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Adenosine methylation (m^6A) in plant mRNA

Methylace adenosinu (m^6A) v rostlinné mRNA

Bachelor´s thesis

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Poděkování

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Prohlášení

Prohlašuji, že jsem závěrečnou práci zpracovala samostatně a že jsem uvedla všechny použité informační zdroje a literaturu. Tato práce ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu.

V Praze

Abstrakt

V eukaryotických organismech je známo více než 200 interních posttranskripčních modifikací RNA. Nejběžnější modifikací v mRNA je *N6*-methyladenosin (m^6A). V rostlinách m6A ovlivňuje mnoho aspektů procesování mRNA, jako je její stabilita, sestřih, alternativní polyadenylace či export z jádra a translace. Za zápis, odstranění a percepci m^6A jsou zodpovědné proteinové komplexy obsahující methyltransferázy (tzv. writery), demethylázy (erasery) a proteiny obecně vázající m^6A (readery). Dynamické regulace pomocí m6A mají významný vliv na vývoj rostlin. m^6A také hraje roli v reakci na abiotický stres a virovou infekci. Tato práce shrnuje současné znalosti o m6A v rostlinách a také s přihlédnutím k nejnovějším poznatkům z živočišných experimentálních modelů.

Klíčová slova

m^6A, úpravy mRNA, metylace mRNA, vývoj rostlin

Abstract

In eukaryotic organisms, there are known more than 200 internal post-transcriptional modifications of RNA. *N6*-methyladenosine (m^6A) is the most common modification in mRNA. In plants, m^6A affects many aspects of mRNA processing, such as mRNA splicing, alternative polyadenylation, export from the nucleus, its overall stability or translation. Adding, removing, and perceiving of m^6A are handled by protein complexes containing methyltransferases (writers), demethylases (erasers), and m6A-binding proteins (readers), respectively. Dynamic regulations of m^6A have a significant effect on plant development. Also, m^6A exerts its role in response to abiotic stress and viral infection. This thesis summarizes current knowledge on m^6A in plants in light of the latest advances in animal experimental models.

Keywords

m^6A, mRNA processing, mRNA methylation, plant development

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List of abbreviations

3'-UTR	3'-untranslated region
5'-UTR	5'-untranslated region
APA	Alternative polyadenylation
m^6A	*N6*-methyl adenosine
m^6A_m	*N6*,2′-O-dimethyladenosine
miRNA	microRNA
mRNA	Messenger RNA
ROS	Reactive oxygen species
SAH	S-adenosyl homocysteine
SAM	S-adenosyl methionine
SG	Stress granule
WT	Wild type

Introduction

In the eukaryotic organisms, there are more than 200 internal post-transcriptional modifications of mRNA known, among them *N1*-methyladenosine (m^1A), pseudouridine (Ψ), *N6*-methyladenosine (m^6A), 5-methylcytidine (m^5C) and others (Figure 1) (Boccaletto et al., 2022). The compilation of all the biochemical modifications of the RNA species in the cell is called epitranscriptome. In mRNA, the most common modification is *N6*-adenosine, or m^6A (Parker et al., 2020; Wan et al., 2015). This modification occurs by the addition of the methyl (CH_3) group to the *N6* position of adenosines present in the mRNA (Shi et al., 2019). This modification is found in numerous eukaryotes, such as mammals, insects, yeast, and plants. In plants, m^6A was first identified in 1976 in maize and later in many other model organisms, including *Arabidopsis thaliana* (Nichols, 1979; Zhong et al., 2008). m^6A was found to be unevenly distributed along the mRNA, being predominantly localized near the stop codons, within 3'-UTRs, and near the start codon (Figure 2) (Bodi et al., 2012; Dominissini et al., 2012; G. Z. Luo et al., 2014; Meyer et al., 2012).

The processes accompanying the m^6A modification involve numerous protein factors. They include protein complexes containing methyltransferases, demethylases, and m^6A-recognizing proteins, commonly called m^6A writers, erasers, and readers, respectively (Figure 3) (Reichel et al., 2019; Shi et al., 2019). m^6A writers form a complex that is responsible for the addition of the methyl group to the *N6* position of adenosine in mRNA. The m^6A erasers are able to enzymatically remove the methyl groups from RNA, making the m^6A modification reversible. Finally, the m^6A readers can recognize and bind m^6A marks on mRNA.

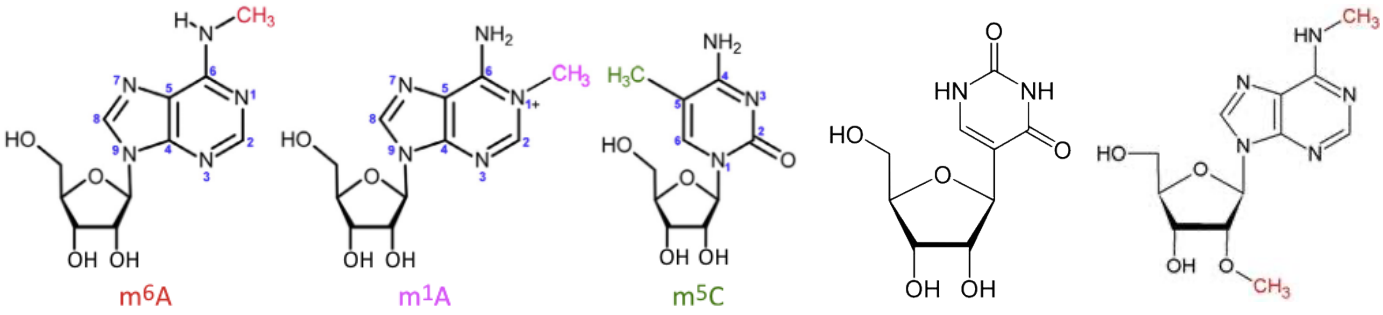

Figure 1 Chemical structure of the mRNA modification (Mauer et al., 2016; Shen et al., 2019)

A large number of studies demonstrated that m^{6}A plays a vital role in many aspects of mRNA processing, such as splicing, alternative polyadenylation, regulation by microRNAs, general stabilization of mRNA, export mRNA from nucleus or translatability (reviewed Reichel et al., 2019; S. Wang et al., 2022). This was underlined by the severe phenotypic defects associated with the deficiency in m^{6}A (reviewed Jiang et al., 2021; Shao et al., 2021). It is also worth noting that m^{6}A plays an important role in stress and viral infection response (Martínez-Pérez et al., 2017; Wan et al., 2015). These findings underline that m^{6}A is the most studied RNA modification in recent years.

