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Photobiological Origins of the Field of Genomic Maintenance†

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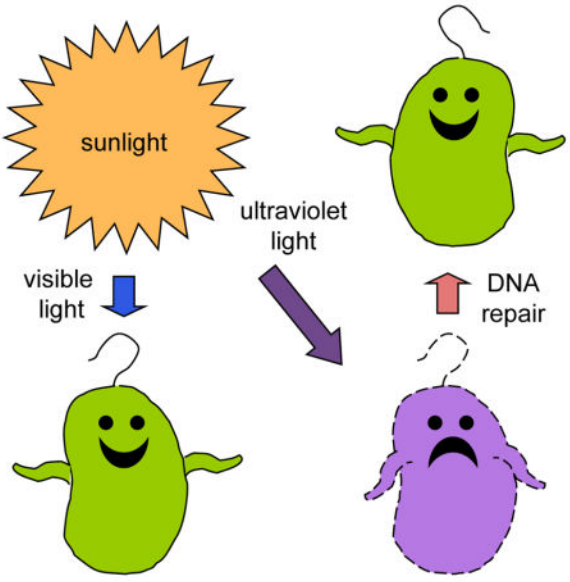
Abstract

Although sunlight is essential for life on earth, the ultraviolet (UV) wavelengths in its spectrum constitute a major threat to life. Various cellular responses have evolved to deal with the damage inflicted in DNA by UV, and the study of these responses in model systems has spawned the burgeoning field of DNA repair. Although we now know of many types of deleterious alterations in DNA, the approaches for studying them and the early mechanistic insights have come in large part from pioneering research on the processing of UV-induced bipyrimidine photoproducts in bacteria. It is also notable that UV was one of the first DNA damaging agents for which exposure was directly linked to cancer; the sun-sensitive syndrome, xeroderma pigmentosum, was the first example of a cancer-prone hereditary disease involving a defect in DNA repair. We provide a short history of advances in the broad field of genomic maintenance as they have emerged from research in photochemistry and photobiology.

Graphical Abstract



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INTRODUCTION

Photochemical processes were surely essential for the early evolution of life on earth, and probably for the actual origin of life as well. They enabled living systems to convert solar energy into chemical energy for purposes of metabolism and growth; indeed, the sun is still the principal source of energy for the biosphere. However, the effects of absorbed UV photons in biological molecules are often more destructive than useful. Very early in evolution, organisms must have evolved in ways to afford protection from UV and for dealing with its damaging effects.

PHOTOCHEMICAL ORIGIN OF LIFE?

The primordial earth was continuously bombarded by a high flux of UV photons, not attenuated by an ozone layer (Figure 1), so it is likely that sunlight photochemistry played some important roles in the origin of life, while paradoxically, it was also one of the main threats to the persistence of early life forms.

The popular “RNA world” hypothesis for early life is based upon two postulates: first, that RNA could fulfill all of the necessary attributes of life, including informational, structural and catalytic functions; and second, that DNA eventually entered the scene and somehow took over from RNA as the principal repository of the genetic blueprint for all living cells. A fundamental problem with this model is that the backbone instability in RNA is such that it might be difficult to maintain the lengths necessary for sufficient information storage. It is also likely that the monomers available in the primordial “stew’ for assembly of informational nucleic acids would have included both ribonucleotides and 2′-deoxyribonucleotides; so both types of monomers may have combined more or less randomly into early nucleic acids, benefitting from the DNA type for backbone stability and the RNA type for purine persistence, since purines are spontaneously lost from DNA, leaving non-instructional abasic sites. Of course, both RNA and DNA suffer spontaneous cytosine deamination, which also reduces information content, but evolving systems must have been able to survive in spite of that instability until there were mechanisms to restore the altered sites to cytosine (1).

