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Neurogenesis, NSCs, pathogenesis and therapies for Alzheimer's disease

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1. ABSTRACT

Neurogenesis occurs in the adult brain and neural stem cells (NSCs) reside in the adult central nervous system (CNS) of mammals. Adult NSCs offer tremendous potential for cellular therapy for the treatment of neurological diseases and injuries, particularly of Alzheimer's disease (AD). The contribution of newly generated neuronal cells of the adult brain to the functioning of the nervous system remains to be elucidated. Neurogenesis is enhanced in the brain of patients with AD. Enhanced neurogenesis would contribute to regenerative attempts in AD, to compensate for the neuronal loss. Adult neurogenesis holds the potential to generate aneuploid cells, a landmark of AD pathology. Aneuploid newly generated neuronal cells in the adult brain would contribute to the pathogenesis of AD. Adult neurogenesis would not only be beneficial, but also detrimental for patients with AD. We will review and discuss the potential of adult NSCs for the treatment of AD and their contribution to the pathogenesis of the disease, as well as the development of novel drugs and therapies for treating AD.

2. INTRODUCTION

Neurogenesis occurs in discrete regions of the adult mammalian brain, in various species including humans (1-3). Newly generated neuronal would originate for a pool of residual stem cells (4). The confirmation that neurogenesis occurs in the adult brain and NSCs reside in the adult CNS has tremendous implications for our understanding of the development and of the physio- and pathology of the nervous system, and for therapy. The adult brain has the potential for self-repair (5). The contribution of adult neurogenesis and newly generated neuronal cells of the adult brain to the physio- and pathology remains to be elucidated and adult NSCs have yet to be brought to therapy.

AD is the most common form of senile dementia. It is a neurodegenerative disease characterized by memory and cognitive deficits, amyloid deposits, neurofibrillary tangles, neurodegeneration and aneuploidy, leading to severe incapacity and death (6). Reports show that neurogenesis is enhanced in the brain of patients with AD

(7). It is proposed that enhanced neurogenesis in the brain of AD patients would represent a regenerative attempt to compensate for the neuronal loss. The process of adult neurogenesis holds the potential to generate populations of cells that are aneuploid, particularly in the neurogenic regions (8). Aneuploid newly generated neuronal cells in the adult brain would contribute to the pathogenesis of AD. Hence, adult neurogenesis might have a dual role in AD. This has tremendous implication for our understanding of AD and for therapy.

3. ADULT NEUROGENESIS AND NEURAL STEM CELLS

3.1. Neurogenesis in the adult brain of mammals

Neurogenesis occurs throughout adulthood in the mammalian brain, primarily in the subventricular zone (SVZ) along the ventricles and in the dentate gyrus (DG) of the hippocampus, in various species including humans (1-5). Newly generated neuronal cells, in the anterior part of the SVZ, migrate through the rostro-migratory stream (RMS) to the olfactory bulb, where they differentiate into olfactory interneurons (9, 10). In the DG, newly generated neuronal cells in the subgranular zone (SGZ), a layer beneath the granular layer, migrate to the granule cell layer, where they differentiate into neuronal cells of the granular layer and extend axonal projections to the CA3 region of the Ammon's horn (11-13). Newly generated neuronal cells in the DG establish synaptic contacts and functional connections with neighboring and target cells (14-16). It is estimated that, in rodents (mice), it takes approximately 15 days for neural progenitor cells of the SVZ to migrate through the RMS, a distance of 3 to 5 mm, and to differentiate into olfactory interneurons, and approximately 4 weeks for newly generated neuronal cells of the SGZ to migrate to the granule cell layer of the DG and to differentiate into granule-like cells (10, 12). Newly generated neuronal cells in the adult hippocampus survive for extended period of time, at least 2 years in humans (1).

The SVZ harbors the largest pool of dividing neural progenitor cells of the adult brain (17, 18). The number of newly generated neuronal cells per day in the adult brain is relatively low, particularly in the DG. In mice, the number of newly generated neuronal cells per day in the DG is estimated at 9,000 new neuronal cells, or about 0.1 percent of the granule cell population (19, 20). In adult macaque monkey, the number of newly generated neuronal cells per day in the DG is estimated at 0.004 percent of the granule cell population (21). Neurogenesis has been reported to occur in other areas of the adult brain, like the CA1 region of the hippocampus, neocortex, striatum, albeit at lower level (22-24).

Hence, neurogenesis occurs in the adult brain. It is a functional neurogenesis and a rare event. Newly generated neuronal cells of the adult brain that survive and extend axonal projections to their target cells may replace nerve cells born during development.

