Single Cell Transcriptome Study in Brain Aging

Xiangru Xu*
Department of Anesthesiology, Yale University School of Medicine, New Haven, USA

The human life expectancy has increased significantly during the past century, due to improvements of the life, changes of lifestyles and treatments for diseases. However, cognitive decline has become one of the greatest health threats of old age. The painful reality is that elderly people not only have deterioration in brain functions, but also are much more susceptible to neurodegenerative diseases such as dementia and Alzheimer’s disease. In fact, almost 50% of adults over the age of 85 are afflicted with Alzheimer’s disease [1]. Developing prevention and therapeutic interventions for such conditions largely demands a deeper understanding of the processes underlying normal and pathological brain ageing. Recent advances in the biology of ageing in model organisms, together with all aspects of -omics level studies in brain tissues and neuronal cells, are beginning to shed new lights on these mechanisms and their potential roles in cognitive decline.

The hippocampus, a major component of the brain and closely associated with the cerebral cortex, is the known target of age-related neurodegeneration. Two generally accepted functions of the hippocampus are as storage and interpreter of spatial information, and as a mediator of consolidation of short term memory into long term memory. During the normal aging process, humans and animals experience age-related memory decline. Historically, it was thought that the primary contribution to the etiology of hippocampus function decline was a massive loss of neurons and dramatic changes in neuronal morphology in pyramidal cell layers [2,3]. However, when it became possible to eliminate many of the confounding factors of the previous studies, this was proved to be a misconception [4]. In fact, neuron numbers and morphologies do not change significantly with normal aging in the hippocampus, suggesting that the functional decline of hippocampal neurons with age is the key alteration. Maintenance of Long Term Potentiation (LTP), a cellular correlate of brain cognitive function, requires gene expression and de novo protein synthesis; therefore, changes of gene expression in neurons are expected to take place with hippocampus aging, and analysis of regions of the hippocampus by microarray has confirmed this [5-7].

Moreover, gene expression studies suggest that hippocampal regional disparity of CA1, CA3 and DG in response to aging and energy intake relates to differences in vulnerability to stressors, the availability of neurotrophic, and cell survival mechanisms, and differences in cell function [8,9]. Major types of hippocampus subregional neurons including CA1 pyramidal neurons, CA3 pyramidal neurons, and DG granule neurons have been studied widely in physiological and pathological conditions, and are believed to play central roles in sustaining learning and memory and cognitive functions of the hippocampus. Importantly, granule neurons in DG are more vulnerable to age-related damage, whereas CA1 and CA3 pyramidal neurons are more susceptible to neurodegenerative disorders such as Alzheimer disease. The mechanism of the selective subregion neuronal vulnerability in hippocampal aging and age-related diseases is not known yet. Also, in the aging brain or age-related disorders such as Alzheimer’s disease, one cell in the brain may clearly be affected, while an adjacent cell appears healthy or unaffected. However, these differences will be masked by the averaging effect of studying pooled cells. Previous technology has allowed us to examine one message at a time, at the level of a single cell (in situ hybridization & qRT-PCR), or multiple messages in a heterogeneous population of cells (northern analysis) or large scale analyses in a single population of cells. But these methods either give information about averages across heterogeneous cell populations or give results for only a few selected genes. The use of genomic scale analyses to define the distribution of these changes in single neurons of various types is supposed to present an unprecedented level of resolution to the study of the effects of aging.

Critical advancement in techniques relevant to single cell transcriptome analysis has been made lately. One individual mammalian cell generally contains ~10 pg of total RNA and ~0.1 pg of mRNA; it is the leading barrier for accurately measuring the transcriptome of one single cell. To overcome this difficulty, various protocols were developed by either T7 RNA polymerase–based In Vitro Transcription (IVT) or PCR to drastically enhance the sensitivity and accuracy of single cell RNAs amplification [10-12]. The superior microarray techniques and the advanced next-generation sequencing methods provide another essential support for one single cell transcriptome analysis. Alternatively, the newly developed microfluidics systems (lab-on-chip) make it possible, in the future, to isolate, track and quantify the expression of genes of thousands of single cells in parallel in a nanoliter of solution [13]. This will very much boost the accuracy and efficiency of analyzing single cells from a range of sources, including brain progenitor cells or neuronal cells.

Results of single cell transcriptome offer the information of cell-to-cell variation, which can reveal novel regulatory mechanisms underlying the phenotypic differences between genetically identical cells. Single cell transcriptome analysis by deep sequencing approach is also providing abundant information about alternative splicing isoforms of messenger RNAs. Gene splicing isoforms in brain play pivotal roles in learning and memory and other cognitive functions. For example, Brain Derived Neurotrophic Factor (BDNF) and its receptor TrkB occur in multiple isoforms. Different BDNF isoforms are predominately expressed in different subtypes of neurons and dysregulation of specific BDNF or TrkB isoforms has been suggested to be important for neurologic and psychiatric disorders [14-16]. In mammalian nervous systems alternative splicing of neural genes in specific cell types is not exhaustively studied but is almost certainly of major importance. Optimistically, the transcriptome insights of single cell mark a new era in genome science and biomedical research including brain aging and age-related neurodegenerative disorders.

*Corresponding author: Xiangru Xu, Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut, 06519, USA, E-mail: xiangru.xu@yale.edu

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