UV radiation was recently found to hinder interferon-γ from exerting its biological effects by inhibiting the phosphorylation of signal transducer and activator of transcription (STAT)-1, a crucial signal transducing protein in the interferon-γ pathway. Because this activity by UV may contribute to its immunosuppressive properties we studied whether this is specific for STAT1 or whether UV also affects other members of the STAT family. STAT5 is crucially involved in signaling of interleukin (IL)-2, enabling up-regulation of the IL-2 receptor α chain, an essential component of the high affinity IL-2 receptor. Exposure of the murine T cell line CTLL to IL-2 caused tyrosine phosphorylation of STAT5 that was remarkably reduced when cells were exposed to UV. Accordingly, STAT5 binding activity was significantly impaired in UV-exposed cells. In contrast, IL-2-induced tyrosine phosphorylation of the kinases Jak1 and Jak3 located upstream of STAT5 was not affected by UV. The effect of UV on STAT5 phosphorylation was antagonized by orthovanadate, implying involvement of a phosphatase in this process. Accordingly, up-regulation of the IL-2 receptor α chain was reduced in cells that were treated with IL-2 plus UV. Because STAT5-mediated IL-2 effects are vital for normal immune functions, inhibition of STAT5 signaling by UV may contribute to its well-known immunosuppressive properties.

UV radiation and, in particular, UVB with a wavelength range between 290 and 320 nm, represents one of, if not the most important environmental danger to human health. Its hazardous effects include the induction of skin cancer (1), suppression of the immune system (2), and chronic skin damage e.g. premature skin aging (3). The effects of UV on the cellular level include the induction of apoptotic cell death (4), the induction of inflammatory processes via the release of inflammatory cytokines (5), and the inhibition of cellular immune responses (2). In particular, the immunosuppressive properties of UV are of major biological relevance, because suppression of the immune system by UV is not only responsible for the exacerbation of infectious diseases following UV exposure, e.g. herpes simplex (6), but also contributes to the induction of skin cancer (7). Hence, understanding of the mechanisms by which UV suppresses the immune system is of primary importance. UV suppresses the immune system in multiple ways (2). Just to name a few, it inhibits antigen presentation by down-regulating the surface expression of accessory molecules (8), it induces the generation of T suppressor cells, which inhibit antigen-specific immune responses (9), and it induces the release of immunosuppressive cytokines e.g. interleukin (IL)-10, tumor necrosis factor α, and transforming growth factor β (reviewed in Refs. 10 and 11).

Recently, we obtained the first evidence that UV does not only have the ability to influence the release of cytokines but that it can also interfere with the biological activity of immunomodulatory mediators. Specifically, we demonstrated that UV is able to hinder the immunomodulatory cytokine interferon-γ (IFNγ) from exerting its biological effects (12). As a consequence of the interaction of IFNγ with its receptor, the signal transducer and activator of transcription protein STAT1 (13, 14) becomes tyrosine-phosphorylated. Phosphorylated STAT1 dimerizes, translocates to the nucleus where it binds to the IFNγ-activated sequences ( GAS) in various promoters, and ultimately induces specific gene transcription. We observed that UV inhibits IFNγ-induced STAT1 phosphorylation and consequently STAT1 binding capacities (15). Because phosphorylation of STAT1 is a critical event in IFNγ signaling, UV inhibits IFNγ from exerting its biological effects via this mechanism. Interestingly, UV had no effect on the phosphorylation of STAT3, which is involved in signaling of IL-6, a potent proinflammatory cytokine whose release is also induced by UV (16). Because IL-6 is an inflammatory mediator and IFNγ is an immunomodulatory molecule, we postulated that the differential effects on cytokine signaling by UV may explain the diverse biological effects of UV, which on the one hand causes inflammation (via induction of the release of inflammatory cytokines) but, on the other hand, inhibits immune reactions (presumably by interruption of the signal transduction of immunomodulatory cytokines). If this hypothesis holds true, the inhibitory effect of UV should not only affect IFNγ signaling but also other immunostimulatory cytokines. Hence, we were interested in finding out whether UV also interferes with IL-2 signaling.

