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DNA damage and repair in plants: A review

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Abstract
Despite stable genomes of all living organisms, they are subject to damage by chemical and physical agents in the environment (e.g., UV and ionizing radiations, chemical mutagens, fungal and bacterial toxins, etc.) and by free radicals or alkylating agents endogenously generated in metabolism. DNA is also damaged because of errors during its replication. The DNA lesions produced by these damaging agents could be due to altered base, missing base, mismatch base, linked pyrimidines, deletion or insertion strand breaks, intra- and inter-strand cross-links Excessive reactive oxygen species may cause irreparable DNA damage, leading to mutagenesis and perhaps cancer. Investigation into the nature of DNA damage and repair have provided valuable insight into aging, human genetics and cancer. Now, there is deep interest in identifying free radical scavengers or antioxidants that inhibit oxidative DNA damage. This review describes all the possible mechanisms of DNA damage and repair in general and recent progress in plants.

Keywords: DNA, reactive oxygen species, radiations, intercalations

Introduction
All the living organisms are made up of cells which get differentiated to form tissues then organs, and finally individuals, but the blueprint for all the living organisms is DNA i.e., Deoxyribonucleic acid which lays a foundation for all life. DNA is made up of three major components *viz,* deoxyribose sugars, phosphates and nitrogen bases. Nitrogen bases are of two types, purines and pyrimidines. Purines include Adenine and Guanine, where pyrimidines are thymine and cytosine. Adenine pairs with thymine and guanine pairs with cytosine with two and three hydrogen bonds respectively. These hydrogen bonds facilitate the stability of DNA intern the genome stability and integrity. Genomes of all the living organisms, including plants, are stable. DNA of genome in the cell replicates during cell division and passes all the genetic information to their progeny hence it is very important for all living organisms to ensure proper functioning and propagation of their genetic information. However, due to constant exposure of the genome to various endogenous and environmental agents, the DNA gets damaged and can produce a large variety of DNA lesions. These lesions can affect the fidelity of DNA replication (Painter, 1985) [4], and transcription (Protic-Sabljic and Kraemer, 1985) [5], which can create mutations in important protein coding sequences. As a result, the produced mutated protein can affect various biological processes leading to the genome instability. In plants if these damages are not repaired properly they can induce proliferation as well as play an important role in the aging of seeds stocks and perennial crops. This unrepaired damage can also lead to the general deterioration of cell function and cell death. DNA repair is not only a fundamental cellular process for protecting cells against the damage, but it is also essential to ensure the faithful transmission of genetic information from one generation to the next.

DNA Damage: Non-heritable physical abnormalities or abnormal chemical modifications in double strand DNA helix are called as DNA damages (Tuteja *et al*., 2001) [6]. DNA damages are produced by endogenous and exogenous agents. Endogenous agent that damage DNA are called as spontaneous damages that include reactive oxygen species, nucleophiles and replication errors. Exogenous factors are various chemicals (Alkylating agents, radiometric agents and heavy metals), radiations (UV rays, IR rays and Gamma rays) and pathogen toxins. All these agents take up different modes of action to induce damage to DNA.

Mode of action of endogenous agents

- **Reactive oxygen species (ROS):** ROS include hydrogen peroxide, hydroxyl radicals, Derivaties of oxygen like singlet oxygen, triplet oxygen and Superoxides. All these will lead to production of free radicals in the cell. Free radicals possess an unpaired electron in their outermost orbital which makes them highly unstable and reactive as a result they interact with surrounding cells and induce damages in DNA.
- **Nucleophiles:** Nucleophiles are the chemical species produced during the process of lipid peroxidation and react with proteins and DNA and induces damages in them.
- **Replication errors and failures:** These are the spontaneous actions in the cell which will result into different kinds of damages.

