ULTRAVIOLET RADIATION AND THE SKIN IMMUNE RESPONSE

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SUMMARY – At present, ultraviolet radiation (UVR) represents one of the most important environmental factors affecting mankind. Besides the beneficial effects of UVR such as vitamin D production, it is known that UVR can lead to adverse effects on human health. The best known harmful effects are sunburns, tumors of the skin and ocular damage. It is noteworthy that UVR effects are not restricted to skin-associated infections, as there is strong evidence for their association with systemic (non-skin-associated) infections as well. Alterations in immune functions that are induced by UVR are initiated by the absorption of light energy by chromophores and their transformation into photoproducts. Some of them are removed by repair mechanisms, others induce signal transduction pathways, whereas some exhibit cytotoxicity. The observable skin response may occur within minutes of light exposure (e.g. urticaria) or may take days (e.g. inhibition of contact hypersensitivity), or much longer periods to be expressed (e.g. tumors). Today, artificial UVR (phototherapy) is used in dermatology for induction of immunomodulation in many forms of autoimmune and/or hyperimmune responses in the skin.

Key words: *Ultraviolet rays, adverse effects; Sunlight, adverse effects; Skin, radiation effects; Photosensitivity disorders, immunology*

Introduction

Although photoimmunology is only twenty years old, it has become one of the most rapidly advancing and expanding fields of biomedicine[1,2]. Anatomically, the first barrier to microbiologic invasion is the skin, a structure that was long considered only a passive barrier against that invasion[1,3]. During evolution, the skin has developed a specific immunologic environment that is known as the skin immune system (SIS)[4]. There are numerous molecular and cellular pathways that originate and terminate in the skin[1,5]. Exposure to ultraviolet radiation (UVR) can lead to immunomodulation that is not restricted to the exposed skin but is also found at other sites, i.e. distant (systemic) immunosuppression[3,6,7]. The best known harmful effects are sunburn, tumors of the skin, and ocular damage. It has been shown that UVR can impair the resistance to bacterial, viral, parasitic and fungal infections not restricted to the skin but may also be associated with systemic infections[3]. UVR induced immunomodulation in the skin might be a protective mechanism against certain forms of autoimmune and/or hyperimmune responses in the skin[6,8].

This paper is divided into four parts dealing with the basic events in the skin immune response, the role of UVR in the pathogenesis of diseases, clinical photoimmunology, and immunologic events during phototherapy[1,9,10].

The Skin Immune Response – Basic Events

The skin is an immunologic microcosmos containing all the cellular and molecular elements needed for initiation, regulation and expression of an immune response[11]. Bone marrow-derived dendritic leukocytes residing in the skin initiate and regulate the immune responses that protect it. In combination with immunomodulatory resident (keratinocytes, mast cells, endothelial cells) and passenger (T lymphocytes recirculating between skin and regional lymph nodes) cells, these leukocytes have been termed skin-associated lymphoid tissues (SALT) and skin immune system (SIS)[1].

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Antigen-presenting cells (APC) are Langerhans cells (LC), and dermal dendritic cells are immunomodulatory resident cells. LC are dendritic cells of bone marrow derivation that reside mainly within stratified squamous epithelia but have also been shown to occur in mesenchymal tissues such as the dermis and lymph nodes. In the epidermis, they are usually located at a suprabasal level and constitute approximately 2%-4% of all epidermal cells. Ultrastructurally, LC exhibit unique trilaminar cytoplasmic organelles (Birbeck granules) that allow their identification. Dermal dendritic cells are primarily located in perivascular areas of the dermis, and are member of the 'dermal microvascular unit'. They conceivably receive signals from the other cellular components of this unit, i.e. endothelial cells, pericytes, mast cells and T cells. While LC may also have occasional encounters with melanocytes and Merkel cells, their most important epidermal partner is unquestionably the keratinocyte. Keratinocytes are capable of producing and secreting growth factors and hormones as well as various mediators of the inflammatory reaction and the immune response, such as eicosanoids and cytokines. The lymphocytes of mammalian skin belong almost exclusively to the T-cell lineage as defined by the surface expression of CD3-associated T-cell antigen receptor (TCR). Lymphocytes are located within the basal layer of the epidermis and acrosyringial epithelium, and are clustered around the postcapillary venule and appendages[1,4].

