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Regenerative Medicine in Alzheimer's Disease

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Abstract

Identifying novel, effective therapeutics for Alzheimer's disease (AD) is one of the major unmet medical needs for the coming decade. Because the current paradigm for developing and testing disease modifying AD therapies is protracted and likely to be even longer with the shift towards earlier intervention in pre-clinical AD, it is an open question whether we can develop, test, and widely deploy a novel therapy in time to help the current at-risk generation if we continue to follow the standard paradigms of discovery and drug development. There is an imperative need to find safe and effective preventative measures that can be rapidly deployed to stem the coming wave of AD that will potentially engulf the next generation. We can broadly define regenerative medicine as approaches that use stem-cell-based therapies or approaches that seek to modulate inherent neurogenesis. Neurogenesis, though most active during pre-natal development has been shown to continue in several small parts of the brain, which includes the hippocampus and the subventricular zone, suggesting its potential to reverse cognitive deficits. If AD pathology impacts neurogenesis then it follows that conditions that stimulate endogenous neurogenesis (e.g., environmental stimuli, physical activity, trophic factors, cytokines, and drugs) may help to promote the regenerative and recovery process. Herein, we review the complex logistics of potentially implementing neurogenesis-based therapeutic strategies for the treatment of AD.

Background

After age 65, the risk of developing Alzheimer's disease (AD) doubles every 5 years, so that by age 85 some studies suggest that ∼50% of individuals will have the disease. The latest estimates suggest that more than 35 million people worldwide suffer from AD today, with predictions that there could be >125 million AD patients by 2050 [1]. Currently, the only approved therapeutics for AD, the acetylcholine esterase inhibitors (Aricept®, Razadyne®, & Exelon®) and the NMDA receptor antagonist (Namenda®), offer transient symptomatic improvement but offer little, if any, benefit in terms of modifying the overall course of disease. It has been just over 20 years since the first studies linking AD to mutations in the amyloid precursor protein (APP) [2] and proteolysis of APP to the development of amyloid plaque pathology [3]. In the ensuing interval, investigators have defined the molecular targets of the proteolytic events that generate amyloid-β (Aβ) peptides, determined that generation of Aβ42 peptides is critical, and developed novel compounds that can prevent the generation of the most damaging peptides. However, to date, some of the heralded Aβ-targeted therapies have reached the clinic only to show little or no efficacy in improving

cognition in patients with clinically diagnosed AD. With the field developing improved methods of biomarker detection and compiling a large correlative dataset to relate biomarkers to cognition, it has become increasingly clear that deposition of Aβ in the form of diffuse and compact amyloid plaques occurs many years before the onset of symptoms; and appears to trigger a cascade of events that includes the misfolding of tau to generate the neurofibrillary tangle pathology of AD [4,5]. The early appearance of these pathologies in the non-symptomatic or prodromal phase of the disease has led to the realization that therapies targeting Aβ, and perhaps tau as well, may prove ineffective unless used as primary preventatives or early in the prodromal phase [6].

In the case of targeting Aβ as a primary preventative therapeutic, we face tremendous challenges in implementation. Even if we were to have, in-hand, safe and effective drugs that lowered Aβ42 production (e.g., γ-secretase modulators [GSMs] or β-secretase [BACE1] inhibitors), it is unclear whether such drugs could be approved solely on the basis of lowering Aβ. It is also unclear how the cost of these drugs to the consumer would be supported; insurance providers might balk at covering such medications without hard proof of efficacy or limit coverage to the subset of individuals carrying known high risk factor genetic mutations. In addition, physiological levels of Aβ may be neuroprotective and inhibition of its production could place patients at a greater risk for other diseases, including traumatic brain injury [7]. In many respects, the future of AD prevention is remarkably similar to that of the ‘lipid hypothesis’ of cholesterol reduction and the introduction of HMG-CoA reductase inhibitors, known as statins. Namely, the hypothesis states that pharmacologic or dietary reduction of the “harmful” cholesterol would benefit the patient by arresting atherosclerosis. At the time, there was no definitive proof that drugs or diet used to lower cholesterol would be the clinical equivalent of patients with “spontaneously occurring” low cholesterol. The key to its eventual success was an intensive post-marketing surveillance and additional directed clinical trials (Phase IV & V).

