Molecular Therapy
Nucleic Acids
Commentary

The regulator of regulators: Understanding the mechanisms behind long noncoding RNA dysregulation

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Long noncoding RNAs (lncRNAs) have been widely recognized for their important roles of gene expression regulation in various biological processes.[1] However, understanding toward their own regulatory mechanisms has remained very limited for some time now. Yin et al. might provide some clue to this question. They report in this issue that the impact of transcription factors (TFs) on lncRNA expression can be modulated by DNA methylation (DNAm) at promoters by conducting a multi-omics integration analysis in the pan-cancer context.[2] The authors reverse engineered the DNAm-mediated TF-lncRNA regulatory circuit and characterized its regulatory patterns and functions in each cancer type from TCGA. By recapitulating the epigenetic scheme involved in transcriptional regulation, this work provides a novel perspective on how DNAm affects the expression of lncRNAs and suggests a framework for dissecting the driving force of lncRNA expression dysregulation related to tumorigenesis and cancer development.

DNAm imbalance has been shown to play critical roles in the occurrence and development of cancer by defining different types of driver events. Alteration of the methylation status at promoter CpG site could influence the transcript abundance of many cancer-related genes by regulating chromatin accessibility and blocking recruitment of upstream TFs.[3] Transcriptional regulatory networks, which are defined as interactions among TFs and their targets, provide detailed maps of gene expression regulations in specific contexts. Previous studies have mainly focused on exploring the detailed machineries of specific genes being regulated by CpG methylation-sensitive TFs in various contexts, whereas the regulatory effects on noncoding RNAs, which constitute a significant part of the cell transcriptome, are rarely reported. LncRNAs bear an uncanny resemblance to protein-coding genes for many characteristics except that they lack the open reading frame and most are transcribed by RNA polymerase II, regulated by upstream TFs, and exhibit tissue- or cell-specific expression patterns; thus, it is not surprising that they may share similar epigenetic regulatory mechanisms with protein-coding genes (Figure 1). This has been confirmed by wide observation of the lncRNA promoter methylation alterations in human diseases. This genome-wide coupling analysis of promoter methylation with the TF regulatory network confirmed that many cancer-related lncRNA dysregulations can be largely attributed to those epigenetically modulated regulatory circuits, which should have substantial value for understanding the intricate expression of regulation machinery in cancers.

By comparison of the global characteristics of methylation-mediated TF regulations on lncRNA and mRNAs, respectively, the authors indicated that there are high similarities between these two different regulatory networks. Generally speaking, the number of mRNAs being regulated by methylation-mediated TFs is about an order of magnitude more than that of lncRNAs in different cancers, whereas a high positive correlation between them can be observed. As for TFs, the number of target mRNAs and lncRNAs also exhibit a strong positive correlation, although some exceptions can be found. Many co-regulated targets of TF regulators are found to share methylation-related motifs, which suggests that these regulatory relations are widespread and conserved. Due to the differences of the regulatory networks among different cancer types, those methylation-mediated TFs and lncRNA targets were further classified as "pan-cancer" or "cancer-specific" according to the number of the cancer types they involved in. As expected, those "pan-cancer" methylation-mediated TFs and lncRNA targets that were conserved in multiple cancers tended to be involved in many core functions related to carcinogenesis, such as cancer hallmarks and signaling pathways.

One of the key findings for those methylation-mediated TF regulations is that they are widely involved in cancer immunity, particularly for those pan-cancer TFs and lncRNAs. Many of them are found to have a strong correlation with infiltrate levels of immune cells, including M1/M2 macrophages and CD4+ and CD8+ T cells, as well as some immune hallmarks, such as major histocompatibility complex (MHC) and cytolytic activity (CYT) level, which have been widely associated with tumor immune response. Moreover, by using unsupervised clustering on the intersection to the significantly correlated immune cells, the authors identified regulatory modules that are correlated with immune therapy response and further applied for cancer subtyping and patient prognosis. This demonstrates the potential value of this tool for clinical applications.

