Adult Neurogenesis, Neural Stem Cells and Alzheimer's Disease: Developments, Limitations, Problems and Promises

Philippe Taupin*

School of Biotechnology, Dublin City University, Glasnevin, Dublin 9, Ireland

Abstract: Alzheimer's disease (AD) is an irreversible progressive neurodegenerative disease, leading to severe incapacity and death. It is the most common form of dementia among older people. AD is characterized in the brain by amyloid plaques, neurofibrillary tangles, neuronal degeneration, aneuploidy and enhanced neurogenesis and by cognitive, behavioural and physical impairments. Inherited mutations in several genes and genetic, acquired and environmental risk factors have been reported as causes for developing the disease, for which there is currently no cure. Current treatments for AD involve drugs and occupational therapy, and future developments involve early diagnosis and stem cell therapy. In this manuscript, we will review and discuss the recent developments, limitations, problems and promises on AD, particularly related to aneuploidy, adult neurogenesis, neural stem cells (NSCs) and cellular therapy. Though adult neurogenesis may be beneficial for regeneration of the nervous system, it may underlie the pathogenesis of AD. Cellular therapy is a promising strategy for AD. Limitations in protocols to establish homogeneous populations of neural progenitor and stem cells and niches for neurogenesis need to be resolved and unlocked, for the full potential of adult NSCs to be realized for therapy.

Keywords: Amyloid, aneuploidy, cellular therapy, neurodegenerative diseases, pathogenesis, presenilin.

INTRODUCTION

AD was first described by Alois Alzheimer in 1906. Alois Alzheimer reported the presence of amyloid or senile plaques and neurofibrillary tangles in the brain of patients with severe dementia [1]. AD is a neurodegenerative disease, associated with the loss of nerve cells in areas of the brain that are vital to memory and other mental abilities, like the entorhinal cortex, hippocampus and neocortex. The disease is characterized by progressive cognitive, behavioral and physical impairments [2, 3]. It is the most common form of dementia among elderly, with 50 to 70% of clinical cases confirmed as AD, *post-mortem*. Aging is the major contributing factor for increased risk of developing AD. The risk of developing AD doubles every 5 years after the age of 65. AD affects 30% of individuals of age over 80 [4]. It affects more than 26 millions of patients worldwide; this number is expected to quadruple by 2050 as population age [5].

Neurogenesis occurs throughout adulthood in mammals [6, 7]. It occurs primarily in two regions of the adult brain, the subventricular zone (SVZ) and the dentate gyrus (DG) of the hippocampus, in various species including humans [8-10]. In the DG, newly generated neuronal cells in the subgranule zone (SGZ) migrate to the granule cell layer, where they differentiate into granule-like cells and extend axonal projections to the CA3 region of the Ammon's horn. Newly generated neuronal cells in the anterior part of the SVZ migrate through the rostro-migratory stream to the olfactory bulb, where they differentiate into interneurons, granule and periglomerular neurons [11]. Newly generated neuronal cells in the adult brain originate from residual stem cells [12]. NSCs are the self-renewing multipotent cells that generate the main phenotypes of the nervous system. Newly generated neuronal cells of the adult brain may be involved in a broad range of physio- and pathological processes, like learning and memory, AD, epilepsy and schizophrenia [13-16]. The confirmation that adult neurogenesis occurs in the adult brain and NSCs reside in the adult central nervous system (CNS) has tremendous implications for our understanding of development, physio- and pathology and for cellular therapy. On the one hand, newly generated neuronal cells of the adult brain would contribute to plasticity and regeneration of the nervous system [17]. The adult CNS has the potential to self-repair. On the other hand, they may be involved in the pathology and pharmacology of neurological diseases and disorders, and particularly AD [18].

In this manuscript, we will review and discuss the potential contribution of newly generated neuronal cells of the adult brain to the pathogenesis of AD and of adult NSCs for cellular therapy, for the treatment of AD.

ALZHEIMER'S DISEASE PATHOLOGY AND PATHOGENESIS

Clinical and Histopathological Diagnosis

Doctors diagnose AD primarily by symptoms, cognitive impairments, behavioural changes and risk factor assessments [19-21]. There are two forms of the disease. Late-onset AD (LOAD) refers to cases of AD diagnosed after the age of 65. Early-onset AD (EOAD) refers to cases of AD diagnosed at younger age. Most cases of LOAD are sporadic. They are believed to be caused by a combination of

*Address correspondence to this author at the School of Biotechnology, Dublin City University, Glasnevin, Dublin 9, Ireland. Tel: (01) 700-7058; E-mail: philippe.taupin@dcu.ie

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genetic risk factors, like the presence ApoE varepsilon 4 allele (*ApoE4*), acquired risk factors, like hypertension and diabetes, and environmental risk factors, like neuroinflammation and oxidative stress [22]. LOAD accounts for the majority, over 93%, of all cases of AD. In contrast, EOAD is a rare form of the disease and is mostly inherited. Inherited form of AD is also known as familial Alzheimer's disease (FAD). It is caused by mutations in so-called familial Alzheimer genes, like the gene of β-amyloid precursor protein (APP). About 200 families in the world carry the gene mutations that cause EOAD. Once diagnosed, the average life expectancy of patients with AD is 8.5 years, though the disease can last for as many as 20 years.

