Transcriptomic landscape of immune system in brain tumors

Jiin Choi[1], Hee Jin Cho[1,2,*]

[1]Department of Biomedical Convergence Science and Technology, Kyungpook National University, Daegu 41566, Korea

[2]Cell and Matrix Research Institute, Kyungpook National University, Daegu 41944, Korea

Abstract

Brain tumor microenvironment (TME) heterogeneity is a major challenge in brain tumor treatment and many studies tried to unveil its complexity, but it is still unclear. In addition, there are diverse immune related cells in TME, so immunotherapy is recently in the spotlight as a treatment for tumors, by manipulating immune cells in TME to kill tumor cells. Here, we decomposed the population of immune cell signature gene expression among six brain tumor types (meningioma, pilocytic astrocytoma, ependymoma, medulloblastoma, glioblastoma, and lower grade glioma) using publicly available microarray datasets and the cell type heterogeneity in TME using publicly available single cell RNA-seq datasets. This transcriptome-based profiling revealed the different cell infiltration patterns according to each brain tumor type. Also, comparing cell type proportion of each brain tumor type at a single cell level revealed several features related to brain tumor therapeutic method. These results will contribute to realize future precision medicine, providing the basic rationale for the immunotherapy in brain tumors.

Introduction

There are different types of brain tumor according to several features such as age of onset, the malignancy of tumor and the originated locations. In these brain tumor microenvironments, various types of cell are existing, including immune cells, and they contribute to tumor progression or tumor suppression, so they related to the prognosis of patients with brain tumor. For this reason, immunotherapy is emerging as an effective and safe treatment, by utilizing some immune cells that are existing in TME.

Recently, single-cell RNA sequencing (scRNA-seq) has become one of the most widely used technologies in biomedical research by providing an opportunity to quantify the abundance of diverse transcriptome among individual cells.

In this study, we executed transcriptional profiling about different types of brain tumor, including meningioma, pilocytic astrocytoma, ependymoma, medulloblastoma, glioblastoma, and lower grade glioma, to reveal and compare the immune related gene expression and cellular heterogeneity across age, malignancy, and location of development. We estimated the TME immune infiltration pattern of publicly available samples using CIBERSORTx algorithm. Then, we compared cell type proportion of each brain tumor type at a single cell level.

