

DNA damage mutagenicity and genotoxicity

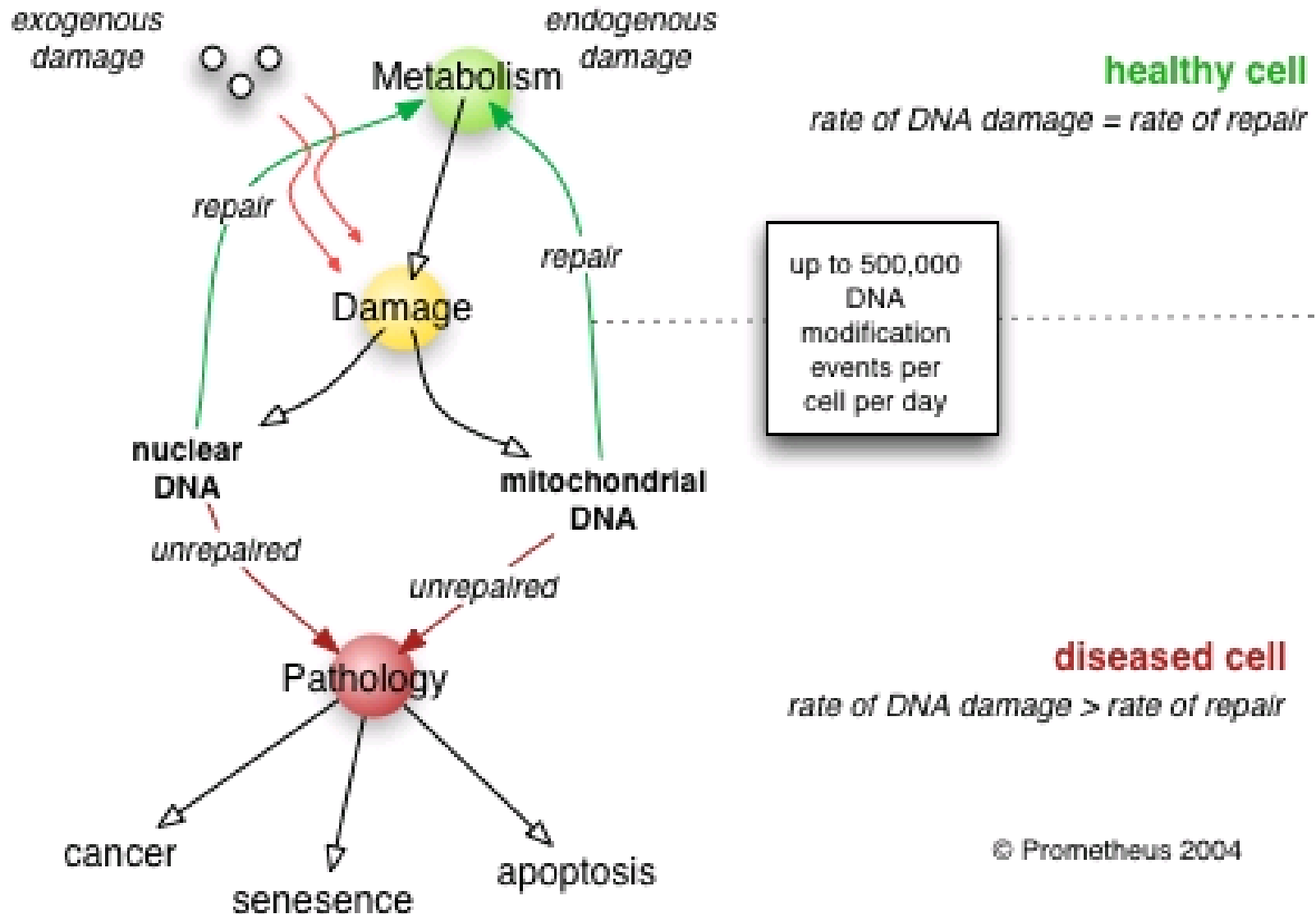
DNA:

- principal molecule for life of the cell
- structure and function carefully checked
- changes rapidly repaired
- irreversible changes -> cell death (*apoptosis*)

Mutagenesis - MUTATIONS

- changes in the sequences of deoxynucleotides
- natural mutations (billions of nucleotides/day)
: variability in genomes; reparations
- chemical-induced mutagenesis

DNA damage



DNA repair

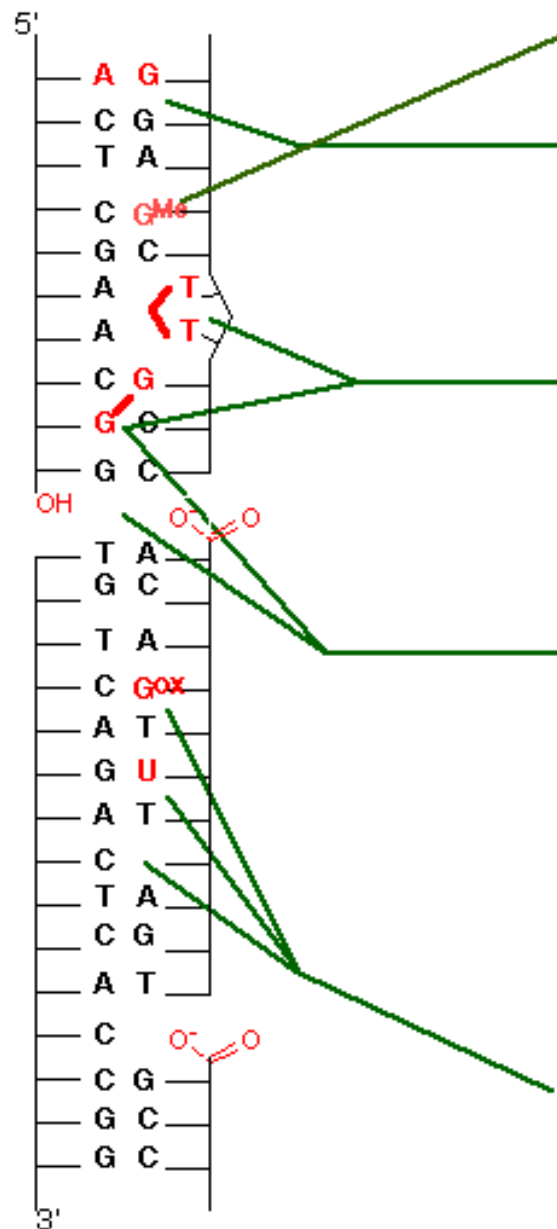
Damage of DNA is carefully controlled
constitutively expressed proteins