Mode of action of endogenous agents

- **Chemicals:** Chemicals of different groups induces different types of damages. Chemicals either alters the topology of DNA double strand or interfere with chemical properties of DNA and its components to cause different types of damages.
- **Radiations:** Radiations disrupt the physical structure of the DNA and interact with chemical components of DNA like oxidization and hydration of DNA bases.
- **Bacterial and fungal toxins:** These behave more like chemical compounds and causes systemic necrosis and also other damages.
- Types of DNA damages

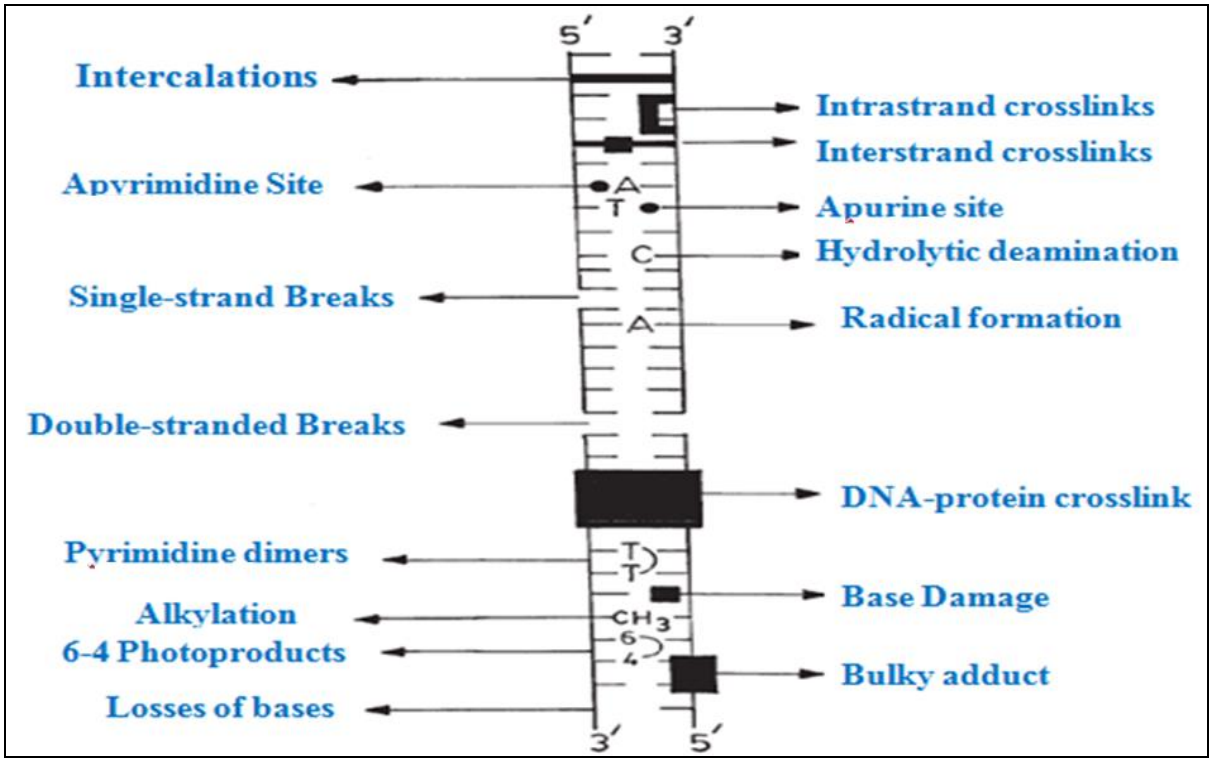

Fig 1: The intercalations and measurement

- **Intercalations:** Insertion of chemical molecules of an appropriate size and nature between the planar bases of DNA are called as intercalations. Such damages induce rigidity of DNA structure and leads to disruption of configuration during replication and results into strand breaks. Commonly involved intercalates are berberine, ethidium bromide, proflavine, daunomycin, doxorubicin and thalidomide.
- **AP Sites (Apurinic/Apyrimidinic Site):** Location in DNA that has neither purine nor pyrimidine. It may occur spontaneously or due to radiations, alkylating agents or/and enzymatically as an intermediate in the repair of modified or abnormal bases.
- **Cross links:** DNA damaging agents form a covalent adducts with bases on either of the strand (Intrastrand) or on both strand (Interstrand) to form cross links. These crosslinks prevents DNA strand separation during replication and blocks replication and further transcription.
- **Strand breaks:** Breaks in the DNA strands in a cell are called as strand breaks. Single strand and double strand breaks are two kinds of breaks where double strand breaks are common and harmful in plant cells. Strand breaks are commonly induced endogenously due to topoisomerases, nucleases, replication fork "collapse", and repair processes. Such breaks are also induced by exogenous agents like alklating agents, UV rays and pathogen toxins.
- **Dimers:** Dimmers are the resultants of photochemical reactions. Photons released by light sources causes two consecutive bases on one strand to bind together, destroying the normal base pairing of double strand structure. Dimers may induce in purine or pyrimidine bases bit pyrimidine dimmers are most common in plant cells.
- **Alkylation:** Addition of alkyl chemical groups into DNA double strand is called as alkylation. Alkyl groups form permanent covalent bonds with nucleophilic substances and prevents proper replication. Alkyl groups bind with phosphodiesters and convert them into phototriesters which get easily hydrolysed from DNA and leads to dissosciation of DNA structure.
- **Other damages**
  a. Loss of bases is a spontaneous action.

