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MOLECULAR AND CELL BIOLOGY

Deep learning resolves cell-type specific transcriptomes and unveils synaptic changes associated with neurodegeneration

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Abstract

Background: Single nucleus RNA sequencing (snRNA-seq) has revolutionized our ability to dissect transcriptional profiles in specific cell types. While nuclear sequencing enhances analysis robustness, it captures only 20-50% of the cellular transcriptional information, limiting our comprehensive understanding of the cellular transcriptional ensemble. Therefore, we propose a computational approach to extract the cellular signal from bulk transcriptomic data from brain tissue, allowing us to investigate cell type-specific transcriptomic programs underlying neurodegeneration.

Method: We adapted Cellformer - a deep learning deconvolution model for ATAC-seq data - to RNA-seq data. We leverage an excitotoxicity mouse model to detect cell-type specific transcriptomic responses to injury.

Result: Cellformer accurately deconvoluted mouse brain bulk RNA into 9 major cell types (mean Pearson correlation of 0.97) (**Figure 1A**). Validation with single nucleus datasets reveals a significantly higher correlation (0.85) within the same cell type compared to different cell types (0.20) (P-value < 1e-6) (**Figure 1B**).

We applied Cellformer to bulk RNAseq data obtained from both tissue and nuclei isolated from the hippocampus of the same mouse. We compared these cell-type-specific transcriptomic signatures between healthy mice and those exposed to a low dose of Kainic Acid (KA), a potent toxin for excitatory neurons (**Figure 1C**). More shared information was found between snRNA and deconvoluted RNA from nuclei compared to deconvoluted tissue (**Figure 1D**). Interestingly, differential expression analysis revealed a greater effect of low-dose KA exposure on deconvoluted bulk tissue compared to nuclei, pinpointing synaptic and lysosomal signaling to excitatory neuronal cells (**Figure 1E-F**).

Conclusion: In this study, we introduce a computational approach utilizing the Cellformer algorithm to deconvolute bulk RNA sequencing data into cell-type-specific profiles, enabling in-depth analysis of bulk RNAseq datasets. We demonstrate

Cellformer's proficiency in recovering cell-type-specific RNA expression patterns. By comparing deconvoluted profiles between healthy and injured hippocampi, we unveil insights previously masked by the limitations of snRNA-seq, revealing intricate synaptic signaling dynamics. Cellformer offers the unprecedented ability to investigate extranuclear signaling in neurodegeneration.