Changes in DNA

induction of reparation enzymes ("SOS-repair")
= biomarker of DNA damage

DNA DAMAGE

DNA REPAIR SYSTEM

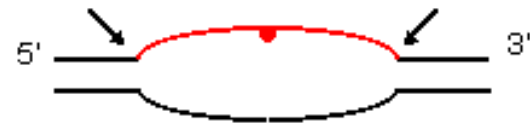


DIRECT REVERSAL

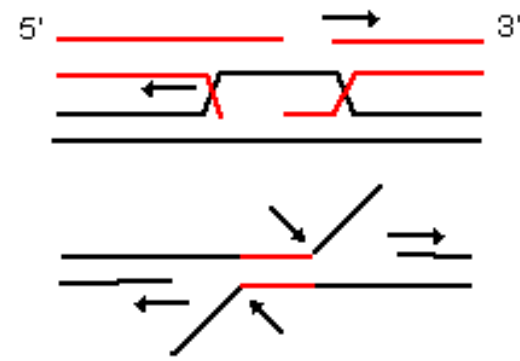
MISMATCH REPAIR



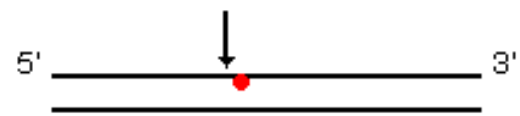
NUCLEOTIDE EXCISION REPAIR



RECOMBINATIONAL REPAIR



BASE EXCISION REPAIR



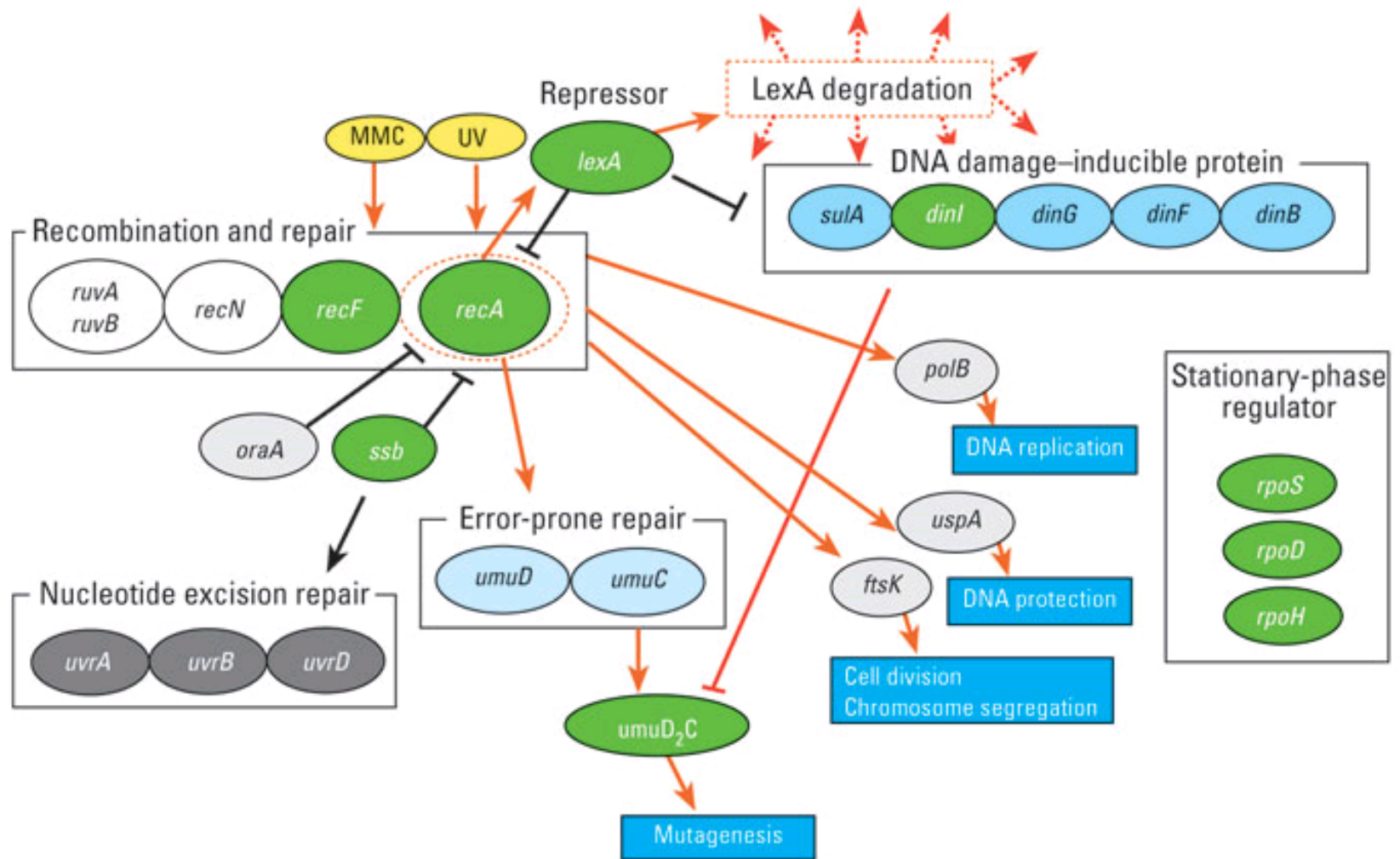


Figure 3. A literature-based linkage map between genes in the SOS response in *E. coli*. The map represents inducible genes/proteins in the SOS response for repair from DNA damage. Black lines indicate pathways in the normal repair process and red lines with arrows activation/induction due to an exposure to damaging agents. Recombination and repair, DNA damage-inducible protein, nucleotide excision repair, error-prone repair, and stationary-phase regulator have family molecules in each box. Green circles are genes used for the analysis.

Induced mutations

MUTAGENS

- ionizing radiation and UV
- chemicals

Base analogs - inserted into the DNA strand during replication in place of the substrates.

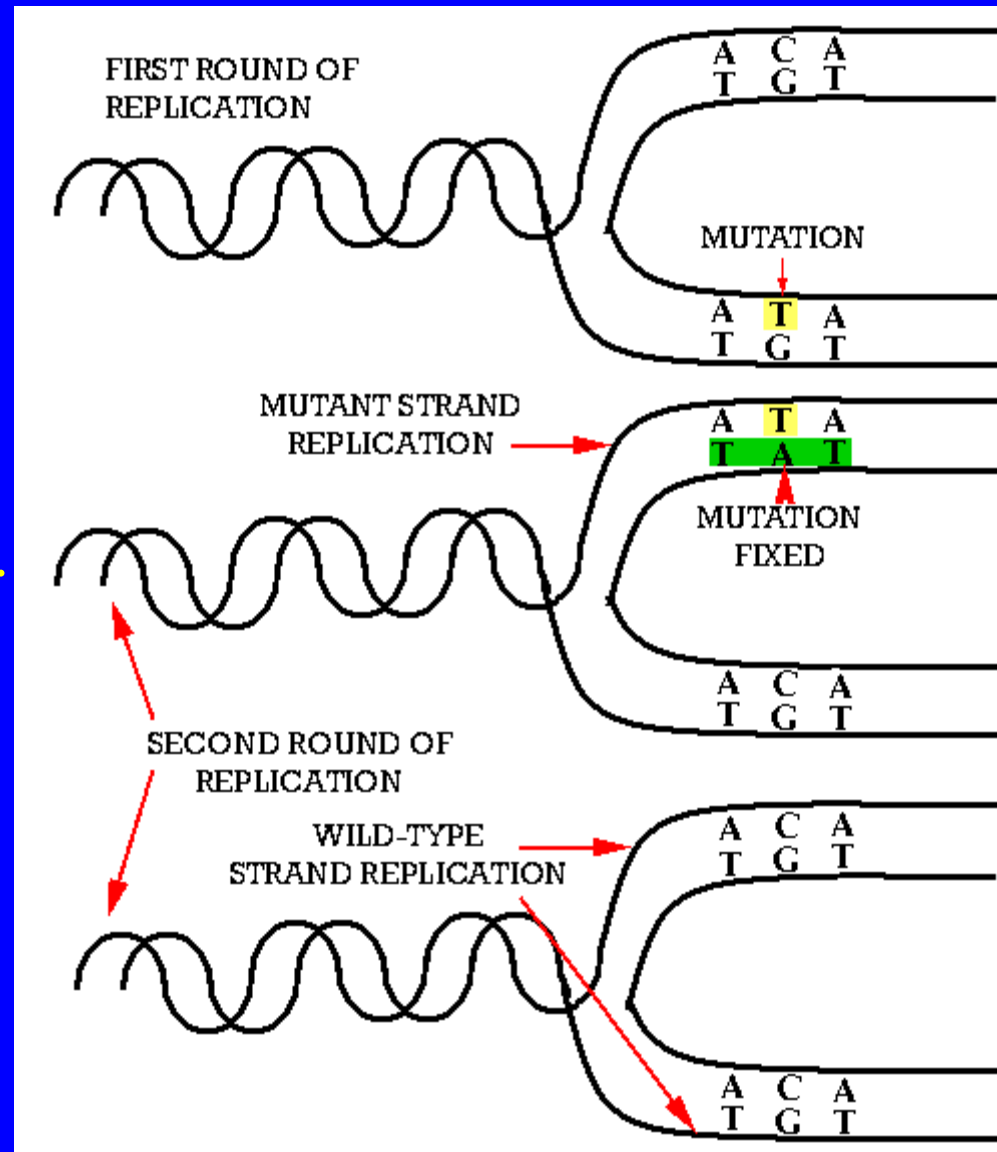
Agents reacting with DNA - structural changes leading to miscopying of the template strand

