Chromatin dynamics during DNA damage and repair in plants: new roles for old players

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Highlight

In this review, we summarize recent data demonstrating that chromatin modifying enzymes are crucial during the DNA damage response.

Abstract

The genome of plants is organized into chromatin. The chromatin structure regulates the rates of DNA metabolic processes such as replication, transcription, DNA recombination and repair. Different aspects of plant growth and development are regulated by changes in chromatin status by the action of chromatin remodeling activities. Recent data have also showed that many of these chromatin associated proteins participate in different aspects of the DNA damage response, regulating DNA damage and repair, cell cycle progression, programmed cell death and the entry to the endocycle. In this review, we present different examples of proteins and chromatin modifying enzymes with roles during DNA damage responses, demonstrating that proper and fast changes in the chromatin structure are essential to maintain genome stability.

Keywords: chromatin remodeling, plant development, flowering time, histone modification, DNA damage response, recombination, transposon activation.

Introduction

Genetic information in the DNA of eukaryotic organisms is compacted into chromatin to allow the genome to fit inside the nucleus (for a revision, see Pfluger and Wagner, 2007). The basic unit of chromatin is the nucleosome core particle, which is formed by wrapping 147 bp of DNA around an octamer of histone proteins composed of two H3-H4 dimers, flanked by two heterodimers of histones H2A and H2B. The structure of each histone consists of a characteristic globular domain, called a histone fold motif that mediates its interaction with other histones or the DNA. These histone fold domains are flanked by short flexible domains, corresponding to the amino-terminal and carboxy-terminal tails, which extend beyond the nucleosome core particles. These histone tails are critical for the regulation of diverse biological processes, as several post-translational modifications occur at different amino acid residues of these tails. These post-translational modifications directly affect chromatin organization, modulating intramolecular and intermolecular folding of nucleosomes and affecting compaction to different levels and/or serving as platforms to recruit other factors that can, in turn, mediate chromatin changes (Dorigo *et al.*, 2003; Gordon *et al.*, 2005; Gardner *et al.*, 2011; Peterson and Almouzni, 2013). In addition, the exchange of canonical histones with variant forms provides an additional contribution to the diversity of nucleosome types present in the genome (Gurard-Levin *et al.*, 2014; Maze *et al.*, 2014; Otero *et al.*, 2014). These variants directly alter nucleosome stability, the interaction between nucleosomes or between chromatin fibers at different moments during the cell cycle or in particular cell types (Probst *et al.*, 2020).

The nucleosome structure is a barrier to proteins that participate in DNA metabolic activities, including transcription, replication, and DNA recombination and repair. To allow these processes to occur, chromatin must be restructured, and this is accomplished by three distinct processes: first, covalent modification of histones, predominantly in the tails, by histone modifying enzymes; second, chromatin remodeling complexes that alter histone–DNA interaction, facilitating nucleosome sliding to a different position, and inducing conformational changes in histone–DNA interactions, and histone loss or nucleosome disassembly; and third, methylation of DNA cytosine residues that alters binding of proteins (Pfluger and Wagner, 2007; Eberharter and Becker, 2002; Vaillant and Paszkowski, 2007). The epigenome, which consists of the genome-wide distribution of the epigenetic marks, can be considered as a signal integration platform that can respond to both intracellular and environmental signals by changing dynamically the local chromatin structure (Badeaux and Shi, 2013; Reinders *et al.*, 2009). This plasticity is essential for cell differentiation and development; and epigenome

maintenance is critical for the robustness of phenotypic traits, as failure to maintain epigenome integrity can have deleterious consequences (Zane et al., 2014, Meinke, 2020). Among DNA metabolic activities, DNA damage repair is unique because it is generally non-programmed, as DNA damage can occur anywhere in the genome at any time. In addition, DNA repair mechanisms are also versatile, as different types of DNA lesions can happen (Britt, 1996). After DNA damage takes place in plants, the activation of the DNA damage response pathway (DDR) occurs. The DDR is modulated by the activation of two related kinases: ATAXIA-TELANGIECTASIA MUTATED (ATM), which is mostly activated by double-strand breaks in the DNA, and ATAXIA TELANGIECTASIA-MUTATED AND RAD3-RELATED (ATR), which is mostly active when single-strand breaks or stalled replication forks occur, such as CPDs and 6-4PPs (Culligan *et al.*, 2006). Both ATM and ATR can then modulate the activation of different downstream regulators involved in distinct responses like DNA repair, cell cycle arrest, endoreduplication, or programmed cell death (Culligan *et al.*, 2006).

Therefore, differentiation, growth and development of plants can be significantly affected after DNA damage, which can occur after exposure to multiple genotoxic agents to which plants are naturally exposed to, such as UV radiation, microbial pathogens and other biotic and abiotic stresses. Moreover, different pathways in plant development are modulated by changes in the epigenome, and many of these changes are also modulated by environmental conditions that can produce DNA damage. Thus, in this review, we present and discuss recent data that show how chromatin remodeling proteins that regulate different aspects of DNA metabolism can also participate in the DDR. We review recent progress in delineating by which mechanisms and to what extent epigenome integrity is affected and restored after DNA damage, and how this is related to other pathways and processes important in plant growth and development.

Role of chromatin dynamics in the control of DNA repair genes expression

While chromatin structure can affect DNA repair rates, it can also modulate the expression patterns of transcription of DNA repair enzymes. This has been demonstrated for different Arabidopsis mutants in genes encoding distinct chromatin remodeling activities, which showed altered expression of transcripts encoding proteins in the DNA damage response. For example, in *Arabidopsis thaliana*, FASCIATA 1 (FAS1) and FASCIATA 2 (FAS2), together with MULTICOPY SUPRESSOR OF IRA1 (MSI1), are subunits of the Chromatin Assembly Factor (CAF-1) complex (Kaya *et al.*, 2001; Henning *et al.*, 2003). CAF-1 is a histone

chaperone complex that mediates nucleosome formation by tetramerizing and depositing histones H3 and H4 onto the DNA during and after replication and DNA repair. Interestingly, these mutants show DNA damage-related phenotypes and also altered expression of some genes, including transcripts for DNA repair activities, suggesting that, at least in part, some of the altered DNA damage responses in CAF-1 deficient plants could be due to improper expression of DNA repair enzymes (Jiang and Berger, 2017; Muñoz-Viana *et al.*, 2017; Otero *et al.*, 2016).

