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UV light affects cell membrane and cytoplasmic targets

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Abstract

For a long time DNA has been regarded as the only molecular cellular target for UVB and UVC. However, evidence is accumulating that ultraviolet light (UV) can also affect cytoplasmic and membrane structures. It has been shown that UV can directly affect cytoplasmatically located transcription factors, kinases closely located to the cellular membrane and even membrane receptors. The identification of additional cellular UV targets and the mechanisms by which these targets transduce the UV signal will increase the understanding of the biological effects of UV. Recently, we observed that UV can interfere with cytokine signalling and induce apoptosis via direct activation of apoptosis-related surface receptors. These findings will be briefly reviewed in the paper.

Keywords: Ultraviolet light; Molecular targets; DNA; Transcription factors; Surface receptors; Signal transduction

1. Introduction

After having obtained detailed knowledge about the biological effects which ultraviolet light (UV) exerts when hitting a cell, one of the current mainstreams of photobiology research focuses on the identification of the molecular UV targets within the cell. Based on its absorption spectrum, DNA was for a long time regarded as the only molecular target. Functional evidence for this assumption was provided by elegant experiments demonstrating that acceleration of DNA repair reverses or inhibits particular biological effects of UVB light. Studies with the marsupial *Monodelphis domestica*, which has the ability to repair DNA damage by a photoreactivating enzyme, implied that DNA damage is the initiating event in UVB-induced immunosuppression [1]. In this study, UVB-induced suppression of contact hypersensitivity was prevented by exposing the animals to photoreactivating light immediately after UV exposure. The critical role of DNA damage in this type of UVB-mediated immunosuppression was further confirmed by the finding that the immunosuppressive effects of UVB can be suppressed by applying T4N5 endonuclease incorporated into liposomes, which enables penetration into the cell both in vitro and in vivo [2]. When DNA-repair-enhancing T4N5 endonuclease was applied topically on UVB-exposed murine skin, inhibition of the induction of contact hypersensitivity was prevented. There is also evidence that DNA damage triggers cytokine release because UVB-induced secretion of interleukin (IL) 10 by keratinocytes was significantly suppressed after additon of T4N5 endonuclease [3]. Taken together, these data strongly suggest that DNA is an important molecular target for UVB.

In addition, it was observed that UV can activate the transcription factors AP-1 and NFκB [4,5]. NFκB is located in the cytoplasm bound to an inhibitory protein, called IκB. Upon activation, IκB is split off and free NFκB migrates into the nucleus where it binds to specific responsive elements in various genes, thereby initiating transcription. When postulating that DNA is the primary and even the only molecular target for UV within the cell initiating the UV response, this would imply that UV has to enter the cell, penetrate the cytoplasm, 'ignore' the cytoplasmatically located transcription factor NFκB, enter the nucleus and damage the DNA. Consequently, a nuclear signal has to be transferred to the cytoplasm to activate NFκB [6]. This rather complicated scenario is hard to envisage. Therefore, the question was addressed whether UV can directly activate NFκB. By using dominant negative mutants, Devary et al. could show that tyrosine kinases and Ha-Ras are involved in NFκB activation by UVC. Furthermore, utilizing enucleated cells, the authors could demonstrate that activation of NFκB does not require a nuclear signal [6]. Based on these findings, it was concluded that the UV signalling cascade that activates NFκB is initiated at or near the plasma membrane and is not elicited by DNA damage in the nucleus. Our group could confirm

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these findings by using another approach. By UVB irradiating cytoplasmic protein extracts which contain NFκB in its inactive form, we observed activation of NFκB [7]. The activation process was dependent on the presence of membranes in the protein extracts, suggesting a signalling pathway for the early UVB response, including a component of the pathway residing at the cell membrane. Taken together, these findings are in accordance with previous ones obtained by Devary et al., who could show that the earliest detectable step in the UVC response was activation of Src tyrosine kinases, followed by activation of Ha-Ras and Raf-1 [8]. This response could be blocked by tyrosine kinase inhibitors and dominant negative mutants of v-src, Ha-ras and raf-1. Furthermore, increased phosphorylation of c-jun on two serine residues was observed [8]. These findings strongly suggested that the UVC response is initiated at or near the plasma membrane rather than the nucleus. Although many similarities exist between the UVC and the UVB response, one has to be aware that the effects following UVC irradiation may not accurately reflect what occurs following UVB and may not be physiological, unless formally proven.

