Module: Molecule, Gene and Disease
Semester: 2
Session: 10
Lecture: 1

Lecture Title:

Mutagenesis & its Effects

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This Lecture was loaded in blackboard and you can find the material in:
(Lippincott's Illustrated Reviews: Cell and Molecular Biology Chapter 5)
For more detailed instructions, any question, or you have a case you need help in, please post to the group of session

Learning Objectives (LO)

1. Explain the relationship between changes in nucleotide and amino acid sequences.

2. Describe the different types of mutational changes, e.g. point mutation, insertion, deletion.

3. Predict and explain the effect that different mutations may have, e.g. silent, missense, nonsense&frameshift mutation.

4. Describe how spontaneous and induced mutations may occur.

5. Describe the genetic link between mutation and mutant and explain how some mutations can be inherited.

6. Describe the process and the role of DNA repair.

7. Explain the relationship between DNA damage and cancer.

This lecture covers

- the phenotypic effects of mutations
- the mechanisms of mutagenesis.
- Types of mutations
- Relation between mutations & cancer

The session demonstrates how the position of a single base change in a nucleotide sequence can determine whether there is no phenotypic effect, a relatively minor effect such as a single amino acid change or a drastic effect such as chain termination.

LO. 1

Gene mutation

❖ Is a change in the nucleotide sequence of an gene, mutation generally show up as altered phenotype due to change in genotype.

As a definition of a gene, a distinct of nucleotides translated to a specific amino acid sequences. So any changes in the nucleotide sequence will mostly lead to change in the amino acid sequence.

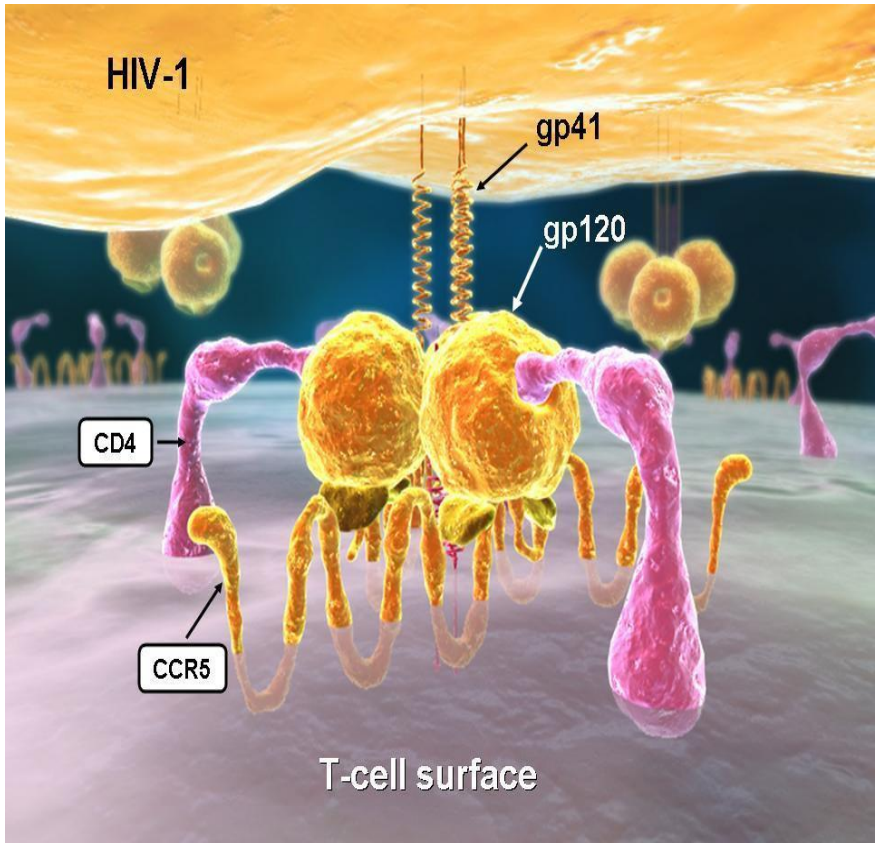
Mutation can be classified into three types according to the effect:

LO. 2

1-Beneficial mutation:

This type of mutation produce anew genotype whose phenotype may be better adapted to the environment or protection.

Ex. Mutation protect against HIV.



https://www.khanacademy.org/test-prep/mcat/biomolecules/genetic-mutations/v/the-different-types-of-mutations

Mutation can be classified into three types according to the effect:/ cont LO.2

2- Neutral mutation:

This type of mutation produce either unaffected or affected on the phenotype but ,in both conditions do not can confer any advantage or disadvantage to the organism

Ex. **Red hair**.

3- Harmful mutation:

This type of mutation produce
changes in the amino acids sequence of protein. Even minor ones can affect its function in a negative way.

Ex. **Thalassemia(Cooly's), Mediterranean anemia**

Mutation can be classified into three types according to the chemical effect: LO. 3

A-Base substitution(point mutation): can be either a **transition** (purine to purine or pyrimidine to pyrimidine) or a **transversion** (purine to pyrimidine or pyrimidine to purine).