IL-2 is a key regulator of normal immune function and acts on a variety of lymphoid cells including T lymphocytes, B lymphocytes, and natural killer cells (17, 18). Blockade of IL-2 or the IL-2 receptor (IL-2R) results in pronounced impairment of antigen-specific proliferative T cell responses (17, 18). To exert its biological effects, IL-2 must interact with the specific IL-2 receptor, which consists of at least two subunits. Het-

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1 The abbreviations used are: IL, interleukin; IFNγ, interferon-γ; IL-2R, interleukin-2 receptor; STAT, signal transducer and activator of transcription; γc, cytokine receptor γ chain; EMSA(s), electrophoretic mobility shift assay(s); PCR, polymerase chain reaction.
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Erudition of the constitutively expressed IL-2Rb chain and the common cytokine receptor γ chain (γc) forms an intermediate affinity receptor for IL-2-mediated signaling. Although the IL-2Rα chain is not necessarily required for IL-2 binding or signaling, it is essential for forming high affinity receptors (19, 20). IL-2Rα expression is tightly regulated by the extracellular binding of IL-2 to the intermediate affinity receptor (21), resulting in intracellular phosphorylation of the activated β chain or γc. Recruitment of the janus kinases Jak1 to IL-2Rβ and Jak3 to γc results in tyrosine phosphorylation, which in turn triggers downstream tyrosine phosphorylation of STAT5 proteins (22, 23). Upon phosphorylation, the STAT5 molecules dimerize and translocate to the nucleus where they serve as transcription factors for their responsive elements. Positive regulatory elements responsive for STAT5 binding are located in the IL-2Rα chain gene promoter region and serve as enhancers of IL-2Rα gene expression (24, 25).

Here, we demonstrate that UV inhibits IL-2-mediated tyrosine phosphorylation of STAT5 and consequently inhibits STAT5 binding activity. In contrast, phosphorylation of the upstream-located kinases Jak1 and Jak3 was not affected by UV. As a consequence of impaired STAT5 phosphorylation, IL-2-mediated up-regulation of the IL-2Rα chain was reduced in T cells exposed to UV at both the mRNA and the protein level. Hence, UV may inhibit immune responses by interfering with the signaling of IL-2. Together, these data indicate that interference of UV with the signal transduction of immunostimulatory cytokines represents an additional pathway by which UV compromises the immune system.

EXPERIMENTAL PROCEDURES

Cells and Reagents—The murine T cell line CTLL (ATCC, Manassas, VA) was cultured in RPMI 1640 supplemented with 10% fetal calf serum, 5 × 10−5 M β-mercaptoethanol and IL-2. Supernatants obtained from concanavalin A-stimulated rat splenocytes were used as a source for IL-2 at a final concentration of 10% (26). IL-2 containing supernatant was added to the culture medium every 24 h. IL-2 (100 units/ml) supplementation was stopped 60 h before experiments were performed. For stimulation, recombinant murine IL-2 was used (R & D Systems Inc., Minneapolis, MN). The tyrosine phosphatase inhibitor sodium orthovanadate (Na3VO4) and the serine phosphatase inhibitor o-acetyl fluoride were purchased from Sigma.

UV Irradiation of Cells—UV irradiation was performed as described previously with slight modifications (5). Briefly, cells (1 × 106/ml) were washed with phosphate-buffered saline and exposed to UV radiation through colorless medium without fetal calf serum. For UV irradiation a bank of fluorescent bulbs (TL12; Philips, Eindhoven, the Netherlands) was used that emit most of their energy within the UVB range (290–320 nm) with an emission peak at 313 nm. Throughout this study a dose of 400 J/m2 was used. This dose was used, because it is in the range of the physiologically relevant doses usually used for in vitro studies when investigating UVB (27). Control cells were subjected to the identical procedure without being exposed to UV.

