General Microbiology
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Introduction to the Oncoviruses

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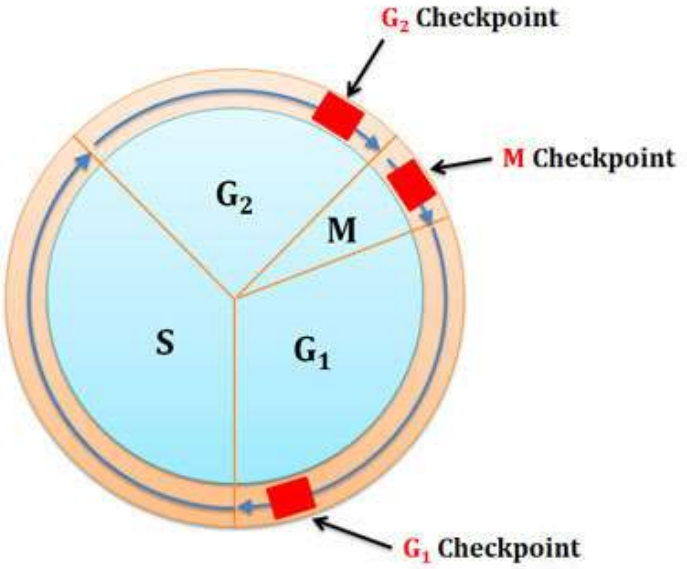
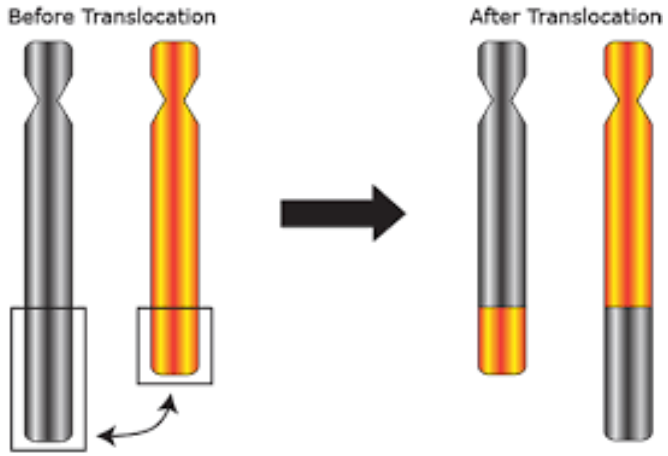
Introduction

- **Cell growth:** is the increase in cell numbers.
- **The cell growth is regulated by two groups of genes:**
  A. Proto-oncogenes (cellular oncogene, c-onc)
    - are normal genes control cell proliferation
    - When altered, they change into oncogenes which contribute to cancer development..
    - codes for:
      i. Growth factors
      ii. Receptors
      iii. Signal transduction proteins.
    - **Activation of proto-oncogenes**
      - **Chromosomal translocation**
      - **Mutation of the proto-oncogene.**
      - **Transduction of the proto-oncogene by an oncovirus**