Point mutations in the coding region of a protein can be a:

1- silent mutation: There is no noticeable effect because both of those codons cods for the same amino acid.

Type of Change	Mutation in the DNA	Example
None	None	5′–A–T–G–A–C–C–G–A–C–C–C–G–A–A–A–G–G–G–A–C–C–3′* Met – Thr – Asp – Pro – Lys – Gly – Thr –
Silent	Base substitution	5′–A–T–G–A–C–C–G–A–C–C–C–C–A–A–A–G–G–G–A–C–C–3′ Met – Thr – Asp – Pro – Lys – Gly – Thr –

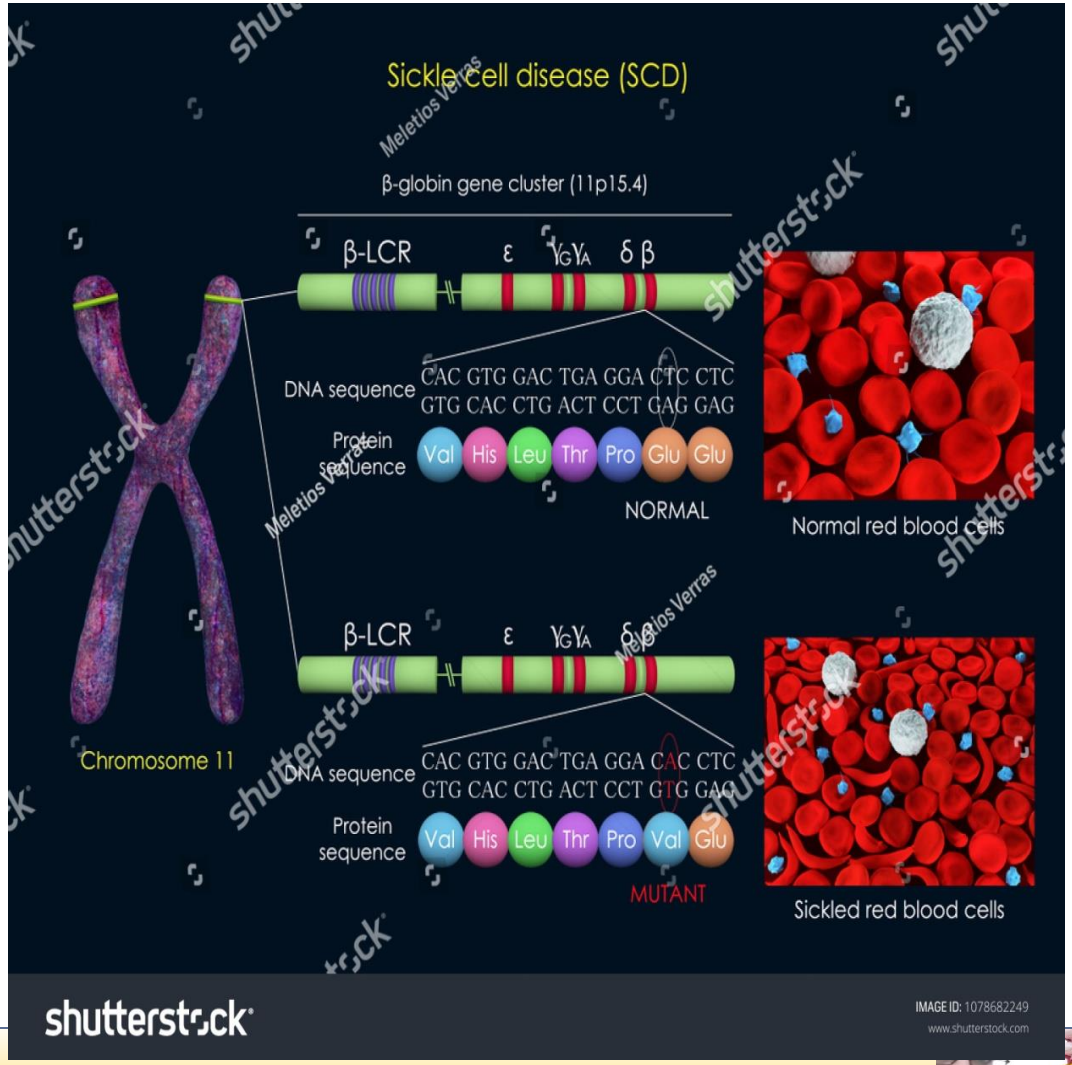
LO. 3

Point mutations

2-Missense mutation:

These are base changes that alter the codon for an amino acid resulting in its substitution with a different amino acid. This substitution may or may not affect the function of the gene product.

Example, GAG (glu.) to GUG (val.) result in **sickle cell anemia**.



LO.3

3- Sense mutation: Produce longer than normal proteins by changing a stop codon into one that codes for amino acids.

