PRINCIPE FELIPE
CENTRO DE INVESTIGACION

Doctoral Thesis

Study of the SAGA deubiquitination module: Identification of new modulators and its implication on Spinocerebellar Ataxia Type 7

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Abstract: Regulation of chromatin by epigenetic modifications is a fundamental step during the control of gene expression in eukaryotic cells. The participation of different factors including histone chaperones, chromatin remodeling complexes and histone-modifying complexes regulate chromatin dynamics and ensure the correct metabolism of transcripts that need to be exported to the cytoplasm. In these lines, post-translational modifications including monoubiquitination of histone H2B ($H2Bub^1$) and methylation of histone H3 represent a well-studied histone cross-talk which is required for chromatin integrity and transcription. Additionally, the transition from $H2Bub^1$ to its deubiquitinated form by Ubp8, the DUB enzyme from SAGA (Spt-Ada-Gcn5-acetyltranferase) co-activator complex, is fundamental to obtain a correct gene expression. In this work, we demonstrate that the histone chaperone Asf1 and the Ran-binding protein Mog1, participate in maintaining correct levels of $H2Bub^1$. We show that Mog1 is required for the trimethylation of histone H3 at lysine 4 ($H3K4me^3$), hence, acting as a modulator of histone cross-talk. Mog1 role into gene expression is also demonstrated by its physical and genetically interaction with transcription factors including SAGA and COMPASS complexes. Indeed, we demonstrate that Mog1 interacts genetically with TREX-2 subunits and affects mRNA export. During this work, we have also focused in understanding the molecular mechanisms surrounding Spinocerebellar Ataxia Type 7 (SCA7) which is a rare disease caused by amino acid glutamine (Q) repeats within the DUBm component, ATXN7. Therefore, our interest has been directed towards the study of new mechanisms that trigger SCA7 such as the DUB activity from SAGA complex, protein-protein interaction networks and metabolic profiles.

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