International Journal of Pharmacology

ISSN 1811-7775

science alert

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Asian Network for Scientific Information

OPEN ACCESS International Journal of Pharmacology

ISSN 1811-7775
DOI: 10.3923/ijp.2017.762.772

Review Article
Pentatricopeptide Repeat-directed RNA Editing and Their Biomedical Applications

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Abstract

RNA editing is an important process that deaminates specific cytidines (C) to uridines (U). Wide-ranging organisms, such as plants, viruses, and animals are receiving the advent of different kinds of RNA editing. Site recognition and enzymatic editing mechanism are two distinct processes of RNA editing machinery. Cis elements and trans-factors empower the site recognition in target RNA molecule. Most RNA editing events can reinstate the evolutionarily conserved amino acids in mRNAs or generate translation start/stop codons, thus an essential process to preserve genetic information at the RNA level. Regulating gene expression in mitochondria and chloroplast is mediated by a large family of Trans-factors RNA-binding proteins, known as pentatricopeptide repeat (PPR) proteins. Notably, several critical molecular functionalities including, splicing, RNA processing, cleavage and translation are facilitated by these plant-specific PRP proteins. Functioning in synergy, these proteins has systematic effects on organelle biogenesis and therefore, on respiration, photosynthesis, plant development, and environmental responses. Mostly, PPR proteins are confined to mitochondria or chloroplasts, where they possess a unique role in RNA metabolism. It is worth to mention that correct RNA editing maintains the cell functionality and organism development and any imbalance in RNA editing machinery may provoke diseases and cancers. Recently, RNA editing has been recognized to be a potential target for therapeutic purposes and several reports targeting RNA editing for disease and cancer therapy have been documented. In this review, a comprehensive literature overview of the RNA editing, evolution and application of PPR proteins and RNA editing on gene expression, diseases, cancers and drugs has been provided.

Key words: RNA editing, deamination, PRP protein, molecular functions, gene expression, cancer

Citation: Danial Hassani, Muhammad Khalid, Muhammad Bilal, Yi-Dong Zhang and Danfeng Huang, 2017. Pentatricopeptide repeat-directed RNA editing and their biomedical applications. Int. J. Pharmacol., 13: 762-772.

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Blueprint for life is an expression often used to represent DNA molecule that entails the wisdom of primary sequence in DNA nucleotides. Nevertheless, these nucleotide sequences serve as the key starting materials for generating genes and transcripts molecules. Most organisms subject these materials to several modification processes before they build organisms[1]. One of the processes which nucleotides will undergo before being translated to their putative proteins is RNA editing[2]. RNA editing refers to a post-transcriptional process in which some cells can reorganize several nucleotide sequences within the transcripts molecules. Base substitution, deletion and insertion within the edited transcripts distinguish the RNA editing from common forms of RNA processing such as polyadenylation, 5′ capping and splicing[2,3]. Initial studies of RNA edition focused on the program alteration of the nucleotide sequence of an RNA species, about the sequence of encoding DNA in kinetoplasts from the mitochondria of Trypanosoma brucei through the insertion of 4 uridylates[4-7]. Since the original discovery, many such processes of nucleotide insertions, deletions and exchanges have been identified in different groups of living organisms such as plants, animals, fungi, protists, bacteria and viruses[8,9].

Mitochondria and plastids are the organelles of choice which are normally subjected to RNA editing. Coding regions of mRNA molecules is the most preferred fragment being subjected to edition, however other RNA molecules such as tRNA, rRNA, miRNA, certain viral RNA as well as the intronic region of transcripts are occasionally altered by editing machinery[3,10]. Formation of translational start or stop codon, frameshift correction, alteration of amino acid sequences as well as the destruction of stop codon are the consequences of mRNAs edition in the level of protein-coding and trypanosomatid mitochondrial transcripts[11]. Production of guanosine, adenosines, cytidine and possibly inosine within the edited transcripts is another phenomenon controlled by RNA editing process and can be obtained either by insertion-deletion or conversion mechanisms[2]. These facts recommend that RNA editing in plants restore codons altered by mutation to (again) encipher the amino acids that are required for the functioning of several supermolecules. The RNA editing will be believed to act as an indirect repair mechanism that amends DNA mutations on the RNA level.