4- Nonsense mutation: Change codons that specify amino acids into one of the three stop codons (UAA,UAG,UGA), produce shortened polypeptide chains.

Example: blood clotting disorder changes one GAA coding for glutamic acid to UAA stop codon.

Point mutations in non-coding regions (introns) can of course also be detrimental as they can change protein binding sites, promoter sequences, splice sites etc. **LO.3**

5- Splice site mutation: can changes the phenotype if an intron is translated into amino acids ,or if an **exon** is skipped instead of being translated, shortening the protein.

In cystic fibrosis, a splice site mutation alters an intron site so that it is not removed.
The encoded protein is too bulky to move to its normal position in the plasma membrane, where it should enable salt to exit the cell. As a result, chloride accumulates in cells and water move in ,drying and thickening the mucus outside.

Mutation can be classified into three types according to the chemical effect:/cont LO. 3

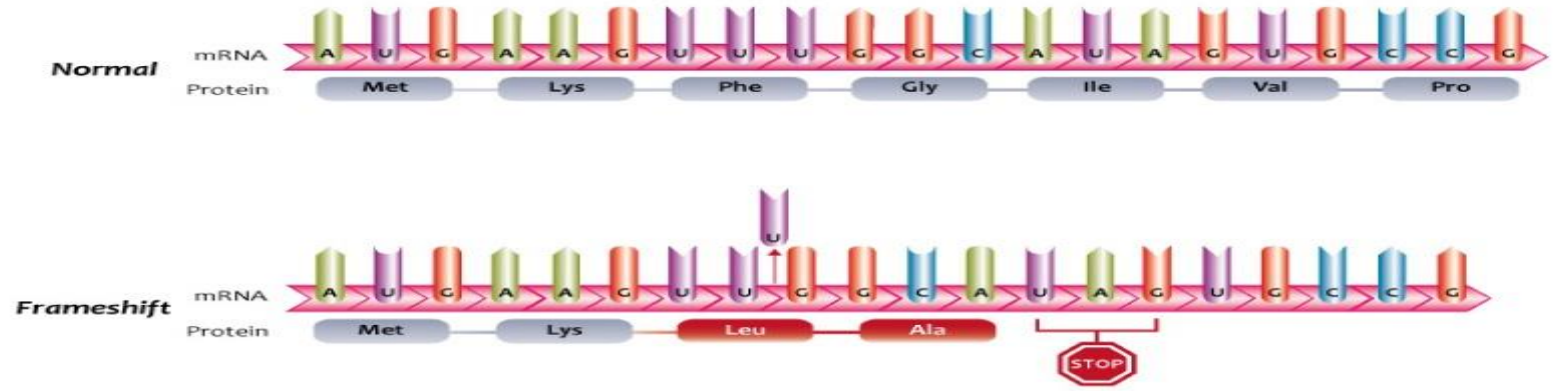
B-Base deletion: Which involve elimination one or two bases. For example: many cases in male infertility are caused by tiny deletions in Y-chromosome.

C-Base insertion: Which involve addition of one or more bases in a gene. For example: In Gaucher disease, an inserted single DNA base prevents production of an enzyme that normally breaks down glycolipids in lysosomes. The resulting build up of glycolipid enlarges the liver and spleen and causes easily fractured bones and neurological impairment.

LO. 3

The deletion and insertion of also called **frame-shift mutation** can be a completely non function protein because the sequence of codons completely altered.

Diseases caused by frameshift mutations in genes include Crohn's disease, cystic fibrosis, and some forms of cancer.



Adapted from Campbell NA (ed). Biology, 2nd ed, 1990.

Spontaneous(intrinsic) mutation occurs may due to LO. 4

- Abnormalities in crossing over
- Aberrant segregation of chromosomes during meiosis.
- Mistakes by DNA polymerase during replication
- Alteration of DNA by chemical products of normal metabolic processes(Ros).
- Spontaneous changes in nucleotide structure
- Guanine pairs with the rare enol form of thymine is considered as hot spot for spontaneous point mutations.

Induced (extrinsic)mutation occurs may due to LO. 4

Resulting from exposure of organisms to mutagenic agents such as:

A-Radiation: such as x-ray and/or ultraviolet, that causes free radicals in the form of ionized hyderogen, or (OH) radicals derived from water.

B-Mutagenes (some chemicals cause mutations): these bind directly to DNA can results in frame shift mutations rather than base substitutions .

These cause DNA strand breaks(single ,double, or both) and cross linking within or between strands.

Genetic link between mutation and mutant

LO. 5

Many mutations are spontaneous; mutations can also be induced (by mutagens).

Mutations are either somatic or germ++line.

Mutations are a source of genetic variation.

A mutation in a gene causes a mutant allele, which is an allele that differs from the common allele in the population (the wild type allele).

a mutant allele inherited from parents to the offspring.