Results

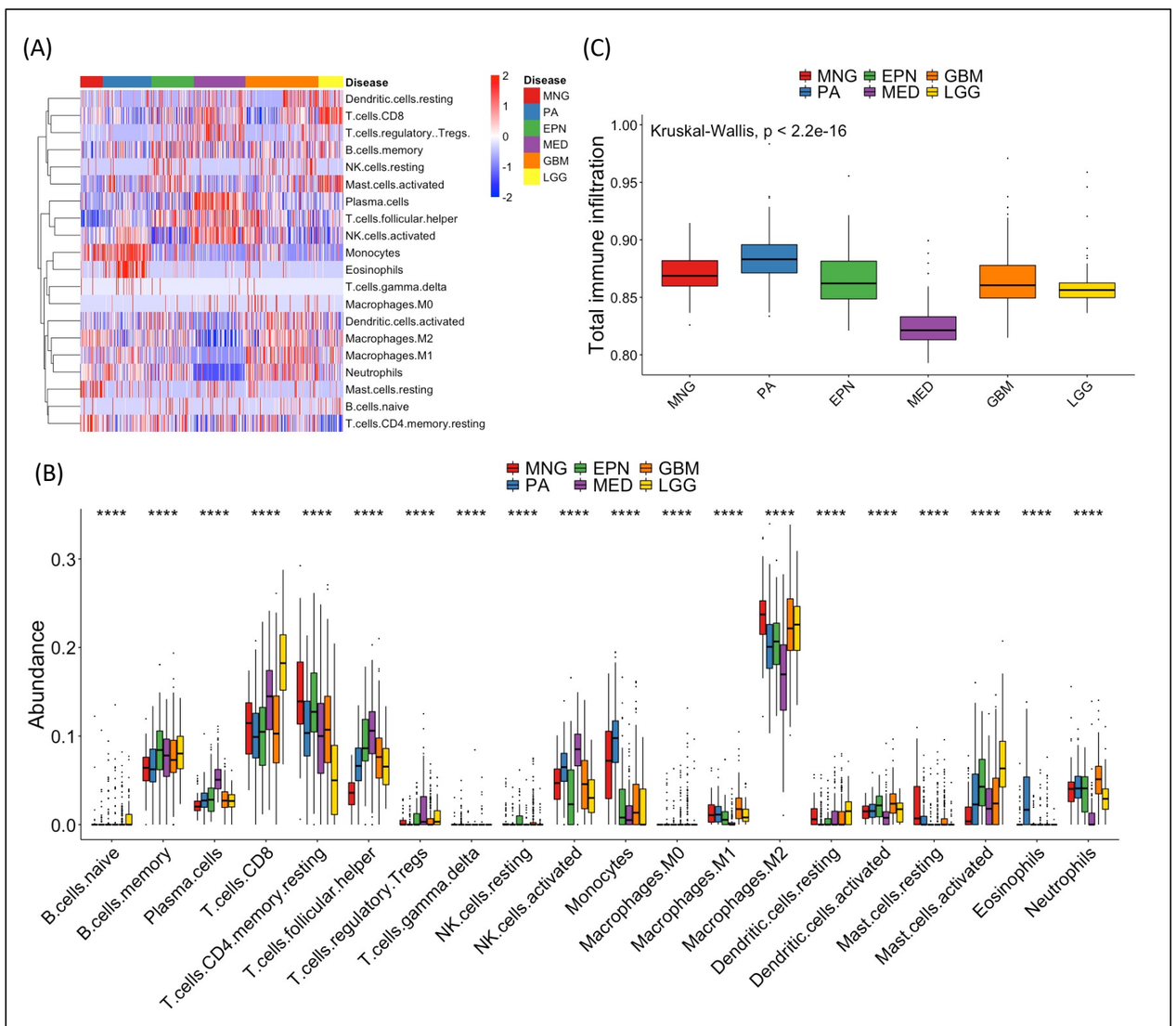

Figure 1. The overall landscape of immune signature expression abundance in brain tumors.

To reveal immune infiltration patterns in each brain tumor TME, publicly available microarray datasets in GEO were used with CIBERSORTx algorithm. (A) CIBERSORTx delineated LM22 gene signature expressions. A heatmap representing the overall immune signature expression of six types of brain tumor by Z-score. (B) A boxplot illustrating the immune signature expression abundance of each brain tumor type. (C) A boxplot showing the total immune infiltration abundance of each type of brain tumors from CIBERSORTx. The thick line represents the median value. The statistical difference was calculated through the Kruskal-Wallis test. ****, $P < 0.0001$. MNG, Meningioma; PA, Pilocytic astrocytoma; EPN, Ependymoma; MED, Medulloblastoma; GBM, Glioblastoma; LGG, Lower grade glioma