Electrophoretic Mobility Shift Assay (EMSA)—15 min after stimulation, nuclear proteins were extracted as described previously (12). Binding reactions were carried out in the presence of 2 μg of poly(dI-dC) (Roche Molecular Biochemicals), 10⁶ cpm of 32P-labeled double stranded oligonucleotide with a consensus binding site for STAT5 (sc-2565; Santa Cruz Biotechnology, Santa Cruz, CA), and 20 μg of nuclear protein extract for 20 min at 22°C. Reaction samples were separated electrophoretically on native high ionic gels at 150 V for 1.5 h and detected by autoradiography. Competition analysis was performed by the addition of the unlabeled consensus oligonucleotide in a 50-fold molar excess. Supershifts were carried out utilizing specific antibodies directed against either STAT5a (sc-108X) or STAT5b (sc-835X), both Santa Cruz.

Immunoprecipitation and Western Blot Analysis—15 min after stimulation cells were lysed in lysis buffer (50 mM Hepes, pH 7.5, 150 mM NaCl, 10% glycerol, 1% Triton X-100, 1.5 mM MgCl2, 1 mM EGTA, 100 mM NaF, 10 mM pyrophosphate, 0.01% NaN3, and Complete™ protease inhibitor mixture) by sonication. After centrifugation, supernatants were collected, and the protein content was measured using a Bio-Rad protein assay kit (Bio-Rad, Hercules, CA). Immunoprecipitations were carried out with 1 ml of a 1 mg/ml protein solution supplemented with 5 μg of the corresponding antibody directed against Jak1 (AF602; R & D Systems), Jak3 (05-406; Upstate Biotechnology, Lake Placid, NY), or STAT5 (PA-ST5A; R & D Systems) and with 50 μl of protein A/G-agarose (Santa Cruz) at 4°C overnight. Samples were washed 3 times with lysis buffer with centrifugation being performed at 13,000 rpm for 5 s. Precipitated proteins were released from protein A/G-agarose beads at 95°C in sample buffer containing 5% β-mercaptoethanol. The protein samples were subjected to 6% SDS polyacrylamide gel electrophoresis, blotted onto nitrocellulose membranes, and incubated with an antibody directed against phosphoostrogen (sc-7020; Santa Cruz). Membranes were stripped and reprobed with different antibodies detecting Jak1 (sc-1677; Santa Cruz), Jak3 (06-667; Upstate Biotechnology), or STAT5 (sc-1656, Santa Cruz). Signals were visualized with an ECL™ kit (Amersham Pharmacia Biotech).

Semiquantitative Reverse Transcription Polymerase Chain Reaction (PCR)—2 h after stimulation total RNA was extracted from cells according to the protocol described by Chomczynski and Sacchi (28). 1 μg of total RNA was reverse transcribed with SuperScript RNase H reverse transcriptase (Life Technologies, Inc.). The amount of template needed was titrated by β-actin PCR in a 20-μl reaction utilizing the RedTaq polymerase system from Sigma and evaluated densitometrically. A murine IL-2 receptor α-amplimer set from CLONTECH (Palo Alto, CA) was used as primers for the amplification of the IL-2 receptor α chain.

Flow Cytometry—Aliquots of 2 × 10⁷ cells were incubated with fluorescein isothiocyanate-conjugated rat anti-mouse antibodies directed against either the IL-2 receptor α-chain (CD25) or the IL-2 receptor β-chain (CD122; both from Southern Biotechnology Associates Inc., Birmingham, AL) for 45 min on ice. Purified rat IgG was used as an isotype control. Cells were then washed twice in phosphate-buffered saline, propidium iodide (100 μg/ml) was added, and cells were analyzed in a flow cytometer (Epics XL, Coulter, Miami, FL).

RESULTS

UV Interferes with Phosphorylation of STAT5—To address the question whether UV interferes with the phosphorylation of STAT5, proteins from lysates of CTLL cells were immunoprecipitated with an antibody against STAT5, and Western blot analysis was performed using antibodies against phosphotyrosine and STAT5, respectively (Fig. 1). In untreated CTLL cells (lane 1) STAT5 was barely phosphorylated if at all, whereas stimulation with IL-2 induced a strong phosphorylation of STAT5 (lane 2). However, in cells that, in addition to IL-2, were also exposed to UV, IL-2-induced STAT5 phosphorylation was remarkably reduced (lane 4). Exposure of CTLL cells to UV alone did not affect the phosphorylation status of STAT5 (lane 3).

