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Review Article

Research progress of the Elongator complex in plant

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Abstract

The Elongator complex consists of six subunits (ELP1-ELP6), where ELP1-ELP3 forms the core subcomplex and ELP4-ELP6 forms the auxiliary subcomplex. Deletion of any of the six subunits results in an almost identical phenotype, suggesting that all six subunits are essential for cellular function. All six subunits are evolutionarily conserved in terms of sequence and their interactions with other subunits. The most striking features are the structural conservation of the protein complexes and the phenotypic similarity caused by loss-of-function mutations in any protein subunit. Similar to elongation factors in translation, there is a strong interaction between the Elongator complex and RNA polymerase II during transcription. The Elongator complex is also involved in a variety of cellular pathways, including histone modification/acetylation, DNA methylation, tRNA nucleoside modification, etc. Here, we summarized the functions and mechanisms of the Elongator complex in plant growth and development, molecular pathways, and gene regulation. In this way, we aimed to provide a reference for an in-depth study of the Elongator complex.

Keywords: DNA methylation; Elongator complex; histone acetylation; RNA polymerase II; tRNA modification

Introduction

The Elongator complex (ELP) was first identified in 1999 and shown to interact with RNA polymerase II (RNA pol.II) in yeast (Otero *et al.*, 1999; Pokholok *et al.*, 2002; Jarosz *et al.*, 2020). The ELP is composed of six protein subunits (Figure 1), the corresponding proteins and their molecular masses are approximate: ELP1-150, ELP2-90, ELP3-60, ELP4-50, ELP5-35, and ELP6-30 kDa (Otero *et al.*, 1999; Winkler *et al.*, 2001; Dalwadi et al., 2018;). ELP1, the largest subunit of ELP, is highly conserved in eukaryotes and can be phosphorylated, and phosphorylation of ELP1 at two sites regulated by the casein kinase Hrr25 and the phosphatase Sit4 (Ser-1198 and Ser-1202) is critical for the tRNA modification activity of ELP (Petrakis *et al.*, 2005). ELP2 serves as an assembly scaffold for the ELP (Fichtner *et al.*, 2002), The *elp2* deletion mutant exhibits a similar phenotype to the *elp1* and *elp3* mutants in yeast, suggesting that it is essential for the complex function of ELP (Mehlgarten *et al.*, 2003), Some mutations in these subunits in yeast produce phenotypes consistent with aberrant tRNA modifications, suggesting a role for this region in tRNA modification (Fichtner

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et al., 2003; Abdel-Fattah *et al.*, 2015; Abbassi *et al.*, 2020). The ELP3 is the functional center of the ELP, which contains a C-terminal GNAT-type histone acetyltransferase (HAT) domain and an N-terminal iron-sulfur (Fe-S) radical S-adenosine-methionine (SAM) domain (Fichtner *et al.*, 2003). In yeast, the SAM radical domain of the ELP3 was shown to be a subunit required for the structural integrity of the ELP (Fichtner *et al.*, 2002). The subcomplex ELP4-6 all share the same RecA-like protein fold, but have no ATPase common sequence, and in vitro ELP4-6 was shown to hydrolyze ATP and use this reaction to bind tRNA. The hexameric NTPase structure is common to other nucleic acid-binding proteins (e. g., Rho GTPase) (Fichtner *et al.*, 2002; Dalwadi *et al.*, 2018). ELP4/5/6 assembles into a heterotrimer, which dimerizes to form a heterohexameric ring (Fichtner *et al.*, 2003; Nelissen *et al.*, 2005; Dalwadi *et al.*,2018). This crystal structure also suggests that all three subunits adopt the same RecA ATPase-like fold, containing a largely parallel and twisted β fold, flanked by the α helix. Analysis of electrophoretic mobility variations showed that ELP4/5/6 hexamers bind directly to tRNA (Fichtner *et al.*, 2003; Dauden *et al.*, 2019).

Studies in *Arabidopsis* show that the structure of the ELP and its function are highly conserved between plants and yeast (Otero *et al.*, 1999; Kojima *et al.*, 2011; Xu *et al.*, 2012; Jarosz *et al.*, 2020). In order to further study the evolution mode and phylogenetic relationship of ELPs protein in different species, using MEGA7.0 software for S. cerevisiae, human, *Arabidopsis*, maize and rice ELPs protein sequence construction phylogenetic tree (Figure 2), *Arabidopsis*, maize and rice ELP gene each subunit gene relationship is close, suggesting that its function may have some similarities in different species.

