Cell Cycle 11:16, 2997-3002; August 15, 2012; © 2012 Landes Bioscience

DNA excision repair

Where do all the dimers go?

Michael G. Kemp and Aziz Sancar*
Department of Biochemistry and Biophysics; University of North Carolina School of Medicine; Chapel Hill, NC USA

Exposure of cells to UV light from the sun causes the formation of pyrimidine dimers in DNA that have the potential to lead to mutation and cancer. In humans, pyrimidine dimers are removed from the genome in the form of ~30 nt-long oligomers by concerted dual incisions. Though nearly 50 y of excision repair research has uncovered many details of UV photoproduct damage recognition and removal, the fate of the excised oligonucleotides and, in particular, the ultimate fate of the chemically very stable pyrimidine dimers remain unknown. Physiologically relevant UV doses introduce hundreds of thousands of pyrimidine dimers in diploid human cells, which are excised from the genome within ~24 h. Once removed from the genome, "where do all the dimers go?" In a recent study we addressed this question. Although our study did not determine the fate of the dimer itself, it revealed that the excised ~30-mer is released from the duplex in a tight complex with the transcription/repair factor TFIIH. This finding combined with recent reports that base and oligonucleotide products of the base and double-strand break repair pathways also make stable complexes with the cognate repair enzymes, and that these complexes activate the MAP kinase and checkpoint signaling pathways, respectively, raises the possibility that TFIIH-30-mer excision complexes may play a role in signaling reactions in response to UV damage.

Keywords: UV radiation, DNA repair, nucleotide excision repair, TFIIH, RPA, cell signaling, pyrimidine dimers

Abbreviations: UV, ultraviolet; ssDNA, single-stranded DNA; TFIIH, transcription factor II H; RPA, replication protein A; CPD, cyclobutane pyrimidine dimer; ATM, ataxia telangiectasia mutated; MRN, Mre11-Rad50-Nbs1; ATR, Ataxia telangiectasia-mutated and Rad3-related; XP, xeroderma pigmentosum; SLE, systemic lupus erythematosus

Submitted: 06/07/12

Revised: 06/13/12

Accepted: 06/13/12

http://dx.doi.org/10.4161/cc.21126

*Correspondence to: Aziz Sancar;
Email: aziz_sancar@med.unc.edu

Ultraviolet (UV) radiation from the sun is the most common environmental carcinogen that leads to skin cancer in humans. UV causes the formation of pyrimidine dimers, cyclobutane pyrimidine dimers (CPDs) and pyrimidine-pyrimidone (6–4) photoproducts [(6–4)PPs] between adjacent bases in DNA (**Fig. 1**). These lesions interfere with both replication and transcription and hence are potentially toxic and mutagenic to cells. In humans and other placental mammals, the sole mechanism for removing pyrimidine dimers from the genome is nucleotide excision repair. Individuals with the disease xeroderma pigmentosum (XP) have mutations in genes that encode nucleotide excision repair proteins and, as a consequence, have a greater than 5,000-fold increased risk of developing skin cancers.[1] Furthermore, there are other diseases, such as systemic lupus erythematosus (SLE), that are characterized by hypersensitivity to UV and are often precipitated or exacerbated by exposure to sunlight. Therefore, detailed understanding of excision repair is of importance to human health.

Excision Repair of UV-Damaged DNA

Excision repair was discovered in the 1960s, and its molecular mechanism was elucidated in the 1980s in *E. coli* and in the 1990s in humans. Initial studies, first in *E. coli* and then human cells, revealed that in cells labeled with ^{3}H-thymidine, exposure to UV irradiation followed by an incubation period resulted in transfer of radiolabel from the acid-insoluble high molecular weight DNA fraction to the acid-soluble oligonucleotide fraction of cells.[2-4] These findings, together with

