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)*

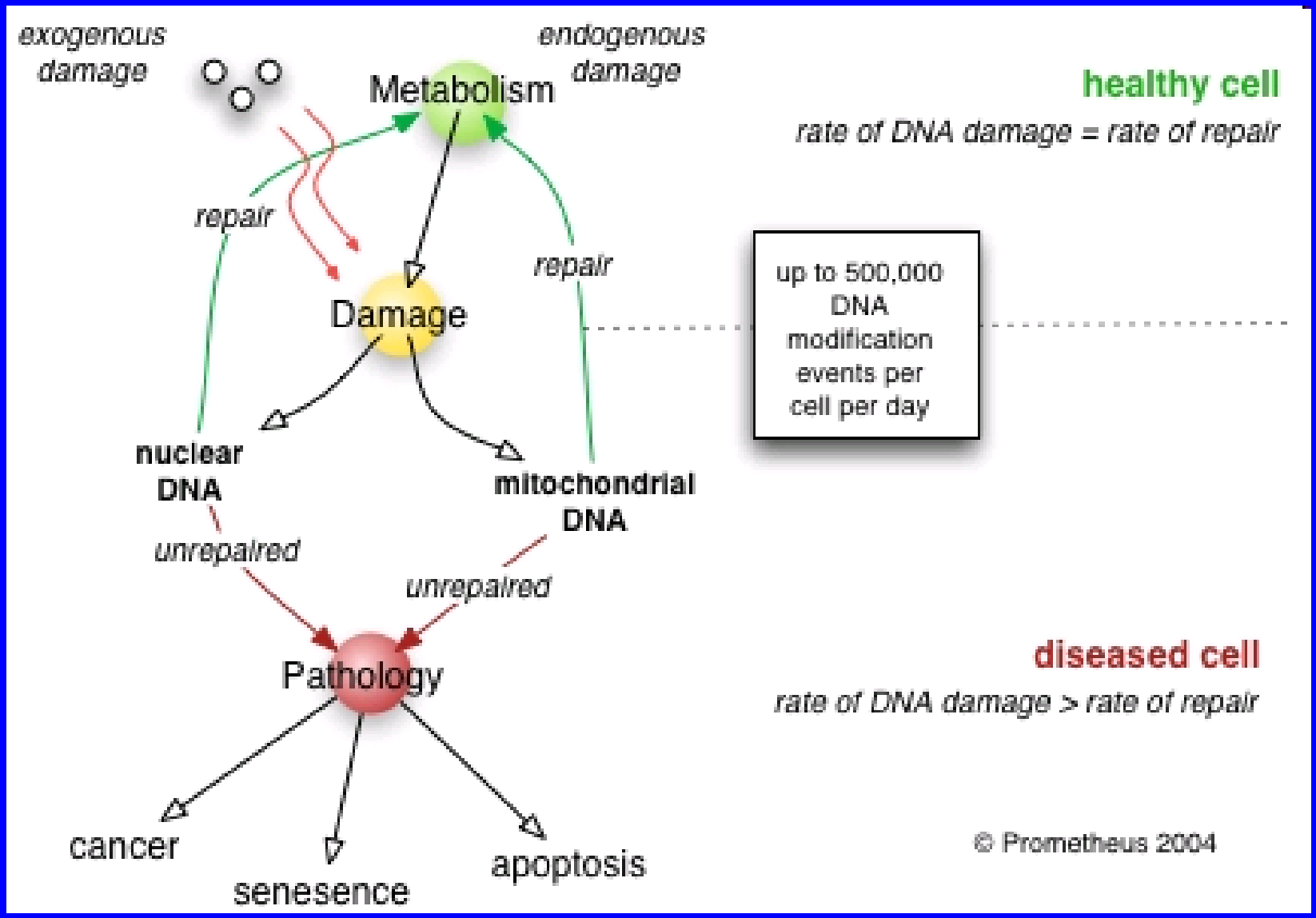
Mutagenesis - MUTATIONS

- changes in the sequences of deoxynucleotides

- natural mutations (billions of nucleotides/day)
: variability in genoms; reparations

- chemical-induced mutagenesis

DNA damage


exogenous damage
endogenous damage
Metabolism
repair
repair
Damage
nuclear DNA
mitochondrial DNA
unrepaired
unrepaired
Pathology
cancer
senescence
apoptosis
healthy cell
rate of DNA damage = rate of repair
up to 500,000 DNA modification events per cell per day
diseased cell
rate of DNA damage > rate of repair
© Prometheus 2004

DNA repair

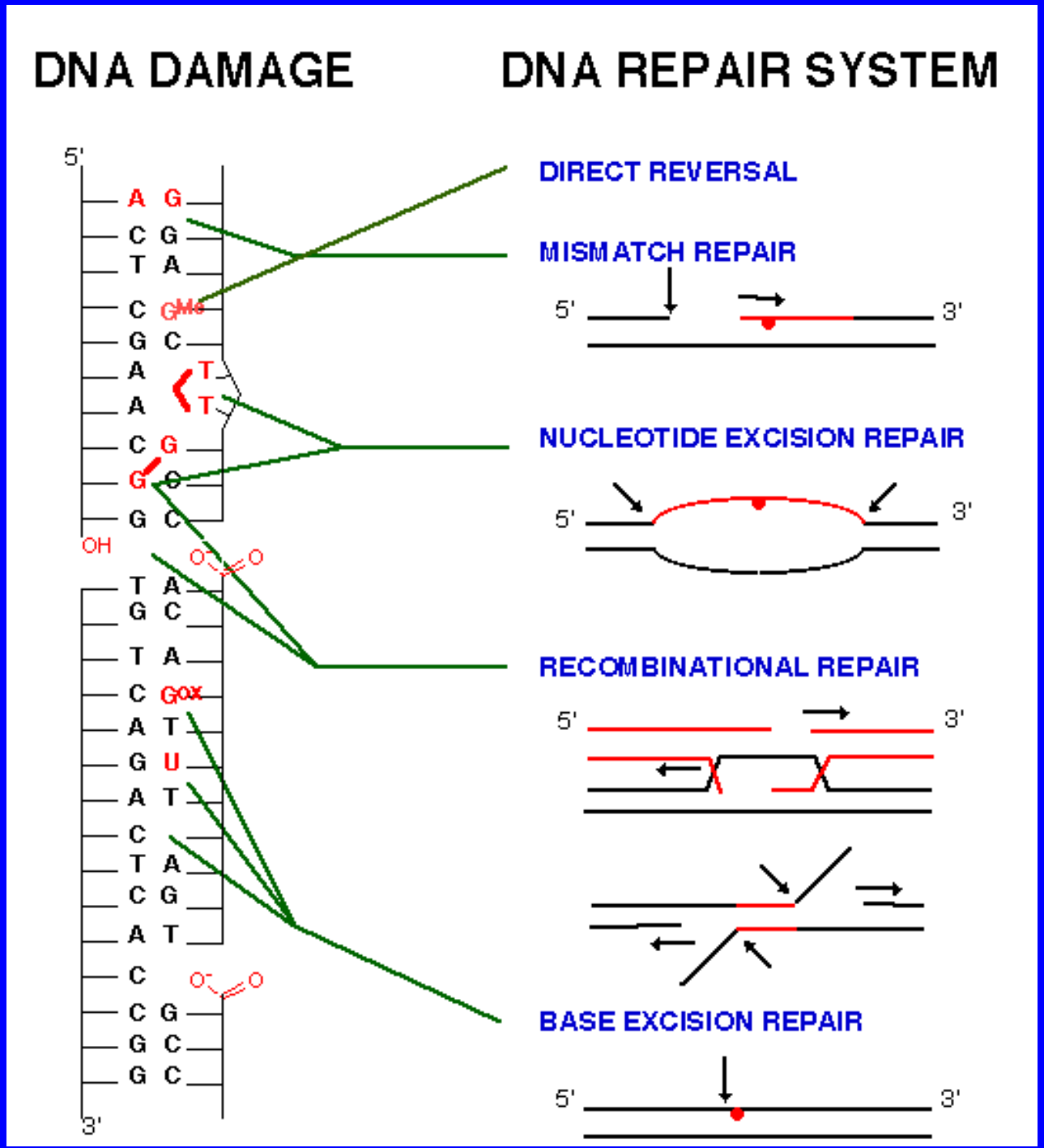
Damage of DNA is carefully controlled

constitutively expressed proteins

Changes in DNA

induction of reparation enzymes ("SOS-repair")