The normal function of ELP requires synergy with other proteins, which is most closely related to KTI12. Both genetic and biochemical evidence suggests a functional overlap between KTI12 and ELP (Zhou *et al.*, 2009; Xu *et al.*, 2012), KTI12 can physically interact with the ELP3 and ELP5 proteins, but the absence of KTI12 does not affect the assembly of the ELP. KTI12 is an ancient ATP/GTP-binding protein (Nelissen *et al.*, 2010). The KTI14 belongs to the casein kinase family for post-translational regulation of ELP function (Xu *et al.*, 2012). In the presence of KTI12, KTI14 can bind to ELPP (Chen *et al.*, 2006), and no physical interaction with ELP was found between the KTI11 or KTI13 proteins (Leitner *et al.*, 2015). Genetic evidence suggests that KTI11 involves KTI11 in the negative regulation of ELP (Leitner *et al.*, 2015), The presence of ELP3 is required for the process of protein interactions between ELP1-ELP2, ELP2-KTI12, ELP2-KTI13, and KTI12-KTI13, illustrating the important role of ELP3 in elongating its structure and function (Leitner *et al.*, 2015).

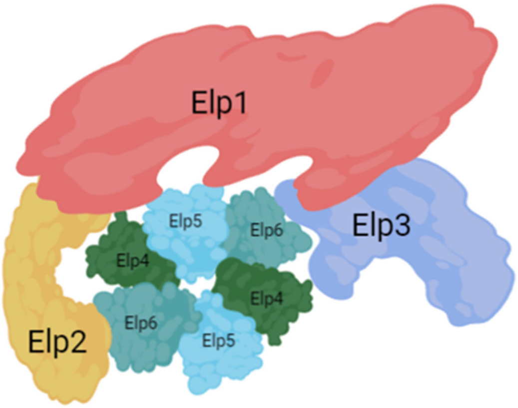

Figure 1. Model of the proteome structure of the Elongator complex

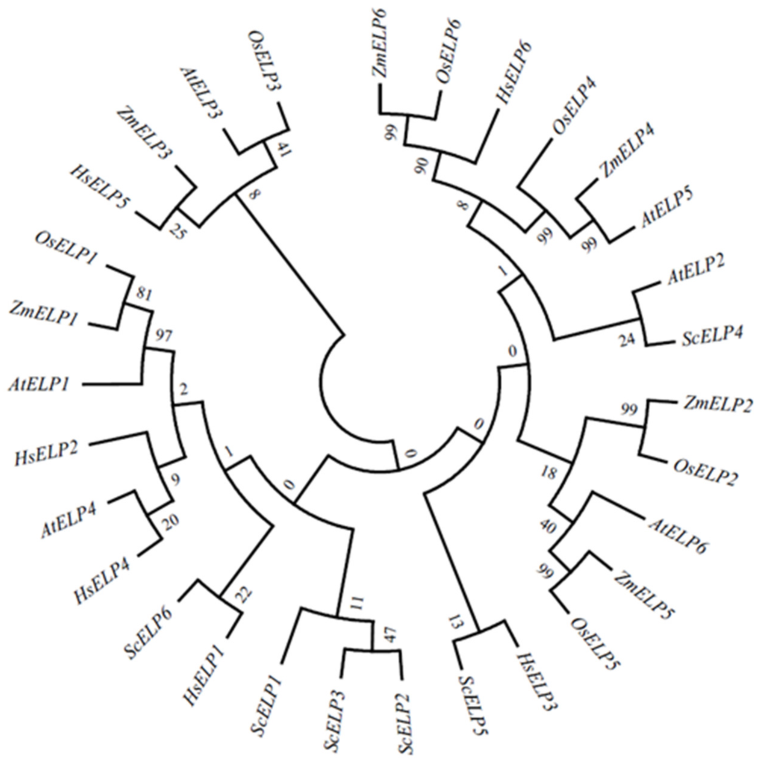

Figure 2. Phylogenetic trees of ELP proteins

The main role of ELP in higher plants

Mutations in ELP genes in *Arabidopsis* (*Arabidopsis thaliana*) produce multiple phenotypes, including leaf stenosis, enlarged hypocotyl, delayed primary root growth, decreased seed germination, delayed flowering time, and decreased root tips (Fellows *et al.*, 2000; Wang *et al.*, 2015). Fistissue cells were reduced in leaf cross sections of *elp* and *kti12* mutants (Fellows *et al.*, 2000; Myat *et al.*, 2022). Reduced stacking particles, decreased vacuole osmotality, and increased exocytosis in the *atelp4* mutants were observed by transmission electron microscopy. The same mutants have different growth kinetics and gene expression for sucrose. Apical-dominant phenotype is attributed to biosynthetic or transport phytohormones (mainly including phytoauxin, abscisic acid (ABA), anthocyanins, etc.) (Fellows *et al.*, 2000; Wang *et al.*, 2015). Studies have shown that the auxin biosynthesis, transport, sensing, and signal transduction genes of the *elp* mutants are severely affected (Kojima *et al.*, 2011). The content of free indoacetate acid (IAA), ethylene, jasmonate (JA) and anthocyanins in *elp1*, *elp2*, *elp4* and *elp6* mutants is higher than in the wild type, which may involve the regulation of transcription factors (Wang *et al.