If regulatory issues regarding targeting Aβ as a biomarker of a risk factor cannot be resolved, then preventative therapeutics aimed at lowering Aβ may be limited to high-risk individuals. Although there are several highly predictive genetic risk factors known, with ApoE genotype being the most common, these risk factors presently predict only 20-25% of late-onset AD [http://www.alz.org/research/science/alzheimers_disease_causes.asp]. Thus, for most cases of AD, it is not possible to predict who is at risk for late-onset sporadic AD. Moreover, if a preventative trial were undertaken in APOE ε4 carriers, and if the standard of proof were to be that lowering Aβ in at risk populations does indeed reduce the incidence of AD (which one could argue is what should be required), then we are looking potentially at very protracted clinical trials. Under this scenario, anyone currently 50 to 70 years of age faces a possible future in which there will be no effective means to lower the risk of developing AD in time to have an impact.

With increasing uncertainty regarding how best to use Aβ targeting therapies, currently in the pharmaceutical pipeline, or how to test their potential as preventatives, the picture today for therapeutics for AD remains as uncertain as it did 20 years ago when the relationship between Aβ and AD was first described. Moreover, the timelines involved in the testing of preventatives virtually ensures a future in which AD remains a dreaded, untreatable disease. The shifting emphasis on earlier pharmaceutical intervention, there is an urgent need to look towards novel therapeutics that could benefit patients whose disease has progressed beyond the early window of clinical intervention. Therapeutic approaches based on biologics may offer one of the few viable therapeutic avenues. One such approach that continues to offer promise for later stages of AD is regenerative medicine, which can be broadly defined as approaches that use stem cell-based therapies or approaches that seek to modulate inherent neurogenesis.

Several recent reviews have more than adequately described the existing literature for pre-clinical studies of stem cell based therapies in models of Alzheimer's disease [8-13] and we will not re-review this work here. Instead, this review will focus on gaps in knowledge that could propel the field towards improved therapeutics and issues regarding translation of these therapies to advanced clinical testing.

Cell-based therapeutics for AD

With advances in stem cell biology and regenerative medicine, it is not unreasonable to construct scenarios that improve the treatment options for mild to moderate AD. There are, however, multiple hurdles to the wide-spread implementation of cell-based therapies for AD: the most obvious being that delivery of these biologic therapies require invasive techniques. Therapeutic benefit in humans may require wide-spread dissemination of transplanted cells throughout the cortex and hippocampus and it is not entirely clear how one might achieve such distribution when injecting such cells into the brains of aged adults. It could be possible to disseminate the cells more broadly through multi-site injection, but the risk of adverse effects from multiple injections may prove unacceptably high. Such potential for adverse effects can be estimated from studies of patient outcomes after implantation of electrodes for deep brain stimulation (DBS) [14]. Continual improvement in imaging techniques and surgical practice may ultimately lower the risk of adverse effects to more acceptable levels [15, 16], thus enabling approaches involving multi-site injections.

Initial attempts at cell replacement by transplantation will likely use well characterized cells, potentially derived from a single source, and long-term immunosuppression [17]. Neural stem and progenitor cells, from embryonic and fetal donors (both human and animal), can produce neurons with varying phenotypes that form functional neuronal connections in culture; integrate into existing normal networks, as well as facilitating repair when transplanted into the injured rodent CNS [18-20]. Advances in induced pluripotent cell technology may make it possible for “transplantation” of autologous progenitor cells. However, at present there is broad recognition that variability in the pluripotency of these cells could limit their efficacy. Inducing the formation of neurons directly from non-neural (e.g., fibroblast) cells can now be accomplished with small numbers of reprogramming transcription factors [21]. Additionally, it may soon be possible to induce reprogramming pharmacologically [22]. In this rapidly progressing area of research, it is difficult to predict how soon cell-based therapies will gain wide usage in the clinic.

In considering the future of cell-based therapies, it is important to consider whether such therapies may be more efficacious as neuroprotectives or whether they can be used to actually replace at-risk populations of neurons and glia in cortical regions involved in higher cognitive functions. With the former, it might be possible to use grafted neural or non-neural stem, and progenitor, cells to deliver protective agents, such as growth factors, or amyloid-degrading molecular therapeutics to reduce burden of extracellular toxic proteins that appear to mediate cognitive functional deficits (e.g. see [23]). However, the prospect of introducing modified or unmodified progenitor cells into relatively healthy patients as a preventative raises the bar for safety to a fairly high standard. It seems unlikely that such approaches would be widely employed if less invasive approaches were available. Instead, it seems far more likely that if these approaches are to gain wide acceptance, they will be used in patients to mitigate the cell loss that contributes to severe cognitive deficits in the later stages of the disease.