Indirect mutagens - affect cells that synthesize chemicals with direct mutagenic effect

Point mutations

BASE - EXCHANGE:

- Silent mutations:
 - code for the same amino acid.
- Missense mutations:
 - code for a different amino acid.
- Nonsense mutations:
 - which code for a stop



Point mutation

INSERTION

DELETION

Change of the reading frame

Insertion

5'	AUG	CGA	UUA	UAC	GGG		3'
	Met	Arg	Leu	Tyr	Gly		

↓

5'	AUG	CGA	UUA	UUA	CGG	G	3'
	Met	Arg	Leu	Leu	Arg		

Deletion

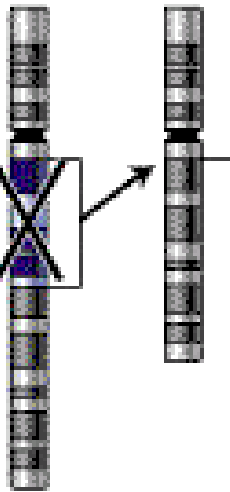
5'	AUG	CGA	UUA	UAC	GGG	AAA	3'
	Met	Arg	Leu	Tyr	Gly	Lys	

↓

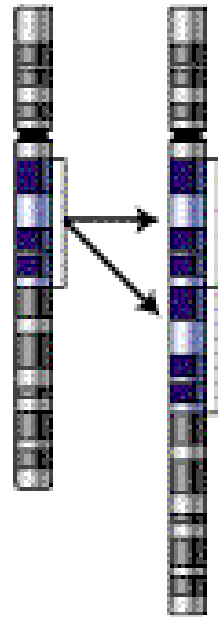
5'	AUG	CGA	UUA	UAG	GGA	AA	3'
	Met	Arg	Leu	Stop			

