Towards cell-type-specific gene regulation in heterogeneous cancer cells

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Introduction

Background and significance:
- The heterogenous gene regulatory mechanisms determine the cell types in disease inducing the diverse drug responsiveness;
- A cell-type-specific regulon (**CTSR**) is defined as a group of genes that are co-regulated by the same transcription regulator (**TR**) and specifically expressed in a cell type;
- CTSRs can provide an effective way to characterize the heterogenous gene regulatory mechanisms in the same or across different cell types;
- scRNA-Seq technologies and data provide an unprecedented opportunity to predict CTSRs.

Challenges:
- The identification of CTSRs is not intuitive;
- Existing tools require programming experience, and no web-server has been developed to directly generate CTSRs.

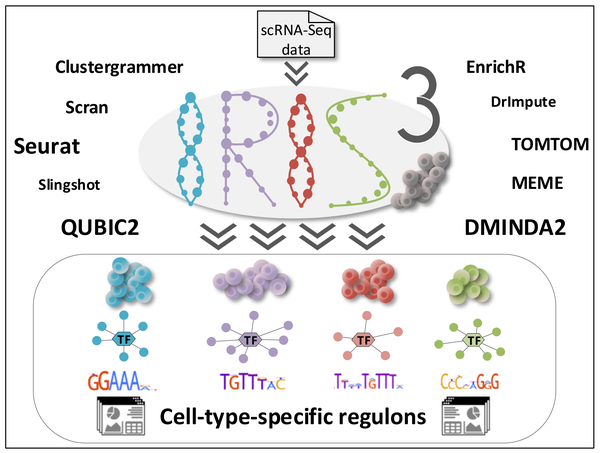

Figure 1. The depiction of IRIS3.

We developed the first-of-its-kind computational web server for CTSR inference from human and mouse, named **IRIS3** (Integrated Cell-type-specific Regulon Inference Server from Single-cell RNA-Seq).

Highlights and impacts:
- Provides informative CTSR interpretations with interactive visualizations;
- No coding background knowledge is required;
- Hold great promise for improving the immune therapy in pinpointing the specific regulatory signatures responsible for diseased cell types, and further determine cell-type-specific drug responses for personalized medicines.

The IRIS3 Workflow

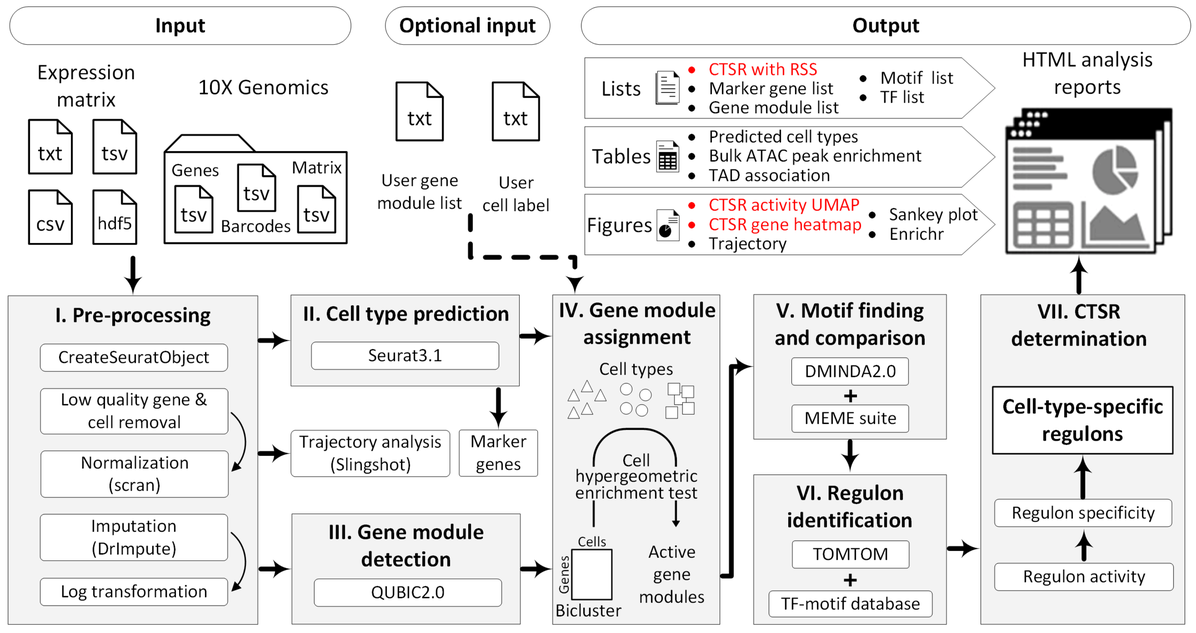

Figure 2. The workflow of IRIS3. IRIS3 uses scRNA-Seq expression files and seven steps to predict CTSRs. A comprehensive and informative HTML analysis report is generated to report the results of IRIS3.

