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Effects of ultraviolet radiation on Langerhans cells

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Abstract

Research on penetration of ultraviolet (UV) radiation into human skin shows that about 20% of UVA and 10% of UVB can reach the basal layer of the epidermis. As a consequence, Langerhans cells (LCs), located in suprabasal layers, are subject to the influence of the two types of UV radiation. This phenomenon leads to quantitative and qualitative alterations in LCs, including reduction in their number in the epidermis and modifications in morphology and immune functions. Studies show that two mechanisms may be responsible for their depletion from epidermis, namely, migration to the lymph nodes or induction of cell necrosis or apoptosis. UV radiation also affects the phenotype of LCs and their functions as antigen presenting cells. In recent years, the role of LCs in the UV-dependent immunosuppression and immune tolerance has been emphasized. The aim of the study is to review the literature about the influence of ultraviolet radiation on Langerhans cells.

Key words: *UVA, UVB, Langerhans cells, skin.*

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Langerhans cells (LCs), dendritic cells of epidermis, are one of key components of the skin immune system. However, in recent years, views on their role and immune properties have significantly evolved. Previously, LCs were regarded as main initiators of immune response to infectious and sensitizing agents. Now it is known that also other types of dendritic antigen-presenting cells are present in the skin. These cells perform functions attributed earlier exclusively to LCs. Moreover, in many experiments selective removal of LCs from epidermis resulted in an increase in immune response, indicating regulatory functions of these cells and their ability to modulate an immune response not only towards immunity, but first of all tolerance [1]. This revision of views on LCs creates the need for a new look and also for redefining of their role in the processes occurring in the skin after exposure to ultraviolet (UV) radiation.

Research on penetration of UV radiation into human skin shows that about 20% of UVA (320-400 nm) and 10% of UVB (290-320 nm) can reach the basal layer of the epidermis. Therefore, LCs found in suprabasal layers are subject to the influence of the two types of UV radiation [2, 3]. Consequently, it results in quantitative and qualitative alterations in LCs, including reduction in their number in the epidermis and modifications in morphology and immune functions [4]. The aim of the study is to review the literature about the influence of ultraviolet radiation on LCs. The résumé of the state of knowledge may become the basis for further investigations of LCs contribution to processes occurring in the skin, following exposure to UV radiation.

Effects of UV radiation on the number of LCs in the epidermis

Numerous studies showed a decrease in the number of LCs in the epidermis caused by exposure to UV radiation, including sunlight [5], solar simulated radiation (SSR) [6], UVA [7, 8] and UVB [9, 10]. Two mechanisms are considered responsible for this effect: mobilization and migration of LCs to the lymph nodes or induction of necrosis or apoptosis processes by UV [9-12]. Those mechanisms were investigated by Kölgen *et al.* [9]: the volunteers' buttock and forearm skin was exposed to 6 minimal erythema dos-

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es (MED) of UVB (58% of radiation within 280-315 nm). Next, the presence of apoptotic markers within LCs was examined but only few apoptotic LCs were found (less than 3%). In the same experiment, the assessment of LCs in fluid obtained from suction blisters showed that disappearance of these cells from epidermis could be mainly attributable to migration.

Czernielewski *et al.* [5] demonstrated that there were fewer LCs in the skin exposed to sunlight (e.g. hand) than in covered areas of the skin (e.g. buttocks). Other authors also showed a reduced number of LCs in the epidermis caused by solar simulated radiation (SSR) – UVA + UVB, 290-400 nm – both in humans after exposure to a single dose of UV-SSR (2 MED, 3 MED) [6, 7] and in mice after multiple suberythematous doses of irradiation (3.7 J/cm^2, from 10 to 60 days) [13]. According to Novakovic *et al.*'s study, the decrease in the number of LCs was the greatest 72 hours after irradiation with 2 MEDs of SSR [6]. McLoone *et al.* observed an increase in the dendritic cells in the lymph nodes [13] with a simultaneous reduction of LCs number in murine epidermis.

A statistically significant reduction in LCs density was also found in human volunteers after irradiation with UV simulated daylight (UV-DL, UVA:UVB approximately 24 : 1). The effect was observed after a single dose equal to or greater than 1.5 MED and after 19 irradiations with 1.5 MED [14].

