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# Recent Advances in Plant DNA Repair

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## 1. Introduction

Plants are sessile organisms that are continuously exposed to different environmental factors, which may affect their development and production. In order to support this, plants change their metabolic pathways through different signal transductions in order to survive or set seeds to propagate the next generation [1, 2]. Due to this, it may be said that plants have a sophisticated perception of stress conditions. Moreover, these stress conditions might be biotic (caused by animals, insects, bacteria or virus), abiotic (caused by heat, temperature, drought, flood, salt, sunlight, soil contamination (chemicals mutagenic in soil or air), or endogenous metabolism (Figure 1). The response from plants to these conditions is usually associated with change in gene regulation, gene expression, protein translation, and post-translational modifications. These changes generated a change in plant metabolism, which is correlated to keep plant homeostasis, DNA repair, cell division, cell growth, and expansion [3, 4].

Regarding environmental conditions, plants are exposed continually to sunlight, which has a deleterious UV component. Then, in order to avoid this negative effect these organisms produce phenolic compounds such as flavones to reduce the amount that reaches the plant cells and they have DNA repair pathways to correct lesions and then keep the genome integrity [5-7].

In general, biotic or abiotic stresses are correlated with an increase in the Reactive Oxidative Species (ROS), and this has been associated as a type of oxidative stress [1]. ROS may be produced due to oxygen presence during plant metabolism (photosynthesis), or a consequence of biotic and abiotic stress. The presence of ROS may produce other forms that are more reactive such as superoxide, $H_2O_2$, $OH^-$, and singlet oxygen [8-9]. Normally, plants keep a balance between ROS production and degradation with an antioxidant system [9-10]. This system is

formed by superoxide dismutase (SOD), catalase, and ascorbate peroxidase (APX) and others proteins. Furthermore, when plants are exposed to a stress condition (biotic or abiotic), the ROS production is accelerated and then a different physiological response [9-15]. It has been observed in some crops that the oxidative stress unbalances the ROS equilibrium in cells that may promote growth reduction, late development, decrease seed production [11-15].
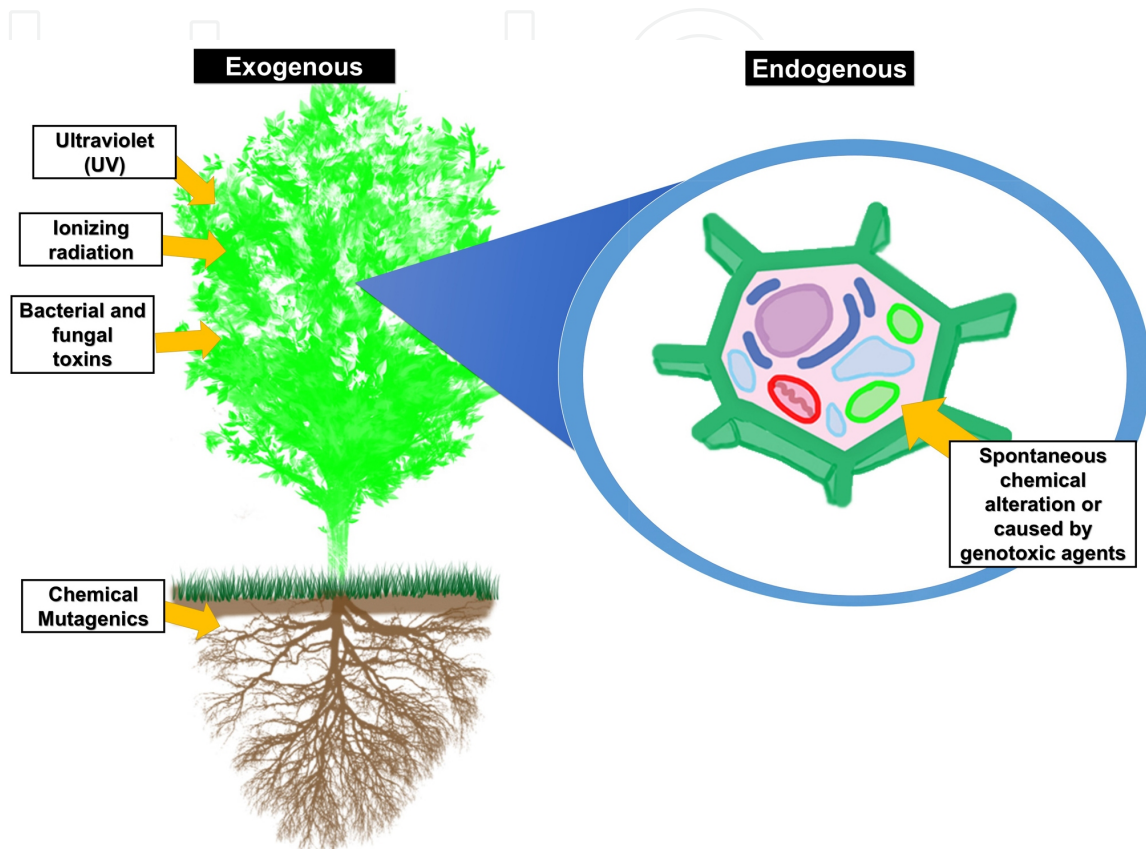


**Figure 1. Schematical representation of agents that act in plant organisms.** These agents are divided into biotic, abiotic, and endogenous agents. The biotic is formed by bacteria, insects, and virus. The abiotic is formed by sunlight (UV component), chemical mutagenics. And the endogenous components can be spontaneous lesions that happen during DNA replication or during photosynthesis.

When the ROS fine balance is not maintained, then these molecules may interact with DNA and this may produce DNA lesions and lipid peroxidation in membranes [9, 13-15]. Then, in order to avoid the DNA lesions and keep the genome integrity, plants have different DNA repair pathways to detect DNA lesions and correct them [15-16]. The effects of biotic and abiotic stresses on DNA repair have been observed (Figure 2). *Arabidopsis ku80* mutants had an increase in homologous recombination (HR) [16]. But, when these mutants were exposed to abiotic stress, this increase in HR was not observed. It was proposed an independent NHEJ and HR pathways in response to abiotic stress [16]. Another example of the connection between DNA repair and stress was observed by [17]. In this work, they observed an increase in DNA Polymerase $\lambda$ protein when plants were grown in the presence of $H_2O_2$ and NaCl. Another protein that has a role in DNA repair and stress is DNA helicase. In rice, it was verified that *OsSUV3* expression (a DNA helicase) increased when rice plants were exposed to 200 mM

NaCl (abiotic stress). Its expression increased fivefold in the first hour and then an interactome analysis indicated that *OsSUV3* plays an important role in other pathways [18]. These are some examples that show the connection among the DNA repair machinery, stress tolerance, and the ROS production (Figure 2) [11-15].

"Omics" are a powerful tool to identify genes/proteins/metabolites that are involved in the plant response to a specific stress and/or to a DNA repair pathway [19]. Besides, transgenic and mutant plants are also helping in the gene characterization function. The data have shown that plant response is more complicated than previously thought. Not only is the presence of transcript (tissue or time presence) important, but also the signals are important for gene regulation, post-translation modifications (ubiquitination or sumolation), protein degradation, and protein targeting. All these may change when plants are exposed to different environmental conditions [19-23]. Furthermore, the *next generation sequence* data have shown that the signal transduction pathways actually form a network and the different networks are interconnected [24-25]. miRNAs have also been connected as a key factor for plant response to the stress and tolerance mechanism [25-28].

Considering the importance of the plants for food production, it is important to identify which genes/proteins/pathways are involved in these different mechanisms. This knowledge is important for plant breeders to produce new cultivars [17, 28]. Moreover, considering all that was explained above, plants are an interesting model to study stresses and DNA repair (Figure 2) due their sessile condition, genome plasticity, and the fact that these organisms do not have a germinative cell lineage. The apical meristem cells (shoot or root) suffer division continually during plant development and then genome integrity is extremely important [2]. Then, this chapter will focus on DNA repair pathways in plants.

