The module: Molecules, Genes and Diseases (MGD)

Session 10

Lecture 17

Duration: 2 hour

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Lecture Title: Mutagenesis and Its Effects

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- **Relevant reading can be found in, for instance:**
- ***Human Heredity Chapters 10, 11, 12, 14***
- ***Marks' Basic Medical Biochemistry Chapters 13, 15***
- ***For more detailed instruction, any question, cases need help please post to the group of session.***

The Learning Outcomes

- Explain the relationship between changes in nucleotide and amino acid sequences. (LO 10.1)
- • Describe the different types of mutational changes, e.g. point mutation, insertion, deletion. (LO 10.2)
- • Predict and explain the effect that different mutations may have, e.g. silent mutation, missense mutation, nonsense mutation, frameshift mutation. (LO 10.3)
- • Describe how spontaneous and induced mutations may occur. (LO 10.4)
- • Describe the genetic link between mutation and mutant and explain how some mutations can be inherited. (LO 10.5)
- • Describe the process and the role of DNA repair. (LO 10.6)
- • Explain the relationship between DNA damage and cancer. (LO 10.7)

LO. 10.1

Gene, protein and phenotype

- Proteins are the link between genes and the phenotype
- Changes in proteins → Changes in phenotype
- Mutated genes can produce either:
  - Abnormal nonfunctional protein
  - Partially functional protein
  - No protein at all

Mutation that affects an enzyme

LO. 10.1

Phenylketonuria (PKU)

- PKU is caused by a mutation in a gene for the enzyme phenylalanine hydroxylase (PAH), which normally converts phenylalanine to tyrosine.
- PKU is an autosomal recessive disorder of amino acid metabolism that results in mental retardation.

LO. 10.1

Defects in Hemoglobin: Sickle cell anemia

- Sickle cell anemia is inherited as an autosomal recessive trait.
- It is caused by a mutation in the beta globin gene.
- The red blood cells became have characteristic sickle shape.

LO. 10.1

Sickle cell anemia

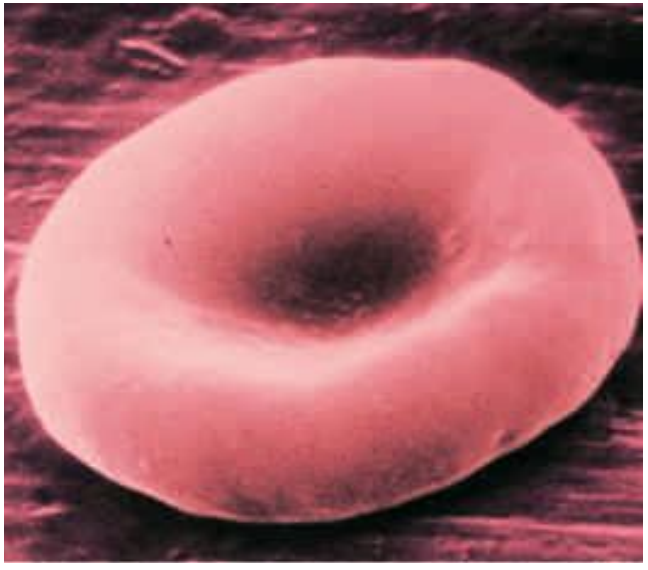
- The sickled cells break easily ⟶ anemia.
- The sickled cells also clog capillaries and small blood vessels ⟶ pain, tissue damage, heart attacks, and strokes.
- The only difference between normal hemoglobin (HbA) and sickle cell hemoglobin (HbS) is a change in the amino acid at position 6 in the beta chain.