= biomarker of DNA damage


DNA DAMAGE
DNA REPAIR SYSTEM
5'
A G
C G
T A
C GMe
G C
A T
A T
C G
G O
G C
OH
O
O
T A
G C
T A
C Gox
A T
G U
A T
C
T A
C G
A T
C
O
O
C G
G C
G C
3'
DIRECT REVERSAL
MISMATCH REPAIR
5'
3'
NUCLEOTIDE EXCISION REPAIR
5'
3'
RECOMBINATIONAL REPAIR
5'
3'
BASE EXCISION REPAIR
5'
3'

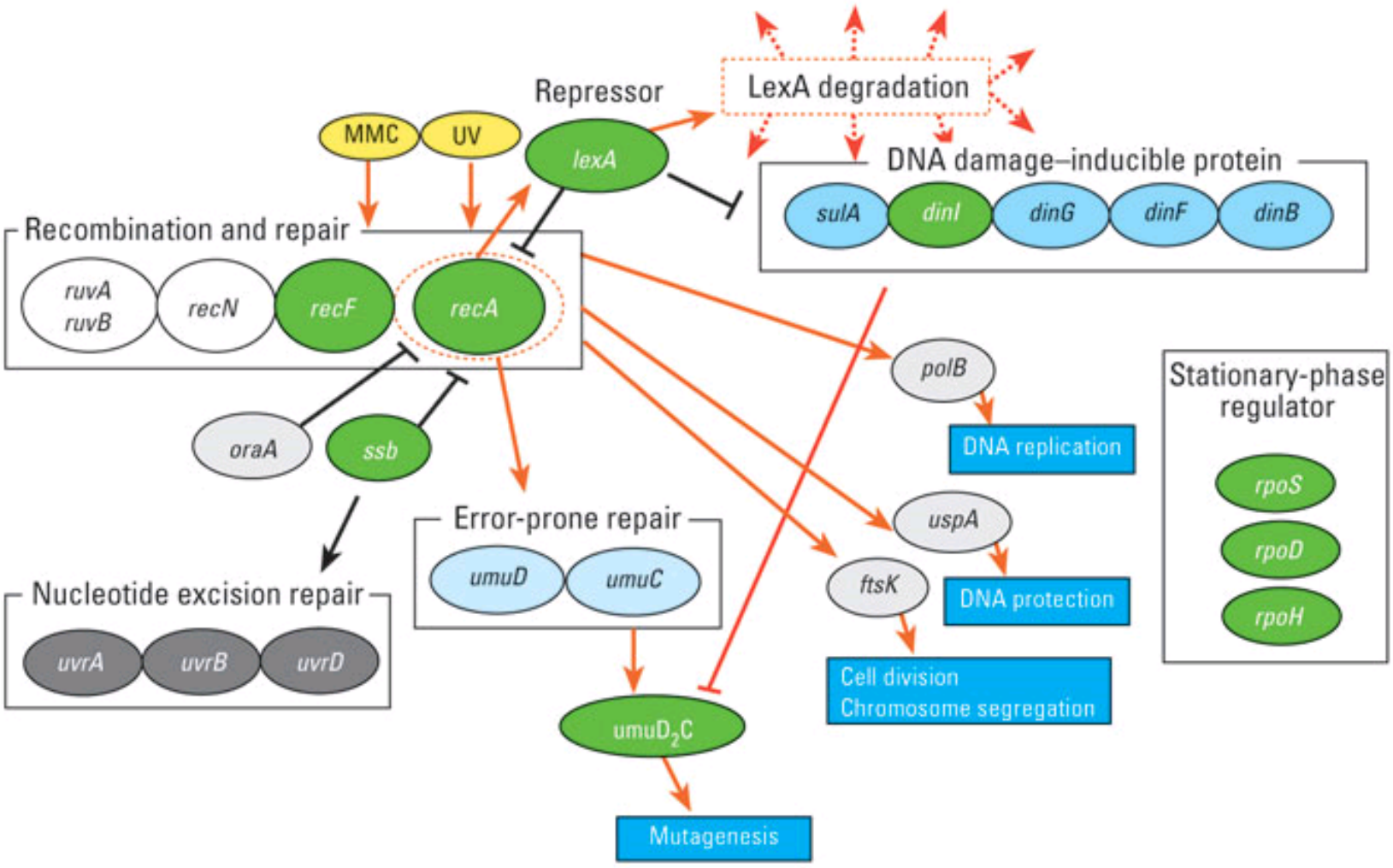


Figure 3. A literature-based linkage map between genes in the SOS response in *E. coli*. The map represents inducible genes/proteins in the SOS response for repair from DNA damage. Black lines indicate pathways in the normal repair process and red lines with arrows activation/induction due to an exposure 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

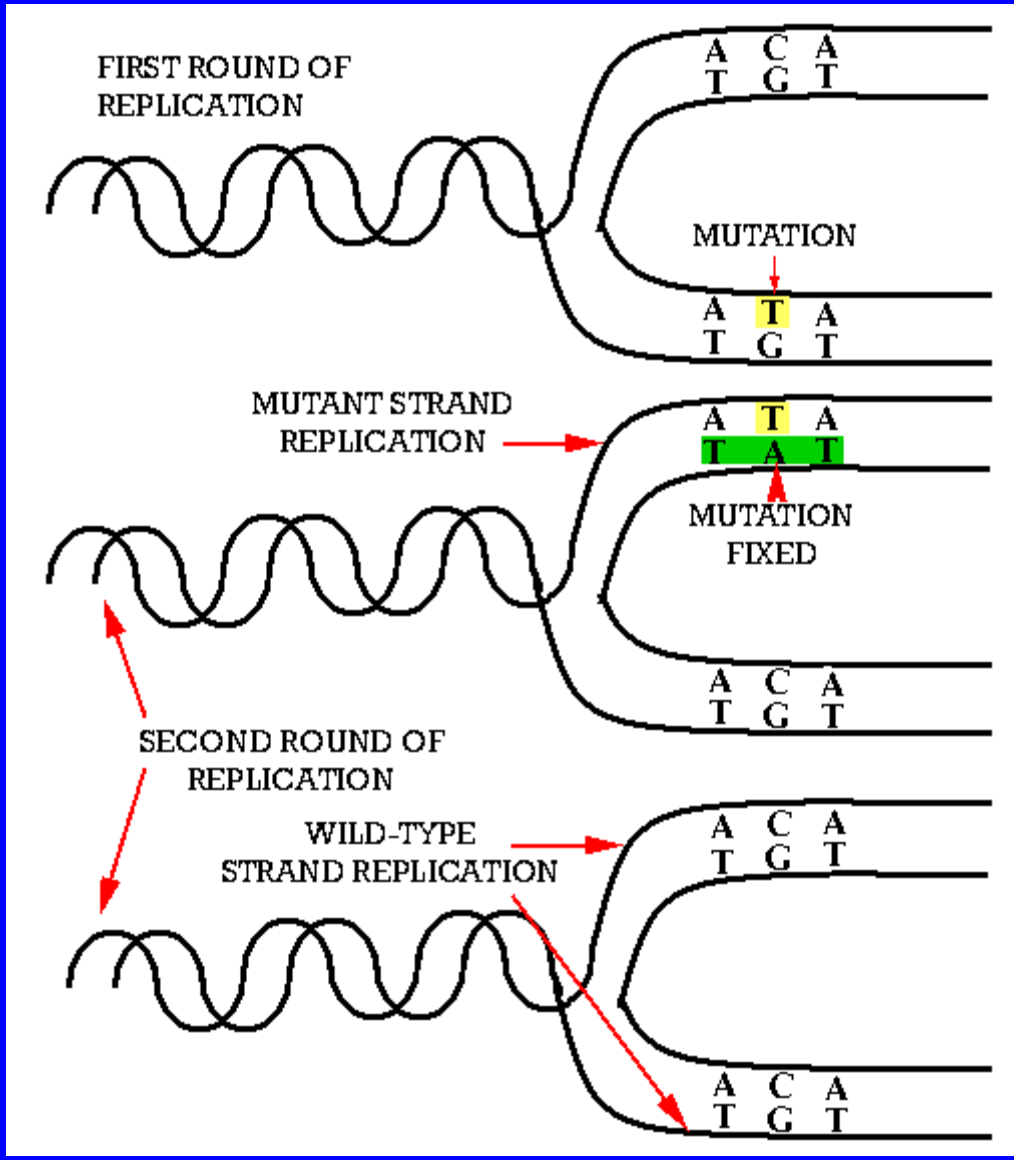
  Indirect mutagens - affect cells that synthesize chemicals with direct mutagenic effect

