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How important is DNA repair?

DNA is:

- the repository of hereditary information
- the blueprint for operation of individual cells.

Nearly all DNA damage is harmful. Therefore, it is essential to reduce this damage to a tolerable level. The importance of repair can be seen from the facts that

- *DNA is the only biomolecule that is specifically repaired. All others are replaced.*
- *>100 genes participate in various aspects of DNA repair, even in organisms with very small genomes.*
- *Cancer is caused by mutations. In most cases, "genetic instability" (elevated mutation rate) is required to permit accumulation of sufficient mutations to generate cancer during a human lifetime. DNA repair mechanisms promote genomic stability and prevent cancer. Many, perhaps most, cancers are at least partially attributable to defects in DNA repair.*

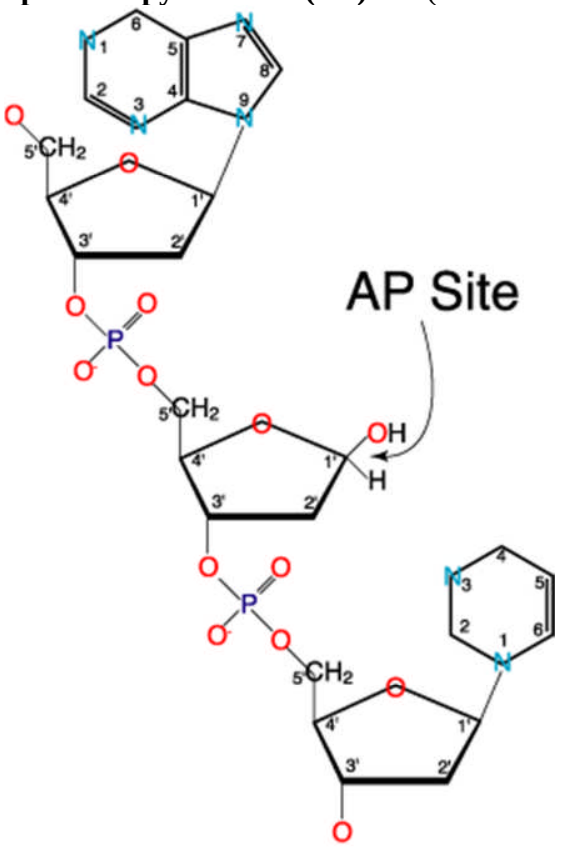
Types of damage

Note that many types of DNA damage are generated spontaneously, in some cases at very high frequency. Thus defects in DNA repair systems are likely to cause problems even in the absence of additional damage caused by environmental factors.

Base loss

The glycosyl bond linking DNA bases with deoxyribose is labile under physiological conditions. Within a typical mammalian cell, several thousand purines and several hundred pyrimidines are spontaneously lost per diploid genome per day. Loss of a purine or pyrimidine base creates an

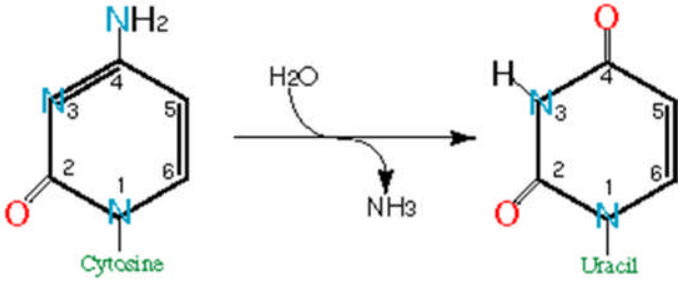
apurinic/apyrimidinic (AP) site (also called an **abasic** site):



Base modification

Deamination

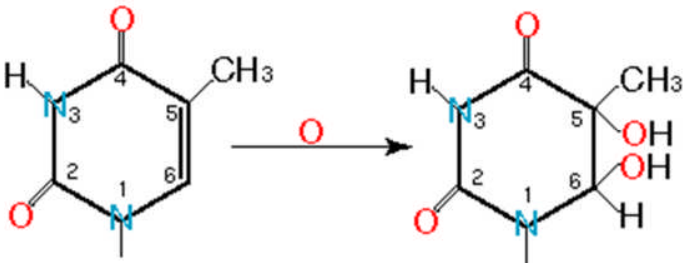
The primary amino groups of nucleic acid bases are somewhat unstable. They can be converted to keto groups in reactions like the one pictured here:



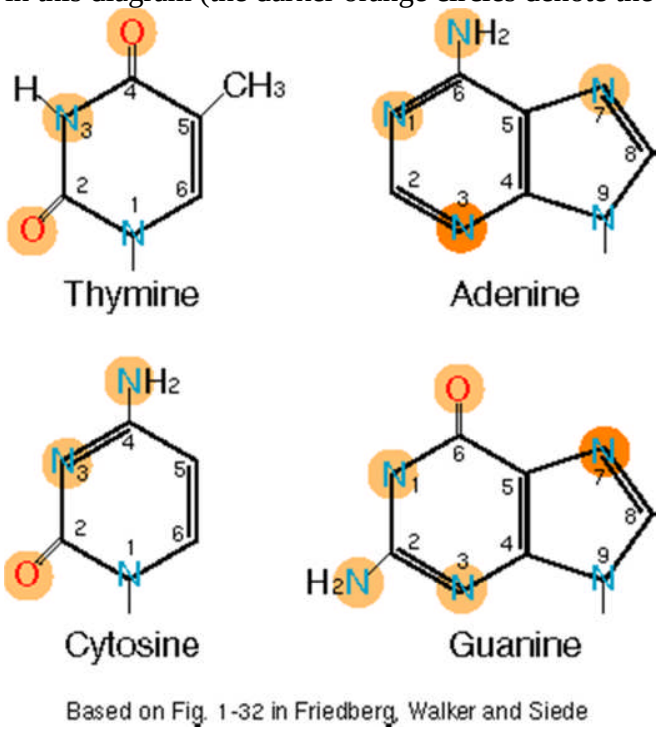
In a typical mammalian cell, about 100 uracils are generated per haploid genome per day in this fashion. Other deamination reactions include conversion of adenine to hypoxanthine, guanine to xanthine, and 5-methyl cytosine to thymine.

Chemical modification

The nucleic acid bases are susceptible to numerous modifications by a wide variety of chemical agents. For example, several types of hyper-reactive oxygen (singlet oxygen, peroxide radicals, hydrogen peroxide and hydroxyl radicals) are generated as byproducts during normal oxidative metabolism and also by ionizing radiation (X-rays, gamma rays). These are frequently called Reactive Oxygen Species (ROS). ROS can modify DNA bases. A common product of thymine oxidation is thymine glycol:



Many environmental chemicals, including "natural" ones (frequently in the food we eat) can also modify DNA bases, frequently by addition of a methyl or other alkyl group (alkylation). In addition, normal metabolism frequently leads to alkylation. It has been shown that S-adenosylmethionine, the normal biological methyl group donor, reacts accidentally with DNA to produce alkylated bases like 3-methyladenine at a rate of several thousand per day per mammalian diploid genome. Alkylation occurs most readily at the nucleophilic positions shown in this diagram (the darker orange circles denote the most reactive positions):

