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Complex brain circuitry revealed using new single-cell sequencing technology

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The complexity of the human brain presents scientists with immense challenges as they try to find new treatments for a host of diseases and conditions. But the advent of a new technology known as single-cell RNA sequencing is opening a window into how the brain works.

Researchers at the Translational Genomics Research Institute (TGen), an affiliate of City of Hope, and a Silicon Valley startup called Circuit Therapeutics Inc. have combined to look deep inside the brain at a structure known as the striatum, which not only is responsible for controlling how we move, but also contributes to the brain's decision-making and the initiation of action.

Nearly 95 percent of the cells that make up the striatum are known as medium spiny neurons (MSN), whose health or malfunction is associated with many psychiatric and neurodegenerative diseases, including Parkinson's disease, Huntington's disease, schizophrenia, drug addiction and ADHD.

In one of the first investigations of its kind, TGen and Circuit Therapeutics have developed exacting methods for examining these MSN cells, and in the process identified a specific gene known as Chrm4 as one of several potential therapeutic drug targets, according to a study published June 15 in the journal *Frontiers in Cellular Neuroscience*.

"Understanding the molecular composition and gene expression of

individual MSN cells are of critical importance to gaining insights into how they work and how we can identify drug targets to treat neurological dysfunctions," said Dr. Matt Huentelman, TGen Professor of Neurogenomics. "In this study, we analyzed and simplified methods for isolating single MSN cells in the striatum, using newly available technology to examine them with unprecedented resolution."

By using single-cell RNA sequencing, the team redefined previous understandings of how MSN cells work, and added to the list of MSN marker genes previously discovered using older technologies that analyzed gene expression by studying bulk portions of striatal tissue.

"Understanding the molecular properties of neural circuitry in the brain is of great interest to neuroscience drug discovery," said Dr. Thomas Portmann, Director of Neurobiology and Transcriptomics at Circuit Therapeutics Inc. "Being able to understand how individual cells form key neural circuits is rapidly advancing our knowledge about the molecular signatures of the brain, and about druggable targets for development of future therapies."

More information: Hanson Ho et al, A Guide to Single-Cell Transcriptomics in Adult Rodent Brain: The Medium Spiny Neuron Transcriptome Revisited, *Frontiers in Cellular Neuroscience* (2018). DOI: 10.3389/fncel.2018.00159

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