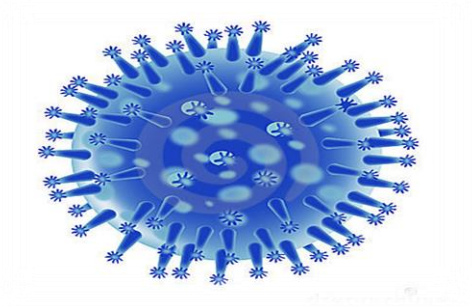


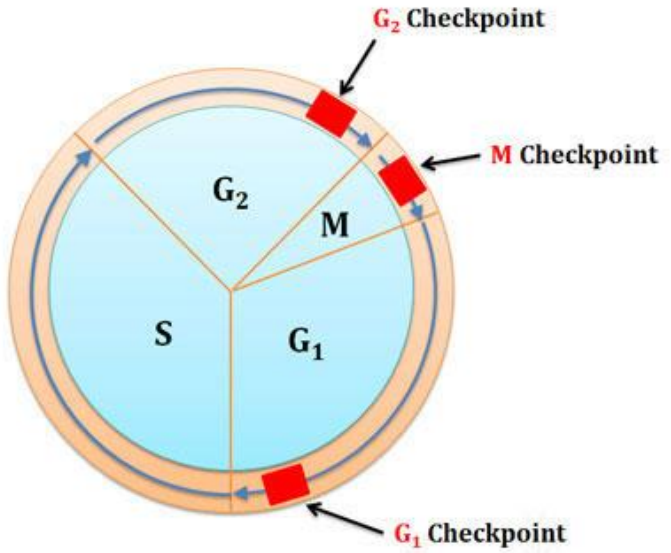
General Microbiology
Lecture 14
2022-2023

Introduction to the Oncoviruses

Dr. Mohammad Odaibat
Department of Microbiology and Pathology
Faculty of Medicine, Mutah University

Introduction

- **Cell growth:** is the cell proliferation (the increase in cell numbers that occurs through repeated cell division).
- Cell growth is regulated by two groups of regulatory genes:
  - A. **Proto-oncogenes (cellular oncogene, c-onc)**
    - are normal genes which control cell proliferation, but which have the potential to contribute to cancer development if their expression is altered **(changed into oncogenes).**
    - codes for:
      - i. Growth factors
      - ii. Receptors
      - iii. Signal transduction proteins.



Cell Cycle Checkpoints

Proto oncogenes vs tumor suppressor genes

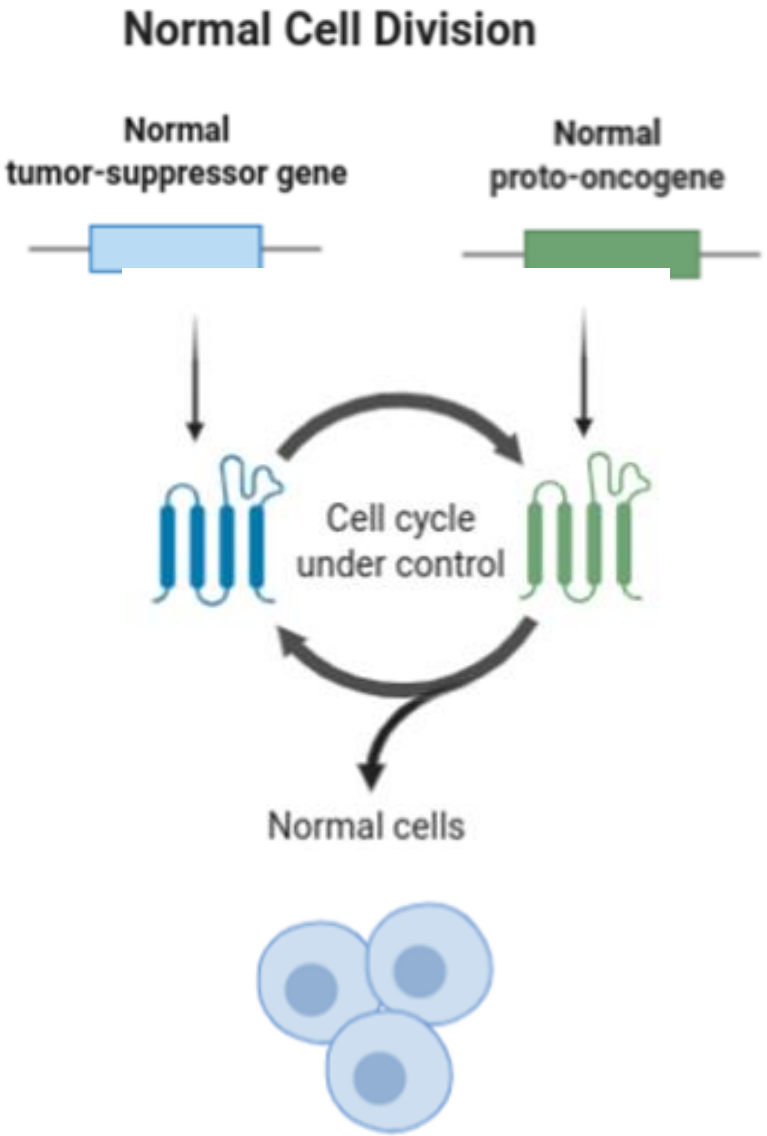
- **Tumor Suppressor Genes** (**Gatekeepers and Caretakers):**