Reduced STAT5 Binding Activity in UV-exposed CTLL Cells—To determine whether inhibition of phosphorylation of STAT5 by UV is functionally relevant, EMSAs were performed using nuclear protein extracts from CTLL cells that were exposed to IL-2 alone or to IL-2 plus UV (Fig. 2). Low constitutive binding activity was observed in untreated cells (lane 1), and this activity was considerably induced upon stimulation of cells with IL-2 (lane 2). UV treatment did not alter the low constitutive binding activity (lane 3) but significantly reduced IL-2-induced STAT5 binding (lane 4). Competition analysis using excess amounts of unlabeled specific oligonucleotides is shown in lane 7. In addition, as demonstrated in Fig. 3, the specificity of the binding activity was proven by incubating the extracts with antibodies directed against either STAT5a (lane 5) or STAT5b (lane 6). Both antibodies caused a supershift of the activated STAT5 bound to its specific consensus oligonucleotide, indicating that both STAT5a and STAT5b proteins heterodimerize upon tyrosine phosphorylation to form active STAT5.
phosphatase inhibitor orthovanadate (Fig. 3). Orthovanadate enhanced IL-2-induced binding activity of STAT5 (lane 3), whereas the serine phosphatase inhibitor okadaic acid did not augment IL-2-mediated STAT5 binding (lane 4). The inhibitory effect of UV on STAT5 binding was also reduced by orthovanadate (Fig. 2, lane 6). The same effect was observed when checking for STAT5 phosphorylation. Inhibition of IL-2-induced STAT5 phosphorylation was prevented in the presence of orthovanadate (Fig. 1, lane 6). Together, these data suggest that the activation of a phosphatase may be involved in the inhibitory effect of UV on IL-2-induced STAT5 phosphorylation and binding.

**UV Does Not Inhibit IL-2-induced Jak1 and Jak3 Phosphorylation**—Because phosphorylation of STAT5 is a consequence of the binding of IL-2 to the intermediate receptor consisting of IL-2Rβ and γc (19, 20), UV could indirectly inhibit STAT5 phosphorylation simply by down-regulating IL-2Rβ and γc. To determine whether IL-2-mediated phosphorylation of STAT5 is directly inhibited by UV or rather a consequence of down-regulation of IL-2Rβ and γc, the effect of UV on the receptor-associated tyrosine kinases Jak1 and Jak3 was analyzed. Jak1 and Jak3 are both required for the IL-2 response and are tyrosine-phosphorylated upon ligand binding (22). Proteins extracted from CTLL cells were immunoprecipitated with an antibody directed against either Jak1 or Jak3, and Western blot was performed using an antibody directed against phosphotyrosine (Fig. 4). Jak1 and Jak3 were found to be tyrosine-phosphorylated upon IL-2 stimulation. However, neither Jak1 nor Jak3 phosphorylation was inhibited or reduced upon UV irradiation.

**UV Suppresses IL-2-induced Up-regulation of the IL-2Ra Chain**—In contrast to the constitutively expressed IL-2Rβ and γc molecules, which form the intermediate-affinity receptor, the inducible IL-2Ra chain contains a STAT5-responsive positive regulatory element within its promoter region (24). Hence, inhibition of STAT5 phosphorylation by UV should result in a reduced transcription rate of the IL-2Ra chain gene. To prove this hypothesis, semiquantitative PCR analysis using specific primers for the IL-2Ra chain was performed (Fig. 5). Untreated CTLL cells expressed low amounts of IL-2Ra chain transcripts, which were enhanced upon stimulation with IL-2 within 2 h. IL-2-induced up-regulation of the IL-2Ra chain transcripts was remarkably reduced following UV exposure of IL-2-treated CTLL cells. Again, orthovanadate prevented the inhibitory effect of UV on IL-2Ra chain mRNA expression.