3.2. Neural progenitor and stem cells *in vitro*

NSCs are the self-renewing multipotent cells that generate, through a transient amplifying population of cells, the main cell types of the nervous system: nerve cells, astrocytes and oligodendrocytes (4, 5). Self-renewing multipotent NSCs have been isolated and characterized *in vitro*, from various regions of the adult brain, including the SVZ, hippocampus and spinal cord, and from various mammalian species, including from human biopsies and *post-mortem* tissues (25-29). The isolation and characterization of neural and progenitor cells from the adult brain reveal that NSCs reside in the adult CNS and that it has the potential for self-repair. Adult-derived neural progenitor and stem cells also provide a source of tissue that may be used for cellular therapy, for transplantation.

Stem cells are defined by the following main attributes: i) self-renewal over an extended period of time, ii) generation of a large number of differentiated progenies and iii) regeneration of the tissue following injury. Progenitor cells are cells that do not fulfill the attributes of stem cells (30). One of the limitations of the established protocols to derive self-renewing multipotent NSCs *in vitro* is that they lead to heterogeneous cultures of neural progenitor and stem cells. After 4 days *in vitro*, 62 percent of the adult derived-neural progenitor and stem cells in culture originate from 23 percent of the plated cells, revealing the existence of different populations of cells with different properties of growth in the culture. Overtime the fast-dividing neural progenitor and stem cells represent a majority of the cells in culture reflecting the heterogeneity of adult derived-neural progenitor and stem cells *in vitro* (31). A second limitation of neural progenitor and stem cells *in vitro*, but also *in vivo*, is the lack of specific markers of NSCs. Molecular markers, like the intermediate filament nestin, the transcription factors sox-2, oct-3/4 and the RNA binding protein Musashi 1, are expressed by neural progenitor and stem cells of the adult brain *in vitro* and *in vivo*. However, they are also expressed by other cell types in the brain, like glial cells and reactive astrocytes, and in gliomas (32-37). Hence, adult NSCs remain elusive and the heterogeneity of the established protocols to derive self-renewing multipotent NSCs *in vitro* limits their potential therapeutic use.

3.3. Modulation of adult neurogenesis *in vivo*

Neurogenesis is modulated in the adult brain, particularly in the hippocampus. It is modulated by a broad range of environmental stimuli, physio- and pathological conditions, trophic factors/cytokines, neurotransmitters and drugs, including enriched environment, learning and memory tasks, physical activity, AD and epilepsy (38). Environmental enrichment, learning and memory tasks and physical activity stimulate hippocampal neurogenesis in adult rodents (19, 39-41). Neurogenesis is enhanced in the adult hippocampus of animal models of epilepsy (42), strokes (43) and traumatic brain injuries (44). It is enhanced in the SVZ and hippocampus in the brain of patients with Huntington's disease and AD, respectively (7, 45). This suggests that neurogenesis in the adult brain is involved in various physio- and pathological conditions and processes of the nervous system, including neurological diseases and pharmacology (46). The role and contribution of newly generated neuronal cells of the adult brain to these processes remains to be elucidated. Newly generated

Table 1. Potential therapeutic approaches for the treatment of Alzheimer's disease

Cellular therapy	Stimulation/Transplantation	Therapy
Endogenous neural progenitor or stem cells	Local	Regeneration
	SVZ	Regeneration/Reverse deficits
	Hippocampus	Reverse deficits
Adult-derived neural progenitor and stem cells	Intracerebral	Regeneration
	Intracerebral	Regeneration
Pharmacology	Target	Therapy
Drugs	Newly generated neuronal cells	Reverse deficits/Regeneration
	Aneuploid newly generated neuronal cells	Prevent deleterious effects

The confirmation that adult neurogenesis occurs in the adult brain and NSCs reside in the adult CNS opens new opportunities to repair and restore the damaged or degenerated nervous system: the stimulation of endogenous neural progenitor or stem cells and the transplantation of adult-derived neural progenitor and stem cells. Neural progenitor and stem cells of the SVZ may be stimulated to repair and restore distant brain regions through their migration to the sites of degenerations and injuries. The modulation of adult neurogenesis may be applied to promote the regenerative and recovery processes, as well as to reverse deficits, associated particularly with the hippocampus. Adult-derived neural progenitor and stem cells may be transplanted in local areas of the adult brain. Intravenous injection provides a strategy for delivering neural progenitor and stem cells in the adult CNS applicable for neurological diseases and injuries, with widespread neurodegeneration or damages, like in AD. Adult neurogenesis and newly generated neuronal cells of the adult brain are the target of drugs used for treating neurological diseases and disorders and contribute to their activities. Drugs targeting the newly generated neuronal cells of the adult brain and adult neurogenesis carry the risk of promoting the generation of aneuploid neuronal cells in the adult brain. Therapeutic strategies will aim at discovering and developing novel drugs that specifically target the newly generated neuronal cells of the adult brain to compensate or reverse deficits, particularly associated with the hippocampus. Such strategy will involve limiting the potential deleterious effects of the generation of aneuploid neuronal cells, without disrupting the regenerative capacity of adult neurogenesis.

neuronal cells of the adult brain would contribute to the plasticity of the nervous system and regenerative attempts after injuries (47, 48).