What are the causes of genetic variation occurs during life?

https://www.khanacademy.org/science/ap-biology/gene-expression-and-regulation/mutations-ap/v/mutagens-and-carcinogens

Some mutations can be inherited LO. 5

Hereditary mutations are **inherited** from a parent and are present throughout a person's life in virtually every cell in the body. These **mutations** are also called germline **mutations** because they are present in the parent's egg or sperm cells, which are also called germ cells.

Genetic alterations that occur in more than 1 percent of the population are called **polymorphisms**. Polymorphisms are responsible for many of the normal differences between people such as eye color, hair color, and blood type.

https://www.khanacademy.org/science/ap-biology/gene-expression-and-regulation/mutations-ap/v/an-introduction-to-genetic-mutations

DNA repair

LO. 6

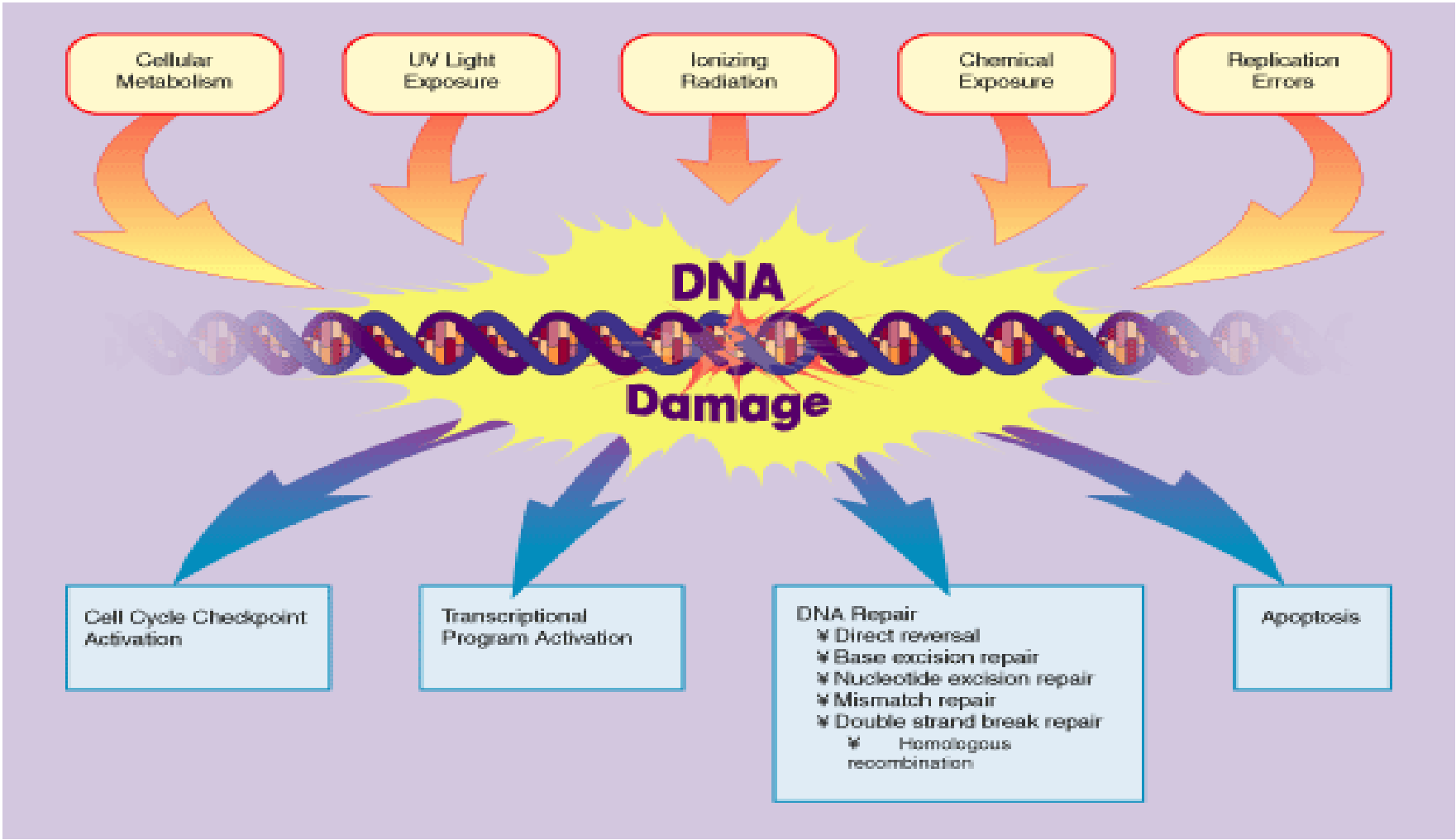
➢Is a collection of processes by which a cell identifies and corrects damage to the DNA molecules that encode its genome.

Damage to DNA alters the configuration of the helix, these alterations can be detected by the cell.

Specific DNA repair molecules bind at or near the site of damage. Inducing other molecules to bind and form a complex that enables the actual repair to take place.