*, 2015). The ventral/abaxial polar changes in leaves in *Arabidopsis elp* mutants, are likely due to reduced cell division and DNA replication and regulation of chromatin structure through histone modifications (Zhu *et al.*, 2015). The crosstalk between salicylic acid (SA), JA/ethylene (ET), and ABA also partially explains the pleiotropic phenotype of the *elp* mutants in higher plants (Zhu *et al.*, 2015), And the secondary effects of hormonal imbalance on the expression of genes involved in abiotic stress, pathogen response, and anthocyanins biosynthesis (Kojima *et al.*, 2011). Some *Arabidopsis elp* mutants were found to be more tolerant to oxidant reagents and H_2O_2, and leaf stomatal closure and root elongation in *elp1* and *elp2* mutants were more sensitive to the phytohormone ABA (DeFraia *et al.*, 2010; Wang *et al.*, 2015). The *elp4* and *elp6* mutants do not have a stomatal closure and water-retaining phenotype similar to the *elp1* and *elp2* mutants (Kojima *et al.*, 2011; Wang *et al.*, 2015), Gene expression in *elp* mutants induced insignificant changes in expression levels of ABA-responsive genes and several drought stress-related genes compared to wild-type, suggesting that enhanced tolerance to drought and oxidative stress may not be transcription but translation (DeFraia *et al.*, 2010). In another study, the two transcription factors and three genes involved in oxidative and abiotic stress were expressed in different amounts in *Arabidopsis elp* mutants under ABA-treated and untreated conditions (Wang *et al.*, 2015).

In the nucleus of the major ELP site (Kojima *et al.*, 2011). And the tissue-specific expression pattern of the *ELP2*, *ELP4*, and *ELP6* genes is very similar to that of *ELP1* in *Arabidopsis* (DeFraia *et al.*, 2010; Wang *et al.*, 2015). This result precisely validates the co-localization of *Arabidopsis* ELP3 with euchromatin, finding a low level of histone H3K14 acetylation on auxin-related genes, resulting in the downregulation of target genes (Kojima *et al.*, 2011). Since H3K14 is the major substrate for ELP3 HAT activity, the epigenetic regulation of auxin biogenesis and transporter genes partially explains the phenotypes of *Arabidopsis elp* mutants related to auxin biology, for example, reduced apical dominance, altered leaf order, altered vein structure and reduced root growth (Kojima *et al.*, 2011).