Large scale mutations / chromosomal

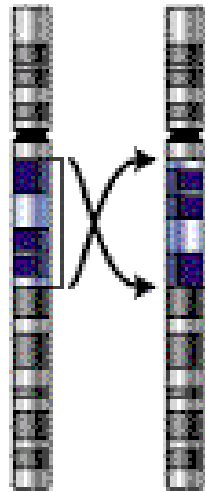
Deletion



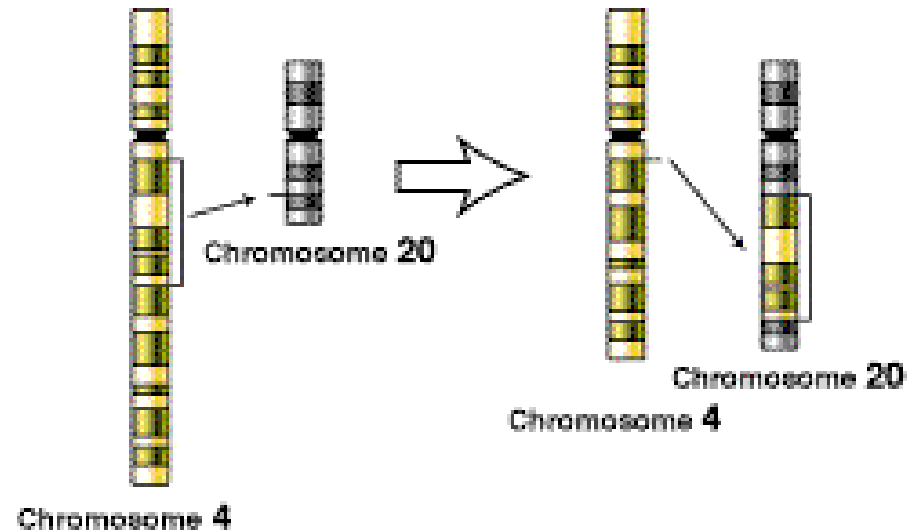
Duplication



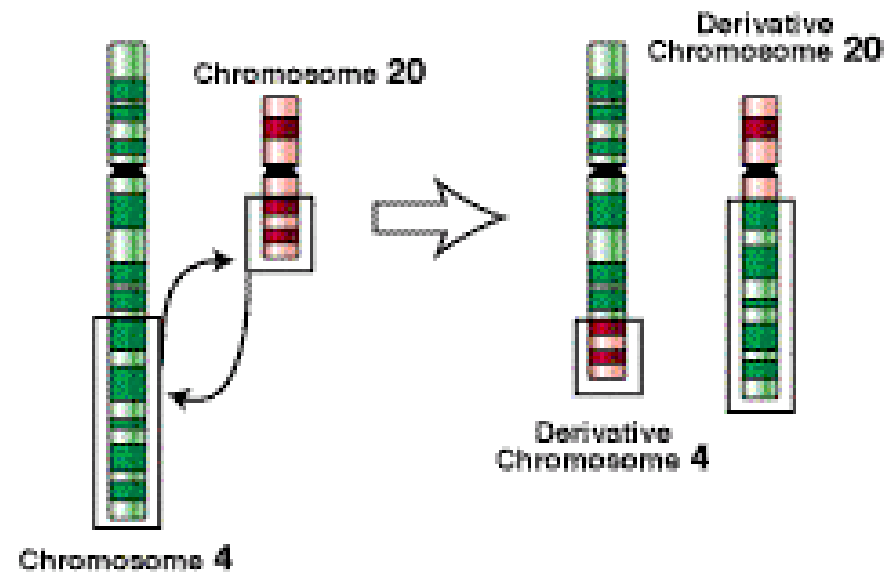
Inversion



Insertion



Translocation



Physical factors & DNA damage

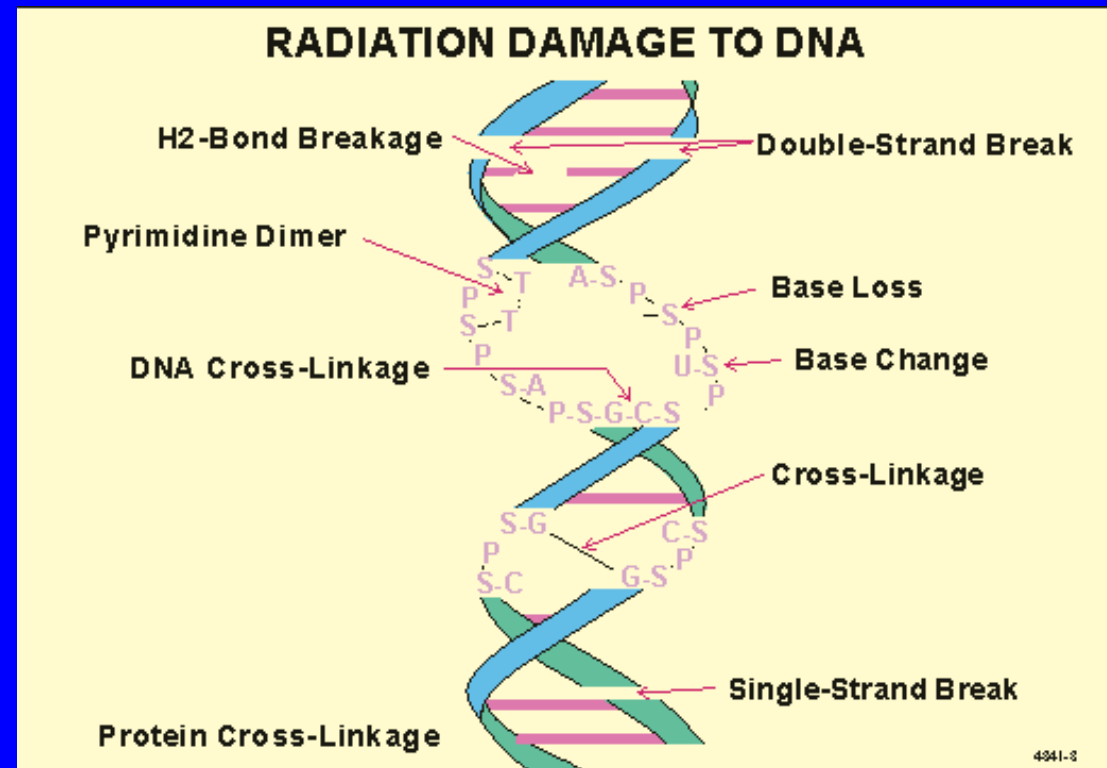
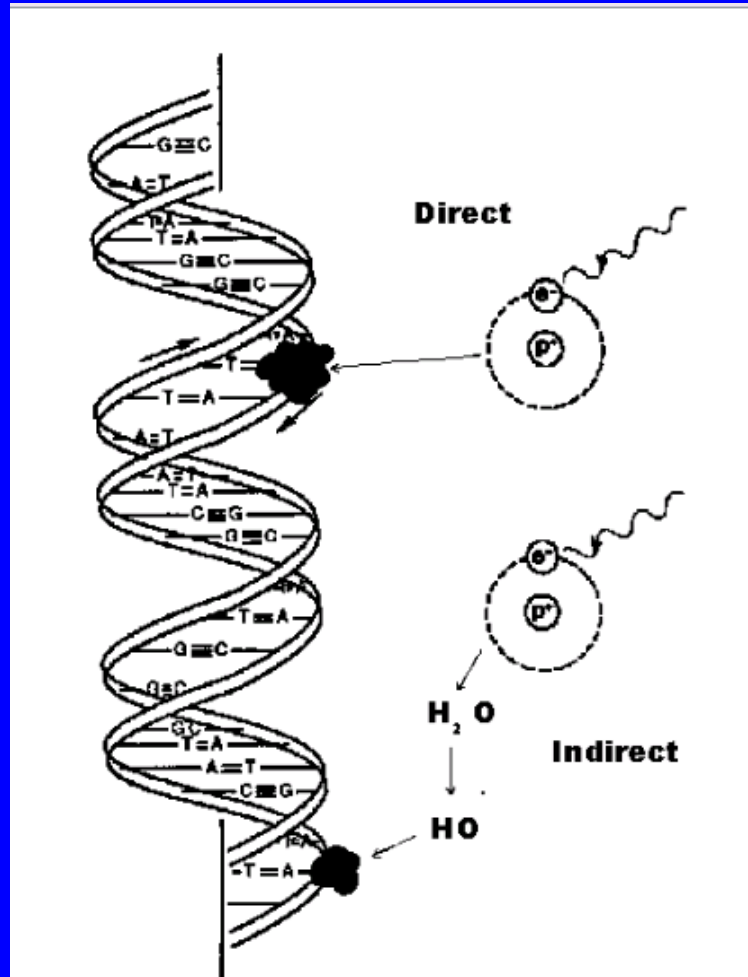
Ionizing radiation

- direct interaction with hydrogen atoms in water (and bases)
 - > OH* radicals; H₂O₂, O₂⁻
- oxidation of bases; dimerization ...

UV radiation

- interaction with aromatic cycles (bases)
- base dimerization (T=T)

Ionizing radiation effects on DNA

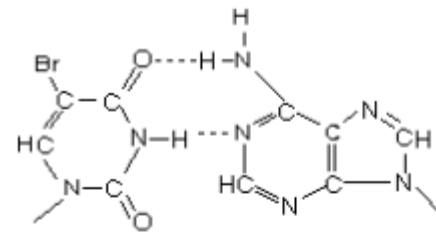


Chemical induced DNA damage

Bases analogs

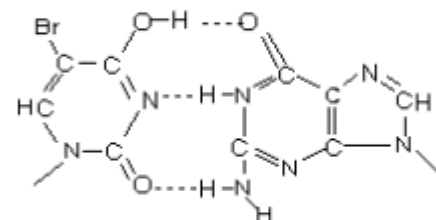
- incorporation into DNA during replication

(5-Br-Uracil: AT → GC)



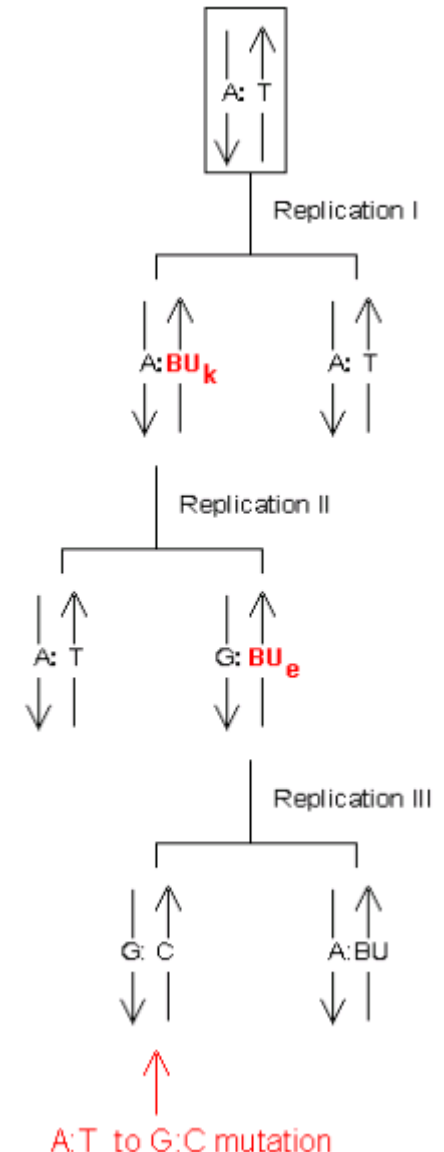
5-Bromouracil
keto form (BU_k)