Bromodeoxyuridine (BrdU)-labeling and immunohistochemistry for markers of the cell cycle are the main methods used for studying cell division and neurogenesis in the adult brain of rodents and primates. BrdU is a thymidine analog used for birth dating and monitoring cell proliferation (49). It is a mutagenic and toxic substance. As a thymidine analog, it is a marker of DNA synthesis, not of cell proliferation. Drug treatments and various physio- and pathological conditions affect the cerebral flow and the permeability of the blood-brain barrier and the availability of BrdU in the brain (50-52). Markers of the cell cycle, like proliferating nuclear antigen, Ki-67 and phosphorylated histone H3, reveal that quiescent cells have re-entered the cell cycle and resumed DNA synthesis, but does reveal whether they have completed the cell cycle. Hence, there are limitations and pitfalls over the use of BrdU-labeling and immunohistochemistry for markers of the cell cycle to study cell proliferation and neurogenesis (53, 54). Studying neurogenesis with BrdU-labeling and immunohistochemistry for markers of the cell cycle requires distinguishing cell proliferation and neurogenesis from other events involving DNA synthesis and cell cycle re-entry, like abortive cell cycle re-entry, leading to apoptosis, and gene duplication, without cell division, leading to aneuploidy (55). Therefore, studies involving BrdU-labeling and immunohistochemistry for markers of the cell cycle, for studying adult neurogenesis must be carefully analyzed and discussed.

3.4. Cellular therapy

Cellular therapy is the replacement of tissues by new ones. Because of their potential to generate the main phenotypes of the nervous system, NSCs hold the potential to treat and cure a broad range of neurological diseases and injuries, particularly neurodegenerative diseases, like AD and Parkinson's disease, cerebral strokes and spinal cord injuries. The confirmation that adult neurogenesis occurs in the adult brain and NSCs reside in the adult CNS opens new opportunities to repair and restore the damaged or degenerated nervous system: the stimulation of endogenous neural progenitor or stem cells and the transplantation of adult-derived neural progenitor and stem cells (3, 4, 5, 48) (Table 1).

Neural progenitor and stem cells of the adult brain may be stimulated locally, by trophic factors or cytokines, to repair and restore the degenerated or injured nerve pathways. Alternatively, new neuronal cells are generated at sites of degeneration in the diseased brain and after CNS injuries, like in Huntington's disease and in experimental models of cerebral strokes. They originate from the SVZ. They migrate partially through the RMS to the sites of degenerations and injuries (56, 57). Neural progenitor and stem cells of the SVZ may be stimulated to repair and restore distant brain regions through their migration to the sites of degenerations and injuries. Adult neurogenesis is modulated in discrete regions of the adult brain, the hippocampus and SVZ, by a broad range of environmental, physio- and pathological stimuli and processes, by trophic factors/cytokines and drugs (38). The modulation of adult neurogenesis may be applied to promote the regenerative and recovery processes, as well as to reverse deficits, associated with those areas of the brain, particularly the hippocampus (Table 1).

Adult-derived neural progenitor and stem cells may be transplanted in local areas of the adult brain, to repair and restore the degenerated or injured nerve pathways. Alternatively, adult-derived neural progenitor and stem cells administered intravenously migrate to

diseased and injured sites of the brain (58, 59). Intravenous administration of neural progenitor and stem cells is a non-invasive procedure for transplantation, particularly promising to deliver neural progenitor and stem cells in the CNS, for the treatment of brain diseases and tumors. The intracerebral transplantation of neural progenitor and stem cells may be applicable to treat neurological diseases and injuries for which the neurodegeneration or the damages are not widespread, like Parkinson's disease. It may not be applicable for the treatment of neurological diseases and injuries, with multiples site of neurodegeneration or damages, like AD. In contrast, intravenous injection provides a strategy for delivering neural progenitor and stem cells in the adult CNS applicable for neurological diseases and injuries, with widespread neurodegeneration or damages, like in AD and multiple sclerosis (59).

