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REVIEW

An insight into understanding the coupling between homologous recombination mediated DNA repair and chromatin remodeling mechanisms in plant genome: an update

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ABSTRACT

Plants, with their obligatory immobility, are vastly exposed to a wide range of environmental agents and also various endogenous processes, which frequently cause damage to DNA and impose genotoxic stress. These factors subsequently increase genome instability, thus affecting plant growth and productivity. Therefore, to survive under frequent and extreme environmental stress conditions, plants have developed highly efficient and powerful defense mechanisms to repair the damages in the genome for maintaining genome stability. Such multi-dimensional signaling response, activated in presence of damage in the DNA, is collectively known as DNA Damage Response (DDR). DDR plays a crucial role in the remarkably efficient detection, signaling, and repair of damages in the genome for maintaining plant genome stability and normal growth responses. Like other highly advanced eukaryotic systems, chromatin dynamics play a key role in regulating cell cycle progression in plants through remarkable orchestration of environmental and developmental signals. The regulation of chromatin architecture and nucleosomal organization in DDR is mainly modulated by the ATP dependent chromatin remodelers (ACRs), chromatin modifiers, and histone chaperones. ACRs are mainly responsible for transcriptional regulation of several homologous recombination (HR) repair genes in plants under genotoxic stress. The HR-based repair of DNA damage has been considered as the most error-free mechanism of repair and represents one of the essential sources of genetic diversity and new allelic combinations in plants. The initiation of DDR signaling and DNA damage repair pathway requires recruitment of epigenetic modifiers for remodeling of the damaged chromatin while accumulating evidence has shown that chromatin remodeling and DDR share part of the similar signaling pathway through the altered epigenetic status of the associated chromatin region. In this review, we have integrated information to provide an overview on the association between chromatin remodeling mediated regulation of chromatin structure stability and DDR signaling in plants, with emphasis on the scope of the utilization of the available knowledge for the improvement of plant health and productivity.

Abbreviation: ADH: Alcohol Dehydrogenase; AGO2: Argonaute 2; ARP: Actin-Related Protein; ASF:1- Anti-Silencing Function-1; ATM: Ataxia Telangiectasia Mutated; ATR: ATM and Rad3-Related; AtSWI3c: *Arabidopsis thaliana* Switch 3c; ATXR5: Arabidopsis Trithorax-Related5; ATXR6: Arabidopsis Trithorax-Related6; BER: Base Excision Repair; BRCA1: Breast Cancer Associated 1; BRM: BRAHMA; BRU1: BRUSHY1; CAF:1- Chromatin Assembly Factor-1; CHD: Chromodomain Helicase DNA; CHR5: Chromatin Remodeling Protein 5; CHR11/17: Chromatin Remodeling Protein 11/17; CIPK11- CBL- Interacting Protein Kinase 11; CLF: Curly Leaf; CMT3: Chromomethylase 3; COR15A: Cold Regulated 15A; COR47: Cold Regulated 47; CRISPR: Clustered Regulatory Interspaced Short Palindromic Repeats; DDM1: Decreased DNA Methylation1; DRR: DNA Repair and Recombination; DSBs: Double-Strand Breaks; DDR: DNA Damage Response; EXO1: Exonuclease 1; FAS1/2: Fasciata1/2; FACT: Facilitates Chromatin Transcription; FT: Flowering Locus T; GMI1: Gamma-Irradiation And Mitomycin C Induced 1; HAC1: Histone Acetyltransferase of the CBP Family 1; HAM1: Histone Acetyltransferase of the MYST Family 1; HAM2: Histone Acetyltransferase of the MYST Family 2; HAF1: Histone Acetyltransferase of the TAF Family 1; HAT: Histone Acetyl Transferase; HDA1: Histone Deacetylase 1; HDA6: Histone Deacetylase 6; HIRA: Histone Regulatory Homolog A; HR-Homologous recombination; HAS: Helicase SANT Associated; HSS: HAND-SLANT-SLIDE; ICE1: Inducer of CBF Expression 1; INO80: Inositol Requiring Mutant 80; ISW1: Imitation Switch 1; KIN1/2: Kinase 1 /2; MET1: Methyltransferase 1; MET2: Methyltransferase 2; MINU: MINUSCULE;

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Supplemental data for this article can be accessed here

MMS: Methyl Methane Sulfonate; MMS21: Methyl Methane Sulfonate Sensitivity 21; MRN: MRE11, RAD50 and NBS1; MSI1: Multicopy Suppressor Of Ira1; NAP1: Nucleosome Assembly Protein 1; NRP1/NRP2: NAP1-Related Protein; NER: Nucleotide Excision Repair; NHEJ: Non-Homologous End Joining; PARP1: Poly-ADP Ribose Polymerase; PIE1: Photoperiod Independent Early Flowering 1; PIKK: Phosphoinositide 3-Kinase-Like Kinase; PKL: PICKLE; PKR1/2: PICKLE Related 1/2; RAD: Radiation Sensitive Mutant; RD22: Responsive To Desiccation 22; RD29A: Responsive To Desiccation 29A; ROS: Reactive Oxygen Species; ROS1: Repressor of Silencing 1; RPA1E: Replication Protein A 1E; SANT: Swi3, Ada2, N-Cor and TFIIIB; SEP3: SEPALLATA3; SCC3: Sister Chromatid Cohesion Protein 3; SMC1: Structural Maintenance of Chromosomes Protein 1; SMC3: Structural Maintenance of Chromosomes Protein 3; SOG1: Suppressor of Gamma Response 1; SWC6: SWR1 Complex Subunit 6; SWR1: SWI2/SNF2-Related 1; SYD: SPLAYED; SMC5: Structural Maintenance of Chromosome 5; SWI/SNF: Switch/Sucrose Non-Fermentable; TALENs: Transcription Activators Like Effector Nucleases; TRRAP: Transformation/Transactivation Domain-Associated Protein; ZFNs: Zinc Finger Nucleases

Introduction

All living organisms are facing the continuous challenge of maintaining the integrity of their genome, which is controlled by the coordinated network among cell cycle-regulated DNA replication, repair, and recombination to avoid mutations and thus genome instability. Various environmental genotoxic stress factors, natural chemical agents, or other endogenous processes frequently induce diverse forms of DNA damage, disrupt cell cycle progression, and eventually lead to genome instability. Therefore, with the evolutionary progress, living organisms have developed highly remarkable and robust DNA repair and recombination (DRR) pathways to repair or to tolerate lesions in their genetic material to maintain genome integrity [1–3]. Thus, besides the key cellular functions for protecting cells against damage, DDR, repair, and recombination pathways are also vital for ensuring the faithful transmission of genetic information over the generations. Interestingly, two fundamental and contrasting functions have been suggested for these partly redundant repair and recombination machineries, firstly to protect the genome from permanent alterations and secondly, to allow for a certain level of mutations during evolution. The delicate and remarkable balance between these two activities is reflected by the high levels of conservation of DNA damage repair and recombination-related proteins across all the three domains of life, the Bacteria, Archaea, and Eukarya [4–6].

Plants, due to their sessile lifestyle, are continuously facing different environmental assaults like solar UV radiation, high soil salinity, drought, chemical mutagens, and free radicals generated by endogenous processes [2,7,8], which frequently challenge the integrity and stability of plant genome. In addition to the damaging effects of various environmental stress factors, endogenous factors like reactive oxygen species (ROS), which are frequently generated as a by-product of metabolic processes, induce highly mutagenic oxidative damage to DNA bases (7, 8-dihydro-8-oxoguanine, and 1,2-dihydro-2-oxoadenine). These DNA lesions, if remain unrepaired due to error-prone or slow repair process, may lead to the formation of more harmful damages, including DNA single and double-strand breaks (DSBs), inter-strand cross-links, and collapse of the replication forks [9,10]. Among the various forms of DNA damage, DSBs in the DNA double helix are considered as one of the most serious forms of DNA damage, as these lesions cause loss of DNA segment and therefore, induce genome instability [11]. Unrepaired DSBs in the actively dividing meristematic cells interfere with DNA replication and transcription, compromises cell viability, and subsequently impair plant growth and productivity [7]. Therefore, efficient detection, signaling, and repair of DSBs in the genome are crucial for the survival of all organisms, including plants [2,12]. To counteract these adverse effects, plants have evolved with highly potent and multi-dimensional signaling responses, collectively known as DDR [3,13–16] for the highly efficient detection and repair of DNA lesions for maintenance of genome stability. Over the past couple of decades, extensive molecular genetic analyses mainly in the model plants, including *Arabidopsis thaliana* and rice (*Oryza*

sativa) have facilitated to achieve significant progress in understanding the molecular mechanisms of various DNA damage repair pathways in higher plant genome [1,17]. Like the other eukaryotic systems, the plant genome possesses an extensive array of DNA repair machinery to eliminate the chances of permanent genetic alterations for maintaining genome stability [18]. Because of their absolute necessity for exposure to sunlight, plants effectively utilize photoreactivation repair to eliminate the UV-B induced lesions on daily basis. In addition, plants also employ two other very essential excision repair pathways, including base excision repair (BER) and nucleotide excision repair (NER) (also known as the light-independent or "dark repair") for the repair of diverse forms of DNA lesions [19]. The recombination-mediated DSB repair pathways, including the homologous recombination (HR) and non-homologous end joining (NHEJ) mechanism, have been shown to play a crucial role in maintaining plant genome stability [7,11,12,20]. In addition, the plant genome also employs the mismatch repair (MMR) pathway for the elimination of incorrectly incorporated nucleotides and removal of other solar UV-induced photoproducts [21–23].

