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Review Article

Effect of transplantation of human embryonic stem cell-derived neural progenitor cells on adult neurogenesis in aged hippocampus

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Abstract: Adult neurogenesis occurs within the special microenvironment in the subgranular zone of the hippocampus and the subventricular zone of the lateral ventricle of the mammalian brain. The special microenvironment is known as neurogenic niches. Multiple cell types, including endothelial cells, astroglia, ependymal cells, immature progeny of neural stem cells, and mature neurons, comprise the neurogenic niche. Differentiation of embryonic stem cells towards the neural lineage results in the generation of different neuronal subtypes and non-neuronal cells (mainly astrocytes). Therefore, it is reasonable to hypothesize that transplantation of human embryonic stem cell-derived neural progenitor cells can be used to modify neurogenic niches for facilitating adult neurogenesis. Furthermore, if generated new neurons are functionally integrated into the existing circuits of the aged hippocampus, synaptic plasticity in the hippocampus and learning/memory functions in aged mice should be enhanced. In this article, we provide a comprehensive review of the concepts in the regulation of adult neurogenesis by neurogenic niches and discuss the molecular mechanisms underlying the effect of stem cell transplantation on adult neurogenesis in aged hippocampus.

Keywords: Adult neurogenesis, aged hippocampus, neurogenic niche, neural progenitor cells

Introduction

Tomorrow's America will be an aging society because enormous "baby boom" generation will reach retirement age over the next decade. The number of individuals older than 65 years is projected to exceed 71.5 million in 2030, which is twice the number alive during 2000 [1]. A significant proportion of those older than 65 years will have to cope with alterations in memory function that are associated with normative aging [1]. Memory loss that increases with age is known clinically as age-associated memory impairment (AAMI). Although AAMI is common and is not a sign of a serious neurological disorder, it can be frustrating and cause reduction of productivity. Hippocampus is a critical brain region for learning and memory functions. We have known that adult neurogenesis occurs in the subgranular zone (SGZ) of the hippocampus [2-4]. Adult neurogenesis is the development of new functioning neurons in the adult central nervous system (CNS) of all mammals, including humans. However, adult neurogenesis in the SGZ of the hippocampus gradually diminishes with increasing age. To date, specialized microenvironments or "niches" have been sh own to play important roles in maintaining and regulating adult neurogenesis [3, 4]. The neurogenic niche is able to sense and response to the activity of the existing circuits, leading to changes in adult neurogenesis. Several cellular components have been implicated in constructing the neurogenic niche for adult neurogenesis [5]. Astroglia, immature progeny of neural stem cells (NSCs) and mature neurons are among those components. Astrocytes within the neurogenic niche contribute to the properties of the niche to promote the proliferation of NSCs. The release of some neurotransmitters from neuroblasts and mature neurons regulates adult n eurogenesis by activation of their receptors.

N-methyl-D-aspartic acid (NMDA) receptor activation in newborn neurons by glutamate released from mature neurons regulates competitive survival and synaptic plasticity of these new neurons [6, 7]. Embryonic stem (ES) cell-derived neural progenitor cells (NPCs) are capable of producing neurons and non-neuronal cells (mainly astrocytes), and thus they not only directly increase the number of functioning neurons, but also can be used to modify the neurogenic niche for improving adult neurogenesis after transplantation. Previous studies from our laboratory and others have demonstrated that postsynaptic density protein-95 (PSD-95), a scaffolding protein, can attach NMDA receptors to internal signaling molecules through the protein-binding module PDZ domain-mediated protein-protein interactions at neuronal synapses and is involved in many physiological and pathophysiological functions, including regulation of synaptic plasticity, triggered via the activation of NMDA receptors in the CNS [8-15]. Therefore, it is very significant to determine whether intrahippocampal transplantation of human ES cell-derived NPCs improves adult hippocampal neurogenesis in aged mice and whether generated new neurons are functionally integrated into the exi sting circuits of the aged hippocampus. Fu rthermore, it is critical to explore whether PDZ domain-mediated interactions between PSD-95 and NMDA receptors at neuronal synapses contribute to the molecular mechanism by which NPC transplantation modifies neurogenic niches and then enhances learning/memory functions in aged mice. These studies will provide important experimental evidence to support the notion that transplantation of h uman ES cell-derived NPCs can modify neurogenic niches to improve adult hippocampal neurogenesis during aging.

