

Review Article

Research on Plants for the Understanding of Diseases of Nuclear and Mitochondrial Origin

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Different model organisms, such as *Escherichia coli*, *Saccharomyces cerevisiae*, *Caenorhabditis elegans*, *Drosophila melanogaster*, mouse, cultured human cell lines, among others, were used to study the mechanisms of several human diseases. Since human genes and proteins have been structurally and functionally conserved in plant organisms, the use of plants, especially *Arabidopsis thaliana*, as a model system to relate molecular defects to clinical disorders has recently increased. Here, we briefly review our current knowledge of human diseases of nuclear and mitochondrial origin and summarize the experimental findings of plant homologs implicated in each process.

1. Introduction

Sequencing of the human genome has been fundamental to progress in the study of genetic diseases. In recent years, the research on various human disorders and the influence of protein and gene interactions to disease state have increased. Several model systems have been used to investigate different human diseases such as cell lines (i.e., fibroblasts, human, and mammalian cell lines), yeast (i.e., *Saccharomyces cerevisiae*), as well as other organisms such as *Caenorhabditis elegans* and *Drosophila melanogaster* [1]. Besides these organisms, plants, especially *Arabidopsis thaliana*, have proven to be a powerful additional model system to study eukaryotic mechanisms that might act similarly in the onset of human diseases [2]. In fact, *Arabidopsis* encodes several orthologs of human proteins [2]. In addition, *Arabidopsis* present some advantages for the study of human diseases: (i) short life cycle, (ii) fast and simple growth on MS medium, (iii) availability of mutants and homozygous lines for almost all genes, (iv) fast and simple plant transformation techniques,

(v) fast and easy cell culture methods, and (vi) few ethical requirements [1].

The following sections review aspects of some human diseases of nuclear and mitochondrial origin and describe experimental advantages and recent studies of plant homologs implicated in each process.

2. DNA Repair Genetic Disorders

2.1. MMR Pathway

2.1.1. Hereditary Nonpolyposis Colon Cancer. Hereditary nonpolyposis colon cancer (HNPCC) or Lynch syndrome is an autosomal dominant disease characterized by the early occurrence of cancers of colon, endometrium, and other organs. Tumors are recognized by a high occurrence of microsatellite sequence instability (MSI) [3]. Microsatellites are tandem repeat nucleotides comprising 1–6 bp that occur ubiquitously throughout the genomes. These sequences undergo changes in the number of repeat units due to

slippage and inefficient proofreading activity of replicative DNA polymerases and to failure of mismatch repair (MMR) system.

The MMR system is best known for its role in the correction of mispaired and unpaired bases that arise during DNA replication and genetic recombination [4–10]. The system involves several nuclear proteins, which function in sequence. First, MutS proteins recognize DNA damage. Subsequently, MutS proteins recruit MutL proteins at the DNA lesion site in the presence of ATP. Then, proteins implicated in multiple DNA metabolic pathways (exonuclease I (Exo I), proliferating cell nuclear antigen (PCNA), replication factor C (RFC), single-strand binding protein RPA, high-mobility group box 1 (HMGB1), DNA polymerase δ and DNA ligase) excise the damaged DNA section and resynthesize the correct DNA sequence.

MutS and MutL proteins form heterodimers in eukaryotes. MutS heterodimers are composed of MutS homologs (MSH) subunits, which assemble as MSH2-MSH6 (MutS α) and MSH2-MSH3 (MutS β). MutS α recognizes base-base mismatches and short insertion/deletion loops (IDLs) [11–16], while MutS β binds larger IDLs [11, 14, 17–20]. MutL heterodimers are composed of MutL homologs (MLH) and postmeiotic segregation (PMS) subunits, which in humans assemble as MLH1-PMS2 (MutL α), MLH1-MLH3, and MLH1-PMS1 [7, 21, 22].

Inherited mutations in one of four different MMR genes (*MSH2*, *MSH6*, *MLH1*, and *PMS2*) are responsible for predisposition to HNPCC development [23]. Germline mutations in *MSH2* or *MLH1* lead to complete loss of DNA MMR activity, whereas inactivation of *MSH6* or *PMS2* shows a less severe form of cancer associated to the functional redundancy of *MSH3* and *MLH3* genes, respectively (Table 1). Once MMR activity is reduced, genes are prone to base and frameshift mutations and loss of function. The most critical mutated genes are either involved in the regulation of growth, the regulation of apoptosis, or in MMR system itself, which leads to a progressive inactivation of the entire system [23].

