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A Computational Pipeline to Profile the Metabolic Landscape of the Tumor Microenvironment

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Tumors are heterogeneous cellular environments with entwined metabolic alterations to support continual growth and evade immune destruction. The importance and ubiquity of the deregulated metabolic pathways and properties in the tumor microenvironment (TME) is gaining considerable attention from the scientific community, especially those interested in designing new drug targets and cancer therapies. Despite large scale studies of single cell transcriptomics data to profile reaction networks and metabolite concentrations in the TME, there is a noticeable lack of systematic analytical workflows available to profile paired multi-omics datasets and identify interactions that may approximate the metabolic rewiring patterns. To address this, we propose a data-driven computational pipeline to identify the complex interactions of metabolic pathways within the TME using multi-omics data.

Previous studies on standalone single-cell transcriptomics analyses are insufficient for profiling metabolic pathways[1], due to limitations in the assumptions of metabolite concentrations and a lack of sensitivity for detecting metabolic changes in heterogenous tissues. We will utilize multiple metabolic modeling approaches at varying levels of complexity such as: pathway level-, constraint-based-, kinetic model-, knowledge-primed neural network-, and graph-based analyses. These approaches will provide a wide range of insights into the modeled metabolic layers, scales and cellular resolutions which are then suitable for various model systems. Moreover, we believe that a combination of these approaches will enable efficient modeling at the multi-omics level, which will be applied to multiple case studies using data from public atlases. The entire workflow will be wrapped within a Nextflow framework, with all software dependencies made available as Singularity containers for exact reproducibility, and the pipeline will be published publicly on GitHub.

Taken together, the automated Nextflow-based pipeline will be scalable and portable and will function as a resource for researchers to characterize metabolic reprogramming, and the distinct metabolic signatures that shape the TME.

[1] Hrovatin K, Fischer DS, Theis FJ, Toward modeling metabolic state from single-cell transcriptomics, Molecular Metabolism, Volume 57, 2022, 101396, ISSN 2212-8778, https://doi.org/10.1016/j.molmet.2021.101396