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Review

How DNA lesions are turned into powerful killing structures: Insights from UV-induced apoptosis

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ABSTRACT

Mammalian cells treated with ultraviolet (UV) light provide one of the best-known experimental systems for depicting the biological consequences of DNA damage. UV irradiation induces the formation of DNA photoproducts, mainly cyclobutane pyrimidine dimers (CPDs) and (6-4) pyrimidine-pyrimidone photoproducts [(6-4)PPs], that drastically impairs DNA metabolism, culminating in the induction of cell death by apoptosis. While CPDs are the most important apoptosis-inducing lesions in DNA repair proficient cells, recent data indicates that (6-4)PPs also signals for apoptosis in DNA repair deficient cells. The toxic effects of these unrepaired DNA lesions are commonly associated with transcription blockage, but there is increasing evidence supporting a role for replication blockage as an apoptosis-inducing signal. This is supported by the observations that DNA double-strand breaks (DSBs) arise at the sites of stalled replication forks, that these DSBs are potent inducers of apoptosis and that inhibition of S phase progression diminishes the apoptotic response. Reactive oxygen species, generated after exposure of mammalian cells to longer UV wavelengths, may also induce apoptotic responses. In this regard, emphasis is given to the formation of 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-OxoG), but indirect induced lesions such as lipoperoxide DNA adducts also deserve attention. ATR is the main established sensor molecule for UV-induced DNA damage. However, there is evidence that ATM as well as the MAPK pathway also play a role in the UV response by activating either the death receptor or the mitochondrial damage pathway. Adding more complexity to the subject, cells under stress suffer other types of processes that may result in cell death. Autophagy is one of these processes, with extensive cross-talks with apoptosis. No matter the mechanisms, cell death avoids cells to perpetuate mutations induced by genotoxic lesions. The understanding of such death responses may provide the means for the development of strategies for the prevention and treatment of cancer.

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1. Historical view on ultraviolet (UV) light and DNA damage

DNA is the molecule responsible for the maintenance and transmission of genetic information over time. Therefore, it is of paramount importance to protect it from damaging insults. However, due to its physicochemical constitution it becomes the main target for genotoxic agents, able to alter its structure and eventually giving rise to mutations leading to improper functioning and enhancing cancer risk. These agents and their effects on the cellular genome have been the subject of intensive studies for decades. Due to its evolutionary and environmental significance, UV light has been historically one of the most studied DNA damaging agents [1], and exposure of cells to UV radiation is one of the best-known models for depicting the biological consequences of DNA damage [2]. Undeniably, the fact that UV irradiation of cells can easily be achieved through the use of common germicidal lamps has been one of the major factors contributing to its wide use by several laboratories worldwide. In addition, the well known effects on DNA, with the generation of few types of damage, has also contributed to the use of this practical tool in the very earliest experiments on gene mutagenesis and cell killing, from the first decades of the last century until today.

UV light represents 45% of the total sunlight spectrum. It is further subdivided into three segments, according to their wavelengths: UVA, ranging from 320 to 400 nm, UVB, ranging from 295 to 320 nm and finally UVC, ranging from 100 to 295 nm. The earth's ozone layer efficiently absorbs UV radiation up to about 310 nm, thus consuming all UVC and most of UVB light before it reaches the surface of the planet [3]. However, current depletion of the ozone layer is significantly increasing the amount of UVB irradiation that reaches the surface, a matter that deserves much consideration [4]. In fact, both melanoma and non-melanoma skin cancers are among the most deleterious effects of UV light [5]. This will not be the focus of this review, since several recent publications have summarized the current knowledge on the subject [6–8]. UV irradiation also suppresses responses of the immune system, which was shown in the pioneering work of Fisher and Kripke that established the field of photoimmunology [9]. It is now well-recognized that UV-induced immunosuppression has considerable implications in skin cancers, infectious diseases and vaccination, autoimmune diseases, as well as photoprotection and phototherapy (for a recent review see Ref. [4]).

On the other hand, although UVC irradiation has no environmental significance, the fact that the maximum absorption peak of the DNA molecule is 260 nm has lead to extensive use of UVC lamps in laboratory studies (typically these lamps emit mainly at the 254 nm wavelength, which has the additional advantage of not being efficiently absorbed by proteins). Although it is now well-known that irradiation with different UV spectra leads to different biological consequences, as will be discussed in this review, many of the same lesions in DNA are produced at longer wavelengths of UV radiation, including UVA and UVB [10]. However, due to the high energy of UVC, these lesions are more efficiently produced in this UV spectra [11].

2. UV absorption and biological consequences

The first step in the induction of DNA damage by UV irradiation is the absorption of energized UV photons either by a cellular chromophore (direct pathway) or by a photosensitizer (indirect pathway) [12]. In the latter, the absorption of UV photons energy changes the distribution of the electrons in the photosensitizer molecule, thus creating an excited singlet state. Cellular damage by an excited molecule may occur either through direct interaction with the DNA molecules, thereby resulting in free radical formation, or through energy transfer to molecular oxygen, leading to the production of reactive oxygen species (ROS) that will then provoke the biological responses [13]. This indirect pathway is particularly relevant in UVA irradiation and will be discussed in more detail later on in this review.

As mentioned above, the DNA absorption peak of UVC is 260 nm, for which DNA is the major cellular chromophore. This absorption leads to photo-induced reactions in DNA bases, generating lesions usually referred to as photoproducts, among which the most common are cyclobutane pyrimidine dimers (CPDs) and (6-4) pyrimidine-pyrimidone photoproducts [(6-4)PPs] [13]. In addition, a third type of UV-induced photoproduct, called Dewar valence isomers (DewPPs), may be generated by photoisomeration of (6-4)PPs by absorption of UVA irradiation (at 320 nm) [14,15]. Fig. 1 shows the chemical structure of these lesions.