Like the natural plant populations, crop plants also encounter a variety of environmental stress factors when they are grown in agriculture fields. Furthermore, unpredictable climatic behavior along with global warming has severely affected crop growth and yield for the past couple of decades [24,25]. Abiotic stresses, such as drought, high soil salinity, heavy metal contamination, cold, heat, etc. have a huge negative impact on agriculture, reducing the average productivity by about 50% for major crop plants [26,27]. Moreover, sessile plants also defend themselves from the attack of a wide range of biotic factors, such as bacteria, viruses, fungi, nematodes, and insects [28]. The increase in global temperature has been predicted to greatly influence the habitat range of the pests and pathogens, which will eventually lead to disease outbreaks covering wide geographic areas [29]. It has been observed that the occurrence and severity of pathogens and insects mediated stress has been further influenced by abiotic stresses, mainly drought, high and low temperature, and salinity [30,31].

During the second half of the twentieth century, the green revolution emerged as one of the most remarkable and successful technological achievements for the enhancement of crop health and productivity, resulting in the availability of high-yielding varieties of rice, wheat, and maize globally. This has led to improvement of food crop production with more than doubled in rate than before and tremendously helped to feed the growing population particularly in the developing countries [32]. The green revolution at the beginning of the 1960s, though has significantly increased yield in some crop species [33,34] limited to few geographical locations [32,35], the subsequent rapid growth rate in the global population [36] has considerably modified the agricultural practice with the enhanced use of agrochemicals and pesticides. These factors have further caused increased susceptibility of modern-day crops to various stress factors.

Accumulating evidence has indicated that many of the agronomic traits are complex and governed by multiple genes and also associated with complicated interactions of different proteins, which respond to various environmental cues [37]. Therefore, the improvement of specific traits requires the integration of multiple transgenes to create a modular trait stacking platform [38,39]. In the transgenic approach for crop improvement, trait stacking is associated with the integration of multiple genetic modifications or traits in a single crop variety. Because of modification for multiple traits, including tolerance to pesticides along with nutritional enrichments, the crop varieties with stacked traits appeared to become more popular to the farmers and consumers than the traditional mono-trait varieties [40]. Although traditional breeding approaches have utilized such trait stacking, the success appeared to be limited due to the problem in organization and deregulation of multiple unlinked transgenes [41]. On the other hand, in addition to the environmental and social issues, crop improvement via transgenic approach also faced limitations because of the nonspecific site of integration of transgene and difficulty in maintaining copy number of integrated transgene. In contrast, for the past couple of years, designed nucleases have emerged as one of the potential and more acceptable molecular tools for gene

targeting for transgenic modification and integration of the transgene at the specific genomic location. Designed nuclease mediated gene targeting operates through the introduction of targeted DSBs into a specific genomic site, which subsequently activates cellular DNA repair machinery for the site-specific integration of the transgene. With the further technological advancement, precise editing of plant genome (genome editing) utilizing site-directed Zinc finger nucleases (ZFNs), transcription activators like effector nucleases (TALENs) and clustered regulatory interspaced short palindromic repeats (CRISPR/Cas) related systems have emerged as important tools in recent years for very specific modification of target gene function for crop improvement [42,43]. Both transgenic approaches, as well as genome editing method using designed site-specific endonuclease, introduces DSBs in the genome, followed by subsequent activation of DDR, repair, and recombination pathways [44,45].

For the past couple of years, understanding the role of chromatin dynamics and remodeling activities in the context of DDR and repair have occupied one of the contemporary domain of research in plants [16,46,47]. Previously, multiple authors have extensively reviewed the impact of chromatin structure and dynamics on DNA replication, transcription and repair events in the context of chromatin remodeling activity [48,49]. Stadler and Richly [50] have provided an important insight into the link between chromatin environment and DDR, highlighting the various crucial regulatory components of DDR signaling. Recently, Wang et al. [51], have provided an extensive update on the functional aspects of Inositol Requiring Mutant 80 (INO80) and SWI2/SNF2-Related 1 (SWR1) groups of chromatin remodeler complexes in plants. Recently, Verma et al. [10], have extensively reviewed the DDR pathway and emphasized the importance of understanding the structural aspects of the key DDR proteins in plants concerning crop improvement. In this review, we have mainly focused on the role of ATP-dependent chromatin remodeling activity in the maintenance of chromatin structure stability and its impact on the HR mediated DSB repair pathway, which is considered as one of the most error-free mechanisms of DSB repair and very essential source of new allelic combination in plants in the context of crop improvement. We have further emphasized the functional aspects of various ATP-dependent chromatin remodelers and discussed how mutations in chromatin remodeler subunits affect the DSB repair in chromatin, HR frequency, and eventually plant growth and development, which also unveils the cross-talks among chromatin remodeling activity, DSB repair pathways and phytohormones signaling in the plant genome.

DNA damage response is tightly coupled with chromatin structure stability

Completion of *Arabidopsis* genome sequencing has identified several homologues of DDR signaling components in plants and indicated their remarkable similarities with the animal system in terms of the general organization of DDR signaling network and the conservation in the functioning of the initial components, including the sensors and signal transduces [8]. As like in the animal system, the initial response to DNA damage in the plant genome is governed and transduced by the two key regulators, Ataxia Telangiectasia Mutated (ATM) and ATM and Rad3-related (ATR), the two phosphoinositide 3-kinase-like kinase (PIKK) family protein kinases [1,13,52]. ATM kinase is activated under genotoxic stress, which induces DSBs, leading to transcriptional regulation of DDR (ATM pathway). On the other hand, DNA lesions associated with collapsed replication forks and replication stress predominantly activate the ATR kinase activity (ATR pathway) [53]. The conserved ternary protein complex, comprising of MRE11, RAD50, and NBS1 (known as MRN complex) is involved in sensing DSBs in the plant genome, while the C-terminal domain of NBS1 activates and recruits ATM kinase at the site of damage chromatin in the ATM pathway [54]. However, activation of both ATM and ATR pathways plays a crucial role in regulating DNA damage signaling in plants through direct or indirect phosphorylation of several downstream targets, including the phosphorylation of histone 2A isoform H2AX, NBS1, and the other checkpoint associated protein kinases [53]. Furthermore, the plant genome possesses a NAC [NO APICAL

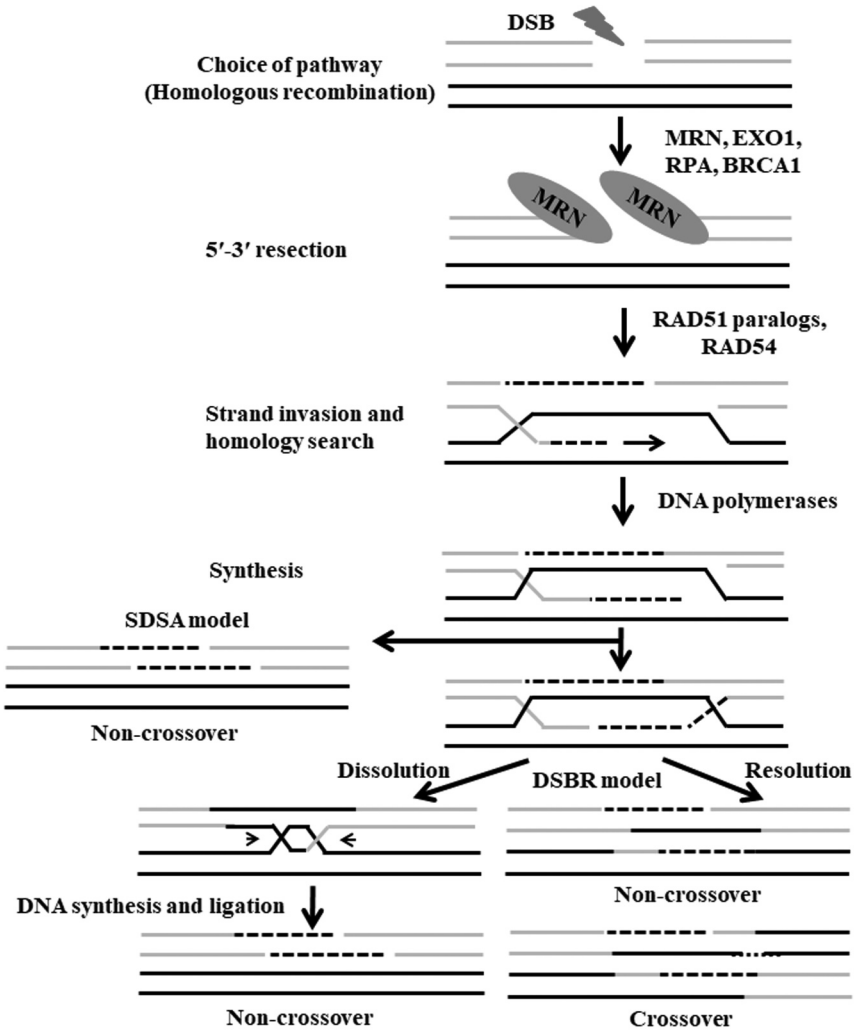

Figure 1. There are two major homologous recombinations (HR) pathways, which repair double-strand breaks (DSBs) in DNA, namely synthesis-dependent strand annealing (SDSA) and double-strand break repair (DSBR). BRCA1 promotes the HR pathway. following the induction of DSBs, DNA ends are processed for the generation of 3 single-strand DNA (ssDNA) overhangs through the action of MRN (MRE11-RAD51-NBS1) complex, CtIP, EXO1, and replication protein A (RPA). the 3 overhangs are then targeted by HR repair machinery for the execution of strand invasion with homologous chromosomes. RAD51-mediated homology search and strand invasion create a nascent D-loop structure. the subsequent activity of DNA polymerases promotes repair DNA synthesis. synthesis-dependent strand annealing (SDSA) represents the primary recombination-based DSB repair pathway in plants. In SDSA mediated repair, the D-loop is displaced, resolving into an unaltered non-crossover product. The DSBR model explains the chromosome crossovers, which occur during meiosis. this mechanism is associated with second end capture, resulting in the heteroduplex extension and formation of a double holliday junction. the DNA intermediates can be resolved by dissolution, resulting in non-crossover products or resolution, which results in both crossover and non-crossover products.

