

# Genotoxicity and cancer

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# Definitions

**Genotoxicity** is a term used by a geneticist for substances possessing destructive effects on a cell's genetic material (DNA, RNA), thus affecting the integrity of the cell.

**Mutagenic agents** comprising the genotoxicity properties are called **genotoxins**.

## **Genetic toxicology**

is the branch of science that deals with the study of DNA and chromosomal damage in the cell due to potential agents or substances.

**Genotoxicity** is sometimes confused with **mutagenicity**.

Not all genotoxic substances possess mutagenic properties; however, every **mutagen** is capable of triggering genotoxicity.

## genotoxic substances

Include both ionizing radiation----- chemical genotoxins.

Organisms are affected primarily by three distinct types of agents, all of which are associated with genetic alterations.

- (i) cancer-causing agents.
- (ii) mutation-causing agents.
- (iii) teratogens, birth defect-causing agents.

## **Defending mechanisms**

**Cells prevent expression of the genotoxic mutation by**

**1- DNA repair machinery**

**2- Induction of apoptosis**

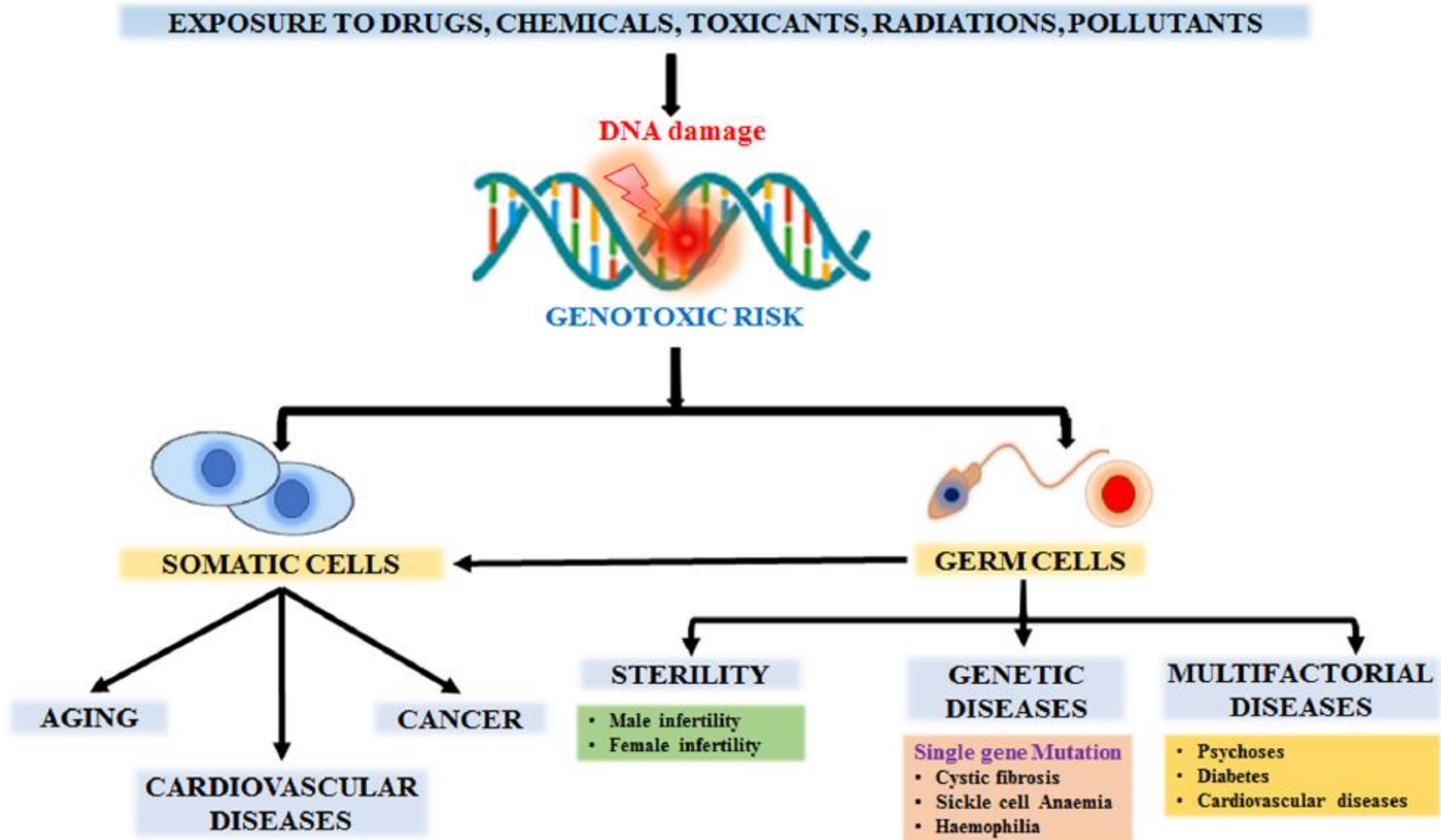
**however, the damage may not always be fixed leading to mutagenesis.**

**Not all genotoxic substances are carcinogenic**

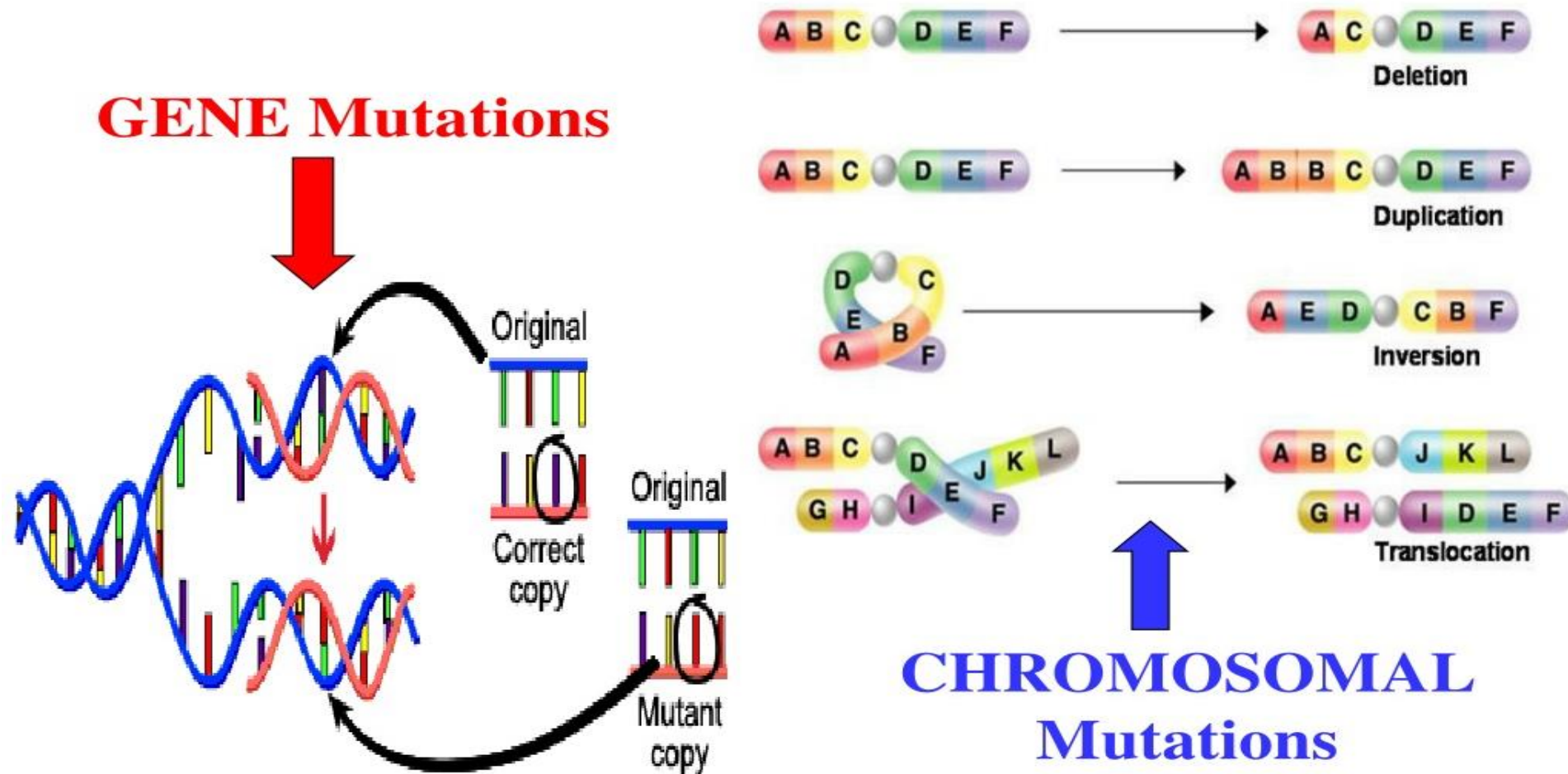
**Not all mutagenic substances are carcinogenic**