In volunteers exposed to a full spectrum of UVA, a significant decrease in the number of LCs was detected by Seité *et al.*, with a 60 J/cm^2 dose, higher than MED. Similarly, single doses of UVA1 caused also a decrease in the number of LCs in human epidermis [7, 8].

Many authors showed a reduction in the number of LCs post-UVB radiation exposure. This effect was observed in mice irradiated with suberythematous doses of UVB. A high single dose of radiation – 50 or 100 mJ/cm^2 – caused a reduction in LC population by 33%; repeated 10 low doses of 10 mJ/cm^2 – by 43% and 4 doses of 25 mJ/cm^2 – by 59% [15]. A similar decrease in LCs density after multiple broad-spectrum UVB irradiation (280-360 nm, a dose of 1500 J/m^2 twice a week for 3 weeks) was detected in mice by Macve *et al.* [10]. Concomitantly, the number of lymph node dendritic cells was reduced by 30%. Moodycliffe *et al.* discovered an increase in the number of dendritic cells in the regional lymph nodes in mice after irradiating with a single dose of 1440 J/m^2, whereas the number of LCs in the epidermis was reduced [16]. In another experiment, involving humans, monochromatic UVB radiation (295 ±5 nm) with a dose of 1.5 MED, single or fractionated over the following 10 days, led to a reduction in LCs number in the epidermis by 30-50% [17]. In an earlier study, involving human volunteers with skin phototypes II-III, irradiation of the buttock skin with a dose of 144 mJ/cm^2 of UVB for 4 days resulted in almost complete depletion of epidermal LCs [18]. According to Rattis *et al.*, *in vitro* UVB irradiation of human LCs with a dose of 200 J/m^2 led to a significant decrease in the number of viable cells after 2 days, which was assigned to the cytotoxic effect of UV and the apoptosis of cells [19].

It should be noted that the reduction in the number of LCs in the epidermis after SSR, UVA, UVA1 and UVB irradiation in the majority of experiments was found to be dose dependent [6, 7, 20].

The results concerning the time of normalization of LCs number in the epidermis after exposure to UV varied depending on the study. In Bacci *et al.*'s experiment with mice irradiated with UVB, it occurred only after 24 hours [21]. However, in Fukunaga *et al.*'s study, after UVB irradiation of mice with a dose of 1000-2000 J/m^2, the number of LCs in the epidermis returned to baseline after 63 days [22].

Effects of UV on morphology and phenotype of LCs

LCs which remained in the epidermis after exposure to UV radiation exhibited characteristic morphological alterations, with a tendency to be more and more evident with an increased radiation dose [6]. The changes included swelling and rounding of the cells, decrease or increase in size and initial shortening and then the loss of dendrites. At the same time, damage at the ultrastructural level, concerning DNA and cell organelles, particularly mitochondria and Birbeck granules, was observed. It can be assumed that it is highly likely that reactive oxygen species play an important role in the induction of these changes [4, 7, 15]. The formation of cyclobutane pyrimidine dimers and 6-4 photoproducts are main UV-dependent DNA modifications [23]. Cyclobutane thymidine dimers were found in about 27% of LCs migrating from the epidermis 18 hours after exposure to UVB (in examination of fluid obtained by blister suction) [8]. It was suggested that the significant damage to mitochondria and formation of numerous reactive oxygen species may lead to apoptosis of cells [7].

In Seité *et al.*'s study with human volunteers, a single exposure to UV-SSR (2 MED) caused a slight reduction in the size of LCs remaining in the epidermis [7]. Novakovic *et al.* observed a 1.7-fold increase in the size of LCs compared with non-irradiated skin, even after exposure to a suberythematous dose of SSR (0.5 MED). The irradiation with a dose of 3 MED resulted in a 2.2-fold increase in the size of LCs; concurrently it caused the loss of dendrites [6]. In mice irradiated with SSR for over 10 days, McLoone *et al.* observed an increase in the length of LCs [13].

