# Tumor origin

- **Genetic disease or “environmental” disease?**
- **What does it mean that a disease is genetic?**
- **What are the environmental causes that induce tumor development?**

# What are the causes of cancer?

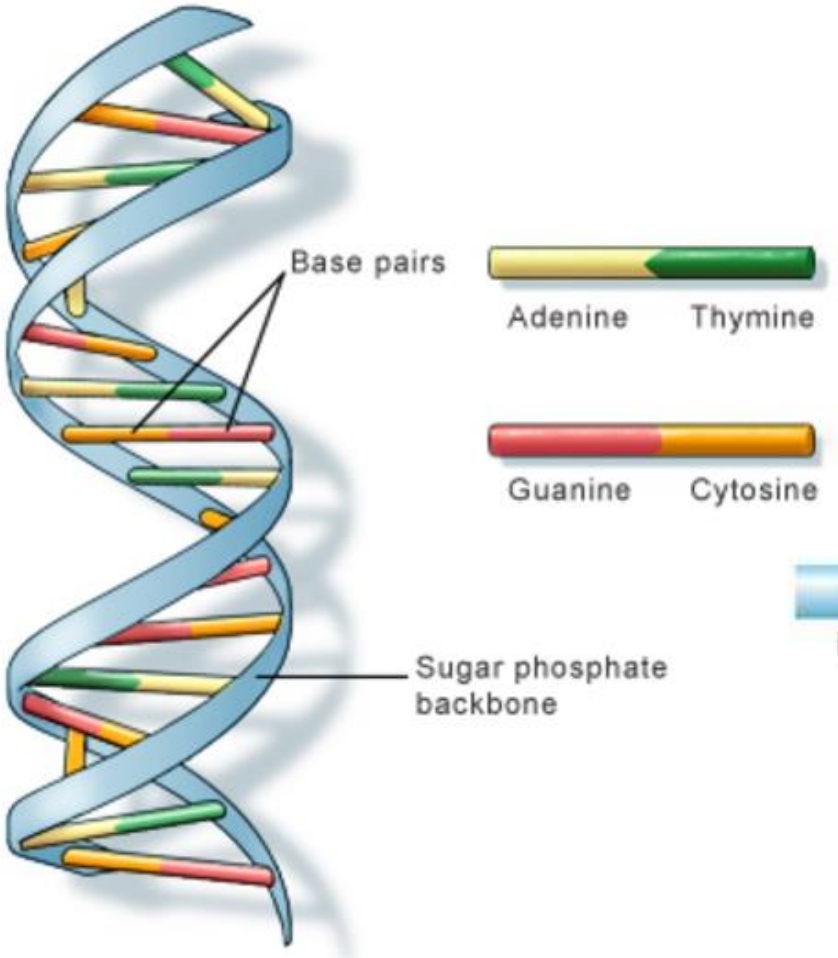
The majority of cancers is not directly inherited (the genes are wt at the birth)

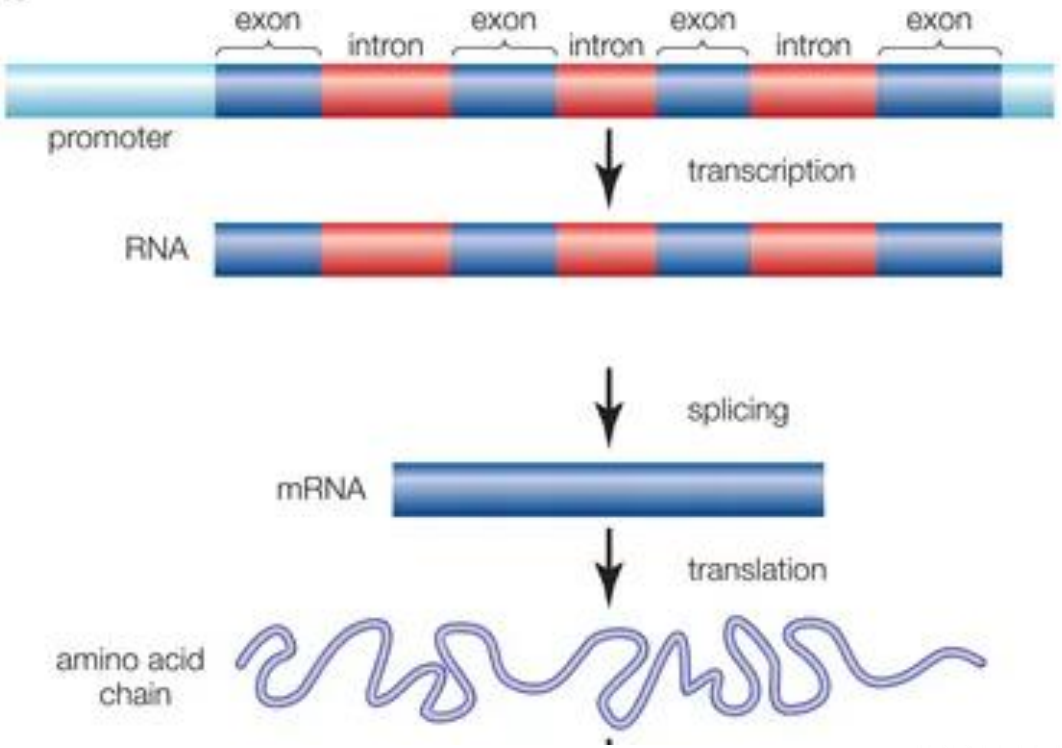
Cancer is, however, a disease of altered gene expression that originates in DNA mutations and results in proteins with modified functions

Cancer development, or carcinogenesis, requires a series of cellular changes. No single gene (mutation) causes cancer. It is a multistep process caused by accumulated errors in the genes of oncogenes and oncosuppressors

Most cancers develop to the stage of being clinically identifiable only years or decades after the initial DNA damage

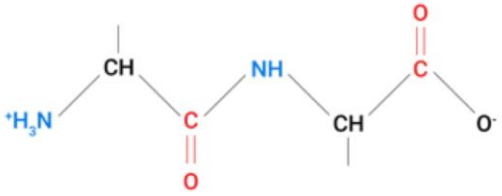
# What is DNA? What is mRNA?



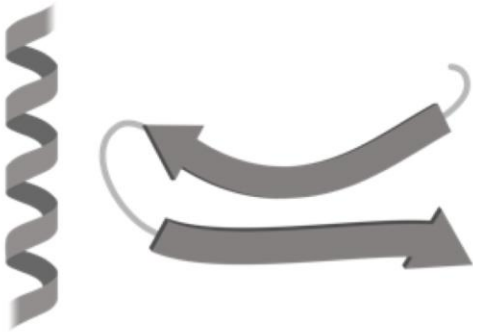



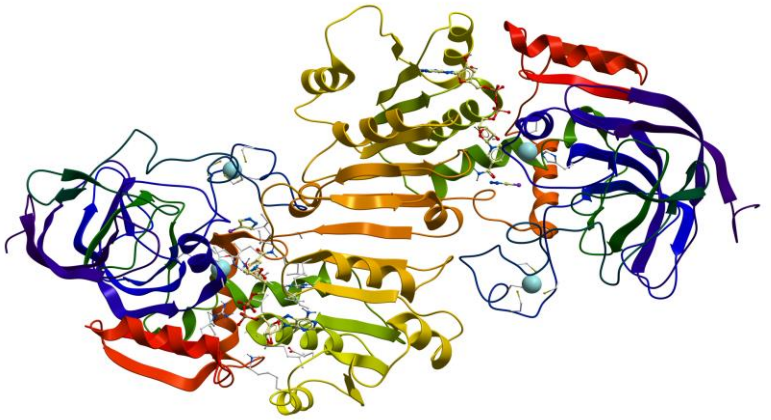
# What is a protein?