Point mutations
BASE - EXCHANGE:

- Silent mutations:
  - code for the same amino acid.

- Missense mutations:
  - code for a different amino acid.

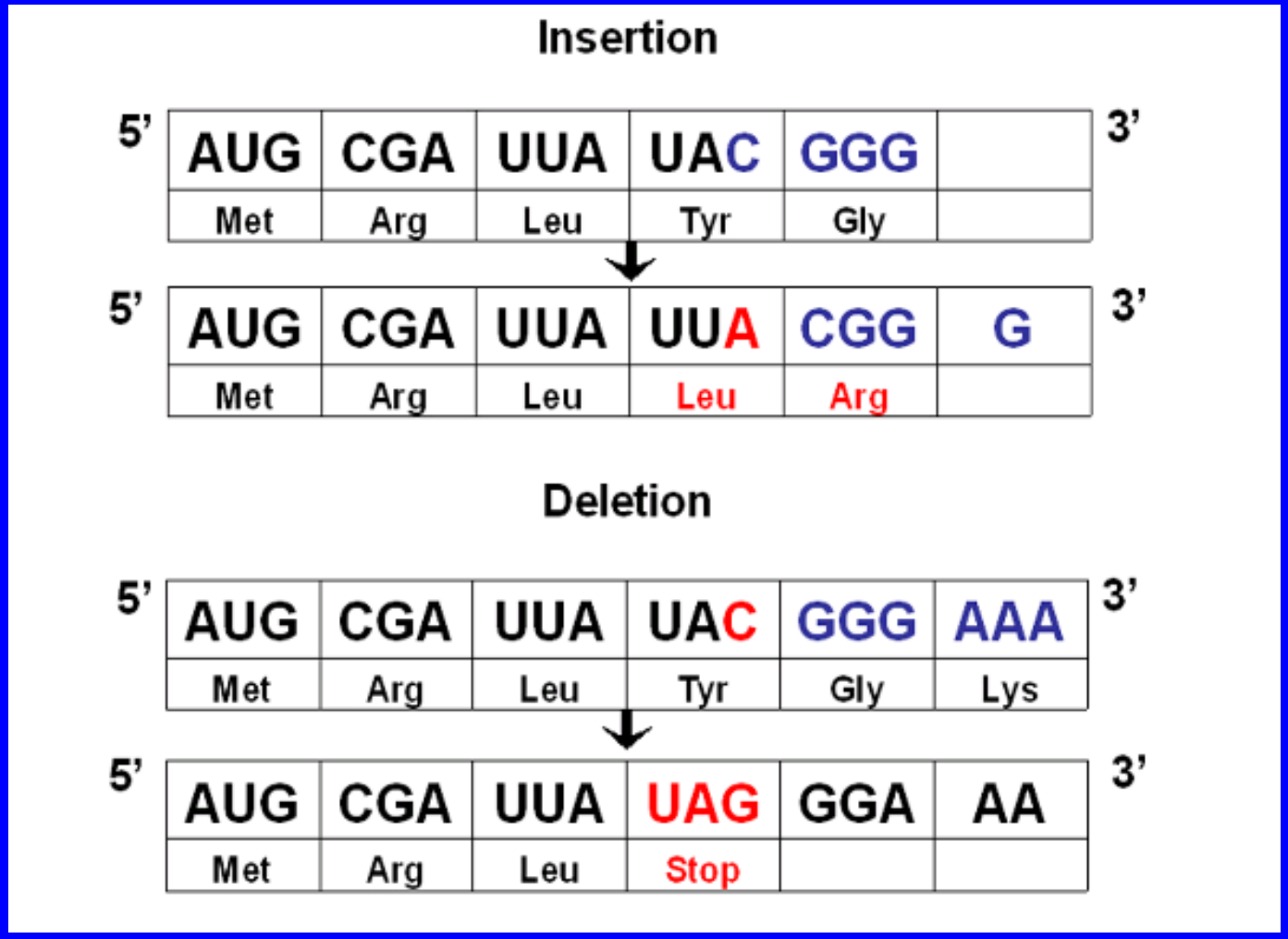
- Nonsense mutations:
  - which code for a stop



