SECTION 5. DNA MUTATION AND REPAIR

LEARNING OBJECTIVES:

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

- Explain the different mechanisms of mutation and how various agents of mutation exhibit their effects on the structure and function of nucleic acids
- Predict the effects of mutagens on DNA and protein sequences
- Describe the various protective mechanisms and repair systems against mutations in cells

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Mutations are changes in the genetic sequence of an organism from what is typically the commonly occurring version. Gene mutations can be classified in two ways:

- **Hereditary mutations** are inherited from a parent and are present throughout an organism's lifetime, in all its cells. Also called germline mutations because they are present in the parent's egg or sperm cells. When the egg and sperm cells unite, the resulting fertilized egg cell receives DNA from both parents. If this DNA has a mutation, the offspring from the fertilized egg will carry the mutation in all of its cells.
- **Acquired (or somatic) mutations** occur at some time during a person's life and are present only in certain cells. These may be caused by environmental factors such as ultraviolet radiation from the sun, or from replication errors. This type of mutation cannot be passed on to offspring.

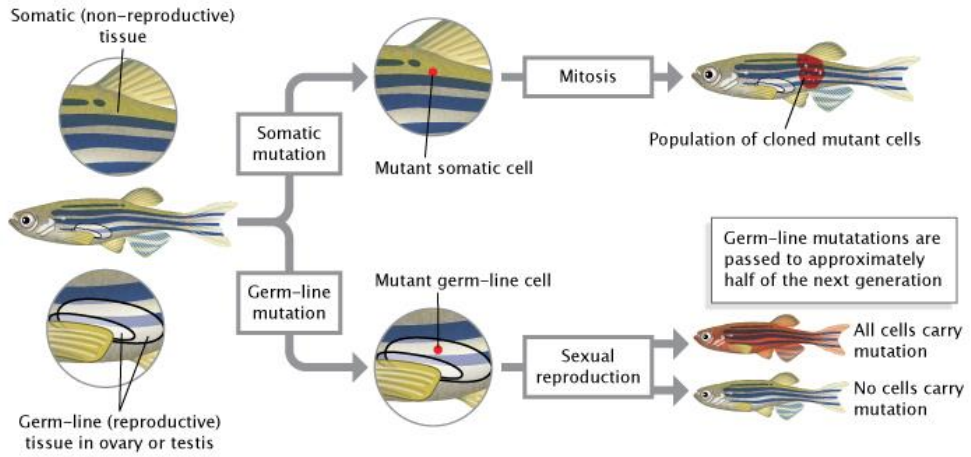


Figure 1: Mutations can occur in germ-line cells or somatic cells.
Germ-line mutations occur in reproductive cells (sperm or eggs) and are passed to an organism's offspring during sexual reproduction. Somatic mutations occur in non-reproductive cells; they are passed to daughter cells during mitosis but not to offspring during sexual reproduction. © 2014 Nature Education Adapted from Pierce, Benjamin. *Genetics: A Conceptual Approach, 2nd ed*

Mutations can have widely differing consequences. For example, many genetic disorders are known to arise from changes in DNA sequences that result in alterations of a protein's

amino acid sequence, and consequently a change in its function. On the other hand, some changes in sequence do not produce any adverse effects at all, or may even be beneficial.

Types of mutation

1. Substitution/point mutation
   - mutation that exchanges one base for another
   - Two types of single base changes:
     - ❑ Transition – change of a pyrimidine to another pyrimidine or a purine to another purine
     - ❑ Transversion - change of a purine to a pyrimidine or a purine to a pyrimidine
   - Can produce three possible outcomes if within a gene
     - ❑ Missense: codon change produces a different amino acid

       e.g., **mRNA 5'-UGU -3' → 5'-UGG -3'**
       Cys → Trp

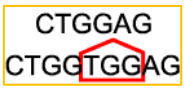
     - ❑ Silent: codon change produces the same amino acid

       e.g., **mRNA 5'-UGU -3' → 5'-UGC -3'**
       Cys → Cys

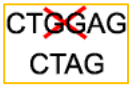
     - ❑ Nonsense: codon change results in a "stop" codon

       e.g., **mRNA 5'-UGU -3' → 5'-UGA -3'**
       Cys → Stop

2. Insertion/deletion mutation
   - **Insertion -** extra base pairs are inserted into a new place in the DNA

   - **Deletion** - one or more bases lost or deleted

   - Both insertions, deletions can produce changes in the mRNA reading frame
     - ❑ frameshift mutations; may generate incorrect or truncated proteins

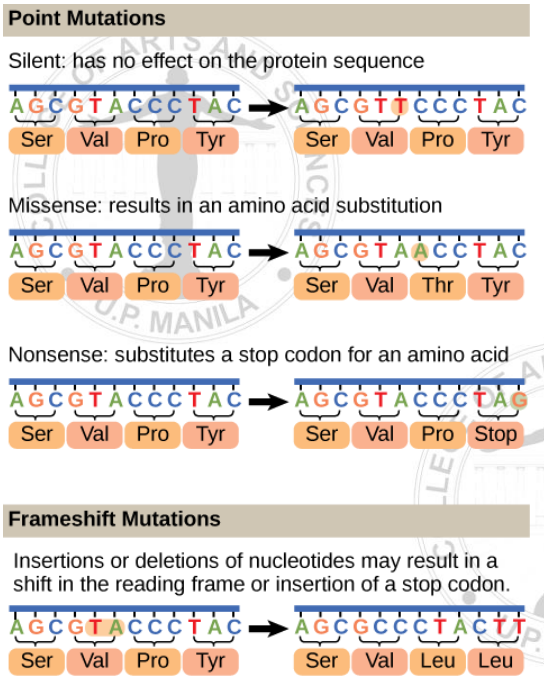


Figure 2: Mutations can lead to changes in the protein sequence encoded by the DNA. From https://courses.lumenlearning.com/wm-biology1/chapter/reading-mutations-in-somatic-cells-and-in-gametes/

CHECK YOUR UNDERSTANDING

• What are the reasons a nucleotide change in a gene for a protein might not have any effect on the phenotype of that gene?
• Is it possible for an insertion of three nucleotides together after the fifth nucleotide in a protein-coding gene to produce a protein that is shorter than normal? How or how not?
• What type of mutation occurs when a gene has two fewer nucleotides in its sequence compared to the unmodified version?

Causes of mutation

DNA interacts with the environment, and sometimes that interaction can be detrimental to the genome. Exposure to a mutagen can increase the rate of mutation more than 1000-fold. Mutagens are often also carcinogen**s**, agents that cause cancer. However, while all carcinogens are mutagenic, not all mutagens are necessarily carcinogens. Modifications of the DNA sequence may also arise from spontaneous mutations and replication errors.

Replication errors

There is a natural—albeit low—error rate that occurs during DNA replication. In most cases, the proofreading function of DNA polymerase, as well as the extensive network of DNA repair mechanisms present in the cell, correct these errors before replication is finished. However, if the repair machinery does not catch the mistake before the complementary strand is formed, the mutation may be passed on to daughter cells.

