

Endogenous Neural stem Cells and Neurological Disorders



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Abstract

Neural stem cells have potential of producing variety of neural cell types And useful to cure neurological conditions .NSCs are also produced from Embryonic Stem Cells (ESCs), induced pluripotent Stem cells in vitro. Ethical problems, immunological problems and Tumorigenic problems makes obstacle during transplantation of these produced Exogenous NSCs. Some years back it was thought that Neurons Are Terminally differentiated Cells which can't further differentiate, but recent Study shows NSCs in Sub ventricular zone (SVZ) have potential to produce glia and new neurons, here we discuss about use of endogenous NSCs in regeneration of damaged brain tissue. These Endogenous NSCs activate when there is traumatic insult to brain which in some cases Shows miraculous recovery.

Keywords: Regenerative medicine; Stem cell; Endogenous Neural Stem Cells (NSCs); Sub ventricular Zone (SVZ); Neuronal regeneration

Introduction

NSCs are multipotent in nature which produces glia and neural cells in human brain. In vitro study shows that Induced pluripotent stem cells (iPSCs) and embryonic Stem cells (ESCs) are capable to produce NSCs [1-5] in animal studies exogenous NSCs transplantation for neurological disorders shows good result which produced from ESC or iPSCs [6-11] these transplanted Exogenous ESC shows immunological response in recipient. in animal study model, few Study shows that ESCs formed tumour in rodents [10-16] in human risk of tumour formation must be evaluated [17]. Space occupying tumour is fatal due to limited space of intracranial cavity. Researchers show that new neurons can be generated from fibroblast cells by Trans differentiation which avoid risk of tumour formation [18].

It was find out that NSCs (Sub ventricular zone of lateral ventricles and Sub granular zone of dentate gyrus) produce new neurons And Glia in human brain in Adult [19-26] if there is trauma or pathological insult to brain then NSCs are stimulated to regenerate glia and new neurons [27,28]. Using endogenous NSCs as treatment for neurological disorders is best option because it avoids ethical issues and immunological responses also there is no chance of tumour formation.

Adult brain and endogenous NSCs

Endogenous NSCs generate neurons continuously in SVZ and SGZ In the adult brain unfortunately Phenotypically there

is no specific marker protein for adult NSCs [29,30], NSCs express electrophysiological and morphological characteristics of astrocytes; express GFAP (glial fibrillary acidic protein) which is marker of Astrocytes.

The NSCs in the SGZ

Learning, memory, emotion, mood are monitored and regulated by hippocampus which is important part of limbic system. Through dentate gyrus, neuronal input passes from neocortex to the hippocampal circuitry. Dentategyrus composed of neurons called granule cells; NSCs in the SGZ produce intermediate neuronal progenitors, which produce new neurons [31,32-34] New neurons differentiate into mature granule cells (glutamatergic neurons) [35].

During functional maturation ,large number of neurons die ,only some of them integrated into neural network [36-38] newly generated immature neurons are unique distinguishable from those of mature granule cells by electrophysiological activities [39]. New neurons are involved in memory and learning task was shown by number of studies [40-42]. Performance of hippocampus dependent learning tasks by animals positively correlates with the amount of new neuron generation, hippocampus-dependent learning tasks increase the proliferation of neuronal progenitors in the SGZ proved

in animal models [40,43] animal model study shows that irradiation and antimetabolic drug reduced proliferation of NSCs [42,44]. Decreased hippocampal neurogenesis shows increase in psychiatric symptoms in rodents and primates [45,46]. Antidepressants, serotonin selective reuptake inhibitors, mood stabilizers drugs increases neurogenesis [47,48]. If neurogenesis got disrupted then it definitely affect behaviour [49].