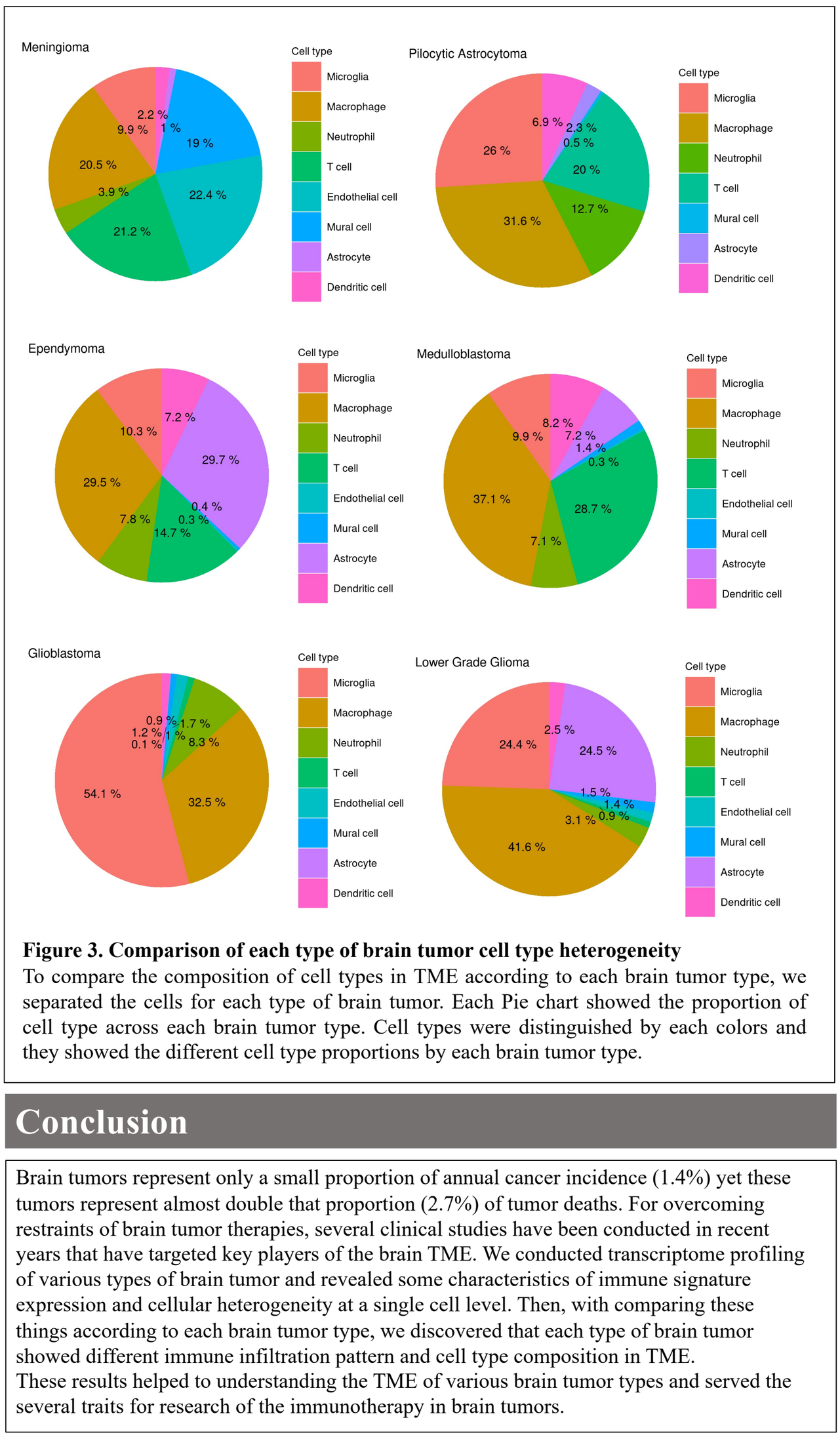

Figure 3. Comparison of each type of brain tumor cell type heterogeneity

To compare the composition of cell types in TME according to each brain tumor type, we separated the cells for each type of brain tumor. Each Pie chart showed the proportion of cell type across each brain tumor type. Cell types were distinguished by each colors and they showed the different cell type proportions by each brain tumor type.