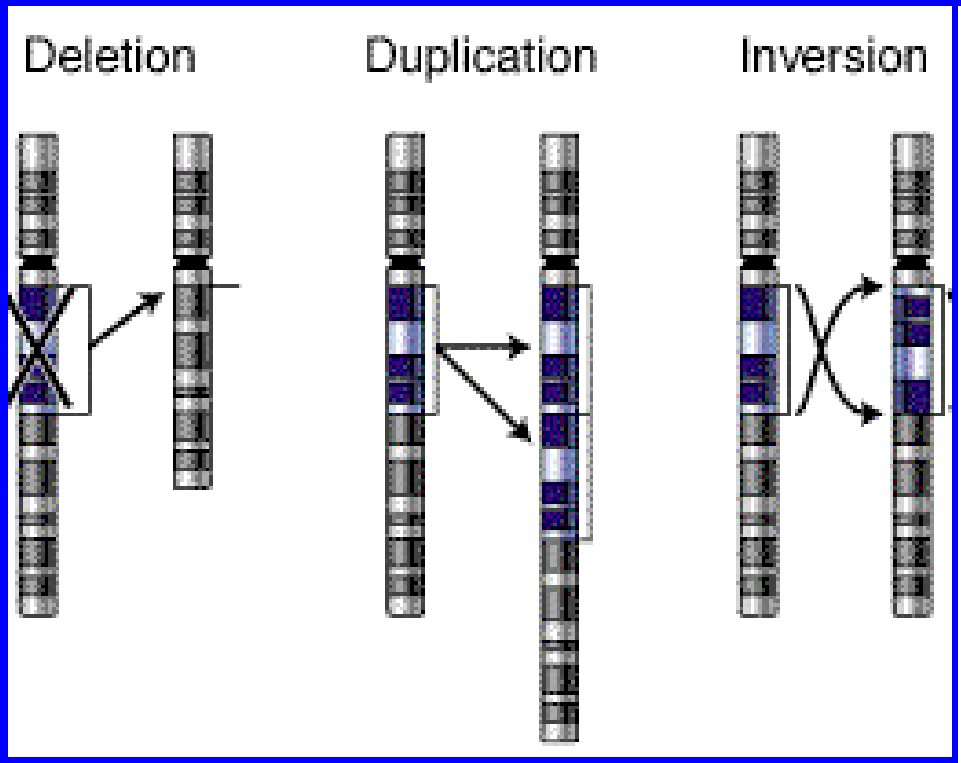
Point mutation

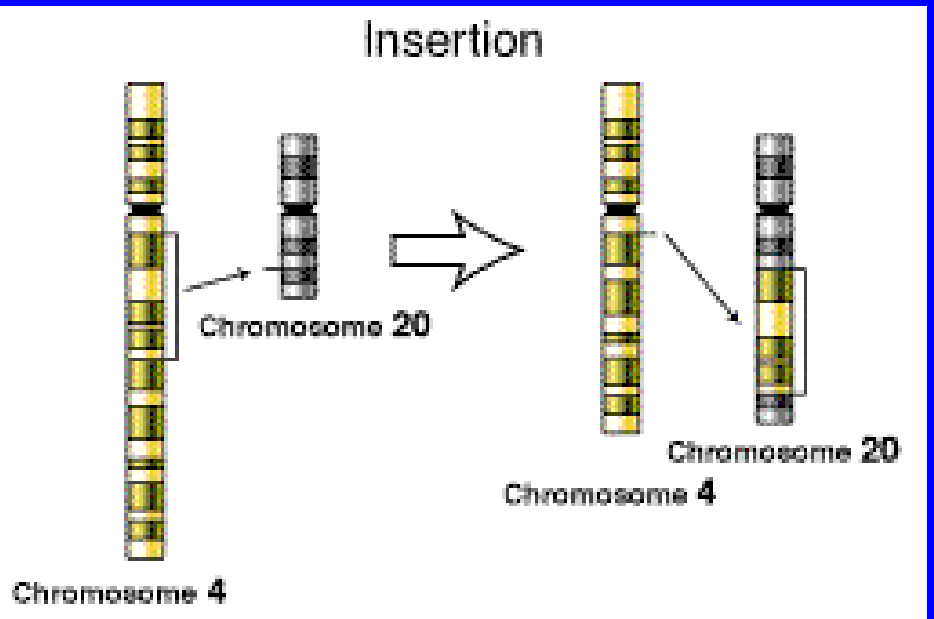
INSERTION
DELETION

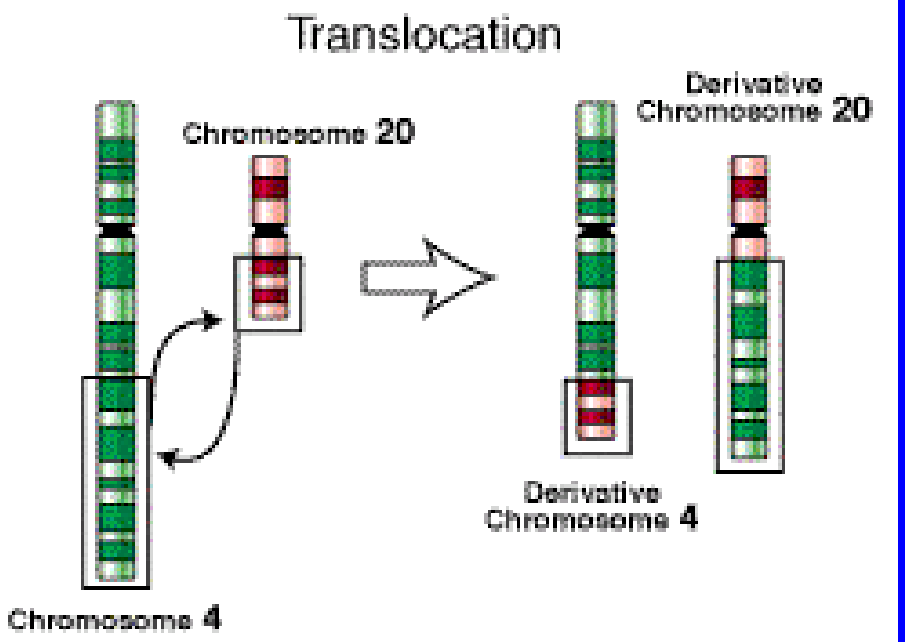
Change of the reading frame



Large scale mutations / chromosomal







Physical factors & DNA damage

Ionizating radiation

- direct interaction with hydrogen atoms in water (and bases)

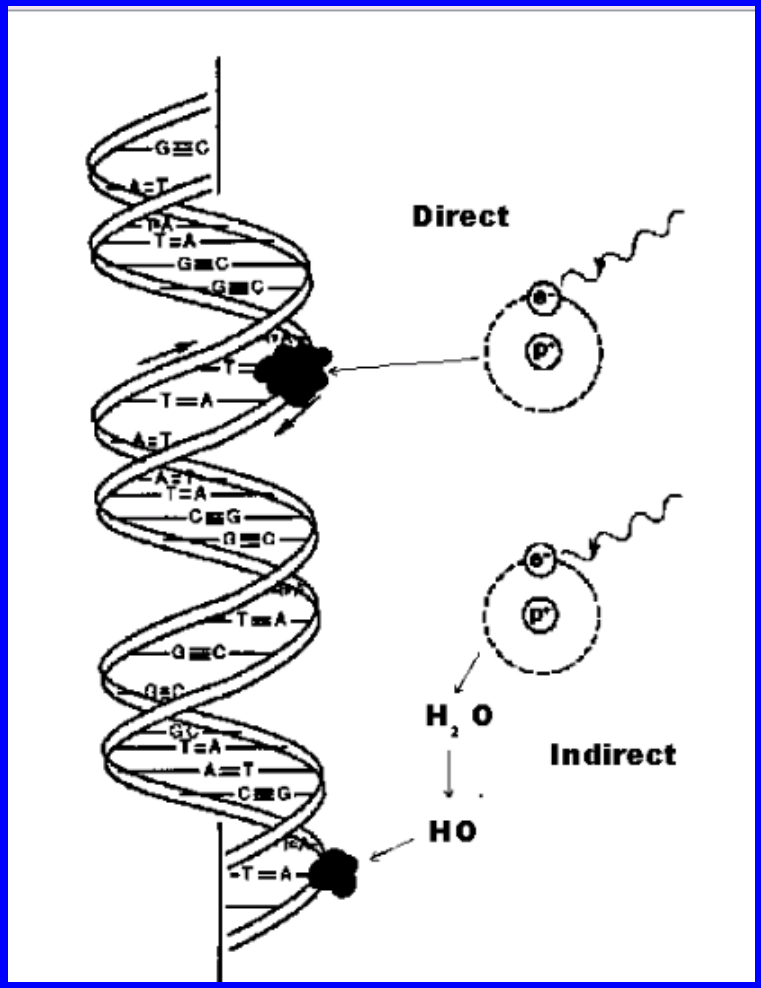
  -> OH* radicals; H_2O_2, O_2-

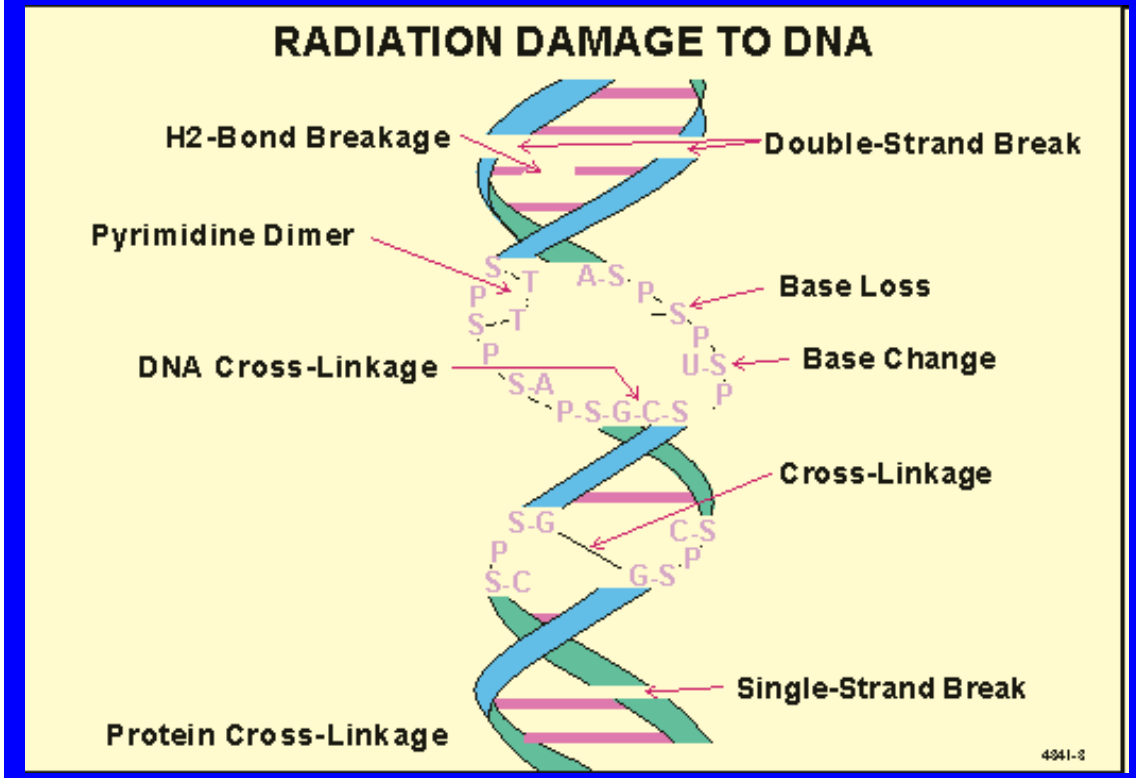
- oxidation of bases; dimerization ...