MERISTEM (NAM), ARABIDOPSIS TRANSCRIPTION ACTIVATION FACTOR (ATAF), CUP-SHAPED COTYLEDON (CUC)] domain transcription factor, SUPPRESSOR OF GAMMA RESPONSE 1 (SOG1), which acts as the central regulator in DDR pathway via modulating the ATM and ATR kinases mediated responses, including transcriptional response, activation of cell cycle checkpoint, DNA repair and programmed death of stem cells [55].

In plants, DSBs are repaired by two major pathways, the HR and NHEJ mechanisms [11,12]. The components of HR and NHEJ pathways are conserved in eukaryotes, while, the efficiency of these two mechanisms shows the appreciable difference between the species and also among cell types [56]. HR is a very precise DSB repair pathway (Figure 1), which utilizes an intact homologous DNA sequence to those flanking the DSB site for the restoration of the damaged segment with the

involvement of Radiation sensitive mutant 52 (RAD52) epistasis groups, including Radiation sensitive mutant 51 (RAD51), Radiation sensitive mutant 52 (RAD52), Radiation sensitive mutant 54 (RAD54), Radiation sensitive mutant 55 (RAD55), Radiation sensitive mutant 57 (RAD57) and the MRN complex [57–59]. The HR pathway is mainly functional during the S and G2 phases of the cell cycle [12] and represents the major DSB repair and recombination pathway during meiosis in higher eukaryotes, including plants, where a programmed induction of DSBs is essential for homologous chromosome pairing and recombination [20,60]. On the other hand, in mammals and plants, the majority of DSBs in somatic cells are predominantly repaired by the NHEJ mechanism, which involves direct ligation of broken DNA ends without any prior knowledge of sequence homology or joining to sequences with microhomologies. Thus, NHEJ is an error-prone and non-precise repair pathway, but this pathway has also been shown to remain functional throughout the cell cycle [61].

As in other eukaryotes, the plant genome is organized into a highly compact chromatin structure. Chromatin has been considered as the functional unit of the basic cellular processes. The chromatin DNA is the template for DNA replication, repair, recombination, and transcription. Therefore, the stability of chromatin structure is crucial for the maintenance of genome stability. Chromatin organization involves the association of histone complexes with DNA to form nucleosomes. The basic building block of chromatin is the nucleosome, which consists of about 147 bp of DNA wrapped around a histone octamer, which contains two copies of each histone (H2A, H2B, H3, and H4) [62] and the linker DNA connecting with H1 histone constituting the less compact region. Thus, nucleosomes with linker DNAs form a “beads-on- a string” structure [63]. To make the structure super stable, DNA in the nucleosome undergoes more than 157 atomic interactions with nucleosome core particles [64,65]. The inaccessibility of DNA within the nucleosome and thus the chromatin, in general, represents a steric barrier for different housekeeping cellular processes, such as replication, transcription, and repair [66].

Nucleosome assembly is regulated by histone gene repressor and chromatin assembly factor-1 (CAF-1) [67,68]. CAF-1, a heterotrimeric chaperone, constituted by FASCIATA1 (FAS1), FAS2, and MULTICOPY SUPPRESSOR OF IRA1 (MSI1) subunits in *Arabidopsis* [69], is strongly coupled with DNA replication [68] and facilitates loading of acetylated histone H3/H4 onto the newly synthesized DNA strand for *de novo* assembly of nucleosomes [67]. In *Arabidopsis, caf-1* mutants are completely viable but showed impaired meristem organization as reported in *fas1* and *fas2* mutants [68]. Similar growth defects in meristem organization were also found in some DSB repair pathway mutants, such as *mre11* and *brca2*, and in the case of wild-type *Arabidopsis* after exposure to high doses of irradiation [61]. Furthermore, in *Arabidopsis, fas1* mutant showed enhanced expression of the DDR and repair-related genes, including, *RAD51, PARP1*, and *BRCA1* and *CYCB1;1* due to epigenetic modifications, such as histone H3 acetylation and methylation in the promoters of these genes, instead of overall alteration in chromatin remodeling activity. Comparable responses were also found in wild-type *Arabidopsis* following treatment with DNA damaging agents. Together, these observations have demonstrated that impairments in chromatin assembly during S-phase and DNA damage response share part of the similar signaling pathway through the altered epigenetic status of the target genes [2,68].

DSB repair pathway requires remodeling of the damaged chromatin

Following the induction of DNA double-strand breaks in the plant genome, DDR-associated genes activate the expression of DSB repair genes. The repair of DNA lesions requires remodeling of the damaged chromatin. Detection and initiation of the DSB repair pathway require the recruitment of epigenetic modifiers for remodeling of the damaged chromatin. Like other highly complex eukaryotes, in plants, chromatin dynamics is necessary for cell cycle progression, which is finely orchestrated by environmental and developmental signals [70]. The regulation of the architecture of chromatin and nucleosome in DDR signaling is

Table 1. Members of ATP dependent chromatin remodelers involved in DDR and DNA repair in plants.

Gene family	Member	Mutant phenotype	Functions
INO80/SWR1	INO80 (AT3G57300)	Smaller plants and organ size with late flowering.	Play important role in the maintenance of genome stability, HR repair of DNA double-strand breaks, meiosis, and somatic homologous recombination.
	ARP5 (AT3G12380)	Dwarf plants and delayed stomatal development.	
	ARP9 (AT5G43500)	Inhibition of plant growth.	
	SWR1 (AT2G47210)	Early flowering and reduced fertility.	Involved in transcriptional regulation of DDR gene expression and play a key role in substitution of nucleosomal H2A by H2AZ.
	ARP6 (AT3G33520)	Abnormal apical stem cell development and organ initiation.	
	ARP4 (AT1G18450)	Inhibition of plant development and delayed flowering.	
	PIE1 (AT3G12810)	Early flowering and extra petal formation.	
	SWC6 (AT5G37055)	Early flowering, altered leaf development, and shortened inflorescence.	
SWI/SNF	BRM (AT2G46020)	Dwarf phenotype, delayed flowering, underdevelopment of floral organs	Involved in regulation of DDR and HR. Also, play important role in the regulation of flowering genes.
	SWI3 (AT2G47620)	Impaired embryo development, root growth, and leaf curling.	
	CHC1 (AT5G14170)	Inhibition of plant growth.	
	RAD54 (AT3G19210)	Increased sensitivity to genotoxic stress but fertile.	Play important role in DDR and HR repair via modulation of chromatin structure through interaction with RAD51.
CHD	CHR5 (AT2G13370)	Dwarf phenotype and impaired seed maturation.	Function in transcriptional gene regulation and nucleosome remodeling.
	PKL (AT2G25170)	Primary root retains embryonic characteristic with "pickle root" phenotype	
	PKR1 (AT5G44800)	Alteration in embryonic to vegetative development	
	PKR2 (AT4G31900)	Suppress seed abortion in other mutants.	
ISWI	MSI4 (AT2G19520)	Late flowering response.	Involved in the distribution of nucleosomes.
	CHR11 (AT3G06400)	Disruption of megagametogenesis, female sterility.	
	CHR12 (AT3G06010)	Temporary growth arrest in overexpression lines.	
	CHR17 (AT5G18620)	Altered floral organ identity.	
Uncategorized	RAD18 (AT5G61460)	Highly sensitive to radiation.	Promote KU-independent NHEJ repair and also involved in sister chromatid cohesion after induction of DSBs and hence facilitating HR repair.
	RAD21.1 (AT5G40840)	Reduced germination with developmental delay.	
	RAD21.2 (AT3G59550)	Disruption of pollen development.	
	RAD21.3 (AT5G16270)	Impaired growth and perhaps delay in flowering.	

mainly carried out by the chromatin remodelers, chromatin modifiers, and histone chaperones (Table 1 and Table 2) [71]. Thus, these epigenetic modifiers work harmoniously as potential gatekeepers and signaling coordinators for the maintenance of genome integrity [72]. Chromatin architecture also maintains the transcriptional regulation of expression of several stress-induced genes in plants [73]. For example, the INO80 chromatin remodeler has been shown to interact with phosphorylated γ-H2AX at DSB sites and enhance the accession of the DDR proteins involved in chromatin mobility and HR repair [74,75]. Therefore, chromatin can be viewed as a multifaceted signaling platform that responds to both intracellular and environmental cues by

Table 2. Functions of different histone modifiers in DNA repair and DDR in plants.