Types of RNA editing: The RNA editing can be categorized into two major types namely nucleotide insertion/deletion editing and nucleotide conversion editing.

Insertion or deletion based editing: The RNA editing through uracil deletion or insertion in kinetoplasts of *T. brucei* mitochondria is a common illustration of this phenomenon[12]. Since this type of editing may involve an oversized fraction of the sites in a gene, it is known as "pan-editing" to differentiate it from topical editing of one or a couple of sites. Moreover, insertion of guanidine nucleotide in mammalian nuclear mRNA mediated by the paramyxoviral RNA genome[12] and the creation of stop codon via poly (A) addition to 3′ end of mRNA in mammalian mitochondria[13], are the other distinctive examples of this kind of editing.

Deamination-based editing

C-to-U editing: This type of editing is enhanced by the involvement of cytidine deaminase that deaminates a cytidine base into a uridine base. In human, the CDAgeneencodes cytidine deaminase which hydrolytically deaminates cytidine to uridine or deoxycytidine into deoxyuridine, rendering them for being catalyzed to homotetramerform[14,15].

In 1987, an APOBEC1 cytidine deaminase 107 mediated tissue-specific C-to-U alterations of apolipoprotein B in mammals was reported which resulted in a CAA-to-UAA in the mRNA. This edition compelled the cellular machinery to synthesize apoB48 (the truncated form of apolipoprotein B) in intestinal cells of rabbits and human[16,17]. The generated UAA stop codon translated a 2152 amino acid corresponding apolipoprotein B, (apo-B48) collinear with the amino-terminal half of hepatic apo-B100-a 2411 amino acid shorter than apo-B100[16].

A-to-I editing: A-to-I RNA editing appears to be the most common type of post-transcription RNA editing process in eukaryotes involving an adenosine to inosine modification in pre-mRNA[18-20]. An enormous family of catalytic proteins and enzymes bearing a separate deaminase or catalytic domain and two or three repeats of a dsRNA binding motif hinder the conversion of genetically-encoded (A) to (I) in dsRNA structures thus making the cellular machinery to read the substitute (I) as a (G). Therefore, sequencing of RNAs containing inosine results in G where the nuclear DNA reads A[21]. These enzymes family are recognized as adenosine deaminases acting on RNA (ADARs) with partially overlapping target specificity.

A-to-I editing can alter a single nucleotide within the dsRNA (specific editing), or it can also realign a large region of the duplex (promiscuous editing). Nishikuran[21], reported that arising pre-or pri-miRNAs from paired repetitive elements as well as duplexes from a transgene or viral expression comprising 50% of the edited adenosines are distinguished

in A-to-I group of editing. ADARs and A-to-I editing are known to play various biological processes which are not hitherto fully elucidated[22]. Alteration of miRNA or siRNA population, formation of heterochromatin, sequestration of cytoplasmic, coding capability alteration, Tudor SN-mediated endonucleolytic cleavage, sequestration of nucleus, alteredsplicingand miRNA and siRNAprocess inhibition are the effects of A-to-I editionembrace[21]. Inarguably, a plethora of studies elucidating the role ofRNAand ADARs involvement ineditingneuronalreceptors andionchannel componentson squid taxalikeflies and vertebrates have been presented in the scientific literature[23].