Sachsenmaier et al. were able to demonstrate involvement of growth factor receptors in the mammalian UVC response [9]. UVC-induced activation of c-fos and c-jun was found to be mediated via cytoplasmic signal transduction, involving Ras and Raf, Src and MAP kinases. The UVC response could be inhibited by prior downmodulation of epidermal growth factor (EGF) receptor signalling upon EGF prestimulation, by suramin, which inhibits receptor phosphorylation, or by expression of a dominant negative EGF receptor mutant. Consequently, UVC was found to tyrosine phosphorylate the EGF receptor. In a follow-up paper on this study, Knebel et al. provided evidence that phosphorylated EGF receptor is rapidly dephosphorylated and that UV inhibits or delays dephosphorylation [10]. Since UV-mediated interference with dephosphorylation was caused by a reversible SH-group oxidation or a non-reversible modification by alkylation, involvement of a phosphatase was supposed. Thus, it was concluded that UV can target membrane-associated protein tyrosine phosphatase [10].

Taken together, these studies confirm the concept that the UV response can be initiated in the cytoplasm or at the cell membrane independently of a nuclear event. Our laboratory recently obtained further findings supporting this concept. In the following, these data will be briefly reviewed.

2. UVB interferes with the signal transduction pathway of interferon γ

When studying the effect of UVB on the release of cytokines, we observed that UVB inhibits interferon-γ (IFNγ)-induced release of IL-7 by murine keratinocytes. IL-7 functions as a survival factor for dendritic epidermal T cells [11]. Since UV exposure of murine skin results in the loss of dendritic epidermal T cells, inhibition of IL-7 release by UV might be biologically relevant [12] and thus we were interested in elucidating the underlying molecular mechanism [13]. Since in contrast to the in vivo situation, the murine keratinocyte cell line Pam212 spontaneously released rather minimal amounts of IL-7, therefore not providing optimal conditions to study a negative regulatory effect of UV, we had to stimulate Pam212 cells with IFNγ before exposure to UV. The IL-7 promoter contains an interferon responsive element [14], accordingly IFNγ significantly upregulated IL-7 transcripts in Pam 212 cells. In contrast, exposure of Pam212 cells to UVB before addition of IFNγ suppressed IL-7 mRNA expression in a dose-dependent manner. We anticipated that the inhibitory effect of UV could be due either to interference of UV with the effect of IFNγ or to the activation of negative regulatory UV-responsive elements in the IL-7 promoter.

To prove or to exclude the first possibility, it was determined whether activation of the IL-7 gene by IFNγ is impaired by UVB. Interferon regulatory factor 1 (IRF-1) is an important transcription factor in this respect. Following stimulation of cells with IFNγ, IRF-1 is induced, which consequently migrates into the nucleus and binds to specific responsive elements called ISREs (interferon stimulatory response elements) in the respective genes, thereby inducing transcription [15]. Electrophoretic mobility shift assays revealed that IFNγ induced IRF-1 in Pam212 cells, while binding activity was significantly reduced when cells were irradiated with UVB before stimulation with IFNγ [13]. Induction of IL-7 gene expression by IFNγ was inhibited by the protein synthesis inhibitor cycloheximide, suggesting that IFNγ-induced IL-7 gene expression requires de novo protein synthesis. Thus, it appeared likely that newly synthesized IRF-1 in response to IFNγ is responsible for inducing IL-7 through the binding to the ISRE located in the IL-7 gene. Accordingly, Northern blot analysis indicated that UVB inhibits induction of IRF-1 mRNA expression by IFNγ. The functional relevance of this inhibition was demonstrated by a CAT assay using the minimal promoter of the ISRE of the IL-7 gene. Upon UV exposure IFNγ-induced CAT activity was found to be reduced, suggesting that downregulation of IRF-1 expression might contribute to the suppression of the IFNγ-induced activation of the ISRE of the IL-7 gene. Taken together, these data indicated that the downregulatory activity of UV on IFNγ-induced IL-7 gene expression cannot be attributed to an effect on the IL-7 promoter, but to altered IRF-1 gene expression [13]. Furthermore, these findings imply that UVB, by inhibiting expression of IRF-1, may antagonize biological effects of IFNγ and thus demonstrate that UV cannot only modulate the secretion of cytokines but can also interfere with the biological effects of these mediators. Moreover, this was the first demonstration that UV can negatively interfere with transcription factors. Therefore, further studies were performed to elucidate the molecular mechanisms underlying this unique effect.