While CPDs are the result of the covalent linkage between adjacent pyrimidines by the formation of a four-member ring-structure resulting from saturation of the pyrimidine 5,6 double-bond, (6-4)PPs arise from the linkage of the C6 position of the 5′-pyrimidine in an adjacent pair, to the C4 position of the 3′-pyrimidine [16]. Although several studies have shown that the overall formation ratio between CPDs and (6-4)PPs after UVC irradiation is approximately 3:1 [17], this is in fact related to the specific DNA sequence. Accurate determination of the distribution of bipyrimidine photoproducts has shown that TT and TC sequences are much more photoreactive than CT and CC, and the ratio between the yield of CPDs and (6-4)PPs was found to be strongly dependent on the two adjacent bases involved in the dimeric lesions [18]. In addition, it has been shown that the proportion of TT CPDs generated by UVA is higher than upon UVB irradiation [14]. Accordingly, Besaratinia et al. have elegantly shown that although CPDs are the main type of lesion generated in the p53 gene after UVA and UVB irradiation, the specific sites of lesion in this gene are not the same, demonstrating that the mechanism of formation of CPDs is different for these two wavelengths [19].

The presence of these lesions in the DNA double-helix drastically alters metabolic processes in DNA, since they represent a physical blockage for both replication and transcription machinery [20,21]. It is well accepted that replication blockage is not only a passive consequence of this physical blockage, but an active response in the form of a S phase checkpoint by which replication errors are avoided, that could otherwise lead to mutagenesis, chromosomal breakage and DNA recombination [22]. Most importantly, UV photoproducts in the DNA molecule are the main cause for cell death by apoptosis following UV irradiation, and the focus of this work is precisely on how these DNA lesions are capable of terminating the cell's life.

3. Photoproducts-induced apoptosis

In order to deal with UV photoproducts in their genome, mammalian cells have evolved a dedicated and extremely efficient DNA repair system, capable of removing these types of lesions from DNA, called Nucleotide Excision Repair (NER). This repair pathway requires approximately 30 proteins that act in a sequential manner to excise the DNA region containing the lesion [23]. It is composed of two sub-pathways: global genomic repair (GGR) and transcription-coupled repair (TCR) [20,24]. GGR repairs helix-distorting lesions throughout the entire genome. It is initiated by the action of the damage-sensing XPC-HR23B complex and DDB (DNA damage-binding) factor (composed of two protein subunits, p48 and p127) [22]. TCR preferentially removes transcription-blocking DNA lesions, presumably with stalled RNA polymerase II (RNApol II)

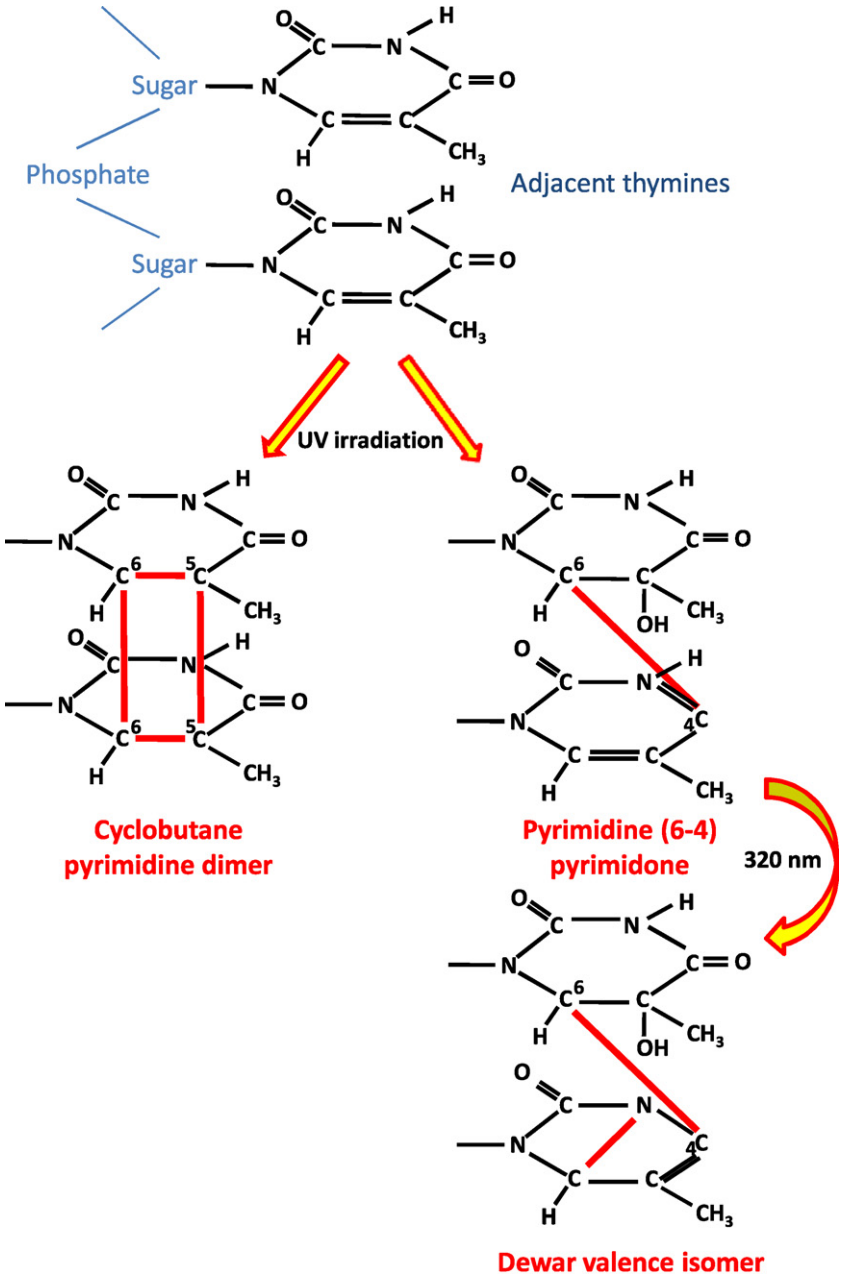

Fig. 1. Chemical structure of the main DNA lesions induced by UV light.

complexes being the damage sensor [25]. Therefore, TCR acts as an efficient backup system for lesions that are slowly or not at all repaired by GGR [26]. Another well-known mechanism of UV-photoproducts repair is photoreactivation. It is performed by photolyases, enzymes that specifically remove CPDs (CPD photolyase) or (6-4)PPs (6-4PP photolyase) from the double-helix, by using the energy of blue light to directly revert the damage in a one-step reaction [27,28]. Although this type of repair is very efficient (absolutely error-free), during the evolution of mammals the photolyase genes were lost and, as a consequence, placental mammals depend only on NER for the removal of these photoproducts from DNA [27].