On the other hand, ANTI-SILENCING FUNCTION1 (ASF1) is another histone H3/H4 chaperone that participates in various DNA- and chromatin-related processes. Arabidopsis has two ASF1 encoding genes, *AtASF1A* and *AtASF1B* (Zhu *et al.*, 2011; Lario *et al.*, 2013). *ASF1A* and *B* deficient plants accumulated more DNA damage after hydroxyurea or UV-B treatments than WT plants (Zhu *et al.*, 2011; Lario *et al.*, 2013); and *asf1ab* double mutants showed altered expression of some genes, including cell cycle genes, DNA damage checkpoint and repair genes, such as *ATM*, *ATR*, *PARP1* and *PARP2*, and genes of the homologous recombination pathway (Zhu *et al.*, 2011). Similarly as CAF-1 deficient plants, altered expression of DDR genes could be responsible for the increased sensitivity of these plants to genotoxic stress. However, neither CAF-1 nor ASF1 deficient plants showed altered expression of photolyases or nucleotide excision repair enzymes, which are the most important repair pathways of UV-B induced damage (Lario *et al.*, 2013; Maulion *et al.*, 2019). Thus, at least during the repair of cyclobutane pyrimidines dimers (CPDs) that are produced after UV-B exposure, these histone chaperones probably participate in DNA repair mostly by altering chromatin structure. Therefore, it is possible that this could be the case for at least some of the chromatin remodeling proteins with a role in the DDR. Thus, some chromatin remodeling proteins can participate in the DDR by regulating the expression of proteins in this pathway, by altering chromatin structure to facilitate repair, or both.

Histone covalent modifications regulating plant development also modulate the DNA damage response

Flowering at a correct moment during plant development is crucial for proper plant reproduction. Flowering time is dependent not only on endogenous parameters but also on environmental conditions. Different pathways regulate flowering time, many of them are modulated by changes in the chromatin structure of flowering time genes. One of the pathways that regulate flowering time is the autonomous pathway, which promotes floral

transition independently of the day length through the repression of the central flowering repressor FLOWERING LOCUS C (FLC). FLC blocks floral transition by repressing flowering time integrators such as FLOWERING LOCUS T (FT). One important regulator of the autonomous pathway is NUCLEOSOME/CHROMATIN ASSEMBLY FACTOR GROUP C4/MULTICOPY SUPPRESSOR OF IRA4 (NFC4/MSI4), which reduces *FLC* expression. NFC4/MSI4 is also known as FVE and represses *FLC* expression through its interaction with a CLF-Polycomb Repressive Complex 2 (PRC2) in Arabidopsis. FVE is necessary for H3K27 trimethylation which occurs locally on *FLC* and *FT*, decreasing the expression of both genes, and therefore regulating flowering time (Pazhouhandeh *et al.*, 2011).

Interestingly, FVE is also important during DNA damage after UV-B exposure. *FVE* is significantly induced by UV-B radiation; and Arabidopsis plants deficient in its expression, and also maize plants with decreased expression levels of the FVE-homologue gene *NFC102*, accumulated more damaged DNA than WT plants. In addition, these plants were affected in the accumulation of pigments by UV-B (Campi *et al.*, 2012). In fact, decreased *FVE* levels impaired the increase in global histone acetylation that accompanies DNA damage after UV-B exposure in maize and Arabidopsis (Casati *et al.*, 2008; Campi et al., 2012). This increase in histone acetylation has been proposed to be required for proper DNA repair after UV-B exposure; as plants treated with an inhibitor of histone acetyltransferases, curcumin, previous to the UV-B treatment, showed deficiencies in DNA repair (Casati *et al.*, 2008; Campi *et al.*, 2012).

Moreover, Arabidopsis mutants in two histone acetyltransferases from the MYST family, *ham1* and *ham2*, also showed increased accumulation of CPDs after UV-B exposure (Campi *et al.*, 2012). In Arabidopsis, HAM1 and HAM2 work redundantly to acetylate histone H4 lysine 5 (H4K5ace) *in vitro* (Earley *et al.*, 2007). In humans, a very well characterized member of the MYST family is TIP60 (Tat-interacting protein of 60 kD), which has important roles during DNA repair acetylating histone H4 when DNA is damaged, and also trans-activating genes in response to DNA damage (Squatrito *et al.*, 2006). Thus, the role of MYST acetyltransferases in DNA damage repair seems to be conserved through evolution (Campi *et al.*, 2012). Interestingly, *amiRNA-HAM1/2* transgenic plants with decreased expression of both *HAM1* and *HAM2* showed early flowering and reduced fertility (Xiao *et al.*, 2013). These plants showed decreased expression of *FLC* and its homologues, *MADS-box Affecting Flowering genes 3/4* (*MAF3/4*). In contrast, *HAM1* overexpression caused late flowering and elevated expression of *FLC* and *MAF3/4*. H4 hyper-acetylation at *FLC* and *MAF3/4* associated chromatin was decreased in *amiRNA-HAM1/2* and increased in *HAM1* overexpression lines, suggesting that HAM1 and HAM2 may regulate flowering time by acetylating histone H4 associated to *FLC* and *MAF3/4* (Latrasse *et al.*, 2008; Xiao *et al.*,

2013). These results demonstrate that the regulation of flowering time is highly associated with DNA damage responses through chromatin changes, in particular by altering the acetylation state of histones. Thus, increased acetylation in particular histone residues may make chromatin more accessible both for repair and activation of transcription to allow flowering.

