Novel mechanisms controlling the interplay between SUMOylation, chromatin remodeling and transcription

Ingress: A study of the functional interaction between the SUMO-protease SENP1, the chromatin remodeler CHD3 and the pioneer transcription factor c-Myb

Roza Berhanu Lemma and her colleagues reported a novel functional interaction between SUMOylation, chromatin remodeling and transcription that give insights on how different gene programs and chromatin dynamics are regulated and dysregulated with potential implications in different diseases and cancer.

The central part of our existence, the different characters we have, how we respond to changes in our environment and what kind of diseases we are prone to are all encoded in our genes, in our DNA. In order for these traits to come into existence, the gene has to go through a series of processes. The information encrypted in the DNA is transferred into an RNA molecule through transcription, which then is transferred into a protein molecule through a process of translation. In each of the above stages, the gene expression process is challenged with several types of regulatory mechanisms to ensure proper expression of that gene. A DNA molecule in a cell, if stretched can reach 2 m long. In order to fit such a long molecule into the microscopic space of a cell's nucleus, it should be coiled, wrapped and condensed into chromatin. This is achieved by wrapping the DNA around nucleosomes, which are made up of histone proteins followed by several levels of compaction. The process of gene regulation involves a combinatorial and coordinated action of several proteins that are found in the nucleus (nuclear proteins) and that have roles in gene regulation and chromatin dynamics.

These work combines studying regulation of gene expression at the transcriptional level with regulators known as transcription factors (TFs), at the post translational level with a specific type of protein modification and at the chromatin level with chromatin remodelers and pioneer TFs as players. SUMOylation is a post translational modification by proteins named SUMOs (small ubiquitin-like modifiers) that become attached to other proteins to control their properties. The main outcome of SUMOylation of nuclear proteins is transcriptional repression. SUMOylation is a reversible process, where proteins (enzymes) called SENPs remove SUMO from the modified proteins. Using different lines of research, Lemma and her colleagues investigated the role of SENP1 in gene activation by targeting it with some of its novel interaction partners. Using a variety of biochemical and genome-wide methods Lemma and colleagues showed that SENP1 and one of its novel interaction partner, a chromatin remodeler named CHD3 physically interact and functionally operate together to affect the accessibility of shared loci (genomic locations). They also affect the expression of significant number of shared genes. Another novel interaction partner of SENP1 named UXT was similarly shown to physically interact with SENP1 and functionally inhibit its activity. In this study the TF c-Myb, which itself is modified by SUMO was used to investigate the interplay between transcriptional activation and repression. In addition, Lemma and colleagues reported that c-Myb has a novel role in chromatin dynamics, where it acts as a pioneer factor by accessing closed (nucleosome occluded) chromatin and causing chromatin opening.

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