Spontaneous mutations

- May arise from tautomeric shifts; *e.g.,* the common amino tautomeric form of cytosine base pairs with guanine but its rare imino form of cytosine base pairs with adenine.

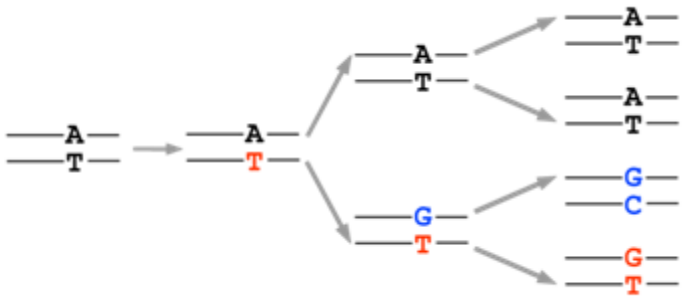


Figure 3: **Mispairing of bases (e.g. G with T) can occur due to tautomerism, alkylating agents, or other effects.** As a result, in this example the AT base pair in the original DNA strand will become permanently substituted by a GC based pair in some progeny. The mispaired GT basepair will likely be repaired or eliminated before further rounds of replication. (Original-Deyholos-CC:AN). From https://bio.libretexts.org/Courses/University_of_Arkansas_Little_Rock/BIOL3300_Genetics/03%3A_Mutation/3.01%3A_Origins_of_Mutations

- Deamination, or the removal of an amine group from a base. Deamination of cytosine converts it to uracil, which will pair with adenine instead of guanine at the next replication, resulting in a base substitution.
- depurination, in which a purine base is lost from a nucleotide, can occur without an explicit insult from the environment. The apurinic nucleotide cannot act as a template for complementary base-pairing during replication.

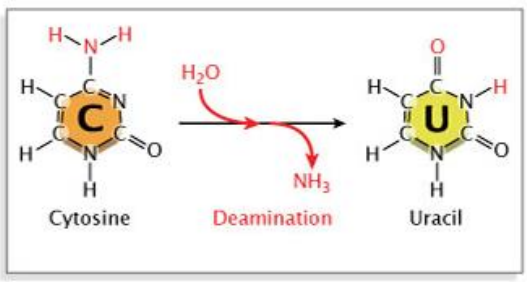


Figure 4: Deamination is a spontaneous mutation that occurs when an amine group is removed from a nitrogenous base. Cytosine is converted to uracil after the loss of an amine group. Because uracil base-pairs with adenine and cytosine base-pairs with guanine, conversion of cytosine to uracil causes base substitutions. © 2014 Nature Education Adapted from Pierce, Benjamin. *Genetics: A Conceptual Approach*, 2nd ed.

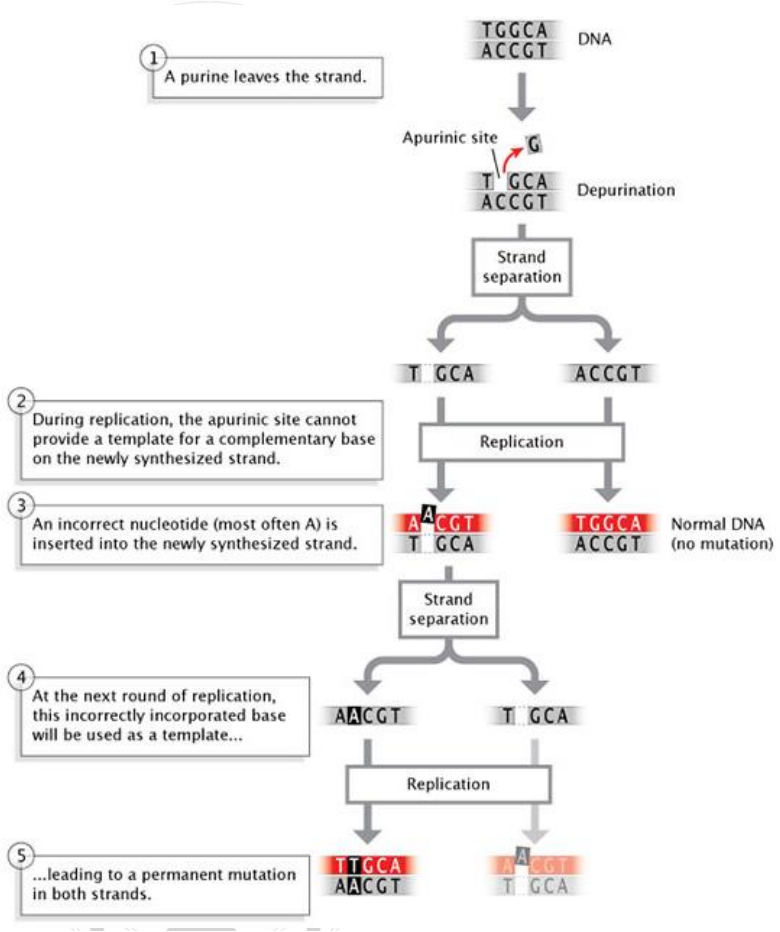


Figure 5: Depurination occurs when a nucleotide loses a purine base. The apurinic site on this strand cannot provide a template for complementary base-pairing during replication. An incorrect nucleotide (*e.g.*, adenine) is inserted into the newly-synthesized strand, across from the apurinic site, producing a normal ds DNA molecule and a mutant ds DNA molecule. When the mutant DNA undergoes a 2nd round of replication, the incorrect base is used as a template for synthesizing a new DNA strand. The resulting point mutations will be passed on in subsequent replications. © 2014 Nature Education Adapted from Pierce, Benjamin. *Genetics: A Conceptual Approach*, 2nd ed.

Physical mutagens

- ultraviolet light
  - ❑ can cause formation of covalent bonds between adjacent prymidine bases. These pyrimidine, or thymine, dimers can stall replication and transcription, leading to frameshift or point mutations
  - ❑ Can also trigger hydrolysis of a cytosine base to a hydrate form, causing it to mispair with adenine
- ionizing radiation (cosmic rays, gamma rays, X-rays) can cause double-stranded breaks in DNA

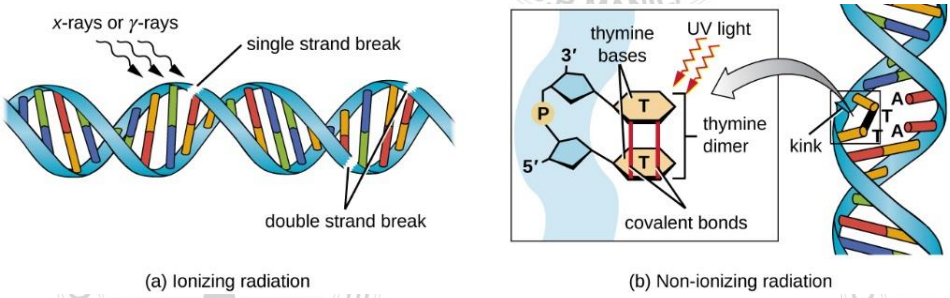


Figure 6. DNA damage caused by physical mutagens. (a) Ionizing radiation may lead to the formation of single-stranded and double-stranded breaks in the DNA sugar-phosphate backbone (b) Nonionizing radiation like ultraviolet light can lead to the formation of thymine dimers, which can stall replication and transcription

and introduce frameshift or point mutations. From https://courses.lumenlearning.com/wm-biology1/chapter/reading-mutations-in-somatic-cells-and-in-gametes/

Chemical mutagens

- **Base analogs**
  - ❑ structurally similar to normal nucleotide bases; *e.g.,* 5-bromouracil and 2-aminpurine
  - ❑ can be incorporated into DNA during replication and form transient tautomers, leading to transition mutations
  - ❑ e.g., 5-bromouracil in keto form will H-bond to adenine, but in enol form instead H-bonds with guanine. This can result in a TA to CG substitution mutation.