b. Bulky adducts are the intermediary products of metabolic process which results in bulky addition into DNA.
c. Base damages occur spontaneously or by any other agents.
d. Radical formation due to exposure to UV radiation or due to unstable electron release in cells.
e. Mis-match of bases occurs due to errors in DNA replication, in which the wrong DNA base is stitched into place in a newly forming DNA strand, or a DNA base is skipped over or mistakenly inserted.

Consequences of DNA damage: The DNA damage can have genotoxic and cytotoxic effects on the cell. The real biological consequences of these damaged products usually depend on the chemical nature of the lesion. In plants if this damage are not repaired properly they can induce proliferation as well as play an important role in the aging of seeds stocks and perennial crops. This unrepaired damage can also lead to the general deterioration of cell function and cell death. (Tuteja *et al*., 2001) [6].

Response of plants to damages: Plant cells respond to chromosomal insults or DNA damages by activating a complex damage response pathway. The DNA damage response pathway is a kind of signal transduction pathway consisting of sensor, transducers, and effectors. Damages in plant cells will be recognized by sensor proteins that initiate a network of signal transduction pathway. The identities of sensors are not yet known, but the DNA-break binding protein such as poly (ADP-ribose) polymerase (PARP) and DNA-dependent protein kinase (DNA-PK) are the kind of DNA damage sensors. Transducers are less known in plants but well known in mammalian system. Signal transduction pathway ultimately results in the activation of effector proteins that execute the functions of DNA damage response, including recruitment of DNA repair proteins, cell cycle arrest, damage induced transcription and, or induction of apoptosis.

Repair mechanisms and their significance: Collection of processes by which cell identifies and corrects damage to the DNA molecules that encode its genome. It is a multiple process involving, (a). Recognition of damage by sensor proteins or proof reading. (b). Removal of damage by help of exonucleases or endonucleases. (c). Synthesis of normal DNA by DNA polymerase.
Cells take up two different types of repair mechanisms. They are classified as follows-

a. Direct reversal
1. Photoreactivation
2. Removal of alkyl groups.

b. Excise repair
1. Base excision repair
2. Nucleotide excision repair.
3. Mis –match repair.
4. Non homologous end joining.
5. Homologous recombination.

Direct reversal: The direct reversal of DNA damage is by far the simplest repair mechanism that involves a single polypeptide chain, with enzymatic properties which binds to the damage and restores the DNA genome to its normal state in a single-reaction step.

Photo reactivation: DNA photolyases are the enzymes responsible for removing damages from DNA in a light-dependent process called as photo reactivation. DNA photolyases are enzymes coded by PHR/PRE genes with cofactor folic acid and binds to damaged area in dark. When light falls on cell, folic acid absorbs the light and energy it breaks the bonds of damage and then the photolyase falls off. (Hu *et al.*, 2015) [2].

Removal of alkyl groups: Alkyl trnasferases are the enzymes that removes the alkylated regions of a DNA. Enzymes go and bind to damaged areas and remove off the damaged bases and then fall off from the DNA. (Hu *et al.*, 2015) [2]

Excision repair: Certain damages in plant cells cannot be repaired directly by any enzymes. Hence cells have adopted a excision mechanisms to remove the damaged areas of DNA. When damages are in single strand, cells go for base excision repair, nucleotide excision repair and mismatch repair. Non homologous end joining and homologous recombination methods will be adopted when damages are in both the strands.