Adenine



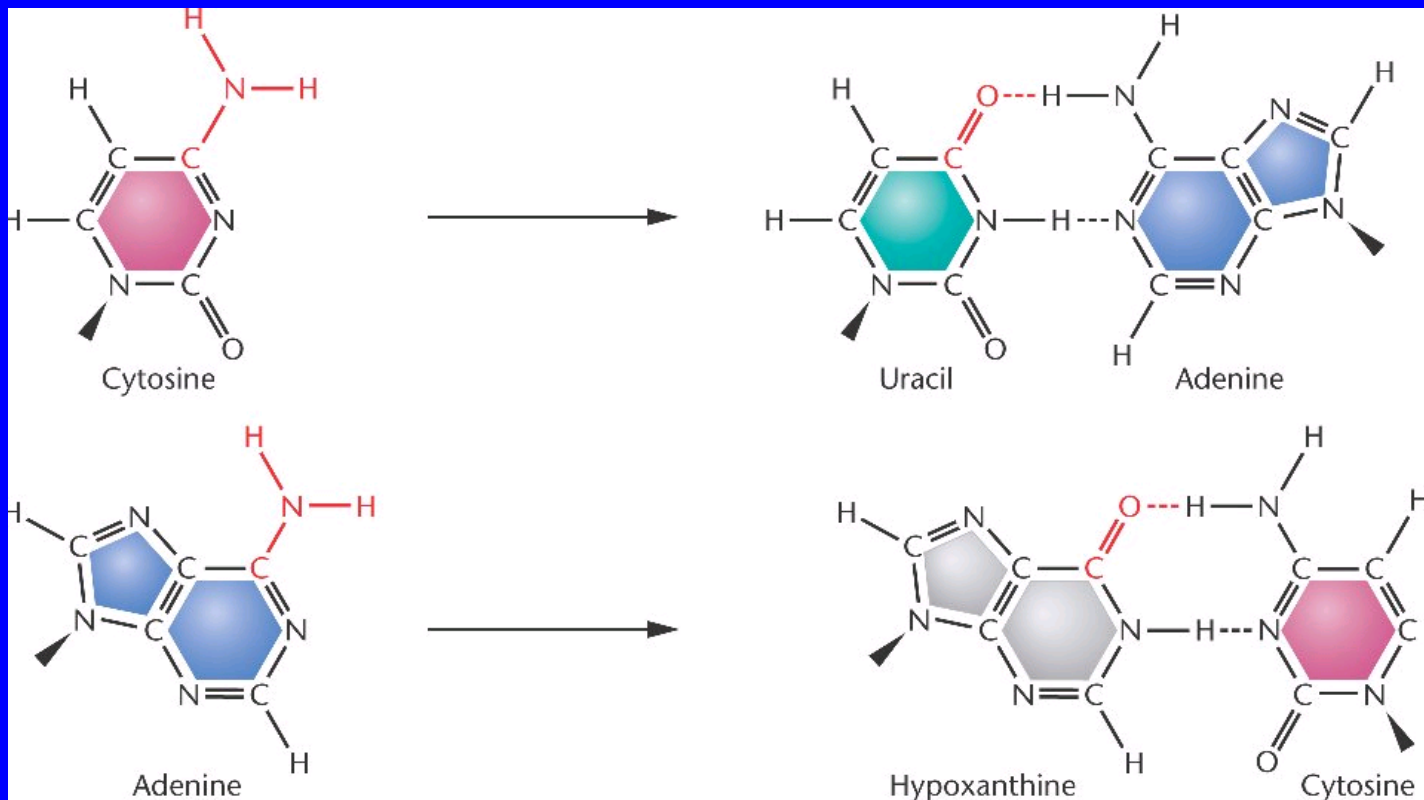
5-Bromouracil
enol form (BU_e)

Guanine



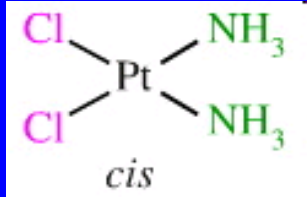
Chemical induced DNA damage

HNO_2 , HSO_3^- , Hydroxylamine, Methoxyamine
deamination of bases
(GC \rightarrow AT)

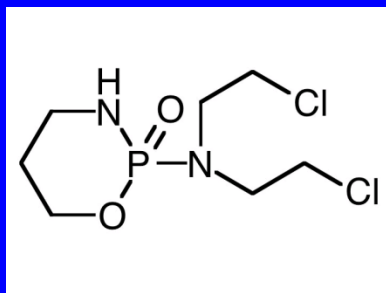


Chemical induced DNA damage

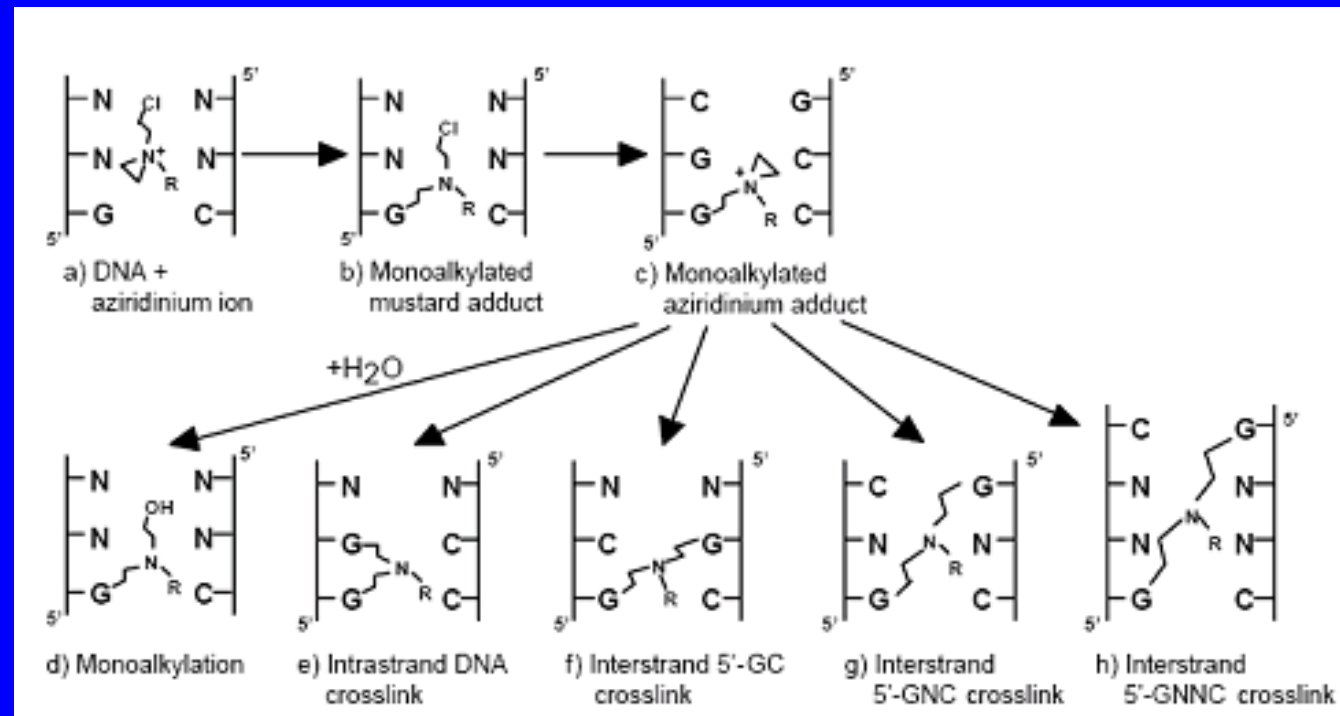
Alkylsulphates, N-nitroso-alkyles, cis-platinum
- alkylation of bases; crosslinks of dsDNA