Recent studies have implicated UV and hydrogen sulfide in key reactions in which precursors of ribonucleotides, amino acids, and lipids can all be derived from the reductive homologation of hydrogen cyanide and some of its derivatives (2). It has also been shown that ribose can be converted to 2′-deoxyribose and that a derivative of uracil can be reduced to thymine through UV photoredox chemistry (3). One of the next challenges in this “primordial soup that cooks itself” (4) would have been the polymerization of nucleotides into sets of short polymers (oligomers) with different sequences. This would have eventually yielded a large variety of oligomers; the hybridization of these to form double-stranded molecules with overlapping 3′ and 5′ ends could then have facilitated their further aggregation into much longer polynucleotides. The oligomers might have been covalently linked by UV-induced cyclobutane pyrimidine dimers (CPDs) at their abutting ends, as documented in a proof-of-principle experiment (5). Once a suitable collection of large polynucleotides became available, the “final” challenge would have been to couple them to

some evolutionary processes for maintenance and replication of the most “useful” ones. Meanwhile, the accumulation of RNA species as ribozymes might have included molecules that could catalyze polynucleotide chain elongation and replication. Some simple polypeptides might also have provided important enzymatic functions. Then, all that would be needed would be for this stew to “cook” for a few billion years until something emerged that could grow and duplicate itself. Because thymine dimers can pair to some extent with two adenines in a complementary nucleic acid strand, the presence of these photoproducts in nucleic acids should not have posed a serious issue for a rudimentary level of fidelity in a relatively basic replication process. It is not our purpose to speculate further about life’s origins, but rather to move on to consider the maintenance of evolved life forms once they have emerged.

EARLY STUDIES OF INACTIVATION AND RECOVERY FROM UV EXPOSURES

Most of our early understanding of DNA damage and repair phenomena was based upon analyses of the responses of bacteria to UV irradiation. Downes and Blunt (6) reported in 1877 that bacteria were inactivated by light. Fifty years later, Gates (7) showed that the relative effectiveness of killing bacteria by different wavelengths paralleled the absorption spectrum of nucleic acid, as early evidence from action spectra that RNA and/or DNA might be the targets for lethality. A hint that “repair” of UV induced damage might occur appears in a brief report by Hollaender and Curtis (8), who accounted for the eventual growth resumption of UV-irradiated *Escherichia coli* by cautiously suggesting that “the possibility of recovery of the irradiated bacteria is not entirely excluded.” This observation was followed by the finding that higher survival levels of UV-irradiated fungal spores could be obtained if they were held in liquid medium for a period before plating on nutrient agar (9). Action spectra also implicated nucleic acids in UV-induced mutagenesis (10; 11). Roughly a decade later, there was a series of significant discoveries, including the phenomenon of photoreactivation of UV-irradiated bacteria and bacteriophage (12; 13), the revelation that the shapes of survival curves could be altered by varying the treatment of UV-irradiated bacteria *after* the irradiation (that challenged the classical “target theory” for the deleterious effects of UV photons) (14), and the enhanced survival of UV-irradiated bacteriophage if the host cells were also irradiated (an early example of what is now known as the SOS response) (15). In addition, the isolation of bacterial mutants with altered sensitivity to UV by Evelyn Witkin, Ruth Hill and Paul Howard-Flanders provided genetic evidence for recovery mechanisms (e.g., (16–20)).

In the 1950s, a number of researchers began to focus on the effects of UV on macromolecular synthesis in bacteria. Kelner (21) and Kanazir and Errera (22) reported that DNA synthesis was inhibited in UV irradiated *E. coli*. Iverson and Giese (23) followed DNA synthesis over a period of 8 hr after UV irradiation of *E. coli*, using the indole method of Dische for quantitation, and found that DNA synthesis resumed roughly in parallel with the resumption of cell division. Hanawalt and Setlow (24), using radioactive labeling, showed that monochromatic 265 nm UV inhibited DNA synthesis for a period roughly proportional to the dose and concluded that “it is evident that recovery mechanisms can

eventually restore the DNA synthesis rate to nearly that of the unirradiated control except after very high doses." Photoreactivating light had the effect of reducing the length of the lag in the recovery of DNA synthesis, and it also enhanced recovery of RNA synthesis following UV irradiation, as though inhibitors were being destroyed or blockages were being removed (25).

THE DISCOVERY THAT UV GENERATES CYCLOBUTANE THYMINE DIMERS

The landmark discovery that thymines could be dimerized by UV exposure ((26); reviewed in (27)) facilitated the next fundamental advances in our understanding of recovery from DNA damage. Studies of *Hemophilus influenza* transforming DNA showed that thymine dimers produced in DNA irradiated with UV *in vitro* caused biological damage and could be removed by photoreactivation (28; 29). Bollum and Setlow (30) found that thymine dimers interfered with synthesis by DNA polymerase *in vitro*. Now there was a specific chemical lesion, the CPD (31), produced by UV in DNA that needed to be processed to avoid mutagenesis and to promote the survival of UV irradiated organisms.