Relationship between ELP and plant growth and development

Genes encoding ELP subunits have been well studied in *Arabidopsis*, as well as in environmental responses, and also showed important roles in leaf and root development (Fellows *et al.*, 2000; Kojima *et al.*, 2011; Jia *et al.*, 2015). Similar to rice *CUR1*, the *Arabidopsis* ELO genes (e. g., *ELO2* / *AtELP1* and *ELO3* / *AtELP4*) are expressed in the apical meristems and leaf primordia (Kojima *et al.*, 2011; Matsumoto *et al.*, 2020), In contrast to these *Arabidopsis ELO*/*AtELP* genes showing local paraxial expression in the leaf primordium, the rice *CUR1* gene was expressed uniformly in the leaf primordium (Selvadurai *et al.*, 2014). The narrow-leaf phenotype and the altered ventilation pattern in the rice *cur1* mutants were similar to those of the *Arabidopsis elo*/*elp* mutants. But unlike the rice *cur1* mutants, an *elo* mutant phenotype was observed in the leaves, independent of the growth stage of *Arabidopsis* (Fellows *et al.*, 2000; Kojima *et al.*, 2011; Selvadurai *et al.*, 2014). In tomato (*Lycopersicon esculentum*), the silenced *ELP2* gene (*SlELP2L*) can promote leaf senescence in addition to inhibiting leaf and plant growth (Karlsborn *et al.*, 2014). Leaf senescence has not been observed in ELP mutants in rice or *Arabidopsis*, so ELP activity depends on plant species and affects different plant development, but it has been proposed that ELP plays multiple roles at the phenotypic level of various organisms (Falcone *et al.*, 2007; Woloszynska *et al.*, 2018). Interestingly, in addition to the functional differences in the ELP genes between rice and tomato, the genes encoding the E3 ubiquitin ligase were highly up-regulated in the plants silenced by *SlELP2L* (Karlsborn *et al.*, 2014). Auxin-associated phenotypes and an altered distribution of auxin have been observed in the *elo* mutants found in *Arabidopsis* (Fellows *et al.*, 2000; Li *et al.*, 2009; Kojima *et al.*, 2011). Combined transcriptome and proteome analysis in future studies may provide some light on the molecular mechanisms of ELP during plant growth and development.

Molecular pathways and genes for ELP action in plants

In plants, the phenotype of *elp* mutants reveals the molecular pathways of ELP, namely growth and cell proliferation, leaf and root development, immune response, cell cycle, tissue differentiation, ABA response, antioxidative stress, and anthocyanins biosynthesis (Fellows *et al.*, 2000; Frohloff, 2001; Lu *et al.*, 2005; DeFraia *et al.*, 2010; Fang *et al.*, 2015; Leitner *et al.*, 2015; Wang *et al.*, 2015; Dalwadi *et al.*, 2018;). Plant growth, immune response, and root development pathways were found to be regulated by histone acetylation of the ELP during transcription, DNA demethylase activity, and uridine modification at the tRNA wobble position (Stirnimann *et al.*, 2010; Kojima *et al.*, 2011; Fang *et al.*, 2015; Dalwadi *et al.*, 2018).

Histone acetyltransferase activity of ELP in plants

The effect of the histone acetyltransferase activity of the ELP on the transcriptional activation of plant genes in plants is well established. Two growth-regulating genes associated with auxin, *SHY2* and *LAX2*, five genes of the salicylic acid (SA) defense pathway, *NPR1*, *PAD4*, *EDS1*, *PR2*, and *PR5*, and three genes of the jasmonate/ethylene (JA/ET) defense pathway, *WRKY33*, *ORA59*, and *PDF1.2*, the four transcription factor genes responsible for root development, *PLT1*, *PLT2*, *SHR*, and *SCR*, were identified as the HAT activity targets of ELP (Huang, 2005; Stirnimann *et al.*, 2010; Kojima *et al.*, 2011; Fang *et al.*, 2015; Dalwadi *et al.*, 2018). Using chromatin immunoprecipitation (ChIP-qPCR), histone H3 acetylation was much less detected in the coding region of the *Arabidopsis elp*/*elo* mutants than in the wild-type, using both antibodies, and the ELP-targeted genes H3K14Acand H3K9/14Ac were identified (Kojima *et al.*, 2011; Dalwadi *et al.*, 2018). The finding that decreased histone H3 acetylation was found in both elp3 and elp2 mutants suggests that ELP is required for HAT activity in plants similar to yeast (Huang *et al.*, 2008). It is therefore suggested that histone acetylation activates the basis or induced expression of selected genes through ELP by promoting transcription elongation. Recently, it was found that wheat *TaELP4* negatively regulates the plant response to freezing stress by increasing the histone acetylation levels of *ACS2* and *ACS6* and increasing their transcription and ethylene accumulation(Wang *et al.*, 2020).