Cell Cycle Checkpoints



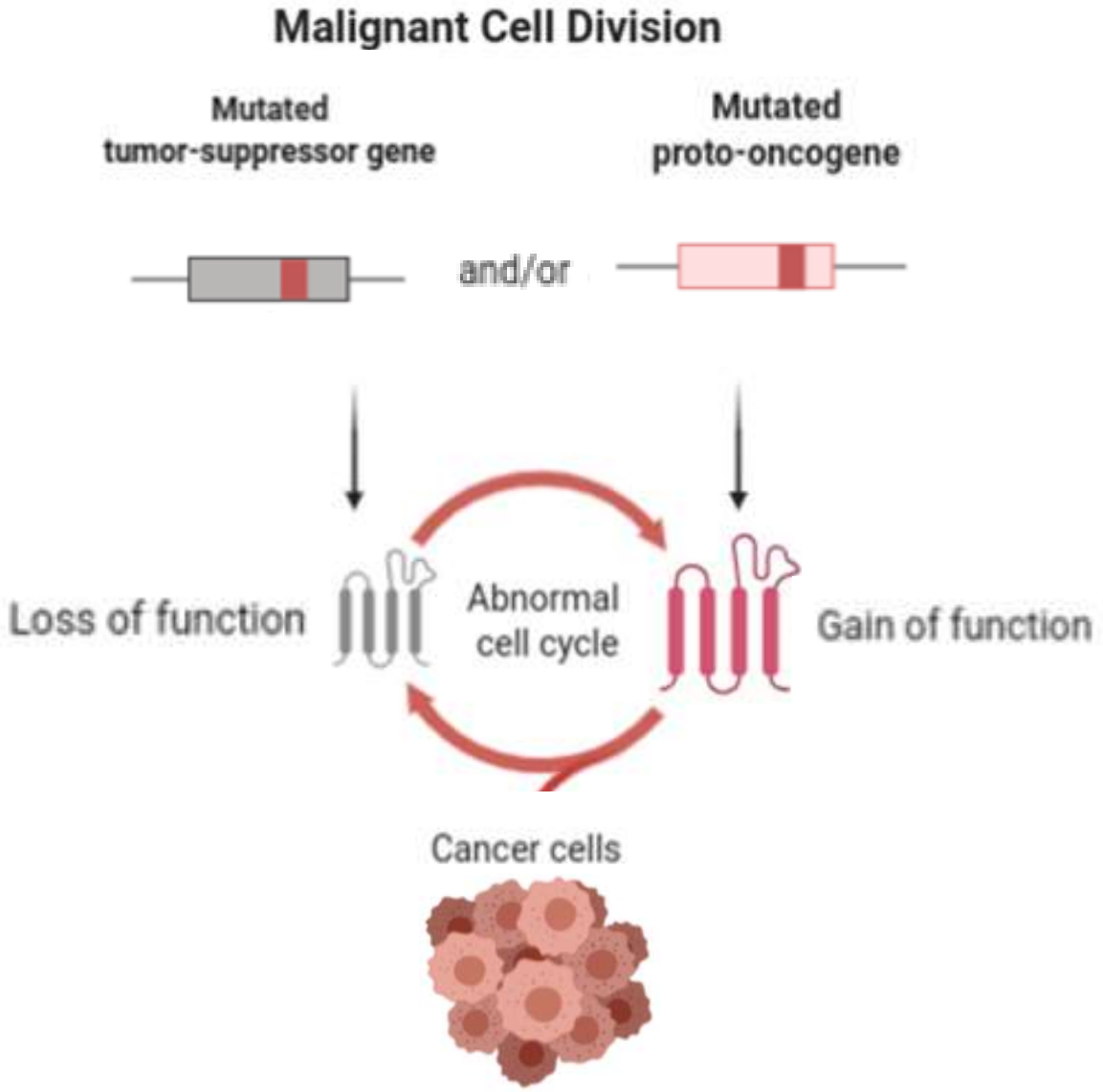
Proto oncogenes vs tumor suppressor genes

- **<u>Tumor Suppressor Genes</u> (Gatekeepers):**

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

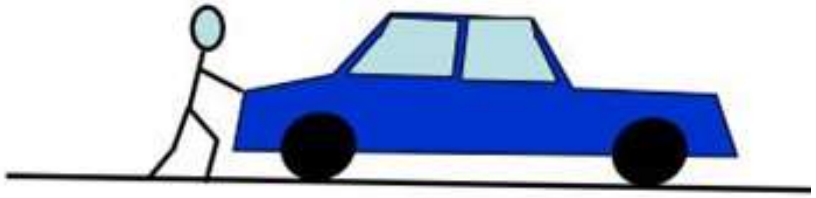
- inhibiting cell growth,
- fixing broken DNA,
- or causing a cell to die.
  - Examples: P53, Rb

Tumor= **activation of proto-oncogenes into (oncogenes (gain of function) +** turning off tumor suppressor genes (loss of function).

