Adult neurogenesis and Alzheimer's disease

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Until recently, progressive neurodegenerative diseases such as Parkinson's or Alzheimer's disease (AD), as well as acute brain injuries like stroke were thought to result in an irreversible loss of neurons with no possibility of neuronal regeneration. In the last few years, this belief has been challenged by numerous studies that have demonstrated that specialized areas of the brain retain pluripotent precursors with the capacity to regenerate neurons in adult mammals such as rodents[1-3], non-human primates[4], and humans[5,6]. The function of neurogenesis in the adult brain is still unknown, and we are far from understanding the processes regulating it. The available knowledge indicates that significant limitations at all key steps in the process will have to be overcome to achieve functionally relevant replacement of lost brain networks from endogenous neuronal stem cells. However, that new neurons are added continously to the adult brain is a discovery that has already changed the way we think about neurobiology and may soon change the way we understand and approach neurodegenerative diseases.

1. Alzheimer's disease

Overview

Alzheimer's disease, the most common dementing disorder, is a remarkably pure cognitive impairment[7] whose anatomical hallmarks are the so-called amyloid plaques, neurofibrillary tangles, and a profound loss of synapses and neurons in the brain. Cognitive impairment in AD can be attributed to the loss of specific populations of neurons and the breakdown of vulnerable brain networks, particularly those involved in memory formation. Mutations associated with familial AD have been mapped to the amyloid precursor protein (APP) gene or to genes whose products participate in the proteolytic processing of the APP protein[8]. Familial forms of AD have early onset and progress to moderate and severe stages in a relatively short time. Sporadic AD, which has a later age of onset, accounts for 98 % of cases and varies considerably in its rate of progression. The underlying pathogenic processes, however, are thought to be shared by both forms of the disease. Proteolytic processing of APP gives rise to amyloid ß(Aßa peptide which aggregates into insoluble amyloid plaques. The hypothesis that has dominated the field for the last 15 years proposes that the accumulation of Aß and the deposition of amyloid plaques is the main cause for the toxicity observed in AD. This hypothesis, however, has been questioned by a number of recent studies showing that the level of soluble Aß, but not the degree of Aß deposition, correlates with functional impairment in humans[9], and that synaptic anatomical and functional deficits occur much before Aß deposition in humans[10,11] and in transgenic mouse models[12,13]. Furthermore, we have shown that AD-like pathology in transgenic mice can be independent of the accumulation and deposition of Aß[14]. In humans, a decrease in synaptic density number is the strongest correlate to degree of cognitive impairment[10,11,15,16]. These observations strongly suggest that plaque deposition may be secondary to functional deficits, and that soluble Aß and possibly

other factors in addition to Aβ accumulation have a crucial role in the early pathogenesis of the disease.

At its earliest clinical phase, AD manifests itself as an amnestic mild cognitive impairment (or minimal cognitive impairment, MCI) whose identification poses a considerable challenge to the clinician[17]. The impairment may affect any or a number of memory functions. In those individuals who will progress to AD, MCI evolves into the so-called prodromal phase which is characterized by a further progressive deterioration of memory functions which may interfere with normal social functioning. Other forms of cognitive impairment such as language disorders and impaired visuospatial learning skills and executive functions are added over the course of several years after diagnosis, and changes at these stages frequently involve profound alterations in personality. Eventually, patients progress into clinical dementia in which many brain functions are affected. Definitive diagnosis, however, is possible only at the time of autopsy, when the co-occurrence of amyloid plaques and neurofibrillary tangles (NFT), and particularly of NFTs in the neocortex, are indicative of AD when consistent with the individual's clinical history.

The regions of the brain that are most affected at the early stages of the disease are the associative cortexes, particularly the hippocampus and the entorhinal cortex, which are thought to have a fundamental role in associative memory functions and in spatial contextual memory encoding[18,19]. At early stages, the circuits affected are fundamentally glutamatergic and cholinergic, consistent with damage to the septal-hippocampal and basal forebrain-neocortical pathways and their projection neurons[20]. Olfactory dysfunction is a feature that sometimes accompanies preclinical AD and it has been proposed that it may serve as a predictor of the development of cognitive symptoms[21-23]. As the disease progresses, other cortical regions are affected, involving at first high-order association regions much more frequently than the primary motor and sensory regions. At later stages in the progression of the disease, the loss of medium-sized pyramidal neurons effecting corticocortical connections, together with neurons throughout the cerebral cortex, add other spheres of cognitive impairment such as language disorders, impaired visuospatial skills and executive functions to the gradual memory loss as the disease progresses into its moderate and severe stages[17].

