19.9: Mutation

Skills to Develop

1. Define the following:
   a. genotype
   b. phenotype
   c. allele
   d. mutation
   e. spontaneous mutation
   f. induced mutation
2. Describe two different mechanisms of spontaneous mutation and, in terms of protein synthesis, describe the four possible results that may occur as a result of these mutations.
3. Briefly describe three ways chemical mutagens work.
4. Compare ultraviolet radiation and gamma radiation in terms of how they induce mutation.

As we learned earlier, the sequence of deoxyribonucleotide bases in the genes that make up a bacterium's DNA determines the order of amino acids in the proteins and polypeptides made by that organism. This order of DNA bases constitutes the organism's genotype. A particular organism may possess alternate forms of some genes. Such alternate forms of genes are referred to as alleles. The physical characteristics an organism possesses, based on its genotype and the interaction with its environment, make up its phenotype.

Mutation is an error during DNA replication that results in a change in the sequence of deoxyribonucleotide bases in the DNA. Spontaneous mutation occurs naturally (a normal mistake rate) about one in every million to one in every billion divisions and is probably due to low level natural mutagens normally present in the environment. Induced mutation is caused by mutagens, substances that cause a much higher rate of mutation.
Mechanisms of Mutation

There are two general mechanisms of mutation.

1. Substitution of a nucleotide (point mutations): substitution of one deoxyribonucleotide for another during DNA replication (see Figure 1). This is the most common mechanism of mutation. Substitution of one nucleotide for another is a result of tautomeric shift, a rare process by which the hydrogen atoms of a deoxyribonucleotide base move in a way that changes the properties of its hydrogen bonding. For example, a shift in the hydrogen atom of adenine enables it to form hydrogen bonds with cytosine rather than thymine. Likewise, a shift in the hydrogen atom in thymine allows it to bind with guanine rather than adenine.

2. Deletion or addition of a nucleotide (frameshift mutations): deletion or addition of a deoxyribonucleotide during DNA replication (see Figure 2 and Figure 3).

Results of Mutation

One of four things can happen as a result of these mechanisms of mutation and the resulting change in the deoxyribonucleotide base sequence mentioned above:

- A missense mutation occurs. This is usually seen with a single substitution mutation and results in one wrong codon and one wrong amino acid (Figure 4).

- A nonsense mutation occurs. If the change in the deoxyribonucleotide base sequence results in transcription of a stop or nonsense codon, the protein would be terminated at that point in the message (Figure 5).

- A sense mutation occurs. This is sometimes seen with a single substitution mutation when the change in the DNA base sequence results in a new codon still coding for the same amino acid (Figure 6). (With the exception of methionine, all amino acids are coded for by more than one codon.)
• A frameshift mutation occurs. This is seen when a number of DNA nucleotides not divisible by three is added or deleted. Remember, the genetic code is a triplet code where three consecutive nucleotides code for a specific amino acid. This causes a reading frame shift and all of the codons and all of the amino acids after that mutation are usually wrong (Figure 7); frequently one of the wrong codons turns out to be a stop or nonsense codon and the protein is terminated at that point.

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**YouTube movie illustrating frameshift mutations** ([https://www.youtube.com/v/o-otJT3N_E](https://www.youtube.com/v/o-otJT3N_E))

Induced mutation is caused by mutagens, substances that cause a much higher rate of mutation. Chemical mutagens generally work in one of three ways.

1. Some chemical mutagens, such as nitrous acid and nitrosoguanidine work by causing chemical modifications of
purine and pyrimidine bases that alter their hydrogen-bonding properties. For example, nitrous acid converts cytosine to uracil which then forms hydrogen bonds with adenine rather than guanine.

2. Other chemical mutagens function as base analogs. They are compounds that chemically resemble a nucleotide base closely enough that during DNA replication, they can be incorporated into the DNA in place of the natural base. Examples include 2-amino purine, a compound that resembles adenine, and 5-bromouracil, a compound that resembles thymine. The base analogs, however, do not have the hydrogen-bonding properties of the natural base.

3. Still other chemical mutagens function as intercalating agents. Intercalating agents are planar three-ringed molecules that are about the same size as a nucleotide base pair. During DNA replication, these compounds can insert or intercalate between adjacent base pairs thus pushing the nucleotides far enough apart that an extra nucleotide is often added to the growing chain during DNA replication. An example is ethidium bromide.