UVR alters the APC function of the skin by two distinct mechanisms: directly by the effect on APC population, and indirectly by the production of soluble mediators that act indirectly on APC[12].

Effects of UVR on the signals provided by APC are released at all four levels of antigen-presenting (AP) function, that include:

(i)   cell-surface expression of major histocompatibility complex (MHC) class II determinants (UVR leads to depression in class II antigen positive LC);

(ii) antigen-processing (UVR leads to reduction in the proliferative response of the responding T-cell lines);

(iii) the production of various cytokines such as IL-1 and IL-6 (UVR leads to deficiency in IL-1 production and it is responsible for the loss of epidermal antigen presenting function); and

(iv) the expression of various adhesion molecules such as intercellular adhesion molecule (ICAM-1), B7/BB1 and LFA-3 adhesion molecules (UVR leads to down-regulation in the expression of ICAM-1 molecules and inhibition of B7/BB1 adhesion molecules)[1].

UVR suppresses the development of contact hypersensitivity (CHS) and results in the development of long lasting antigen specific unresponsiveness. UVR converts epidermal LC from immunogenic to tolerogenic APC for the subset of T cells responsible for mediation of delayed-type hypersensitivity (DTH) responses[1,13]. The effect of UVR and visible radiation on the immune system is initiated absorption of photons by specific chromophores. These chromophores are DNA, aromatic amino acids, 7-dehydrocholesterol, cytochromes, melanin and bilirubin[1].

UVR causes chromophores to transform into photoproducts. Some photoproducts are removed by repair mechanisms, others induce signal transduction pathways, and some of them are toxic to cells[14].

UVR also contributes to DNA damage and leads to the production of DNA photoproducts such as pyrimidine dimers (most frequent), pyrimidine-(6-4) pyrimidon photoproducts, and Dewar isomer[1].

The observable responses in skin may occur within minutes of light exposure (i.e. urticaria), or it may take days (i.e. inhibition of contact hypersensitivity) or much longer to express (i.e. tumors)[1,15].

There is ample evidence for a *close relationship between the immune and the neuroendocrine system*. The pro-opiomelanocortin (POMC) derived peptides exert potent immunomodulating functions and interact strongly with the cytokine network. On the other hand, cytokines were also found to be able to modulate the production and function of these peptide hormones. There is recent evidence that within the epidermis keratinoncytes, melanocytes and LC are able to produce POMC peptide. The constitutive production of both cytokines and neuroendocrine hormones by keratinocytes is quite low, but can be enhanced by injurious stimuli. UV light is one of these inducers[1,16].

PUVA-therapy suppresses IL-1, IL-6, IL-8 and tumor necrosis factor α (TNFa), which inhibit the migration of LC to lymph nodes[14,15].

UVB light upregulates IL-10 production, and there is evidence that keratinocyte derived IL-10 is involved in systemic immunosuppression. UV light is known to inhibit inflammatory and immune reaction, and the selective nature of the UV-induced suppression, similar to the biological activity of IL-10. UVR leads to the cutaneous release of colony-stimulating factors (CSFs) in amounts sufficient to reverse acute myelosuppression[7,16-18].

The Role of UVR in the Pathogenesis of Diseases

This part will present experimental aspects of photo-immunology. UVR may induce skin cancers, cutaneous melanoma and infectious diseases[16]. In fact, UVR leads to DNA damage that may cause **non-melanoma and melanoma skin cancers**. UVR may lead to mutations to tumor suppressor genes as well as to systemic immunosuppression (due to the generation of tumor antigen-specific T-suppressor cells that permit tolerance of normally highly antigenic tumors)[19,20]. UVR may play a role in the transformation of normal melanocytes into malignant melanoma cells, inhibit local immunity by modifying local immunologic environment, and facilitate the metastatic spread of melanomas[21]. **UVR triggers latent herpes simplex virus (HSV) infection** by impairment of LC in the UV-irradiated epidermis[1,22]. Also, UVR induces human immunodeficiency virus (HIV) gene expression and replication by direct interaction with the infected cells[1,22].

Recent studies suggest that soluble mediators released by UV-irradiated keratinocytes are involved in the suppression of systemic immunity to bacille Calmette-Guérin (BCG) by UVR and that the mediators may act, al least in part, by altering macrophage function. However, much more information is needed before we fully understand how UVR alters resistance to BCG infection[1].

