# Mechanistic dissection of long non-coding RNA chromatin association in mammalian cells

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## ABSTRACT

Long non-coding RNAs (lncRNAs) are a large group of non-coding RNAs, involved in important processes, such as genome organization, chromatin remodeling and gene expression regulation. lncRNAs can function in cis, while attached to their transcription site or near to it, or by interacting with other molecules such as RNA-binding proteins. In either case, lncRNAs are responsible for regulating the expression of target genes through various mechanisms. It has been observed that some lncRNAs transcribed from enhancer-like regions, are functioning in cis, to regulate target gene expression[1]. However, cases like that of the lncRNA A-ROD, which is enhancer-associated, function in cis, but the functionality comes from the chromatin-dissociated form, suggesting that chromatin dissociation is a crucial step in determining the function of those lncRNAs, and thus the regulation of target gene expression. Recent computational analysis aiming at modeling chromatin (dis-) association of nascent RNA transcripts, combined with machine learning, led to the identification of potential functional features that define chromatin release of enhancer-transcribed lncRNAs, in comparison to mRNAs[2]. During my PhD studies, I aim to experimentally validate those features derived as significant from the modeling, and then characterize their impact on cognate enhancer activity and target gene expression. Specifically, I will try to gain mechanistic insights into the role of co-transcriptional splicing and its potential effects on chromatin dissociation of lncRNAs, by modulating splicing of poorly spliced, chromatin retained lncRNAs. Also, I will try to identify RNA-binding protein interactions that affect lncRNA's release or retaining, focusing on factors that were derived as significant from machine learning, such as NONO, CSTF2T, XRN2 and KHSRP. Understanding how chromatin (dis-) association of developmentally regulated or cell type-specific lncRNAs is shaping cognate enhancer activity and target gene expression holds promise for the development of effective RNA-based therapeutic strategies in several disease-associated conditions, such as cancer.

### REFERENCES

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