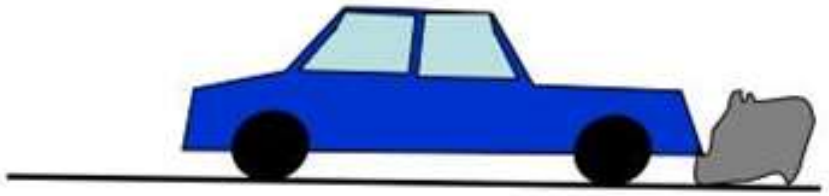


Protooncogenes vs tumor suppressor genes

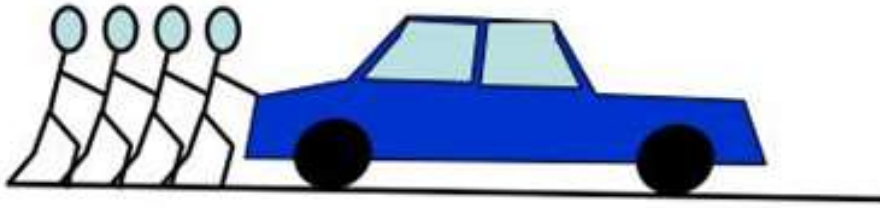
Wild-type proto-oncogene



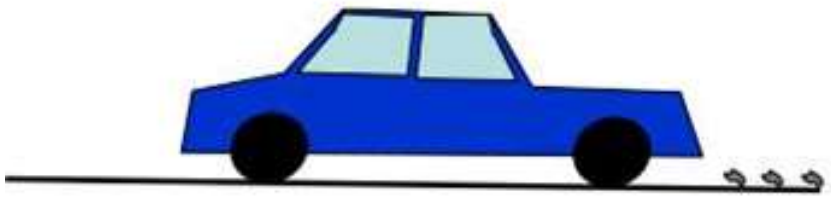
Wild-type Tumor suppressors



Activated oncogene



Inactivated Tumor suppressors



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.
- 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

1. **Insertion of its genetic material into the host cell's genetic material (retroviruses).**
2. **Targeting host cell tumor suppressor genes by viral proteins without the need to integrate (DNA viruses)**

Indirect acting carcinogenic viruses

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

B. By immunosuppression.

C. By both A and B.

Mechanisms of viral oncogenicity

Types of viruses based on their ability to integrate:

1. Retroviruses: can integrate due to the presence of integrase.
2. Other viruses: can not integrate (no integrase).

Types of retroviruses:

Retroviruses without an oncogene:

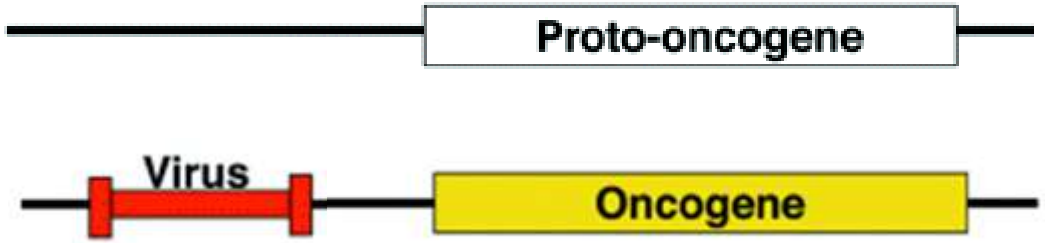
A viral active promoter's presence and integration close to the host cell protooncogene will heighten its expressivity ("promoter insertion hypothesis").

Retroviruses with an oncogene:

In most cases, the viral oncogene is overexpressed. This leads to the rapid development of acute malignancies.