Amyloid plaques and neurofibrillary tangles are hallmarks of AD, Fig. (**1**). They are deposits of proteins distributed throughout the brain of patients with AD, particularly in the entorhinal cortex, hippocampus, temporal, frontal and inferior parietal lobes. Their density increases as the disease progresses. However, the correlation between the density of amyloid plaques and the severity of the dementia is not clearly established [23]. Amyloid plaques are thought to be the first histological changes that occur in AD [24]. AD is associated initially with the loss of nerve cells in areas of the brain that are vital to memory and other mental abilities, like the entorhinal cortex, hippocampus and neocortex, but also in regions of the brain important to sense of smell. As the disease progresses, other regions of the brain are affected, including the medial temporal area, lateral hemisphere, basal forebrain and locus coeruleus. This leads progressively to the overall shrinkage of the brain, severe incapacity and death [25]. Autopsies are performed to assess the presence of amyloid plaques and neurofibrillary tangles, the extent of the degeneration and to confirm earlier diagnosis.

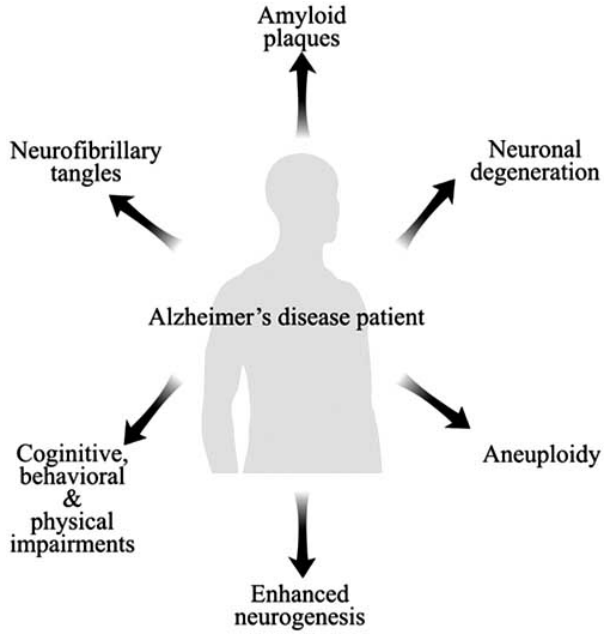

Fig. (1). Alzheimer's disease is the most common form of dementia among elderly. AD is characterized in the brain by amyloid plaques, neurofibrillary tangles, neuronal degeneration, aneuploidy, enhanced neurogenesis and cognitive, behavioural and physical impairments. The origin and contribution of these processes to the etiology and pathogenesis of AD remain mostly unknown.

Amyloid Plaques and Neurofibrillary Tangles

Amyloid plaques are extracellular deposits of proteins, surrounded by degenerating nerve cells in the brain of patients with AD and in the retina of patients with aged-related macular degeneration [26]. They are composed of amyloid fibrils and α1-antichymotrypsin (ACT), a serine protease inhibitor. Protein β-amyloid is a 42 amino acid β-peptide originating from the post-transcriptional maturation of APP [27]. It is synthesized and secreted by nerve cells, as a soluble peptide. The gene for APP is located on chromosome 21q21 [28, 29]. Protein β-amyloid is an amyloidogenic protein; proteins forming amyloid fibrils [30]. Amyloidogenic proteins are monomer and soluble in their physiological state. Under pathological conditions, they form insoluble extracellular aggregates or deposits of amyloid fibrils [31]. Deposit of amyloid fibrils in the brain of patients with AD results from aggregation of protein β-amyloid. They arise when protein β-amyloid is induced to form filaments by amyloid-promoting factors expressed in certain regions of the brain or under certain gene mutations, including in *APP*. The aggregation of protein amyloid results from the abnormal processing of *APP*. According to the amyloid hypothesis, protein β-amyloid deposit may cause AD. As the amyloid deposits develop in the brain, the brain cells start dying and the signs and symptoms of AD begin [32, 33]. Alternatively, the over-expression of protein β-amyloid or of mutated form of the protein may be the cause leading to the pathology of AD [34]. In support of this contention, the correlation between the density of amyloid plaques and the severity of dementia is not clearly established [23]. In this latter model, the deposit of protein β-amyloid would be a consequence rather than a cause of AD. The contribution of protein β-amyloid to the etiology and pathogenesis of AD remains to be fully understood and determined.

