Abstract

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Title: Understanding the functional regulation of the RNA Polymerase II elongation factor, ELL

Over the last decade, studies on eukaryotic transcription have focused on the role of the Super Elongation Complex (SEC) in transcription control. The SEC is important as the expression of several of its members are found to be misregulated in terminal diseases such as mixed lineage leukemia (MLL). Hence the detailed study of SEC components becomes essential and critical. Of all the SEC components identified and described, ELL1 (also known as ELL) is the only factor capable of stimulating RNA Pol II-mediated transcription elongation *in vitro*. However, the mechanisms of regulation of ELL are completely unknown. In our studies, we report a novel interaction between ELL and the protein DBC1, which acts to regulate ELL stability and its functions within mammalian cells. Mechanistically, we show that ELL is acetylated by the lysine acetyltransferase, p300, which provides it stability and makes it functionally active. Upon deacetylation, mediated by HDAC3, ELL is targeted for polyubiquitination by the E3 ubiquitin ligase Siah1 and undergoes proteasomal degradation. DBC1 competes with HDAC3 for binding to ELL by virtue of possessing the ability to interact with the same region of ELL, thereby preventing ELL deacetylation and providing it stability. A similar mode of ELL regulation is seen in the case of EAF1/EAF2 as well, wherein, in the presence of EAF1/2, HDAC3-ELL interaction is displaced. The ELL-DBC1 axis serves to regulate the expression of SEC-affected genes, influencing genes involved in metabolism, cell cycle regulation, and immunity. Our studies show that dysregulation of these genes can lead to the development of diseases like cancer or type 2 diabetes, a phenomenon confirmed by studies in PBMCs from diabetic patients. In contrast, ELL-EAF1 functions are more prevalent in the genotoxic stress response. Our assays show that two independent factors, DBC1 and EAF1 work in tandem to maintain the protein levels of ELL for cellular response to stimuli in a context-dependent manner.

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