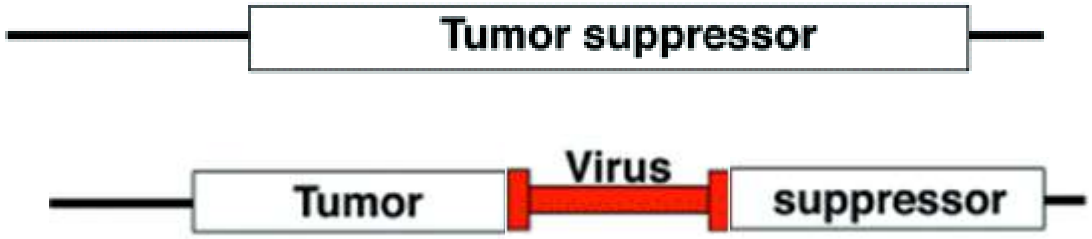
Mechanisms of viral oncogenicity

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

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

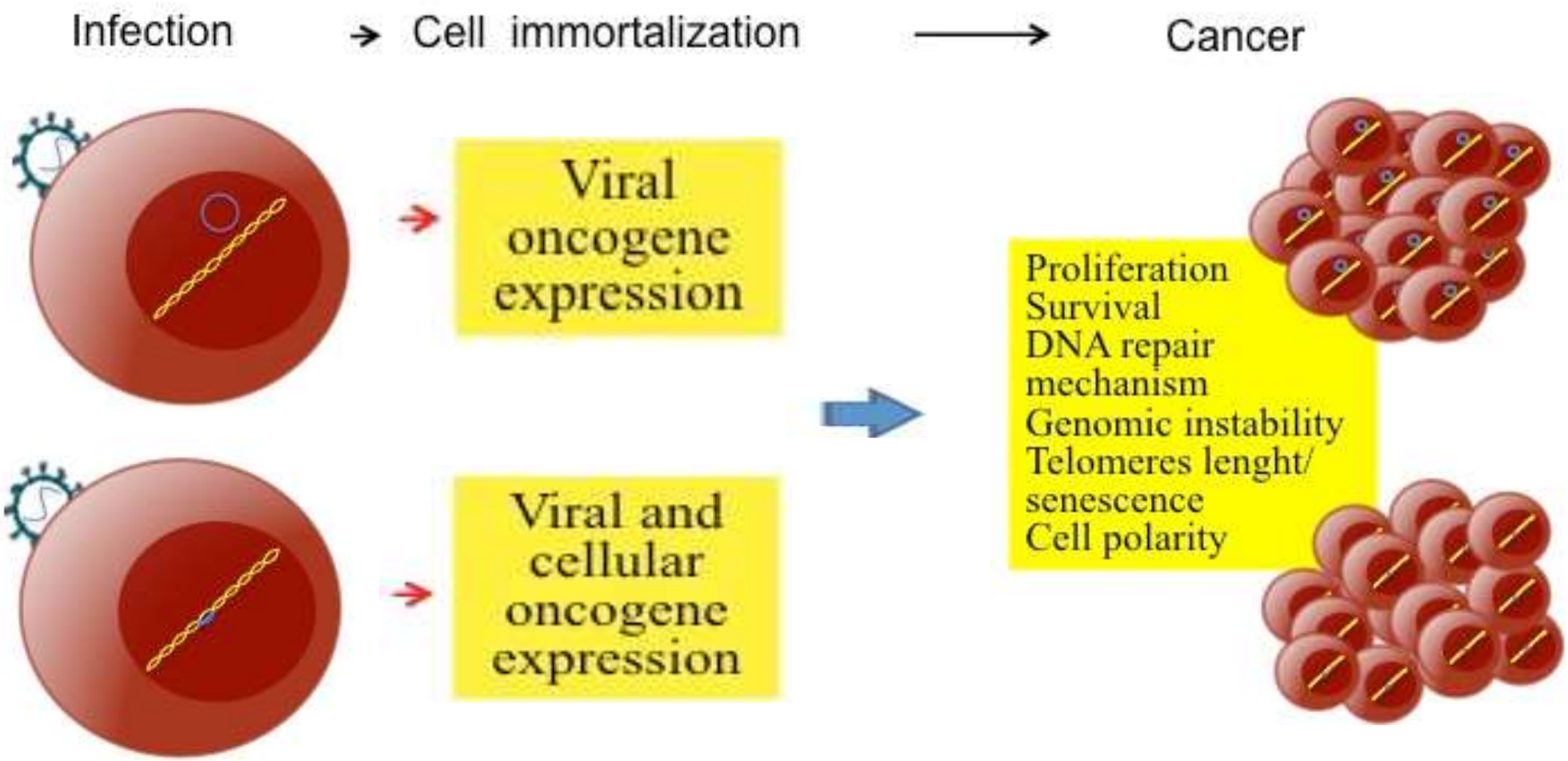
Direct acting carcinogenic viruses

DNA Tumor Viruses

- Genes have also been found in DNA tumor viruses that induce a malignant transformation of the host cell.
- They code for viral regulator proteins.
- They are produced early in the viral replication cycle and assume essential functions in viral DNA replication.
- Their oncogenic potential is through their negative effect on tumor suppressor genes such as p53, Rb and can thus inhibit their functions.
- DNA viruses are important inducers of human tumors (example: HHV8, papovaviruses, hepatitis B viruses, Epstein-Barr viruses).

Mechanisms of viral oncogenicity

Direct acting carcinogenic viruses



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 Kaposi sarcoma (KS) infection.