DNA repair

LO. 6



DNA Repair Mechanisms

LO. 6

1-Direct reversal: do not involve breakage of the phosphodiester backbone.

By the action of the enzyme **photolyase**, the photoreactivation process directly reverses this damage(captures the light) upon irradiation with UV light(**pyrimidine dimers**).

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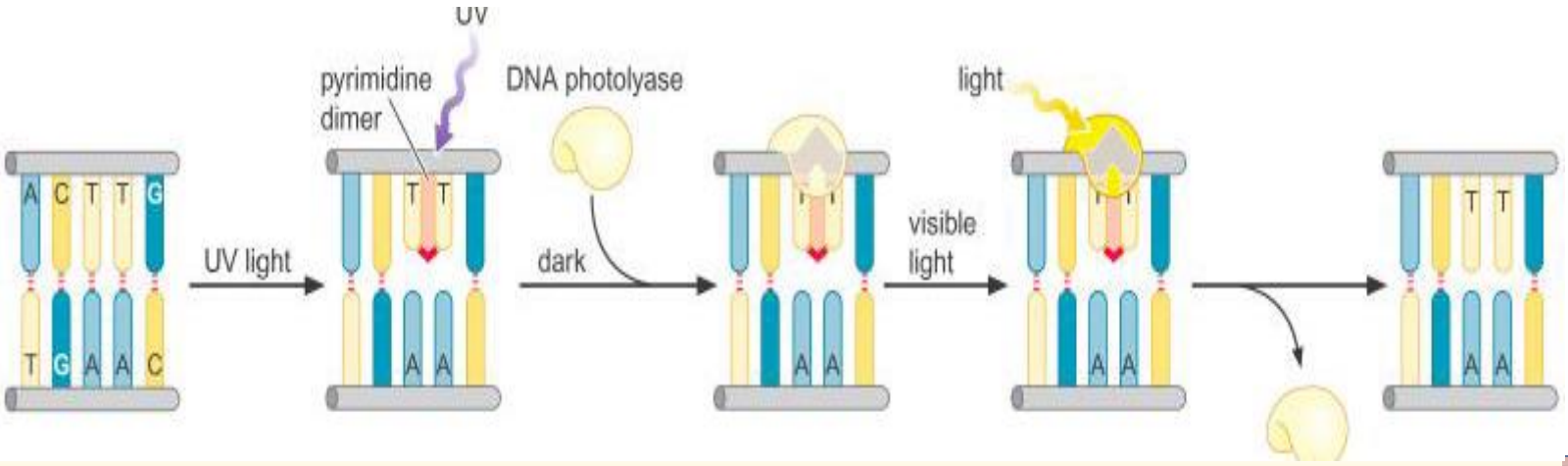


DNA Repair Mechanisms/cont

LO. 6

2- Indirect reversal:

A. Excision repair mechanisms (base excision repair)that remove the damaged nucleotide in single strand and replace it with an undamaged nucleotide complementary to that found in the undamaged DNA strand.