Potential of NSCs in sub ventricular zone

NSCs in SVZ area are derived from radial glia which is subpopulation of astrocytes [33,50,51]. Notch 1, sonic hedgehog (SHH), Galectin-1, Noggin, hepatocyte growth factor (HGF), basic fibroblast growth factor (FGF2), ciliary neurotrophic factor (CNTF) all these signalling molecules are important in self-renewal and forming niche [52-59]. "Transit-amplifying cells" known as intermediate progenitors generated from NSCs, which proliferate and form progeny of immature new neurons which identified Wnt- β -Catenin signal molecule [60,61].

New neurons migration mechanism from SVZ

Along rostral migratory stream (RMS) pathway, migration of immature neurons to olfactory bulb occurred within a week period which generated in the SVZ [62,63]. Imaging studies in animal shows migration of iron-oxide-labelled new neurons [64,65]. These bipolar migrating new neurons form chains so new neurons slide over [22,66]. Cytoskeletal modifications occurred in new migrating neurons, active cytoskeletal modification occurs in the new neurons during migration in the chain, cyclin-dependent kinase 5 help in the chain formation of new neurons in the Sub ventricular zone and Rostral Migratory Stream [67]. New neurons expressed β 1-integrin, PSA-NCAM [68,69]. laminins, Metalloproteases and tenascin-C, proteoglycans like molecules help in adhesion between new neurons in the chain and help them to slide over [68,70,71].

New neurons used blood vessel as scaffold for migration [72] in the lateral ventricle, new neurons migration occurs in parallel with CSF flow [73] factors like glial cell line derived neurotrophic factor (GDNF), netrin1, prokineticin2, brain derived neurotrophic factor (BDNF) attract new neurons toward the olfactory bulb [68,74-76]. Chains of new neurons move through tunnel formed by astrocytes [66,71]. It was noted in mutant mice that aberrant astrocytic tunnel formation disrupts the migration of new neuron chains [77-81]. Due to proper interaction between new neurons and astrocytes, neuronal migration occurred. GABA secreted by migrating neurons took by astrocytes in the RMS and control the migration of new neurons also trapping endothelial cell-derived BDNF [82-85]. Proteins slit 1 derived from new neuron acts on RMS astrocytes expressing slit1 receptor robo which guide astrocytes to form the tunnels [86].

Process of new neuron generation in the Olfactory Bulb

Chain of new neurons ultimately reach to olfactory bulb where new neurons detach themselves from chain and migrate

to granule cell layer (GCL) and glomerular layer (GL), at last they differentiate into granule cells, periglomerular cells, olfactory interneurons by the help of tenascin-R and glycoprotein Reelin [87,88]. Some of these neurons remain longer than year [89,90]. Newly added interneurons are involved in odour discrimination but their actual function is unclear in the olfactory circuit [91,92].

Regeneration of neurons by endogenous NSCs

Trauma, stroke, neurodegenerative diseases are pathological insult in which NSCs proliferation increases and newly formed neurons appeared at damaged area. Recent study on human post mortem brain revealed that new neurons produce after insult in cerebral infarction patients [93-95] these findings show that neuronal regeneration in mammalian brain is possible, but spontaneous regeneration of neuron should not compensate loss of neurons. In adult gerbil model and rat model of insult-induced neurogenesis studies showed that global ischemia causes death of pyramidal neurons in the CA1 region of hippocampus activate proliferation of NSCs in SGZ region and increases number of new granule neurons in the GCL [96,97]. In ischemic stroke model, induced by middle cerebral artery occlusion (MCAO), small striatal projection neurons regenerated [98,99]. SVZ is the potential reservoir of NSCs, these neurons form new progeny with strong migratory capacity and which can compensate loss neuron in pathological conditions of brain. SVZ need to be target to restore and replenish lost function by producing new neurons.

Alterations in the microenvironment play important role in NSCs activation after insult to brain in ischemic stroke due to sudden onset, causes immune responses immediate after lesion, in which microglia and astrocytes activate surrounding infarcted area with T-lymphocytes infiltration into the damaged brain [100-102] these cells produce growth factors and cytokines which affect neurogenic function of NSCs [103,104]. NSCs proliferation stimulate by growth factors and cytokines in the SVZ [59,105,106] angiogenesis is important to activate NSCs after stroke, study shows that vasculature is important component of stem cell niche which activate proliferation of NSCs [53,107,108].