Consistent to the essential genome maintenance function performed by MMR system, evolutionary conservation of MMR genes in plants is not surprising. Besides *MSH2*, *MSH3*, *MSH6*, *MLH1*, *MLH3*, and *PMS1* (ortholog to human *PMS2*), plants encode a unique mismatch-recognition protein named *MSH7* [24–29]. *MSH7* forms heterodimers with *MSH2* leading to the formation of MutSy. MutSy preferentially recognizes some base-base mismatches and plays a specific role in meiotic recombination [25, 30–32]. Like human MMR proteins, plant counterparts are critical to efficiently promote genomic stability (Table 1). Inactivation of Arabidopsis *MSH2* by T-DNA insertion or RNA interference generated microsatellite instability at several dinucleotide repeat alleles [33]. These insertion/deletion mutations accumulated during propagation since the fifth generation of mutant plants showed up to 3-fold more allele shifts per plant than the first generation [34]. Cumulative mutations over generations produced abnormalities in morphology and development, fertility, germination efficiency, seed/silique development, and seed set [34]. Loss of

a functional Arabidopsis *MLH1* gene also led to a significant reduction in fertility in both homozygotes and heterozygotes [35].

Some advantages of Arabidopsis as a model system to study DNA repair mechanisms are worth mentioning: (i) short generation time for propagating progeny, (ii) availability of both homozygous and heterozygous seeds for comparison, and (iii) different reporter systems based on histochemical staining, bioluminescence generation, or herbicide resistance for mutagenesis analysis. In this regard, several reporter constructs were developed to examine Arabidopsis thaliana MMR function *in vivo* (reviewed in [36]). Assays were designed to analyze microsatellite instability or monitor the frequency of somatic recombination by restoring β -glucuronidase activity or conferring tolerance to the herbicide phosphinothricin. Results confirmed that frameshift mutations were dependent on *MSH2* [37]. In addition, *MSH2*, *MLH1*, or *PMS1* were suggested to play essential roles in suppressing recombination between diverged sequences and indicated the involvement of *MLH1* and to a lesser extent *MSH2* in the stimulation of plant homologous mitotic recombination [35, 38–41].

Research in Arabidopsis MMR also included overexpression of functionally impaired mutated proteins. Transgenic plants harboring a truncated form of human *PMS2*, first identified in kindreds affected with HNPCC, exhibited a dominant negative effect [42]. A similar strategy was used to analyze the role of the highly conserved ATP binding domain of AtPMS1. Introduction of mutant alleles were shown to inhibit the MMR system in Arabidopsis [43].

A better understanding of MMR genes, and the mechanisms in which they contribute, requires the isolation and characterization of the proteins they encode. We successfully overexpressed AtMSH2 and AtPMS1 in *Escherichia coli* and raised polyclonal-antibodies against these subunits [44, 45]. In addition, in studies to be reported elsewhere, we found that expression of MutL α or MutSy in *Saccharomyces cerevisiae* leads to a clear increase in yeast mutator rate, suggesting that the expression of the plant proteins somehow affects yeast MMR mechanism.

Taken together, the above-cited studies indicate that MMR system shows high conservation from humans to plants. Disruption of plant MMR genes, either by inactivation or dominant negative inhibition, confirmed the function of their orthologs in humans. Studies can be further extended to analyze DNA damage induction and repair. Considering that human MMR proteins also recognize modified bases generated in response to endogenous or exogenous DNA damaging agents and that Arabidopsis seedlings are relatively sensitive to chemical mutagens and reasonably transparent to UV light, Arabidopsis MMR research promises to yield insights into the processing of such lesions. Recently, the contribution of Arabidopsis and maize MutS α (*MSH2*–*MSH6*) to UV-induced DNA lesion repair was investigated [46]. *MSH2* and *MSH6* genes were reported to be upregulated by UV-B. Consistent with these results, *Atmsh2* and *Atmsh6* mutant plants accumulated more DNA lesions relative to wild-type plants. These data

TABLE 1: Overview of studies linking DNA repair pathways and disorders in humans and plants.

