Course Name: Human Cytogenetics

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Unit 5: Mutation and Repair of DNA

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Mutation

Introduction:

- Sudden change in genetic material or character of an organism is known as mutation.
- Individuals showing these changes are known as mutants.
- A mutation occurs when a DNA gene is changed or damaged in such a way as to alter the genetic message carried by that gene.
- An individual showing an altered phenotype due to mutation are known as variant.
- Factor or agents causing mutation are known as mutagens.

- A mutagen is an agent of substance that can bring about a permanent alteration to the physical composition of a DNA gene such that the genetic message is changed.
- Mutation which causes change in base sequence of a gene are known as gene mutation or point mutation
- Gene mutations have the exclusive effect of adding to the number of alleles available at a locus, and so increasing the gene pool.
- The gene mutations are the only source of new genetic variability, and without them evolution could not progress for a long time.
- Mutant gene do not become expressed immediately because most of them are recessive.

History

- Seth Wright recorded case of mutation first time in 1791 in male lamb with unusual short legs.
- 1901- Hugo deVries first used the term mutation to describe the sudden heritable phenotypic change in evening primrose *Oenothera lamarckiana.*
- Systematic study of mutation was started in 1910 when Morgan genetically analyzed white eye mutant of *Drosophila.*
- H . J. Muller induced mutation in Drosophila by using X-rays in 1927; he was awarded with Nobel prize in 1946.

Spontaneous Mutation

- Spontaneous mutation occur frequently in nature without any cause.
- During the study heredity since1900, Spontaneous mutation have been recognized in a large number of organisms.
- Various species of *Drosophila* have contributed the greatest number of gene mutations. Hundreds of normal genes and their mutant alleles are known in these flies.
- The known gene mutations in *Drosophila* are those causing white eyes, pink eyes, black body colour, yellow body colour and vestigial wings.
- Similarly in man, many characters as hair colour, eyes colour, skin pigmentation and several body deformities are due to mutant gene.

Induced Mutations

- Induced mutations are alterations in the gene after it has come in contact with mutagens and environmental causes.
- Induced mutations artificially through the use of radiations, chemicals and other agent.
- It has been shown that the mutation rate can be raised well above the spontaneous' rate by various experimental procedures.
- Temperature shocks were one of the first methods used to raise the mutation rate.
- In *Drosophila,* short exposures to both low and high temperature extremes outside the normal range result in higher rate of mutation.

- X-rays and other ionizing radiations (alpha, beta and gamma rays) induce mutations and cause chromosomal breakage. At present, X-rays are considered to be the most effective physical mutagens.
- Several chemicals are also strongly mutagenic. The chemicals like formaldehyde and urethane when mixed with food on which *Drosophila* larvae grow cause mutations.
- Triazine diepoxide, caffeine, phenol and several cancer producing compounds cause mutations.
- Mutations are also produced by the analogues of DNA bases e.g., 5-Bromouracil, 5 Chlorouracil, which are incorporated into newly formed DNA strands.

Types of Mutation

- Chromosomal Mutation

i) Deletion
ii) Duplication
iii) Inversion
iv) Translocation
v) Nondisjunction

- Gene Mutation

i) Point Mutation
   Silent
   Missense
   Nonsense
ii) Frameshift Mutation
   Insertion
   Deletion

Chromosome Mutation

- A chromosome mutation is missing extra or irregular portion of a chromosomal DNA. It can be from an atypical number of chromosomes or a structural abnormality in one or more chromosomes.

Types of Chromosome Mutation

Deletion:

- Deletion occurs when nucleotides are left out of a gene.
- They also usually cause a shift in reading frame that will ultimately truncate the protein.
- Deletions can be caused by errors in chromosomal crossover during meiosis, which causes several serious