To determine whether mRNA expression correlates with the cell surface expression of the IL-2Ra chain, flow cytometric analysis using an antibody directed against the IL-2Ra chain was performed. In accordance with the PCR results, IL-2 caused an up-regulation of the IL-2Ra chain, which was reduced to control levels upon exposure to UV (Fig. 6). UV alone did not affect IL-2Ra expression. Exposure of cells to orthovanadate prevented the inhibitory effect of UV on IL-2-induced IL-2Ra expression. Neither IL-2 nor UV had an effect on the constitutive expression of the IL-2Ra chain (data not shown).

**DISCUSSION**

STAT proteins are cytoplasmically located transcription factors that, upon activation by tyrosine phosphorylation, dimerize, translocate to the nucleus, and bind to specific regulatory elements that control gene expression. Several of the STAT members are involved in the signal transduction of immunomodulatory cytokines (31); e.g. immune responses to IL-4 and IL-12 are mediated by STAT6 and STAT4, respectively. IFNγ signaling is critically dependent on STAT1, and STAT5 plays an important role in the signal transduction of IL-2 (25). Hence, disruption of or interference with STAT signaling may be an effective way to compromise an immune response. Recently, we observed that UV radiation, a potent immunosuppressor, may interfere with STAT signal transduction and thereby antagonizes the biological effects of IFNγ (12, 15). Here, we show that the same seems to apply to IL-2 signaling.

A crucial step in IL-2 signal transduction is the phosphoryl-
ation, subsequent dimerization, and nuclear translocation of STAT5 (25). Hence, disturbances in the STAT5 pathway results in severe alterations of immune responses as the phenotypes of STAT5a/STAT5b double knockout mice clearly show (24, 32–34). Our results demonstrate that UV interferes with IL-2-mediated STAT5 signaling by inhibiting tyrosine phosphorylation of STAT5. Accordingly, STAT5 binding activity as demonstrated by EMSA is significantly reduced when CTLL cells are exposed to UV in the presence of IL-2.

Jak1 and Jak3 are required for normal IL-2-mediated STAT5 activation (35–38). In contrast to STAT5 phosphorylation, IL-2-induced tyrosine phosphorylation of Jak1 and Jak3 was not affected by UV. This excludes the possibility that UV affects components in the IL-2 signaling pathway located upstream of STAT5 phosphorylation. Hence, it is unlikely that UV exerts its inhibitory effect by down-regulating the IL-2 receptor, e.g. by inducing shedding of one of the IL-2 receptor chains. Along this line, STAT3 phosphorylation, which also appears to be involved in IL-2 signaling, was not significantly affected by UV (data not shown). In this context it is important to mention that it was previously observed that IL-6-mediated phosphorylation of STAT3 was also not inhibited by UV (15).

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These findings and the fact that UV is a well known activator of nuclear factor-κB and AP-1 both in vitro and in vivo (39–41)
UV exhibits the ability to induce the release of a variety of cytokines, among these transforming growth factor-β (11). Transforming growth factor-β was recently found to exert its immunosuppressive effects by inhibiting IL-2-induced tyrosine phosphorylation and the activation of Jak1 and STAT5 in T lymphocytes (42). However, it is unlikely that the inhibitory effect of UV on IL-2 signaling observed in our system is indirectly mediated by transforming growth factor-β, because in our hands, phosphorylation of Jak1 was not affected by UV. In addition, UV did not significantly induce the release of transforming growth factor-β in CTLL cells (data not shown).