UV radiation

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

Ionizing radiation effects on DNA



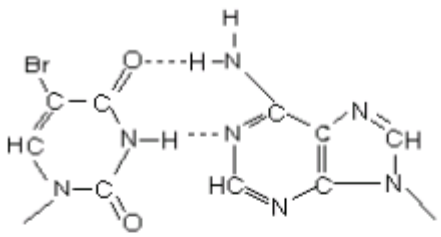


Chemical induced DNA damage

Bases analogs

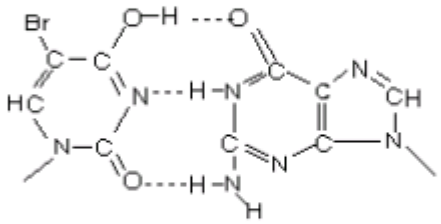
- incorporation into DNA during replication

(5-Br-Uracil: AT -> GC)



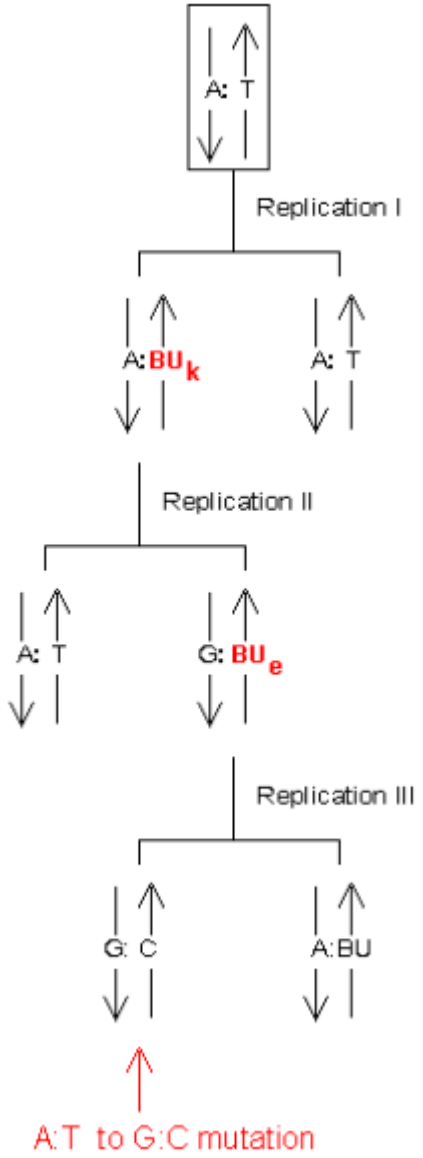
5-Bromouracil
keto form (BU_k)

Adenine



5-Bromouracil
enol form (BU_e)

Guanine

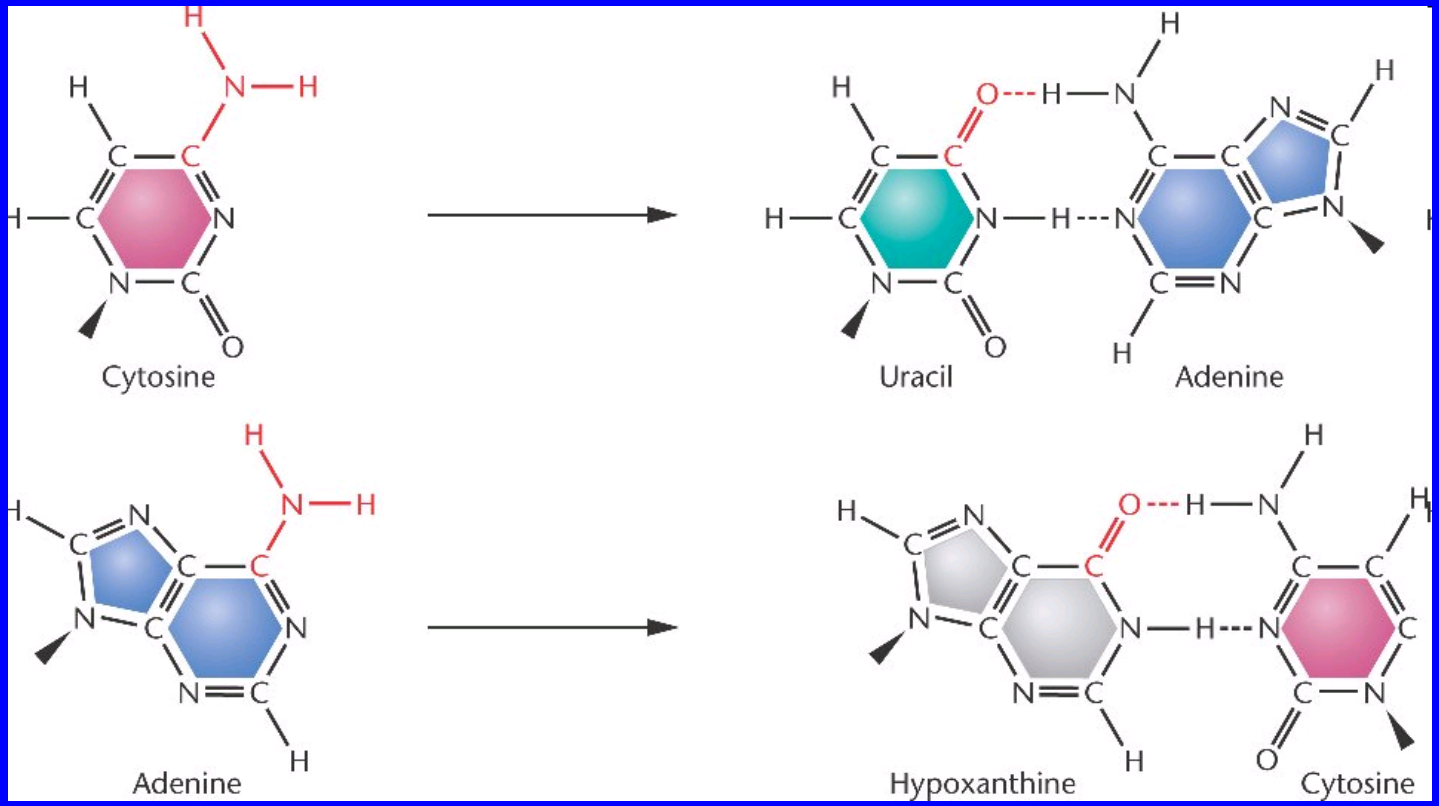


Chemical induced DNA damage

HNO_2, HSO_3^-,Hydroxylamine, Methoxyamine

deamination of bases

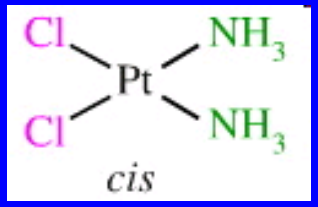
(GC -> AT)