## Primary

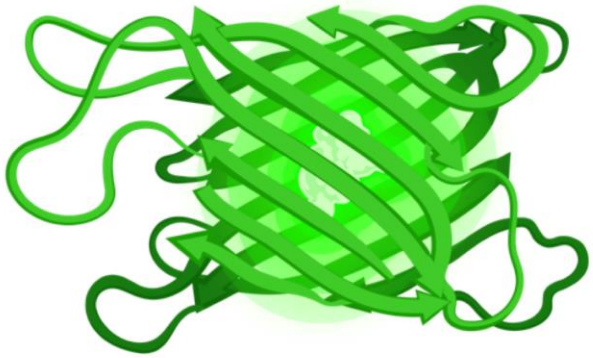



## Secondary

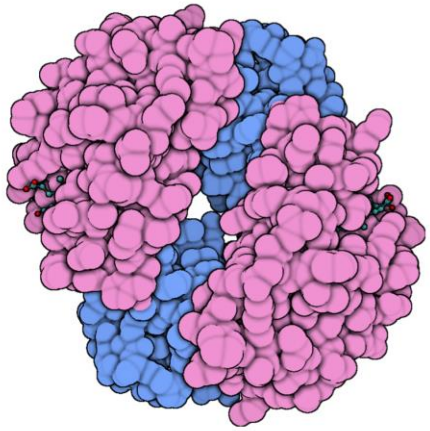


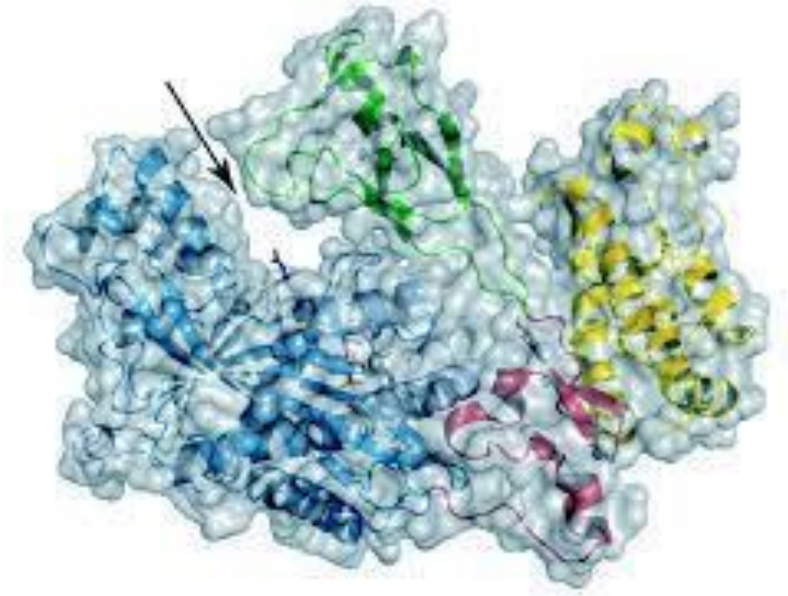


## Tertiary

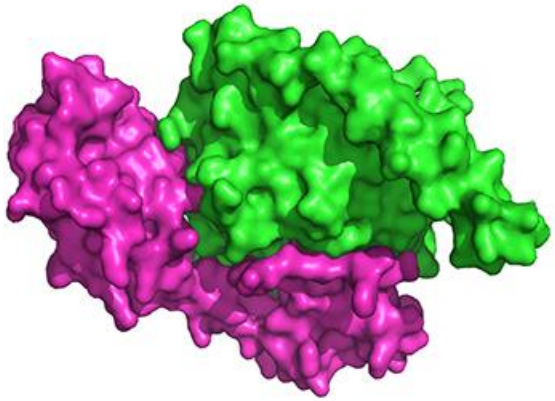


## Quaternary

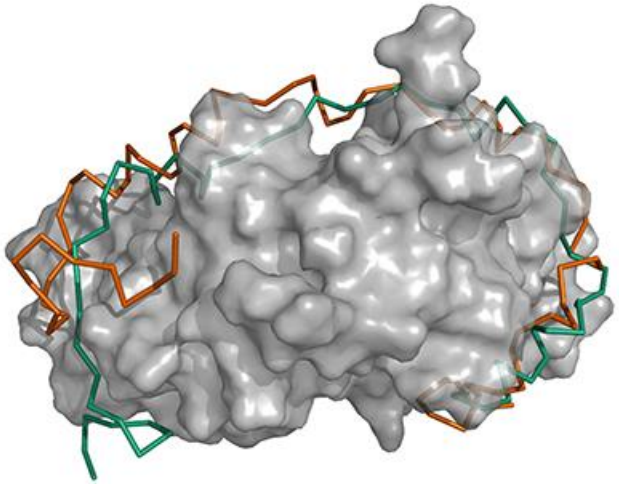




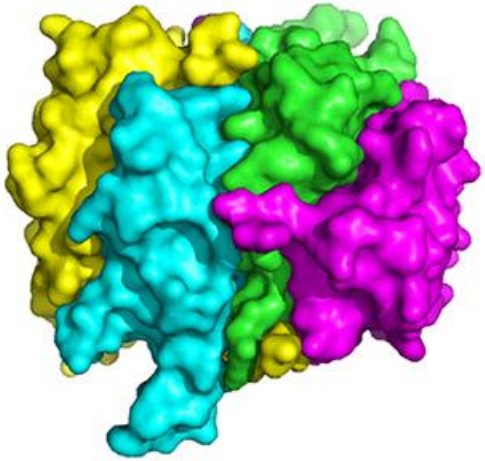
# Proteins: the structure dictates the function



