



Alzheimer's Disease and Stem Cell

El Shawarby A and Omar SMM*

Department of Histology and Cell Biology, Faculty of Medicine, Ain Shams University, Egypt

*Corresponding author: Department of Histology, Ain Shams University & Armed Forces College of Medicine, Cairo, Egypt, Tel: 00201001428289; Email: saharhistology@gmail.com

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Abstract

Aging causes many changes in the human body, as a mechanism responsible for maintaining proper protein composition starts to decline with age. Proteins lose their stability, and the autophagy process failed, which resulted in the accumulation of misfolded proteins, which in turn resulted in diseases.

Keywords: Alzheimer's; Stem cell; Beta-Amyloid

Introduction

Dementia, a common age-related disease, is a clinical disorder triggered by neurodegeneration. Numerous conditions can cause dementia. However, the most common form of dementia is Alzheimer's disease (AD) [1,2]. Alois Alzheimer in 1907 was the first to describe this type of dementia. Approved medication that provides symptomatic relief does not affect the disease progression [3].

According to World Alzheimer's disease report 2018, about 50 million people have dementia due to the accumulation of microscopic brain protein fragment called beta-amyloid (AB), a sticky compound that aggregates in the brain, disrupting communication between brain cells and eventually killing them [4]. Some researchers believe that defects in the processes governing production, accumulation, or disposal of beta-amyloid are the primary cause of Alzheimer's. This theory is called "the amyloid hypothesis." Excessive accumulation of toxic proteins as extracellular senile amyloid-beta plaque (AB) and intracellular neurofibrillary tangles are the hallmarks of AD. Neurofibrillary tangles are caused by the hyper-phosphorylation of Tau proteins. Tau proteins are microtubule-associated proteins. They usually help in the stabilization of neural microtubules [5].

Oxidative stress, vascular dysfunction due to loss of vascular endothelium growth factors (VEGF), and

mitochondrial dysfunction play a role in the pathophysiology of AD [6].

Because of the absence of effective treatment, stem cell therapy could have promising therapeutic potential, which might be attributed to stem cells induction of neurogenesis (proliferation of endogenous stem cells) [7]. Besides, stem cells have anti-inflammatory action, immune-modulatory action, anti-amyloidogenic potential in addition to the release of neurotrophic factors. Moreover, AD is considered, to some extent, a stem cell disease, due to the deposition of senile plaque which harms stem cell proliferation. Also, newly generated neurons and glia cannot survive in the AD environment [8,9].

Adult neurogenesis carries the potential of brain self-repair by the formation of new neurons. However, it declines with aging. Strategies to improve symptoms of aging is to stimulate neurogenesis both pharmacologically and naturally. Stem cells neurogenesis might provide the basis for grafted stem cell therapy [10,11].

The Role of Neuroglia in Alzheimer Disease

The Role of Microglia

Microglia are resident macrophages of the brain. They develop either from mesenchyme or monocytes. They sense

neural activity and regulate synaptic plasticity, learning, and memory mechanisms. They also clear amyloid plaque. Excessive accumulation of AB peptide results in gliosis. During inflammation, ATP is released in extracellular space resulting in increased expression of receptors (P2X7) of microglia with a subsequent increase in their activity. The decrease in the phagocytic function of microglia with the release of proinflammatory cytokines. Increasing the expression of these receptors in microglia results in the generation of inflammation in AD [12-14].

Two types of microglia are present in CNS classically activated macrophages M1(proinflammatory) and alternatively activated macrophages M2(anti-inflammatory). M2microglia are involved in improving senile plaque and enhance AD-associated neuroinflammation. Moreover, stem cell treatment works through the polarization of M1 to M2 [15].

The Role of Astrocytes in AD

Astrocytes are neuroglia cells involved in the release and cycling of neurotransmitters, modulation of synaptic transmission. Aggregated amyloid can induce increase calcium uptake by astrocytes resulting in its activation [16]. Astrocytes express receptors that bind amyloid and degenerate amyloid extracellularly by secretion of enzymes like insulin and metalloproteinases [17].

Oligodendrocytes

AD has a toxic effect on oligodendrocytes with the deterioration of myelin integrity and axonal destruction [18].

Nerve-Glial Antigen 2 (NG2-Glia cells)

It is a newly discovered Precursor of oligodendroglia (OPCs). They are immature cells present in all brain regions. They represent the subtype of glial cells in CNS. They are smaller than neurons and express proteoglycan. They are one of the most proliferative glial cells. They can renew themselves or generate new oligodendrocytes. They can differentiate into neurons or astrocytes following CNS injury. They are playing an essential role in the pathology of AD. Peptide plaque activates enzymes that lead to phosphorylation of beta-catenin and its degradation, which results in decrease WNT signaling and inhibition of differentiation of oligodendrocytes precursors [19].

