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DNA Repair in Plants

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Contents

1. Introduction

Plants are affected by various environmental stresses which they cannot avoid by moving. DNA in plants is continuously damaged by the ultraviolet (UV) irradiation in sunlight (Figure 1). Green plants obtain energy through photosynthesis and cannot survive without light. Plants generally have a higher tolerance for UV than animals due to the absorption of UV by waxy substances on leaf surfaces, cell walls, and intracellular chemical compounds such as flavonoids.[1−7] The UV that is not absorbed induces DNA damage such as the formation of cyclobutane pyrimidine dimers (CPDs) and (6−4) photoproducts. Field-grown crops such as wheat are also known to suffer continuous UV-induced DNA damage.[9] Furthermore, due to the formation of reactive oxygen species (ROS) in cells by UV irradiation, biotic stresses, and secondary metabolism, cellular components, including DNA, are oxidized and are thus susceptible to oxidative modifications. In addition, the fidelity and integrity of DNA are constantly challenged by chemical substances in the environment, ionizing radiation, and errors that occur during DNA replication or proofreading (Figure 1). This accumulated damage blocks a number of critical processes, such as

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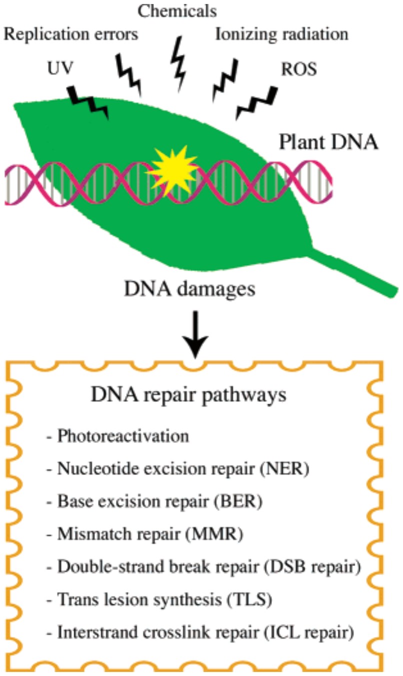

Figure 1. Plant DNA damage and DNA repair. DNA in plants is constantly damaged by environmental stresses. Plants have several DNA repair pathways to protect themselves.

transcription and replication, and can eventually cause cell death, which leads to undesirable effects on the growth and yield of plants.[10−13]

Plants have evolved several DNA repair pathways (Figure 1). While previous studies on DNA repair have mostly focused on animals and yeast cells, recent analyses of UV tolerance and DNA repair have addressed the responses of plants to environmental factors and to the mechanisms of stress resistance in plants.[14−18] An additional basis for molecular analyses has been provided by the completion of genome sequencing projects in model plants such as rice and *Arabidopsis*.[19−21] Completed genome sequences allow the identification of entire gene groups related to DNA repair in higher plants. The recent advances in understanding the mechanisms of protection against DNA damage and of plant DNA repair will be described here.

2. Genome Projects and Plant DNA Repair

Completion of the model dicot *Arabidopsis* and monocot rice genome sequencing projects[19−21] gives researchers access to complete genomic sequences and structures, and has introduced a new phase in the study of DNA repair in higher plants. The availability of high quality nucleic acid sequences has provided a powerful tool for genetic research, but the inherent limitations of genomic sequence databases, such as the amount of nonannotated sequence that will need to be identified by proteomics or traditional genetics, means that some genes that are unique members of a DNA repair system may go undetected for the present.

2.1. Species Used for the Study of DNA Repair in Higher Plants

Arabidopsis is a small plant with a short generation time (about 6 weeks), that has been used extensively as an experimental model in plant genetics for a long time (Figure 2), in part because of its exceptionally small genome (130 MBp, $n = 5$). The *Arabidopsis* genome sequencing project was completed in 2000 and was the first completed in higher plants.[19] In addition to the full genomic sequence, a number of research tools such as a series of T-DNA insertion mutants are available in this species, making it the most suitable model dicotyledonous plant for research. Many UV-sensitive and UV-resistant mutants have been isolated, and DNA repair has been studied in *Arabidopsis*.[15]


Arabidopsis thaliana


Oryza sativa

Figure 2. Species used for the study of DNA repair in higher plants. *Arabidopsis thaliana* and *Oryza sativa* (rice) are mainly used for the study of plant DNA repair.

About half of the world's population uses rice as staple food, making rice the most important food crop. Rice, however, is subject to a number of devastating diseases, it is sensitive to environmental conditions such as soil salinity and heavy metals, and it has some critical nutritional shortcomings. Therefore, molecular studies of rice are increasingly important for the world's agriculture.[22] Rice has a small genome (430 Mbp, $n = 12$) compared to other staple grain crops such as wheat (15 Gbp) or maize (2.5 Gbp). The rice genome sequencing project, with Japanese initiative, was finished in 2004.[20,21] The genome sequence of rice has a high degree of synteny with wheat and maize. Therefore, the understanding of genetic and physiological processes obtained in rice is largely applicable to other cereals, making rice an ideal model crop.[22,23] Research databases such as the full-length cDNA project database (KOME; knowledge-based *Oryza* molecular biological encyclopedia)[21] and libraries of transposon-induced mutants are also available for rice.[24] Furthermore, the mechanisms of tolerance to stresses such as disease, low temperature, and drought are being studied in rice. The study of DNA repair in rice will likely play a significant role in the future development of practical agronomic applications.

Recently, increases in UV radiation (especially UV-B) on the surface of the earth because of ozone depletion have become a serious problem.The depletion of the ozone layer became evident as the so-called ozone hole expanded over the Antarctic in the 1980s. The total amount of atmospheric ozone has continued to decrease, making DNA repair in the world's most important food crop even more important in the future.

Table 1. DNA Repair Genes in Rice

pathway	gene	function/remarks	accession
photoreactivation	*CPD photolyase*	removal of CPD	AK111418
	(6-4) photolyase	Rremoval of (6-4) photoproduct	AP005008
nucleotide excision repair (NER)	*(XPA)*	binds to DNA damage	
	XPB	DNA helicase, subunit of THIIH	AK060447
	XPC	binds to DNA damage	AK102608
	XPD	DNA helicase, subunit of THIIH	AK099724
	XPF (Rad1)	5′ incision	AK068556
	ERCC1 (Rad10)	5′ incision	AK070764
	XPG (Rad2)	3′ incision	AC123568
	UV-DDB1	UV damaged DNA binding protein-1	AK065508
	UV-DDB2	UV damaged DNA binding protein-2	AB082381
	Rad23	binds to DNA damage	AK064881
	Rad23	binds to DNA damage	AK069065
	Rad23	binds to DNA damage	AK103728
	Rad23	binds to DNA damage	AK061556
	CSA	transcription-coupled NER	AK111811
	CSB	transcription-coupled NER	AK064456
	CSB	transcription-coupled NER	AK071717
	CSB	transcription-coupled NER	AK099822
	XAB2	transcription-coupled NER	AK066726
	MMS19	transcription-coupled NER	AK070264
	TF2H1	TFIIH subunits p62	AK068124
	TF2H2	TFIIH subunits p44	OSJN00169
	(TF2H3)	TFIIH subunits p34	
	TF2H4	TFIIH subunits p52	OSJN00017
	Cyclin H	kinase subunit THIIH	AK101854
	CDK7	kinase subunit THIIH	AK068916
	CDK7	kinase subunit THIIH	AK064909
	CDK7	kinase subunit THIIH	AK067238
	CDK7	kinase subunit THIIH	AK072696
	CDK7	kinase subunit THIIH	AK101089
	CDK7	kinase subunit THIIH	AK073808
	MAT1	kinase subunit THIIH	AK103771
	MAT1	kinase subunit THIIH	AK065754
base excision repair (BER)	*TagI*	glycosylase	AK063273
	TagI	glycosylase	AK110707
	TagI	glycosylase	AK065590
	TagI	glycosylase	AK069193
	TagI	glycosylase	AK109346
	MutM	glycosylase	AK063295
	MutM	glycosylase	AK065376
	AlkA	glycosylase	AK073046
	Ung	glycosylase	OSJN00095
	(Ogg)	glycosylase	
	MutY	glycosylase	AC138002
	AP endonuclease	DNA-(apurinic or apyrimidinic site) lyase	AK101426
	AP endonuclease	DNA-(apurinic or apyrimidinic site) lyase	AK102132
	AP endonuclease 2	DNA-(apurinic or apyrimidinic site) lyase	AK103074
	PARP	poly(ADP-ribose) polymerase	AK103479
	PARP	poly(ADP-ribose) polymerase	AK102681
mismatch repair (MMR)	*MSH1*	MutS family	AK110146
	MSH2	MutS family	AK111168
	MSH3	MutS family	AK065300
	MSH5	MutS family	AK101127
	MutS homologue	MutS family	AK067042
	MutS homologue	MutS family	AK105809
	(PMS1)	MutY family	
	PMS2	MutY family	AK102601
	MLH1	MutY family	AK103319
	(MLH3)	MutY family	
homologous recombination (HR)	*Rad51*	recombination protein, RecA homologue	AK064759
	Rad51B	Rad51 homologue	AK107571
	Rad51C	Rad51 homologue	AK060971
	(Rad51D)	Rad51 homologue	
	RecA	similar to *E. coli* RecA	AK103365
	RecA	similar to *E. coli* RecA	AK099587
	DMC1	Rad51 homologue, meiosis	AK110641
	(XRCC2)	DNA break and cross-link repair	
	XRCC3	DNA break and cross-link repair	AP005883
	(Rad52)	involved in recombination	
	Rad54	involved in recombination	AK111184
	Rad54	involved in recombination	AK068327
	(BRCA1)	involved in recombination	
	(BRCA2)	involved in recombination	

