Molecular Therapy
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Commentary

Landscape and perturbation of enhancer-driven core transcription regulatory circuits in cancer

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Enhancers are emerging as critical regulatory regions in regulating gene expression across diverse tissues and cell types. Perturbation of enhancer-driven transcriptional regulatory circuits has been observed in cancer and other human complex diseases. Systematic analyses of the landscape of core enhancer- or super-enhancer-driven regulatory circuits (CRCs) will provide novel insights into the regulation of gene expression. In this study, Feng et al. have identified the CRCs in large cell/tissue samples.[1] The authors analyzed the sequence conservation, CRC activity, and genome binding affinity for common transcription factors (TFs), moderate TFs, and specific TFs, which exhibited distinct biological features. Moreover, network analysis highlighted the potential as prognostic biomarkers of the CRC module in cancer. A user-friendly resource named CRCdb (http://www.licpathway.net/crcdb/index.html) was developed for aiding analysis of CRCs.

The transcriptional activity of a gene is usually regulated by the crosstalk among enhancers and various *cis*-regulatory elements bound by TFs and RNA binding proteins. Recent developments of high-throughput sequencing technologies have generated valuable multiple-omics data resources (Figure 1A), which accelerated the studies of CRCs in diverse tissues and complex diseases contexts. TRANSFAC is widely used for identification of TF-gene binding and ChIP-Base has been developed with >10,000 curated ChIP-seq datasets. In addition, enhancers and super-enhancers are usually identified based on the H3K27ac and H3K4me1 signals. The Encyclopedia of DNA Elements Project and Roadmap Epigenomics Project provide rich histone modification datasets across diverse tissues and cell types. Moreover, the development of biological methods (e.g., Hi-C, 3C, and ChIA-PET) to investigate the 3D chromatin organization is pivotal for understanding the enhancer-gene interactions.[2] However, these experimental data are generally considered to be tissue- or cell-type specific. Increasing omics data allows genome-wide identification of the CRCs constituted by enhancers, TFs, and genes, which would be a valuable resource in biomedical research.

The increases of high-throughput sequencing data have provided foundational resources for modeling the CRCs across diverse tissues and complex diseases. Experimental determination of the CRCs is time-consuming and laborious. Thus, numerous computational methods have attempted to map the CRCs by efforts to integrate global information regarding these resources (Figure 1A). CRC mapper was developed to construct the core regulatory circuitry models across human cell types.[3] The python package Coltron (https://pypi.python.org/pypi/coltron) has also been developed to identify CRCs by integrating H3K27ac ChIP-seq and ATAC-seq data. FIMO is widely used for scanning TF motifs in gene sequences. Moreover, SCENIC is a recently developed computational method for simultaneous gene regulatory network reconstruction and cell-state identification from single-cell RNA-seq data.[4] These computational methods for constructing core circuitry models should prove valuable tools for further investigating CRCs in healthy and diseased contexts. In this study, Feng et al. identified the CRCs and core TFs by integrating the results of CRC mapper and Coltron,[1] generating a comprehensive landscape of CRCs driven by super-enhancers across diverse tissues and cell types. However, the landscape of CRCs across diverse cancer types is still largely unknown.

The CRCs are under intricate regulation in physiological conditions but could go awry upon genome instability caused by genetic and epigenetic alterations. A detailed understanding of the molecular mechanisms of CRC perturbations in cancer still remains an important question. In the past decade, thousands of genomic mutations have been identified by high-throughput sequencing technologies in a variety of cancer patients. A large number of genomic mutations and structural alterations were observed in enhancers, TFs, and target genes (Figure 1B). Moreover, copy number variations may impact the activities of a variety of oncogenic or tumor-suppressive pathways by perturbing the CRCs in cancer. For example, Xiao et al. have performed an integrative analysis of the enhancer-centered regulatory circuit perturbations in gliomas and revealed the potential CRC biomarkers.[5] DNA methylation is the most widely studied epigenetic regulation (Figure 1B), which could also drive the tissue-specific enhancer basal transcription and target gene expression in human cancers.[6]

Gene expressions are regulated by the complex model of CRCs, represented as "nodes" and "edges" in the regulatory network model, respectively. Genetic and epigenetic alterations not only perturbed the nodes but also exhibited edge-specific alterations (edgetic). The edgetic alterations of CRCs might improve our understanding of gene expression regulation in cancer. The gene

