Light, Including Ultraviolet

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Abstract

Ultraviolet (UV) light is intricately linked to the functional status of the cutaneous immune system. In susceptible individuals, UV radiation can ignite pathogenic inflammatory pathways leading to allergy or autoimmunity. In others, this same UV radiation can be used as a phototherapy to suppress pathogenic cutaneous immune responses. These vastly different properties are a direct result of UV light's ability to ionize molecules in the skin and thereby chemically alter them. Sometimes these UV-induced chemical reactions are essential, the formation of pre-vitamin D_3 from 7-dehydrocholesterol, for example. In other instances they can be potentially detrimental. UV radiation can ionize a cell's DNA causing adjacent pyrimidine bases to chemically bond to each other. To prevent malignant transformation, a cell may respond to this UV-induced DNA damage by undergoing apoptosis. Although this pathway prevents skin cancer it also has the potential of inducing or exacerbating autoreactive immune responses by exposing the cell's nuclear antigens. Ultaviolet-induced chemical reactions can activate the immune system by a variety of other mechanisms as well. In response to UV irradiation keratinocytes secrete cytokines and chemokines, which activate and recruit leukocytes to the skin. In some individuals UV-induced chemical reactions can synthesize novel antigens resulting in a photoallergy. Alternatively, photosensitizing molecules can damage cells by initiating sunburn-like phototoxic reactions. Herein we review all types of UV-induced skin reactions, especially those involving the immune system.

Keywords

Ultraviolet radiation; skin; phototoxic reaction; photoallergic reaction; phototherapy; atuoimmunity

The basic principles of light

Although *light* is commonly thought of as something visible, in physics *light* actually refers to all electromagnetic radiation. The frequency, wavelength, and energy of an electromagnetic wave are related to one another with wavelength being inversely proportional to both frequency and energy (Figure 1). The huge spectrum of electromagnetic radiation can therefore be organized conceptually by decreasing wavelength into radio waves, microwaves, terahertz

radiation, infrared radiation, visible light, UV radiation, X-rays, and gamma rays (Figure 1). The sun emits mainly visible light and infrared radiation, but it also emits some UV radiation, which will be the focus of much of the discussion herein.

UV Radiation

The term *ultraviolet* means "beyond violet" and refers to electromagnetic radiation with a wavelength shorter than visible violet light but longer than x-rays (Figure 1). Radiation within the UV spectrum can be further divided by wavelength into UVC (200–280 nm), UVB (280–320 nm) and UVA (320–400 nm) (Figure 1). An important property of UV radiation that separates it from the visible spectrum is that UV light can ionize molecules and thereby induce chemical reactions. Ultraviolet light is a strong environmental mutagen and the reactions it induces in the skin can precipitate or exacerbate immune-mediated diseases or even worse, cause a fatal cancer. However, not all UV-induced reactions are pathogenic. For example, in the epidermis, UVB induces a 6-electron conrotatory electrocyclic reaction to synthesize pre-vitamin D_3 from 7-dehydrocholesterol, a derivative of cholesterol (Figure 2).

In the earth's atmosphere, ozone (O_3), dioxygen (O_2) and water vapor (H_2O) selectively filter out both UVC and UVB radiation (Figure 3A). Due to this, UVA makes up about 95% of the UV radiation that reaches the earth. Currently, almost no UVC radiation penetrates the atmosphere and approximately 90% of the UVB is absorbed, depending on geographic location and time of day. As the ozone layer is depleted by chlorofluorocarbon (CFC) pollution, more UVB and even some UVC radiation will reach the earth.

Although relatively little reaches the earth's surface, UVB radiation possesses much more energy than UVA (remember that energy is inversely proportional to wavelength). By some estimates UVB is 1,000 times more erythematogenic than UVA. In other words, although more UVA reaches the earth, it is mainly UVB that burns the skin. In contrast, the ability to penetrate the skin is proportional to the wavelength of the radiation. Thus, UVA, with its longer wavelength, can penetrate deep into the dermis of the skin while UVB is absorbed superficially in the epidermis (Figure 3B). This fact will be important later during our discussion of UV-induced inflammatory reactions.

The cutaneous immune system: a brief overview

An intact skin barrier is our first defense against invading microbes and environmental allergens. The importance of the skin's barrier function has been highlighted recently by evidence linking atopic dermatitis and allergy to mutations in filaggrin, a major barrier-forming protein responsible for organizing keratin filaments in the skin [1]. However, the skin is not merely a physical barrier to microbial pathogens and allergens. When breached, components of the innate immune system such as defensins and cathelicidins are poised to prevent pathogen invasion; these are antimicrobial cationic proteins and peptides, respectively.

In addition to a very complex innate immune system, the skin also hosts a highly efficient adaptive immune system equipped with a specialized antigen presenting cell, the Langerhans cell, as well as unique T cells bearing skin-homing receptors. Receptors that target T cells for migration to the skin include the cutaneous lymphocyte antigen (CLA) and the chemokine receptors CCR4 and CCR6.

When activated keratinocytes can interact so closely with skin-resident immune cells that they can be considered components of the cutaneous immune system. Specifically, keratinocytes can secrete cytokines, chemokines [2], and express costimulatory adhesion molecules such as the intercellular adhesion molecule 1 (ICAM-1). They can also express major

histocompatibility complex (MHC) class II molecules, allowing them to present antigen to T cells.

Ultraviolet radiation can activate components of the cutaneous immune system and precipitate an inflammatory response by a variety of mechanisms. For example, UV radiation can: (1) directly activate keratinocytes and other cells to release inflammatory mediators such as cytokines and chemokines, (2) cause redistribution and release of sequestered autoantigens from UV-damaged cells, (3) alter self-proteins to make them more immunogenic (Figure 4), (4) enhance the immunogenicity of externally applied molecules, and (5) chemically alter systemically administered medications whose distribution includes the skin. We will discuss each of these in detail below.

UV radiation causes DNA damage, apoptosis and release of autoantigens from keratinocytes

When UV radiation strikes the skin, its ionizing energy can be absorbed. There are a variety of molecules within the skin that can absorb this energy and be chemically altered by it. One of the major UV-absorbing molecules is DNA itself. Over time, the absorption of ionizing radiation by a cell's DNA will result in the accumulation of genetic mutations and eventually the malignant transformation of the cell. The immune system is responsible for destroying these UV-induced skin malignancies. Evidence in support of this is the fact that immunosuppressed individuals are predisposed to developing aggressive skin cancers. However, cancer surveillance by the immune system is more of a final safeguard rather than a primary method of preventing skin cancer; many earlier defenses must fail before malignant transformation occurs.

The first UV defense is melanin, a UV-absorbing pigment that is able to dissipate UV radiation as harmless heat. This pigment is made in melanocytes and then transferred to keratinocytes via long dendritic processes. UV radiation that escapes melanin absorption may induce DNA damage by either creating reactive oxygen species or by directly inducing chemical reactions within DNA. For example, ionizing UV radiation can induce the creation of cyclobutane pyrimidine dimers (CPD) within DNA. Figure 5 depicts two adjacent thymine residues being altered in this fashion. In addition to CPD dimers, UV radiation can also induce the formation of (6-4) photoproducts (6-4PP) (Figure 5). UVB is the most common cause of 6-4PPs. To prevent malignant transformation, cells have specific defense mechanisms to seek out pyrimidine dimers for repair. Patients with xeroderma pigmentosa develop multiple skin cancers because they have a defect in a nucleotide excision repair system that normally recognizes and repairs UV-induced mutations [3]. Even in people with normal DNA repair systems some dimers fail to be corrected, eventually resulting in a permanent DNA mutation. As the cell accumulates more DNA mutations, malignant transformation will eventually occur. For example, squamous cell carcinomas and their precancerous precursors have mutational hotspots within the p53 tumor suppressor gene that correspond to sites where sunlight-induced CPD dimers occur [4,5]. Thus, there is a direct link between CPD dimer formation and skin cancer.