Adult NSCs that have limited ethical and political constraints offer a promising model and a model of choice for cellular therapy. However, there are limitations over the use of adult NSCs for cellular therapy. First, the heterogeneity of established protocols to isolate and propagate, *in vitro*, neural progenitor and stem cells from the adult brain is a factor limiting their therapeutic potential. Second, stem cells reside in specialized microenvironments or "niches" (60, 61). An astroglial and an angiogenic niche for neurogenesis have been identified and characterized in the adult brain (62, 63). The microenvironment controls the developmental potential of stem cells and their proliferation and maturation. As such, it plays a key role in the therapeutic potential of stem cells, whether endogenous or transplanted. Future investigations will aims at establishing homogeneous population of self-renewing multipotent NSCs *in vitro* and unraveling the molecular and cellular mechanisms underlying the developmental potential of NSCs in the adult brain (64).

4. ALZHEIMER'S DISEASE

4.1. A senile dementia and neurodegenerative disease

AD was first described by Alois Alzheimer in 1906 (65). It is the most common form of senile dementia. AD is characterized by memory and cognitive deficits, but also anosmia (66, 67). Age is the principal risk factor for AD and the incidence of the disease doubles every 5 years after age 65 (68). AD is a neurodegenerative disease. It is initially associated with the loss of nerve cells in areas of the brain that are vital to memory and other cognitive abilities, like the enthorhinal cortex, hippocampus and neocortex. As the disease progresses, other regions of the brain are affected, leading to severe incapacity and death (69). Beside, neurodegeneration, AD is characterized in the brain by the presence of amyloid plaques, neurofibrillary tangles and aneuploidy (6, 65, 69). Amyloid plaques and neurofibrillary tangles are the histopathological hallmarks of AD.

There are two forms of the disease. The early onset form of AD (EOAD) is a rare form of the disease. It is diagnosed before age 65. EOAD is primarily an inherited disease. It runs is about 200 families in the world. The late onset form of AD (LOAD) is diagnosed after the age of 65. Most cases of LOAD are sporadic forms of the disease. LOAD is the most common form of the disease, accounting for over 93 percent of all cases of AD (6, 69). Doctors diagnose AD primarily by symptoms of cognitive impairments, behavioural changes and risk factor assessments (71, 71). There is no cure for AD which leads to death within 3 to 9 years after being diagnosed (68, 69). The disease affects more than 35 million of individuals worldwide.

4.2. Amyloid plaques and neurofibrillary tangles

Amyloid plaques are distributed throughout the brain of patients with AD, particularly in the regions of degeneration, like the entorhinal cortex, hippocampus and temporal, frontal and inferior parietal lobes (72). Their density increases as the disease advances. Amyloid plaques are thought to be the first histological change to occur in the brain of patients with AD (6). They are composed of extracellular deposits of amyloid fibrils or protein beta-amyloid and of alpha 1-antichymotrypsin, in the brain of AD patients (73). Alpha 1-antichymotrypsin is a serine protease inhibitor.

Protein beta-amyloid is a beta-peptide. It originates from the post-transcriptional maturation of the amyloid precursor protein (APP) (74). Protein beta-amyloid is synthesized and secreted by nerve cells, as a soluble peptide. It aggregates to form deposits of amyloid fibrils or amyloid plaques after abnormal processing of APP under certain conditions, like in the presence of specific gene mutations for example. In physiological conditions, APP is cleaved primarily by the alpha- and gamma-secretases into a 40 amino acid beta-peptide (74). Under pathological conditions, there is an increase in the cleavage of APP, by the beta- and gamma-secretases. This results in an increase in the synthesis of a 42 amino acid beta-amyloid peptide. This latter form of protein beta-amyloid aggregates into insoluble amyloid deposits or amyloid plaques, particularly in the brain (Figure 1).

According to the hypothesis knows as the amyloid hypothesis, deposits of protein beta-amyloid may be a causative factor of AD. As the amyloid deposits in the brain, nerve cells start dying, and the signs and symptoms of the disease appears. This hypothesis is the source of debates and controversies (75). The main argument against the amyloid hypothesis is the lack of correlation between the density of amyloid plaques in the brain and the severity of the disease (76).

Neurofibrillary tangles are distributed throughout the brain of patients with AD. They are composed of intracellular deposits of hyperphosphorylated Tau proteins, in the brain of patients with AD (77). Tau protein is microtubule-associated phosphoprotein (78). Microtubules are involved in cell structure, intracellular transport and cell division. The hyperphosphorylation of Tau proteins results in their aggregation and in the breakdown of microtubules (79). This leads to the formation of neurofibrillary tangles and cell death (80, 81) (Figure 1).