It was soon reported that photoreactivation requires an enzyme that can bind to thymine dimers in the dark and then split them *in situ* upon exposure to visible light, without breaking the phosphodiester backbone (32). The earliest form of a photoreactivating entity could have been a tripeptide of lysine-tryptophan-lysine, which has been shown to reverse dimers at low efficiency upon irradiation with visible light (33). Subsequently, the elongation of the polypeptide and the addition of a blue-light "antenna" may have led to the amazing sensitivity and specificity of current-day photoreactivating enzymes (reviewed in (34)).

In the early studies of UV irradiated bacteria (e.g., (35)), the CPD content of DNA was typically assayed by hydrolyzing DNA with a strong acid and then analyzing the hydrolysis products by chromatography. Subsequently, enzymes that specifically recognize dimers in DNA were identified (36–39). These enzymes were originally thought to be endonucleases, but later studies revealed that they were glycosylases with associated AP lyase activities (40; 41). The enzyme purified from *E. coli* infected with the bacteriophage T4 proved especially useful. This enzyme, called T4 endonuclease V (TEV) or T4 pyrimidine DNA glycosylase (T4 PDG) is a small, relatively stable enzyme that does not require a Mg^{++} cofactor. The purified enzyme specifically nicks a DNA strand at the site of a CPD in duplex DNA. This meant that a variety of assays could be developed based upon measuring the length (size) of the DNA strand before and after exposure to the enzyme, or by assessing the relative amount of DNA resistant to the enzyme. In the case of plasmids, a single nick converts superhelical molecules to open circles, which can be separated from the superhelical molecules by agarose gel electrophoresis. In the case of linear molecules, the nicked DNA can be separated from the unnicked DNA by centrifugation in alkaline sucrose gradients or by electrophoresis in alkaline gels (42–44). The sensitivity of this kind of assay depends upon the size of the DNA being analyzed; the larger the DNA, the lower the UV dose that can be used to produce detectable levels of CPDs. In some cases, a dose as low as 2 J/m^2 can be studied (42; 45). By employing appropriate probes for specific genomic regions, repair in

those regions (including transcriptionally active genes and inactive regions) can be studied, even in the individual DNA strands (44; 46)). The development of these techniques led to the discovery of transcription coupled repair (TCR) and its distinguishing features in comparison to global genome repair (GGR) as discussed below.

THE DISCOVERY OF NUCLEOTIDE EXCISION-REPAIR (NER)

In addition to photoreactivation, another type of repair, which did not require light, was identified in *E. coli* in 1963-'64. This dark recovery mode was absent in the UV sensitive *E. coli* B_{S-1}, in which DNA synthesis did not recover following irradiation (47). The selective release of CPD-containing fragments from the DNA in UV resistant strains but not in UV sensitive derivatives prompted the suggestion of an excision-repair mechanism for removing these lesions (35; 48). Density labeling the replicating DNA with 5-bromouracil in UV irradiated bacteria provided evidence for the patching step in the postulated repair pathway (a non-conservative mode of synthesis in which the nascent DNA patches are much shorter than the DNA fragments containing them) (49; 50). The essential last step in nucleotide excision repair (NER) required joining the repair patch to the contiguous parental DNA strand. The needed enzyme, polynucleotide ligase, was discovered several years later (51). Subsequently, it was shown that excision deficient mutants of *E. coli* did not carry out repair replication (52).

The isolation and study of mutants of *E. coli* K-12 led to the identification and characterization of the different biochemical steps in NER and the proteins involved (20; 53); reviewed in (54). The NER pathway in *E. coli* is illustrated in Figure 2, in which it is shown that only six proteins are required for global genomic repair (GGR). It is noteworthy that each step in this excision-repair pathway creates another lesion until the final ligation step has been completed. The subpathway of transcription-coupled repair (TCR) is targeted to the transcribed strands of expressed genes and is initiated by the blockage of RNA polymerase translocation at the sites of the lesions. In bacteria, all the proteins involved in GGR also participate in TCR; however, in eukaryotes, the XPC protein is needed for the initiation of GGR, but it does not participate in TCR. The number of proteins and protein complexes involved in NER in eukaryotes is much larger than that in prokaryotes and includes those involved in dealing with the chromatin structures (for reviews see (55–58).