The amyloid precursor protein

APP is an integral membrane protein that is axonally transported to nerve terminals and accumulates at presynaptic sites[24,25]. APP's transmembrane region contains the carboxyterminal portion of the Aβ peptide, flanked by a short intracytoplasmic C-terminal domain and a much larger extracellular domain at its N-terminus. Proteolytic processing at the proximal region of the extracellular domain and within the transmembrane region by βΒ, αvδΥ-secretases gives rise, in different combinations, to the soluble extracellular domain, the poorly soluble Aβ1-42 (as well as Aβ1-40), the soluble p3 peptide and a 99-amino acid carboxyterminal fragment as major cleavage products[26,27]. The cytosolic region of APP has a caspase recognition site at Asp 664 that generates a cytotoxic 31-amino acid C-terminal fragment, C3128-33 This peptide encompasses a YENPTY clathrin-pit internalization signal34 that acts as a binding site for several APP-interacting proteins[35-41].

Accumulating evidence suggests that the intracellular carboxy (C)-terminus of APP is involved in multiple cellular processes[35,40,41] and our studies have implicated it directly in the pathogenesis of the AD-like phenotype in transgenic mice[14].

The most abundant cleavage of APP in non-pathological conditions is by α-secretase within the Aβ sequence[8]. This cleavage releases the soluble ectodomain of APP, sAPP, which is present in brain tissues and in cerebrospinal fluid and has been shown to enhance synaptogenesis, neurite outgrowth, cell adhesion and cell survival[42]. Even though the processes involved in the generation of Aβ through cleavage of the amyloid precursor protein (APP) are being elucidated, the function of APP and that of Aβ remain unclear. APP is a member of a family of proteins that includes the amyloid precursor-like protein 1 (APLP1) and 2 (APLP2)[43,44]. Whereas APP null mice show relatively mild brain abnormalities[45], the APP, APLP2 double knockout has a lethal phenotype[46] suggesting a fundamental role for the APP family and functional redundancy between APP and the APLPs in mammalian development.

2. Neurogenesis in the adult mammalian brain

Neurogenesis in rodents and primates

Until recently, a central assumption in neuroscience had been that new neurons do not arise in the adult mammalian brain. This had been the accepted belief[47] since the idea was proposed by Ramon y Cajal[48] and others at the beginning of the last century. This view firmly prevailed in spite of sporadic reports that showed that new cells could arise in certain specialized areas of the brain[49-54]. The thorough historical review by C.G. Gross[55] provides an illuminating example of a 'paradigm shift'[56] and shows how the weight of authority and the engraftment of a ruling belief in a field can completely block discovery and make researchers blind to the evidence for almost a century. About ten years ago, studies that firmly established that new neurons are continuously born in the adult mammalian brain[57,58] including non-human primates[4] and humans[5,6] were published[59,60]. It is now widely accepted that undifferentiated neural stem/progenitor cells (NPCs) are maintained in specialized microenvironments or 'niches' in some brain regions[61] in which these cells may undergo symmetrical division at a very low rate[62,63] maintaining their multipotency, or alternatively undergo asymmetric division to differentiate into neuronal precursors. In rodents, it was shown that neurogenic stem cells are concentrated in the subventricular zone (SVZ) of the lateral ventricle wall[3] and the subgranular zone of the dentate gyrus (SGZ) of the hippocampus[64]. Cells born in the SVZ during adult life travel anteriorly through the rostral migratory stream along tubular structures formed by astrocytes that envelop the neuronal progenitors into the olfactory bulb (OB), where they differentiate into interneurons[65]. This process is referred to as "chain migration"[57]. Cells born in the SGZ of the dentate gyrus of the hippocampus migrate a short distance to integrate in the granular layer[60].