Types of RNA editing in plants: The RNA editing has been identified in both mitochondria and chloroplasts of land plants which lead to modifying the genetic information and post-transcriptional conversion of C-U and U-C in the sequences of many transcripts[24-27]. Mitochondria and chloroplasts are the archaic endosymbioses commenced organelles from free-living bacteria[28]. Previous investigations on plant mitochondrial genes indicated the presence of CGG (arginine) codons in CDS region of the gene, where UGG (tryptophan) is supposed to be in the corresponding genes of any plant species. Further identification and sequencing of a Trp tRNA demonstrated the inability of this particular tRNA in decoding CGG codon[26]. Reportedly, there are about 500 editing sites in mitochondrial and 40 editing sites in flowering plants plastids, which are individually addressed by specific proteins during organelles RNA editing[29,30]. In Arabidopsis, 43 and 619 sites have been reported to be edited in the chloroplasts[31] mitochondria[32], respectively. These editions induce amino acid alterations, indispensable for the expression of functional proteins[33]. The RNA editing, typically occurs in coding regions, is extremely important for producing functional proteins by creating new codons (either initiation or stop codon) and consequently, ensures the preservation of functionally valuable amino acids[34-36]. The first observation of RNA editing in flowering plants was described in 1989 that some U nucleotides in the RNA were substituted with C sequences and led to differences in DNA and RNA[24]. The specified amino acids following edition displayed a considerable similarity to those presented at the respective position of orthologous proteins in other organisms[37]. Identical RNA splicing has been documented to occur in plastids[37]. The observations mentioned above were further corroborated by comparing the sequence of subunit 9 (atp 9) of wheat mitochondrial ATP synthase (ATPase) and its consonant genes[38]. In the majority of the RNA editing events, the position of the given codon in the genome is altered and subsequently transcribed to the premature mRNA, resulting in a new amino acid introduction within the polypeptide chain which is variable and barely predictable from genomic DNA. Given the probability of alteration in any C containing codon by C-to-U RNA editing, generation of initiation codon or translational termination signals can be expected[39]. In contrast, generation of CAA triplet codon of amino acid glycine as a substitute of UAA termination signals in mosses and ferns by U-to-C editing can lead to the synthesis of a distinguishable protein which is not compatible with its putative genomic sequence[29]. The RNA editing regulation does not occur only in CDS regions of the messenger RNA molecules but also in untranslated regions as well as intronic sites[40,41]. Several reports are demonstrating the inevitability of RNA editing for restoring the functionality of tRNAs and precursor RNA molecules[42]. Nonetheless, due to the rapid compartmentalization of rRNA with proteins, the RNA editing in ribosomal RNA (rRNA) appears to be negligible or very scarce[29].

The significance of RNA editing in restoring the functionality of mutant codon of polypeptide complexes of the respiration pathway has been elaborated. Therefore, it is possible that the synthesized protein from unedited RNAs would not function optimally resulting in the alteration of both mitochondria and plastids activity[43].

Mechanism of RNA editing

Site recognition by Cis elements and trans-acting factors: When RNA editing discovered, it was not clear how the information could be manipulated to RNA molecule from a gene. Many years of exploration into different sorts of RNA editing initiated to uncover their underlying mechanisms[44,45]. Mechanistically, the RNA editing can be classified into two steps of site recognition, facilitated by trans-acting factors interacting with their corresponding, cis-acting elements. The steps of editing mechanism are mediated by a catalyzing enzyme that modifies the specific nucleotides to be spliced[25,46,47]. The synthesis of a functional protein in plants depends on the precise recognition of C nucleotide to be edited and distinguishing that from unedited C. Due to lacking a common denominator and the presence of hundreds of editing sites in plants, this process requires a unique sequence pattern which can guide the editing machinery[48]. In all instances, stretches of 20-25 nucleotides in RNA, particularly in upstream (5′) of the editing site provide a specific context, which in turn is distinguished by the editing machinery. One noteworthy inquest is to comprehend the cis-element characterizing the C residue to be edited[49].