Neurofibrillary tangles are deposits of proteins present inside neuronal cells in the brain of patients with AD. They are composed of hyperphosphorylated Tau proteins [35]. Tau protein is a microtubule-associated phosphoprotein. It is an axonal protein involved in the formation of microtubules [36]. Tau proteins interact with tubulin to form the microtubules [37]. Microtubules are involved in the structure, transport and division of cells. The *TAU* gene is located on chromosome 17q21.1 [38]. The phosphorylation of Tau is modulated by phosphatases and kinases. It regulates the binding of Tau to microtubules. The phosphorylation of Tau decreases the binding of Tau to microtubules. It results in instability of the microtubules and aggregation of Tau proteins. In AD and tauopathies, Tau protein is hyperphosphorylated by kinases [39]. It leads to the dissociation between Tau and tubulin. This triggers the breakdown of microtubules and the polymerization and aggregation of Tau proteins [40]. It results in the formation of neurofibrillary tangles and cell death [41].

These mechanisms underlying the formation of amyloid plaques and neurofibrillary tangles are not fully understood. They are likely to be different depending on whether AD is caused by genetic mutations or genetic, acquired or environmental risk factors.

Genetic Factors

EOAD is a rare form of AD, mostly inherited, caused by mutations in familial Alzheimer genes [42]. Mutations in these genes almost always result in the individual developing the disease [43]. The patients generally have a family history with EOAD. Three genes have been identified for the FAD. These are the *APP* gene, the presenilin-1 (*PSEN-1*) gene and the presenilin-2 (*PSEN-2*) gene [44]. In contrast, no single causal genetic mutation has been identified for LOAD [45]. LOAD is believed to be caused by a combination of genetic, acquired and environmental risks factors [46-50]. These risk factors increase the probability of developing the disease. Their absence does not mean that AD will not develop. The identification of gene mutations linked to LOAD has mainly been performed by single-nucleotide polymorphism studies to link the genetic polymorphism to the disease. The apolipoprotein E (*APOE*) gene is the best established genetic risk factor for LOAD. It accounts for the vast majority of causes and risks to develop AD [51].

Familial Alzheimer genes. APP is a 695-770 amino acid protein. It is normally synthesized and present in the brain and other tissues. APP plays a role in various cell functions, like cell adhesion and neurite growth. APP is processed by α-, β- and γ-secretase enzymes. In physiological conditions, it is cleaved by the α and γ-secretase enzymes into a 40 amino acid β-peptide. Mutations in the APP gene cause excessive cleavage of APP, by the β- and γ-secretase enzymes. This results in increased production of the 42 amino acid β-amyloid peptide; this latter form of protein β-amyloid aggregates into insoluble amyloid deposits, particularly in the brain. The presenilin proteins are components of the γ-secretase complex. These enzymes play a role in the maturation of APP into the 42 protein β-amyloid [52]. Mutations in the *PSEN-1* gene and *PSEN-2* gene lead to excessive cleavage by γ-secretase enzyme, resulting in increased production and aggregation of protein β-amyloid [53]. The *PSEN-1* gene and the *PSEN-2* gene are located on chromosome 14q24.3 and 1q31–q42, respectively [52]. Among the cases of EOAD for which a genetic mutation has been identified as cause of the disease, 30-70% of the mutations are in the *PSEN-1* gene, 10-15% in the *APP* gene and less than 5% in the *PSEN-2* gene [21]. For many individuals/families with cases of EOAD, the genetic mutation causative of the disease has not been determined. There are other gene mutations involved in EOAD to be identified.