Metabolic Disorder

Aberrant lipid metabolism is associated with AD. Aberrant lipid metabolism is also associated with neurogenesis defects. Lipid droplets accumulate in subventricular zone

destroy NSC and their daughter neuroblasts [20].

Stem Cell Therapies

Stem cell-based therapy is under development but has therapeutic potential for reversing neurodegenerative changes and improve cell structure. Stem cells have several paracrine and neurotrophic factors for neuro-modulation [21].

In Vivo Neurogenesis & Neural Stem Cells (NSC)

Stem cell niches in the brain are present in the subventricular zone of lateral ventricles and granular layer of the hippocampal dentate gyrus. In this region, star-shaped astrocytes (double-positive for GFAP and nestin) with ultrastructural properties of astrocytes are present. They are derived from radial glial cells. These astrocytes divide producing cell like itself and another small transit amplifier cell that divide at a high rate producing neural progenitor cells and migrate to specific areas while differentiating [22].

Adult neurogenesis is a dynamic process. Signaling molecules, neurotrophic factors, and neurotransmitters like glutamate and GABA could Successful regulate neurogenesis. Neurogenesis is also affected by trauma, ischemia, and aging and neurodegenerative diseases [10].

AD in the senile brain triggers neurogenesis to replace the lost neurons leading to an increasing number of immature neurons in the granular cell layer. In the Pre-senile brain, AD showed no increase in neurogenesis but an increase in the name of neuroglia cells [23].

Monomeric AB42 showed no significant effect on NSCs proliferation and differentiation at low concentrations but inhibited proliferation and differentiation at high levels. In the early stage of AD oligomeric AB, increases proliferation and differentiation of [24].

Fibrillary AB42 in the late stage of AD decreases progenitor cells in culture at high concentrations due to cortical cholinergic loss. Depletion of neural progenitor cells in AD by pushing their cell fate into immature neurons or glial cells [25].

In AD, Neurogenesis in the subgranular zone of dentate gyrus may be an endogenous repair mechanism via Wnt signaling pathway. The in vitro studies of the role of fibroblasts growth factor 2 (FGF2) in neurogenesis, declared that FGF2inhibits neural differentiation and maturation in the absence of neurotrophic factors [26]. FGF2 increases the number of immature and dividing neurons while decreasing the mature neurons. It does not affect neuroglia lineage [27].

In another study, injection of neural precursor cells in the subventricular zone resulted in activation of neurogenesis in the ipsilateral subventricular region and not in the contralateral subventricular zone or subgranular zone in aged rats [28].

Stem Cells Transplantation in AD

Administration of MSCs derived from Wharton's jelly of the umbilical cord and their transdifferentiation into neurons like cells have been used. This reduced amyloid load and increase cognitive function via microglia activation and expression of amyloid degrading and insulin-degrading enzymes. MSCs administration caused hippocampal neurogenesis and increased differentiation of neuroprogenitor cells [29].

Exosomes secreted by stem cells can transmit function proteins and genetic information to the diseased cells in AD patients. They can send tissue repair regenerative segments. Adipose-derived MSCs secrete exosomes contain active enzyme neprilysin (zinc-dependent metalloproteinase) that degrade amyloid peptides [30].

Neural stem cells isolated from mouse embryo or Human olfactory bulb express nerve growth factors Placenta and amniotic membrane-derived MSCs can be used. Adipose-derived MSCs cross blood-brain barrier reduced memory loss and upregulated VEGF [31].

Epidermal neural crest stem cells increase granules cells in the hippocampus and express GFAP [32].

Transplantation of genetically altered NSC rescued cognitive dysfunction in an animal model of AD but failed to improve AB deposition. Some scientists proposed to allow NSC to deliver essential disease modulating proteins [33].

Using a genetically engineering NSC that releases beta-amyloid degrading enzymes resulted in augmentation of synaptic plasticity and amelioration of amyloid deposition [34].

Overexpression of neprilysin, which is AB degrading enzymes in the transplanted MSC, reduces synaptic loss and AB level [35].

The NSC's overexpression of brain-derived neurotrophic factors resulted in better recovery, increased synaptic density, and cognitive function [36].

Overexpression of IGF-1 in cortical neurons resulted in increased GABAergic neuron differentiation and increased VEGF production [37].

Transplantation of neural stem cells into aged transgenic mice that express mutant tau and APP resulted in improvement of learning and memory loss without altering beta-amyloid and tau pathology. The mechanism of action of stem cells was related to release of neurotrophic factors [38].

Administration of mesenchymal stem cells from cord blood in transgenic mice (presenilin (Ps1) and APP) led to the activation of microglia (M2 anti-inflammatory) with the improvement of learning and memory loss [39].

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