The fact that NER-deficient cells are extremely sensitive to the killing effect of UV light [29–31] is a clear indication that unrepaired photoproducts constitute the main apoptosis-triggering signal after UV irradiation. This has been shown not only in cultured cells, but also with NER-deficient mouse models [32,33]. The following discussion involves the contribution of each specific lesion, CPDs and (6-4)PPs, to the induction of apoptosis following UV irradiation. Although TCR and GGR contribute to the removal of CPDs and (6-4)PPs, the efficiency of removal varies [17,34]. On the one hand, it has been shown that both lesions block the progression of RNA polymerase II [35] and can be removed by TCR with equal efficiency *in vivo*. On the other hand, GGR can remove (6-4)PPs from the genome much faster than CPDs [36] which is probably related to the fact that the XPC-HR23B complex has a higher affinity for 6-4PP than for CPD [37]. This, together with the already mentioned fact that the number of CPDs induced by UVC is approximately three times higher than the number of (6-4)PPs, accounts for the observation that the mutagenic and carcinogenic potential of UV light is expected to arise mainly from CPDs [38–41]. Interestingly, studies with plasmids containing site-

specific lesions have shown that (6-4)PPs are more mutagenic [17], which might be due to the stronger helix-distorting potential of this lesion when compared to CPDs. As to the induction of apoptosis, experiments with CPD-photolyase transfected cells showed that the removal of this lesion from DNA efficiently avoids apoptosis induction [38,39]. This was confirmed *in vivo* [33], where the authors showed that the enhanced repair of CPDs by CPD-photolyase transgenic mice leads to enhanced UV resistance. More recently, experiments with transgenic mice that express CPD-photolyase, 6-4PP photolyase, or both, have shown that CPDs, rather than (6-4)PPs form the main trigger for UV-induced cell death, transcription inhibition and carcinogenesis [32]. It is important to mention that this work was performed in a NER-proficient background, which may affect the relative role of (6-4)PPs, since these are rapidly removed by NER [42]. In fact, studies performed with NER-deficient cell lines transfected with either CPD-photolyase, 6-4PP photolyase or both, concluded that 6-4PP lesions are several times more toxic than CPD lesions unless they are repaired by NER [43]. The authors reached this conclusion based on the fact that both CPDs or (6-4)PPs removal contributes almost equally to an increase in cell survival and, since (6-4)PPs represent only one fourth of the total number of UV-induced lesions, this indicates a higher toxicity for this type of lesion. An even more striking result came from the work of Lo et al. [44], where the authors observed that in XPA deficient fibroblasts the removal of CPDs reduced apoptosis by 40%, whereas the removal of (6-4)PPs alone reduced apoptosis by 70%. A different approach to address this specific problem was recently published by Lima-Bessa et al. [45]. Human fibroblasts were transduced by recombinant adenoviruses carrying the CPD-photolyase or 6-4PP photolyase cDNAs. Both photolyases were able to prevent UV-induced apoptosis in cells deficient in NER to a similar extent, while in NER-proficient cells UV-induced apoptosis was prevented only by CPD-photolyase, with no effects observed when (6-4)PPs were removed by the specific photolyase [45]. Moreover, photorepair prevents apoptosis even when performed up to 8 h after UV irradiation, indicating that lesions need to be processed before the cells are definitely compromised to cell death. Therefore, the fast kinetics of (6-4)PPs removal in NER proficient cells may account for its small impact on the deleterious consequences of UV irradiation. This leads to the assumption that skin photosensitivity in most of the xeroderma pigmentosum (XP) patients, unable to remove these lesions, is not only a quantitative aspect, but may also depend on the rate of damage removal of each kind of lesion in skin cells. This assumption, however, needs further experimentation with photolyase transgenic NER-deficient *in vivo* models, in order to ascertain the relative importance of each UV-photoproduct in sunlight induced skin tumors in XP patients.

4. Replication and transcription blockage are triggers of UVC-induced apoptosis

So far we have focused on how UV light generates DNA lesions and how important each of these lesions is for the induction of apoptosis. But an even more intriguing point is how these DNA lesions trigger the apoptotic response, a phenomenon carried out mainly outside the cell nucleus [46]. In the last few years it became clear that the induction of apoptosis by UV light is avoided if DNA lesions are quickly photorepaired from the genome, i.e., up to 8 h after irradiation in HeLa cells [39] and in NER-deficient XP cells [45]. After this time point, the removal of photoproducts is no longer efficient in protecting cells from apoptosis; in other words, cells become committed to cell death. These data lead to two important conclusions: (i) the presence of photoproducts is the initial signal for apoptosis and (ii) these lesions are recognized and somehow processed by cellular enzymatic systems, to only then generate the cytotoxic effect. Since replication and transcription machineries are largely disturbed by UV photoproducts, major attention has been given to disturbances of these processes as a starter of the apoptotic response after UV-induced DNA damage.

The hypothesis that UV-induced apoptosis depends on a blockage of transcription due to unrepaired DNA lesions rests on a large amount of data. Initial experiments with cell lines impaired in different proteins of NER showed that CSB mutant cell lines, which are deficient in TCR, are provoked to undergo apoptosis at much lower doses of UVC than cells deficient in XPC, characterized by impaired GGR but proficient in TCR [47]. Moreover, recovery from RNApol II arrest by photorepair causes prevention of apoptosis in CHO cells, which correlates well with the fact that the deleterious effects of UVC light are related to transcription impairment [38]. These findings have been extended with the use of mouse models with specific genetic defects in GGR or TCR, where it was shown that TCR is the dominant trait in the protection against UVB irradiation in mouse cells [48]. Since transcription occurs during all phases of the cell cycle, except for mitosis, the scanning for lesions by the transcription machinery is permanent. Thus, it is reasonable to conclude that protection against the deleterious effects of UV-light may occur on two fronts: by repairing the damage by TCR, or if TCR is unable to deal with the amount of lesions present in DNA, by signaling apoptosis.

