DOI: 10.1002/alz.075032

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Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

Immunomodulating mechanisms of human neural stem cell transplantation in a transgenic Alzheimer's disease mouse model

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Abstract

Background: Many pathways are implicated in pathogenesis of Alzheimer's disease (AD). Stem cells are a promising strategy to simultaneously correct multiple pathways; however, therapeutic mechanisms of stem cells are not well described. Here, we used spatial transcriptomics to quantitate gene expression following intracranial transplantation of human neural stem cells (hNSCs) in a mouse model of AD.

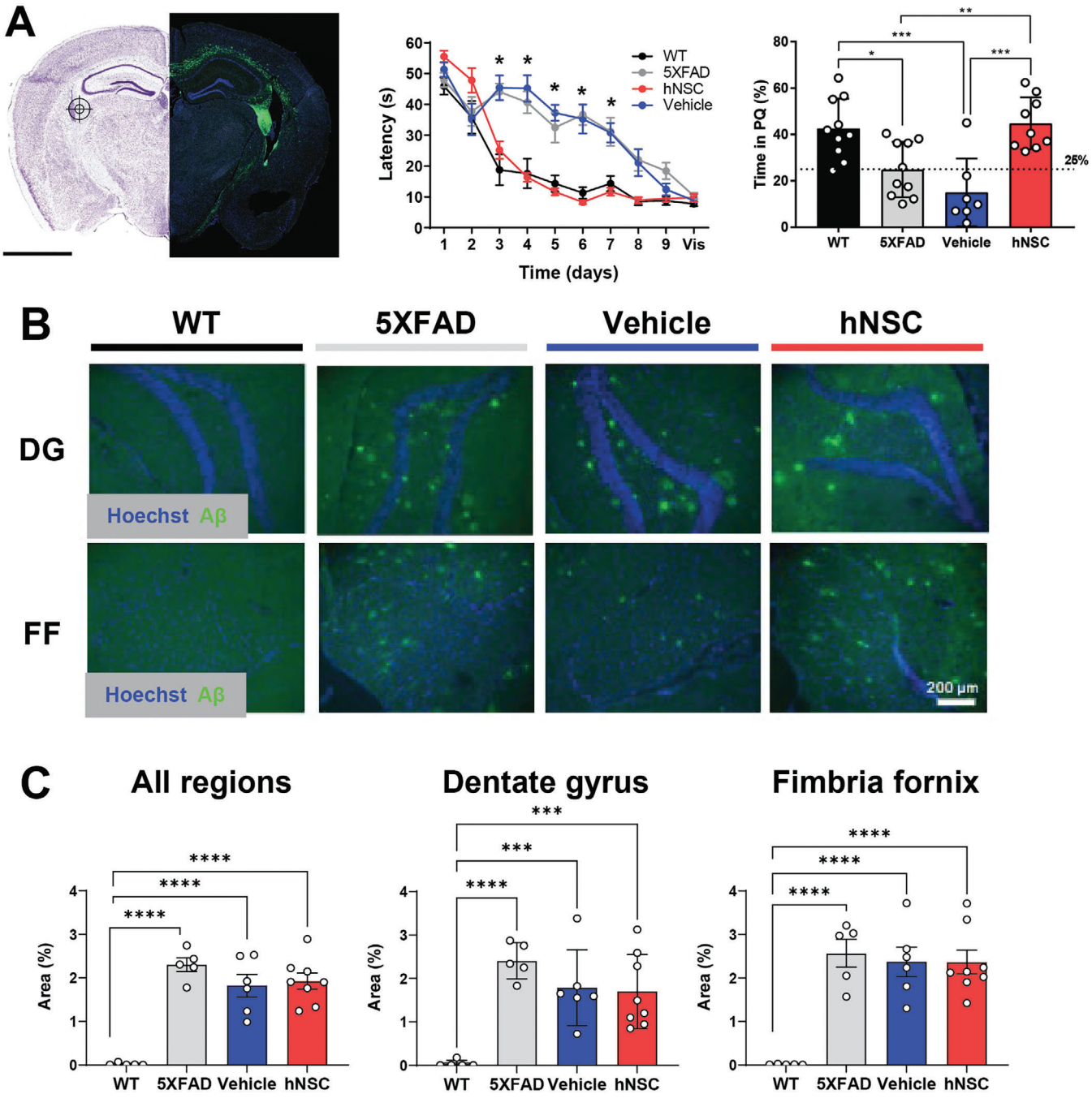
Method: The 5XFAD mouse model was utilized. An hNSC cell line (HK532-IGF1, Palisade Bio) was transplanted into fimbria fornix of the hippocampus (6 total injections, 180,000-600,000 total cells). Spatial memory was assessed by Morris water maze. Amyloid plaques were assessed by immunofluorescence and ELISA. Hemibrains were submitted for spatial transcriptomics (Visium 10X, 10X Genomics) and significant differentially expressed genes (DEGs) were identified ($p < 0.05$). Pathway enrichment was performed using the Kyoto Encyclopedia of Genes and Genomes (KEGG), and CellChat network analysis examined communication between cell populations.

Result: hNSC transplantation restored learning curves of 5XFAD mice in Morris water maze, mimicking wild-type performance (Fig 1A). However, there were no changes in amyloid-beta burden (Fig 1B-C). Spatial transcriptomics elucidated non-amyloid hNSC therapeutic mechanisms. In hippocampal subregions, we discovered 1061 normalized DEGs. KEGG pathway analysis revealed significant impact on protein processing ("ubiquitin mediated proteolysis", "protein export", and "proteosome"), "long-term potentiation," and "metabolic pathways" (Fig 2). Plaque induced genes were normalized upon hNSC transplantation, particularly in microglia (Fig 3A). A reduction in stage 1 and stage 2 disease associated microglia (DAM) was seen, without affecting homeostatic microglia (Fig 3B). CellChat analysis showed hNSCs interacted with stage 1 and stage 2 DAM along many pathways (Fig 3C). Pathologic signaling between hippocampus and DAM upregulated in the 5XFAD model was again normalized upon hNSC transplantation.

Conclusion: Transplantation of hNSCs rescued memory in 5XFAD mice. No change in amyloid plaque burden was noted, but spatial transcriptomics revealed many genes

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dysregulated in 5XFAD that were normalized with hNSC transplantation. hNSCs interacted with and normalized populations of stage 1 and stage 2 DAM. Our results suggest that hNSCs exert beneficial effects in part by modulating microglia-mediated neuroinflammation in AD.



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