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REVIEW

Recent Advances in the Role of the Elongator Complex in Plant Physiology and tRNA Modification: A Review

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Abstract

The Elongator complex is a multifunction protein complex which has been shown to be involved in transcriptional elongation, DNA replication and repair, tubulin and histone acetylation, gene silencing and tranfer RNA uridine modification. The composition of the Elongator complex is found to be highly conserved in eukaryotes, protein homologs of various subunits have been identified in fungi, plant, animal, and human. Remarkably, mutation in genes encoding the Elongator complex structural components all results in defects of transfer RNA wobble uridine modification, and this function of the Elongator complex is also conserved in eukaryotes. The Elongator complex mutants in higher plants have pleiotropic phenotypes including defects in vegetative growth, abiscisic acid hypersensitivity, elevated tolerance to drought and oxidative stress. What is the relationship between the Elongator complex's function in nucleoside modification and its activity in other cellular pathways? This review summarizes the recent advances in study of function of the Elongator complex, in the aspects of cell physiology and molecular biology.

Key words: the Elongator complex, transfer RNA, nucleoside modification

INTRODUCTION

From the first report of the Elongator complex in 1999 (Otero *et al*. 1999) from *Saccharomyces cerevisiea*, protein homologs of various subunits have been found in various eukaryotic systems including *Caenorhabditis elegans*, *Arabidopsis thaliana*, *Drosophila melanogaster*, and *Homo Sapiens* (Hawkes *et al*. 2002). The most striking feature of all is the structural conservation of the protein complexes, as well as the phenotype similarity resulting from loss-of-function mutation in any of the protein subunits. With analogy to the elongation-factors in translation, the Elongator complex associates with RNA polymerase II (RNA pol. II) during transcription process. The strong physical interaction between the Elongator complex and RNA pol. II has been shown by *in vitro* immunoprecipitation assay, and this interaction relies on the hyper-phosphorylated status of the CTD domain of RNA pol. II (Jablonowski *et al*. 2001b).

However, after the initial discovery, the Elongator complex have been suggested to participate in diverse cellular pathways, including histone modification/acetylation (Wittschieben *et al*. 1999), exocytosis (Rahl *et al*. 2005), tubulin acetylation (Creppe *et al*. 2009), response to DNA damage (Li *et al*. 2009), transcriptional silencing (Li *et al*. 2009), and tRNA nucleoside modification (Huang *et al*. 2005; Esberg *et al*. 2006).

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The dysfunction of the Elongator complex proteins in *D. melanogaster* and *C. elegans* result in defect of embryo development (Chen *et al*. 2009; Walker *et al*. 2011), and several neural degenerative diseases have been associated with different alleles coding for the Elongator complex subunits (Anderson *et al*. 2001; Crolla and van Heyningen 2001; Kleinjan *et al*. 2002; Strug *et al*. 2009). Most of these phenotypes have been attributed to translational defect, for instance neural cells are particularly sensitive to translational defects due to their high demand of protein synthesis, and also over-expression of certain tRNA isoacceptors harbouring the affected nucleoside can partially rescue the phenotype (Chen *et al*. 2011).

So far all mutants in the structural components of the Elongator complex lead to specific tRNA nucleoside modification defects at position 34 (wobble position), which harbours xm^{5}U (including ncm^{5}U: 5-carbomoylmethyluridine and mcm^{5}U: methoxycarbonylmethyl-uridine) type of uridine modifications in *S. cerevisiea* (Huang *et al*. 2005), *C. elegans* (Chen *et al*. 2009) and *A. thaliana* (Mehlgarten *et al*. 2010). The connnection between the Elongator complex's role in tRNA wobble uridine modification and metabolic and physiological duties is still a mystery. In this review, we focus on the recent advance in the Elongator complex function in higher plants, particular associated with tRNA uridine nucleoside modifications.

STRUCTURAL COMPOSITION OF THE ELONGATOR COMPLEX AND FUNCTIONAL ASSOCIATION

The Elongator complex is composed of six protein subunits, the corresponding protein and their molecular mass are: Elp1-150, Elp2-90, Elp3-60, Elp4-50, Elp5-35, and Elp6-30 kDa (Otero *et al*. 1999; Winkler *et al*. 2001, Table). Elp1-3 form the core complex, the Elp4-6 subcomplex forms a hetero-hexameric ring-like structure which is essential for the binding of anticodon stem-loop of substrate tRNAs (Fig., Glatt *et al*. 2012). Contrary to its primary role in transcriptional elongation and histone modification, the subcellular localization of the Elongator complex subunits are mainly cytoplasmic, except for the catalytic subunit Elp3 (Fichtner *et al*. 2002b; Creppe *et al*. 2009; Miśkiewicz *et al*. 2011).

