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mRNA methylation at the crossroads of translation, transport, and decay in plant development and stress responses

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Modified nucleotides on RNAs have been investigated for over six decades for their potential role in regulating gene expression and protein synthesis across a wide range of organisms, from animals to plants and fungi, as well as in viral genetic materials. Among them, mRNA methylation stands out with its dynamic nature, which underscores the adaptability of the epitranscriptome in developmental transitions and response to environmental stress, especially in plants. Advances in next-generation sequencing methods have revealed the specific sequence contexts of mRNA methylation, uncovering their involvement in gene regulatory networks. Additionally, genetic perturbations on the writers, erasers, and readers of m^6A and m^5C expanded our understanding of the physiological function and the mode of action of these modifications. In this review, we highlight recent advances in understanding how mRNA fate decisions, mainly determined by m^6A and m^5C RNA methylation, shape stress response and development in plants.

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Introduction

To date, more than 170 different RNA modifications have been identified. Among them, N^7-methylguanosine and 5′ nicotinamide adenine dinucleotide (NAD^+) caps, and N^6-methyladenosine (m^6A), 5-methylcytosine (m^5C), pseudouridine, N^1-methyladenosine, 2′-O-methylation, N^4-acetylcytidine, N6,2′-O-dimethyladenosine, uridylation, 5-hydroxymethylcytosine, and inosine have been detected in plant mRNA [1–3]. The dynamic nature of the RNA methylation marks, particularly m^6A and m^5C, has drawn considerable attention, as it highlights the versatility of the epitranscriptome in the course of organismal development and in environmental stress conditions [4–6]. Moreover, the elucidation of the role of RNA modifications in plant domestication and trait improvement implicates its potential in novel agricultural applications [7–9].

Hundreds of m^5C sites were detected on mRNAs in plants via RNA bisulfite sequencing. Later on, antibody-based m^5C-RIP-seq and antibody- and bisulfite-independent Nanopore direct RNA sequencing (DRS) expanded the list of m^5C-modified mRNAs to several thousand [10,11]. Recently, the TET-associated chemical labelling method (m^5C-TAC-seq) has been applied to animal cells to detect m^5C, but not yet to plant systems [12]. m^5C is deposited(written) onto mRNAs by NOP2/Sun RNA METHYLTRANSFERASE FAMILY MEMBER 2 (NSUN2), tRNA-SPECIFIC METHYLTRANSFERASE 4B (TRM4B), and in specific cases, DNA METHYLTRANSFERASE 2 (DNMT2) [13,14]. The m^5C sites are recognized(read) by ALYREF and YBX1 in animals [15]. ALYREF family nuclear export factors ALY2 and ALY4 are shown to act like m^5C readers in plants, but direct binding of ALY2 or ALY4 to m^5C has not been proven yet [16]. Although specific m^5C modifications were associated with mRNA stability in animal systems, the comparison of m^5C sites across tissues and species suggests that the vast majority of mammalian m^5C modifications on mRNAs are due to imprecise m^5C deposition errors and they are nonadaptive [17,18]. In plants, the m^5C modification has been proven to regulate the nuclear export and mRNA mobility of three transcripts. Yet, the little overlap between m^5C and mobile RNAs in cucumber and pumpkins suggests a lack of a

strong association between m^5C modification and mRNA mobility across different plant species [19,20].