Several years after the identification of CPDs in DNA, another UV induced dipyrimidine lesion was discovered, the helix distorting 6-4 pyrimidine-pyrimidone photoproduct (6-4 PP) (59). It is produced in DNA with a lower quantum efficiency than that for the CPD, and it is more easily recognized by NER in bacteria and mammalian cells (60–62). Although this lesion is not recognized by T4 PDG, sensitive assays using the *E. coli* UvrABC incision complex or antibodies have been developed to detect it (63–65). The 6-4PP is rapidly converted to the Dewar valence isomer upon further UV irradiation and it can be sensitively assayed by high-performance liquid chromatography-electrospray ionization tandem mass spectrometry to study its repair rate, as well as that of the other bipyrimidine photoproducts (66). Yet another unique type of dipyrimidine photoproduct is generated in UV irradiated bacterial spores (67, 68).

MOST PATIENTS WITH XERODERMA PIGMENTOSUM ARE DEFICIENT IN NER

Simultaneous with the studies reporting NER in bacteria, evidence for the patching step in the NER pathway was identified in UV irradiated mammalian cells as “unscheduled DNA synthesis” (UDS) in non-S-phase human cells. This phenomenon was detected by autoradiography (69) and then validated as repair replication by carrying out DNA density labeling analyses in parallel with UDS determinations (70). James Cleaver, a post-doctoral fellow in Robert Painter’s laboratory, happened to read a feature story by David Perlman in the San Francisco Chronicle, describing a rare human hereditary disease, xeroderma pigmentosum (XP), in which the victims are sun-sensitive and suffer high levels of cancer in their sun exposed skin. Suspecting that the etiology might involve a defect in DNA repair, Cleaver studied epidermal cells from an XP patient and discovered that they were extremely sensitive to UV and deficient in repair replication (71). This was the first example of a human disease caused by a defect in DNA repair, and it stimulated studies in many laboratories to elucidate the details of the mammalian DNA repair pathways. Setlow et al. (72) confirmed Cleaver’s discovery by showing that an XP cell line cannot carry out the first nicking step in NER. Another form of XP, called the “variant”, turned out to be due to a deficiency in a translesion DNA polymerase, Pol eta, which may have evolved for the specific purpose of bypassing CPDs, since its fidelity is much higher when it copies dimerized thymines than when it replicates through adjacent thymines in undamaged DNA (73–75).

THE DISCOVERY OF POST-REPLICATION REPAIR (DAUGHTER STRAND GAP REPAIR) AND INDUCIBLE RESPONSES TO UV IRRADIATION

The isolation of recombination deficient *E. coli* K-12 mutants (76), which were sensitive to UV, led to the identification of another mechanism for mitigating the effects of UV. This mechanism has been referred to by several terms, including recombination repair, post-replication repair and daughter strand gap repair (77) (reviewed in (78)). Although this mechanism does not directly result in the removal of CPDs, it contributes to the survival of UV-irradiated bacteria and allows cells to tolerate persisting DNA damage. A similar mechanism has been described in the cells of other organisms, including *Drosophila*, mammalian cells, and yeast. Extensive analysis of the recombination deficient *recA* mutants of *E. coli* K-12 and the pleotropic RecA protein led to the characterization of a complex regulatory network originally called the LexA regulon and subsequently termed the SOS response. Although a variety of DNA damaging agents have been shown to elicit the SOS response, it was the study of UV irradiated bacteria and bacteriophage that initially revealed this network (reviewed in (79). One of the many interesting findings was the relationship of *recA* and *lexA* to NER. Originally, it was thought that daughter strand gap repair, dependent on *recA*, was separate from NER, which required the *uvr* genes. However, as the SOS hypothesis developed, it became clear that *recA* and *lexA* have important regulatory roles in NER. The RecA protein has both ATPase and co-protease activities. The co-protease activity facilitates the self-cleavage of several other proteins, including the lambda repressor and the LexA protein. The LexA protein represses the transcription of more than 40 genes in

E. coli (80; 81) by binding to a sequence in the promoter region known as the LexA or SOS box (reviewed in (82)). When RecA is activated by binding to single stranded DNA generated at blocked replication forks after UV irradiation, it forms a filament that facilitates the self-cleavage of LexA, which then dissociates from the DNA allowing transcription of the regulated genes to occur. The genes repressed by LexA include *uvrA* and *uvrB*, which code for two of the subunits of the NER incision complex. The induction of these two genes facilitates GGR of CPDs but has little effect on the repair of 6-4 PPs (83).