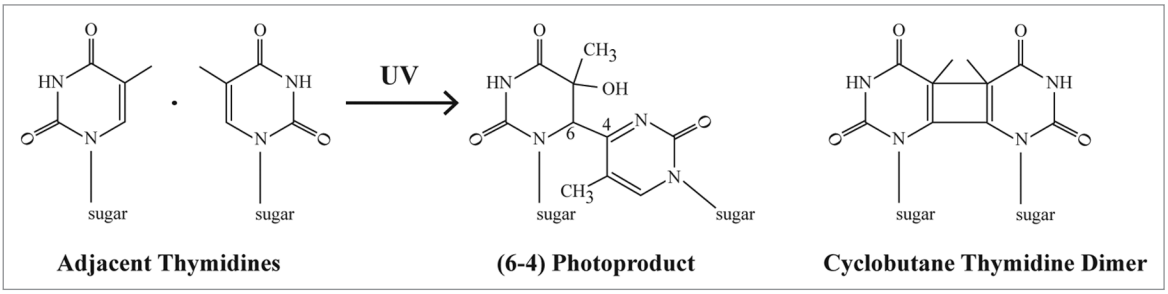

Figure 1. DNA base damage induced by UV. Exposure of adjacent thymidine bases in DNA results in formation of (6–4) photoproducts and cyclobutane thymidine dimers.

chromatographic approaches examining the nature of the soluble material, suggested that CPDs were essentially "cut out" (excised) and released from duplex DNA in the form of short, single-stranded (ssDNA) oligonucleotides. UV-sensitive bacterial strains and XP patient cell lines, which were later identified to contain mutations in nucleotide excision repair genes, failed to release radiolabeled thymidine into the acid-soluble fraction.[2,3,5] Thus, the ability of both bacterial and human cells to remove CPD-containing oligonucleotides from their genomes seemed to be correlated with their sensitivity to UV radiation as measured by mutation rate and clonogenic survival.

The release of dimer-containing oligonucleotides from duplex DNA is expected to leave a corresponding ssDNA tract (gap) in the duplex that could be restored to a fully double-stranded state through DNA synthesis (patch) across the gap. Coincident with the measurement of dimer release studies, investigations using density labeling and centrifugation and radiolabeling and autoradiography identified the predicted non-conservative mode of DNA replication in UV-treated *E. coli* and human cells, respectively.[6,7] Now termed unscheduled DNA synthesis (UDS), repair replication or repair resynthesis, this replication mechanism (and hence excision repair) was further shown to be defective in human patients with XP.[8] In fact, XP genes can be legitimately considered the first tumor suppressor genes to have been identified. These and subsequent studies on UV excision repair led to the following consensus model[9]: the UV damage is recognized by a repair endonuclease that makes an incision 5' to the photoproduct; a 5' to 3' exonuclease releases the dimer in oligonucleotides 4–6 nt in length; and the resulting gap may or may not be enlarged by exonuclease action before being refilled and ligated to produce the repair patch.

The identification and cloning of the genes responsible for excision repair and the development of in vitro repair assays with both cell-free extracts and purified proteins ultimately led to reconstitution of both *E. coli* and human nucleotide excision repair with purified components and elucidation of molecular mechanisms of excision repair in both organisms.[10-12] Importantly, these studies revealed that, contrary to the prevailing views at the time, CPDs are removed by concerted dual incisions (rather than endonuclease/exonuclease action) in the form of 12–13 nt-long oligomers in *E. coli*[10] and 24–32 nt-long oligomers ("canonical 30-mer") in humans.[13] Interestingly, though the principle of excision and repair synthesis are nearly identical in these two divergent organisms, the specific proteins that perform the damage recognition and excision steps are not conserved from prokaryotes to eukaryotes. A schematic of the human nucleotide excision repair system and its core repair factors is shown in **Figure 2**. Comprehensive reviews of nucleotide excision repair have been published,[14-16] and the human repair system will be described only briefly here. Recognition of thymine dimers occurs by stochastic order assembly of RPA, XPA and XPC-TFIIH at sites of damage, and specificity is achieved in part by cooperative protein-protein interactions among these factors and mainly by the kinetic proofreading activity of TFIIH. Helicase action by the XPD subunit of TFIIH generates a bubble around the photoproduct and creates the requisite branched DNA substrates for the structure-specific endonucleases XPF and XPG, which incise the damaged strand 20 ± 5 phosphodiester bonds 5' and 6 ± 3 phosphodiester bonds 3' of the lesion, respectively. These dual incision events therefore generate an oligonucleotide 24–32-nt in length (also known as the "canonical 30-mer") that dissociates from the duplex. Release of the canonical 30-mer leaves a canonical 30-mer gap that is then filled in and ligated by a DNA polymerase and ligase. Though the DNA damage recognition, dual incision and repair synthesis steps of nucleotide excision repair have been examined in considerable detail, the fate of the excised canonical 30-mer has not been explored to any significant extent. In our recent study,[17] we addressed three interrelated questions: (1) How is the canonical 30-mer released; (2) Does the canonical 30-mer constitute a signal for an intracellular signaling pathway; and (3) What is the ultimate fate of the canonical 30-mer and, most intriguingly, of the cyclobutane pyrimidine dimer? Our study has answered some of these questions and has provided the conceptual framework for answering the others.