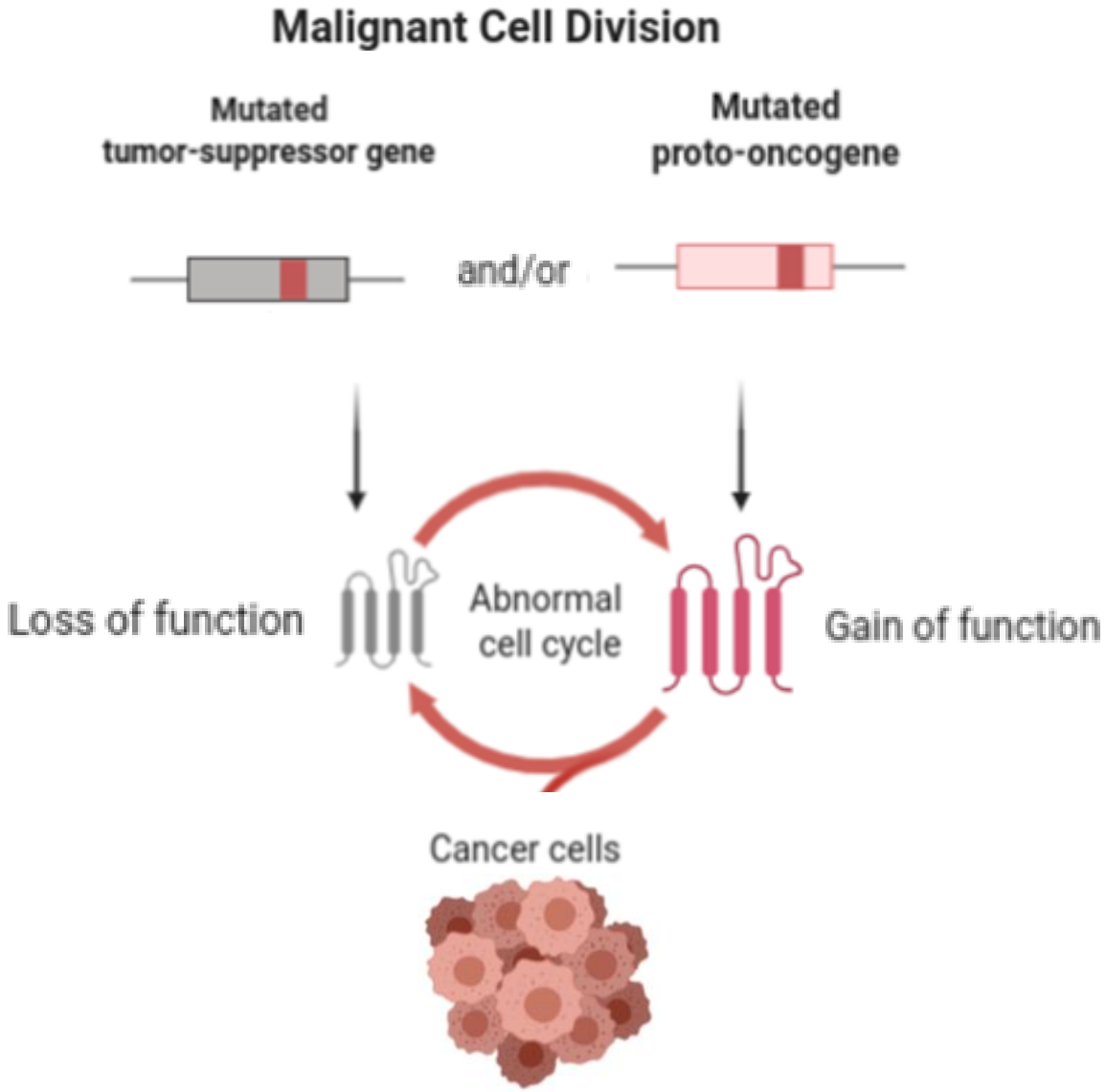
They function as the "brakes" of the car in three primary ways by:

- inhibiting cell growth,
- fixing broken DNA,
- or causing a cell to die.
  - Examples: P53, Rb

An important difference between oncogenes and tumor suppressor genes is that **oncogenes result from the activation (turning on) of proto-oncogenes**, but tumor suppressor genes cause cancer when they are inactivated (turned off).

Proto oncogenes vs tumor suppressor genes

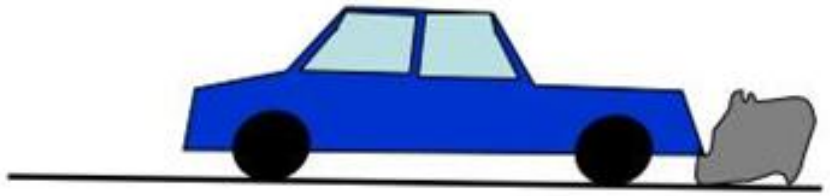




Protooncogenes vs tumor suppressor genes

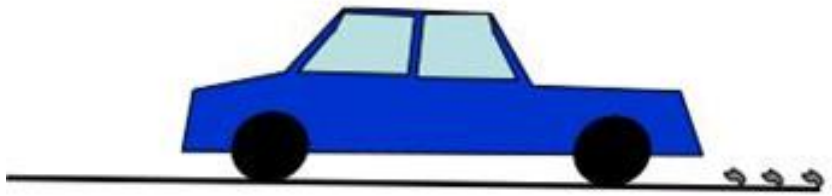
Wild-type proto-oncogene

Wild-type Tumor suppressors

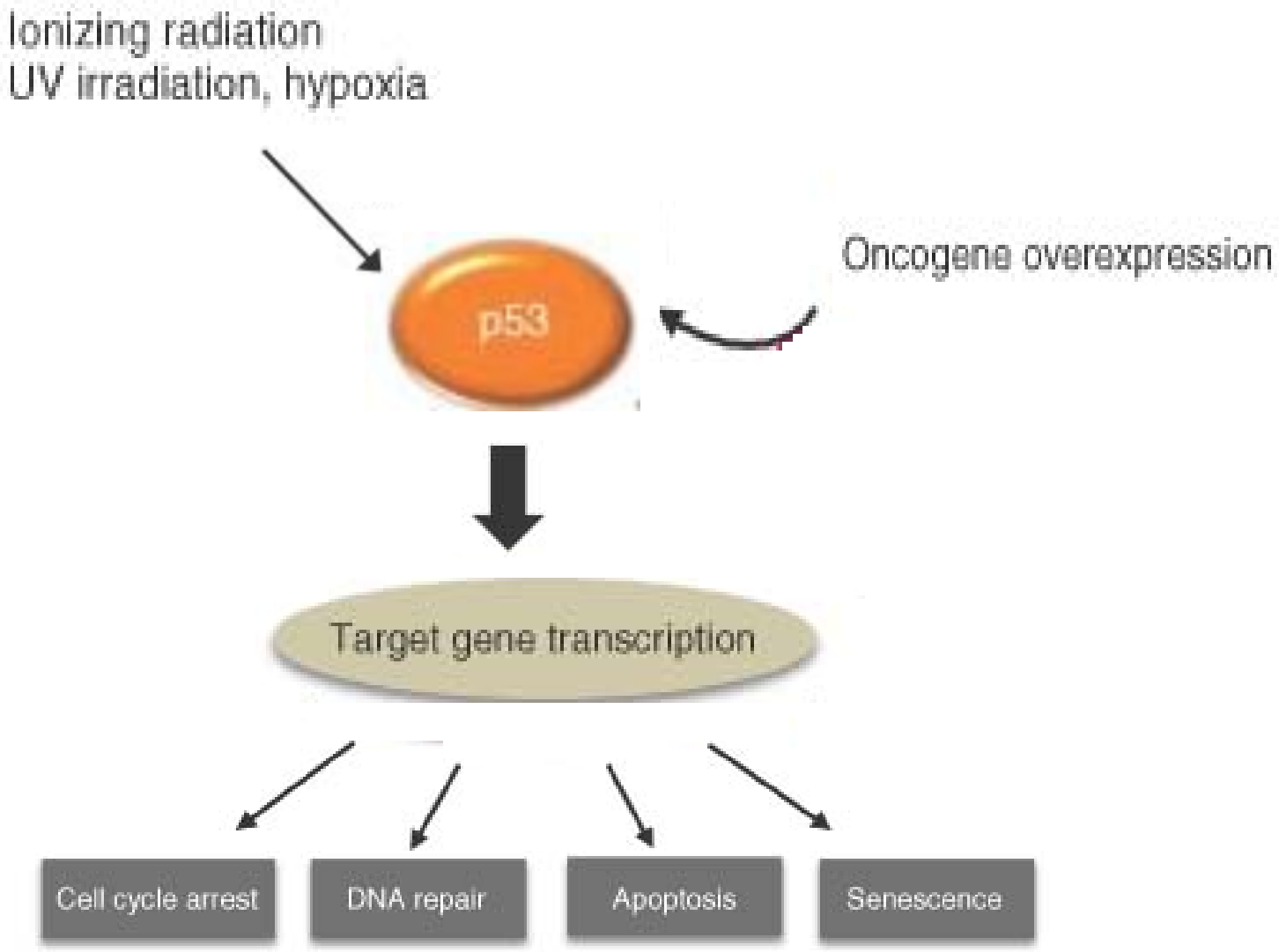


Activated oncogene

Inactivated Tumor suppressors



p53 signaling pathway



Changes in cell that leads to transformation

- Mutations
- Deletions
- Recombinations
- Transpositions
- Epigenetic alterations (DNA methylation, imprinting)
- Viral infections (oncoviruses)

Early History of Oncoviruses

- The theory that cancer could be caused by a virus began with the experiments of Oluf Bang and Vilhelm Ellerman in 1908 who first show that avian erythroblastosis (a form of chicken leukemia) which is caused by avian erythroblastosis virus could be transmitted by cell-free extracts.
- This was subsequently confirmed for solid tumors in chickens in 1910-1911 by Peyton Rous.
- Later on they called oncoviruses.

Oncoviruses

- An oncovirus is a virus that can cause cancer.
- It refers to any virus with a DNA or RNA genome causing cancer and is synonymous with "tumor virus" or "cancer virus".
- Most viruses are non-transforming - however, they may play a role in reducing the host cell’s ability to inhibit apoptosis.
- Cells that are resistant to apoptosis with help of the viral genes that they express are more likely to survive genomic damage that will predispose to later neoplastic changes.

Human Oncoviruses Replication Strategies

1. **Create Conditions for replication:**
   - Metabolic reprogramming.
   - Inducing angiogenesis.

2. **Maximize virus production:**
   - Prevent apoptosis until virion matures.
   - Immune evasion.

3. **Multiply latent proviruses:**
   - Cell survival.
   - Cell immortalization.

Mechanisms of viral oncogenicity

Two mechanisms that an oncovirus can cause cancer

Direct acting carcinogenic viruses

Insertion of its genetic material into the host cell genetic material.