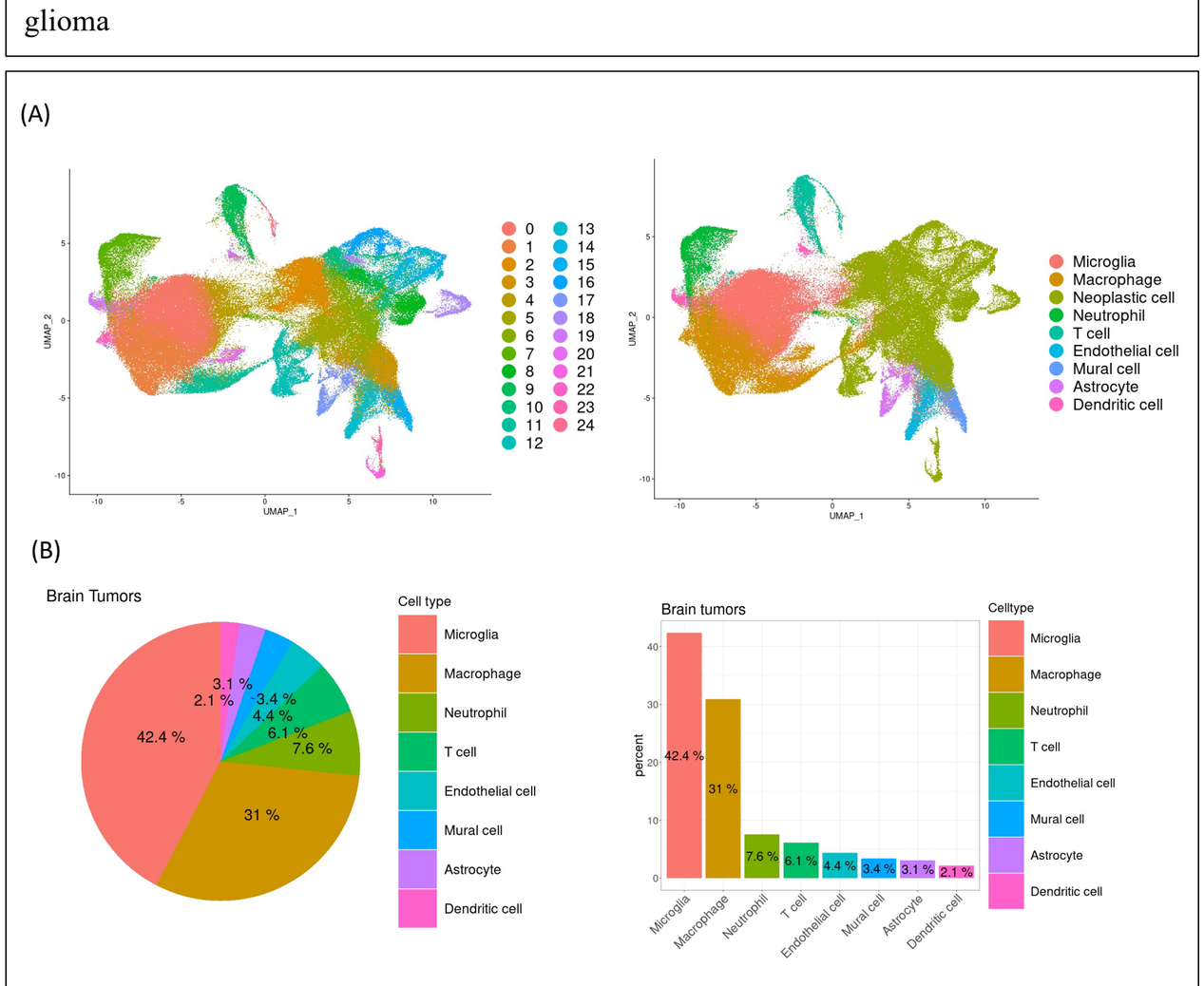

Figure 2. Single cell characterization via scRNA-seq datasets in brain tumors.

Publicly available scRNA-seq datasets were used to show brain tumor microenvironment cellular heterogeneity at a single cell level. scRNA-seq data processing was carried out by Seurat R package. (A) UMAP plot of total scRNA-seq datasets showing 25 cell clusters processed by the KNN algorithms and on the right side, UMAP plot showed the cell annotated with cell types by each cluster's marker gene and cell type clusters were denoted by distinct color. (B) Bar graph and pie chart representing the proportion of each cell type in all brain tumors. X-axis of bar graph represented cell type and Y-axis of bar graph represented percent of each cell type. UMAP, Uniform Manifold Approximation and Projection; KNN, K-nearest neighbor; scRNA-seq, single cell RNA sequencing

Conclusion

Brain tumors represent only a small proportion of annual cancer incidence (1.4%) yet these tumors represent almost double that proportion (2.7%) of tumor deaths. For overcoming restraints of brain tumor therapies, several clinical studies have been conducted in recent years that have targeted key players of the brain TME. We conducted transcriptome profiling of various types of brain tumor and revealed some characteristics of immune signature expression and cellular heterogeneity at a single cell level. Then, with comparing these things according to each brain tumor type, we discovered that each type of brain tumor showed different immune infiltration pattern and cell type composition in TME.

These results helped to understanding the TME of various brain tumor types and served the several traits for research of the immunotherapy in brain tumors.

Reference

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Acknowledgement

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