H3K27 acetylation as a key regulator of onco-lncRNA expression in lung cancer

C. Ayala-Roldán[1,2,3]*, L. Gisella Bermúdez Liscano[1,4], J. Romero Simmonds[4], R. R. Ariza[1,2,3], T. Roldán-Arjona[1,2,3], T. Morales-Ruiz[1,2,3], & A. P. Rojas Moreno[1,2,3]

[1] Department of Genetics. University of Cordoba, Córdoba, Spain.
[2] Maimonides Biomedical Research Institute of Cordoba (IMIBIC), Córdoba, Spain
[3] Reina Sofia University Hospital, Córdoba, Spain
[4] Institute of Human Genetics, School of Medicine, Pontificia Universidad Javeriana, Bogotá, Colombia
* b82ayroc@uco.es

Background: Lung cancer is the leading cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for approximately 85% of cases. Beyond genetic alterations, epigenetic mechanisms play a central role in tumor progression by modulating gene expression programs. Long non-coding RNAs (lncRNAs), which are transcripts longer than 200 nucleotides that do not encode proteins, are emerging as key regulators of cancer-associated cellular processes, acting as either oncogenes or tumor suppressors. However, the epigenetic mechanisms that govern their transcription process remain poorly understood.

Aim: To investigate whether histone H3 lysine 27 acetylation (H3K27ac), a chromatin mark associated with transcriptional activation, regulates the expression of a deregulated onco-lncRNA identified in lung cancer models.

Methods: H3K27ac enrichment at putative regulatory regions of the lncRNA locus was first assessed. To determine the functional relevance of this modification, targeted acetylation was induced using a CRISPR/deactivated Cas9 (dCas9)-p300 epigenome editing system in HEK293 cells, which lack endogenous expression of the lncRNA. Guide RNAs were designed to direct the dCas9-p300 complex to specific regulatory regions. Following transfection, lncRNA expression levels were quantified by reverse transcription quantitative polymerase chain reaction (RT-qPCR). A catalytically inactive p300 construct was used as a control.

Results: Regulatory regions of the lncRNA locus displayed enrichment of H3K27ac. Targeted acetylation of individual regulatory regions significantly increased lncRNA expression compared with control conditions.

Conclusions: These findings demonstrate that H3K27 acetylation directly regulates the transcriptional activation of this lncRNA and highlight the utility of epigenome editing tools to dissect the regulatory mechanisms governing lncRNA expression in lung cancer.