LO. 10.1

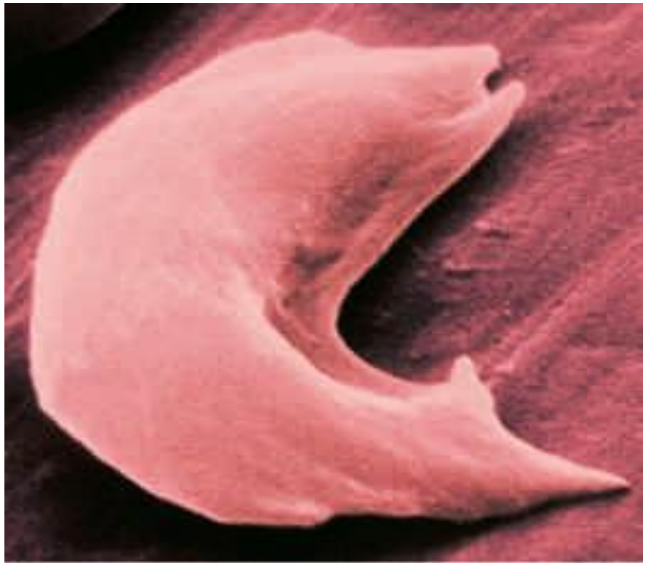
		1	2	3	4	5	6	7	8
Normal hemoglobin A (HbA)	DNA	CAC	GTG	GAC	TGA	GGA	CTC	CTC	TTC
	mRNA	GUG	CAC	CUG	ACU	CCU	GAG	GAG	AAG
	Amino acid	Val	His	Leu	Thr	Pro	Glu	Glu	Lys
Hemoglobin in sickle cell anemia (HbS)	DNA	CAC	GTG	GAC	TGA	GGA	CAC	CTC	TTC
	mRNA	GUG	CAC	CUG	ACU	CCU	GUG	GAG	AAG
	Amino acid	Val	His	Leu	Thr	Pro	Val	Glu	Lys

At the DNA level, the only difference is a T → A substitution in triplet 6. At the protein level, this causes substitution of valine for glutamic acid at amino acid 6 in the beta globin protein, which contains 146 amino acids.

LO. 10.1



Normally shaped red blood cells



Sickled red cells from people with sickle cell anemia

Stanley Fleger/Visuals Unlimited

LO. 10.2

Mutation

- A change in a nucleic acid sequence, which can be the addition of one or many nucleotides (insertion), the removal of one or many nucleotides (deletion), or one nucleotide base is replaced by another in the DNA sequence (substitution).

Types of mutation

LO. 10.2

1. **Point mutations** can be either **transition** or **transversion**.
2. **Frameshift mutations** can be either **insertion** or **deletion**

Point mutation

LO. 10.2

Point mutation: A change of a single nucleotide in a nucleic acid sequence.

Transition: A point mutation where a purine has replaced another purine or a pyrimidine has replaced another pyrimidine.

Transversion: A point mutation where a purine has replaced a pyrimidine or vice versa.

Point mutation

LO. 10.3

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

Silent mutation: a mutation that does not alter the amino acid specified.

Missense mutation: a mutation that replaces one amino acid with another in a protein.

Nonsense mutation: a mutation that changes the amino acid specified to a stop codon.

Sense mutations change a termination codon into one that codes for an amino acid. Such mutations produce elongated proteins.

LO. 10.3

Frameshift mutation

- Mutational events in which a number of bases are added to or removed from DNA, causing a shift in the codon reading frame.
- A frameshift mutation changes the amino acid sequence of the protein from the site of the mutation to the end of the protein.

Frameshift mutation

LO. 10.3

Suppose that a codon series reads as the following sentence:

THE FAT CAT ATE HIS HAT

A nucleotide (in this case, an A) inserted in the second codon destroys the sense of the remaining message:

insertion

THE FAA TCA TAT EHI SHA T

Similarly, a deletion in the second codon can also generate an altered message:

THE FTC ATA TEH ISH AT

A deletion

Beta thalassemia 0 caused by nonsense mutation: LO. 10.3

- A single nucleotide substitution creates a UAG stop codon at position 39 in beta globin mRNA.
- This truncated mRNA is not functional, reducing the production of beta globin and causing a serious disorder called beta thalassemia 0.

Causes of Mutation

LO. 10.4

- **Spontaneous Mutation** result from mistakes that occur during DNA replication or from the action of agents that attack DNA. These agents can originate from inside (free radicals)
- **Induced mutation** caused by radiation or chemicals (mutagens)
- **Carcinogen**: A chemical causing cancer.

Radiation

LO. 10.4

- Cells are about 80% water; radiation often splits water into hydrogen ions (H+) and hydroxyl radicals (OH).
- Free radicals can produce mutations if they interact with DNA.
- If too many mutations accumulate in a cell in a short time, the repair system can be overwhelmed.