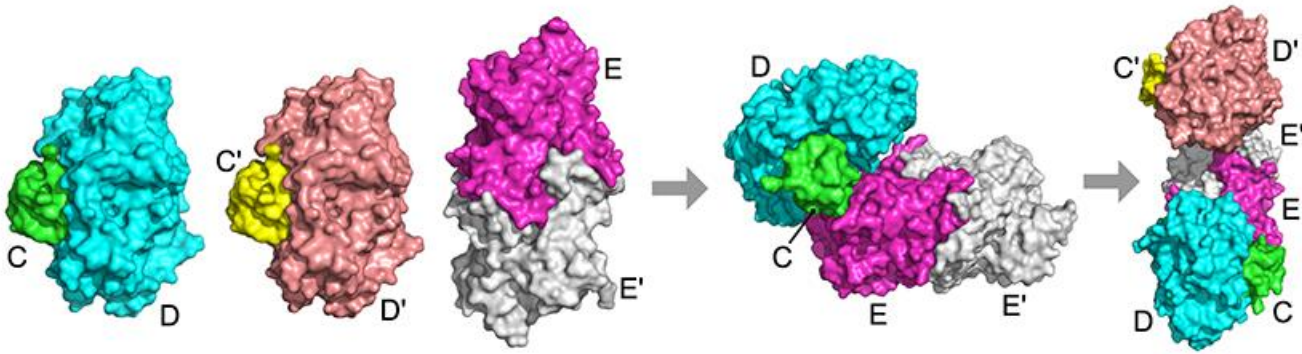
Pairwise Protein Docking



Docking with Disordered Protein

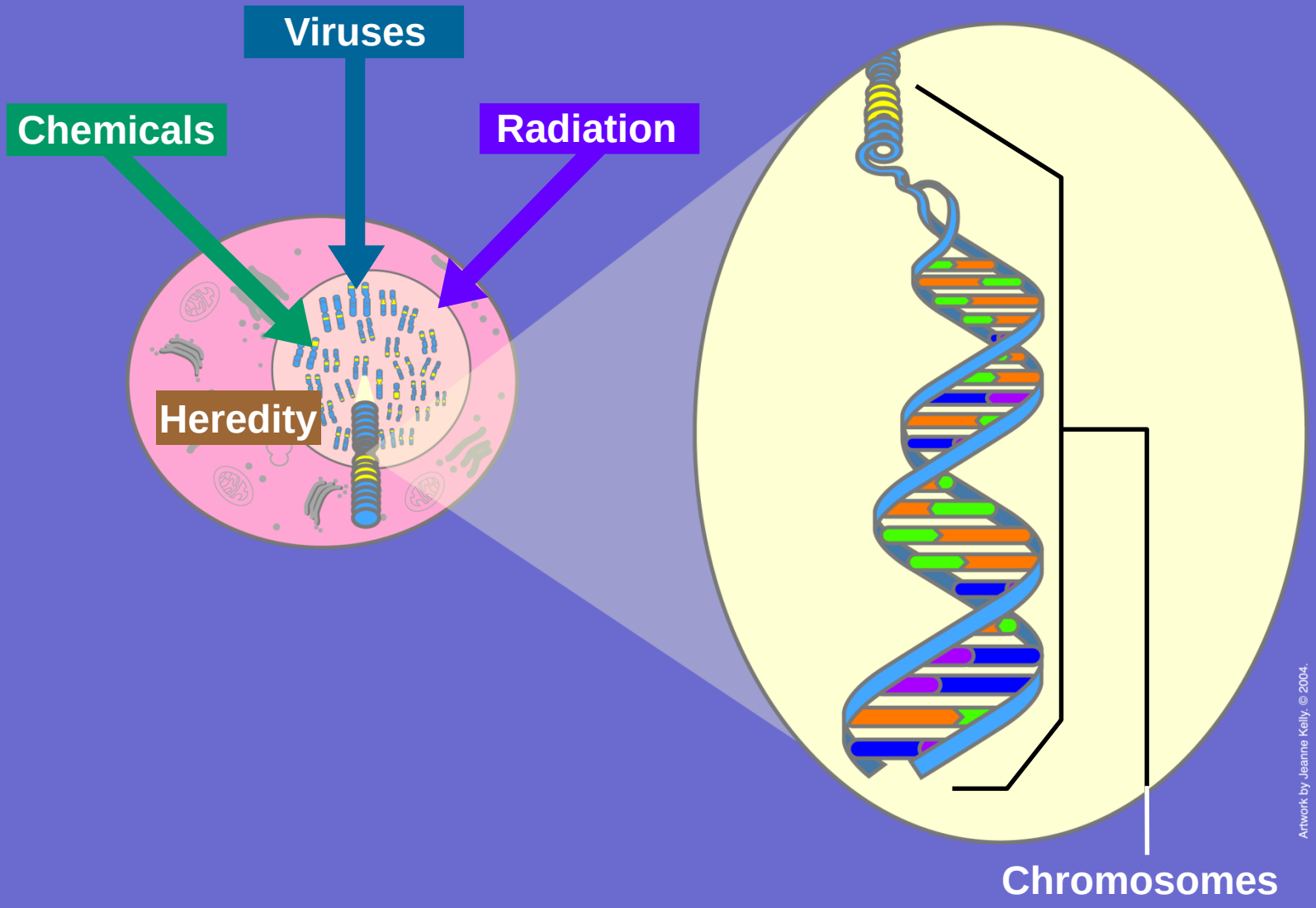


Multiple Protein Docking

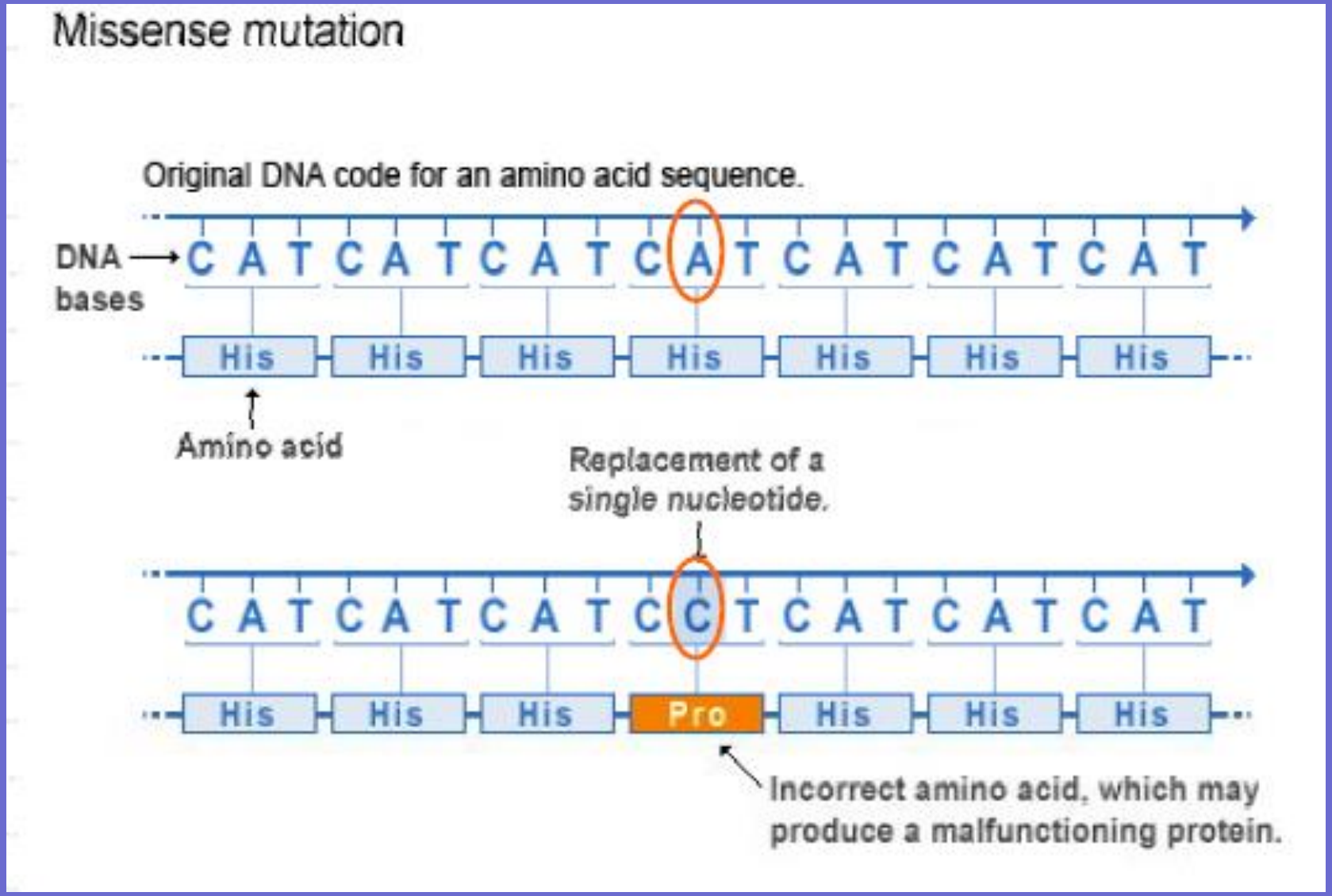



Prediction of Docking Order

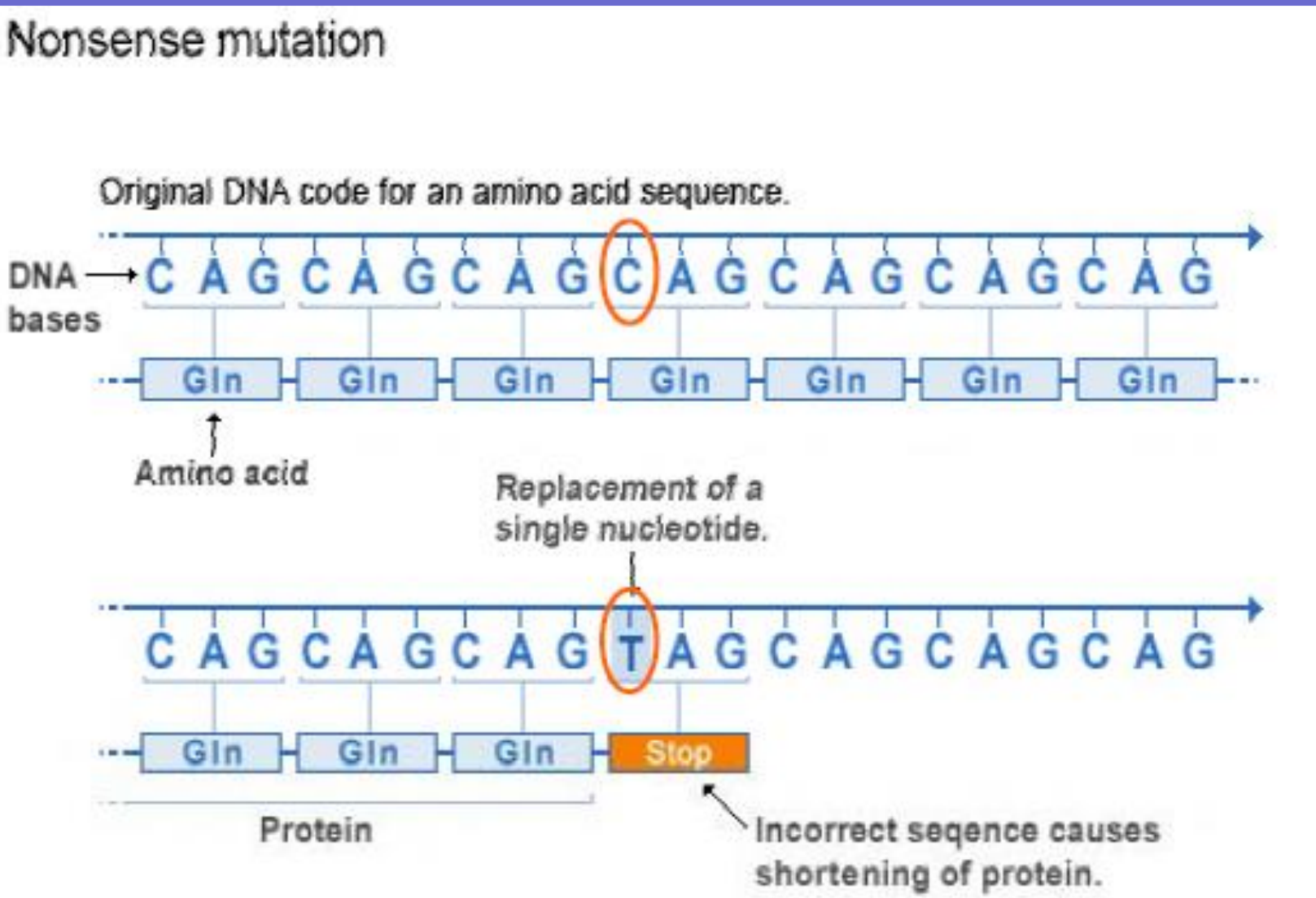
# Genes and Cancer



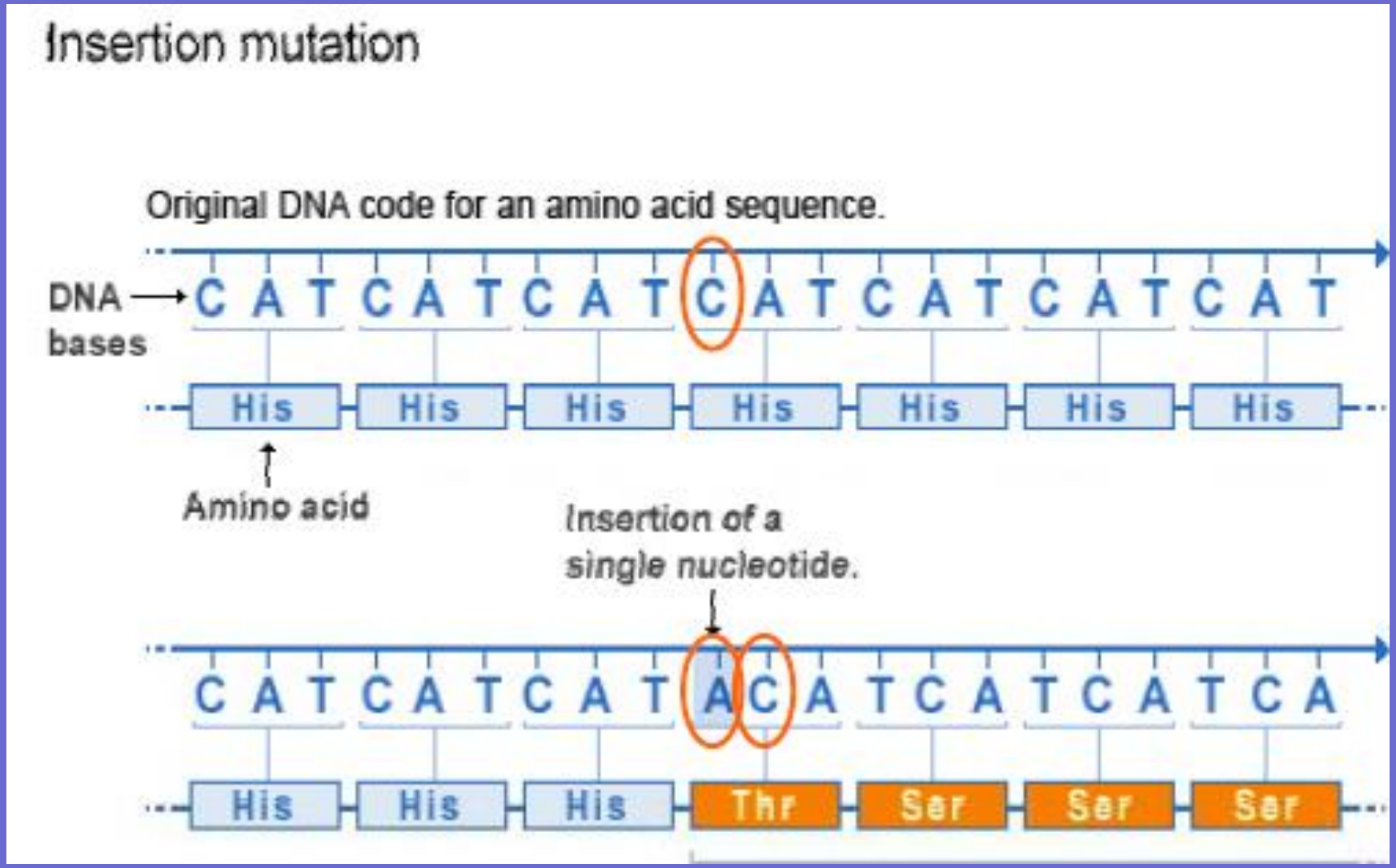
# Point Mutations



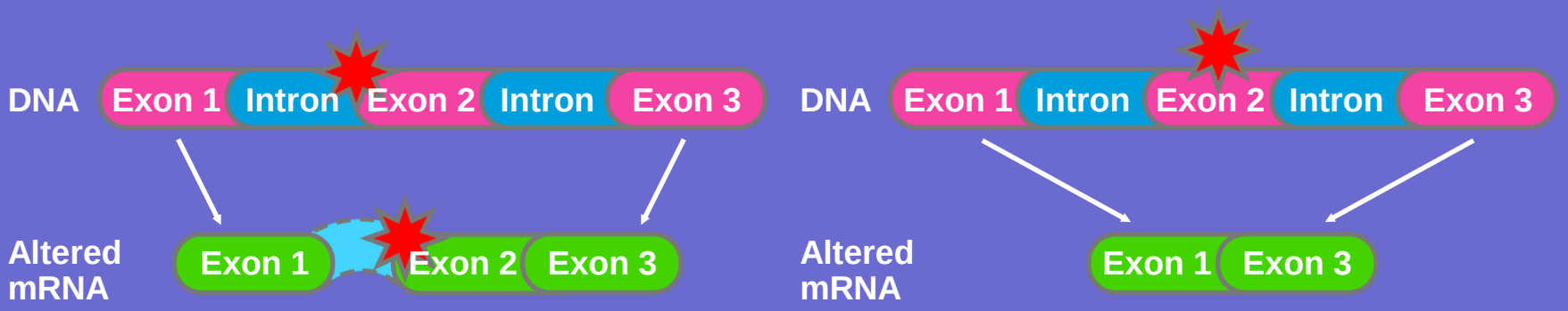
# Point Mutations



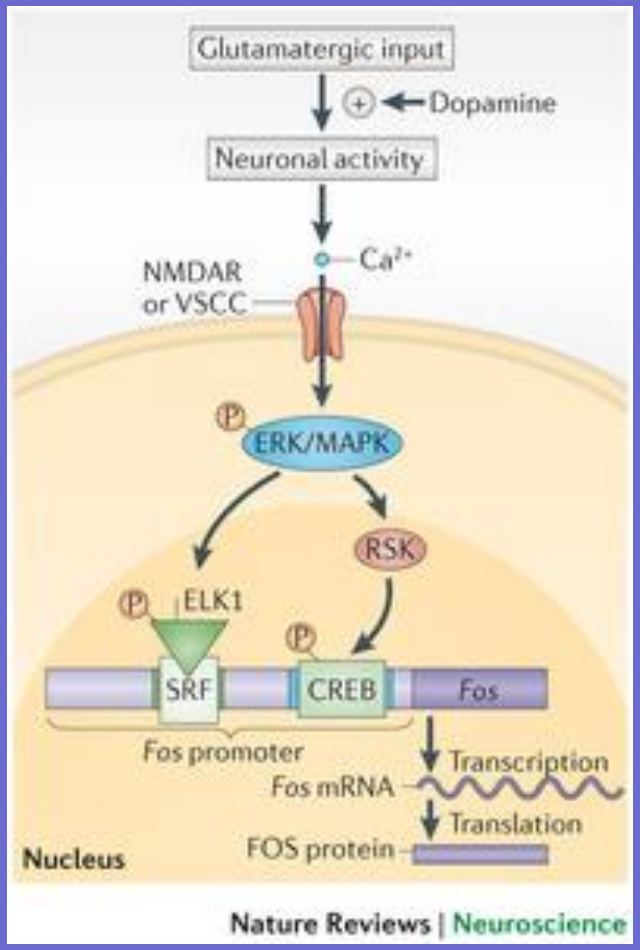
# Insertion/deletion mutations

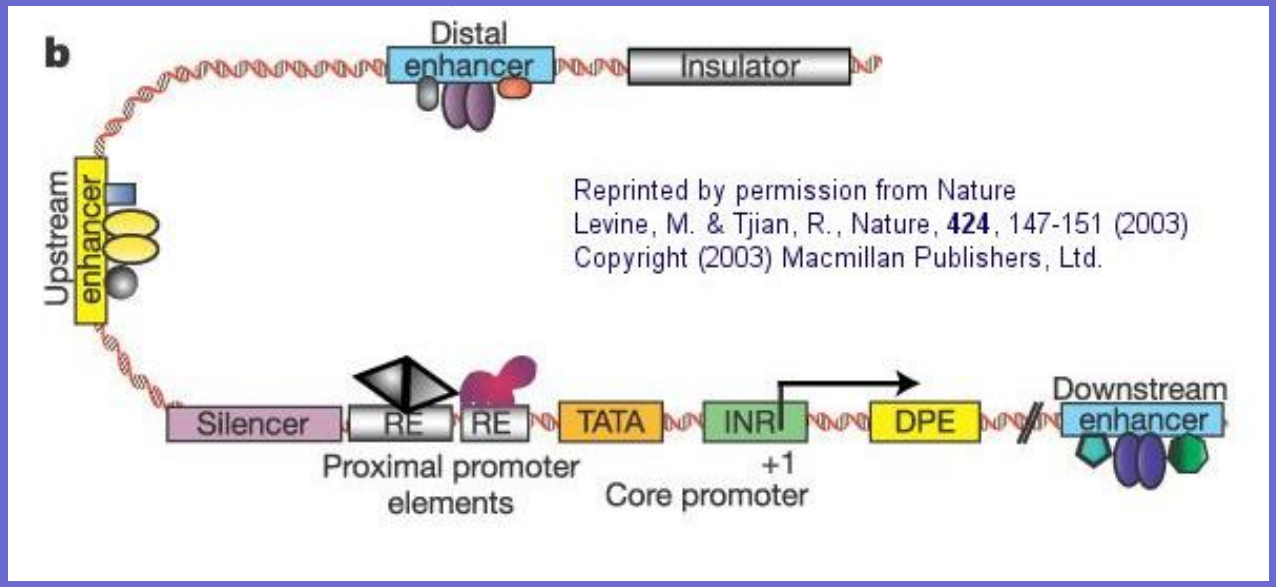