Together with the dethronement of the paradigm of 'brain constancy', the 'neurocentric' view of the brain is also being reconsidered. The fundamental role of glia in the adult brain was further underscored by the studies of Alvarez-Buylla and coworkers[57] and other groups[66] that demonstrated that astrocytes in the SVZ and SGZ are neurogenic stems cells in mammals[67] and that radial glia function as

progenitors for the majority of mammalian CNS neurons[66]. The neurogenicity of SVZ and SGZ progenitors in the adult mammal brain is restricted by signals from their local tissue environment, as astrocytes outside these zones do not show neurogenic properties in vivo[61]. Highlighting the importance of cues from their microenvironment, transplantation experiments demonstrated that SVZ cells loose their neurogenic potential when placed into non-neurogenic regions of the brain[61]. Thus, groups of astrocytic cells both contain neural progenitors and participate in the creation of the microenvironment that stimulates neurogenesis[61,66]. Not surprisingly, well-established developmental signal molecules and morphogens such as Notch, BMPs, Noggin and sonic hedgehog have been implicated in the maintenance of these adult neurogenic microenvironments[68] that involve endothelial cells[69].

That neural stem/progenitor cells also exist in adult primate and human brain has now been firmly established[4,6,70,71] for the subependymal zone[72] and for the hippocampus[5,73]. Sanai et al.[74] described an astrocyte band along the lateral ventricles of adult human brains ages 19-68 years that had not been described in other mammalian species. Although explant cultures of adult human SVZ astrocytes could produce multipotent, self-renewing neurospheres both in the presence and in the absence of exogenously added growth factors, no evidence of chain migration could be found in the SVZ or in the human olfactory peduncle in this study. The substantial loss of functional olfactory receptor genes in the human genome when compared to rodents suggests that the sense of smell in humans has long lost part of its adaptive value. Consistent with this idea, the rostral migratory stream that continues to supply replacement interneurons to the rodent olfactory bulb is weak or undetectable in humans, possibly reflecting the reduced functionality of the human OB. A recent report by Bedard and Parent[75], however, reported the presence of cells expressing cell cycle markers and markers for immature neurons in the human olfactory bulb (OB), suggesting that precursor proliferation may also occur, albeit at a much reduced rate, in this region of the adult human brain. In contrast, the dentate gyrus and the hilus in cornus ammonis 4 region (CA4) of the human hippocampus are possibly the most active areas of progenitor proliferation in adult primates[76,77] and humans[5].

In a seminal paper, Eriksson et al.[5] examined hippocampal sections of non-metastatic cancer patients that had received bromo-deoxyuridine (BrdU) as part of their treatment. This study revealed a relatively high percentage of proliferating progenitors (as evidenced by BrdU incorporation in their DNA) in the granular cell layer and the subgranular zone of the dentate gyrus and in CA4. Remarkably, and albeit the sample number precluded drawing quantitative conclusions, the highest number of proliferating precursors in the granule cell layer and in the hilus were found in human adults of middle and advanced age. Other studies have shown a decrease in the levels of adult progenitor proliferation with increasing age in rodents, but a stronger response to its stimulation when compared to young hippocampus[78].

A role for neurogenesis in learning and memory

The function of adult neurogenesis is still not known. In 2001, however, Shors et al. demonstrated that performance of a hippocampus-dependent learning task was dependent on the presence of replicating progenitors, suggesting that neurogenesis in the adult hippocampus has a role in learning memory[79]. The number of new cells generated in the hippocampus of rat is in the order of the thousands per day[80] and a high proportion of them differentiate into neurons[81,82]. However, only about half of these newly generated neurons will survive after the first few weeks[83,84]. Those that survive seem to integrate into preexisting hippocampal circuits and may permanently replace granule cells born during development[84]. Survival of new neurons is significantly enhanced by exposure to hippocampal-dependent learning tasks[84,85], by environmental enrichment, and by running[86]. Most remarkably, production overweights loss of proliferating progenitors in the rat hippocampus such that neuronal cell numbers increase continously throughout life[87]. A central idea that long supported the assumption of 'cerebral constancy' was the proposed need for the organism to preserve memories of experiences throughout a relatively long lifespan; however, a fundamental feature of memory is that it is selective, so that not all memories are preserved, and those that are preserved are not static but are reprocessed continously in a dynamic fashion[88]. Moreover, a memory is associated with a pattern of activation[88], not with an individual neuronal circuit in its physical sense. Thus, the preservation of memories may not necessarily require the preservation of individual neurons.