In addition to their role in causing cancer, UV-induced CPDs and 6-4PPs have multiple other effects on cells as well. In melanocytes, they up-regulate melanin production and invoke the tanning response [6]. Also, CPDs can cause cell cycle arrest and 6-4PPs can induce apoptosis [7]. Thus, UV-induced DNA damage will signal the cell to stop dividing and if needed to undergo apoptosis. In keratinocytes cell surface death receptors such as Fas respond to UV-induced damage and trigger apoptosis [8]. In fact, Fas can initiate UV-induced apoptosis even in the absence of its ligand [9]. As part of the keratinocyte's program for cell death, cytochrome *c* and other pro-apoptotic factors are released from the mitochondria. This signals the formation

of the apoptosome and subsequent activation of caspase-9, which in turn cleaves caspases-3 and/or -7.

The term *sunburn cell* refers to keratinocytes undergoing apoptosis (Figure 6) [10,11]. It is important to understand that programmed cell death of UV-damaged skin cells is a definitive cancer-preventing pathway. Transgenic animals designed to be resistant to the development of UV-induced sunburn cells can tolerate more UV radiation without burning, but they are predisposed to developing skin cancers [5,12].

In the setting of sunburn, large numbers of keratinocytes will undergo apoptosis to prevent malignant transformation (Figure 5). The skin is chalked full of Langerhans cells that can easily pick up autoantigens released by dying keratinocytes. Therefore, disposing of UV-damaged cells without igniting autoimmunity is a delicate balance. Fortunately, there are multiple safeguards in place to prevent the induction of autoimmunity. For example, as a keratinocyte undergoes apoptosis, it attempts to keep everything private and ordered. During the initial 24 hours following the induction of apoptosis, the cells release only low levels of nuclear material [13]. This provides a window for the keratinocytes to self-process their cellular contents and then be cleared by phagocytosis. Autoimmunity is favored if there is a defect in cellular processing of the autoantigens [14], an increase in nucleosomal antigen release [13] or a decrease in clearance of the apoptotic cells [15] (Figure 6). Thus, although exposure to potential autoantigens in the setting of UV-induced apoptosis is common, efficient processing and disposal mechanisms minimize the antigenicity of this material.

One revelation in our understanding of autoimmunity was the discovery that autoantigens targeted in systemic lupus erythematosus (SLE) are clustered on the surface of apoptotic cells (Figure 6) [16]. Likewise, UV radiation induces the redistribution of nuclear autoantigens to the surface of keratinocytes [17]. For example, SS-A/Ro and SS-B/La are found on the surface of keratinocytes following UV exposure. The presence of Ro on the surface of UV-exposed keratinocytes is of particular interest because anti-Ro antibodies are indicative of enhanced photosensitivity [18]. They are seen in many patients with SLE and in the overwhelming majority of patients with subacute cutaneous lupus erythematosus (SCLE). Binding of anti-Ro antibodies to UV-exposed keratinocytes may increase cell death via complement-mediated cytotoxicity, resulting in the premature release of nuclear antigens before they have been adequately processed. Naively one might predict that knocking out Ro in an experimental system would result in less autoimmunity. Surprisingly, this is not the case. Animals deficient in Ro are more sensitive to UV radiation and develop a spontaneous lupus-like autoimmune disease [19]. Thus, Ro evidently plays a role in cell survival following UV exposure. Some have suggested that it may sequester ribonuclear proteins following DNA damage and thereby help to prevent autoimmunity [19].

Immunosuppressive effects of UV light

Although UV light can induce strong inflammatory responses in susceptible individuals, under chronic or minimally erythematogenic doses its immunosuppressive effects are dominant. The mechanism of this immunosuppression involves both cellular components and soluble mediators. Langerhans cells are very sensitive to UV radiation. These cells are antigen presenting dendritic cells that have a cell surface phenotype poised to simulate T cells, including autoreactive and allergen-specific T cells [20]. Highlighting their role as antigen presenting cells, Langerhans cells express molecules such as: MHC class II, lymphocyte function-associated antigen-3 (LFA-3), ICAM-1, ICAM-3, B7, CD1a and CD40. In the absence of Langerhans cells a state of antigen unresponsiveness predominates. For example, Langerhans cell density correlates with the ability of the hapten DNFB to induce contact hypersensitivity [21]. These cells are more sensitive to UV radiation than keratinocytes. This

helps prevent immune recognition of nuclear antigens released by dying keratinocytes. Prior to the appearance of UV induced sunburn cells, Langerhans cells in the skin are lost or at least severely altered. Langerhans cell loss following UV exposure is partially due to UV-induced apoptosis [22]. However, UV radiation also induces these cells to migrate out of the skin to draining lymph nodes [23,24] and there is a dramatic reduction of the immunologic markers expressed by Langerhans cells following UV exposure [25,26]. Reduced markers include: MHC class II, ICAM, and B7. Lastly, UV radiation alters the shape of Langerhans cells, destroying their dendritic processes (Figure 7) [23]. Thus, the residual Langerhans cells after UV exposure have drastically altered antigen-presenting capabilities. Some believe that UV-treated Langerhans cells preferentially stimulate T helper type 2 (Th2) cells and suppress T helper type 1 (Th1) cells, which might explain some of UV light's immunosuppressive effects [27]. Studies have also demonstrated that UVB can induce T cell apoptosis directly [28].

Following UV exposure a systemic immunosuppressive state is induced that cannot be explained solely by local loss of Langerhans cells and T cells. For example, UV radiation on the dorsum of a mouse will prevent a delayed-type hypersensitivity (DTH) response on the mouse's ventral surface [29]. This state of global immunosupresion is due in part to soluble inflammatory mediators. One of these molecules is IL-10; IL-10 is an anti-inflammatory cytokine that can inhibit the production of proinflammatory cytokines such as IFN-γ. It also can inhibit the surface expression of MHC class II and co-stimulatory molecules that are important for T cell activation and antigen recognition. Following UV exposure, some IL-10 may be secreted by keratinocytes [30], but the majority likely comes from skin-infiltrating bone marrow derived macrophages that can express large amounts of IL-10 (Figure 7) [31]. These cells begin infiltrating the skin as early as six hours following UV exposure, reaching their peak numbers at 48 to 72 hours [32].

Apart from IL-10 there are likely many other immunosuppressive mechanisms induced by UV radiation. For example, urocanic acid is found within the epidermis at relatively high levels because the enzyme, urocanase, that usually processes this molecule is missing in the skin [33]. The absorption spectrum that causes the transformation of urocanic acid from its *trans* to *cis* isomer closely matches the absorption spectrum that induces immunosuppression. This identified the *cis* isomer of urocanic acid as a possible immunosuppressive agent. Correlating with this observation, the administration of UV-irradiated urocanic acid suppresses DTH to herpes simplex virus in the mouse [34]. Still other mechanisms of UV-induced immunosuppression include the induction of CD4+ CD25+ T regulatory cells [35].