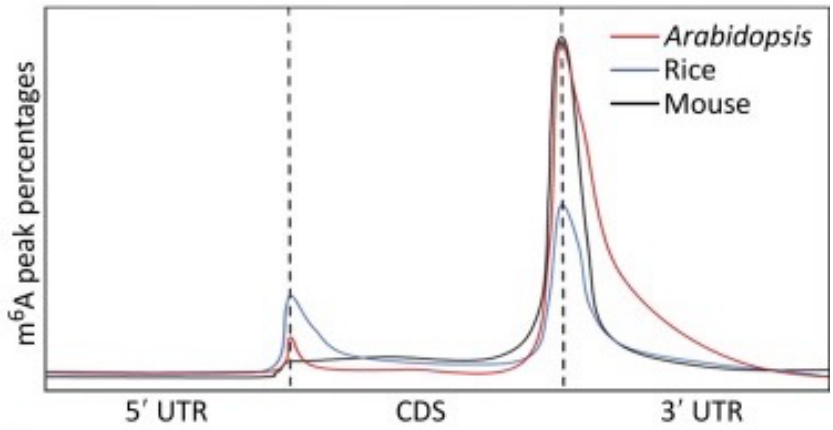

Figure 2 Comparison of the m^{6}A distribution in mRNA of Arabidopsis, rice, and mouse, based on several m^{6}A-seq studies (Shen et al., 2019).

This thesis aims to review the latest research on the role of m^{6}A in plants, including the effects of m^{6}A on mRNA processing or maturation, and highlights the role of m^{6}A in plant development, response to abiotic stress and plant viral infections. Moreover, the status of knowledge about m^{6}A-dependent processes in plants was compared to the information from animals' systems where relevant.

Table 1: m^{6}A writers, erasers, and readers in *Arabidopsis thaliana*, in mammals and in *Drosophila melanogaster*, if relevant.

	Arabidopsis	Homologs in mammals (*Drosophila*)
Writer complex	MTA (Zhong et al., 2008)	METTL3 (J. Liu et al., 2013)
	MTB (Růžička et al., 2017)	METTL14 (J. Liu et al., 2013)
	FIP37 (Shen et al., 2016; Zhong et al., 2008)	WTAP (fl(2)d) (Ping et al., 2014)
	VIRILIZER (VIR) (Růžička et al., 2017)	VIRMA (vir) (J. Liu et al., 2018)
	FPA (Parker et al., 2021)	RBM15/15B (nito) (Patil et al., 2016)
	HAKAI (Růžička et al., 2017)	HAKAI (Hakai) (J. Liu et al., 2018)
	HIZ1 (M. Zhang et al., 2022)	Information about (possible) homologs missing
	HIZ2 (M. Zhang et al., 2022)	Zc3h13 (Flacc) (Knuckles et al., 2018)

	Information about (possible) homologs missing	Zfp217 (Aguilo et al., 2015)
Erasers	ALKBH9B (Duan et al., 2018) ALKBH10B (Duan et al., 2018)	ALKBH5 (Zheng et al., 2013a) ALKBH5
	no homolog present (Mielecki et al., 2012)	FTO (Jia et al., 2011)
Readers	ECT2 (Arribas-Hernández et al., 2018) ECT3 (Arribas-Hernández et al., 2018) ECT4 (Arribas-Hernández et al., 2018) CPSF30 (P. Song et al., 2021)	YTHDF1/2/3 (Dominissini et al., 2012) YTHDF1/2/3 YTHDF1/2/3 YTHDC1/2
	Information about (possible) homologs missing	IGF2BPs (Huang et al., 2018)
	Information about (possible) homologs missing	Prrc2a (R. Wu et al., 2018)

Proteins directly associated with the m^{6}A modification

m^{6}A writers

The methyltransferase complex responsible for adding the m6A marks on mRNA is commonly called m6A writer complex. Since its components are evolutionarily conserved, most m6A writers show orthologs across the main eukaryotic lineages. Particularly human, Drosophila melanogaster and Arabidopsis thaliana model systems proved to be instrumental in uncovering their identity. Mammalian m6A writer complex includes methyltransferase-like proteins 3 and 14 (METTL3 and METTL14) (J. Liu et al., 2013), Wilms tumor 1 associated protein (WTAP) (Ping et al., 2014), virilizer (VIRMA, also known as KIAA1429) (J. Liu et al., 2018), RNA-binding motif protein 15 (RBM15/15B) (Patil et al., 2016), HAKAI (J. Liu et al., 2018) and Zinc finger CCCH domain-containing protein 13 (Zc3h13) (Figure 3) (Knuckles et al., 2018). Plants writer complex consists of the mRNA ADENOSINE METHYLASE A (MTA; orthologue of METTL3) (Zhong et al., 2008) and B (MTB; orthologue of mammalian METTL14), VIRILIZER (VIR; orthologue of VIRMA/KIAA1429), FKBP12 INTERACTING PROTEIN 37 KD (FIP37; orthologue of WTAP), HAKAI (Růžička et al., 2017), Flowering time control protein FPA (Parker et al., 2021) and HAKAI-interacting zinc finger proteins (HIZ2) (M. Zhang et al., 2022). m6A writers are localized in the nuclear domains called

nuclear, or splicing, speckles. They contain the proteins that regulate several stages of RNA processing, from the site of transcription to the nuclear export (Galganski et al., 2017; Ping et al., 2014; Růžička et al., 2017).

The first component of the writer complex identified in mammals was METTL3 (Bokar et al., 1997). Later, the METTL3 ortholog, METTL14, was revealed, as interacting with METTL3 to form a stable METTL3-METTL14 dimer (Schöller et al., 2018; P. Wang et al., 2016). It was shown that only METTL3 is active as methyltransferase, while METTL14 likely functions in the dimer as an essential component facilitating the RNA binding. Both METTL3 and METTL14 have the methyltransferase catalytic domains and bind S-adenosyl methionine (SAM) (Bokar et al., 1997; P. Wang et al., 2016; X. Wang et al., 2016). SAM is a product of the methionine cycle of one-carbon metabolism, and a universal methyl donor in the cellular methylation processes. After the m^{6}A methylation, SAM turns into S-adenosyl homocysteine (SAH) that can allosterically inhibit methyltransferase activity of METTL3 (Kim & Lee, 2021).