The largest subunit of the Elongator complex is the Elp1 protein, which can be phosphorylated. Actually the phosphorylation status of Elp1 is regulated by several proteins including Sit4 and Sit4-associated proteins-Sap185 and Sap190 (Jablonowski *et al*. 2001a, 2004), Kti11-Kti14 (Mehlgarten *et al*. 2009). Elp3 is the functional centre of the Elongator complex, the histone acetyl transferase (HAT) activity for histone modification directly links the chromatin structure deformation with elevated transcription activity mediated by RNA pol. II. The presence of an iron-sulphur cluster on Elp3 protein allows for the binding of S-AdoMet (Paraskevopoulou *et al*. 2006). The radical shoot apical meristem (SAM) activity of Elp3 was indicated to be involved in DNA methylation/demethylation at specific cytidine positions in paternal zygotic cells (Okada *et al*. 2010). The sub-complex Elp4-6 all share a same RecA like protein fold but without the ATPase consensus sequence, and it has been shown *in vitro* that Elp4-6 could hydrolyse ATP and use this reaction to bind tRNA. The hexameric NTPase structure is common to other nucleic acids-binding proteins such as Rho GTPase (Glatt *et al*. 2012).

The proper function of the Elongator complex need the collaboration with other proteins, among all Kti12 is the most tightly related. Both genetic and biochemical evidence suggest there is considerable functional overlap between Kti12 and the Elongator complex (Frohloff *et al*. 2001; Petrakis *et al*. 2005), Kti12 could physically interact with Elp3 and Elp5 proteins, however deletion of *KTI12* does not influence the assembly of the Elongator conplex. Kti12 is an ancient ATP/GTP binding protein which has also been found in Achaea *Methanopurus kandleri* (Fichtner *et al*. 2002a). All Kti12 homologs contain conserved P-loop motif, but the plant Kti12 protein also contains a calmodulin binding domain at the C-terminus (Nelissen *et al*. 2005). Kti14 protein belongs to casein kinase family, it has been suggested for post-translational regulation of the Elongator complex's function (Mehlgarten and Schaffrath 2003). Kti14 could bind the Elongator complex in the presence of Kti12 (Fichtner *et al*. 2003; Mehlgarten *et al*. 2009), however no physical interace tion has been shown between Kti11 or Kti13 protein