New Steps in Nucleotide Excision Repair

In our study, which in part was motivated by the question "where do all the dimers go?," we first wished to know, rather, "where do all the canonical 30-mers go?" To this end, we used an in vitro excision assay with a radiolabeled dimer-containing model DNA substrate and cell-free extract or purified repair factors and identified new steps in excision repair that occur following the dual incision event. As shown

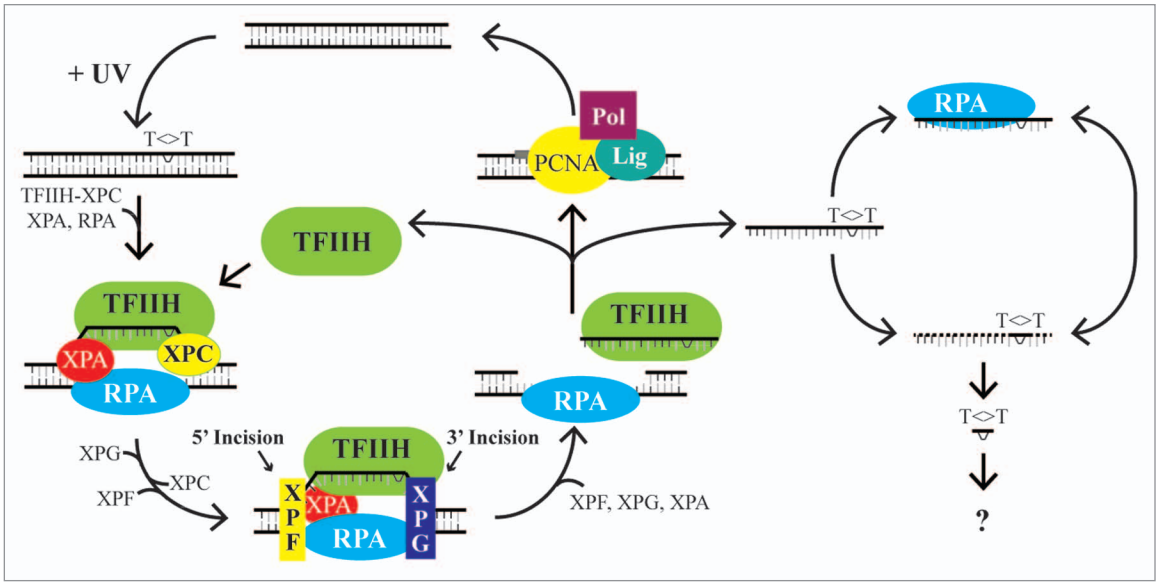

Figure 2. Model of human nucleotide excision repair. UV-induced thymine dimers (T<>T) are recognized by the actions of XPA, RPA, and XPC-TFIIH and DNA is unwound around the dimer by the helicase activity of TFIIH. Following dual incisions by the XPF and XPG nucleases, an oligonucleotide ~30 nt in length is released from the duplex in complex with TFIIH. The remaining gap is filled in by the actions of DNA polymerase (Pol) and DNA ligase (Lig). Release of the excised oligonucleotide from TFIIH recycles TFIIH for new rounds of repair. The released 30-mer can then be targeted for degradation by nucleases or bound by RPA, which limits its degradation.

in **Figure 2**, contrary to current models of excision repair, we discovered that the excised canonical "30-mer" is released from the DNA duplex in complex with the repair factor TFIIH. Next, in a reaction dependent on ATP but not ATP hydrolysis, the canonical 30-mer excision product is very slowly released from TFIIH ($t_{½}$ of 3.3 h), whereafter it can become bound by RPA and/or partially degraded by nucleases present in the cell-free extract. Consistent with a purported role for RPA in preventing single-stranded DNA degradation by cellular nucleases, we further observed that addition of excess RPA to canonical 30-mers provided significant protection of the excision products from degradation by nucleases present in cell-free extract. Though this in vitro system may not accurately reproduce all of the processing events and reaction rates inside the cell, the release of the excised canonical 30-mer in complex with TFIIH is almost certainly an elementary step in the excision repair reaction, because it represents an enzyme-product complex. However, new methods are needed to monitor the kinetics of release of the excised oligomer and its processing in vivo.

