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Cytokine Polymorphisms Play a Role in Susceptibility to Ultraviolet B-Induced Modulation of Immune Responses after Hepatitis B Vaccination

Annemarie Sleijffers,²*‡ Berran Yucesoy,† Michael Kashon,‡ Johan Garssen,* Frank R. De Gruijl,§ Greet J. Boland,‖ Jan Van Hattum,‖ Michael I. Luster,‡ and Henk Van Loveren*

UVB exposure can alter immune responses in experimental animals and humans. In an earlier human volunteer study, we demonstrated that hepatitis B-specific humoral and cellular immunity after vaccination on average were not significantly affected by UVB exposure. However, it is known that individuals differ in their susceptibility to UVB-induced immunomodulation, and it was hypothesized that polymorphisms in specific cytokines may play a role in this susceptibility. In this respect, we previously demonstrated that immune responses after hepatitis B vaccination are influenced by the minor allelic variant of IL-1β in the general population. For all volunteers, single nucleotide polymorphisms were determined for the following UV response-related cytokines: IL-1 receptor antagonist (+2018), IL-1α (+4845), IL-1β (+3953), TNF-α (−308), and TNF-α (−238). Exposure to UVB significantly suppressed Ab responses to hepatitis B in individuals with the minor variant for the IL-1β polymorphism. Increased minimal erythema dose values (just perceptible), which resulted in higher absolute UVB exposures, were observed in the same individuals. There were no associations observed between UVB-induced immunomodulation and the other cytokine polymorphisms examined. This study indicates that individual susceptibility to UVB radiation needs to be considered when studying the effects of UVB in the general population. The Journal of Immunology, 2003, 170: 3423–3428.

Over the last few decades it has become evident that UVB exposure (280–315 nm) influences specific and nonspecific immune responses (1). This immunomodulation may have positive health effects, such as in UVB phototherapy of psoriasis patients and potentially of other cell-mediated autoimmune diseases (such as multiple sclerosis) and the impairment of delayed-type allergies (2–5). However, by the same token, UVB-induced immunosuppression can also have adverse consequences. For example, UVB-induced immunosuppression has been shown to play an important role in photocarcinogenesis (6). In addition, UVB exposure has been demonstrated to impair resistance to bacterial, viral, parasitic, and fungal infections. Importantly, the effects of UVB are not restricted to skin-associated infections, but are also found in systemic infections (7–13).

The mechanisms that have been proposed to play a role in UVB-induced immunomodulation (14, 15) involve cytokines in a regulatory capacity. Epidermal cytokines are involved in acute dermatotoxicity as well as in immunomodulation induced by UV. IL-1α is present in the stratum corneum of normal human skin, but not in the basal layer. After UVB exposure, IL-1α appears in the basal layer and is increased in the more exterior regions (16). However, the anti-inflammatory cytokine IL-1 receptor antagonist (RA)3 is also up-regulated by UV. This increment is 100-fold more compared with IL-1, so the biological activity of IL-1 is suppressed by the competitive inhibitor IL-1RA. Thereby, IL-1RA is possibly an important mediator of immunomodulation in the skin (17).

TNF-α is also an important cytokine in UVB-induced immunomodulation as well as in sunburn (18, 19). UV radiation up-regulates the expression of TNF-α by keratinocytes directly (20) and through IL-1α (21). In addition, UV induces release of intracellular TNF-α from dermal mast cells (22). TNF-α helps regulate the migration of Langerhans cells from the skin toward the lymph nodes (23). These Langerhans cells show a diminished or altered presentation of Ags after UV exposure (24). IL-1 and TNF-α can be detected in serum after UV radiation and are thought to be responsible, at least in part, for UVB-induced suppression of systemic immunity (20, 25).

Recent studies have focused on differences in cytokine levels among individuals and have ascribed these differences, in part, to inheritable single nucleotide polymorphisms (SNPs) present within the regulatory elements of cytokine genes (26–30). In humans, the gene encoding for TNF-α is located on chromosome 6 between HLA-B and DR within the class III region of the major histocompatibility complex (31). Two SNPs containing a G→A substitution have been described in the promoter region at positions −308 and −238, which influence TNF-α expression (32, 33). The IL-1 family consists of three genes located on the long arm of chromosome 10.