Pharmacologic stimulation of endogenous neurogenesis

An alternative approach that may be more amenable to wide-spread implementation in patients may be to identify processes to augment endogenous neurogenesis [24] in early to

mid-stages of the disease. In rodent models, neurogenesis has been directly associated with cognitive functions [25,26] including pattern separation [27]. Neurogenesis occurs in the adult human brain [28-31]; and recent studies have demonstrated links between neurogenesis and declarative memory function [32]. The importance of adult human neuropoiesis in the context of AD is that both indigenous programs for support of precursor cell growth and their progeny, as well as a microenvironment that can also sustain the growth of grafted neural stem/progenitor cells, clearly exist throughout adulthood. This offers considerable hope for exploiting these cells and inherent programs for repair and re-establishment of circuits that have been damaged as a result of the disease course in AD.

Reynolds and colleagues were among the first to demonstrate the existence of adult neural stem cells [33] and that growth factor infusions enhance endogenous neurogenesis in the periventricular subependymal zone [34], opening the door for using or controlling these cells for reparative programs. Since the initial report, numerous studies have reported the discovery and use of so-called neuropoietins [35], including epidermal growth factor (EGF), fibroblast growth factor (FGF), and transforming growth factor (TGF). In addition, a growing list of developmentally morphogenetic gene products have been identified including ERK2, a mitogen-activated protein kinase that plays an important role in cortical neurogenesis and cognitive functions [36], and the orphan nuclear receptor TLX, that regulates adult neural stem/progenitor cell proliferation in a “cell-autonomous manner by controlling a defined genetic network implicated in cell proliferation and growth” [37]. The list of developmentally regulated morphogens affecting neural stem/progenitor cell fate decisions and giving rise to differentiated neural progeny, neurons and glia, is too long to summarize here but together clearly support a notion that we understand how to make both endogenous and grafted populations of precursor cells give rise to potential replacement cells in AD. Intracerebral injections of morphogens, including certain transcription factors [38], some of which contribute to dedifferentiation through reprogramming [39], could be used to attempt to chemically reconstitute adult forebrain neurogenesis, including within the cerebral cortex [40]. This could be accomplished without the need for *in vitro* enrichment or preconditioning and transplantation of *ex vivo*-derived cells.

There are existing pharmacologic interventions that have the potential to encourage or sustain neurogenesis in the normal adult and AD forebrain. Anti-depressant drugs such as Prozac® (fluoxetine) have been shown to increase adult hippocampal neurogenesis in rodent models, as well as enhancing memory function and cognition in AD patients [41-44]. Presumably this occurs by increasing the generation of neuronal progenitor cells [41]. There has been at least one study with AD patients using a stem/progenitor cell growth factor, granulocyte colony stimulating factor (G-CSF), which was previously reported to improve spatial learning performance as well as reducing amyloid deposition in the hippocampus and entorhinal cortex of a mouse model of AD [45]. In the human study, the authors reported that G-CSF positively affected a hippocampal-dependent task of cognitive performance in AD patients.

A fair amount of effort by both the pharmaceutical industry and academic researchers has been put into identifying novel compounds that have effects on neurogenesis as well as neuroprotection [46]. This includes not only synthetic chemicals but also naturally derived compounds [46,47]. The latter not only includes isolated naturally occurring compounds but also the identification and use of, e.g., plants and herbs used in traditional Chinese medicine (TCM) and ayurvedic medicine native to the Indian subcontinent [47-50]. Natural product extracts can function as disease-modifying therapies, but this potential has rarely been critically evaluated *in vivo*; and as traditional medicines, many TCM and ayurvedic products have not been tested in rigorous scientific studies and clinical trials. If primary prevention for AD is largely unrealistic with therapies that do not have history of human exposure, then

we are left with few alternatives in the short-term. Botanical extracts with long histories of human exposure may provide a novel form of potentially "safe-enough" prophylactic therapy as well as their cognitive-enhancing or anti-dementia activities [51]. The plant materials are reported to contain several active compounds that have effects on cognitive function, resulting from the fact that cognitive dysfunctions are not solely dependent on the decreased activity of cholinergic neurotransmitter system [52].

