

Embassy Sweden)

Telomerase and Aging

Cells that undergo cell division continue to have their telomeres shortened because most somatic cells do not make telomerase. This essentially means that telomere shortening is associated with aging. With the advent of modern medicine, preventative health care, and healthier lifestyles, the human life span has increased, and there is an increasing demand for people to look younger and have a better quality of life as they grow older.

In 2010, scientists found that telomerase can reverse some age-related conditions in mice. This may have potential in regenerative medicine.² Telomerase-deficient mice were used in these studies; these mice have tissue atrophy, stem cell depletion, organ system failure, and impaired tissue injury responses. Telomerase reactivation in these mice caused extension of telomeres, reduced DNA damage, reversed neurodegeneration, and improved the function of the testes, spleen, and intestines. Thus, telomere reactivation may have potential for treating age-related diseases in humans.

Cancer is characterized by uncontrolled cell division of abnormal cells. The cells accumulate mutations, proliferate uncontrollably, and can migrate to different parts of the body through a process called metastasis. Scientists have observed that cancerous cells have considerably shortened telomeres and that telomerase is active in these cells. Interestingly, only after the telomeres were shortened in the cancer cells did the telomerase become active. If the action of telomerase in these cells can be inhibited by drugs during cancer therapy, then the cancerous cells could potentially be stopped from further division.

14.6 DNA Repair

By the end of this section, you will be able to do the following:

- Discuss the different types of mutations in DNA
- Explain DNA repair mechanisms

DNA replication is a highly accurate process, but mistakes can occasionally occur, such as a DNA polymerase inserting a wrong base. Uncorrected mistakes may sometimes lead to serious consequences, such as cancer. Repair mechanisms correct the mistakes. In rare cases, mistakes are not corrected, leading to mutations; in other cases, repair enzymes are themselves mutated or defective.

Most of the mistakes during DNA replication are promptly corrected by the proofreading ability of DNA polymerase itself. (Figure 14.17). In **proofreading**, the DNA pol reads the newly added base before adding the next one, so a correction can be made. The polymerase checks whether the newly added base has paired correctly with the base in the template strand. If it is the right base, the next nucleotide is added. If an incorrect base has been added, the enzyme makes a cut at the phosphodiester bond and releases the wrong nucleotide. This is performed by the 3' exonuclease action of DNA pol. Once the incorrect nucleotide has been removed, it can be replaced by the correct one.

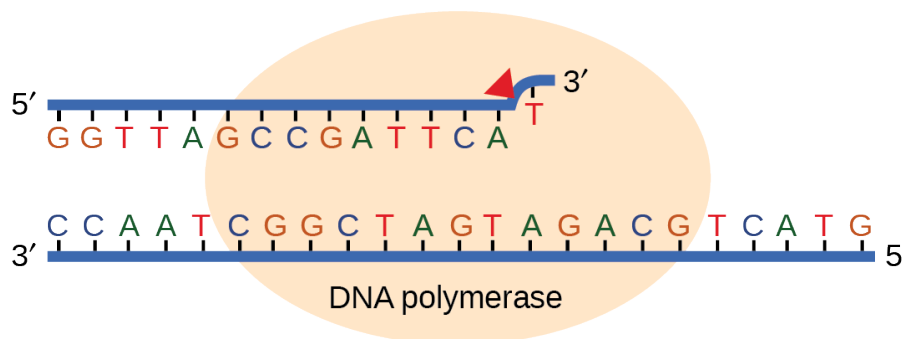


Figure 14.17 Proofreading by DNA polymerase corrects errors during replication.

Some errors are not corrected during replication, but are instead corrected after replication is completed; this type of repair is known as **mismatch repair** (Figure 14.18). Specific repair enzymes recognize the mispaired nucleotide and excise part of the strand that contains it; the excised region is then resynthesized. If the mismatch remains uncorrected, it may lead to more permanent damage when the mismatched DNA is replicated. How do mismatch repair enzymes recognize which of the two bases is the incorrect one? In *E. coli*, after replication, the nitrogenous base adenine acquires a methyl group; the parental DNA

²Jaskelioff et al., "Telomerase reactivation reverses tissue degeneration in aged telomerase-deficient mice," *Nature* 469 (2011): 102-7.

strand will have methyl groups, whereas the newly synthesized strand lacks them. Thus, DNA polymerase is able to remove the wrongly incorporated bases from the newly synthesized, non-methylated strand. In eukaryotes, the mechanism is not very well understood, but it is believed to involve recognition of unsealed nicks in the new strand, as well as a short-term continuing association of some of the replication proteins with the new daughter strand after replication has completed.