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3 Abbreviations used in this paper: RA, receptor antagonist; SNP, single nucleotide polymorphism; MEDjp, minimal erythema dose (just perceptible); HBsAg, hepatitis B surface Ag.
chromosome 2 that encode for IL-1α, IL-1β, and IL-1RA (34). Each of these genes possesses exonic SNPs that also affect their expression by increasing either message stability or the rate of mRNA synthesis. For example, individual homozygous for the IL-1β +3953 allele produce approximately fourfold more IL-1β, and heterozygous cells produce approximately twofold more IL-1β, than do individual homozygous for the wild-type allele (26).

The IL-1RA exon 2 (+2018) (T and heterozygous cells produce approximately twofold more IL-1β, than do individual homozygous for the wild-type allele (26).

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The study revealed that UVB exposure before hepatitis B vaccination associated with several autoimmune and inflammatory diseases (36–41).

Whether genetic differences in susceptibility to UV-related dermatotoxicity or carcinogenicity exist is not known. However, Yoshikawa et al. (42) demonstrated that humans differ in their susceptibility to UV-induced suppression of contact hypersensitivity responses and photocarcinogenesis. From animal models they concluded that there are at least two different susceptibility genes for UV-induced immunosuppression, i.e., LPS and TNF-α, in mice (19). In view of the fact that cytokine polymorphisms seem to be associated with several autoimmune and inflammatory diseases, it would be consistent that these differences play a role in the modulation of immune responses by UV radiation.

Recently, we investigated the effects of UVB exposure on immune responses in humans vaccinated against hepatitis B. This study revealed that UVB exposure before hepatitis B vaccination did not alter the humoral or the cellular responses to hepatitis B surface Ag, when averaged over the investigated group (43). Because humans differ in their susceptibility to acute skin effects of UV radiation as well as immunomodulating effects, we investigated whether cytokine polymorphisms could play a role in interindividual differences in minimal erythema doses and susceptibility to UV-induced immunomodulation of hepatitis B vaccination responses.

Materials and Methods

Subjects

Healthy volunteers (students and staff) were recruited from the local university hospital to study the influence of repeated UVB exposures on hepatitis B vaccination responses (43). The total number of volunteers in this prospective cohort was 191, 61 males and 130 females. Ninety-seven were randomised to either receive the UVB exposure or act as an unexposed control. Each volunteer was fully informed about the procedures and gave written informed consent before entering the study. The study was approved by the medical ethical committee of the University Medical Center Utrecht and by the National Institute for Occupational Safety and Health/ Centers for Disease Control Human Studies Review Board.

UVB exposure protocol

Volunteers were exposed to UVB as previously described (43). Briefly, subjects were UVB irradiated while standing in an upright cabinet equipped with TL12 lamps (Philips, Eindhoven, The Netherlands) for 5 consecutive days, with a previously determined minimal erythema dose (just perceptible) (MEDp) per day. MEDp was defined as the UVB dose that induced a just perceptible (hence “jp” as subscript) erythema at 24 h after exposure. MEDp ranged from 186.3 to 1040.0 J/m² UVB (Table I).

Immune responses

Three days after the last UVB exposure, volunteers were vaccinated to hepatitis B by i.m. injection in the upper arm with a commercial vaccine containing 20 μg of recombinant hepatitis B surface Ag (HBsAg) (Engerix-B, GlaxoSmithKline Biologicals, Rixensart, Belgium). At multiple time points, blood was collected to obtain PBMCs and serum to measure hepatitis B-specific lymphocyte proliferation in a lymphocyte stimulation test and to measure hepatitis B-specific Ab titers, respectively. Materials and methods are previously described (43).

DNA preparation and genotyping

Uncoagulated blood was spotted evenly using a sterile Pasteur pipette onto a clean sheet of filter paper. This was left to dry overnight and stored at room temperature. DNA freshly obtained from human skin samples was used as an internal quality control.

Genotyping was performed using a PCR RFLP technique. Briefly, PCR mastermix containing 10 mM Tris-HCl, 50 mM KCl buffer, and 0.2 mM each dNTP and 0.05%/W-1 detergent was prepared where Taq polymerase was omitted. This was aliquoted in reaction tubes (20 μl), and ~1 mm² of the blood spot was cut out and placed into the reaction mix. Samples are then heated at 98°C for 15 min. After cooling for a few minutes, the rest of the mastermix (30 μl) containing 1.25 U of Taq polymerase was added and standard PCR cycling followed.