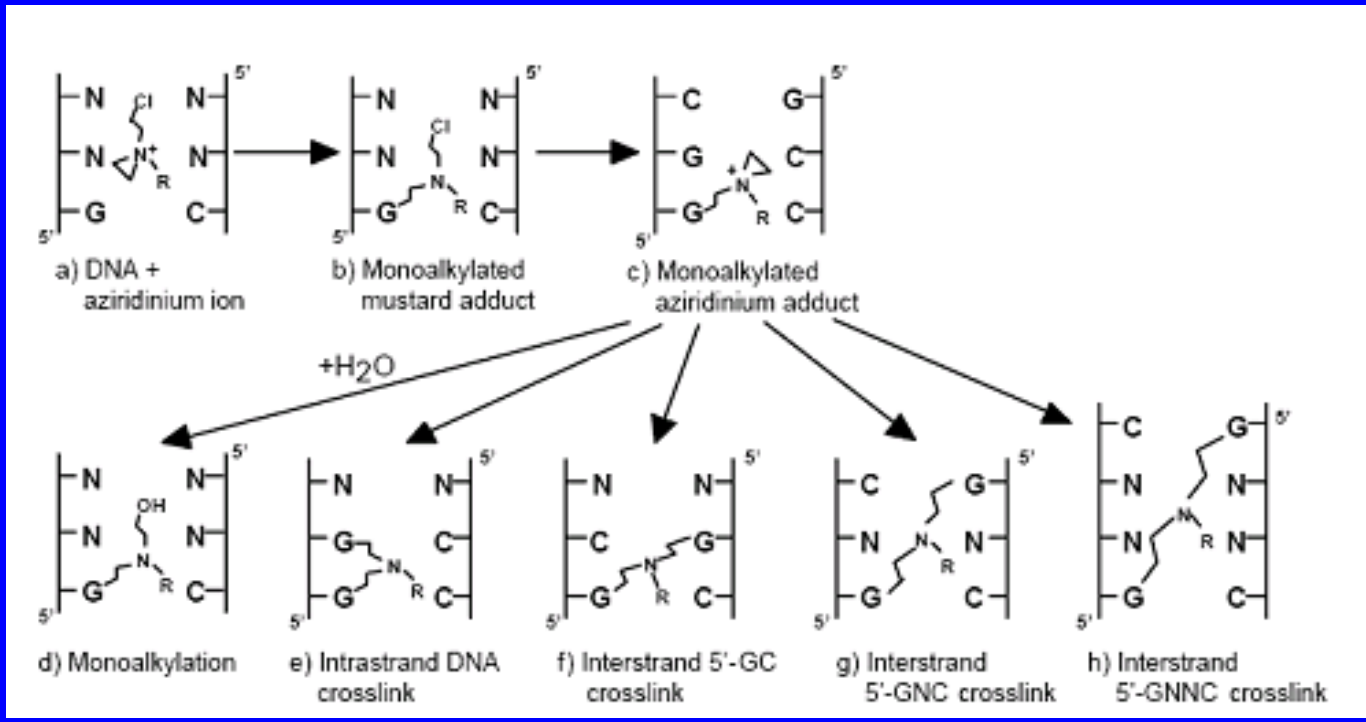
Chemical induced DNA damage

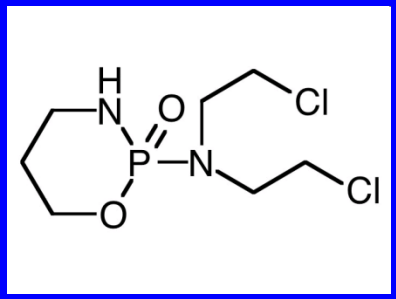
Alkylsulphates, N-nitroso-alkyles, cis-platinum

- 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) aduct formation with DNA (*biomarkers*)

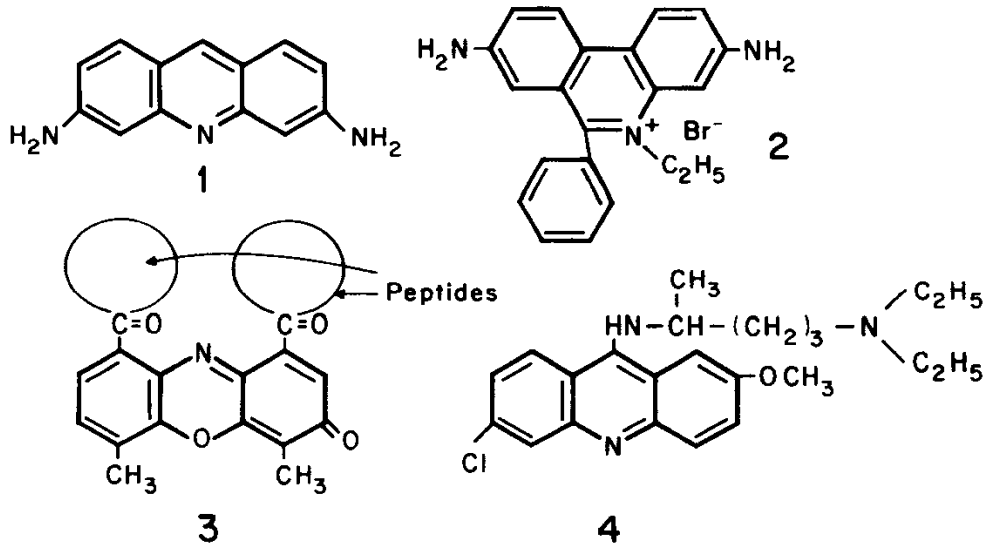
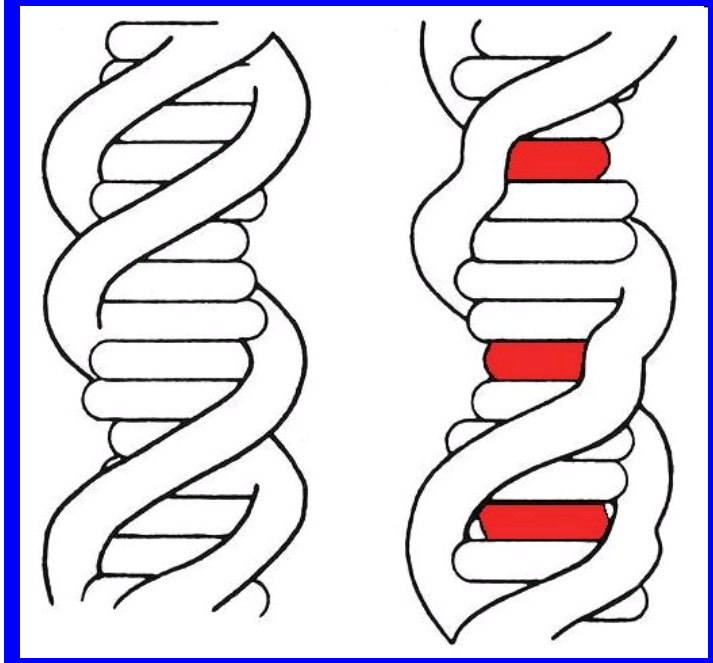
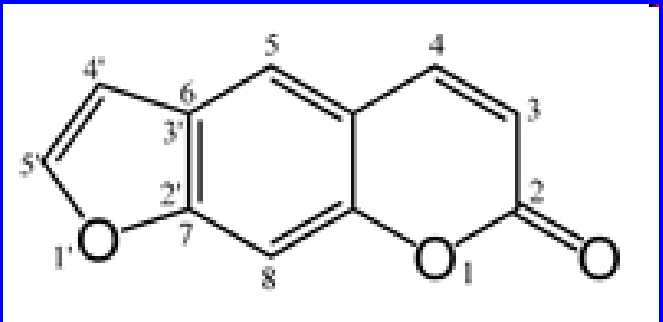
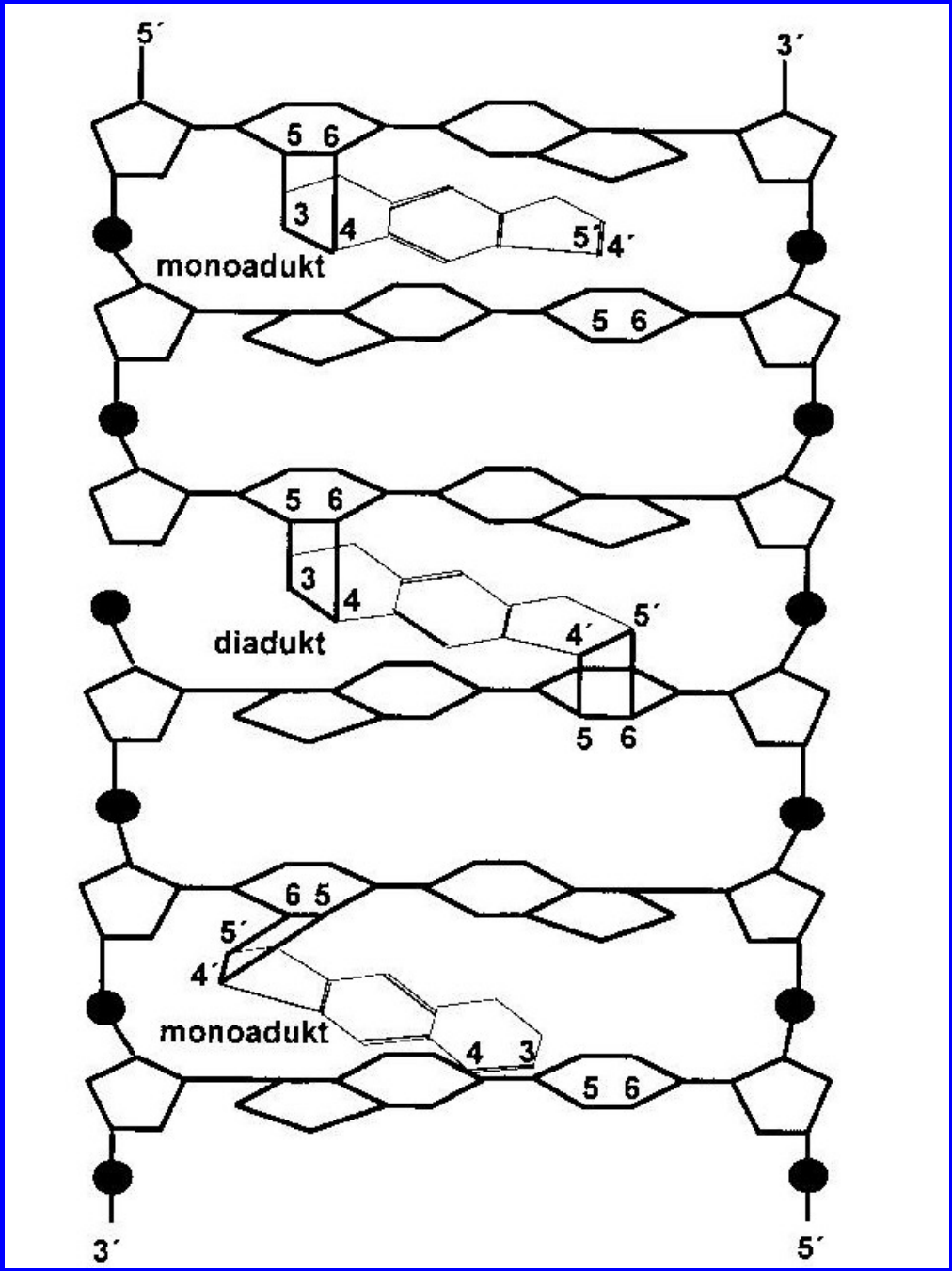