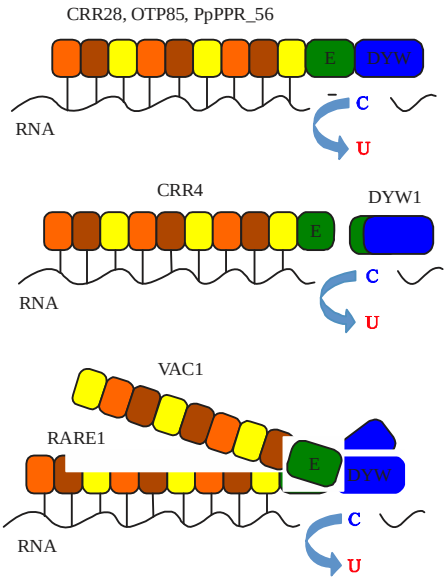

Fig. 1: RNA editing requires a single or multiple PPR editing factors Ichinose and Sugita[119], an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC-BY) license (http://creativecommons.org/licenses/by/4.0/)

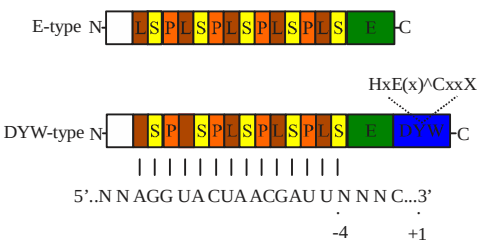

Fig. 2: Plant organellar pentatricopeptide repeat (PPR) editing proteins and a model for their binding to the editing site Ichinose and Sugita[119], an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC-BY) license (http://creativecommons.org/licenses/by/4.0/)

To accomplish the editing procedure, the recognition of a cis-element surrounding the 20-25 nucleotides in the vicinity of target C by trans-acting factor is necessary for initiation of RNA editing machinery[50,51]. In this model, cis-element is recognized by a trans-acting factor that recruited the RNA editing machinery to the site[52]. Trans-acting factors were first suggested in tobacco plastids by in-vitro approaches[48]. Trans-acting factors that specifically bind to the cis-elements were determined by experiments with an in vitro RNA editing system (Fig. 1). In tobacco, psbL, psbE and petB cis-elements are circumscribed by the proteins of 25, 57 and 70 kDa, respectively[52-54].

Pentatricopeptide repeat (PPR) proteins: The PPR proteins are among the largest nucleus-encoded helical repeat protein family in plants that specifically binds to RNA present in mitochondria and chloroplasts[55] (Fig. 2). The PPR protein family was first identified by Small and Peeters, in *A. thaliana* nuclear genome. The PPR proteins are made up of tandem repeats of a variable number of PPR motifs, each consisting of approximately 35 amino acids[55-57].

The PPR proteins are found only in eukaryotes and the size of PPR family fluctuates among different organisms. For instance, angiosperm genomes encoding >400 PPR proteins, over 400 genes in *A. thaliana* and 477 genes in Oryza sativa have been identified[58,59]. The majority of the PPR proteins are predicted to be localized in chloroplast or mitochondria. In contrasting with higher plants, all other eukaryotes including humans, Drosophila, protists and algae encompass a small set of PPR proteins, suggesting that the number of these factors dramatically increased during plants evolution period[59,60]. Undeniably, the unique role of PPR protein family in physiology and organism development, organelles and plastid RNA metabolism including splicing, RNA cleavage, translation and RNA stabilization, many researchers have rekindled their research interest explore this family in plants[61]. Based on their repeats, PPR proteins have been classified into two broad families namely P family, which lacks any other conserved domains and PLS, which is further divided into three subfamilies of E, E + and DYW based on C-terminal motifs[62]. The P classes of PPR protein essentially comprise only canonical 35-amino-acid PPR repeats. Contrarily, the PLS class proteins contain characteristic triplets of P, PPR-like L (L for long, generally 36 amino acids) and PPR-like S (S for short, generally 31 amino acids) motifs and equally characteristic C-terminal domains[60,63]. Some PPR proteins contain E-domain (for extended), which is further classified into two smaller motifs explicitly E and E+. Another additional domain is defined as DYW domain by a C-terminal aspartic acid, tyrosine and tryptophan-tripeptide. This motif always follows the E and E+ motifs[63] .