This figure illustrates different abiotic factors such as drought, heavy metals, light, heat, ozone, lack of nutrients, cold, freezing, etc. Plants are able to perceive these different conditions or signals (on the right side) and then promote different molecular and physiological responses, which involve changes in gene expression, protein translation, post-translation modifications, degradation, epigenetic changes, and miRNAs. All these together produce a plant response that helps plants to tolerate this stress condition. Represented on the left side are the effects of an imbalance of ROS in DNA repair and the different DNA repair and genes that are involved in these different processes. The DNA repair presented in this figure includes mismatch repair (MMR), excision repair (NER and BER), and double strand breaks (HR and NHEJ).

## 2. Photoreactivation

Due to the sessile habits of plants, they are exposed continually to sunlight that is composed by UV-A (315 – 400 nm), UV-B (280-315 nm), and UV-C (200 -280 nm). However, due to the ozone layer, the UV-C does not penetrate. Furthermore, it is known that UV-B light affects photosynthesis, reduces productivity, and is also responsible for promoting lesions in DNA, such as (6-4) photoproducts and cyclobutane pyrimidine dimmers (CPDs). Moreover, plants produce compounds such as phenol compounds that act as filters in order to reduce the UV
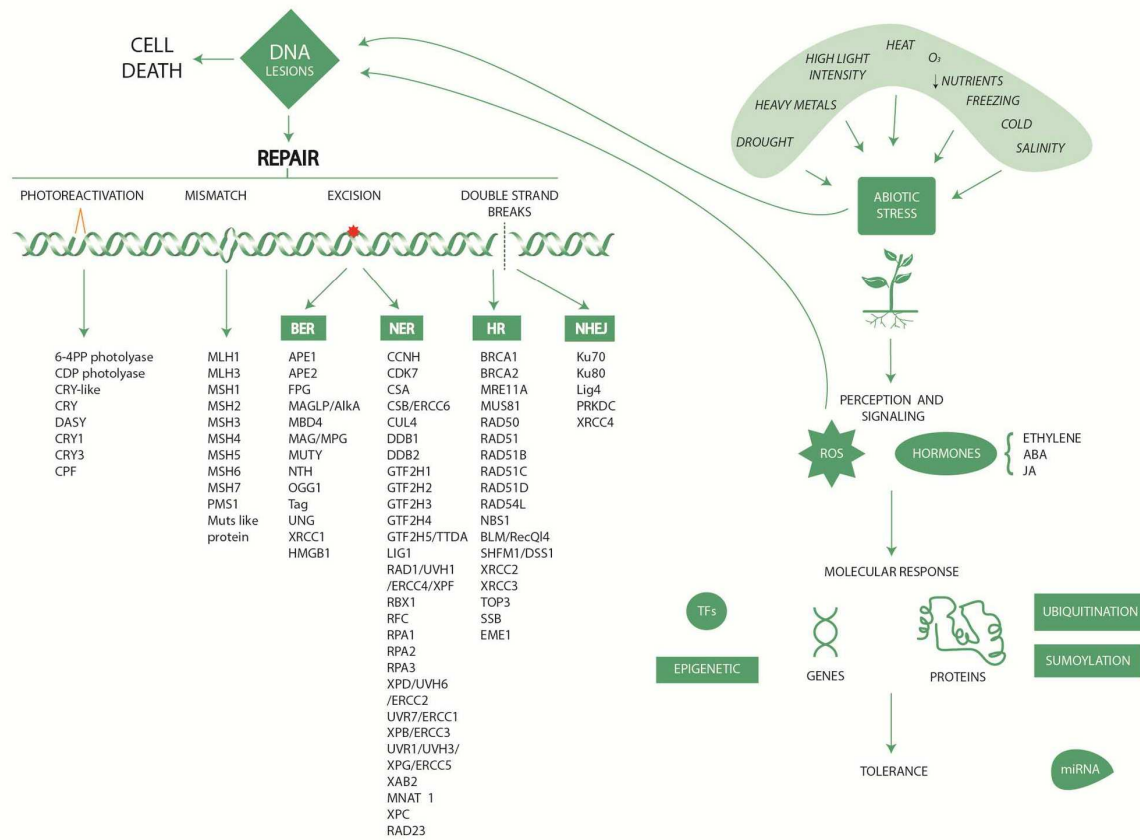
**Figure 2.** Schematical representation of environmental and endogenous factors and different plant responses.

light in plant cells [15]. Besides this, plant DNA also suffers DNA lesions. In rice cultivars was reported that CPDs may be the principal lesion that affects growth [29]. In *Arabidopsis* seedlings was observed that plants have photorepair mediated by photolyase proteins similar to what had been observed with other organisms [29-32]. The photolyase binds to damaged DNA and it uses the blue light photon to correct these lesions [33]. Furthermore, it was also observed that photolyase enzymes were not affected by the environmental temperature to which plants are exposed [34]. In cucumber leaves it was verified high expression of photolyase between the period of 9 am to 12 pm, and the photoreactivation activity was high between 12 pm to 15 pm [35]. The dark repair was done by Mismatch Repair (MMR), Nucleotide Base Excision (NER), and Base Excision Repair (BER) [1, 35].

The cryptochrome/photolyase superfamily (CPF) is a group of flavoproteins that includes photolyases and cryptochrome (CRY). Photolyases are DNA enzymes that are activated by light and when they recognize the CPD lesion, they are called CPD photolyases; and when they recognize the (6-4) pyrimidine-pyrimidone photoproducts, they are called (6-4) photolyases. CRY proteins do not have DNA repair activity, but they have a photoreceptor or transcription regulation functions [33]. Moreover, by phylogenetic analysis using the genomic data available, the CPF superfamily was divided into the following groups: 1- Class II CPD (involved in CPD DNA repair); 2- Class I and II CPDs and CRY photoreceptors (blue light receptors involved in circadian clock regulation; plant development); 3- Cry

DASHs (proteins that are able to do DNA repair); and 4- 6-4 photolyase (diverse group of proteins that includes DNA repair, photoreceptors, and transcriptional regulators) [33]. Although CPF is a diverse group, these proteins have a conserved photolyase homology region (PHR), with two non-covalent bound chromophoros (FAD and 8-HDF/MTHF). The CPFs may also have an N or C-terminal extension that might be associated with different functions such as signalling, regulation, post-translational modifications, protein target-ing, circadian clock regulation [30, 32].

It has been shown that some rice cultivars have different UVB sensitivity, which is related to CPD lesion, photolyase activity, and ability to correct these lesions [29, 36]. It was observed that overexpression of photolyases increases biomass production under UV-B light in *Arabidopsis* [37]. Furthermore, data from the rice photolyase overexpression in different rice cultivars showed that rice UV-B resistance is associated with photolyase activity [38]. It was identified only one nuclear CPD photolyase gene in rice that produces only one mRNA [39]. However, this mRNA is translated in one protein that may be target to nuclei, chloroplast, or mitochondria. This is an example of a protein with triple targeting. Furthermore, their data showed that OsCRY-DASH carried some sequence at the N-terminal region that may be important for the mitochondria and chloroplast target [39].

## 3. Mismatch repair — MMR

The mismatch repair pathway is important for the genome stability during replication and it has been associated with the correction of the incorrect base incorporation by DNA polymerase during DNA replication or during the process of recombination [1, 49, 50] as well as to correct the photoproducts [42-43]. The other function of this pathway is to reduce recombination events between diverged genomes [42, 44-45].

It has also been observed that MMR is conserved from bacteria, yeast, humans, and plants. This pathway is formed by the following proteins: MutS (recognizes the base-base mismatch and deletion or insertion that promotes mismatch on a DNA strand, ATPase activity); MutL (interacts with MutS, helps in the mismatch detection, recruits and activates MutH, ATPase activity); MutH (an endonuclease - identifies the hemi-methylated sequence and produces a nick on the DNA strand); DNA helicase II (MutU or UvrD); exonucleases (ExoI, ExoVII, ExoX, RecJ); SSB protein (single strand-binding protein); PCNA (important for lagging strand); DNA polymerase III (fill the gap), and DNA ligase (ligates the DNA ends) [41, 47]. Also observed in human cells hemi-methylated sites that may act as important signals for discriminating the strand where nicks is produced. Despite this conservation, some differences have been observed between bacteria, yeast, and humans, and plants, which may be related to the life style where plants are sessile organisms [41, 46].