# Major effects on human health on exposure to genotoxins.

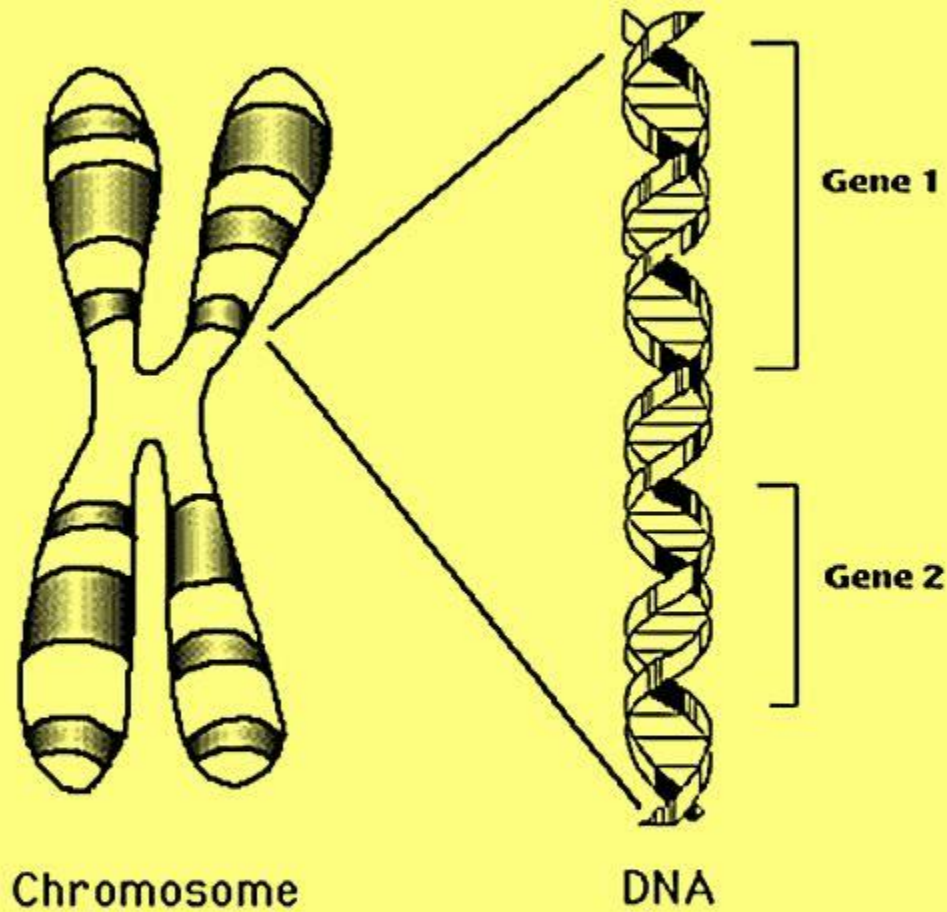


# Types of DNA mutations





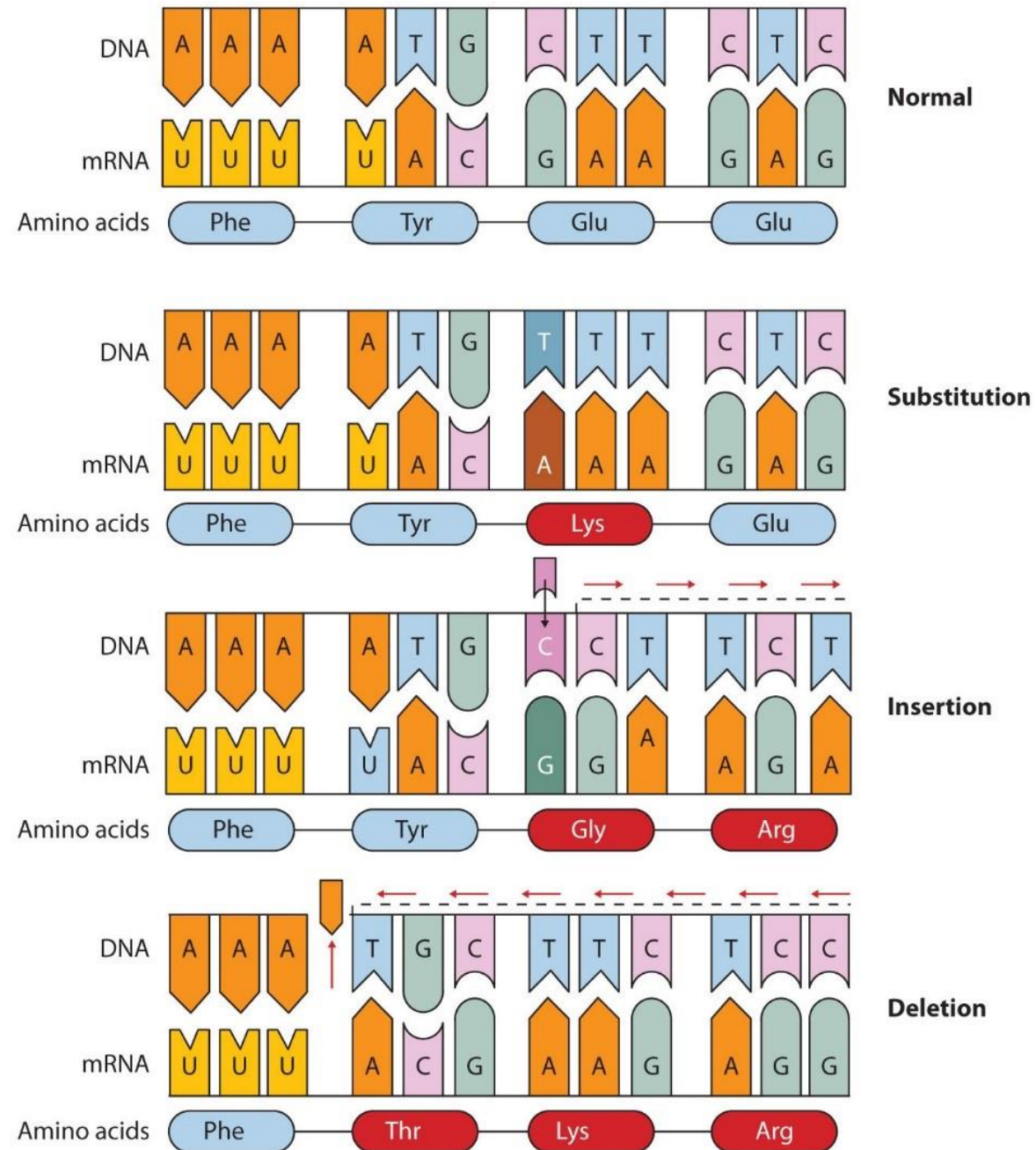
# Types of mutations



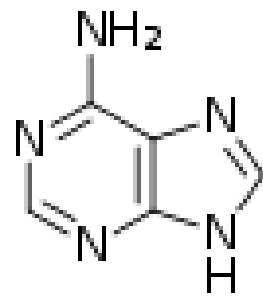
**Genes**

**Chromosomal mutation:**  
affecting whole or a part  
of a chromosome

**Gene mutation:** changes  
to the bases in the DNA of  
one gene

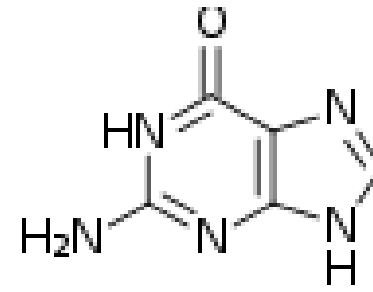




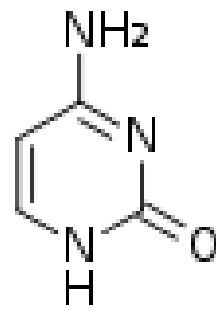