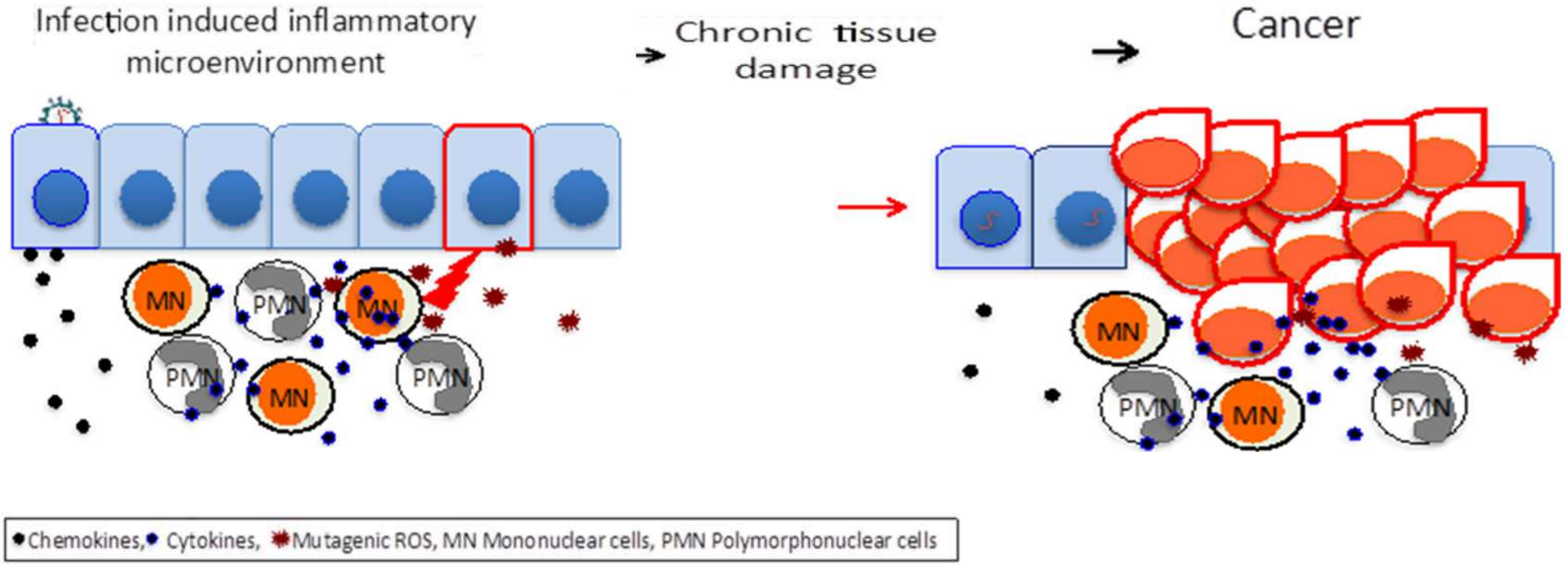
C. **By both mechanisms (A and B):**

Example: HBV and HCV

Mechanism of Oncogenecity