Genetic risk factors. Several genes have been identified as risk factors for LOAD. Among them, the *ApoE* gene and the neuronal sortilin-related receptor (*SORL1*) gene [54, 55]. ApoE is a plasma protein. It plays a role in the transport and metabolism of lipids. ApoE is a ligand for the low density lipo-protein receptors. Through interaction with these receptors, it participates in the transport of cholesterol and other lipids, to various cells of the body [56]. There are three major isoforms of ApoE, ApoE2, ApoE3 and ApoE4, encoded by different alleles in humans. The ApoE2 isoform occurs in 10%, ApoE3 in 74% and ApoE4 in 16% of white populations. Individuals who have the *ApoE4* allele have increased risk of developing AD. Up to 50% of people who have AD have at least one *ApoE4* allele. People who have two *ApoE4* alleles have a higher risk of developing AD, after age of 65 [57]. It is estimated that one copy of the *ApoE4* allele reduces the age of onset by 7-9 years [58]. The role of ApoE4 in the etiology and pathogenesis of AD remains to be established. In patients with AD, ApoE is localized in amyloid plaques and neurofibrillary tangles. ApoE4 may promote the formation of amyloid plaques, by a mechanism yet to be determined [59]. The *ApoE* gene is located on chromosome 19q13.2. SORL1 belongs to a family of proteins termed retromer. Retromers are involved in intracellular trafficking. SORL1 is involved in the trafficking and recycling of APP [60]. Reduced expression of the *SORL1* gene is associated with an increase in the risk for LOAD. It is also associated with an increase in density of amyloid plaques. The decreased expression of SORL1 is linked to variants in at least two different clusters of intronic sequences in the *SORL1* gene. The variants of *SORL1* may promote AD by suppressing the activity of the gene. This may affect the processing of APP and increase its production [55]. Variants for the genes coding for α2-macroglobulin, monoamine oxidase A and myeloperoxidase have been linked with the occurrence of LOAD. α2-Macroglobulin is a protease inhibitor found in neuritic plaques. The α2-macroglobulin gene is located on chromosome 12p13.3. Monoamine oxidase A is a regulator of the metabolism of neuroactive and vasoactive amines within the CNS. Myeloperoxidase is an enzyme present in circulating monocytes and neutrophils; it catalyses the production of the oxidant hypochlorous acid. Myeloperoxidase is thought to contribute to the pathology of AD through oxidation of either protein β-amyloid or ApoE. Studies have reported a linkage between the polymorphism of the gene for cystatin C (*CST3*) with LOAD [61]. There are also evidences that polymorphisms within the genes of the folate methionine and homocysteine metabolic pathways are involved in the pathogenesis of AD [45, 62, 63].

Other genes have been identified as promoting the risk factors of identified genetic risk factors. GRB-associated binding protein 2 (GAB2) belongs to a family of proteins that plays a central role in signalling by receptor protein-tyrosine kinases [64]. Mutations in the GAB2 gene are linked with increasing risk of LOAD, in people with ApoE4 allele [65]. *GAB2* gene may offset some of the ApoE4 associated risks for developing AD, by inhibiting the formation of amyloid plaques, whereas mutation in the *GAB2* gene would promote the formation of amyloid plaques, in people with *ApoE4* allele.

Sporadic forms of AD are the most common cases of AD. They most generally develop after age 65. They correspond to most cases of LOAD. The genetic risk factors in sporadic forms of AD present an unclear mode of inheritance. Sporadic cases of EOAD can occur, with no family history and no identified causal genetic mutations. Cases of FAD can occur after age of 65 [66]. The causal mutations involved in these forms of LOAD remain unidentified.

Chromosome 21 and Aneuploidy

Several studies reveal that cells from patients with AD elicit aneuploidy, particularly for chromosome 21. Preparations of lymphocytes of patients with sporadic form of AD elicit an elevation in aneuploidy for chromosomes 13

and 21, particularly for chromosome 21 [67, 68]. Preparations of lymphocytes of patients with AD, familial and sporadic forms, elicit a 2-fold increase in the incidence of aneuploidy for chromosomes 18 and 21 [69]. Deposit of protein amyloid is one of the histopathological features of AD and one of the probable cause for the pathogenesis of AD. The *APP* gene is located on chromosome 21 [28, 29]. Aneuploidy for chromo-some 21 has been proposed as one of the mechanisms underlying the pathogenesis of AD [70]. The synthesis and deposit of protein amyloid could have for origin the overexpression of mutant or wild type amyloid protein in aneuploid cells, due to the duplication of the *APP* gene that resides on chromosome 21, in patients with FAD or sporadic form of AD respectively.

Patients with Down's syndrome develop, during their 30^s and 40^s, dementia and neuropathology that share characteristics with AD [71-73]. Down's syndrome has for pathogenic cause trisomy for the chromosome 21 [74]. Aneuploidy for chromosome 21 would underly the pathogenesis of the dementia that occurs in Down's syndrome and AD patients [70]. Cells that are the most likely to develop aneuploidy are dividing cells. Aneuploidy results from the non-disjunction of chromosomes during mitosis or meiosis [75]. A wide range of cells elicit aneuploidy in patients with AD [67-69]. The non-disjunction of chromosomes, particularly of chromosome 21, in stem cells and/or populations of somatic cells that retain their ability to divide could be at the origin of aneuploidy in patients with AD. The origin of aneuploidy in patients with Down's syndrome would result from the non-disjunction for chromosome 21 in germ cells, during meiosis [70].