A recent study by Deiseroth et al.[89] has addressed for the first time the question of whether activity and neurogenesis are coupled, a process that would implement a form of network plasticity that would be conceptually analogous to the well-known forms of plasticity at the synaptic level, but occurring at the cellular network level[89]. Using an in vitro model, the authors demonstrated that excitatory stimuli act directly on adult hippocampal proliferating NPCs to favour adoption of the neuronal phenotype. The generation of new neurons was strongly dependent on Cav1.2/1.3 type of HVA channels and on NMDA receptor activity. These in vitro results strongly suggest excitation-neurogenesis coupling, and are consistent with a proposed model for frequent memory turnover in the hippocampus, a critical locus for temporary memory storage[90,91]. Indeed, organismal-level stimuli that entail an increase in neuronal activity such as learning[85,92], exposure to environmental enrichment[86,93], and voluntary running[86] have been shown to stimulate neurogenesis and enhance the survival of new neurons in the adult mammalian hippocampus. Although neither of these behavioral interventions increase adult neurogenesis in the SVZ/OB[93], proliferation in these areas can be influenced by olfactory sensory stimuli[94]. These observations strongly suggest a need for local network activity for the stimulation of neurogenesis and the survival of differentiated progenitors[94]. Thus, neurogenesis may have a role in plasticity at a cellular network level[89] in a manner that is in turn regulated by activity-induced excitation of those networks.

3. Brain injury and neurogenesis

Neurogenesis and acute injury

Acute injury, such as hipoxia following middle artery occlusion in rat, induces the proliferation of neuronal precursors after extensive damage has occurred as consequence of infarctum in the striatum and parietal cortex[95]. These new neurons are generated in the SVZ and tend to migrate towards the site of the lesion. It has been proposed that the migration of precursors is guided by a migration-inducing activity produced by astrocytes at the ischemic site[96]. Only a small fraction of the cells generated in the initial proliferative response, however, survives 6 weeks after the insult[95] and it is not clear how or if these cells can contribute to functional recovery of neuronal networks. However, recent studies[97-99] showed that stimulation of NPC proliferation and possibly survival may be enhanced by growth factors even in older rodents[99], suggesting that the endogenous neurogenic response to acute injury could in principle be modulated exogenously. In agreement to the findings by Eriksson et al. for endogenous neurogenesis in human brains[5], the responsiveness of aged mouse brains to growth factor-stimulated neurogenesis was comparable to that of young animals, even when the overall level of endogenous neurogenesis in older mice were decreased. Neurogenesis following acute injury, however, has in most cases been described for regions close to the SVZ, suggesting that the SVZ preferentially contributes new neurons to the lesioned area by activation and migration of its progenitors, with a much smaller contribution of progenitor cells from the damaged area itself or from other regions of the brain. A variety of other forms of acute brain injury, such as mechanical lesions, elicit similar effects on the proliferation of neuronal precursors[100].

Neurogenesis and chronic damage

The activation of neurogenic processes as a response to chronic damage is much less well documented. In most cases of activation of neurogenesis as a response to injury, the origin of the proliferating precursors can be traced to the SVZ and the SGZ in the dentate gyrus. However, other regions of the brain for which endogenous multipotent precursors have not been described, such as the postnatal mouse cortex, have been found to respond to injury with the proliferation of endogenous neural precursors as well[101]. Targeted photolytical degeneration of corticothalamic neurons in layer VI of anterior cortex in adult mice activated the production of new neuronal cells that could form appropiate long-distance corticothalamic connections[101]. In contrast to the massive losses of cells that generally accompany acute injury, only 20% of the total number of neurons in the treated area were targeted in these experiments. Thus, the induction of de novo neurogenesis in areas of the brain in which it does not normally occur may follow the induction of a synchronous “neurodegenerative-like” lesion.