Indirect acting carcinogenic viruses

A. Triggering chronic inflammation and oxidative stress: that persistently damage local tissues.

B. By producing immunosuppression.

C. By both mechanisms (A and B).

Mechanisms of viral oncogenicity

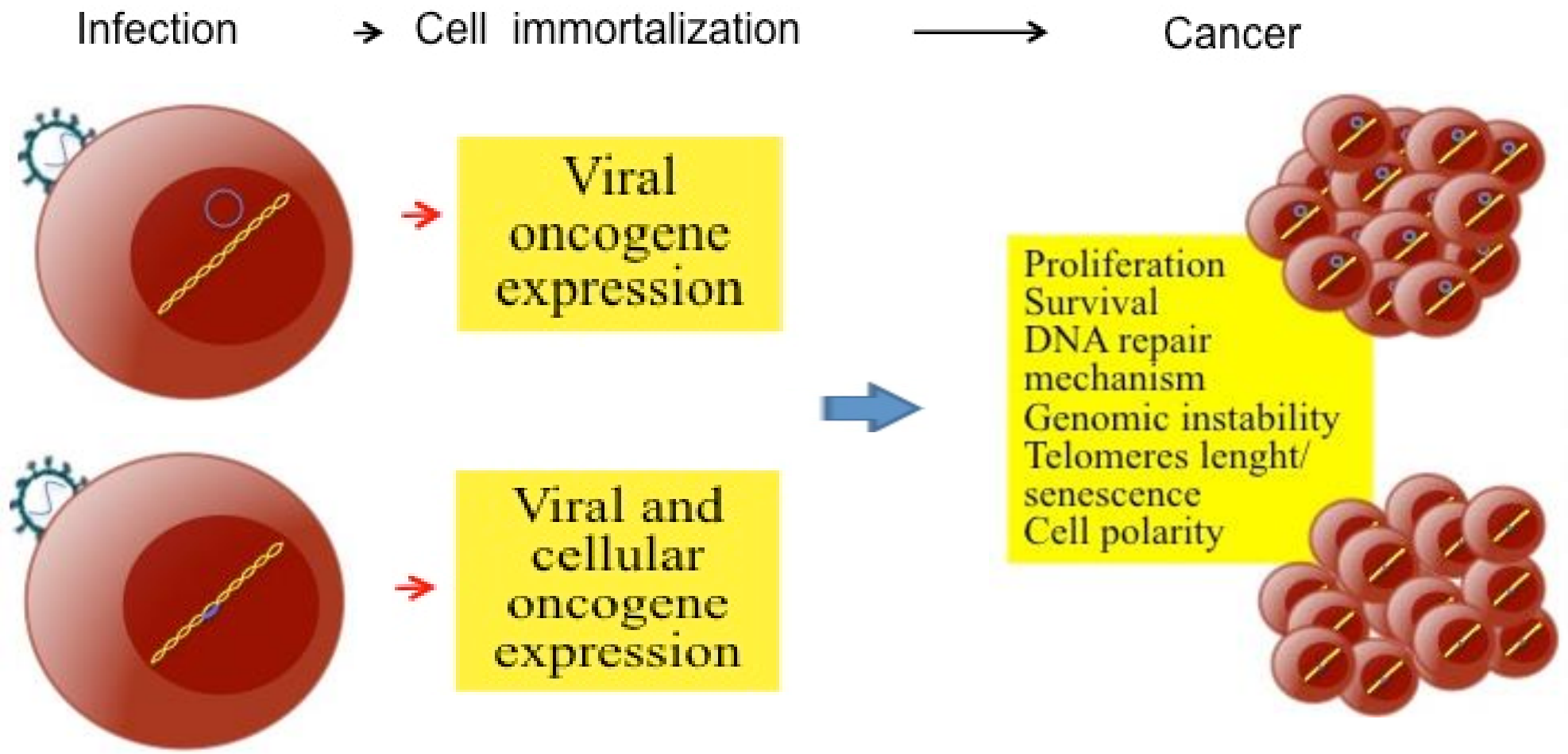
Direct acting carcinogenic viruses

The **Direct acting carcinogenic viruses can directly trasform cells by:**

1. Some viruses replication cycle require the integration of the viral genome into the host genome, commonly transform because integration deregulates expression of cellular oncogenes or tumor suppressor genes (insertional mutagenesis).
2. Through the expression of its own oncogenes without the need to integrate (Ex, EBV).

Mechanisms of viral oncogenicity

Direct acting carcinogenic viruses



Mechanisms of viral oncogenicity

Direct acting carcinogenic viruses

No Integration

For most viruses

↓

Lytic Life Cycle

↓

Genome viral proteins

↓

Replication

↓

Lysis → **Progeny virions**

Integration

Virus

↓

Cell

↓

Integration

↓

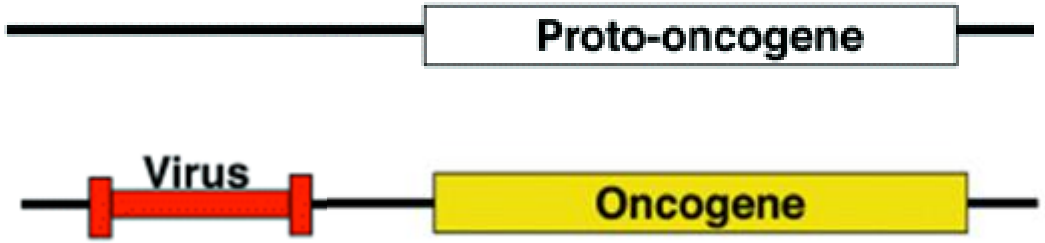
Virus-specific proteins expressed - No mature virus