Base excision repair: A DNA glycosylase recognizes a damaged base and cleaves between the base and deoxyribose in the backbone that results into AP site. AP endonuclease cleaves the phosphodiester backbone near the AP site. DNA polymerase I initiates repair synthesis from the free 3’ OH at the nick, removing a portion of the damaged strand (with its 5’→3’ exonuclease activity) and replacing it with undamaged DNA. The nick remaining after DNA polymerase I has dissociated is sealed by DNA ligase.

Nucleotide excision repair: Two exonucleases (excision endonucleases) bind DNA at the site of bulky lesion. One exonuclease cleaves the 5’ side and the other cleaves the 3’ side of the lesion. DNA segment is removed by a helicase. DNA polymerase fills in the gap based on complementarity. DNA ligase seals the nick.

Mis-match repair: It corrects a single mismatch base pair or a short region of unpaired DNA. The defective region is recognized by an endonuclease that makes a single-strand cut at an adjacent methylated GATC sequence. Strands will me methylated to detect he mismatched base. The DNA strand is removed by exonucleases, replaced by DNA polymerase and relegated by DNA ligase.

Non-homologous end joining (NHEJ): It is a complex process of repairing when damages are in both the strands of DNA. It is a two step process, DNA end recognition and stabilization of the core NHEJ factors. DNA double strand break (DSB) are induced. *Ku* proteins quickly binds to the ends of the broken DNA molecule. *Ku* serves as a scaffold to recruit the core NHEJ machinery to the DNA DSB. *DNA-PKcs*, *XRCC4*, *XLF*, DNA Ligase IV and *APLF* are independently recruited to the Ku-DNA complex. The core NHEJ factors interact with each other to form a stable complex at the DSB. Ligation of the DNA ends and dissolution of the NHEJ complex. Autophosphorylation and/or *ATM* mediate phosphorylation of DNA-*PKcs* resulting in the opening up of the DNA-*PKcs* resulting in its release from the DSB. DNA ends are ligated by DNA-Ligase. *Ku* released from the repaired DSB via ubiquitylation and results

in degradation of Ku. The DNA DSB is repaired.

Homologous recombination: The procedure for homologous recombination repair mechanism is same as that of nonhomologous end joining mechanism but the two strand break ends are joined initially based on their recombination pattern followed by interaction with *ku* complex. Its mechanism is not well known in plant system.

Significance of repair mechanisms: In both dividing and non-dividing cells, DNA is vital to their everyday functioning. The code in DNA is read by special enzymes and "translated" into the proteins that carry out all of our cellular and other bodily processes hence to ensure faithful or error free transmission of genetic information from parents to daughter cells hence facilitate the genome integrity and normal functioning of plants. DNA damage caused by various genotoxins in *Arabidopsis* can be detected when suitable comet protocols are used. These protocols will elicit the up- or down-regulation of genes involved in the response to genotoxic stress and gene expression profiling will show which known genes contribute to mutagenesis, DNA repair and recombination in plants after exposure to different types of genotoxins. DNA damages in all the organisms including plants are unavoidable as there is exponential rate of increasing pollution, changing food habits etc. Hence all the living organisms has to build up a mechanism to tolerate, sustain or/and repair these damages to have a stable genome in them. Although the study of the molecular mechanisms controlling the plant DNA damage response lags behind those of yeast and mammals, plants offer a unique model system: Compared with mammals, in which mutations in checkpoint regulators often cause embryo-lethal phenotypes, such mutations in plants still allow the plants to complete their life cycles and lead to only conditional phenotypes. This feature provides unique possibilities to isolate the downstream components of the ATM and ATR signaling cascades through genetic approaches. Such approaches are of particular interest for the identification of signaling cascade components that connect plant development and environmental stresses to DNA checkpoint control. Additionally, the absence of embryo-lethal phenotypes allows studies of the effects of defective checkpoints over multiple generations. As discussed above, plants appear to use different adaptation strategies to prevent the spread of DNA mutations, including activation of cell cycle checkpoints, stem cell death, and endoreplication. Through whole-genome sequence comparisons of mutant plants grown for one or more generations under DNA stress–inducing conditions, the contributions of these different mechanisms to genome integrity can be quantified. In the long run, such information might result in the development of new crop species that can withstand genotoxic growth condition.

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