Another protein that is part of the SOS response and subject to self-cleavage facilitated by RecA is the UmuD protein. A dimer of UmuD is activated by cleavage to UmuD′ which associates with UmuC to form an error prone polymerase, UmuD′$_2$C (also known as polV). This polymerase is one of three polymerases in *E. coli* that can perform translesion synthesis (TLS); they are “error prone” and can insert nucleotides opposite lesions in DNA (reviewed in (84)). In some cases (especially opposite TT dimers) the inserted nucleotides are correct (e.g., AA), but in other cases they are not and result in mutations. In the case of polV, the active, mutagenic form of the complex (polV mut) contains RecA and ATP (UmuD′$_2$C-RecA-ATP) (85).

INDUCIBLE RESPONSES TO UV IRRADIATION IN MAMMALIAN CELLS

Following the characterization of the SOS response in *E.coli*, inducible responses to DNA damage in UV irradiated mammalian cells were identified. The UV stimulated activation of the p53 tumor suppressor in human fibroblasts was shown to have an effect remarkably similar to that of the SOS response in bacteria; it was required for the efficient GGR of CPDs but not the 6-4 PPs (86; 87). It was also established that the accumulation and activation of p53 in response to DNA damage can lead to apoptosis or arrest of the mammalian cell cycle, presumably to provide time for the repair of damage before the cell divides or initiates a new round of replication (for review see (88). Skin fibroblasts derived from tumors in patients with the cancer-prone Li-Fraumeni syndrome are homozygous for mutations in the p53 gene. These fibroblasts are defective in GGR of CPDs, compared to the related heterozygous mutants and normal cells (86), and this defect can be complemented by the expression of a stably integrated tetracycline-regulated p53 cDNA (87). The p53 effect is mediated in part through the activation of p48 (DDB2), an accessory lesion-recognition factor that is upregulated in UV-irradiated human cells in a p53 dependent manner (89; 90). Upon recognition of CPDs in DNA, DDB2 recruits the essential factor XPC to initiate NER (91). Rodent fibroblasts, typically deficient in the expression of DDB2, are also deficient in repair of CPDs (92; 93). However, it is important to appreciate that the efficiency of CPD repair in cultured cells may be much less than that in the intact epidermis (94).

EFFECTS OF CHROMATIN STRUCTURE ON DNA DAMAGE AND REPAIR

Interstrand crosslinking of DNA with photoactivated psoralens contributed importantly to the early analysis of chromatin structure (95; 96). Smerdon, Tlsty and Lieberman (97) found greater amounts of repair synthesis in nuclease sensitive than in nuclease resistant regions of chromatin in UV irradiated human cells, and the rearrangement of nucleosomes in mammalian chromatin was then demonstrated during UV-induced repair replication (98;

99). It was later shown that UV-induced 6-4 PPs were largely restricted to the inter-nucleosome regions, whereas CPDs were more uniformly distributed in chromatin ((100); reviewed in (101)). The studies of the repair of UV induced DNA photoproducts in chromatin stimulated broad interest in genomic heterogeneity in repair.

GENOMIC HETEROGENEITY IN REPAIR

Zolan et al. (102) showed that CPDs in the highly-repetitive alpha DNA 179 bp sequence were almost as accessible to repair as CPDs in the bulk DNA, while psoralen monoadducts and crosslinks were repaired much less efficiently in the alpha DNA than in the overall genome. This observation supported the view that different types of lesions are recognized with different efficiencies by the proteins involved in NER, an idea suggested by the difference in the rates of repair of the two UV photoproducts, CPDs and 6-4 PPs. The difference in the rate of repair of psoralen adducts in the alpha DNA and the rest of the genome also provided the first evidence for different rates of repair in different domains of the genome. Jonathan Mansbridge discovered that in XPC mutants, deficient in GGR, there were selected domains in which CPDs were being repaired (103). Bohr et al. (44; 104) extended this finding by showing that CPDs in a transcriptionally active gene in UV irradiated Chinese hamster ovary (CHO) cells were removed from DNA more rapidly than CPDs in adjacent silent regions of the genome. The same phenomenon was confirmed in human cells (105). In addition, repair was found to be more rapid in the transcribed strands of active genes than in the non-transcribed strands or in the genome overall in mammalian cells and in bacteria (46; 106). This observation led to the identification of the two branches of NER, GGR, which depends upon recognition of DNA damage by DDB2 and XPC, and TCR, which depends upon the recognition of damage by a translocating RNA polymerase blocked at a lesion. TCR was also demonstrated in yeast (107; 108). The documentation of strand specificity of TCR in bacteria eliminated the hypothesis that the preferential repair in active genes could be fully explained by chromatin structure. However, it has become clear that there is also a component of lesion accessibility due to features of chromatin structure in actively transcribed genomic domains.