According to this model, genetic, acquired and environmental factors that promote or contribute to aneuploidy, particularly for chromosome 21, would increase the risk of developing AD. Mutated forms of PSEN-1 are detected in the centrosomes and interphase kinetochores of dividing cells. Mutated PSEN-1 may then be involved in the segregation and migration of chromosomes [76]. Mutation in *PSEN-1* is a causative factor for EOAD. Mutated PSEN-1 may contribute to the pathogenesis of FAD not only by abnormally processing APP, but also by promoting the non-disjunction of chromosomes and aneuploidy in cells. In AD and tauopathies, Tau is hyperphosphorylated by kinases, leading to the dissociation between Tau and tubulin and the breakdown of microtubules [39, 40]. The breakdown of microtubules, by hyperphosphorylated Tau, could promote aneuploidy by causing defects in the mitotic spindle during mitosis. Hyperphosphorylated Tau is a component of neurofibrillary tangles, a histopathological hallmark of AD and a probable cause for cell death in AD patients. Hyperphosphorylated Tau protein may contribute to the pathogenesis of AD not only by the polymerization and aggregation of Tau proteins, resulting in the formation of neurofibrillary tangles and cell death [41], but also by promoting the non-disjunction of chromosomes and aneuploidy in cells. Hence, mutated PSEN-1 and hyperphosphorylation of Tau could promote aneuploidy in somatic cells, particularly for chromosome 21, leading to AD.

The *PSEN-1* and *TAU* genes are located on chromosomes 14 and 17, respectively [38, 52]. Aneuploidy for chromosomes 14 and 17 could lead to an over-expression of mutated PSEN-1 and Tau, respectively, further increasing the risk of aneuploidy and of the formation of neurofibrillary tangles. Aneuploidy for chromosomes 14 and 17 may therefore also contribute to increase the risk of developing AD and the progression of the disease. Oxidative stress promotes aneuploidy for chromosome 17 [77]. Oxidative stress is an environmental risk factor for developing AD [22]. It may act as a risk factor for AD, by promoting the expression of Tau proteins, which hyperphosphorylation causes the formation of neurofibrillary tangles. β-Amyloid, reactive oxygen species and oxidative stress induce cell cycle re-entry and neuronal death [78-81]. A "two-hit hypothesis" has been proposed to conciliate the activity of oxidative stress and abnormal mitotic signalling, like abortive cell cycle re-entry or gene duplication without cell division leading to cell death, as causative factors of AD. Oxidative stress and abnormal mitotic signalling can act independently as initiators; however both processes are necessary to propagate the pathogenesis of AD [82]. Abnormal mitotic signalling may lead to a small population of aneuploid cells that over-express genes that contribute to the development of the disease, like *APP* and *TAU*. As these cells undergo cell death, they trigger an inflammatory reaction in the regions of amyloid and neuritic plaques formation. This further promotes the development of the disease. In this model, individuals may eventually develop the disease, over a longer period of time.

In all, chromosomes non-disjunction and aneuploidy are contributing factors for the pathogenesis of AD by promoting the expression of genes involved in AD; this primarily by promoting the formation of amyloid deposits and neurofibrillary tangles.

Enhanced Neurogenesis in the Brain of Patients with Alzheimer's Disease

The expression of markers of immature neuronal cells, like doublecortin and polysialylated nerve cell adhesion molecule, is increased in hippocampal regions, particularly the DG, in the brain of patients with AD [83]. In animal models of AD, neurogenesis is enhanced in the DG of transgenic mice that express the Swedish and Indiana APP mutations, a mutant form of human APP [84]. It is decreased in the DG and SVZ of mice deficient for PSEN-1 and/or APP, in transgenic mice over expressing variants of APP or PSEN-1 [85-89]. It is decreased in the DG of PDAPP transgenic mouse, a mouse model of AD with age-dependent accumulation of protein β-amyloid [90]. Transgenic mice that express the Swedish and Indiana APP mutations, mice deficient for PSEN-1 and/or APP and transgenic mice over expressing variants of APP or PSEN-1 are transgenic mice that express variants of FAD genes. The discrepancies of the data observed on adult neurogenesis in autopsies and animal models of AD may originate from the validity of the animal models, particularly transgenic mice, as representative of AD and to study adult phenotypes [91]. Mice deficient for APP and PSEN-1 provide information on the activities and functions of the proteins involved in AD. They do not represent the disease. The effects of genetic mutations during development may have adverse effects on adult phenotypes, like adult neurogenesis. Aggregation of protein β-amyloid

affects adult neurogenesis and may be an underlying of the modulation of neurogenesis in AD brain and animal models of AD [92]. These results indicate that neurogenesis is enhanced in the brain of patients with AD. It would result from damaged or stimulation induction of neurogenesis. It may be a consequence, rather than a cause, of the disease [18]. Enhanced neurogenesis in AD may contribute to a regenerative attempt, to compensate for the neuronal loss [84, 93].

Early Diagnosis and Treatments

Since FAD and sporadic forms of AD have a genetic component, it is possible to detect causative mutations and genetic risk factors for developing AD in patients, by genetic testing. A broad range of tests are being developed and validated to improve the diagnosis of AD, including the measurement of amyloid deposits by brain imaging and the proteomic analysis of cerebrospinal fluid [94-99]. These tests aim to improve the diagnosis of AD and detect AD, or the susceptibility to AD, at early stages. Early diagnosis of AD will allow providing the patients with better treatment, assistance and care [100]. AD patients could be treated earlier, in the aim to curb the progression of the disease, by identifying who is at risk and prescribing drugs and lifestyle changes to keep them healthy. However, until such knowledge is available, the use of these tests is not without ethical and moral issues for the physicians and patients [21].