One model for the MMR pathway is: MutS/MSH (this complex recognizes mismatches or insertions/deletions on the DNA strand and bind to the DNA strand); and MutL/MLH (this complex has been associated with ligation to the DNA strand and the DNA repair complex is assembled). The MutL/MLH protein complex interacts with MutS in helping the detection

of the mismatch and the complex assembling. Then, both proteins activate the MutH protein. This protein now will recognize the hemi-methylation strand and produce a nick in the unmethylated DNA strand in a process that requires ATP-dependent proteins [41- 42]. After these steps, there is the association of PCNA, DNA helicases II, exonucleases, SSB, DNA polymerases, DNA synthesis and DNA ligation; then the mismatch lesion will be correct-ed. One difference between bacteria and eukaryotes is that MutS and MutL proteins work as homodimers and in the case of eukaryotes these proteins work as heterodimers (Table 1) [41-42].

This MMR pathway is able to identify a mismatch on the DNA strand, remove it, and replace it with the correct base [1, 40, 42]. Mutants in mice have shown that MMR proteins are associated with cancer as well as fertility as some mice mutants were sterile, and then it has been suggested that the MMR may also have a role in meiosis [47]. As plants are sessile organisms and do not have specific germ cells, these organisms have meristematic cells that divide to form gametes. These meristematic cells go through division during the life cycle of the plant and then these cells may accumulate spontaneous mutations that need to be recog-nized and corrected in order to keep the genome integrity. Due to this aspect, MMR has an important role in the plant genome [1, 40, 42].

The genome projects have allowed researchers to identify gene sequences and it has been observed that in plants some MMR genes were duplicated when compared to a bacteria genome (Table 1). Phylogenetic work on MSH proteins (bacteria MutS homolog) has observed the division into two distinct groups [48]. The idea is that the MutS from eubacteria present in mitochondria suffered duplication, and this new copy was transferred to nuclei where other duplication and specialization processes gave rise to MSH2, MSH3, MSH4, MSH5, and MSH6 in the nuclei. It has been observed that these sequences were related to recognizing and correcting DNA replication errors, and some proteins became involved in meiotic recombi-nation. It has been proposed that these events occurred before the evolution of plants [49]. Furthermore, it was observed that sequence from MSH7 is specific to plants (Table 1).

Considering the role of MMR in recombination, in *Arabidopsis* when the level of genome divergence was 1.6% or 1.9%, a reduction in somatic recombination by to 3.6 or 9.6 fold was observed [50, 51]. Then, it has been proposed that the MMR pathway is also involved in reducing recombination frequency (or plays a role in anti-recombination) between diverged species or in cases of interspecies hybrids [52]. On the other hand, mutation in the MMR pathway has shown an increase in the recombination frequency. One difference in MMR between animals and plants is that it has been observed that many knockouts in animals are lethal; however, in plants it was observed in most cases that knockout may cause some problems in fertility, but a few had embryo lethality. These results shown that plants have plasticity for these lesions, as these organisms may tolerate these mutations [46].

For the MSH genes, it has been proposed that MSH2 is an important gene for MMR pathway and for the recombination repression [52]. This protein has a role in recognition of mismatch lesions (Table 1) and it forms dimmers to MSH3 or MSH6 proteins. The mutation only in the MSH2 sequence increases the homologous recombination by ninefold [52]. It has been observed that mutants in the MSH2 gene had problems in setting seeds and siliques were

abnormal; embryo lethality was also observed. These phenotypes suggested that these mutants probably accumulated many mutations, as it was not able to correct mismatch errors from DNA replication or normal metabolism [53].

In maize and in *Arabidopsis*, it was observed an increase in MSH2 and MSH6 transcriptional levels in leaves after UV-B irradiation. The MSH$\alpha$ (MSH2-MSH6) heterodimer may be involved in DNA repair by UV-B radiation in special to CPD lesions [43]. These authors also investigated the influence of other stress conditions as drought, cold, salt, heat, wounding and osmotic stress (all abiotic stress conditions). It has been observed that all these conditions down-regulated MSH2. On the other hand, the gene MSH6 was only down-regulated by drought, heat, and genotoxic stress. Both sequences were up-regulated by UV-B radiation. The hormone influence was also analyzed, and it was verified that the MSH2 sequence only responds to brassinolides, but MSH6 responds to all hormones tested [43]. Then these results showed that this heterodimer has a regulation to UV-B radiation on leaves, but each gene responds to different abiotic and hormone conditions. The authors also analyzed the cell cycle effect and they verified that MSH6 expression may be regulated by E2F transcription factors during the cell cycle [43].

The MSH7 protein (specific to plants) may interact to MSH2 as well as MSH3 and MSH6 [48]. It has been shown that this protein plays an important role in maintaining the genome integrity in plants and meiotic recombination [49; 54]. In tomato plants was showed a role of MSH7 in anti-recombination activity [55]. It was also shown that the heterodimer MSH2-MHS7 was able to recognize G/T or A/C mismatches, and this heterodimer may have a role in mismatches that arose from cytosine deamination or by UV or oxidative lesions [56].

The heterodimer MUTL$\alpha$ (MLH1-PMS1) has been considered an important heterodimer. The MLH1 has been associated with homologous recombination, as a decrease of 72% was observed [45]. Mutant plants for this sequence had problems in setting seeds, and a problem in pollen formation has also been observed. Then, it was proposed that the MLH1 gene may be important for recombination as well as in limiting the recombination frequency between diverged sequences [45]. For MLH2 it was observed that mutants also had problems in recombination, but the frequency reduction was only 22% [52]. The MLH3 mutants also had a reduction in seed production, but also a verified decrease in frequency of crossovers. MLH3 has a role in meiosis and is expressed in reproductive tissues. The immunolocalization identified the presence of this protein as foci on the chromosome axes during prophase I in meiosis, suggesting a role in Holliday resolution. Furthermore, AtMLH1 protein is dependent on AtMLH3 protein [57]. For the *PMS1* gene, it has been observed that the loss of the *PMS1* sequence creates problems in correcting the loopout (deletion/insertion mispairs), increasing the frequency in mutation in microsatellites [58]. *AtPMS1* mutants also showed problems in setting seeds, suggesting that this may be a characteristic of MUTL mutants. Furthermore, these mutants showed problems in pollen formation; however, the data obtained proposed that the *AtPMS1* gene has an anti-recombination activity as these mutants had an increase in homeologous recombination [58]. This observation is the opposite of what had been observed in yeast.

The comparative genome analysis between *UVRD* sequence from *Arabidopsis* and the rice genome showed that these enzymes may be involved in the following processes: DNA replication, DNA repair, DNA transcription, and DNA recombination. In this work, it was observed that both protein sequences of AtUVRD (129 KDa) and OsUVRD (130 KDa) share identity with E. *coli* REP helicases and both sequences have the ATP binding and helicase C-terminal domains that are important for its activity [18]. Furthermore, the structural modelling from these two sequences showed conservation in their structure to *E. coli* ReP helicases. This protein is an important component from MMR and these data showed the conservation domains, suggesting that the plant proteins may work in a way similar to the *E.coli* protein.

| E. coli | Plant | Function | Localization |
|---|---|---|---|
| **MutS** | MSH4 | meiotic recombination | nuclei |
| | MSH5 | meiotic recombination | nuclei |
| | MSH1 | replication errors | mitochondria |
| | MSH2 | replication errors | nuclei |
| | MSH3 | replication errors | |
| | MSH6 | replication errors | |
| | MSH7 **(sequence found only in plants)** | replication errors | ? |
| | MSHα – MSH2-MSH6 | mismatch error and 1-2 bases of deletion/insertion loopout | |
| | MSHβ – MSH2-MSH3 | 2-12 bases of deletion/insertion loopout | |
| | MSHγ – MSH2-MSH7 | preference for G/T or A/C base/base mispairs and meiotic recombination | |
| **MutL** | MLH1 | homologous recombination | |
| | MLH2 | | |
| | MLH3 | | |
| | MUTLα - MLH1-PMS1 | endonuclease activity, protein/DNA complex | |
| | MLH6 | | |
| **Uvr** | UVRD | DNA helicase | |
| **PCNA** | PCNA | Interacts with MSH2, MLH1, MSH6 | |

**Table 1.** MMR sequences identified in plant genomes

These data in plants showed the importance of MMR components and that many of these mechanisms are not clear yet, especially related to meiotic recombination and homeologous recombination.

