General Toxicology

Non-Organ Directed Toxicity (Part II)
Mutagenesis

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Objectives of this lecture are to:

- Define mutagenesis & its mechanisms.
- Explain damage to DNA caused by alkylating electrophiles, &
- Determine DNA repair mechanisms.

Mutagenesis:

The reaction of a carcinogen with genomic DNA either directly or indirectly may result in DNA adduct formation or DNA damage, & frequently produces a mutation.

Mechanisms of mutagenesis:

- Transitions & transversions
- Frame shift mutations
- Broken DNA strands

Transitions & transversions:

- Transitions are a substitution of one pyrimidine by the other or one purine by the other (changes within a chemical class).

- A transversion occurs when a purine is replaced by a pyrimidine or a pyrimidine is replaced by a purine (changes across a chemical class) as shown in (Figure 1).

  An example of transition & transversion is shown in (Figure 2).

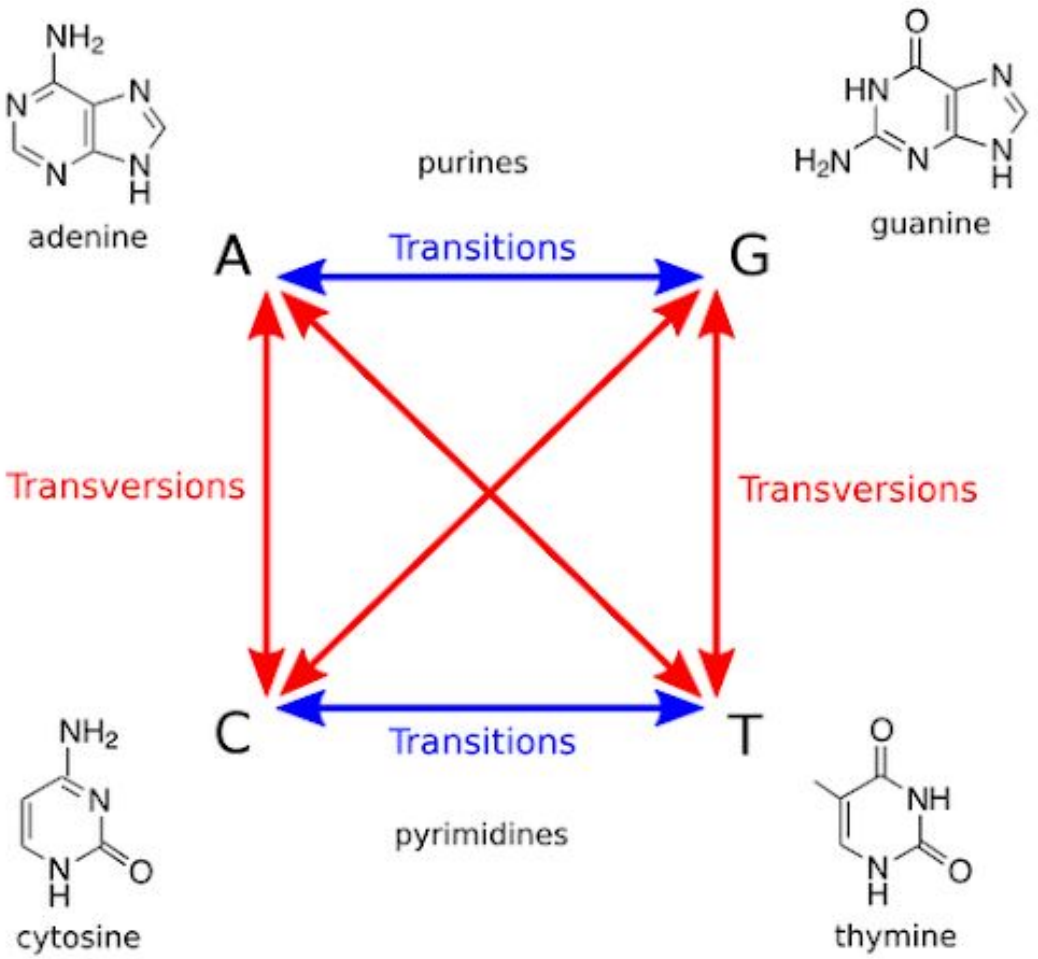

Figure 1. Transitions and transversions.