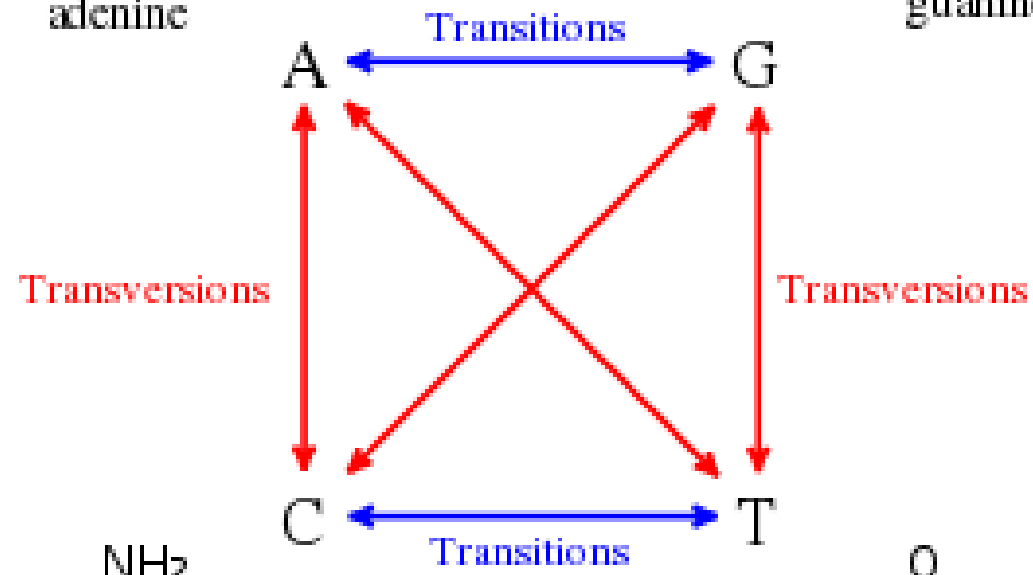


adenine

purines

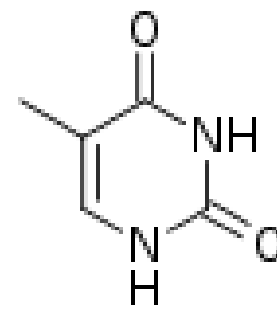


guanine



cytosine

pyrimidines



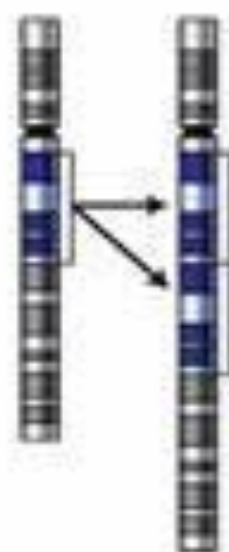
thymine

## Types of Mutations

Deletion



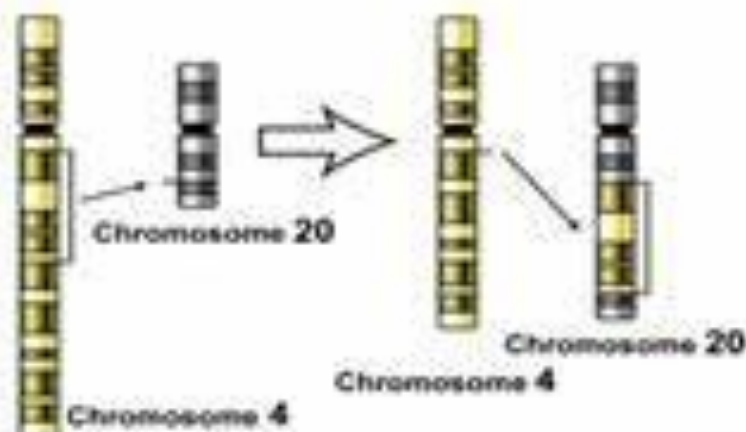
Duplication



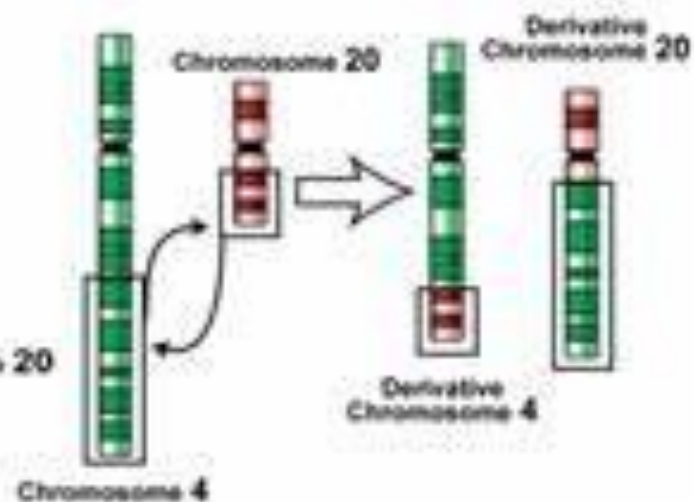
Inversion



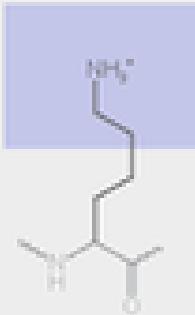
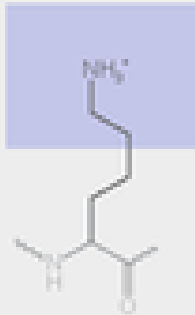
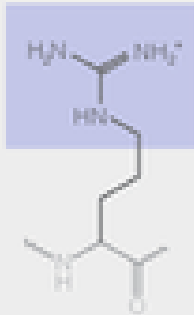
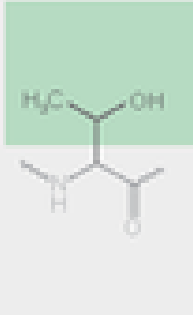
Insertion