In addition, a few other factors have been found as parts of the writer complex. WTAP associates with METTL3 and is required for the m^{6}A writer complex assembly and binding to RNA. Firstly, this association was seen in *Arabidopsis thaliana* by Zhong et al. (2008) and only later was it shown in mammals (Ping et al., 2014; Zhong et al., 2008). Another protein of the m^{6}A writer complex is VIRMA. VIRMA knockdown

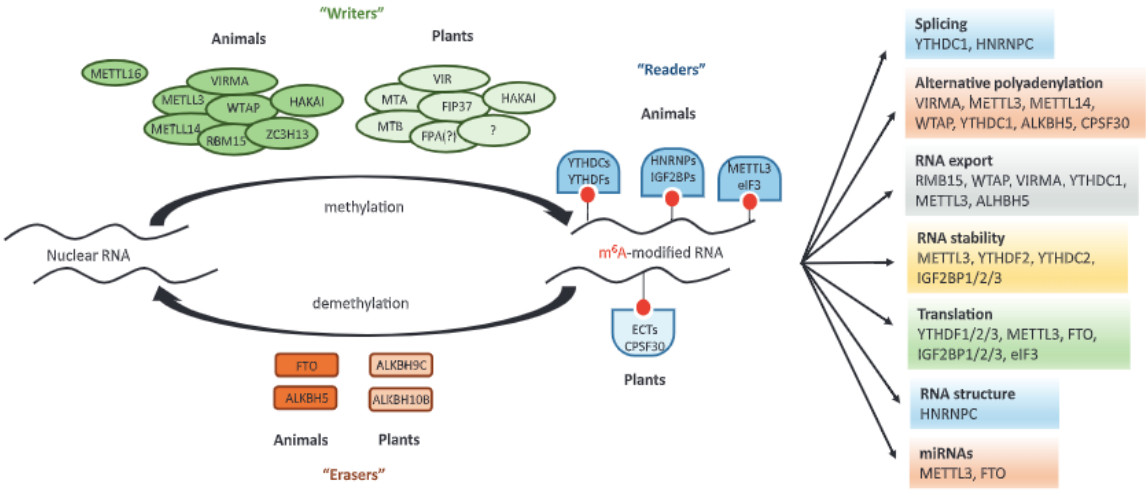

Figure 3 Schematic illustration of the m^{6}A machinery in plants and animals, highlighting the aspects of mRNA processing in which m^{6}A is involved (Reichel et al., 2019).

displays loss of m^{6}A enrichment in 3′UTR and near the stop codon and to the extension of 3′-UTRs for certain groups of transcripts (J. Liu et al., 2018).

HAKAI protein was first described as a component of the m^{6}A writer complex in the model organism *Arabidopsis thaliana* (Růžička et al., 2017). Further studies on human Studies on HeLa and U2OS cells and *Drosophila melanogaster* revealed that disrupting the HAKAI expression causes an overall destabilization of the WTAP and VIRMA proteins (Bawankar et al., 2021). Additionally, Patil et al. (2016) found that the mammalian RNA-binding motif protein 15 (RBM15) and related RBM15B (respectively, the *Drosophila* homolog called Nito) interact with the WTAP and METTL3 proteins (Lence et al., 2016; Patil et al., 2016). Originally, it was known that RBM15 and RBM15B bind the U-rich regions in mRNA (Patil et al., 2016). However, since the knockdowns of *RBM15/15B* and Nito show the reduced levels of m^{6}A of numerous transcripts, it was concluded that these proteins indeed participate in the mRNA methylation, too (Lence et al., 2016; Patil et al., 2016).

The next component of the mammalian writer complex is the zinc finger CCCH domain-containing protein (Zc3h13), respectively its *Drosophila* homolog Flacc (Knuckles et al., 2018), later described in *Arabidopsis* as HIZ2. Zc3h13 interacts with WTAP, VIR and HAKAI and appears to be required for the nuclear localization of Zc3h13-WTAP-VIR-Hakai complex (Wen et al., 2018). Moreover, Zc3h13 (Flacc) contributes to the stabilization of interaction between WTAP and RBM15, which increases the efficiency of the m^{6}A writing (Knuckles et al., 2018). Some data also suggest that Zc3h13 (Flacc) could contribute via m^{6}A to the regulation of alternative polyadenylation (Knuckles et al., 2018; Wen et al., 2018).

Similar to the animal proteins, MTA and MTB appear to form a heterodimer and interact with FIP37 (Růžička et al., 2017; Zhong et al., 2008), as a part of the molecular complex containing MTA, MTB, FIP37, VIR, HAKAI (Růžička et al., 2017). It was also found that the FLOWERING TIME CONTROL PROTEIN FPA co-purifies with MTA, MTB, FIP37 and VIR, and although FPA not affect global m^{6}A levels, it perhaps plays direct role in m^{6}A (Parker et al., 2021). There are also two HAKAI-INTERACTING ZINC FINGER PROTEINS (HIZ1 and HIZ2). HAKAI is required for interaction between

HIZ1 and MTA, while HIZ2 can interact with MTA even in absence of HAKAI. Disrupting the expression of HIZ1 protein has almost no effect on the plant growth and development, while the knockout of HIZ2 (homolog of the Zc3h13 (Flacc) protein) led to decrease in the m^6A levels and plant developmental defects (M. Zhang et al., 2022). In sum, the quantification of the total m6A levels along with the phenotypic assays indicates that MTA, MTB, FIP37 and VIR are the core m^6A components required for the full methylation levels. In contrast, HAKAI and HIZ2 seem to have rather auxiliary role and FPA, and HIZ1 has no significant effect on the total m^6A pools (Růžička et al., 2017; M. Zhang et al., 2022).