After irradiation with a dose of UVA greater than 30 J/cm^2 (MED of about 48 J/cm^2) LCs were reduced in size by 22% (more than after UV-SSR) and after 60 J/cm^2 by 45%. Moreover, shortening or fragmentation of dendrites, rounding of cell bodies and lower HLA-DR expression were observed. A similar decrease in the size of LCs was noted after exposure to UVA1. Under a transmission elec-

tron microscopy, alterations in size and shape of cell organelles, concerning mitochondrial membranes and endoplasmic reticulum were visible after a single UVA dose of 60 J/cm^2 [7].

After UVB irradiation of mice with a single suberythematous dose (50, 100 mJ/cm^2), a decrease in the number of LCs and dendrite shortening were observed. Then, after 10 irradiations with 10 mJ/cm^2 and 4 irradiations with 25 mJ/cm^2 LCs lost their dendritic morphology [15]. As early as 2 hours after UVB irradiation with a single dose of 400 J/m^2 in mice *in vivo* and in murine skin biopsies ex *vivo*, Bacci *et al.* reported shortening and partial fragmentation of dendrites of LCs remaining in the epidermis [6]. At the ultrastructural level, a reduction of Birbeck granules, their shortening and loss of rocket shape [15] and even disappearance of cytoplasmic organelles, except lysosomes [6], were noted.

LCs remaining in the epidermis after UV exposure may also exhibit alterations in expression of surface molecules. It was proved by Dumay *et al.* that UVA1 (340-400 nm) with a dose of 60 J/cm^2 resulted in a lower HLA-DR expression [8]. After exposure of LCs in mice to UVB with a dose 200 J/m^2, Denfeld *et al.* observed an altered expression of costimulatory molecules CD80 (B7.1) and CD86 (B7.2) (ligands for CD28 in the interaction between LCs and T cells) [24]. 2 days after UVB irradiation of LCs *in vitro* with a dose of 100 J/m^2 UVB, Rattis *et al.* observed a decreased CD54 and CD86 expression, whereas the level of CD80 was comparable to the control group [11]. Other researchers also noted a reduction in HLA-DR expression and co-stimulating molecules on the surface of LCs [25, 26].

Damage to cell membrane and loss of characteristic features of LCs were also observed, making identification of these cells difficult [26]. According to Ishitsuka *et al.*, repetitive suberythemal UVB irradiation had a greater effect on the number and morphology of LCs than a single high dose of radiation, to a much higher degree inhibiting their regeneration in the epidermis [15].

The consequence of morphological alterations is the loss of the integrity of LCs network – "guards" of the epidermis. It may contribute to the impairment of the immune surveillance mechanisms in the skin, resulting in lower efficacy in eliminating transformed or infected cells [23].

Effects of UV on immunological functions of LCs: maturation, migration, antigen-presentation and T cells stimulation

UV radiation significantly affects the functions of LCs, however, the experimental results of various research groups differ in this respect. Nakagawa *et al.* [4] described two different effects on LCs after *ex vivo* irradiation of human skin sections with UVB (doses of 200, 400, 600, 800, 1600 J/m^2). Two separate subpopulations of LC were distinguished: large-sized LCs with a high HLA-DR expression, and HLA-DR-low, small LCs. UVB stimulated the maturation of the former LC subset as demonstrated by enhanced up-regulation of CD80, CD86, CD54, CD40, and CD83, a reduced CD1a expression and release of proinflammatory cytokines. In contrast, the latter LC exhibited little or no up-regulation of these molecules except for a high CD1a expression indicating that they were apoptotic. These results suggested a dual action of UVB on LC when irradiated in situ: immunosuppression in part of LC, and immunopotentiation in another part. HLA-DR-high population retained the ability to stimulate T cells, nevertheless to a lesser extent than non-irradiated cells. It seems that this dual effect (immunosuppression plus inhibition of maturation versus immunostimulation plus maturation) may be triggered by different doses of radiation, below or above a threshold leading to a cytotoxic or cytostatic effect. It was revealed that with the increasing UV dose the number of HLA-DR-low cells increased and the number of HLA-DR-high cells decreased. The location of target LCs within the layers of the epidermis may be also important – the closer to the basal layer, the lower penetration and lower cytotoxicity of UVB radiation.