# Splice-Site Mutations



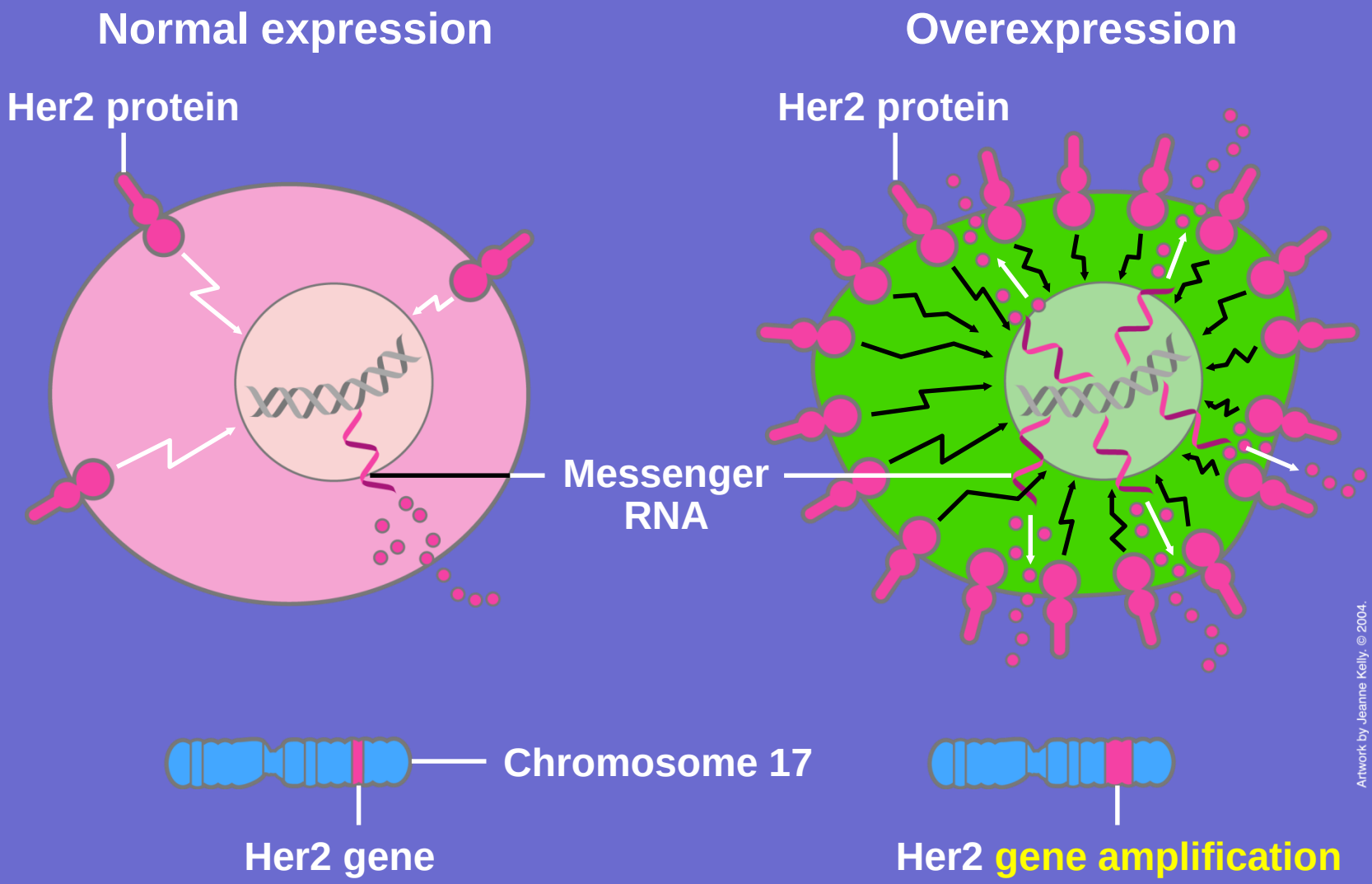
# Regulatory Mutations



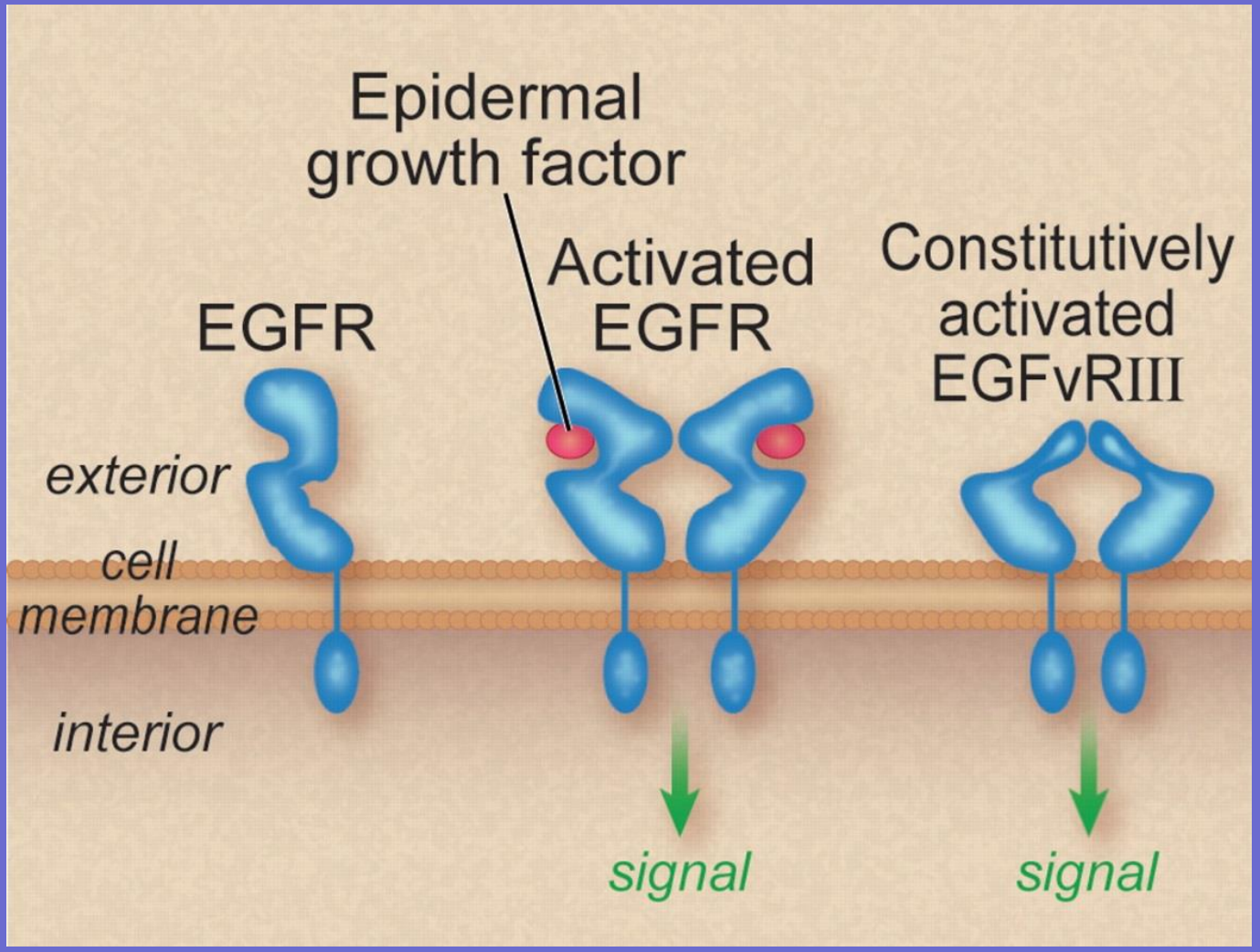

**Promoter activation**

# Regulatory Mutations



# Regulatory Mutations

**The level of expression remains normal, but the receptor is constantly activated**



# Oncogenes and tumor suppressors

Oncogenes and tumor suppressor genes are present in all cells, and in their normal, non-mutated form contribute to the regulation of cell division and death

In cancer, both types of gene are often mutated, and these alterations contribute to the cancer process