IL-2-induced up-regulation of the IL-2Rα chain is largely dependent on STAT5 signaling (24). Hence, we analyzed IL-2Rα expression to determine whether the inhibition of STAT5 signaling by UV is also biologically relevant. Indeed, RT-PCR revealed that UV inhibits IL-2-mediated up-regulation of IL-2Rα chain transcripts. In addition, as determined by fluorescence-activated cell sorter analysis, IL-2Rα protein expression was affected in a similar fashion; IL-2-induced up-regulation was completely prevented when cells were exposed to UV. However, the effects of UV on IL-2Rα protein expression were less pronounced than the inhibitory effects on STAT5 phosphorylation and its binding activity. This may be because of the fact that the CTLL cells constitutively express relatively high amounts of the IL-2Rα chain. Because CTLL cells are strictly IL-2 dependent, they are permanently cultured in the presence of IL-2. To yield IL-2 responsiveness, IL-2 supplementation was stopped 60 h before performance of experiments. This time interval was too short to allow complete loss of the IL-2Rα chain. This explanation would imply that CD25 expressed on the surface of CTLL cells has a quite long half-life. In this context it is important to mention that Nakajima et al. (24) showed that anti-CD3-induced expression of CD25 on CD4+ splenocytes is only minimally reduced if the cells are cultured for an additional 48 h without any further stimulus. Accordingly, we presume that because of the high constitutive expression of CD25 the effect of IL-2 on IL-2Rα chain induction was not as pronounced as one would have expected from the immunoprecipitations and EMSAs, both of which revealed remarkable phosphorylation and activation of STAT5 upon stimulation with IL-2. Nevertheless, although moderate, the induction of IL-2Rα expression by IL-2 was completely prevented by UV, indicating that the inhibition of IL-2 signaling by UV may also be functionally relevant.

The observation that UV inhibits IL-2-induced STAT5 phosphorylation but leaves Jak1 and Jak3 phosphorylation unaffected points to the STAT5 protein as a direct target for UV. However, we have no evidence as yet whether phosphorylation of STAT5 is directly inhibited by UV. Data are accumulating that show that the amount of phosphorylated STAT proteins does not only depend on the rate of phosphorylation but also on the rate of dephosphorylation. It has been demonstrated that STAT1 signaling can be abrogated by dephosphorylation of the conserved tyrosines through tyrosine phosphatases (29). Similar observations were recently made for STAT5 phosphorylation. Using CTLL-20 cells as a model system, Yu et al. (30) provided evidence that tyrosine dephosphorylation of STAT5 after IL-2-induced phosphorylation occurs in the absence of nuclear translocation and new protein synthesis, indicating the constitutive presence of a STAT5-specific tyrosine phosphatase activity in the cytosolic compartment. In addition, using an in vitro tyrosine phosphatase assay with purified proteins Yu et al. (30) demonstrated that SHP-2, but not SHP-1, directly dephosphorylates STAT5. UV-mediated suppression of STAT5 phosphorylation was inhibited by adding the phosphatase inhibitor sodium orthovanadate, suggesting involvement of a tyrosine phosphatase. However, these findings should be interpreted with caution, because orthovanadate also had a slight stabilizing effect on IL-2-activated STAT5 itself (Figs. 1–3). Therefore, in this experimental design it is difficult to differentiate whether the increase of binding active STAT5 in the UV sample by orthovanadate is because of inhibition of the UV effect or depends on the inhibition of dephosphorylation of phosphorylated STAT5. If UV mediates this effect via dephosphorylation this would imply that UV activates a vanadate-inhibitable phosphatase. The effect of UV on phosphatases, however, appears to be heterogenous. Using protein-tyrosine phosphatase-overexpressing cells, Gross et al. (43) recently observed that four defined protein-tyrosine phosphatases, SHP-1, RPTPα, RPTPβ, and DEP-1, are partially inactivated upon UV irradiation. How SHP-2, the phosphatase most likely to be involved in STAT5 dephosphorylation (30), is affected by UV remains to be determined.

STAT5 proteins have also been reported to be phosphorylated at serine residues (44). However, it is not yet clear whether serine phosphorylation is important for transactivation activity (25) as reported for STAT1 and STAT3 (45). The addition of ocdacic acid, an inhibitor of serine phosphatases, did not stabilize STAT5 binding activity in our hands. Thus, it appears unlikely that UV targets serine phosphorylation of STAT5 resulting in its inhibitory effect.