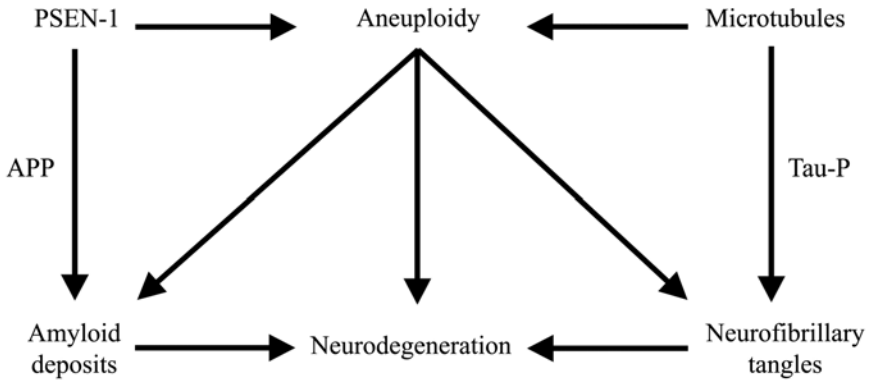

Figure 1. Neurogenetic events in Alzheimer's disease. Alzheimer's disease is characterized by genetic instability. Genetic mutations, genetic risk factors and aneuploidy are causative factors and landmarks of the disease. Protein beta-amyloid originates from the post-transcriptional maturation of the amyloid precursor protein (APP). As the amyloid deposits in the brain, nerve cells start dying. The presenilin (PSEN) proteins are components of the gamma-secretase complex that plays a role in the maturation of APP into protein beta-amyloid. Neurofibrillary tangles are composed of intracellular deposits of hyperphosphorylated Tau proteins (Tau-P). The hyperphosphorylation of Tau proteins results in the aggregation and in the breakdown of microtubules. This leads to the formation of neurofibrillary tangles and cell death. Mutated forms of PSEN-1 are detected in interphase kinetochores and centrosomes of dividing cells, where they may be involved in the segragation and migration of chromosomes during cells division. The breakdown of microtubles causes the disruption in the mitotic spindle and promotes aneuploidy during cell division. Aneuploidy for genes involved in the pathology of AD, like *APP*, *PSEN-1*, *PSCN-2*, *TAU* and *ApoE*, would contribute to the pathogenesis of the disease, e.g. to the formation of amyloid plaques, neurofibrillary tangles and neurodegeneration, as a result of the over expression of those genes.

4.3. Genetic mutations and risks factors in Alzheimer's disease

Three genetic mutations causative for inherited forms of AD have been identified: mutations in the gene of APP, of presenilin-1 (PSEN-1) and of presenilin-2 (PSEN-2) (82). APP is a 695-770 amino acid protein coding for the protein beta-amyloid. Mutations in *APP* cause excessive cleavage of APP by the beta- and gamma-secretases. This results in an excessive production of the 42 amino acid beta-amyloid peptide and the formation of amyloid deposits. The PSEN proteins are components of the gamma-secretase complex that plays a role in the maturation of APP into protein beta-amyloid (83). Mutations in *PSEN-1* and *PSEN-2* lead to excessive cleavage of APP by gamma-secretase enzyme, resulting in an excessive production of the 42 amino acid beta-amyloid peptide and the formation of amyloid deposits (84) (Figure 1). Individuals carrying mutations in these genes, also known familial Alzheimer's disease (FAD) genes, will almost always develop AD or FAD, before age 65, or EOAD (85). EOAD is primarily a genetic inherited disease. Cases of FAD can occur after age of 65 (86). The causal mutations involved in these forms of LOAD remian unidentified.

Some of the genetic, acquired and environmental risk factors causative for the sporadic forms of AD have been identified, like the presence of certain alleles, such as the apolipoprotein E varepsilon 4 allele (*ApoE4*), in the genetic makeup of the individuals, hypertension, diabetis and oxidative stress (87-89). ApoE is a plasma protein that is involved in the transport of cholesterol and lipids in the blood (90). There are three major alleles of ApoE gene in humans: ApoE2, ApoE3 and ApoE4. Up to 50 percent of people who have AD have at least one *ApoE4* allele in their genetic make-up (91). Individuals who have two *ApoE4* alleles have a higher risk of developing AD (92). The presence *ApoE4* in the genes of the individuals accounts for most causes and risks to develop LOAD. Other genes have been been linked with the occurence of LOAD, among them variants for the genes coding for alpha2-macroglobulin, myeloperoxidase, cystatin C, the gene coding for neuronal sortilin-related receptor, the gene coding for FKBP52 and polymorphisms in the cholesteryl ester transfer protein gene (93-96). These risk factors increase the probability of developing AD after age 65, or LOAD. However, sporadic cases of EOAD can occur, with no family history and no identified causal genetic mutations.