Ultraviolet light induces inflammation

In contrast to the immunosuppressive mechanisms just described, UV radiation can also activate the immune system. The activation is mediated in part through UV-induced cytokine production, though the mechanism by which this occurs is debatable. It is possible that DNA damage is the inducing signal. This theory has been investigated by a variety of groups.

Exposure to UV radiation induces the activation of nuclear factor kappa B (NF-κB). This in turn induces the secretion of a variety of inflammatory mediators including: IL-1, IL-6, TNF-α and VEGF. Furthermore, blocking NF-κB inhibits the secretion of these molecules [36]. The hypothesis that UV-induced DNA damage is responsible for NF-κB activation was directly tested. Investigators found that enucleated cells were fully responsive to UV-induced NF-κB activation. Thus, a signal cascade based upon UV-induced DNA damage seems unlikely for NF-κB [37]. In contrast to NF-κB, the wavelength dependence (action spectrum) for UV-induced TNF-α production correlates with the *in vivo* action spectra for UV-induced CPD formation [38]. In other words, the production of TNF-α correlates with the amount of DNA damage, making a link between the two likely.

Together with IL-1, TNF was one of the first cytokines found to be upregulated in the skin following UV irradiation [39,40]. It was subsequently discovered that keratinocytes and mast cells were the sources of TNF-α [41,42]. Once expressed, TNF-α has effects on a variety of cell types. It increases MHC class I expression on endothelial cells and dermal fibroblasts [43]; induces the production of IL-1α [44]; increases the expression of adhesion molecules, including ICAM-1, VCAM-1 and E-selectin [45]; and it promotes formation of sunburn cells [46]. By upregulating adhesion meolcules on endothelial cells, TNF-α helps support the migration of neutrophils and macrophages to UV-exposed skin. Although these skin-infiltrating macrophages can secrete IL-10, they are also effective at antigen presentation [32]. Thus, if their local inflammatory milieu changes, they can become more pathogenic, capable of participating in an autoreactive immune response.

Given that TNF-α supports the formation of sunburn cells, it is not surprising that polymorphisms within its promoter have been linked to lupus. The TNF-α -308A promoter polymorphism increases susceptibility to SLE and SCLE. When a reporter gene was placed under the regulation of this polymorphism an abnormal photoregulation of gene expression was observed; the combination of UVB plus IL-1α resulted in a dramatic increase in transcription over wild type levels. This finding helps to link together the TNF-α -308A promoter polymorphism with UV photosensitivity, formation of sunburn cells, and the photosensitive diseases SLE and SCLE [47].

It has been proposed that UV damage can be considered a "danger" signal. Recent data linking IL-1β production to "inflammasomes" supports this notion. IL-1β is normally expressed in human keratinocytes as an inactive precursor. Upon exposure to UV radiation, the precursor is then cleaved by caspase-1 to yield active IL-1β. Caspase-1 activation is dependent upon its recruitment to inflammasomes, which links UV-induced cytokine production to the innate immune system. Inflammasomes are composed of NOD-like receptor (NLR)-family proteins [48]. These intracellular proteins contain a nucleotide-binding oligomerization domain called NACHT and several leucine rich repeats domains that may bind to microbial ligands similar to Toll-like receptor family proteins. The relationship between inflammasomes and UV-induced IL-1β production demonstrates that this pathway can also sense tissue injury. This is especially interesting in light of the recent findings linking NLR proteins to autoimmune disease [49]. IL-1β is a proinflammatory cytokine that has also been linked to a variety of inflammatory diseases, including contact hypersensitivity [50].

Keratinocytes have also been shown to produce a variety of other cytokines in response to UV radiation. Interleukin-8 is a chemotactic cytokine that is upregulated in response to UV exposure [51]. This cytokine is partially responsible for the dramatic influx of inflammatory cells into the skin following UV irradiation. Some other UV-induced cytokines have very specific action spectra. For example, IL-12 is upregulated in response to UVA, but not UVB, exposure [52].

Phytophotodermatitis, UV-induced altered self, and other UV eruptions

Photosensitizers can absorb photons of a particular wavelength, enter a transient activation state, and then elicit a chemical reaction by transferring the photon's energy to another molecule. By capturing photons and releasing their energy, photosensitizers increase the sensitivity of the skin to light. The physical manifestation of this increased photosensitivity will depend on the specific photosensitizer; some will reduce the threshold to sunburn while others may induce a photoallergy in susceptible individuals.

Photosensitizers may be a variety of substances including: light-sensitizing botanicals, such as the psoralens responsible for phytophotodermatitis; systemically distributed medications, such as tetracyclines; endogenous light absorbing molecules, such as porphyrins; and externally

applied chemicals, such as aminolevulenic acid, the chemical used in photodynamic therapy (Figure 8). The action spectrum for most photosensitizers affecting the skin lies in the UVA range but may also include UVB or even visible light. Importantly, UVA can penetrate deeper into the dermis to excite photosensitizers whose distribution does not include the more superficial epidermis (Figure 3B).

In broad terms, photosensitizers induce two types of reactions: phototoxic and photoallergic (Figure 8). Phototoxic reactions are sunburn type reactions that occur in all individuals exposed to the photosensitizer. They occur quickly, within a few hours of sun exposure, and unlike photoallergic reactions, do not require an allergic sensitization period. Clinically, the eruption is similar to an exaggerated sunburn with erythema and possibly some blistering (Figure 9). The erythema usually resolves within a few days, but a residual postinflammatory hyperpigmentation may last for several weeks. The two main types of phototoxic reactions are phytophotodermatitis and phototoxic drug.

In phytophotodermatitis the photosensitizer is a botanical substance, most commonly a psoralen (furocoumarins), which is ingested or externally applied to the skin. Plants in the families Umbelliferae (e.g. parsley) and Rutaceae (e.g. limes) are common sources of photoactive psoralens. In the skin, the psoralen causes cellular damage upon excitation by UVA radiation. This damage is caused by either direct photosensitizer-target interactions or indirectly through reactive oxygen species. The most common type of direct psoralen-target interaction is the formation of DNA-psoralen photoadducts that are induced by UVA radiation. In this example, the psoralen absorbs UVA energy and then interacts directly with DNA to form a cross-link or a single strand adduct. Alternatively, the psoralen can transfer the photon's energy to oxygen creating reactive oxygen species (e.g. $^1O_2$, O_2^-, ·OH). The reactive oxygen species can then injure cells by interacting directly with: cellular DNA; lipid-rich membranes, including the plasma and mitochondrial membranes; and enzymes vital for cell survival, e.g. cytochrome P450 enzymes (Figure 8) [53]. Psoralens can be found abundantly in our environment making phytophotodermatitis extremely common, especially amongst chefs and gardeners.

Phototoxic drug reactions can be due to topical or internal exposure to photosensitizing medications. Oral medications causing phototoxic reactions include but are not limited to: tetracyclines, especially doxycycline and demeclocycline; fluoroquinones; sulfa medications, e.g. lasix; amiodarone; and NSAIDS, all types. Phototoxic drug reactions are usually dose-dependent, both in terms of the medication's dose and the amount of UV exposure. To avoid phototoxic drug reactions, patients should be educated on the risk of sun sensitivity when they start the medication.