Nonetheless, transcription occurs only in a small portion of the entire genome. If the transcription machinery were to be the only mechanism responsible for lesion-recognition, a large region of the genome would be unprotected against the presence of lesions, increasing the chance for chromosomal mutations during the following DNA replication cycle. Therefore, GGR is also of utmost importance for avoiding replication blockage and resulting mutations, and defects in GGR are likely to cause elimination of damaged cells by apoptosis. Consistent with a role of DNA replication signaling for cell death, it was shown that UV-induced apoptosis is dependent on S phase progression [49,50]. Likewise, confluent primary DNA repair deficient fibroblasts are more resistant to apoptosis induction by UVC light [51,52]. Moreover, although primary CS-deficient cells (TCR defective) enter into apoptosis at lower UV doses, they also present higher resistance to UV irradiation when in confluence, even though RNA transcription blockage is not restored under these conditions [53]. Since confluent cells are quiescent, not replicating their genome, these data point to DNA replication blockage by DNA damage as also being an important player for triggering cell death. In fact, working with CHO cells proficient in NER or mutated in the XPB gene, it was shown that inhibition of replication by low concentrations of aphidicolin, a drug that inhibits the progression of the replication forks, prevents UV-induced apoptosis, even in a DNA repair deficient background [54]. This suggests that protection conferred by replication inhibition is not only a passive process that simply allows more time for the DNA repair machinery to act, but somehow protects the cell against apoptosis induction, even if the lesions are not removed. An explanation of this protection was proposed by Dunkern and Kaina [50]. They observed that after UVC irradiation of cells, DNA double-strand breaks (DSBs) are formed, arising from replication of damaged DNA. In cells where replication was inhibited, a significantly smaller amount of DSBs was formed, which coincided with a lower frequency of UV-induced cell death. It is reasonable to hypothesize that initial photoproducts are converted, during DNA replication, into DSBs, due to a complex, not well-defined process called "collapse of replication forks" [55]. In fact, the generation of DSBs in UV-irradiated cells, specifically in replicating DNA, has been known for a long time [56]. We obtained similar data, shown in Fig. 2, with SV40 transformed human cell

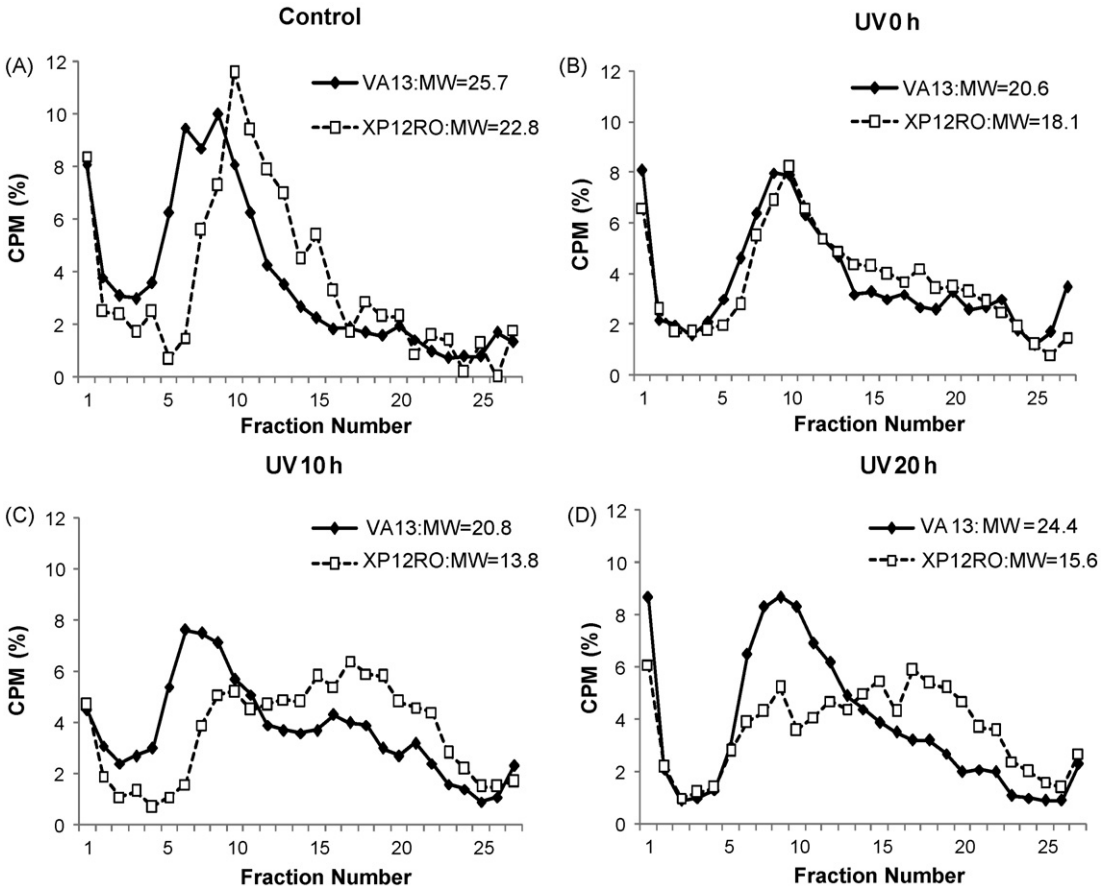

Fig. 2. Double-strand breaks in replicating DNA of UV-irradiated DNA-repair proficient and deficient cells. Cells were UV-irradiated (0 J/m^2, A, or 12.5 J/m^2, B–D) and pulse-labeled with ^{3}H-thymidine (50 μCi/mL, for 45 min) immediately (A and B), 10 h (C) or 20 h (D) after irradiation. Cells were then harvested, and DNA was extracted and analyzed in neutral sucrose gradients, as previously described [53]. Sedimentation is from right to left. VA13 and XP12RO are SV40 transformed human cell lines normal or deficient for DNA repair (mutated in the *xpa* gene), respectively. MW values correspond to the molecular weight of DNA $\times 10^{-6}$. Note that for XP-A cells DNA is smaller when labeled several hours after UV irradiation, due to DSBs specifically in replicating DNA. The figure represents original unpublished data.

lines, by checking DNA size in neutral sucrose gradients [57]. Basically, these breaks are observed when replicating DNA is labeled with radioactive precursors after UV irradiation, and NER-deficient cells have increased number of DSBs, when compared to NER proficient cells. Very few DSBs are observed in the control DNA, probably because only a small fraction of the DNA is replicating, which also discards the possibility that these breaks are related to internucleosomal DNA cleavage caused by apoptosis itself. These results are consistent with the notion that DSBs are produced during the replication of unrepaired UV-induced DNA lesions, and that these lesions may trigger apoptosis. Clearly further experiments have to be done to confirm this, but the fact that DSBs are extremely strong apoptotic (but not necrosis-inducing) lesions, as shown by electroporation of restriction enzymes in living cells [58], is a good indication of the feasibility of this hypothesis. In addition, the fact that DSBs are able to block the activity of topoisomerases during S phase progression in mammalian cells adds further support to this theory, since this is a well-described apoptosis-inducing factor after induction of different sort of DNA damages [59–62].