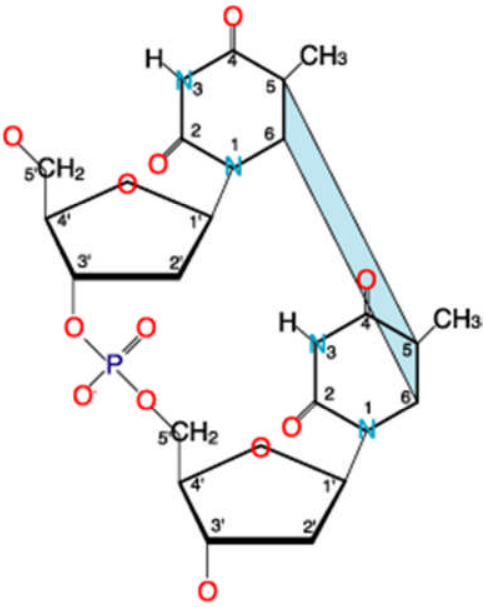


Based on Fig. 1-32 in Friedberg, Walker and Siede

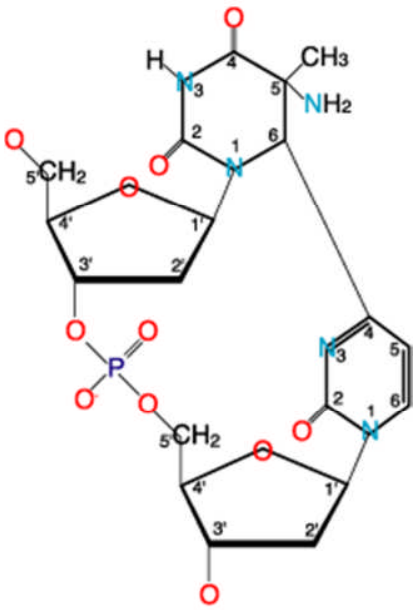
Photodamage

Ultraviolet light is absorbed by the nucleic acid bases, and the resulting influx of energy can induce chemical changes. The most frequent photoproducts are the consequences of bond

formation between adjacent pyrimidines within one strand, and, of these, the most frequent are cyclobutane pyrimidine dimers (CPDs). T-T CPDs are formed most readily, followed by T-C or C-T; C-C dimers are least abundant. One can obtain an idea of the extent of distortion of DNA chain structure caused by CPDs by noting that, in the diagram of a T-T CPD below, the cyclobutane ring, shaded in light blue, should have sides of approximately equal length. Thus the two adjacent pyrimidines must be pulled closer to each other than in normal DNA.



Dimers can also be produced by formation of a single covalent bond between the 6 position of one pyrimidine and the 4 position of the adjacent pyrimidine on the 3' side. The order of abundance of such pyrimidine (6-4) pyrimidone photoproducts (6-4PPs) is T-C>>C-C>T-T>C-T. Although only one bond attaches the adjacent pyrimidines, there is nevertheless extensive distortion of the normal DNA structure. In the diagram below of the T-C 6-4PP, notice that the amino group, originally from the 4 position of the cytosine, ends up at the 5 position of the thymine. Although it is not evident from this crude diagram, the structural distortion generated by 6-4PPs (a DNA bend of 44°) is greater than that produced by CPDs (bend of 30°).



Replication errors

Another major source of potential alterations in DNA is the generation of mismatches or small insertions or deletions during DNA replication. Although DNA polymerases are moderately accurate, and most of their mistakes are immediately corrected by polymerase-associated proofreading exonucleases, nevertheless the replication machinery is not perfect. As we shall see later, efficient repair mechanisms correct most of these problems.

Inter-strand crosslinks

By attaching to bases on both strands, bifunctional alkylating agents such as the psoralens can cross-link both strands. Cross-links can also be generated by UV and ionizing radiation.

DNA-protein crosslinks

DNA topoisomerases generate covalent links between themselves and their DNA substrates during the course of their enzymatic action. Usually these crosslinks are transient and are reversed as the topoisomerase action is completed. Occasionally something interferes with reversal, and a stable topoisomerase-DNA bond is established. Bifunctional alkylating agents and radiation can also create crosslinks between DNA and protein molecules. All of these lesions must be repaired.

Strand breaks

Single-strand and double-strand breaks are produced at low frequency during normal DNA metabolism by topoisomerases, nucleases, replication fork "collapse", and repair processes.

Breaks are also produced by ionizing radiation. In fact, Hermann Müller's discovery in 1927 that X-rays can cause mutations (as a consequence of occasional failure to properly repair damage induced by ionizing radiation) was the first experimental demonstration that environmental factors can affect genome stability.

Summary of types of DNA damage

DNA molecules, like all other biomolecules, can be damaged in numerous ways. Spontaneous damage due to replication errors, deamination, depurination and oxidation is compounded in the real world by the additional effects of radiation and environmental chemicals. The number of ways that DNA molecules can be damaged is very large. Since repair systems must be capable of recognizing and dealing with each type of damage, it is not surprising that there is a large number of different types of repair system.