Amplification of the IL-1RA (+2018), IL-1α (+4845), IL-1β (+3953), TNF-α (−308), and TNF-α (−238) polymorphisms was similar to that previously described (33, 35, 37, 44, 45) with minor modifications. The MgCl2 and primer concentrations varied in each type of reaction as detailed below.

| IL-1RA (+2018): primers, 5’-CTA TCT GAT GAA CAA CAA ACT AGT ACCG-3’ and 5’-TAG GAC ATT GCA CCT AGG GTT TGTG-3’ | 1 μM, 1.75 mM MgCl2; cycling, 35 cycles at 94°C for 1 min, 57°C for 1 min, 70°C for 2 min followed by 96°C for 1 min, then a final 5 min at 70°C. Digestion was performed at 37°C for 2 h with 5 units of AluI and 5 units of MspI. AluI digestion gave allele 1 (28 + 26 bp) and allele 2 (154 + 125 bp) products. MspI digestion yielded allele 1 (154 bp) and allele 2 (154 + 125 bp) products. |
| IL-1α (+4845): primers, 5’-ATG TTA GAA ATC ATC AAG CTT CCT AGG GGA GTA GGA GGA GGA AGG GGA TGG TGTG-3’ and 5’-GGT TTG TCG TGC TCA TGG GGA TGG TGTG-3’ | 0.8 μM, 1 mM MgCl2; cycling, 1 min denaturation at 95°C followed by 35 cycles of 94°C for 1 min, 56°C for 1 min, 72°C for 2 min, and a final 5-min extension at 72°C. The products were digested with 2.5 U of Fnu I at 37°C for 2 h. This gave allele 1 (124 + 76 + 29 bp) and allele 2 (153 + 76 + 29 bp) products. |
| IL-1β (+3953): primers, 5’-CTC AGG TCT CCT CGA AGG ATG ACC AAT A-3’ and 5’-GCT TTT TTG TGT TCG TGA GTC CGG 3’ | μM, 2.5 mM MgCl2; cycling, 95°C for 2 min followed by 35 cycles at 95°C for 1 min, 57.5°C for 1 min, 72°C for 1 min, and then a final 5 min at 72°C. Digestion with 10 U of Taq restriction enzyme at 65°C for 2 h yielded allele 1 (85 + 97 bp) and allele 2 (182 bp) products. |
| TNF-α (−308): primers, 5’-GGT ATG GCA TAG TGG TTT TGT TGG TGA GTC CGG 3’ and 5’-TCC TCC TTC CGA CGA CGG GCA TGG TGTG-3’ | 0.2 μM, 1.5 mM MgCl2; cycling, 35 cycles at 94°C for 1 min, 60°C for 1 min, 72°C for 1 min followed by 95°C for 1 min and 72°C for 5 min. PCR product was digested at 37°C for 2 h with 6 U of NcoI, resulting in allele 1 (87 and 20 bp) and allele 2 (107 bp) products. |
| TNF-α (−238): primers, 5’-GGA GCC CCT CCT AGG TCT ATC CCT CAA-3’ and 5’-GCT TTT TTG TGT TCG TGA GTC CGG 3’ | 0.8 μM, 1.5 mM MgCl2; cycling, 35 cycles at 94°C for 1 min, 61°C for 1 min, 72°C for 1 min followed by 94°C for 3 min, and then a final 5 min at 72°C. Digestion with 5 U of AvaI at 37°C for 2 h yielded allele 1 (63 + 49 + 21 bp) and allele 2 (70 + 63 bp) products. |

All PCR products were electrophoresed into 10% polyacrylamide-Tris-borate/EDTA gel (Bio-Rad, Hercules, CA) at 150 V for 30 min and visualized by UV illumination after staining with ethidium bromide.

Table I. Minimal erythema doses (MEDp) and total UVB exposures

<table>
<thead>
<tr>
<th>MEDp (J/m²)</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>440.0</td>
<td>146.0</td>
<td>424.2</td>
<td>186.3</td>
<td>1040.0</td>
<td>4095.0</td>
</tr>
</tbody>
</table>

Dose = 5 consecutive days, 1 MEDp per day, n = 97.