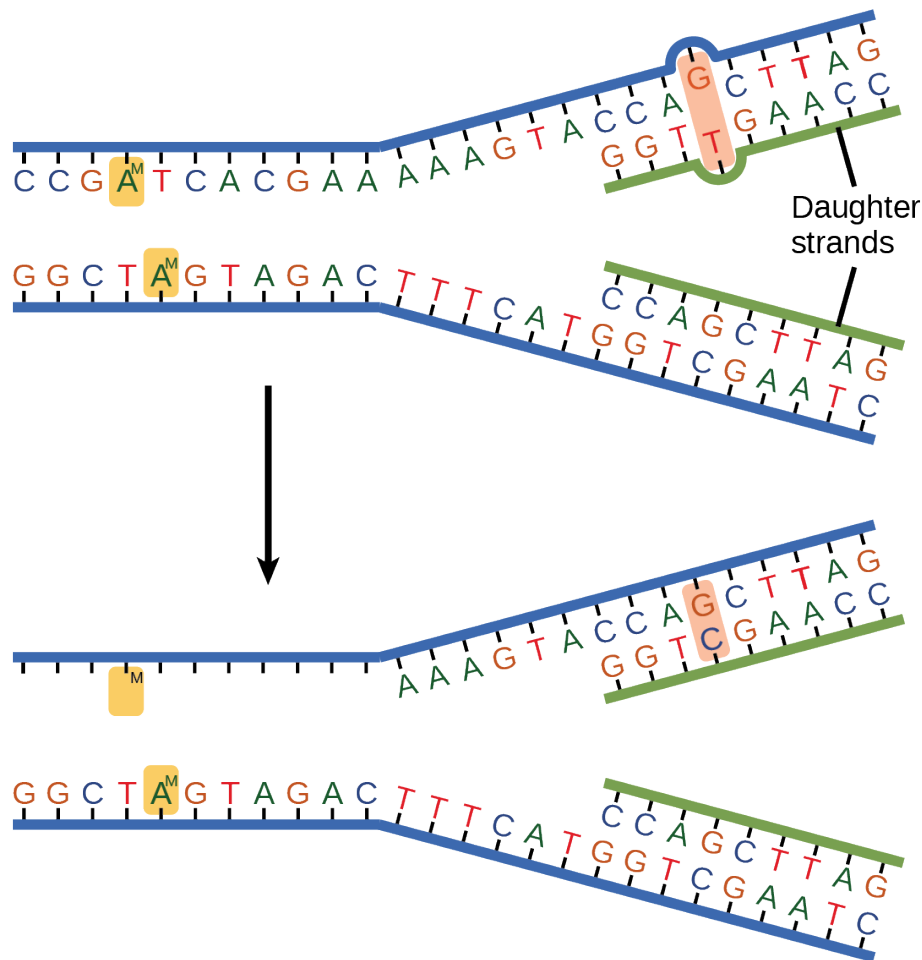


Figure 14.18 In mismatch repair, the incorrectly added base is detected after replication. The mismatch repair proteins detect this base and remove it from the newly synthesized strand by nuclease action. The gap is now filled with the correctly paired base.

Another type of repair mechanism, **nucleotide excision repair**, is similar to mismatch repair, except that it is used to remove damaged bases rather than mismatched ones. The repair enzymes replace abnormal bases by making a cut on both the 3' and 5' ends of the damaged base (Figure 14.19). The segment of DNA is removed and replaced with the correctly paired nucleotides by the action of DNA pol. Once the bases are filled in, the remaining gap is sealed with a phosphodiester linkage catalyzed by DNA ligase. This repair mechanism is often employed when UV exposure causes the formation of pyrimidine dimers.

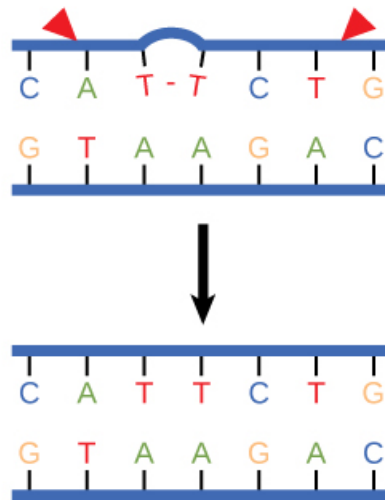


Figure 14.19 Nucleotide excision repairs thymine dimers. When exposed to UV light, thymines lying adjacent to each other can form thymine dimers. In normal cells, they are excised and replaced.

