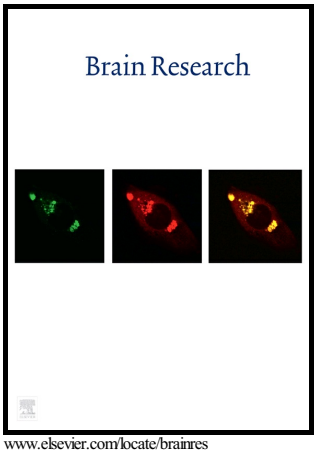

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Induced pluripotent stem cells as a discovery tool for Alzheimer's disease

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ABSTRACT
The ability to accurately and systematically evaluate the cellular mechanisms underlying human neurodegenerative disorders such as Alzheimer's disease (AD) should lead to advancements in therapeutics. Recent developments in human induced pluripotent stem cells (iPSCs) has afforded the opportunity to use human neurons and glia to study cellular changes involved in neurological diseases. iPSCs have the potential to be differentiated into AD-relevant cell types, including forebrain neurons, astrocytes, and microglia. This permits the evaluation of individual cell types in isolation or in concert, thus modeling the interdependence of cell types within the brain. When discussing the potential of modeling AD with iPSCs, it is important to remember that the umbrella diagnosis of "Alzheimer's disease" represents a disease that is heterogeneous in terms of age of onset, underlying causes, and at times precise pathology. The ability of iPSCs to be derived from an array of AD patients allows for a closer examination of the mechanism of disease progression in particular subsets of subjects, who may have different mutations and allelic variants affecting their risk for disease. Disease mechanisms can be probed both by the genetic manipulation of iPSCs and by modifications to the cellular environment by chemical treatment. These studies may lead not only to the refinement of known pathways implicated in AD, but also to the identification of novel pathways heretofore unaffiliated with disease pathology. In this review, we describe the potential of iPSC models to transform our understanding of AD and to lead to valuable advancements in therapeutics.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by dysfunction and deterioration of neurons within the cerebral cortex resulting in loss of memory and progressive cognitive decline. According to the Alzheimer's Association, AD is the 6th leading cause of death in the United States and the number one cause of dementia (Thies and Bleiler, 2013). The earliest symptoms of AD are subtle difficulties with memory storage and recall. Episodic memory impairment becomes more striking as