In contrast to phototoxic reactions, photoallergic reactions are true immunologic reactions. Similar to the above description, the photosensitizer absorbs light energy and then transfers this energy to another molecule that then induces a chemical reaction. This time, however, the result is the creation of a novel allergen, a photoallergen. For the most part the proteins involved in the formation of these photoallergens are unknown. It is possible that the photosensitizer acts like a hapten. When irradiated, the energy absorbed is used to chemically bond the photosensitizer/hapten to a self-protein, resulting in a novel immunogenic compound. After repeat exposure, a DTH reaction to the new photoallergen occurs. As is the case in other DTH responses, there is a delay in onset, sometimes in the range of weeks. This makes it difficult for patients to associate UV exposure with the eruption, which makes the photodistribution of the rash key to its diagnosis.

In photoallergic reactions the photoallergen can be external, in which case the reaction would be called photoallergic contact dermatitis, or it may be internal as seen in photoallergic drug

reactions. Clinically, the lesions of photoallergic reactions are eczematous pruritic plaques distributed over sun-exposed areas. Histopathologically they show features of contact dermatitis. Although cross reactivity to similar antigens may occur, photoallergic reactions are not as common as phototoxic reactions. Implicated medications include: thiazide diuretics, sulfonamide antibiotics, sulfonylureas, phenothiazides, quinine, quinidine, tricyclic antidepressants, antimalarials, and NSAIDs.

There are also a variety of immune mediated DTH-like reactions that occur hours or days after sun exposure in which the photoallergen is unknown but believed to be an endogenous self molecule. These photodermatoses are called idiopathic or primary photosensitivity disorders. Among this group, polymorphous light eruption (PMLE) is the most common. PMLE is characterized by an erythematous, mildly pruritic, papulovesicular eruption that appears on sun-exposed skin, especially the chest and upper extremities. Following sun exposure there is a delay in the onset of these eruptions, from hours to days. Thus, some patients do not attribute their rash to sun exposure. Once present, the eruption will last for days. PMLE is most common in the spring and summer and may recur annually. A variant of PMLE, called juvenile spring eruption, presents with vesicles on helices of ears of young boys. Most authorities consider UVA to be the main cause of PMLE, but UVB, or occasionally even visible light, may also be responsible. Mild cases of PMLE are prevented and treated with photoprotection. More severe cases, ironically, may require phototherapy.

Actinic prurigo (AP) is a persistent HLA-restricted variant of PMLE. Its incidence is highest in the Native American population, especially young Native American girls. Clinically, it differs from PMLE by: (1) the presence of papules and nodules that are sometimes lichenified or excoriated due to pruritis, (2) a distribution that may include non-sun-exposed areas, and (3) the presence of cheilitis or conjunctivitis that may accompany the skin lesions or be the only presentation of the disease.

Chronic actinic dermatitis (CAD) is another type of idiopathic or primary photosensitivity disorder. This persistent eczematous dermatitis of chronically sun-exposed skin commonly affects middle-age to elderly men. CAD can be caused by UVA, UVB, or even visible ight, which makes strict sun avoidance essential.

Phototherapy: Inhibiting the Immune System with Light

Phototherapy is defined as the use of UV radiation in the treatment of skin disease. There are many types of phototherapy including: broadband UVB (280–320 nm), narrowband UVB (311-313nm), UVA1 (340–400 nm), and combination therapy of psoralen plus UVA (PUVA). Weighing the type of disease being treated, the depth of disease pathology, and the risk of skin carcinogenesis helps to determine the best phototherapy treatment modality for a particular patient. Once the appropriate modality has been chosen, the treatment is then individualized based upon the patient's minimal erythema dose (MED). MED is defined as the minimum amount of radiation that produces erythema 24 hours after exposure.

Use of phototherapy with psoralens revolutionized the treatment of patients with severe psoriasis. Although the psoralens used in PUVA photochemotherapy are highly purified medications, their mechanism of action is the same as the environmental psoralens responsible for phytophotodermatitis. By titrating the exact dose of psoralen and the amount and type of UV radiation, the physician is able to maximize the immunosuppressive effects of the treatment and minimize the risk of photoburn. PUVA is the most powerful phototherapy and just about any immune-mediated skin disease, including cutaneous T cell lymphoma, will respond to PUVA therapy. The main concern associated with PUVA is the increased risk of skin cancer, including melanoma [54].

Take-home messages:

- The ultraviolet spectrum is further divided by wavelength into UVC (200–280 nm), UVB (280–320 nm) and UVA (320–400 nm). More UVA reaches the Earth's surface but it is mainly UVB that causes sunburn. Almost no UVC reaches the Earth's surface.

- UV radiation causes local and systemic immunosuppression by: disrupting Langerhans cell function, inducing the formation of the *cis* isomer of urocanic acid, inducing anergy or deletion of Th1 cells, and promoting the influx of IL-10-secreting macrophages.

- Ultraviolet radiation induces keratinocytes and other cells to produce a variety of cytokines, including IL-1β and TNF-α.

- Transgenic animals designed to be resistant to the development of UV-induced sunburn cells can tolerate more UV radiation without burning, but they are predisposed to developing skin cancers. Sunburn cells are essential to prevent skin cancer but may induce or exacerbate an autoimmune disease state because their nuclear antigens are redistributed to their cell surface.

- Photosensitizers, absorb photons and release their energy. They induce two types of skin reactions: phototoxic and photoallergic. Phototoxic reactions are sunburn type reactions whereas photoallergic reactions are true immune mediated reactions that occur in sensitized individuals. UVA plays an important role in both phototoxic and photoallergic reactions.

- Phototherapy is the use of UV radiation in the treatment of skin disease. Types of phototherapy include broadband UVB (280–320 nm), narrowband UVB (311–313nm), UVA1 (340–400 nm), and combination therapy of psoralen plus UVA (PUVA).

