CHAPTER 1

Recent Perspective About the Amyloid Cascade Hypothesis and Stem Cell-Based Therapy in the Treatment of Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is a complex neurodegenerative condition that is clinically characterized by impaired cognitive functions. The major morphologically observed lesion of AD encompasses the accumulation of extracellular amyloid aggregates (plaques) formed of amyloid-β (Aβ) protein and of intracellular neurofibrillary tangles (NFT) of hyperphosphorylated Tau protein. According to the currently accepted amyloid cascade hypothesis, the major induction factor underlying the loss of cholinergic neurons in the cortex and hippocampus is the pathological accumulation of a smaller protein fragments known as amyloid-β which in turn is

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derived from a larger membrane protein called amyloid precursor protein (APP). Based on this hypothesis, several diagnostic and drug-based therapeutic interventions were suggested, mostly targeting amyloid-β and hyperphosphorylated Tau proteins. Several data have emerged that might indicate the inconsistency of the amyloid cascade hypothesis. Moreover, due to the purely palliative nature of AD drugs used so far, new stem cell-based therapy has been suggested as a promising potential therapeutic approach. Several cell sources have been used, such as embryonic stem cells, neural stem cells, mesenchymal stem cells, and induced pluripotent stem cells. While this suite of cell-based trials has shown promising results in preclinical paradigms, stumbling blocks still exist in the current treatment regimens. The present review highlights the recent perspective that argues against the long standing amyloid cascade hypothesis as well as the major efforts in the experimental application of stem cell-based therapies used as treatment options for AD, and discusses the major impediments against their successful translation into clinical.

Keywords: Aβ42 peptides, Alzheimer's disease, Amyloidogenesis, Amyloid precursor protein (APP), Neuronal stem cells, Pathogenesis, Senile, plaques, Stem cells-Therapy.

ALZHEIMER'S DISEASE PATHOPHYSIOLOGY

Since the discovery of Alzheimer's disease (AD) in 1907, two major pathological AD associated proteins composed of amyloid β (Aβ), a small fragment of a larger precursor protein called amyloid precursor protein (APP) and a microtubule-associated intraneuronal tau protein have been incriminated as the major etiology underlying the massive loss of cholinergic neurons in the cortex and hippocampus of the brain [1 - 3]. Using Sephadex G-100 column chromatography, and by high performance liquid chromatography, a purified protein was derived from fibrils in cerebrovascular amyloidosis associated with Alzheimer's disease has been isolated. This protein have no homology with any protein sequenced, and may provide a diagnostic test for Alzheimer's disease and a means to understand its pathogenesis [4].

A monoclonal antibody to the microtubule-associated protein tau (tau) labeled some neurofibrillary tangles and plaque neurites, the two major locations of paired-helical filaments (PHF), in Alzheimer disease brain. [5].

Massive neuronal loss is associated with major synaptic losses reflected clinically

as gradual loss of recent memory functions and late-life dementia [6]. Based on the observed AD-associated pathology, the "amyloid cascade hypothesis," was proposed [7, 8]. Major evidence for this hypothesis included the discovery that mutations of APP genes are among the major genetic makeup of AD [9, 10].

During the last century, the amyloid cascade hypothesis represented the roadmap by which AD can be diagnosed and treated. Unfortunately, in most cases, this simple straightforward linear hypothesis failed to explain the complex biological and molecular pathways associated with the perplexing and devastating AD pathology. Smith *et al.* [11] stated that alternate interpretations of old data as well as new evidence indicates that amyloid-beta, far from being the harbinger of disease, actually occurs secondary to more fundamental pathological changes and may even play a protective role in the diseased brain. These findings bring into doubt the validity of the Amyloid Cascade Hypothesis as the central cause of Alzheimer disease and, consequently, the potential usefulness of therapeutic targets against amyloid-beta protein. This became more clear when many of Aβ and tau-protein-based preclinical and clinical trials failed to restore lost neuronal and cognitive functions associated with AD pathology [12, 13].

The palliative nature of AD drugs developed so far and the failure of amyloid and tau-based therapeutic protocols have prompted several investigators not only to point out the possible inconsistency of the amyloid cascade hypothesis, but also to start searching for novel non-drug based therapeutic protocols such as stem cell-based therapy [14]. In this respect, several cell sources have been used with the aim to provide an ample supply of suitable progenitor cells that might restore the lost neuronal and synaptic elements associated with AD [15, 16].

This review explores novel data that may modify or replace the amyloid cascade hypothesis, and presents major experimental findings relevant to stem cell-based therapy for AD.

GENERAL VIEW ABOUT AD

AD represents one of the major public health burdens in elderly population. The ratio of AD occurence is approximately one to nine in individuals of age < 65 year old and such figures worsen as the population of the world ages to approximately

one in three over 85 years age [17]. AD pathology as collected and depicted in Fig. (**1**) include massive loss of cholinergic neurons in different brain areas such as the substantia nigra, subcortical structures such as the basal nucleus of Meynert and the locus coeruleus are also damaged [18].