The UVC component (200–280 nm) of solar radiation is completely absorbed by the ozone layer and is therefore biologically irrelevant. We therefore used the UVB range (290–320 nm) that causes a variety of biological effects in vivo including immunosuppression, inflammation, and induction of skin cancer. UVB is primarily absorbed in the epidermis, and therefore keratinocytes are the major cellular target in vivo for UVB. However, there is clear-cut evidence that UVB also reaches the dermis where lymphocytes and endothelial cells reside. (46, 47). Young et al. (48) recently observed pyrimidine dimers in dermal nuclei induced by 300 nm of UV, providing clear evi-
FIG. 6. UV irradiation inhibits IL-2-induced surface expression of the IL-2Rα chain on CTLL cells. CTLL cells were left untreated (Co), stimulated with 100 units/ml IL-2, irradiated with 400 J/m² UV, or treated with UV plus IL-2 (IL-2/UV). Histograms presented in the bottom lane are from cells that were preincubated with 1 mM Na₃VO₄ for 2 h before stimulation with IL-2 (IL-2/Na₃VO₄) or with UV plus IL-2 (IL-2/Na₃VO₄/UV). 8 h after stimulation cells were incubated with a fluorescein isothiocyanate-conjugated antibody directed against the IL-2Rα chain (CD25). Purified rat IgG was used as an isotype control (dotted lines). Histograms show fluorescence intensity (x axis) versus cell number (y axis).
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To UVB enters the dermis and can therefore directly affect lymphocytes.

The immunosuppressive properties of UV/solar radiation may have important biological implications. Chronic UV exposure can lead to exacerbation of infectious disease (6). UV-induced immunosuppression, however, may also contribute to carcinogenesis, because it impairs the immune response of the host against tumor cells (7). Accordingly, chronically immunosuppressed individuals, e.g. renal or cardiac transplant patients, exhibit a dramatically increased risk for cancer, and this risk strongly correlates with the intensity of solar exposure (49). On the other hand, UV radiation is used therapeutically to treat numerous inflammatory skin diseases with great success. Although the exact mechanisms for this beneficial effect still remain to be determined, it is the immunosuppressive effect of UV radiation that is regarded to be most important, because the majority of diseases responsive to UV can also be treated with steroids or other immunosuppressive drugs like cyclosporin A (50). In this context, it is important to mention that one mechanism by which steroids suppress immune reactions is by inhibiting IL-2-induced STAT5 phosphorylation (51). In psoriasis, a common chronic inflammatory dermatosis responding favorably to UV therapy, IL-2 appears to be crucially involved, because cyclosporin A, which targets IL-2 transcription (52), or the application of antibodies directed against the IL-2R alpha chain (anti-CD25) are effective treatments (53, 54). Interruption of IL-2 signaling by UV as demonstrated in this study may represent a mechanism that explains why phototherapy improves psoriasis so effectively. In addition, the present observation that UV can antagonize IL-2 effects may also explain why UV preferentially and very effectively suppresses T cell-mediated immune reactions.

