Repair mechanisms

Prevention of errors before they happen

detoxification of reactive oxygen species & oxygen radicals

$2O_2^{\cdot} + 2H^+ \xrightarrow{\text{superoxide dismutase}} O_2 + H_2O_2$

(superoxide)

$2H_2O_2 \xrightarrow{\text{catalase}} O_2 + 2H_2O$

(Hydrogen peroxide)

Direct reversal of damage

■ **Pyrimidine dimers :-**

Exposure to sunlight ⇒ UV light hit the DNA ⇒ formation of a covalent interaction (50-100 reactions per second) between two adjacent pyrimidine bases "commonly between two thymines" forming structures known as cyclobutane pyrimidine dimers. are reversed by enzymes known as photolysas (covalent interaction are removed).

■ **Specific mispairing :-**

Alkylating agents can transfer methyl group to guanine forming 6-methyl guanine, which pairs with thymine, after replication, you will have (AT) instead of (GC).

• Addition of large chemical ⇒ Carcinogens.

• Repair of O^6- methylguanine :-

O^6-methylguanine $\xrightarrow{O^6\text{-methylguanine methyl transferase}}$ Guanine

Excision repair pathways

Base excision repair

DNA glycosylases :-

They remove damaged base (don't cleave phosphodiester bonds, but instead cleave N-glycosidic "base-sugar" bonds of damaged base)

→ generating an apurinic or apyrimidinic site (both are called AP sites) and then this base can be repaired (AP site is repaired) by AP endonuclease repair pathway.

Example: uracil-DNA glycosylase, removes uracil from DNA.

→ AP endonucleases cleave the phosphodiester bonds at AP sites

→ The deoxyribose is removed.

← DNA pol. : بحط بدالها "C"

إذا الـ "U" ما تصلحت وصار عنا

DNA replication ← (U/A) بدل (C/G)

وبالتالي الـ "U" ممكن تتصلح لـ (T)

Nucleotide excision repair

• Include the breaking of a phosphodiester bond.

• In bacteria, the Uvr(A/B/C) protein complex does this work.

• Helicase removes the strand.

• In human cells, defect in this mechanism causes Xeroderma pigmentosum (XP) is caused by defective genes designated as XPA to XPG

XP proteins have different functions including damage recognition and enzyme activities (endonuclease, helicase)

• The UV light cause cell death in xeroderma pigmentosum.

Transcription coupled repair

• RNA pol. pauses (stalls) when encountering a lesion.

TFIIH and other factors carry out the incision, excision and repair reactions.

Then, transcription can continue normally.

• Cockayne's Syndrome: a condition caused by mutation in a CSB protein which recognizes that the RNA pol. is stalled due to a mutation.

• It recruits XPA, RPA and TFIIH

Mismatch repair and post-replication repair

In prokaryotes

• This is mediated by the (mut) protein system

• Original DNA strands are methylated

• The newly synthesized strands aren't methylated (takes place at the adenine)

وبتأخر السلسلة الجديدة بعملها DNA methylation

In humans

Two proteins, hMSH2 and hMLH1 are very similar to MutS / MutL, respectively

Except: it's not post-replication repair rather it's co-replication mechanism, so as replication takes place mismatches are repaired.

• The newly synthesized lagging strand could be identified by nicks at either end of okazaki fragments.

• The leading strand might be identified by its growing 3' end.

• mutation in MSH followed by MLH ↳ HNPCC.

Translesion DNA Synthesis

• (DNA pol. synthesize DNA over the lesions.

• They have low fidelity, lack proofreading mechanism.

Recombinational repair

Ionization reaction

when double strand breaks of DNA occur (→) takes place by NHEJ/HR

• BRCA 1 activates homologous recombination repair.

• BRCA 2 can recruit Rad51 to the ssDNA