

# 20 Years After – Milestones in Molecular Photobiology

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Ultraviolet radiation represents one of the most relevant environmental factors because of its hazardous health effects, which include induction of skin cancer, premature skin aging, and exacerbation of infectious diseases. The biologic effects exerted by ultraviolet radiation have been well characterized by a variety of *in vitro* and *in vivo* studies. The events taking place inside the cell during the ultraviolet response, however, remained unclear for quite a long time. Molecular photobiology has increased our knowledge about ultraviolet-induced signal transduction enormously within the last 10 years. For a long time, nuclear DNA has been regarded as the only chromophore for ultraviolet radiation. Today we

know that ultraviolet radiation can affect also other molecular targets located in the cytoplasm and at the cell membrane. These targets include cell surface receptors, kinases, phosphatases, and transcription factors. Detailed knowledge about ultraviolet-induced signal transduction will certainly increase our understanding of how ultraviolet radiation exerts its biologic effects and furthermore will provide us with tools to interfere with these pathways, thereby reducing the adverse effects of ultraviolet radiation. **Key words:** apoptosis/DNA damage/receptors/signal transduction/ultraviolet radiation. *JID Symposium Proceedings 7: 46–50, 2002*

Ultraviolet (UV) radiation represents one of the most important, if not the most important, environmental factor influencing humans, especially with regard to its hazardous health effects, which include induction of skin cancer (de Gruijl *et al*, 1993), premature skin aging (Fisher *et al*, 1997), and exacerbation of infectious diseases, e.g., herpes simplex (Chapman *et al*, 1995). UV radiation is arbitrarily separated into three ranges: UVC (200–290 nm), UVB (290–320 nm), and UVA (320–400 nm). UVC is biologically not relevant as it is completely absorbed by the stratospheric ozone layer. In contrast, both UVA and UVB reach terrestrial surfaces at significant levels and are therefore able to mediate biologic effects. The present paper will mostly focus on the effects of UVB radiation. One of the most burning issues that puzzled photobiology for the last two decades was the identification of the molecular targets for UV radiation within the cell. Recognition of these targets is a prerequisite for the understanding of the molecular mechanisms by which UV radiation mediates its biologic effects.

## DNA, THE MAJOR CHROMOPHORE FOR UVB RADIATION, MEDIATES UVB EFFECTS

To exert its biologic effects, UVB radiation must be first absorbed by a cellular chromophore, which transduces the energy into a biochemical signal. Among a variety of cellular chromophores

(porphyrins, aromatic amino acids, urocanic acid), DNA has been regarded as the most important one for quite a long time. DNA absorbs UV radiation in the UVC and UVB range. The wavelength dependence of some UVB effects, e.g., erythema induction and carcinogenesis, is similar to that for DNA absorption. Exact determination of action spectra for *in vivo* effects of UV radiation, however, is extremely difficult to perform due to a lack of appropriate UV devices allowing such studies. UVB radiation induces primarily two types of photolesions in DNA, cyclobutane pyrimidine dimers and (6–4)-photoproducts. Usually, UV-induced DNA lesions are removed by nucleotide excision repair (NER) (de Laat *et al*, 1999). Two modes of NER can be distinguished: repair of lesions over the entire genome, designated as global genome NER, and repair of lesions present in transcribed DNA strands, thus referred to as transcription-coupled NER. In global genome repair, UV-induced DNA lesions are recognized by the protein xeroderma pigmentosum (XP) group C, whereas in transcription-coupled repair damage is detected by the elongating RNA polymerase II complex when it encounters a DNA lesion. XPA is crucial in the assembly of the remaining components of the repair machinery. Replication protein A stabilizes the opened DNA complex and helps to position XPG and XPF. Incision involves the proteins XPF, XPG, and TFIIH, which contains the repair proteins XPB and XPD. After excision of the damaged strand, repair is completed by replication factors DNA polymerase and DNA ligase. Both the efficacy and the importance of the NER is impressively demonstrated by the dramatically enhanced rate of skin cancer in patients suffering from xeroderma pigmentosum, which is based on genetic defects in various components of the NER machinery. The fact that lower UVB doses are sufficient to achieve the same biologic effects in DNA repair-deficient than repair-proficient cells also supports the crucial role DNA damage plays in UV-induced signaling (Petit-Frere *et al*, 2000).

