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REVIEW

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

YAN Xu[1], JIN Xiao-huan[1], WANG You-mei[1], ZHENG Bo[2] and CHEN Peng[1]

[1] *Biomass and Bioenergy Research Centre, College of Plant Sciences and Technology, Huazhong Agricultural University, Wuhan 430070, P.R.China*
[2] *College of Horticulture and Forest Sciences, Huazhong Agricultural University, Wuhan 430070, P.R.China*

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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Correspondence CHEN Peng, Tel: +86-27-87281399, Fax: +86-27-87281765, E-mail: chenpeng@mail.hzau.edu.cn

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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