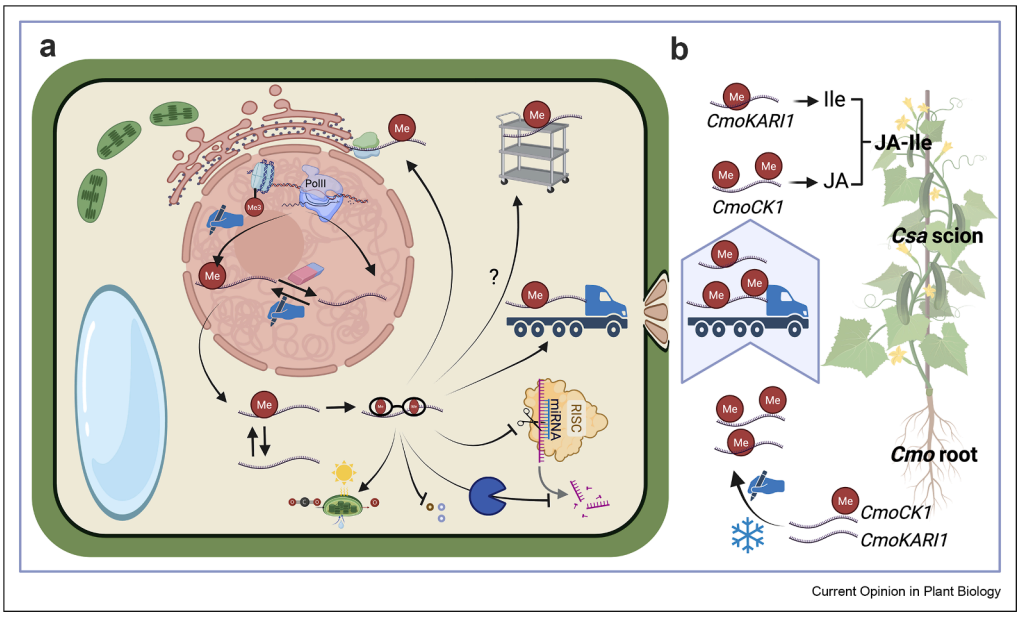
m^6A has been the most abundant and most studied epitranscriptomic mark. While antibody-dependent m^6A-seq/MeRip-seq and miCLIP-seq show the abundance of m^6A-modified mRNAs, antibody-independent m^6A -sensitive enzymatic methods, such as mazF RNase-assisted sequencing (MAZTER-seq), RNA-Endoribonuclease-Facilitated sequencing (m^6A-REF-seq), m^6A-selective allyl chemical labeling and sequencing (m^6A-SAC-seq), FTO-assisted m^6A selective chemical labeling (m^6A-SEAL-seq), Nanopore direct RNA sequencing (DRS), deamination adjacent to RNA modification targets (DART-seq), Glyoxal and nitrite-mediated deamination of unmethylated adenosine (GLORI) were developed to map m^6A sites to single-nucleotide resolution [21,22]. The most common m^6A motif RR(m^6)ACH (R = A/G, H = A/C/U) is shared between animals and plants, although some plants, such as cotton, lack it [23]. m^6A modifications in plants are the most abundant at the 3′ untranslated regions (3′UTRs), in the vicinity of the stop codon, and they are relatively low in the inner exons and at the 5′UTR [1]. Besides the sequence composition and the position of the motif, gene structures also affect m^6A deposition. For example, introns contain more abundant m^6A sites than the inner exons. In addition, a positive correlation between longer inner exons and higher m^6A levels has been observed in both animals and plants, but the suppression of m^6A at the exon junctions in animals does not apply to plants [21,24]. In addition to the shared structural features of m^6A-modified mRNAs, those containing m^6A in their 3′UTRs are enriched for Gene Ontology (GO) terms related to RNA metabolic processes and translation. In contrast, mRNAs harboring m^6A outside the 3′UTR are predominantly associated with development and stress response pathways [21].

In plants, m^6A is deposited (written) predominantly co-transcriptionally by the catalytic heterodimer core of the m^6A methyltransferase complex (MTC), consisting of mammalian METHYLTRANSFERASE LIKE 3 (METTL3) homologue mRNA ADENOSINE METHYLASE A (MTA), and mammalian METTL14 homologue mRNA ADENOSINE METHYLASE B (MTB). MTA and MTB form the m^6A METTL complex (MAC). In addition to the methyltransferases, MTC contains multiple accessory subunits: FKBP12 INTERACTING PROTEIN 37 KD (FIP37), VIRILIZER (VIR), the E3 ubiquitin ligase HAKAI, and HAKAI-INTERACTING ZINC FINGER PROTEIN 2 (HIZ2), which form m^6A-METTL-associated complex (MACOM) [25—27]. Furthermore, FIONA1 (FIO1) is postulated to be an independent m^6A writer, but the exact mode of action of FIO1 requires further studies [28,29]. In plant *mta*, *fip37*, *mtb*, *vir*, and *hiz2* mutants, global m^6A levels drop substantially, whereas *fio1* and *hakai* mutants have a subtle effect on total m^6A abundance [26]. It is noteworthy that different writers may methylate distinct m^6A sites resulting in an opposing effect on mRNA stability and splicing. For example, the FLOWERING LOCUS C (FLC) is a well-established transcription factor that suppresses flowering. High *FLC* transcript levels are associated with late flowering, while low *FLC* level leads to an early flowering phenotype. *FLC* transcript carries m^6A modification in wild-type *Arabidopsis*. *fio-1* mutants exhibit an early flowering phenotype due to a specific reduction in the transcript level of the major splice variant of *FLC*. However, *vir-1* mutants have a late flowering phenotype and extremely high levels of *FLC* transcript [30,31]. Therefore, it is postulated that VIR and FIO1 deposit m^6A on *FLC* at distinct sites, which have opposite effects.