Chemicals can cause mutations

LO. 10.4

1. Base analogs
2. Chemical modification of bases
3. Chemicals that insert into DNA

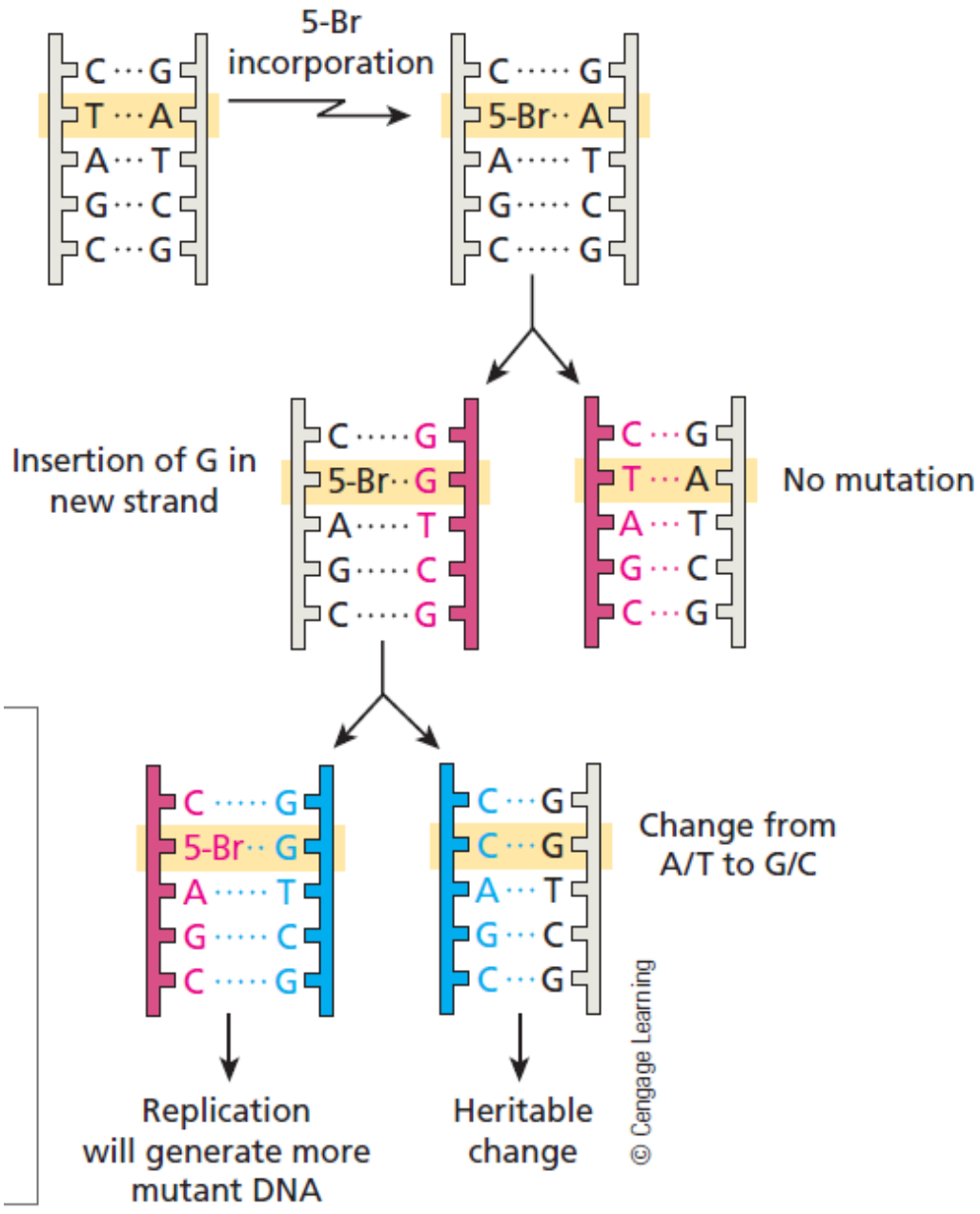
LO. 10.4

Base analogs

- Mutagenic chemicals that resemble nucleotides and are incorporated into DNA during synthesis are called base analogs.
- 5-bromouracil (5-Br) has a structure similar to that of thymine and is inserted into DNA in place of thymine but serve as a template for guanine.
- The original A/T → G/C mutation