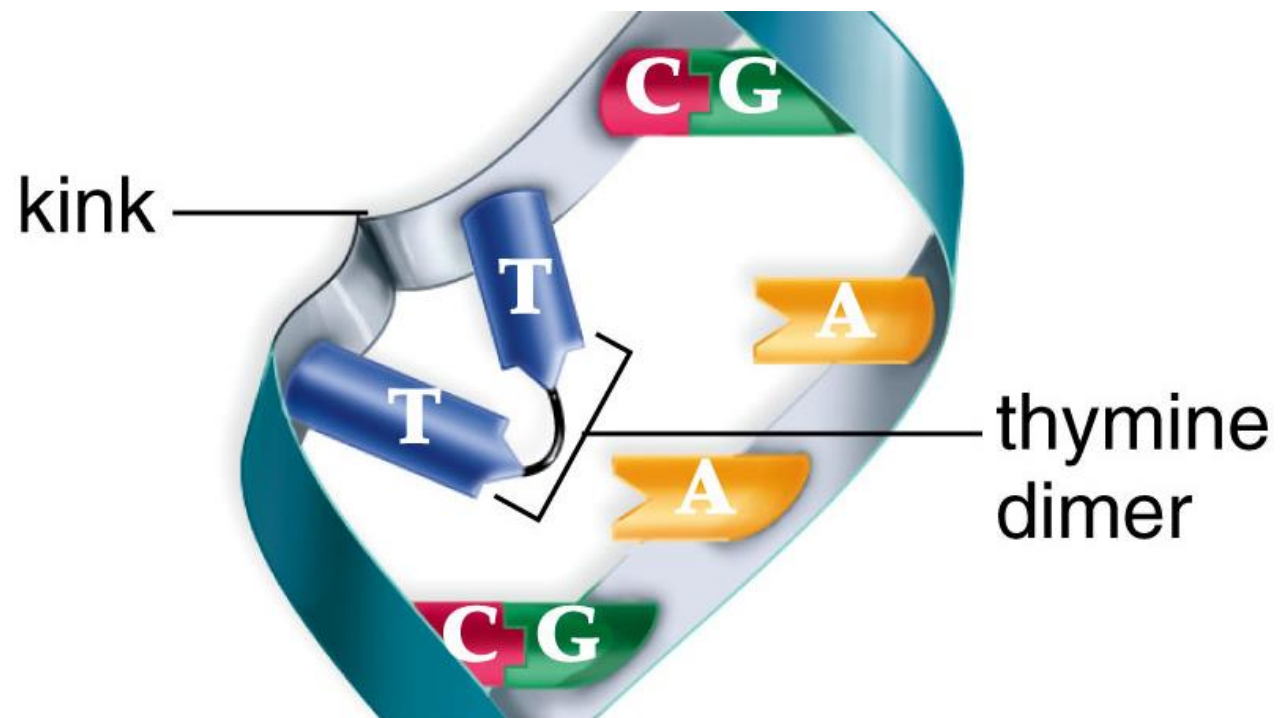
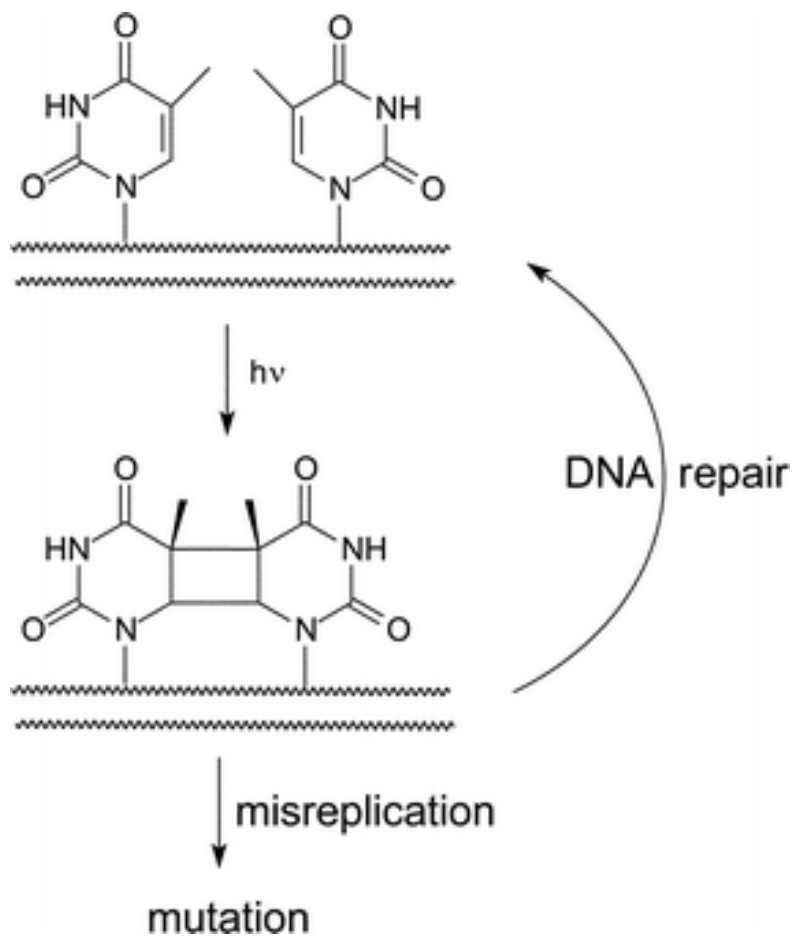


Translocation

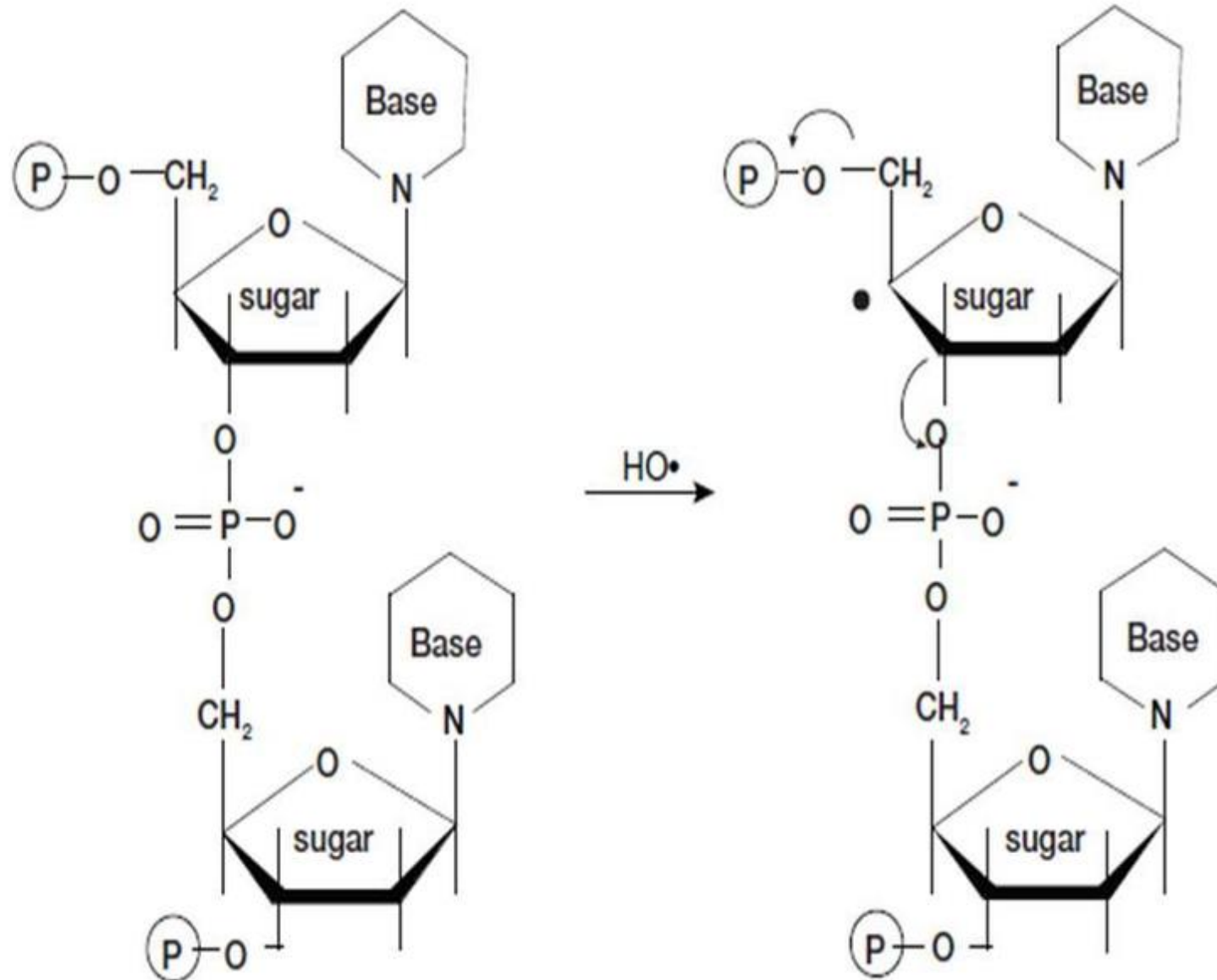


A **point mutation** or substitution is a genetic mutation where a single nucleotide base is changed inserted or deleted from a DNA sequence