Gene family	Member	Mutant phenotype	Function
Kinase	ATM (AT3G48190)	Altered seed genome stability and germination.	Involved in phosphorylation of γH2AX at DSB sites and thereby initiate DDR.
	ATR (AT5G40820)	Hypersensitive to genotoxic stress otherwise viable.	
Acetyltransferase/ Deacetylase	HAM1 (AT5G64610)	Seeds non-viable and impaired gametophyte development.	Involved in gene regulation associated with development and UV-B induced DDR.
	HAM2 (AT5G09740)	Seeds non-viable and impaired gametophyte development.	
	HAC1 (AT1G79000)	Alteration of flowering time.	
	HAF1 (AT1G32750)	Altered male gametophyte development.	
	HDA1 (AT4G38130)	Impaired embryogenesis and root shoot development.	Involved in chromatin modification under abiotic stress.
	HDA6 (AT5G63110)	Increased auxin-responsive gene expression and abnormal cotyledon.	
Methyltransferase/ Demethylase	CLF (AT2G23380)	Curled and involuted leaves with ectopic expression of AGAMOUS and APETALA3.	Function in somatic and meiotic HR repair and prevent over-replication associated heterochromatic DNA damage.
	ATXR5 (AT5G09790)	Impaired plant growth while overexpression lines are sterile.	
	ATXR6 (AT5G24330)	Impaired growth and leaf development.	
	MET1 (AT5G49160)	Late flowering phenotype.	
	MET2 (AT4G14140)	Retarded growth like auxin pathway impairment.	
	DDM1 (AT5G66750)	Hypersensitive response to gamma irradiation and increased mortality of root cells.	
	CMT3 (AT1G69770)	Single mutants without any visible phenotype but *drm1/drm2/cmt3* triple mutants are partially sterile.	
	ROS1 (AT2G36490)	Various developmental abnormalities at later stages.	Act as a Transcriptional Gene Silencing repressor under genotoxic stress.
Chaperone	CAF-1 (AT1G65470)	Abnormal leaf and flower morphology with disorganization of shoot and root meristem.	As H3/H4 chaperones they are involved in transcriptional regulation of HR/NHEJ genes and confer genome stability.
	ASF-1 (AT1G66740)	Aborted ovules with collapsed embryo sac.	
	HIRA (AT3G44530)	Impaired embryo development	
	NAP1 (AT4G26110)	Hypersensitive to genotoxic stress.	As H2A/H2B chaperones they play a key role in the regulation of nucleosome structure and dynamics.
	NRP1 (AT1G74560)	Shortened root with Hypersensitivity to genotoxic stress.	
	NRP2 (AT1G18800)	Shortened root with Hypersensitivity to genotoxic stress.	
	FACT (AT3G28730)	Impaired leaf growth and flower development.	

dynamic alteration of the epigenetic marks [76]. Thus, maintenance of plasticity of the epigenome is necessary for cellular differentiation and expression of phenotypic traits [77]. However, considering the importance of DDR signaling in the life process for the maintenance of genome stability with potential application in crop improvement, information on the chromatin structure remodeling and chromatin-mediated regulation of DDR and signaling remain mostly segmented in plants.

The ATP-dependent chromatin remodelers (ACRs)

The chromatin architecture modulates the expression of different DDR-associated genes in multiple ways. The ACRs are one of the key modulators of chromatin ultrastructure, regulating several DNA repair-associated genes. Previously, a plethora of studies has been conducted predominantly focused on the repair of DNA lesions via epigenetic regulators in yeasts and mammals [78–80], while corresponding information in plants remains far from

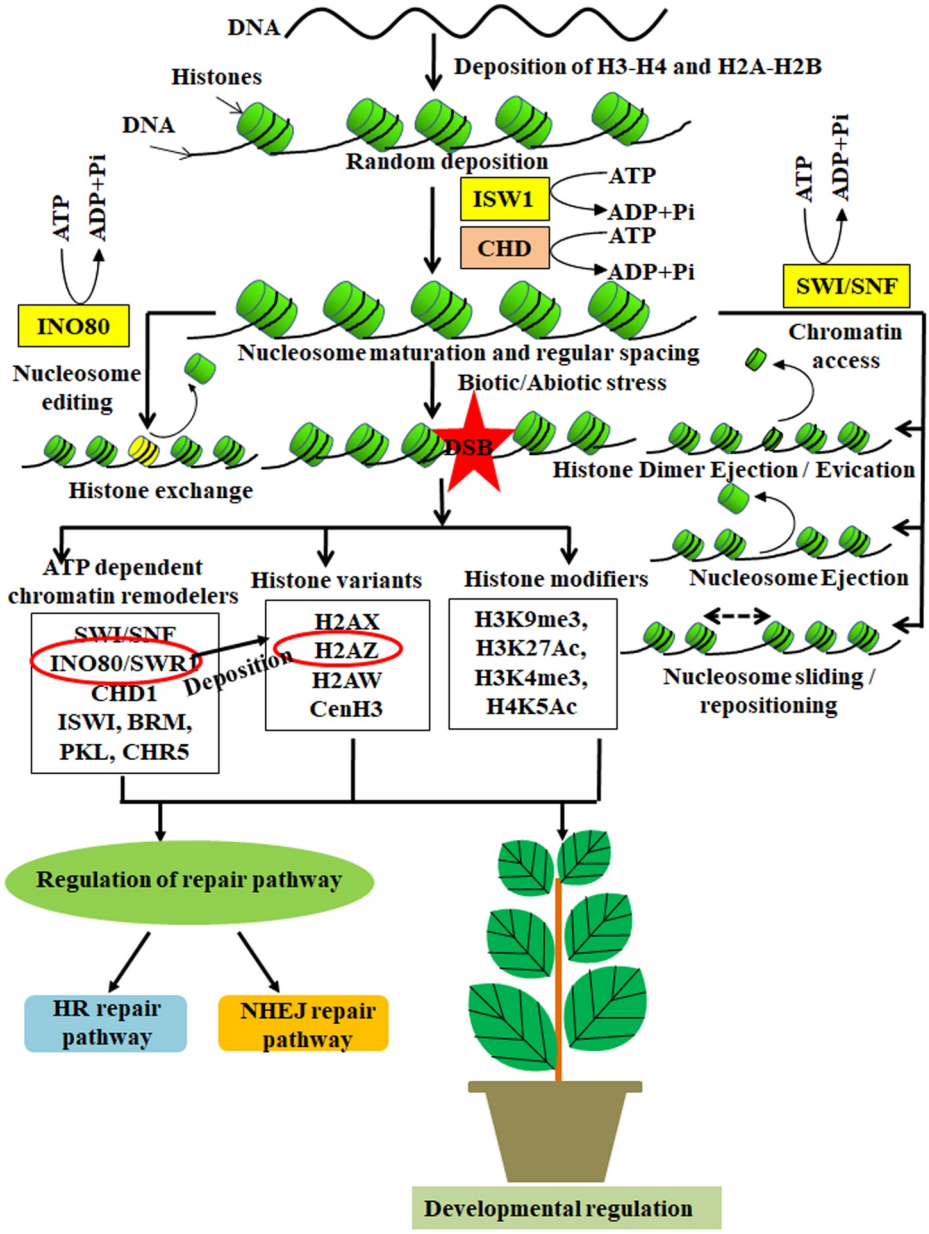

Figure 2. Schematic representation of ATP dependent chromatin remodelers (ACRs) associated with DNA damage response (DDR) in plants. following the replication of DNA molecules, the assembly histone dimers and tetramers are facilitated by two ACRs, namely ISW1 and CHD. these ACRs play a dual role, including histone maturation followed by nucleosome spacing. meanwhile, the SWI1/SNF family of remodelers promote the sliding and eviction of nucleosomes or a part of nucleosome through ATPase activity. the INO80 remodelers regulate the exchange of histones within the nucleosome. moreover, the INO80 family of ACRs regulates the genome-wide deposition of the histone H2AZ variant (marked in red circle). following the accumulation and detection of DSB in the plant genome, the ACRs, histone modifiers, and histone variants appear to regulate both plant growth response and repair machinery (HR and NHEJ), through alteration of chromatin dynamics.

being understood. The association of chromatin structure with DNA is modulated in three different ways, including, (a) chromatin remodeling via the activity of ATP-dependent chromatin remodelers (ACRs); (b) exchange of histones with histone variants, and (c) post-translational modifications (PTMs) in the nucleosome core particle [62]. Among the various forms of chromatin remodeling complexes, the ACRs use ATP to slide, exchange, evict or dismantle the nucleosomal organization and can alter histone composition at the sites of DNA lesion (Figure 2) [81,82]. The ACRs have different domain compositions with a common central ATPase (comprised of DExx