LO. 10.4

Mechanism of mutation by Base analogs



LO. 10.4

Chemical modification of bases

- Chemical mutagens can modify the bases in a DNA molecule and alter their base pairing properties.
- Some mutagens do this directly by attacking the bases in a DNA molecule, changing one base into another.
- For example, treatment of DNA with nitrous acid (HNO_2) changes cytosine into uracil.
- Uracil has the base-pairing properties of thymine (T).
- After another round of replication, a G/C → A/T mutation will be created.

Chemicals that insert into DNA

LO. 10.4

- These chemicals called intercalating agents such as acridine orange
- This molecule is about the same size as a purine/pyrimidine base pair and insert itself into DNA, distorting the shape of the double helix.
- When replication takes place in this distorted region, deletion or insertion of single base pairs can take place.

LO. 10.5

Mutation

- A **mutation** is a change in the DNA sequence of an organism.
- A **mutant** is an organism that carries a mutation in its DNA, especially when the mutation results in a visible or detectable difference from the typical (or "**wild-type**") form.

- **Mutation** = the change in DNA
- **Mutant** = the individual that has the change

LO. 10.5

How some Mutations can be Inherited?

1. Germline Mutations (Heritable)

These occur in the reproductive cells (sperm or egg). If a germline cell with a mutation contributes to a new embryo, every cell in that offspring will carry the mutation. These mutations are inheritable and can be passed to future generations.

2. Somatic Mutations (Non-Heritable)

These occur in non-reproductive cells (e.g., skin, liver, lung cells). They can cause diseases like cancer in the individual, but aren't passed to offspring.

LO. 10.5

Example of inherited mutation

Sickle cell anemia:

- **It's caused by a single point mutation in the gene that codes for hemoglobin.**
- **This mutation can be inherited if it's present in the DNA of the sperm or egg.**
- **Individuals who inherit the mutation from both parents show symptoms, while those who inherit it from just one parent may be carriers.**

Mutation and DNA damage can be repaired

LO. 10.6

- Not every mutation becomes a permanent genomic change.
- Mutations happen very frequently but are being recognized and repaired very frequently too.
- Failure of DNA repair can have serious consequences to the cell, and can cause disease.
- In a healthy cell there is a fine balance between DNA damage and DNA repair.
- If the rate of DNA damage is so high, it is easy to overload the repair systems.

Fates of cells have DNA damage

LO. 10.6

Cells that accumulate a lot of DNA damage can have several fates:

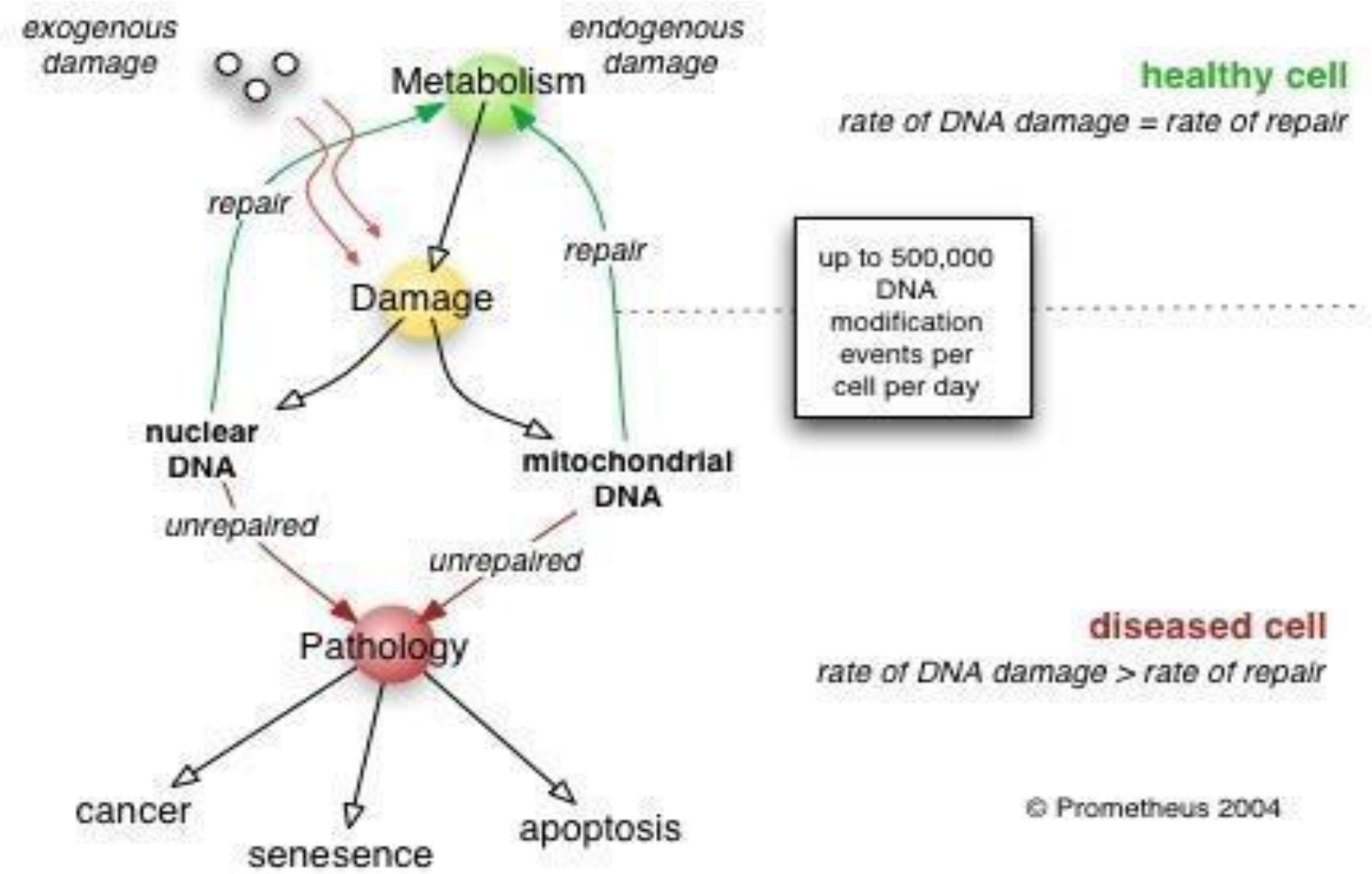
1. The cells can become dormant, a condition called **senescence**.

2. Control systems in the cell can induce cell suicide, a process called **apoptosis**.

3. The accumulated damage can cause the cell to escape the normal controls of the cell cycle and become **cancerous**.

Fates of cells have DNA damage

LO. 10.6



DNA repaired

LO. 10.6

- To maintain the integrity of DNA, cells have a collection of enzyme systems that monitor and repair mutations and DNA damage.
- All cells have enzyme systems that repair mutations and damage to DNA.
- Humans have several highly efficient DNA repair systems.

Cells have several DNA repair systems

LO. 10.6

- One of these systems corrects errors made during DNA replication.
- Other enzyme systems recognize and repair DNA damage in other phases of the cell cycle.

DNA repair system during DNA replication

LO. 10.6

- During replication, an incorrect nucleotide can be inserted into the newly synthesized strand, producing a potential mutation.
- DNA polymerase has a proofreading function.
- If an incorrect nucleotide is inserted, the enzyme can detect the error and reverse direction, move backward and remove nucleotides until the incorrect nucleotide is eliminated.
- Then the enzyme inserts the correct nucleotide and moves forward, resuming replication.
- The few mistakes that elude the proofreading function of DNA polymerase remain as newly created mutations.

Other DNA repair systems

LO. 10.6

- These systems fall into several categories, each controlled by a number of system specific genes.
- For example, exposure of DNA to UV light causes thymine bases adjacent to each other in the same DNA strand to pair with each other, forming thymine dimers.
- Thymine dimers distort the DNA molecule and can interfere with normal replication, producing mutations.
- These dimers are corrected by several different DNA repair mechanisms.