LPS and TNF-α expression by increasing either message stability or the rate of mRNA synthesis. For example, individuals homozygous for the IL-1β +3953 allele produce approximately fourfold more IL-1β, and heterozygous cells produce approximately twofold more IL-1β, than do individuals homozygous for the wild-type allele (26).
Statistical analysis

All analyses were performed using SAS version 8.2 (SAS Institute, Cary, NC). MED$_i$, UVB dose, and HBsAg Ab titers were transformed using the natural log function before the analysis to meet the assumptions of the statistical models. All analyses were performed using mixed model ANOVA, followed by Fisher’s least significant difference for pair-wise comparisons where appropriate. A two-way repeated measures ANOVA was used to examine the effects of UVB radiation and time on HBsAg titers independent of genotype. One-way ANOVAs using genotype as the classification variable were used for the MED and UVB dose data, and three-way repeated measures ANOVAs were used for the Ab titer and lymphocyte proliferation assays, taking into account genotype, UVB exposure, and time. For the HBsAg Ab titer data, only data from T38, T46, and T60 were used due to predominantly undetectable levels before T38.

Results

Genotyping of study population

Tables II and III illustrate the distribution of genotypes and allelic frequencies for IL-1RA (+2018), IL-1α (+4845), IL-1β (+3953), TNF-α (−308), and TNF-α (−238) for control volunteers (Table II) and UVB-exposed volunteers (Table III). The allelic frequencies of the IL-1 and TNF-α polymorphisms were comparable to those reported by others (29, 37, 46–48).

MEDs and total amount of received doses of UVB

Table IV shows the mean values of personally tested MED values or the total amount of received doses in 5 consecutive days of UVB in J/m² per genotype per cytokine polymorphism tested. Individuals with the minor variant of IL-1β (+3953) polymorphism showed statistically significant increased MED values compared with individuals possessing the wild-type allele (1.1; p = 0.029) or that are heterozygous for this polymorphism (1.2; p = 0.024). No difference was found between the 1.1 and the 1.2 alleles (p = 0.842). The same association existed for the dose of UVB received (1.1 vs 2.2, p = 0.071; 1.2 vs 2.2, p = 0.065; 1.1 vs 1.2, p = 0.905), though statistical significance was not reached. IL-1RA (+2018), IL-1α (+4845), TNF-α (−308), and TNF-α (−238) allele polymorphisms did not reveal associations with MED values or received doses of UVB.

Total Ab titers against HBsAg after hepatitis B vaccination

Serum samples were obtained and total HBsAg Ab levels were determined at eight different time points. Ab titers were not significantly different between UVB-exposed and control volunteers when HLA-DR1 and HLA-DR7 alleles, which are associated with a high or low response to the hepatitis B vaccination (49), were taken into account (data not shown).

Fig. 1 shows total Ab titers against HBsAg for the cytokine variants at the day 38, 46, and 60 time points. Before these time points, Abs were not detectable (data not shown). As would be expected, a significant increase in HBsAg Ab titer, independent of the genotype, was observed over the time period examined (p < 0.0001).

Analysis of the influence of IL-1β (+3953) polymorphisms on the production of HBsAg-specific Ab titers revealed a significant increase in Ab titers in control (nonirradiated) volunteers with the 2.2 allele compared with those with the 1.1 allele (p < 0.0001) and compared with those with the 1.2 allele (p = 0.0002). However, when volunteers possessing the 2.2 allele were exposed to UVB before their hepatitis B vaccination, the significant increase no longer existed, and suppression of HBsAg-specific Ab titers was observed at the different time points. At T38 and T60, 6 and 30 days after the second vaccination, respectively, UVB-irradiated volunteers with the 2.2 allele (p = 0.022 and p = 0.007, respectively) showed statistically significant lower Ab titers compared with nonirradiated volunteers with the 2.2 allele (p = 0.022 and p = 0.007, respectively).

UVB radiation did not show any interactions with genotype or UVB exposure in 5 consecutive days in J/m² of UVB-irradiated volunteers per genotype per interleukin polymorphism

Table III. Distribution of genotypes and allele frequencies of UVB-exposed individuals

<table>
<thead>
<tr>
<th>SNP</th>
<th>Allelic Frequency*</th>
<th>Allele 2 Frequency*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1RA (+2018)</td>
<td>52 29</td>
<td>11 (43.5%)</td>
</tr>
<tr>
<td>IL-1α (+4845)</td>
<td>4736</td>
<td>92 (48.9%)</td>
</tr>
<tr>
<td>IL-1β (+3953)</td>
<td>50 37</td>
<td>5 (45.6%)</td>
</tr>
<tr>
<td>TNF-α (−308)</td>
<td>60 29</td>
<td>3 (34.8%)</td>
</tr>
<tr>
<td>TNF-α (−238)</td>
<td>84 8</td>
<td>92 (8.7%)</td>
</tr>
</tbody>
</table>

*1.1, Homozygous for wild-type allele; 1.2, heterozygous for both alleles; 2.2, homozygous for polymorphic allele.