There is currently no cure for AD. Actual treatments consist in drug and occupational therapies [101]. Three types of drugs are currently used to treat AD: i) blockers of the formation of amyloid deposits, like alzhemed, ii) inhibitors of acetylcholine esterase, like tacrine, galantamine and rivastigmine, and iii) N-methyl-D-aspartate glutamate receptor antagonists, like memantine [102-106]. Acetylcholine esterase inhibitors are thought to improve cognitive functions by enhancing cholinergic neurotransmission, that are affected in brain regions of AD and that are important for learning and memory. N-methyl-D-aspartate glutamate receptor antagonists confer protection against excitotoxic neurodegeneration. These drugs produce improvements in cognitive and behavioural symptoms of AD. Other treatments that are considered involve secretase inhibitors, drugs for lowering cholesterol levels, chelators of metals, anti-inflammatory drugs and protein β-amyloid vaccination, to stimulate the immune system to clean up the amyloid [107-109].

DISCUSSION

AD is the most common form of dementia among elderly. Amyloid plaques, neurofibrillary tangles, neurodegeneration, aneuploidy and enhanced neurogenesis are landmarks of AD pathology, Fig. (**1**). The origin and contribution of these processes to the etiology and pathogenesis of AD remain mostly unknown. Among the causes of AD are genetic mutations and genetic, acquired and environmental risk factors, neuroinflammation and oxidative stress. The confirmation that adult neurogenesis occurs in the adult brain and NSCs reside in the adult CNS not only brings new opportunities for the treatment of AD, but also raises the question of the involvement of newly generated neuronal cells of the adult brain in the etiology and pathogenesis of AD.

Aneuploid Cells in Regions of Degeneration in the Brain of Patients with Alzheimer's Disease

The adult brain contains a substantial number of cells that are aneuploids; 5 to 7% of the cells in the brain of adult mice [110, 111]. Aneuploidy may originate from non-disjunction of chromosomes during cell division, abortive cell cycle re-entry, cells undergoing DNA duplication without cell division and cell fusion [75, 112]. In the brain of patients with AD, 4 to 10% of neurons in regions of degeneration, like the hippocampus, express proteins of the cell cycle and some at-risk neurons are aneuploids [113, 114]. The marker of the phase G2 of the cell cycle, cyclin B, is expressed in neurons in regions of degeneration, particularly the hippocampus, in patients with AD [115]. Nerve cells are post-mitotic cells in the adult brain. Hence, the characterization of cyclin B and aneuploidy in neurons suggests that cells entered the cell cycle and underwent DNA replication, but did not complete the cell cycle, in regions of degeneration in the brain of AD patients. It is proposed that the genetic imbalance in aneuploid cells signifies that they are fated to die [116]. Their relatively high percentage at any one time in regions of degeneration in AD brains suggests that they will undergo a slow death process. Unlike apoptosis, these cells may live in this state for months, possibly up to 1 year [117, 118]. The deregulation and/or re-expression of proteins controlling the cell cycle of nerve cells, triggering cycle re-entry with blockage in phase G2, would underlie the neurodegenerative process and pathogenesis of AD.

Aneuploidy for chromosome 21 has been proposed as one of the contributing factors for the pathogenesis of AD [70]. APP is located on chromosome 21 and over-expression of APP would promote the formation of amyloid plaques. According to the "amyloid hypothesis", this would underlie cell death and the pathogenesis of AD. Hence, aneuploidy for chromosome 21 in neurons in regions of degeneration would underlie the pathogenesis of AD in two ways, by promoting the process cell death and neurodegeneration and the formation of amyloid plaques. The *TAU* gene is located on chromosome 17. Aneuploidy for chromosome 17 in neurons in regions of degeneration would underlie the pathogenesis of AD, by promoting the process neurodegeneration and the formation of neurofibrillary tangles.

Abortive Versus Beneficial Neurogenesis in the Adult Brain

Cells that are the most likely to develop aneuploidy are dividing cells [75]. Aneuploidy for chromosomes 21, 14 and/or 17 is a contributing factors to the pathogenesis of AD, by increasing the risk of amyloid plaques formation, aneuploidy and neurofibrillary tangles formation. It has been proposed that the non-disjunction of chromosomes, particularly of chromosomes 21, 14 and 17, in stem cells and/or populations of somatic cells that retain their ability to divide is at the origin of aneuploidy in patients with AD [70]. In the adult brain, neurogenesis occurs primarily in the SGZ and SVZ. Newly generated neuronal cells of the adult brain would originate from stem cells. Newly generated neuronal cells of the adult brain would contribute to plasticity and regeneration of the nervous system. The process of adult neurogenesis holds the potential to generate populations of