Table Structural and regulatory components of the Elongator complex

Gene	Annotation	Mutant phenotype	Mutant modification	References
ELP1	Elongator core subunit	Yeast: slow growth, G1 cell cycle delay, Ts, zymocin resistance, calcofluor, and 6-AU sensitive *Arabidopsis*: narrow leaf and reduced root growth, ABA hypersensitivity, tolerance to drought and oxidative stress, accumulation of anthocyanin, reduced apical dominance *Caenorhabditis elegans*: neuronal defect Human: FD disease	Lack ncm^5U, mcm^5U	Fellows (2000); Frohloff *et al*. (2001); Anderson *et al*. (2001); Huang *et al*. (2005) Nelissen *et al*. (2005); Chen *et al*. (2006); Zhou *et al*. (2009); Nelissen *et al*. (2010); Chen *et al*. (2009)
ELP2	Elongator core subunit	Yeast: slow growth, G1 cell cycle delay, Ts, zymocin resistance, calcofluor, and 6-AU sensitive *Arabidopsis*: accumulation of anthocyanin, ABA hypersensitivity, tolerant to oxidative stress, narrow leaf, and reduced root growth	Lack ncm^5U, mcm^5U	Fellows (2000); Frohloff *et al*. (2001); Huang *et al*. (2005); Zhou *et al*. (2009)
ELP3	Elongator core subunit	Yeast: slow growth, G1 cell cycle delay, Ts, zymocin resistance, calcofluor, and 6-AU sensitive *Arabidopsis*: narrow leaf and reduced root growth, reduced apical dominance, MMS sensitivity *C. elegans*: neuronal defect Drosophila: larval lethality	Lack ncm^5U, mcm^5U	Fellows (2000); Frohloff *et al*. (2001); Huang *et al*. (2005); Melhgarten *et al*. (2010); Nelissen *et al*. (2005); Nelissen *et al*. (2010); Xu *et al*. (2012); Chen *et al*. (2009); Walker *et al*. (2011)
ELP4	Elongator sub-complex	*Arabidopsis*: narrow leaf and reduced root growth, accumulation of anthocyanin, ABA hypersensitivity, tolerant to oxidative stress, reduced apical dominance	Lack ncm^5U, mcm^5U	Huang *et al*. (2005); Nelissen *et al*. (2005); Zhou *et al*. (2009); Nelissen *et al*. (2010)
ELP5	Elongator sub-complex	Yeast: zymocin resistance, slow growth, G1 cell cycle delay, Ts, calcofluor, and 6-AU sensitive	Lack ncm^5U, mcm^5U	Frohloff *et al*. (2001); Huang *et al*. (2005)
ELP6	Elongator sub-complex	*Arabidopsis*: narrow leaf and reduced root growth, accumulation of anthocyanin, ABA hypersensitivity, tolerant to oxidative stress	Lack ncm^5U, mcm^5U	Huang *et al*. (2005); Zhou *et al*. (2009)
KTI11		Yeast: G1 cell cycle arrest, zymocin resistance	Lack ncm^5U, mcm^5U	Fichtner *et al*. (2002c); Huang *et al*. (2005)
KTI12	ATP/GTP binding	Yeast: zymocin resistance, slow growth, G1 cell cycle delay, Ts, calcofluor and 6-AU sensitive *Arabidopsis*: narrow leaf and reduced root growth, defect in leaf polarity	Lack ncm^5U, mcm^5U	Frohloff *et al*. (2001); Fichtner *et al*. (2002a); Huang *et al*. (2005); Nelissen *et al*. (2003); Nelissen *et al*. (2005)
KTI13		Yeast: G1 cell cycle arrest, zymocin resistance	Lack ncm^5U, mcm^5U	Fichtner *et al*. (2002c); Huang *et al*. (2005)
KTI14		Yeast: G1 cell cycle arrest, zymocin resistance, calcofluor, and 6-AU sensitive, MMS sensitive	Lack ncm^5U, mcm^5U	Mehlgarten *et al*. (2003); Huang *et al*. (2008)
TRM9		Yeast: zymocin resistant, paramycin senstive	Lack mcm^5U	Jablowski 2006; Kalhor and Clarke (2003); Huang *et al*. (2008); Leihne *et al*. (2011)
SIT4		Yeast: G1 cell cycle arrest, zymocin resistance, 6-AU sensitive, Ts	Lack ncm^5U, mcm^5U	Huang *et al*. (2008); Jablowski *et al*. (2001a)
SAP185,190		Yeast: G1 cell cycle arrest, zymocin resistance, 6-AU sensitive, Ts	Lack ncm^5U, mcm^5U	Huang *et al*. (2008); Jablowski *et al*. (2001a)

with the Elongator complex (Fichtner and Schaffrath 2002c). Genetic evidence points to a negative regulation of Kti11 on Kti12 (Fichtner and Schaffrath 2002c); whereas Kti13 acts as a positive regulator by serving as a potential guanosine-exchange-factor (GEF) for Kti12. Kti13 belongs to RCC1 protein family involved in chromatin-remodelling and condensation (Fichtner and Schaffrath 2002c). Finally, protein interactions between Elp1-Elp2, Elp2-Kti12, Elp2-Kti13 and Kti12-Kti13 need the presence of Elp3 (Fichtner *et al*. 2002b), emphasizing the important role of Elp3 both for structural integrity and function of the Elongator complex.

