Review Article

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Harnessing the Tremendous Power of Adult Neural Stem Cells for Neurodegenerative Diseases

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Abstract

In almost all neurodegenerative diseases, progressive neuronal loss is a common phenomenon. Hence neurodegenerative diseases are customarily defined by the progressive loss of neurons. Traditionally the novel treatment strategies focused on replacing the lost neurons by neural precursor cells (NPCs)/neural stem cells (NSCs). Huge amount of research reports demonstrate the proof-of concept that transplantation of NSCs has therapeutic potential and have been used for Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic Lateral Sclerosis (ALS), Multiple Sclerosis (MS) and other neurodegenerative diseases. The basic concept stand out in this point and question arises what happens to the self-renewing and multi-potent properties of NSCs that subsist in the adult brain. How adult NPCs/NSCs loss their capacity to overcome the effect of amyloid plaque pathology that cause AD, Lewis body that cause PD etc. It is not yet clear, whether prominent alteration of adult neurogenesis happens simultaneously during the initiation stage of plaque deposit (pre-plaque) stage. Parallel observations of generation of adult new neuron might affect by early hippocampus dysfunction which in turn follow the plaque deposit. This review article will try to define novel therapeutic strategies for neurodegenerative disorders and novel tools for high scale generation of adult NPCs/NSCs in vivo as well as in vitro. More importantly it will focus to explain the regulatory switches of adult neurogenesis and the factors that regulate adult neurogenesis.

Keywords: Adult Neurogenesis; Sub-Ventricular Zone; Sub-Granular Zone; Neural Stem Cell; Neural Precursor Cell.

Introduction

Until 1960, it was believed that the adult brain is a quiescent organ and no new neurons produced in adult brain. A group of neuroscientists challenged to change the dogma and brought the new vision to world that new neurons are generated in the adult brain throughout life. The neurogenesis confined to specific areas of the adult brain is sub-ventricular zone (SVZ) of fore brain and sub-granular zone (SGZ) of the dentate gyrus of hippocampus. With increasing life expectancy, the neurodegenerative diseases like Alzheimer's disease (AD), Huntigton's disease (HD) and Parkinson's disease (PD) becoming a considerable burden for the society. The diagnosis of age related neurodegenerative diseases is predicted to increase 12% by 2030 (WHO, 2006). Hence there is urgent need to support the adult brain of aging population with novel treatments.

A number of recent studies reveal the role of adult neurogenesis phenomenon in the process of learning, memory and brain plasticity [1-4]. To bring the significant promising and intriguing chapters in the contemporary neurobiology of aging, numerous studies yet to be explained. In several neurological diseases like, bipolar disorder, Schizophrenia [5], anxiety disorder and particularly depression [6], the critical relationship between adult neurogenesis and neuropathogenesis have broadly discussed. There is some assumption that the attenuation of neurogenesis has close association between the disturbances in proliferation and differentiation of NSCs and severe neurological diseases like Alzheimer's and Parkinson's have been postulated since long time [7] [8]. It seems decreased of self renewal of certain NPCs

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in hippocampus, substantial niagra and some areas of neocrtex. Also proliferation rate and survival of mature neuron decreased in chronic stress. There observed a stimulation of adult neurogenesis as a consequence of ischemic stroke and traumatic brain injury [9,10]. Currently there are no widely available treatments to slow down the progression of neurodegenerative diseases or to prevent the diseases like AD, PD or HD. A new view of protecting the neuronal loss and damaged neuron through NPCs now becoming deemed to provide trophic support to vulnerable neurons rather than merely replacing lost neurons. This emphasizes the need for improving and providing novel therapy. Multi-dimensional interactions among stem cells, stem cell niches and the system environments have considerable effect on adult neurogenesis. Although sometimes stem cells behave as double edged weapon, for therapeutic interventions, their combined power of responding to systemic signals and extrinsic factors illustrate the responsiveness of stem cells that control stem cell fate [11]. Also neural precursor cells sense and respond to injury or physiological changes. Focal cerebral ischemia leads to increase proliferation of NPCs in SVZ and SGZ and inhibition of ischemia-induced proliferation in the SVZ and SGZ in vivo [12]. Many more future questions still remain unclear and need to be addressed by meticulous investigators, such as (I) How stem cells intellect the tissue damage and modulate cell proliferation (II) Can stem cells aggressively redirect the fate of their progeny (III) Could it be possible to adapt the fate determination process of stem cells for therapeutic purposes.