*Percentage that are carriers of allele 2 is shown in parentheses.

Table IV. MED values and received UVB dose on 5 consecutive days in J/m² of UVB-irradiated volunteers per genotype per interleukin polymorphism

<table>
<thead>
<tr>
<th>MED UVB (J/m²)</th>
<th>Dose UVB (J/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allele*</td>
<td>Mean SD</td>
</tr>
<tr>
<td>IL-1RA (+2018)</td>
<td>1.1 441.2 138.8</td>
</tr>
<tr>
<td></td>
<td>1.2 433.3 168.6</td>
</tr>
<tr>
<td>IL-1α (+4845)</td>
<td>2.2 463.2 102.1</td>
</tr>
<tr>
<td></td>
<td>1.1 426.6 138.2</td>
</tr>
<tr>
<td>IL-1β (+3953)</td>
<td>1.2 455.0 158.4</td>
</tr>
<tr>
<td></td>
<td>2.2 429.3 121.3</td>
</tr>
<tr>
<td>TNF-α (−308)</td>
<td>1.2 565.3* 104.7</td>
</tr>
<tr>
<td>TNF-α (−238)</td>
<td>2.2 446.0 145.5</td>
</tr>
</tbody>
</table>

*1.1, Homozygous for wild-type allele; 1.2, heterozygous for both alleles; 2.2, homozygous for polymorphic allele.

* p = 0.029 compared with 1.1.

* p = 0.024 compared with 1.2.
Lymphocyte proliferation responses of PBMCs against HBsAg

Immunity to the hepatitis B vaccination was also determined by measuring the in vitro proliferation response of PBMCs to HBsAg of volunteers who were included in the second cohort ($n = 11005$). The variants revealed no significant differences in lymphocyte proliferation responses after UVB exposure in any of the subgroups tested (data not shown).

**Discussion**

In an earlier study, we demonstrated that UVB exposure before hepatitis B vaccination altered neither humoral nor cellular immune responses to hepatitis B in human volunteers, taking into account the entire group that was investigated (43). The present study indicates that cytokine polymorphisms, notably IL-$1\beta$ (+3953), IL-1RA (+2018), IL-$1\alpha$ (+4845), TNF-$\alpha$ (−308), and TNF-$\alpha$ (−238). The horizontal axis shows the different time points during the protocol: T38, T46, and T60 are 6, 14, and 30 days after the second hepatitis B vaccination, respectively. The vertical axis shows the natural log of Ab titers ± SE.

**FIGURE 1.** HBsAg-specific Ab titers after hepatitis B vaccination in control and UVB-exposed volunteers. Pictures represent the different gene variants: IL-$1\beta$ (+3953), IL-1RA (+2018), IL-$1\alpha$ (+4845), TNF-$\alpha$ (−308), and TNF-$\alpha$ (−238). The horizontal axis shows the different time points during the protocol: T38, T46, and T60 are 6, 14, and 30 days after the second hepatitis B vaccination, respectively. The vertical axis shows the natural log of Ab titers ± SE.