m^6A erasers

The organisms can enzymatically remove the methyl groups from mRNA using m^6A demethylases, making the m^6A modification reversible. The m^6A demethylases identified in mammals are the Fat mass and obesity-associated protein (FTO) and AlkB homolog 5 (ALKBH5) (Jia et al., 2011; Zheng et al., 2013a). FTO was the first found mammal m^6A demethylase which was also shown to demethylate *N6,2′*-O-dimethyladenosine (m^6A_m; Figure 1), the mRNA modification located near the 5'-cap of mRNA (Jia et al., 2011; Mauer et al., 2016). FTO is localized in the nucleoplasm, particularly in nuclear speckles, however, unlike ALKBH5, it was also found in the cytoplasm of some cell lines (Gulati et al., 2014; Jia et al., 2011) In contrast to ALKBH5, there were no closer homologs of FTO found in plants (Mielecki et al., 2012). ALKBH5, as m^6A demethylase, was found when Zheng et al. (2013a) biochemically tested human FTO paralogs for the m^6A demethylation activity. Influence of ALKBH5 on mammalian organisms was also studied through the changes in the ALKBH5 expression in mice mutant lines. In HeLa cells, *ALKBH5* knockdowns show increase in the m^6A levels in total mRNA. Similar to the proteins of the m^6A writer complex, ALKBH5 is localized in the nucleoplasm, particularly in the nuclear speckles (Zheng et al., 2013a).

A protein called ZFP217 is a negative regulator of mRNA methylation in mammals. It is involved with the m^6A eraser Fat mass and obesity-associated protein (FTO) that is a target transcript of the ZFP217 protein. ZFP217 activates transcription of genes

related to pluripotency in embryonic stem cells and regulates m^{6}A deposition on the corresponding transcripts by interaction with METTL3 by the activation of expression the m^{6}A demethylase FTO. As a result, the degradation of these transcripts is observed, which prevents differentiation of the embryonic stem cells (Aguilo et al., 2015; T. Song et al., 2019). Also, activity of FTO can be inhibited by m^{6}A reader YTHDF2 activity. And to maintain the demethylase activity of FTO, ZFP217 interacts with the YTHDF2 (T. Song et al., 2019).

Plant demethylases identified so far belong to the AlkB family. 13 members of the AlkB family were found in *Arabidopsis thaliana* (Mielecki et al., 2012). Duan et al. (2018) identified five orthologs of ALKBH5 in *Arabidopsis*: AtALKBH9A, AtALKBH9B, AtALKBH9C, AtALKBH10A, and AtALKBH10B, and demonstrated that the *Arabidopsis alkbh9b* and *alkbh9c* mutants did not show significant changes in m^{6}A levels. However, the *alkbh10b* mutants had increased m^{6}A levels (Duan et al., 2018). It shows that the functions of AtALKBH9B and AtALKBH9C proteins compared to AtALKBH10B may differ. In particular, the change in AtALKBH9B expression was shown to play an important role in protecting plant organisms from viral infections, such as alfalfa mosaic virus (AMV) and cucumber mosaic virus (CMV) (Martínez-Pérez et al., 2017).

m^{6}A readers

Eukaryotic organisms are able to specifically perceive m^{6}A marks with the proteins called m^{6}A readers. The canonical m^{6}A readers have been identified with RNA affinity chromatography and are characterized by the presence of domain YTH (YT512-B homology) (Dominissini et al., 2012; Stoilov et al., 2002). YTH domain binds single-mRNA motif consisting of six nucleotides, with the hydrophobic contacts to the sugar and base moieties as well as salt bridges to the phosphate oxygens of the RNA back-bone. YTH domain can specifically bind the GA-containing RNA sequences even in absence of *N6*-adenosine methylation but shows an increased affinity for the m^{6}A-containing RNA. YTH domain recognizes *N6*-methyladenine using the binding pocket that consists of two or three conserved aromatic side chains. After the recognition, the *N6*-methyl group is located inside the hydrophobic pocket (Theler et al., 2014).

There are two families of mammalian proteins with RNA-binding YTH domains, including five proteins that bind m^{6}A: YTHDC protein family, which includes the YTHDC1 and YTHDC2 proteins, and YTHDF protein family, which consists of 3 members (YTHDF1-3) (Dominissini et al., 2012; Z. Zhang et al., 2010). The YTHDC and YTHDF protein families show no sequence homology besides their YTH domain (Stoilov et al., 2002). The YTH-containing protein first found in vertebrates was YT512-B (YTHDC1) (Stoilov et al., 2002; Z. Zhang et al., 2010). YTHDC1 is a nuclear m^{6}A reader that binds m^{6}A and regulates pre-mRNA splicing and alternative polyadenylation (Kasowitz et al., 2018; Xiao et al., 2016). YTHDC2 influences mRNA translation efficiency and provides mRNA stability (Hsu et al., 2017). YTHDF are predominantly cytoplasmic proteins that contribute to mRNA decay (Patil et al., 2018). The proteins of YTHDF family were also found to contain the YTH domain in the C-terminal (Patil et al., 2018).

Apart from the proteins containing YTH domain, also other m^{6}A readers were found in human cancer cells. They include the insulin-like growth factor 2 mRNA-binding proteins (IGF2BPs; including IGF2BP1/2/3). Similar to the proteins containing YTH domain, the binding sites of IGF2BP are the sequences rich in GA-containing m^{6}A motif. IGF2BPs are proteins whose function is to provide mRNA stability and promote mRNA translation in stress response (Huang et al., 2018). Another mammalian m^{6}A binding protein is Proline rich coiled-coil 2 A (Prrc2a), that was first found in mouse neural cells and shown to regulate brain development and functions. Prrc2a localizes to cytoplasm (R. Wu et al., 2018). Unfortunately, the information about possible homologs of IGF2BPs and Prrc2a in plants is missing.

13 proteins with the YTH RNA-binding domain were found in *Arabidopsis thaliana* (Stoilov et al., 2002). In eleven plant m6A readers, the YTH domain is located near the C-terminus, in contrast to the two remaining proteins with the YTH domain located in the internal regions (D. Li et al., 2014). The members of the former group are the EVOLUTIONARILY COSERVED C-TERMINAL REGION 1-11 proteins (ECT1-11) in *Arabidopsis* (Arribas-Hernández et al., 2018) and belong to the YTHDF family. The other two proteins are members of the YTHDC family (ECT12 and CLEAVAGE AND POLYADENYLATION SPECIFICITY FACTOR30 - CPSF30) (Figure 4) (Scutenaire et

al., 2018; P. Song et al., 2021). ECT1 and ECT2 proteins predominantly localize in nucleus (Ok et al., 2005). The ECT2, ECT3 and ECT4 are localized to cytosol, similar to the animal YTHDF proteins (Arribas-Hernández et al., 2018, 2020). Moreover, they can form cytoplasmic aggregates in certain conditions, for example, upon osmotic stress (Arribas-Hernández et al., 2018).