PHENOTYPE OF *elp* AND *kti* MUTANTS IN YEAST AND HIGHER PLANTS SUGGESTS FUNCTIONAL CONSERVATION

Zymocin resistance in yeast

The original identification of *KTI* genes was from isolation of killer-toxin-insensitive *S. cerevisiea* towards

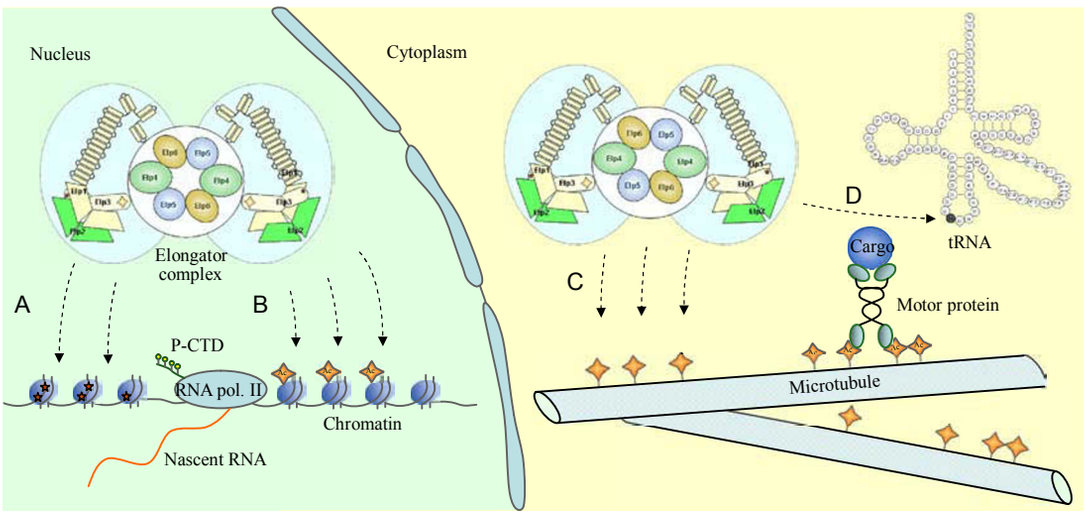

Fig. Role of the Elongator complex. A, DNA methylation or demethylation mediated by SAM activity of Elp3 is represented by stars. B, the HAT activity in Elp3 protein and corresponding histone acetylation are illustrated by diamonds. C, microtubulin acetylation by the Elongator complex. D, tRNA wobble uridine (in dark gray circle) modification regulated by elongator.

zymocin (Fichtner and Schaffrath 2002c; Frohloff 2001), which is secreted by *Kluyveromyces lactis* to inhibit the growth of other sensitive yeast (Butler *et al*. 1991, 1994). Most strikingly *kti11-14* mutants in *S. cerevisiea* all shared zymocin-resistant phenotypes as the *elp* mutants (Mehlgarten and Schaffrath 2003), the data supported the idea of zymocin as a general translation inhibitor which poisons the RNA pol. II *via* the Elongator complex (Frohloff *et al*. 2001; Jablonowski *et al*. 2001b; Li *et al*. 2001). The zymocin resistant phenotype of *kti14* mutants is dependant on the C-terminal region integrity of the protein (Fichtner *et al*. 2002b), further more the expression of Urm1 and Uba4 in *elp* mutants (Fichtner *et al*. 2003). All these proteins were involved in wobble uridine nucleoside modification at position 34 of certain tRNA molecules (see below).

On gene expression, almost 100 genes were regulated in *elp* mutants, and the profile of up- or down-regulation of the target genes was very similar (Krogan and Greenblatt 2001). Chromotin immunoprecipitation (ChIP) and Re-ChIP assay suggested that the Elongator complex could bind to the elongating transcript after the RNA pol. II is hyper-phosphorylated (Métivier *et al*. 2003). In other words, the Elongator complex starts its mission after the commitment of RNA pol. II. Recent study with ChIP assay also showed that the Elongator complex could associate with genomic DNA regions within replicons and DNA replication-coupled histone acetylation (Xu *et al*. 2012). Since genes in different cellular pathways were affected in *elp* mutants, pleiotropic phenotype was illustrated in higher eukaryotes during the process of embryogenesis and organ development.