Table 1 (Continued)

pathway	gene	function/remarks	accession
homologous recombination (HR)	*Rad50*	complex with Mre11 and Xrs2	AK106581
	Rad50	complex with Mre11 and Xrs2	AK109956
	Mre11	3′ to 5′ exonuclease	AK070546
	(Xrs2)	complex with Rad50 and Mre11	
	NBS1	Nijmegen breakage syndrome	AK069561
	RadA (sms)	similar to RadA/Sms	AK102866
nonhomologous end-joining (NHEJ)	*Ku70*	binds to DNA end	AK099980
	Ku80	binds to DNA end	AK064097
	(DNA-PKcs)	DNA-dependent protein kinase	
DNA polymerases	*DNA polymerase α*	primer function in DNA replication	AB004461
	(*DNA polymerase β*)	BER, meiosis	
	(*DNA polymerase γ*)	mitochondrial DNA replication and repair	
	DNA polymerase δ	DNA replication, NER, BER	AB037899
	DNA polymerase δ	DNA replication, NER, BER	AK110500
	DNA polymerase δ2	*DNA polymerase δ* small subunit	AK067991
	DNA polymerase ϵ	DNA replication, cell cycle regulation	AK107241
	DNA polymerase ζ	translesion DNA synthesis	AP004570
	Rev 7	subunit of *DNA polymerase ζ*	AP004592
	DNA polymerase η	translesion DNA synthesis, XPV	AK101271
	DNA polymerase θ	DNA repair of cross-links, MUS308	CNS09S4U
	(DNA polymerase ι)	translesion DNA synthesis, Rad30	
	DNA polymerase κ	translesion DNA synthesis	AK066372
	DNA polymerase λ	BER, contains a BRCT domain	AB099525
	(*DNA polymerase μ*)	somatic hypermutation	
	DNA polymerase σ	sister-chromatid cohesion	AK070718
	DNA polymerase V	similar to *S. pombe* Pol V	AK110065
	(TdT)	terminal deoxyribonucleotidyltransferase	
	Pol I-like	chloroplast DNA polymerase	AK103236
	Pol I-like	family A DNA polymerase	AK065360
	Rev1	deoxyribonucleotidyl transferase	AK068150
	Rev1	deoxyribonucleotidyl transferase	AK110206
proliferating cell nuclear antigen	*PCNA*	accessory protein of DNA polymerases	AK071591
	PCNA	accessory protein of DNA polymerases	AK063098
replication factor C	*RFC1*	accessory protein of DNA polymerases	AK070564
	RFC2	accessory protein of DNA polymerases	AK103718
	RFC3	accessory protein of DNA polymerases	AK069984
	RFC4	accessory protein of DNA polymerases	AK069025
	RFC5	accessory protein of DNA polymerases	AK103751
replication protein A	*RPA70a*	ssDNA binding	AK101212
	RPA70b	ssDNA binding	AK060582
	RPA70c	ssDNA binding	AK073598
	RPA32	ssDNA binding	AK103235
	RPA32	ssDNA binding	AK073723
	RPA32	ssDNA binding	AK102353
	RPA14	ssDNA binding	AK058837
Rad2 nuclease family	*XPG*	NER	AC123568
	FEN-1a	removal of Okazaki fragment, BER	AK103819
	FEN-1b	class II member of Rad2 nuclease family	AK062149
	FEN-1	class II member of Rad2 nuclease family	AK063534
	EXO1	involved in DNA repair	AC135159
	SEND-1	plant specific Rad2 family nuclease	AK102542
Rad6 pathway	*Rad6*	ubiquitin-conjugating enzyme	AK067703
	Rad6	ubiquitin-conjugating enzyme	AK070524
	(Rad18)	postreplication repair	
	MMS2	ubiquitin-conjugating enzyme	AK073729
	MMS2-like	ubiquitin-conjugating enzyme	AK068060
	UBC13	ubiquitin-conjugating enzyme	AK104148
RecQ helicase	*RecQ homologue*	RecQ-like helicase	AK101124
	RecQ homologue	RecQ-like helicase	AK072117
	RecQ homologue	RecQ-like helicase	AK073504
	RecQ homologue	RecQ-like helicase	AK072977
	WRN-like exonuclease	WRN-like exonuclease	AK063585
topoisomerase	*topoisomerase I*	type I topoisomerase	AK070325
	topoisomerase II	type II topoisomerase	AK072471
	topoisomerase III α	type I topoisomerase	AC104428
	topoisomerase III β	type I topoisomerase	AK066999
	topoisomerase VI subunit A	type II topoisomerase	AC135594
	topoisomerase VI subunit B	type II topoisomerase	AK101452
	Spo11	topoisomerase, meiosis	AK073344
	Spo11	topoisomerase, meiosis	AK073184
DNA ligase and related gene	*DNA ligase I*	ligates DNA ends	AK110056
	(DNA ligase III)	ligates DNA ends	
	XRCC1	interacts with DNA ligase III	AK068998
	DNA ligase IV	ligates DNA ends	OSJN00168

Table 1 (Continued)

pathway	gene	function/remarks	accession
DNA ligase and related gene	*XRCC4*	interacts with DNA ligase IV	AK071772
	DNA ligase	ligates DNA ends	AK064463
other DNA repair genes	*Rad1(S. pombe) homologue*	PCNA-like damage sensor	AK074010
	Rad9(S. pombe) homologue	PCNA-like damage sensor	AK065579
	(Hus1(S. pombe) homologue)	PCNA-like damage sensor	
	(Rad17)	RFC-like damage sensor	
	ATM	Ataxia telangiectasia	AK109634
	ATR	ATM-like kinase	AK110033

2.2. Plant DNA Repair Genes Identified by Genomics

The genome sequence generated by the Rice Genome Project and the results of the full-length cDNA Project have both been made public,[21] which has made the identification of DNA repair genes in the rice genome by database searches possible (for a summary, see Table 1).[14] The genes involved in DNA repair and recombination in *Arabidopsis* have also been made public in a database called DNAMETAB (http://www.ag.arizona.edu/dnametab/).