Acknowledgments

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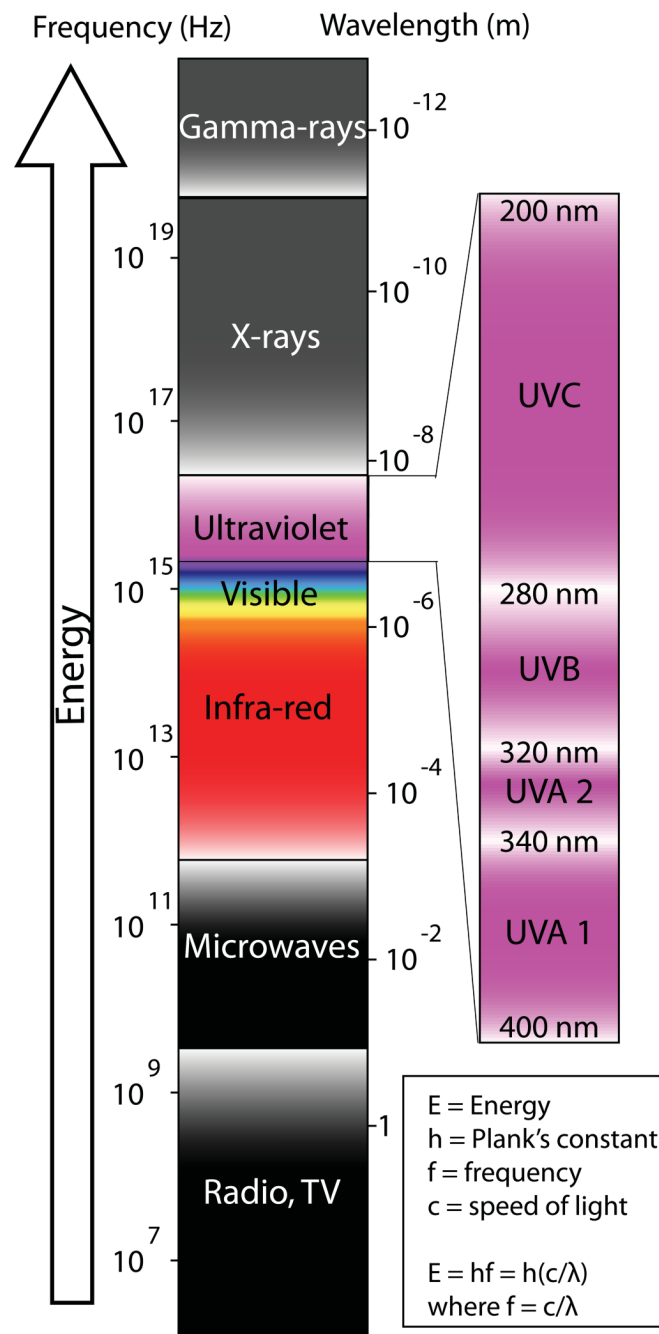
Figure 1. The electromagnetic spectrum
Ultraviolet radiation can be further devided into UVC, UVB, and UVA. Wavelength decreases as the frequency of the electromagnetic waves increases. As the frequency increases the energy of the emitted photons also increases. With a shorter wavelength, UVB radiation possesses much more energy than UVA.
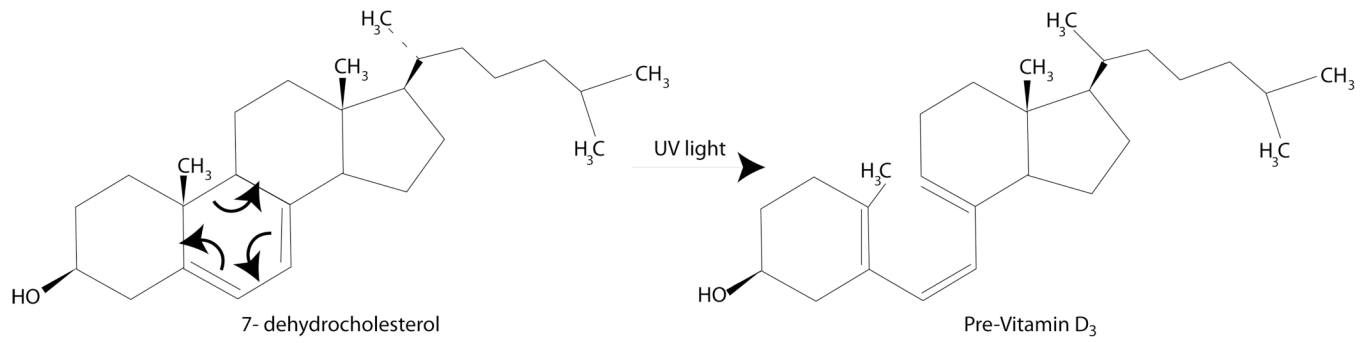
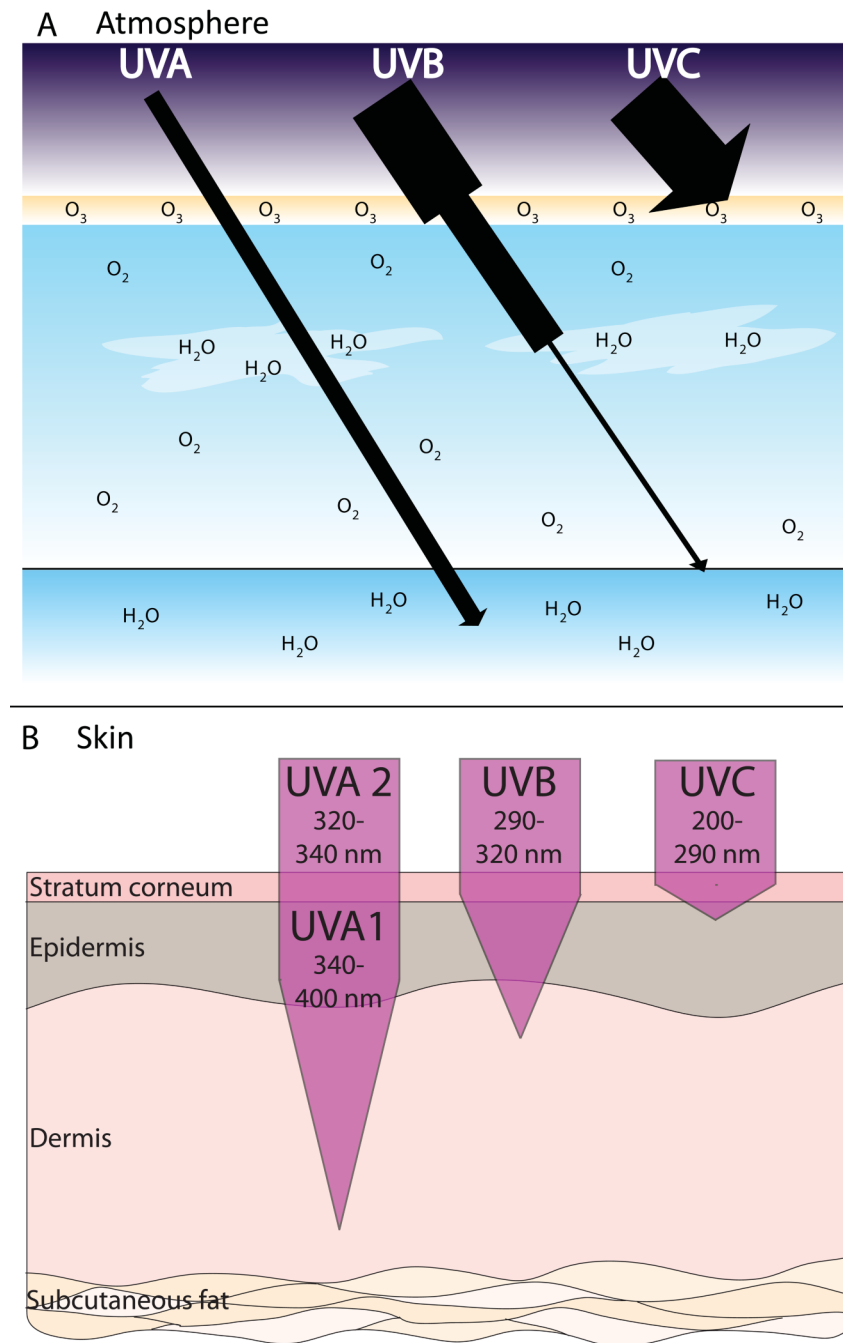**Figure 2. UVB induces a 6-electron conrotatory electrocyclic reaction to synthesize pre vitamin D$_3$ from 7-dehydrocholesterol, a derivative of cholesterol**