Ennormous Potential of NPCS

More than two decades, sufficient evidences give us the information that endogenous stem cell populations in adult hippocampus are the brain's endogenous reservoir of stem cells. This view implicates that newborn neurons in adult may help overcome the loss of neural and cognitive functions that occur during neurodegenerative disorders and illness of brain. The endogenous stem cell populations in adult hippocampus are large pools of neural stem cells that stay in a latent stage and these cell populations can be stimulated to produce new neuron. There is a possibility for the treatment of incurable neurological diseases by the production of new neurons at required specific sites [13]. The research of this translation from animal models to human application may take few years, but understanding of detail cellular and molecular mechanisms that regulate endogenous neurogenesis offers the enormous potential to use these innate reservoirs of adult neural stem cells to produce neuron that may be able to protect the diseases brain from cognitive decline and mood disorders [14,15].

Proneurogenic & Prosurvival Signals

The role of neural stem cells or precursor cells in adult brain for repairing of damage neuron remains an open question. In neurodegenerative diseases, when damage happens, the rapid migration of neuroblasts towards the damage site has been observed and the activation of endogenous neural precursor cells has been explored [16]. Using suitable magnetic resonance imaging , endogenous neural stem cell populations have been traced in vivo and migration of specifically labeled endogenous neuroblasts niches been detected in the site of lesion [17,18]. The identification of endogenous neural precursors in vivo and migration of these NPCs to lesion site in diseased brain is a characteristic that need to be explored in live animal model in detail. The factors that facilitate the regenerative mechanism and activation of endogenous neural precursors are yet to be summarized in detail. Neural precursors have the ability to support their own survival independent of any exogenous growth factor. These important aspects facilitate self repair processes in the adult brain. These powerful neurotrophic properties of NPCs can give therapeutic values of NPCs in neurodegenerative diseases [19] and in chronic neurological disorders, the neurotrophic properties of transplanted neural stem cells are limited in time [20]. The long term survival and their enduring functional properties of NPCs hold the key for NPC therapy for neurodegenerative diseases.

Effect of Extracellular Matrix Proteins

The role of matrix composition highly influences the stem cell niche and a myriad of signals within the niche regulate stem cell behavior. Multiple factors required for survival and differentiation of adult neural stem cells, among which extracellular matrix composition which contain fibrin, fibronectin, gelatin, growth factors and hyalunoric acid are essential on which NSCs can home, multiply and differentiate. Laminin, netrin-4 and reelin regulate axon guidance during development [21]. The huge amount of research study established the fact that composition of matrix protein is required for differentiation of neurons, astrocytes and oligodendrocytes. Various components expressed in ECM promote cell homing, survival and differentiation of adult neural precursor cells before onset of neurodegeneration. The levels of ECM protein upshot the expression of different

receptors that are likely responsible for changes in ECM microenvironment and NSC behaviour [22].

Balanced Cell Cycle Activity

The expedition of neural stem cell research has started since three decade ago. Huge amount of literature available on embryonic neural precursor cells, while very little is known about the cell cycle parameters of adult neural precursors. It is very essential to understand the long journey of neural stem cell from embryonic development to adult homeostasis and how adult neural stem cells and their cell cycle length as well as quiescent state that regulate the physiological condition and neurological disorders. Short cell cycle length found to correlate with a higher proliferative potential of NPCs and lengthening the cell cycle leads for differentiation and neurogenesis [23].

The regulation of NPC proliferation in the adult brain has been widely studied; however the intrinsic cell cycle machinery underlying NPC proliferation remains largely unexplored. The cell cycle components such as CDKs, cyclins and inhibitors of cell cycles are involved in the regulation of NPC proliferation in both neurogenic areas (dentate gyrus and in the subventricular zone of the lateral ventricles) of the adult brain. To design new strategies for cell replacement after injury or neurodegeneration, a better understanding of the molecular factors that regulate the generation or cell cycle activity in the adult DG is essential. Cell cycle related protein those interacting with cdk2 and specific requirements of Cdk2 in hippocampus has been reported by several investigator [24-26].