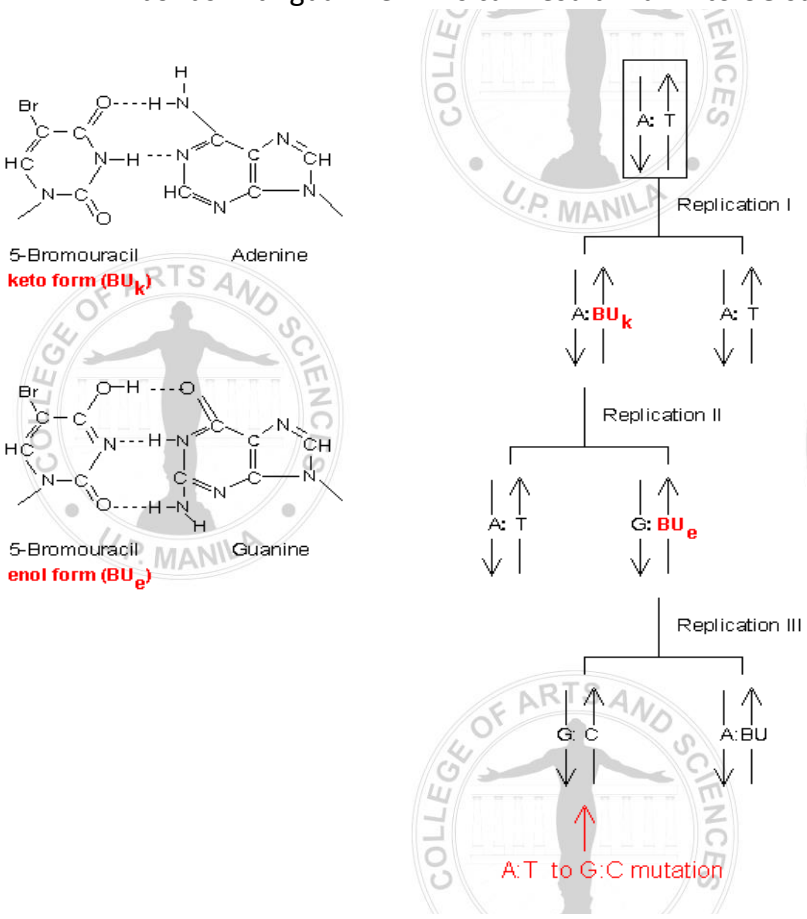


Figure 7: Effect of a base analog. 5-bromouracil (5BU) is a thymidine analog, and usually basepairs with A. If it shifts to its rate enol tautomeric form right before replication, it will basepair with G instead, and will results in a TA base being convereted to a CG base pair.

- **Base modifiers -** Chemically modify DNA bases, which can lead to altered base-pairing capabilities
  - ❑ alkylating agents – largest class of "potential" mutagens present in man's environment
    - ➢ *e.g.,* N - nitrosamines found in cigarette smoke; metabolized by liver enzymes, such as the cytochrome P450 enzyme systems, to form alkylating agents.
    - ➢ Addition of an alkyl group to G changes its base pairing properties so that the next time the alkylated DNA strand is replicated, alkylated G basepairs with a T instead of a C, leading to a substitution mutation.

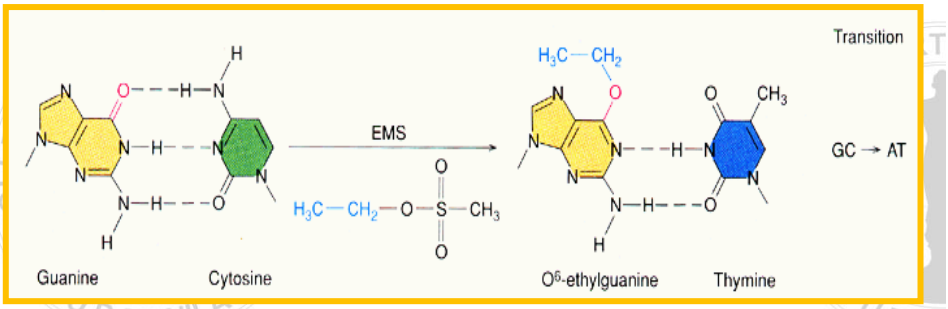


Figure 8. Alkylation of G allows G to bond with T, rather than with C.
From https://openstax.org/books/microbiology/pages/11-5-mutations

- deaminating agents
  - *e.g.*, nitrous acid produced from ingested sodium nitrite, which is used as a preservative, color enhancer, and color fixative in bacon, tocino, etc.
  - Nitrous acid can cause changes in basepairing; *e.g.*, cytosine, when deaminated, is converted to U, which basepairs with A instead of G. In a subsequent round of replication, U then pairs with A, resulting in the conversion of a GC to an AT base pair.

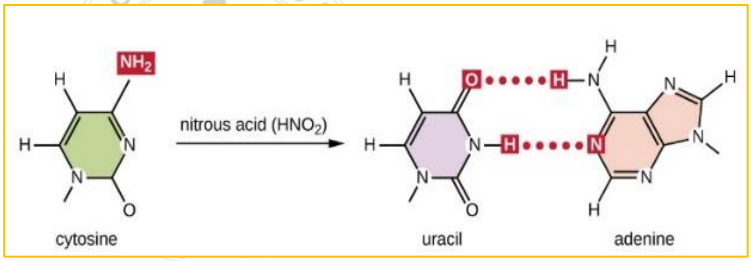


Figure 9. Nitrous acid is a chemical mutagen that modifies already existing nucleoside bases like C to produce U, which base pairs with A. This chemical modification, as shown here, results in converting a CG base pair to a TA base pair. From https://openstax.org/books/microbiology/pages/11-5-mutations

- **DNA intercalators –** can slip in between adjacent base pairs in dsDNA. This can lead to insertion or deletion of an extra base pair following the next round of DNA replication
  - ***e.g.***, benzo(a)pyrene, found in automotive exhaust and cigarette smoke; benzene, an organic solvent, and aflatoxin, a metabolic product of molds in peanuts, oils, and grains