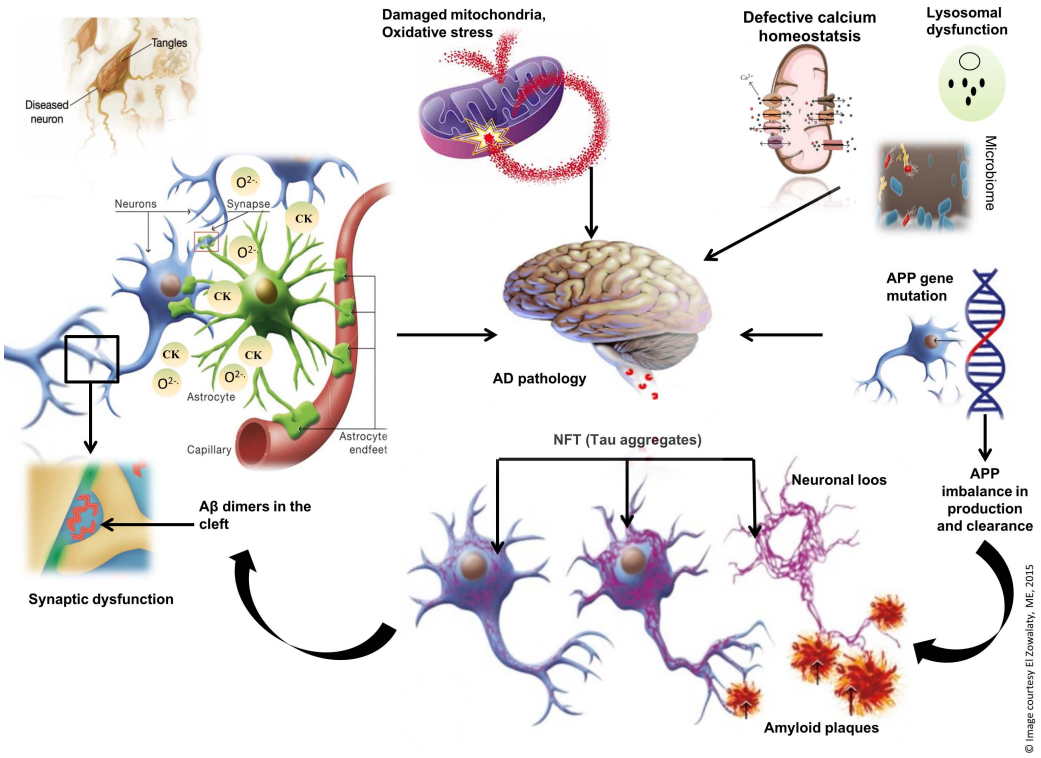


Fig. (1). Schematic representation of the pathology of Alzheimer's disease depicting the multifactorial perplexed feature of AD disease. The figure depicts the role of amyloid-β (Aβ) in the formation of extracellular amyloid aggregates which in turn will results in the formation of Tau aggregates and neurofibrillary tangles (NFTs) which contribute to the neuronal loss, synaptic dysfunction, and diseased neurons characteristic of AD. In addition, the periplaque activation of astrocytes, resulting in the release of various cytokines (CK), and microglia, leading to the generation of superoxide radicals (O^{2-}). The contribution of damaged mitochondria due to aging plays a role in the accumulation of free radicles which leads to change in the energetic efficiency of neuron. The loss of Ca^{2+} homeostasis explained by the excitotoxic activity is a core contributing cause in AD pathogenesis. Changes in the gut microbiome composition may also contribute to AD pathology. [Parts of the figure were reproduced with permission from references [17, 27, 32]].