In addition, it was recently demonstrated that Arabidopsis plants grown under UV-B conditions show a delay in flowering time (Dotto *et al.*, 2018; Arongaus *et al.*, 2018). Interestingly, UV-B radiation downregulates the expression of *MSI1* and *CURLY LEAF* (*CLF*), two of the components of the Polycomb repressive complex 2 (PRC2; Dotto *et al.*, 2018). As a consequence, after UV-B exposure, there is a decrease in H3K27me3 histone methylation of *MIR156* and *FLC* genes, therefore modifying the expression of several flowering time genes that causes a delay in flowering time. Also, *CLF,* which encodes the methyl-transferase subunit of PRC2, has a role during DNA damage after UV-B exposure (Ré *et al.*, 2020). In fact, *clf* mutants show increased Argonaute 1 (AGO1) ubiquitination and enhanced degradation of this protein in specific tissues. AGO1 selectively recruits mostly microRNAs but also other siRNAs regulating gene silencing at the post-transcriptional level. In plants, ~21 nucleotide long miRNAs are loaded into AGO1 to assemble a functional RNA-induced silencing complex that scans for mRNAs with sequence complementarity to the loaded miRNA; this triggers mRNA silencing by cleavage or by translation inhibition (Achkar *et al.*, 2016). Recently, AGO1 was shown to participate in Global Genome Repair after DNA damage (Schalk *et al.*, 2017). After UV irradiation, AGO1 forms a complex bound to chromatin with DNA DAMAGE-BINDING PROTEIN 2 (DDB2), which participates in this pathway of DNA repair, facilitating the recognition of CPDs by specific 21-nt small interfering RNAs. Interestingly, CLF-mediated AGO1 also regulates DNA damage responses after UV-B exposure (Ré *et al.*, 2020). *clf* mutants are more sensitive to UV-C than WT seedlings, show increased programmed cell death in the root meristematic cells after irradiation with UV-B, and this phenotype is reverted in transgenic *clf-28* plants expressing AGO1 constitutively (Ré *et al.*, 2020). This result further validates the existence of a crosstalk between flowering regulation and DNA damage responses by chromatin remodeling activities. In particular, histone pos-traslational modifications seem to have a major role in this crosstalk.

Histone chaperones and their roles during DNA damage

Histone chaperones are a group of proteins that are able to bind histones and therefore regulate nucleosome assembly. Interestingly, a number of Arabidopsis mutant plants deficient in different histone chaperone activities have been shown to have defects in normal vegetative development, suggesting that these activities are essential for proper plant growth (Leyser and Furner, 1992; Zhu *et al.*, 2011; Kandasamy *et al.*, 2009). For instance, Arabidopsis *fas1* and *fas2* mutants were first identified because they showed stem fasciation and abnormal leaf shape, root growth, and flower organ number (Leyser and Furner, 1992). CAF-1 deficient mutants show severely disturbed organization of both shoot and root apical meristems, with an altered expression of both WUSCHEL and SCARECROW, each of these genes play important roles in the organization of shoot and root apical meristems, respectively (Kaya *et al.*, 2001). Interestingly, these mutants also show inhibition of mitosis, cell cycle arrest and an increase in endoreduplication, which are also responses activated during the DNA damage response (Chen *et al.*, 2008; Exner *et al.*, 2006; Ramirez-Parra and Gutierrez, 2007). In fact, CAF-1-deficient Arabidopsis plants show DNA damage-related phenotypes, which include shortening of telomeres, loss of 45S rDNA, increased homologous recombination and an altered DNA damage response after UV-B exposure (Mozgova *et al.*, 2010; Muchova *et al.*, 2015; Endo *et al.*, 2006; Gao *et al.*, 2012; Kirik *et al.*, 2006; Varas *et al.*, 2015; Maulion *et al.*, 2019). UV-B inhibition of leaf and root growth requires the participation of CAF-1, as *fas1* and *fas2* proliferating leaves show a lower inhibition of cell proliferation and decreased cell area; while *fas1* and *fas2* mutants show significantly shorter primary roots after UV-B exposure than WT plants (Maulion *et al.*, 2019). In this way, plant growth and development is regulated by the activity of chromatin remodeling complexes like CAF-1, and this regulation is affected under DNA damage conditions. As described before, CAF-1 deficient plants not only have modified positioning of nucleosomes, but they also show altered expression of some genes, including transcripts for DNA repair activities (Jiang and Berger, 2017; Muñoz-Viana *et al.*, 2017; Otero *et al.*, 2016). Therefore, these changes could both affect development and DNA repair.

As mentioned above, ASF1 is a histone H3/H4 chaperone that has two ASF1 encoding genes, *AtASF1A* and *AtASF1B* in Arabidopsis (Zhu *et al.*, 2011; Lario *et al.*, 2013). While single *asf1a* or *asf1b* Arabidopsis mutants did not show obvious phenotypic defects, double *asf1ab* mutants showed a dramatic inhibition of plant growth and abnormal vegetative organ development (Zhu *et al.*, 2011). These plants also had decreased leaf cell number, an S-phase delay in the cell cycle and reduced polyploidy levels. *ASF1A* and *B* deficient plants

accumulated more DNA damage after treatment with different genotoxic agents (Zhu *et al.*, 2011; Lario *et al.*, 2013). Interestingly, *ASF1A* and *ASF1B* are targets of regulation of E2F transcription factors, suggesting that ASF1A and ASF1B roles during cell cycle progression are through activation by E2F transcription factors (Lario *et al.*, 2013). Taken together, AtASF1A and AtASF1B have crucial roles both in the maintenance of genome integrity and also controlling cell proliferation during plant development. In addition, ASF1 plays a critical role in gametophyte development in Arabidopsis (Zhu *et al.*, 2011; Min *et al.*, 2019). ASF1 deficient plants are impaired in gametophyte development and in the acquisition of fertilization competency (Min *et al.*, 2019). In female gametophytes, ovules show aberrant development leading to gamete degeneration; while on male organs, *asf1* mutant pollen tube growth is inhibited, showing impaired fertilization to ovules (Min *et al.*, 2019). The role of ASF1 during reproduction seems to be different to that during cell cycle progression, as for gametophyte maturation and fertilization ASF1 is required for nuclei differentiation. Thus, the function of ASF1 during DNA damage responses is more related to its role during vegetative growth than to that during reproduction.