Following interaction of IFNγ with its receptor, the Janus kinases Jak1 and Jak2, which are associated with the receptor,

become tyrosine phosphorylated (Fig. 1). This enables tyrosine phosphorylation of the signal transducer and activator of transcription (STAT) protein STAT1 [16,17]. Phosphorylated STAT1 dimerizes, migrates to the nucleus, and there binds to the IFNγ-activated sequences (GAS) in the IRF-1 promoter. Consequently, transcription of IRF-1 is induced [18,19].

Since STAT1 needs to be tyrosine phosphorylated to bind to the GAS element [20], we investigated whether UVB interferes with the phosphorylation of STAT1 [21]. Immuno-precipitates from cells that were UV exposed before stimulation with IFNγ revealed STAT1 not to be tyrosine phosphorylated, suggesting that UV indeed inhibits IFNγ-induced IRF-1 expression by preventing phosphorylation of STAT1. Since all STAT proteins bind to receptor phosphotyrosine via Src homology region (SH2) domains which result in the phosphorylation of STAT and ultimately enable DNA binding [19], the question arose whether interference with phosphorylation of STAT proteins by UV is a general phenomenon. This, however, appears to be unlikely, since UV had no effect on IL-6-induced phosphorylation of STAT3. IL-6 is an inflammatory mediator which is produced by keratinocytes. Since UV significantly induces its release, IL-6 appears to play an important role in UV-induced local and systemic inflammation [22,23]. The failure of UV to suppress the IL-6 signal transduction pathway is not surprising, since it would be strange that UV on the one hand induces the secretion of IL-6, but on the other hand would prevent this cytokine from mediating its effects by interfering with its signalling. Since IL-6 is an inflammatory mediator and IFNγ an immunomodulatory one, the detection of differential effects on cytokine signalling by UV may explain the diverse biological effects of UV, which causes inflammation (via induction of the release of inflammatory cytokines) on the one hand, but inhibits immune reactions (presumably by interruption of the signal transduction of immunomodulatory cytokines) on the other hand [21]. However, it remains to be determined whether these findings are specific for IL-6 and IFNγ or whether they are also valid for other inflammatory and immunomodulatory mediators.

Inhibition of phosphorylation of STAT1 by UV does not appear to be due to downregulation or downmodulation of the IFNγ receptor, because UV had no effect on IFNγ-induced phosphorylation of Jak1 and Jak2 [21]. Phosphorylation of Jak1 and Jak2 is an early event following interaction of IFNγ with its receptor and thus is located