The combined effect of activation of oncogenes and inactivation of tumor suppressor genes is an important driver of cancer progression

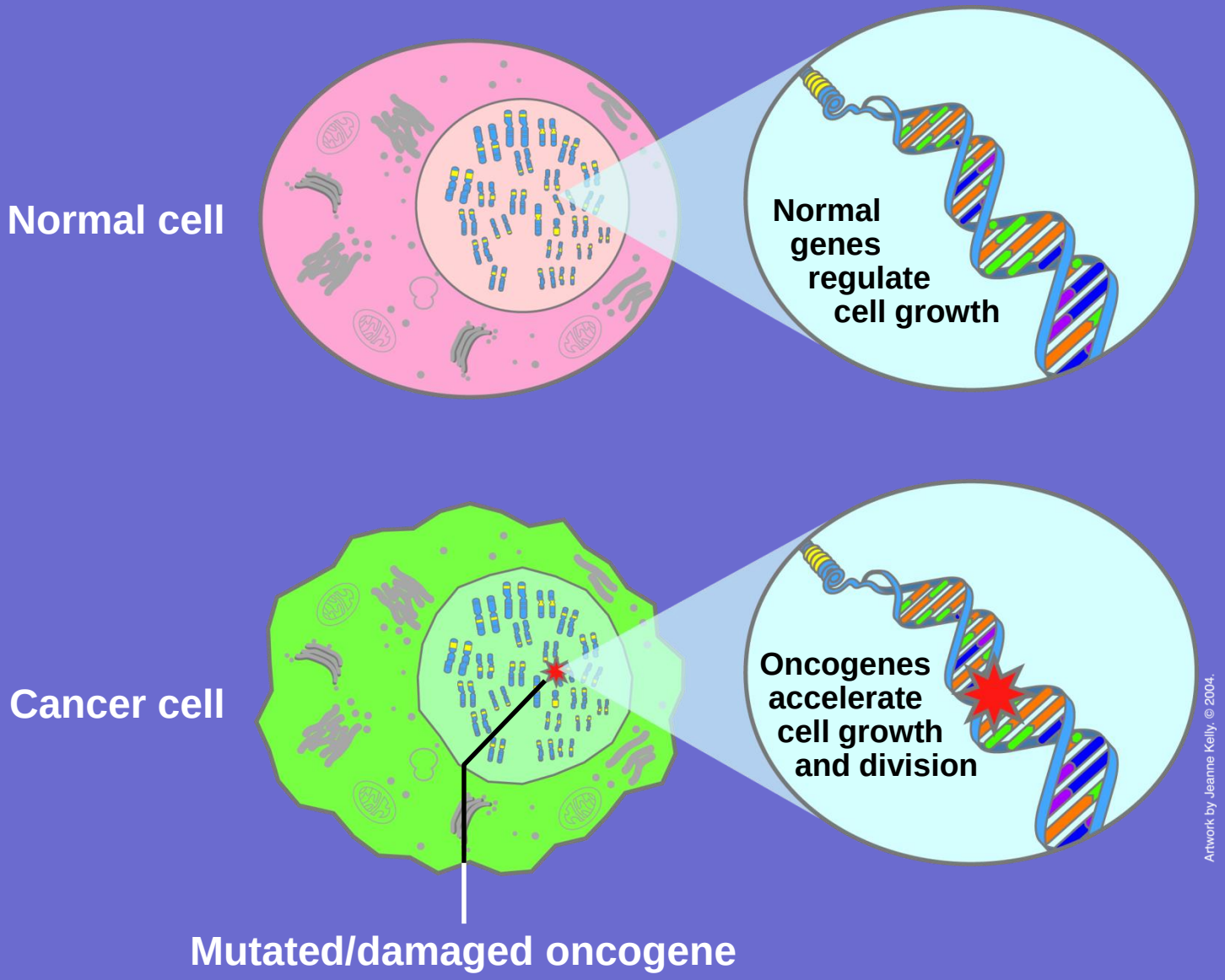
# Oncogenes

Oncogenes increase the rate of transformation from a normal to a cancerous cell

Oncogene function is changed by mutations so that the protein is produced either in greater quantities or has increased activity

The normal, non-mutated form of an oncogene is called a proto-oncogene. More than 100 oncogenes have been identified

