21. Mammalian Elongin A complex mediates DNA-damage-induced ubiquitylation and degradation of Rpb1

Takashi Yasukawa[1], Takumi Kamura[2], Aya Tsutsui[1], Yasufumi Kondo[1], Shigetaka Kitajima[3], and Teijiro Aso[1]

[1]Department of Functional Genomics, Kochi Medical School, [2]Division of Biological Science, Graduate School of Science, Nagoya University, [3]Department of Biochemical Genetics, Medical Research Institute, Tokyo Medical and Dental University

The Elongin complex stimulates the rate of transcription elongation by RNA polymerase II (pol II) by suppressing transient pausing of the pol II at many sites along the DNA. Elongin is composed of a transcriptionally active A subunit and two small regulatory B and C subunits, which bind stably to each other to form a binary complex that interacts with Elongin A and strongly induces its transcriptional activity. We have recently shown that Elongin A homozygous mutant (Elongin $A^{-/-}$) mice are embryonic lethal, and primary fibroblasts derived from Elongin $A^{-/-}$ embryos display not only increased apoptosis but also senescence-like phenotypes accompanied by the activation of p38 mitogen-activated protein kinase and p53. In this report, we have shown that both the ubiquitylation and proteasomal degradation of the largest subunit of pol II (Rpb1) following UV-irradiation are significantly suppressed in Elongin A-deficient cells, however those suppressions are rescued by transfection of wild-type Elongin A. Moreover, using recombinant proteins expressed in insect cells, we have demonstrated that the Elongin A-Elongin BC complex is capable of assembling with the Cul5/Rbx2 module, and this hetero-pentamer complex efficiently ubiquitylates Rpb1 *in vitro*. Mechanistic studies indicate that colocalization of Elongin A and Cul5 in cells and the interaction of Elongin A with the Ser5-phosphorylated form of Rpb1 are strongly enhanced following UV-irradiation. Taken together, our results suggest that mammalian Elongin A is directly involved in ubiquitylation and degradation of Rpb1 following DNA damage.

Reference

Yasukawa T, Kamura T, Kitajima S, Conaway RC, Conaway JW, and Aso T. Mammalian Elongin A complex mediates DNA-damage-induced ubiquitylation and degradation of Rpb1. EMBO J. 27, 3256-3266, 2008.