↓

Changes in the properties of host cell - TRANSFORMATION

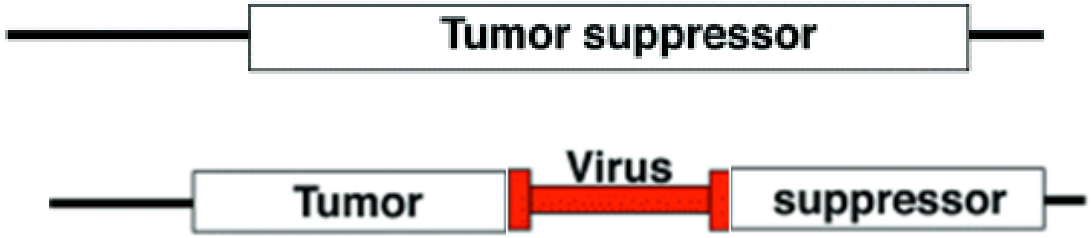
Mechanisms of viral oncogenicity

Direct acting carcinogenic viruses



Insertion of a viral gene close to the protooncogene leads to its activation

Gain of function



Insertion of a viral gene within the tumor suppressor gene leads to its inactivation

Loss of function

Mechanisms of viral oncogenicity

Indirect acting carcinogenic viruses

This happened through two main mechanisms:

A. **triggering chronic inflammation and oxidative stress:** that persistently damage local tissues;

Example: HBV and HCV; chronic inflammation produced by persistent infection is a major risk to develop hepatocellular carcinoma (HCC).

B. **by producing immunosuppression:** that reduces or eliminates anti-tumor immune surveillance mechanisms.

Example: HIV ; patients with low T cell counts frequently develop lymphomas associated with EBV or KSV infection.