As shown in Table 1, plants possess homologues of most of the genes involved in the widely conserved DNA repair pathways such as nucleotide excision repair (NER) and base excision repair (BER). However, some of the genes involved in well-characterized DNA repair pathways are absent. The genes in parentheses in Table 1 were not found in the sequence information available for rice. For example, the genes involved in Fanconi anemia were not present, nor was *XPA* (xeroderma pigmentosum, complementation group A), which is involved in NER. *DNA polymerase* β, which is involved in BER, is also not found in plant genomes. The absence of these important genes suggests a basic difference in the mechanisms of DNA repair between plants and animals.

Several DNA repair-related genes are present in multiple copies in plant genomes. For example, there are three homologues of *CSB* (Cockayne syndrome, type B), which is involved in the transcription-coupled repair (TCR) of NER, three homologues of *RPA* (replication protein A),[25−27] and two homologues of *PCNA* (proliferating cell nuclear antigen) and *FEN-1* (Flap endonuclease-1)[28] which function in DNA repair and replication. *Arabidopsis thaliana* harbors a duplication of the *XPB*(*AtRad25*) homologue.[29] In general, plants contain more multiple gene copies than animals. Therefore, multiple copies of DNA repair genes may simply reflect this general trend. However, it may also be possible that the presence of multiple DNA repair alleles increases a plant's UV tolerance.[29] Moreover, without gene duplication, any functional differentiation would result in the loss of the original function and would thus limit the possibility of evolving more efficient repair systems, since there could be no allelic variation. In fact, our own data indicate that each of the three homologues of *RPA* has a different role.[25−27]

Several DNA repair genes that appear to be specific to plants, or that are limited to the *plantae* among the eukaryotes, were recognized in the completed genome sequences. The presence of these genes suggests plant-specific pathways of DNA repair, a topic of great interest.

3. DNA Repair Pathways in Higher Plants

Recent research on the mechanisms of DNA repair has provided additional insights which will be described in the following sections.

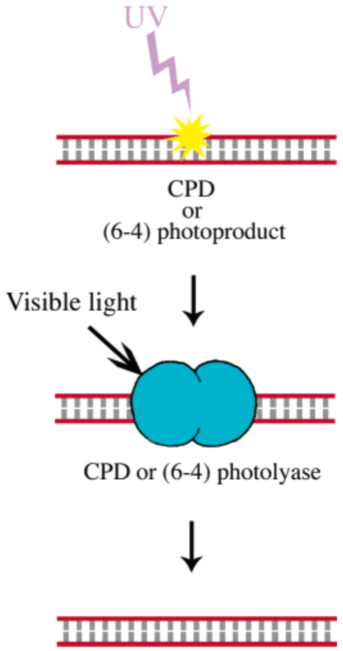

Figure 3. Photoreactivation. Photolyases bind to pyrimidine dimers (CPDs or (6−4) photoproduct) and directly cleave the dimers using the energy of visible light.

3.1. Photoreactivation

Photoreactivation is a mechanism of repair of UV-damaged DNA that is carried out by photolyases using the energy of visible light (Figure 3). Cyclobutane pyrimidine dimers (CPDs) and (6−4) photoproducts, both induced by UV irradiation, have thymine dimer structures that are directly cleaved by either CPD lyase or (6−4) phytolyase.

Photolyase genes have been identified in several plant species.[30−36] In *Arabidopsis*, the presence of both *CPD photolyase* and *(6−4) photolyase* was demonstrated by an analysis of UV-sensitive mutants.[31−36] In rice, a *CPD photolyase* gene was isolated by Hirouchi et al.[37] No cDNA clone of the rice *(6−4) photolyase* has been isolated, but a homologue has been identified on chromosome 6. A light-dependent decrease of (6−4) photoproducts with time was observed by direct determination of DNA damage by the ELISA method, which indicated that (6−4) photolyases operate in rice.[38] The expression of photolyase genes in cucumber (*CsPHR*) was highest during morning light (9:00 a.m. to 12:00 p.m.), and photoreactivation activity in cucumber leaves was highest during the afternoon (12:00 p.m. to 3:00 p.m.), when the plants received full sunshine.[39] These results suggested that photolyase expression was regulated to prevent the suppression of growth by UV irradiation.[39] It is also evident that the major pathway of DNA repair operating in nonproliferating organs, such as mature leaves, is photoreactivation.[38]

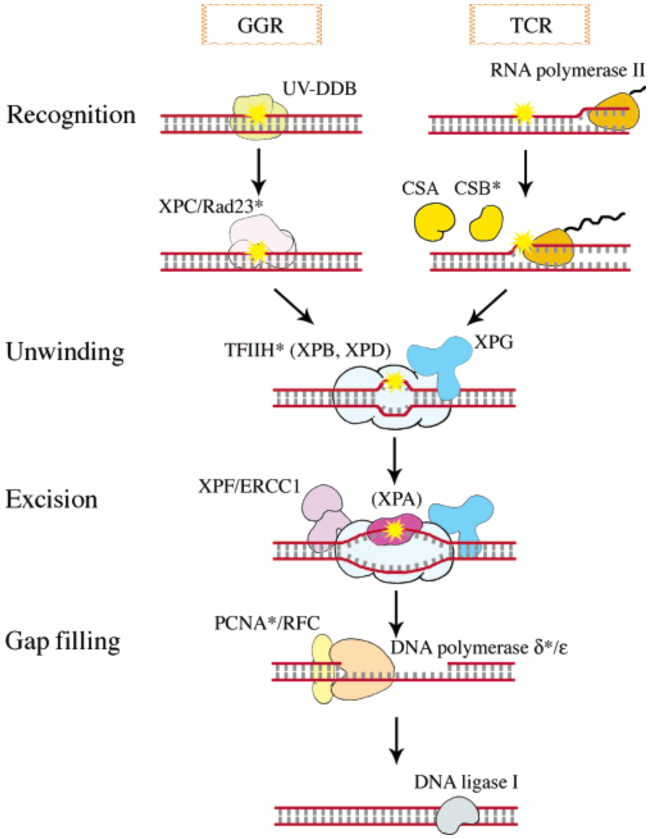

Figure 4. Nucleotide excision repair (NER). NER pathways can be classified into two groups, global genome repair (GGR) and transcription-coupled repair (TCR). The NER pathway consists of a series of reactions: recognition of DNA damage, unwinding double-stranded DNA in the neighborhood of the damage, excision of the damaged nucleotides, and filling the gap by DNA synthesis and ligation. The proteins in parentheses have not been found in plants. The proteins marked by asterisks are present in multiple copies.

Sensitivity to UV-B radiation varies widely among rice cultivars.[40] Differences in UV tolerance between the *Japonica* rice cultivar Nipponbare and the *Indica* rice cultivar Kasalath appear to be due to natural variation. The CPD photolyase gene contributes most to UV tolerance, as demonstrated by QTL (quantitative trait loci) analysis and map-based cloning.[41,42] There are also differences in UV tolerance between *Japonica* rice cultivars. For instance, cv. Norin 1 is less UV tolerant than cv. Sasanishiki, due to differences in the functioning of CDP photolyase.[43] These results suggest that allelic variation in the CPD photolyase gene is associated with different degrees of sensitivity to UV-B.[40]

3.2. Nucleotide Excision Repair (NER)

Nucleotide excision repair (NER) recognizes and repairs various types of DNA damage caused by UV irradiation, cisplatin, and other damaging agents. NER pathways can be classified as either global genome repair (GGR), which repairs DNA damage anywhere in the genome, or transcription-coupled repair (TCR), which specifically restores DNA strands that are being transcribed (Figure 4).