Two non-heme Fe(II)- and α-KG-dependent dioxygenase AlkB family proteins, fat mass and obesity-associated protein (FTO) and ALKBH5, were discovered as m^6A demethylases in animals [32]. In plantae, only green algae have homologous genes to FTO [33], while ectopic expression of FTO alone in rice is shown to be sufficient to reduce global m^6A levels [8]. Most plants have multiple homologous genes to ALKBH5. Among them, ALKBH10B, ALKBH8B in *Arabidopsis thaliana*, ALKBH9 in rice, ALKBH2 in tomato, and ALKBH1B in barley have been shown to remove (erase) the m^6A mark [32,34,35]. *Atalkbh10b* mutant yields over a thousand hypermethylated transcripts, and overexpression of ALKBH8B leads to m^6A hypomethylation [36,37]. Besides the effect of "erasers" on global m6A level, ALKBH9B also acts as an eraser of m^6A, specifically in alfalfa mosaic virus (AMV), suggesting a specialized role of ALKBH9B in defense against viruses [38]. Hence, the m^6A methylation state of transcripts depends on the interplay between MTC and ALKBH activity, as m^6A writers and erasers, and their respective target genes in plants (Figure 1a).

m^6A modification on mRNAs is preferentially recognized (read) by the YT521-B homology (YTH) domains in animals and plants. YTH domain contains a methyl-group-binding hydrophobic aromatic cage, which is typically composed of a combination of tryptophan (W), phenylalanine (F), and tyrosine (T) [39]. YTH domain family (YTHDF) EVOLUTIONARILY CONSERVED C-TERMINAL REGION (ECT) proteins are mostly cytosolic m^6A readers, controlling mRNA stability, decay, and translational efficiency, and mobility (Figure 1). In addition, CLEAVAGE AND POLYADENYLATION SPECIFICITY FACTOR 30 (CPSF30) and DC1 are structurally distinct YTH domain-containing (YTHDC) m^6A readers, which predominantly appear in nuclear speckles and control mRNA splicing, export, and possibly the stability of mRNAs via alternative polyadenylation. Although its

Figure 1



mRNA methylation dynamics influence transcript fate and mobility in plants.
(**a**) mRNA fate by RNA methylation. RNA methylation can be a co-transcriptional and post-transcriptional modification. RNA methylation on mRNAs is deposited by the core "writer" complex, and it is removed by "eraser" proteins. RNA methylation is recognized by readers (spectacles), which determines the fate of the mRNA in development and stress conditions. mRNA methylation (e.g., m^6A) is often established co-transcriptionally and is tightly coordinated with the local chromatin environment (e.g., H3K4me3). After export from the nucleus, mature mRNAs may be directed to ribosomes for efficient translation, targeted to the RNA-induced silencing complex (RISC) for gene silencing, sequestered into condensates (brown small circles) or processing bodies (P-bodies) (lilac small circles), degraded (Pac-Man figure), or stabilized for certain cellular processes such as photosynthesis (chloroplast). Subcellular localization of mRNA (trolley) was shown to be regulated by m^6A in neurons, but the effect of m^6A on the subcellular localization of mRNAs in plants remains elusive. Some mRNAs evade these canonical fates and instead undergo long-distance transport (truck). (**b**) The importance of mRNA transport in cold stress and the involvement of RNA methylation in mRNA mobility is shown. In a cucumber(*Csa*)/pumpkin(*Cmo*) heterograft system, m^5C was detected on *CmoCK1* in vascular sap, whereas m^6A was detected only in total seedling samples. Under ambient temperature, *CmoCK1* was marked by m^5C and loaded into vascular tissues, but was not identified as a mobile transcript, likely due to degradation during transport. Notably, m^5C methylation was not cold-responsive. By contrast, m^6A methylation of *CmoCK1*, induced specifically under chilling stress, enhanced its stability and enabled its detection following unloading from the vasculature [50]. Another cold-responsive mobile transcript, *CmoKARI1*, was annotated as an m^5C-modified transcript only in the vasculature and was also transported from the pumpkin rootstock to the cucumber scion. Together, CmoCK1 and CmoKARI1 promoted jasmonoyl-isoleucine (JA-Ile) biosynthesis, thereby enhancing the chilling tolerance of the heterograft [51]. Created in BioRender (2025).