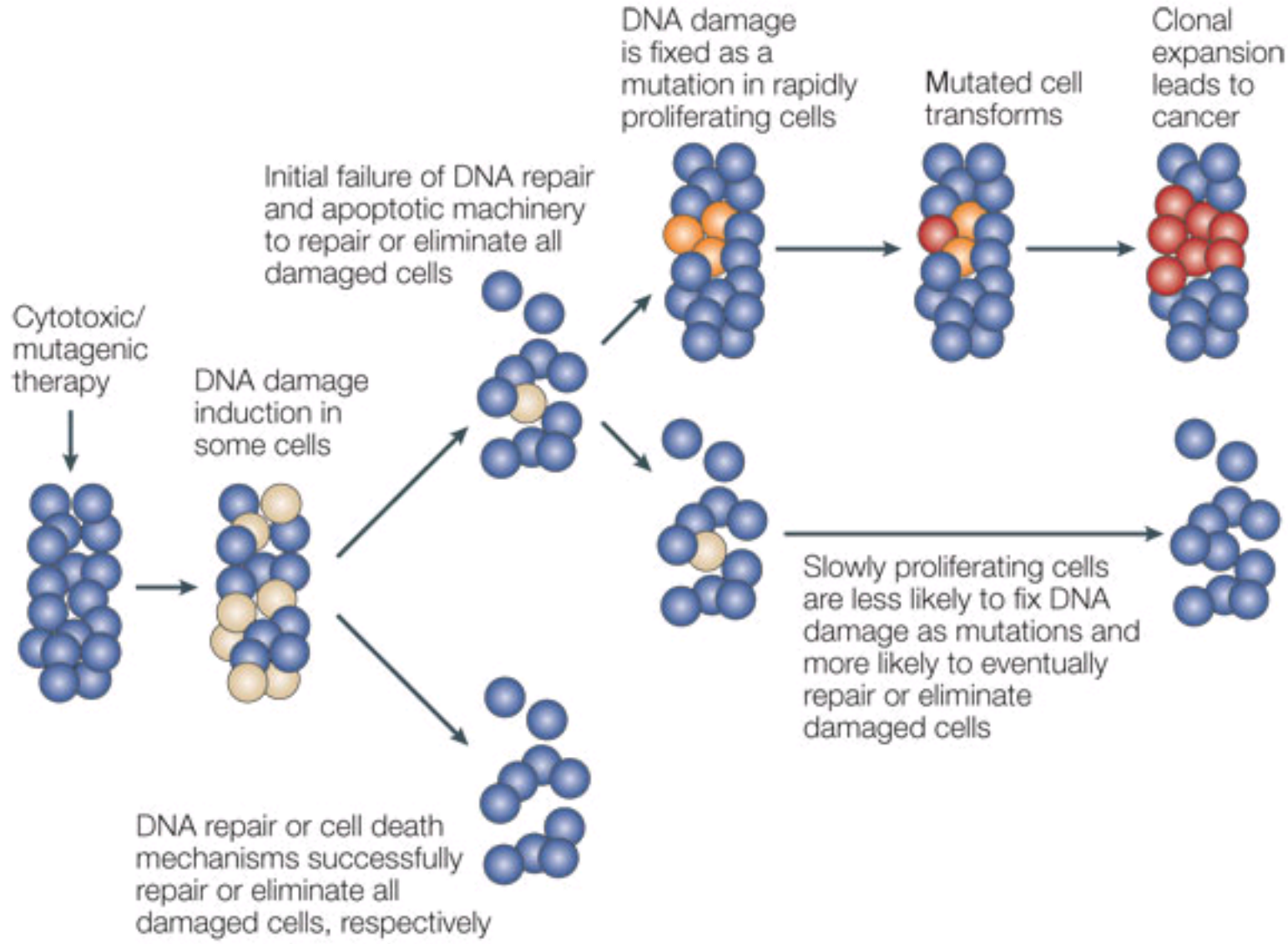
Chart 5.8. Examples of intercalating agents. Key: 1, acriflavine; 2, ethidium bromide; 3, actinomycin; 4, quinacrine.