Another plant m^{6}A reader, CPSF30 (specifically, the longer of its two splice isoforms called CPSF30-L, which contains the m^{6}A binding YTH domain near the C-terminus), is an RNA-binding zinc-finger protein (Barabino et al., 1997; Delaney et al., 2006). It was earlier found to play a role in the regulation of alternative polyadenylation and gene expression (Addepalli & Hunt, 2007). RNA-binding ability of CPSF30 protein can be inhibited by the interaction with the calcium sensor calmodulin in the presence of calcium (Delaney et al., 2006). Based on this and the fact that in plants calcium operates as secondary messenger in cellular signaling cascades, Chakrabarti & Hunt (2015) in their review suggest that CPSF30 is associated with calmodulin-mediated cellular signaling (Chakrabarti & Hunt, 2015; J. Zhang et al., 2008). AtCPSF30 is known to localize in the cytoplasm in *Arabidopsis* cells, but it can also have nuclear localization where it interacts with itself and other polyadenylation factors, such as AtCSP160 and AtCSP73 (Rao et al., 2009). Song et al., 2021 revealed that binding sites of CPSF30 predominantly are located within the 3'-untranslated regions (3' UTR) of mRNA. Moreover, *cpsf30-1* mutants show extension of the transcript 3'-UTR regions, which causes the faster degradation of the transcripts. It was also shown that the m^{6}A binding ability of CPSF30-L, with participation of other polyadenylation factors, contributes to the formation of unspecific aggregates inside the nuclei (P. Song et al., 2021).

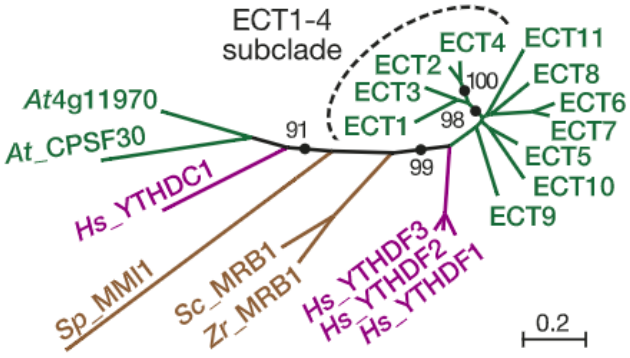

Figure 4 Phylogenetic relationship of *Arabidopsis* YTH domain proteins (green) (Arribas-Hernández et al., 2018)

m^{6}A in mRNA processing

Role of m^{6}A in animals

In animals, *N6*-adenosine methylation affects stability and structure of mRNA as well as many other steps of mRNA processing and maturation, including splicing of mRNA, alternative polyadenylation, nuclear processing and export, translation, and degradation (N. Liu et al., 2015; X. Wang et al., 2014). m^{6}A can influence both increase of mRNA stability and destabilization of mRNA: for example, the activity of m^{6}A readers IGF2BPs is known to increase mRNA stability, while the activity of YTHDF2 and YTHDC2 has been shown to contribute to destabilization of m^{6}A-containing transcripts and their subsequent degradation (Hsu et al., 2017; Huang et al., 2018; X. Wang et al., 2014). m^{6}A has been found to change the local structure of mRNA, thus helping some RNA-binding proteins to access their target motifs (N. Liu et al., 2015).

In mammals, m^{6}A modification and m^{6}A-related proteins are capable of regulating the alternative splicing (Gulati et al., 2014; Ping et al., 2014; Zheng et al., 2013a). Geula et al. (2015) have shown that the disruption of the *METTL3* gene in mouse embryonic stem cells can lead to exon skipping and intron retention in mRNA (Geula et al., 2015). Activity of m^{6}A eraser, ALKBH5, is necessary for correct alternative splicing in the nuclei of spermatocytes in mouse (Tang et al., 2017). Also, m^{6}A reader YTHDC1 was shown to interact with the pre-mRNA splicing factor SRSF3 to regulate splicing (Xiao et al., 2016).

m^{6}A density peaks early in the 3′ UTR, and also in the last exons. In knockdowns of m6A writer complex components were found some transcripts with altered APA use. All these show that m^{6}A can affect the choice of alternative polyadenylation (APA) sites (Ke et al., 2015). VIRMA binds not only the core writer catalytic components METTL3/METTL14/WTAP by directing m^{6}A methylation in the 3′UTR, but it is able to interact with the polyadenylation cleavage factors CPSF5 and CPSF6, connecting the writer complex with the polyadenylation process (J. Liu et al., 2018). Further, YTHDC1 is able to interact with CPSF6 as well, and *YTHDC1* knockdown was shown to increase APA rates (Kasowitz et al., 2018).

m^{6}A was also shown to regulate the nuclear export of mRNA. The knockdowns of m^{6}A writers, such as METTL3, WTAP and VIRMA display the delay in the mRNA export from the nucleus and accumulation of methylated mRNA transcripts. Similar has been shown for the knockouts of YTHDC1 (Fustin et al., 2013; Lesbirel et al., 2018; Roundtree et al., 2017). The knockdowns RBM15 show decreased nuclear export of mRNA as well (Zolotukhin et al., 2009), and, in accord, the disruption of ALKBH5 leads to the accumulation of mRNA in cytoplasm (Zheng et al., 2013a).

It was shown that the presence of m^{6}A residues within 5′UTR can promote the cap-independent translation (Meyer et al., 2015). Knockdowns of m^{6}A eraser FTO in axons lead to increase in m6A levels and decreased local translation of axonal target transcripts, which points out that m^{6}A can negatively regulate mRNA translation (Yu et al., 2018). Further studies have shown that activity of m^{6}A readers YTHDC2 and YTHDF1 promotes the translation of methylated mRNAs (Hsu et al., 2017; X. Wang et al., 2015). However, the influence of YTHDF1 on translation remains controversial, as other studies have shown that the activity of YTHDF family proteins does not induce translation in HeLa cells (Zaccara & Jaffrey, 2020). On the other hand, there is a strong possibility that results of Zaccara & Jaffrey (2020) studies are right since they are based on multiple analyses of YTHDF1 influence on translation also inspecting theory of X. Wang et al. (2015).