NER mechanisms rely on a series of reactions: recognition of DNA damage, unwinding double-strand DNA in the neighborhood of the damage, excision of the damaged nucleotides, and filling of the single-stranded gap by DNA synthesis (Figure 4). In GGR, DNA damage is recognized by XPC/Rad23 (*xeroderma pigmentosum*, complementation group C/Rad23) or UV-DDB (UV-damaged DNA binding protein). In contrast, during TCR, contact of the transcribing RNA polymerase II with damaged nucleotides triggers recognition of the DNA damage by the CSA (Cockayne syndrome, type A) or CSB (Cockayne syndrome, type B). The DNA region that contains the recognized damage is unwound by TFIIH (transcription factor IIH), including XPB (*xeroderma pigmentosum*, complementation group B), XPD (*xeroderma pigmentosum*, complementation group D), XPA (*xeroderma pigmentosum*, complementation group A), and RPA (replication protein A). Then, the structure-specific endonucleases XPF/ERCC1 (*xeroderma pigmentosum*, complementation group F/excision repair complementing defective repair in Chinese hamster 1) and XPG (*xeroderma pigmentosum*, complementation group G) excise oligonucleotides of about 20 to 30 bases containing the damaged part of the DNA. The gap formed by the excision is filled through PCNA (proliferating cell nuclear antigen) and RFC (replication factor C)-dependent DNA synthesis carried out by *DNA polymerase* δ/ϵ. NER is completed by rejoining the repaired DNA strand with DNA ligase I.

NER in plants has been studied mainly using *Arabidopsis*.[44] NER-related genes were isolated by analysis of UV-sensitive mutants (*UVH*).[45] The genes responsible for *UVH1*, *UVH3*, and *UVH6* mutations were found to be *XPF* (*AtRad1*), *XPG* (*AtRad2*), and *XPD* (*AtRad3*), respectively.[46−50] In addition, the NER-related genes *XPB* (*AtRad25)*, *AtUV-DDB2*, *AtRad23*, and *ERCC1* (*AtRad10)* have been isolated from *Arabidopsis*.[51−56] The T-DNA insertion *XPB* (*AtRad25)* mutant showed retarded growth,[57] and the T-DNA and RNAi mutants of *UV-DDB2* developed dwarf phenotypes.[51] These results stressed the important role of DNA repair in growth and development. An *ERCC1* (*AtRad10)* mutant of *Arabidopsis* was sensitive to γ irradiation,[52] an *XPB* (*AtRad25)* mutant was sensitive to hydrogen peroxide and MMS (methyl methanesulfonate),[57] and *XPG* (*AtRad2)* mutants were sensitive to hydrogen peroxide and ionizing radiation.[47] The involvement of *XPF* (*AtRad1*) in the repair of oxidatively damaged DNA was demonstrated by an in vitro DNA repair assay using cell extracts of *Arabidopsis*.[58] Moreover, *XPF* (*AtRad1*) and *ERCC1* (*AtRad10)* have key roles in homologous recombination.[59,60] From these results, it can be concluded that NER is involved in the repair of a number of different types of DNA damage in plants. The NER-related genes *UV-DDB*,[61] *FEN-1*,[28,62,63] *PCNA*,[62] *DNA polymerase* δ,[64] *RPA*,[27] and *CSB*[38] have been isolated and characterized in rice. It is apparent, then, that plant NER is essentially, but not entirely, the same as NER in animals. However, though *XPA* is not found in plants, multiple homologues of *CSB* are present (Table 1). This indicates subtle but potentially important differences between the mechanisms of DNA repair in plants and animals.

The *Arabidopsis* UV-DDB1 enzyme, which recognizes DNA damage in GGR, was shown to form a CDD complex with COP10 (constitutive photomorphogenic 10) and DET1 (de-etiolated 1), which are negative regulators of photomorphogenesis.[65,66] COP10 was reported to enhance the activity of ubiquitin-conjugating enzymes, thus promoting the ubiquitination of proteins.[65] Moreover, UV-DDB1 assembles DET1, COP1, Cullin 4A, and Roc1 (regulator of Cullins-1) to regulate c-Jun ubiquitination in mammals.[67] Thus, UV-DDB1 is probably involved in the regulation of ubiquitin/proteasome-mediated proteolysis. The ubiquitin/proteasome-

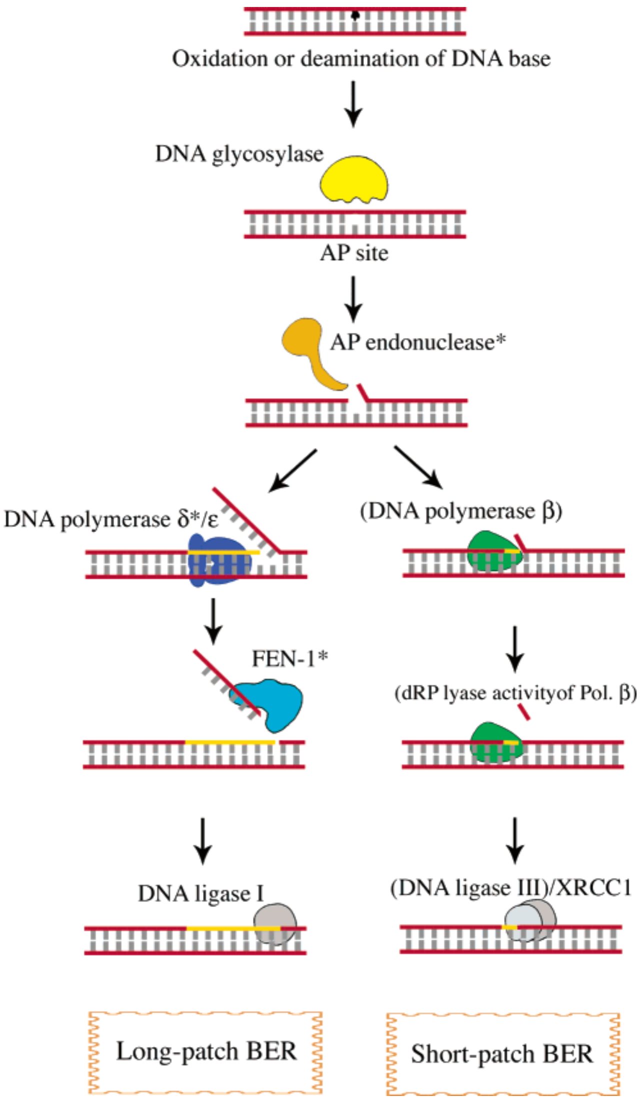

Figure 5. Base excision repair (BER). DNA damage such as oxidative DNA damage, deamination of DNA bases, or apurinic/apyrimidinic sites (AP site) is corrected by base excision repair (BER). DNA glycosylases initiate this process by releasing the damaged base through cleavage of the sugar−phosphate chain and excision of the abasic residue or of the abasic residue containing oligonucleotides, followed by DNA synthesis and ligation. There are two subpathways for BER. Short-patch BER is *DNA polymerase β*-dependent, while long-patch BER is *DNA polymerase δ/ϵ*-dependent. The proteins in parentheses are not found in plants. Proteins marked by asterisks are present in multiple copies.

mediated proteolysis has a number of central roles in cellular processes, including cell cycle control and the regulation of transcription.[65,66,68−71] Thus, NER-related genes might function in a wide range of cellular events in addition to DNA repair.