Functions of PPR proteins: Among various eukaryotes PPR proteins, many of them have specialized roles in organelles gene expression. Some of PPR proteins in fungi, animals and plants act in gene expression of mitochondrial and chloroplast. Therefore dysfunctioning of any particular PPR protein often leads to severe phenotypes, suggesting the central roles in plant organelle physiology[64,65]. Bentolila *et al.*[64] reported an albinism and lethality following by a significant defect in the chloroplast development which was occurred after the suppression of (OsPPR1) gene in rice chloroplast[64].

Given promoting the role of PPR proteins in expressing genes required for synthesis or functioning of the energy transducing machinery, PRP proteins have been characterized to perform diverse biological functions in plant organelles including, photosynthesis or respiration. Recent research conducted by Kamel Hammani and coworkers, indicated the loss of plastids ribosome due to the mutation in PPR103 gene of Zea maize[66]. Despite their crucial roles in plant development and physiology, the molecular functions of PPR proteins revealed their involvement in a diverse range of purposes including splicing, stability, editing and translation of various transcripts[60,67-69]. Table 1 comprehensively illustrates the molecular functions of PPR proteins in Arabidopsis thaliana and Zea mays. The role of PPR proteins in all stages of RNA metabolism has been elucidated and interestingly, the structurally similar PPR proteins are particularly involved in different physiological and molecular functions[70]. A remarkable example of this phenomenon is the pentatricopeptide repeat protein CRR4-a sequence- specific RNA binding protein- that enhances the site recognition in plastids during RNA editing process[71,72]. However, in Arabidopsis thaliana, the absence of translational initiation codon for plastid ndhD gene (the ndhD-1 site) was reported in CRP4 mutant lines[34,71]. Studies have evidenced the attachment of PPR proteins to various kinds of RNA molecule with target sequences in 5 untranslated regions (UTRs), introns and an intergenic spacer[73,74]. Enormous numbers of introns and editing sites in different taxa highlighted that editing and splicing have gone through evolutionary tracks in various chloroplast descent. The PPR proteins are recognized as acentral player[75] involving in organellar RNA splicing directly or indirectly. In Physcomitrella patens, the PPR protein PPR_38 has shown to play a role in splicing of chloroplast clpP mRNA encoding the ClpP protease[76]. The processing of petD mRNA from a polycistronic precursor is mediated by CRP1 protein in maize, suggesting an unusual mode of RNA binding for PPR proteins. It also showed that the translational regulation might be a particularly common function of PPR proteins[74].

RNA editing and biomedical applications: As mentioned above, the RNA editing is crucial in regulating gene expression of any organism, imbalance of RNA editing may cause defective functioning of proteins involved in normal physiology such as immuno-neural functions. A significant number of nervous system targets such as ion channels and neurotransmitter receptors undergo A-to-I RNA editing by ADARs[18]. Moreover, the ADAR-assisted RNA editing in nervous tissues may occur both in coding as well as non-coding transcriptomes[77]. As a result, perfect and controlled RNA editing is essential for proper functioning of nervous system and circumventing neural disorders[78]. The RNA editing and replication of hepatitis delta virus might be regulated by ADAR (ADAR1). For instance, the two forms of ADAR1 namely ADAR1-S and ADAR1-L are associated with HDV editing (Fig. 3), where the ADAR1-S and ADAR1-L functions in unstimulated cells and IFN-alpha stimulated cells, respectively[79].

The control and regulation of ADAR depend on the differentiation status of pluripotent human embryonic stem cells, demonstrating that RNA editing is involved in human embryogenesis. Therefore, any interference in apoptosis and

Table 1: Molecular functions of PPR proteins in *Arabidopsis thaliana* and *Zea mays*