## 4. Base Excision Repair (BER)

This pathway is responsible for identifying and correcting lesions associated with alkylation, oxidation, deamination, DNA replication, and base adducts that sometimes block DNA replication and transcription [59-60]. This pathway is a multistep, beginning with the lesion recognition by DNA glycosidase. These enzymes remove the base by an incision on DNA strands at the N-glycosidic bond that connects the base to the deoxyribose-phosphate residue. Then, this incision creates an abasic site or AP site [61, 62]. There are different DNA glycosylases (mono or bifunctional), each one specific to a different type of base lesion. The AP sites may also be produced by spontaneous depurination or by hydrolysis of N-glycosidic bond [63]. After that, the AP site is processed by a bifunctional DNA glycosylase (3´AP lyase function) or by AP endonuclease. This excision creates a gap, which is filled with nucleotides by DNA polymerase and then ligated to the DNA strand by DNA ligase (Figure 3) [59].

The BER may be divided into two pathways: short-patch and long-patch (Figure 3). Choosing the short or long patch will be associated with which type of lesion and which DNA glycosylase will be used in the DNA repair. The short patch is responsible for correcting the lesion of only one nucleotide, and the long-patch will correct a lesion from 2 to 13 nucleotides [64]. The other difference is that in the short-patch the DNA polymerase that acts in this process is Polβ (mammals) or PolI (bacteria) [65]; and the DNA sealing is done by XRCC1 and LigIII (mammals) or LigI (bacteria) [66-67]. It is known that for the long patch Polβ probably introduces the first nucleotide, but the other nucleotides are processed by Polδ or Polε [64]. The short and long-patches were discovered by *in vitro* and *in vivo* experiments [68-72].

Different work using the *Arabidopsis thaliana* has shown that there are homologous sequences for BER pathway in plants [2]. However, one difference found was related to the correction of the 8-oxo-7, 8-dihydroguanine lesion. In bacteria this lesion is corrected by MutM/Fpg (formamidopyrimidine DNA glycosylase) and in eukaryotes by OGG1 (8-Oxoguanine DNA-glycosylase). And it was found that plants have both sequences/proteins in their genome. But, the real function of these proteins is not clear, although an overlap for the lesion subtract was observed [73-74].

The other interesting component of this pathway is the enzyme fosfodiesterase-DNA tirosil (TDP1), which is involved in the repair of lesions *topo I-mediated damage* [75]. The TDP1 enzyme is responsible for hydrolyzing the phosphodiester ligation from DNA at the 3´end ligated to the tirosil radical and this enzyme has been associated with the repair of the topoisomerase complex I (TOP1)-DNA. Some data have shown that TPD is important for oxidative lesions in mitochondrial DNA [76]. This enzyme has been identified in plants. It has been observed in two sequences of the *Medicago truncatul*a genome: MtTDP1α and MtTDP1β. These isophorms are up-regulated in leaves and roots in response to heavy metals and osmotic stress [77].

Another difference observed in plants is related to AP endonuclease. This protein is necessary for survival, as it has been observed that homozygote knockout mice are lethal. [78]. Furthermore, APE1 (also known as HAP1 or APEX) has two types of functions – AP endonuclease and a redox function to *jun* and *fos* transcription factors [79]. In plants at least three sequences

of the *Arabidopsis* genome have been observed: *AtAPE1*, *AtAP2*, and *AtARP*. However, only the *AtARP* has been shown to have the AP endonuclease activity [80]. In sugarcane, two sequences were identified, one directed to nuclei (*ScARP1*) and the second one (*ScARP3*) directed to chloroplast and/or mitochondria [81]. Furthermore, at least nine genes that codified bifunctional DNA glycosylase have been identified, seven of which were characterized by *in vivo* experiments - *AtMMH*, *AtNTH1*, *AtOGG1*, *DME*, *ROS1*, *DML2*, and *DML3* [82-86].
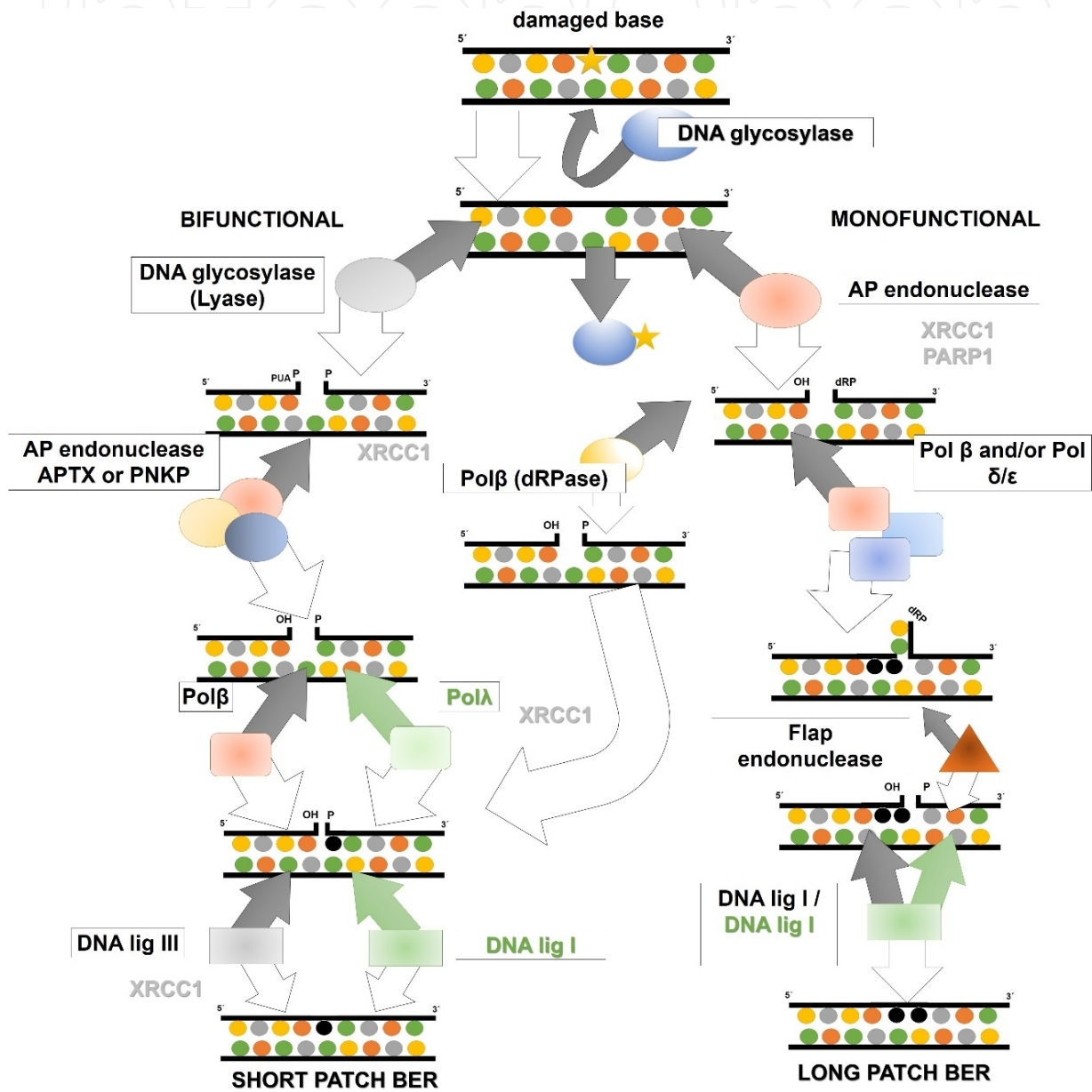


**Figure 3.** Schematical representation of BER pathway.

The short-patch needs the DNA polymerase β and DNA ligase III, but as these sequences were not identified in *Arabidopsis* and rice genomes, it was thought that plants do not have this pathway, only the long-patch [87] (Figure 3). However, experiments showed by *in vivo* that

plants have both pathways [88]. Another difference verified in plants is related to DNA polymerase$\lambda$, which is a member of the polymeraseX family [89]. Then, DNAPol$\lambda$ is the only member of this family identified up to now in plants [87]. Furthermore, for DNA ligase only the presence of DNA ligase I was observed in plants. It has been proposed that DNA ligase I may have the function of all DNA ligase in plants for both patches [90]. In XRCC a lack of domains responsible for the interaction to DNAPol$\beta$ and LigIII has been observed. One reason for this reinforces the observation that in the plant genome these two sequences were not found. But the presence of the domain PARP1 was observed. Although plants have only DNAPol$\lambda$ and not DNAPol$\beta$, no protein interaction was observed between XRCC and Pol$\lambda$, but rather only the interaction from XRCC to PCNA (Figure 3) [91-92].