role in flowering has long been known, FLOWERING LOCUS K (FLK) has recently been discovered as an unusual m^6A reader, which does not contain a YTH domain but binds to m^6A sites via one of its three KH domains [26,30,40]. *Arabidopsis thaliana flk* mutant leads to unusually high spliced *FLC.1* transcript, similar to *vir-1* and in contrast to *fio1* mutants, as mentioned above, suggesting that specific readers may act downstream of specific writers and determine the fate of the m^6A-modified mRNAs accordingly [30].

mRNA methylation in plant growth, development, and fruit ripening

The role of the m^6A and m^5C modifications has been established through extensive genetic and molecular studies. m^6A plays essential roles in various developmental processes. Disruption of key components of the m^6A machinery—whether writers, erasers, or readers—can perturb this regulatory network, leading to abnormal growth and reproductive development [41].

m^6A writer proteins (MTA, MTB, FIP37, FIO1), reader proteins (YTHDF, CPSF30-L, ECTs) and erasers (ALKBH10B) are also involved in the circadian rhythms, root meristem activity, organogenesis, hypocotyl elongation and floral transition via post-transcriptional regulation independently of light [40,42–44], promoting chromatin remodeling and gene activation, ultimately improving photosynthetic efficiency and yield [8,45]. m^6A methylation also exhibits species-specific roles in regulating fruit ripening. In climacteric fruits like tomato and kiwifruit, the m^6A modification on fruit-ripening related genes is inversely correlated with transcript abundance of these genes. Therefore, m^6A eraser *AcALKBH10* demethylase expression increases the abundance of these genes and thereby the process of

fruit ripening [30,46,47]. By contrast, in the non-climacteric strawberry, m^6A writers MTA and MTB promote natural strawberry ripening by stabilizing mRNAs of key ABA biosynthesis and signaling transduction pathways [9], underscoring the essential role of m^6A recognition in both vegetative growth and crop yield enhancement.

mRNA methylation in stress and immune responses

mRNA modification acts as a rapid and dynamic regulator of plant responses to abiotic stress and immune challenges. Its regulatory functions are closely coordinated by methyltransferases, demethylases, and reader proteins.

m^5C has been implicated in adaptation to heat stress, associated with the upregulated transcript level of the heat-induced m^5C writer NSUN2 in rice [48]. The cytosolic m^6A methylome stabilizes photosynthesis-related transcripts and enhances the translation efficiency of cold-responsive genes, thereby sustaining cold tolerance in Arabidopsis [28,49]. In the cucumber and pumpkin heterograft system, where the cucumber scion is grafted on a pumpkin root, the global m^6A level—but not the m^5C level—increased and positively contributed to the chilling tolerance of cucumber scions (Figure 1b). m^6A modification within the coding sequence (CDS) promoted the mobility of a cold-responsive pumpkin transcript, *CmoCK1*, which is involved in jasmonic acid (JA) biosynthesis, following chilling stress [50]. In our recent study, we identified another cold-specific mobile mRNA, *CmoKARI1*, a single-copy gene involved in isoleucine biosynthesis. Together with CmoCK1, CmoKARI1 contributes to JA-Ile biosynthesis, enhancing chilling tolerance. This study ruled out a role for transported isoleucine itself [51]. A previous study also demonstrated that JA can be transported from the shoot to the root but not from the root to the shoot [52]. Collectively, these findings highlight the advantage of mRNA as a specific and efficient long-distance signaling molecule. In contrast, metabolite transport is often constrained by diffusion-related losses and lacks directional specificity (Figure 1b). Furthermore, the accumulation of certain metabolites in the source organ can trigger pleiotropic effects before their long-distance movement. *CmoKARI1* is reported to have m^5C modification specifically in the vascular tissue, albeit a mechanistic link between *CmoKARI* m^5C mark and its mobility requires further investigation [51].