Role of m^{6}A in plants

The impact of m^{6}A on plant mRNA processing is less known up to now. Numerous studies examined the effects of m^{6}A on the stability of plant mRNA. Similar to the animal model systems, it was concluded that m^{6}A can promote both stabilization and degradation of mRNA under given conditions. Thus, studies in *Arabidopsis thaliana* have shown that m^{6}A inhibits the local ribonucleolytic cleavage, and the absence of the m^{6}A mark leads to the transcript destabilization, but also m^{6}A can destabilize some specific target mRNAs. It was shown that the knockdowns of MTA lead to the transcripts' destabilization (Anderson et al., 2018; Duan et al., 2018). Further studies have shown that the knockouts of m^{6}A readers ECT2 and CPSF30 accelerated the degradation of target transcripts, which indicates the positive role of these proteins in

the mRNA stabilization (P. Song et al., 2021; Wei et al., 2018). In contrast, the activity of m^{6}A writer FIP37 decreases the stability of transcripts of the key shoot meristem genes (Shen et al., 2016), and demethylation caused by ALKBH10B can increase the stability of its target mRNAs (Duan et al., 2018). Also, m^{6}A was shown to affect the plant mRNA structure under certain conditions, for example during the salt stress. The m^{6}A increase in mRNA stability leads to a subsequent decrease in mRNA complexity (secondary structures of mRNA) and following response to salt stress (Kramer et al., 2020).

The regulatory role of m^{6}A modification in splicing in plants has not yet been fully studied, although several studies have shown that mutants with defects in m^{6}A writers FIP37, VIR in *Arabidopsis* and rice did not display remarkable changes in splicing (Růžička et al., 2017; Shen et al., 2016; F. Zhang et al., 2019). m^{6}A modification can be related to decision on poly(A) site choice in *Zea mays*, which points to a role of m^{6}A modification in APA (J. H. Luo et al., 2020). Further, in *Arabidopsis*, the reduced *VIR* expression led to the defects in the mRNA 3' end formation, resulting in the preferential proximal poly(A) sites selection (Parker et al., 2020). Moreover, the CPSF30 reader itself regulates the alternative polyadenylation and controls poly(A) site choice as well (Hou et al., 2021; P. Song et al., 2021). Also, studies of FIP37 activity by of Pontier et al. (2019) have shown the importance of m^{6}A in targeting APA pathway. Also was shown that CPSF30-L are required for the optimal APA process (Pontier et al., 2019).

It was shown effect of MTA on microRNAs (miRNAs). MTA is capable of methylating pri-miRNA and effects miRNA processing. This has demonstrated by decrease in levels of miRNAs and accumulation pri-miRNAs in *MTA* knockdowns (*mta* mutants). And also, was shown decrease in secondary structure within stem–loop regions of pri-miRNA transcripts (Bhat et al., 2020).

It was shown that m^{6}A modification correlates with the translational status in different manners and that correlation varies in the context of m^{6}A strength and genic location (J. H. Luo et al., 2020; Murik et al., 2020). In *Zea mays*, m^{6}A levels show negative correlation with the translational status at the global scale, but when m^{6}A modifications are located near the start codon, this correlation is reversed (J. H. Luo et al., 2020).

Physiological role of m^{6}A in plants

m^{6}A in plant development

m^{6}A plays an important role in various stages of plant development and the disruption of the m^{6}A-related genes leads to various pleiotropic phenotypes (Figure 5) (Arribas-Hernández et al., 2020; Růžička et al., 2017; Shen et al., 2016; Zhong et al., 2008). m^{6}A participates in the plant development as early as at the embryo development stage. The knockouts of the Arabidopsis core m^{6}A writer genes *MTA*, *MTB*, *FIP37* and *VIR* display embryo-lethal phenotype and did not pass the globular stage of embryo development in Arabidopsis and rice (Růžička et al., 2017; Vespa et al., 2004; Zhong et al., 2008).

Shen et al. (2016) have shown that the reduced expression of m^{6}A writer FIP37 leads to the increased proliferation of shoot apical meristem and the delayed leaf production. FIP37 expression was found to be elevated in actively proliferating tissues such as shoot apices, young leaves, and developing floral organs and seeds. This protein has been found to destabilize the expression levels of the two key shoot apical meristem regulators, *WUSCHEL* (*WUS*) and *SHOOT MERISTEMLESS* (STM). MTA can in a similar way regulate the shoot apical meristem proliferation. Thus, it was proposed that FIP37 and MTA are required for the prevention of the excessive shoot apical meristem proliferation (Bodi et al., 2012; Shen et al., 2016).

m^{6}A has a role in the development of trichomes and leaves as well. Bodi et al. (2012) have shown that the reduction in m^{6}A levels in *MTA* knockdown mutants leads to the abnormality in trichome branching (Bodi et al., 2012). Plants overexpressing FIP37 show phenotypes with a high number of highly branched trichomes as well (Vespa et al., 2004). Later studies have shown that the plants with reduced expression of HIZ2 also have phenotypes with abnormal branched trichomes (M. Zhang et al., 2022). Further, m^{6}A readers ECT2, ECT3 and ECT4 also participate in the regulation of trichome branching and cellular proliferation of leaves. ECT2 was shown to regulate the trichome development by binding the transcripts related to the trichome morphogenesis and stabilizing them. The disruption of ECT2 leads to the phenotypes