The DNA demethylation activity of ELP in plants

The ELP 3 subunit of ELP contains a free-radical SAM domain, and was initially thought to be associated with histone demethylation (Mehlgarten *et al.*, 2009). But recent studies in the mouse (*Mus musculus*) show that the demethylation of the paternal DNA in zygotes requires the SAM domain of ELP 3 in the ELP (Creppe *et al.*, 2009). Assuming that the ELP3 SAM activity can form a strong oxidant 5 ′ -deoxyadenosine, this activity may extract the hydroxyl group of the 5-methylcytosine to produce powerful free radicals for further reactions (Creppe *et al.*, 2009). The experiment supported model of modified tRNA by ELP3 SAM and HAT activity is extremely similar in the first reaction step, where the ELP3 SAM activity generates the SAM-derived 5 ′ -deoxyadenosine group that extracts hydrogen atoms-CoA from the methyl group of the acetyl group for binding to the ELP3 HAT domain and reacts with the C5 of U34 tRNA (Esberg *et al.*, 2006). Thus, the seemingly distinct activities of the ELP3 SAM domain in DNA demethylation and tRNA modification may share common biochemical properties. Modified DNA methylation levels were identified both by gene-specific and genome-wide approaches in plant *elp* / *elo* mutants (Fang *et al.*, 2015). Two defense genes, *NPR1* and *PAD4*, were examined, which showed reduced expression in *elp2* mutants and regulated DNA methylation levels by ELP via histone acetylation (Fang *et al.*, 2015). The *NPR1* promoter and *PAD4* coding regions were more methylated in the *elp2* mutants than in the wild-type, but not in the coding portion of *NPR1*. Methylation levels in both the promoter and coding regions were reduced in the *elp2* mutants (Dalwadi *et al.*, 2018). Analysis of methylation patterns in *elp2* mutants and wild-type cytosine by deep sequencing indicates that there was more cytosine methylation in *elp2*, but with lower average methylation levels than in wild-type. When analyzing specific cytosines, increased or decreased methylation levels were detected in the *elp2* mutants, suggesting that ELP is involved in methylation and demethylation. ELP can not only directly affect DNA methylation through the activity of its SAM domain, but can also affect DNA methylation by regulating the transcriptional levels of DNA methyltransferases, as indicated by enhanced expression. Although the cytosine methylation pattern suggests that ELP regulates DNA methylation, it is unclear whether the complex is involved in cytosine methylation, demethylation or both, and how these modifications affect gene expression levels.

The tRNA wobble uridine modification of ELP in plants

Growing evidence from plants suggests that ELP mainly plays a role in tRNA modification, and some studies suggest that its tRNA modification activity is conserved in *Arabidopsis* (Versées *et al.*, 2010; Chen *et al.*, 2011). In budding yeast (*Saccharomyces cerevisiae*), the gene encoding ELP is not required, but its deletion leads to a large set of common phenotypes (Zhou *et al.*, 2009; Lin *et al.*, 2012), One of them is resistant to Zymocin toxin, a protein toxin secreted by Kruviyeast lactate (*Kluyveromyces lactis*) (Mehlgarten *et al.*, 2009). Zymocin is a tRNA anticodon nuclease that efficiently cleaves $tRNA^{Glu}$ (UUC) and cleaves $tRNA^{Lys}$ (UUU) and $tRNA^{Gln}$ (UUG), containing 5-methoxymethyl-2-thiuridine (mcm^5s^2U) in these three tRNA anticodon swing positions (Lin *et al.*, 2013). Yeast mutants of ELP1-6 and KTI11-14 both lack 5-aminomeylmethyl uridine (ncm^5U) and mcm^5s^2U at position 34 (wobble position) of total tRNA (Frohloff *et al.*, 2001; Bauer *et al.,* 2012). All of these mutants showed a resistance phenotype to Zymocin in budding yeast mcm^5s^2U modification is essential for substrate recognition by Zymocin, which targets $tRNA^{Glu}$ (UUC) to cleave at the 3' sides of the wobble position (Lin *et al.*, 2013). The ELP mutant strain lacks a 5-methoxymethyl (mcm^5) and 5-carbamylmethyl (ncm^5) modification on the tRNA-containing swing uridine, and the absence of the mcm5 fraction protects them from Zymocin recognition and cleavage in the case of the Zymocin substrate tRNA (Frohloff *et al.*, 2001). Thus, for the early steps of synthetic mcm^5 and ncm^5 modifications on a tRNA containing a swinging uridine, ELP use is required (Frohloff *et al.*, 2001). In yeast, 11 out of the 42 tRNA species carry these ELP-dependent modifications, as required for efficient decoding at the wobble position during translation (Frohloff *et al.*, 2001). The main role of ELP in yeast is now thought to be a uridine modification in tRNA swing: increased expression of $tRNA^{Lys}$ (UUU) and $tRNA^{Gln}$ (UUG) is sufficient to rescue most of the elp mutant phenotypes tested to date (Versées *et al.*, 2010; Fernandez-Vazquez *et al.*, 2013). The study by Lin et al revealed that the modified uridine is the in vitro recognition site of the Zymocin tRNA endonuclease, and thus the mutants lacking these wobble uridine modifications are resistant to Zymocin (Lin *et al.*, 2013). Overly modified $tRNA^{Glu}$ (UUC) and $tRNA^{Lys}$ (UUU) can inhibit the growth phenotype and exocytosis defects in the *elp* mutants (Fernandez-Vazquez *et al.*, 2013), This suggests that this phenotype is mainly due to reduced translation efficiency. Overexpression of the three tRNA containing low-modified mcm5s2U also suppressed defects in telomeric gene silencing and the DNA damage response in C. elegans (*C. elegans*) *elp* mutants (Versées *et al.*, 2010), There are therefore at least two cases that suggest that translation defects may be the main cause of this defect. This evidence suggested that the mutant phenotype is caused by common translational defects. The effect of ELP on tRNA wobble uridine modification was also retained in microorganisms, plants and animals (Miskiewicz *et al.*, 2011), Studies in *Arabidopsis* suggest that ELP may play a role in tRNA modification in plants (Versées *et al.*, 2010; Dauden *et al.*, 2017). But the link between ELP in tRNA modification, plant development, abiotic and biotic stress response is difficult to determine. A variety of biological processes can be regulated by ELP tRNA modification, such as telomeric gene silencing, cell cycle control and oxidative stress responses that are also present in *Arabidopsis* (Versées *et al.*, 2010; Bauer *et al.*, 2012; Fernandez-Vazquez *et al.*, 2013), Thus the binding of ELP to RNAPII in yeast is not just a coincidence.