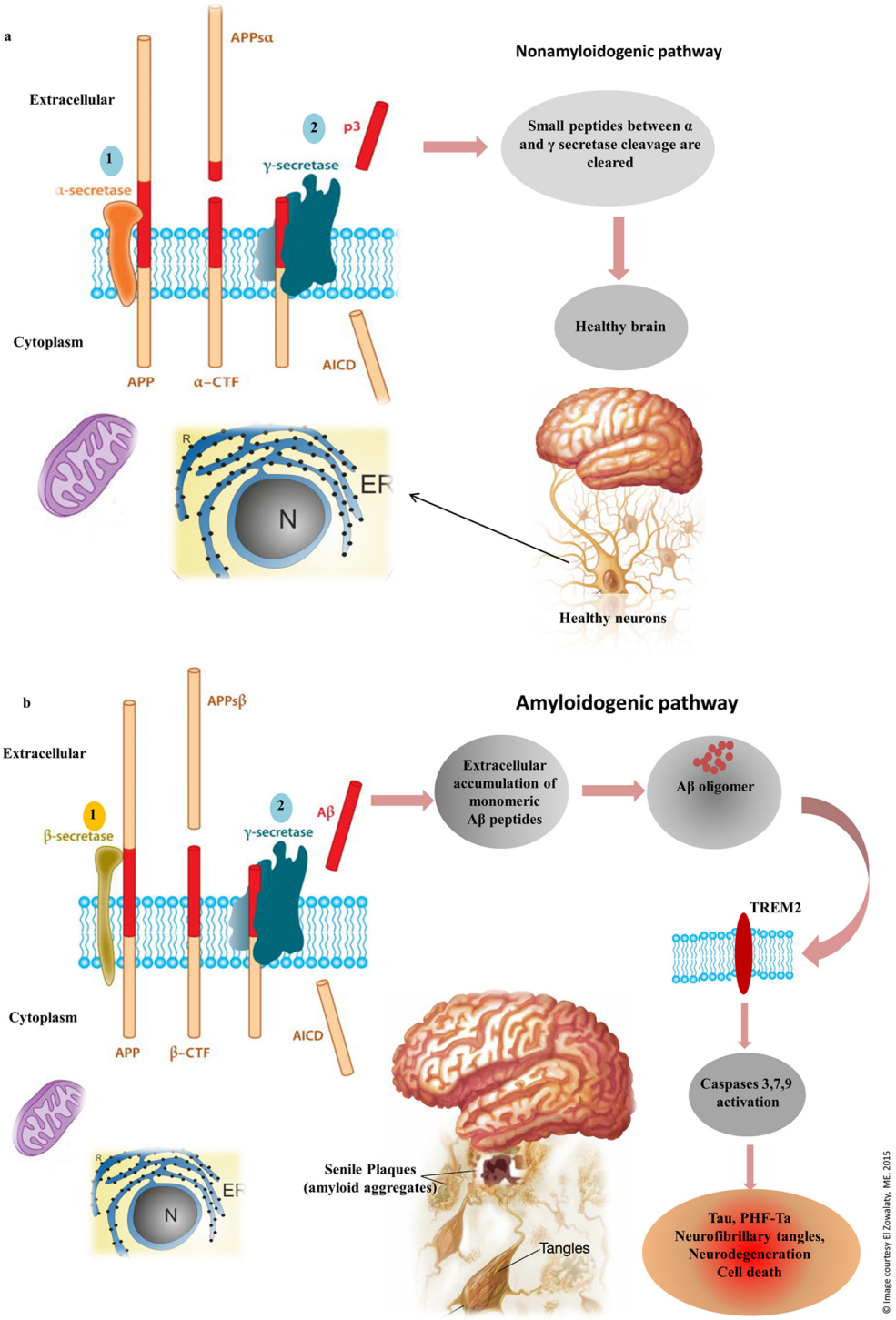
A major hallmark of AD pathology is the deposition of amyloid β and

hyperphosphorylated tau; this is usually associated with dramatic synaptic loss [2, 19]. These lesions explains the well-known AD symptoms ranging from loss of memory for recent events to complete dementia with severe behavioral symptoms such as apathy and depression [20, 21]. It is important to indicate that the inclusion of such hallmarks is arbitrary and perpetuates the difficulty of properly studying the etiology of AD, because it is nothing more than a tautological element in support of the amyloid cascade hypothesis: amyloid must be present in the brain in order for a patient to be defined as suffering from dementia of the AD type. That, by definition, eliminates the sub-population of clinically diagnosed AD patients with no amyloid load from the AD category, and hampers progress on our understanding of the disease.

GENETIC BASIS OF AD AND AMYLOID CASCADE THEORY

First, it is important to highlight that he pathogenic sequence of familial and sporadic AD are very different, and that there is no published evidence indicating that the latter begins with amyloid accumulation. Thus, the genetic basis of AD only applies to the familial form of the disease. A detailed discussion of this issue can be found in Ageing Research Reviews [21]. AD is a genetic disease and the two forms of the disease are recognized as early- and late-onset AD. Mutations in the amyloid precursor protein (APP) gene interfere with the normal cleavage process of APP leading to the formation of pathologic proteins especially in early onset AD [22].

Under normal conditions, the micro processing of APP involves two consecutive cleavage events [12, 24]. The first cleavage as was shown in Fig. (**2a**) occurs close to the outer cellular membrane and is mediated by the extracellular protease α-secretase leading to the formation of a soluble extracellular fragment sAPPα [10]. The second cleavage occurs within the membrane by an enzyme known as γ-secretase and leads to the formation of an intracellular peptide known as amyloid intracellular domain (AICD) and smaller peptides between the α- and γ-secretase cuts [10]. The benign nature of the second cut is mediated by one of the presenilin proteins, encoded by either *psen1* or *psen2* genes which affect the catalytic subunit of γ-secretase [10].


a
APPsα
Extracellular
1
α-secretase
2
p3
γ-secretase
Cytoplasm
APP
α–CTF
AICD
R
ER
N
Nonamyloidogenic pathway
Small peptides between α and γ secretase cleavage are cleared
Healthy brain
Healthy neurons
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APPsβ
Extracellular
1
β-secretase
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Aβ
γ-secretase
Cytoplasm
APP
β–CTF
AICD
R
ER
N
Amyloidogenic pathway
Extracellular accumulation of monomeric Aβ peptides
Aβ oligomer
TREM2
Caspases 3,7,9 activation
Senile Plaques (amyloid aggregates)
Tangles
Tau, PHF-Ta Neurofibrillary tangles, Neurodegeneration Cell death
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Fig. (2). The amyloid cascade hypothesis of Alzheimer's disease representing the classic theory of the origination of Alzheimer's disease (AD). The amyloid protein precursor (APP) is processed by two consecutive proteolytic pathway events. The first cleavage (**a**) occurs close to the outer membrane and is mediated by membrane embedded α-secretase which leads to the release of soluble extracellular domain (sAPP- α) and smaller peptides between α and γ secretase cuts, which are cleared in normal neurons. In AD (**b**), the APP metabolism is shifted from alpha to beta cleavage products by β- and γ-membrane embedded secretases. leading to the formation of extracellular Aβ monomers and oligomers which contribute to the formation of the senile plaques or amyloid aggregates, the enzymatic activation of caspases through TERM 2 receptor, formation of neurofibrillary tangles, neurodegeneration, and eventually cell death. Both processes produce identical intracellular C-terminal fragments (AICD), C-terminal fragment (CTF), and N-terminally truncated Aβ (p3). Parts of the figure were reproduced with permission from reference [20, 23]. Additional part of the figure were used with permission from Mayo Foundation for Medical Education and Research, Rochester, Minnesota, USA.

