Chapter 14

Mutation, DNA repair, and Cancer
Mutation

A heritable change in DNA sequence
Mutation

Examples

- Change base sequence
  - Base substitution

  5’ – CCCGCTAGATA – 3’  →  5’ – CCCGCGAGATA – 3’
  3’ – GGGCGATCTAT – 5’  →  3’ – GGGCGCTCTAT – 5’

- Add or remove a single base pair

  5’ – GGCGCTAGATC – 3’  →  5’ – GGCAGCTAGATC – 3’
  3’ – CCGCGATCTAG – 5’  →  3’ – CCGTCGATCTAG – 5’
Mutation

Examples

1) Point mutation: substitution, insertion or deletion of single base pair

- Single base substitution

  5’ – CCCGCT\text{TAGATA} – 3’ → 5’ – CCCGC\text{GAGATA} – 3’

  3’ – GGGCG\text{ATCTAT} – 5’ → 3’ – GGGGC\text{GCTCTAT} – 5’

- Add (insertion) or remove (deletion) a single base pair

  5’ – GGCG\text{CTAGATC} – 3’ → 5’ – GGC\text{AGCTAGATC} – 3’

  3’ – CCG\text{CGATCTAG} – 5’ → 3’ – CG\text{TGATCTTAG} – 5’
Consequences of mutations

1) Silent mutation

ATG AGC GAC CCC UAU GGG
---
Met  Ser  Asp  Pro  Tyr  Gly

ATG AGT GAC CCC UAU GGG
---
Met  Ser  Asp  Pro  Tyr  Gly

No changes in aa sequence

This happens because genetic code is degenerate
Consequences of mutations

2) Missense mutation

ATG AGC GAC CCC UAU GGG

Met Ser Asp Pro Tyr Gly

ATG AGA GAC CCC UAU GGG

Met Arg Asp Pro Tyr Gly

-changes in a single amino acid

-May or may not alter the function of protein based on the importance of original amino acid
Consequences of mutations

2) Missense mutation

Example: sickle-cell disease  Blood disorder caused by abnormal shape of RBC

Normal RBC: disc shape  Sickle red blood cells; Crescent

=> Deliver less oxygen, easily stick to small blood vessels

Fig 14.1
Consequences of mutations

2) Missense mutation

Example: sickle-cell disease

Wt b-globin

Mutant b-globin

Normal hemoglobin

Sickle Cell hemoglobin forms long, inflexible chains
Example of missense mutation

2) Missense mutation

Example: sickle-cell disease
Example of missense mutation

2) Missense mutation

Example: sickle-cell disease

Symptom

1) Pale skin

2) Delayed growth

3) Bone and joint pain

etc……
Consequences of mutations

3) Non-sense mutation

ATG AGC GAC CCC UA\textcolor{red}{U} GGG \rightarrow \textcolor{red}{A} GG\textcolor{red}{G}

Met Ser Asp Pro Tyr Gly \rightarrow Met Ser Asp Pro \textcolor{red}{Stop} Gly

- Changes to stop codon
- Produce a truncated polypeptides
Consequences of mutations

4) Frame shift mutation

- Produce a completely different amino acid sequence
mutations
## Mutations

<table>
<thead>
<tr>
<th>Mutation in the DNA</th>
<th>Effect on polypeptide</th>
<th>Example*</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>None</td>
<td><img src="#" alt="DNA and amino acid sequence" /></td>
</tr>
<tr>
<td>Base substitution</td>
<td></td>
<td><img src="#" alt="DNA and amino acid sequence" /></td>
</tr>
<tr>
<td>Base substitution</td>
<td>1</td>
<td><img src="#" alt="DNA and amino acid sequence" /></td>
</tr>
<tr>
<td>Addition (or deletion) of single base</td>
<td>-</td>
<td><img src="#" alt="DNA and amino acid sequence" /></td>
</tr>
</tbody>
</table>

*DNA sequence in the coding strand. This sequence is the same as the mRNA sequence except that RNA contains uracil (U) instead of thymine (T).*
Mutations outside of coding sequences

May alter transcription

e.g. Mutations in promoter of amyloid protein => increase in amyloid protein => association with Alzheimer disease

Table 14.2
Germ line or somatic mutation

- Germ line mutation
  - Inherited to offspring
  - Entire organism carries the mutation.