Figure 3. Penetrating abilities of UVA, UVB and UVC
A) Approximately 90% of UVB and nearly all of UVC is absorbed by O_3, O_2, and H_2O in the Earth's atmosphere. UVA makes up 95% of the UV radiation that reaches the Earth. B) With its longer wavelength, UVA can penetrate deeper into the skin than UVB.
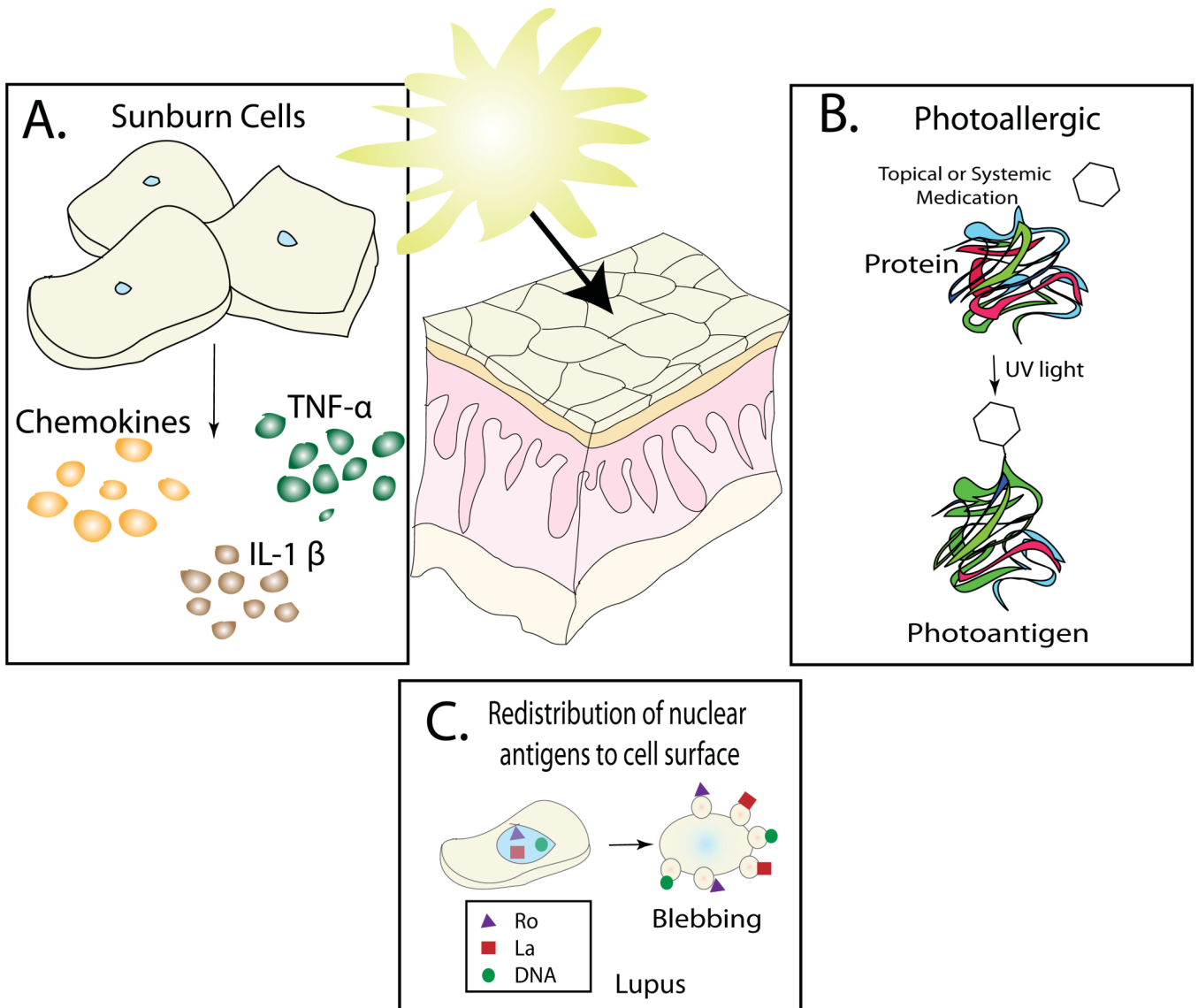
Figure 4. Mechanisms by which UV radiation can activate the immune system
A) In response to UV irradiation keratinocytes secrete a variety of different cytokines including TNF-α and IL-1β. B) Ionizing radiation from ultraviolet light can induce chemical reactions in the skin. Depicted here is a drug forming a covalent bond to a self-protein resulting is a novel antigen. In this example the drug can be considered