cisplatin



cyclophosphamide



Chemical induced DNA damage

INTERCALATION & ADDUCT FORMATION

Polycyclic aromatic hydrocarbons (PAHs) & derivatives (N-acetyl-2-aminofluorene (AAF), benzo[a]pyrene)

Mycotoxins (aflatoxins) adduct formation with DNA (biomarkers)

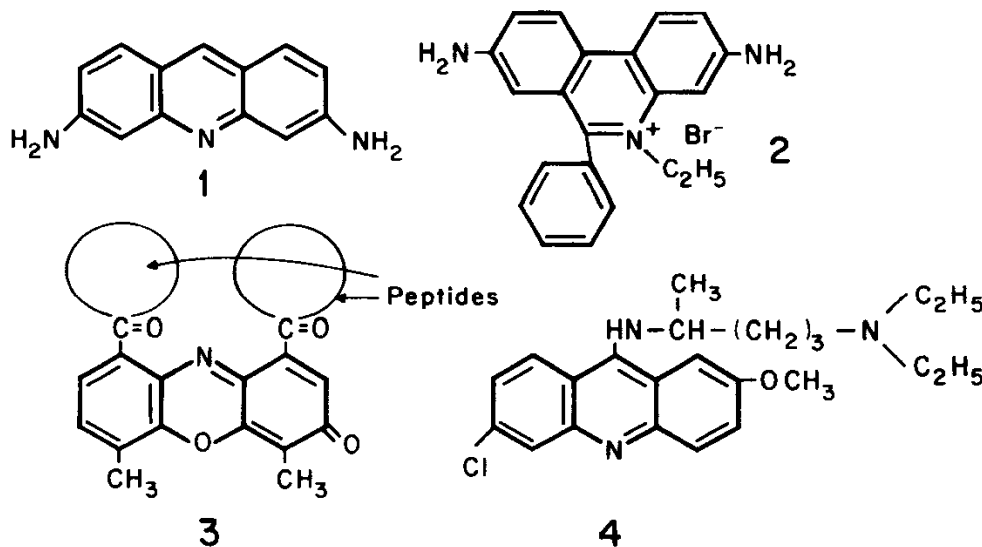
