Reconstruction of Cell Type-Specific Genome-Scale Metabolic Models using Single-cell RNA-Seq Data to Investigate Tumor Metabolism

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Cancer is a global health problem with high mortality and increasing prevalence. Mathematical modeling strategies have a great impact on the pharmaceutical industry through their cost and time-saving effects in drug discovery and development processes. Genome-scale metabolic models (GEMs) have been used to investigate complex disease mechanisms by integrating them with omics data [1].

Cancer has complex and dynamic biology including interactions between tumor cells and microenvironments. Each cell type has a different driver role in the clinical progression of cancer. Cell-specific computational strategies are crucial in exploring complex interactions in cancer mechanisms [2]. Through the single-cell RNA (scRNA) sequencing technologies, gene expression values of each cell that are taken from the same microenvironment can be measured. In this study, we used lung and liver cancer scRNA transcriptome datasets [3,4], which are publicly available in Gene Expression Omnibus (GEO) [5], to reconstruct cell type-specific genome-scale metabolic models for tumor and control tissues.

Normalization and annotation of scRNA data were carried out in Seurat package in R [6]. iMAT (Integrative Metabolic Analysis Tool), an algorithm that can reconstruct context-specific GEMs based on the expression level of genes, was used to reconstruct cell type-specific GEMs [7]. Human-GEM version 1.11.0 model, consisting of 13,069 reactions, 3067 genes, and 8366 metabolites were used as a template model [8]. Basically, transcriptome data of each cell type was mapped to Human-GEM by iMAT to identify the reactions that are active in each cell type. After reconstruction of models, flux balance analysis (FBA) [9] was applied for each cell type specific model to predict their metabolic flux rates. Each cell type was found to have distinct metabolic rates in terms of growth rate and lactate production rate, and some cell types were observed to have differences in their metabolic pathway activities between control and tumor conditions.

Keywords: Cancer, Tumor, Genome-scale Metabolic Model, Single-cell, Transcriptome

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