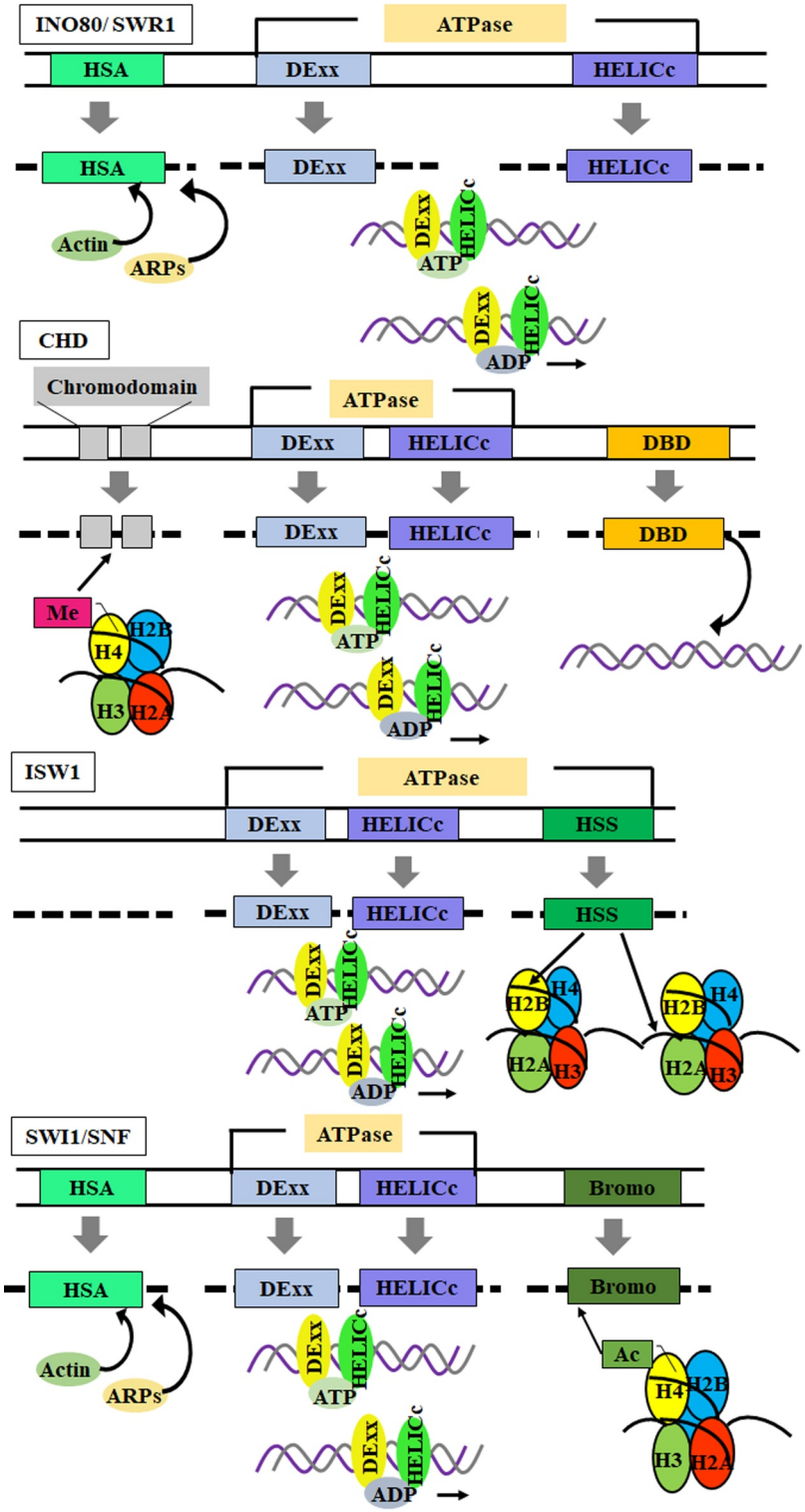

Figure 3. The ACRs can be categorized into four families based on their similarities and differences in domain composition and organization. the ACRs contain different functional domains, which perform diverse activities. the conserved ATPase domain (DExx and HELICc) confers translocase activity and helps them move toward the site of DNA damage (as indicated in black arrows). this ATPase domain is present in all the ACR families. The SWI1/SNF and INO80/SWR1 group of ACRs contain an HSA domain, which is involved in mediating the interaction with actin or actin-related proteins (ARPs). The bromodomain of SWI1/SNF remodelers interacts with acetylated lysine of histone H3/H4 (marked in a green-colored box). The CHD family of ACRs contains two tandemly arranged chromodomains, which facilitate the interaction with methylated histone H3/H4 (marked in pink-colored box). The DNA binding domain (DBD) facilitates the binding of CHD with DNA. The HSS domain of ISW1 interacts with nucleosomal or internucleosomal DNA. moreover, the HSS and DBD help to measure the distance between the nucleosomes through interaction with the linker DNA.

and HELICc) and HAS (Helicase SANT Associated), HSS (HAND-SLANT-SLIDE), chromodomain, and bromodomain [83] (Figure 3), which enable ACRs to interact with diverse groups of DDR proteins and DNA lesions. ACRs are multi-subunit complexes consists of a central DNA-dependent ATPase subunit similar to the SNF2-like family ATPases [84]. In plants and animals, the fate of stem cell differentiation is determined by chromatin remodeling factors. Plant chromatin remodelers differ from their animal counterpart in terms of the position and occurrence of the different domains, such as the chromodomain, bromodomain, and SANT domain [85]. The ATPase domain is related to the translocases of DEAD/H helicase. However, the function of true helicases is absent in ACRs. They cannot separate two annealed DNA strands, while can only recognize the different chromatin marks with the help of other protein domains of the remodeler complex [86] (Figure 3).

ACRs regulate a wide range of fundamental processes, including replication, transcription, and DNA damage response. Thus, the mutants lacking major chromatin remodelers display increased sensitivity to DNA damage with impaired DNA repair activity. Previously, Attikum and Gasser [87] have extensively reviewed the importance of ATP-dependent chromatin remodeling activity in facilitating the repair of DSBs. The nucleosomal occupancy is changed surrounding the DNA lesions by the activity of chromatin remodelers, ensuring accessibility of DNA repair proteins at the site of damage [88]. In yeast (*Saccharomyces cerevisiae*), ACRs have been shown to enhance the HR repair efficiency by increasing nucleosomal mobility [89]. In general, the chromatin remodeling complexes are highly conserved throughout evolution [88,90]. In plants, the ACRs are orthologs of yeast and mammalian counterparts and loss of function mutants display a similar response as in the case of DDR pathway-related mutants [91], suggesting functional conservation. However, as compared to yeast and mammals, in plants, information on the structure-function characteristics of chromatin remodelers and their association with DDR remains still limited. As like yeast and mammalian system, the plant genome possesses four conserved families of ATP dependent chromatin remodelers, namely INO80/SWR1, Switch/Sucrose non-fermentable (SWI/SNF), Chromodomain helicase DNA (CHD), and Imitation switch 1 (ISW1), which also play a key role in DDR signaling and DNA repair [92–94]. In addition, molecular-genetic studies mainly in the model system *Arabidopsis thaliana* have demonstrated that besides playing a crucial role in the regulation of chromatin structure stability, ACRs are important components in modulating plant growth and development, as discussed in the subsequent sections.

INO80/SWR1

One of the important members of ACRs is INO80/SWR1 family and the members are conserved in both animals and plants. The INO80/SWR1 chromatin remodelers regulate the expression of DSB repair pathway-associated proteins and modulate chromatin ultrastructure at the sites of DNA lesions. The INO80 subfamily chromatin remodeling complex was originally purified and characterized by yeast [95]. The INO80 complex contains a central ATPase subunit and 13–16 additional sub-units, which may vary among different species [81]. In yeast, mouse, humans, and *Arabidopsis*, the INO80 and SWR1 chromatin remodelers regulate the genome-wide distribution of H2A.Z at the transcriptional start sites (Figure 2) [72]. Recently, Wang et al., (2019) [51] have provided an extensive update on the functional aspects of INO80 and SWR1 chromatin remodeling complexes in plants. In *Arabidopsis, INO80* (*AtINO80*) was found to be involved in a dual role in the regulation of both transcription and HR repair [96]. In *Arabidopsis*, both HR and NHEJ mediated DSB repair is defective in the *atino80* mutant, but *atswr1* mutants show impaired NHEJ repair only [96], indicating interactions of INO80/SWR1 family of remodelers with the DSB repair pathway. Defect in *AtINO80* expression in *Arabidopsis* leads to error-prone HR mediated DSB repair [96]. The Actin-related protein 5 (ARP5), a subunit of INO80, has been shown to play an important role in multicellular development and genome stability in *Arabidopsis* [97]. *Arabidopsis* mutant lacking the *ARP5* subunit

function showed hypersensitivity to several genotoxic agents, including hydroxyurea, methyl methanesulfonate (MMS), and bleomycin than the wild-type plants [97]. The *arp5-1* mutant has been found to display reduced plant height with shorter hypocotyl and primary root length than wild-type plants, while the complementation lines with *gARP5* transgene (*arp5-1/gARP5*) exhibited significant recovery of such growth defects. Again, in *Arabidopsis*, loss of function of other INO80 subunits, including actin-related protein 4 (*arp4*), actin-related protein 6 (*arp6*), actin-related protein 7 (*arp7*) resulted in delayed floral organ development and flowering time along with retardation of root growth [98]. On the other, the *Arabidopsis atswr1-c* mutant exhibits an early flowering phenotype due to the dysfunction of several genes associated with flowering [99,100]. In addition, loss of function of other subunits of AtSWR1, *arp6*, PHOTOPERIOD INDEPENDENT EARLY FLOWERING 1 (*pie1*), and SWR1 COMPLEX SUBUNIT 6 (*swc6*) (involved in H2A substitution by H2A.Z) have shown enhanced sensitivity to DNA damage [101,102]. Furthermore, the reduced fertility phenotype associated with the *atswr1-c* mutant has indicated its role in meiosis [102]. Taken together, these observations have demonstrated the crucial role of INO80/SWR1 family chromatin remodelers in influencing DDR and HR-mediated DSB repair with subsequent profound influence on plant growth and development.