# Proto-Oncogenes to Oncogenes

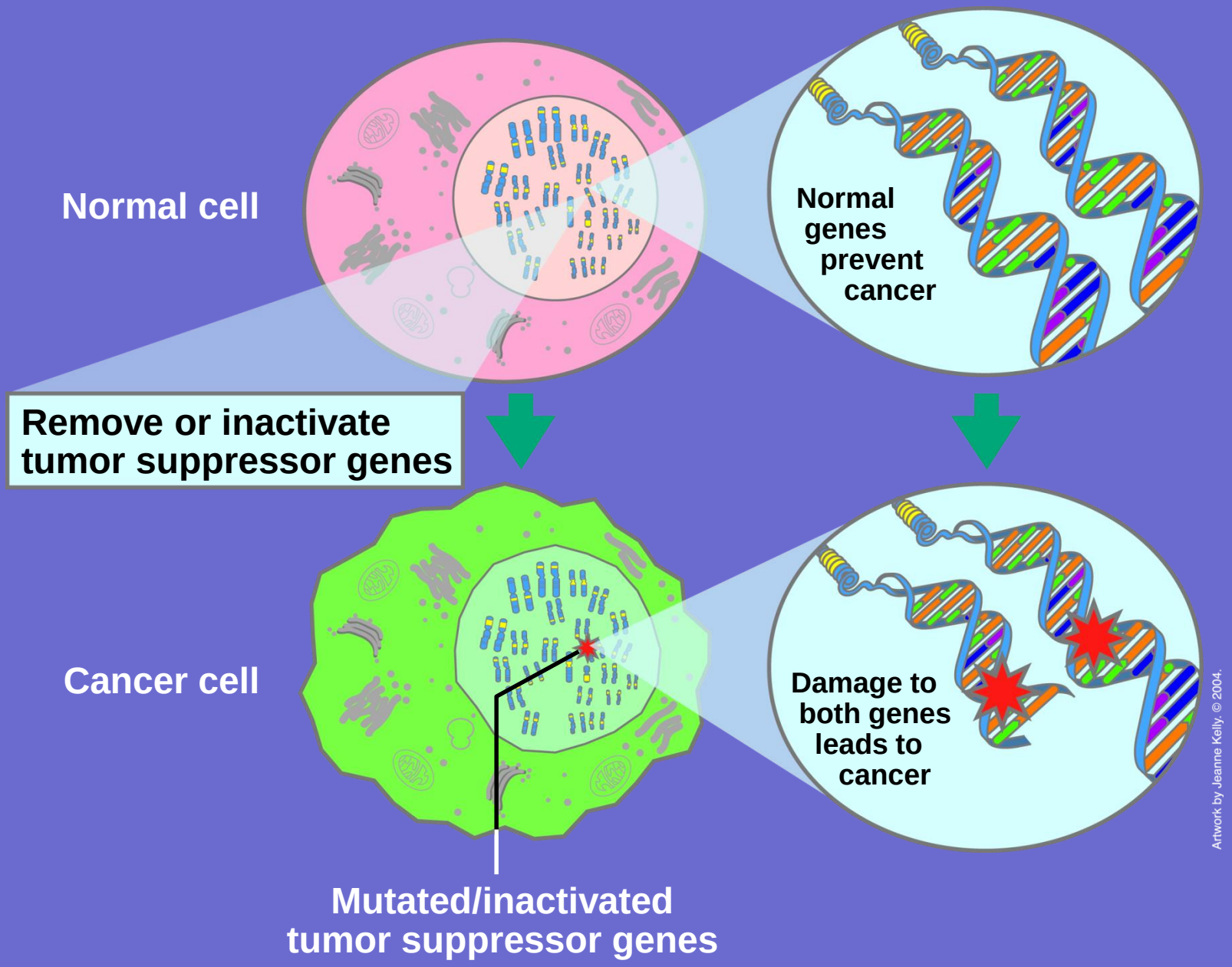


# Tumor suppressors

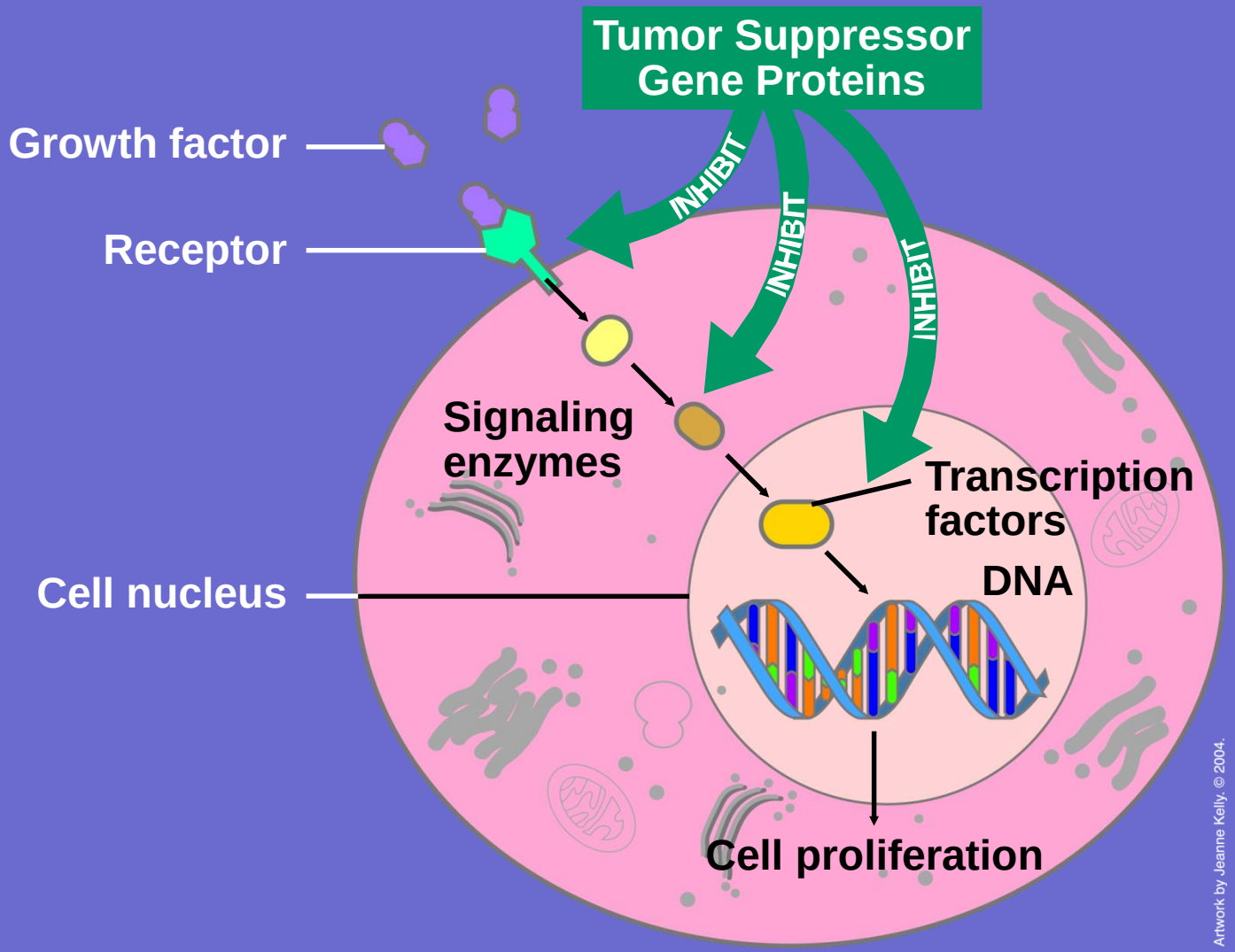
Tumor suppressor genes prevent excessive growth of a cell, either by controlling cell proliferation or by controlling DNA repair and genomic stability

Mutation of a tumor suppressor gene results in the loss of function of the protein product