Indirect acting carcinogenic viruses

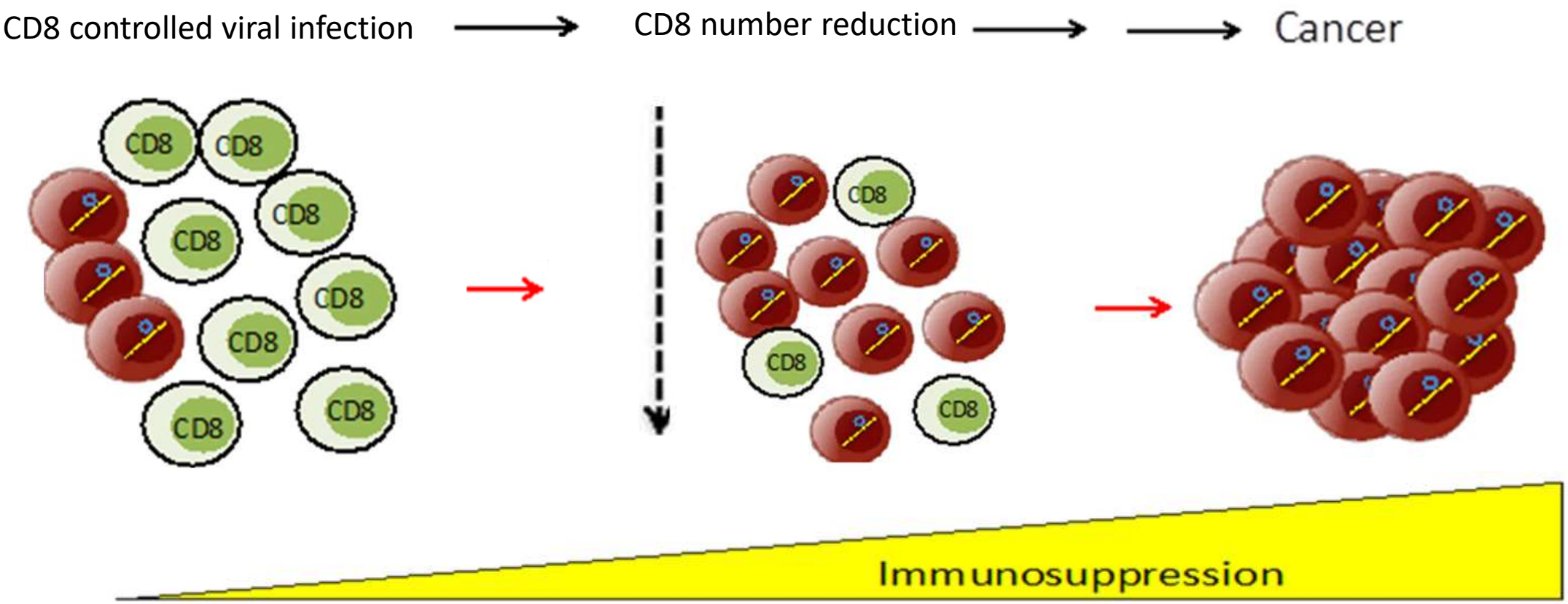
A. triggering chronic inflammation and oxidative stress