CHD

The CHD group of chromatin remodelers also play a key role in the regulation of chromatin architecture and thus regulate plant growth and development like the INO80/SWR1 family of ACRs. The CHD proteins are divided into three subfamilies, namely Chromodomain helicase DNA 1 (CHD1), Chromodomain helicase DNA 3 (CHD3), and Chromodomain helicase DNA 7 (CHD7) [103]. *Arabidopsis* genome encodes four families of CHD chromatin remodelers, such as Chromatin Remodeling Protein 5 (CHR5), which is a CHD1 homolog and the other three are CHD3 homolog [103]. Deletion of *CHD1* negatively affects the transcription of highly active genes in yeast [104]. CHD1 protein is negatively regulated by chromodomains. Deletion or point mutation that disrupts the chromodomain of the interface of both chromodomain and translocase domain, enhances the DNA binding and DNA mediated ATP depletion efficiency. In *Arabidopsis, CHD1* directly induces the expression of several genes involved in seed maturation [105], while CHD1 protein mutants for the SANT-SLIDE domain showed lower DNA and nucleosomal occupancy [106]. The CHD3 homologs, PICKLE (PKL), PICKLE related1 (PKR1), and PICKLE related2 (PKR2) are involved in plant development and the induction of stress-responsive genes [92,103]. The chromodomain associated with CHD3 interacts with H3K4me3 (Figure 3) and regulates the stress response in both *Drosophila* and humans [92]. Interaction of mammalian CHD1 and Amplified in liver cancer 1 (ALC1) complexes have been correlated with DDR [88] and their ATPase subunits are encoded as CHR5 and Chromatin Remodeling Protein 10 (CHR10) in *Arabidopsis*. Recent studies have also demonstrated the role of *AtCHR5* in the maintenance of nucleosomal occupancy and plant immune response [107]. *CHR5* has been shown to promote the enhanced level of H3K27me3 formation and upregulation of genes related to seed maturation [105], while *CHR5* acts antagonistically with Decreased DNA Methylation1 (*DDM1*) and mutants of *CHR5* display dwarf phenotype [108].

ISW1

The ISW1 represents a small family of chromatin remodelers in plants. The ISW1 group of enzymes was originally discovered in *Drosophila* [109]. Subsequently, homologs of ISW1 were identified in plants, yeast, mice, and humans [108,110]. In *Arabidopsis*, two ISW1 chromatin remodelers Chromatin Remodeling Protein 11 (CHR11) and Chromatin Remodeling Protein 17 (CHR17) directly act as a repressor of FLOWERING LOCUS T (FT) and SEPALLATA3 (SEP3). Mutation of both these genes results in an early flowering phenotype [92,111]. The phenotypes of *chr11/chr17* double mutant line have indicated the involvement of *CHR11* and *CHR17* in the regulation of floral organ identity [112]. Expression

studies revealed that *CHR11* is highly expressed in gametophytic and sporophytic tissues than *CHR17*. During the period of callus regeneration, *CHR11* showed enhanced expression, suggesting phytohormone independent activity [113]. Plants under continuous environmental stress, with the overexpression of Chromatin Remodeling Protein 12 (*CHR12*) displayed temporary inhibition in primary bud formation and primary stem growth [114]. ISW1 interacts with both the upstream and downstream coding regions of different genes in *Arabidopsis*, facilitating transcriptional machinery to communicate with the cis-elements [81]. In *Saccharomyces cerevisiae*, knockout mutations of *ISW1* and *CHD1* lead to loss of histone position as well as increased histone exchange [115]. Moreover, the ATPase and C-terminal domains of ISW1 (HAND, SANT, and SLIDE (HSS) (Figure 3) also play an important role in chromatin remodeling. *In vitro* studies in *Arabidopsis thaliana* have revealed that *ISW1* promotes chromatin assembly and also regulates nucleosome spacing and organization after replication [116]. However, in plants, a direct link of ISW1 proteins with DDR needs further investigation.

SWI/SNF

SWI/SNF is another large family of ACRs and is involved in the regulation of chromatin dynamics in the plant genome. The SWI/SNF complex comprises 9–13 subunits. The central ATPase subunit is composed of an ATPase domain (DExx and HELICc) with additional flanking domains, like bromodomain and HSA (Helicase SANT Associated) (Figure 3). The SWI/SNF complexes play a major role in transcriptional regulation, chromosome stability, and maintenance of the nuclear organization. From the screening of 14 *Arabidopsis* SWI2/SNF2 RNAi lines, 11 remodeling genes were identified and shown to be involved in DNA repair to confer resistance against genotoxic agents [7,91]. In general, all land plants encode three types of SWI/SNF subfamily ATPases: BRAHMA (BRM), SPLAYED (SYD), and MINUSCULE (MINU) [117]. However, the *Arabidopsis* genome possesses four SNF2 family members, including BRM, SYD, MINUSCULE 1 (MINU1), and MINUSCULE 2 (MINU2). The C-terminal bromodomain of BRM participates in the interaction with acetylated lysine residues in the N-terminal tails of H3 and H4 histones [117]. Previously, the role of Sucrose Non-Fermenting 2 (SNF2) protein in histone eviction for facilitating RNA PolII elongation process has been characterized [118]. Besides, SNF2 appeared to be involved in the telomeric gene silencing and DSB repair process [119]. The BRM proteins are post-translationally modified and stabilized by sumoylation via *Arabidopsis thaliana* methyl methanesulfonate sensitivity 21 (AtMMS21). Therefore, downregulation of *AtMMS21* leads to depletion of BRM proteins. BRM and histone H2AZ are colocalized at several loci regulating gene transcription [120]. It was also observed that *brm* mutant exhibit dwarf phenotype, delayed flowering, and underdeveloped floral organs, similar to gibberellin responses [121]. Single mutants of either *brm* or *syd*, though showed normal embryo development, double mutants of *brm/syd* showed significant developmental defects and growth arrest at the heart stage of embryo development. The knockout mutants of *Arabidopsis thaliana* Switch 3 c (*atswi3c*) gene exhibit similar phenotypic defects like *brm* mutants except that they are not sterile. However, *atswi3c/brm* double mutants exhibit functional sterility, indicating their involvement in post-embryonic development [122]. In *Arabidopsis*, BRM interacts and regulates the activity of histone deacetylase, HD2C, responsible for the repression of several heat-activated genes [123]. The chromatin remodeler *AtBRM* complex is involved in DDR and HR repair [91] but their specific role in the DDR pathway in plants remains to be experimentally characterized [92]. The plant-specific protein, SWI1 regulates the switch between mitosis to meiosis. Histone H3 (H3K4me2) interacts with a plant homeodomain (PHD) protein Male meiocyte death 1 (MMD1), which regulates the transcription during *Arabidopsis* male meiocyte development [124]. Mutants of *swi1* exhibit altered distribution of H3K4me2 [125]. In animal cells, SWITCH 3B (SWI3B), a subunit of SWI/SNF complex, interacts with Structural Maintenance of Chromosomes protein 5 (SMC5) protein. SMC5 is recruited at the locus of DNA DSB repair [62]. It has been found that SWI3B helps to dissociate SMC5 from its original location to move toward the DSB site. Downregulation of *SWI3B* results in the inefficiency of SMC5 to move toward the DSB site with

subsequent enhancement of DNA damage accumulation [126]. Various cold stress response genes, including Alcohol dehydrogenase (*ADH*), Cold Regulated 15A (*COR15A*), Cold Regulated 47 (*COR47*), Kinase 1 (*KIN1*), Kinase 2 (*KIN2*), Responsive to Desiccation 29A (*RD29A*), and Responsive to Desiccation 22 (*RD22*) showed differential expression (upregulated or downregulated) in *swi3c* mutant plants [127]. The *swi3c/ice1* double mutant of *Arabidopsis* exhibits a severely dwarf phenotype with complete sterility [128]. Overall, these results have indicated the important role of ACRs in modulating chromatin structure stability in DDR and also play an essential function in regulating plant growth and development.

Chromatin remodeling in plants vs. mammals: plant genome lacks topologically associating domains and chromatin loops

The chromatin remodelers are associated with multiple essential functions in both animals (mammals) and plants and the structural components of ACRs are highly conserved in all eukaryotes. Various features of chromatin remodeling proteins are common in both animals and plants, with some distinct differences in their function [16]. In both plants and animals, chromatin remodelers are involved in the regulation of stem cell differentiation, developmental transitions, and stress responses [92]. For example, the conserved subunits of *INO80* and *ARP5* in yeast, mammals, and plants are involved in the regulation of DNA repair and development [94]. Moreover, several small non-coding RNAs, involved in epigenetic modifications of DDR-associated genes, are found to be common in both animals and plants [129]. Although chromatin conformation and remodeling activities have been widely investigated in mammals, information remains still limited in plants. Recent techniques, which combine chromosome conformation capture (3 C), known as Hi-C, and high-throughput sequencing, have revealed that mammalian chromatin folding has three hierarchical levels, compartment, domains, and loops, which are crucial for transcriptional regulation. Similar structures were also found in plants; however, appeared to be functionally different [130]. Moreover, polyploidy is a natural phenomenon in the plant kingdom. It is an important characteristic for speciation and crop domestication. Recent studies have revealed that epigenetic modification can alter homologous gene expression, which helps the polyploid plants to adapt to changing environments [131].

There has been a lack of substantial information regarding the relationship between genome size and chromatin remodeling. Heterochromatin condensation in the context of the size of the nucleus was found to play a crucial role in photomorphogenesis [132]. Moreover, the dye incorporation studies have revealed a positive correlation between genome size and chromatin compaction, probably affecting gene expression [133]. The Hi-C-based approaches have revealed that topologically associating domains (TADs), which demarcate the boundary of genome territories in *Drosophila* and mammals do not seem to be present in *Arabidopsis* [134,135]. Moreover, the open region of chromatin in plants exhibits less tissue-specific dynamics than mammals [136]. The lack of TADs and chromatin loops in plants may be responsible for the distinct pattern of gene regulation, differentiating them from mammals [130]. This probably represents one of the unique features of the plant genome, differentiating them from other eukaryotic organisms. However, further research is essential to understand the link between the chromatin remodeling mechanism in plants and mammals and the impact of genome size on the efficiency of chromatin remodeling activity.