An alternative way to reduce UV-mediated DNA damage is the application of exogenous DNA repair enzymes. Yarosh *et al*

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Abbreviations: COX, cyclooxygenase; NER, nucleotide excision repair; NFκB, nuclear factor κB; T4N5, T4 endonuclease V; XP xeroderma pigmentosum.

(1994) showed that the bacterial DNA repair enzyme T4 endonuclease V (T4N5) can be delivered into cells both *in vitro* and *in vivo* via liposomes. Topically applied T4N5 liposomes penetrate the skin and the enzyme enters the nucleus and increases the removal of cyclobutane pyrimidine dimers, thereby preventing DNA mutations. In the XP transformed fibroblast line XP12BE, treatment with T4N5 liposomes reduced the mutagenesis rate by 99% and in the normal transformed fibroblast line GM637 by 30% (Yarosh, 2002). Accordingly, UV-irradiated mice treated with these liposomes exhibited a dose-dependent decrease in the incidence of squamous cell carcinomas compared to controls (Yarosh *et al*, 1992). In addition, photolyase, another repair enzyme that repairs DNA damage via photoreactivation, was also delivered successfully into the skin via liposomes (Stege *et al*, 2000). A recently published randomized, placebo-controlled study demonstrated that topical application of T4N5 liposomes significantly reduced the rate of new actinic keratoses and basal cell carcinomas in XP patients within the period of 1 y (Yarosh *et al*, 2001).

The application of DNA repair enzymes via the liposome route, however, not only represents a major therapeutic breakthrough for these patients, but provides us with a nice tool to elucidate the crucial role of UV-induced DNA damage in mediating the biologic effects of UV radiation. Accordingly, it was shown that removal of DNA damage by application of T4N5 endonuclease reduces UV-induced immunosuppression, in particular systemic suppression of contact hypersensitivity (Kripke *et al*, 1992). Furthermore, the T4N5 approach demonstrated that unrepaired cyclobutane pyrimidine dimers in DNA are a direct cause for the UV-mediated release of cytokines. UV-induced expression of the immunosuppressive cytokine interleukin-10 (IL-10) and of the inflammatory mediator tumor necrosis factor  $\alpha$  was found to be decreased upon application of T4N5 endonuclease (Nishigori *et al*, 1996; Kibitel *et al*, 1998; Wolf *et al*, 2000). Taken together, these studies demonstrated that DNA is the major target of UV radiation in the generation of immunosuppression and suggested that the primary molecular event mediating these effects is the formation of cyclobutane pyrimidine dimers.

Another important biologic effect of UVB radiation is the induction of apoptosis of keratinocytes, which appear as sunburn cells *in vivo* (Kulms and Schwarz, 2001). Although the phenomenon of sunburn cell formation has been appreciated for decades, its functional relevance was mostly unclear for quite a long time. A major advance in the understanding of the functional role of sunburn cells was the discovery of the link between sunburn cell formation and the tumor suppressor gene *p53*. Irradiation with UV arrests cells during the G1-phase in a *p53*-dependent manner in order to allow DNA repair prior to DNA synthesis (Campbell *et al*, 1993; Levine, 1997). *p53* was recognized to be critically involved in the formation of sunburn cells as mice lacking functional *p53* revealed significantly fewer sunburn cells upon UV exposure compared to wild-type mice (Ziegler *et al*, 1994). This gave rise to the concept that UV-damaged keratinocytes that fail to repair their DNA damage will die as sunburn cells, thereby escaping the risk of malignant transformation. Therefore, the formation of sunburn cells was proposed to be a scavenging event that under control of the *p53* gene protects the individual from developing UV-induced skin cancer (Brash *et al*, 1996). Consequently, *p53*-mutated keratinocytes should be more susceptible to the tumor promoting effects of UV radiation. Due to diminished *p53*-mediated apoptotic cell death these cells should survive, whereas other cells carrying damaged DNA but wild-type *p53* will be eliminated by apoptosis (Brash *et al*, 1996; Kraemer, 1997). UV radiation preferentially mutates *p53* (Brash *et al*, 1991); thus it may exert a selective pressure for the mutated, damage-resistant keratinocytes, thereby allowing these cells to clonally expand and to form actinic keratosis (Ziegler *et al*, 1994). Accordingly, *p53* knockout mice exposed to chronic UV radiation revealed significantly increased susceptibility to skin cancer induction compared to wild-type mice (Jiang *et al*, 1999). In this context it is important to mention that application of sunscreens with a sun protection factor of 15 to mouse skin prior to each UV irradiation nearly

abolished the frequency of *p53* mutations, demonstrating the efficacy of sunscreens in the prevention of skin cancer (Ananthaswamy *et al*, 1997).

