Human prefoldin modulates co-transcriptional pre-mRNA splicing

Laura Payán-Bravo[1,2], Sara Fontalva[1,2], Xenia Peñate[1,2,], Ildefonso Cases[3], José Antonio Guerrero-Martínez[5], Yerma Pareja-Sánchez [1], Yosu Odriozola-Gil[1], Esther Lara[1], Silvia Jimeno-González[2,5], Carles Suñé[4], Mari Cruz Muñoz-Centeno[1,2], José C. Reyes[5] and Sebastián Chávez [1,2,*]*

[1]Instituto de Biomedicina de Sevilla, Universidad de Sevilla-CSIC-Hospital Universitario V. del Rocio, Seville, Spain,
[2]Departamento de Genética, Facultad de Biología, Universidad de Sevilla, Seville, Spain,
[3]Centro Andaluz de Biología del Desarrollo, CSIC-Universidad Pablo de Olavide, Seville, Spain,
[4]Department of Molecular Biology, Institute of Parasitology and Biomedicine "López Neyra" IPBLN-CSIC, PTS, Granada, Spain
[5]Andalusian Center of Molecular Biology and Regenerative Medicine-CABIMER, Junta de Andalucia-University of Pablo de Olavide-University of Seville-CSIC, Seville, Spain

Prefoldin is a heterohexameric complex conserved from archaea to humans that plays a co-chaperone role during the co-translational folding of actin and tubulin monomers. Additional functions of prefoldin have been described, including a positive contribution to transcription elongation and chromatin dynamics in yeast. Here we show that prefoldin perturbations provoked transcriptional alterations across the human genome. Severe pre-mRNA splicing defects were also detected, particularly after serum stimulation. We found impairment of co-transcriptional splicing during transcription elongation, which explains why the induction of long genes with a high number of introns was affected the most. We detected genome-wide prefoldin binding to transcribed genes and found that it correlated with the negative impact of prefoldin depletion on gene expression. Lack of prefoldin caused global decrease in Ser2 and Ser5 phosphorylation of the RNA polymerase II carboxy-terminal domain. It also reduced the recruitment of the CTD kinase CDK9 to transcribed genes, and the association of splicing factors PRP19 and U2AF65 to chromatin, which is known to depend on CTD phosphorylation. Altogether the reported results indicate that human prefoldin is able to act locally on the genome to modulate gene expression by influencing phosphorylation of elongating RNA polymerase II, and thereby regulating co-transcriptional splicing.