The RAD epistatic group of genes and maintenance of chromatin dynamics via homologous recombination

The *RAD* epistatic group of genes are conserved in both plants and animals. Various studies have revealed that the *RAD* group of genes play a crucial role in HR-based repair pathways and mutation of any one of this group of genes leads to increased sensitivity to various genotoxic agents. In eukaryotes, Radiation sensitive 54 (RAD54), a member of the SWI2/SNF2 family of chromatin remodelers play an important role in HR-mediated DSB repair via its intrinsic DNA dependent ATPase and DNA translocase activity. In *Arabidopsis*, RAD54 modulates chromatin structure via interaction with RAD51 and is

mainly involved in synthesis-dependent strand annealing (SDSA) mechanism of DSB repair by HR pathway (Figure 1) [91,137,138]. Plants, deficient in RAD54 function show increased sensitivity to gamma irradiation, disruption of HR, and altered DDR in mitotic cells due to lack of DNA supercoiling and chromatin stability [139]. Multiple studies have indicated the key role of RAD54 in the regulation of spatiotemporal arrangement of homologous foci with DSB sites and its accumulation at the damaged sites, resulting in the formation of RAD54 foci [140]. In eukaryotes, RAD54 is involved in strand exchange and modulation of chromatin ultra-structure during HR (Figure 1) [141]. RAD54 stabilizes RAD51 and stimulates strand invasion and exchange in HR in both mitotic and meiotic cells [142]. In *Arabidopsis*, RAD54 loss of function leads to impairment of strand pairing activity though the plants remain viable. In plants, RAD55 and RAD57 are the RAD51 paralogue in yeast and play a crucial role in HR-mediated repair during meiosis. RAD17, another RAD group of protein in *Arabidopsis* shows increased expression in irradiated seedlings. AtRAD17 along with AtRAD9 directly participate in HR repair after induction of DSBs [143].

Cohesin is a large multi-subunit protein complex and is consisting of two structural maintenance groups of proteins, including Structural maintenance of chromosomes protein 1 (SMC1) and Structural maintenance of chromosomes protein 1 (SMC3) and two α-kleisins, namely Sister chromatid cohesion protein 1 (SCC1, also known as Radiation sensitive mutant 21 or RAD21) and Sister chromatid cohesion protein 3 (SCC3). Previous studies have established functional involvement of α-kleisins in the regulation of HR-mediated DSB repair [144]. In *Arabidopsis, RAD21* is a small family of three homologous genes comprising *AtRAD21.1, AtRAD21.2, AtRAD21.3* [145]. Earlier studies in *Arabidopsis* have implicated the function of the *RAD21* group of genes in the regulation of the dynamic nature of chromatin structure and DDR. Imbibed seeds of *atrad21.1* mutant displayed hypersensitive response following induction of DSBs by genotoxic agents, like gamma radiation. The phenotype was found to be more severe in the case of *atrad21.1/atrad21.3* double mutants [144]. *De novo* synthesis of AtRAD21.1 and AtRAD21.3 at the G2/M phase was observed after the induction of DSBs. After induction of DSBs, *de novo* cohesion between two sister chromatids is mediated by RAD21 homologs in eukaryotes. Like other chromatin remodeler proteins, *atrad21.3* mutants exhibit growth defects, mainly delayed flowering response [144]. Additional studies have demonstrated the role of the RAD21 group of proteins in chromosomal segregation via sister chromatid entrapment [146], chromatin alignment, and post-meiotic pollen development [147].

Strong association of chromatin remodeling and homologous recombination frequency and regulation of plant growth and developmental response

The chromatin remodeling complexes appear to play an essential role in the regulation and activation of the HR repair machinery in plants. Moreover, the *RAD* epistatic group of genes is closely associated with HR-mediated repair. Among the two major pathways of DSB repair, although the NHEJ pathway represents the predominant mechanism of DSB repair in somatic cells of plants, the HR-based repair pathway is considered the most error-free mechanism of DSB repair and represents one of the essential sources of genetic diversity and new allelic combinations. Therefore, understanding the HR pathway and its interactions with other repair pathways is essential for the implications of the DDR signaling cascade for the manipulation of HR events as part of the crop improvement program. The dynamic nature of chromatin elicits the potentiality of plant survival against different stress conditions. Multiple pieces of evidence have indicated that chromatin remodelers play an important role in controlling plant response under stress conditions. ATP-dependent chromatin remodelers are involved in the maintenance of genome stability through changing the dynamics of chromatin in the context of regulation of HR events.

Accumulating evidence has revealed that in plants, defects in expression of chromatin remodelers or subunit mutants of chromatin remodelers lead to enhanced sensitivity to various genotoxic agents along with impaired DSB repair [94,97]. These effects were found to be strongly linked with defects in growth and developmental response in plants, with impaired apical meristem organization, dysfunction of floral genes, and flowering response [92,100,148]. Together, these observations have indicated the crucial role of chromatin remodelers and DDR signaling in regulating normal growth and developmental events in plants. Chromatin remodelers are also involved in the cross-talk with the phytohormones biosynthesis pathway. The SWI/SNF ATPases family members are directly involved in regulating phytohormone biosynthesis and responses [149]. The *syd* and *brm* loss of function mutations in *Arabidopsis* showed impaired gibberellic acid (GA) and auxin signaling networks [150]. Both PKL and BRM positively regulate GA-mediated signaling pathways [121]. Phosphorylation and dephosphorylation of BRM regulate ABA synthesis and thereby be involved in the regulation of seed dormancy [151]. In *Arabidopsis*, CHD1 directly induces the expression of several genes involved in seed maturation [105]. Again, in *Arabidopsis*, two ISW1 chromatin remodelers, CHR11 and CHR17 directly act as a repressor of *FT* and *SEP3*, and mutation of both these genes results in early flowering phenotype [92,111]. The *chr11/chr17* double mutant phenotypes have suggested a link with floral organ identity [112]. Together, these observations have provided strong evidence on the key role of the chromatin remodelers in regulating several important genes involved in controlling plant growth and development through direct and indirect interactions with the plant growth regulators.

The interplay between epigenetic regulators and chromatin remodelers regulates DDR signaling

The pluripotent epigenetic factors, including the chromatin remodeling activity, post-translational modifications of histone proteins, and histone chaperones play a crucial role in maintaining the structural stability of chromatin in a coordinated manner and thus regulate the DDR signaling and repair pathways. The dynamic nature of chromatin at the point of DNA lesion is crucial for the efficient detection and repair by DDR machinery [152]. Post-translational modifications (PTMs), in general, affect the chromatin structure in three ways- either through intrinsic effects on histone–histone interaction, through extrinsic effects on inter-nucleosome contacts, or by providing binding sites for effector molecules. PTMs of histones have a profound impact on chromatin structure to increase the accessibility of DDR factors to DNA strands to facilitate the repair of DNA lesions. Various forms of post-translational histone modifications, including methylation, phosphorylation, acetylation, and ubiquitylation [153,154] facilitate the accessibility of repair machinery at the damage site on the chromatin. In *Arabidopsis*, after irradiation with gamma-ray, expression of DDR related genes, such as CBL- Interacting Protein Kinase 11 (*CIPK11*), Replication Protein A 1E (*RPA1E*), Gamma-Irradiation and Mitomycin C Induced 1 (*GMI1), RAD51*, Argonaute 2 (*AGO2*) are associated with H3K4me3 or H3K9ac [155]. Acetylation of histone H3 and H4 facilitate the accession of DDR proteins at the site of damage after induction of DNA damage [93,156].

The histone chaperones modify the nonspecific interaction between DNA and histones. In general, histone chaperones have been divided into two types, H2A-H2B and H3-H4 and both types are evolutionarily conserved [157]. Chromatin Assembly Factor-1 (CAF-1), ANTI-SILENCING FUNCTION1 (ASF1), and HISTONE REGULATORY HOMOLOG A (HIRA) are the H3-H4-type chaperones, whereas the Nucleosome Assembly Protein1 (NAP1) and Facilitates Chromatin Transcription (FACT) belong to the H2A-H2B group (Figure 4). ASF-1 contributes to the maintenance of chromosome integrity, heterochromatin formation, and transcriptional regulation of repair genes by targeting acetylated H3 and H4 onto newly synthesized DNA, allowing *de novo* assembly of nucleosomes (Figure 4) [67,158]. In *Arabidopsis*, BRUSHY1 (*BRU1*), which encodes a CAF protein, is involved in the regulation of

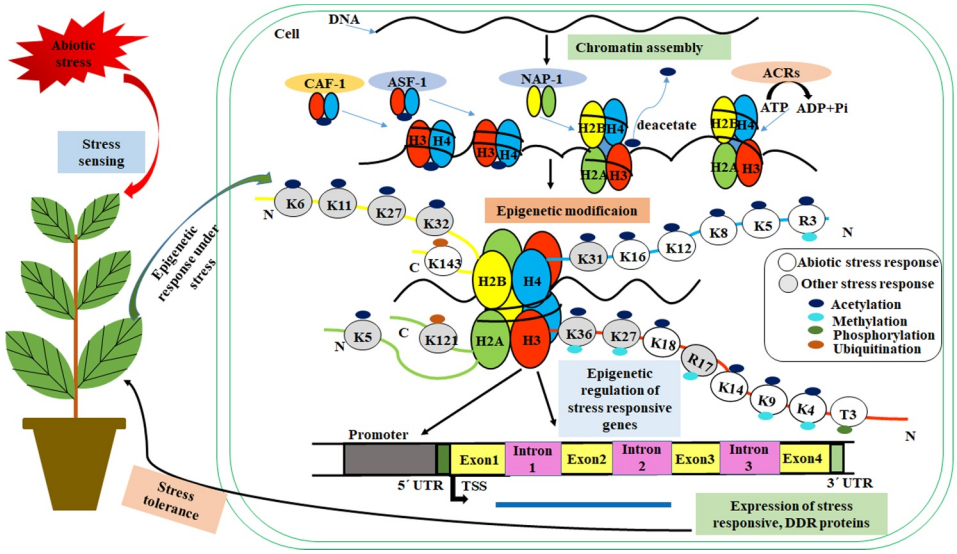

Figure 4. Schematic representation showcasing the function of histone chaperones and epigenetic marks of histones in plants under abiotic stress. the assembly of histones and their organization into nucleosomes is regulated by histone chaperones. two daughter DNA molecules are organized into chromatin in a stepwise manner. initially, H3-H4 chaperone proteins CAF-1 and ASF-1 deposit H3-H4 tetramers on nascent DNA strand, followed by the deposition of histone H2A-H2B dimers via NAP1 (H2A-H2B chaperone protein). the ACRs also play a crucial role in the construction of the final nucleosome structure. the acetylated H3-H4 becomes deacetylated in their final configuration. following abiotic stress, various epigenetic modifications occur at the N and C terminal amino acids of H2A, H2B, H3, and H4 (shown in white circles). different forms of epigenetic modifications (acetylation, methylation, phosphorylation, and ubiquitination) are indicated by different colors in the figure. the epigenetic modifications related to other stresses are indicated by the gray circle. these epigenetic modifications regulate the activity of different stress-responsive and DDR-associated genes involved in developing stress tolerance in plants.