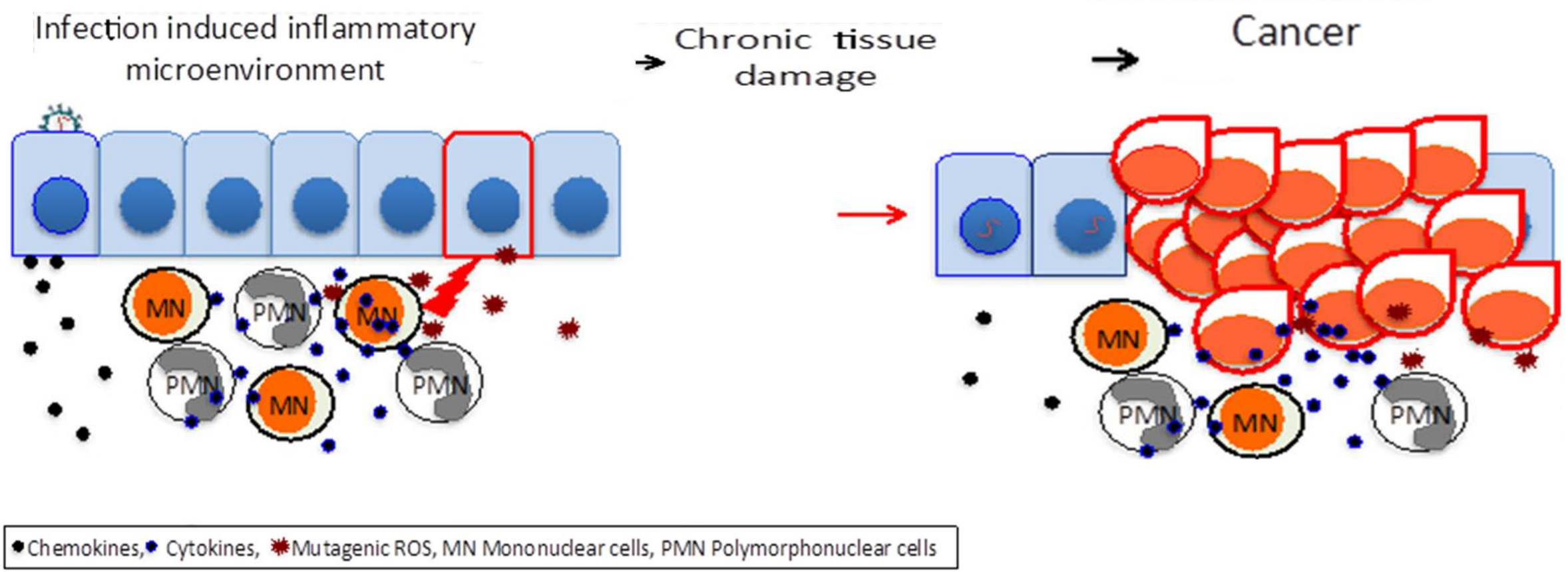
C. **By both mechanisms (A and B):**

Example: HBV and HCV

Mechanism of Oncogenecity

Indirect acting carcinogenic viruses

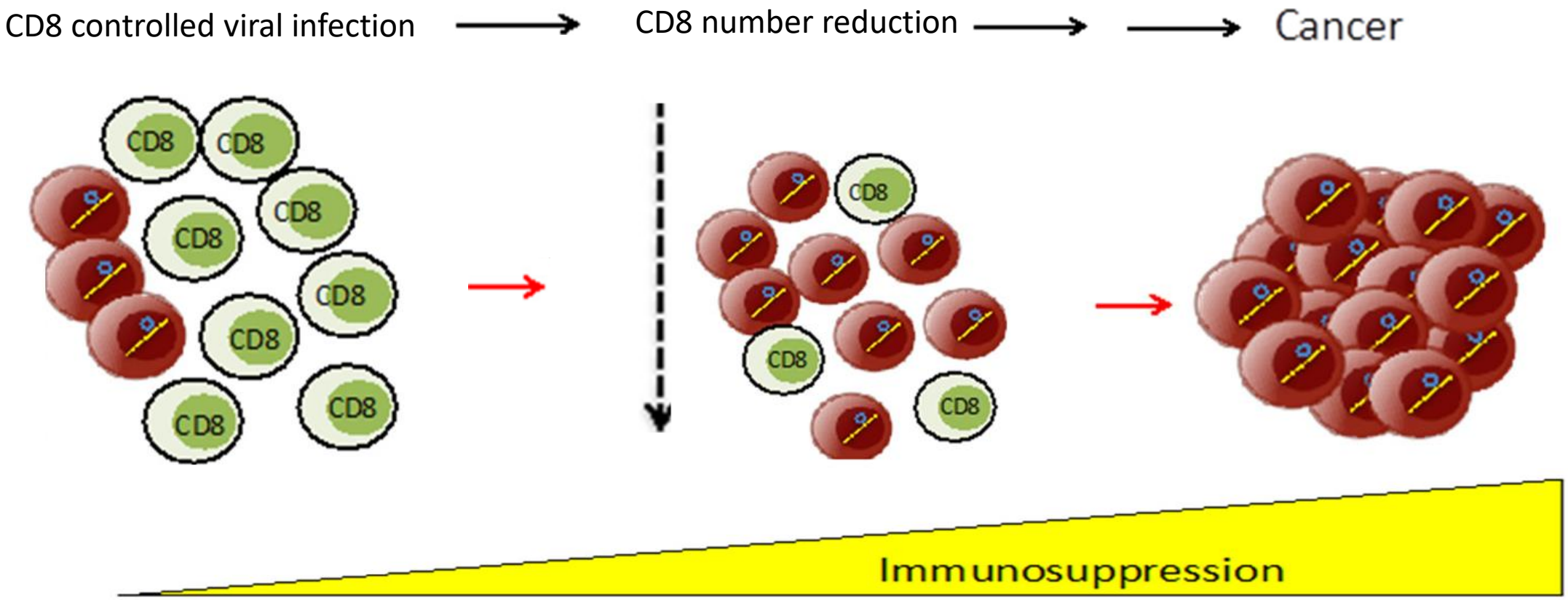
A. triggering chronic inflammation and oxidative stress



