TENET+: a tool for reconstructing gene networks by integrating single cell expression and chromatin accessibility data

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Abstract

Gene expression is regulated by multiple epigenetic factors including chromatin structure. Single cell chromatin accessibility data combined with transcription factor (TF) binding motif information enhances our understanding of gene expression regulation. However, enhancer-driven gene regulation remains limited due to the lack of promoter-enhancer interaction data. Here, we developed TENET+, a tool for reconstructing enhancer-driven gene regulatory networks (eGRN) by integrating single cell transcriptome and chromatin accessibility data. By leveraging causal relationship inference based on pseudo-time-ordered gene expression and chromatin accessibility, TENET+ predicts interaction between TF expression, target gene expression, and open chromatin regions including long-range enhancer. Applying TENET+ to a paired scRNAseq and scATACseq dataset of human peripheral blood mononuclear cells, we identified critical regulators and their epigenetic regulations. Interestingly, TENET+ exhibited a superior performance to predict promoter-enhancer interactions provided by cell type-specific Hi-C datasets compared with other motif-based GRN reconstruction tools. Notably, TENET+ demonstrates competitive performance in ChIP-seq validation compared to other tools, even without relying on motif information We identified key regulatory factors in CD4 T cell, and subsequent siRNA knockdown experiments confirmed that their target genes were indeed regulated by these identified factors. Overall, TENET+ provides a robust framework for reconstructing eGRN with a single-cell resolution.