

### Articles:

**DNA Replication and Causes of Mutation** - Leslie A. Pray, Ph.D.

**DNA Damage & Repair: Mechanisms for Maintaining DNA Integrity** - Suzanne Clancy, Ph.D.

**Write a short (1 page) summary of the cellular damage caused by UV light, including how DNA replication errors are sensed and one mechanism that can repair them, either in humans or bacteria.**

Among the three solar types of UV radiations that can penetrate Earth's atmosphere, UV-A and UV-B radiations are the most important environmental factors involved in skin cancer. Such UV light can cause crosslinks within the same strand or between opposite strands of double-stranded DNA. These mutations interfere with DNA replication or transcription. Two common UV by products are cyclobutene pyrimidine dimers (CPDs) and 6-4 photoproducts resulting from crosslinks within a strand of DNA between two pyrimidine residues, generally two thymine residues, causing kinks in the double helix DNA structure. Studies have shown that human skin efficiently protects against UVB-induced DNA damages, but there is no efficient protection against UVA. There are at least five major DNA damage response pathways: base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), homologous recombination (HR), and non-homologous end joining (NHEJ) which are active throughout the different stages of the cell cycle. Crosslinks are repaired primarily by NER. In eukaryotes, NER is a multistep process which relies on about 30 genes and 18 proteins complexes. NER consists of two pathways [1][2]:

- **Global genome nucleotide excision pathway (GG-NER):** detects and eliminates bulky damages, including transcribed and untranscribed DNA strands in active and inactive genes. At high level, NER requires four steps: 1) detection of damage, 2) excision of DNA and surroundings, 3) filling the gap by DNA polymerase, 4) sealing of the nick. "Damage sensing" is controlled by the damage proteins XPC-rad23B and DDB1-DDB2 heterodimer (XPE factor) which recognize helix distortions.
- **Transcription-coupled nucleotide excision repair (TC-NER):** contrary to GG-NER, does not require XPC or DDB proteins to recognize DNA distortion, and is initiated when RNA polymerase is stalled at the damaged sites of a transcribed DNA strand. Instead of XPC, CSA and CSB proteins can bind to some types of DNA damages.

Genetic mutations in the NER pathway genes are responsible for genetic disorders including xeroderma pigmentosum (XP), the Cockayne syndrome (CS), and trichothiodystrophy (TTD). In prokaryotes, the excision process is similar to the one in eukaryotes, but is controlled by less proteins; the Uvr proteins (UvrA, UvrB, UvrC), and the motor protein DNA helicase II. TC-NER also exists in bacteria and is activated by the TRCF protein. In addition, bacteria, and many other organisms including fungi, plants, fruit flies and frogs but not humans, have another UV incurred DNA damage repair mechanism: photoreactivation. During photoreactivation, the enzyme photolyase binds to CPDs and the chromophore molecules convert light into chemical energy required to revert the DNA damages.

Excision repair pathways such as NER and BER can be bypassed: translesion synthesis polymerases can substitute for a DNA polymerase that has stalled at the replication fork due to DNA damage, and allow DNA replication process to continue. These DNA polymerases are

tightly regulated. Translesion mutations and slippages can accumulate over time and cause cancer. In some cases, these mutations are beneficial for the survival of the population and also source of genetic variation required by evolution.

- [1] “Cyclobutane pyrimidine dimers are predominant DNA lesions in whole human skin exposed to UVA radiation.” <https://www.pnas.org/doi/10.1073/pnas.0604213103> (accessed Apr. 14, 2022).
- [2] N. Chatterjee and G. C. Walker, “Mechanisms of DNA damage, repair and mutagenesis,” *Environ Mol Mutagen*, vol. 58, no. 5, pp. 235–263, Jun. 2017, doi: 10.1002/em.22087.