Adult neurogenesis and neurogenic niches

It was believed that the adult mammalian brain was completely unable to regenerate after insults and neurogenesis occurred only during embryonic stages in the CNS [16]. However, accumulating evidence in the field of stem cell biology has shown that active neurogenesis continues throughout life in discrete regions of the adult brain of all mammals [2, 17, 18]. Adult neurogenesis is mainly restricted to two specific brain regions: the SGZ of the hippocampus and the subventricular zone (SVZ) of the lateral ventricle [3, 4, 19-23]. Our understanding of adult neurogenesis has progressed enormously over the past decade. Currently we have known much more about the biology of adult neurogenesis, including the identity of adult NSCs, proliferation and fate specification of NPCs, migration, neuronal maturation, and synaptic integration of new neurons in the adult brain niche [3, 4, 17-27]. The differentiation of NSCs towards a neuronal phenotype is determined by the extracellular and intracellular factors that form the neurogenic niche. The unique neurogenic niche architectures present in above-mentioned two brain regions permit functional neurogenesis from NSCs in vivo [3, 5, 21]. To date, five major cellular components have been implicated in constructing the neurogenic niche for adult NSCs, including endothelial cells, astroglia, ependymal cells, immature progeny of NSCs, and mature neurons [5]. These components in the neurogenic niche regulate different steps of adult neurogenesis. For instance, astrocytes within the neurogenic niche may promote the proliferation of NSCs; mature neurons may release glutamate to regulate neuronal survival and synaptic plasticity of newly generated neurons in the adult brain by activation of NMDA receptors [6, 7]. The neurogenic niche is a dynamic signaling center that can be modified in response to both physiological and pathological stimulations [4, 5]. Thus, neurogenic niches are potential targets to develop novel approaches for improving adult neurogenesis and enhancing neuronal f-unctions.

ES cells have been demonstrated to be able to spontaneously differentiate towards many cell types in vitro, including neuron-like cells [28]. Differentiation of ES cells towards the neural lineage results in the generation of different neuronal subtypes and non-neuronal cells (mainly astrocytes). Previous studies have shown that human ES cell-derived NPCs differentiate into mature neurons after transplantation and functionally integrate into the host brain [29, 30]. One defining characteristic of adult neurogenesis is its regulation by activity of mature neurons in the exiting circuits [4, 5]. Some neurotransmitters released from mature neurons, such as glutamate and γ-aminobutyric acid, can regulate adult neurogenesis by activation of their receptors. Therefore, it is possible that transplantation of human ES cell-derived NPCs can be used to modify neurogenic niches for facilitating adult neurogenesis (**Figure 1**).

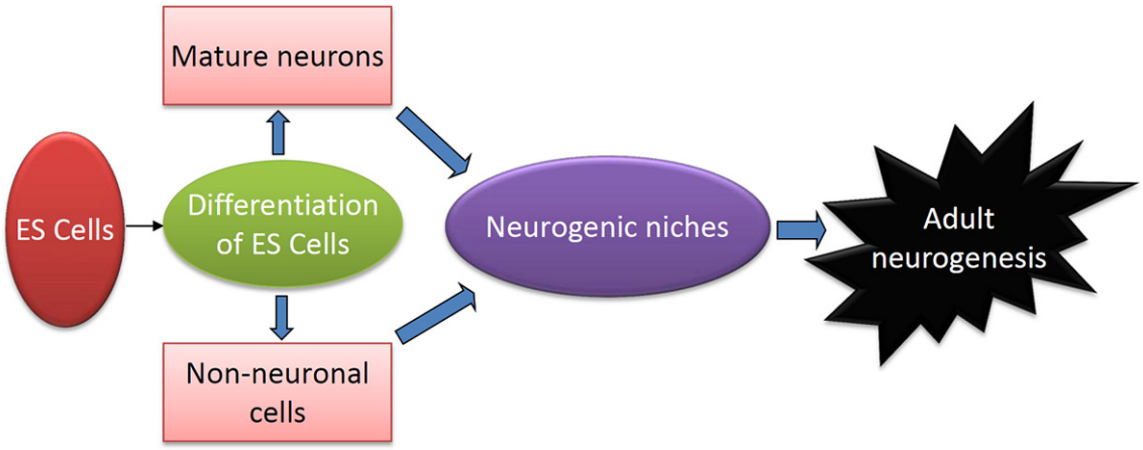

Figure 1. Stem cell transplantation and adult neurogenesis.