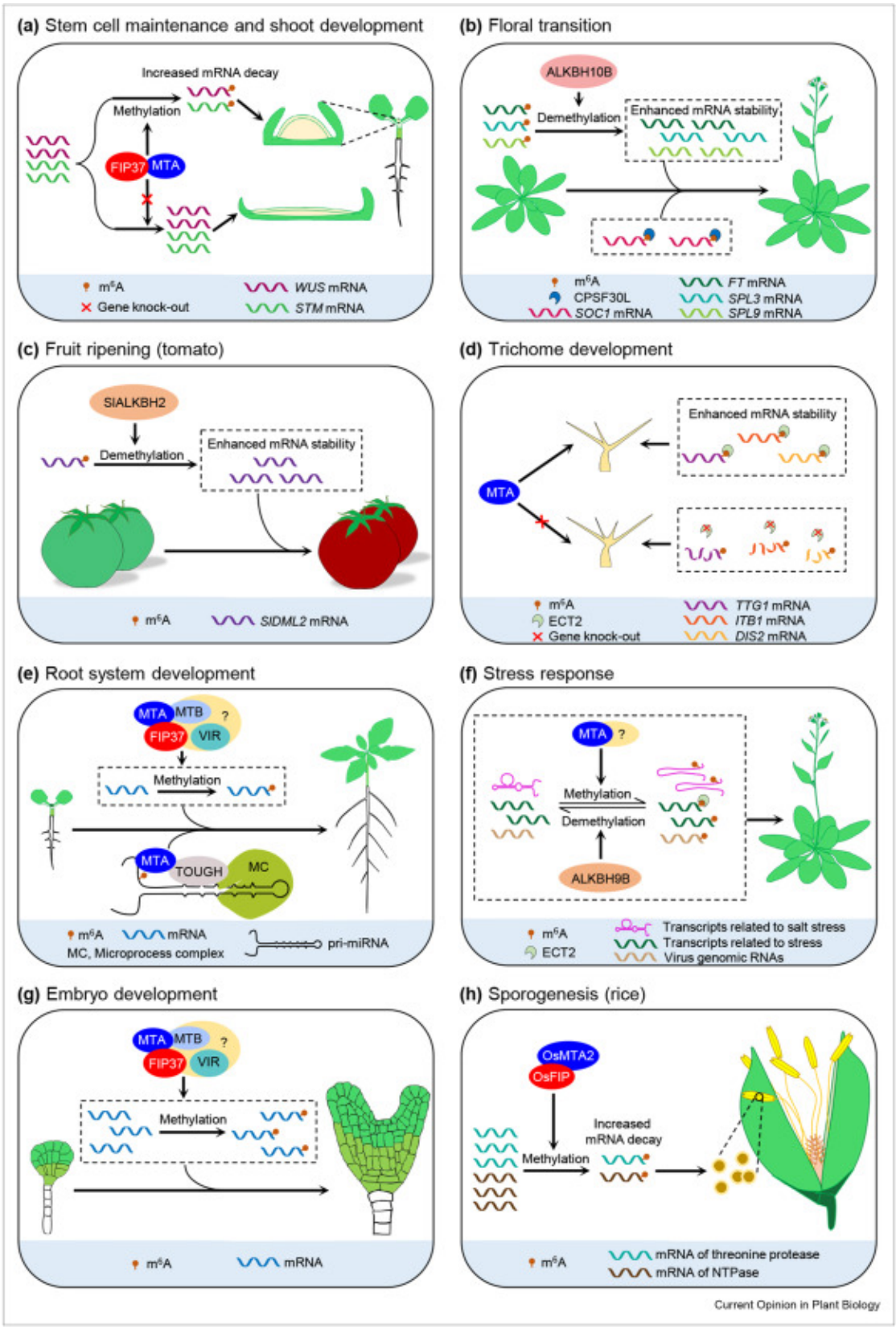

Figure 5 Role m^{6}A modification and m^{6}A-related proteins in various process of plant development. Please expand the legend a bit (Shao et al., 2021)

with abnormal trichome branching (Wei et al., 2018). *ect2 ect3 ect4* triple mutant shows the defective leaf growth, including deformed leaf blades (Arribas-Hernández et al., 2020). J. Wu et al. (2020) have also shown that the plants with overexpressed ECT2 protein have smaller leaves compared to WT (J. Wu et al., 2020). Finally, the ALKBH10B knockout shows the reduction of leaf growth rate (Duan et al., 2018). The phenotypes of the *ect2 ect3 ect4* and *alkbh10b* mutants can be related to the fact that functions of ECT2 and ECT3 in leaves depend on intact m^6A binding sites and therefore control the timing of leaf emergence and contribute to normal leaf development (Arribas-Hernández et al., 2018).

The root and vascular development are also dependent on m^6A. The knockdowns of *MTA*, *MTB, FIP37* and *VIR* display developmental defects in overall root growth and root vasculature (Růžička et al., 2017). ECT2, ECT3 and ECT4 were shown to enhance cell division rate of provascular stem cells. The hypomorphic *mta*, *mtb, fip37* and *vir* mutants, as well as *ect2 ect3 ect4* knockouts, also show a reduced formation of lateral roots (Arribas-Hernández et al., 2020).

m^6A proteins also affect plant reproduction and regulate flowering time. AtALKBH9B, AtALKBH9C and AtALKBH10B are known to have pronounced expression in flowers (Duan et al., 2018). *alkbh10b* mutants show late flowering, while the lines overexpressing *ALKBH10B* flowered sooner compared to WT. Moreover, ALKBH10B demethylates the transcripts encoding the key flowering time regulators *FLOWERING LOCUS T* (*FT*), *SQUAMOUSA PROMOTER BINDING PROTEIN-LIKE* (*SPL*) *3* and *9* and stabilize their expression (Duan et al., 2018). The reduced expression of CPSF30-L also leads to the delay in flowering, consistent with the results seen on erasers lines. Moreover, by recognizing the m^6A marks, CPSF30-L can control the choice of polyadenylation site of *SUPPRESSOR OF OVEREXPRESSION OF CONSTANS 1* (*SOC1*) transcript. As a result, short 3'UTRs are formed on *SOC1*, contributing to stabilization of the *SOC1* mRNA, thus regulating normal floral transition (P. Song et al., 2021). Studies in rice have shown that m^6A is instrumental in early sporogenesis and revealed that OsFIP37 has a role in rice male gametogenesis. Hence, the *Osfip37* and *Osmta* knockouts are sterile and exhibit degradation of microspores at the vacuolated pollen stage (F. Zhang et al., 2019).

Role of m^{6}A in stress response

Several studies have reported significant changes in the expression of the m^{6}A-related genes in response to various kinds of stress in *Arabidopsis* (Bodi et al., 2012; Wan et al., 2015). Under stress conditions, so-called stress granules (SGs) are formed. SGs are cytoplasmic non-membranous granules consisting of RNA and proteins (Ivanov et al., 2019). ECT2 and ECT4 were shown to localize to the SGs upon osmotic and heat stress. Ok et al. (2005) have found that ECT1 and ECT2 interact with CALCINEURIN B-LIKE-INTERACTING PROTEIN KINASE 1 (CIPK1). CIPK1 is a target of CALCINEURIN B-LIKE PROTEIN 1 (CBL1), playing an important role in reaction to various external environmental stimuli, such as cold, drought and high salt stress or wounding (Ok et al., 2005).

