A new, multidisciplinary approach to classify cell types in the brain

December 21 2015

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Despite its importance, scientists still do not understand all of the different cell types that make up the brain. A group of researchers from Baylor College of Medicine (Drs. Andreas and Kimberley Tolias' laboratories), the Karolinska Institutet (Dr. Rickard Sandberg's laboratory), and the University of Tübingen (Dr. Matthias Bethge's laboratory) have developed a novel technique that allows, for the first time, the anatomical and functional properties of single neurons to be directly linked to their gene expression profiles. Their findings, which

can be found in the latest edition of *Nature Biotechnology*, may provide vital clues for understanding neuropsychiatric disorders such as autism and schizophrenia.

For years, scientists have used a technique known as whole-cell patch-clamp recording to measure the electrical activity of neurons, including their unique patterns of activation and their connectivity to other neurons, and to relate these physiological properties to the cell's morphology.

However, individual neurons also differ at the genetic level. While all cells within an organism have the same genetic 'blueprint' of DNA, each individual cell only uses a subset of the available genes, which are 'expressed' in the form of mRNA and ultimately proteins. Until now, techniques to study genetic variability at the single-cell level have been impossible to combine with patch-clamp recording, and thus it has been difficult for neuroscientists to directly relate cellular physiology with gene expression profiles.

A multidisciplinary team led by Dr. Andreas S. Tolias, associate professor of neuroscience at Baylor, and Dr. Rickard Sandberg, professor of molecular genetics at the Karolinska Institute, developed a new method called 'patch-seq' that combines patch-clamp recording with single-cell RNA sequencing to study the morphology, physiology and gene expression profiles of individual neurons. Their study focused on the outermost, very thin layer of the neocortex, which is known to contain two morphologically distinct types of neurons.

"We found that individual neurons express approximately 7,000 genes," said Cathryn R. Cadwell, student in the M.D/Ph.D program at Baylor and co-first author. "Many of these genes are thought to be important for specifying the morphological and physiological characteristics of a neuron."

"The patterns in gene expression were used to sort cells into two genetic classes, which corresponded almost perfectly to the two known morphological cell types," added co-first author Athanasia Palasantza of Karolinska Institutet. "In addition, several quantitative physiological properties of the neurons could be predicted based on their gene expression profiles."

Interestingly, the study also found that four genes that have been previously associated with autism and schizophrenia were expressed by neurons of a particular cell type. Sandberg and Tolias believe that their technique can allow a systematic identification of the specific brain cell types that may be dysregulated in neuropsychiatric illness. This can provide a novel path forward for developing cell-types specific therapeutic interventions.

Others who contributed to the study include Xiaolong Jiang, Jacob Reimer, Shan Shen and Kimberley F. Tolias, all with Baylor College of Medicine; Qiaolin Deng and Marlene Yilmaz with the Karolinska Institutet; Philipp Berens with University of Tübingen; and Matthias Bethge with the University of Tübingen and Max Planck Institute.

More information: Electrophysiological, transcriptomic and morphologic profiling of single neurons using Patch-seq, *Nature Biotechnology*, DOI: 10.1038/nbt.3445

Provided by Baylor College of Medicine