As *p53* becomes activated proportionally to DNA damage it was concluded that the formation of sunburn cells is linked to the severity of UV-induced DNA damage (Ziegler *et al*, 1994). If DNA damage is causally related to UV-mediated apoptosis, an increase in DNA repair should result in reduction of the apoptotic response to UV exposure. Therefore, the epithelial cell line HeLa was exposed to UV radiation and subsequently DNA repair was enhanced by adding the repair enzyme photolyase via liposome delivery (Kulms *et al*, 1999). Accordingly, the rate of apoptosis was remarkably but not completely reduced. In addition, *in vivo* studies showed that enhancement of DNA repair by topical application of the repair enzyme T4N5 in liposomes reduced the number of sunburn cells (Wolf *et al*, 1995). A very recent study extended these observations to normal human individuals, demonstrating that topical application of photolyase not only decreased the number of UV-induced cyclobutane pyrimidine dimers but also suppressed erythema and sunburn cell formation (Stege *et al*, 2000). Taken together, these data clearly indicated that UV-induced DNA damage is indeed an important mediator of a variety of biologic effects caused by UV radiation.

In addition, there is evidence that not only the DNA damage itself but also products generated during DNA repair may cause UV effects. Eller *et al* showed that production of melanin in melanocytes by UV radiation is not reduced by induction of DNA repair via T4N5 endonuclease but significantly enhanced. As the number of excised short DNA fragments increases with the efficacy of DNA repair the effect of pyrimidine dimers (pTpT) on melanin synthesis was tested. Application of pTpT induced melanin production both *in vitro* and *in vivo* in guinea pigs (Eller *et al*, 1994). In addition, it was shown that pTpT enhance repair of UV-induced DNA damage (Eller *et al*, 1997). Enhanced repair resulted in a 2-fold increase in expression of a UV-damaged chloramphenicol acetyltransferase expression vector transfected into pTpT-treated fibroblasts and keratinocytes. As both melanogenesis and enhanced DNA repair are photoprotective responses, these data suggest the existence of an SOS response in mammalian cells analogous to that described in prokaryotes (Sancar and Sancar, 1988).

A very recent publication provided a potential connection between DNA damage and the immunostimulatory cytokine IL-12 (Schwarz *et al*, 2002). Quite surprisingly, it was observed that IL-12 reduced UVB-induced DNA damage both *in vitro* and *in vivo*. Apparently, reduction of cyclobutane pyrimidine dimers was mediated via NER, as IL-12 did not exert this activity in *Xpa* knockout mice, which are deficient in NER. IL-12 is known to antagonize UVB-induced immunosuppression (Schwarz *et al*, 1996). As UVB-induced DNA damage is the primary mediator of UVB-induced immunosuppression (Kripke *et al*, 1992), it remains to be determined whether at least some of the immunoreconstitutive effects of IL-12 are due to its ability to reduce DNA damage. The observation that IL-12 inhibits UVB-induced IL-10 release (Schmitt *et al*, 2000), which is clearly mediated via DNA damage (Nishigori *et al*, 1996), strongly supports this assumption.

Although UV-induced DNA damage and the subsequent mutations are certainly the main factor causing skin cancer, other mechanisms may contribute to photocarcinogenesis as well. There is evidence that UV-induced prostaglandin synthesis may also be of relevance. Prostaglandin synthesis is mediated by two major enzymes, a phospholipase that releases arachidonic acid from membrane phospholipids and a cyclooxygenase (COX) that converts the free arachidonic acid into prostaglandins (Smith *et al*, 1996; Leslie, 1997). Two isoforms of COX have been described: COX-1 and COX-2. Whereas COX-1 is primarily constitutively expressed, COX-2 can be induced by a variety of stimuli, including UV radiation (Buckman *et al*, 1998). Accordingly, it was demonstrated that application of the COX-2 inhibitor celecoxib significantly reduced the development of skin tumors in murine

photocarcinogenesis models (Fischer *et al*, 1999; Pentland *et al*, 1999).