The level of Cdk2 protein and its kinase activity seems to decrease throughout brain development, paralleling the diminution of NPC proliferation [27,28] and Cdk2 is dispensable in crucial proliferative events of the adult brain. Several studies have highlighted the importance of intrinsic cell cycle components in regulating NPC proliferation in the adult neurogenic niche. It is believed that an improved knowledge of the intrinsic cell cycle regulation of adult NPCs will be necessary to develop new cell based regenerative therapies. As key regulators of adult neurogenesis, the cell cycle constituents such as Cdk5 plays predominant role in post mitotic neurons [29]. It is widely accepted that the hallmark feature of adult stem cells in their capacity to self renew over the life-span with a very slow rate of cell division as compared to their fetal counterpart and the adult stem cells are functionally linked to quiescent state where quiescent can be defined as non-dividing state outs the cell cycle where a cell can remain in static condition until activated by appropriate proliferative signal. The molecular characterization and regulation of NPCs specific CDK inhibitors may provide insights into the signaling pathways underlying quiescence of adult NPCs.

Regulator of Adult Neurogenesis

Adult neurogensis is the process of generating new hippocampal neurons and subventricular zone where the proliferations of neural precurssors cells follow the caution of potential side effect by the regulators. Metatonin is a circardian rhythm-promoting molecule secreted by pineal gland and has a variety of biological functions, including control of sleep-awake cycle, which may have beneficial effect in stimulating endogeneous neural stem cells [30].

Neuronal cell expressed developmentally down regulated (NEDD9) polymorphism seems to regulate the neural process outgrowths/ neuritis and affect the number of synapses in neural cells in brain under stressful conditions [31] and allelic variants of NEDD9 have been implicated in late-onset AD [32]. Phagocytosis of neural cell debris and beta amyloid get supported by a primary microglia cell receptor protein, signal regulatory protein beta (SIRP beta1) and act as passive regulator of neurodegenerative diseases such as AD [33].

In the hippocampus, ATXN1 plays an intrinsic regulatory role of precursor cell proliferation and loss of ATXN1 affect hippocampal function, potentially contributing to cognitive deficits and depression, which indicates the novel impact of ATXN1 on hippocampal function [34].

Region Specific Environmental Support

Host brain micro-environments get rejuvenated by significant neurorescue of transplanted NSCs. Investigators illustrated that, transplantation of NSCs provides neuro-protection against depletion of specific vulnerable neuronal population by recruiting endogenous cells to establish a favorable niche [35].

Among many other regulatory factors, 5-HT released at subependymal plexus is part of an intrinsic brain mechanism which controls the subventricular zone cell proliferative capacity by modulating 5-HT release [36].

The fate of adult neural progenitor cells is determined by regional environmental cues present in the adult brain and ectopic expression of growth factors promote the proliferation and neuronal differentiation of adult neural progenitor cells.

Genetic and Epigenetic Control of Adult Neurogenesis

Various physiological, pathological and pharmacological stimuli dynamically regulate the adult neurogenesis process. Other than the SVZ and SGZ, whether neurogenesis occurs in any other areas of adult mammalian brain is an important question remains controversial [37]. In a variety of non-mammalian vertebrates such as song birds, adult neurogenesis has been extensively studied [38,40]. Neurogenesis in aged animals can be restored to a certain extent by voluntary exercise, enriched environment and learning new things, which suggest that these cells still have the capacity to respond to extrinsic stimuli [40]. Physical activities and exercise enhance hippocampal neurogenesis by growth factor gene expression [41] and synaptic plasticity [42]. Increased angiogenesis and increased blood flow and endothelial cell proliferation intimately related to enhancement of neurogenesis. Many crucial questions remain so far unanswered, how NPCs will revenue the successful achievements in neurological diseases. Hence intensive basic research in the field is essential.

Future Prospective

Fully understanding of the biology of adult neurogenesis/adult neural precursor would provide the crucial insights in terms of both the etiology and potential therapeutic interventions of major brain disorders and neurodegenerative diseases. Functional role of endogenous adult neurogenesis needs to be understood clearly to develop the sophisticated strategy of regenerative medicine for neurological diseases in human.

Key Messages

Adult neurogenesis is regulated by multiple factors and several limitations withheld the proliferative capacity of NSCs. Successful progression of neurological diseases can be achieved through the NSC induced neural integrity and synaptic plasticity. The therapeutic treatment of neurodegenerative diseases is possible through NSCs.

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