a hapten. C) In response to UV-induced DNA damage, keratinocytes undergo apoptosis as a definitive mechanism to prevent malignant transformation. Following UV irradiation there is a redistribution of nuclear antigens to the surface of the keratinocyte.
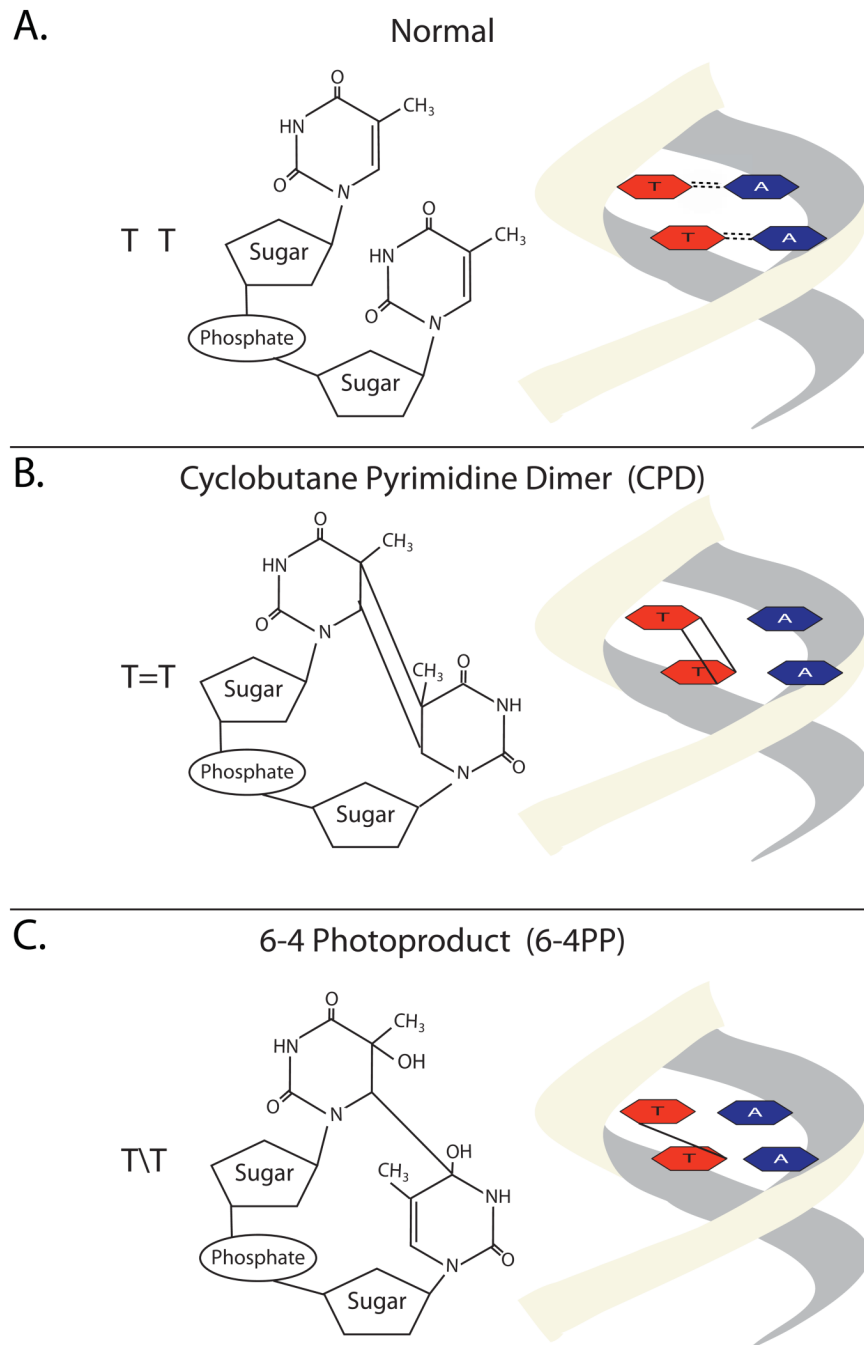
Figure 5. Formation of cyclobutane pyrimidine dimers and (6-4) photoproducts photoproducts
A) Two normal thymidine residues. B&C) DNA can absorb the ionizing radiation of ultraviolet light and undergo chemical modifications including the formation of cyclobutane pyrimidine dimers (CPD) or 6-4 photoproducts (6-4PPs).
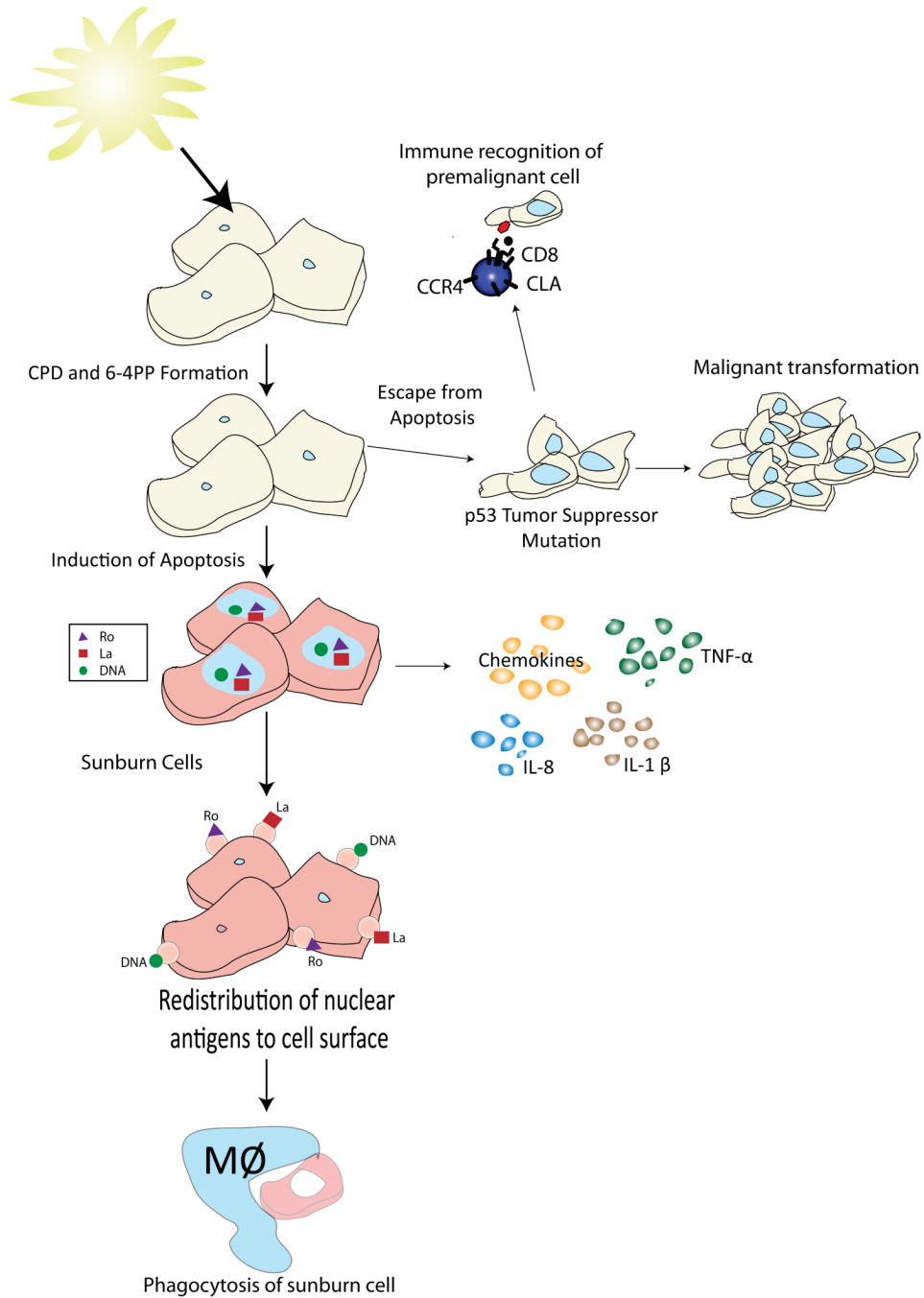
Figure 6. Following UV irradiation there are several pathways to eliminate DNA-damaged keratinocytes