#### UV RADIATION AFFECTS ALSO EXTRANUCLEAR MOLECULAR TARGETS

Despite the undisputed crucial role of UV-induced DNA damage in the mediation of UV effects, there is increasing evidence that UV radiation also affects extranuclear molecular targets and that this seems to be of functional relevance (Schwartz, 1992). UV radiation activates the transcription factors AP-1 and nuclear factor  $\kappa$ B (NF $\kappa$ B) (Stein *et al*, 1989; Devary *et al*, 1991). NF $\kappa$ B is located in the cytoplasm coupled to an inhibitory protein, called I $\kappa$ B. Upon activation, I $\kappa$ B is split off; free NF $\kappa$ B then translocates into the nucleus where it targets specific responsive promoter elements of various genes, thereby initiating transcription. When postulating that DNA is the primary and even the only molecular target for UV radiation within the cell initiating the UV response, this would imply that UV radiation has to enter the cell, penetrate the cytoplasm, "ignore" the cytoplasmically located transcription factor NF $\kappa$ B, enter the nucleus, and damage the DNA. Consequently, a nuclear signal has to be transferred to the cytoplasm to activate NF $\kappa$ B. This rather complicated scenario is hard to reconcile with nature's straightforwardness. Therefore, it was obvious to study whether UV radiation can directly activate NF $\kappa$ B. Using dominant negative mutants, Devary *et al* showed that cytoplasmically located tyrosine kinases and Ha-Ras are directly involved in NF $\kappa$ B activation by UVC. Furthermore, utilizing enucleated cells, it was demonstrated that activation of NF $\kappa$ B does not require a nuclear signal (Devary *et al*, 1993). These observations were confirmed by another experimental approach. Simon *et al* (1994) irradiated cytoplasmic protein extracts that contained NF $\kappa$ B in its inactive form and observed activation of NF $\kappa$ B. The activation process was dependent on the presence of membranes in the protein extracts, suggesting a signaling pathway for the early UVB response, including participation of a component of that pathway residing at the cell membrane. Taken together, these findings suggested that the UV signaling cascade that activates NF $\kappa$ B is initiated at or near the plasma membrane and is not elicited by DNA damage in the nucleus. These observations were in accordance with previous findings obtained by Devary *et al* (1992) who observed that the earliest detectable step in the UVC response was activation of Src tyrosine kinases, followed by activation of Ha-Ras and Raf-1. This response was inhibited by tyrosine kinase inhibitors and dominant negative mutants of v-src, Ha-ras, and raf-1. These findings strongly suggested that the UVC response is initiated near the plasma membrane rather than in the nucleus.

Sachsenmaier *et al* (1994) demonstrated involvement of the epidermal growth factor (EGF) receptor in the mammalian UVC response. 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. This response appeared to be mediated via the EGF receptor as prior downmodulation of EGF receptor signaling upon EGF prestimulation inhibited the kinase activation. The same was observed upon pretreatment with suramin, which inhibits receptor phosphorylation, or upon expression of a dominant negative EGF receptor mutant. Consequently, UVC was found to phosphorylate the EGF receptor on tyrosine residues. According to this line, Miller *et al* (1994) demonstrated that UVB radiation reduces prostaglandin release via EGF receptor activation. Extending the findings of Sachsenmaier and coworkers, Knebel *et al* (1996) showed that the phosphorylated EGF receptor is rapidly dephosphorylated and that UV radiation inhibits or delays dephosphorylation. In other words, this means that EGF receptor activation by UV radiation is not due to enhanced phosphorylation but to reduced dephosphorylation. As UV-mediated interference with dephosphorylation was caused by a reversible SH-group oxidation or a nonreversible modification by alkylation, involvement of a phos-

phatase was supposed. There is recent evidence for an inactivation of a receptor-directed tyrosine phosphatase through an unknown reactive intermediate that oxidizes the conserved cysteine in the active site of the phosphatase (Gross *et al*, 1999).

UV radiation was also shown to be able to interfere with cytokine signaling. UV inhibits interferon- $\gamma$  and IL-2 from exerting particular biologic effects through interference with signal transduction. UV radiation reduces the phosphorylation of STAT-1 and STAT-5, which are involved in signaling of interferon- $\gamma$  and IL-2, respectively (Aragane *et al*, 1997; Kulms & Schwartz, 2001). There are indications that UV radiation may mediate this suppressive effect via activation of a phosphatase. Although the detailed mechanism involved remains to be determined, this effect may contribute to the immunosuppressive activities of UV, as both interferon- $\gamma$  and IL-2 are important immunostimulatory cytokines.