A well-studied example of mistakes not being corrected is seen in people suffering from xeroderma pigmentosa ([Figure 14.20](#)). Affected individuals have skin that is highly sensitive to UV rays from the sun. When individuals are exposed to UV light, pyrimidine dimers, especially those of thymine, are formed; people with xeroderma pigmentosa are not able to repair the damage. These are not repaired because of a defect in the nucleotide excision repair enzymes, whereas in normal individuals, the thymine dimers are excised and the defect is corrected. The thymine dimers distort the structure of the DNA double helix, and this may cause problems during DNA replication. People with xeroderma pigmentosa may have a higher risk of contracting skin cancer than those who don't have the condition.



Figure 14.20 Xeroderma pigmentosa is a condition in which thymine dimerization from exposure to UV light is not repaired. Exposure to sunlight results in skin lesions. (credit: James Halpern et al.)

Errors during DNA replication are not the only reason why mutations arise in DNA. **Mutations**, variations in the nucleotide sequence of a genome, can also occur because of damage to DNA. Such mutations may be of two types: induced or spontaneous. **Induced mutations** are those that result from an exposure to chemicals, UV rays, x-rays, or some other environmental agent. **Spontaneous mutations** occur without any exposure to any environmental agent; they are a result of natural reactions taking place within the body.

Mutations may have a wide range of effects. Point mutations are those mutations that affect a single base pair. The most common nucleotide mutations are substitutions, in which one base is replaced by another. These substitutions can be of two types, either transitions or transversions. **Transition substitution** refers to a purine or pyrimidine being replaced by a base of

the same kind; for example, a purine such as adenine may be replaced by the purine guanine. **Transversion substitution** refers to a purine being replaced by a pyrimidine, or vice versa; for example, cytosine, a pyrimidine, is replaced by adenine, a purine. Some point mutations are not expressed; these are known as silent mutations. Silent mutations are usually due to a substitution in the third base of a codon, which often represents the same amino acid as the original codon. Other point mutations can result in the replacement of one amino acid by another, which may alter the function of the protein. Point mutations that generate a stop codon can terminate a protein early.

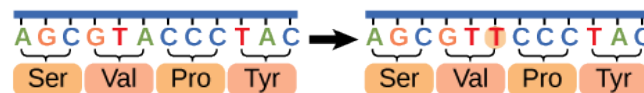
Some mutations can result in an increased number of copies of the same codon. These are called trinucleotide repeat expansions and result in repeated regions of the same amino acid. Mutations can also be the result of the addition of a base, known as an insertion, or the removal of a base, also known as deletion. If an insertion or deletion results in the alteration of the translational reading frame (a frameshift mutation), the resultant protein is usually nonfunctional. Sometimes a piece of DNA from one chromosome may get translocated to another chromosome or to another region of the same chromosome; this is also known as translocation. These mutation types are shown in [Figure 14.21](#).



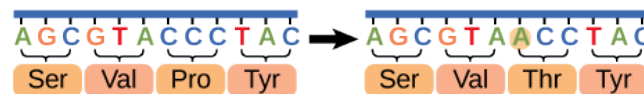
VISUAL CONNECTION

Point Mutations

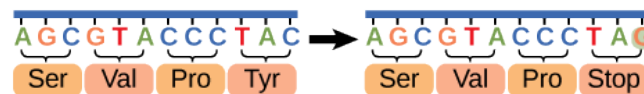
Silent: has no effect on the protein sequence



Missense: results in an amino acid substitution



Nonsense: substitutes a stop codon for an amino acid



Frameshift Mutations

Insertions or deletions of nucleotides may result in a shift in the reading frame or insertion of a stop codon.

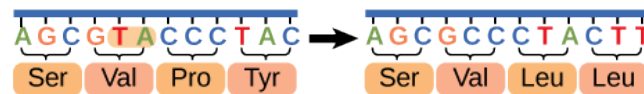


Figure 14.21 Mutations can lead to changes in the protein sequence encoded by the DNA.

A frameshift mutation that results in the insertion of three nucleotides is often less deleterious than a mutation that results in the insertion of one nucleotide. Why?

Mutations in repair genes have been known to cause cancer. Many mutated repair genes have been implicated in certain forms of pancreatic cancer, colon cancer, and colorectal cancer. Mutations can affect either somatic cells or germ cells. If many mutations accumulate in a somatic cell, they may lead to problems such as the uncontrolled cell division observed in cancer. If a mutation takes place in germ cells, the mutation will be passed on to the next generation, as in the case of hemophilia and xeroderma pigmentosa.