The α-secretase first cut is defective in case of AD as was shown in Fig. (**2b**) and APP is cleaved farther from the membrane by an aspartyl protease enzyme known as β-secretase, followed once again by γ-secretase cleavage [10]. The amino acid residue between the two cuts is mediated by β and γ cleavage sites form the amyloid-β (Aβ) peptide. The Aβ accumulates in the form of oligomers leading to the formation of amyloid plaques [25, 26].

The main genetic predisposition factor of AD encompasses three main genes APP, PSEN1, and PSEN2 which are implicated in the early onset, familial AD (fAD) [10]. Various mutations of these key player genes are known to interfere with APP cleavage, leading to increased production of $A\beta_{42}$ which is implicated in AD pathology [10]. This observation argues in favor of the amyloid cascade theory. Other supporting evidence for the amyloid cascade theory stems from the recent observation that mutation of APP near the β-secretase cleavage site interferes with the function of β-secretase, leading to decrease of Aβ production, and thus presumably having a protective role against AD pathology [27].

The Amyloid Cascade Hypothesis

The AD pathology develops gradually over a considerable period of time and it is explained by the imbalance in Aβ production and/or clearance. The amyloid hypothesis model was first proposed by Glenenr and Wong [28, 29]. The oligomeric and fibrillar forms of Aβ are the main driving factors behind the development of AD pathology which includes neuronal loss, synaptic dys-

function, and formation of neurofibrillary tangles [30].

Argument Against the Amyloid Cascade Hypothesis

The amyloid cascade hypothesis was poorly supported as summarized in Fig. (**3**) solely on the basis that AD genetics, involvement of APP, and its processing by presenilin. The amyloid cascade model did not provide a direct enough evidence for the involvement of Aβ as the main cause behind the initiation of AD pathology [31 - 33].

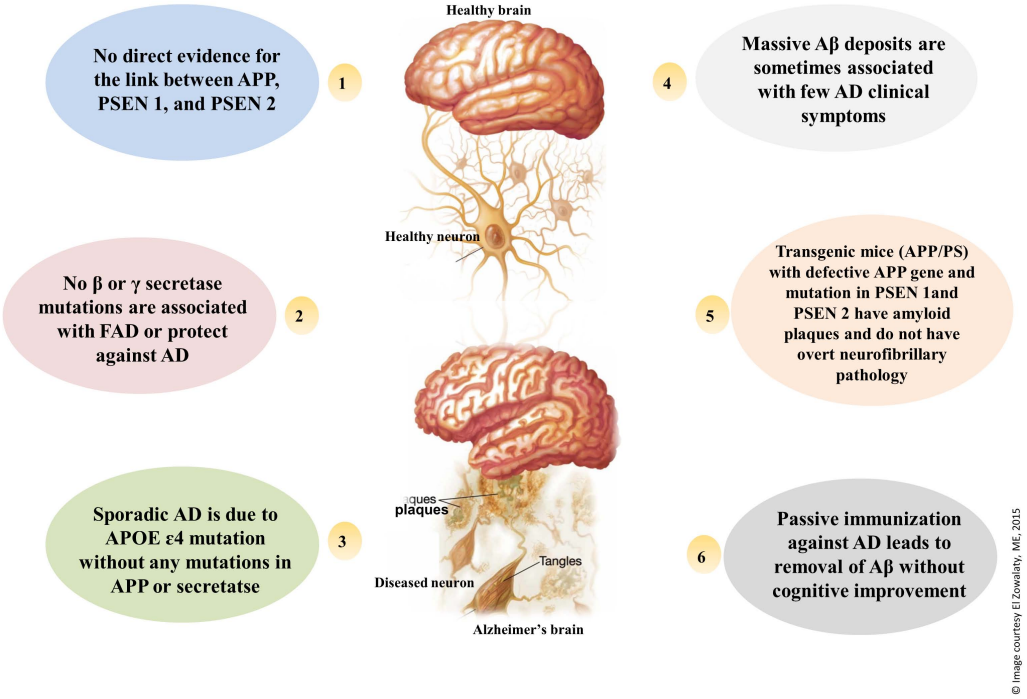

Fig. (3). Challenges to accept the amyloid cascade hypothesis. The figure depicts the different observations, controversies, and anomalies that have important implications in explanation of the pathogenesis of AD on the sole basis of amyloid β protein concept. [Parts of the figure were used with permission from Mayo Foundation for Medical Education and Research, Rochester, Minnesota, USA].