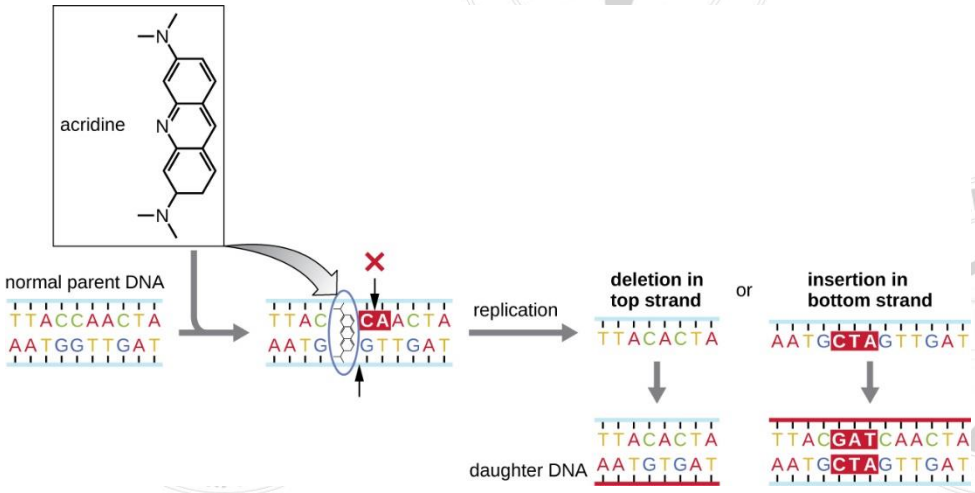


Figure. 10. Intercalating agents, such as acridine, introduce atypical spacing between base pairs, resulting in DNA polymerase introducing either a deletion or an insertion, leading to a potential frameshift mutation.

Biological mutagens

Mutations can also be caused by biological agents such as viruses. Because they are acellular and need to infect a cellular a host to survive and reproduce, viruses are not considered living organisms.

Viral genomes may consist of circular or linear molecule of nucleic acid, and may be single-stranded or double-stranded DNA or RNA. RNA viruses are also called retroviruses since their genome needs to be reverse transcribed into DNA (using the reverse transcriptase enzyme). The reverse transcribed DNA is then incorporated into the host's genome, and then undergoes the usual transcription and translation processes to express the genes carried by the virus. Technically, retroviruses are exceptions to the central dogma, since retroviral genes generate the corresponding proteins via the sequence: RNA → DNA → RNA → protein.

Examples of RNA viruses include SARS-CoV2, the causative agent of COVID-19, and HIV, which causes AIDS.

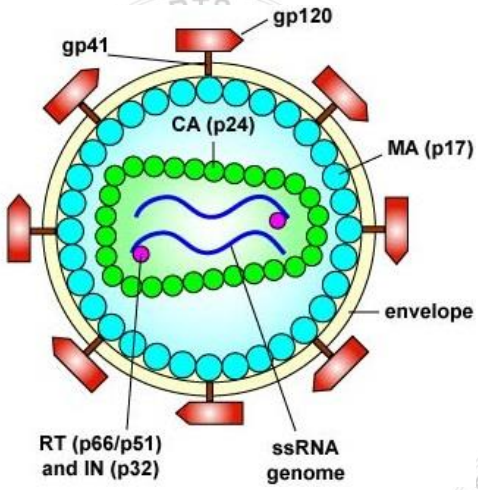


Figure 11. The structure of HIV, an RNA virus (or retrovirus)

When the viral genome enters a host cell, it may undergo either a lytic or lysogenic cycle. In lysogeny, the virus inserts its genome into the host cells and replicate along with it fairly harmlessly. The genomic material may be inserted at random positions in chromosomes. When the host cell reproduces, the viral genome is also reproduced in the cell's offspring. The virus remains dormant until host conditions deteriorate; for example, when nutrients become depleted, at which point the phage shifts to the lytic phase. The phage takes over the cellular machinery of the host cell, and directs the production of the viral components, proteins and nucleic acids, needed to form new virus particles. Once formed, the new viral particles leave the host cell, causing cell lysis.

Integration of the viral genome into host genome may result in gene alteration, especially if the point of integration is a coding or regulatory sequences of a gene. Some viruses are known to cause cancer, either by either introducing genes that stimulate unregulated cell growth or by interfering with the expression of genes that inhibit cell growth. Examples of cancers known to be associated with viral infections include cervical cancer caused by human papillomavirus (HPV), liver cancer caused by hepatitis B virus, T-cell leukemia, and several types of lymphoma. Oncogenic viruses can be either DNA or RNA viruses.

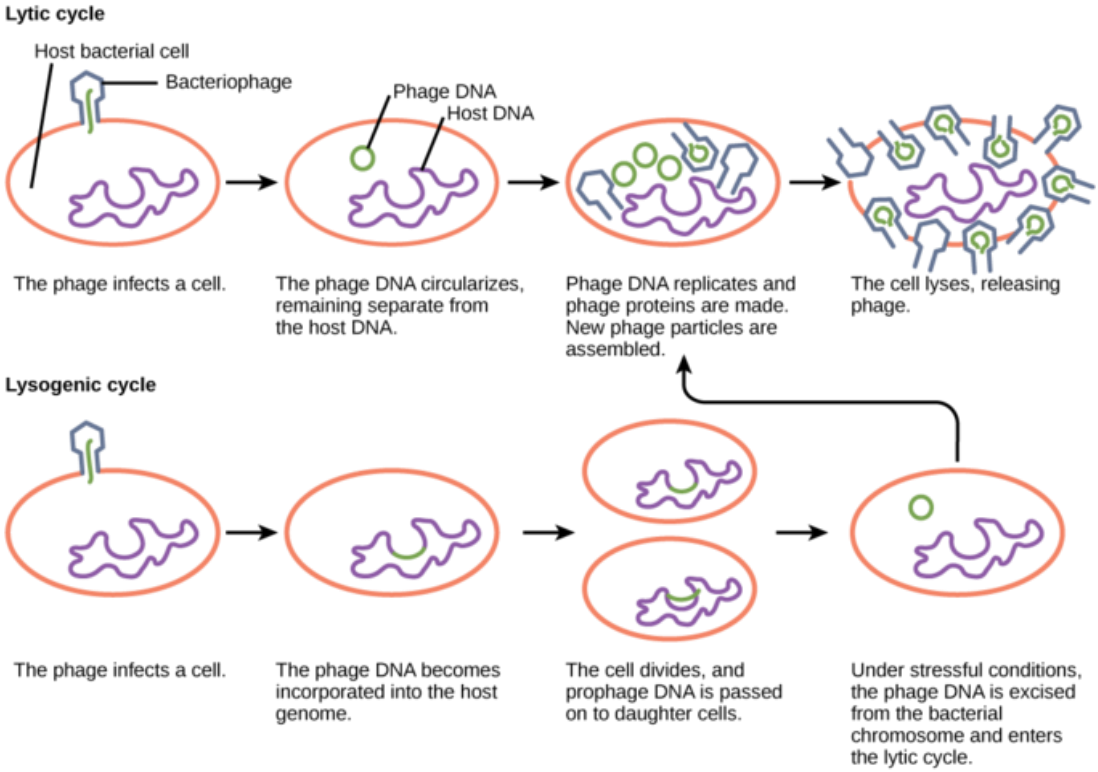


Figure 12: Lytic versus lysogenic cycle. In the lytic cycle, the phage replicates and lyses the host cell. In the lysogenic cycle, phage DNA is incorporated into the host genome, where it is passed on to subsequent generations. Environmental stressors such as starvation or exposure to toxic chemicals may cause the prophage to excise and enter the lytic cycle. **From https://bio.libretexts.org/Bookshelves/Introductory_and_General_Biology/Book%3A_General_Biology_(Boundless)/21%3A_Viruses/21.2%3A_Virus_Infections_and_Hosts/21.2B%3A_The_Lytic_and_Lysogenic_Cycles_of_Bacteriophages**

CHECK YOUR UNDERSTANDING

1. Adding or removing bases in multiples of three will not cause a frameshift mutation. Why is this?
2. The chemical EMS adds an ethyl group to G, which then pairs with T instead of C. What would be the effect of EMS exposure on the DNA sequence …CARGTCA… ?