On the other hand, NUCLEOSOME ASSEMBLY PROTEIN1 (NAP1) is a conserved histone chaperone in yeast, humans and plants, and binds histones H2A and H2B *in vivo*. Multicellular organisms, including plants and animals, have several *NAP1* and *NAP1-RELATED PROTEIN* (*NRP*) genes, particularly Arabidopsis genome encodes 2 NRPs and 4 NAP proteins. In *Arabidopsis thaliana*, knockout mutants in the two *NRP* genes, *NRP1* and *NRP2*, are impaired in postembryonic root growth (Zhu *et al.*, 2006). The double mutant shows a disordered cellular organization in the root tips, which is probably due to an altered expression of genes involved in root proliferation and patterning in these plants. Besides the requirement of NRP1 and NRP2 in postembryonic root growth, these histone chaperones also participate in DNA damage responses and transcriptional gene silencing; and NRP1 accumulates in the chromatin of Arabidopsis plants after DNA breaks (Zhu *et al.*, 2006). During the DNA damage response, NRP1 also binds to cytochrome c, this binding with cytochrome c comptes with its binding to histones (Gonzalez-Arzola *et al.*, 2017). In addition, some NAP1 deficient plants also show sensitivity to DNA damaging agents such as UV-C. Interestingly, AtNAP1, 2 and 3 bind to genes that encode proteins that participate in DNA repair; in particular, binding is enriched at some genes involved in the Nucleotide Excision Repair (NER) pathway, whose expression is decreased in the triple mutants (Liu *et al.*, 2009). Moreover, plants with decreased levels of either *NAP1* or *NRP* show a reduction in homologous recombination (HR), which contrasts with the hyper-recombinogenic phenotype shown by CAF-1 deficient plants that are also deficient in root development (Gao *et al.*, 2012; Maulion *et al.*, 2019). Interestingly, simultaneous knockout mutants in the four *NAP1* and the

two *NRP* genes increased hypersensitivity to UV or bleomycin in Arabidopsis plants, demonstrating that NAP1 and NRP act synergistically activating somatic HR (Zhou *et al.*, 2016). On the other hand, NAP1 interacts with other chromatin remodeling factors to promote nucleosome assembly and disassembly in order to facilitate DNA repair (Kuryan *et al.*, 2012; Cho *et al.*, 2013). One of NAP1 interactors is INOSITOL AUXOTROPHY 80 (INO80) ATP-dependent chromatin-remodeling complex, which has a positive role regulating HR (Fritsch *et al.*, 2004). Recent data has shown that, in Arabidopsis, NRP and NAP1 synergistically promote HR upstream of INO80, and this occurs by mediating chromatin remodeling during DNA damage repair (Zhou *et al.*, 2016). Moreover, there is also a genetic interplay between INO80 and NRP1/2 regulating the root apical meristem activities (Kang *et al.*, 2019). Arabidopsis plants deficient in these 3 proteins were deficient in the auxin pathway, showing decreased histone H3 levels associated to PIN1, which encodes an important auxin efflux carrier. The triple mutant displayed a severe short-root phenotype, with increased programmed cell death in the root tips, double-strand break DNA damage and cortex cell enlargement. Therefore, this demonstrates that, despite these chromatin remodeling activities have different roles, they not only show a functional coordination during growth and development, but also they regulate DNA repair in plants.

Different chromatin remodeling activities are required during DNA repair

Various chromatin remodeling activities have been shown to have a role during plant development, for example ACTIN-RELATED PROTEIN 5 (ARP5), which is a subunit of the INO80 ATP-dependent chromatin-remodeling complex. *arp5* mutants are dwarf with smaller organs than those from WT plants and have smaller cells (Kandasamy *et al.*, 2009). Interestingly, these mutants showed a higher ratio of leaf stomata to epidermal cells and a delayed stomatal development compared to WT plants. Interestingly, *arp5* plants were hypersensitive to DNA-damaging reagents such as hydroxyurea, methylmethane sulfonate and bleomycin, demonstrating that ARP5 is required for both proper development and DNA repair. These common phenotypes are not shared by other chromatin remodeling proteins such as ARP4, which is also a component of the INO80 complex, demonstrating that there is specificity in the roles of different chromatin remodeling activities in plants.

In plants, DNA methylation and chromatin silencing regulate different aspects of DNA metabolism, such as transcriptional silencing of transposons and transgenes, regulation of imprinting and gene silencing (Vongs *et al.*, 1993; Bender, 2004; Chan *et al.*, 2005). Different

proteins have been demonstrated to participate in DNA silencing, and recent data have shown that some proteins that participate in this process also have a role in the DNA damage response. For example, *DECREASE IN DNA METHYLATION1* (*DDM1*) is an ATP-dependent SWI2/SNF2 chromatin remodeling factor which is required for DNA methylation in Arabidopsis plants (Vongs *et al.*, 1993). When *DDM1* is mutated, there is a rapid loss of cytosine methylation, both at heterochromatic repetitive sequences and also at euchromatic low-copy sequences over successive generations (Kakutani *et al.*, 1996). In *ddm1* mutants, DNA methylation and methylation of lysine 9 in histone H3 are lost (Gendrel *et al.*, 2002). DDM1 regulates 5S rDNA methylation, gene imprinting, transposon, gene and transgene silencing, and possibly also the occurrence of paramutations (Kurihara *et al.*, 2008, Jeddeloh *et al.*, 1998; Vielle-Calzada *et al.*, 1999; Hirochika *et al.*, 2000). In Arabidopsis, *ddm1* mutants show genomic DNA hypomethylation and the release of silencing of transposons, demonstrating that one important function of this silencing is the suppression of transposons; and DDM1 has been shown to stabilize the activity of transposons (Hirochika *et al.*, 2000; Lippman *et al.*, 2003; Miura *et al.*, 2001). On the other hand, DDM1 has also been reported to have a role during the DDR. For example, *ddm1* plants are deficient in homologous recombination and in the repair of DNA damaged by methyl methane sulfonate, γ and UV radiation (Shaked *et al.*, 2006; Yao *et al.*, 2012; Qüesta *et al.*, 2013a), suggesting that the regulation of DNA silencing is intimately coordinated with the repair of damaged DNA.