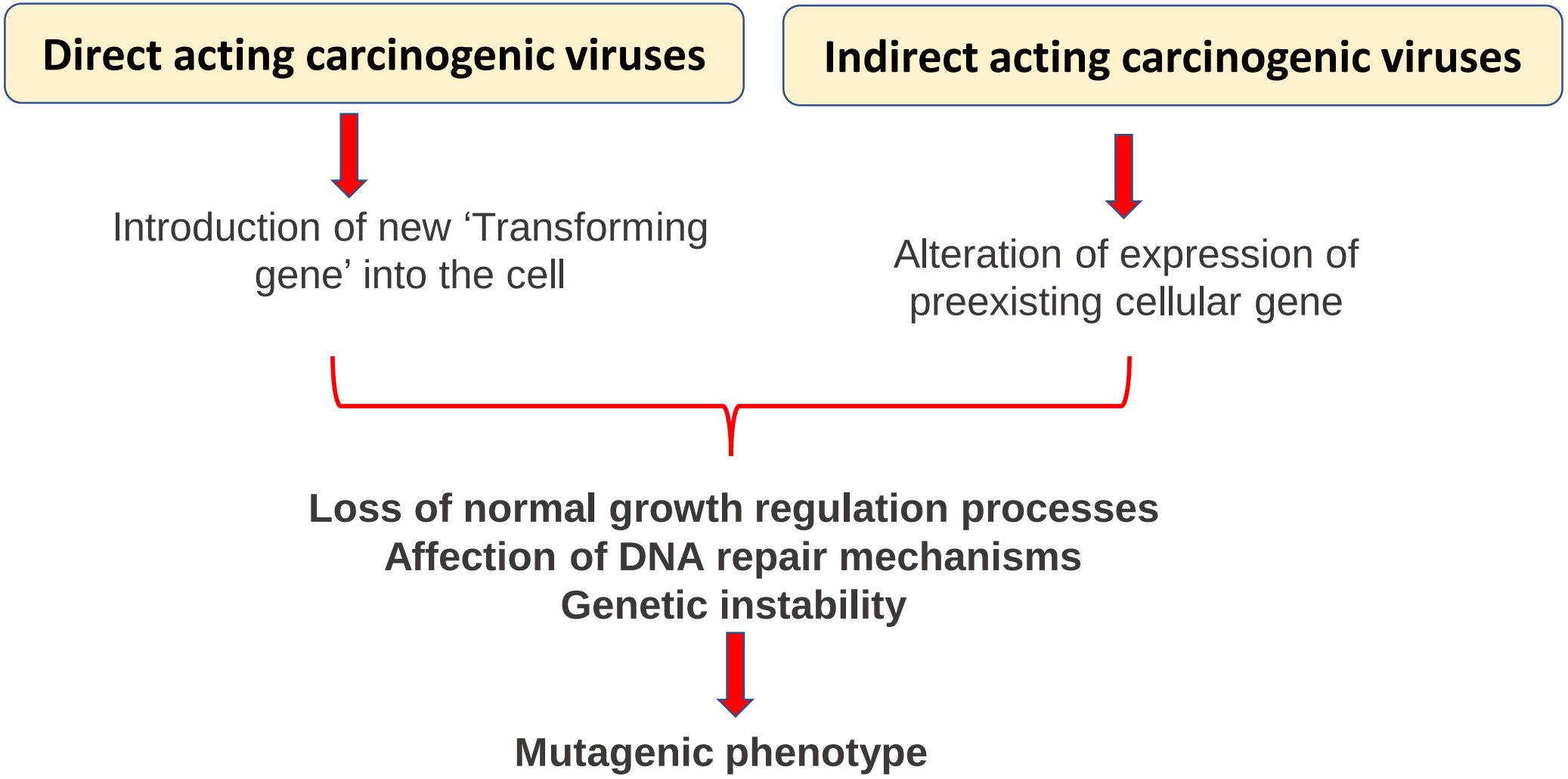
Mechanism of Oncogenecity

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