		Silent	Nonsense	Missense	
				conservative	non-conservative
DNA level	TTC	TTT	ATC	TCC	TGC
mRNA level	AAG	AAA	UAG	AGG	ACG
protein level	Lys	Lys	STOP	Arg	Thr
					
				basic	polar

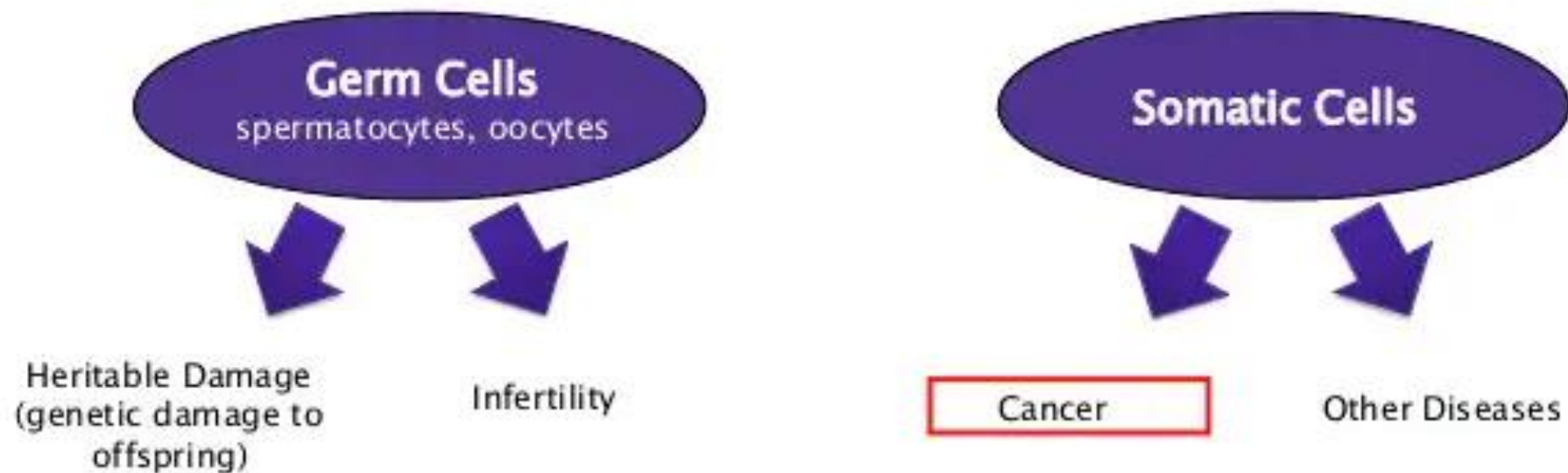


DNA single-strand breaks are the most common damage inflicted by **ROS**

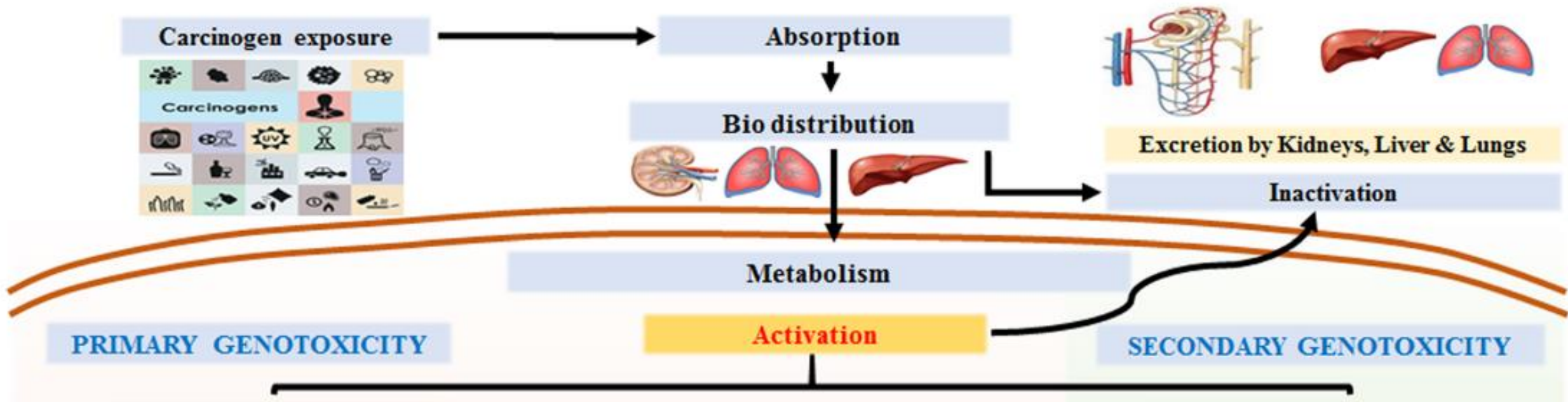




## DNA damage is associated with many human diseases



# Schematic representation of mechanisms of carcinogenesis due to genotoxicity.



## PRIMARY GENOTOXICITY

## Activation

## SECONDARY GENOTOXICITY

### Genotoxic mechanisms

#### Direct DNA damage

- DNA lesions
- Strand breaks

#### Indirect DNA damage

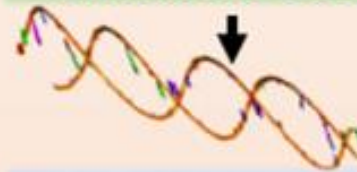
##### Damage to:

- DNA replication enzymes
- DNA repair enzymes
- Cell cycle control proteins
- Spindle apparatus
- Centrosome

- Mitochondrial damage
- Antioxidant depletion

- ROS

#### Oxidative DNA Damage



## GENOTOXICITY

- Hyper mutability
- Gene instability
- Abortive Apoptosis
- Loss of proliferation control