4.4. Aneuploidy in region of neurodegeneration

Lymphocyte preparations of patients with AD, EOAD and LOAD, reveal an increase in aneuploidy, particularly for chromosomes 13, 18 and 21 (97, 98). Four to 10 percent of nerve cells in regions of neurodegeneration of the brain, like the hippocampus, of patients with AD are aneuploid and express proteins of the cell cycle, like cyclin B (99-101). The nondisjunction of chromosomes during cell division in stem cells or somatic cells that retain their ability to divide is at the origin of aneuploidy in lymphocytes of patients with AD. In the adult brain, most nerve cells are post-mitotic. The characterization of markers of the cell cycle, like cyclin B, in nerve cells in regions of degeneration reveals that cell cycle re-entry and DNA duplication, without cell division, is at the origin of aneuploidy in those cells in the brain of AD patients (102, 103). Aneuploid nerve cells originating from the re-expression of proteins of the cell cycle are fated to die.

They may live in this state for months, undergoing a slow death process (104, 105). Cell cycle re-entry and DNA duplication, without cell division, leading to aneuploidy would be an underlying mechanism of the neurodegenerative process in AD.

The genetic imbalance in aneuploid cells results in the over expression of genes by the cells. The genes for ApoE, APP, PSEN-1, PSEN-2 and TAU are located on chromosomes 19, 21, 1, 14 and 17, respectively (106-109). Cells of AD patients elicit an elevation of aneuploidy for chromosomes 13, 18 and 21, particularly (97, 98). Aneuploidy for genes involved in the pathology of AD would contribute to the pathogenesis of the disease, as a result of the over expression of those genes. Aneuploidy for chromosome 19 would result in the over expression of ApoE and in an increase risk for individuals who have *ApoE4* in the genetic make-up of developing the sporadic form of AD. Aneuploidy for chromosome 21 would result in the overexpression of APP and promote the formation of amyloid plaques. Aneuploidy for chromosomes 1 or 14 would promote the formation of amyloid plaques in patients carrying FAD mutations on PSEN genes and contribute to the pathogenesis of EOAD. Aneuploidy for chromosomes 17 would result in the overexpression of Tau protein and promote the formation of neurofibrillary tangles.

Protein beta-amyloid induces cell cycle re-entry and neuronal death (110). Hence, aneuploidy for chromosome 21 would not only promote the formation of amyloid plaques, it would also promote cell cycle re-entry and DNA duplication, without cell division, leading to aneuploidy and neuronal cell death in regions of neurodegeneration in the brain. Hence, aneuploidy is landmark of the pathology of AD. It underlies the process of neurodegeneration and contributes to the pathogenesis of AD, by over-expressing genes involved in the disease and triggering a cascade of events amplifying the development of the disease.

5. ADULT NEUROGENESIS AND THE PATHOGENESIS OF ALZHEIMER'S DISEASE

Neurogenesis is enhanced in the brain of patients with AD (7). This reveals adult neurogenesis and newly generated neuronal cells of the adult brain play a role in the pathogenesis and pathology of AD, the contribution of which remains to be elucidated and determined.

5.1. Neurogenesis in Alzheimer's disease

The expression of markers of immature neuronal cells, particularly doublecortin, is enhanced in the hippocampus of the brain of patients with AD, mostly patients with LOAD (7). In animal models, adult neurogenesis is enhanced in the hippocampus of transgenic mice that express the Swedish and Indiana APP mutations. It is decreased in the hippocampus of mice deficient for APP or PSEN-1, of transgenic mice over expressing variants of APP or PSEN-1 and of PDAPP transgenic mice, a mouse model with age-dependent accumulation of protein beta-amyloid (111-115). BrdU-labeling and/or immunohistochemistry for makers of the cell cycle were conducted to study and quantify neurogenesis in the adult hippocampus of AD patients and of animal models of AD. As such, due to the limitations and pitfalls over the use of BrdU-labeling and immunohistochemistry for makers of the cell cycle for studying cell proliferation and neurogenesis, these studies remain to further evaluated and confirmed (59, 60, 64). In addition, the various animal models of AD used in those studies are not representative of complex diseases like AD, EOAD and LOAD, but rather of the genes deficient or mutated in AD (116). Genetic modifications in transgenic mice may also have adverse effects during development, altering adult phenotypes, particularly adult neurogenesis.

