In silico Analysis of the Immunological Landscape of Hippocampi in Alzheimer's Disease

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Keywords

Dendritic cells · Neuroinflammation · Hippocampi · Alzheimer's disease

Abstract

Introduction: Accumulating evidence suggests a relationship between neuroinflammation and neurodegenerative pathologies such as Alzheimer's disease (AD). This study sought to investigate the immunological composition of hippocampi in patients afflicted with AD. **Methods:** CIBERSORTx RNA deconvolution was applied on gene expression data developed from hippocampi of 38 AD patients and 17 controls to infer the relative proportions of 22 subsets of immune cells. **Results:** AD-afflicted hippocampi were found to have greater relative abundances of M2 macrophages and CD8 T cells. AD-afflicted hippocampi were also composed of significantly more active dendritic cells and significantly fewer resting dendritic cells than control samples. **Conclusion:** AD-afflicted hippocampi present with a distinct immune signature and dendritic cells may play a critical role in the pathogenesis of AD in this brain component.

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Introduction

Alzheimer's disease (AD), a common cause of neurodegenerative dementia in the elderly, is pathologically characterized by neurofibrillary tangle formation, β -amyloid deposition creating senile plaques, and neuroinflammation [1]. Although neuroinflammation has been shown to play a critical role, the specifics of immune cell recruitment and infiltration into the brain parenchyma to perpetuate neuroinflammation are only recently being elucidated but are still poorly understood [2–6]. However, the spatiotemporal pattern of neurofibrillary degeneration and progression in AD has been resolved and starts with brain areas primarily involved in memory and learning, notably the hippocampus [7]. Moreover, there has been no investigation to date specifically examining the total immune cell infiltrate of initially affected brain structures in AD. To address this gap, the study presented herein explored the immune composition of 38 AD-afflicted hippocampi through digital cytometry.

Fig. 1. **a** Heat map showing relative abundances of immune cell subsets in AD hippocampi. **b** Violin plot showing relative abundances of active dendritic cells. Asterisk denotes significance at $p < 0.05$. **c** Violin plot showing relative abundances of resting dendritic cells. Asterisk denotes significance at $p < 0.05$.

Materials and Methods

CIBERSORTx, an established in silico RNA deconvolution approach, was used to provide an estimation of the relative abundances of immune cells from a previously published gene expression dataset [8]. The dataset consists of hippocampi gene expression for 38 AD patients and 17 controls [9]. The data was generated using Affymetrix 133AB platform and was downloaded from Synapse database (<https://www.synapse.org/>) under accession syn3157699.

A validated signature matrix for distinguishing 22 human hematopoietic cell subsets was used to deconvolute the bulk hippocampi gene mixture matrix [8]. The CIBERSORTx algorithm was run with bulk-mode batch correction and quantile normalization with 500 permutations in relative mode. Deconvoluted samples were deemed significant if CIBERSORTx p value was < 0.05 , which represents the significance of the deconvolution results across all cell subsets for goodness of fit [8].

After CIBERSORTx, data was downloaded and analyzed with R programming language. Normality was not assumed and no values were excluded, thus the nonparametric Mann-Whitney U test was used for comparisons. A p value < 0.05 was deemed significant.

Results

After RNA deconvolution for immune cell subset identification, all samples met the p value < 0.05 cutoffs. Overall, AD hippocampi were enriched mainly for T follicular helper cells, a specialized subset of CD4+ T cells (shown in Fig. 1a). CD8 T cells and M2 macrophages also

showed greater relative abundance. When comparing relative abundances between AD and control samples, AD hippocampi were significantly enriched for more activated dendritic cells (shown in Fig. 1b) but also had significantly fewer resting dendritic cells (shown in Fig. 1c).

Discussion/Conclusion

This digital dissection of the immunological landscape from existing gene expression data has shown a distinct immune profile for AD-afflicted hippocampi. Importantly, these results support findings from previous studies. Prior studies have proposed a role for T follicular helper cells in AD [10, 11] and have shown that increased T cell and macrophage recruitment into brain parenchyma of AD patients may modulate AD-associated inflammation [4, 12]. Furthermore, the novel finding of increased active dendritic cells and decreased resting dendritic cells in hippocampi of AD patients has not previously been directly characterized. However, prior studies have shown decreased levels of dendritic cells in the blood of AD patients, possibly indicating their recruitment to the brain [5, 13].

In conclusion, the unbiased computational approach used herein demonstrated immune infiltrates in AD-afflicted hippocampi, suggesting that dendritic cells, along with other immune cell subtypes, may play a significant

role in the hippocampi during AD. Further studies examining dendritic cells in AD are warranted to develop rational therapeutic strategies.

Statement of Ethics

Ethical approval is not applicable. This article does not contain any studies with human participants performed by the author.

Disclosure Statement

The author has no conflict of interest to declare.

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