- Somatic mutation
  - Affect part of organism (depending on when mutation occurs)

Every single cell in the body carries same mutation

Germ line or somatic mutation

Gametes

Embryo

Organism

Patch of affected area
Causes of mutations

1) Abnormal biological process
   => Spontaneous mutations

   A. During DNA replication

   B. Toxic metabolic products => alter DNA structure
      e.g., free radical
Causes of mutations

2) Environmental agents => Induced mutations

**Mutagen**: mutation-causing agents

A. Chemical agents

- Base analog
  
  e.g. 5Bromo-uracil

During the replication

5BU can be incorporated

Instead of T

Replication

5BU can switch to isoform

Also see Table 14.4 and Fig 14.5
2) Induced mutations

**Mutagen**: mutation-causing agents

A. Chemical agents

-DNA intercalating agents
  e.g. Ethidium Bromide

. Ethidium Bromide intercalated

. Changes in DNA structure
  ⇒ Inhibition of Replication and/or transcription
2) Induced mutations

**Mutagen**: mutation-causing agents

B. Physical agents

- UV

. Causes dimeration of adjacent Ts

=> Changes in DNA structure

⇒ Inhibition of transcription
2) Induced mutations

**Mutagen**: mutation-causing agents

**B. Physical agents**

*Radiation*  
Causes DNA breaks
DNA Repair System

Recognize mutations and fix

Mutation in DNA sequence → Mutant protein
DNA repair

Types of DNA repair

1) Direct repair

- Enzyme removes a modification

  e.g., Removal of an alkyl group

![Diagram of Alkylation caused by Some chemical agents]

- Alkylation caused by Some chemical agents

  3-Methyl Cytosine → Cytosine
Types of DNA repair

2) Altered DNA strand removed and new segment synthesized: more common

- Nucleotide excision repair (NER)

Most common DNA repair system

e.g. E.coli

UvrA, B, C and D: involved in ultraviolet light repair of thymine dimers
Nucleotide excision repair (NER)

**Thymidine Dimer**

1. **UvrA-B complex tracks along the DNA**
2. **UvrA-B complex identifies a damaged site**
3. **UvrA are released and Uvr C comes in**
4. **Uvr C cuts one strand in both sides of DNA**
5. **Uvr C is released. Uvr D comes in and unravels DNA**
6. **=> Release damaged DNA**
7. **DNA pol comes in and fill in the gap**
Xeroderma Pigmentosum (XP)

Genetic disease

- Defective in DNA repair system

=> Hyper sensitivity to sun light, greater risks of developing skin cancer
Cancer

A class of diseases caused by abnormal cells with uncontrolled cell growth and invasive properties
Cancer

Tumor ≠ Cancer

Tumor: solid lesion formed by abnormal growth of cells

- Benign state: harmless
- Pre-malignant state: will progress if left untreated
- Malignant state: invade surrounding tissues and spread to other organs

Malignant Tumor = Cancer
## Cancer - Leading cause of death

> 20,000 people die from cancer everyday = 1 death every 4 seconds

> 30,000 people are diagnosed with cancer everyday

<table>
<thead>
<tr>
<th>Disease</th>
<th>% of total death</th>
<th>US</th>
<th>% of total death</th>
<th>South Korea</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Heart disease</td>
<td>26%</td>
<td></td>
<td>26.7%</td>
<td></td>
</tr>
<tr>
<td>2. Cancer</td>
<td>23%</td>
<td></td>
<td>12.7%</td>
<td></td>
</tr>
<tr>
<td>3. Strokes</td>
<td>5.6%</td>
<td></td>
<td>7.9%</td>
<td></td>
</tr>
</tbody>
</table>
Causes of Cancers