aneuploid cells particularly in the neurogenic areas. The non-disjunction of chromosomes during the process of cell division of newly generated progenitor cells of the adult brain could lead to newly generated neuronal cells that are aneuploids or to a population of aneuploid cells that would not proceed with its developmental program, Fig. (**2**). Such aneuploidy, particularly for chromosomes 21, 14 and/or 17 and particularly in the hippocampus, would contribute to the pathogenesis of AD. Cell death is a normally occurring process in the adult brain especially in the neurogenic zones, as a significant proportion of newly generated cells in the SVZ and SGZ are believed to undergo apoptosis rather than achieving maturity [119, 120]. The number of newborn neuronal cells generated in the adult brain is relatively low, particularly in the DG. It is estimated that 0.1% of the granule cell population is generated per day in the DG of young adult rodents [120, 121]. Hence, aneuploidy in newly generated neuronal cells would be a rare event. It would most likely contribute to the pathogenesis of AD, in individuals predisposed to develop the disease. This suggests that newly generated neuronal cells of the adult brain and adult neurogenesis could be involved in the pathogenesis of AD, and not only in a regenerative process.

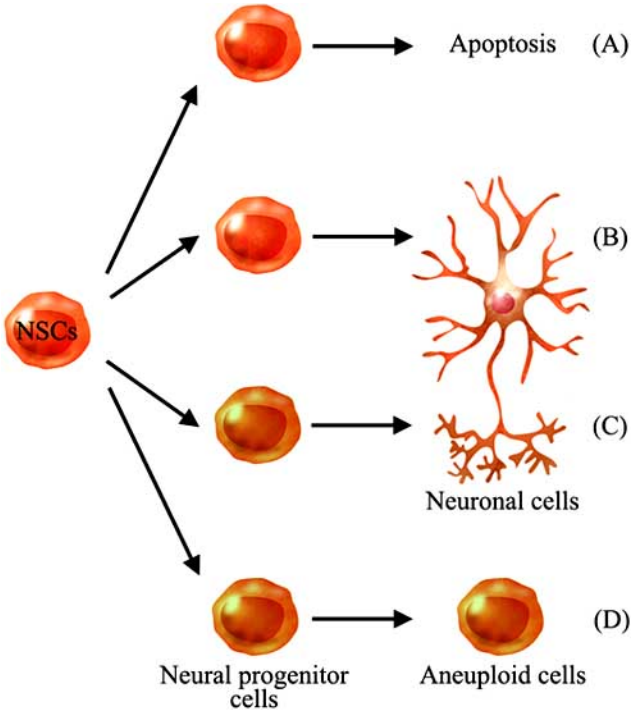

Fig. (2). Abortive versus beneficial neurogenesis in the adult mammalian brain. In the adult brain, neurogenesis occurs primarily in the SGZ and SVZ. Cell death is a normally occurring process in the neurogenic zones, as a significant proportion of newly generated cells are believed to undergo apoptosis rather than achieving maturity (A). Newly generated neuronal cells of the adult brain would originate from stem cells (B). Newly generated neuronal cells of the adult brain would contribute to plasticity and regeneration of the nervous system. The process of adult neurogenesis holds the potential to generate populations of aneuploid cells, particularly in the neurogenic areas. The non-disjunction of chromosomes during the process of cell division of newly generated progenitor cells of the adult brain could lead to newly generated neuronal cells that are aneuploids (C) or to a population of aneuploid cells that would not proceed with its developmental program (D). The genetic imbalance in aneuploid cells signifies that they are fated to die. Aneuploidy in newly generated progenitor cells of the adult hippocampus, particularly for chromosomes 21, 14 and/or 17, would contribute to the pathogenesis of AD. Newly generated neuronal cells of the adult brain and adult neurogenesis could be involved in the pathogenesis of AD, and not only in a regenerative process.

Abortive Cell Cycle Re-Entry and Cells Undergoing DNA Duplication without Cell Division Versus Neurogenesis in Animal Models of Alzheimer's Disease