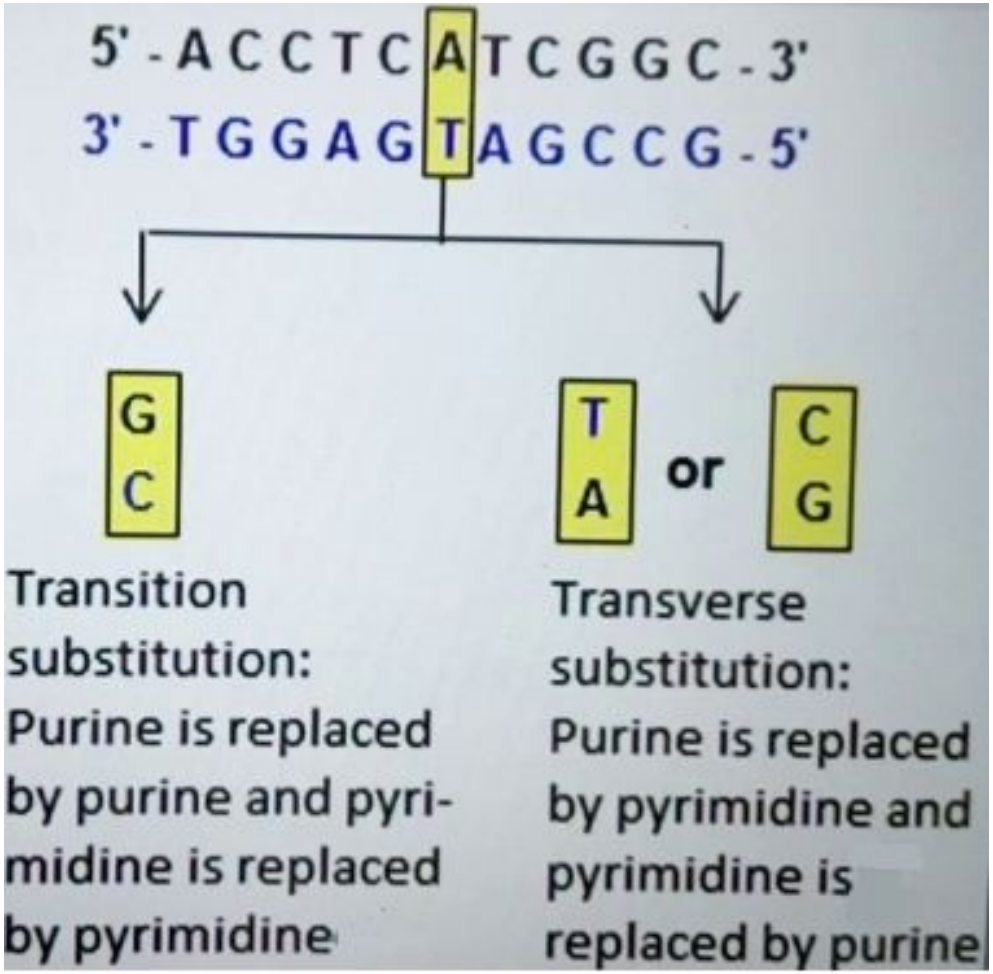

Figure 2. Diagram illustrating transition and transversion.

Frame shift mutations:

Frame shifting mutations are the addition or deletion of one or a few base pairs in protein coding regions.

Broken DNA strands:

These may arise either as a result of:

- excision repair mechanisms that are incomplete during DNA replication, or

- via direct alkylation of the phosphodiester backbone leading to backbone cleavage.

Note: the phosphodiester bond is the bond between phosphoric acid & two sugar molecules (Figure 3).