The *Arabidopsis* oxidative stress-tolerant mutant (*oxt6*) with the defective *CPSF30* gene is tolerant to the oxidative stress. J. Zhang et al. (2008) suggested that accumulation of Ca^{2+} in cells following the oxidative stress leads to the inhibition of RNA-binding activity of CPSF30. This, according to the proposed model, activates the expression of genes regulated by the reactive oxygen species (ROS), which leads to the subsequent tolerance to the oxidative stress (J. Zhang et al., 2008).

Recent studies indeed demonstrated that changes in m^{6}A epitranscriptome play role in salt and osmotic stress. Following the stress stimulus, the methylation levels of the respective abiotic stress response-related transcripts tend to increase, which leads to stabilization of the transcripts, reflected also by the decrease in the mRNA complexity. It was proposed that this leads to the increased expression levels particularly of proteins required for the response to salt and osmotic stress (Anderson et al., 2018; Kramer et al., 2020). Additionally, Hu et al. (2021) shown that knockdown mutants of MTA, MTB, FIP37 and VIRILIZER (VIR) and HAKAI, show sensitivity to salt stress that is connected to the decrease in m^{6}A levels of their mRNAs; among them, the *vir-1* knockdowns exhibit phenotype hypersensitive to salt stress. The loss of m^{6}A in 3'UTR all over the transcriptome can stabilize transcripts of some negative regulators of the salt response. Eventually, this leads to the accumulation of ROS in plants and

subsequent hypersensitivity to salt stress. Results of these studies indicate the connection between m^{6}A levels, length of 3'UTR and stress response (Hu et al., 2021).

m^{6}A participates in the abiotic stress response in many other plant species. For example, in *Populus trichocarpa*, the plants overexpressing *PtrMTA* are more tolerant to the drought stress (Lu et al., 2020). In *Triticum aestivum L.*, most of the *TaYTH* genes show altered expression upon the abiotic stresses, such as phosphorus starvation, cold stresses, and heat stress that can suggest on possible functions of TaYTH proteins in stress response (Sun et al., 2020).

Role of m^{6}A in plant interaction with viruses

m^{6}A modification can be found not only on eukaryotic mRNA but also on viral RNA (Beemon & Keith, 1977; Brocard et al., 2017). Several studies have shown that m^{6}A and m^{6}A-related proteins can impact the processes of viral infection and replication (Martínez-Pérez et al., 2017; K. Zhang et al., 2021). In case of plant viruses, during the Tobacco mosaic virus (TMV) infection, the presence of the virus led to the increased expression levels of *Nicotiana tabacum* m^{6}A-demethylases, and, as a result, the plant m^{6}A levels were reduced (Z. Li et al., 2018). Similarly, in *Arabidopsis,* the total m^{6}A levels increased after the infection with Alfalfa mosaic virus (AMV) (Martínez-Pérez et al., 2021).

Martínez-Pérez et al. (2017) studied the ALKBH9B demethylase and its effect on the interaction of the host plant with two m^{6}A-containing viruses, AMV and Cucumber mosaic virus (CMV). Indeed, the activity of ALKBH9B affected the virulence of AMV but not CMV. Moreover, ALKBH9B directly interacts with the coat proteins of AMV, but not those of CMV. Consistently, the reduced ALKBH9B levels in *Arabidopsis* mutant infected by AMV were shown to increase the methylation levels in the virus genome and decrease the virus infectivity; these changes were not observed in the mutant line infected by CMV (Martínez-Pérez et al., 2017). These observations are closely linked solely with the activity of ALKBH9B, as the other ALKBH9B paralogs show no impact on the AMV infection (Martínez-Pérez et al., 2021).

Summary and discussion

In recent years, the research of m^{6}A started to belong to the hottest topics in RNA biology. Significant progress has been made in studying the epitranscriptomic changes and accompanying molecular factors and processes. m^{6}A is predominantly eukaryotic mRNA modification but was also found in bacterial mRNA and viral RNA. m^{6}A-related proteins are evolutionary conserved, as well as their overall distribution over the transcript primary sequence (Deng et al., 2015; Dominissini et al., 2012; Krug et al., 1976; G. Z. Luo et al., 2014).

Several enzymes classified as m^{6}A writers, erasers, and readers have been experimentally characterized (reviewed Reichel et al., 2019). But it is still possible to discover new m^{6}A-related proteins, as exemplified recently on mammalian writers Zfp217 and readers IGF2BPs and Prrc2a. It should also be noted that at the present time, there is insufficient information about the regulation of m^{6}A processing and evolutionary relationship between proteins related to m^{6}A. Therefore, it will be an interesting and important theme for the future research.

In mammals, m^{6}A plays a role in almost all aspects of mRNA processing. It affects mRNA stability, splicing, alternative polyadenylation, export from nucleus and translation. In contrast, in plants, the overall functional knowledge is more fragmentary (reviewed Shao et al., 2021). The most studied is the effect of m^{6}A on mRNA stability. However, the data regarding the influence of m^{6}A on mRNA stability are contradictory. Mainly, studies have shown the mRNA-stabilizing effect of m^{6}A (Anderson et al., 2018; P. Song et al., 2021; Wei et al., 2018). But it was also shown that in some cases m^{6}A can destabilize transcripts (Duan et al., 2018; Shen et al., 2016). Regrettably, we know little about exact mechanisms connected with these relatively contradictory observations. Considering the evolutionary conservation of well-known m^{6}A-related proteins, perhaps plant m^{6}A proteins have similar mechanisms and that will help in their future study.

The disruption of m^{6}A-related genes has demonstrated their significant role in different processes such as formation of embryos, apical meristems, trichomes, vasculature and reproductive organs (reviewed Shao et al., 2021). Also, m^{6}A plays its role in

abiotic stress and viral infection response (reviewed Shao et al., 2021). However, despite an immense effort, the exact molecular mechanisms underlying these processes are still largely unknown and represent thereby a highly promising and attractive research topics for the future.

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