Most studies conducted in animal models of neurological diseases and disorders, and particularly in animal models of AD, use bromodeoxyuridine (BrdU) labelling, as a paradigm to study adult neurogenesis. BrdU is a thymidine analog used for birth dating and monitoring cell proliferation [122, 123]. There are pitfalls and limitations over the use of thymidine analogs, and particularly BrdU, for studying neurogenesis [124-126]. BrdU is a toxic and mutagenic substance. It triggers cell death, the formation of teratomes, alters DNA stability, lengthens the cell cycle and has mitogenic, transcriptional and translational effects on cells that incorporate it. All of which have profound consequences on neurogenesis. In addition, as a thymidine analog, BrdU is not a marker for cell proliferation, but a marker for DNA synthesis. Therefore, studying neurogenesis with BrdU requires distinguishing cell proliferation and neurogenesis from other events involving DNA synthesis, like DNA repair, abortive cell cycle re-entry and gene duplication without cell division, leading to aneuploidy [127, 128]. In addition, despite earlier reports [129], the permeability of the blood-brain barrier may be affected in AD [130]. In these conditions, an increase in BrdU labelling in the brain could originate from an increase in BrdU uptake rather than an increase in cell proliferation and neurogenesis [127, 128]. Cell cycle proteins, like cyclin B the marker of the phase G2, are expressed in neurons, in regions in which degeneration occurs, and some at-risk neurons in regions of degeneration are aneuploids in the brain of AD patients [113, 114]. The evidence that cell cycle re-entry and DNA duplication, without cell division, precedes neuronal death in degenerating regions of the CNS suggests that when using immunohistochemistry for proteins of the cell cycle to study adult neurogenesis, this paradigm does not allow discriminate between cells undergoing DNA duplication, without cell division, as part of their pathological fate and newly generated neuronal cells [127, 128]. Hence, data involving the use of BrdU-labelling and immuno-histochemistry for proteins of the cell cycle, as paradigms for studying adult neurogenesis in neurological diseases and disorders, and particularly in AD, must be carefully assessed and analyzed.

Potential and Limitations of Adult Neurogenesis and Neural Stem Cells for the Treatment of Alzheimer's Disease

The confirmation that neurogenesis occurs in the adult brain and NSCs reside in the adult CNS, opens new opportunities for cellular therapy for a broad range of neurological diseases, disorders and injuries, particularly for neurodegenerative diseases like AD [18]. The adult CNS may be

amenable to repair. To this aim, two strategies are being considered: the stimulation of endogenous neural progenitor or stem cells of the adult brain, and the transplantation of adult-derived neural progenitor and stem cells, to repair the degenerated or injured pathways [131]. There are limitations to the potential of adult NSCs for therapy. On the one hand, stem cells reside in specialized microenvironments or "niches", particularly in the adult brain [132, 133]. An angiogenic niche and an astroglial niche for neurogenesis have been identified and characterized in the adult brain. These niches regulate and control the self-renewal and differentiation activities of NSCs. The microenvironment plays therefore a key role in the therapeutic potential of adult stem cells, whether endogenous or transplanted. Unravelling and unlocking the mechanisms underlying the neurogenic niches for neurogenesis will contribute to the realization of the therapeutic potential of adult NSCs [134]. On the other hand, protocols currently established to isolate and culture neural progenitor and stem cells from the adult brain yield to heterogeneous populations of neural progenitor and stem cells, limiting their therapeutic potential [135]. Identifying markers of neural stem/ progenitor cells and conditions to maintain such culture homogeneous will enhance the therapeutic potential of adult-derived neural progenitor and stem cells.

Cell grafting targets local areas of the brain. The intracerebral transplantation of adult-derived neural progenitor and stem cells may not be applicable for the treatment of AD, where the degeneration is widespread. Neural progenitor and stem cells, administered intravenously, migrate to diseased and injured sites of the brain [136, 137]. Systemic injection provides a non-invasive strategy for delivering neural progenitor and stem cells in the adult CNS. Experimental studies reveal that systemic injection of neural progenitor and stem cells promote functional recovery in an animal model of multiple sclerosis [137]. This shows that systemic injection provides a model of choice for delivering NSCs for the treatment of neurological diseases and injuries and may provide a paradigm of choice for the treatment of AD. Adult neurogenesis is modulated by a broad range of environmental and physio- and pathological stimuli and processes, as well as trophic factors/cytokines and drugs [138]. Conditions that stimulate endogenous neurogenesis in the adult brain may be applied to promote the regenerative and recovery processes.

CONCLUSION AND PERSPECTIVES

AD is characterized in the brain by amyloid plaques, neurofibrillary tangles, neurodegeneration, aneuploidy and enhanced neurogenesis. The role and contribution of these processes to the etiology and pathogenesis of AD remain to be elucidated and fully understood. The confirmation that neurogenesis occurs in the adult brain and NSCs reside in the adult CNS opens new perspectives and opportunities for the treatment and cure, but also for our understanding of the etiology and pathogenesis of AD. Chromosomes non-disjunction and aneuploidy are contributing factors for the pathogenesis of AD. The non-disjunction of chromosomes during the process of cell division of newly generated progenitor cells of the adult brain could lead to newly generated neuronal cells that are aneuploids or to a population of aneuploid cells that would not proceed with its developmental program. Hence, newly generated neuronal cells of the adult brain would not only contribute to plasticity and regeneration of the nervous system, but also to the pathogenesis of neurological diseases and disorders, particularly AD. Future studies will aim at understanding the role and contribution of adult neurogenesis to the pathology of AD and to design protocols and strategies to treat and cure AD with adult NSCs.

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