Nonetheless, these new steps of excision repair have important implications for understanding the efficiency of UV photoproduct removal from the human genome. For example, exposure of naked DNA to 1 h of mid-day summer sun yields a number of pyrimidine dimer photoproducts comparable to that generated by 10–20 J/m^2 of UV-C from a germicidal lamp (254 nm). In the pseudotetraploid HeLa cell line, this dose of UV-C generates approximately 1.2 million photoproducts, of which 75% are CPDs and 25% are (6–4)PPs. Because HeLa cells can remove nearly all of the (6–4)PPs and approximately 10% of the CPDs within 2–3 h, approximately 400,000 canonical 30-mer excision products are generated within this time frame. However, HeLa cells contain only 100,000 molecules of TFIIH and 200,000 molecules of RPA.[18] Thus, there must be additional mechanisms to effectively recycle these proteins and to allow them to participate in other DNA metabolic processes, including transcription, cell cycle regulation, DNA replication, recombination and DNA damage checkpoints. These considerations also raise the possibility that the inhibition of replication and transcription known to occur after UV exposure may be due in part to formation of protein-excision product complexes that titrate TFIIH and RPA away from gene promoters, replication forks and recombination intermediates.

Signaling Roles for Excision Products

Recent studies have raised the possibility that DNA repair products, whether in the form of oligonucleotides or a modified base, when in complex with the cognate repair enzyme, may activate intracellular signaling pathways. One example involves homologous recombination-mediated repair of double-strand breaks. In this repair pathway the DNA ends are resected by the MRN nuclease in preparation for Rad51 assembly and the subsequent reactions that generate and resolve joint molecules. Remarkably, it was found by co-immunoprecipitation that exonucleolytically generated oligonucleotides 4–12 nt in length were associated with the MRN complex, and that this association was necessary for activation of the ATM kinase and the ATM-mediated DNA damage signaling pathway[19] (**Fig. 3**, left panel). In support of this conclusion, it was reported that degradation of the MRN-associated oligonucleotides with a phosphodiesterase

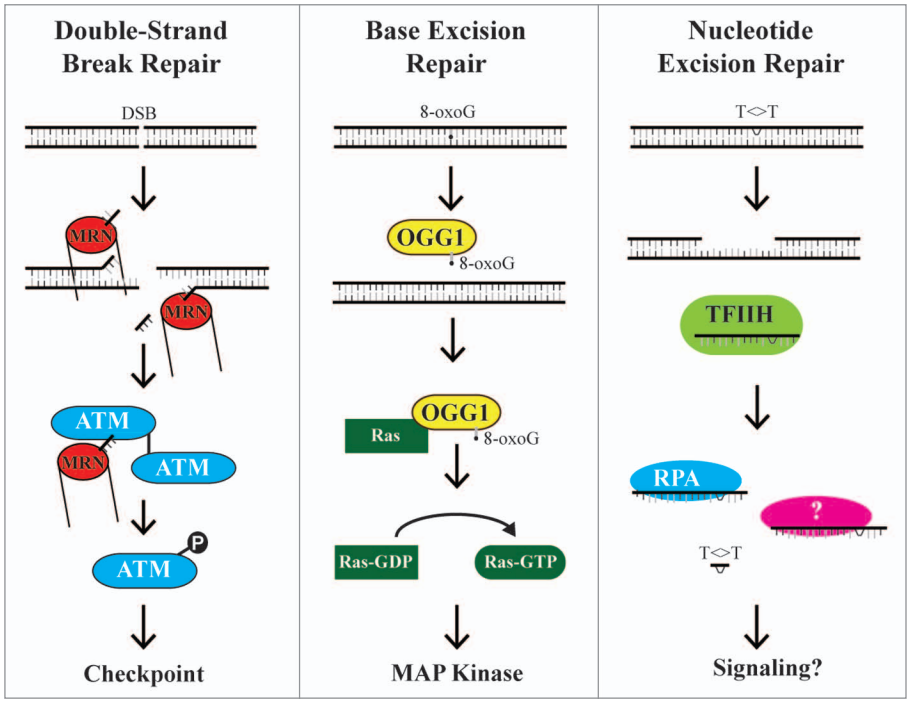

Figure 3. Roles of DNA repair intermediates in cell signaling. Processing of double-strand breaks by the MRN complex generates short oligonucleotides that remain associated with MRN and stimulate ATM kinase activity (left panel). Repair of 8-oxoguanine (8-oxoG) lesions by OGG1 during base excision repair leads to the formation of a stable OGG1–8-oxo-G complex that binds Ras and stimulates nucleotide exchange (middle panel). Nucleotide excision repair of thymine dimers releases oligonucleotides from the duplex that are initially in complex with TFIIH. This complex may activate an intracellular signaling pathway. After release from TFIIH, these oligonucleotides may bind RPA or other factors that may impact the cellular response to UV (right panel).