In terminally differentiated human neurons, TCR is proficient, and GGR of CPDs is generally deficient except in an expressed gene (109). Originally termed differentiation associated repair, the definition of this mode of preferential repair was then broadened when it was documented in actively growing cells that otherwise displayed poor GGR (110; 111), and it is now termed transcription domain associated repair (DAR). Within an expressed gene, DAR operates upon both strands, while TCR is superimposed upon DAR in the template strand (110).

Complementation assays *in vitro* (112; 113) led to the reconstitution of mammalian GGR with purified proteins (114; 115). TCR has not yet been demonstrated in eukaryotic systems *in vitro*, although it has been reconstituted in *E. coli* (116; 117).

The locations of GGR and TCR of UV induced CPDs and 6-4 PPs have recently been mapped at single-nucleotide resolution throughout the entire human genome (118).

PHOTOSENSITIVE HUMAN GENETIC DISEASES AND CANCER SUSCEPTIBILITY

As described above, NER deficient cells from victims with xeroderma pigmentosum are strikingly sensitive to UV induction of cutaneous cancers. There are a number of other photosensitive human syndromes (119; 120). Several of these are characterized by defects in the TCR pathway and the patients do not develop any cancers upon sunlight exposure. (A caveat is that these are very rare diseases with relatively few patients to study.) They include Cockayne syndrome (CS), UV sensitive syndrome ($UV^{S}S$) and tricothiodystrophy (TTD). Whereas CS and TTD patients typically suffer severe developmental and neurological abnormalities, patients with $UV^{S}S$ only present with sunburn and freckles (for review see (121). Although cells from CS and $UV^{S}S$ have been shown to be equally deficient in TCR of very low levels of CPDs and 8-oxo-guanine (122), the CS cells exhibit sensitivity to reactive oxygen species, whereas $UV^{S}S$ cells respond like normal cells to reactive oxygen species (123; 124).

The UVA wavelengths have been shown in recent studies to generate CPDs but not 6-4PPs (66). Melanin is known to protect epidermal DNA from the UV induced generation of CPDs and other photoproducts, thereby reducing the frequency of the highly lethal cancer, melanoma. Most mutations in cells from melanoma have the signature of UV induced CPDs. Recent studies have shown that CPDs are generated in melanocytes many hours following exposure to UVA irradiation. This has been shown to be due to activation of melanin and energy transfer in the dark (125). This work provides new insights about the etiology of melanoma and raises concerns about effective protection from UV in the UVA range.

SUMMARY AND CONCLUSIONS

The study of the effects of UV on various organisms, including bacteria and humans, has been fundamental to our understanding of the biological mechanisms that ameliorate the effects of DNA damage and help to maintain genetic integrity. From the experimental point of view, UV is an extremely useful agent. Exposures can be accurately timed, and therefore the relationship between dose and lesion yield can be precisely determined. In addition, unlike some agents (e.g., ionizing radiation), UV produces a relatively restricted variety of lesions in DNA. The most frequent lesion, the CPD, is chemically stable, which has made it possible to obtain accurate estimates of the amounts present in irradiated DNA even following harsh treatments. The subsequent development of enzyme and antibody-based assays enhanced the sensitivity of detection so that the effects of very low UV doses could be studied.

The other frequent lesion produced by UV, the 6-4 photoproduct, is more easily recognized than the CPD by NER and provides an opportunity to investigate mechanisms for recognizing specific types of DNA damage with unique characteristics that differ from the canonical CPD.

Finally, from the biological perspective and relevance to human health, UV continues to be a very significant environmental threat. With the destruction of the ozone layer, a major increase in UV induced skin cancer can be anticipated.