Formed new neurons form chain and migrate towards damaged area [99,109] vascular endothelial cells produced stromal derived factor 1 (SDF1) and angiopoietin 1 (Ang1) which control migration of new neurons and also controlled by monocyte chemo attractant protein 1 (MCP1) which expressed by activated astrocytes and microglia in the damaged area [109-113] the receptors of signals of these molecules like CXCR4, Tie2, CCR2 respectively expressed on migrating new neurons. Hence interaction of glia and vasculature regulate migration of new neurons in the injured brain.

SVZ derived GFP labelled cells possess long processes, express NeuN and form synaptic structures in the damaged striatum 90 days after ischemia induction under electron

microscope [99] gliogenic proliferation of NSCs occurs more after insult than neurogenic [114] migrating new neurons die before differentiating into mature neurons in the damaged area [98]. NSCs don't show neurogenic differentiation in SVZ [115,116]. Apparently there are limitations of regeneration of damaged brain tissue by activating endogenous NSCs, some of studies shows beneficial effect in which neurogenesis promoted such as treatment with erythropoietin, statins, activated protein C, HDAC inhibitors and EGF/FGF-2 [117,119-124].

Regeneration of myelin by endogenous NSCs

Myelin sheath covers axons and nerve conduction is important function of it which carries electrical impulses. Oligodendrocyte form myelin sheath in central nervous system. In multiple sclerosis demyelination occurred. Demyelination impairs nerve impulse conduction, causes variety of neurological impairments. NG 2 chondroitin sulphate expressing endogenous oligodendrocyte progenitor cells regenerate oligodendrocyte [125,126]. NSCs in SVZ are also involve in regeneration of oligodendrocyte, recent study shows it [127-129].

Oligodendrocyte lineage transcription factor Olig2 express by NSCs and progenitors in the SVZ under physiological conditions, generate oligodendrocyte progenitors. These oligodendrocyte progenitors cells express PSA-NCAM marker but not beta3 tubulin which is neuronal lineage marker and migrate to fimbria fornix, striatum, corpus callosum where they differentiate into nonmyelinating progenitors and mature myelinating oligodendrocyte [127,128].

Demyelination in rodents model induced by chemical markedly promotes this process [127,129]. Mature oligodendrocyte formed by oligodendrocyte progenitors after migration and regenerate myelin on the affected axons. Researchers find out factors involved in this process are namely EGF, IGF-1, Wnt- β -catenin mediator Tcf4, notch1, erythropoietin [130-138]. In animal demyelination model and in patients with chronic MS, Phenomenon of Remyelination is disturbed [120,139-141].

Demyelination is the process in which regeneration of myelin sheath is required to restore normal function, in these conditions spontaneous regeneration of myelin will not completely recover injury. Allograft transplantation of exogenous cells shows myelination in animal model of demyelination. For successful neuronal regeneration, the appropriate regeneration of oligodendrocyte is also needed

Conclusion

SVZ is the store house of NSCs which produce new neurons that ultimately travel to damaged part of brain and regenerate damaged tissue of brain. NSCs differentiate into mature neurons and in oligodendrocyte which contribute to Remyelination. It was observed in traumatic injury or in hypoxic condition to brain tissue that NSCs in SVZ proliferate and regenerate intermediate new neuron which transforms into mature neuronal cells; these

mature neuronal cells travel to injured site and contribute to restore function of that damaged part. Using of exogenous NSCs induced from ESCs or iPSCs are facing ethical problem, shows immunological responses in recipient and having ability of tumour formation. Application of endogenous NSCs needs to be evaluated on the basis of molecular study in preclinical animal model. Need to be evaluating exact molecular mechanism which control endogenous NSC and their progeny in near future. Self-repair strategy governed by Endogenous NSC is needed to be established for clinical application in brain tissue damage.

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