DNA methylation during DNA silencing and repair

Interestingly, while *ddm1* mutants show increased accumulation of damaged DNA after UV-B exposure, plants with decreased expression of *REPRESSOR OF SILENCING1* (*ROS1*) accumulate less pyrimidine dimers in the DNA than WT plants after UV-B exposure (Qüesta *et al.*, 2013a). ROS1 is a 5-meC DNA glycosylase that specifically removes 5-meC from DNA, which is then replaced by an unmethylated cytosine through a Base Excision Repair mechanism (Ponferrada-Marín *et al.*, 2009). In Arabidopsis plants, ROS1 regulates the DNA methylation pathway at specific regions of the genome, protecting the genome from excess methylation (Zhu, 2009). *ros1* mutants show increased silencing of repetitive transgenes and increased telomere length in Arabidopsis plants (Gong *et al.*, 2002; Liu *et al.*, 2010). In these mutants, expression of both *UVR2* and *UVR3* photolyases is increased, suggesting that the lower accumulation of photoproducts by UV-B in the mutants is due to higher photorepair (Qüesta *et al.*, 2013a). Despite this, *ros1* plants accumulate high levels of oxoproducts in the

DNA, indicating that this glycosylase not only has a role in removing 5-meC in the DNA, but it also participates in the repair of oxidative DNA damage (Qüesta *et al.*, 2013a). Interestingly, the DNA repair factor DNA damage-binding protein 2 (DDB2) is able to represses the enzymatic activity of ROS1, suggesting that this protein that participates in DNA repair is also a regulator of ROS1-mediated DNA demethylation (Córdoba-Cañero *et al.*, 2017).

Moreover, the development of seeds, in particular in maize and Arabidopsis, is under control of epigenetic regulation, specifically genomic imprinting (Bai and Settles, 2015), a type of epigenetic regulation in which identical alleles of genes are expressed in a parent-of-origin dependent manner. Imprinted gene expression primarily occurs in the endosperm, and imprinted genes will express either the maternal or paternal allele even though the primary sequences of these alleles may be identical. Therefore, developing seeds show chromatin changes due to imprinting and also because they are usually under stressful conditions that can produce DNA damage (Waterworth *et al.*, 2015). In fact, several reports have demonstrated that genome stability maintenance influence seed development and survival. For example, mutants in a gene encoding the single strand DNA LIGASE1 (LIG1) show a strong maternal endosperm developmental phenotype (Andreuzza *et al.*, 2010). These mutants also show DNA hypermethylation at the regulatory sequences of imprinted genes that regulate endosperm development, which are usually DNA demethylated in the maternal genome during early seed development, for example in sequences that regulate the expression of a key endosperm developmental regulator *MEDEA* (Li *et al.*, 2015). LIG1 was shown to participate in the Base Excision Repair (BER) pathway in Arabidopsis (Córdoba-Cañero *et al.*, 2011), suggesting that a non-canonical BER pathway specialized in eliminating DNA methylated cytosines may also participate in gene imprinting in plants. Similarly, the bifunctional 5-methyldeoxycytosine-specific glycosylase DEMETER (DME) which is involved in DNA repair, is expressed in the vegetative cell in pollen and the central cell in ovules, and *dme* mutants are deficient in seed development, demonstrating that DME has a role both in DNA repair and in seed development (Choi *et al.*, 2002).

Another protein with a dual role in DNA repair and epigenetic silencing is BRUSHY1 (BRU1). BRU1 is a nuclear protein with tetratricopeptide-repeat and leucine-rich repeats protein interaction domains with a proposed role in the epigenetic inheritance of chromatin states (Suzuki *et al.*, 2005). *bru1* mutants show a release of transcriptional gene silencing, increased intrachromosomal homologous recombination and are also highly sensitive to genotoxic stress (Takeda *et al.*, 2004). These mutants also show high expression of poly ADP-ribose polymerase-2, which is usually related with high DNA damage. Despite *bru1* mutants show heterochromatin organization instability, they do not show changes in DNA methylation (Takeda *et al.*, 2004). Interestingly, *bru1* mutant plants have a similar phenotype

as CAF-1 deficient plants, suggesting that cooperative roles in DNA repair, stabilization of chromatin structure and regulation of plant development exist.

Silencing of transposable elements (TE) have a fundamental role to alleviate the deleterious impact of active TE on the genome. Most TE contain tandem or inverted repeats, and these regions can form double-stranded RNA regions that trigger silencing when processed into small interfering RNAs (Lippman *et al.*, 2004). siRNAs are associated with post-transcriptional degradation of target mRNAs and with transcriptional silencing of target genes via DNA methylation and histone modification. In maize, spontaneous silencing of mutator transposons occurs in ~10–100% of the progeny of an active plant, and once the transposons are silenced, their reactivation is very rare. However, UV-B radiation is able to reactivate Mutator transposons (Walbot, 1999; Qüesta *et al.*, 2013b). After UV-B exposure, different chromatin remodeling events occur in inverted repeats of Mutator elements, which include the increase in histone H3 acetylation and the decrease in DNA and H3K9me2 methylation, suggesting that these modifications contribute directly to transposon reactivation by UV-B in maize (Qüesta *et al.*, 2010). Interestingly, maize plants with decreased expression of the METHYL-CpG BINDING DOMAIN PROTEIN 101 (MBD101) regulate chromatin structure associated to Mutator transposon elements (Qüesta *et al.*, 2015). Methyl-CpG binding domain proteins usually interact with DNA when it is methylated in cytosine bases; however, *Zm*MBD101 binds DNA even if not methylated. Transgenic maize plants with reduced *MBD101* expression show induction of Mutator genes after UV-B exposure, and this up-regulation is accompanied with decreased accumulation of histone repressive marks H3K9me2 and H3K27me2, suggesting that *Zm*MBD101 is required to maintain the levels of these marks under UV-B conditions (Qüesta *et al.*, 2015). Interestingly, cytosine methylation at Mutator TIRs is not modified in *Zm*MBD101 deficient plants. On the other hand, *Zm*MBD101 deficient plants show increased DNA damage accumulation and visible symptoms of damage after UV-B exposure (Campi *et al.*, 2012; Casati *et al.*, 2008). These results demonstrate that epigenetic mechanisms to silence transposable elements can also participate in the repair of damaged DNA.