Acknowledgments

We wish to dedicate this review to the memory of Jane Setlow and Dick Setlow, for their friendship and for their seminal contributions to UV photobiology and DNA repair. We also express our appreciation to many students and colleagues for their contributions to this field, and we apologize for the limited citations in this short article. We owe particular gratitude to Charles Allen Smith, whose ideas and generous mentoring are woven into most of the publications from our laboratory. Our research has been supported by grants from the National Institutes of Health, the American Cancer Society and the Department of Energy.

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Biographies

Philip Hanawalt is the Dr. Morris Herzstein Professor of Biology at Stanford University. He graduated from Oberlin College, completed his Ph.D. at Yale and joined Stanford faculty in 1961. He co-discovered excision-repair of damaged DNA in 1964 and transcription-coupled repair was discovered in his lab several decades later. He is a member of National Academy of Sciences and a Fellow of the American Academy of Arts and Sciences, American Academy of Microbiology and American Association for Advancement of Science, as well as a Foreign Associate of EMBO. He has research awards from the American Society for Photobiology, Environmental Mutagen Society, and an AACR-Princess Takamatsu Cancer Research Lectureship.

Ann Ganesan studied genetics with Joshua Lederberg and received an MSc in Genetics from the University of Wisconsin and a PhD from Stanford University. She spent 35 years as a Senior Research Scientist in the stimulating and convivial atmosphere of Phil Hanawalt's laboratory, where she developed a sensitive enzymatic assay for cyclobutane pyrimidine dimers in DNA, and employed this to study various aspects of DNA repair, including recombinational mechanisms and the dedicated pathway of transcription-coupled repair. She also served as an expert mentor to students and postdocs in Hanawalt's group, and taught them how to write understandable manuscripts for publication.

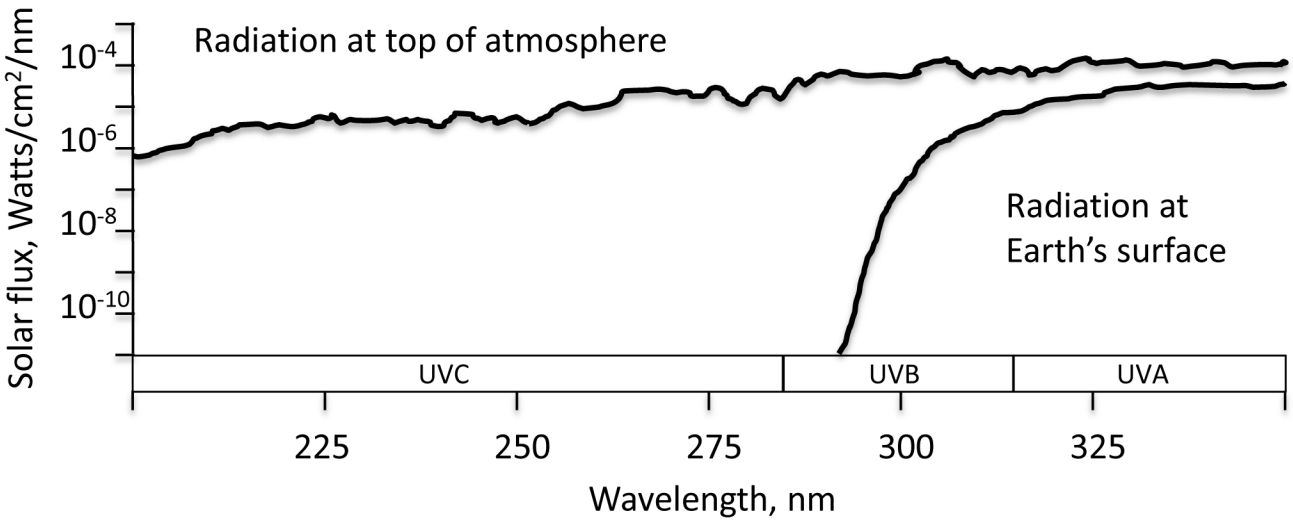

Figure 1.

Wavelength distribution of sunlight impacting earth's atmosphere and the selective attenuation of short UV wavelengths by ozone, molecular oxygen and water vapor. (Ranges: UVA, 315–400 nm; UVB 280–315 nm; UVC 100–280 nm). Adapted by Graciela Spivak from http://ozonewatch.gsfc.nasa.gov/facts/SH.html.