Hence, these studies show that neurogenesis is enhanced in the hippocampus of patients with AD, but report conflicting data in animal models of AD. Studies of neurogenesis in the adult hippocampus of AD patients and of animal models of AD need to be confirmed and validated. Enhanced neurogenesis in the brain of patients with AD may contribute to regenerative attempts, to compensate for the neuronal loss.

In the SVZ, studies in patients with AD report a reduction in the number of neural progenitor cells in the SVZ, as revealed by immunohistology for nestin and Musashi1 (117). Protein beta-amyloid stimulates neurogenesis in the SVZ of young APP/PS1 transgenic mice, but not of 12-month-old APP/PS1 transgenic models of AD (118). The reduction in the number of neural progenitor cells in the SVZ of AD brain and the lack of stimulation of neural progenitor and stem cells of the adult SVZ by protein beta-amyloid suggest depletion in the pool of stem cells in the adult SVZ in AD. It may underlie the compromised olfaction also associated with the disease.

5.2. Aneuploid newly generated neuronal cells in the adult brain with Alzheimer's disease

The hyperphosphorylation of Tau by kinases leads to the breakdown of microtubles and to the formation of neurofibrillary tangles (79). The breakdown of microtubles causes the disruption in the mitotic spindle and promotes aneuploidy during cell division. Mutated forms of PSEN-1 are detected in interphase kinetochores and centrosomes of dividing cells, where they may be involved in the segragation and migration of chromosomes during cells division (119, 120). Oxidative stress, an environmental risk factor for LOAD, promotes aneuploidy, particularly for chromosome 17 that carries the *TAU* gene (121). Cells that are the most likely to develop aneuploidy are dividing cells. Hence, somatic cells that retain their ability to divide in AD are at high risk of aneuploidy. The process of adult neurogenesis holds the potential to generate populations of cells that are aneuploid, particularly in the neurogenic regions. The neurogenic regions are therefore sites of the adult brain with AD that are at particularly high risk of aneuploidy (Figure 1). The nondisjunction of chromosomes during the process of cell division of neural progenitor and stem cells of the adult brain could lead to newly generated neuronal cells that are aneuploid and/or to newly generated neuronal precursor

cells that are aneuploid and would not proceed with their developmental program (8, 122). These aneuploid cells may have their lifespan shortened, further contributing to the neurodegenerative process in AD, or they may survive for extended period of time, potentially contributing to the formation of amyloid plaques, neurofibrillary tangles, neurodegeneration and aneuploidy, locally, in the neurogenic regions of the adult brain, particularly the hippocampus (Figure 1).

The generation of new neuronal cells represents a relatively low frequency event in the adult brain of mammals, estimated that 0.1 and 0.004 percent of the granule cell population is generated per day in the DG of adult mice and macaque monkeys, respectively (19-21). Hence, the generation of newly generated neuronal cells that are aneuploids and/or of newly generated neuronal precursor cells that are aneuploid and would not proceed with their developmental program in the adult brain would concern a relatively low fraction of cells of the hippocampus. Nonetheless, their pathological activity may be critical to the pathogenesis of AD, since these aneuploid neuronal cells are generated particularly in the hippocampus, a region involved in learning and memory and particularly affected in patients with AD. In addition, reports show that neurogenesis is enhanced in the brain of patients with AD (7). So, adult neurogenesis may be a preferential target for generating aneuploid neuronal cells in the adult brain.

In all, causative factors of AD, like Tau protein, mutated PSEN-1 proteins and oxidative stress, may not only contribute to the pathogenesis of AD by promoting the formation of amyloid plaques and neurofibrillary tangles, the process of neurodegeneration, but also by promoting the generation of neuronal cells that are aneuploids in the brain with AD, particularly in the hippocampus. Enhanced neurogenesis may further contribute to the risk of generating neuronal cells that are aneuploids in the brain of patients with AD (123). This reveals that neurogenesis in the adult brain may have a dual activity. On the one hand, it may contribute to regenerative attempts. On the other hand, it may contribute to the generation of aneuploid neuronal cells and the pathogenesis of AD. Adult neurogenesis would not only be beneficial, but also detrimental for patients with AD. This has important implications for therapeutic strategies for AD.