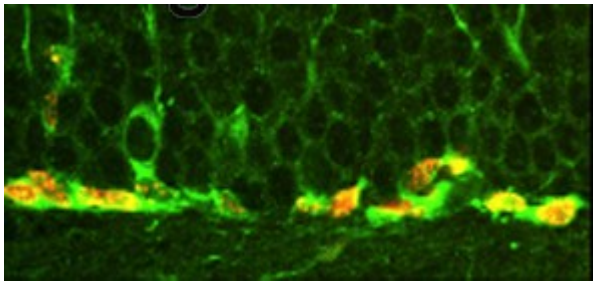

Figure 1. Bromodeoxyuridine-labeled nuclei (red) of cells expressing the immature neuronal marker doublecortin (DCX) (green) in the subgranular zone of the dentate gyrus of mice that model Alzheimer's disease.

Supporting the idea that slow damage as that leading to neurodegeneration may also induce progenitor proliferation, we have described higher numbers of replicating neuronal progenitors in the molecular layer of the dentate gyrus of transgenic mice that model AD[102] (Figure 1). This is in contrast to prior findings from different transgenic mouse models of AD in which transgenic mice showed impaired, rather than increased, neurogenesis[103-105]. These disparities raise the possibility that different forms of AD may differ with respect to their association with neurogenesis, especially when considering that sporadic AD accounts for the great majority of the cases and is thought of as a heterogeneous disorder. Supporting our observations in transgenic mouse models, Jin et al. recently demonstrated that increased levels of neuronal progenitors expressing high levels of markers of immature neurons could also be found in the dentate gyrus and in the CA1 regions of the hippocampus of human AD patients when compared to age-matched normal controls[106]. These results suggest that proliferation of neuronal precursors may take place in aged patients with AD and that this process may be exacerbated by the ongoing neurodegenerative process. The evidence for de novo neurogenesis induced by chronic injury, however, is far from being definitive.

That the two regions that remain ostensibly neurogenic in the adult brain are part of the structures supporting higher-level functions affected at the early stages of AD (olfaction and associative memory) may be interpreted as pointing out to deficits in endogenous neurogenesis as a contributing factor in the early pathogenesis of the disease. This may suggest that sporadic AD may have a component of insufficient neurogenic replacement or insufficient neurogenic stimulation. This view is consistent with epidemiological data suggesting that higher education and increased participation in intellectual, social and physical aspects of daily life are associated with slower cognitive decline in healthy elderly and may reduce the risk of AD[107]. These aspects of life experience have been dubbed "cognitive reserve" as they seem to point out not to a specific decrease in anatomical pathology but to a higher tolerance to such pathology.

Some studies in AD brains[106] and in mouse models of AD[102], however, revealed increased, not decreased, levels of dividing neuronal progenitors. That we observed increased neurogenesis in young animals, at ages well before the onset of overt pathology and in the absence any detectable increase in cell death[13], suggests that synaptic abnormalities in transgenic mice may be sufficient to stimulate neurogenesis[102]. Synaptic loss is possibly the earliest anatomical deficit detectable

in the progression to AD. The number of presynaptic objects present in frontal cortex of mildly impaired patients is decreased by 25% with respect to age-matched controls[10,15], and the degree of synaptic loss is more robustly correlated to cognitive impairment than any other morphological indicator in the disease (number of plaques or tangles, degree of neuronal perykaryal loss, or extent of cortical gliosis)[7]. Whether changes in rates of progenitor proliferation occur in brains of MCI or early AD patients is still not known; studies aimed to answer this question should provide valuable information as to whether synaptic deficits in early AD might also be sufficient to stimulate neurogenic processes.

At first glance, the recent findings of coupling between excitation and neurogenesis seem to be at odds with the observed decrease in the number of synapses early in the pathogenesis of AD, which would be expected to result in a decrease in overall network activity. However, as suggested by the studies of Deiseroth et al., the activity-dependent proliferative bursts of progenitors in the hippocampus precede the excitation-induced bias for the choice of neuronal fates, which is dependent on NMDA receptor activity in vitro[89]. It has been proposed that while excess glutamate will be toxic to established, mature neurons, differentiating neuronal precursors will respond to this stimulus by the production of new neurons[89]. If, as it has been proposed[108] and the available AD data suggest[102,106], the loss of small numbers of mature neurons or a decrease in the numbers of presynaptic terminals signal the proliferation of neuronal precursors, then the increased levels of dividing neuronal precursors found in AD brains and in mouse models of AD are likely to represent the response of the local network to these synaptic alterations. However, even though progenitor proliferation might be activated by synaptic deficiencies, their survival heavily depends on function[89,92]. Moreover, the proportion of surviving progenitors that will adopt a neuronal fate is also dependent on their integration in circuits with active excitatory synaptic connections. Notwithstanding these caveats, that the neurogenic response remains functional in the framework of ongoing neurodegeneration is encouraging for the prospects on intervention.

