[BIOINFO 2023]

Revealing cell type-specific transcriptional signatures of hippocampal circuit in fear memory network

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Contextual fear conditioning (CFC) is a leading behavioral paradigm used for studying the neurobiological basis of fear learning and memory. The neural circuitry encompassing the hippocampal subregions dentate gyrus (DG), CA3, and CA1 are referred to as the 'trisynaptic circuit', which represents a major component of fear memory network. However, there is limited research that simultaneously investigates such gene expression across all subregions. In this study, we utilize a comprehensive single-cell dataset to provide novel insights into the transcriptomic and gene regulatory landscape of fear memory in the hippocampus at a single-cell resolution. We constructed our dataset by integrating publicly available single-cell RNA sequencing data from the hippocampus of mice that underwent CFC. Differentially expressed gene (DEG) analysis showed the largest transcriptional response to CFC in cells within the trisynaptic circuit compared to other cell types. DEGs of CA1, CA3, and DG showed both common and cell type-specific enriched pathways. Weighted gene co-expression network analysis showed that co-expressed modules in the trisynaptic circuit cell types were significantly regulated by CFC. A strong correlation among synapse-associated modules in the three cell types suggests a fear memory-related gene network that encompasses the hippocampal circuit. We performed gene regulatory network analysis to highlight cell type-specific transcription factors enriched by CFC, focusing on target genes that also show CFC-induced differential expressions. Through this research, we provide a greater understanding of the molecular mechanisms underlying fear memory within the hippocampal circuit.