3.3. Base Excision Repair (BER)

Reactive oxygen species from endogenous and environmental sources induce oxidative damage to DNA. Deamination of DNA bases can occur spontaneously, generating highly mutagenic modifications of DNA bases into uracil, hypoxanthine, and xanthine, which are corrected by base excision repair (BER) (Figure 5). AP sites (apurinic/apyrimidinic) are also thought to be repaired by this pathway. BER is initiated by the removal of the damaged base(s), which is mediated by DNA glycosylase. The AP site formed by the removal reaction is incised by AP endonuclease. Some DNA glycosylases are known to have AP endonuclease activity. There are two pathways known for the DNA synthesis following the incision: long-patch BER, in which DNA is synthesized by *DNA polymerase δ/ϵ*, and short-patch BER, in which synthesis is catalyzed by *DNA polymerase β*. In long-patch BER, PCNA and FEN-1 act in coordination with *DNA polymerase δ/ϵ* in the synthesis of relatively long DNA chains**,** which are eventually ligated by DNA ligase I. In the case of short-patch BER, the 5′-dRP residue is removed by the dRP lyase activity of *DNA polymerase β*. DNA chains are then joined by DNA ligase III/XRCC1 (X-ray repair complementing defective in Chinese hamster 1) to complete the repair.

BER in plants, including the presence of uracil-DNA glycosylase, was demonstrated in a study using carrot cells.[72,73] The cDNA of 3-methyladenine glycosylase, one of the DNA glycosylases, was first isolated from *Arabidopsis*[74] and was found to be strongly expressed in developing tissues.[75] Several additional types of DNA glycosylases have since been isolated and characterized.[76−81] In addition, homologues of *DNA polymerase δ* and *FEN-1*, which are involved in BER, have been isolated.[28,63,64] Ten types of DNA glycosylases and three types of AP endonucleases were identified in the rice genome (Table 1). Though *XRCC1* was present, *DNA ligase III*, which probably forms a complex with XRCC1 in animal systems, was absent. Similarly, *DNA polymerase β*, which is assumed to be essential in short-patch BER, has not yet been found in any plant genome (Table 1). On the other hand, *DNA polymerase λ*, which belongs to the same family as *DNA polymerase β*, seems to be present,[82,83] suggesting that *DNA polymerase λ* may serve the same function as *DNA polymerase β* in plant short-patch BER.

Recently it was demonstrated that DEMETER, a DNA glycosylase domain protein, was required for endosperm gene imprinting and seed variability in *Arabidopsis*,[84] likely because of its role in transcriptional regulation of the gene required for gene imprinting.[85] Furthermore, the repressor of transcriptional gene silencing in *Arabidopsis*, ROS1, encodes a DNA glycosylase/lyase.[86] Thus, as for the case of NER, some of the genes involved in BER have functions in addition to DNA repair.

3.4. Mismatch Repair (MMR)

Mismatch repair (MMR) restores the correct match in mismatched base pairs formed by incorporation of an incorrect base by DNA polymerase or during recombination. The template DNA chain, which has the correct sequence, is methylated and can be distinguished from the unmethylated, newly synthesized strand. In *E. coli*, MutS and MutL recognize a mismatch, and MutH introduces a nick on the new, nonmethylated strand. Exonuclease removes the newly formed chain, DNA polymerase fills the gap, and DNA ligase rejoins the DNA. Numerous homologues of MutS and MutL are present in eukaryotes, and MMR is regarded as an important path of DNA repair. However, several steps in eukaryotic MMR are not yet understood, including the mechanism of recognition of the newly formed DNA strand.

MSH genes, which are homologues of *E. coli MutS*, have been isolated from plants, mostly from *Arabidopsis*.[87−90] *Mus1* and *Mus2*, homologues of *MutS*, were isolated from *Zea mays*. [91] *MLH1*, a homologue of *MutL*, was also isolated from *Arabidopsis*.[92] The MSH2/MSH6 and MSH2/MSH7

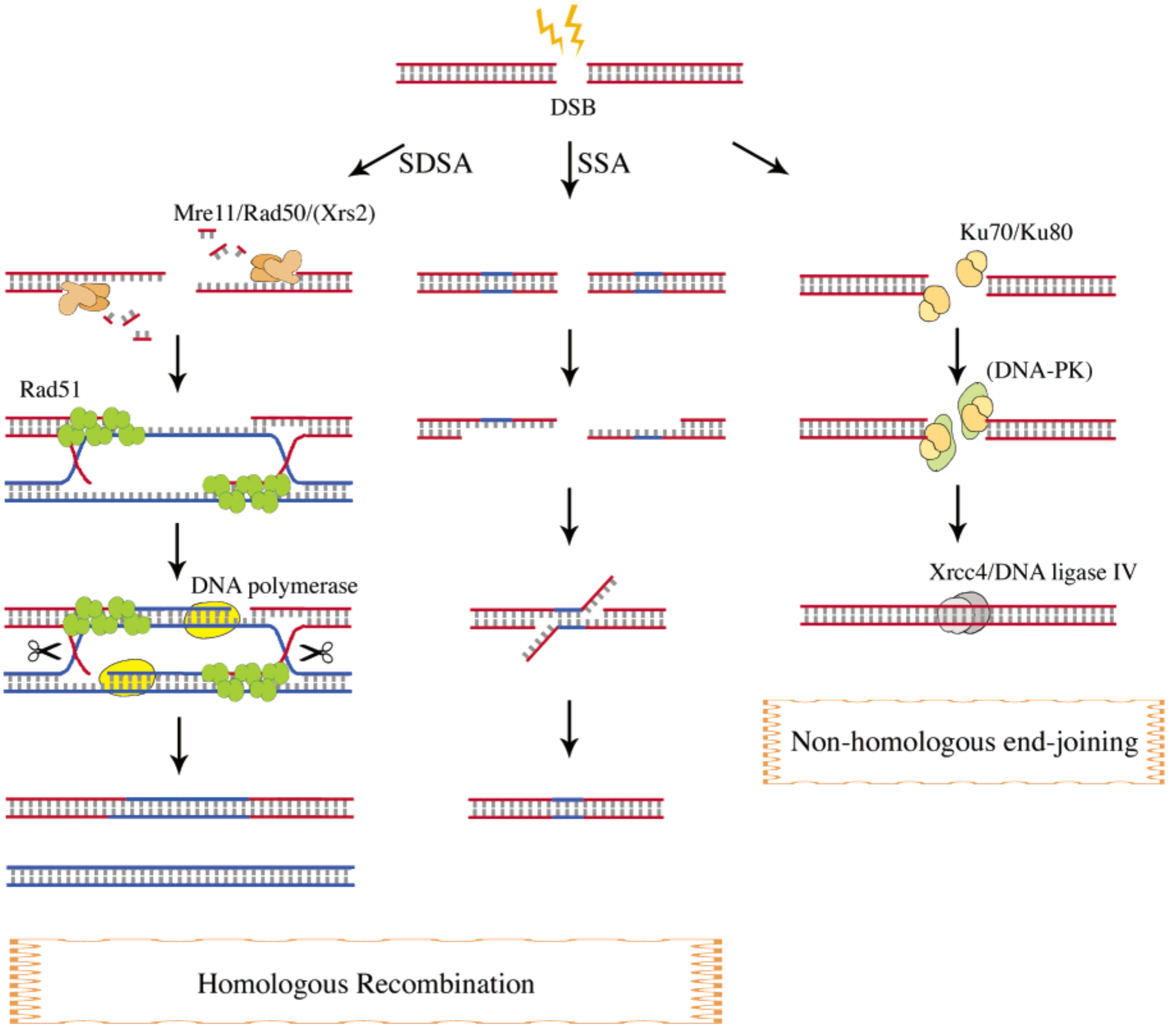

Figure 6. Double-strand break repair (DSB repair). DSBs are rapidly repaired in cells either by homologous recombination (HR) or nonhomologous end-joining (NHEJ). HR is a repair process carried out through the recombination of homologous DNA regions. In NHEJ, the ends of the severed chains are joined directly. The proteins in parentheses are not found in plants.

complexes in *Arabidopsis* recognize different nucleotide mismatches [88,93] The presence of multiple *MutS* homologues may increase the range of recognized mismatches. Involvement of *MSH2* in the maintenance of stability of the *Arabidopsis* genome has also been reported.[94] Rapid accumulation of mutations during seed-to-seed propagation was observed in *MSH2* mutants of *Arabidopsis*.[95] The *AtMSH2* mutant lines rapidly accumulated a wide variety of mutations and had abnormalities in morphology and development, fertility, germination efficiency, seed/silique development, and seed set. These results clearly indicated that crippling MMR has pleiotropic effects, likely due to the accumulation of uncorrected mismatch events and the concomitant loss of many normal cellular functions.