- Genetic inheritance

- Exposure to external carcinogens

- Or in combination

- In about 10% of cancers (depending on the types of cancers) => people with certain inherited traits have a higher predisposition to develop the disease

- Most cancers do not involve genetic changes that are passed from parent to offspring
• Contribution of Genetic inheritance to cancer development

• 20% - 30% Breast cancer cases

BRCA1: Breast cancer 1
CHEK2: Cell cycle checkpoint kinase 2
- Genetic inheritance

• The mechanism of BRCA 1 mutation in Breast cancer

BRCA 1 involved in interactions with several DNA repair proteins

Commonly mutated sites

Truncated or non-functional proteins

Defects in DNA damage checkpoint signaling and repair

Genomic instability (Aneuploidy, DNA amplification, and etc)
Most of cancers are related to the exposure to carcinogens

1) UV or ionic irradiation

- Direct DNA damage
- Indirect DNA damage by producing free radical

Exposure to UV
- Dimerization of adjacent T
- Distortion of DNA
- Inhibition of transcription
1) UV or ionic irradiation

2) Chemical carcinogen:
   - In prepared food: Burnt foods contain many potent carcinogens e.g., benzopyrene (also found in Tabacco smoke)

Benzopyrene $\rightarrow$ Processed in liver

Benzopyren-7,8-dihydrodiol-9,10-epoxide (BEP) $\rightarrow$

Covalent binding to Guanine $\rightarrow$

Disruption of DNA replication
2) Chemical carcinogen:

-Tobacco smoke:
Carcinogens cause alterations in DNA sequences or structure

=> Affect expression of **genes critical** in maintaining normal cell growth
Two classes of genes that can cause a cancer when mutated

1) Onogenes
   : Genes that have the potential to cause a cancer

2) Tumor suppressor genes
   : Genes that protect a cell from forming a cancer
Two classes of genes that can cause a cancer when mutated
Two classes of genes that can cause a cancer when mutated

Mutations that cause

- Hyperactivation of oncogenes
- Loss of functions of tumor suppressor genes

Uncontrolled cell growth

Tumor
Two classes of genes that can cause a cancer when mutated

1) Onogenes

Proto-oncogene:

- involved in normal cell growth and differentiation

- A large number of proto oncogenes encode proteins that function in cell growth signaling pathways

=> if mutated, can become an oncogene
Two classes of genes that can cause a cancer when mutated

How proto-oncogenes become oncogenes?
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- Missense mutations
How proto-oncogenes become oncogenes?

- Missense mutations

  e.g. Ras protein - involved in various signaling pathway including cell growth
How proto-oncogenes become oncogenes?

- Missense mutations e.g. Ras protein - involved in various signaling pathway including cell growth

1) Cell growth signal

2) Signal Receptor

Cell growth
Missense mutations e.g. Ras protein - involved in various signaling pathway including cell growth

How proto-oncogenes become oncogenes?

1) Cell growth signal
2) Signal Receptor

Cell growth
How proto-oncogenes become oncogenes?

- Missense mutations e.g. Ras protein - involved in various signaling pathway including cell growth

![Diagram showing the conversion of GDP to GTP in Ras protein and its role in cell growth regulation.](Image)
How proto-oncogenes become oncogenes?

- **Gene amplifications**
  - Abnormal increase in copy number => too much of the encoded protein
  - Many human cancers are associated with the amplification of particular proto-oncogenes
How proto-oncogenes become oncogenes?

- **Chromosomal translocations**
  - Two different chromosomes break, and the ends of the broken chromosomes fuse with each other incorrectly.
  - Very specific types of chromosomal translocations have been identified in certain types of tumors.
  - Chimeric genes are composed of two gene fragments fused together.
Chromosomal translocations

How proto-oncogenes become oncogenes?

Bcr-Abl fusion protein: hyperactive

In Normal cells

In leukemia

Protein kinase involved in cell growth
How proto-oncogenes become oncogenes?

Chromosomal translocations

e.g. Bcr-Abl
How proto-oncogenes become oncogenes?

1) Missense mutation
2) Gene amplification
3) Chromosomal translocations