Three-dimensional genome organization during TGFB-induced transcription requires nuclear microRNA and G-quadruplexes

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Résumé

Studying the dynamics of three-dimensional (3D) chromatin structure is essential to understand biological processes in the cell nucleus. Recent publications based on integrative analysis of multi-omics studies have provided comprehensive and multilevel insights into 3D genome organization emphasizing its role during transcriptional regulation. While enhancers are regulatory elements that play a central role in the spatiotemporal control of gene expression, chromatin looping has been broadly accepted as a means for enhancer-promoter interactions allowing them to stablish cell-type-specific gene expression signatures. On the other hand, G-quadruplexes (G4s) are non-canonical DNA secondary structures that are both, enriched at promoters and related to increased gene expression. However, the role of G4s in promoter-distal regulatory elements, such as super-enhancers (SE), as well as in 3D genome organization and chromatin looping mediating long-range enhancer-promoter interactions has remained elusive. Here we show that mature microRNA 9 (*miR-9*) is enriched at promoters and SE of genes that are inducible by tissue growth factor beta 1 (TGFB1) signaling. Further, we found that nuclear *miR-9* is required for chromatin features related to increased transcriptional activity, such as broad domains of the euchromatin histone mark H3K4me3 (histone 3 tri-methylated lysine 4) and G4s. Moreover, we show that nuclear *miR-9* is required for promoter-super-enhancer looping. Our study places a nuclear microRNA in the same structural and functional context with G4s and promoter-enhancer interactions during 3D genome organization and transcriptional activation induced by TGFB1 signaling, a critical regulator of proliferation programs in cancer and fibrosis.
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