Pleiotropic phenotype in higher plants

Mutation in both structural and regulatory components of the Elongator complex in *A. thaliana* results in multiple phenotypes including narrow leaves, enlargement of hypocotyl, retarded primary root growth, decreased seed germination, delay of flowering time, and reduced apical dominance (Nelissen 2003, 2005; Chen *et al*. 2006; Zhou *et al*. 2009). The growth phenotypes were associated with decreased cell division rate, defect in control of cell cycle and meristem polarity setup (Xu *et al*. 2012). Transverse section of *elp* and *kti12* mutants showed fewer and larger palisade cells (Nelissen 2003, 2005). By transmission electron microscopy, Falcone *et al*. (2007) observed that the *atelp4* mutant had fewer stacked-grana in chloroplast, a hypotonic vacuole and massive exocytosis; and the same mutant displayed different growth dynamics and gene expressions in response to sucrose. The apical dominance phenotype was attributed to misregulation in biosynthesis or transport of plant hormones including anthocyanin, abiscic

acid, auxin, and abscisic acid (ABA) (Nelissen 2005, 2010; Zhou *et al*. 2009). Auxin biosynthesis, transport, perception, and signalling genes were severely affected according to the microarray data from *elp* mutants (Nelissen *et al*. 2010), gene ontology (GO) clustering also revealed significant change for genes in chromatin assembly, pattern specification and vascular tissue development. Free indoleacetic acid (IAA), ethelene, jasmonic acid (JA) and anthocyanin content in mutants of *ELP1*, *ELP2*, *ELP4*, and *ELP6* were higher than that in wild type, which might involve regulation by transcriptional factors (Zhou *et al*. 2009) and epigenetic modification on genomic sequence by H3K14 (Nelissen *et al*. 2010). Leaf abaxial/adaxial polarity was altered in *Arabidopsis elp* mutants, possibly due to decreased cell division and DNA replication coupled with regulation of chromatin structure by histone modification (Xu *et al*. 2012). The crosstalk between salicylic acid (SA), JA/ethylene (ET) and ABA also partially explained the pleiotropic phenotypes of *elp* mutants in higher plants (DeFraia and Mou 2011), along with secondary effect of hormone imbalance on gene expression involved in abiotic stress, pathogen response and anthocyanin biosynthesis (Nelissen *et al*. 2010).

Drought and other abiotic stress can cause similar changes in cellular pathways as oxidative stress. Surprisingly several *Arabidopsis elp* mutants were found to be more tolerant to oxidative reagent methyl-viologen and H_2O_2 (Chen *et al*. 2006; Zhou *et al*. 2009), further more *elp1* mutant was more drought tolerant than wild type (Chen *et al*. 2006). Leaf stomata closure and root elongation of *elp1* and *elp2* mutants were more sensitive to plant hormone ABA (Chen *et al*. 2006; Zhou *et al*. 2009). It is noteworthy that *elp4* and *elp6* mutants did not have stomata closure and water retention phenotype as that in *elp1* and *elp2* mutants (Zhou *et al*. 2009; Nelissen *et al*. 2010), suggesting functional difference between the Elongator complex core-subunit and sub-complex. On gene expression, both ABA responsive genes and several drought-stress related genes were less induced in *elp* mutants than in wild type (Chen *et al*. 2006), suggesting the elevated tolerance for drought and oxidative stress might not be transcriptional but translational instead. In another study, two transcriptional factors and three genes involved in oxidative and abiotic stress were differently expressed in *Arabidopsis elp* mutants, either with or without ABA treatment (Zhou *et al*. 2009). Therefore it is still on debate whether regulation of gene expression by the Elongator complex is mostly transcriptional or translational.

By constructing double mutants of the *KTI12* and various *ELP* genes and comparing the phenotype of double mutant (DM) with their parents, epistatic relationships between the Elongator complex subunits and regulatory components were determined as the following: 1) *KTI12* is epistatic over *ELP* genes; 2) subcomplex gene *ELP4* is epistatic over core complex genes *ELP1-3*; 3) within core complex *ELP1* is epistatic over *ELP3* (Nelissen *et al*. 2005). Considering the hetero-hexameric ring-like structure of the Elp4-6 subcomplex with the Elp1-3 core-complex (Lin *et al*. 2012), in addition with the regulatory components either with or without direct physical interaction with the Elongator complex proteins, these data suggests the significant role of regulatory proteins and the importance of Elp1 as scaffold protein for the proper function of the whole Elongator complex. The Elongator complex proteins were found to be located mainly in cytoplasm except for Elp3 (Nelissen *et al*. 2010), and the tissue specific expression patterns of *ELP2*, *ELP4* and *ELP6* genes were very similar to that of *ELP1* in *Arabidopsis* (Chen *et al*. 2006; Zhou *et al*. 2009). Co-localization of *Arabidopsis* Elp3 protein with euchromatin was verified, acetylation level of histone H3K14 on auxin-related genes was found to be reduced which resulted in down-regulation of the target genes (Nelissen *et al*. 2010). Because H3K14 is the predominant substrate of Elp3 HAT activity, the epigenetic regulation of auxin biogenesis and transport genes partially explained the auxin-biology-related phenotypes of *Arabidopsis elp* mutants such as reduced apical dominance, changed phyllotaxy, defective leave venation patterning, and reduced root growth (Nelissen *et al*. 2010).