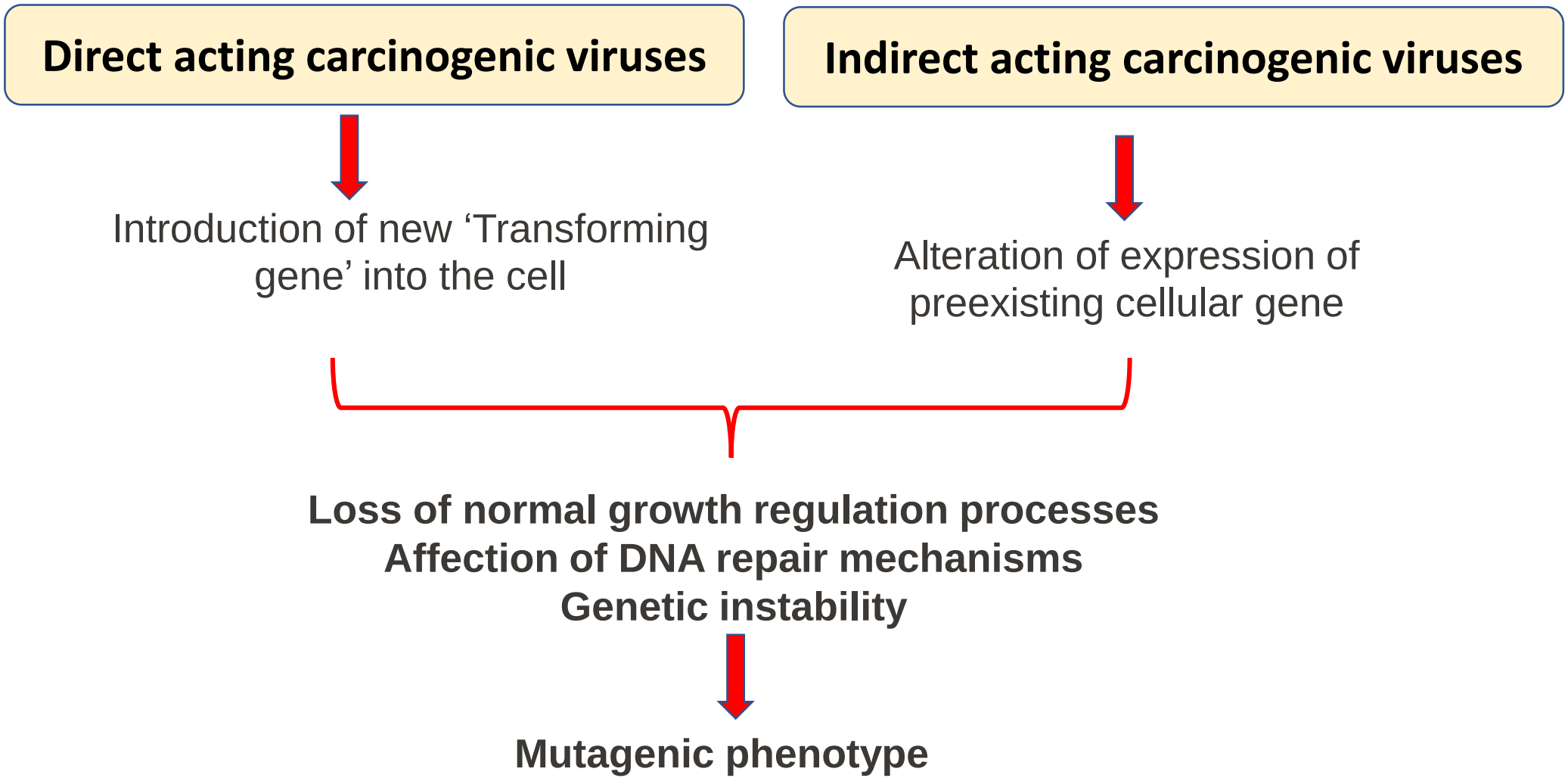
Mechanism of Oncogenecity

Indirect acting carcinogenic viruses

B. by producing immunosuppression:



Mechanisms of viral oncogenecity



Calcification of oncogenic viruses

DNA viruses

1- Human papilloma virus (HPV):

- ✓ Causes transformation in cells through interfering with tumor suppressor proteins such as p53.
- ✓cause cervical cancer.

2- Kaposi's sarcoma-associated herpesvirus (KSHV or HHV-8):

- is associated with Kaposi’s sarcoma, a type of skin cancer.

3- Epstein-Barr virus (EBV or HHV-4): is a herpes virus that’s spread through saliva. EBV infection increases the risk of Burkitt lymphoma, some types of Hodgkin’s and non-Hodgkin’s lymphoma and stomach cancer.

4- Human cytomegalovirus (CMV or HHV-5) is associated with mucoepidermoid carcinoma and possibly other malignancies.

DNA viruses associated with the development of human neoplasia

Virus	Neoplasms
Human papilloma virus	Cervical Ca , warts, ano- genital carcinoma
Herpes simplex virus II	Cervical carcinoma
Epstein-Barr virus	Nasopharyngeal carcinoma, Burkitt's lymphoma
Herpes virus 8	Kaposi's sarcoma
Hepatitis B virus	Hepatocellular Ca
Herpes simplex virus 6	Certain B cell (HBLV) lymphomas

RNA viruses associated with the development of human neoplasia

Virus	Neoplasms
Human T-cell leukemia virus I	Some T-cell leukemia, Lymphoma
Human T-cell leukemia virus II	Some cases of hairy cell leukemia
HIV	Lymphoma; Kaposi's sarcoma