3.5. Double-Strand Break Repair (DSB Repair)

External effects, such as ionizing radiation and chemical substances, and internal factors, such as errors during DNA replication, can induce DNA double-strand breaks (DSBs). DSB is a very severe type of DNA damage which can jeopardize the survival of the organism. DSBs are rapidly repaired in cells by either of two mechanisms: homologous recombination (HR) or nonhomologous end-joining (NHEJ) (Figure 6).[96−99]

HR is a repair process that uses the recombination of homologous DNA regions (Figure 6). An intact copy of the damaged region, which may be located on a sister chromatid or a homologous chromosome, is used as a template to repair the damage. In the synthesis-dependent strand annealing mechanism (SDSA; Figure 6, left), single-stranded DNA is formed by the action of the Mre11/Rad50/Xrs2 (meiotic recombination11/Rad50/X-ray sensitive 2) complex at DSB sites. Recombination is mediated by RecA homologues such as Rad51. A Holliday structure formed during recombination is incised by nucleases and dissociates into two DNA chains. However, the process of dissociation is not well understood in eukaryotic organisms. In the DSB repair mediated by NHEJ, Ku70/Ku80 recognizes the ends formed by DSBs. Then, DNA-PKcs (DNA-dependent protein kinase) binds to these ends. Finally, Xrcc4 (X-ray repair complementing defective repair in Chinese hamster cells 4)/DNA ligase IV joins the two ends to complete the repair (Figure 6, right). In NHEJ, the ends of the severed chains are joined directly and deletions or insertions can occur (Figure 6, right).

Higher plants are generally more tolerant to ionizing radiation than mammals, and it has been suggested that radiation tolerance is due not only to a lower induction of DNA damage but also to more efficient repair of the induced DSBs.[100] Information on mechanisms of DSB repair in higher plants is mainly from studies in *Arabidopsis*.[97,101,102] *AtRad51*,[103−108] *AtRad50*,[109,110] and *AtMre11*,[111] which are all involved in HR, have been isolated and analyzed. Differing requirements for the activities of *Arabidopsis AtRad51* paralogues in DNA repair and meiosis have been observed.[104,106] In addition to *Rad51*, rice and *Arabidopsis* possess the genes *OsRadA* and *AtRadA*, respectively, which have a high degree of homology with RadA/Sms, a eubacterial homologue of RecA.[112] These genes, too, may have a functional role in HR. *AtKu70*, *AtKu80*, *Arabidopsis DNA ligase IV*, and *AtXRCC4* are involved in NHEJ and have been isolated and analyzed in plants.[113−116] Because mutations in these genes introduced sensitivity to ionizing radiation, they are thought to play key roles in DSB repair. [113−116] Furthermore, telomere lengthening in AtKu80 mutants suggests that one function of AtKu80 is the maintenance of telomere length.[117]

It remains unclear how a particular repair pathway, HR or NHEJ, is activated and how the two pathways are regulated when a DSB occurs. In yeast, most DSBs are repaired through HR, while in humans NHEJ is predominant.[96−99,118] In this respect, plants are more like animals than yeasts, but the relative activity of plant HR seems to be much lower than that of animals.[96,97,118−122] The *Arabidopsis* plant line with the loss of function mutant homologue of *Rad51*, *AtRad51*, exhibits normal vegetative and flower development and has no detectable mitotic abnormality.[106] Also, the *Arabidopsis* line carrying the *MRE11* allele is viable, though it exhibits growth defects and is infertile.[111] These results suggest that the HR pathway is not essential for vegetative plant growth. *INO80*, a member of the SWI/SNF ATPase family, was shown to control HR in *Arabidopsis*.[123] The mutant line affected in the expression of *INO80* showed a reduction in HR frequency.[123] Species-dependent differences in the repair of DSBs in plants have been reported.[124] HR was shown to be influenced by temperature and day-length.[125] In addition, multiple sub-pathways seem to be part of the plant HR pathway. Thus, DSB repair appears to be quite complex.[96,97,101,126−130]

The differences in DSB repair between animals, yeast, and plants and also between plant species may contribute to the evolution of genomes.[97,101,131,132] In NHEJ, deletions and/or insertions can take place when DNA chains are joined. HR (SDSA) is most likely to provide an error-free repair, as DNA is repaired by using a homologous DNA region. When a homologous DNA region, such as a sister chromatid, is not used for HR, homologous sequences proximal to the DSB can be interposed, leading to sequence deletions (SSA, single-strand annealing mechanism; Figure 6). Therefore, the relative frequency of occurrence of these DSB repair pathways may influence the rate of genomic evolution.[97,101]

Two NER-related genes, *AtXPF* and *At*ERCC1, were also shown to be involved in plant DSB repair.[52,59,60] The two proteins encoded by these genes form a complex which functions as a structure-specific endonuclease. In NER, it incises DNA strands on the 5′-end side of the damage (Figure 4). In HR, XPF/ERCC1 is probably involved in the removal of nonhomologous tails. The analysis of a mutant with a high frequency of HR led to the isolation of CENTRIN2 (caltractin-like protein).[133] The CENTRIN2 mutant showed changes in the expression profiles of genes involved in DNA repair pathways such as NER. These findings indicate an interconnection between the early steps of NER and HR.

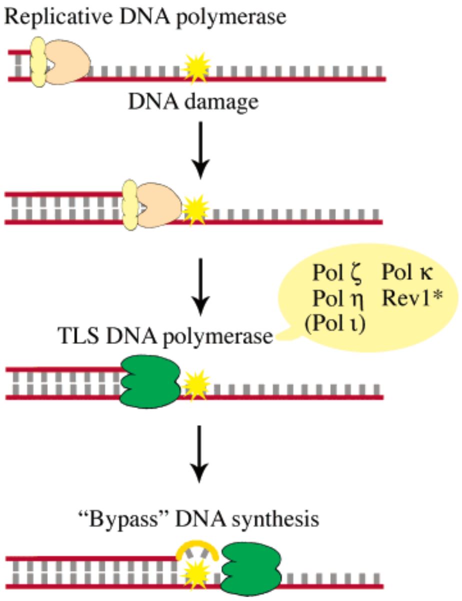

Figure 7. Trans lesion synthesis (TLS). When DNA damage blocks the DNA synthesis mediated by replicative DNA polymerases (*DNA polymerase* δ/ε), an exchange of DNA polymerases takes place. In this case, TLS DNA polymerases, such as *DNA polymerases* ζ, η, ι, and κ and *Rev1*, synthesize DNA to overcome the DNA damage. The proteins in parentheses are not found in plants. Proteins marked by asterisks are present in multiple copies.

Gene knockout mutagenesis by gene targeting is extremely difficult in plants,[118,134−136] and there are few successful cases.[137] This lack of success has been interpreted to be due to the low frequency of HR in plant cells. To make gene targeting more successful in plants, homologous recombination has been stimulated in plant cells by overexpression of recombination genes such as *RecA*, *RuvC*, *RecQ*, *Rad54*, *and Zinc-finger* nucleases.[118,134−136,138−143] If the frequency of HR can be raised by controlling DSB repair, the useful technique of gene targeting could become practicable in plants.