replication and the DDR pathway [159]. Another H3/H4 chaperone, HISTONE REGULATOR A (HIRA), which is conserved in plants, is mainly involved in the deposition of nucleosomes at damaged sites and the regulation of transcriptional dynamics [160]. Together, this information has suggested that understanding chromatin configuration at the sites of DNA damage is an important characteristic of the genome in the regulation of the DDR process [152]. The molecular mechanism of DDR pathways and their regulation via chromatin modification has been significantly advanced in plants after the completion of the *Arabidopsis* genome project. It should also be kept in mind that, plants in the field conditions are exposed to multiple stress factors. Several studies have suggested that the interplay of epigenetic regulators through changing the configuration of chromatin and DNA damage repair effector genes play a crucial role in the efficient detection, signaling, and repair of the DNA lesions [94,161,162] (Figure 4).

Chromatin remodeling during seed germination and role of TRRAP pseudo-kinase

Dynamic changes in chromatin ultrastructure were observed at the time of germination of seeds. Both chromatin remodelers and epigenetic modifiers are strongly associated with chromatin modifications during seed germination. The epigenetic modifiers are not only associated with DDR and DNA repair in plants but also regulate plant development. Seed germination is influenced by multiple exogenous and endogenous factors. Uniform seed germination and the successful establishment of the seedling are intimately associated with crop yields. Early imbibition stages of seed germination involve coordinated and complex response, which includes the activation of antioxidant mechanisms and various DNA repair pathways to constitute the pre-germinative metabolism cascade [163]. Earlier studies in *Arabidopsis* and also in *Medicago truncatula* have demonstrated up-regulated expression

of DNA repair genes [164,165] and emphasized the key role of ATM kinase in the maintenance of seed embryo genome stability [166]. In addition, distinct transcriptional changes and chromatin remodeling activities, including the histone acetylation/deacetylation mechanism play a crucial role in the developmental transition during seed germination. The chromatin remodelers facilitate the recruitment of the DNA repair machinery at the site of DNA lesions through disruption of DNA-histone interactions [167]. Recent studies in *Arabidopsis* have demonstrated that after accumulation of DNA breaks, the histone chaperone NRP1 (NAP (NUCLEOSOME ASSEMBLY PROTEIN)-RELATED PROTEIN) binds to chromatin, allowing destabilization of nucleosome and recruitment of the repair enzymes at the damaged sites in DNA [168]. Recent studies in *Drosophila* and human have revealed the role of a transcriptional activator TRRAP (TRANSFORMATION/TRANSACTIVATION DOMAIN-ASSOCIATED PROTEIN), an ATM/R-related pseudokinase in scaffolding several histone acetyltransferase (HAT) complexes and their recruitment to chromatin during DNA repair [169,170]. The DDR components have been suggested to preferentially recruit the TRRAP-containing HAT complexes at the sites of DSBs in DNA. However, corresponding information on TRRAP mediated chromatin modification remains still limited in plants. Recent studies in *Medicago truncatula* have revealed the correlations between DNA Repair, antioxidant response, and chromatin remodeling activities in the context of seed repair response during germination and demonstrated the link between DNA repair and chromatin remodeling through 8-OXOGUANINE GLYCOSYLASE/LYASE 1 (*OGG1*) and *TRRAP* genes [171].

Outlook and conclusion

Crop improvement is intimately associated with genetic diversity to achieve the generation of the novel combination of genes for desired phenotypes [172]. Spontaneous mutations, which occur via the activity of endogenously generated ROS, transposon insertions, replication defects, and cosmic radiations represent some of the potential and natural sources of induction of genetic

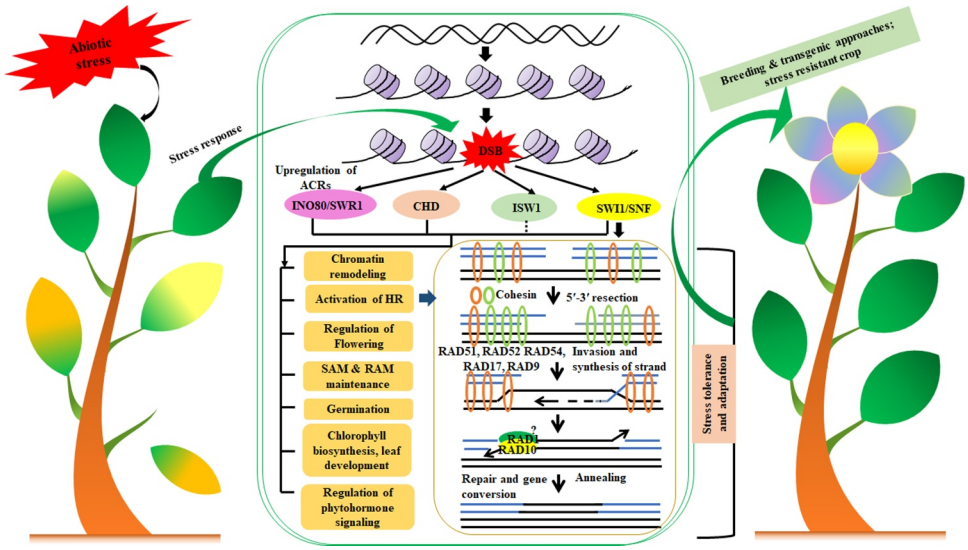

Figure 5. Schematic representation illustrating the ACRs can be the potential targets of breeding and transgenic approaches for the generation of stress-resistant transgenic crops. the DSBs are formed in the plants' genome under different abiotic stresses, which upregulates the expression of different families of ACRs in the plant genome. however, a direct link between ISW1 and DDR has not been observed in plants (indicated with dotted line). the ACRs modulate the expression of different repair genes and also some other genes involved in plant development. the HR repair pathway is considered the most error-free repair mechanism, where the RAD epistatic group of genes and cohesin play a crucial role in repairing the damaged strand via interacting with different DDR proteins. The interplay between DDR mechanism and growth responses develops stress tolerance and adaptation in plants. therefore, breeding and transgenic approaches targeting ACRs and HR repair machinery provide a novel approach for the generation of stress tolerance in crops (see text for details).

variations in plants. However, the rate of spontaneous mutation is very slow and over time, many of the present-day crop plant species have already reached a status of low genetic diversity. Together, these situations have evoked the need for the introduction of more efficient and potential crop improvement methods [173] to keep pace with the ever-increasing demand for global food production. It has been suggested that the future crops will probably express multiple transgenes as targeted and highly complex stacked trait crops to provide tolerance to a wide range of abiotic and biotic stress factors. Moreover, it has now been realized that crop improvements by modification of the transgenic events via gene targeting and precise genome editing approaches have several advantages over random transgenic events (Figure 5). To overcome the limitations of breeding and plant transformation processes, technologies also continue to emerge to provide highly efficient, flexible, and more potential gene targeting approaches based on the manipulation of intra genomic HR events with designed nucleases for the precise introduction of desired DNA sequence through the induction and repair of DSBs. Therefore, crop improvement through gene targeting and genome editing depends on the intrinsic DDR signaling and interplay between DDR signaling and chromatin structure stability (Figure 5). In plants, DDR, signaling, and repair constitute robust machinery and interlinked, highly complicated crosstalks exist between various repair and recombination pathways. The DDR cascade and the different repair pathways are regulated in a cell-cycle, tissue-specific, and developmental stage-dependent manner. Considering the highly potential error free-repair of DSBs, much emphasis has been given in recent years to understand the various facets of the HR repair pathway, including the nature of the broken DNA ends in DSBs and the regulatory switch which controls the cellular decision to select between the HR and NHEJ pathway of repair after the induction of DSBs in the genome [174]. Apart from the studies on the interactions between the HR and NHEJ pathways, significant progress has been made during the past couple of years to unveil the crosstalk between phytohormones and DSB repair pathways [175], between HR and other major repair pathways, including MMR [176], NER [177] and BER [178]. Based on these, emphasis has been given to enhancing the recombination frequencies through the manipulation of the existing crosstalk between various recombination-mediated DNA repair pathways [179]. Therefore, in-depth study on various aspects of DDR and associated signaling cascade, different repair pathways, and the dynamic chromatin remodeling activity is essential to further provide meaningful information for the improvement of the current approaches and designing potential strategies for the improvement of crop health and productivity in an efficient and environment-friendly manner.

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