Genetic deficiency ^a	DNA repair pathway defect ^b	Human disease ^c	Reference	Plant disorder ^d	Reference
MSH2 MSH6 MLH1 PMS2(1)	MMR	HNPCC	[23]	MSI Homeologous recombination	[33, 34, 37–41]
XPA XPB XPC XPD XPE XPF XPG					
	NER	XP	[48]	Hypersensitivity to UV	[90, 93–95, 97, 98]
ATM					
	DSB	AT	[101]	Hypersensitivity to γ radiation, X-ray, radiomimetic agents	[115, 117, 118]

^aMSH: MutS homolog; MLH: MutL homolog; PMS: postmeiotic segregation; XPA-XPG: xeroderma pigmentosum A-G; ATM: ataxia telangiectasia mutated.

^bMMR: mismatch repair; NER: nucleotide excision repair; DSB: double-strand break.

^cHNPCC: hereditary nonpolyposis colon cancer; XP: xeroderma pigmentosum; AT: ataxia telangiectasia.

^dMSI: microsatellite instability.

provide evidence that plant MutS α is associated with the repair of UV-induced DNA lesions.

2.2. NER Pathway

2.2.1. Xeroderma Pigmentosum. Xeroderma pigmentosum (XP), meaning parchment pigmented skin, is a rare, autosomal inherited neurocutaneous disorder. XP patients are extremely sensitive to sun exposure (ultraviolet radiation, UV): 45% develop skin cancer, comprising mostly basal and squamous cell carcinomas, and to a lesser extent melanomas, angiomas, and sarcomas [47–49]. Besides skin cancers, 20% of the XP patients can develop progressive neurological disabilities. These patients are unable to repair UV-induced DNA damage because they are deficient in nucleotide-excision repair pathway (NER). Different genetic variants occur, thus patients are classified into eight complementation groups of XP named XP-A through XP-G for the respective mutated gene and XP-V for the variant form (Table 1). XP-C and XP-A are the most common complementation groups [50].

The NER pathway removes bulky DNA adducts, including cyclobutane pyrimidine dimers (CPDs) and pyrimidine (6-4) pyrimidinone dimers (6-4 PPs) caused by UV radiation. The repair of DNA damage occurs through different steps: (i) damage recognition, (ii) assembly of a preincision complex, (iii) excision of the damaged strand, and (iv) gap-filling DNA synthesis. Two subpathways that differ in the initial damage recognition step operate in parallel. The global genome NER (GG-NER) removes lesions throughout the genome, while the transcription-coupled NER (TC-NER) functions on actively transcribed strands [51, 52].

The GG-NER subpathway involves recognition of the lesion by a heterotrimeric complex containing XPC, HR23B, and centrin together with damaged DNA-binding protein

1 and 2 (DDB1, DDB2, or XPE) [53]. The initial damage detection process involves cycles of XPC (together with DDB1 and DDB2) binding and dissociation from the DNA in search of structure distortions [54–57]. Once a lesion is encountered, XPC changes its conformation and binds DNA with single-stranded character opposite the lesion [56, 58–62].

The TC-NER involves recognition of the lesion through a stalled RNA-polymerase II, which triggers the recruitment of Cockayne syndrome type A (CSA), Cockayne syndrome type B (CSB), and XPA binding protein 2 (XAB2) to the damage [59, 63].

After DNA recognition, the ten-subunit complex transcription factor IIIH (TFIIH, comprising XPD and XPB among others) is recruited and GG-NER and TC-NER converge into the same pathway. The DNA helicases XPB and XPD facilitate the partial unwinding of the DNA duplex leading to the recruitment of XPA, RPA, and XPG proteins and formation of a stable preincision complex around the damage site [64–69]. Then, ERCC1-XPF and XPG make DNA incisions, which result in the excision of a 24–32 nucleotide single-strand fragment containing the damaged site [70]. The gap formed is filled by DNA polymerases δ , ϵ , or κ and associated factors [71]. NER is completed by nick sealing by DNA ligase I or III α [72].

