


Chapter 15

Glial Cell Biology and Their Multifaceted Functions in Alzheimer's Disease: New Therapeutic Prospects


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ABSTRACT

Although the pathophysiology of Alzheimer's disease (AD) is exceedingly complex and poorly understood, the illness is nonetheless of great interest to the scientific community. Recent advances in AD research have allowed for the possibility that further treatment advantages might be found, which would assist patients all around the world. However, recent studies suggest that glial cells, such as microglia, astrocytes, oligodendrocytes, and oligodendrocyte progenitor cells (NG2 glia), are linked to the pathogenesis of AD and may offer several potential therapeutic targets against AD. Previous research on AD has focused primarily on neurons. Glial cells are essential to the structural integrity of neurons and are necessary for regulating homeostasis (concentration of ions, neurotransmitters) within the central nervous system. This chapter investigates the following topics: (i) the function of glial cells in the pathogenesis of AD; (ii) the intricate functions of the constituent parts; and (iii) prospective therapeutic targets that may one day improve the quality of life for AD patients.

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INTRODUCTION

Alzheimer's disease (AD), a crippling neurological condition, is characterized by hyperphosphorylated tau protein aggregation in the brain and β -amyloid ($A\beta$)-induced senile plaques, which eventually cause patients to lose their cognitive function and develop dementia (Cummings et al., 2014). Age is one of the biggest risk factors for AD, which is why it is becoming common to see older people worldwide. In 2010, there were 35 million AD patients worldwide; by 2030, that number is expected to increase to 65 million. When compared to females, human males have about twice as many cases of AD, and around the age of 85, over 50% of males have the disease (Cummings et al., 2014). Considering the age at which the disease manifests itself, there are two subcategories of Alzheimer's disease. Sporadic AD (SAD) develops at a much later age than familial AD (FAD), which manifests itself earlier in life.

The amyloid cascade theory, initially put forward in 1992, holds that aberrant amyloid beta ($A\beta$) deposition in numerous brain regions is an essential stage leading to neuronal death and AD (Hardy & Higgins, 1992). According to O'Brien & Wong, (2011), β -secretase (BACE1) and γ -secretase are involved in the production of A from $A\beta$ from amyloid precursor protein (APP). Aside from having a negative impact on neighboring neurons, $A\beta$ accumulation in the brain can also result in a number of processes, including tau hyperphosphorylation and the formation of neurofibrillary tangles (NFTs), which are important players in the neurodegenerative processes associated with AD (Mohandas et al., 2009; Niedowicz et al., 2011). There are presently no therapies or medications that may reverse or stop the progression of AD, despite countless research illuminating the cellular and molecular processes underlying its pathogenesis (Poon et al., 2020).

Multiple studies currently suggest that inflammation may be the primary neuropathological hallmark causing neurodegeneration in AD, despite the fact that the amyloid cascade theory is still the most popular explanation for how AD pathogenesis occurs. Increased cytokine levels have also been seen in the brains of AD patients (Ojala et al., 2009) and animal models of the disease (Benzing et al., 1999; Apelt et al., 2001; Patel et al., 2005). Numerous studies have also shown that the mechanism of neurodegeneration-associated inflammatory signaling heavily depends on the activation of glial cells (Wang et al., 2015). The creation and maintenance of synapses, the creation of the axonal myelin sheath, the maintenance of normal levels of neurotransmitters, and mitochondrial activities are just a few of the critical jobs that glial cells play in the central nervous system (CNS) (Wong et al., 2020). According to Overmyer et al (1999), microglia, the main immune cell in the CNS, are intimately linked to aging. Microglia's contributions in the development of AD have been the subject of several research (Swanson et al., 2020; Schwabe et al., 2020; Streit et al., 2004). Alterations in microglial gene expression and the emergence of dystrophic microglia, a sign of cellular senescence, have been related to aging (Streit et al., 2004). Glial cells are thought to be directly related to cognitive impairments and the pathogenesis of AD, according to an increasing body of research (Dossi et al., 2018; Uddin & Lim, 2022). In the brains of people with AD, reactive astrocytes and microglia have been observed in higher concentrations close to senile plaques (McGeer et al., 1987; Zotova et al., 2011), suggesting these immune cells may be involved in the etiology of AD.

There is established correlation between the degree of cognitive impairment and brain shrinkage and the level of glial cell activation and their interaction (Cagnin et al., 2001). Therefore, it seems sense to hypothesize that glial neuroinflammatory responses, namely those of microglia and astrocyte, worsen the neurodegeneration linked to AD.

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