Psoralen
DNA intercalation

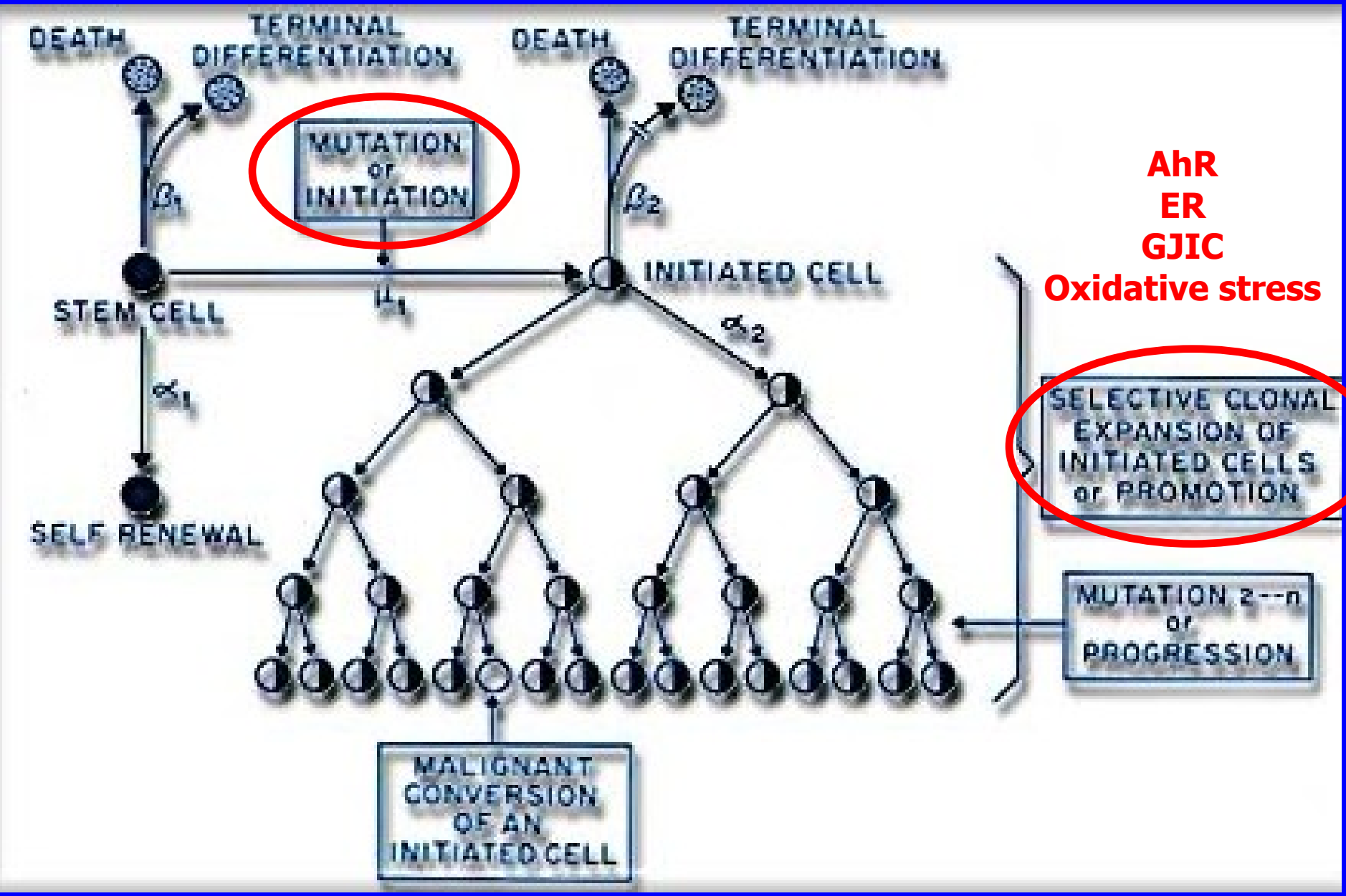




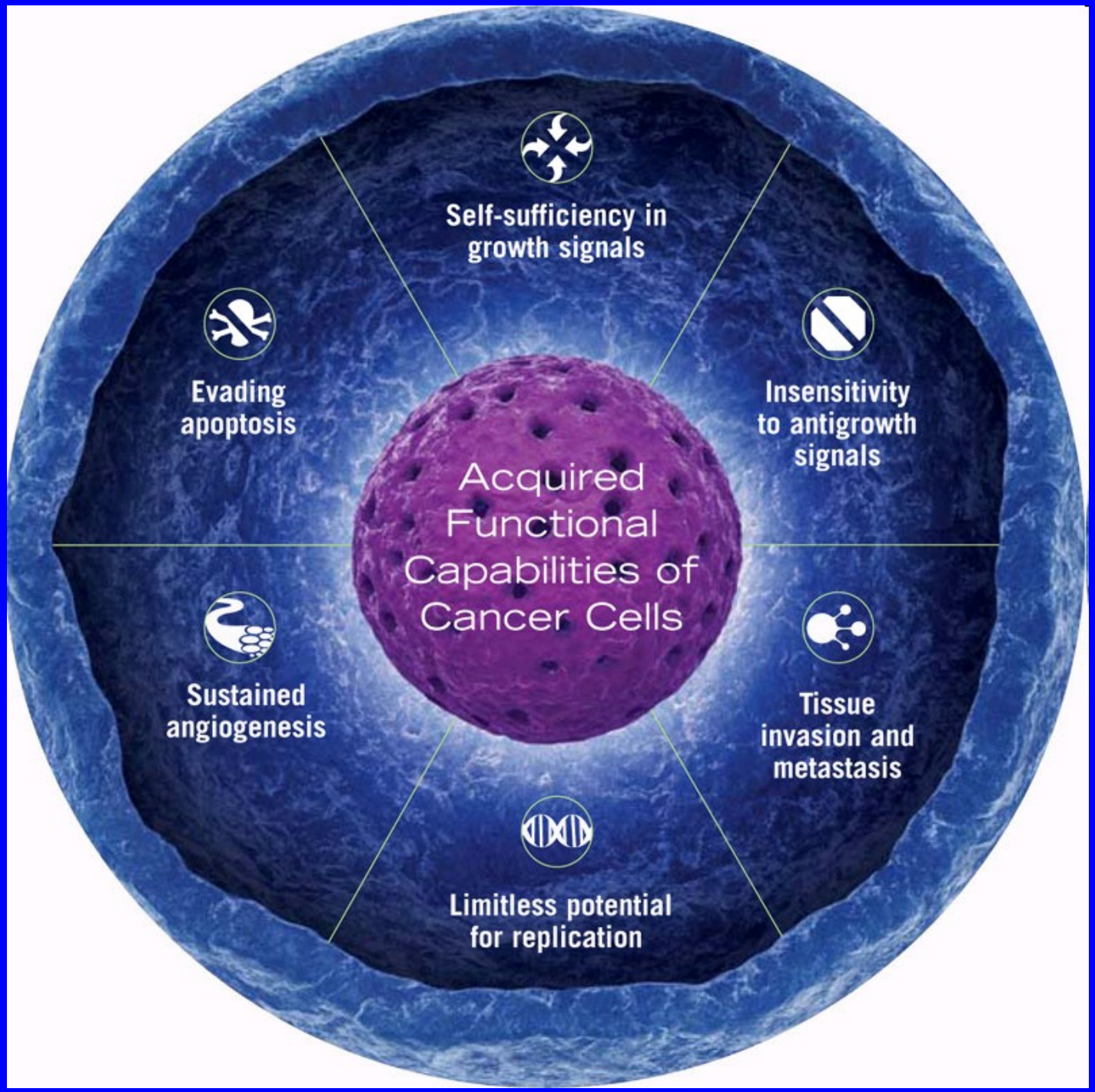


Nature Reviews | Cancer

IMPORTANT PROCESSES IN CANCEROGENESIS



Trosko and Ruch 1998, Frontiers in Bioscience 3:d208


Self-sufficiency in growth signals
Insensitivity to antigrowth signals
Tissue invasion and metastasis
Limitless potential for replication
Sustained angiogenesis
Evading apoptosis
Acquired Functional Capabilities of Cancer Cells

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 !!!)*