NMDA receptor signaling in adult hippocampal neurogenesis

New neurons are continuously integrated into existing neural circuits in adult dentate gyrus of the mammalian brain [22, 31-33]. These new neurons are involved in learning and memory [34-37]. The survival of new neurons is competitively regulated by their own NMDA receptors during a short and critical period soon after neuronal birth [6]. This critical period is associated with a high degree of morphological change in new neurons, including synapse formation [38-40]. This temporal association suggests that the NMDAR-dependent regulation of survival is closely related to synapse formation, although synapse formation itself does not require functional NMDA receptors. In many parts of the developing brain, the death of immature neurons has been found to occur around the peak period of synaptogenesis [41, 42], which parallels the maturational stage of new neurons during the critical period for the NMDA receptor-dependent survival/death in the adult brain. Therefore, NMDA receptor-dependent, cell-specific regulation of neuronal survival might be a general mechanism involved in the formation of functional circuits in the developing and adult brain. Synaptic NMDA receptor activation promotes neuronal survival in physiological conditions [43]. Thus, the construction of new circuits through selective survival/death of new neurons is probably regulated by synaptic activity, and in an information-specific manner [6]. This information-specific construction of new circuits could be a unique mechanism by which newborn neurons in adult dentate gyrus contribute to information storage related to learning and memory [6]. Ge *et al.* also identify a critical period between 1 and 1.5 months of the cell age when adult-born dentate granule neurons exhibit enhanced long-term potentiation with increased potentiation amplitude and decreased induction threshold [7]. Furthermore, such enhanced plasticity in adult-born neurons depends on developmentally regulated synaptic expression of NR2B-containing NMDA receptors [7]. This study demonstrates that adult-born neurons exhibit the same classic critical period plasticity as neurons in the developing nervous system. The transient nature of such enhanced plasticity may provide a fundamental mechanism allowing adult-born neurons within the critical period to serve as major mediators of experience-induced plasticity [7].

At neuronal synapses, NMDA receptors are li nked to downstream molecules [*e.g.,* neuronal nitric oxide synthase (nNOS)] via PDZ domain-mediated protein-protein interactions [8, 9, 14, 15]. PSD-95 is a major scaffolding protein at excitatory synapses and it contains three tandem PDZ domains at the N-terminus [44-46]. This protein can bind both NMDA receptors and nNOS through its second PDZ domain [8, 9, 14, 15], and then form NMDA receptor signaling in the postsynaptic density of the CNS. Nitric oxide (NO), the product of nNOS, is an important modulator of axon outgrowth and guidance, synaptic plasticity, neural precursor proliferation as well as neuronal survival [47].

Previous study has shown that a functional NO-cyclic guanosine monophosphate (cGMP) signaling is operative early during the differentiation of ES cells [47]. Therefore, PSD-95 PDZ domain-mediated protein-protein interactions might be involved in the effect of NPC transplantation on modification of neurogenic niches.

Conclusion and perspective

It has been known that many aged individuals will exhibit deficits in memory that are unrelated to neuropathologies. With a rising population older than 65 years, it becomes increa singly imperative to search for a feasible a pproach to treat memory decline with normative aging. In recent years, experimental studies on the molecular and cellular mechanisms underlying adult neurogenesis in the SGZ of the hippocampus [3, 4, 19-23], a critical brain region for learning and memory, have emerged and sparked tremendous interest in this once obscure field. Several lines of evidence indicates that specialized neurogenic niches play essential roles in maintaining and regulating adult hippocampal neurogenesis [3-5]. We hypothesize that the neurogenic niche can be modified to promote adult hippocampal neurogenesis by transplantation of human ES cell-derived NPCs into aged mice, because transplantation of NPCs can produce several cellular components including mature neurons and astrocytes that construct the neurogenic niche and then may recreate the neurogenic niche-like microenvironment to support active neurogenesis in aged hippocampus. Future studies can observe the effect of intrahippocampal transplantation of human ES cell-derived NPCs on adult hippocampal neurogenesis, synaptic plasticity, and learning/memory functions in aged mice; future studies can also explore whether PDZ domain-mediated interactions between PSD-95 and NMDA receptors at neuronal synapses contribute to the underlying mechanism. These studies will provide important experimental evidence to support our hypothesis that intrahippocampal transplantation of human ES cell-derived NPCs can modify neurogenic niches to improve adult hippocampal neurogenesis during aging and will help us develop a neurogenic niche-based approach for enhancing learning and memory functions in aged people.

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Disclosure of conflict of interest

None.

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