When taken all together, the available data suggest that apoptosis induction by UVC light is related to both inhibition of transcription and replication of DNA. How can these different hypotheses be consolidated? On trying to find an answer to this intriguing question, Ljungman and Lane [63] proposed the "collision hypothesis", claiming that the normal level of collisions observed between RNA and DNA polymerases [64] would be largely increased by DNA damage that blocks the elongation of RNA polymerases during the S phase. Although this hypothesis has the merit of bringing together the two potential processing of DNA damage as necessary for cell death signaling, it still requires direct experimentation to be confirmed.

5. Role of UV light generated reactive oxygen species in apoptosis

UVA irradiation is poorly absorbed by DNA, but causes the formation of ROS. Therefore, the genotoxic effects of UVA have been mainly attributed to the induction of oxidative stress. Strong emphasis is given to the generation of 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-OxoG) [13,65], which is formed in large quantities as compared to other oxidative lesions. The formation of 8-OxoG can be explained in terms of the predominant production of $^1O_2$ upon UVA irradiation, since this excited molecule is known to induce mainly 8-OxoG [13]. This lesion is highly mutagenic and may also be cytotoxic [66], thus its rapid removal from the genome is fundamental for normal cell development (for a recent review on this subject see Ref. [67]). It has also been shown that 8-OxoG induced by different stimuli is able to induce apoptosis in mammalian cells [68,69]. However, it is unlikely that 8-OxoG is the predominant lesion leading to apoptosis in mammalian cells upon UVA irradiation, for the following reasons: firstly, studies performed with the recently developed HPLC–MS/MS method (liquid chromatography–tandem

mass spectrometry operating in electrospray ionization (ESI) detection mode) indicated that the predominant lesions induced by UVA irradiation are CPDs (for a comprehensive review on the challenges and advances in the measurement of DNA photodamage see Ref. [11]). The formation of CPDs was shown to be higher than the amount of oxidative DNA lesions in cultured cells [14,34,70] and also in whole skin samples [10]. Secondly, in contrast to CPDs and (6-4)PPs, 8-OxoG is not a strong replication and transcription-blocking lesion, only slowing down the progression of the polymerases [71–73]. Therefore, its potency to trigger apoptosis is likely to be very low, whereas in UVA, UVB and UVC irradiated cells, CPDs and (6-4)PPs are most likely the main lesions responsible for apoptosis induction. This hypothesis also needs further verification, and experiments with UVA and heterologous photolyase-expressing cells can potentially provide definite answers to the role of these lesions in UVA induced apoptosis. Other potential toxic DNA lesions may occur by lipid peroxidation of cell membrane components by ROS induced by UVA light. The major end-products of lipid peroxidation are malondialdehyde (MDA) and 4-hydroxynonenal (HNE), which may react with DNA, generating adducts [74]. Although the real consequences of such adducts needs further investigation, they certainly may lead to mutagenesis, carcinogenesis and even to cell death [75].

UVA can also induce apoptosis independent of DNA damage, through the generation of singlet oxygen, H_2O_2, superoxide and hydroxyl free radicals [48,76]. These interact and can cause damage to cellular proteins, lipids and saccharides [12]. ROS-induced lipid-damage causes changes in the structure of the outer cell membrane [77–79]. It also damages the inner mitochondrial membrane, which results in a loss of membrane potential and subsequent release of cytochrome *c* into the cytoplasm [80], a pivotal event of the intrinsic apoptotic pathway [81,82]. On the basis of these insights, efforts are being made in order to investigate the potential of new compounds with radical scavenger activity to reduce the toxic effects of UVA irradiation [6,83–86]. Interestingly, UVA irradiation itself has been shown to reduce the apoptotic effects of UVB radiation in hairless mouse skin [87]. These authors used a series of UV sources that provided a constant UVB dose, while increasing the UVA fluency. Apoptosis was markedly reduced with higher amounts of UVA, indicating that UVA is able to induce protective functions. A gene induced by oxidative stress is heme oxygenase 1 (HO1) and, in fact, the protection observed correlated with the induction of HO1 by UVA [87–89].

For UVB, ROS may also play a role in triggering apoptosis. Apoptosis of HeLa cells was shown to be dependent on ROS formation, although to a small extent [90,91]. In these studies, HeLa cells that were UVB irradiated in the presence of the radical scavenger pyrrolidene-dithiocarbamate (PDTC), presented a partial inhibition of apoptosis. The apoptotic response could be completely blocked, when, in addition to PDTC treatment, DNA repair capacity was enhanced by liposomal transfection of a CPD-photolyase gene. Furthermore, it was necessary to inhibit the FAS/CD95 death-receptor pathway since, as it will be discussed in the next item, this can be directly activated by UVB light.

6. DNA damage-independent apoptosis induced by UV light

The term "death receptors" is commonly used to describe members of the tumor necrosis factor (TNF) receptor super-family, which includes a variety of related molecules consisting of similar cysteine-rich extra-cellular domains and a homologous cytoplasmic sequence termed "death domain" [92]. Members of this family include the TNF receptor-1, TNF-α related apoptosis-inducing ligand (TRAIL) receptors, death receptors-3, 4 and 5 (DR-3, DR-4 and DR-5) and CD95 (FAS/APO-1). Upon binding of their natural ligands, these monomeric receptors trimerize, thus forming receptor clusters that are considered to be intracellular activated death domains [93]. Recruitment of Fas-associated protein (FADD) to this activated death domain, in turn, recruits and activates caspase-8/FLICE, which cleaves and activates caspase-3 and its downstream targets, thereby leading to cell death by apoptosis [81,94–96]. This pathway of apoptosis signaling is usually referred to as the "extrinsic pathway", since it is mediated trough the activation of external membrane receptors of the cell.