Clinical Photoimmunology

This part is devoted to clinical photoimmunology with the emphasis on the pathogenesis of the disease.

Polymorphous light eruption (PLE). PLE is the most common photodermatosis. Its etiology is still elusive, and so is its pathogenesis. Currently, a delayed-type immunoreaction induced by electromagnetic irradiation and maintained by defective immunoregulatory mechanisms is proposed as the pathogenesis of PLE. Additional evidence has come from the investigation of expression of ICAM-1 that is also found in PLE. A recent investigation demonstrated stimulation of autologous mononuclear cells of peripheral blood by UV-irradiated epidermal cells. Currently, heat shock proteins are being discussed as the possible antigens expressed in the epidermis after brisk UVR[1,23].

A delayed type of immunoreaction induced by UVR and maintained by defect immunoregulatory mechanisms seems likely. Although a DTH reaction is postulated as the pathomechanism, the putative photoallergen has not yet been identified[1,15].

Photoallergy. Photoallergic reactions require not only the allergen (a chemical substance) but also light for their manifestation. Consequently, this type of reaction involves only uncovered areas of the skin exposed to light. Among photoallergic reactions, type IV reactions predominate[1].

Chronic actinic dermatitis (actinic reticuloid). Although the pathogenesis has not yet been fully clarified, the immunophenotype of the infiltrate and the therapeutic response to immunomodulatory drugs suggest an immune pathogenesis compatible with DTH, conceivably to a cutaneous photoallergen. Cellular hypersensitivity to UVR has also been proposed as an alternative pathogenic basis for the disease, and humoral immunity appears to be normal[5,9].

Solar urticaria. In solar urticaria, the proposed pathogenesis is an immediate-type hypersensitivity reaction. A precursor (chromophore) is activated by electromagnetic irradiation, thus forming a photoproduct (photoallergen). Specific IgE directed against the photoallergen is bound to the surface of mast cells. Bridging of IgE molecules by the photoallergen leads to the release of histamine and probably also of other mediators[1].

UVR produces striking changes in the immunologic environment of the epidermis promoting the specific immune reactions that are believed to be involved in different types of lupus erythematosus (LE) skin lesions. The proposed mechanisms of photosensitivity in LE include UVR induced proinflammatory mediators (PGE2, PGE2α, PGD, LTC4) necessary for the activation and mobilization of leukocytes involved in LE skin lesion. The mechanisms also include cytokines (IL-1, IL-6, TNFα, GM-CSF, IL-8), UVR induction of adhesion molecules (ICAM-1), enhanced cytotoxicity, and translocation of nuclear and/or cytoplasmic antigens recognized by antibodies associated with LE[24].

Immunologic Events in Phototherapy

This part reviews photoimmunology as a therapeutic modality.

Extracorporeal photochemotherapy (photopheresis) is used in erythrodermias and later stages of cutaneous T-cell lymphoma (CTCL) and graft-*versus* host disease (GvHD). PUVA (psoralen and UVA) therapy interacts with cellular DNA, lipids and protein, and leads to the formation of photoadducts that inhibit DNA synthesis. PUVA therapy leads to apoptosis, mutagenicity (cumulative exposure to PUVA may result in the development of squamous cell

carcinoma) and antigenicity (cell membrane photomodifications result in the formation of new antigenic moieties). The cell surface changes induced by PUVA therapy render cells susceptible to immune surveillance and destruction. Also, changes in antigen presentation due to altered processing of cellular proteins, or enhanced expression of class I MHC, may also contribute to therapeutic response[1,25].

UVA-1 radiation as therapy for atopic dermatitis. UVA-1 therapy was originally designed as monotherapy to treat patients with atopic dermatitis (AD). UVA-1 was found to functionally affect epidermal Langerhans cells, a cell population that appear to be of pathogenic relevance for AD. UVA-1 irradiation was highly efficient in improving clinical symptoms in patients with AD. Elevated serum levels of eosinphil cation protein ECP undergoing UVA-1 therapy are significantly decreased[26].

UVA-1 affects keratinocytes by modulating the expression of immunologically relevant surface molecules (e.g., expression of MHC and ICAM-1). UVA-1 radiation affects T-cell-derived cytokine expression by induction of IL-10 as a potent inhibitor of interferon-gamma (IFN-γ) produced by Th1 cells. UVA-1 also affects epidermal LC by modulating LC morphology and function (due to the depletion of epidermal LC surface markers)[27].