Heterochromatin is usually associated with silenced transcription. However, mutations in particular genes or environmental changes can alter heterochromatin-associated silencing without changing most of the repressive epigenetic marks in histones or the DNA. This occurs by the action of proteins that activate transcription in a nonpermissive chromatin context. One example is the MEDIATOR SUBUNIT 14 (MED14) in Arabidopsis (Bourguet *et al.*, 2018). MED14 is the central subunit of the MEDIATOR complex, which is a large protein complex necessary for the early steps of transcription initiation (Soutourina, 2018). In Arabidopsis, MED14 has been shown to participate in the regulation of the expression of cold-regulated

and biotic stress–induced genes (Hemsley *et al.*, 2014; Wang *et al.*, 2016). MED14 is also required for heterochromatin transcription during heat stress in Arabidopsis, together with UVH6, releasing heterochromatin transcriptional silencing (Bourguet *et al.*, 2018). UVH6 is the Arabidopsis orthologue of the human XPD and yeast RAD3 proteins (Liu *et al.*, 2003), and it is part of the transcription factor IIH complex that participates both in transcription initiation and also in DNA repair by the Nucleotide Excision Repair system (Compe and Egly, 2016). In Arabidopsis, UVH6 is required for tolerance to UV and heat stress (Jenkins *et al.*, 1995 and 1997). Bourguet *et al.* (2018) showed that when heterochromatin silencing is destabilized by mutations in silencing factors, UVH6 is dispensable for transcription, while MED14 is still necessary for transcription. MED14 also targets highly methylated transposon elements under normal growth conditions, suggesting that repressive chromatin may recruit MED14. In this way, MED14 and the DNA repair enzyme UVH6 would be simultaneously involved in the transcription and the formation of heterochromatin, demonstrating that there is a clear crosstalk between transcription, repair and silencing of the DNA.

Chromatin remodeling proteins that participate in homologue recombination during DNA repair

Meiosis is a specialised cell division that sexually reproducing organisms undergo in order to reduce the chromosome number by half before gamete formation. Most diploid cells contain two homologous sets of chromosomes, one from the mother and one from the father; and during meiosis each of them are replicated, recombined and distributed to four daughter cells in two rounds of cell division. During the first division of meiosis, and before homologous chromosomes are separated, homologous recombination occurs, resulting in the formation of chromosomes consisting of both paternal and maternal DNA sequences, this contributes to the genetic diversity of the four haploid cells that are the products of meiosis (Page and Hawley, 2003). Meiotic recombination is initiated by the formation of DNA double strand breaks (DSBs), which are catalyzed by the topoisomerase-like enzyme SPO11 (Grelon *et al.*, 2001). The repair mechanism preferentially uses the homologous chromosome as a template to produce crossovers (COs) and noncrossovers (NCOs) and is mediated by two recombinases, RAD51 and DMC1 (Okada and Keeney, 2005; Hunter and Kleckner, 2001; Shrivastav *et al.*, 2008). In Arabidopsis, as well as in other eukaryotes, ATM is also involved in meiotic recombination, particularly in the formation of COs (Yao *et al.*, 2020). Furthermore, some DSBs are repaired through inter-sister recombination. In *dmc1* single mutants, COs are not observed, suggesting that meiotic DSBs are completely repaired via RAD51-mediated inter-sister recombination. In contrast, *atm dmc1* double mutants show a severe chromosome fragmentation phenotype, suggesting that in the absence of ATM, inter-sister repair by RAD51 is impaired in the *dmc1* background. In contrast, *atm rad51* double mutants show similar

chromosome fragmentation levels as those of the *rad51* single mutant (Yao *et al.*, 2020). This genetic analysis demonstrates that *At*ATM, a key regulator of the DNA damage response, also functions in meiotic recombination mediating DSBs repair during meiosis.

Interestingly, there seems to be meiotic recombination hotspots, as recombination events are not distributed evenly; these hotspots are associated to particular chromatin structures. For example, in yeast and mammals, the initiation of meiotic recombination was linked to the presence of open chromatin sites upstream from genes and to trimethylation of lysine 4 in histone H3 (H3K4me3), a mark of active chromatin (Pan *et al.*, 2011; Berchowitz *et al.*, 2009). In maize, which has a large genome that is rich in repetitive DNA, double strand breaks during meiotic recombination were frequent in all chromosome regions, included in repetitive DNA, while only one-quarter of hotspots are located near genes (He *et al.*, 2017). Interestingly, maize hotspots overlapped regions of low nucleosome occupancy, suggesting that chromatin remodeling activities could have a role in meiotic recombination. Despite this, there was very low correlation with H3K4me3 sites, in contrast to what it was described in other eukaryotes (He *et al.*, 2017).

Besides its participation during meiotic recombination, RAD51 also has a role in somatic recombination. By yeast two-hybrid analysis, RAD51 was demonstrated to bind RAD54, which belongs to the SWI2/SNF2 family of DNA-stimulated ATPases (Osakabe *et al.*, 2006). AtRAD54 is expressed in different tissues; with a high expression in flower buds, suggesting that, although this has not been demonstrated yet, AtRAD54 may also have a role during meiosis. On the other hand, AtRAD54 was also induced by ɣ-irradiation, and *rad54* mutants showed increased sensitivity to ɣ-irradiation and cisplatin, and the efficiency of somatic homologous recombination in the mutant plants was reduced, demonstrating that this chromatin remodeling protein also participates in DNA repair (Osakabe *et al.*, 2006). In *Arabidopsis thaliana* plants, RAD54 is able to form subnuclear foci after induction of DNA double-strand breaks (Hirakawa *et al.*, 2017). These RAD54 foci are dependent on the activation of the DNA damage response pathway, and co-localized with phophorylated H2AX (ɣ-H2AX) signals, which are usually associated with damaged DNA. Moreover, in living cells, RAD54 was specifically accumulated at damaged sites in the DNA, suggesting that RAD54 foci correspond to DNA repair foci (Hirakawa *et al.*, 2017). The dissociation of RAD54 at damaged sites during homologous recombination repair is regulated by the histone demethylase LYSINE-SPECIFIC DEMETHYLASE1-LIKE 1 (LDL1); LDL1 functions as a histone demethylase that targets H3K4me2 (Hirakawa *et al.*, 2019). When LDL1 is depleted, there is an overaccumulation of RAD54 at damaged DNA sites that recognizes histone H3K4 methylation deposited in double strand breaks. Interestingly, and in contrast with yeast and animals, H3K4me2 levels but not H3K4me1 or H3K4me3 levels are associated to