As demonstrated by Rosette and Karin [97], UVB is able to directly activate TNF receptor-1 by inducing receptor clustering without the need of the respective ligand. Several other reports indicated that this was also true for the CD95/FAS receptor, which was not only activated by UVB [90,98], but also by UVC light [99]. However, the direct activation of receptor clustering by UV radiation, independently of its ligand (Fas-L), does not seem to be relevant *in vivo*, since mice that are deficient in this ligand have decreased levels of apoptotic cells in the skin after chronic exposure to UV light [100]. Moreover, as outlined above, NER defective mutants are more sensitive and photolyase-expressing cells that photorepair CPDs and (6-4)PPs lesions are much more resistant to UV-induced apoptosis [45], stressing again the key role of DNA damage as a trigger of this type of cell death.

7. Cellular responses to UV-light induced DNA damage: the role of DNA damage-sensing by phosphoinositide 3-kinase-related kinases (PIKKs)

After the early signals provided by DNA damage processing, cellular response to genotoxic stress occurs, which involves a cascade of events. Microarray experiments revealed that UV irradiation induces significant changes in the expression of hundreds of genes, in a timely manner that can be divided into three waves of activation: early, intermediate and late [101]. The use of microarray technologies demonstrate the complexity of the transcriptional profile of the UV response, since they describe several cellular processes previously not known to be affected by UV irradiation. For instance, significant increases were seen in the expression of genes involved in basal transcription, splicing, and translation as well as in the proteasome-mediated degradation pathways after UVB irradiation in primary human keratinocytes [102]. Interestingly, the expression pattern after UV irradiation is also dependent on the DNA repair status of the cell, indicating that the efficiency of removal of UV photoproducts generates different cellular responses [103].

For the sake of clarity, the proteins behind the UV-induced damage response can be divided into (1) *sensors* that will detect DNA lesions, (2) *transducers* that will transmit the signal to effector structures, and (3) *effectors* that will finally execute cellular functions relating to cell-cycle progression and apoptosis [104]. At the top of this pathway are members from the PIKK family of proteins. Three of the PIKK proteins involved in the DNA damage response are DNA-PK (DNA-dependent protein kinase), ATM (Ataxia Telangiectasia Mutated) and ATR (ATM and Rad3 related) [105–107]. Interestingly, while ATM is recruited to DSBs by the Mre-Rad50-Nbs1 (MRN) complex [108], ATR is recruited to single-stranded DNA (ssDNA) regions that arise at stalled replication forks, or during the processing of bulky lesions such as CPDs and (6-4)PPs [109,110]. ATR is recruited to RPA-coated ssDNA regions via its interacting partner ATRIP (ATR-interacting protein) [111], and it has been shown that ATR binds to UV-damaged DNA with higher affinity than to undamaged DNA [112]. Therefore, ATM was considered to be relevant only for DSBs inducing agents, such as ionizing radiation (IR), and ATR mainly for UV-induced damage. However, recent reports indicated that not only ATM but also ATR can be activated

following IR [113,114], and that ATM can be phosphorylated by ATR upon UV treatment, which occurs independent of DSBs formation [115]. Furthermore, it was observed that UVA, unlike UVC, triggers ATM kinase activity, and that this activation is dependent on ROS production in the cells [116].

One of the most important targets of ATR following DNA damage is p53 [117–119]. Following activation by ATR-dependent phosphorylation, p53 regulates a myriad of proteins that control cell death by apoptosis [120]. Therefore, it is not surprising that ATR is involved in apoptosis induction in a p53 dependent manner [55,107]. Interestingly, DNA repair-deficient primary human fibroblast confluent cells were shown to have a strong and stabilization of p53 after UV irradiation, although apoptosis induction was very low [52]. In fact, it has been observed that p53 activation in DNA damaged quiescent cells is part of a RNA transcription-based stress response that includes a DNA damage sensor mechanism linked to ATR and RPA [117]. However, the resistance of confluent cells to UV irradiation indicates that in quiescent cells p53 activation is not related to apoptosis induction [52]. This result seems to be contrary to previous findings, that demonstrated that p53 accumulation in the cell nucleus after DNA damage [121,122] is usually associated with apoptosis induction [47,63]. Taken all together, these results are a clear indication that the participation of p53 in cell-decision of life-or-death after DNA damage is still a complex and largely unknown phenomenon, and this specific topic has been recently reviewed by different authors [123–125]. In addition, the participation of other proteins of the p53 family (p63 and p73) in this intricate process and the recent discovery of nine different isoforms of p53, add a further hurdle in the understanding of how this key protein determines cell-fate [126,127].

8. Cellular responses to UV-light induced DNA damage: the role of signal transduction by mitogen-activated protein kinases (MAPKs)

UV irradiation triggers the activation of signaling pathways that, collectively, are termed MAPK pathway [128]. MAPKs are involved in regulating cell proliferation, differentiation, cancer formation and cell death by apoptosis [129]. Activation of MAPKs is mediated by a sequential protein phosphorylation module. First, serine/threonine MAP kinase kinase kinases (MAPKKKs) will phosphorylate serines in the activation loop of MAP kinase kinases (MAPKKs), which will in turn phosphorylate threonine-X-tyrosine motifs within the activation loop of MAPKs [130,131]. The classic MAPK family consists of three sub-families: extra-cellular signal-regulated kinase (ERK; ERK1 and ERK2), c-Jun N-terminal kinase (JNK; JNK1, JNK2, and JNK3), and p38-MAP kinase (α, β, δ and γ) [132]. While ERKs are usually activated by mitogenic stimuli, JNK and p38 MAPKs are activated by environmental stresses, such as UV irradiation (for a recent review on this subject see Ref. [133]). They are, therefore, collectively termed SAPK (stress activated protein kinases). A central question that still needs to be answered is whether the activation of these stress kinases is DNA damage dependent or independent. Current evidence supports both views, since it has been proposed that the immediate early response is due to receptor activation whereas the late response is due to DNA damage [97,134–138].