Preliminary results

- Tested 35 scRNA-Seq datasets including 11 10X Genomics data;
- Regulon specificity score (**RSS**): formulates regulon activity entropy within and out of the selected cell type;
- IRIS3 identified CTSRs controlled by signature TFs (e.g. SP1 and EGR3) in effector CD8 T cells;
- SP1 and EGR3 CTSRs may be involved in regulating cell proliferation, effector function, and maintaining the chromatin accessibility CD8 T cells.

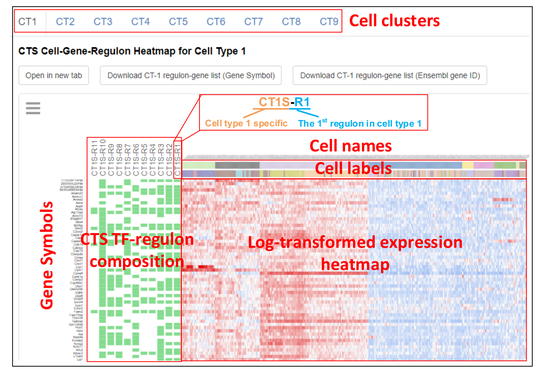

Figure 3. An example of CTSR results demonstration using Clustergrammer heatmap in IRIS3.

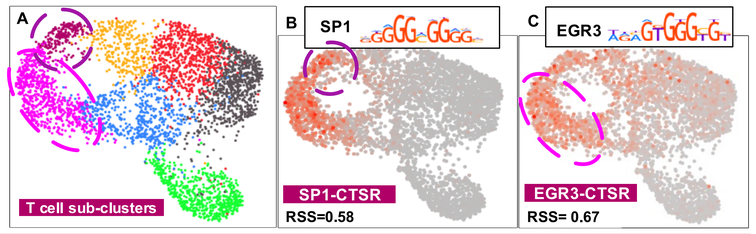

Figure 4. IRIS3 result on a 10X scRNA-Seq dataset consisting 4,958 effector CD8 T cells. (A) Seven sub-clusters were predicted in effector T cell populations. (B) and (C) CTSR activities of SP1 and EGR3 TF controlled CTSRs, respectively.

Discussion

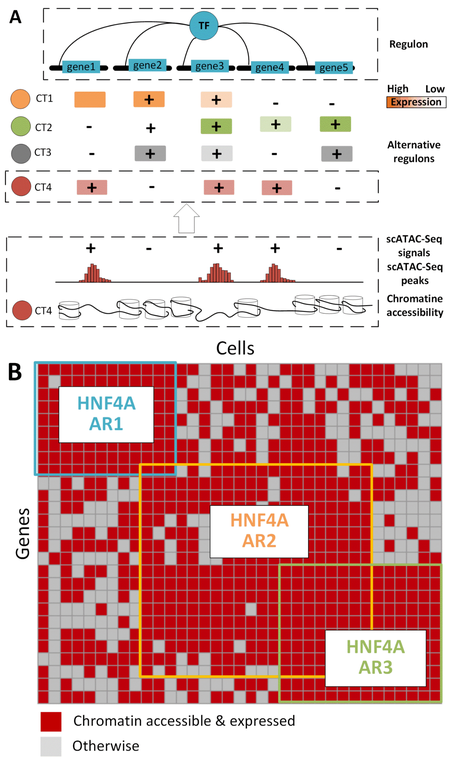

Figure 5. (A) The alternative regulon pattern. (B) The alternative regulon pattern identified in matched mouse kidney scRNA-Seq and scATAC-Seq data (1,414 cells). HNF4A TF: related to kidney development and diabetes.

- IRIS3 can provide comprehensive and meaningful CTSR predictions;
- CTSRs can reveal the heterogeneity in immune cells and enable the discovery of key regulators for immune therapy;
- Dynamic transformations of a CTSR in different cell types, in terms of gene co-expression and chromatin accessibility patterns, were named as Alternative Regulons (**ARs**);
- ARs can elucidate dynamic global GRNs coding in specific cell types and construct heterogeneous regulatory landscape in complex disease.

Links

- **IRIS3**: https://bmbl.bmi.osumc.edu/iris3/
- **BMBL**: https://u.osu.edu/bmbl/

Reference

Anjun Ma, et al., (2020), IRIS3: Integrated Cell-type-specific Regulon Inference Server from Single-cell RNA-Seq. *Nucleic Acids Research*. In press.

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