Multi-omics data analysis to characterize metabolic shifts during embryo development

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Abstract:
Recent findings suggest that cell metabolism may be key to understanding miscarriages and developmental abnormalities in early embryonic development [1-6]. To explore metabolic differences between pre- and post-implantation embryonic cells, we analyzed single-cell RNA-seq data from various 3D culture models, integrating data from two studies: one using Inner Cell Mass Cells [7] and another using human Embryonic or induced Stem Cells [8]. Using metabolic network reconstructions, constraint-based methods [9], and machine learning techniques [10], we estimated metabolic fluxes and assessed shifts in cellular metabolic activity. Metabolic fluxes are calculated using COBRA-based models. Transcriptomic data are preprocessed and denoised using the MAGIC imputation algorithm. The processed data are used to calculate Reaction Activity Scores, which, along with Flux Variability Analysis results, define the metabolic model constraints. Metabolomics data constrain exchange reactions before flux calculation. The model is sampled using the Constrained-Based Sampling technique with randomly defined objective functions. The fluxes are averaged to generate a flux distribution representing the metabolic activity of each cell. Preliminary findings revealed significant variations in biomass production and glucose consumption between stages. However, inconsistencies across experiments indicate the need for further investigations. Similar analyses can now be performed on any dataset using COBRAxy, a Galaxy-based tool that extends the Marea platform [11]. COBRAxy enables users to analyze cellular metabolism using transcriptomic and metabolomic data, comparing gene expression and metabolite differences through the Reaction Activity Score and Reaction Propensity Score, visualized on a metabolic map. It also allows users to calculate metabolic fluxes and compare these across different cell groups, offering insights into metabolic changes during development. In the next future, we aim to develop dynamic metabolic maps that represent stage-and sex-specific metabolic changes during human embryonic development, by integrating multi-omics data, including transcriptomics, proteomics, and exo-metabolomics. Beyond flux sampling, we will explore alternative approaches, such as geometric neural networks. This integrative approach could provide valuable insights into the metabolic landscape of early development, enhancing our understanding of growth anomalies and embryonic viability.

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