Organism	Protein	Target RNA	Localization	Function	Reference
Arabidopsis thaliana	HCF152	psbB-psbT-psbH-petB-petD	Chloroplast	RNA Processing	Nishimura and Shikanai[85]
Arabidopsis thaliana	CLB19	clpP, rpoA	Chloroplast	RNA editing	Chateigner Boutin *et al.*[86]
Arabidopsis thaliana	OTP43	Nad1	Mitochondria	RNA splicing	Delannoy *et al.*[67]
Arabidopsis thaliana	OTP82	ndhB/ndhG	Chloroplast	RNA editing	O'Toole *et al.*[59]
Arabidopsis thaliana	CRR2	Rps7, ndhB	Chloroplast	RNA Processing	Hirose *et al.*[46]
Arabidopsis thaliana	CRR4	ndhB	Chloroplast	RNA editing	Kwak and Kawahara[87], Oguchi *et al.*[88]
Arabidopsis thaliana	CRR21	ndhB	Chloroplast	RNA editing	Nishikura[21]
Arabidopsis thaliana	CRR22	ndhB, ndhD, rpoB	Chloroplast	RNA editing	Nishikura[21], Okuda *et al.*[89]
Arabidopsis thaliana	CRR28	ndhB, ndhD,	Chloroplast	RNA editing	Okuda *et al.*[90]
Arabidopsis thaliana	PGR3	petL	Chloroplast	RNA stabilization	Yuan and Liu[90]
Arabidopsis thaliana	P67	ND	Chloroplast	RNA Processing	Lurin *et al.*[63]
Arabidopsis thaliana	LOJ	ND	Chloroplast	Lateral organ development	Lurin *et al.*[63]
Arabidopsis thaliana	PPR40	Cytochrome C	Mitochondria	RNA stability	Yagi *et al.*[91]
Arabidopsis thaliana	At1g 53330	ND	Mitochondria	Embryo development	Kazama *et al.*[73]
Arabidopsis thaliana	MRL1	petA	Chloroplast	RNA stabilization	Lahmy *et al.*[92]
Arabidopsis thaliana	PpPPR38	ClpP1	Chloroplast	RNA stabilization	Hattori and Sugita[76]
Arabidopsis thaliana	MPPR6	rps	Mitochondria	RNA Processing	Maier *et al.*[2]