3.6. Trans Lesion Synthesis (TLS)

Trans lesion synthesis (TLS) is a newly discovered pathway of DNA repair (Figure 7). When UV-induced DNA damage cannot be adequately corrected by DNA repair processes such as NER and the DNA synthesis mediated by DNA polymerases of the DNA replication type (*DNA polymerase* δ/ε) is halted at the site of DNA damage, an exchange of DNA polymerases takes place. In this case, *DNA polymerases* ζ, η, ι, κ, and *Rev1* (*Reversionless 1*) synthesize DNA to overcome the DNA damage. These DNA polymerases have been identified only recently, but it is known that the fidelity of these DNA polymerases varies. When a low-fidelity DNA polymerase cannot insert a correct base into the site opposite to the damaged base, an incorrect base might be inserted resulting in a base substitution point mutation. However, the details of TLS, including how the multiple DNA polymerases are used, are not clear in any organism. Studies are currently underway to elucidate this intriguing type of DNA repair.

The gene responsible for the UV-sensitive *Arabidopsis* mutant (*rev3−1*) obtained by ion beam mutagenesis was shown to encode a catalytic subunit of *DNA polymerase* ζ.[144] In addition to UV sensitivity, this mutant was sensitive to γ irradiation and mitomycin C (a cross-linking agent). Furthermore, the elongation of roots was suppressed by UV irradiation, and the incorporation of BrdU after UV irradiation was decreased compared to the case of the wild type. These observations are the first report of TLS in plants and suggest the involvement of *DNA polymerase* ζ in TLS. Similarly, *DNA polymerase* κ (*AtPol*κ) was identified in *Arabidopsis*[145] and thought to be involved in TLS. *AtPol*κ was able to extend primer–terminal mispairs. It is interesting that *AtPol*κ was expressed in endoreduplicating cells, indicating a possible role in this process. In addition, the *Arabidopsis* homologues of *REV7* (*AtREV7*, subunit of *DNA polymerase* ζ) and *REV1* (*AtREV1*) were isolated and shown to be involved in TLS and to have important roles in tolerance against DNA damaging agents.[146]

TLS-associated genes, including *DNA polymerases* ζ, η, and κ and *Rev1*, have been found in the genomes of rice (Table 1) and *Arabidopsis*. The presence of these genes suggests the possibility of DNA repair by the trans lesion mechanism in plants.

3.7. Interstrand Cross-link Repair (ICL Repair)

Interstrand cross-links (ICLs) are a highly toxic form of DNA damage.[147,148] ICLs can be induced by bifunctional alkylating agents such as nitrogen mustard and mitomycin C. Numerous genes are involved in the repair of ICLs.[147–149] ICL repair involves proteins that also act in NER[148,149] and HR.[149,150] *Snm1* (sensitive to nitrogen mustard) is thought to function specifically in ICL repair. It was first identified in yeast by screening for mutants sensitive to nitrogen mustard.[151,152] *Snm1* proteins are nuclear proteins[153,154] and have 5′-exonuclease activity.[155] Thus, *Snm1* appears to be involved in processing intermediate structures of the ICL repair mechanism.

Recently, the *Arabidopsis* and rice homologues of *Snm1* (*AtSNM1* and *OsSnm1*) were identified and characterized.[156,157] Interestingly, *AtSNM1*-deficient mutants were not hypersensitive to mitomycin C (MMC), but showed a moderate sensitivity to bleomycin and H_2O_2. The mutants exhibited a delayed repair of oxidative DNA damage and did not show any increase in the frequency of somatic homologous recombination with exposure to H_2O_2. These results suggest the existence in plants of *Snm1*-dependent recombinational repair processes of oxidatively induced DNA damage.[157]

4. DNA Repair Genes Specific to Plants

A search of the rice and *Arabidopsis* genomes indicated the presence of DNA repair genes that were unknown from animals and yeast. DNA endonucleases belonging to the Rad2 nuclease family have key roles in processes of DNA repair such as NER. Rad2 family nucleases can be grouped into three classes: class I (XPG), class II (FEN-1), and class III (ExoI). Several genes belonging to these families have been studied in plants.[28,47,62,63,158–160] We identified a new nuclease with endonuclease activity on ssDNA that did not fit into any of these classes, and we designated it *OsSEND-1* (*Oryza sativa* single-stranded DNA endonuclease-1).[159] Its amino acid sequence was similar to, but shorter than, that of XPG. As rice and *Arabidopsis* possess *XPG* homologues different from *OsSEND-1*, the latter was considered to be a new gene, which is unique to plants. Overexpression of *OsSEND-1* was increased by UV irradiation and MMS (methyl methanesulfonate) treatment**,** [161] indicating that *OsSEND-1* is involved in DNA repair.[161]

RecA catalyses strand exchange reactions in prokaryotes and is involved in repair and recombination of DNA. Eukaryotic organisms possess the *RecA* homologues *Rad51* and *Dmc1*. Rad51 functions in both somatic and meiotic cells, while Dmc1 acts specifically in meiotic cells. *RadA/Sms* is a highly conserved eubacterial protein with homology to *RecA*.[162,163] We identified a gene that has a high degree of homology to *RadA/Sms* in the rice genome and named it *OsRadA* (*Oryza sativa* RadA).[112] In addition to *OsRadA*, rice also carries *Rad51* and *Dmc1*. The presence of *RadA* homologues appears limited to plants among eukaryotic organisms. OsRadA is located in the cell nucleus and has strand exchange activity. *OsRadA* RNAi mutants are sensitive to UV and MMS. These results suggest that *OsRadA*, too, is involved in DNA repair in plants.

Among the many uncharacterized plant-specific genes that are present in the genomes of plants, there may be many more genes involved in uncharacterized DNA repair pathways. Moreover, the multiplicity of DNA repair genes in plants also suggests plant-specific mechanisms of DNA repair. The functions of these genes will have to be scrutinized to provide a full understanding of these mechanisms.

5. DNA Repair in Organelles

Chloroplasts and mitochondria have their own DNA and systems of DNA repair and replication. Given the hypothesis that these organelles have prokaryotic origins, the repair and replication of DNA in chloroplasts and mitochondria of plants may be quite different from nuclear mechanisms. Because of their critical role in the production of photosynthate and energy for the cell, it would be useful to fully understand the unique as well as the common features of DNA repair in the non-nuclear genomes.

5.1. DNA Repair and Replication in Chloroplasts

The photosynthetic apparatus in chloroplasts is one of the largest sources of reactive oxygen species produced by UV irradiation. Chloroplast DNA repair mechanisms and the stabilization of the chloroplast genome are mostly obscure.

We succeeded in isolating a new plastidal DNA polymerase gene.[164] This gene was named *OsPolI-like* (*Oryza sativa* DNA polymerase I-like DNA polymerase), as it has a high degree of homology to *DNA polymerase I* of cyanobacteria. Fractionation of subcellular components and analysis of transient expression of a GFP fusion protein showed that *OsPolI-like* was localized in plastids.[164,165] *OsPolI-like* was actively expressed in the meristems of shoot apexes, root apexes, and leaf primordia. In these tissues, plastids are present as undifferentiated proplastids. Plastids develop into chloroplasts in leaves. In roots and tubers, plastids differentiate into amyloplasts which store starch. Replication of plastid DNA is activated as the first step in the process of chloroplast differentiation. After an increase in the number of copies of the plastid genome, the plastids divide and photosynthetic activities commence. The active expression of *OsPolI-like* coincides with the period of plastid genome replication, indicating that *OsPolI-like* is involved either in DNA replication or in the repair of errors occurring during replication.