4. Neurogenesis and AD

The ultimate requirement for neurogenesis to be beneficial in the adult is that it contributes to function at the systemic level according to the cognitive and psychological definition of function[109]. The different levels of analysis in adult neurogenesis have been adequately described by Kempermann et al.[109], and we refer the reader to this review for further information. All available evidence indicates that continous hippocampal neurogenesis may be involved in learning[92,110]. It is possible that increases in continuous neurogenic processes may be activated by relatively ‘mild’ injuries such as a decrease in synaptic numbers, as it appears to be the case in transgenic mice[102]. If this is also true in early AD, an unique window of opportunity may exist in which neurogenesis could potentially be tapped on to contribute to functional ‘repair’ of the adult brain. However, many factors are required for neurogenic processes to contribute to function. Survival and acquisition of a neuronal phenotype by NPCs are dependent not only on network activity, but also on the existence of a complete environment capable of supporting survival, maturation and function by the production of neurotrophins and other regulators of proliferation and differentiation[111-114]. When the network structures in

which NPCs can integrate are compromised, increased proportions of proliferating progenitors may die. If death of moderate numbers of cells can activate neurogenesis[101], increased numbers of dying precursors may signal further activation of NPC proliferation. Would ongoing neurogenic processes contribute to 'repair' at all stages in AD, or might there be a requirement for a minimal degree of integrity of the network structure for neurogenesis to be beneficial? It is conceivable that a temporal distinction exists in the role of neurogenesis during the course of a slow degenerative disease, one dictated by the degree of permissibility of the environment in which the process is taking place.

The role of APP

The processes that underlie the initial loss of functional synaptic elements early in the progression to AD are not known. The "amyloid hypothesis", which has considerable experimental support, states that increases in the amounts of low and high order oligomers of the Aβ peptide released by proteolytic cleavage of APP can induce deleterious processes at the cellular and network level. Unfortunately, the investigation of the biological role of Aβ has long been out of the main focus of interest, possibly as a consequence of a widespread misconception of Aβ as a wholly undesirable endogenous "toxin". Consistent with its presence at synaptic sites, however, many studies have suggested a role of oligomeric Aβ in the modulation of glutamatergic synaptic transmission and plasticity in vivo[115-120] and all amyloidogenic Aβ peptides have been reported to enhance Ca^{2+} entry or destabilize intracellular Ca^{2+} storage[8,42,121,122]. Moreover, Kamenetz et al. recently showed that neuronal activity can be regulated by Aβ and in turn regulate the production and secretion of Aβ by controlling the proteolytic processing of APP[123]. Their observations strongly indicate on a role of Aβ as a negative feedback regulator of neuronal activity and it is thus conceivable that alterations in this feedback process may result in increased Aβ levels, decreased local network activity, and a decrease in numbers of functional synaptic sites, which may in turn further decrease network activity.

On the other hand, the soluble secreted derivatives generated when APP is cleaved by β-secretase on the pathway to Aβ generation and by α-secretase in the non-amyloidogenic pathway (β-sAPP and α-sAPP respectively), that encompass APP's extensively glycosylated ectodomain, have been implicated in the enhancement of synaptogenesis, neurite outgrowth, cell survival and cell adhesion[42], and recently in the modulation of neurogenesis in the SVZ[124]. Thus APP may serve two separate functions, one possibly local at synaptic sites and another one at the network/system level through the action of sAPP as a survival/neurogenic factor. Interestingly, a recent report has suggested that aggregated $Aβ_{1-42}$ may also have a neurogenic effect in fate choice of NPCs in culture[125].