In current cancer omics studies, lncRNAs have always emerged as regulators of other

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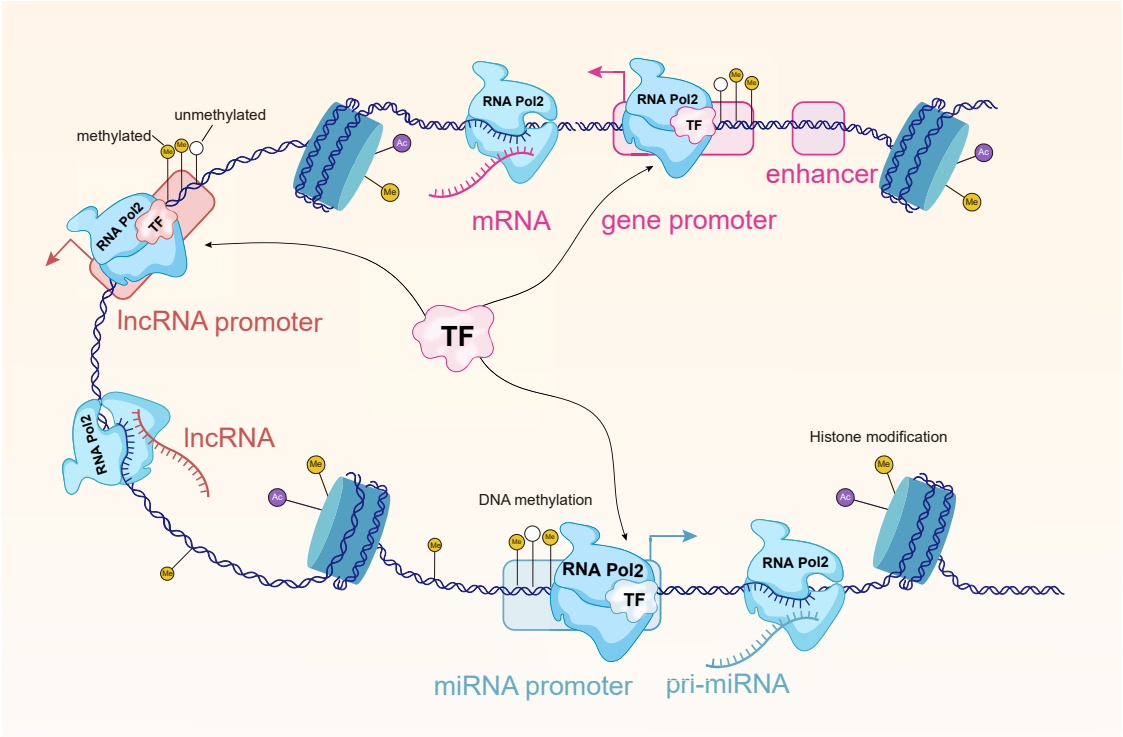

Figure 1. Schematic diagram for the methylation-mediated TF regulations

Yin et al. reveal that lncRNAs are regulated by the coupled interaction of promoter methylation and TF binding. Combining their data with previous work, different regulations of complexity become apparent: methylation-mediated TF regulation may widely involve expression regulation of different RNA species, including mRNA, lncRNA, and miRNA. By integrating other epigenetic mechanisms such as histone modification, we may obtain a more comprehensive and detailed landscape to depict the mechanism behind transcriptional regulation.

mechanisms, including DNAm and TF binding. As for the transcription products, however, we should bear in mind that lncRNAs are also tightly regulated by other upstream elements. Therefore, investigation into the mechanisms involved in their expression regulation could be the fundamental way for us to get a deeper insight into the intrinsic driving forces of tumorigenesis and may also provide more effective targets for cancer prognosis and treatment. Yin et al. provide a good example for further exploring toward this end. At the same time, we should also keep in mind that expression regulation is a complex process at multiple steps and layers. Only focusing on the proximal regulatory elements may not be sufficient for us to fully understand the landscape of lncRNA expression regulation. Distal machineries such as the enhancer CpGs or other regulatory regions should not be excluded from further integrative analysis. Furthermore, integration with other epigenetic machineries such as histone modification and chromatin remodeling, which have been widely involved in gene expression regulation, also provide opportunities for a deeper understanding of lncRNA expression regulation and to construct more precise expression prediction models.[4]

Furthermore, regulations to other types of noncoding RNAs and their associated functions should not be neglected, such as circular RNAs and small RNAs including microRNA (miRNA). The transcriptional regulation of miRNA has always been the focus due to its similarity to that of protein-coding genes. However, for the vague annotation of the promoter region of miRNA genes, studies on their expression regulation have been difficult for a long time. This barrier is being removed with the increasing availability of computational tools and high-throughput data for accurate identification of miRNA promoter regions.[5] With the development of similar studies, we can expect to get a better understanding of the biogenesis and regulation of different transcriptional products (Figure 1). Combined with computational models based on their downstream functional mechanisms, such as RNA-protein interaction, RNA-chromatin interaction, or interaction with other RNAs, we will also be able to characterize their action mechanisms more accurately and comprehensively in different biological processes and lay the foundation to further study their roles in different diseases.

DECLARATION OF INTERESTS

The author declares no competing interests.

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