Besides HAT activity, Elp3 protein also contains a radical shoot apical meristem (SAM) domain, which has been shown recently in mice for paternal DNA demethylation (Okada *et al*. 2010). As the Elongator complex works as a whole functional unit, knock out of other structural genes also lead to similar results on DNA methylation status. Recent study suggests role of *ELP2* in plant immune response towards certain pathogenic bacteria (Defraia *et al*. 2010). *Arabidopsis elp2* mutant

showed much less of free SA upon pathogen attack, because SA is important for defense-related signal transduction in plants, Elp2 is considered as an accelerator of defense response. Although not required for systematic acquired resistance, *AtELP2* regulates both SA accumulation and kinetics of defense gene induction, therefore it is considered as a component for basal immunity (Defraia *et al*. 2010). *elp2* mutant in *Arabidopsis* also influenced pathogen-induced DNA methylation/demethylation on at least two defense genes at specific sites, and histone H3 acetylation levels in several defense genes were also compromised (Wang *et al*. 2013). Both increased DNA methylation and decreased H3 acetylation contribute to the delayed defense gene induction, this epigenetic regulation both in zygotic cell and somatic cell adds an additional level of gene regulation by the Elongator complex. However the epistatic relationship between histone acetylation and DNA methylation/demethylation need further investigation.

Association with embryogenesis and human disease

Human familial dysautonomia (FD) is a neurodegenerative disease, IKAP/hElp1 protein level was found to be very low in brain tissues from FD patients (Anderson *et al*. 2001). Elp3 protein is unstable without association with Elp1, therefore Elp3 level is also reduced in FD patients (Close *et al*. 2006). Cells with low levels of the Elongator complex display defects in cell motility and migration, it has been shown that Elp3 promotes α-tubulin acetylation and also physically interacts with it (Creppe *et al*. 2009). Elp1 and Elp3-mediated tubulin acetylation is found in *C*. *elegans* (Chen 2009; Solinger 2010), human and mouse (Creppe *et al*. 2009), which was manifested by defects in early embryogenesis or neurological dysfunction. Since several neurodegenerative disease including Alzheimer's, Parkinson and ALS have been linked to defects in intracellular trafficking, the loss of elongator-mediated tubulin acetylation can lead to defective intracellular cargo transport therefore survival of neuronal cells (DeFraia and Mou 2011). Alternatively, dysfunction of the Elongator complex also results in general translation defect which is more sensitive for neural cell development. Elp3 dysfunction causes embryo-lethality in *D*. *melanogaster*, microarray analysis suggested considerable overlap of gene expression involved in neuronal development with *domino* mutant (Walker *et al*. 2011).