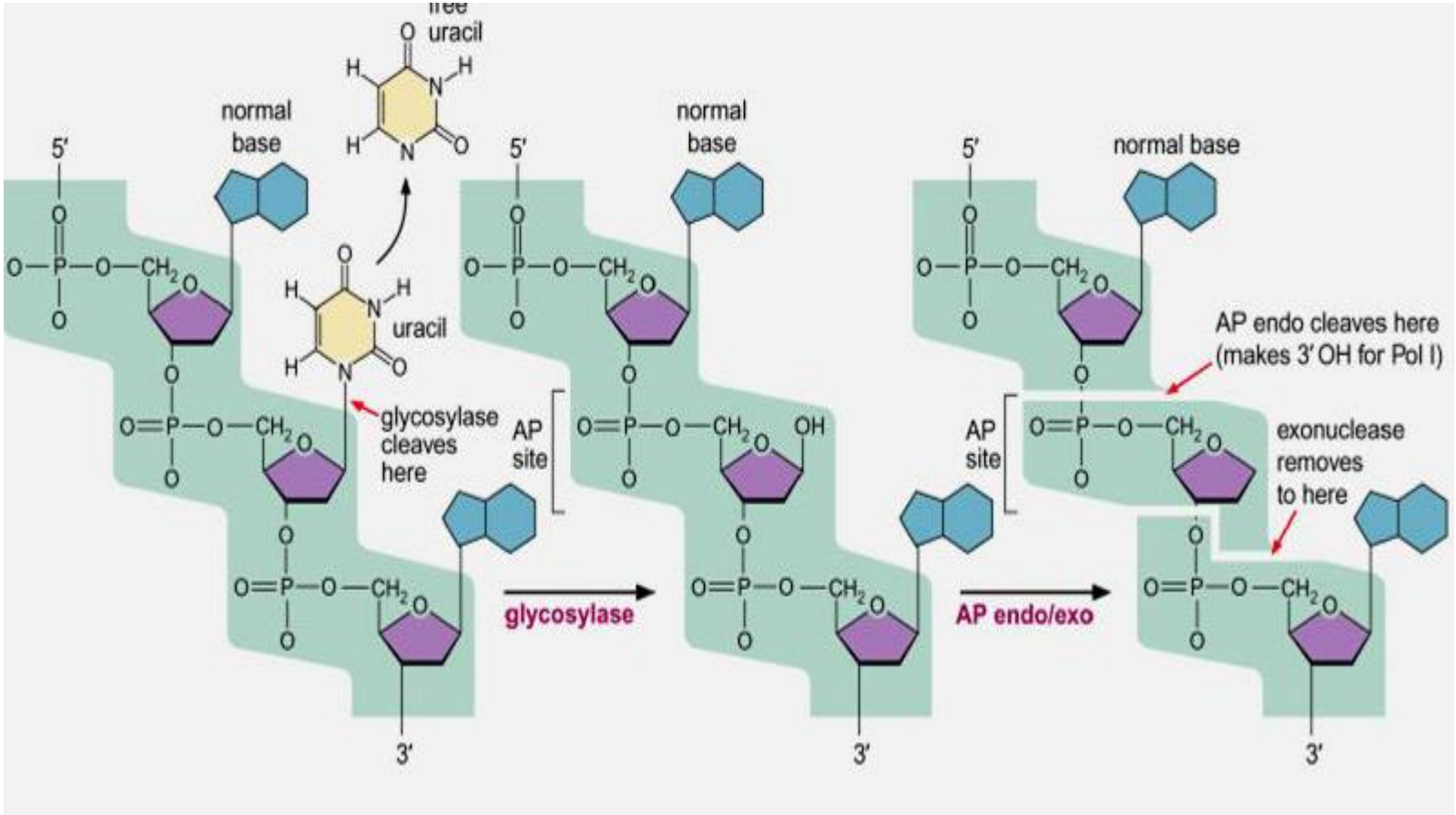
The damaged base is removed by a DNA glycosylase.

- Then recognized by an enzyme called endonuclease , which cuts the phosphodiester bond .
- The missing part is then resynthesized by a DNA polymerase,
- a DNA ligase performs the final nick-sealing step.