Intracellular factors, such as cytokine polymorphisms, play a significant role in the susceptibility to UVB-induced acute skin effects as well as immunomodulation in humans. With respect to the IL-$1\beta$ polymorphism, we demonstrated earlier that Ab production and lymphocyte proliferation responses to HBsAg in volunteers vaccinated against hepatitis B are statistically significantly influenced by the minor allelic variant of IL-$1\beta$ (+3953) (50). In this study, Ab responses to HBsAg were statistically significantly suppressed in individuals homozygous for the minor variant (2.2) of the IL-$1\beta$ polymorphism (+3953) when they were irradiated with UVB before hepatitis B vaccination. The allele dose-dependent adjuvant effect of IL-$1\beta$ on Ab responses was suppressed when volunteers were exposed to UVB before their first hepatitis B vaccination. Individuals homozygous for the minor variant (2.2) of the IL-$1\beta$ polymorphism (+3953) also were associated with higher MED values compared with individuals homozygous for the wild-type allele (1.1) or individuals heterozygous for the IL-$1\beta$ polymorphism (1.2). Thus, UVB-irradiated individuals with the minor variant for the IL-$1\beta$ polymorphism had significantly higher MEDs, which means less susceptibility for acute skin effects, viz erythema. In these same individuals with the minor variant (2.2) of the IL-$1\beta$ polymorphism (+3953), decreased Ab titers were found compared with those of control volunteers. This indicates that the MED does not correlate directly with the minimal immunosuppressive dose of UVB, and it is consistent with earlier data obtained in mice (51).
UVB radiation of keratinocytes causes increased production of various cytokines, including IL-1β (52), IL-1RA (53), and TNF-α (20). In fact, increased levels of IL-1 and TNF-α have been found in the serum of human volunteers after total body UVB irradiation (20, 25). Pentland and Mahoney (54) showed that keratinocyte-derived IL-1 may be partially responsible for induction of PGE₂ synthesis by keratinocytes after UVB radiation. PGs contribute to erythema and may modulate the cytokine production of dendritic cells and thereby influence their Ag presentation capacity. Indeed, elevated levels of PGE₂ promote in vitro a Th2 immune response by impairing the ability of human dendritic cells to produce IL-12 and by stimulating their production of IL-10 (55). In addition, Shreedhar et al. (56) suggested that UVB exposure activates a cytokine cascade involving PGE₂, IL-4, and IL-10, which can then modulate systemic the function of APCs (57).

Thus, increased levels of IL-1β, as occur in individuals with certain polymorphisms, might result in increased levels of PGE₂, which may in turn elevate IL-10 levels via IL-4 and exacerbate UVB-induced systemic immune suppression. However, individuals homozygous for the IL-1β polymorphism showed higher MED values, i.e., less sensitivity for UVB-induced erythema.

TNF-α is a major contributor of UVB-induced immunomodulation (18, 19). The less common TNF-α-2 allele (–308) is associated with an increased constitutive and inducible transcription rate for TNF-α. Therefore, this is associated with higher expression of TNF-α upon stimulation (58). However, other studies have failed to confirm any functional significance for this polymorphism (59). In addition, literature data about the TNF-α (–238) polymorphism are contradictory with regard to expression of this cytokine. These may be explanations why an effect of these polymorphisms on UVB-induced immunomodulation was not observed in the present study. However, individuals heterozygous for the TNF-α (–238) allele showed a tendency to higher MED values. It is possible that this polymorphism is associated with less sensitivity for UVB-induced erythema and that it could not be demonstrated in this study because of the low prevalence of homozygous individuals with the TNF-α (–238) polymorphism. Additional studies with larger populations should be performed to investigate this.

In addition, Streilein and colleagues (60) did find significant associations between susceptibility to UVB-induced suppression of contact hypersensitivity responses and different TNF-α polymorphisms. However, other polymorphisms were investigated in this study compared with our study. Future research on UVB-induced modulation of immune responses should consider determination of these polymorphisms.

Genetic factors, such as HLA class II alleles, which have been demonstrated to be associated with Ab responses to hepatitis B vaccination (49), were not a predisposition for an increased or decreased susceptibility to UV. HLA-DR1 and HLA-DR7, which are associated with high and low responders, respectively (49), were tested, and a subdivision into high or low vaccination responders did not reveal differences in susceptibility to UVB-induced immunomodulation either (data not shown).

In conclusion, the presence of SNPs in cytokine genes, which influence their expression, may play a role in individual susceptibility to UVB-induced acute skin effects and modulation of immune responses in humans. These findings should be treated with caution, because prevalence of the minor variant of the IL-1β polymorphism is low. Additional studies with large populations will be needed to confirm these observations. In addition, studies should be performed in which polymorphisms of other cytokines that play a role in UVB-induced immunomodulation are determined, to further elucidate the cytokine cascade initiated by UVB and ultimately leading to modulation of the immune system. Nevertheless, differences in cytokine expression, particularly of IL-1β, due to the presence of SNPs, may play a role and therefore must be taken into account when effects of exogenous factors, such as UV, are determined on the human immune system.

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