abolished double-strand break-induced ATM activation. It was further suggested that these ssDNA oligonucleotides may serve as an alarm signal to sustain ATM-dependent DNA damage response signaling events until double-strand break repair and ssDNA degradation are complete.

A second example of a DNA repair product-dependent signaling event was recently reported for 8-oxoguanine glycosylase (OGG1), which excises the abundant oxidative lesion 8-oxoguanine (8-oxoG) from DNA as the initial step of the base excision repair pathway.[20,21] The excised 8-oxoG is in a tight complex with OGG1, and the OGG1-8-oxoG complex binds with high affinity to the Ras MAP kinase signaling protein.[22] Ras is a GTPase and is activated by nucleotide exchange factors that coverts inactive Ras:GDP complex to the signaling Ras:GTP form. Strikingly, it was found that the OGG1-8-oxoG complex was capable of serving specifically as a nucleotide exchange factor for Ras, converting it from the inactive GDP-bound state to the GTP-bound state and stimulating downstream signaling events (**Fig. 3**, middle panel).

Taking into account these reports that link DNA repair enzyme-base/oligonucleotide complexes as activators of MAP kinase and checkpoint intracellular signaling pathways, it is quite conceivable that the excised UV photoproducts, either in the canonical 30-mers or their degradation products, may impact the cellular response to UV. Further work is needed to determine whether the TFIIH- and RPA-canonical 30-mer excision product complexes stimulate any specific DNA damage response or cell signaling pathways (**Fig. 3**, right panel). We suggest that the ATR kinase signaling pathway may be a potential target for dimer-containing oligonucleotides, particularly because ATR activation after UV radiation in quiescent cells has been reported to require the dual incisions of the nucleotide excision repair system.[23-25] Though the prevailing view has been that checkpoint activation is due to the assembly of checkpoint proteins on ssDNA and ss/dsDNA junctions at the gapped DNA intermediate that is generated in DNA duplex following excision of the photoproduct, it is plausible that the canonical 30-mer in complex with TFIIH or RPA may also directly contribute to ATR activation in a manner analogous to that of MRN and ATM. Though our recent report identified only TFIIH and RPA as canonical 30-mer-associated proteins in our cell-free system, we expect that there may be additional proteins that associate with the excised oligonucleotide, particularly after release from TFIIH. Interestingly, based on the finding that ~30 nt-long oligomers bound to the non-specific DNA binding site of p53 and stimulated its specific binding to target DNA sequences,[26] it was proposed that UV radiation may activate the p53-mediated cellular response to damage by association of the canonical 30-mer excision product with p53. In light of these new developments in the excision repair field, this hypothesis deserves a critical experimental testing.

Lastly, innate immunity and inflammatory responses to UV may also be impacted by the excised oligonucleotide. Mutations in enzymes responsible for ssDNA degradation, such as DNase1 and Trex1, are known to be associated with systemic lupus erythematosus and other autoimmune diseases.[27-30] Of particular relevance to nucleotide excision repair, photosensitivity is often an early manifestation in SLE patients. Thus, the slow or improper degradation of canonical 30-mer excision products after excessive sun exposure may lead to altered inflammatory and immune responses that result in photosensitivity. Though the molecular mechanisms of such a response are not known, we note that it may be analogous to the response of cells to short, bacterial DNA-mimicking CpG oligonucleotides,[31] which are well-recognized regulators of intracellular immune and inflammatory responses in many tissues, including skin. Thus, it will be interesting to determine whether excised, pyrimidine dimer-containing oligonucleotides contribute to inflammation and intrinsic immune responses after exposure to UV radiation.

Where Do All the Dimers Go?