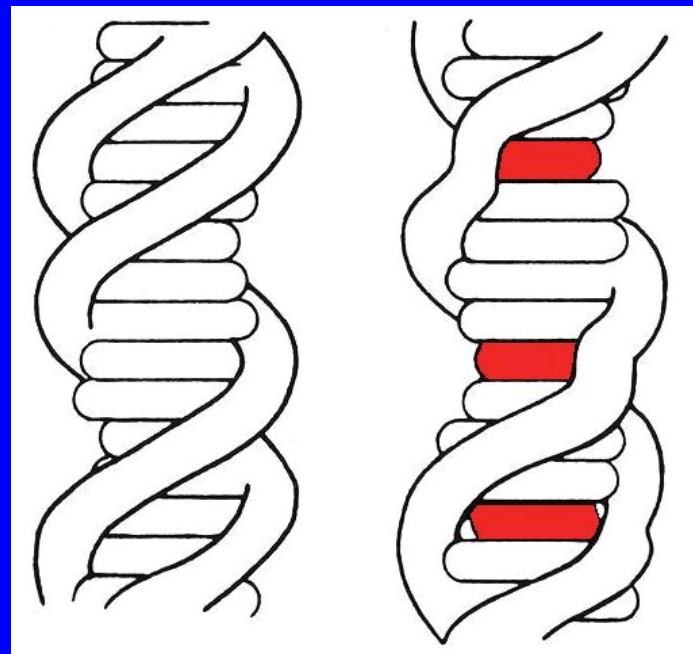
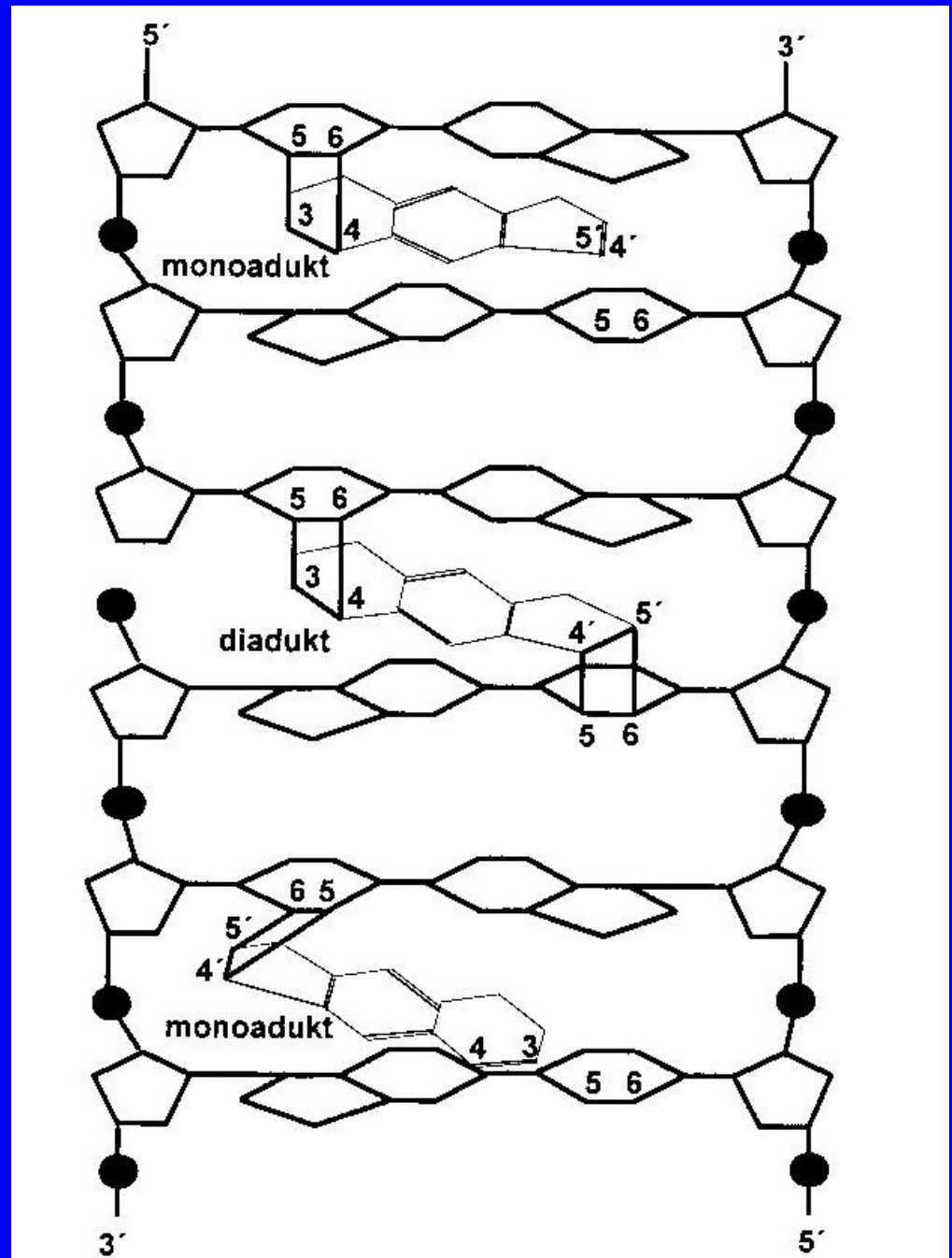
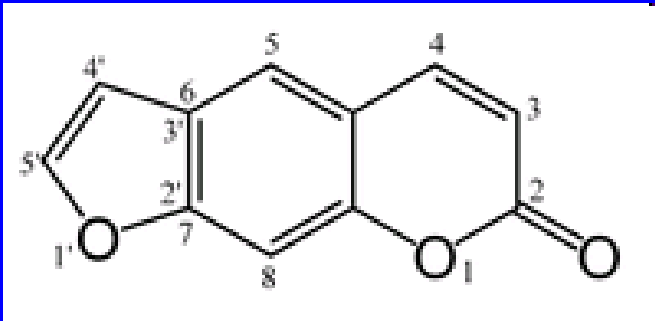
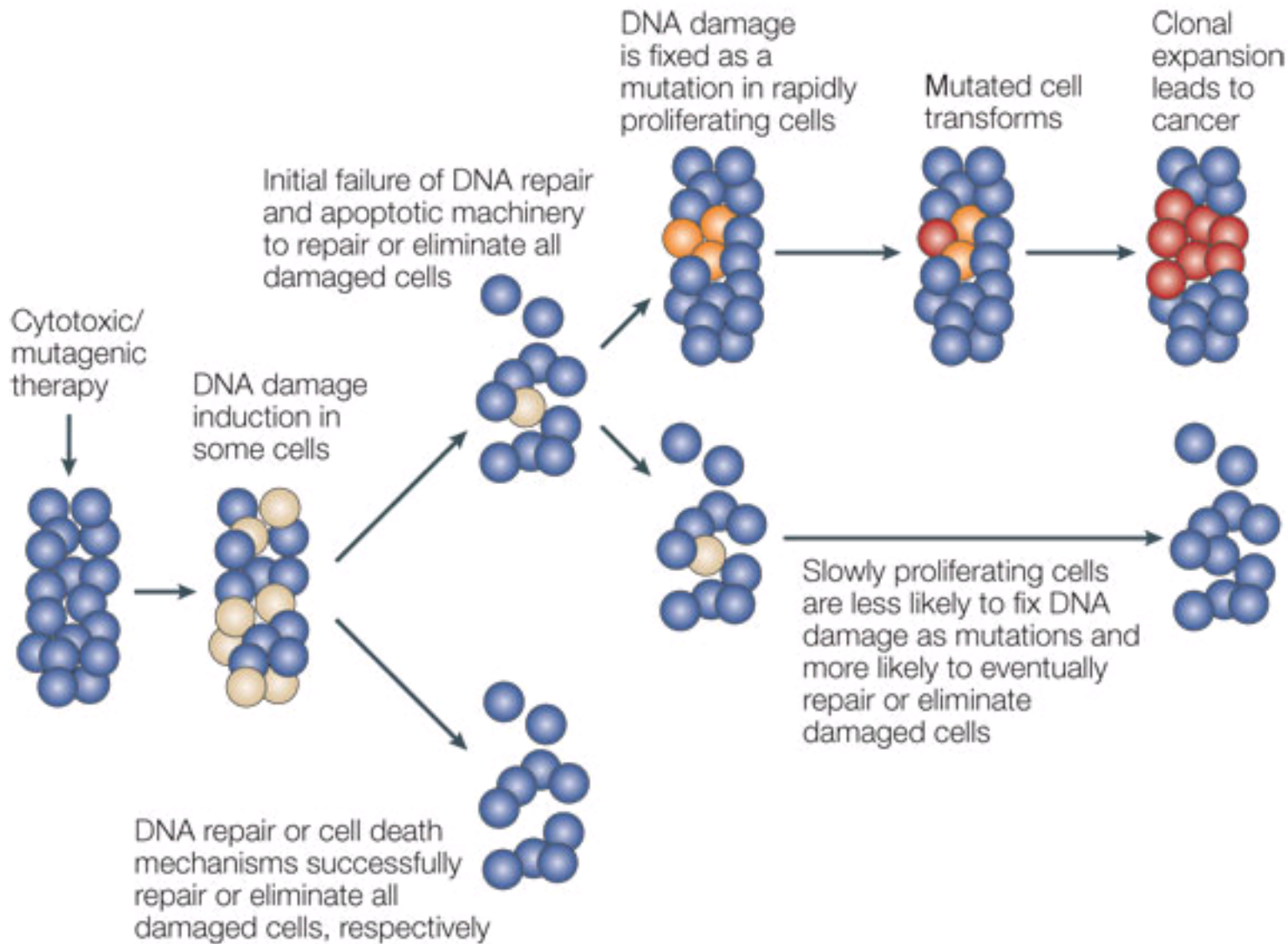


Chart 5.8. Examples of intercalating agents. Key: 1, acriflavine; 2, ethidium bromide; 3, actinomycin; 4, quinacrine.