DNA Repair Mechanisms/cont

LO. 6

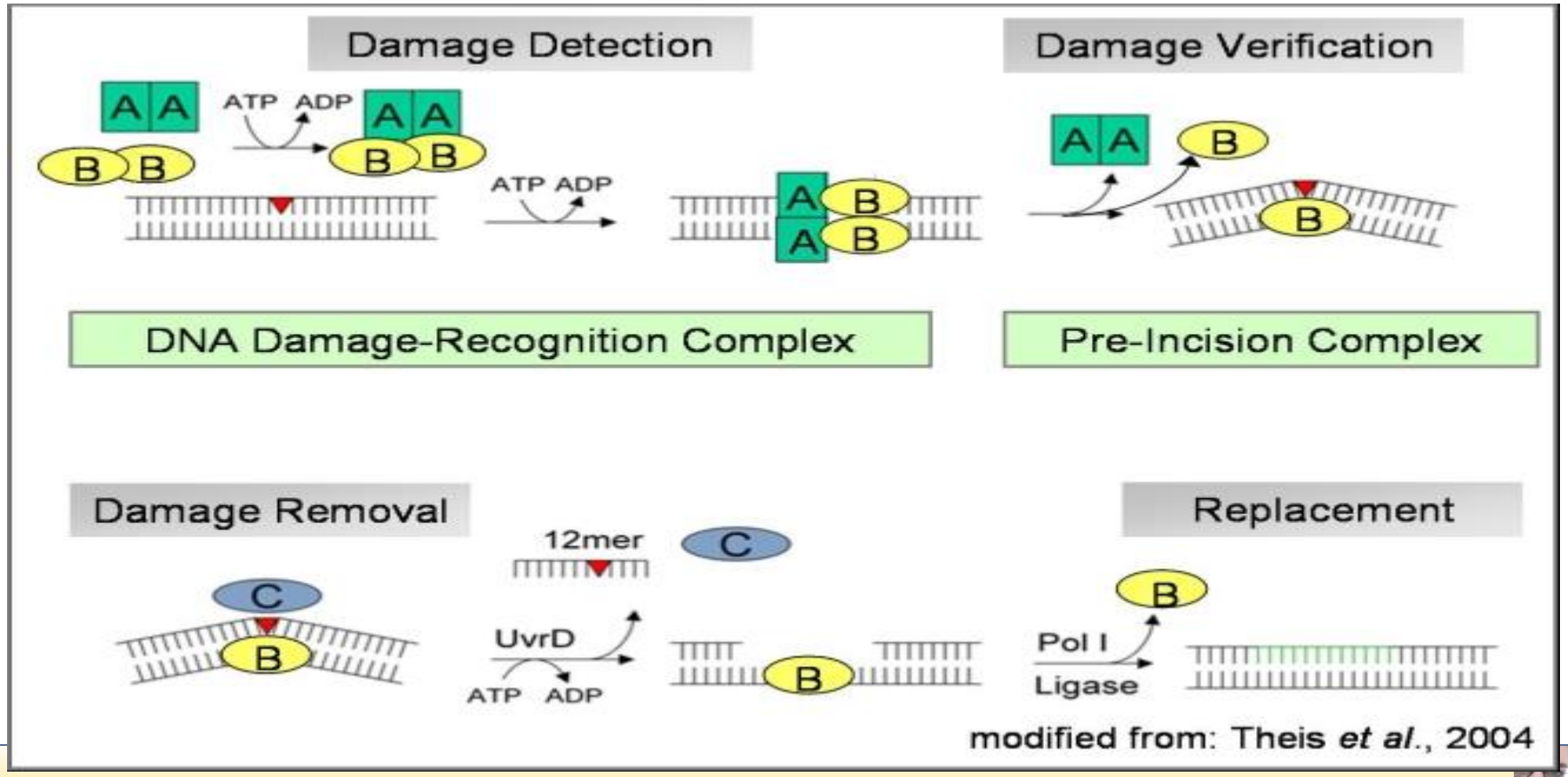
Base excision pathway



DNA Repair Mechanisms

LO. 6

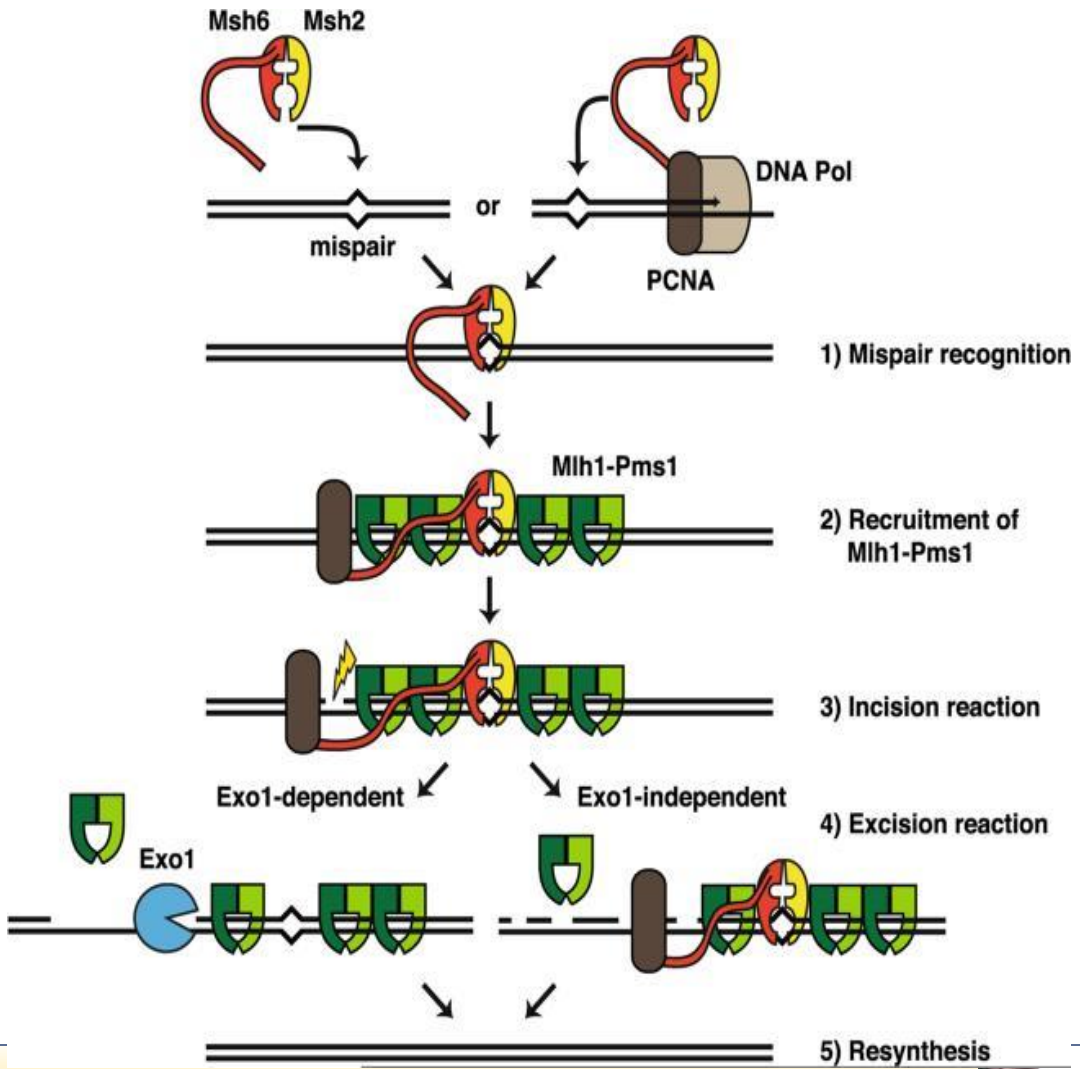
B- Nucleotide Excision repair mechanisms,
which recognize damages , then removal and replacement.