Moreover, MTA/ECT-mediated m^6A methylation contributes to mRNA transcription stability and translation in *Arabidopsis* and apple under either drought stress or salinity stress [53–55]. Additionally, m^6A modification and ECT1 also stabilize immune-related mRNAs and fine-tune their translation during pattern-triggered immunity, further underscoring their involvement in pathogen defense [55,56]. Collectively, these findings establish mRNA methylation as a key regulator of post-transcriptional gene expression in plant immunity and highlight its potential for biotechnological applications in developing stress-tolerant crops.

The effect of mRNA methylation on mRNA fate

After export from the nucleus, properly processed mRNAs are typically directed to ribosomes for translation. Alternatively, they may be targeted to the RNA-induced silencing complex (RISC) for gene silencing, sequestered in processing bodies (P-bodies) for storage, or degraded (Figure 1a). Interestingly, some mRNAs escape these canonical fates and are instead subjected to long-distance transport. The fate of mRNA is tightly regulated by numerous cis-acting elements, such as secondary structures and upstream open reading frames (uORFs), as well as trans-acting factors, including eukaryotic initiation factors (eIFs) and components of the nonsense-mediated decay (NMD) pathway. Over the past several years, mRNA methylation has emerged as a crucial layer of post-transcriptional regulation influencing mRNA destiny [10,57].

As mentioned above, m^6A has been implicated in the regulation of various developmental processes and environmental responses in plants. Depending on the context, m^6A can either enhance or suppress mRNA translation efficiency and stability [28,30,49,53,55,56,58–63]. The interaction between the m^6A reader protein ECT2 and poly(A)-binding proteins (PABPs) may provide mechanistic insight into how m^6A modulates these processes [44,62]. The interaction between the ECT2 and PABPs is intriguing and suggests a potential crosstalk between m^6A deposition and the function of poly(A) tails on mRNA stability and translation efficiency [21]. Yet, the exact mechanism is still not fully understood.

A recent study sheds light on the molecular mechanisms of epitranscriptomic regulation impinging on fruit elongation and fruit domestication in cucumber. A synonymous mutation on *aminocyclopropane-1-carboxylic acid synthase 2* (*ACS2*) coding sequence reveals that YTH1 reader weakens the structural conformation of the *ACS2* mRNA by binding to m^6A-modified target site on the coding sequence. The translational efficiency increases upon unwinding of the *ACS2* mRNA and leads to higher ACS2 protein levels and shorter cucumbers [7]. Enrichment of such synonymous m^6A-site disruptive mutations in tumor suppressors in cancer genomes, and changes in the structure and abundance of mRNAs upon loss of m^6A sites in animals, suggest that epitranscriptome-mediated mRNA stability is an ancient mechanism [64,65].