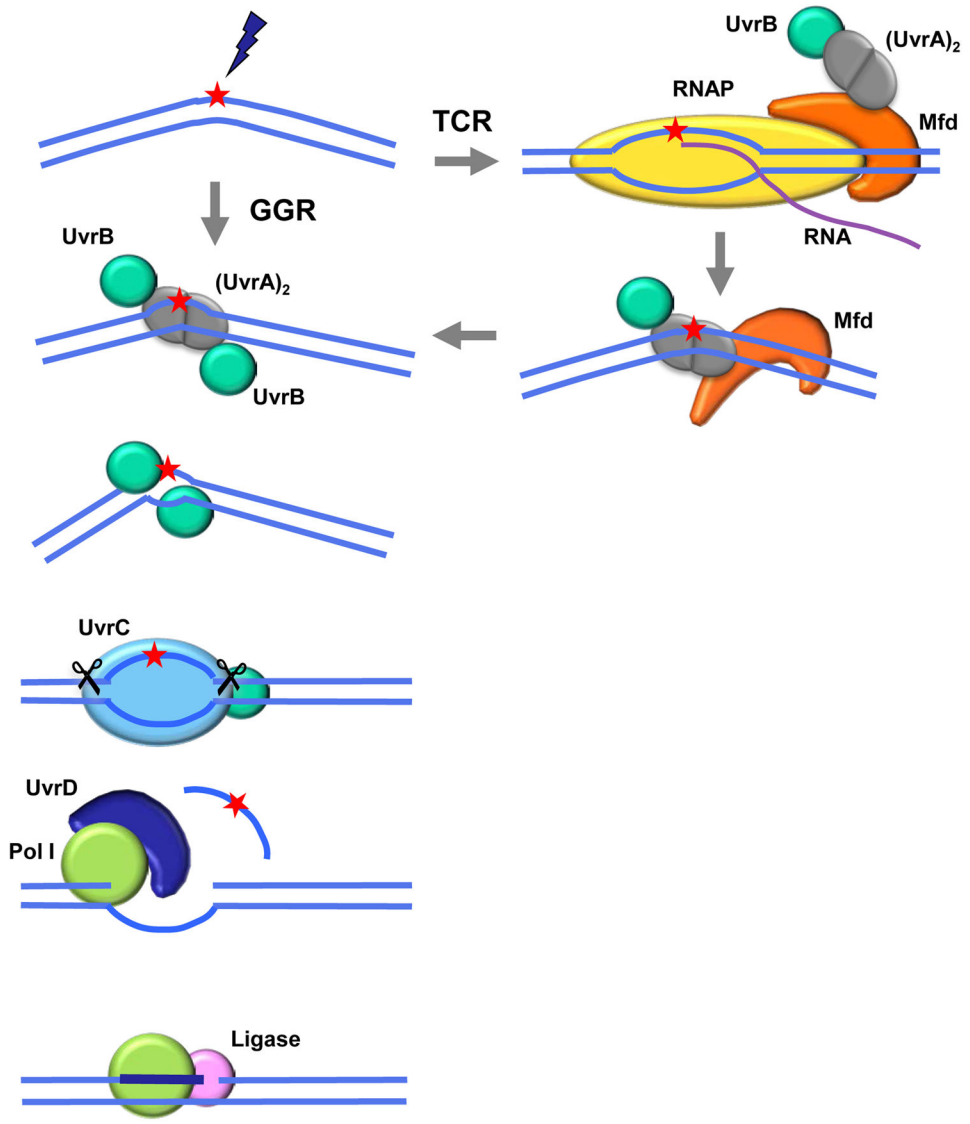

Figure 2.

Schematic representation of NER in *Escherichia coli*. Damage can be recognized either by sensing instability of the duplex DNA structure (for GGR) or by the arrest of a translocating RNA polymerase upon encountering the damaged site (for TCR). In the latter case Mfd binds the arrested polymerase and recruits UvrA, which then further recruits UvrB, as the polymerase and RNA product are released. From then on the pathway proceeds in the classic manner in which the recognition proteins recruit UvrC, which catalyzes dual incisions (~ 13 nt) in the damaged strand. UvrD and DNA Pol I excise the damaged stretch and Pol I synthesizes a repair patch that is eventually ligated to the contiguous parental strand. The relative sizes of the nucleic acids and proteins depicted in this figure are not meant to reflect their actual sizes and conformations.