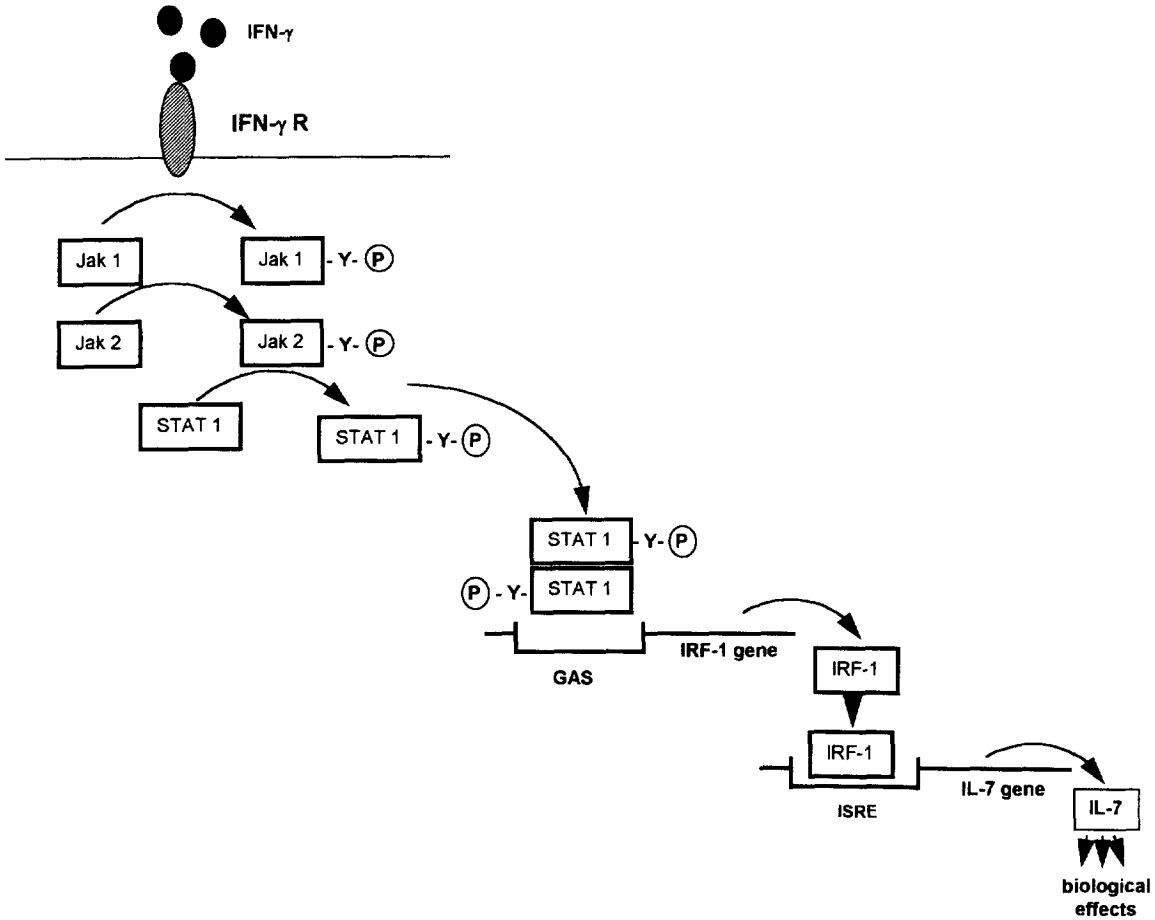

Fig. 1. Simplified scheme of signalling by interferon-γ. Upon activation of the IFN-γ receptor, the receptor-associated tyrosine kinases Jak1 and Jak2 become tryosine phosphorylated (-Y-P), which leads to tyrosine phosphorylation of STAT1. Phosphorylated STAT1 dimerizes and binds to the GAS element in the IRF-1 promoter, thereby initiating transcription of IRF-1. IRF-1 binds to the ISRE element in the IL-7 promoter, thereby inducing transcription of IL-7.

upstream of STAT1 phosphorylation (Fig. 1). We have no evidence yet whether UV directly prevents the phosphorylation of STAT1; alternatively, one has to consider enhanced dephosphorylation. Kim and Maniatis [24] could show that the amounts of phosphorylated STAT1 in IFNγ-treated cells are controlled by the proteasome pathway. Since proteasome inhibitors did not prevent the suppressive effect of UV on STAT1 phosphorylation, it appears unlikely that this pathway is involved [21]. Furthermore, it was currently found that protein tyrosine phosphatases control the amount of phosphorylated STAT1 in the nucleus [25]. Since the phophatase inhibitor vanadate at least partially prevented UV-mediated inhibition of STAT1 binding, involvement of phosphatase(s) may be responsible for the inhibitory UV effect [21]. However, these data have to be interpreted with caution, since vanadate is not a specific phophatase inhibitor and may interfere with a variety of other cellular processes.

While these data suggest activation of one or more phosphatases by UV, inhibition of phosphatase activity by UV was reported recently, causing functional EGF receptor and platelet-derived growth-factor receptor autophosphorylation by inhibiting dephosphorylation of these receptors [10]. The differences between these two studies could be due to the fact that different phosphatases may be involved in these two systems. Furthermore, the UV doses applied in these studies differ remarkably. Nevertheless, both studies identify phosphatases as an additional UV target located within or close to the cell membrane.

3. Direct activation of the CD95 receptor by UVB

Rosette and Karin identified another cell-membrane-associated pathway by which UV can mediate its effects [26]. They observed that UV light or osmotic shock activates multiple growth factor and cytokine receptors, consequently activating the JNK cascade. Confocal laser scanning microscopy studies revealed that exposure of HeLa cells to UV induced clustering and internalization of the cell surface receptors for EGF, tumour necrosis factor and IL-1 [26]. Based on these findings, we became interested in studying whether by this pathway UV can also activate the apoptosis-related surface receptor CD95 and whether activation of this receptor may be functionally relevant for UV-mediated apoptosis of keratinocytes. CD95, also called Fas or APO-1, is a death-inducing receptor belonging to the tumour necrosis factor receptor family [27,28]. Activation of CD95 either by agonistic antibodies or by its natural ligand CD95L, also called FasL, causes apoptosis [29] (see Fig. 2). Binding of the ligand induces trimerization of CD95; subsequently the trimerized cytoplasmic region transduces the signal by recruiting a molecule called FADD (Fas-associating protein with death domain) [30]. FADD recruits the cysteine protease FLICE (FADD like ICE) [31], which induces a cascade of other cysteine proteases (caspases) ultimately executing apoptosis.