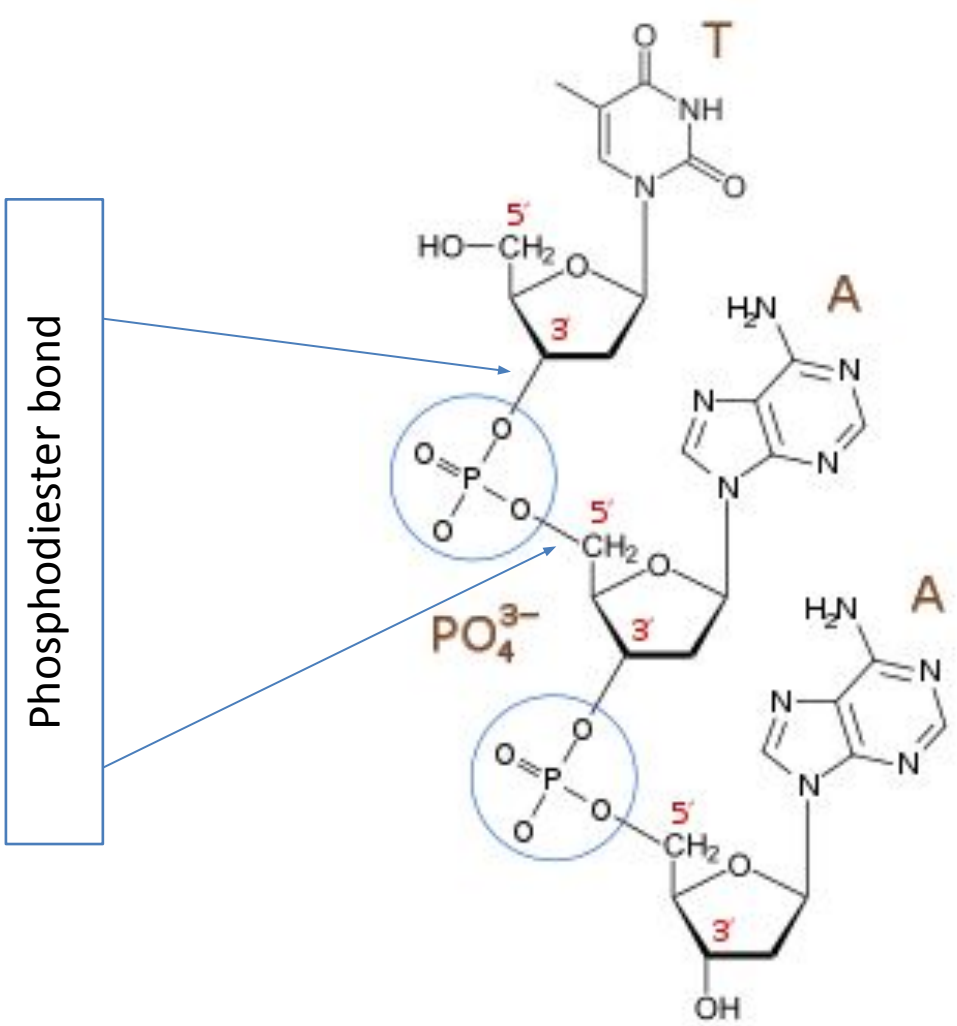

Figure 3. Diagram of phosphodiester bonds between three nucleotides.

Damage by alkylating electrophiles:

- Most chemical carcinogens require metabolic activation to exert a carcinogenic effect.

- The ultimate carcinogenic forms of these chemicals are frequently strong electrophiles (e.g., carbonium ions, free radicals, epoxides & sulfonates) that can readily form covalent adducts with nucleophilic targets.

- An important & abundant source of nucleophiles is contained not only in the DNA bases, but also in the phosphodiester backbone.

- Another common modification to DNA is the hydroxylation of DNA bases.

- Oxidative DNA adducts have been identified in all our DNA bases. The source of oxidative DNA damage is typically formed from free radical reactions that occur endogenously in the cell or from exogenous sources.

- Chemical carcinogens may inhibit DNA methylation by several mechanisms including:

  forming covalent adducts, &

  inactivation of the DNA methyltransferase responsible for methylation.

DNA repair mechanisms:

- Although cells posses mechanisms to repair many types of DNA damage, these are not always completely effective.

- These mechanisms include:

- Mismatch repair of single-base mispairs
- Excision repair, &
- Double-strand break repair

Mismatch repair of single-base mispairs:

- Depurination is a fairly common occurrence & spontaneous event in mammals, & results in the formation of apurinic sites.

- All mammalian cells possess apurinic endonucleases that function to cut DNA near apurinic sites.

- The cut is then extended by exonucleases, & the resulting gap repaired by DNA polymerase & ligase.

Excision repair:

DNA regions containing chemically modified bases, or DNA chemical adducts, are typically repaired by excision repair processes.

Double-strand break repair:

There are two general pathways for repair of DNA double-strand breaks:

- homologous recombination &
- nonhomologous end-joining (NHEJ).

Homologous recombination:

In homologous recombination, the double-strand break on one chromosome is repaired using the information on the homologous, intact chromosome.

Nonhomologous end-joining (NHEJ):

- A cell that has double-strand breaks can be repaired by joining the free DNA ends.

- The joining of broken ends from different chromosomes, however, will lead to the translocation of DNA pieces from one chromosome to another, translocations that have the potential to enable abnormal cell growth.


Thank
you