Genes and Cancer

LO. 10.7

- Cancer is a genetic disorder of somatic cells.
- Mutation is a universal feature of all cancers.
- Mutations in the genes regulating cell division are important in cancer development
- Mutations in cancer cells disrupt cell-cycle regulation

Genes regulate cell division

LO. 10.7

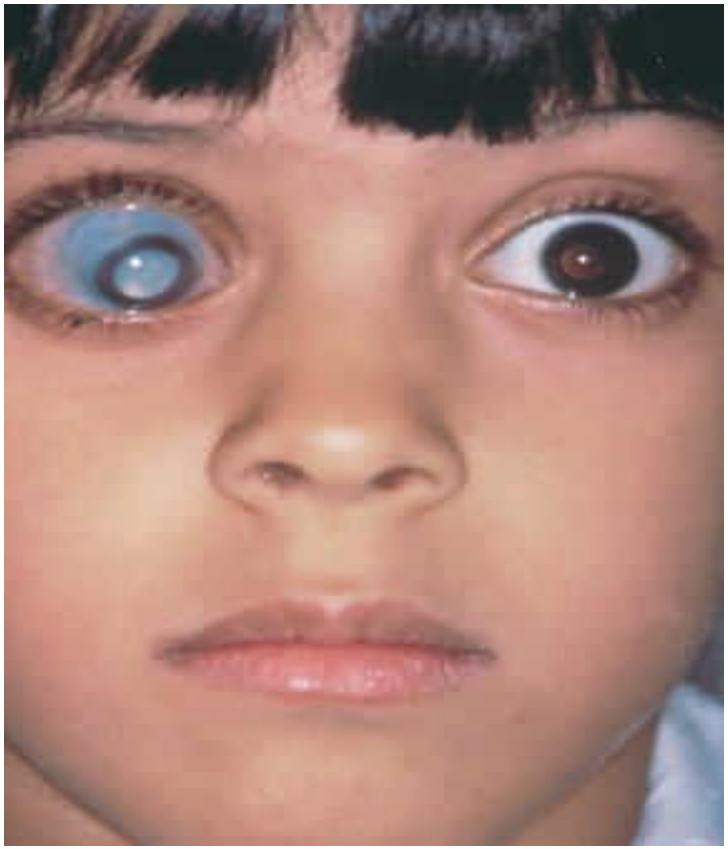
- **Tumor-suppressor genes** that turn off or decrease the rate of cell division
- **Proto-oncogenes** that turn on or increase the rate of cell division.
- Mutation in these genes ⟶ Cancer
- Mutant forms of proto-oncogenes are called **oncogenes**.

Retinoblastoma

LO. 10.7

Mutation in the tumor-suppressor gene (*RB1*) lead to retinoblastoma

Retinoblastoma: A malignant tumor of the eye arising in retinoblasts



LO. 10.7

DNA repair genes and cancer

- Mutant DNA repair genes (*BRCA1* and *BRCA2*) cause a predisposition to breast cancer
- Failures in DNA repair cause a hereditary nonpolyposis colon cancer
- Mutations in DNA repair genes do not directly lead to cancer but do increase the mutation rate across the genome.

