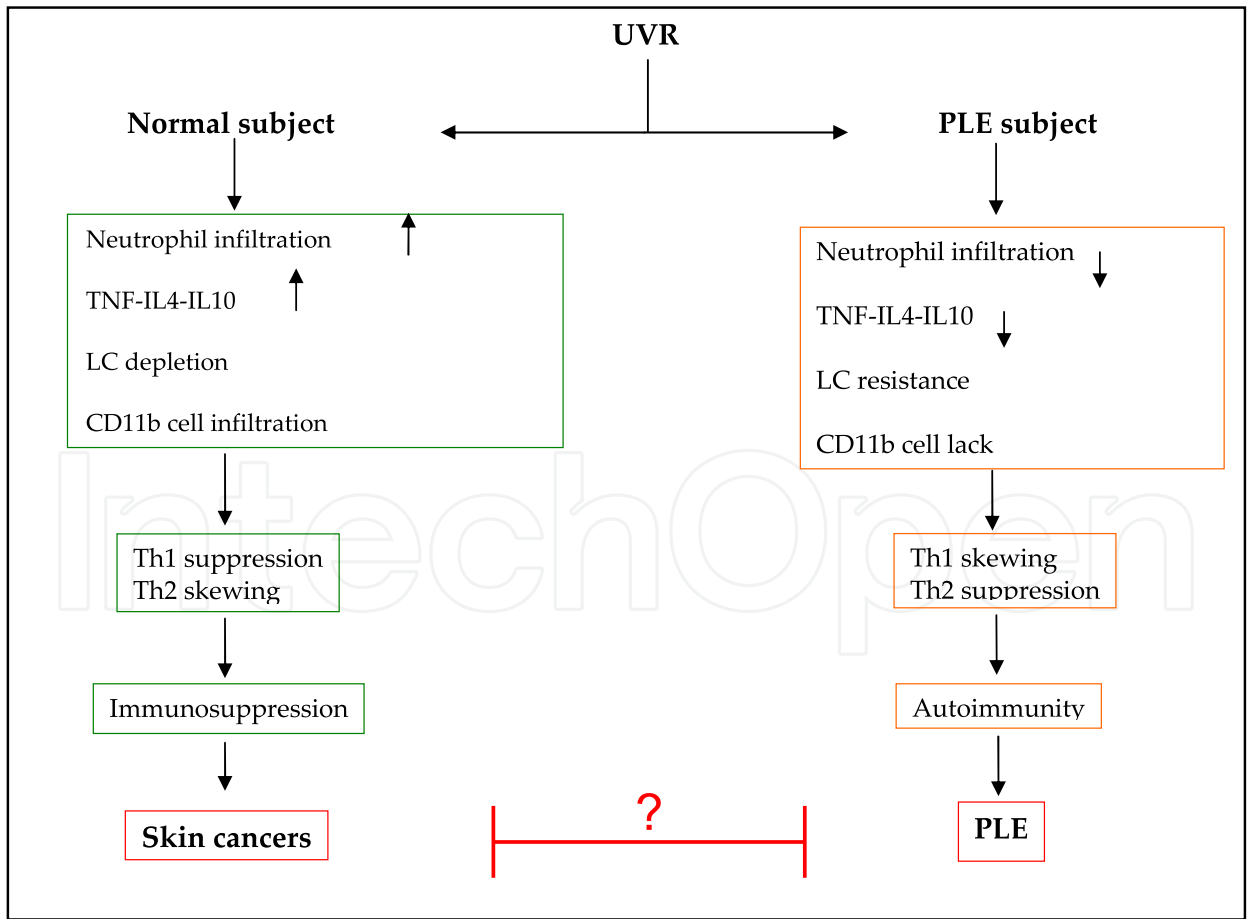

Fig. 2. Pathogenesis of skin cancers and PLE.

The schematic diagram highlights the potential pathway of inhibited ultraviolet radiation (UVR)-induced immune suppression in patients with polymorphic light eruption. In patients with PLE, a persistence of Langerhans cells and failure of UV-induced immune suppression may favour the occurrence of autoimmunogenic skin rashes. In normal subjects, concurrent UV-induced immunosuppression represent a risk factor for the skin cancers. The resistance to UVR-induce immunosuppression of PLE may prevent skin cancers risk as the immunosuppression that occurs in skin cancer may prevent PLE development.

6. Conclusion

A better understanding of UV-induce immunosuppression, leading to SC, and UV-induce immunoactivation, provoking PLE, may be helpful in preventing and treating these conditions. Therefore, it would be very useful to have a reliable cumulative sun exposure dose biomarker, which, related to every single case, could be a predictive factor for SC development. SC, up to date, remains the most common human malignancy and, its occurance is manly linked to UVR exposure. Immunosurveillance inefficiency or disruption of biological pathways of damage repair or programmed cells death, are additive mechanisms permitting progression of the neoplastic process initiated by UVR.

Despite these new insights, in fact, excessive and chronic natural, as well as artificial UVR exposure will, however, remain one of the major environmental threats for human health. Various skin cancer task forces have proposed several important guidelines to decrease the rising skin cancer incidence. These briefly include the following: (1) the establishment of policies that reduce exposure to UVR; (2) providing and maintaining physical and social environments, which support sun safety and are consistent with the development of other healthful habits; (3) professional pre-service and in-service skin cancer education for school administrators, teachers, physical education teachers and coaches, nurses, and others working in healthcare; (4) health services and organizations to increase skin cancer prevention education, sun-safety environments and making these policies readily available to the public; (5) lastly, the promotion of free skin cancer screening programs are also highly encouraged. Primary care physicians can have greater role in preventing skin cancer if they are trained to recognize it and able to educate patients to appropriate sun exposure and periodical dermatological consults. Therefore, there is a need for education related to UV exposure and skin cancer risk. To address this issue, it would be beneficial to implement educational programs tailored for schools/workplaces, homes and doctors' visits. Patient education can include advice pertaining to sunscreen usage, reapplication methods, risk factors and tanning bed dangers. In addition to this, visual aids can be valuable in physicians' offices, as they can display the results of people after receiving a great deal of UVR. Sun protection strategies utilized for promote safe sun behaviours are resumed in: (1) setting a date to end intentional tanning, (2) determining which past behaviors were helpful in protecting against sun exposure and trying to incorporate them (as well as other techniques) in the future, (3) making strategies to overcome obstacles and (4) involving family members so everyone would remind each other about using sun protection. Application and promotion of sun protective techniques in children will reduce their cumulative lifelong sun exposure and intense episodic sun exposure, hence reducing their risk for skin cancer.

7. References

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Skin Cancer Overview

Edited by Dr. Yaguang Xi

The book Skin Cancer Overview is divided into three sections to cover the most essential topics in skin cancer research: Etiology, Diagnosis and Treatment, and Prevention. Due to the complexity of skin cancer, this book attempts to not only provide the basic knowledge, but also present the novel trends of skin cancer research. All chapters were written by experts from around the world. It will be a good handbook for researchers with interests in skin cancer.

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