Plants have developed different strategies to counteract UV-induced DNA damage: the accumulation of UV absorbing flavonoids and related phenolic compounds in the upper epidermal layers of leaves [73–77], and the excision of UV-induced DNA adducts by photoreactivation or NER [2, 78–81]. Photoreactivation is mediated by photolyases. Arabidopsis contains two photolyase genes, the *UVR2* gene which encodes a CPD photolyase [82, 83], and the *UVR3* gene, which encodes a 6-4 PP photolyase [84]. In addition to this direct repair process, NER also contributes to maintain genome integrity in plants [85]. Orthologs of XPB and

XPD helicases have been isolated. Unlike other eukaryotic organisms, *A. thaliana* genome contains two *XPB* copies, named *XPB1* and *XPB2*, arranged as tandem repeats in head-to-tail fashion [86–89]. Expression of both genes varies with developmental stages and across tissues and is modulated by light [88]. *Atxpb1* mutant plants are viable but exhibit growth delay, lower seed viability, and loss of germination synchrony, indicating a partially functional redundancy of both *XPB1* and *XPB2* in DNA repair and transcription [87].

XPD was also shown to function in plant DNA repair. Liu et al. [90] characterized two *Arabidopsis* mutant lines. A T-DNA disruption of *XPD* was found to be homozygous lethal. However, plants harboring a point mutation in the *XPD* gene, which resulted in a substitution of a highly conserved glycine residue (G521E), are viable. These plants show growth defects, decreased UV resistance, and excision of UV photoproducts [90]. Results thus suggest that *XPD* gene is essential for plant development and is required for UV resistance.

DDB2 (XPE) is also critical for UV-B tolerance in plants. The transcript was reported to be expressed in rice and *Arabidopsis* proliferating tissues [91, 92] and anthers of *Arabidopsis* flowers [92]. These transcripts are rapidly induced after UV irradiation [91, 92]. Consistent with these results, *ddb2* mutant plants demonstrated a hypersensitivity to UV radiation [93, 94] and a dark repair deficiency of UV-induced DNA damage [94]. Combining the *ddb2* mutation with a CPD photolyase mutation (*uvr2*) further sensitized the plants to UV. These findings suggest the involvement of NER system besides photolyases for the repair of UV-induced DNA damage in plants.

Orthologs of human XPF (AtRAD1/UVH1) and XPG (AtRAD2/UVH3) endonucleases have also been characterized in *Arabidopsis*. *AtRAD1* transcript is expressed in all tissues but strongly accumulates in meristems and flowers [95, 96]. *AtRAD1* defective plants (*uvh1*) display a higher sensitivity to DNA damaging agents than wild-type [95, 97, 98]. More specifically, γ radiation of *uvh1* plants generated cell expansion but inhibited cell division [98]. This response was reported to be due to a G2-phase cycle arrest [97].

Finally, *AtRAD2* transcript appears to be ubiquitously expressed at moderate levels [99]. Plants deficient in *AtRAD2* (*uvh3* mutant) are substantially more UV-sensitive than the wild-type parent, exhibiting severe leaf yellowing and tissue damage after UV irradiation [99].

Overall, these findings indicate essential roles of XP genes in suppressing toxic effects of UV and another DNA-damaging compounds (Table 1). There are, however, differences among human and plant NER pathways. *Arabidopsis* has 2 copies of *XPB* and seems to lack *XPA*. In addition, *AtXPF* confers sensitivity to γ radiation while the corresponding human gene does not. Further studies are needed to understand NER pathway in higher plants.

2.3. Double-Strand Break Repair

2.3.1. Ataxia Telangiectasia. Ataxia telangiectasia (AT) is a rare human autosomal recessive neurodegenerative disorder that is characterized by ataxic movements due to cortical

cerebellar degeneration and ocular and cutaneous telangiectasia (dilation of small blood vessels) [100, 101]. Other features of the disease include increased risk of cancer, with ~70% of malignancies being lymphomas and T cell leukemias [100], immunodeficiency [102], sterility, and extreme cellular and chromosomal sensitivity to ionizing radiation [103].