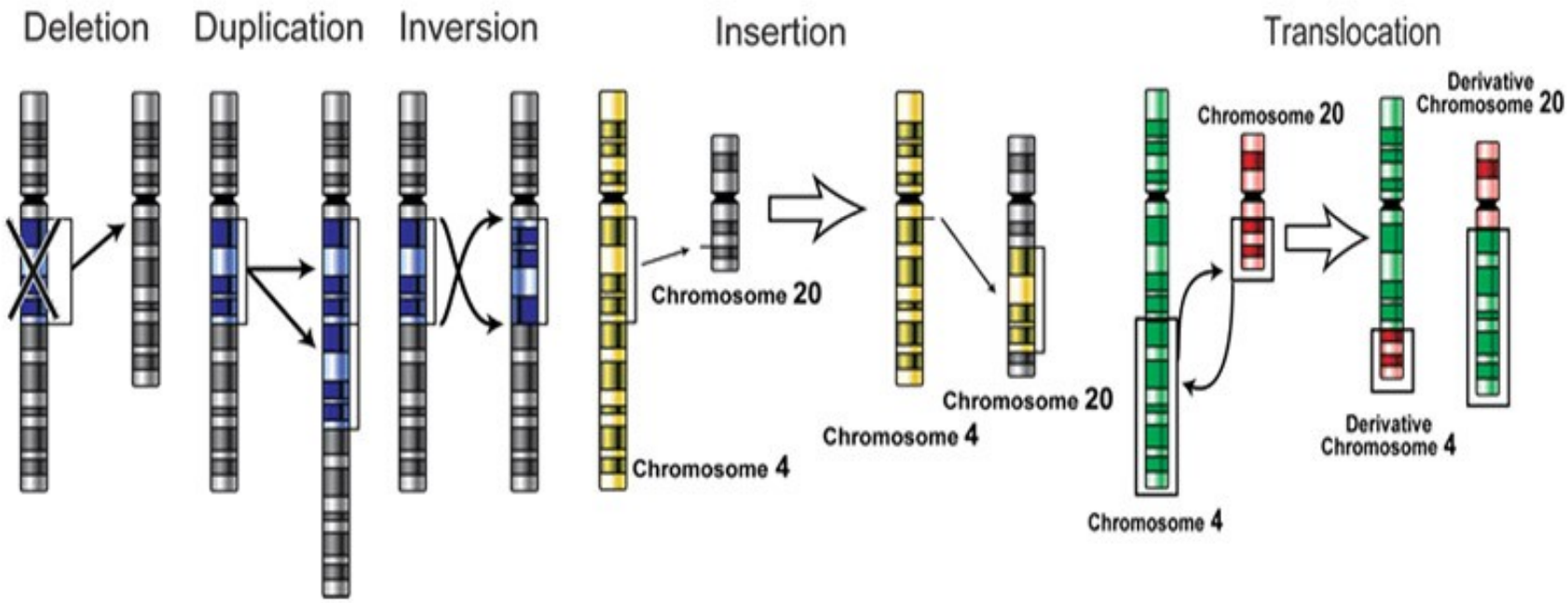
Duplication:

- A portion of the chromosome is duplicated, resulting in extra genetic material
- Duplications arise from an event termed unequal crossing-over that occurs during meiosis between misaligned homologous

Inversion:

- A portion of the chromosome has broken off, turned upside down, and reattached, therefore, the genetic material is inverted.

Types of Mutations



Translocation :

- Chromosome translocation is caused by rearrangement of parts between non homologous chromosome.

Nondisjunction:

- Failure of chromosome to separate during meiosis
- Causes gamete to have too many or too few chromosomes
- Disorder:

- Down syndrome
- Turner syndrome
- Klinefelter's syndrome

Gene Mutation

- A gene mutation is a permanent alteration in the DNA sequence that makes up a gene, such that the sequence differ from what is found in most people.
- Mutation range in size; they can affect anywhere from a single DNA building block (base pair) to a large segment of a chromosome that include multiple genes.

Types of Gene Mutation

Point mutation:

- Point mutation are the most common type of gene mutation. Also called a base-pair substitution, this type of mutation changes a single nucleotide base pair. Point mutation can be categorized into three types:

i) Missense Mutation:

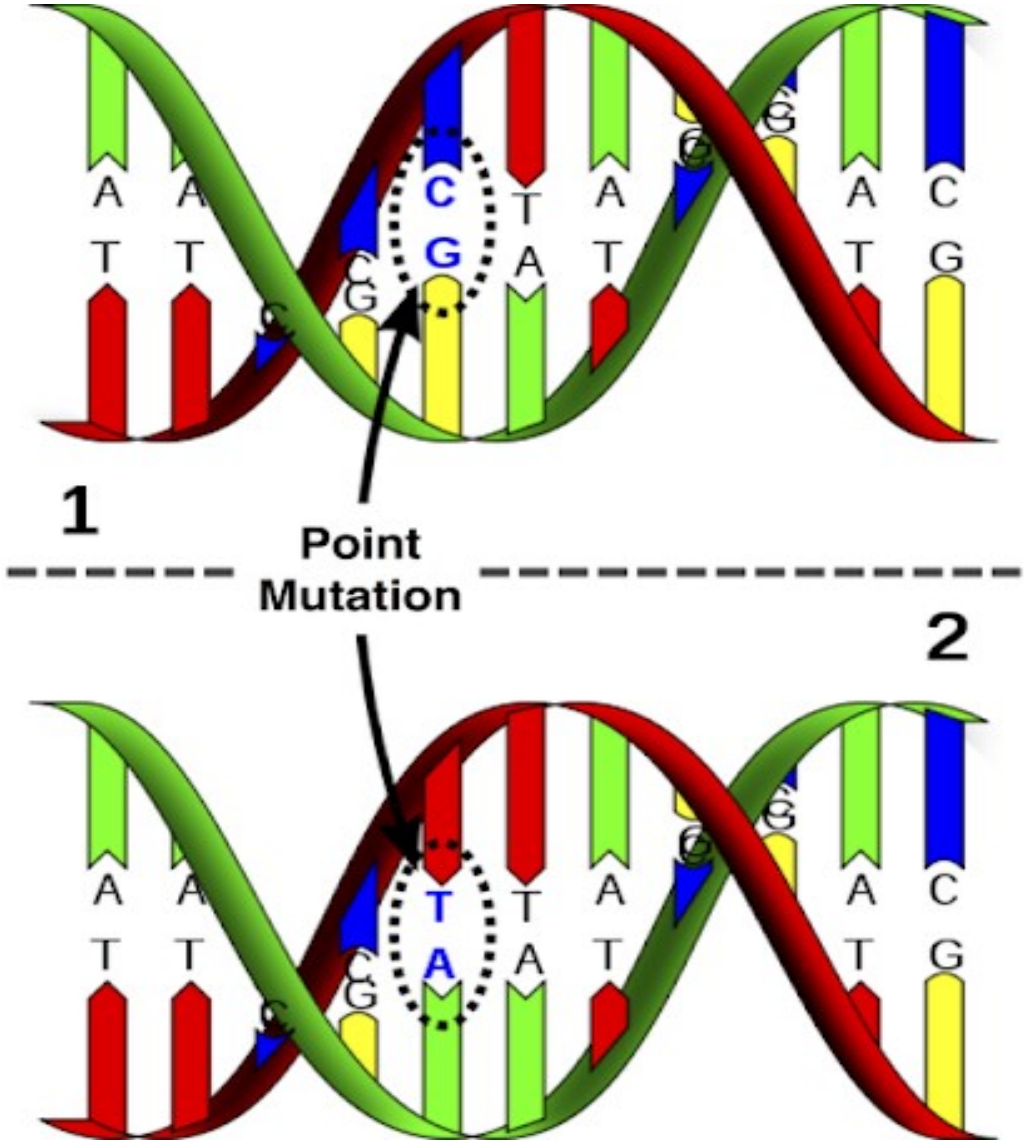
Change in nucleotide sequence brings different types of protein.