READING SUPPLEMENT: REAL WORLD EFFECTS OF MUTATIONS

PGC SARS-CoV-2 Bulletin No.1: Philippine Genome Center Reports Detection of the D614G Variant of SARS-CoV-2 Virus in the Philippines

https://pgc.up.edu.ph/pgc-sars-cov-2-bulletin-no-1-philippine-genome-center-reports-detection-of-the-d614g-variant-of-sars-cov-2-virus-in-the-philippines/

COVID-19 or the Coronavirus Disease 2019 is caused by SARS-CoV-2 virus, the genome of which is a single-stranded positive sense RNA that is about 30,000 bases long. It contains 11 genes and several regions have been known to be immunogenic, including different parts of the Spike (S) protein, the Nucleocapsid (N) protein, as well as the Membrane (M) and Envelope (E) proteins, which have therefore been targeted for vaccine development.

In the context of vaccine design and diagnostic assays, it is important to track and study the mutations of the virus as it spreads around the world. Epidemiologists likewise study the random mutations occurring in circulating viruses to inform containment measures.

Coronaviruses including the SARS-CoV-2 are characterized by the presence of spikes surrounding the virus core. These spikes enable the virus to attach to human cells through the ACE2 receptor. Since the spike protein mediates the entry of the coronavirus into host cells, insights into mutations affecting this region is important to understand its infectivity as well as its antigenicity.

The Global Initiative on Sharing All Influenza Data (GISAID) records show that among the most frequently observed amino acid replacements from high quality genomes deposited in its database, the D614G mutation at the spike protein is the most common, with 16,254 occurrences reported as of July 14, 2020[1]. In the D614G variant of the virus, the "D" amino acid aspartate at position 614 of the spike protein has mutated to the "G" amino acid glycine. The G614 variant of SARS-CoV-2 has been reported to have become the dominant strain of the virus in circulation around the world[2].

As part of the validation study of the locally developed SARS-CoV-2 RT-PCR kit, the Philippine Genome Center has done whole genome as well as targeted sequencing of the SARS-CoV-2 virus in the Philippines. Among COVID-19 positive samples from the Philippine General Hospital collected last March 2020 during the early stages of the pandemic in the Philippines, 13 local isolates that were sequenced show the wild type or the original D614 genotype. Six (6) of these were sequenced to near completion and are now deposited in GISAID. In addition, seven (7) samples deposited by the RITM in GISAID also show the D614 wild type strain. All in all, a total of 20 Philippine isolates collected in March 2020 with available sequences spanning the spike protein region show the D614 genotype.

In contrast to the coronavirus collected in March, we now report the detection of the D614 variant among nine (9) randomly selected COVID-19 positive samples collected in Quezon City in July. In the month of June, both the D614 as well as the G614 have been detected in a small sample of positive cases. Although this information confirms the presence of G614 in the Philippines, we note that all the samples tested were from Quezon City and may not represent the mutational landscape for the whole country.

Data from an *in vitro* study suggest that viruses with the D614G mutation appear to have higher levels of viral RNA and higher titers of pseudo viruses[2]. Together with the observation that G614 is now the dominant viral state, the authors claim that the said mutation can increase the viral rate of transmission[2]. However, there is still no definitive evidence showing that carriers of the G614 variant are actually more transmissible than those with D614, and the mutation does not appear to substantially affect clinical outcomes as well[3]. Nevertheless, considering the presently wide geographic spread of G614, continuous monitoring of the said mutation – and other frequently observed mutations for that matter – must be done in order to better understand the evolutionary trajectory of SARS-CoV-2 to inform containment, diagnostic, and therapeutic strategies.

Table 1. A Summary of mutagenic agents. From https://openstax.org/books/microbiology/pages/11-5-mutations

Mutagenic Agents	Mode of Action	Effect on DNA	Resulting Type of Mutation
Nucleoside analogs			
2-aminopurine	Is inserted in place of A but base pairs with C	Converts AT to GC base pair	Point
5-bromouracil	Is inserted in place of T but base pairs with G	Converts AT to GC base pair	Point
Nucleotide-modifying agent			
Nitrous oxide	Deaminates C to U	Converts GC to AT base pair	Point
Intercalating agents			
Acridine orange, ethidium bromide, polycyclic aromatic hydrocarbons	Distorts double helix, creates unusual spacing between nucleotides	Introduces small deletions and insertions	Frameshift
Ionizing radiation			
X-rays, γ-rays	Forms hydroxyl radicals	Causes single- and double-strand DNA breaks	Repair mechanisms may introduce mutations
X-rays, γ-rays	Modifies bases (e.g., deaminating C to U)	Converts GC to AT base pair	Point
Nonionizing radiation			
Ultraviolet	Forms pyrimidine (usually thymine) dimers	Causes DNA replication errors	Frameshift or point

DNA Repair

Because DNA is the repository of genetic information in each living cell, its integrity and stability are essential to life. However, DNA is not a stable molecule. It slowly decays over time, and it is subject to damage and modification due to exposure to various environmental factors. For life to exist, there must be repair mechanisms that can minimize the number of mutations that persist, and which may lead to disease. DNA repair processes exist in both prokaryotic and eukaryotic organisms, and many of the proteins involved have been highly conserved throughout evolution.

Proofreading

Most of the mistakes introduced during DNA replication are promptly corrected by the proofreading function of DNA polymerases even before replication is finished. DNA polymerase checks that the newly added base forms the appropriate H-bonds to the template base before adding the next one. If an incorrect base has been added, it utilizes its 3' to 5' exounuclease function to excise the incorrect nucleotide, and adds the correct one.