Although in our recent study we did not identify the nuclease(s) that degrade canonical 30-mer excision products, both our study and earlier studies revealed that the excision product is degraded to gradually smaller products,[32,33,34] and based on properties of a number of mammalian endo- and exonucleases, it is reasonable to assume that the canonical 30-mer will be eventually degraded to mononucleotides and a pyrimidine dimer. Indeed, even though the in vitro *E. coli* and human nucleotide excision repair systems reveal that CPDs are removed in the form of 12–13 nt- and 24–32 nt-long oligomers, respectively, analyses of the excision products from cells indicate that nearly all CPDs are in 3–4 nt-long oligomers both in *E. coli* and humans.[2,3,34] Importantly, during this processing, the CPDs are retained intracellularly, never exported into the medium. In contrast, in the extremely radioresistant *Deinococcus radiodurans*, following excision, the dimers are exported into the medium in the form of 2–4 nt-long oligomers.[35] However, in all model systems tested, whether the dimers are retained intracellularly or exported into the extracellular space, as of now, there appears to be a rule of conservation of the total dimers (dimers in genome + dimers removed = constant),[2,3,35,36] indicating that none of the model organisms investigated so far has an enzyme capable of breaking down cyclobutane dimers. Thus the question arises: "Where do all the dimers go?" We present some facts pertinent to this question and a potential answer below.

In cyclobutane pyrimidine dimers, the pyrimidines, as a consequence of the cyclobutane ring between C5-C5 and C6-C6 of adjacent pyrimidines, have lost their aromaticity and no longer absorb the UV component of sunlight (> 300 nm) and thus are not subject to direct photoreversal in nature. Moreover, the loss of aromaticity also makes the dimers resistant to non-enzymatic degradation by extreme heat or pH that they may encounter in nature. As an illustration of this latter point, the following is a standard procedure for measuring CPDs in DNA[2,3]: the material is dissolved in 98% formic acid and hydrolyzed in sealed glass tubes by heating at 175°C for 90 min. Then the dimers are separated from monomeric bases by various chromatographic methods. Thus, it is quite likely that chemical degradation of CPDs does not play a major role in maintaining the CPD balance in nature, and that it must be removed enzymatically before depleting the carbon reserve of the biosphere.[37] We therefore predict that some organisms must possess an enzyme that is capable of breaking down CPDs into simpler constituents that can be processed by common metabolic enzymes.

Conclusion

Our recent work revealed that the oligonucleotide removed by dual incision from UV damaged DNA is released in a tight complex with TFIIH. Further work is needed to determine (1) the effect of sequestering TFIIH with the excised oligomer on cellular physiology, (2) the potential of the TFIIH-excised oligomer to activate an intracellular signaling pathway, (3) the identity of nucleases that degrade the excised canonical 30-mer to 3–4 nt-long oligomers and (4) the discovery of an enzyme that degrades cyclobutane dimers and thus provides an answer to "where do all the dimers go?"

Acknowledgments

We are grateful to Stuart Linn (University of California, Berkeley) who on September 7, 2006 sent A.S. an e-mail asking "where do all the dimers go?" Our study was, to a large extent, motivated by our attempt to answer this question. This work was supported by National Institutes of Health grant GM32833 to A.S.