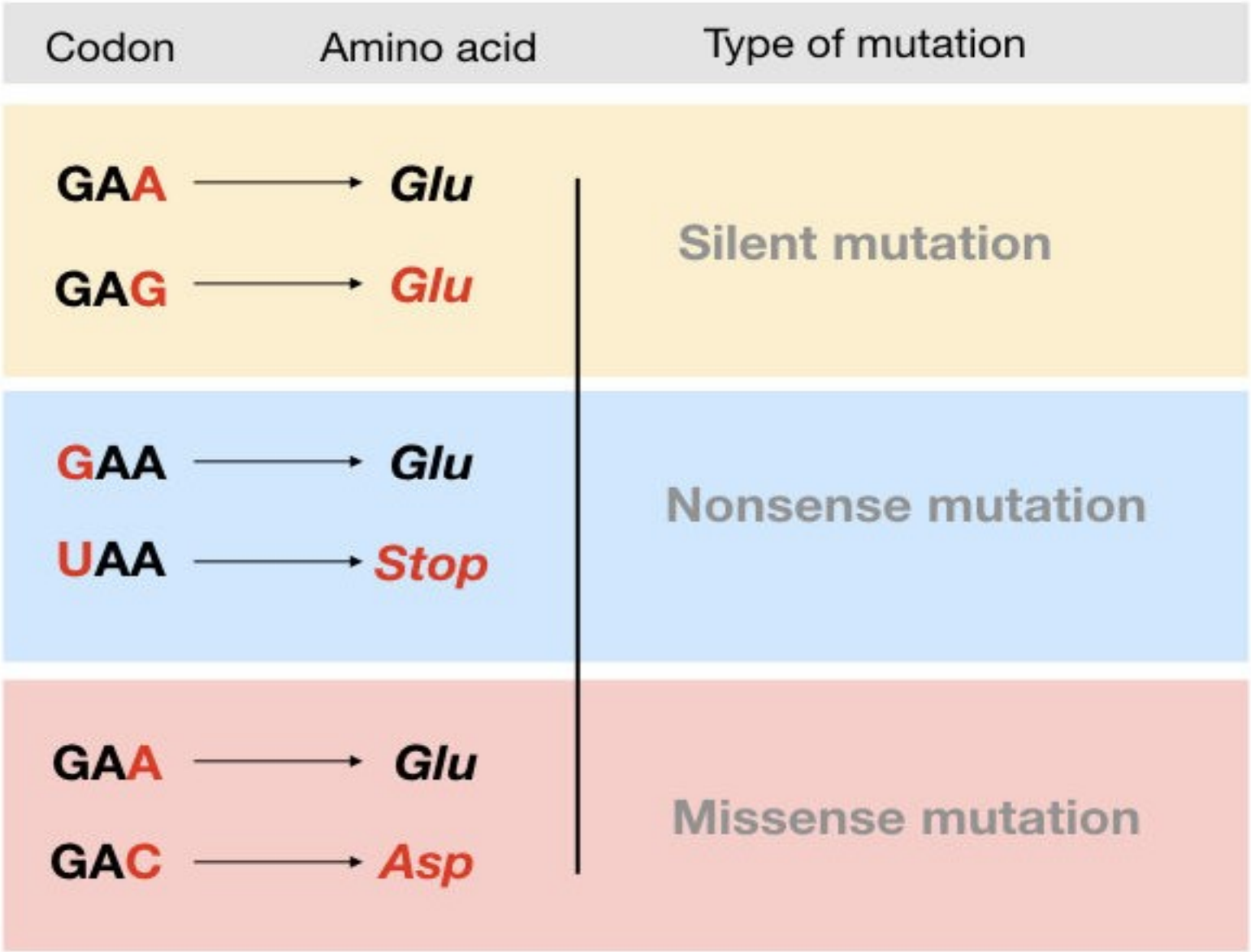
ii) Silent Mutation:

Change in nucleotide sequence brings no change in protein type. It is due to degeneracy of genetic.

iii) Non- Sense Mutation:

Change in nucleotide sequence brings non-sense codon (UAA, UAG, UGA) at a new position in the mRNA as a result, protein synthesis adversely stops.