Table 1: Continue

Organism	Protein	Target RNA	Localization	Function	Reference
Arabidopsis thaliana	Rf1a	Atp6, orf79	Mitochondria	RNA Processing	Kazama *et al.*[73]
Arabidopsis thaliana	RPF1	Nad4	Mitochondria	RNA Processing	Hashimoto *et al.*[93]
Arabidopsis thaliana	RPF2	Nad9, cox3	Mitochondria	RNA Processing	Jantsch and Ohman[23]
Arabidopsis thaliana	RPF3	ccmC5	Mitochondria	RNA Processing	Jonietz *et al.*[94]
Arabidopsis thaliana	RPF5	Nad6, atp6, rrn26	Mitochondria	RNA Processing	Hogg *et al.*[78]
Arabidopsis thaliana	OTP70	Rpoc1	Chloroplast	RNA splicing	Chateigner Boutin *et al.*[95]
Arabidopsis thaliana	THA8	ycf3	Chloroplast	RNA splicing	Khrouchtchova *et al.*[96]
Arabidopsis thaliana	ABO5	nad2	Mitochondria	RNA splicing	Liu *et al.*[97]
Arabidopsis thaliana	BIR6	nad7	Mitochondria	RNA splicing	Liu *et al.*[97]
Arabidopsis thaliana	DYW1	ndhD	Chloroplast	RNA editing	Belcher *et al.*[75]
Arabidopsis thaliana	LPA66	psbF	Chloroplast	RNA editing	Cai *et al.*[98]
Arabidopsis thaliana	OTP80	rpl23	Chloroplast	RNA editing	Hammani *et al.*[99]
Arabidopsis thaliana	OTP81	rps12	Chloroplast	RNA editing	Hammani *et al.*[99]
Arabidopsis thaliana	OTP84	ndhB, ndhF, psbZ	Chloroplast	RNA editing	Hammani *et al.*[99]
Arabidopsis thaliana	OTP85	ndhD	Chloroplast	RNA editing	Hammani *et al.*[99]
Arabidopsis thaliana	OTP86	rps14	Chloroplast	RNA editing	Hammani *et al.*[99]
Arabidopsis thaliana	RARE1	accD	Chloroplast	RNA editing	Schmitz-Linneweber *et al.*[74]
Arabidopsis thaliana	YS1	rpoB	Chloroplast	RNA editing	Schmitz-Linneweber *et al.*[74]
Arabidopsis thaliana	MEF19	ccmB	Mitochondria	RNA editing	Takenaka *et al.*[100]
Arabidopsis thaliana	MEF20	rps4	Mitochondria	RNA editing	Takenaka *et al.*[100]
Arabidopsis thaliana	MEF21	cox3	Mitochondria	RNA editing	Takenaka *et al.*[100]
Arabidopsis thaliana	MEF22	nad3	Mitochondria	RNA editing	Takenaka *et al.*[100]
Arabidopsis thaliana	MEF25	nad1	Mitochondria	RNA editing	Arenas-M *et al.*[101]
Arabidopsis thaliana	MEF29/PPR2263	cob, nad5	Mitochondria	RNA editing	Sosso *et al.*[102]
Arabidopsis thaliana	OTP71	ccmFN2	Mitochondria	RNA editing	Chateigner Boutin *et al.*[103]
Arabidopsis thaliana	OTP72	rpl16	Mitochondria	RNA editing	Chateigner Boutin *et al.*[103]
Arabidopsis thaliana	OTP87	atp1, nad7	Mitochondria	RNA editing	Hammani *et al.*[104]
Arabidopsis thaliana	REME1	mttB, nad2	Mitochondria	RNA editing	Bentolila *et al.*[105]
Arabidopsis thaliana	REME2	rps3, rps4	Mitochondria	RNA editing	Bentolila *et al.*[32]
Arabidopsis thaliana	SLG1	nad3	Mitochondria	RNA editing	Yamazaki *et al.*[69]
Arabidopsis thaliana	SLO1	nad4, nad9	Mitochondria	RNA editing	Sung *et al.*[106]
Arabidopsis thaliana	SLO2	mttB, nad1, nad4L, nad7	Mitochondria	RNA editing	Zhu *et al.*[43]
Arabidopsis thaliana	AtECB2	accd	Mitochondria	RNA editing	Yu *et al.*[107]
Arabidopsis thaliana	MEF1	Rps4, nad7, naad2	Mitochondria	RNA editing	Yu *et al.*[107]
Arabidopsis thaliana	MEF9	Nad7	Mitochondria	RNA editing	Takenaka *et al.*[100]
Arabidopsis thaliana	MEF11	cox3, nad4, ccb203	Mitochondria	RNA editing	Verbitskiy *et al.*[108]
Arabidopsis thaliana	AtC401	ND	Mitochondria	Clock controlled	Oguchi *et al.*[88]
Arabidopsis thaliana	PTAC2	N/A	Chloroplast	Transcription	Pfalz *et al.*[109]
Arabidopsis thaliana	MTSF1	nad4	Mitochondria	RNA Stability	Haili *et al.*[110]
Arabidopsis thaliana	OTP51	ycf3	Chloroplast	RNA Splicing	Longevialle *et al.*[111]
Arabidopsis thaliana	PRORP1	PRORP	Mitochondria chloroplast	RNA processing	Gobert *et al.*[112]
Arabidopsis thaliana	PRORP2/PRORP3	PRORP	Nucleus	RNA processing	Gutmann *et al.*[113]
Arabidopsis thaliana	SVR7	atpB, atpE, rbcL	Chloroplast	Translation	Moreira and Philippe[114]
Zea mays	Crp1	petA, psaC, petD	Chloroplast	Translation processing	Fisk *et al.*[115]
Zea mays	PPR2263	nad5, cob	Mitochondria	RNA Editing	Sosso *et al.*[102]
Zea mays	PPR2	Ribosome	Chloroplast	RNA	Williams and Barkan[116]
Zea mays	PPR4	Rps12	Chloroplast	RNA	Schmitz-Linneweber *et al.*[117]
Zea mays	PPR5	*TurnG-UCC*	Chloroplast	RNA	Williams-Carrier *et al.*[72]
Zea mays	PPR10	*Atpl, atph*	Chloroplast	RNA	Prikryl *et al.*[118]

