LETTER

Transcriptional changes in single cells in neurodegenerative diseases

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ABSTRACT

Our understanding of the molecular changes involved in neurodegenerative diseases has evolved dramatically in recent decades. The technologies of single-cell RNA sequencing and single-nucleus RNA sequencing have been used to provide cellular and molecular details of the brain at the single-cell level. This has increased our understanding of the central nervous system and provided insights into the molecular vulnerability of different types of brain cells as well as the underlying mechanisms in neurodegenerative diseases.

We highlight recent advances and findings related to neurodegenerative diseases using these cutting-edge technologies in this article.

Key Words: *Central Nervous System*

INTRODUCTION

Neurodegenerative diseases are chronic and progressive illnesses of the Central Nervous System (CNS), characterized by neuron loss loss in the brain. Many efforts have been made at the molecular level to understand the fundamental biological mechanisms that contribute to neurodegeneration. Although the primary focus has been on the role of protein metabolism and aggregates in Neurodegenerative Diseases (NDDs), researchers are attempting to decipher the role of transcriptomic changes in the pathogenesis of these diseases.

Understanding the pathogenesis of neurodegenerative diseases and brain ageing is complicated by the need to identify the body's intrinsic mechanisms that may be causal or protective against neurodegeneration. For example, growing evidence suggests that Disease-Associated Microglia (DAM), a recently identified subset of microglia found in damaged areas, may play a protective role. This subpopulation was discovered using single-cell RNA-seq in an Alzheimer's disease mouse model.

DAMs are molecularly identified by the expression of microglial markers such as Iba1, Cst3, and Hexb, as well as the downregulation of homeostatic microglial genes such as.

DAMs also increase the expression of genes involved in lysosomal, phagocytic, and lipid metabolism pathways, including Apoe, Ctsd, Lpl, Tyrobp, and Trem2. This subset of cells has been proposed to have a dedicated sensory mechanism to detect damage within the damaged brain, which has been thoroughly discussed elsewhere. In this section, we go over the various cell types' roles in neurodegeneration in greater depth.

Amyotrophic Lateral Sclerosis (ALS) is recognized as a multisystem neurodegenerative disorder with clinical, genetic, and neuropathological heterogeneity. Adult-onset focal muscle weakness and wasting, which tends to spread with disease progression, are typical clinical features of ALS. In addition to their motor problems, approximately 50% of patients experience extra motor manifestations. Approximately 15% of ALS cases have a secondary diagnosis of frontotemporal dementia, and nearly 40% have mild behavioural and/or cognitive impairments. Almost 20% of ALS cases have a familial history. The cytoplasmic aggregation of TDP43 protein, encoded by the TARDBP gene, is the most common neuropathological signature of ALS, and it is present in nearly 95% of ALS cases. TDP43 is normally found in the nucleus, but in ALS it is mislocalized to the cytoplasm, where it aggregates and becomes pho-

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-sphorylated. Other aggregating proteins, such as SOD1 and FUS, are found in patients who have SOD1 or FUS mutations. Patients with C9orf72 hexanucleotide repeat expansions have dipeptide repeat protein accumulations that are translated from the GGGGCC repeats, despite the fact that this repeat is located in a noncoding region of the gene. Transcriptome profiling has also been used to investigate transcriptional changes at the single-cell resolution in ALS. scRNA-Seq of degenerating motor neurons derived from ALS patients has recently been used to unravel key disturbed pathways in ASL pathogenesis. In ALS-motor neurons, genes involved in synaptic structure, neuromuscular junction, neuronal cytoskeleton, and mitochondrial function were significantly downregulated. Interneurons, on the other hand, did not exhibit the same suppression of these homeostatic functions. Data from single cells revealed a context-specific transcriptional network relevant to ALS neurons. This network's master regulator analysis identified key transcriptional factors driving the ALS disease signature. Suppression of the HOXA1 and HOXA5 genes, in particular, was linked to synaptic dysfunction in ALS motor neurons. This suggests that HOX gene suppression is a common occurrence in SOD1 ALS. Despite these significant findings, more research is needed in the future to determine the relationship between transcriptional dysregulation in brain cell types and the mechanism of ALS pathogenesis.

To summarize, technologies such as scRNA-Seq and snRNA-Seq can be used to advance our understanding of brain health and disease. These technology's data could be used to re-evaluate hypotheses about differences between pre-defined sample groups at the single-cell level, regardless of their original classification. The use of these technologies in future human studies to analyze transcriptomic changes throughout disease stages could provide detailed molecular vulnerability of specific cell types in the brain as an advantage over bulk RNA-Seq. In this regard, scRNA-Seq databases will make it easier to access neurodegenerative-related findings. Another goal could be to create a single-cell resolution molecular atlas of the brain, which would help us understand the spatiotemporal structure and connectivity of cell types and subpopulations in the brain. Despite the fact that sc-RNA-Seq operates at the most fundamental level, mapping cell types and states at a specific level of resolution of interest may be difficult: Achieving the desired level of resolution for the intended cell map may necessitate significant methodological efforts. Importantly, scRNA-Seq and snRNA-Seq technologies will make it easier to identify sensitive diagnostic and prognostic biomarkers by looking at differences between patients and healthy people as well as using animal models. In this line, much research has been focused on understanding transcriptional changes in AD, but there is still room for other neurodegenerative diseases to be investigated further. Ultimately, the goal is to find novel molecular targets in the CNS using scRNA-Seq and snRNA-Seq to develop effective treatments.