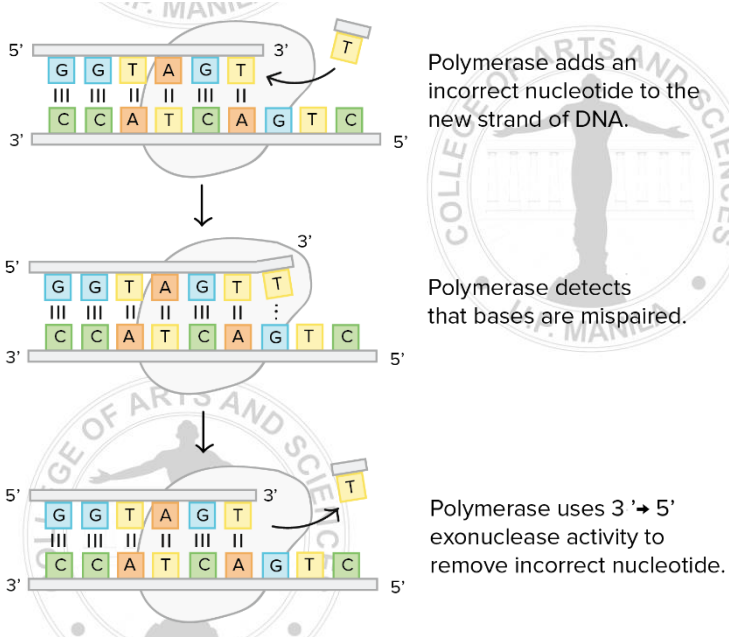


Figure. 13. Proofreading by DNA polymerase corrects errors during replication. From https://www.khanacademy.org/science/high-school-biology/hs-molecular-genetics/hs-discovery-and-structure-of-dna/a/dna-proofreading-and-repair

Mismatch Repair

Some errors introduced during replication are corrected shortly after the replication machinery has moved. An important mechanism for this is methyl-directed mismatch repair. In *E. coli*, a special methylase called the "Dam methylase" adds a methyl group to all adenines that occur within 5' GATC sequences. A newly synthesized double – stranded DNA is hemimethylated, which means that the parental strand is methylated while the newly synthesized daughter strand is not. It takes several minutes before the new strand is methylated. It is during this window of time that the mismatch repair proteins MutS, MutL, and MutH bind to the unmethylated site containing the incorrect nucleotide. MutH cuts the unmethylated strand, and an exonuclease removes a portion of the strand, including the incorrect nucleotide. The gap formed is then filled in by DNA pol III and ligase.

In eukaryotes, the mechanism to distinguish the template strand from the new strand is still unclear.

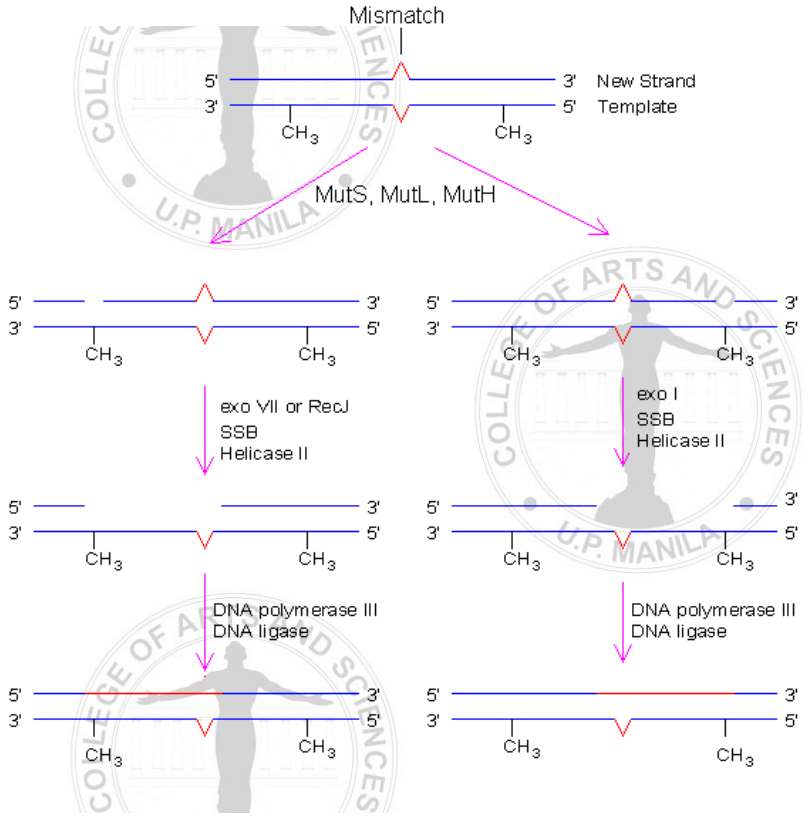


Fig. 14. In mismatch repair, the incorrectly added base is detected after replication. The mismatch repair proteins detect this base and remove it from the newly synthesized strand by nuclease action. The gap is now filled with the correctly paired base, and adjacent nucleotides are covalently linked by DNA ligase.

From https://www.web-books.com/MoBio/Free/Ch7G.htm

Repair of Thymine Dimers

Because many organisms cannot avoid ultraviolet light, the formation of thymine dimers is quite common. Two mechanisms have evolved to repair these lesions.

- **nucleotide excision repair** (also called dark repair): Enzymes remove the pyrimidine dimer and replace it with the correct nucleotides. If a distortion in the double helix due to the presence of a pyrimidine dimer is found, an enzyme complex cuts the sugar-phosphate backbone several bases upstream and downstream of the dimer, and the segment of DNA between these two cuts is enzymatically removed. DNA pol I replaces the missing nucleotides with the correct ones and DNA ligase seals the gap in the sugar-phosphate backbone.
- **direct repair** (also called light repair) occurs in the presence of visible light through the process of photoreactivation. Photolyase enzyme recognizes the distortion caused by the thymine dimer and binds to the dimer. Visible light changes the enzyme's conformation, allowing it to breaks apart the thymine dimer.