THE ELONGATOR COMPLEX IN ASSOCIATION WITH tRNA WOBBLE URIDINE MODIFICATIONS

Yeast mutants of *ELP1-6* and *KTI11-14* all lack ncm^{5}U (5-carbomoylmethyluridine) and mcm^5(s^2)U (methoxycarbonylmethyl-(thio-)uridine) at position 34 (wobble position) in total tRNA (Huang 2005, 2008). All of these mutants displayed zymocin resistance phenotype in *S*. *cerevisiea*. Study by Lu *et al*. (2005) revealed that modified uridine is the recognition site of the zymocin tRNA endonuclease *in vitro*, therefore mutants lacking these wobble uridine modification were resistant to zymocin. In *S*. *cerevisiea* 11 tRNA species carried either ncm^{5}U or mcm^{5}U derivatives at position 34 (Johansson *et al*. 2008), overexpression of hypomodified $tRNA^{Glu}_{mcm^5s^2UUC}$ and $tRNA^{Lys}_{mcm^5s^2UUU}$ suppressed growth phenotypes as well as exocytosis defects in *elp* mutants (Esberg *et al*. 2006) and partial resistance towards zymocin, suggesting that the phenotype is mainly due to inefficient translation. Overexpression of three tRNA species containing hypomodified mcm^{5}s^{2}U also supressed the defects in telomeric gene silencing and DNA damage response in *C*. *elegans elp* mutants (Chen *et al*. 2011), therefore at least two cases have suggested translational defects might be the primary reason for the various phentoypes observed in *elp* and *kti* mutants. According to sequenced tRNA data from Modomics database (http://modomics.genesilico.pl/sequences/list/tRNA/), higher plants also contain mcm^5(s^2)U and mnm^5(s)^{2}U wobble uridine modifications, for example in tRNA-Gln-UUG or tRNA-Glu-UUC species from *Hordeum vulgare* and *Triticum aestivum*, respectively. Since the genome sequence of *A*. *thaliana* is known, the corresponding tRNA coding genes could be identified, and most likely these tRNAs also contain similar wobble uridine modifications. It would be very interesting to see if overexpression of hypomodified tRNA-Gln-!UG (!UC represents the anticodon, ! stands for cmnm^{5}U) or tRNA-Glu-SPC (S stands for mnm^{5}s^{2}U and P stands for pseudouridine) could rescue some of the phenotypes in *Arabidopsis elp* mutants.

The function of the Elongator complex is found to be conserved from yeast to higher plant, not only because the *Arabidopsis* Elp1 and Elp3 protein can both substitute for protein-protein interaction and complement yeast mutant for zymocin resistance, but also that *elp1*, *kti12* and *elp3* knock-out mutants lacks ncm^{5}U and mcm^{5}U modified nucleoside in total tRNA (Chen *et al*. 2010; Mehlgarten *et al*. 2010). *elp1* and *elp3* mutants of *C*. *elegans* also resulted in deficiency for ncm^{5}U and mcm^{5}U nucleoside modifications in total tRNA (Chen *et al*. 2009), supporting the view that the function of the Elongator complex in tRNA wobble uridine modification is conserved.

The codon bias in mRNA results in regulation of specific protein level mediated by the presence of modified nucleoside, *Cdr2* which is a central regulator for mitosis and cytokinesis is under such translational control by Elp3 due to the lysine codons that are decoded by mcm^{5}s^{2}U -containing tRNAs (Bauer *et al*. 2012). Similarly, yeast exocytosis was affected in *elp1* mutant in a process independent of the transcriptional elongation (Rahl *et al*. 2005). However, as more substrates were found for the HAT activity of the Elongator complex, and with radical SAM activity recently discovered, both tRNA nucleoside modification, DNA and proteins could be affected by the Elongator complex. The phenotype caused by lack of ncm^{5}U and/or mcm^{5}U modifications on tRNA is a translational effect; however the central role of the Elongator complex in association with RNA pol. II and histone modifications is transcriptional. Why mutation in *ELP* and *KTI* genes all lead to defect in wobble uridine modification is not understood, at least the involvement of ATP/GTPase activity was suggested for energy supply of the modification reaction.

Besides Elp1-6 and Kti1-14, Trm9 (Kalhor and Clarke 2003) and ALKBH8 (Leihne *et al*. 2011) proteins were further identified for the mcm^{5}U and mchm^{5}U modifications. It is suggested that Trm9 methylation facilitates the recognition of target tRNA by zymocin (Jablowski *et al*. 2006), the defect in translation also renders the mutant sensitive to paramycin at high temperature (Kalhor and Clarke 2003). However no obvious phenotype was observed under normal growth conditions for *TRM9* and *ALKBH8* mutants in *Arabidopsis*, which lacks mcm^{5}U and mchm^{5}U modified nucleosides, respectively (Leihne *et al*. 2011).

Acetylation of histone by the Elongator complex also need the expression of Sit4 together with its associated protein Sap185 and Sap190 (Jablowski *et al*. 2004), moreover yeast *sit4* mutant and *sap185*, *sap190* double mutant resembled phenotypes in lack of ncm^{5}U, mcm^{5}U and mcm^{5}s^{2}U modified nucleoside and zymocin resistance (Huang *et al*. 2008). The phosphorylation status of Elp1 was suggested to be regulated by Sit4 phosphatase with the help of Sap185/Sap190, which is antagonized by Kti12 and Kti14 (Mehlgarten *et al*. 2009).