Natural product botanical extracts have many classes of compounds that might have many beneficial actions in AD. For example, polyphenolic compounds in the extracts might function as anti-aggregation agents or anti-oxidants, and plant sterols could have numerous neuroprotective actions or anti-inflammatory actions and possibly directly impact Aβ production [50,53,54]. Thus, it is entirely possible that an extract could prove more efficacious *in vivo* because it contains multiple agents that target multiple pathologies. Memory enhancing extracts have been identified [48,50,55,56] and may play a role in neurogenesis; which can directly impact learning and memory [57]. The major hurdle to moving plant extracts into clinical settings is uncertainty over the composition of such extracts and a lack of information on the identity of bioactive components. Still, the fact that plant extracts have a long history of use in humans leads one to believe that it may be possible to implement use of these preparations in at-risk individuals much sooner than could be possible with synthetically-derived small molecules, which will require long periods of testing before approval for wide-spread use.

Environmental modulation of neurogenesis

Perhaps the least invasive and most widely implementable approach to enhancing endogenous neurogenesis may be through environmental manipulation [for recent reviews see [58,59]]. Both physical and mental exercises increase the numbers of newly generated neurons in the adult rodent hippocampus [60,61]. Multiple studies have demonstrated that exposing mice that develop the amyloid pathology of AD to environmental enriching factors such as exercise wheels or "enriched" environments can either lower the burden of disease-related pathology [62] or mitigate associated cognitive deficits [63]. The concept of exercising the brain has stimulated the genesis of cottage industries (e.g., www.luminosity.com) that promise improvements in brain health and performance through cognitive exercise. Indeed, leading scientists have begun to develop self-help approaches to improving brain function and health through non-pharmacologic methods [64].

Although data on the efficacy of non-pharmacological intervention is still limited, there have been a number of pilot clinical trials that have attempted to provide hard evidence to support this approach. A recent meta-analysis of 14 random-controlled-trials that involved 1,695 MCI patients aged 65 to 95 years concluded that there is limited evidence to support the idea that exercise alone markedly improved cognitive function [65]. In this study, improvements were noted in a single measure, verbal fluency, with no significant improvements in executive function, memory, or information processing. By contrast, there considerable evidence that providing various types of cognitive training, or memory training, can provide some level of benefit to patients. A recent review of neuropsychological outcomes in AD patients concluded that there was good evidence that interventions such as cognitive training or cognitive stimulation provided benefit in language and memory [66]. A recent clinical trial involving 104 Taiwanese subjects reported that activities described as music-therapy, orientation-training, and art-cognitive activities, with physical activities, produce broad benefits in multiple symptoms associated with dementia [67]. To our knowledge, it has not been possible to discern whether the mechanism for these benefits involves neurogenesis per se, but the data clearly indicate that it is possible to tap into other regenerative processes,

such as the inherent plasticity of the brain, in patients with dementia as a means to provide some level of symptomatic relief.

Prospects of replacing lost cell function

Replacement therapies involving several sources of neural precursor cells have been shown to generate long-distance projecting cortical pyramidal cells (one of the cell types most at risk in AD), including induced pluripotent stem cells (iPSC), as discussed above, embryonic stem cell-derived neural precursors [20,68], or stimulation of endogenous cortical oligodendroglial progenitor cells [69]. For example, Ideguchi et al., [68] have shown that mouse ES cells can give rise to pyramidal neurons that integrate and appropriately project to subcortical targets. This last study suggests that it might not be necessary to supplement growth conditions involved in axonal growth and synaptogenesis from such newly generated neurons in the AD brain with supportive factors like IGF-1 [70]. It has been presumed that axon growth would be inhibited in the adult brain, due to myelin-associated inhibitors [71], as well as extracellular matrix and other putative repulsive molecules associated with white matter and the mature brain in general [72]. However, these inhibitory factors may not be the insurmountable deterrent once thought for the formation of new and appropriate connections that arise from newly generated neurons. Still, it is certain that fate choice decisions of subtypes of cortical pyramidal neurons is dependent on both intrinsic programs (e.g. neuronal subtype-specific genes, see [73]) in addition to the aforementioned environmental factors. Together, these factors modulate appropriate connectional arrangements involving both newly generated neurons and pre-existing neurons in the AD brain. Additionally, it is certain that enhancing neurogenesis and circuitry reconstitution in the AD brain will require behavioral rehabilitation on many levels to secure appropriate function of formerly compromised memory circuits following the successful functional integration of newly generated neurons. The continuing struggle to identify effective therapeutics for AD, and other dementias, heightens the need to explore a broad spectrum of approaches including regenerative therapies that could repair damaged circuits and provide significant symptomatic improvements for the large number of patients that will soon be living with dementia.

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