Despite the fact that amyloid cascade hypothesis is largely dependent on the presence of mutations of APP genes, uptill now there hypothesis was no evidence

that clearly link mutations in APP, and AD symptome. Moreover, no mutations were reported in either the β- or α-secretase, major enzymes responsible for cleavage of APP, that either lead to inductions of fAD or guard againist it [33].

Furthermore, the sporadic form of AD (sAD) is more prevalent that fAD, and its high risk is caused mainly by mutation in the apolipoprotein E (*APOE*) gene leading to a two-amino-acid switch in its normal amino acid sequence, thus producing the APOE4 variant of the protein [31]. Thus, sAD does not appear to involve genes for either APP or secretases as risk factors which might argues against the amyloid cascade hypothesis [10, 34].

Results from several experimental and clinical trials argue against the amyloid cascade hypothesis. In some individuals, massive amounts of amyloid aggregates could be localized in the brain with few if any clinical AD symptoms; thus amyloid is not sufficient to cause disease [35, 36]. Transgenic mice that carry a variant defective human APP gene together with a mutated form of presenilin 1 and 2 produce substantial amounts of amyloid in their brain and despite their poor performance in tests of spatial memory (such as the Morris water maze) they never develop any of the well-known AD pathology [37]. Moreover, transgenic mice that express amyloid-β peptide only, with no APP expression, develop a considerable amount of amyloid-β with no cognitive deficits [37], such data thus provide a strong suggestion that Aβ alone is not sufficient to cause the complex AD symptoms and pathology.

Beside apoE polymorphisms which are being linked to differential AD risks, current genome-wide association studies (GWAS) expand the early findings on apoE and highlight three key pathways as being linked to AD risk: cholesterol dysregulation, immune response and endocytosis. An increasing number of results implicating cholesterol metabolism in the pathophysiology of AD. Cholesterol, its transporter in the brain, apolipoprotein E, amyloid precursor protein, and amyloid-beta all interact in AD pathogenesis [38].

Removal of macroscopic plaques in mice through active and passive immunization against the Aβ peptide and the use of anti-inflammatory drugs was shown to be effective in removing amyloid plaques from the brain [39, 40]. The

clearance of Aβ plaques was associated with improvement in behavioral performance and restoration of the damaged neural networks. The rapid and nearly complete restoration of normal behavior may indicate that although these models may reproduce some of the early stages of AD, they do not fully represent the massive permanent damage that occurs along the course of AD in human patients [39, 41].

Immunization against Aβ in humans was tested in sAD subjects. Several participants have developed anti-amyloid antibodies and the plaque pathology was reported to be drastically reduced [42, 43]. Despite the great reduction in plaque load, the associated cognitive impairment did not improve, and in most cases the dementia appeared to be aggravated [44]. The most likely reason for this phenotype is the proposed protective role of amyloid in the brain. Understanding such role would clearly provide the intellectual framework that is currently missing in the discussions on the amyloid cascade hypothesis. In that regard, amyloid can be protective against upstream pathogenic triggers, such as cholesterol, inflammation and oxidative stress that are more solidly linked to AD than amyloid itself, both by GWAS as well as by population studies. This notion is a significant conceptual contribution to the debate, first proposed by the Perry lab, and has been discussed at length in the following references [21, 45].

Further arguments against the amyloid cascade hypothesis were deduced from repeated failure of clinical trials to demonstrate possible beneficial effects of anti-amyloid-β antibody therapy even after as much as 80 weeks of therapy [46, 47].

Therefore, AD pathology cannot be only explained based on a simple linear model such as the amyloid cascade hypothesis. Instead, there are alternative hypothesis to account for the development of the disease [48]. AD is a complex array of the lesions including damage in the brain's neuronal circuits, synaptic failure, neuritic atrophy, tauopathy, failure of autophagy, and lysosomal functions [49 - 51], and a loss of Ca^{2+} homeostasis which may be explained by the excitotoxic activity. These are considered the core mechanisms of AD [52 - 57]. Other studies have suggested that AD is associated with a failure of neuronal cell cycle control [58 - 67], neuroinflammation [68 - 73], progressive oxidative damage [74] that accumulates with age [75], DNA damage [76 - 83], loss of

mitochondrial function [84 - 86], or a complex senescence phenotype [87]. More recently, the involvement of human microbiota including bacteria and fungi in the secretion of lipopolysaccharides (LPS) and other related pro-inflammatory and neurotoxic substances which significantly contribute to AD-related neuro-degeneration and age-related neuroinflammation has been described [88 - 91]. Other possibilities include impairment in glucose metabolism [92, 93] or a general metabolic compromise [94 - 96]. Although Aβ was believed to be the most frequent underlying cause concomitant of the AD disease process, much evidence suggests that it is neither necessary nor sufficient alone to induce the AD associated damage. Each of the aforementioned processes may contribute in important pathways towards the development and progression of AD disease [31]. Recent GWAS studies have provided the strongest available evidence that other, non-amyloid factors are involved in late onset AD. This topic has been discussed at length in our recent paper [97].