Pharmacological inhibition of JNK and/or p38 MAPK has been demonstrated to result in marked attenuation of apoptosis in UV irradiated cells [139–142]. It has been proposed that the proapoptotic role of JNK after UV irradiation is independent of c-Jun mediated transcription, since it was not affected by the protein synthesis inhibitor actinomycin-D [142]. On the other hand, MEFs isolated from knockout mutant mice deficient in c-Jun were resistant to UV-induced cell death, indicating that c-Jun is required for UV killing [143]. However, it is important to note that primary c-Jun knockout MEFs hardly proliferate (BK, unpublished data) which points to the role that proliferation plays in the conversion of UV-induced DNA damage into apoptosis-triggering secondary lesions. Another reason for the proapoptotic function ascribed to JNK lies in its role in the intrinsic apoptotic pathway [144]. It has been reported that the release of cytochrome *c* from mitochondria after UV irradiation is dependent on JNK activation [142]. To further support the role of JNK in the regulation of the intrinsic apoptotic pathway, it was recently shown that the pro-apoptotic proteins Bax/Bak are targets of the JNK-induced apoptotic signaling pathway [145,146]. Also, anti-apoptotic proteins belonging to the intrinsic apoptotic pathway have been shown to be phosphorylated and inhibited by JNK [147].

Additionally, an important point to be mentioned is that Fas-L is transcriptionally regulated by the Activator Protein-1 (AP-1) [148,149], a homo- or heterodimeric transcription factor composed of proteins of the Jun, Fos and ATF family [150]. Recently, it was shown that inhibition of JKN attenuated Fas-L induction upon UVC irradiation in cells that do not express c-Fos, indicating that c-Jun/ATF2 is majorly involved in Fas-L regulation [151]. Therefore, the induction of SAPK by UVC is likely to up-regulate Fas-L. It is conceivable that this, together with the up-regulation of the FAS receptor induced by p53 [152,153], provides a powerful signal for triggering the receptor driven apoptotic pathway.

The findings noted above seem to be contrary to the observation that c-fos knockout cells are hypersensitive to UVC [154] showing a high frequency of apoptosis [155]. Obviously, heterodimeric AP-1 containing c-Fos (e.g. Fos/Jun and Fos/ATF complexes) are not essential for stimulation of apoptosis, but rather protect against it. How can this apparent contradiction be reconciled? The answer was recently provided in studies on DNA repair in *c-fos* knockout cells. It was shown that these cells are impaired in CPD removal due to a defect in the resynthesis of *xpf* and *xpg* [156]. The authors found that both genes are transcriptionally down-regulated in response to UVC. Whereas transcriptional recovery occurred in wild-type, it did not occur in c-Fos deficient cells. Therefore, it was inferred that c-Fos (AP-1) is essential for abolition of the block of transcription of the genes encoding xpf and xpg, which enables NER to continue, removing toxic lesions and, therefore, preventing apoptosis. This data provided evidence that the immediate-early MAPK induction protects against apoptosis by stimulation of DNA repair upon UVC exposure [156].

Also, it is possible to draw a correlation between the specific transcription inhibition of DNA-damage response genes and apoptosis induction. For instance, UVC blocks the transcription of MAP kinase phosphatase 1 (MKP1), which dephosphorylates the EGF receptor (for review see Roos and Kaina [55]). This in turn leads to maintenance of EGF receptor phosphorylation and downstream to sustained JNK activation, which triggers proapoptotic pathways such as the Fas-L. This was shown to be true for cisplatin [157,158] and it is conceivable that at least in repair deficient cells UV light triggers the same response, for which evidence was recently provided [151]. Transcriptional inhibition may also stabilize p53 [117] and, therefore, the p53 driven apoptotic pathway involving up-regulation of the FAS receptor, PUMA, Bax and Bak could also be involved [118,159], amplifying the apoptotic signal evoked by SAPK activation.

9. DNA damage cell death and autophagy

Autophagy is an evolutionary conserved catabolic program for lysosomal degradation of proteins and other subcellular constituents [160]. The process plays a fundamental role in house-

keeping and tissue homeostasis, as it promotes protein turnover and removes damaged proteins and organelles as well as superfluous portions of the cytoplasm [161]. In most circumstances autophagy acts as a prosurvival mechanism, adapting cells to stress conditions by providing metabolic precursors for cellular renewal and maintenance, through the recycling of cellular components [162]. On the other hand, the constitutive activation of autophagy in response to stress can lead to cellular death. Therefore, it has been proposed that programmed cell death can result not only from apoptosis, but also from autophagy [163]. In fact, autophagy has already been implicated as a mechanism of cell death after a variety of different stimuli such as irradiation [164], TNF-α treatment [165], viruses [166] and low potassium conditions [167]. However, the role of autophagy as a mechanism of cell survival or death is still controversial. It has been proposed that the cellular genetic background may determine whether autophagy exerts a pro- or anti-apoptotic effect in response to genomic stress [168]. Furthermore, the type of stress also seems to play a role in this decision, since it was recently shown that even though autophagy sensitizes fibroblasts to apoptosis after FAS and TNF-α treatment, it protects from cell death after UV irradiation [169]. In addition, it has also been shown that deletion of the autophagic gene Beclin-1, while disrupting the autophagic response to nutrient deprivation, has no effect at all in the apoptotic response after UV irradiation in mouse cells [170].

Despite this controversial role of autophagy in cell survival or death, the extensive crosstalk between apoptosis and autophagy is well established. For instance, several pro-apoptotic signals induce