1
Point
Mutation
2

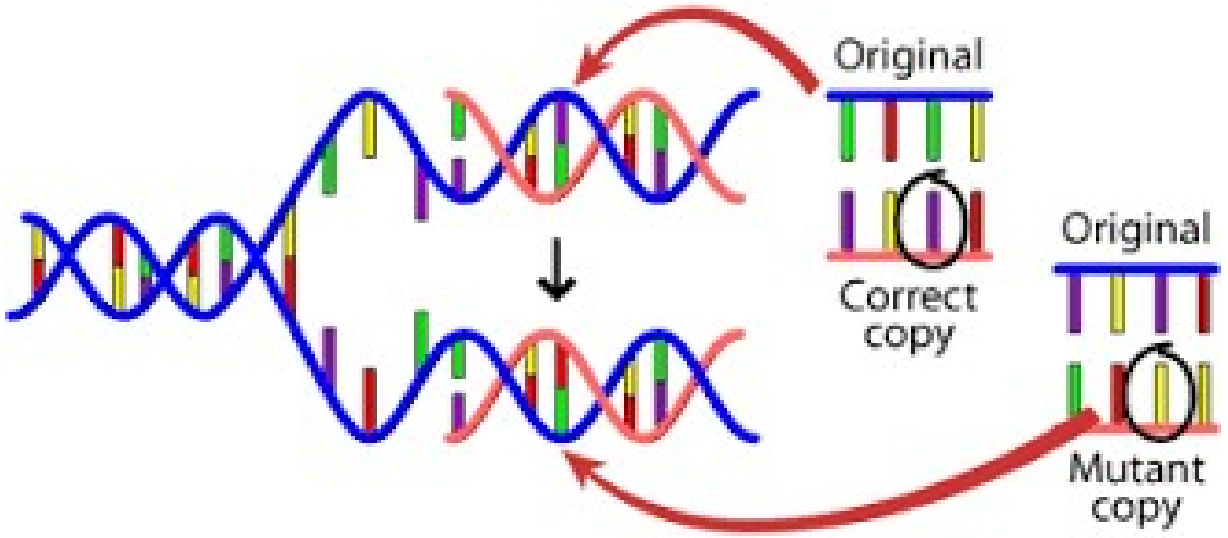

Codon
Amino acid
Type of mutation
GAA
Glu
GAG
Glu
Silent mutation
GAA
Glu
UAA
Stop
Nonsense mutation
GAA
Glu
GAC
Asp
Missense mutation

Frameshift Mutation:

- Mutation caused by the addition or deletion of a base pair or base pairs in the DNA of a gene resulting in the translation of the genetic code in an unnatural reading frame from the position of the mutation to the end of the gene

Causes of mutation

- Acquired mutations occur at sometime during a person's life and are present only in certain cells, not in every cell in the body. These changes can be caused by environmental factors such as ultraviolet radiation from the sun, or can occur if an error is made as DNA copies itself during cell division.
- Mutations can also be caused by exposure to specific chemicals or radiation. These agents cause the DNA to break down. So the cell would end up with DNA slightly different than the original DNA and hence, a mutation.