Many authors concluded that UV radiation was a factor stimulating migration of LCs from the epidermis to the lymph nodes [4, 9, 13, 16, 20]. An increased number of migrating LCs after exposure to UVB (doses of 200, 400, 800, 1600 J/m^2) was shown by Nakagawa *et al.*, but at high doses of radiation this effect was reduced [4]. However, Mizuno *et al.* [26] noted that the ability of LCs to migrate in response to chemokines was diminished as a result of UVB radiation. Observations of irradiated mice by Duthie *et al.* [20] showed that the migration of LCs was different in response to UVB and UVA1. After exposure of mice to 1 MED of UVB radiation, the maximum reduction in the number of LCs in the epidermis was observed after 12 hours (by 45.3%), whereas 1 MED of UVA1 did not cause such an effect at all. Both UVB and UVA1 irradiations resulted in a two-fold increase in the number of dendritic cells in lymph nodes. In the case of UVB irradiation, treatment of mice with anti-TNF-α and anti-IL-1β neutralizing antibodies resulted in a minor reduction in the number of LCs in the epidermis and a lesser increase in dendritic cells in the lymph nodes. In the case of UVA1, the inhibition of accumulation of dendritic cells in lymph nodes occurred only after treatment with anti-IL1β antibodies. These findings suggest slightly different mechanisms of action of UVB and UVA1 on LCs and dendritic cells [20]. Hamakawa *et al.* [27] found that UVB radiation with doses of 20 and 40 mJ/cm^2 resulted in a reduction in the migration of LCs to lymph nodes in mice. This phenomenon may be partly explained by the decreased expression of alpha4 integrin by LCs and its impaired binding to fibronectin as well as the reduction in surface chemokine receptor CCR7. In the study involving mice *in vivo*, Fukunaga *et al.* [22] showed that exposure to UVB (270-290 nm) triggered the migra-

tion of mature LC to the skin draining lymph nodes. The authors also observed prolonged LCs survival in the lymph nodes, i.e. increased number of CD207+ cells 7, 14 and 21 days after irradiation.

Mizuno *et al.* [26] found that UVB radiation impaired the endocytic activity of Langerhans cell-like dendritic cells, obtained by *in vitro* culture. The release of TNF-α, maturation, migration and the ability of LCs to stimulate T cells were subsequently also inhibited [26]. Other experiments also showed that UVB irradiation resulted in impaired antigen presentation by LCs and their reduced ability to stimulate T cells [19, 24]. It may be related to the UV-dependent decrease in expression of HLA-DR and co-stimulating molecules (CD80, CD86), but also decreased formation of the immunologic synapse between LCs (as antigen presenting cells) and T cells. LCs in the forearm skin of the volunteers irradiated three times with a dose of 1 MED of UVB did not upregulate CD86 molecules. Their antigen presenting function was impaired and in a mixed leukocyte reaction they did not show the ability to activate T cells [28]. A similar immunological dysfunction of LCs and inhibition of mixed epidermal cell-lymphocyte reaction, was obtained by exposure of the volunteers to UVB radiation with a total dose of 600 to 3500 J/m^2 applied within 3 weeks [29]. In Denfeld *et al.*'s study, the functional expression of CD80 and CD86 on LCs from mice was distorted by UVB, thereby contributing to the failure of irradiated LCs to stimulate naive T cells [24]. *In vitro* exposure of LCs to UVB radiation (312 nm) with doses of 100 to 200 J/m^2 also resulted in a significant dose-dependent reduction or suppression of proliferation of CD4+ and CD8+ T cells, without any cytotoxic effect of radiation on LCs [19]. Unlike UVB, exposure of forearm skin of human volunteers to UVA1 (with a dose of 3 MED) did not impair either expression of CD86 on the surface of LCs or antigen presenting function or the ability to stimulate T cells proliferation [28]. It may mean that the immune functions of LCs are modified mainly by UVB and to a lesser extent by UVA. [28]. It seems that the UV-dependent inhibition of T cells activation mainly affects Th1 type immune response, without suppression of Th2 type immunity, which results in a reduction in Th1 effector cells and generation of Th2 suppressor cells [25, 26].