References

1. DiGiovanna JJ, Kraemer KH. Shining a light on xeroderma pigmentosum. J Invest Dermatol 2012; 132:785-96; PMID:22217736; http://dx.doi.org/10.1038/jid.2011.426.
2. Boyce RP, Howard-Flanders P. Release of ultraviolet light-induced thymine dimers from dna in E. coli K-12. Proc Natl Acad Sci U S A 1964; 51:293-300; PMID:14124327; http://dx.doi.org/10.1073/pnas.51.2.293.
3. Setlow RB, Carrier WL. The disappearance of thymine dimers from dna: An error-correcting mechanism. Proc Natl Acad Sci U S A 1964; 51:226-31; PMID:14124320; http://dx.doi.org/10.1073/pnas.51.2.226.
4. Regan JD, Trosko JE, Carrier WL. Evidence for excision of ultraviolet-induced pyrimidine dimers from the DNA of human cells in vitro. Biophys J 1968; 8:319-25; PMID:5759918; http://dx.doi.org/10.1016/S0006-3495(68)86490-2.
5. Setlow RB, Regan JD, German J, Carrier WL. Evidence that xeroderma pigmentosum cells do not perform the first step in the repair of ultraviolet damage to their DNA. Proc Natl Acad Sci U S A 1969; 64:1035-41; PMID:5264135; http://dx.doi.org/10.1073/pnas.64.3.1035.
6. Pettijohn D, Hanawalt P. Evidence for repair-replication of ultraviolet damaged dna in bacteria. J Mol Biol 1964; 9:395-410; PMID:14202275; http://dx.doi.org/10.1016/S0022-2836(64)80216-3.
7. Rasmussen RE, Painter RB. Evidence for repair of ultra-violet damaged deoxyribonucleic acid in cultured mammalian cells. Nature 1964; 203:1360-2; PMID:14207310; http://dx.doi.org/10.1038/2031360a0.
8. Cleaver JE. Defective repair replication of DNA in xeroderma pigmentosum. Nature 1968; 218:652-6; PMID:5655953; http://dx.doi.org/10.1038/218652a0.
9. Haseltine WA. Ultraviolet light repair and mutagenesis revisited. Cell 1983; 33:13-7; PMID:6380746; http://dx.doi.org/10.1016/0092-8674(83)90329-X.
10. Sancar A, Rupp WD. A novel repair enzyme: UVRABC excision nuclease of Escherichia coli cuts a DNA strand on both sides of the damaged region. Cell 1983; 33:249-60; PMID:6380755; http://dx.doi.org/10.1016/0092-8674(83)90354-9.
11. Mu D, Park CH, Matsunaga T, Hsu DS, Reardon JT, Sancar A. Reconstitution of human DNA repair excision nuclease in a highly defined system. J Biol Chem 1995; 270:2415-8; PMID:7852297; http://dx.doi.org/10.1074/jbc.270.6.2415.
12. Evans E, Moggs JG, Hwang JR, Egly JM, Wood RD. Mechanism of open complex and dual incision formation by human nucleotide excision repair factors. EMBO J 1997; 16:6559-73; PMID:9351836; http://dx.doi.org/10.1093/emboj/16.21.6559.
13. Huang JC, Svoboda DL, Reardon JT, Sancar A. Human nucleotide excision nuclease removes thymine dimers from DNA by incising the 22nd phosphodiester bond 5' and the 6th phosphodiester bond 3' to the photodimer. Proc Natl Acad Sci U S A 1992; 89:3664-8; PMID:1314396; http://dx.doi.org/10.1073/pnas.89.8.3664.
14. Reardon JT, Sancar A. Nucleotide excision repair. Prog Nucleic Acid Res Mol Biol 2005; 79:183-235; PMID:16096029; http://dx.doi.org/10.1016/S0079-6603(04)79004-2.
15. Sancar A. DNA excision repair. Annu Rev Biochem 1996; 65:43-81; PMID:8811174; http://dx.doi.org/10.1146/annurev.bi.65.070196.000355.
16. Wood RD. Nucleotide excision repair in mammalian cells. J Biol Chem 1997; 272:23465-8; PMID:9295277; http://dx.doi.org/10.1074/jbc.272.38.23465.
17. Kemp MG, Reardon JT, Lindsey-Boltz LA, Sancar A. Mechanism of release and fate of excised oligonucleotides during nucleotide excision repair. J Biol Chem 2012; 287:22889-99; PMID:22573372.
18. Araújo SJ, Nigg EA, Wood RD. Strong functional interactions of TFIIH with XPC and XPG in human DNA nucleotide excision repair, without a preassembled repairosome. Mol Cell Biol 2001; 21:2281-91; PMID:11259578; http://dx.doi.org/10.1128/MCB.21.7.2281-2291.2001.
19. Jazayeri A, Balestrini A, Garner E, Haber JE, Costanzo V. Mre11-Rad50-Nbs1-dependent processing of DNA breaks generates oligonucleotides that stimulate ATM activity. EMBO J 2008; 27:1953-62; PMID:18596698; http://dx.doi.org/10.1038/emboj.2008.128.
20. Klungland A, Bjelland S. Oxidative damage to purines in DNA: role of mammalian Ogg1. DNA Repair (Amst) 2007; 6:481-8; PMID:17127104; http://dx.doi.org/10.1016/j.dnarep.2006.10.012.