In addition to its HAT activity, the ELP3 also contains an S-adenosine methionine-binding domain (SAM), which has more recently been shown to be available for paternal DNA demethylation in mice (Creppe *et al.*, 2009). Since the ELP is a global functional unit, the knockdown of other structural genes also causes similar results in the DNA methylation status. Recent studies have demonstrated the role of *ELP2* in the plant immune response to certain pathogens (Skylar *et al.*, 2013). The *elp2* mutants in *Arabidopsis* also affect pathogen-induced DNA methylation and demethylation at least two defense genes at specific sites, and histone H3 acetylation levels in several defense genes are also compromised (Fang *et al.*, 2015). Both increased DNA methylation and decreased H3 acetylation in plants contribute to the delayed induction of defense genes, and this epigenetic regulation in zygotic and somatic cells increases gene regulation by ELP. However, the epistasis relationship between histone acetylation and DNA methylation and demethylation in plants requires further investigation.

Conclusions

Current studies of plant Elongator provide a large amount of data proving that, unlike in yeast, Elongator in plants combines several roles. The pathways regulated by the ELP also differ between the different plants, reflecting the inducible diversification of the ELP gene itself. Many environmental conditions that induce or inhibit ELP genes were identified in the experimental analysis, which may be the starting point for further experimental studies. Although the intrinsic link between histone acetylation and DNA demethylation and methylation in *Arabidopsis* Elongator mutants is yet to be determined, these results suggest that ELP may epigenetically regulate plant development as well as in response to abiotic and biotic stresses. Although recent structural and biochemical investigations have yielded a wealth of novel information on individual Elongator subunits and the full holo-Elongator, mechanistically how this complex exerts its diverse physiological functions remains unclear. The highly conserved Elongator complex modifies transfer RNAs (tRNAs) in their wobble base position, thereby regulating protein synthesis and ensuring proteome stability. The precise mechanisms of tRNA recognition and its modification reaction remain elusive. Further research might reveal innovative insights into the crosstalk between transcriptional and translational regulation.

Authors' Contributions

XJ conceptualized and prepared the draft of the manuscript. ZZ reviewed and improved the manuscript. YW and YZ provided technical assistance. YP supervised the study. All authors read and approved the final manuscript.

Ethical approval (for researches involving animals or humans)

Not applicable.

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Conflict of Interests

The authors declare that there are no conflicts of interest related to this article.

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