When under stress from antibiotics or other harmful chemicals, some bacteria switch on genes whose protein products can increase the mutation rate within the bacterium 10,000 times as fast as the mutation rate that occurs during normal binary fission. This causes a sort of hyperevolution where mutation acts as a self defense mechanism for the bacterial population by increasing the chance of forming an antibiotic-resistant mutant that is able to survive at the expense of the majority of the population. (Remember that most mutations are harmful to a cell; see SOS repair below.)

Certain types of radiation can also function as mutagens.

1. Ultraviolet Radiation. The ultraviolet portion of the light spectrum includes all radiations with wavelengths from 100 nm to 400 nm. It has low wave length and low energy. The microbicidal activity of ultraviolet (UV) light depends on the length of exposure: the longer the exposure the greater the cidal activity. It also depends on the wavelength of UV used. The most cidal wavelengths of UV light lie in the 260 nm - 270 nm range where it is absorbed by nucleic acid.

In terms of its mode of action, UV light is absorbed by microbial DNA and causes adjacent thymine bases on the same DNA strand to covalently bond together, forming what are called thymine-thymine dimers (see Figure 8). As the DNA replicates, nucleotides do not complementary base pair with the thymine dimers and this terminates the replication of that DNA strand. However, most of the damage from UV radiation actually comes from the cell trying to repair the damage to the DNA by a process called SOS repair. In very heavily damaged DNA containing large numbers of thymine dimers, a process called SOS repair is activated as kind of a last ditch effort to repair the DNA. In this process, a gene product of the SOS system binds to DNA polymerase allowing it to synthesize new DNA across the damaged DNA. However, this altered DNA polymerase loses its proofreading ability resulting in the synthesis of DNA that itself now contains many misincorporated bases. (Most of the chemical mutagens mentioned above also activate SOS repair.)
2. Ionizing Radiation. Ionizing radiation, such as X-rays and gamma rays, has much more energy and penetrating power than ultraviolet radiation. It ionizes water and other molecules to form radicals (molecular fragments with unpaired electrons) that can break DNA strands and alter purine and pyrimidine bases.

Summary

1. The sequence of deoxyribonucleotide bases in the genes that make up an organism’s DNA determines the order of amino acids in the proteins and polypeptides made by that organism. This order of DNA bases constitutes the bacterium’s genotype.

2. A particular organism may possess alternate forms of some genes referred to as alleles.

3. The physical characteristics an organism possesses, based on its genotype and the interaction with its environment, make up an organism’s phenotype.

4. Mutation is an error during DNA replication that results in a change in the sequence of deoxyribonucleotide bases in the DNA.

5. Spontaneous mutation occurs naturally (a normal mistake rate) about one in every million to one in every billion divisions and is probably due to low level natural mutagens normally present in the environment; induced mutation is caused by mutagens, substances that cause a much higher rate of mutation.

6. There are two primary mechanisms of mutation: substitution of a deoxyribonucleotide (point mutations) whereby one deoxyribonucleotide is substituted for another during DNA replication; and deletion or addition of a nucleotide (frameshift mutations) where deoxyribonucleotides are either added or deleted during DNA replication. Point mutations are most common.

7. There are four possible results from a mutation: missense, nonsense, sense, or frameshift.

8. A missense mutation usually seen with a single substitution mutation and results in one wrong codon and one
wrong amino acid.

9. A nonsense mutation occurs when the change in the deoxyribonucleotide base sequence results in transcription of a stop or nonsense codon. The protein would be terminated at that point in the message.

10. A sense mutation occurs is sometimes seen with a single substitution mutation when the change in the DNA base sequence results in a new codon still coding for the same amino acid.

11. A frameshift mutation occurs when a number of DNA nucleotides not divisible by three is added or deleted. This causes a reading frame shift and all of the codons and all of the amino acids after that mutation are usually wrong; frequently one of the wrong codons turns out to be a stop or nonsense codon and the protein is terminated at that point.

12. When under stress from harmful chemicals, some bacteria switch on genes whose protein products can increase the mutation rate within the bacterium 10,000 times as fast as the mutation rate that occurs during normal binary fission. This causes a hyperevolution where mutation acts as a self defense mechanism for the bacterial population by increasing the chance of forming an antibiotic-resistant mutant that is able to survive at the expense of the majority of the population.

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