AT cells are defective in the ataxia telangiectasia-mutated (*ATM*) gene [101, 103, 104] (Table 1). *ATM* is a member of the family of phosphatidylinositol-3-OH-kinase-like kinases (PIKK) of serine/threonine protein kinases [105]. Activation in response to double-strand break (DSB) damage involves autophosphorylation and dimer dissociation [106, 107]. Activated *ATM* phosphorylates different downstream proteins involved in cell cycle arrest and/or apoptosis [100, 108]. Failure to activate *ATM* in response to DNA damage might attenuate repair and prevent apoptosis. This would then cause an accumulation of genetic lesions that eventually compromise cellular function and viability leading to neurodegeneration [109]. Recently, *ATM* has also emerged in the general response to reactive oxygen species [110–113].

Arabidopsis also possesses *ATM* orthologs [114]. *AtATM* is expressed ubiquitously at low levels, slightly higher in flower buds than in other tissues [114]. *atm* knockout mutants are particularly sensitive to DNA DSB induced by γ radiation, X-ray treatment, and radiomimetic agents (Table 1) [115, 116] and are defective in the transcriptional induction of genes involved in DNA metabolism, repair, chromatin, and chromosome structure in response to γ irradiation [115, 117, 118]. While *ATM* function appears to be conserved in plants and humans, the signal transduction pathways in these organisms are not precisely the same. Plants lack apoptotic counterparts of downstream regulators. Transmission of signal from *ATM* depends on a plant-specific transcription factor SOG1 (suppressor of gamma response 1) [119, 120]. Recent reports have demonstrated that *Arabidopsis* root and shoot stem cells undergo cell death as a downstream response to DNA damage mediated by *ATM* [116, 121].

Taken together, the above-cited studies demonstrate that the mechanisms connecting DNA damage to downstream effectors in plants do not mirror those in human cells. In fact, plants are continuously exposed to environmental mutagens; thus plants have evolved different strategies to sustain growth under genotoxic stress.

3. Mitochondrial Disorders

3.1. Friedreich's Ataxia. Friedreich's ataxia (FA) is an autosomal recessive disease in humans [122–124]. FA causes progressive cardio- and neurodegeneration as well as skeletal muscle abnormalities, increased risk of diabetes, and sometimes liver and renal failure [123, 125–128].

This disorder is caused by a GAA triplet expansion, and/or a point mutation in the FA gene, resulting in a deficiency in the expression of frataxin [122, 129, 130]. Frataxin is a nuclear-encoded mitochondrial protein highly conserved across the evolution and with homologues found in prokaryotes and eukaryotes (Figure 1). This protein is

		*	
<i>H. sapiens</i>	107	WENPLMGWASTADPLSN	123
<i>M. musculus</i>	116	WENPLMGWASTADPLSN	132
<i>B. taurus</i>	107	WENPLMGWASTADPLSN	123
<i>D. melanogaster</i>	114	WENPLMGWASSGDPLSN	130
<i>A. thaliana</i>	84	WENPLMGWTSTGDPYAN	100
<i>P. trichocarpa</i>	88	WENPLMGWTSTGDPYAH	104
<i>H. vulgare</i>	86	WENPLMGWTSTGDPYAN	102
<i>Z. mays</i>	86	WENPLMGWTSTGDPYAN	102
<i>O. sativa</i>	88	WENPLMGWTSTGDPYAN	104
<i>G. max</i>	75	WENPLMGWTSTGDPYSH	89

FIGURE 2: Sequence alignment of *NDUFS4* homologues from different organisms showing the high conservation in the flanking region of D119. The amino acid sequence of *Homo sapiens* (accession no. NP_002486.1), *Mus musculus* (accession no. NP_035017.2), *Bos taurus* (accession no. DAA17925.1), *Drosophila melanogaster* (accession no. NP_573385), *Arabidopsis thaliana* (accession no. Q9FJW4), *Populus trichocarpa* (accession no. XP_002310893), *Hordeum vulgare* (accession no. BAK01929), *Zea mays* (accession no. NP_001132398), *Oryza sativa* (accession no. NP_001060126) and *Glycine max* (accession no. NP.001235335) are shown. Alignment was performed by using the CLUSTALW2 method (Protein Weight Matrix Blosum, clustering NJ) (<http://www.ebi.ac.uk/Tools/msa/clustalw2/>). The conserved Asp residue is shown in grey.

aging and cell death, among others [152]. Defects in any of the different mitochondrial pathways can cause mitochondrial diseases. In most of these diseases, the muscle and cerebral function is affected, and because of this, disorders are known as mitochondrial encephalomyopathies [154].