The first step of the BER pathway is the recognition of the lesion (represented by a star on the DNA strand). This lesion recognition is done by a bifunctional DNA glycosylase that makes an incision on the DNA strand and produces an end with 5′P and the other end 3′P or a 3′polinsaturated aldeid (PUA). In the case of the monofunctional DNA glycosylase, the nick is done by AP endonuclease creating 3′OH and 5′dRP. These ends were corrected by Pol$\beta$ (dRPase function). The short-patch (left side) Pol$\beta$ adds one nucleotide, and then XRCC1/LigIII or LigI does the ligation. In the long-patch Pol$\beta$ and/or Pol$\delta$/$\epsilon$ adds the nucleotides (2 to 13); then the lesion is removed by the DNA Flap (FEN) and DNA is sealed by LigI. All the proteins and steps present in BER are represented by gray, and the proteins and steps present only in plants are represented by green color.

## 5. Nucleotide excision repair

Nucleotide excision repair (NER) is the other DNA repair pathway that removes damages caused by UV radiation and bulky covalent adducts that cause helix distortion [5, 93-95]. Furthermore, it has been observed that NER proteins are more conserved considering amino acid identity than the other pathways when compared with bacteria, yeast, humans, and plants [46].

NER is divided into two sub-pathways, each one having distinct damage recognition mechanisms but both using the same machinery to correct the lesion. Transcription-coupled repair (TC-NER) is responsible for the removal of lesions from the transcribed strand of actively expressed genes [96]. This pathway is activated when RNA polymerase is stalled during transcription and it depends on the recruitment of the proteins CSA and CSB (Cockayne syndrome A and B) to the site of the lesion [97]. This process was first discovered in mammals [98] and *E. coli* [99], and then in yeast [100]. CSB interacts with CSA-DDB1(damage-specific DNA binding protein 1)-CUL4 (CULLIN4) E3 ubiquitin ligase [101]. The ubiquitination of CSB in the DNA repair is regulated by the CUL4-DDB1-CSA complex [102].

The regions in the genome that are not actively expressed are repaired by Global Genome repair (GG-NER). In this case, the lesion is detected by the DDB2 (damage-specific DNA binding protein 2)-DDB1-CUL4 complex. The binding of this complex recruits another complex of proteins composed by XPC (*xeroderma pigmentosum* group C), RAD23, and centrin

[94]. After the recognition of the lesion and binding of the protein complex, TCR and GG-NER converge to base reactions common for both pathways. All the components of TC-NER and GG-NER identified in humans are well conserved in the *A. thaliana* and rice genomes, except for the protein XPA (*xeroderma pigmentosum* complementation group A) [46].

In *Arabidopsis* genome, two *DDB1* genes, *DDB1a* and *DDB1b* were found [103], and the protein complex CUL4-DDB1 was also identified in plants [104]. This complex has been associated with different biological processes [104-107]. However, it is not clear yet if plants have a CUL4-DDB1CSA protein complex. It was identified two CSA-like genes from *A. thaliana* (*AtCSA1A* and *AtCS1B*) that form an heterotetramer [107]. A UV sensitivity assay was performed in order to check whether *atcsa-1,1; ddb2-3* and *atcsa-1,1/ddb2-3* double mutants had an increase in UV sensitivity. After the plants had been exposed to UV-B radiation, it was observed that the root growth from single mutants was more severe than in wild-type plants. It was also observed that *atcsa-1, 1* had a stronger reduction in the root growth than *ddb2-3*, and the double mutant did not have an increase in UV treatment sensitivity. These results show the importance of these genes for DNA repair in roots. It has also shown the interaction of ATCSA-1 and DDB1a by two-hybrid assay [108].

For both NER pathways it is important that the TFIIH complex (transcription elongation factor-IIH) unwind the DNA near the lesion site. XPB and XPD proteins are the subunits of this complex that have helicase activity [109]. Orthologs of these two helicases were isolated in *A. thaliana* genome. Furthermore, it is also observed gene duplication for *XPB1* and *XPB2* genes [110-112]. AtXPB1 and AtXPB2 share 95% of amino acid sequence identity and the complementation assay in yeast showed that each protein sequence is able to complement the yeast Rad25 mutant strain in the presence of UV radiation [110-111]. The XPD gene in *Arabidopsis* is essential for plant development, since the *xpd* mutants present yellow-green leaves and their size is smaller than that of the wild-type plants. And after UV plant treatment, these mutants shown brown color and dead leaves in the rosette. These results suggested the involvement of this *XPD* gene to DNA repair [113].

In rice, differential modulation was reported for the genes *OsXPB2*, *OsXPD*, *OsTFIIS*, and *OsTFIIS-like* in response to γ-rays. The expression of the genes *OsXPB2* and *OsXPD* were down-regulated in 5-day-old seedlings and were up-regulated 20-day-old plantlets. The treatment with γ-rays and salinity showed an up-regulation of these two genes in both samples. For the *OsTFIIS* and *OsTFIIS-like* genes a similar pattern was observed [114].

In the study [115] it was observed that OsREX1-S (a TFB5 homolog in yeast and human - a subunit of TFIIH), is involved in NER as it was observed that *Arabidopsis* plants expressing this gene had an UV-B tolerance. Another subunit of TFIIH - MAT1 (ménage à trois 1) from sugarcane gene (ScMAT1) was also characterized. There was sequence conservation between human MAT1 and ScMAT1 for the region related to CAK kinase where XPD and XPB proteins interact to MAT1. This work using yeast two-hybrid assay showed that ScMAT1 interacts with proteins related to stress, but ScMAT1 was not induced by stress conditions such as phosphate deficiency, ABA methyl jasmonate, or cold. Therefore, this data suggest an indirect role of ScMAT1 in NER [116].

Plants also have DNA polymerases that are an important component of the DNA repair machinery. The only family of these proteins known to have a role in DNA repair and recombination is the DNA polymerases X family [117]. It was observed that AtPolλ had the C-terminal and N-terminal motives characteristic of the PolX family [118]. Seedlings from two mutant lines for *AtPolλ* (*AtPoll-1* and *AtPoll-2*) showed growth inhibition when compared to the wild-type lines after UV-B radiation exposure. In the same work, it was observed that the *AtPolλ* overexpression lines had a germination inhibition after UV radiation as well as CPD and DSB lesions. These data reinforce the role of *AtPolλ* in the NER DNA repair pathway [118].

# 6. Double-Strand Break (DSB) repair in plants

Double-strand breaks (DSBs) can be introduced in DNA mainly by metabolic products, ROS, radiation, replication, or transposon excision [119-120]. This structure is also intermediate in several recombination events in eukaryotic cells [121]. When a DSB is detected in the cell, the cell cycle is stopped or arrested for its damage to be repaired [119] to avoid the serious consequences to the cell that an unrepaired DSB can cause, such as chromosome rearrangements, chromosome loss, or cell death [121]. Prokaryotes and eukaryotes have evolved two main pathways to repair DSBs: non-homologous end joining (NHEJ) and homologous recombination (HR) [121-122].