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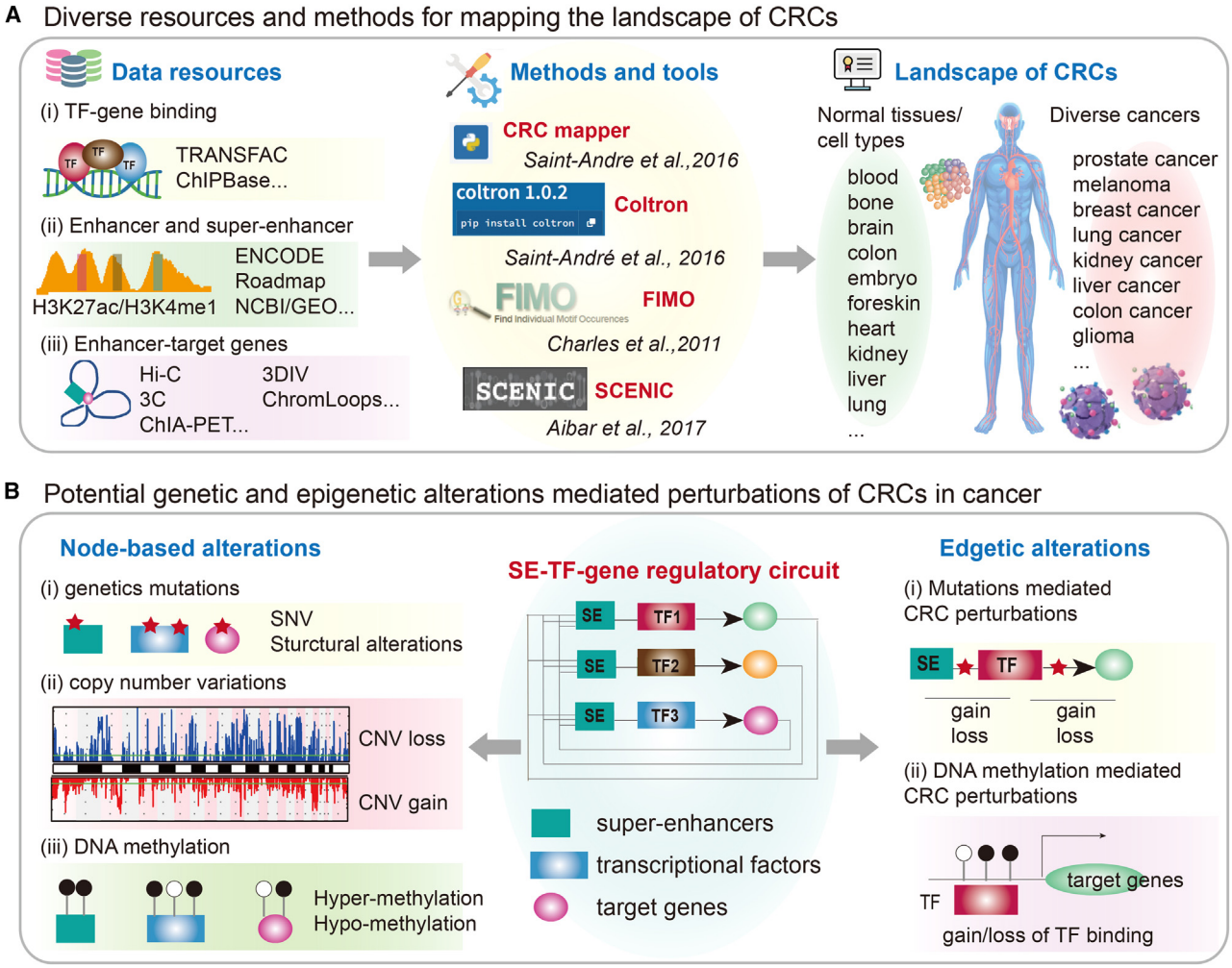

Figure 1. Enhancer-TF-gene regulatory circuits in cancer

(A) Data and methods for constructing the landscape of CRCs across diverse tissue/cell types and cancers. (B) Potential genetic and epigenetic alteration-mediated perturbations of CRCs in cancer. Left panel shows the node removal effects of CRCs, and the right panel shows the edgetic effects of CRCs in cancer.

regulatory network has been observed to be perturbed by genetic and epigenetic variations,[7,8] such as genomic mutations and DNA methylation. Genomic mutations and DNA methylation can regulate gene expression by gain or loss of the binding of transcription factor(s) to DNA (Figure 1B). Such efforts have already been initiated in cancer for understanding the edgetic perturbations of CRCs. The global landscape of DNA methylation-mediated transcriptional dysregulation across 22 human cancer types has been portrayed recently,[9] and a network module that consisted of methylation-sensitive TFs with prognostic potential was identified. Moreover, regulatory network and pathway perturbations analyses help prioritizing cancer driver mutations and genes.[10] Feng et al. also identified the core TFs in tissue-specific CRC networks as potential biomarkers, which have regulatory potential for cancer immunotherapy.[1] Functional characterization of the node and edgetic effects of genetic and epigenetic variants on CRCs will undoubtedly facilitate our understanding of the molecular mechanism of cancer, which will help identifying biomarkers for clinical diagnosis and therapy.

In conclusion, the findings of Feng et al. provided a valuable resource for investigating the CRCs across diverse tissues and cell types. Comprehensive analysis of the enhancer-TF-gene regulatory circuits across diverse tissue/cell types and cancers may thus help better understanding of cancer-associated genetic and epigenetic alterations, leading to potential CRC-directed therapeutic interventions in cancer.

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DECLARATION OF INTERESTS

The authors declare no financial interest.

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