recombination sites in Arabidopsis plants (Hirakawa *et al.*, 2019). Therefore, LDL1 removes RAD54 at damaged sites by demethylating H3K4me2 during homologous recombination repair (Hirakawa *et al.*, 2019). Thus, similarly as described in yeast and mammals (Pan *et al.*, 2011; Berchowitz *et al.*, 2009); recombination was linked to the presence of open chromatin sites associated with H3K4 methylation in Arabidopsis. Moreover, the presence of open chromatin seems to be necessary for both meiotic recombination and homologous recombination during DNA repair. Interestingly, Arabidopsis chromosomes are highly DNA methylated in the centromeres, which are also crossover-suppressed. The suppression of euchromatic crossover in hot spots is associated with an increased nucleosome density and H3K9me2 and loss of CG DNA methylation maintenance. For example, *met1* mutants show increased euchromatic recombination, suggesting that DNA methylation is sufficient to silence crossover hot spots and plays an important role in establishing regions of meiotic recombination (Yelina *et al.*, 2015).

Other chromatin remodeling proteins with roles during meiosis have also been described to be important during DNA repair. For example, plants deficient in the chromatin remodeling SWI2/SNF2-related complex (SWR1), which deposits histone H2A.Z into the DNA, have smaller flowers, altered petal number, short anthers, shortened and thickened gynoecia and siliques, aborted ovules, and a reduced number of seeds per silique (March-Díaz and Reyes, 2009). These mutants have reduced fertility and irregular gametogenesis, these are due to defects in meiosis (Rosa *et al.*, 2013). Moreover, Arabidopsis *swr1* mutants also show hypersensitivity to different DNA damaging agents, even in the absence of any genotoxic stress. These mutants have symptoms of DNA damage accumulation, and the reduced DNA repair observed is due to a decrease in somatic homologous recombination (Rosa *et al.*, 2013). In this way, similarly as RAD54, the SWR1 complex participates both in meiotic recombination and in DNA repair, modifying chromatin structure to facilitate recombination.

Telomere Stability and DNA repair

Eukaryotic chromosomes are linear and have DNA ends. Therefore, if they are not protected, the DNA repair systems recognize these ends as DNA double-strand breaks activating the DDR, producing as a consequence, chromosome fusions. Although there are minor differences in telomeric DNA sequence between species, which are composed by several kilobases of G-rich double-stranded repeats that ends with a 39 single-strand overhang, telomeric proteins are more diverse between species. In plants, several proteins involved in telomere homeostasis have been identified (Valuchova *et al.*, 2017; Surovtseva *et al.*, 2009; Charbonnel *et al.*, 2018). One is GH1-HMGA1, which belongs to the High Mobility Group Protein A (HMGA) family in plants (Charbonnel *et al.*, 2018). GH1-HMGA1 deficient plants

showed telomeric deficiencies; such as a telomere length decrease in the second mutant generation with increased mitotic anaphase bridges and degraded telomeres. In addition, *gh1-hmga1* mutants show increased sensitivity to DNA-damaging agents such as ɣ-radiation, which produces DNA double strand breaks, and mitomycin C, a DNA cross-linking agent, but not to hydroxyurea, which affects DNA replication (Charbonnel *et al.*, 2018), suggesting that GH1-HMGA1 could be involved both in telomere maintenance and in DNA repair allowing the completion of homologous recombination.

Conclusions and perspectives

Plants are sessile and they are therefore constantly exposed to diverse environmental conditions. In order to survive, they must adapt to different conditions such as excessive or inadequate light, water, salt, temperature, and pathogens. Plant growth and development is modulated by these external conditions and by endogenous cellular processes which can affect performance, and can also damage the DNA. Because DNA damage constitutes a serious menace to cell viability and compromises both genome and epigenome integrity, when DNA damage occurs, there are significant modifications of chromatin structure, affecting intrinsic chromatin components and gene expression. Data presented in this review and summarized in Box 1 and Table 1 provides recent evidence that demonstrate that plants have adapted to modulate responses when they are exposed to stressful conditions that can produce DNA damage. In this way, chromatin changes can be activated when DNA damage occurs to regulate plant growth and development under adverse conditions. Future work will need to address how this connection works, and to identify the different players that remodel chromatin structure under genotoxic stress conditions that specifically participate in the regulation of particular aspects of plant growth, and how this specificity is acquired. Results on chromatin changes that occur after DNA damage from animals and yeast could be used as a starting point to investigate the same processes in plants. For example, in plants, data regarding the role of chromatin modifications at the site of DNA damage to signal the damage or promote repair is scarce. Yet in animals there is clear evidence that chromatin modifiers are key to signal and repair various types of damage. In humans, for instance, the PRC2 subunit EZH2 has been demonstrated to be recruited at stalled replication forks, where it

triggers H3K27 methylation and allows the recruitment of the nuclease MUS81 to degrade and repair stalled forks (Rondinelli *et al.*, 2017). Likewise, it was shown that hydroxylation of methyl cytosines in the DNA can mark stalled forks, playing a key role in their destabilization for repair (Kharat *et al.*, 2020). Moreover, how chromatin states are re-established after the repair processes is also not known in plants, while it is an emerging topic in animal systems (Adam *et al.*, 2016). Therefore, a challenge for future work would be to discover the similarities or differences with what occurs in other organisms that would help to understand the links between DNA replication, DNA repair and chromatin dynamics in plants.