RPA (replication protein A) is composed of three subunits of 70, 32, and 14 kDa. It binds to and stabilizes ssDNA formed during DNA repair processes such as NER.[166] Only

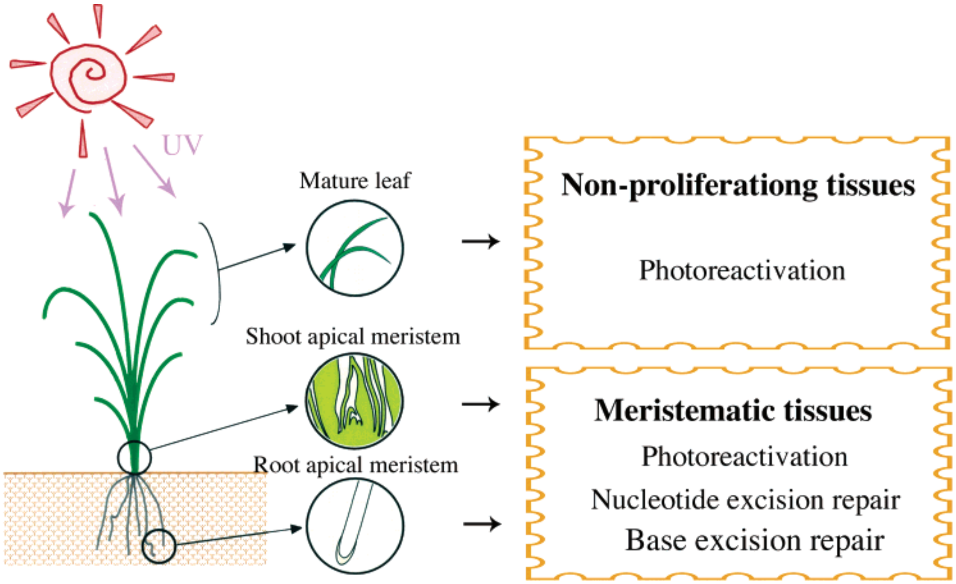

Figure 8. Overview of DNA repair in plants. Photoreactivation is the major DNA repair pathway in nonproliferating cells, while excision repair (nucleotide excision repair and base excision repair) is active in proliferating cells.

one kind of RPA exists in animals and yeast. In contrast, the nuclear genomes of rice and *Arabidopsis* possess three types of RPA.[25,27] Two were localized in nuclei while the third appeared to be specific to chloroplasts.[25−27] These findings suggest that copies of RPA assumed different functions in the organelles following multiplication of the original gene.

DNA polymerase, DNA primase, DNA topoisomerase, DNA helicase, and structure-specific endonuclease proteins have been purified from chloroplasts of higher plants and have been characterized.[167−172] A RecA homologue and DNA gyrase were also shown to be localized in chloroplasts and mitochondria in *Arabidopsis*,[173,174] and many genes that have homology to prokaryotic DNA-metabolizing enzymes are present in the rice genome. It is probable that some of them are located in the chloroplast and are involved in DNA replication and repair.

5.2. DNA Repair and Replication in Mitochondria

The mechanisms of repair of mitochondrial DNA are mostly unclear in animals and yeast, as well as in plants. The presence of DNA helicase, RecA, and DNA gyrase in plant mitochondria has been reported.[173,175,176] *DNA polymerase* γ, which is a mitochondrial DNA polymerase in animals, is not found in plant genomes. Numerous genes that encode proteins which may function in mitochondrial DNA repair are present in plant genomes. In *Arabidopsis*, these genes are clustered on chromosome 3.[177] Similar gene clusters also exist in rice.[177] Some of the repair genes for plastid DNA are included in these clusters. These observations indicate correlations in the evolution of DNA repair gene families for mitochondria and chloroplasts.

6. Relationship between DNA Repair and Cell Proliferation

In our study on the expression of DNA repair genes and localization of proteins in plants, we found a close association between excision repair and cell proliferation.[38] Analyses of the expression patterns of DNA repair genes in rice showed that while photolyase is expressed in mature leaves, the genes involved in excision repair (NER and BER) are expressed predominantly in the proliferating meristems of shoot and root apexes. It was unexpected that the genes for excision repair were not expressed in mature leaves, which receive significant doses of UV radiation. Similarly, expression of these genes in the root apex, which is sheltered from light, seemed odd. In addition, analysis of expression patterns of DNA repair genes using oligo-DNA microarrays demonstrated that photolyase is expressed in mature leaves, while most of the excision repair genes are strongly expressed in shoot apexes (Figure 8).[38] These results suggest that the expression of genes involved in excision repair is associated with cell proliferation (Figure 8).[38] Furthermore, the gene for 3-methyladenine glycosylase, which is involved in BER, is also expressed in proliferating tissues.[75] *In vivo* DNA repair assays of the photoreactivation and dark reactivation in nonproliferating tissues (mature leaves) and proliferating tissues (root apexes) showed that photoreactivation is the major pathway of DNA repair in nonproliferating tissues, whereas photoreactivation as well as dark repair are active in proliferating tissues (Figure 8).[38]

In plants, cells proliferate only in meristems. In addition, plant germ cells are differentiated from meristematic tissue in later stages of development, as opposed to the case for animals, where the germ cell line is continuous throughout development. As a result, mutations generated in shoot apical meristems have a high probability of genetic continuity.[8] Therefore, high fidelity is required from DNA repair in shoot apical meristems. The results described above may suggest that this is indeed the case: genes involved in excision repair have key roles in the maintenance of genomic integrity in active meristems.

Endoreduplication is the major mechanism leading to somatic polyploidisation in plants and can be found in many cell types, especially in those undergoing differentiation and expansion, though cells proliferate (giving a daughter cell) only in meristems. [178−180] Endoreduplication occurs when cells re-replicate chromosomes in the absence of mitosis, and about 30% of the resultant cells are polyploid. It would be interesting to know the relationship between DNA repair and endoreduplication, because many DNA repair genes may be involved in endoreduplication, and endoreduplication could provide a template for homologous recombination.

7. Application of Studies of DNA Repair to Breeding of UV Resistant Plants

The depletion of the ozone layer became evident as the so-called ozone hole expanded over the Antarctic in the 1980s. The total amount of atmospheric ozone has continued to decrease, and the concomitant increase in the level of UV radiation (especially UV-B) on the surface of the earth has become a serious problem.[8,161,181] Although harmful effects of UV on animals, such as the induction of skin cancer, cause serious concern, the adverse effects of UV on plants have not been adequately recognized. The harmful effects of UV irradiation on plants include suppression of growth, lowering of yield, browning and chlorosis of the leaf, and thickening of the leaf. Further increases in UV irradiation may cause serious food shortages, if food production and quality are decreased by the deterioration of the environment.

Genetic engineering could out-compete traditional methods of breeding, as the former can introduce useful characters to plants in a short period. Thus, the practice and acceptance of molecular approaches to plant improvement may help to prevent food shortages in the future. The introduction and contingent expression of DNA repair genes in plant cells by genetic engineering may lead to improved DNA repair activities and to the breeding of UV-tolerant lines.[161]

In one of the ultraviolet-B-resistant mutants (*uvi1*) of *Arabidopsis thaliana*, the improved UV tolerance was due to enhanced transcription of *CPD photolyase* and enhanced capacity for dark repair of (6−4) photoproducts.[182] A UV-hyperresistant rice plant was produced by overexpression of CPD photolyase.[41] The UV tolerance of rice was improved by overexpression of the DNA repair genes *UV-DDB2* and *OsSEND-1*.[161] Thus, it is possible in principle to increase UV tolerance by the increased expression of a DNA repair gene. These examples provide encouragement for our attempts to improve UV resistance by a genetic engineering approach.

8. Concluding Remarks

Despite the recent progress reviewed in this paper, the study of DNA repair and UV tolerance in higher plants is still in an early phase. Understanding DNA repair in higher plants is not only interesting from a purely biological viewpoint but is also likely to make a significant contribution to the solution of impending social and environmental problems.

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