5. The opportunities for intervention

It is likely that continuing neurogenesis has a function in plasticity at the local network and system levels in the adult brain. To the extent that neurogenesis may contribute to function in the adult human CNS, the process does not suffice to preserve function when injury or degenerative processes have ensued. The observation that the mildest form of impairment in new memory formation is correlated with a considerable decrease in synapse number in humans[10] may suggest that during the latent phase, ongoing pathological processes such as an increase in Aβ levels may be tolerated by local neuron/glial networks. If we make the assumption that changes in connectivity that are below ~25% can be absorbed without an overall effect on high-order functions, it is reasonable to expect that interventions before or at those stages will be most effective to prevent further, more drastic changes. The potential for stem-cell derived transplantation therapy as a possible intervention has been the focus of intense research in the last years. We refer the reader to the article by Lindvall et al[126] for a comprehensive review on this subject. The use of endogenous sources for cell replacement, however, offers several key advantages such as the absence of ethical concerns and the avoidance of immunological reactions. A thorough consideration of the challenges to the design of treatment strategies based on the stimulation of endogenous neurogenesis for replacement of affected networks, mainly centered on the delivery of growth factors, can be found in the review article by Lie et al[127].

Insulin-like growth factor I (IGF-I) has neuroprotective and neurogenic effects[128] and it has been shown that peripheral infusion of IGF-I can increase NPC proliferation, selectively induce neurogenesis[129], and ameliorate the age-related decline in hippocampal neurogenesis in rats[130]. Moreover, a comprehensive study by Carro et al.[131] demonstrated that serum IGF-I modulates Aβ levels in brain. IGF-I treatment dramatically reduced Aβ burden in rats and transgenic mice modelling AD[131], suggesting that IGF-I signaling may also have a direct role the pathogenesis of AD[132].

Providing evidence that modulation of the endogenous progenitor cell response to injury may be beneficial for recovery after injury, Nakatomi and colleagues showed that intraventricular infusion of FGF-2 and EGF after selective degeneration of CA1 pyramidal neurons in rats by global ischemia contributed to regeneration of approximately 40% of the pyramidal neurons in this region, which survived at least up to 6 months after injury and were correlated with enhanced improvements in behavioral recovery in growth-factor treated animals[133].

Endogenous augmentation of trophic factor expression (such as BDNF, NGF and FGF) in brains of laboratory animals has been achieved by behavioral interventions[134] such as enriched experience, voluntary exercise[135] and training/learning[136]. Both enriched housing and training have been shown to increase synaptogenesis[132] and neurogenesis[86] as well. In conditions of brain damage, environmental enrichment and physical exercise has been shown to have beneficial effects on the behavioral outcome of the injury irrespective of the origin and type of damage[136,137 137]. The protective effects of physical exercise were shown to be mediated by circulating IGF-I[137]. In most cases, the effects of enriched

experience, physical exercise or training are thought to arise through activation of compensatory effects at the cerebral level.

The discovery of neurogenesis in the adult mammalian brain has opened up avenues of research that will hopefully provide us with knowledge that will enable the development of therapeutic interventions to prevent and treat neurodegenerative diseases such as AD. Even though the gaps in our understanding of the neurogenic process are not insignificant, it is likely that continuing investigation into the basic biology of adult neural stem cells will allow us to modulate cell replacement processes in the adult brain. While efforts are devoted to the study of neural stem cell biology and the development of therapeutics[126,127], it should be kept in mind that the contribution of adult neurogenesis to cognition is most likely a long-term process[109,138]. As behavioral interventions can stimulate neurogenesis in experimental models and possibly in humans, it is reasonable to suggest that lifestyle changes may constitute a therapeutic approach of low risk, albeit of variable efficacy, for the treatment of AD patients, particularly those at the early stages in the progression of the disease. Moreover, behavioral interventions may help societies increase their overall “cognitive reserve” and reduce the human, economic and social burden associated with increased numbers of cognitively impaired elderly in developed societies with high life expectancy. This goal can be achieved through the diffusion of knowledge, required for informed lifestyle choices, and the socialization of institutions providing access to continuing education, creative occupation, physical activity and the enjoyment of the arts.

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