Another cell membrane associated pathway by which UV radiation can mediate its effects was identified by Rosette and Karin (1996). They observed that UV radiation or osmotic shock can activate multiple growth factor and cytokine receptors, subsequently triggering the JNK cascade. Confocal laser scanning microscopy studies revealed that exposure of HeLa cells to UV radiation induced clustering and internalization of the cell surface receptors for EGF, tumor necrosis factor  $\alpha$ , and IL-1 (Rosette and Karin, 1996). Based on their findings, Rosette and Karin predicted that any receptor whose activation mechanism involves multimerization should be activatable by UV radiation. This appears to be the case, as direct activation was recently demonstrated also for the apoptosis-related cell surface receptor CD95 (Fas, APO-1). UV radiation induced clustering of CD95, as demonstrated by confocal laser scanning microscopy (Aragane *et al*, 1998). In addition, CD95 activation was functionally relevant as inhibition of clustering by exposing cells to UV radiation at low temperature (4°C–10°C) was associated with a reduced apoptosis rate. In addition, transfection of cells with a dominant negative mutant of FADD, a crucial signaling protein in the CD95 pathway, partially reduced UV-induced apoptosis. Similar observations were made by Rehemtulla *et al* (1997) reporting that UVC induced CD95 clustering in a breast carcinoma cell line. In addition, there is evidence that triggering of the tumor necrosis factor type 1 receptor by UV radiation is responsible for UV-induced release of IL-6 (Kulms *et al*, 2000).

The above data clearly indicated that UV-induced apoptosis can also be initiated at the cell membrane and were therefore in contrast to the observation that UV-induced DNA damage is the primary event in UV-mediated apoptosis. It is important to note, however, that neither inhibition of death receptor clustering nor removal of DNA damage by induction of DNA repair resulted in a complete prevention of UV-induced apoptosis. Therefore, the relative contribution of nuclear and membrane effects in UVB-induced apoptosis was measured. When the epithelial cell line HeLa was exposed to UVB radiation at low temperature (which inhibited death receptor activation) followed by photoreactivation (which reduced UV-induced DNA damage), UVB-mediated apoptosis was almost completely prevented (Kulms *et al*, 1999). Although activation of death receptors and induction of DNA damage are caused by the same stimulus, i.e., UVB, they independently occur in parallel. As inhibition of both events results in an additive reduction of apoptosis, this indicated that death receptor activation and DNA damage contribute independently to UVB-induced apoptosis. Most importantly, these data showed that nuclear and membrane effects are not mutually exclusive and that both components are necessary to yield the complete UVB response. Very recently, it was reported that reactive oxygen species may be involved in mediating UV-induced apoptosis as well, as radical scavengers reduced UV-mediated cell death (Kulms *et al*, 2002). Furthermore, complete inhibition of apoptosis was observed when, in addition to DNA damage removal via photoreactivation and blockade of CD95 signaling, radical scavengers were added before UV exposure.

## CONCLUSION

In the 1980s we have learned a lot about the biologic effects of UV radiation. These include induction of apoptosis, release of both inflammatory and immunosuppressive soluble mediators, modulation of surface molecule expression, inhibition of antigen presentation, just to name a few. Appreciation of these effects significantly contributed to our understanding of how UV radiation may act both as a pathologic and a therapeutic agent. In those days, however, we had no or minimal understanding of the events taking place inside the cell and how the UV signal is converted into the respective biologic effect. In the last 10 y, molecular photobiology has dramatically increased our understanding of UV-induced signal transduction. We have learned that UV radiation can affect a variety of molecular targets within the cell. Although DNA still is the most important chromophore it is far from being the only molecular target for UV radiation. UV radiation can directly affect surface receptors, phosphatases, and transcription factors. Presumably the list will increase within the next years. Detailed knowledge about UV-induced signal transduction not only will increase our understanding of how UV radiation exerts its biologic effects but will also provide us with tools to interfere with these pathways, which ultimately will allow us to reduce the damaging effects of UV radiation. Application of exogenous repair enzymes via liposome delivery has impressively shown that this is not only a vision but can become reality (Yarosh *et al*, 2001).

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