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Box 1 legend:

Box 1. Plant chromatin dynamic modifications after DNA damage.

After DNA damage occurs, chromatin must be remodeled in order to repair the DNA to maintain plant growth and development. This diagram summarizes the roles that different chromatin remodeling factors play when DNA damage occurs, in particular, the regulation of gene expression, the participation in the alteration of chromatin structure to facilitate DNA repair and their active participation in DNA repair pathways. For more details, see Table 1.

Table 1. Chromatin remodeling activities with roles in DDR and/or DNA repair.

Chromatin remodeling activities	Arabidopsis genes and some homologues in maize (*Z. mays*)	Function in plant growth and development	Function in DDR and DNA repair	References
Histone modifications	*FVE* *NFC102* (*Z. mays*)	Regulator of autonomous pathway. Reduces FLC expression through its interaction with PRC2.	Modulate histone acetylation required for proper DNA repair after UV-B exposure.	Campi *et al.*, 2012 Casati *et al.*, 2008
	HAM1 *HAM2*	Histone Acetyltransferase (H4K5). Regulate flowering time by acetylating H4 associated to *FLC* and *MAF3/4* genes.		Campi *et al.*, 2012 Letrasse *et al.*, 2018 Xiao *et al.*, 2013
	CLF	Methyltransferase, subunit of PRC2. Participates in floral transition control.	Mediates regulation of AGO1 degradation after UV-B exposure. AGO1 participates in Global Genome Repair after DNA damage.	Arongaus *et al.*, 2018 Dotto *et al.*, 2018 Schalk *et al.*, 2017 Ré *et al.*, 2020
Histone chaperones	*FAS1* *FAS2*	Subunits of Chromatin Assembly Factor 1 (CAF-1), a histone chaperone that participates in DNA and chromatin interaction processes.	Regulate cell proliferation, modulate the expression of DNA repair genes and participate in DDR when plants are exposed to different genotoxic agents.	Chen *et al.*, 2008 Endo *et al.*, 2006 Exner *et al.*, 2006 Gao *et al.*, 2012 Henning *et al.*, 2003 Jiang and Berger, 2017

			Kaya *et al.*, 2001 Kirik *et al.*, 2006 Maulion *et al.*, 2019 Mozgova *et al.*, 2010 Muchova *et al.*, 2015 Muñoz-Viana *et al.*, 2017 Otero *et al.*, 2016 Ramirez-Parra and Gutierrez, 2007 Varas *et al.*, 2015
ASF1a *ASF1b*	Histone H3/H4 chaperone that participate in a variety of DNA and chromatin-related processes.		Lario *et al.*, 2013 Zhu *et al.*, 2011
NAP1, NAP2 and *NAP3*	H2A and H2B histone chaperones	Bind to genes that encode proteins of NER pathway. Mediate chromatin remodeling to promote HR after DNA damage caused by UV or bleomycin exposure.	Cho *et al.*, 2013 Kuryan *et al.*, 2012 Liu *et al.*, 2009
NRP1 and *NAP2*		Accumulates in the chromatin after DNA breaks and mediate chromatin remodeling to promote HR after UV or	Gonzalez-Arzola *et al.*, 2017 Kang *et al.*, 2019

			bleomycin exposure.	Zhou *et al.*, 2016 Zhu *et al.*, 2006
Chromatin remodeling	*ARP5*	Subunit of INO80 chromatin-remodeling complex. Participates in multicellular development processes.	Involved in repairing DNA damaged by different DNA-damaging reagents. Participates in DSBs repair via HR and IS recombination. Interacts with RAD54.	Kandasamy *et al.*, 2009
	RAD54	Member of the SWI2/SNF2 family of DNA-stimulated ATPases, involved in somatic HR.	Accumulates at damaged sites in the DNA and co-localizes with ɣ-H2AX. Its function is regulated by LDL1.	Hirakawa *et al.*, 2017 Hirakawa *et al.*, 2019 Osakabe *et al.*, 2006
	SWR1	Chromatin remodeling SWI2/SNF2-related complex, deposits H2A.Z	Participates in meiotic recombination and DNA repair.	Rosa *et al.*, 2013
	GH1-HMGA1	Involved in telomere homeostasis.	Participates in DNA repair after ɣ-radiation and mitomycin C exposure.	Charbonnel *et al.*, 2018
	DDM1	ATP-dependent SWI2/SNF2 chromatin remodeling factor, required for DNA methylation and transposon silencing.	Participates in HR and DDR caused by methyl methane sulfonate, ɣ and UV radiation.	Questa *et al.*, 2013 Shaked *et al.*, 2006 Vongs *et al.*, 1993 Yao *et al.*, 2012
DNA silencing	*ROS1*	5-meC DNA glycosylase, involved in regulation of DNA methylation pathway at specific regions of the	Participates in BER pathway and in repair of oxidative DNA damage caused by UV-B	Córdoba-Cañero *et al.*, 2017 Ponferrada-Marín *et al.*,

		genome.	radiation. Its function is regulated by DDB2.	2009 Questa *et al.*, 2013 Zhu, 2009
	BRU1	Involved in cell division control and plant morphogenesis and may also play a role in epigenetic inheritance and chromatin states	Participates in DNA repair and chromatin stabilization.	Suzuki, *et al.*, 2005 Takeda *et al.*, 2004
	MDB101 (*Z. mays*)	It is important to maintain histone repressive marks H3K9me2 and H3K27me2 and maintain Mutator elements silenced	Participates in DNA damage repair and transposon silencing after UV-B exposure.	Campi *et al.*, 2012 Casati *et al.*, 2008 Questa *et al.*, 2010 Questa *et al.*, 2015 Walbot, 1999
	DME	5-methyldeoxycytosine-specific glycosylase, establishes *MEDEA* gene imprinting.	Participates in BER pathway.	Choi *et al.*, 2002

Figure 1