Stem Cell-Based Therapy for AD

It was previously shown that the pathogenesis of AD is probably multifactorial. Effective therapeutic strategy for the treatment of AD has not yet been available. AD therapy should be comprehensive and tackle the complex multiple factors contributing to the pathogenicity of the disease. Recently, stem cell technologies have succeeded in generating different types of neuronal and glial cells from different types of stem cells. This achievement may be a crucial step in providing hope for the possible use of stem cell therapeutics as a novel treatment for AD [98 - 109].

Neural Stem Cell-Based Therapy for AD

Neural stem cells (NSC) are multipotent progenitor cells located in specific regions of the brains such as the subventricular zone (SVZ), the subgranular layer of the hippocampus, and olfactory bulbs. The cell characteristics fit well with the standards criteria for any viable stem cells, namely: the ability to self-renew, the ability to differentiate into different kinds of nervous tissue-specific cells (including neurons, astrocytes, oligodendrocytes) and the ability to replace damaged tissue following their engraftment as shown in Fig. (**4**). NSC have been

isolated from human fetal brain tissue [110, 111] and from different regions of adult human brain such as the olfactory bulb [112 - 115], cortex, hippocampus, and SVZ of the lateral ventricles [116]. Isolation of NSC from the human olfactory bulb (OB) provides a promising approach to cell-based therapy for AD which overcomes possible immunorejection, avoids ethical issues raised by the use of human embryos, and provides a chance for personalized medicine [117]. NSC can be transplanted either as a wild type or can be genetically engineered to overexpress several active substances of known trophic influences for different elements constituting the CNS tissues [118].

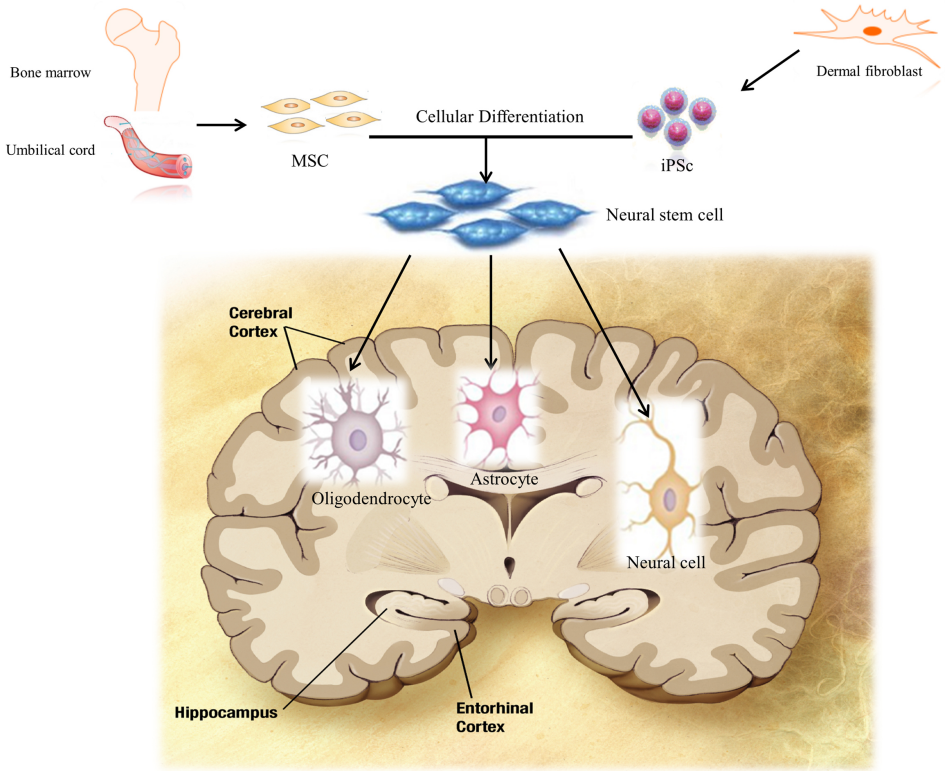

Fig. (4). Schematic representation showing the differentiation of neural stem cells (NSCs) into different types of nervous tissue-specific cells including neurons, astrocytes, or oligodendrocytes and the ability of these cells to replace damaged tissue following their engraftment. NSCs may be genetically programmed to produce neurotrophic factors such as brain-derived neurotrophic factor (BDNF), nerve growth factor, and vascular endothelial growth factor.

The marked ability of NSC to differentiate into neurons, astrocytes, and

oligodendrocytes following transplantation seems to be promising for cell-based therapy. In our previous studies, NSC isolated from the adult human OB (OBNSC) were able to proliferate in culture for several months [118]. The OBNSC differentiated into MAP2-immunoreactive mature neurons (17.5%) in the presence of 1% fetal bovine serum, β-tubulin immature neurons (5%), astrocytes (75%) and fewer oligodendrocytes (2.5%). The human OBNSC were genetically modified to overexpress human NGF (hNGF) and green fluorescent protein (GFP) genes [119]. Engraftment of human OBNSC into the hippocampus of an ibotenic acid-treated AD rat model restored memory deficits and hippocampal histo-architecture [112 - 115, 118]. Transplantation of F3. NGF human NSCs in mice following ibotenic acid-induced hippocampal damage was associated with improved cognitive functions, and restoration of lost neurons within the hippocampal regions, indicating the positive neurotropic effects exerted by the biological action of hNGF [120]. Direct intracerebral engraftment of NSC genetically modified to over-express nerve growth factor (NGF) gene promoted the hippocampal regeneration and restored age-related atrophy of cholinergic neurons [121].