Mismatch Repair Mechanism

LO. 6

C- Mismatch repair, enzymes proofread newly replicated DNA for small loops that emerge from the double helix.
The enzymes excise the mismatched base and then can replaced and correct the error.



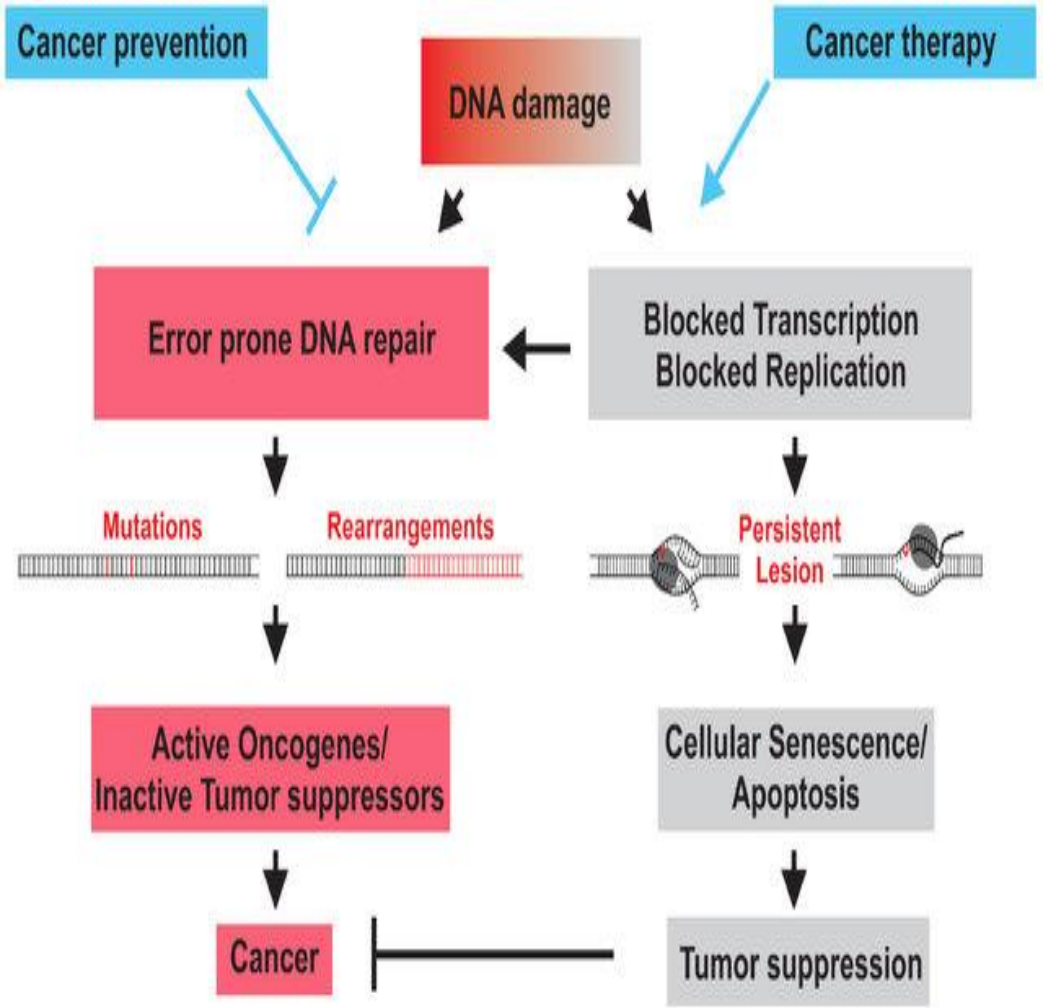
DNA damage and Cancer

LO. 7

In a healthy cell there is a fine balance between DNA damage and DNA repair.

DNA damage causes cancer deve lopment when erroneous DNA re pair leads to mutations of chrom osomal aberration that activate oncogenes or inactivate tumor s uppressors genes.

When DNA damage persists and interferes with replication or transcription, DNA damage checkpoints trigger cellular senescence or



DNA damage and Cancer

LO. 7

apoptosis that inactivate or eliminate damaged cells and thus suppress tumorigenesis. DNA repair mechanisms prevent cancer by preventing mutations. Chemo- and radiotherapy often inflict DNA damage to halt cancer cell proliferation or trigger the apoptotic demise of cancer cells.

All agents that cause cancer (carcinogens) also cause a change in the DNA sequence and thus are mutagens.

The ability of ionizing radiation to cause human cancer (Leukemia) among survivors of the atomic bombs dropped in World War II.


THANK
YOU