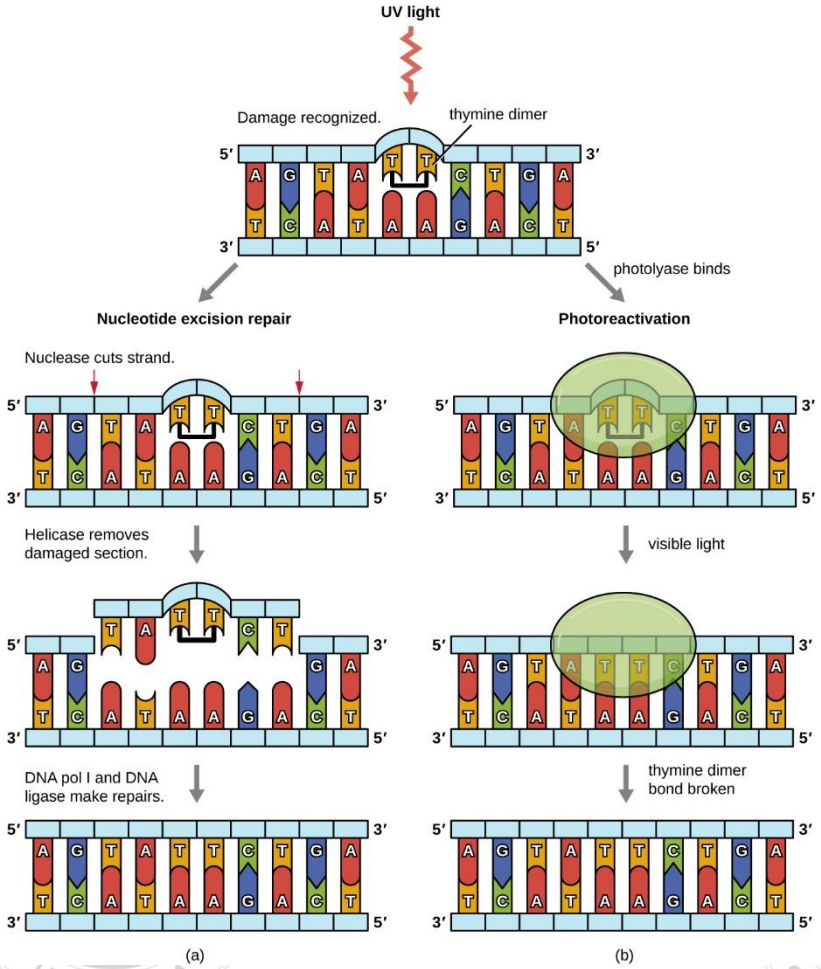


Fig. 15: Bacteria have two mechanisms for repairing thymine dimers. (a) In nucleotide excision repair, an enzyme complex recognizes the distortion in the DNA complex around the thymine dimer and cuts and removes the damaged DNA strand. The correct nucleotides are replaced by DNA pol I and the nucleotide strand is sealed by DNA ligase. (b) In photoreactivation, the enzyme photolyase binds to the thymine dimer and, in the presence of visible light, breaks apart the dimer, restoring the base pairing of the thymines with complementary adenines on the opposite DNA strand. From https://openstax.org/books/microbiology/pages/11-5-mutations

Base excision repair

This repair mechanism is used to fix bases that have become oxidized, alkylated or hydrolyzed due to exposure to free radicals and other reactive species, and therefore must be removed and replaced. This is done by DNA glycosylase enzymes, which cut the defective base from the rest of the nucleotide. The resulting gap is then filled by DNA polymerase I, and adjoining nucleotides are connected by DNA ligase. Various DNA glycosylase enzymes are found in cells, and each is specific to certain types of base alterations.

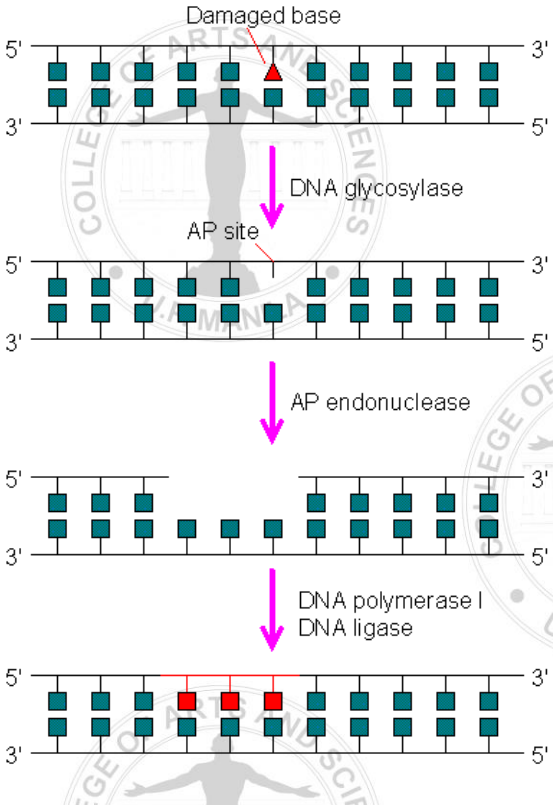


Fig. 16: In the *E.coli* base excision repair system, DNA glycosylase recognizes an apurinic (AP) site and removes its base. The AP endonuclease removes the AP site and its neighboring nucleotides. The gap is filled by DNA polymerase I, and DNA ligase connects adjoining nucleotides. From https://www.web-books.com/MoBio/

Double-stranded break repair

Some types of environmental factors, such as high-energy radiation, can cause double-stranded breaks (DSBs) in DNA. These are more dangerous than damage found in only a single strand, as, for example, large segments of chromosomes, and the hundreds of genes they contain, may be lost if the break is not repaired.

Two pathways are used to repair double-stranded DNA breaks:

1. non-homologous end joining

   The two broken ends of the chromosome are simply glued back together. This typically involves the loss, or sometimes addition, of a few nucleotides at the cut site, and therefore does not return the damaged DNA to its original condition. However, it is better than the alternative, which is loss of part of a chromosome.

2. homologous recombination pathways.

   Information from the homologous chromosome that matches the damaged one (or from a sister chromatid, if the DNA has been copied) is used to repair the DSB. In this process, the two homologous chromosomes come together, and the undamaged region of the homologue or chromatid is used as a template to replace the damaged region of the broken chromosome. Homologous recombination is “cleaner” than non-homologous end joining and does not usually cause mutations.

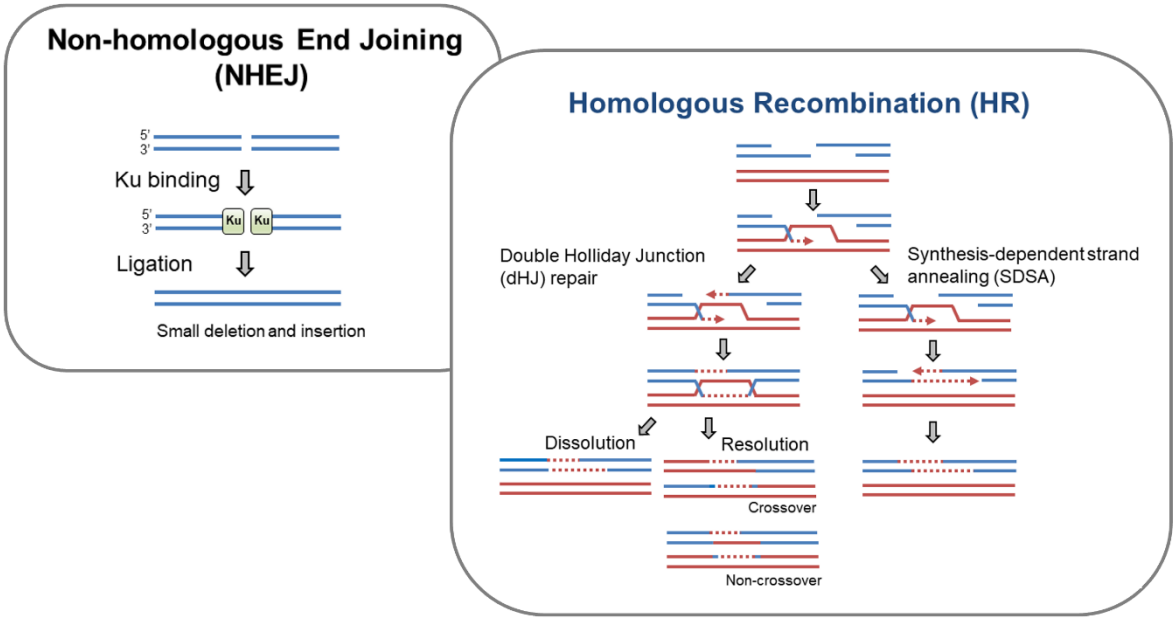


Fig. 17: DSBs can be repaired by different pathways. Non-homologous end joining (NHEJ) and homologous recombination (HR) are two major pathways to repair DSBs. NHEJ is Ku-dependent and ligates DSB ends without using a template. HR uses homologous sequences as repair templates and is considered as the most conserved repair mechanism.
From https://www.scripps.edu/wu/research.html

CHECK YOUR UNDERSTANDING

1. During mismatch repair, how does the enzyme recognize which is the new and which is the old strand?
2. How does an intercalating agent introduce a mutation?
3. What type of mutation does photolyase repair?