OTHER ROLES OF THE ELONGATOR COMPLEX

The Elongator complex has also been implicated to be involved in cytoplasmic kinase signalling and yeast exocytosis, however, there is some controversy with the results from later study, therefore there is still debate concerning whether the Elongator complex is participating in these pathways directly or indirectly (Svejstrup 2007).

The human Elp1 was firstly identified by association with IκB kanases, however this was shown with overexpression of the Elp1 protein (Cohen *et al*. 1998). Later study basically repudiated this conclusion and suggested that Elp1/IKAP had no specificity in cytoplasmic kinase signalling (Krappmann *et al*. 2000). The intereaction of Elp1 with JNK kinase by yeast-two-hybrid was also performed with over-expression approach (Holmberg *et al*. 2002), indeed numerous studies failed to support any involvement of Elp1 or other subunits of the Elongator complex in kinase signalling (Svejstrup 2007).

Using a yeast *sec2-52* mutant which harbours a premature stop-codon in the essential Rab GTPase, Rahl *et al*. (2005) illustrated the possible role of the Elongator complex in exocytosis. Since the author used a Elp1 construct with strong nuclear-localization-signal, the results might be misleading and could not represent the actual function of the Elongator complex in exocytosis. However, Esberg *et al*. (2006) found that the exocytosis defect of yeast *sec2-59* mutant could be overcome by elevated level of hypomodified tRNA-Lys and tRNA-Gln which normally contain mcm^{5}s^{2}U at wobble position, suggesting the phenotype is due to a translational defect. The increase levels of hypomodified tRNA-Lys and tRNA-Gln in the *elp1* mutant strain could restore the po-

larized localization of Sec2 protein which is essential for exocytosis, suggesting the Elongator complex's function in exocytosis is connected with its role in tRNA wobble uridine modification (Esberg *et al*. 2006).

CONCLUSION

The Elongator complex is an important functional unit for transcriptional elongation (Lu *et al*. 2007; Svejstrup *et al*. 2007; Versees *et al*. 2010; Creppe *et al*. 2011). Elp3 is both in a core structural subunit and the catalytic subunit for the whole complex, which is involved in acetylation of H3 and H4 histone lysine residue as well as other substrates including tubulin (Winkler *et al*. 2002; Creppe *et al*. 2009; Solinger *et al*. 2010). Recently an Elp3 protein from insect *Nilaparvata lugens* was indentified, the phylogeny of NlElp3 with homologs of the GNAT superfamily from other organisms was illustrated (Zhu *et al*. 2013). The NlElp3 protein also contains radical SAM domain, possibly also involved in DNA demethylation. It has been shown that affinity binding to DNA and histone substrates need the presence of whole complex (Winkler *et al*. 2002).

Up to date the multifunctional Elongator complex has been shown to be involved in cell cycle control, DNA demethylation and DNA damage repair, regulator of plant abiotic stress and immune response, tubulin acetylation and cytokinesis, neuron development and human neuron degenerative diseases. Elongator-mediated telomeric gene silencing was mainly a translational effect due to defect in mcm^5s^2U modification of certain tRNA (Chen *et al*. 2011), however, association of the Elongator complex with DNA replication, gene silencing and DNA damage response is restricted to the nucleus (Li *et al*. 2009). The misregulation of cell cycle and mitosis in *elp* mutants led to pleiotropic phenotypes in higher plants, such as elongated leaf and petioles, aberrant lateral shoot growth, delayed root growth, and meristem polarity (Xu *et al*. 2012). Elongtor's association with the proliferating cell nuclear antigen (PCNA) was illustrated both in budding yeast and *Arabidopsis*, and this interaction was shown to be necessary for efficient histone acetylation coupled with DNA replication (Li *et al*. 2009; Xu *et al*. 2012).

The crystal structure of Elp4-6 subcomplex was identified recently (Lin *et al*. 2012), however the structure of the holo-elongator complex and the Elp1-3 core subunits still hinders the understanding of the involvement of the Elongator complex in different biochemical pathways. A schematic view of the Elongator complex is represented here based on the present knowledge of the structure and biological functions within eukaryotes (Fig.). The subcellular localization of each subunits and their regulation for protein and gene expression under transcriptional or translational control, in particular the link between dysfunction of particular tRNA modification and downstream targets and phenotype manifestation is a challenging work for the future.

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