Neurotrophins activate a number of signalling pathways relevant to neuro-protection; however, their poor pharmacological properties and their pleiotropic effects resulting from interaction with the p75(NTR)-Trk-sortilin three-receptor signalling system limit therapeutic application [122]. The traditional perspective of applying neurotrophins in the context of Alzheimer's disease is based on the premise that neurotrophins are capable of upregulating cholinergic function and of rendering neurons less vulnerable to certain processes causing degeneration [123]. Neurotrophins have potential for the treatment of neurological diseases. However, their therapeutic application has been limited owing to their poor plasma stability, restricted nervous system penetration and, importantly, the pleiotropic actions that derive from their concomitant binding to multiple receptors. One strategy to overcome these limitations is to target individual neurotrophin receptors — such as tropomyosin receptor kinase A (TRKA), TRKB, TRKC, the p75 neurotrophin receptor or sortilin — with small-molecule ligands [124, 125]. Application of neurotrophic factors able to modulate neuronal survival and synaptic connectivity is a promising therapeutic approach for AD. Ciliary neurotrophic factor (CNTF)

and/or CNTF receptor-associated pathways may have AD-modifying activity through protection against progressive Aβ-related memory deficits [126]. Ciliary neurotrophic factor oral administration in 3xTg-AD and wild type female mice was associated with significant reduction in abnormal hyperphosphorylation and accumulation of tau at known major AD neurofibrillary pathology [127].

NSC can be derived from different primary tissues such as fetal, postmortem, neonatal or adult brain tissues [109], or from ESCs and iPSCs [128 - 130]. In an AD mouse model, the engrafted NSCs survived, differentiated into different neuronal and glial elements, and improved learning and memory function [131, 132]. Transplantation of rat NSC in fimbria-fornix has been shown to improve memory function, and to restore lost cholinergic neurons [133, 134].

The specific microenvironment (niche) of the recipient brain has been shown to have a major impact on the proliferation and differentiation potential of the engrafted NSCs. In this regard, it has been revealed that overexpression of human amyloid precursor protein shifted the differentiation potential of the engrafted NSCs to form more astrocytes than neurons or oligodendrocytes [135]. In contrast, it was previously demonstrated that genetic engineering of NSC to over-express nerve growth factor (NGF) helped promote proliferation and differentiation of engrafted NSC. It was demonstrated that NSCs that are genetically modified to stably express hNGF engrafted well into the cerebral cortex of AD rats and enhanced different cognitive parameters; an effect that was not show upon engraftment of non-genetically manipulated NSC [100].

NSCs have also been used as a vehicle for several amyloid-inhibitory genes such as neprilysin, insulin degrading enzyme, plasmin, and cathepsin B [107]. Fibroblast-delivered neprilysin has been shown to reduce amyloid plaques in AD mice [102, 136]. Engraftment of embryonic NSCs isolated from embryonic medial ganglionic eminence (MGE) into the hippocampal hilus of aged apoE4-KI mice (with or without Aβ accumulation) developed into mature inhibitory interneurons and rescued learning and memory despite the toxic environment created by Aβ and apoE4 [137]. Such inhibitory GABAergic interneurons could connect to more than thousands of excitatory neurons leading to significant improvement of learning and memory functions [138, 139].

Several other cellular sources have been used to treat animal models of AD pathology in addition to NSCs such as embryonic stem cells (ESCs), mesenchymal stem cells (MSCs), and induced pluripotent stem cells (iPSCs) and these cells have been shown to be effective in removal of AD pathology. These cells can improve the cognitive ability of animals [120, 133, 134, 140 - 146] by cell replacement [140, 144], Aβ reduction [133, 134, 141, 142], neurotrophic action [133], and immune modulation [122]. Following engraftments, ESCs, NSCs and MSCs-derived from bone marrow have been shown to survive, migrate, and differentiate into cholinergic neurons, restoring spatial learning and memory ability for AD animal models [142].

Induced Pluripotent Stem Cell-Based Therapy for AD

De novo generation of neurons from iPSCs seems to be a promising approach for AD treatment. New neurons generated from iPSCs from familial AD patients exhibited positive MAP2 and β III-tubulin expression, normal electrophysiological activity *in vitro*, and formed functional synaptic contacts. The genetic background of AD patients from which iPSC-derived neurons originated is reflected in the formed neurons, which displayed similar pathological features [147]. This observation necessitates the final tuning of iPSC technology before translation into AD patients. One possible way to alter the associated mutation is the use of recent genome editing protocols to eliminated associated deleterious AD variants.

Direct programming of somatic cells into functional neurons or induced neurons (iN) seems to be a possibly effective protocol for AD cell-based therapy. The iN might represent a direct source of replacement for lost neurons that are associated with AD pathology. However, such direct differentiation protocols usually provide low yields of non-proliferated, terminally differentiated neurons. The lower cellular yield in this protocol might limit its broad application in cell-based therapy for AD [148]. It is suggested that direct reprograming of somatic cells into induced neural progenitor cell (iNPCs) which have the ability to differentiate into all types of neural cells would be a potential promising therapeutic strategy for AD pathology [149 - 151].