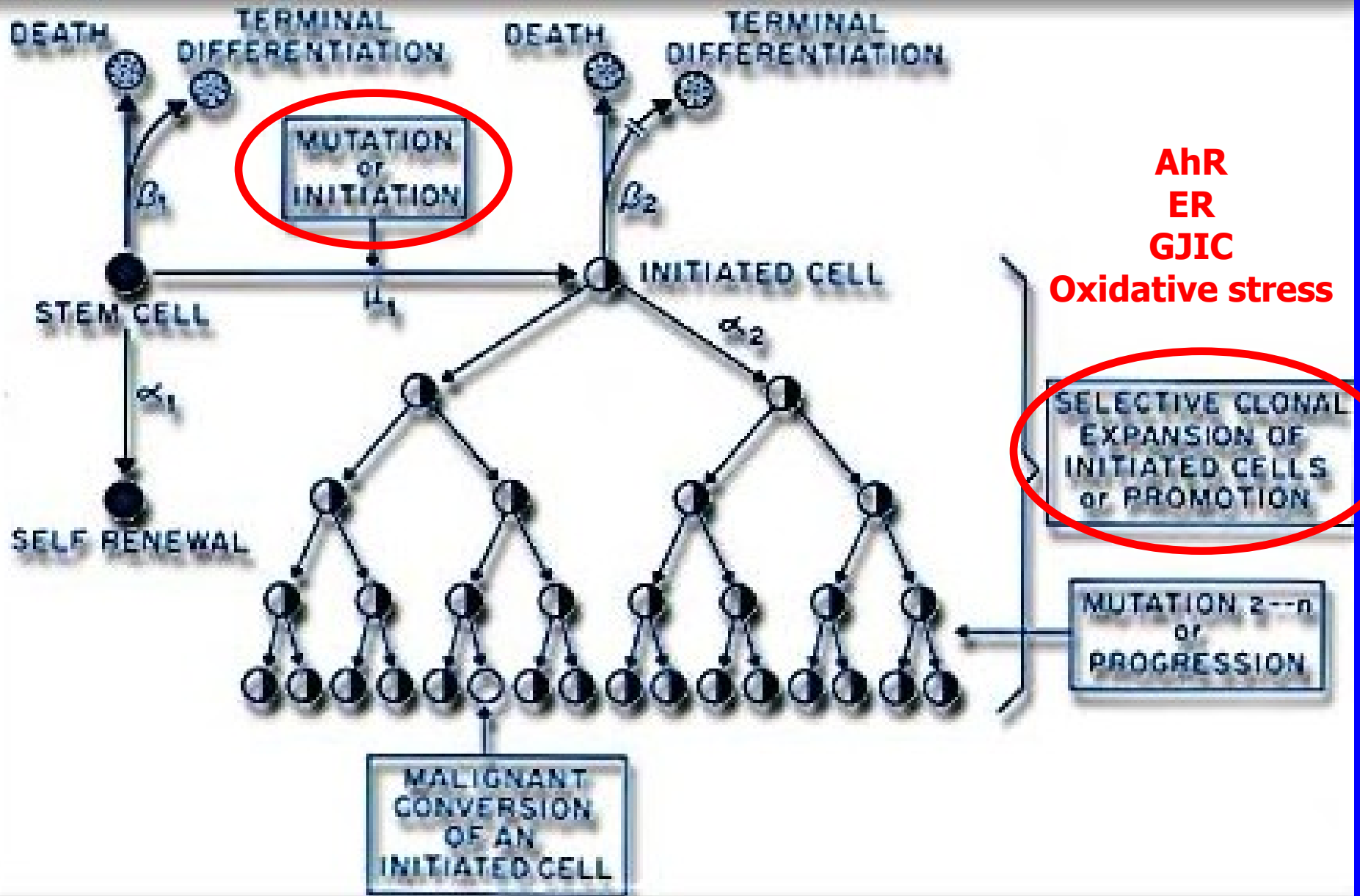


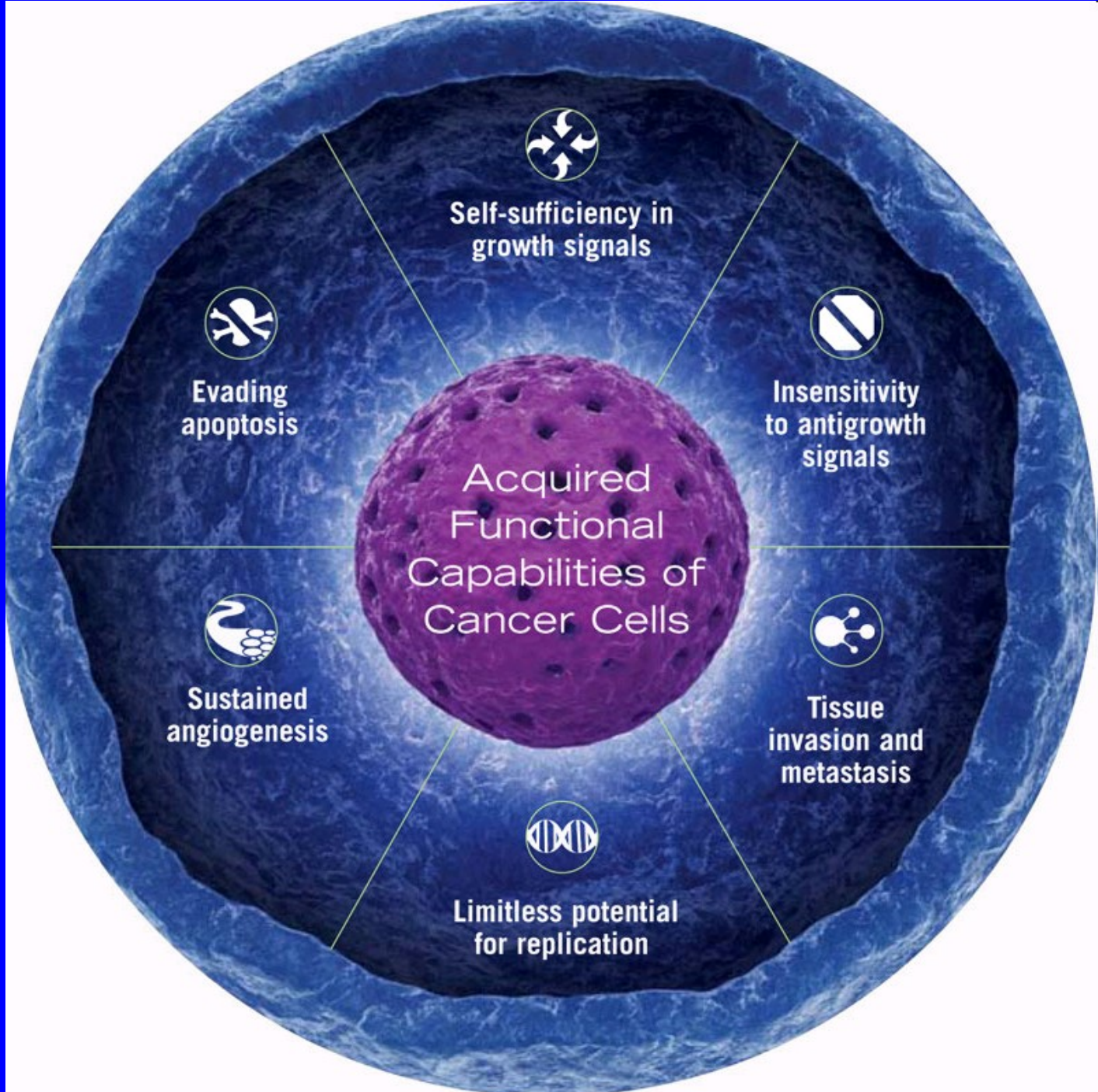
Psoralen DNA intercalation





IMPORTANT PROCESSES IN CANCEROGENESIS





Does **chemically-induced genotoxicity** results in in vivo effects

- adducts from mitochondrial DNA ?
- distance between „source of radicals“ and nuclear DNA ?
- protection mechanisms (mutation -> death/apoptosis)

Rubin (2002) *Oncogene* 21:7392

Thilly (2003) *Nature Genetics* 34(3):255

Mutations are not „primarily“ caused by chemicals

Chemicals only allow „unveil“ previously existing mutations in nuclear DNA (*non-genotoxic events cause cancer !!!*)