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REFERENCES

1. De Gruijl, F. R., Sterenborg, H. J., Forbes, P. D., Davies, R. E., Cole, C., Kelkens, G., van Weelden, H., Slaper, H., and van der Leun, J. C. (1993) Cancer Res. 53, 53–60
2. Beissert, S., and Schwarz, T. (1999) J. Invest. Dermatol. Symp. Proc. 4, 61–64
3. Fisher, G. J., Datta, S. C., Talwar, H. S., Wang, Z. Q., Varani, J., Kang, S., and Schwarz, T. (1998) Nature 395, 355–339
4. Kuhl, D., Poppelmüller, B., Barosh, D., Lugger, T. A., Krumm, J., and Schwarz, T. (1999) Proc. Natl. Acad. Sci. U. S. A. 96, 7974–7979
5. Kuhl, D., Poppelmüller, B., and Schwarz, T. (2000) J. Biol. Chem. 275, 15050–15056
6. Chapman, R. S., Cooper, K. D., De Fabo, E. C., Frederick, J. E., Gelatt, K. N., De Fabo, E. C., Frederick, J. E., Gelatt, K. N., and Russell, S. M., Mess, S. A., Friedmann, M., Erdos, M., Francois, J., Jaques, Y., Adelstein, S., and Leonard, W. J. (1994) J. Immunol. 153, 27018–27024
7. Ozawa, M., Ferenczi, K., Kikuchi, T., Cardinale, I., Austin, L. M., Coven, T. R., Hoffman, A., von Deursen, J., Sangster, M. Y., Bunting, K. D., Grosveld, G. C., and Ilie, J. N. (1999) Immunity 6, 249–259
8. Furue, M., Takahashi, T., Osawa, M., Arase, H., Hirayama, N., Miyake, K., Nakauchi, H., Shirasawa, T., and Saito, T. (1995) Immunity 3, 721–782
9. Rodig, S. J., Merz, M. A., White, J. J., Lampe, P. A., Riley, J. K., Arthur, C. D. K., L., Sheechan, K. C., Yin, L., Penicca, D., Johnson, E. M., Jr., and Schreiber, R. D. (1998) Cell 93, 373–383
10. Thomis, D. C., Gurniak, C. B., Twel, S. H., Shore, A. B., and Berg, L. J. (1995) Science 274, 794–797
11. Abeyama, K., Eng, W., Jester, J. V., Vink, A. A., Edelbaum, D., Cockerell, C. J., Bergstresser, P. R., and Takashima, A. (2000) J. Clin. Invest. 105, 1751–1759
12. Fisher, G. J., Talwar, H. S., Lin, J., Lin, P., McPhileps, F., Wang, Z., Li, X., Wang, Y., Kang, S., and Voorhees, J. J. (1998) J. Clin. Invest. 101, 1422–1440
13. Simon, M., Aragane, Y., Schwarz, A., Lugger, T. A., and Schwarz, T. (1994) J. Invest. Dermatol. 102, 422–427
14. Bright, J. J., Kerr, L. D., and Srikum, S. (1997) J. Immunol. 159, 175–183
15. Ghal, S., Knebel, A., Tener, T., Neisinger, A., Glasser, M., Herrlich, P., and Bohmer, F. D. (1999) J. Biol. Chem. 274, 26378–26386
16. Celano, A., Mez, M., White, J. J., Lampe, P. A., Riley, J. K., Arthur, C. D. K., L., Sheechan, K. C., Yin, L., Penicca, D., Johnson, E. M., Jr., and Schreiber, R. D. (1998) Cell 93, 373–383
17. Thomis, D. C., Gurniak, C. B., Twel, S. H., Shore, A. B., and Berg, L. J. (1995) Science 270, 802–808
18. Ozawa, M., Ferenczi, K., Kikuchi, T., Cardinale, I., Austin, L. M., Coven, T. R., Burck, I. H., and Krueger, J. G. (1999) J. Exp. Med. 189, 711–718
19. Scholzen, T., Hartmeyer, M., Fastrich, M., Brasca, T., Becher, E., Schwarz, T., and Lugger, T. A. (1998) J. Invest. Dermatol. 111, 50–56
20. Young, A. R., Chadwick, C. A., Harrison, G. I., Nikaido, O., Ramsden, J., and Potten, C. S. (1998) J. Invest. Dermatol. 111, 982–988
21. Butt, A., and Roberts, D. J. (1997) Cancer 349, 179–180
22. Schwarz, T., and Grabbe, S. (1996) In The Fundamental Bases of Phototherapy (Honigsmann, H., Jori, G., and Young, A. R., eds) pp. 99–116, OEMF SpA, Milano, Italy
23. Bianchi, M., Meng, C., and Isakivk, L. B. (2000) Proc. Natl. Acad. Sci. U. S. A. 97, 9573–9578
24. Ellis, C. N., Pradin, M. S. M., Messana, J. M., Brown, M. D., Siegel, M. T., Hartley, A. H., Rocher, L. L., Whelan, S., Hamilton, T. A., Parish, T. G., Ellis-Modu, M., Dwell, E., Annesley, T. M., Cooper, K. D., and Voorhees, J. J. (1991) N. Engl. J. Med. 324, 277–284
25. Ozen, M., and Cavanagh, F. V. (2000) Clin. Exp. Dermatol. 25, 195–197
26. Mrowietz, U., Zhu, K., and Christophers, E. (2000) Arch. Dermatol. 136, 655–676
Ultraviolet Radiation Inhibits Interleukin-2-induced Tyrosine Phosphorylation and the Activation of STAT5 in T Lymphocytes

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