A major breakthrough in the field of stem cell-based therapy for AD has been achieved in converting somatic cells into iNSCs using defined transcription factors [152, 153]. The iNSCs elicited in this technique have been shown to share similarities with NSC in proliferation, differentiation, and self-renewal capabilities. The iNPCs were also obtained from mouse embryonic fibroblasts using chemical cocktails under a physiologically hypoxic condition, without overexpression of exogenous genes [154, 155]. Direct conversion of somatic cells into iNPCs may well overcome the ethical issue associated with the collection of cells from human embryos, and at the same time it should help to reduce the tumorigenic nature of the iPSCs [154, 156].

Despite the apparent success in the direct reprogramming of somatic cells into iN, and iNPSc which have proven to be able to give rise to all types of neural cells, efficient induction of cholinergic neurons from NSC and iNPCs remains a challenge. Under typical culture condition, the great majority of NSCs/NPSCs seem to be converted into glial restricted states, with low efficiency for specific neuronal subtypes [157]. Moreover, most of the transplanted NSCs/NPCs tend to be converted into astrocytes, especially in response to injury [158, 159]. Based on these observations, it seems plausible that using AD cell-based strategy that have been primarily directed to produce specific neuronal subtypes, such as forebrain cholinergic neurons, will be more effective, especially the apparent loss of cholinergic neurons associated with AD pathology, and the selective degeneration of septal and hippocampal GABAergic neurons reported in AD mouse models [160]. Thus, direct conversion of somatic cells into GABAergic neuronal progenitor seems to be a promising avenue for further exploration in strategies for AD treatment.

One of the recently discovered protocols that might revolutionize the field of cell-based therapy of AD is the direct *in vivo* conversion of somatic cells such as astrocyte into region-specific iPNCs in the AD brain [161, 162]. These studies will contribute to the conversion of active astrogliosis into neurogenesis, possibly leading to the formation of disease specific neurons, such as forebrain cholinergic neurons. Such novel therapeutic strategy could potentially overcome the need for an invasive transplantation protocol, and also provide an effective tool for personalized medicine.

Expert View and Future Perspectives

The amyloid cascade hypothesis is a relatively simple linear theory that relates most if not all of the AD pathology to the pathological aggregation of amyloid beta in brain regions known to be involved in learning and memory. Defective APP breakdown products formed as result of mutations of key AD-related genes may be at the core of AD pathology. Despite the central role of Aβ in the initiation of AD pathology proposed in the amyloid cascade hypothesis, a number of alternative mechanistic pathways of viewing the disease have been suggested, such as progressive loss of integrity in the brain's neuronal networks, gradual decrease in synaptic density, increasing neuritic atrophy, and eventually widely dispersed cell loss. Moreover, there is enough evidence to support that AD represents a failure of autophagy and/or lysosomal function, loss of Ca^{2+} homeostasis due perhaps to excitotoxic activity. Other alternative causes include failure of neuronal cell cycle control, neuroinflammation, progressive oxidative damage that accumulates with age, DNA damage, loss of mitochondrial function and general metabolic compromise. These have all been argued to be root causes of the disease.

Amyloid is a frequent contributor to the AD disease process, however evidence suggests that it is neither necessary nor sufficient. The biology of AD is perhaps one of the most perplexing systematic malfunctions of the nervous system so far known. Indeed, it is likely that we will need to address all of the listed options if we are to cure AD or completely prevent it.

Cell-replacement therapy for AD has achieved some success in animal models of AD. Although these preclinical studies are promising, many obstacles are required to be addressed before successful translation into therapy for human AD patients can be achieved. Different types of stem cells are used for testing cell-based therapy in animal models of AD, such as embryonic, mesenchymal, and neural stem cells, and recently induced pluripotent stem cells were included. These cells are either engrafted without any genetic manipulation as naive wild type cells or they are genetically engineered to overexpress specific biologically active substances that can alter AD molecular pathways. At the preclinical level, most of the engrafted cells survived, proliferated, and differentiated into different neuronal

subtypes, although the hostile environment of AD in many cases favors the transformation of them into astrocytes rather than neurons. This caveat prompted many investigators to directly reprogram somatic cells into specific cell types such as the cholinergic neurons that are known to be lost in AD brain. The low yield of differentiated neurons also prompted many investigators to find a mechanism by which somatic cells could be transformed into neuronal progenitor cells rather than fully differentiated neurons. Such approaches should enhance the proliferative and differentiating features of the transformed cells to enhance the ability to replace all of the lost neuronal and glial cell types.

Progress in the stem cell research field has also opened new windows to the generation of region-specific and subtype-specific neural progenitors through direct reprogramming from somatic cells, thus creating another new concept for potential AD treatment. Moreover, instead of cell transplantation, directly reprogramming of activated astrocytes already in the pathological site of AD brain into region- or subtype-specific iNPCs by direct injection of defined factors *in vivo*, could be a promising strategy. Development of comprehensive therapeutic protocols for provision of different cell types and stages, together with anti-Aβ, and anti-Tau antibodies will be a crucial step for clinical translational studies in human AD patients.

CONFLICT OF INTEREST

The author confirms that he has no conflict of interest to declare for this publication.

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