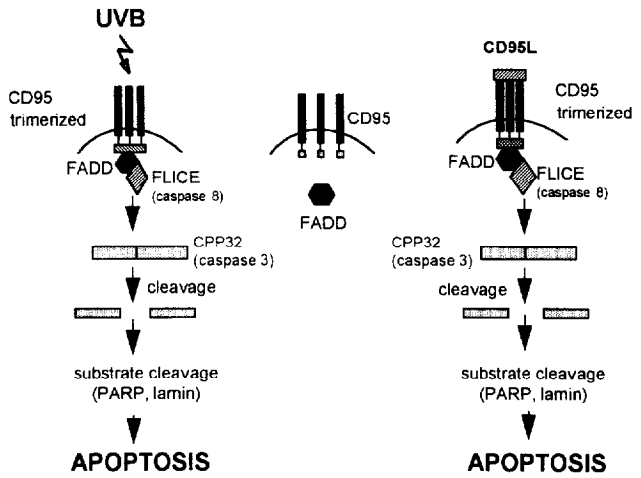

Fig. 2. Simplified scheme of CD95-induced apoptosis. Upon activation either by the natural ligand CD95L or by UVB, CD95 trimerizes, which subsequently transduces the signal by recruiting the FADD protein. FADD recruits the protease FLICE (caspase 8), which activates CPP32 (caspase 3) by cleavage. CPP32 cleaves a variety of substrates including lamin and PARP, which ultimately results in apoptosis.

Since the initial event during activation of CD95 is its trimerization, we addressed whether UV light directly causes CD95 clustering [32]. Therefore, the transformed human keratinocyte cell line HaCaT was exposed to UVB, stained with an antibody against CD95 and subsequently analysed by confocal laser scanning microscopy. While on the surface of untreated HaCaT cells only a very weak and diffuse CD95 staining was detectable, UV-exposed HaCaT cells revealed a marked patchy staining compatible with receptor clustering. A similar staining pattern was found upon treatment of cells with the natural ligand of CD95, CD95L. These data provide strong evidence that UVB triggers the CD95 pathway by directly activating the CD95 receptor [32]. Accordingly, we were able to detect FADD recruitment to the CD95 receptor following UV exposure. Similar observations were made by Rehemtulla et al., reporting that UVC induces CD95 clustering on the breast carcinoma cell line MCF7 [33].

To prove whether clustering of CD95 directly induced by UV is also functionally relevant, HaCaT cells were exposed to UV at 10°C. Rosette and Karin observed that exposing HeLa cells to UV at such low temperatures, which are below the transition temperature of the membrane, prevents JNK activation [26]. Accordingly, exposing HaCaT cells to UV at 10°C significantly reduced the apoptosis rate [32]. Confocal laser scanning microscopy revealed that exposing HaCaT cells to UV at 10°C almost completely prevented CD95 aggregation. Taken together, these data indicate that UV-induced clustering of CD95 is functionally relevant for UV-mediated apoptosis. This conclusion was also confirmed by the observation that HaCaT cells transfected with a FADD dominant negative mutant construct were less susceptible to UV-induced apoptosis than mock transfected cells. However, since neither UV exposure at 10°C nor elimination of the FADD pathway completely prevented UV-induced apoptosis, additional pathways have to be involved. As suggested

by Ziegler et al. [34], one important phenomenon involved might be DNA damage. Therefore according to the findings of Godar [35], two phases of UV-mediated death may exist: an early one due to direct clustering of surface receptors including CD95 and a late one due to DNA damage.

When initially observing the receptor clustering by UV, Rosette and Karin proposed that any receptor the activation of which involves multimerization should be activatable by UV light [26]. This prediction is strongly supported by our and Rehemtulla's observations [32,33]. However, it is presently not clear how UV light causes multimerization of cell surface receptors. Physical perturbation of the plasma membrane or a conformational change caused by energy absorption may be important [26]. Nevertheless, demonstration of direct activation of surface receptors by UV further adds to the concept that UV can affect targets at the plasma membrane and that targeting of such structures is of functional relevance.

4. Abbreviations

EGF	epidermal growth factor
FADD	Fas-associating protein with death domain
GAS	interferon-γ activated sequences
IL	interleukin
IFNγ	interferon-γ
IRF-1	interferon regulatory factor 1
STAT	signal transducer and activator of transcription
UV	ultraviolet light

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