## 6.1. Non-Homologous End Joining (NHEJ)

NHEJ promotes the ligation of two DNA ends without homology between them. If the DNA damaged is repaired by this pathway, the integrity of DNA molecule is re-established, but the sequence is altered because of the nucleotides additions or deletions at the junction [123]. In plants, as in all the higher eukaryotes, DSBs in somatic cells are mainly repaired by NHEJ, but depending on the conditions of the cell, like the phase of the cell cycle and availability of homologous repair templates, DSBs can also be corrected by homologous recombination (HR) [120, 124]. Bacterial homologs of all DNA repair pathways were found in the genomes of *Arabidopsis* and rice, but not for all the proteins that form the NHEJ pathway up to now [46]. There are more data about this repair pathway in mammals. It is known that the KU complex (KU70/KU80) recruits DNA-dependent protein kinases (DNAPKcs) that activate nucleases, DNA polymerases (polymerase λ or μ), and the XRCC4-Lig4 complex to the sites of the lesion [125]. This was identified in plant orthologs of KU70, KU80, LIG4, and XRCC4 [144-126].

Another process of error-prone DSB repair was reported by direct ligation of extremities of DNA, without the participation of the KU proteins—microhomology-mediated end joining (MMEJ). This pathway uses a microhomologous sequence with the length of 5-25 base pair (bp) in the alignment of the DNA ends, before the ligation, which causes deletions in the flanking region of the DSB [127].

It was recently reported that PARPs (Poly-ADP-ribose polymerases) are involved in several processes and play a role in MMEJ in *Arabidopsis thaliana* [128]. Homologs of *PARP1* and *PARP2* were identified in plants by [129]. PARP1 is one of the proteins that have a role at base excision

repair [130]. There is evidence that PARP is also involved in abiotic stress response, as it was observed that transgenic plants of *A. thaliana* and *Brassica napus* with *PARP* overexpression were more resistant to abiotic stress [131]. In order to investigate whether these proteins are involved in MMEJ, mutants *parp1*, *parp2*, *parp1parp2* (*p1p2*), *ku80* and *parp1parp2ku80* (*p1p2ku80*) were analyzed for the MMS sensitivity (a genotoxic agent) and the *in vitro* ability to join linear DNA [128]. It was observed that the *p1p2* double mutant was more sensitive, and this mutant had the root length about half of what was observed in the wild type. The phenotype for the triple mutant *p1p2k80* was stronger than for the double mutant *p1p2*. To test whether the PARP protein had function in MMEJ, an end-joining experiment using a substrate containing 10 bp microhomology sequences was done with cell extracts from wild-type, *ku70*, *ku80*, *p1p2* and *p1p2k80* mutants. It was observed in this experiment that *p1p2* and *p1p2ku80* mutants had two to 20-fold less MMEJ products while *ku70* and *ku80* mutants had four-fold more of these products when compared with the wild type. This demonstrates that PARP proteins are involved in this DNA repair, and a possible competition from PARP and KU proteins may determine which DNA repair pathway may be used to correct these lesions [128].

The *KU70* gene homolog in rice was identified by genome comparative analysis [153]. Studies using two-hybrid and pull-down assays demonstrated an interaction of OsKU70 and OsKU80 proteins, and the importance of OsKU70 for plant development. It was also observed that the *Osku70* mutant was more sensitive to MMS treatment than wild-type plants, suggesting its participation in the DSB repair. Recently, *KU70* from *Vitis vinifera* was cloned and characterized [133]. The mRNA was found in leaves, stem, and roots and its expression increased in response to gamma irradiation.

*Agrobacterium tumefaciens* is known to transfer the T-DNA region to the plant genome. The T-DNA is converted in double-DNA strand and it is integrated into the host genome [134]. One mechanism proposed for this integration involves the DNA repair pathway NHEJ using the KU80 protein [135]. The *Agrobacterium* plant transformation using *Arabidopsis ku80* mutants showed a decrease in stable transformation and the plants overexpressing *KU80* had increased in T-DNA integration and MMS resistance. However, up to now this mechanism is not clear.

It was verified in rice that the NHEJ pathway is involved in the *Agrobacterium* stable transformation. The mutants lacking NHEJ-related genes *ku70*, *ku80*, and especially the *lig4* mutant presented a reduction in frequency of stable transformation [137]. In tobacco, the role of XRCC4, another NHEJ factor, was observed in a complex with Lig4 to seal the two ends of the DSB during in the T-DNA integration [138]. In this work, it was also observed by yeast two-hybrid assay that the protein VirE2 (from *Agrobacterium*) interacts with XRCC4, then it is proposed that the VirE2 protein may act in the inactivation of XRCC4, then delaying the final step of NHEJ repair, creating an opportunity for T-DNA integration [138].

Besides, *AtPolλ* has been associated to the NER pathway in the repair of DSBs induced by high salinity and mitomycin C (MMC - a DNA cross-linker agent) [17, 118]. An increase in the levels of *AtPolλ* was observed after treatment with NaCl or MMC. On the other hand, for *AtPolλ* mutants had an increase in sensitivity to these treatments. These data propose a possible role of DNA polymerase in DNA repair for these two genotoxic agents. Furthermore, results obtained from yeast two-hybrid assays showed a protein interaction between AtPolλ and

XRCC4-Lig4 [17]. All these data have demonstrated the role of NHEJ in plant transformation as well as its role in abiotic stress.

## 6.2. Homologous Recombination (HR)

HR is a repair pathway that uses a homologous donor molecule, being, in principle, a DSB repair pathway which is not mutagenic, since all the genetic information can be recovered in the case that the sequence of the template is identical to the broken site [120]. In the HR process many proteins are recruited. PARP1 and PARP2 proteins are considered a sensor for DSBs and then these proteins are important for the recruitment of the MRN complex, which consists of MRE11–Rad50–NBS1 [139-140].

One of the proteins from the MRN complex, *AtMRE11*, has distinct roles in meiosis [141]. Two *Atmre11* T-DNA mutants (*Atmre11-2* and *Atmre11-4*) were analyzed. These mutants produced truncated forms protein with a small difference in size at the C-terminus region. The *Atmre11-2* had a normal phenotype; on the other hand, the *Atmre11-4* mutant had sterility, yellow leaf margins, and misarranged mesophyll cells. To investigate if these phenotypic differences were associated with abnormalities at the cellular or chromosome level, cytogenetic analysis was performed. After this analysis, it was observed that the mitotic phases for *Atmre11-2* and wild-type plants were fine, but for *Atmre11-4* it was observed chromosomal breaks and fusions suggesting genome instability. Since *Atmre11-4* plants were sterile, it was analyzed the pollen mother cells. It was observed problem in the meiosis process, since the regular prophase was not observed. *In silico* analysis proposes that the *Atmre11-4* T-DNA mutant may not have the RAD50 interaction domain in the sequence [141].

For the homologous recombination process, it is important that a stretch of single strand DNA (ssDNA) be produced before the strand invasion. A 5′-3′ degradation of DSB occurs, generating 3′ssDNA overhangs. This process is called end resection and it requires the action of nucleases and helicases. In yeast and mammals the kinases MEC1/ATR, TEL1/ATM, Rad53/CHK1, Cdc5/PL, and CDKs (cyclin-dependent kinases) are involved in this process [142]. Five RAD51 paralog proteins are involved in the process of recombination repair in mammals: RAD51B [143], RAD51C [144], RAD51D [145], XRCC2 [146], and XRCC3 [147]. RAD51C-XRCC3 form one complex and RAD51B-RAD51C-RAD51D-XRCC2 form another complex [148]. In addition to these five genes, *Arabidopsis* and rice have four more *recA-like* genes [148-150].

In *Arabidopsis*, it was observed that AtRAD51 is necessary for double-strand break repair, as the *Atrad51c* mutant has sensitivity to γ-radiation and cisplatin during development, besides it has lower HR frequency and higher chromosome fragmentation in somatic cells [151]. The *RAD51D Arabidopsis* homolog in rice, *OsRAD51D*, was characterized by [152] and it has an important role for reproductive development. The *Osrad51d* mutant presented normal vegetative growth but it had defects in the reproductive development. The *OsRAD51C* characterization showed that the mutant plants had male and female sterility. The cytological analysis showed that this phenotype was a consequence of fragments produced during early meiosis [153]. The DNA-DAMAGE REPAIR/TOLERANCE 100 (DRT100) is a RECA protein identified in plants [154]. In grapevine, it was observed that this protein plays an important role in DNA damage repair and toleration against UV-B irradiation [155].

