Regulation of Transcription Elongation in the Outer Space

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Summary of Research

(1) Generation of knock-out mouse lacking Elongin A

We have isolated and analyzed the structure of the mouse Elongin A gene. A gene-targeting vector was constructed by replacing exons encoding the transcriptional activation domain of Elongin A with the neomycin cassette. Heterozygous mutant ES cell lines were obtained by homologous recombination technique and, subsequently, homozygous mutant ES cell lines were generated by culturing these heterozygous cells in high concentrations of G418. The obtained homozygous mutant ES cell lines possessed markedly enlarged cell mass and showed a reduced growth rate. FACS analysis revealed that these cells arrested at the G2/M phase of the cell cycle. Moreover, cDNA microarray analyses using the wild-type and Elongin A-deficient ES cells indicated that the expression of only a small percentage of genes is significantly reduced in the mutant cells. These findings suggest that Elongin A is not a general elongation factor and it regulates the expression of a distinct set of genes. We are currently trying to generate the knock-out mouse lacking the both alleles of Elongin A gene. (Aso et al, CCG 1999 and unpublished results)

(2) Identification and functional characterization of novel transcription elongation factors

We have identified two novel transcription elongation factors, Elongin A2 and Elongin A3. Mechanistic studies have demonstrated that both Elongins A2 and A3 stimulate the rate of transcription elongation by RNA polymerase II and are capable of forming a stable complex with Elongin BC. In contrast to Elongin A, however, their transcriptional activities are not activated by Elongin BC. Structure-function analyses using fusion proteins composed of Elongin A3 and Elongin A revealed that the COOH-terminal region of Elongin A is important for the activation by Elongin BC. (Aso et al, JBC 2000 and Yamazaki et al, submitted)

(3) Identification and characterization of proteins interacting with transcription elongation factors

We have identified a novel protein, termed EloA-BP1, which interacts with the NH2-termini of both Elongin A and SII. EloA-BP1 is composed of 1221 amino acids and its mRNA is expressed ubiquitous. As EloA-BP1 possesses the exonuclease domain at its COOH-terminus, this protein may have role to maintain the fidelity of transcriptional products. (unpublished results)
(4) Functional characterization of the Elongin complex

We have shown that the von Hippel-Lindau (VHL) tumor suppressor protein is capable of forming a multi-protein complex containing Elongins B and C, and known components the ubiquitin ligase, Cul2 and Rbx1. In addition, we have found that the VHL-Elongin complex possesses E3 ubiquitin ligase activity and identified hypoxia-inducible factor-1α as one of the ubiquitination target of this complex. (Aso et al, BBRC 2000)

Publication List

Original Articles

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