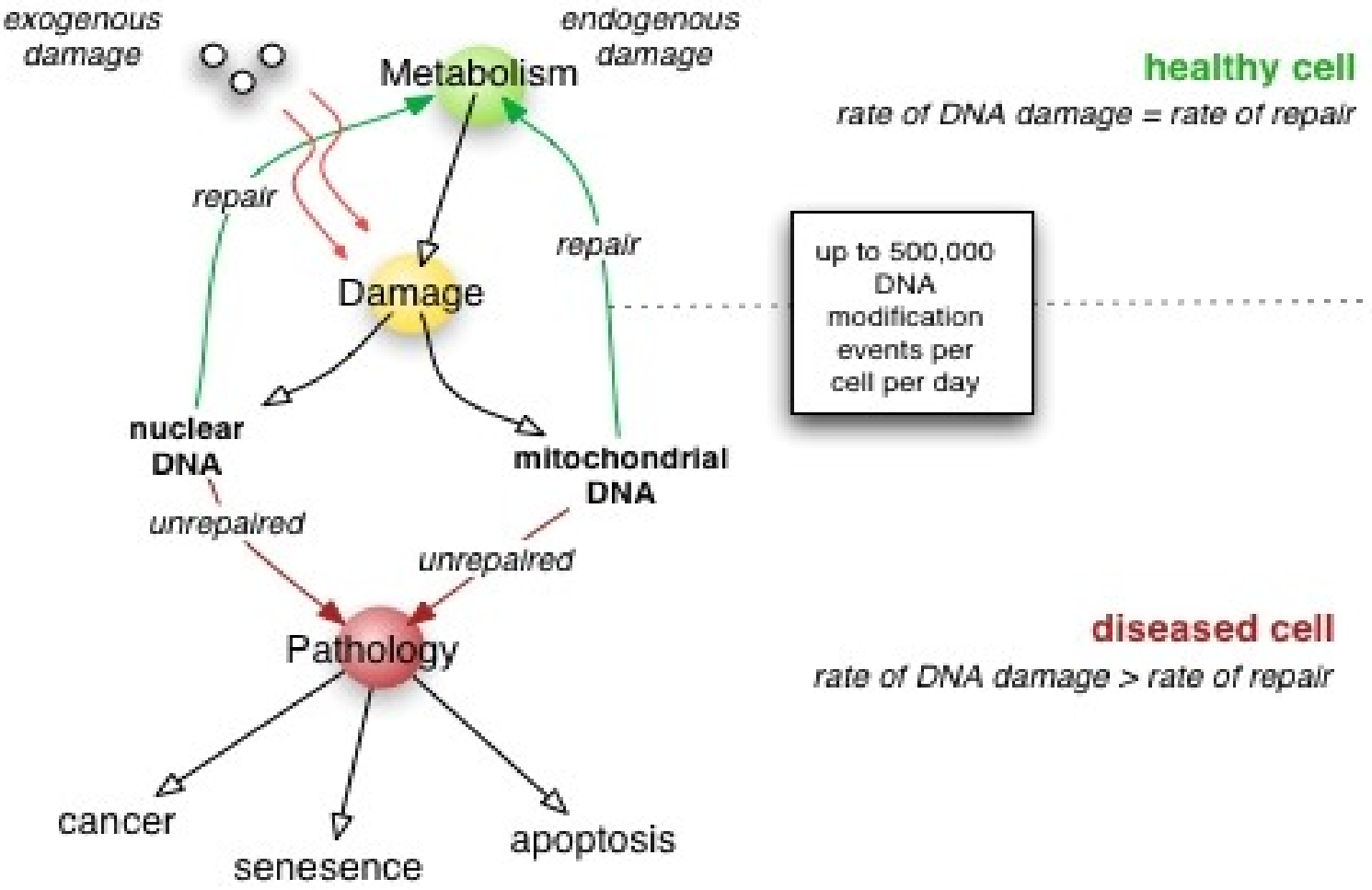
The cause of mutations

Repair of DNA

- In order to repair damage to one of the two paired molecules of DNA, there exist a number of excision repair mechanisms that remove the damaged nucleotide and replace it with an undamaged nucleotide complementary to that found in the undamaged DNA

  strand.
- The different types of DNA repair include direct repair, base excision repair, nucleotide excision repair (NER), double-strand break repair (including homologous recombination and non-homologous end joining), and crosslink repair (Sancar et al., 2004).

- DNA repair is a collection of processes by which a cell identifies and corrects damage to the DNA molecules that encode its genome.
- In human cells, both normal metabolic activities and environmental factors such as radiation can cause DNA damage, resulting in as many as 1 million individual molecular lesions per cell per day.
- Many of these lesions cause structural damage to the DNA molecule and can alter or eliminate the cell's ability to transcribe the gene that the affected DNA encodes. Other lesions induce potentially harmful mutations in the cell's genome, which affect the survival of its daughter cells after it undergoes mitosis.
- As a consequence, the DNA repair process is constantly active as it responds to damage in the DNA structure. When normal repair processes fail, and when cellular apoptosis does not occur, irreparable DNA damage may occur, including double-strand breaks and DNA cross linkages (interstrand cross links or ICLs).This can eventually lead to malignant tumors, or cancer as per the two hit hypothesis.


exogenous damage
endogenous damage
Metabolism
repair
repair
Damage
up to 500,000 DNA modification events per cell per day
nuclear DNA
mitochondrial DNA
unrepaired
unrepaired
Pathology
cancer
senesence
apoptosis
healthy cell
rate of DNA damage = rate of repair
diseased cell
rate of DNA damage > rate of repair

- The rate of DNA repair is dependent on many factors, including the cell type, the age of the cell, and the extracellular environment.
- A cell that has accumulated a large amount of DNA damage, or one that no longer effectively repairs damage incurred to its DNA, can enter one of three possible states:

1. an irreversible state of dormancy, known as senescence
2. cell suicide, also known as apoptosis or programmed cell death
3. unregulated cell division, which can lead to the formation of a tumor that is cancerous

- The DNA repair ability of a cell is vital to the integrity of its genome and thus to the normal functionality of that organism. Many genes that were initially shown to influence life span have turned out to be involved in DNA damage repair and protection.

Thank You