Photodynamic therapy (PDT) is the treatment of tumor or dysplastic tissues with drugs (photosensitizing molecules) that produce cytotoxic metabolites when exposed to light (argon-dye laser). Monocytes and macrophages phagocytize the photosensitizer and then infiltrate tumor tissue resulting in tumor necrosis[1]. In addition, PDT influences the inflammatory response and alters cell-mediated immune response. Also, PDT induces macrophages to produce and secrete cytokines (IL-1) and prostaglandins (PGE2), which are known to inhibit the generation of contact hypersensitivity response. Inflammatory mediators in PDT treatment are vasoactive amines, eicosanoids, eliciting an important stimulus for TNF (that might be a mediator of tumor regression)[28].

PUVA therapy and psoriasis. PUVA has antiproliferative effects on keratinocytes, interferes with cytokine production (IL-6, IL-2), decreases density of intraepidermal-dermal mononuclear cells, diminishes T-cell population, and in combination with cyclosporin results in reduction of ICAM-1 expression[29].

UVB-therapy and psoriasis. UVB therapy can prevent TNFα- or TNFβ-induced ICAM-1 expression by keratinocytes, and may suppress MCP-1 production[30].

Generalized lichen planus has been shown to respond to systemic PUVA treatment by destruction of the epitheliotropic inflammatory mononuclear cells and/or interference with cytokines[31].

PUVA therapy in patients with dermatitis allergica e contactu (CAD) may diminish the induction of CAD due to impairment of LC, it leads to long lasting antigen specific unresponsiveness, and converts epidermal LC from immunogenic to tolerogenic[13].

In *vitiligo, PUVA therapy* induces systemic T-suppressor cell population, and melanocyte destruction could be prevented[32].

PUVA therapy acts as a photochemoprotective agent that induces an 'endogenous sunscreen' and thereby inhibits the photoantigen formation in *polymorphous light eruption*[1,22].

In *CTCL, PUVA therapy* causes cytotoxic effect on the infiltrating T-cells within the epidermis, and downregulation of the 'homing' receptors of epidermotropic malignant cells[33].

In *chronic GvHD, PUVA* is a successful treatment. PUVA therapy interferes with the production and/or release of potent cytokines, and leads to downregulation of class II alloantigen expression by the dendritic cell population[28].

Conclusion

Photoimmunology has already contributed greatly to our understanding of the immunophysiology of the skin, and of the normal regulation and functioning of the immune system. It promises to continue to improve our understanding of the pathogenesis of cutaneous diseases and to provide new avenues for therapy in the future.

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Sažetak

ULTRALJUBIČASTO ZRAČENJE I IMUNI ODGOVOR KOŽE

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Ultraljubičasto zračenje (UVZ) danas predstavlja jedan od najvažnijih čimbenika okoliša koji utječu na ljude. Uz korisne učinke UVZ, kao što je stvaranje vitamina D, poznato je da UVZ može imati i neželjene učinke na ljudsko zdravlje. Najprepoznatljiviji štetni učinci su opekline od sunca, tumori kože i oštećenje očiju. Valja napomenuti kako učinci UVZ nisu ograničeni na infekcije povezane s kožom, nego su isto tako udruženi sa sistemskim infekcijama (koje nisu povezane s kožom), i za to postoje jaki dokazi. Promjene imunosnih funkcija što ih izaziva UVZ započinju apsorpcijom svjetlosne energije od strane kromofora i njihovom pretvorbom u fotoproizvode. Neki se od njih uklanjanju popravnim mehanizmima, drugi izazivaju putanje signalne transdukcije, dok su pak treći citotoksični. Primjetljiva reakcija na koži može se pojaviti u roku od jedne minute izloženosti svjetlu (tj. urtikarija) ili mogu proći dani (tj. suzbijanje kontaktne preosjetljivosti) ili znatno duže vremensko razdoblje (tj. tumori) do njezine pojave. Danas se umjetno UVZ (fototerapija) rabi u dermatologiji za izazivanje imunomodulacije u mnogim oblicima autoimunog i/ili hiperimunog odgovora u koži.

Ključne riječi: *Ultraljubičaste zrake, neželjeni učinci; Sunčeva svjetlost, neželjeni učinci; Koža, imunologija; Koža, učinci zračenja; Poremećaji fotoosjetljivosti, imunologija*