During HR, in a few cases, there is a second strand capture after the strand exchange, forming a structure called Holliday junction (HJ) that consists of four DNA strands of two homologous chromosomes or sister chromatids [156]. The removal of this structure is important to correct chromosome segregation. The enzymatic processing of recognition and cleavage or resolving these structures is done by resolvase proteins [157-158]. In *Arabidopsis*, the resolvase AtGEN1 and AtSEND1 are members of the Rad2/XPG family and these proteins work similar as the resolvase in *E. coli* [159].

One important aspect for plant survival and reproduction is the accurate transmission of chromosomes during meiosis. The **s**tructural **m**aintenance of **c**hromosomes (SMC) proteins are essential for the architecture and organization of chromosomes, and these proteins are also responsible for sister chromatid cohesion, chromosome condensation, and HR during meiosis [160]. The complex SMC5/6 is one of the SMC complexes and it is related to HR damage repair [161]. MMS21, a SUMO 3 ligase, is a subunit of this complex. The function of *AtMMS21* in HR repair was verified by [162]. In this work, it was observed that *Atmms21* mutants presented sensitivity to MMS, cisplatin, and γ radiation. It was also observed that in *Atmms21, atm* double mutant has a severe morphology defect and it was verified that the HR frequency is reduced in this mutant line. It was verified that *mms21* mutants had a disrupted meiosis. All this data support the role of *AtMMS21* in the HR repair pathway [162-163].

# 7. DNA repair in organelles

Plants need to maintain the genome stability of the DNA in three compartments: nuclei, mitochondria, and chloroplast. The endosymbiotic theory postulates that these organelles originated from a prokaryotic organism that developed a symbiotic relationship with a eukaryotic host. In the course of time, chloroplast and mitochondrial genomes have been reduced and studies have shown that the nuclei genome integrated DNA from these organelles' genomes.

Many studies have been done on nuclei, but little is known about plant organelle DNA repair (mitochondria or chloroplast) [15, 31]. Comparative analysis proposed that in the *Arabidopsis* genome 17% and 10% of all genes related to DNA repair and recombination (DRR) have chloroplast and mitochondrial origin, respectively. The same investigation was done in the rice genome and it was seen that 19% and 17% of DRR genes have chloroplast and mitochondrial origin, respectively [46].

## 7.1. Photoreactivation (DR)

This pathway may be an alternative mechanism to correct NER lesions. It has been shown that DR is functional in mitochondrial and chloroplast plant genomes. It was observed that CPDs and 6-4 photoproducts were corrected after *Arabidopsis* leaves were UV radiated and transferred to blue lights (photoreactivation) [164]. In spinach leaf chloroplast no photolyase activity was detected [165]. These data showed that more work is necessary to understand all the mechanism in organelle.

## 7.2. BER

In plant organelles the BER pathway is also not completely understood. Some data have shown that this pathway occurs in mitochondria and chloroplast. It has been observed that the 8-oxoG lesion in mitochondria needs the OGG1 protein to correct it. Furthermore, it was verified that the mitochondria and chloroplast have a functional Uracil-DNA-glycosylase (UNG) [166]. Furthermore, there is also the presence of thymine glycol DNA glycosylase proteins [167]. In relation to AP endonuclease, it was verified in *A. thaliana* and *Solanum tuberosum* that mitochondria and chloroplast have AP functional endonuclease [166].

With regard to short or long patch pathways, at least the short patch was detected in mitochondria [166]. And for chloroplast, it was identified the presence of two homologs for endonuclease III and one AP endonuclease [167]. For DNA polymerase $\gamma$, duplication was observed: POL$\gamma$1 (At3g20540) and POL$\gamma$2 (At1g50840). Both sequences had a dual targeting – chloroplast and mitochondria. On the other hand, it was observed for DNA ligase 1 an alternative splicing producing proteins that were targeting nuclei and mitochondria, but it is not clear about chloroplasts [168].

## 7.3. NER

In yeast it has been proposed that it is possible that the NER pathway does not exist and that some lesions may be corrected by other pathways or alternative mechanisms [37, 169-170].

## 7.4. MMR

The role of the MSH1 sequence was analyzed in *Arabidopsis* mitochondria and it was verified that this protein may have a role in the recombination process. It is not clear how MMR happens in chloroplast and mitochondrial. It is proposed that BER may have an overlap in these organelles [171].

## 7.5. NHEJ and HR

*Arabidopsis* mutants for the polymerase *PolIA* and *PolIB* showed the importance of these genes in organelles as it was observed that these mutants had problems to set seeds [172]. Moreover, single mutant for *polIA or polIB* were viable, showing that each gene partially compensates the function of the other [173]. The observation of higher levels of DNA damage in chloroplasts of *polIB* mutants compared to mitochondria suggests the specialized role of PolIB protein in this organelle [172].

Furthermore, it was identified in the *Arabidopsis* genome five putative homologues of the bacterial RecA that were predicted to be targeted to mitochondria or chloroplasts [148-149, 154, 174-175]. In the study done by [176], two RECA chloroplast-targeted proteins were analyzed using T-DNA mutants. Although *drt100-1* mutant had the same phenotype, it was observed 24-fold reduction in mRNA expression in the *drt100-1* genotype when compared to wild-type plants. However, this reduction did not alter the structure or the amount of cpDNA presented in wild-type and mutant plants [176]. The analysis of another *RECA*

mutant - *cprecA* also showed no morphological difference between immature seedlings and the wild type, but only after the fourth generation it was observed change coloration and tissue necrosis in leaves [176].

Despite the existence of the homologous recombination DNA repair pathway in mitochondria and chloroplasts, it was verified in *Arabidopsis* DSBs caused by ciprofloxacin treatment produced DNA rearrangements with microhomology at their junctions. This suggested a DNA repair pathway through a microhomology-mediated break-induced replication (MMBIR) [177]. One of the proteins that act in this pathway is the single-stranded DNA-binding proteins WHIRLY (WHY) [178]. The role of WHIRLY in the stability of the organelle genome was observed by [179]. Later, it was proposed by [209] that these proteins would prevent the error-prone DNA repair binding and protecting resected ends at break sites, independent of the sequence.

The genomic comparative data from coding and non-coding sequences from the mitochondria genome of two *Arabidopsis* ecotypes showed that DNA mitochondrial is repaired by different pathways and these regions (coding and non-coding) had different mutation rates and spectra [180-181]. Recently, it was verified that coding regions that are repaired by inaccurate mechanisms will be eliminated by natural selection while the consequences of inaccurate DNA repair in non-coding regions (e.g. mutations) will be kept in the genome [182]. Then, this data would explain the low mutation rates and rearrangements in genes observed in non-coding regions.

## 8. Plant-specific factors involved in DNA repair

Triggering the DNA repair machinery in response to lesions in DNA is essential in order to maintain the genome integrity [183]. The cell cycle may be arrested to allow that the DNA damage is repaired before entering the mitosis process. The perception of DNA damage activates proteins that promote the suppression of the cyclin-dependent kinase (CDK) activity and consequently arrest the cell cycle process [184]. B-type CDKs (CDKBs) are plant-specific, under cell-cycle control, and divided into CDKB1 and CDKB2 [185].

Endoreplication or endoreduplication is a common modification of the cell cycle, which consists of multiple rounds of replication from the nuclear genome without cytokinesis [186]. A genotoxic stress may promote endoreduplication in plants and animals, but the function of this process in animals remains unclear, as endoreduplication can block mitosis and may be associated with tumor progression [187]. In plants, the process of endoreplication is important, as it may be observed in *Arabidopsis* trichomes. The precursor cells need the endoreduplication process to complete the development [186]. It has been observed that DSBs enhanced the endoreduplication process in *Arabidopsis* [188]. Also observed was a reduced expression of CDK and cyclin B during endoreduplication in trichomes, cells of the epidermis, or mesophyll cells [189].

One of the largest families of plant-specific transcription factors is NAC, and AtSOG1 is one of the proteins that belong to this family [190]. AtSOG1 protein has been associated with transcription, cell-cycle arrest and programmed cell death, and genome stability [191]. Although there is no similarity in p53 and *AtSOG1* sequences, or in their gene regulation, their functions are similar [192]. The AtSOG1 has also been associated with the endoreduplication process after a genotoxic stress that induces DSBs [188].