### Non- genotoxic mechanisms

#### Chronic inflammatory response

- Inflammation
- Immunosuppression
- Receptor activation
- Epigenetic silencing

- ROS
- RNS

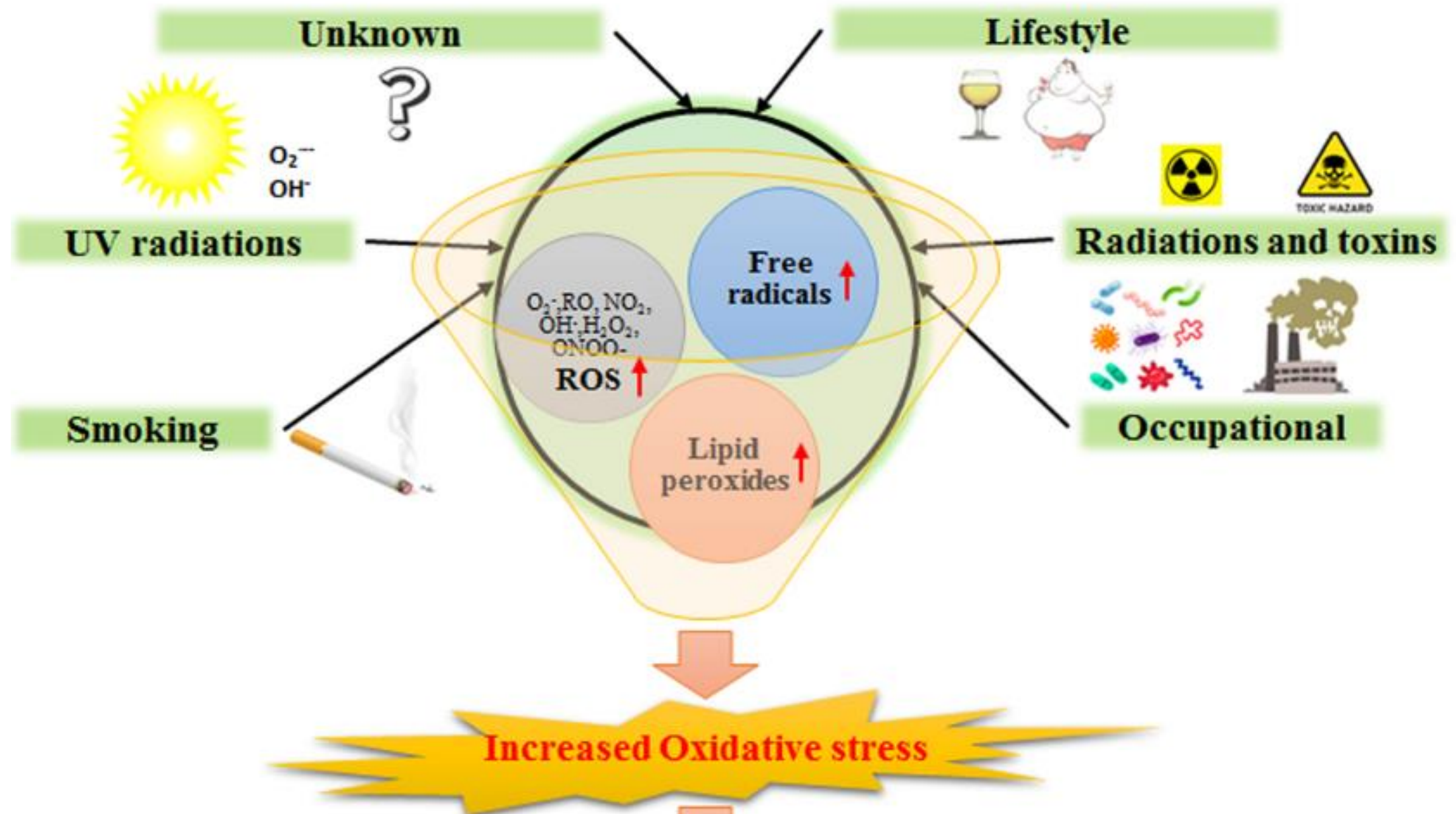
#### Oxidative DNA Damage

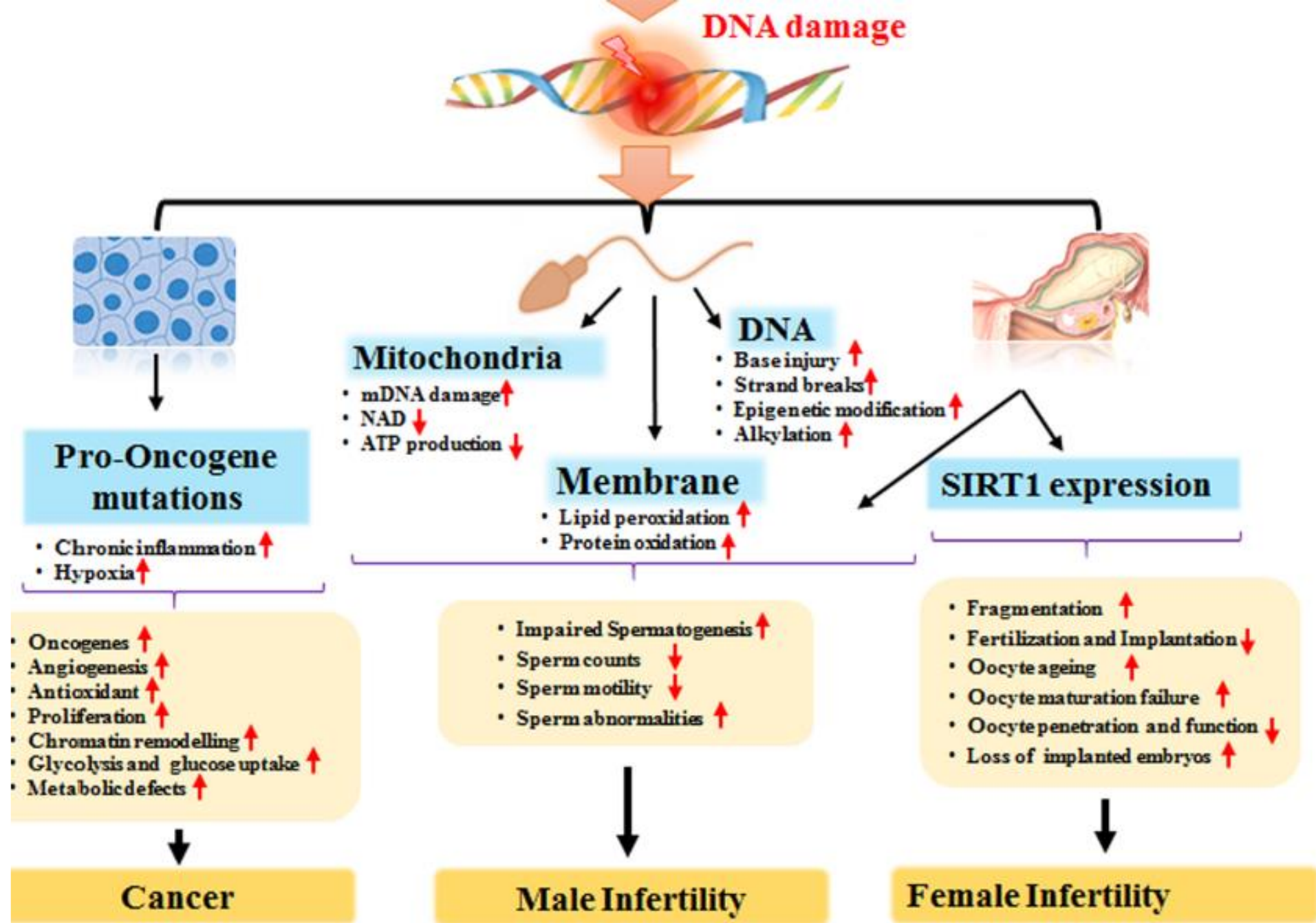
#### Altered signal transduction

**CANCER**



Schematic representation of interplay between increased reactive oxygen species (ROS) and cancer and/or male and female infertility.

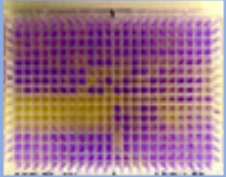




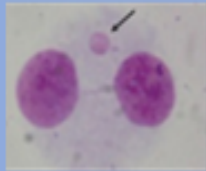


# Test for Genotoxicity

## Genotoxicity assays



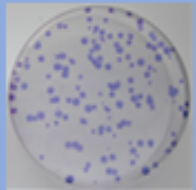
**Mini Ames Test**



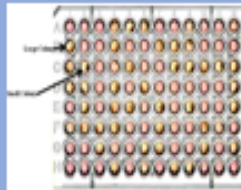
**In Vitro  
micronucleus Test**



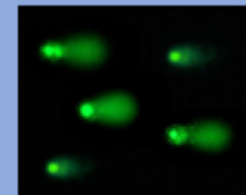
**In Vitro  
Chromosomal  
Aberration Assay**



**In Vitro  
Mammalian Cell Gene  
Mutation Test (HPRT  
Gene)**



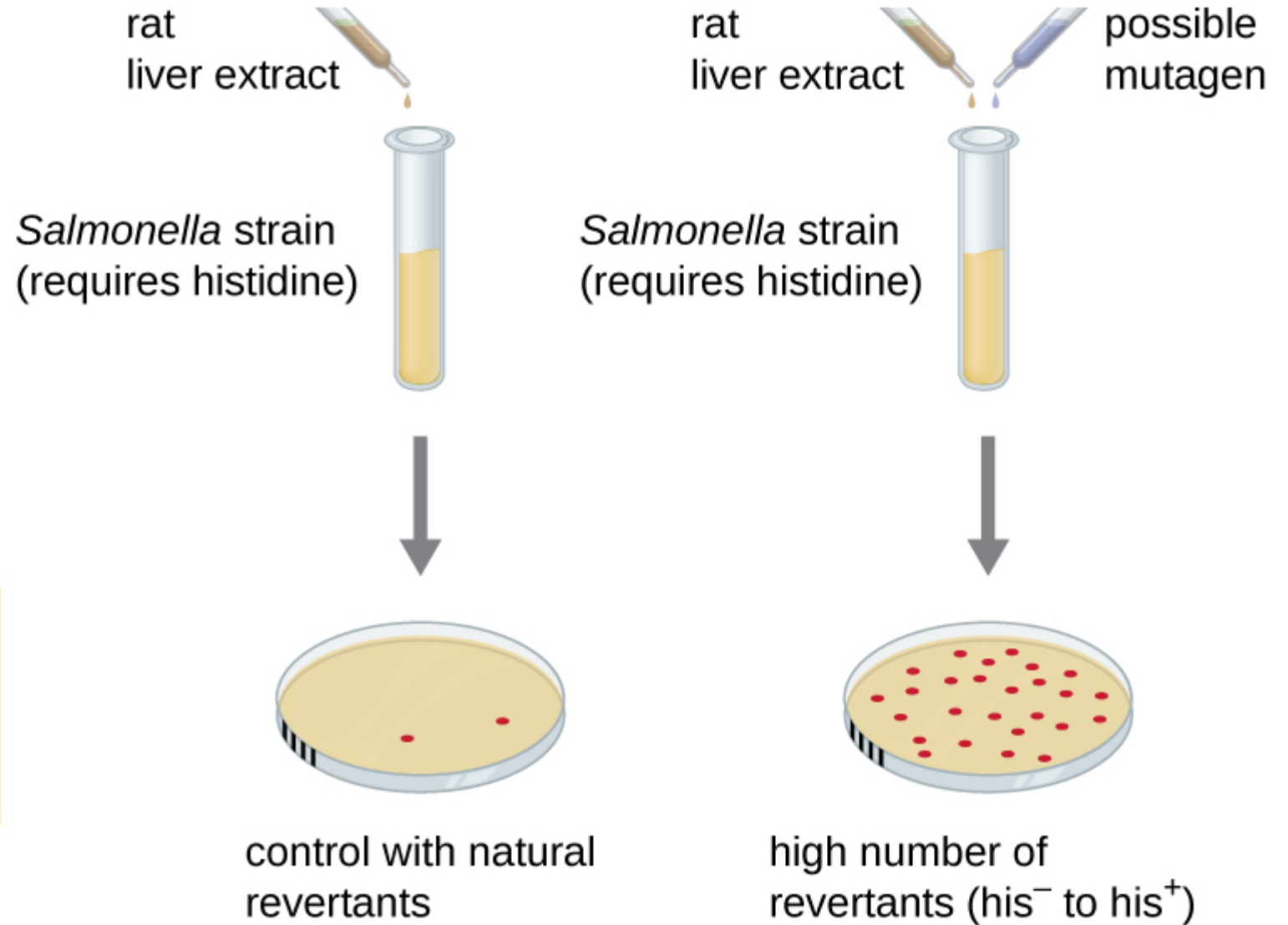
**In Vitro  
Lymphoma  
Thymidine Kinase (TK)  
Gene Mutation Assay**