differentiation regulation may lead to carcinogenesis. It is worth mentioning that RNA regulation can modulate the expression of tumor-suppressing genes[80]. In recent years, some cancer-related RNA editing targets viz. antizyme inhibitor1 (AZIN1) and glioma-associated oncogene 1 (GLI1) have been discovered. A-to-I RNA editing of AZIN1 is enhanced in hepatocellular carcinoma whereas the RNA editing of GLI1 transcription factor associated with Hedgehog signaling is decreased in basal cell carcinoma tumor. Consequently, the discrepancy in ADAR enzyme expression is profoundly interrelated with cancer evolution and expansion[81].

The RNA editing also has a remarkable influence on drug discovery. Besides primary gene products, the isoforms generated as a consequence of RNA editing may apprehend additional drug targets with superior physiological impact[82].

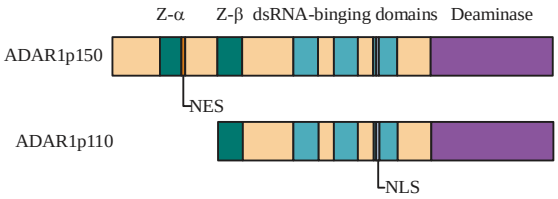

Fig. 3: Gene structures of the two isoforms of ADAR1. Z: Z DNA binding domain, NES: Nuclear export signal, NLS: Nuclear localizations signal Song *et al.*[120], an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC-BY) license (http:// creativecommons.org/licenses /by/4.0/)

Importantly, RNA editing has been advocated to be a therapeutic target for Central Nervous System (CNS) ailments. A-to-I RNA editing can also regulate the drug response of some channels, such as Kv1.1 channel. Hence, RNA editing of these channels and receptor may alter their protein functions and resultantly develop a target for disease therapy[83]. Some drugs acting as inhibitors of RNA editing enzymes have been developed in the recent past. For instance, novel inhibitors of Trypanosoma brucei RNA editing ligase 1 were described to be budding therapeutic drugs of choice[84].

CONCLUDING REMARKS AND PERSPECTIVES

The RNA editing is a well-studied process that may cause sequence diversity of transcripts in chloroplasts and mitochondria of land plants. The mechanisms by which RNA sequences are recognized through PPR motifs accompanied by some components of RNA editing machinery have been discovered. These findings led to researchers in discovering new approaches for manipulating RNA *in vivo*. Importantly, a worthy inquest is to explore how the RNA editing machinery common among different systems. Despite the tremendous progress, exclusively regarding the mechanism of target recognition, understanding the puzzling nature of RNA editing in plants, is necessary to put evolution into perspective. In the upcoming years, it may be promising to deliberate the advancement of editing machinery by comparing genome information. This may provide a solution to the fundamental question of why plants do not correct their genomic information and consequently stop editing their RNA. Moreover, it is believed that RNA editing concept can encourage the scientists to connect the areas of RNA editing research with natural products for drug discovery in cancer therapy.

SIGNIFICANCE STATEMENT

Correct RNA editing is necessary to maintain the cell functionality and organism development and any imbalance in RNA editing machinery may provoke several diseases including cancer. Pentatricopeptide repeat (PRP) proteins are typically targeted to mitochondria or chloroplasts, where they bind one or several organellar transcripts and influence their expression by modifying RNA sequence, turnover, processing, or translation. Their synergistic action has significant effects on organelle functions and resultantly, on respiration, photosynthesis and plant development.

ACKNOWLEDGMENTS

This study was sponsored by National Nature Science Foundation of China (NSFC, 31372079) and Nature Science Foundation of Shanghai (13ZR1422400).

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