ATAXIA TELANGIECTASIA MUTATED (ATM) and RAD3-RELATED (ATR) both are protein kinases that act as DNA damage sensors in mammals [193]. In *Arabidopsis*, mutants were sensitive to γ radiation or other genotoxic agents and these mutants also had problems in DNA replication. However, these mutants were viable [190, 194]. It has been proposed that biogenesis of small interfering RNAs, DNA repair, and tolerance to stress are connected [194, 195].

The work [196] described MAINTANCE OF MERISTEMS (MAIN), one of the 14 members of the DUF1723 protein family in *Arabidopsis*, mainly expressed in meristematic cells. The DUF1723 domains are plant-specific and they were described in a work with WRKY and GCM1 transcription factors [191]. It was proposed that MAIN was essential to the genome stability of meristematic cells because *main* mutants presented a high level of DNA damage when compared to the wild type [196]. Three *MAIN*-related genes are present in *Arabidopsis*, forming a subfamily of plant-specific aminotransferase-like proteins. These genes were named *MAINLIKE 1* (*MAIL1*), *MAIL2* and *MAIL3*, and their proteins are localized in the nuclei [197]. MAIN and MAIL1 proteins had 68% of sequence similarity. The mutant *mail1* presented dead cells in the root apical meristem (RAM), as observed in mutants that display genomic instability. It was not established whether cell death was induced in this mutant or whether DNA damaged led to cell death, because this happened without the participation of the ATM/ATR signaling pathway [197].

Plant mitochondria present a striking homologous recombination activity [181]. Therefore, this organelle has plant-specific ssDNA-binding proteins that function in this process like the Organelle single-strand binding protein (OSB) [198] and the WHIRLY protein (WHY) [199]. OSB1, in *Arabidopsis*, was reported as important to the genome stability of mitochondria [198]. The proteins WHIRLY (WHY) may be found in mitochondria (WHY2) and chloroplasts (WHY1 and WHY3) [199]. The report by [200] described Organellar DNA-binding protein 1 (ODB1), another plant-specific mitochondrial ssDNA-binding protein. The role of OSB1 was similar to that of Rad52, in vitro, in homologous recombination - the stimulation of the pairing of complementary sequences. Moreover, the similarity between the DNA-binding domain of ODB1 and RAD52 suggests that ODB1 is involved in the homologous recombination repair pathway.

# 9. DNA damage in plant cells

Stem cells in plants are maintained in two regions: shoot apical meristem and root apical meristem, both of which may be referred to simply as meristem. The division of meristem

allows plants to grow continually and produce new organs and tissues. These cells may divide for self-renew and also may produce new tissues and organs throughout their lifetime. For example, in shoot apical meristem these cells may produce leaves during the vegetative stage; however, when the plant reaches the reproductive stage, the meristem now produce flowers [200]. Furthermore, like animal stem cells, plant stem cells are kept in microenvironments known as stem cell niches, where signals act to organize and keep the adjacent stem cells [201]. In animals, it is known that stem cells have a low tolerance for DNA lesions. This process leads to apoptosis in order to avoid cancer and protect germline. In plants this process, as well as the tolerance for DNA damage accumulation at meristem cells, is not well-known [200]. There are some differences between animals and plants with regard to programmed cell death (PDC), as some genes/proteins have not yet been identified [202-204]. It has been observed that PDC is dependent on ATM and ATR [205]. [206] identified the *MERISTEM DISORGANIZATION 1* (*MDO* 1) gene that may interact with ATM kinase and is essential for maintenance of plant stem cells by reducing DNA lesions. In *mdo 1-1* mutants an elevated rate of double strand breaks (DSB) was observed, supporting the hypothesis that *MDO* 1 is *ATM* dependent. Furthermore, also observed was the importance of the *MAINTENANCE OF MERISTEMS* (*MAIN*) gene that produces a nuclear protein that acts as a transcription factor or as chromatin remodeling or DNA replication. [207] proposed that this protein may also be important for genome maintenance of division cells.

Considering that plants are sessile organisms, they are exposed to different environmental conditions (abiotic and biotic stress) as well as exogenous mutagens that may increase ROS, which may induce DNA lesion and increase the accumulation of DNA mutations in cells as described above. [208] worked with Arabidopsis mutants at the MMR pathway in order to test the genome maintenance and integrity. They observed in *Atmsh2-1* mutants a low rate of mutation loading, and this was unable to correct errors due to DNA replication. Only at G5 (5$^{th}$ generation) did they observe problems in seed production and morphological changes such as light green leaf, crinkled leaf, early flower, dwarf, stresslike, sterile plants. These authors calculated the mutation frequency and proposed an error rate of $10^{-7}$ to $10^{-6}$, or one base substitution in 30, 000 to 300, 000 bp. [209] also analyzed the mutation frequency in *Arabidopsis* plants exposed to salinity stress. In their experiments they observed variants in mutation and epigenetic variants only at the 10$^{th}$ generation. These were wild-type plants exposed or not (control plants) to saline condition. They analyzed their data by a new sequencing approach (Illumina) and by bisulfate sequencing (for epigenetic variants). The data analysis allowed them to propose three hypotheses to explain the rate and pattern of mutations observed when Arabidopsis plants were exposed to an abiotic stress. The first hypothesis is related to errors occurring because of DNA replication, the second is based on plant metabolism due to ROS, which increases DNA lesions, consequently increasing the rate of mutation; and the third hypothesis is associated with DNA repair. These authors propose similar SOS and SIM mechanisms that permit an increase in DNA mutation in order for the organism to survive. These data showed that this field is not well known, despite its economic importance, and the

environmental factors have a huge influence on this mutation rate. Further study is needed in order to improve new cultivars and increase seed production.

## 10. Final considerations

DNA repair has been studied since 1970 in bacteria, but in plants the first gene was cloned only in late 80. Then, the worry about the ozone layer reduction and UV light that may affect plant production, DNA repair in plants came to have a place in this field. Genomics and comparative genomics were powerful tools for searching for homologous sequences in genes or proteins in plant genomes that are well characterized in bacteria, yeast, and humans. This data allowed identifying that many gene or protein sequences were also present in plant models such as *Arabidopsis* and rice. Considering the results from evolution, it has been observed that gene duplication happened in plants. Some data revealed the Whole Genome Duplication (WGD) process in plants that was responsible for the loss or duplication of some gene sequences. The loss may be different mutations on the sequence and the duplication of these sequences may acquire new functions or new organelle targeting by either a sub-functionalization or a neo-functionalization process [210, 211]. In the case of MMR, for example, it was determined that MutS homologs were duplicated in plants and the different proteins target different organelles (Table 1). The work with AP endonuclease in sugarcane identified gene duplication in the genome; and by *in silico* analysis they observed that one sequence may target chloroplasts or mitochondria and the sequence duplicated may target the nuclei [95]. Moreover, this duplication event also changed gene regulation as observed in gene expression. In rice it was observed a triple targeting [39]; the mRNA may be translated into one protein and according to the N-terminal sequence this protein may target nuclei, mito-chondria, or chloroplasts. Mutants in different genes in DNA repair pathways generally have problems in germination, setting seeds, plant development, or mitoses or meiosis. Even during the *Agrobacterium* T-DNA transfer process, the DNA repair pathways have an important role. Moreover, the data presented here show a connection between stress (abiotic or biotic) and DNA repair. It has been observed that the overexpression of DNA repair genes in transgenic plant makes these plants more tolerant of drought, salinity, and other stress conditions [18, 212-214]. The other aspect of plant metabolism in which DNA repair pathways have importance is the seed germination process, where there is a burst in ROS. Another difference found in plants is that these organisms have FPG and OGG1 sequences [215, 216].

Then, all these data presented here show how important endogenous and exogenous signals are for the plant response and how these signals are connected to make a interconnected network that helps plant make the fine adjustment in their metabolism in order to tolerate the adverse conditions to which these organisms are exposed continually. Moreover, plants have become an interesting model for research because of their sessile style, photosynthesis, the ROS presence and a possible connection among ROS x stress x DNA repair x food importance. Much progress has been made, but a lack of knowledge still remains; consequently, much work needs to be done.

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