**In Vitro Comet Test**

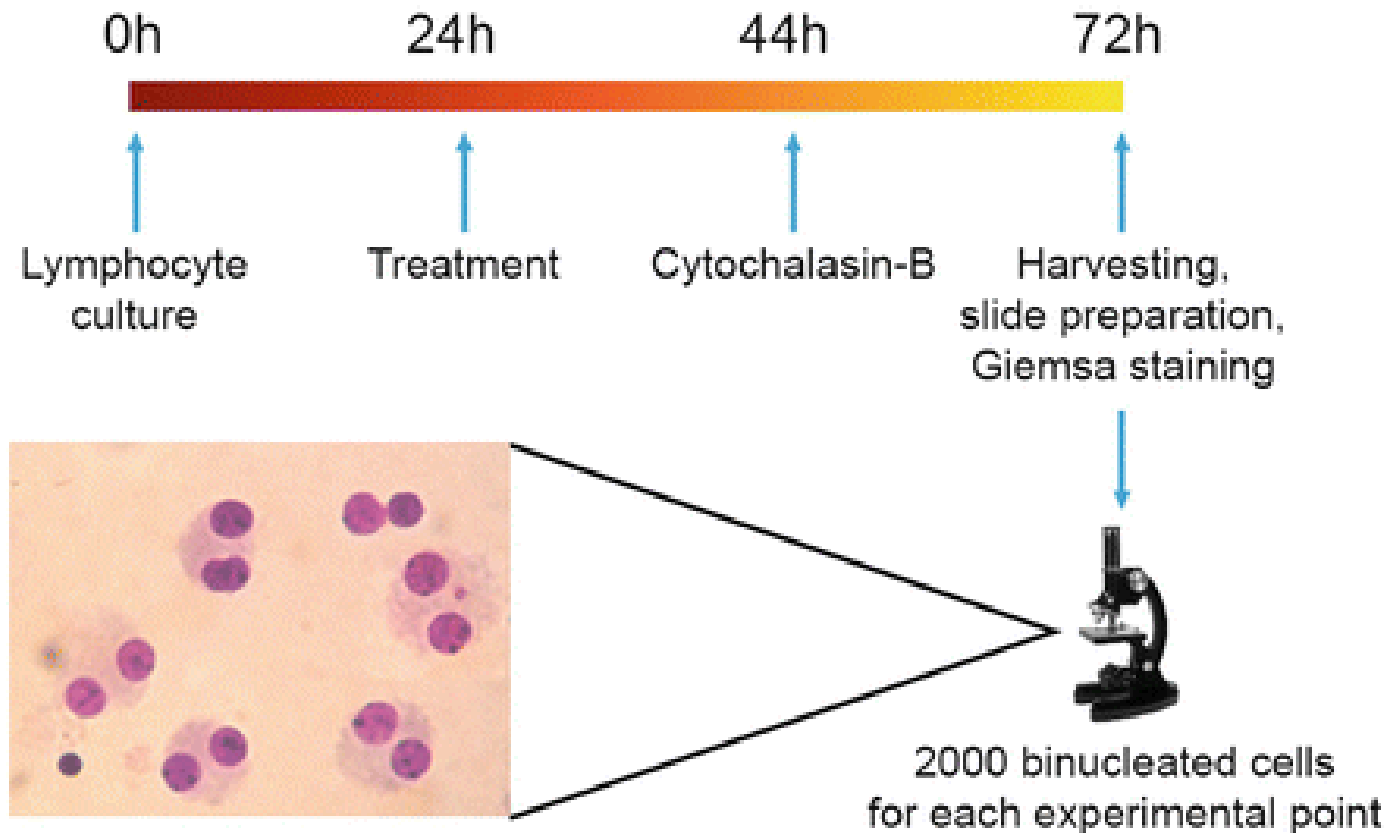
**1** Add rat liver extract and *Salmonella* to top control tube; add rat liver extract, possible mutagen, and *Salmonella* to bottom experimental tube. Plate and incubate both samples using medium lacking histidine.

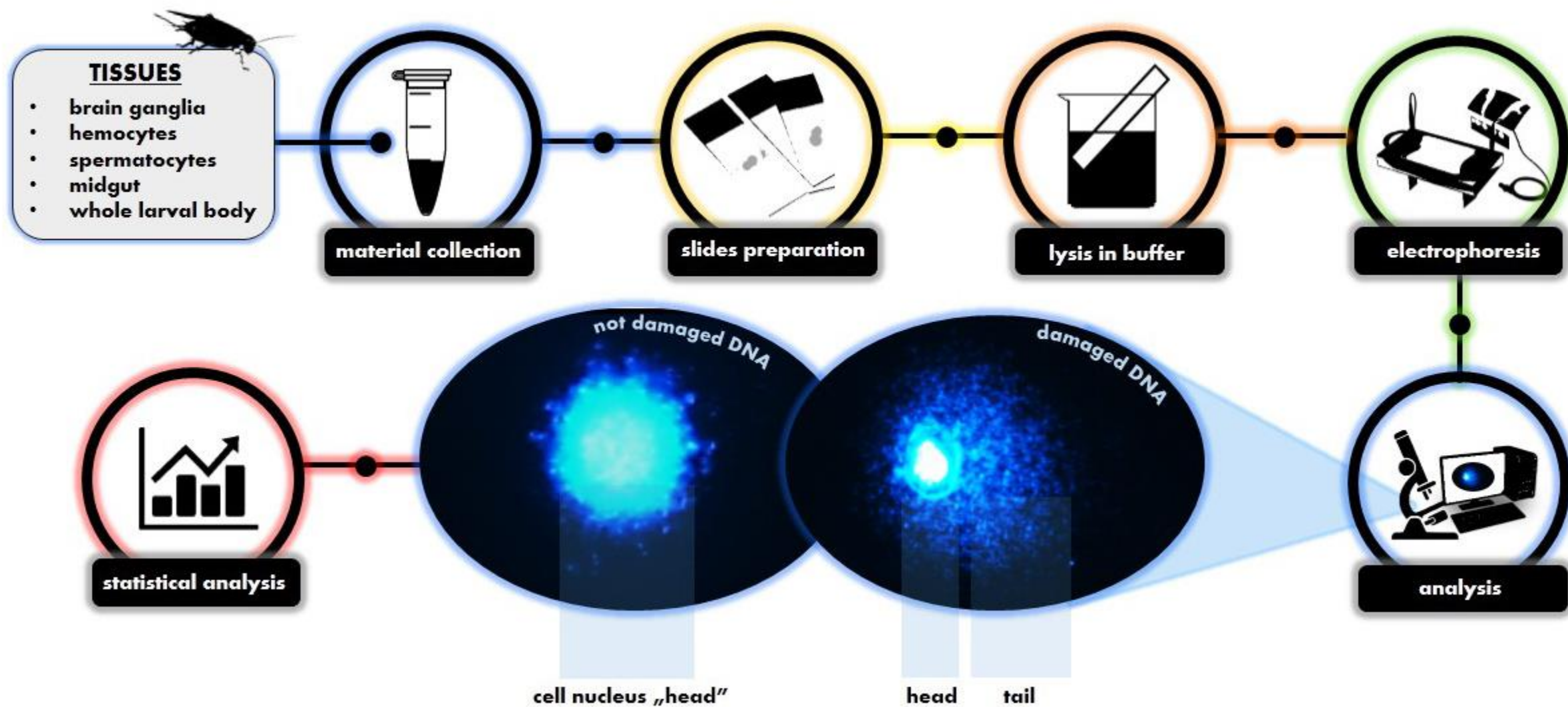
**2** Compare growth on plates to identify revertants, which suggest mutagen causes mutations.