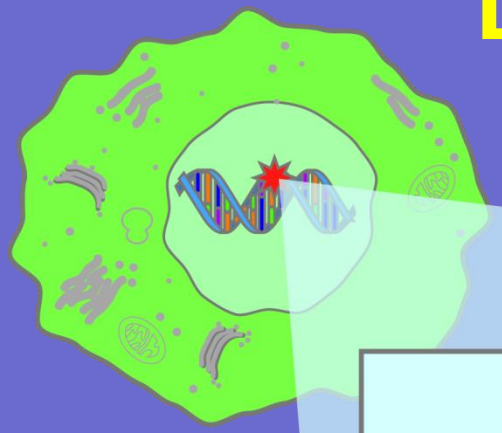
# Tumor Suppressor Genes

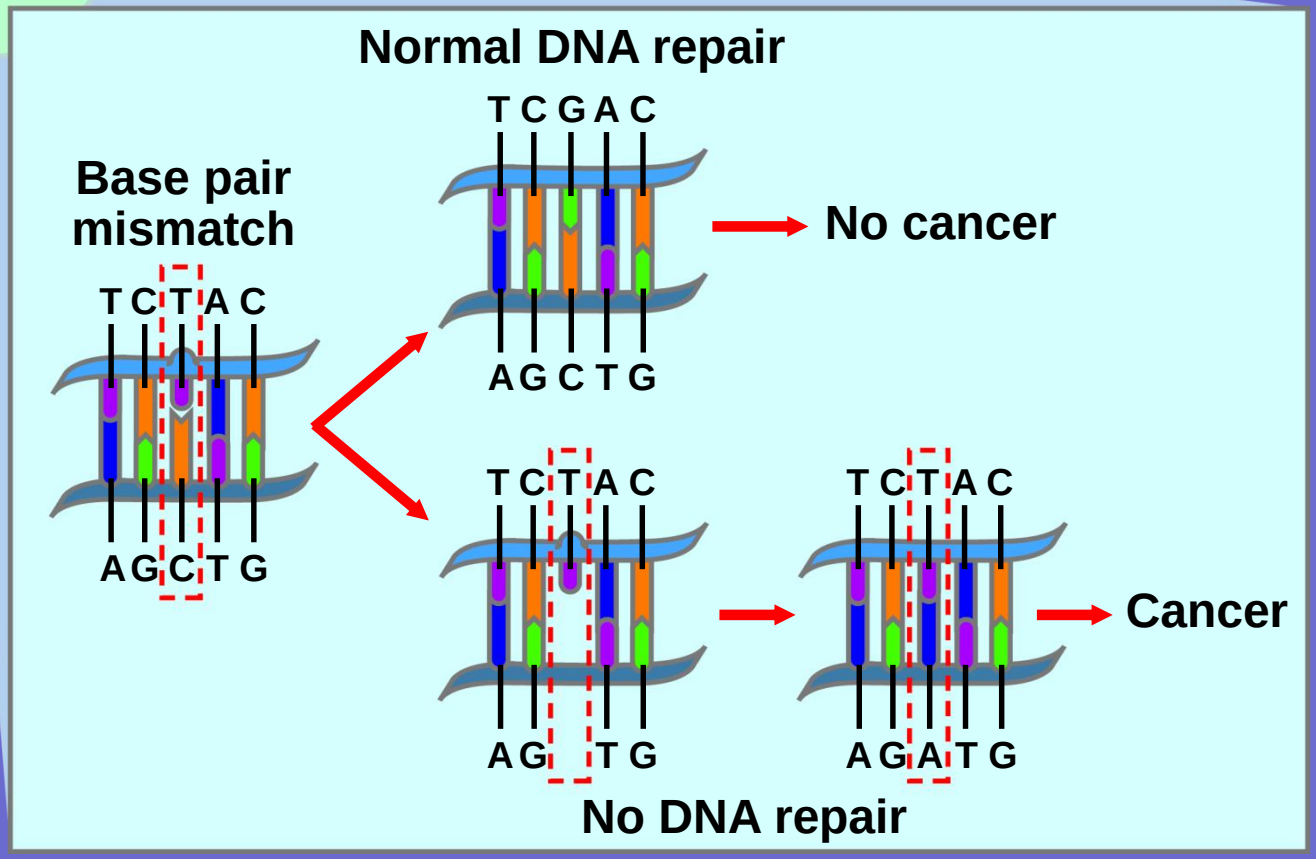


# Tumor Suppressor Genes

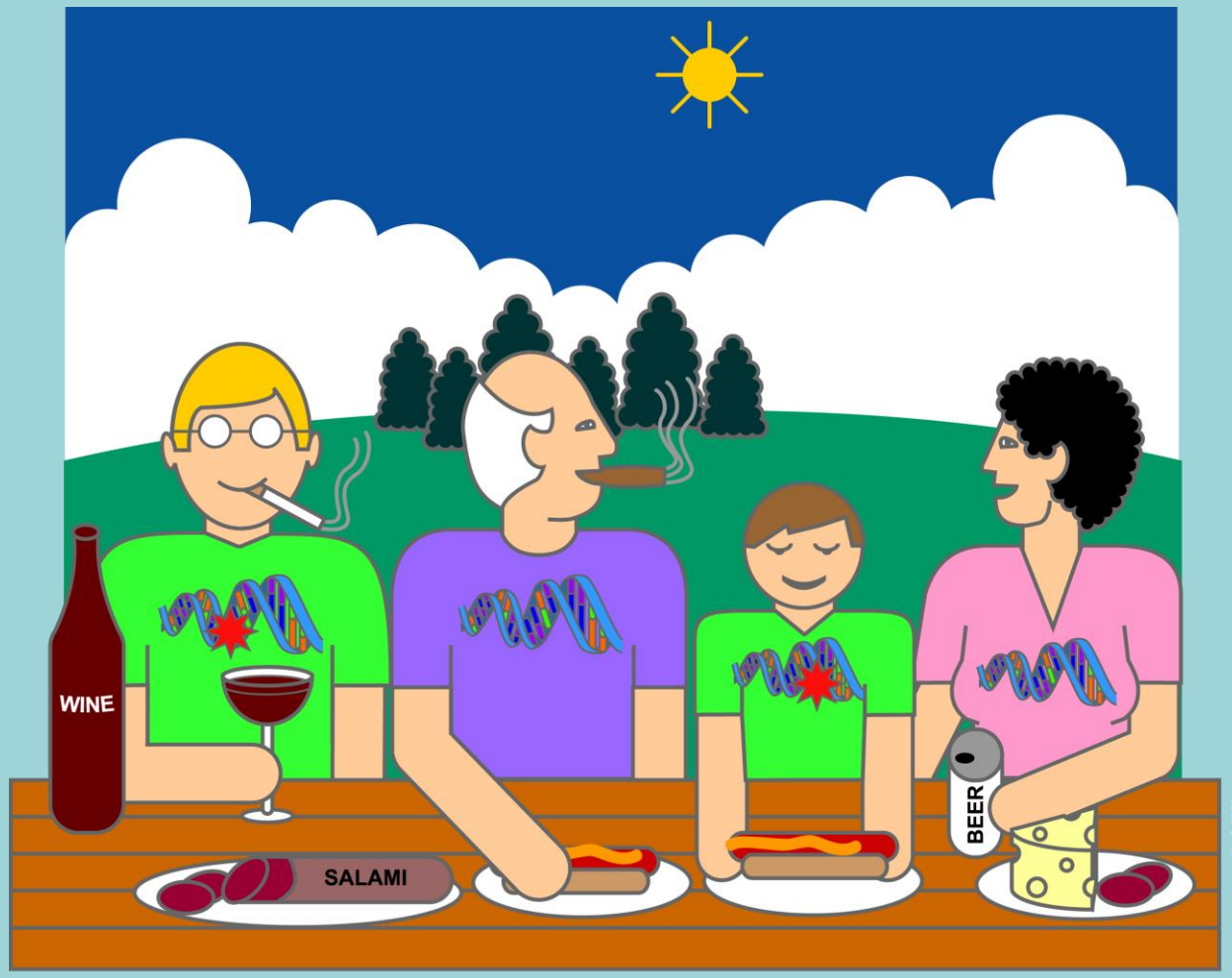


# DNA Repair Genes



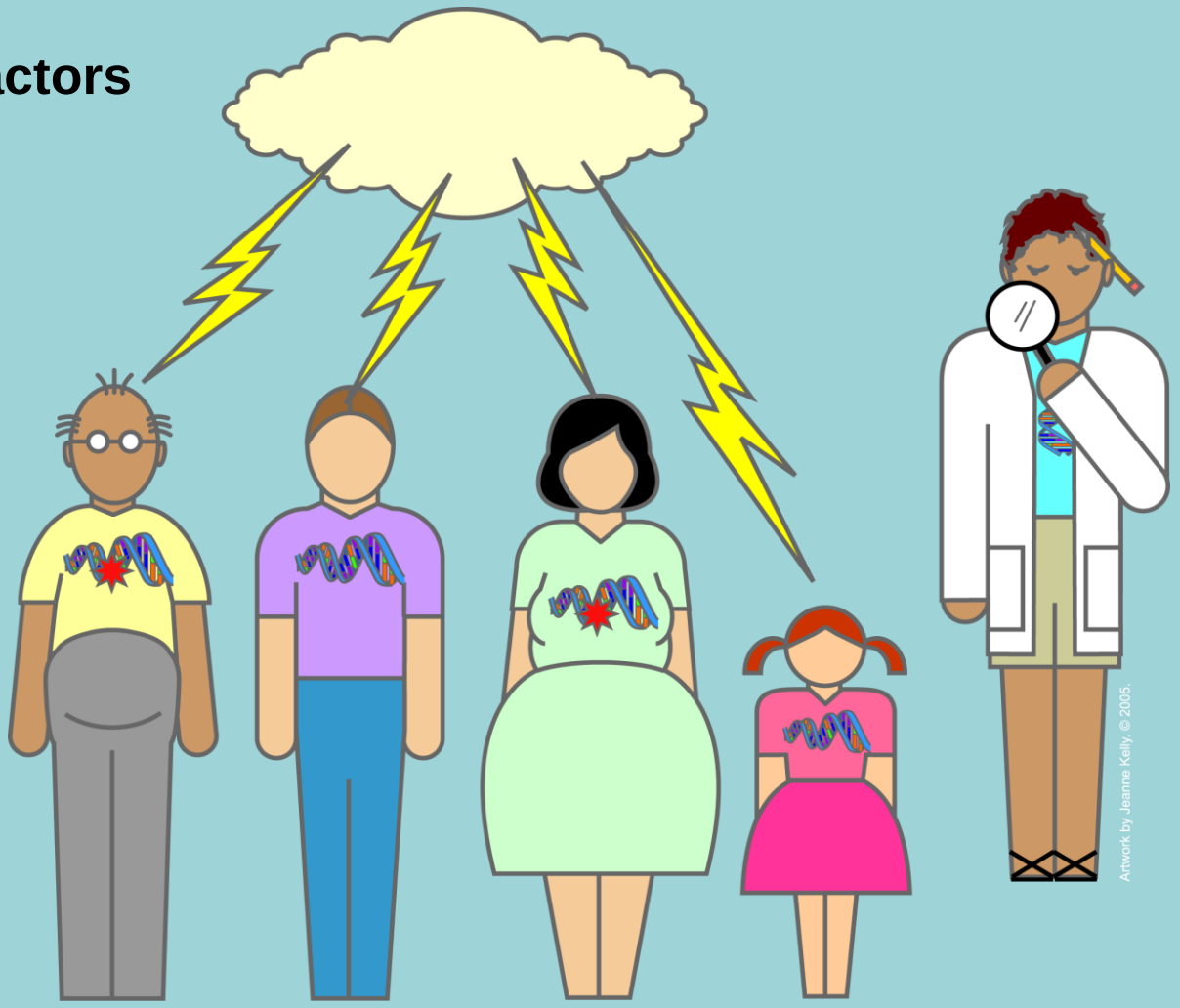


# The Inside Matters:
# Random Gene Changes

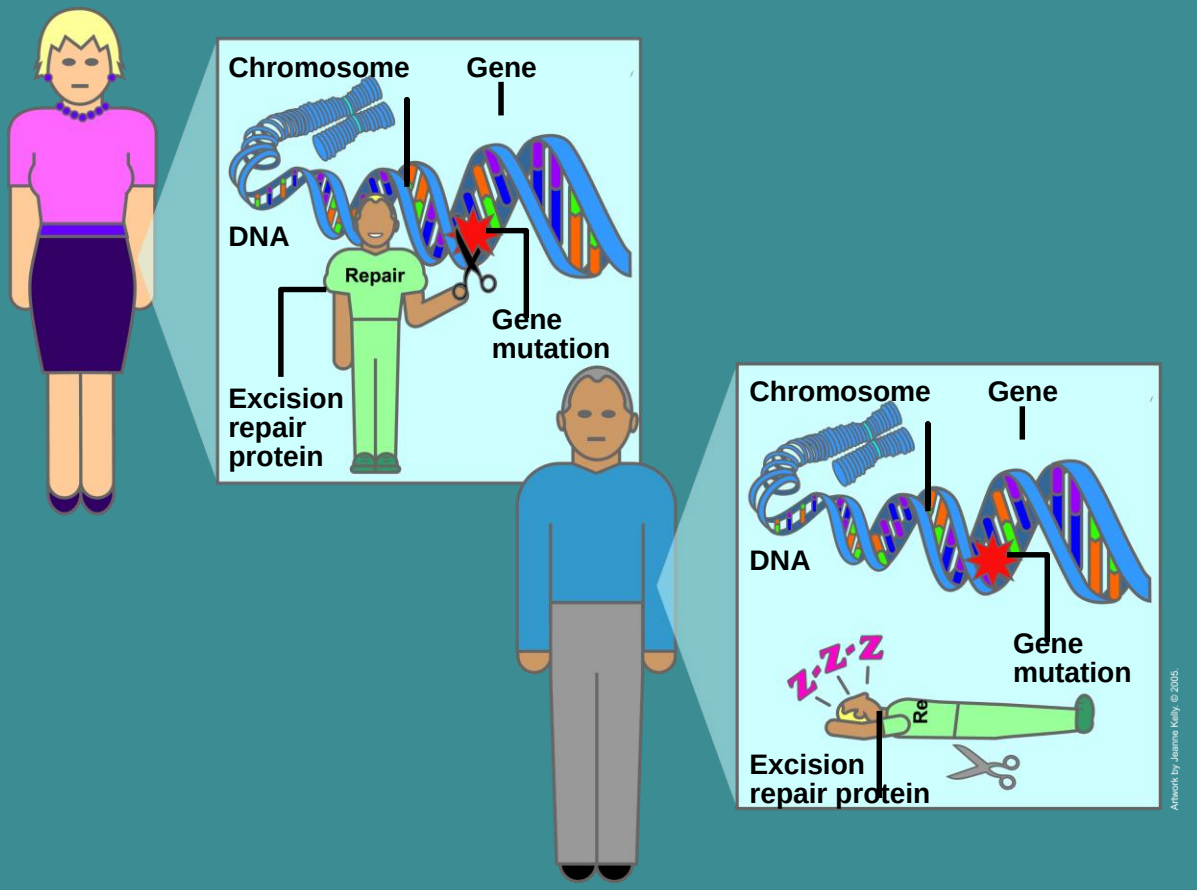


# Chance of Cancer? It Depends…

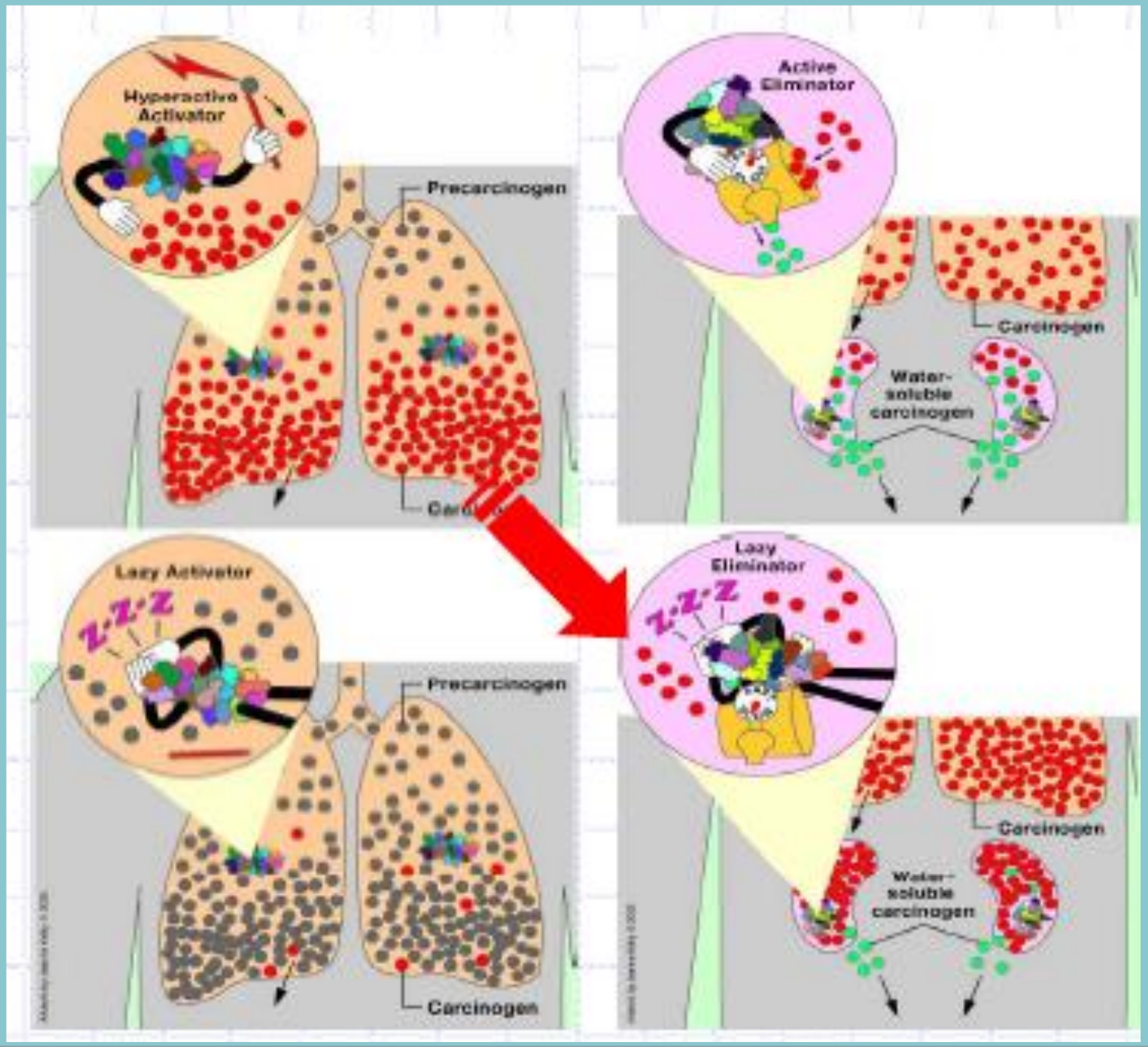
**Environmental factors**



# Faulty Gene Repair Activities



# Individual variability



# Repair Failure

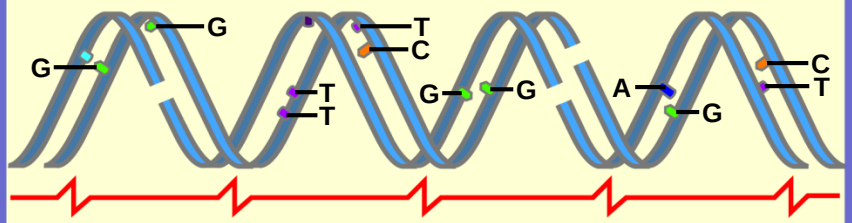
## Damaging Agent

X-rays
Oxygen radicals
Alkylating agents
Spontaneous reactions

UV light
Polycyclic aromatic hydrocarbons

X-rays
Anti-tumor agents (*cis*-Pt, MMC)

Replication errors




Uracil
Abasic site
B-oxoguanine
Single-strand break

(6-4)PP
Bulky adduct
CPD

Interstrand cross-link
Double-strand break

A-G mismatch
T-C mismatch
Insertion
Deletion

Base-excision repair (BER)

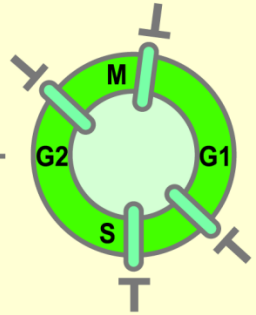
Nucleotide-excision repair (NER)

Recombinational repair (HR, EJ)

Mismatch Repair