DNA MUTATIONS AND DISEASE

Defects in DNA repair underlie a number of human genetic diseases that affect a wide variety of body systems. These include ataxia-telangiectasia (AT), a degenerative motor condition caused by failure to repair oxidative damage in the cerebellum, and xeroderma pigmentosum (XP), which is characterized by sensitivity to sunlight and linked to a defect in an important ultraviolet (UV) damage repair pathway.

DNA damage is a fundamental event in carcinogenesis. Cancer usually results from a series of mutations within a single cell. Mutations leading to cancer often occur in two different types of genes:

1. **Proto-oncogenes**

   Proto-oncogenes are a group of genes that cause normal cells to become cancerous when they are mutated. In their normal form, they encode proteins that function to

stimulate cell division, inhibit cell differentiation, and halt cell death. When mutated, they become oncogenes and contribute to cancer development by stimulating excessive cell growth and cell division. Examples of proto-oncogenes include K-ras and c-myc.

2. **Tumour suppressor genes**

Tumour suppressor genes (TSGs) usually produce proteins that slow down cell division, repair DNA damage, or promote apoptosis, or programmed cell death. When tumor suppressor genes become defective, cells can grow out of control, which can lead to cancer.

For example, the tumor suppressor protein p53 monitors DNA for damage, and triggers repair mechanisms if any is found. If the damage cannot be repaired, p53 initiates apoptosis, thereby preventing the genetically damaged cell from further reproducing. When p53 becomes inactivated by mutation, however, this function is lost; cells divide unchecked and become tumors. Mutated p53 is found in more than half of commonly occurring cancers.

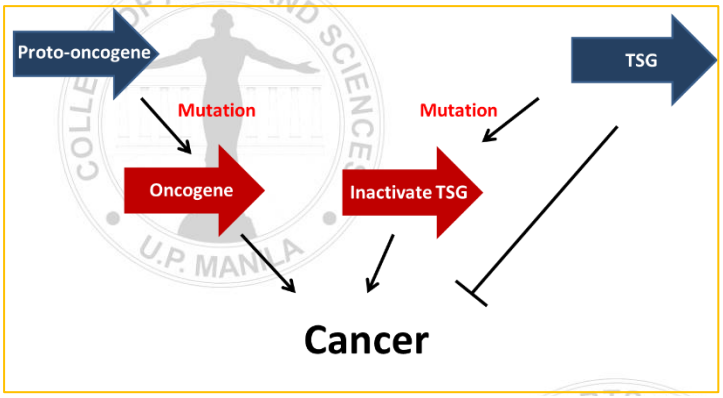


Fig. 18. An important difference between oncogenes and tumor suppressor genes is that oncogenes result from the *activation* (or gain of function) of proto-oncogenes, but tumor suppressor genes cause cancer when they are *inactivated* (or have loss of function). From

https://www2.le.ac.uk/projects/vgec/schoolsandcolleges/topics/genetics-mutation-and-cancer/cancer-genetics

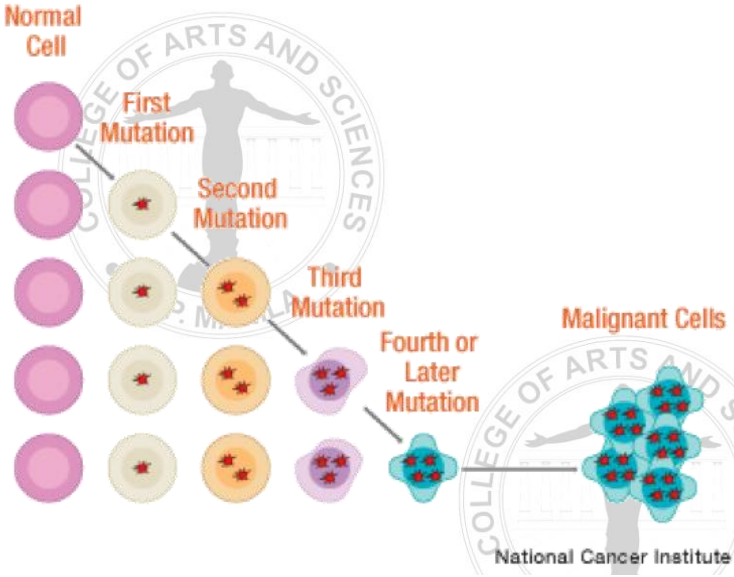


Fig. 19: *C*ancer usually arises from multiple mutational events. Several mutations in both oncogenes and tumour suppressor genes are required for the development of cancerous, malignant tumours. From https://www2.le.ac.uk/projects/vgec/schoolsandcolleges/topics/genetics-mutation-and-cancer/cancer-genetics

Mutations in an organism's DNA are a part of life. Our genome is exposed to a variety of environmental insults that can alter it over the course of our lifetimes. However, a cellular system of checks and balances, in the form of the various DNA repair mechanisms, can mitigate the impact of these alterations. Errors that evade these repair mechanisms may sometimes be associated with disease, but they are also a source of variation that is contribute to longer-term processes, such as evolution and natural selection.

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ADDITIONAL VIDEO RESOURCES

- What happens when your DNA is damaged? - Monica Menesini
  https://www.youtube.com/watch?v=vP8-5Bhd2ag&t=47s
- How this disease changes the shape of your cells - Amber M. Yates
  https://www.youtube.com/watch?v=hRnrIpUMyZQ
- Mutations Animation
  https://www.youtube.com/watch?v=tzSPM9iq7ZU&list=PLYCGVJq0DVwKrmoSIvhzAOh0SpNUgfqFf&index=43
- DNA Mutation by Base Substitution HD Animation
  https://www.youtube.com/watch?v=BvzjqESIcmU&list=PLYCGVJq0DVwKrmoSIvhzAOh0SpNUgfqFf&index=72
- Addition and Deletion Mutations of the DNA HD Animation
  https://www.youtube.com/watch?v=ZHL2ihUDqWY&list=PLYCGVJq0DVwKrmoSIvhzAOh0SpNUgfqFf&index=86
- Thymine Dimers Formation and Repair HD Animation
  https://www.youtube.com/watch?v=SK4MnrgHM-c&list=PLYCGVJq0DVwKrmoSIvhzAOh0SpNUgfqFf&index=13
- Methyl directed mismatch repair HD Animation
  https://www.youtube.com/watch?v=ZoM-HE7Rs6A&list=PLYCGVJq0DVwKrmoSIvhzAOh0SpNUgfqFf&index=46