# The In Vitro Micronucleus Assay

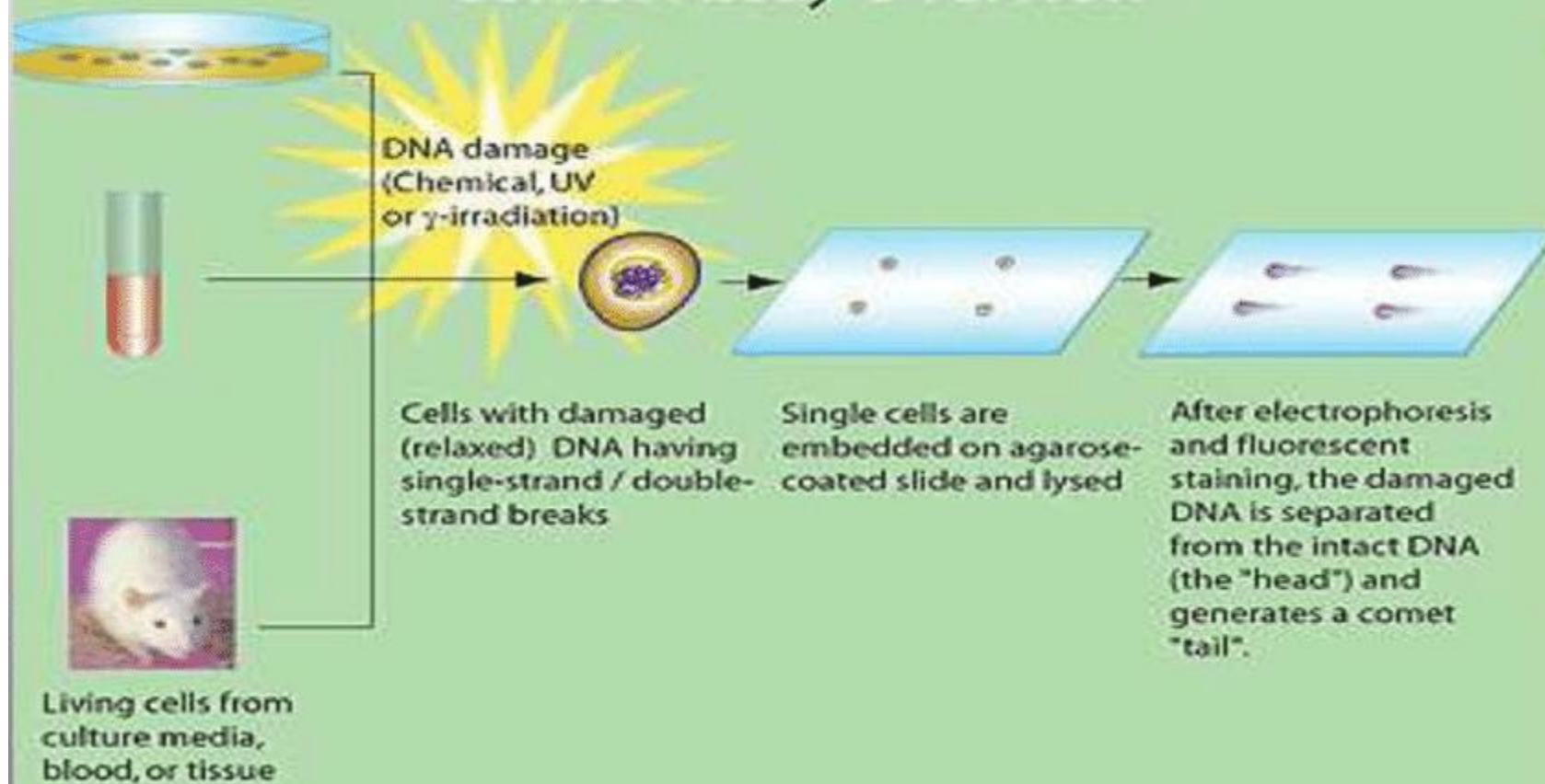
## Cytokinesis-block micronucleus cytochrome assay

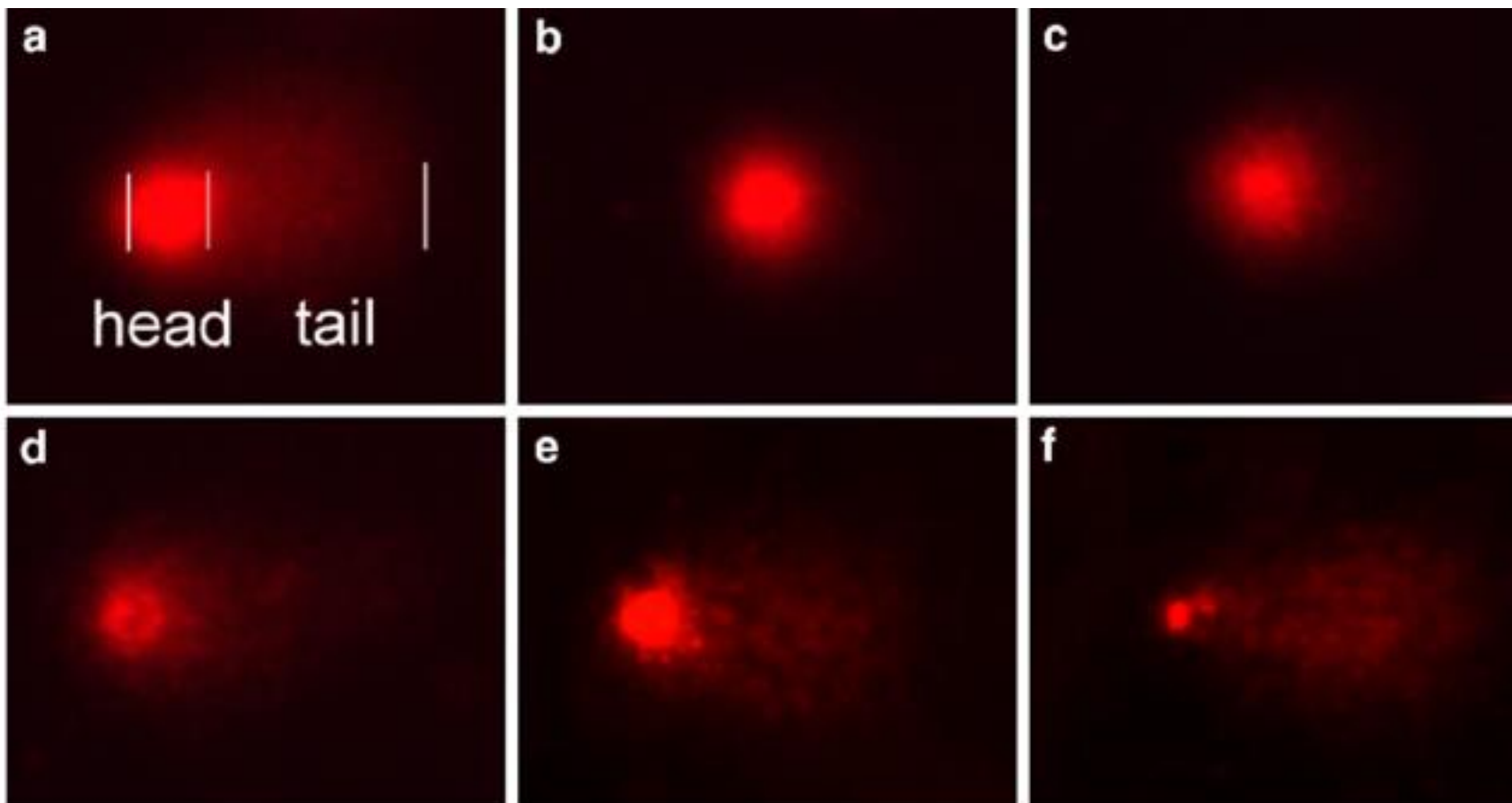






## Comet Assay Overview









THANK  
YOU