21. Mitra S, Hazra TK, Roy R, Ikeda S, Biswas T, Lock J, et al. Complexities of DNA base excision repair in mammalian cells. Mol Cells 1997; 7:305-12; PMID:9264015.
22. Boldogh I, Hajas G, Aguilera-Aguirre L, Hegde ML, Radak Z, Bacsi A, et al. Activation of ras signaling pathway by 8-oxoguanine DNA glycosylase bound to its excision product, 8-oxoguanine. J Biol Chem 2012; 287:20769-73; PMID:22568941; http://dx.doi.org/10.1074/jbc.C112.364620.
23. Marini F, Nardo T, Giannattasio M, Minuzzo M, Stefanini M, Plevani P, et al. DNA nucleotide excision repair-dependent signaling to checkpoint activation. Proc Natl Acad Sci U S A 2006; 103:17325-30; PMID:17088560; http://dx.doi.org/10.1073/pnas.0605446103.
24. Marti TM, Hefner E, Feeney L, Natale V, Cleaver JE. H2AX phosphorylation within the G1 phase after UV irradiation depends on nucleotide excision repair and not DNA double-strand breaks. Proc Natl Acad Sci U S A 2006; 103:9891-6; PMID:16788066; http://dx.doi.org/10.1073/pnas.0603779103.
25. Matsumoto M, Yaginuma K, Igarashi A, Imura M, Hasegawa M, Iwabuchi K, et al. Perturbed gap-filling synthesis in nucleotide excision repair causes histone H2AX phosphorylation in human quiescent cells. J Cell Sci 2007; 120:1104-12; PMID:17327276; http://dx.doi.org/10.1242/jcs.03391.
26. Jayaraman J, Prives C. Activation of p53 sequence-specific DNA binding by short single strands of DNA requires the p53 C-terminus. Cell 1995; 81:1021-9; PMID:7600571; http://dx.doi.org/10.1016/S0092-8674(05)80007-8.
27. Yasutomo K, Horiuchi T, Kagami S, Tsukamoto H, Hashimura C, Urushihara M, et al. Mutation of DNASE1 in people with systemic lupus erythematosus. Nat Genet 2001; 28:313-4; PMID:11479590; http://dx.doi.org/10.1038/91070.
28. Stetson DB, Ko JS, Heidmann T, Medzhitov R. Trex1 prevents cell-intrinsic initiation of autoimmunity. Cell 2008; 134:587-98; PMID:18724932; http://dx.doi.org/10.1016/j.cell.2008.06.032.
29. Fye JM, Orebaugh CD, Coffin SR, Hollis T, Perrino FW. Dominant mutation of the TREX1 exonuclease gene in lupus and Aicardi-Goutieres syndrome. J Biol Chem 2011; 286:32373-82; PMID:21808053; http://dx.doi.org/10.1074/jbc.M111.276287.
30. Napirei M, Karsunky H, Zevnik B, Stephan H, Mannherz HG, Möröy T. Features of systemic lupus erythematosus in Dnase1-deficient mice. Nat Genet 2000; 25:177-81; PMID:10835632; http://dx.doi.org/10.1038/76032.
31. Krieg AM. CpG motifs in bacterial DNA and their immune effects. Annu Rev Immunol 2002; 20:709-60; PMID:11861616; http://dx.doi.org/10.1146/annurev.immunol.20.100301.064842.
32. Svoboda DL, Taylor JS, Hearst JE, Sancar A. DNA repair by eukaryotic nucleotide excision nuclease. Removal of thymine dimer and psoralen monoadduct by HeLa cell-free extract and of thymine dimer by Xenopus laevis oocytes. J Biol Chem 1993; 268:1931-6; PMID:8420966.
33. Huang JC, Sancar A. Determination of minimum substrate size for human excinuclease. J Biol Chem 1994; 269:19034-40; PMID:8034661.
34. Weinfeld M, Gentner NE, Johnson LD, Paterson MC. Photoreversal-dependent release of thymidine and thymidine monophosphate from pyrimidine dimer-containing DNA excision fragments isolated from ultraviolet-damaged human fibroblasts. Biochemistry 1986; 25:2656-64; PMID:3521740; http://dx.doi.org/10.1021/bi00357a055.
35. Boling ME, Setlow JK. The resistance of Micrococcus radiodurans to ultraviolet radiation. 3. A repair mechanism. Biochim Biophys Acta 1966; 123:26-33; PMID:5964047.
36. LaBelle M, Linn S. In vivo excision of pyrimidine dimers is mediated by a DNA N-glycosylase in Micrococcus luteus but not in human fibroblasts. Photochem Photobiol 1982; 36:319-24; PMID:7146108; http://dx.doi.org/10.1111/j.1751-1097.1982.tb04381.x.
37. Dubos RJ. Quest: Reflections on Medicine, Science, and Humanity. New York: Harcourt Brace Jovanovich, 1980.