Damaged cells can undergo apoptosis and be engulfed by macrophages. To facilitate this process UV-irradiated cells secrete pro-inflammatory cytokines. These cytokines help recruit the leukocytes to the skin that participate in the disposal of the dying keratinocytes. T cells can also recognize and destroy the damaged keratinocytes. Receptors that target T cells for migration to the skin include the cutaneous lymphocyte antigen (CLA) and the chemokine receptors CCR4 and CCR6. Finally, if a DNA damaged keratinocye escapes these mechanisms a malignancy may develop. These malignancies almost always have mutations in the p53 tumor suppressor gene.
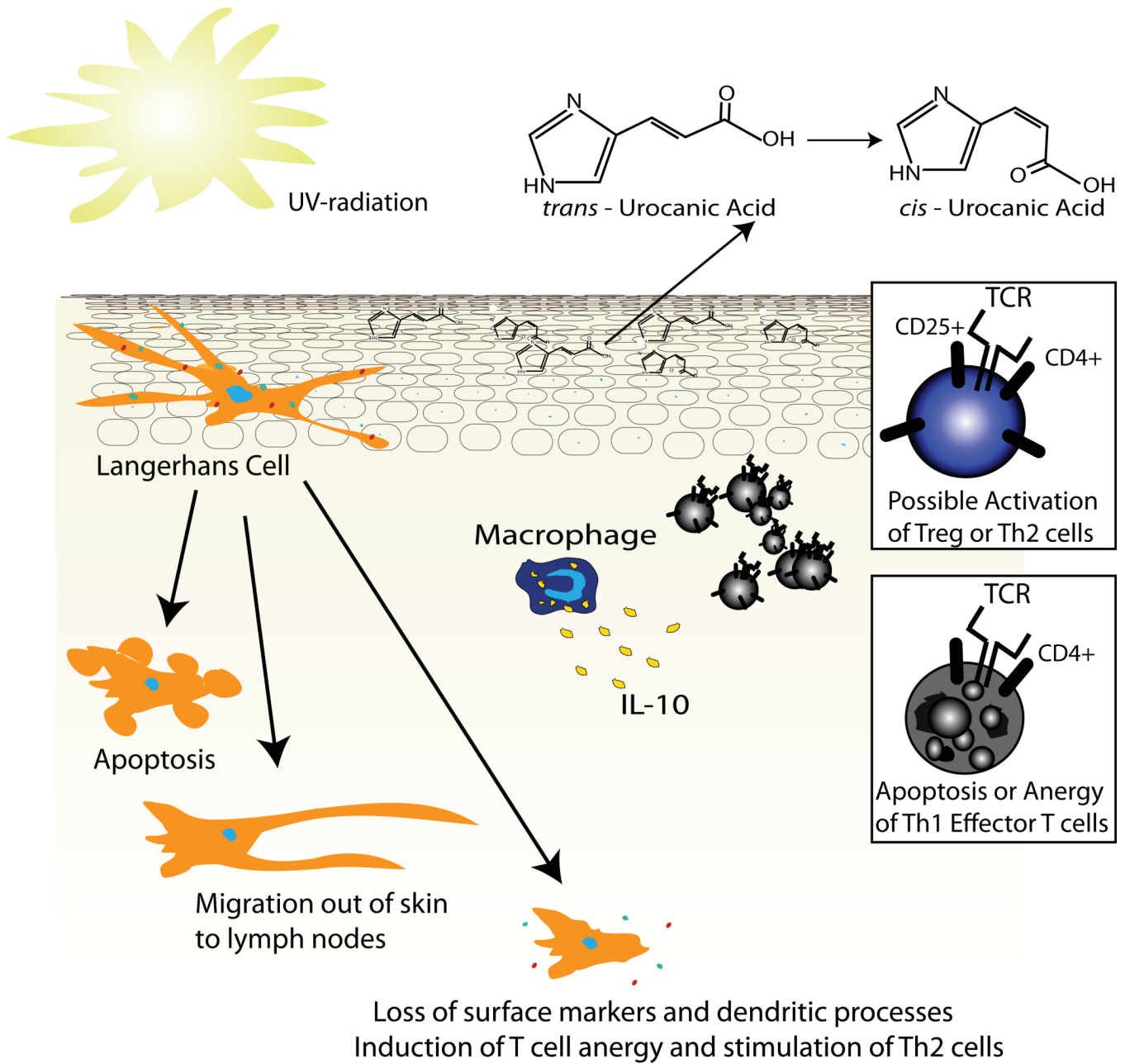
Figure 7. Mechanisms of UV-induced immunosuppression
UV irradiation disrupts Langerhans cell function by: inducing apoptosis, altering their surface phenotype, or by increasing their migration to the lymph nodes. The altered Langerhans cells can induce anergy or deletion of Th1 cells. Urocanic acid is present in large amounts in the epidermis. UV radiation can induce the isomerization of *trans*-urocanic acid to the *cis*-isomer that has immunosuppressive properties. Lastly, skin-infiltrating macrophages secrete IL-10, an anti-inflammatory cytokine.
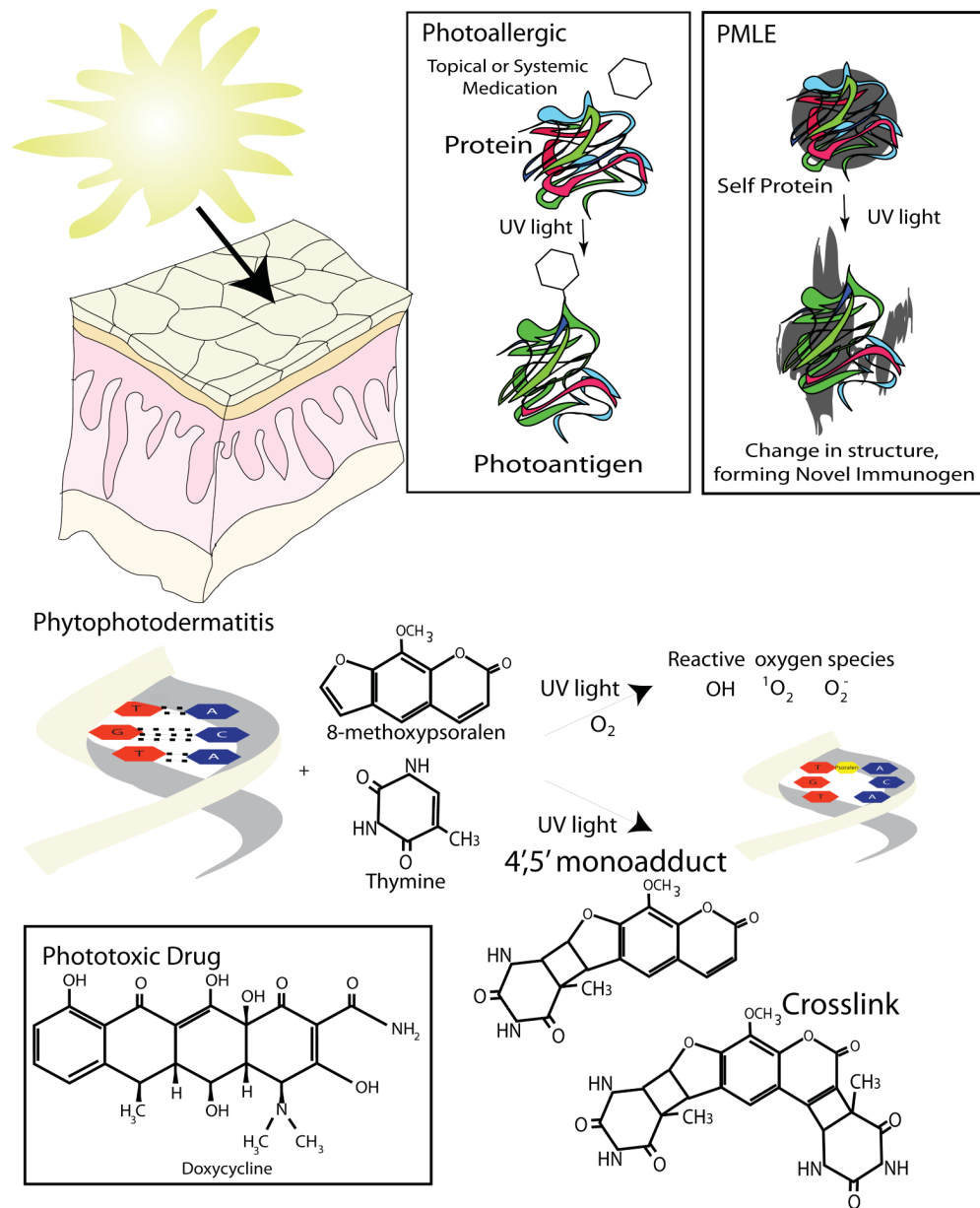
Figure 8. Phototoxic and photoallergic reactions
In photoallergic reactions small photosensitizer can act as a haptens using UV light to attach themselves to larger molecules, forming photoallergens. In PMLE it is believed that there is an endogenous protein or other molecule that can absorb ultraviolet light and be chemically modified by it. The resulting antigen then initiates an immune response. Phytophotodermatitis and phototoxic drug eruptions are examples of phototoxic reactions. In these types of reactions reactive oxygen species can be synthesized by the energy released from light absorbing photosensitizers, such as psoralens. Psoralens can also bind to DNA forming monoadducts or crosslinks.

Figure 9.
A) Phytophotodermatitis in response to lemonade and UV radiation; The linear areas of this rash reveal a likely external cause. B) Picture of hand of the same patient with phytophotodermatitis. The eruption is similar to an exaggerated sunburn, presenting with erythema and bullae. C) A milder case of phytophotodermatitis; The sometimes linear nature of the eruption is more apparent in this photo. D) Phototoxic drug eruption; Note the erythematous photodistributed plaque with hemorrhagic crust. E) Polymorphous light eruption; Notice the photodistribution of this rash. F) Subacute cutaneous lupus; Annular plaques with a ridge of scale and some central clearing or hyperpigmentation. The patient has a positive anti-Ro titer. G) Systemic lupus erythematosus; Acute photodistributed

erythematous plaque with very light scale. The patient has a positive anti-Ro titer. *Photos A, B and D are courtesy of Daniel B. Eisen, M.D.*