6. NOVEL DRUG TARGETS FOR ALZHEIMER'S DISEASE

6.1. Newly generated neuronal cells of the adult brain

Three types of drugs are used for the treatment of patients with AD: blockers of the formation of amyloid plaques, inhibitors of acetylcholine esterase and N-methyl-D-aspartate glutamate receptor antagonists. These drugs improve both cognitive and behavioral symptoms of AD (124-126). The activity of drugs used in the treatment of AD has been assessed for their effects on adult neurogenesis in rodents. Galantamine, an acetylcholine esterase inhibitor, and memantine, an N-methyl-D-aspartate glutamate receptor antagonist, increase neurogenesis by 26 to 45 percent in the hippocampus of adult rodents (127). This reveals that adult neurogenesis may be the target of drugs used for treating AD and contribute to their activities (128). The mechanisms and functions underlying the activities of these drugs on newly generated neuronal cells of the adult brain remain to be elucidated. Drugs may act directly or indirectly on those cells. They may act via their pharmacological activities, on messenger signaling pathways, and/or via a neurogenic activity, by modulating neurogenesis and/or compensating for neuronal loss (129).

6.2. Aneuploid newly generated neuronal cells of the adult brain

The generation of aneuploid new neuronal cells in the adult brain has implications for therapeutic treatments of AD. Factors and conditions promoting adult neurogenesis and aneuploidy would promote the generation of aneuploid new neuronal cells in the neurogenic regions of the adult brain, particularly the hippocampus, and further contribute to the development of AD. Novel drug therapies to treat neurological diseases and disorders aim at targeting the newly generated neuronal cells of the adult brain and at stimulating adult neurogenesis, particularly of the hippocampus (130-132). This to compensate or reverse deficits associated with the hippocampus, like in AD and depression, and to promote functional recovery (46). Such therapies may be associated with the risk of generating of aneuploid neuronal cells in the adult brain of those patients, contributing to pathological developments and deficits.

In all, adult neurogenesis and newly generated neuronal cells of the adult brain are the target of drugs used for treating neurological diseases and disorders and contribute to their activities, particularly in AD (Table 1). Drugs targeting the newly generated neuronal cells of the adult brain and adult neurogenesis carry the risk of promoting the generation of aneuploid neuronal cells in the adult brain (Table 1). Therapeutic strategies will aim at discovering and developing novel drugs that specifically target the newly generated neuronal cells of the adult brain to compensate or reverse deficits, particularly associated with the hippocampus. Such strategy will involve limiting the potential deleterious effects of the generation of aneuploid neuronal cells in the adult brain, without disrupting the regenerative capacity of adult neurogenesis (133).

7. SUMMARY AND PERSPECTIVES

The confirmation that neurogenesis occurs in the adult brain and NSCs reside in the adult CNS has tremendous implications and applications for our understanding of the nervous system and for therapy. Adult NSCs not only offer new opportunities for cellular therapy, to repair and restore degenerated and injured nerve pathways. They also provide novel opportunities for pharmacology, to compensate or reverse deficits, associated with neurological diseases and disorders. Current protocols to establish adult derived-neural progenitor and stem cells yield to heterogeneous populations of cells and the developmental potential of stem cells in under control of the microenvironment. This limits the potential of adult NSCs for cellular therapy for

the treatment of neurological diseases and injuries, and particularly for AD. Neurogenesis is enhanced in the brain of patients with AD. Neurogenesis holds the potential to generate aneuploid new neuronal cells in the adult brain, a pathological hallmark of AD. Hence, adult neurogenesis may have a dual activity. It may be involved in regenerative attempts in AD, but also in the pathogenesis of AD. Adult neurogenesis would not only be beneficial, but also detrimental for patients with AD. This shows that a deep understanding of the mechanisms underlying adult neurogenesis and its contribution to the physio- and pathology of the nervous system is mandated, to bring adult NSCs to therapy. Future directions will aims at generating homogenous population of adult derived-self-renewing multipotent NSCs and to unravel the mechanisms underlying the neurogenic niches. They will also aim at discovering and developing novel drugs that specifically target the newly generated neuronal cells of the adult brain, or neurogenic drugs, to compensate or reverse deficits, particularly associated with the hippocampus; drugs that stimulate neurogenesis, compensate for neuronal loss and elicit potential for regenerative medicine. Such strategy will involve limiting the potential deleterious effects of the generation of aneuploid neuronal cells in the adult brain, without disrupting the regenerative capacity of adult neurogenesis.

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Abbreviations: AD: Alzheimer's disease; ApoE4: apolipoprotein E varepsilon 4 allele; APP: amyloid precursor protein; BrdU: Bromodeoxyuridine; CNS: central nervous system; DG: dentate gyrus; EOAD: early onset AD; FAD: familial Alzheimer's disease; EOAD: early onset AD; NSCs: neural stem cells; PSEN-1: presenilin-1; PSEN-2: presenilin-2; RMS: rostro-migratory stream; SGZ: subgranular zone; SVZ: subventricular zone

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