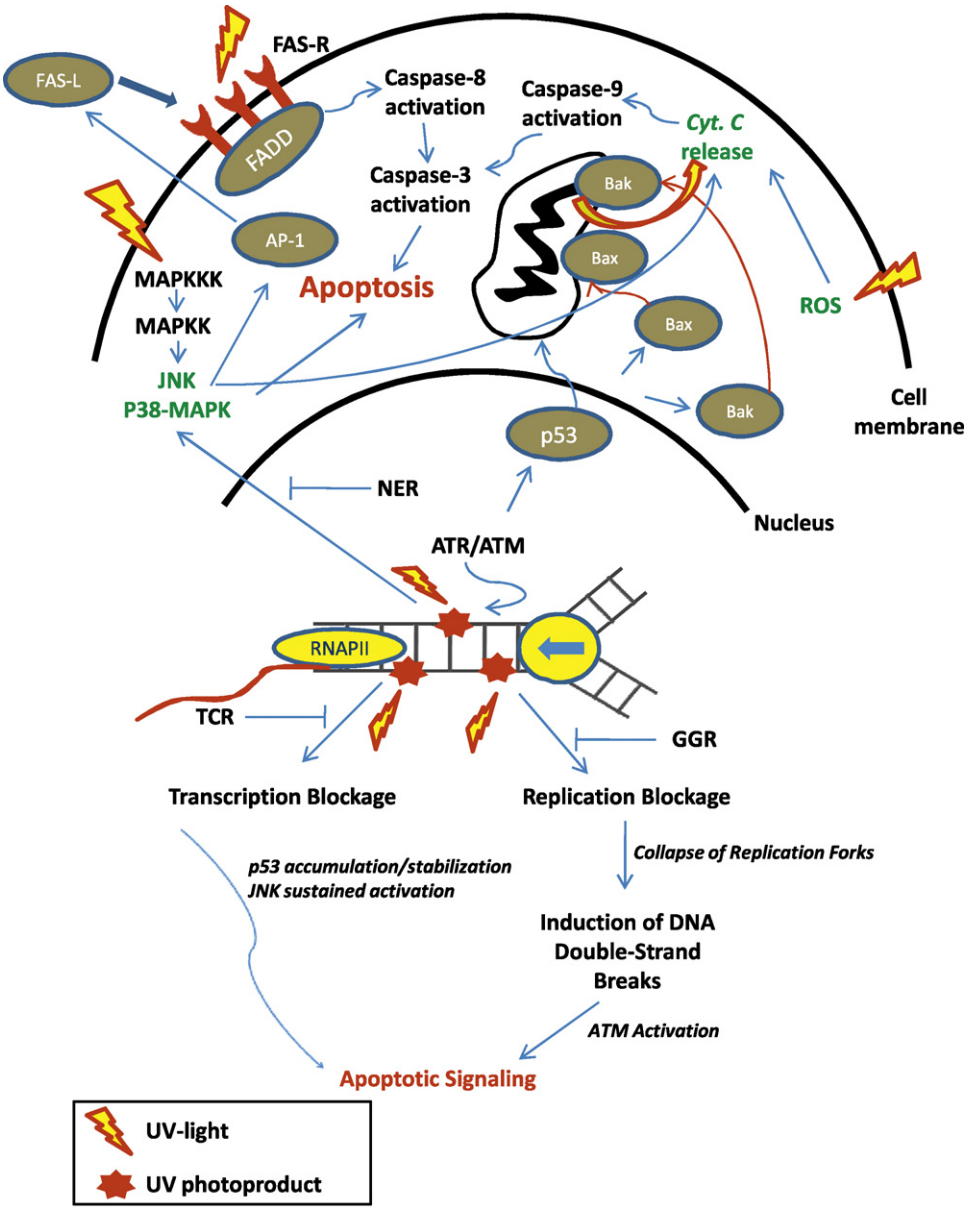

Fig. 3. Summary of the main cellular responses after UV irradiation. UV light targets several different molecules within the cell, leading to cell death by apoptosis. DNA is the main target of UV irradiation, culminating in the formation of photoproducts (CPDs and (6-4)PPs) that represent a blockage to replication and transcription machineries. Interference with DNA metabolism pathways has been shown to be a major factor contributing to UV-apoptosis induction, either through activation of key proteins such as p53, or through formation of DNA DSBs, that will ultimately lead to cell death. UV light (mainly UVA and UVB) is also able to directly activate membrane death receptors and MAPKs that may trigger apoptosis independently of DNA damage. Generation of ROS by UVA is also responsible for the toxic effects of UV irradiation in mammalian cells. Detailed explanations of this figure are depicted throughout the text.

autophagy [165,171] and the anti-apoptotic protein Bcl-2 has been shown to have also an anti-autophagic function [172]. However, it is clear that further experiments are needed to clarify the interrelationship between apoptosis and autophagy, notably upon UV-induced genotoxic stress, which will certainly be a point of high interest in future cell death research.

10. Concluding remarks and future directions

UV irradiation is a powerful and complete carcinogen. It is related to different types of skin cancer that collectively represent approximately 40% of all malignancies diagnosed every year, placing them as the most common tumors known [173]. Therefore it is paramount to elucidate the mechanisms behind cellular responses after UV irradiation. One of these responses is the induction of apoptosis. Our goal in this review was to summarize the knowledge that has been gathered in this field. Fig. 3 shows a model that depicts the main pathways leading to apoptosis after UV irradiation in mammalian cells.

Generation of UV-photoproducts is most likely to be the main reason behind cell killing after UV exposure. This is true not only for UVB and UVC, but also for UVA (as indicated by new lesion-detection methods). The individual contribution of the different DNA photoproducts and ROS to apoptosis is still a matter of controversy. Although different groups have shown that CPDs are the main trigger for apoptosis in NER-proficient cells (because 6-4PP lesions are quickly repaired), (6-4)PPs might play a major role in NER-deficient cells. ROS may also contribute to apoptosis induction, although to a small extent, especially after UVA irradiation. Therefore, considerable efforts are currently being made towards the discovery of new radical scavengers that could help to prevent the deleterious effects of solar radiation on the skin.

Moreover, the cellular signals leading to apoptosis following UV photoproduct formation is still a matter of debate. Despite the well-established role of these lesions as primary structures signaling to cell death, the actual processing of these structures that lead to the formation of toxic signals is still unclear. While some evidence points to transcription blockage as the main reason behind apoptosis induction after UV irradiation, other data indicate that the formation of DNA double-strand breaks during the replication of CPDs-containing DNA is necessary for commitment to cell death. Up to the present moment there is no experimental support for theories that try to reconcile these observations.

An exciting and rather enigmatic line of research is the role played by ATM and ATR in the response to UV-damage. While mounting evidence supports a role of ATR in protection against UV-induced apoptosis, the function of ATM is still a matter of debate. Also several open questions arise when studying the responses of JNK and p38 after UV irradiation. Here, an important question still lacks an answer supported by substantial experimental evidence: are these kinases activated depending or not on DNA damage? Although UV light is able to directly activate the death receptor pathway of apoptosis, most likely DNA damage is the main reason behind cell killing after UV exposure, independent of the wavelength employed. As so, it is important to realize that apoptosis induction after UV irradiation works as a protective mechanism against the presence of unrepaired DNA lesions in the genome. Alternatively, UV-induced DNA lesions, not removed by DNA repair mechanisms and not recognized by apoptosis-inducing proteins, are prone to induce mutations, therefore increasing the risk of cellular malfunction, and carcinogenesis in human beings.

Although we have gained deep insight into the processes regulating UV-induced apoptosis, further knowledge of the molecular mechanisms that regulate this cellular response is required; it is in fact a *sine qua non* condition for the development of new strategies for the prevention and treatment of cancer.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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