It should be noted that in recent years more and more emphasis has been put on the role of LCs in the UV-dependent (mainly UVB 290-320 nm) immunosuppression and immune tolerance [28]. It is considered that UV exposure triggers the migration of LCs from the skin to the draining lymph nodes where they are responsible for inducing immune tolerance [22]. One of its manifestations is the inhibition of contact hypersensitivity (CHS) reaction in the skin exposed to UV radiation. The experiments with LC-deficient mice, with only few exceptions [31], indicate that LCs are necessary for UV-dependent inhibition of contact hypersensitivity as no immune suppression was observed in LC-deficient mice [22, 32]. It was shown experimentally (including studies using a murine model) that skin exposure to UV radiation prior to application of hapten caused suppression of contact hypersensitivity reactions, while the use of DNA repair enzymes prevented this effect [33]. This phenomenon was initially explained by a decreased number of LCs in the epidermis and a lack of effective activation of T cells [34]. It was also suggested that induction of tolerance was related to the immature state of LCs migrating to lymph nodes [35]. In recent years, it has been reported that LCs with UV-induced DNA damage (but still viable) are responsible for immunosuppression. DNA lesions trigger the migration of epidermal LCs to the regional lymph nodes, where during antigen presentation they induce CD4+ CD25+ antigen-specific regulatory T cells. In this way interaction of LCs and effector T cells does not result in sensitization but tolerance [36]. It was also found that LCs, present in murine lymph nodes after exposure to UVB, expressed markers of maturation, including CD80 and CD86. Therefore, a conclusive presumption might be that it is not only an immature phenotype that should be associated with the promotion of tolerance [22]. It is worth noting that immune tolerance induced by LCs and regulatory T cells is antigen-specific [32, 36] and the transfer of LCs from UV-irradiated mice into normal recipient animals causes immune suppression and induced tolerance [22]. Experiments of Fukunaga *et al.* with mice selectively deficient in immune cells showed that LCs, migrating after exposure to UVB, have the ability to activate NKT cells in the lymph nodes. It was suggested that these NKT cells take part in suppression of the immune response [22]. In Simon *et al.*'s study [35], murine LCs exposed to a single UVB dose of 200 J/m^2, underwent the transformation from immunogenic to tolerogenic, causing clonal anergy of Th1 cells that lasted from 8 to 16 days. Experiments carried out with a murine model by Yoshiki *et al.* [37] indicated that under the influence of UVB radiation, LCs underwent maturation, produced IL-10, upregulated OX40L and CD86 and migrated to the lymph nodes [37]. Those activated LCs were essential in the induction of antigen-specific regulatory T cells [37]. The reduction in the number of LCs in the epidermis as well as the induction of a specific cytokine profile also can contribute to immunosuppression, for example IL-10 secreted by keratinocytes and macrophages reduces the expression of CD80, CD86 and CD54 (ICAM1) on LCs [4, 25, 38].

Implications of UV impact on LCs

The participation of LCs in the phenomena occurring in the skin after exposure to UV radiation is complex. LCs participate in a series of processes that consequently lead to local immunomodulation and immunosuppression [39]. These phenomena may play a negative role, for example in UV-dependent carcinogenesis and a positive role, in phototherapy. LCs are considered as important components of skin immune surveillance mechanisms, because of their pos-

sible function of tumor-associated antigens presentation [40]. It was experimentally shown that they were able to induce antigen-specific cytotoxic CD8+ T cells, participating in the elimination of tumor cells [41, 42]. Skin exposure to UV radiation may lead to the impairment of immune surveillance mechanisms, among others through the effect on LCs, including transfer from epidermis to the lymph nodes, disturbances in antigen transport, decrease in IL-1β release and a reduced expression of costimulatory molecules and lower ability to activate T cells [40]. Reduction in the number or depletion of these cells in skin cancers or cutaneous premalignant conditions may indicate that they are indispensable for efficient functioning of immune surveillance mechanisms. On the other hand, depletion of LCs in epidermis, alterations in expression of surface molecules, generation of regulatory T cell, all resulting in local immunosuppression, may contribute to the effectiveness of phototherapy of inflammatory skin diseases as psoriasis, atopic dermatitis or mycosis fungoides.

To summarize, in future research attention should be focused on the detailed role of LCs in UV-dependent phenomena in the skin, especially their contribution to immunosuppression and immunotolerance.

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