## Repair Process

## Consequences




(Transient) cell cycle arrest

Inhibition of:
–Transcription
–Replication
–Chromosome replication

Apoptosis (cell death)

Mutations
Chromosome aberrations

Cancer
Aging
Inborn disease

Hoeijmakers JH. *Nature*. 2001;411:366.

Artwork by Jeanne Kelly © 2004.

# Mutations and Cancer

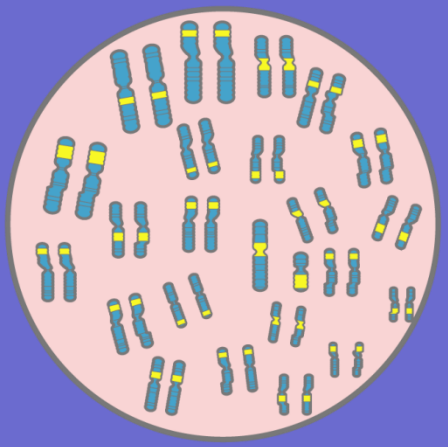
## Genes Implicated in Cancer

| *The prime suspects* | *But* |
|---|---|
| **Mutations in:** | **Other mutations also occur in:** |
| ■ Oncogenes<br>■ Tumor suppressor genes | ■ Cell death genes<br>■ Cell signaling genes |
| ■ DNA repair genes | ■ Cell cycle checkpoint genes |
| | ■ Cellular senescence genes |
| | ■ Cellular differentiation genes |
| | ■ Metastasis/invasion genes |
| | ■ Carcinogen<br>–activating genes<br>–deactivating genes |

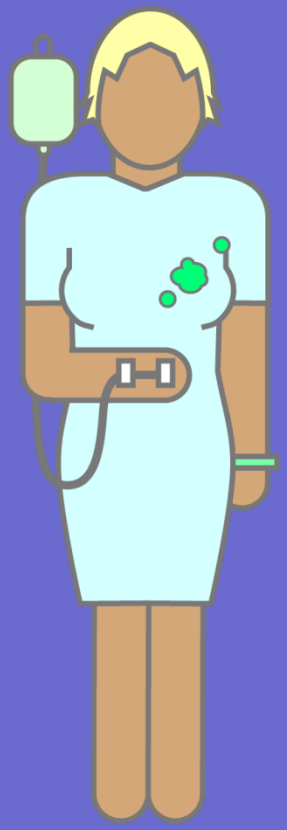
# Genotypes and Phenotypes

A *phenotype* is the physical manifestation of an inherited trait or disease

A *genotype* is the genetic makeup of a person







In cancer, both genotype and phenotype keep changing over time