In addition, it has been described that many mutations on the mitochondrial genome can cause a wide variety of clinical syndromes such as LHON (Leber's hereditary neuropathy), LS (Leigh's syndrome), MELAS (mitochondrial encephalomyopathy), sporadic anemia, encephalomyopathy, among others [154].

Due to the evolutionary conservation of several human proteins that are part of the respiratory complexes, it was possible to develop different models such as yeast mutants [155, 156] and *C. elegans* mitochondrial mutants for CI, CII, and CIII [157] to study the pathogenesis of mitochondrial dysfunction in humans. In addition, the presence of homologous proteins in *Arabidopsis* plants allows us to propose this as a model plant for the study of several mitochondrial diseases related to the mitochondrial respiratory chain dysfunction.

Dysfunction of CI of the mitochondrial respiratory chain is the most common enzyme defect of mitochondrial disorders, and it is involved in more than 30% of the hereditary mitochondrial encephalopathies, including Leigh's syndrome. [158, 159]. CI (NADH: ubiquinone oxidoreductase) is the largest complex of the OXPHOS system. Human CI contains at least 45 protein subunits, 7 encoded by the mitochondrial genome, and 28 by the nuclear DNA [160]. This complex is located on the mitochondrial inner membrane and catalyzes the oxidation of NADH by ubiquinone.

One of the most studied OXPHOS deficiencies is the mutation in the *NDUFS4* gene, a small 18 kD protein of CI highly conserved in different organisms. Mutations in *NDUFS4* result in a loss of the last 10–15 amino acids of its final fifth exon and lead to mitochondrial diseases such as Leber's hereditary optic neuropathy (LHON), Leigh's syndrome (LS), and mitochondrial encephalomyopathy, lactic acidosis, and stroke (MELAS). The mutation affects OXPHOS and metabolism by limiting respiratory substrates such as NADH due to the deficiency in CI function [161].

The first mutation found in *NDUFS4* was a 5-bp duplication in the ORF of the gene that impairs the phosphorylation of the protein leading to an inactivation of the complex [162, 163]. Other mutations in patients with Leigh syndrome were found in *NDUFS4* such as a homozygous G-A transition at nucleotide +44 of the coding sequence [164]. The G44A mutation results in the change of a TGG codon, which encodes for a tryptophan residue, to a TAA stop codon, which causes the premature termination of the protein, thus obtaining a truncated form of *NDUFS4*. A third mutation in *NDUFS4* was reported, a single-base deletion at position 289/290 [165]. Recently, two novel mutations in *NDUFS4* causing Leigh syndrome has been reported [166]. One of these mutations, D119H, is in a conserved region of the protein. Interestingly, the D119 is highly conserved within human, mammals, nematodes, and plant species (Figure 2). All the mentioned mutations were found to be associated with a defect of the assembly of a functional complex in the inner mitochondrial membrane. These data suggest that *NDUFS4* has an essential role in the structure and function of CI.

Recently, Meyer et al. [167] reported the characterization of an *ndufs4* mutant of *A. thaliana*. As mentioned above, At*NDUFS4* is highly conserved, showing a 41% identity respect to the human homolog. *NDUFS4*-deficient plants show low phosphorylation efficiency, sucrose-sensitive germination, delayed growth, a modified respiration pathway, and altered stress responses. The lack of CI has no major influence on the mitochondrial proteome or transcriptome but leads to a lowering of growth-related nuclear transcripts and clearly influences central metabolism [167]. In addition, the deletion of *NDUFS4* prevents the assembly of CI and alters the adenylate control of cellular metabolism without pleiotropic effects on other respiratory components [167]. Taken together, these observations show the essential role of the *NDUFS4* gene in the structure and function of CI. Moreover, due to evolutionary conservation of this protein, it is possible to use different models, including *Arabidopsis*, in order to better understand the mechanism of assembly of this respiratory complex, whose dysfunction is responsible for many mitochondrial human diseases.

4. Concluding Remarks

Plants have preserved most of the pathways essential for life and then represent complementary resources within human disease research. As described in this paper, observations demonstrate that plants encode orthologs of human proteins, which function in mechanisms reminiscent of those in other eukaryotes. Thus, plant research opens new areas regarding drug development and disease therapy, which are crucial to human health.

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