Recent findings in animal systems may offer new perspectives for plant research. In mammals, the m^6A methyltransferase METTL3 (homologue of plant MTA) has been shown to interact with eIF3h, a non-core subunit of the eukaryotic initiation factor 3 complex. This interaction promotes selective translation of m^6A-marked transcripts and has been associated with enhanced ribosome loading, as evidenced by circularized polysomes observed via electron microscopy [66]. Moreover, the exon junction complex (EJC) plays a dual role: it suppresses m^6A deposition in mammals (but not in plants) and, when not removed during the pioneer round of translation, targets the transcript for degradation via the NMD pathway. This is particularly relevant for mRNAs containing upstream open reading frames (uORFs), which are often NMD targets in animals [67]. Interestingly, uORF-containing mRNAs in plants appear to be less susceptible to NMD [67]. Moreover, plant eIF3h has been specifically implicated in the translation of uORF-containing mRNAs [68,69]. It remains unclear whether m^6A deposition in plants is required for this process, as has been observed in animals [66]. Since both METTL3 and eIF3h are conserved across plants and animals, it will be intriguing to investigate whether they physically interact and whether such an interaction is required for translation reinitiation. However, animals and plants employ distinct mechanisms for m^6A deposition, suggesting that the role of m^6A in translation regulation might not be conserved [21]. Nevertheless, m^6A-marked viral mRNAs can be targeted for degradation via the plant NMD pathway, as demonstrated by the interaction between ECT proteins and two nonsense-mediated mRNA decay factor proteins, SUPPRESSOR WITH MORPHOGENETIC EFFECTS ON GENITALIA 7 (SMG7) and UP-FRAMESHIFT-SUPPRESSOR 3 HOMOLOG (UPF3) in *Nicotiana benthamiana* [23]. Given that plant viral mRNAs rely entirely on the host's translational machinery, regulation of their translation is particularly critical. For example, BjeIF2Bβ from *Brassica juncea* recruits the m^6A demethylase ALKBH9B to modulate viral mRNA translation [70]. Additionally, the m^6A reader ECT8 has been shown to promote phase separation and interact with the decapping enzyme DCP5 within P-bodies, facilitating mRNA degradation [54,59]. Collectively, these findings suggest that plants may employ unique and diverse strategies to coordinate m^6A-mediated regulation of translation and mRNA surveillance, highlighting a promising avenue for future research.

Compared to m^6A, m^5C remains much less well characterized in plants. The clearest established function of m^5C to date is its role in inhibiting translation and promoting long-distance mRNA transport [14,19]. This aligns with expectations, as successful transport requires that the mRNA avoid engagement by ribosomes, as mRNAs cannot be systemically mobile when they are loaded onto ribosomes [71]. Another essential prerequisite for transport is mRNA stability. A recent study by Li et al. demonstrated that m^5C influences the likelihood of an mRNA being transported, while m^6A determines the extent to which transported mRNAs remain detectable, effectively reflecting their post-transport stability [50]. Notably, a range of m^6A reader proteins have been identified in plants, each contributing to distinct regulatory processes [72]. In contrast, no promising m^5C reader proteins have yet been discovered in plants, leaving the mechanistic basis of m^5C-mediated regulation largely unresolved.

Future perspectives and open questions

An increasing number of studies focusing on the molecular mechanisms of epitranscriptomic regulation, and the recent studies on the impact of mRNA modifications on crop quality, implicate their pivotal roles in plant growth, development, and stress adaptation. Moving forward, future research should place greater emphasis on the transport dimension of mRNA regulation. Especially, revisiting the roles of RNA methylation in systemic mRNA transport in the light of the novel and more rigorous bioinformatic tools for mobile mRNAs is likely to be fruitful [73]. For instance, RNA stability and mobility are fundamental for the success of exogenous RNA (exoRNA) applications (such as dsRNA or mRNA sprays), and the influence of RNA methylation on the fate of these mobile RNAs could critically determine their efficiency [74,75]. Drawing inspiration from models of small RNA (sRNA) transport, where AGO binding dictates which small RNAs are stabilized in AGO−RNA complexes and which remain mobile, it will be an exciting frontier to explore how translation efficiency and ribosome heterogeneity coordinate the long-distance mobility of mRNAs [76]. Structural features of tRNAs allow their systemic movement in plants [77]. Recently, it has been shown that these tRNA features are transferable to other RNA species. For example, when mRNAs are artificially tagged with such features, they also move from the shoot to root [78]. Therefore, it is promising to investigate mRNA modifications in light of the knowledge from other RNA species. To illustrate, it is possible to hypothesize that 2′-O-methylation in mRNA has a similar impact on mRNA fate to HEN1-mediated 2′-O-methylation in miRNAs, which is known to increase miRNA stability and movement [79]. Furthermore, while intracellular RNA localization has been shown to depend on m^6A in neurons, the role of RNA modifications in subcellular mRNA trafficking beyond nuclear export remains poorly understood in plants [80]. Addressing these knowledge gaps will be essential to unravel how RNA modifications regulate both long-distance transport and intracellular localization, thereby opening new avenues for optimizing crop performance and enabling controlled developmental outcomes through transport-aware epitranscriptomic strategies.

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Declaration of competing interest

There are no competing interests to disclose

Data availability

No data was used for the research described in the article.

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