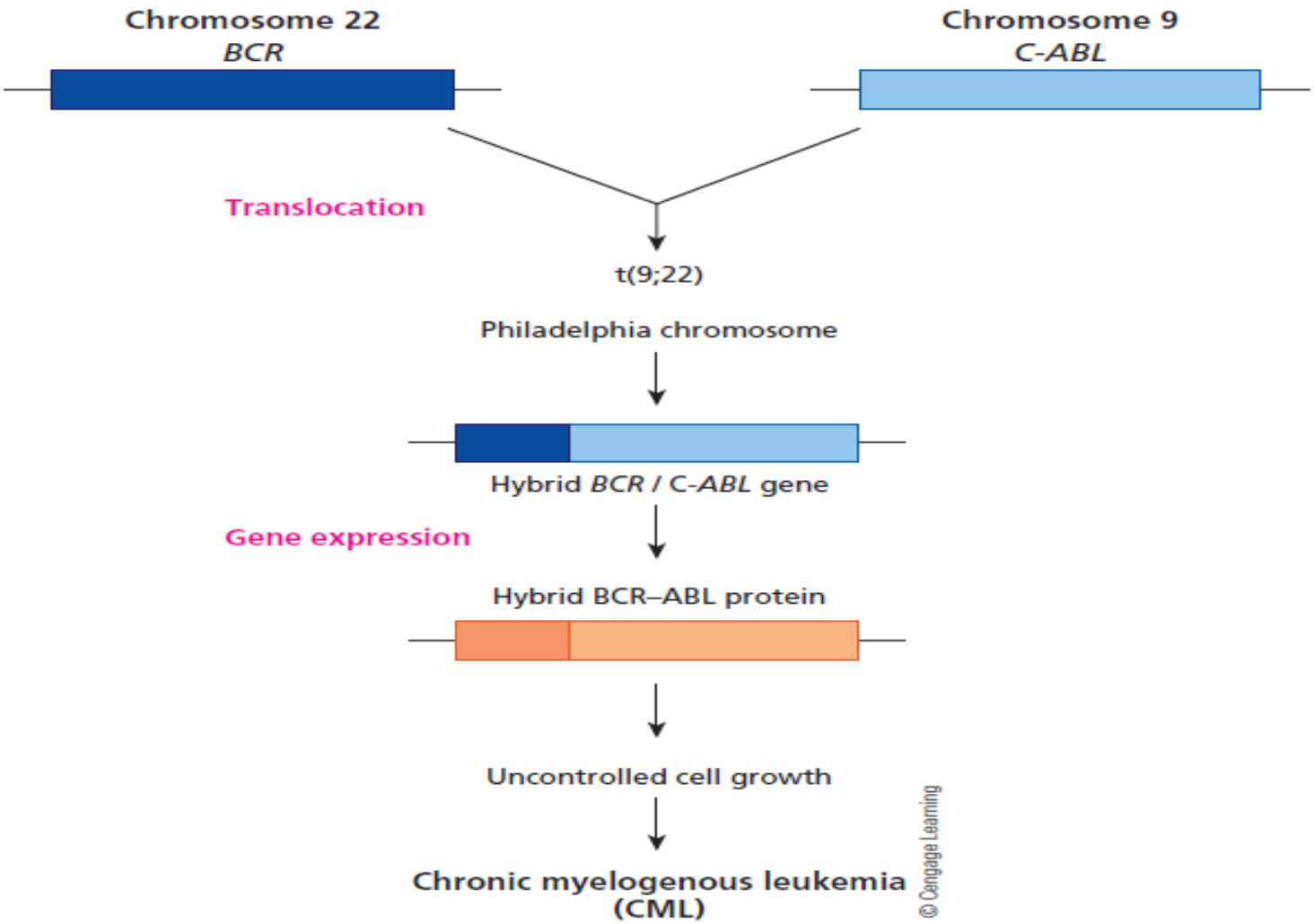
Hybrid Genes and Cancer

LO. 10.7

- **Chronic myelogenous leukemia (CML) associated with translocation between chromosome 9 and chromosome 22 that produce abnormal chromosomal.**
- **This abnormal chromosome is called Philadelphia chromosome**
- **The *C-ABL* gene on chromosome 9 is combined with part of the *BCR* gene on chromosome 22 to form a hybrid gene.**
- **This hybrid gene encodes a unique protein that constantly signals the white blood cell to divide, even in the absence of external signals, resulting in CML.**

Chronic myelogenous leukemia

LO. 10.7



Oncogenic viruses

LO. 10.7

Oncogenic viruses can cause cancer by

- **Genomic Integration**: Some viruses integrate their genetic material into the host cell's DNA, potentially activating oncogenes or inactivating tumor suppressor genes, leading to uncontrolled cell growth.
- **Viral Oncoproteins**: Certain viral proteins can interfere with cell cycle regulation that inactivate tumor suppressor proteins.

Examples

- Human Papillomavirus (HPV): Linked to cervical, anal, and oropharyngeal cancers.
- Human T-cell Leukemia Virus Type 1 (HTLV-1): Causes adult T-cell leukemia/lymphoma

Thank you