

# 신경 줄기세포를 이용한 신경계 질환 치료

## Neural Stem Cells for Neurological Disorders

28

Jae - Kyu Roh, M.D. · Manho Kim, M.D.  
Stroke & Neural Stem Cell Laboratory in Clinical Research Institute  
Department of Neurology  
Seoul National University College of Medicine & Hospital  
E - mail : rohjk@snu.ac.kr · kimmanho@snu.ac.kr

28

3 30 - 3

Kon Chu, M.D.  
Stroke & Neural Stem Cell Laboratory in Clinical Research Institute  
Department of Neurology  
Seoul National University College of Medicine & Hospital  
Seoul National Hospital, Center for Alcohol and Drug Addiction Research  
E - mail : stemgen1@snu.ac.kr

### Abstract

Recent progress shows that neurons suitable for transplantation can be generated from neural stem cells (NSCs) in culture, and that the adult brain produces new neurons from its own stem cells in response to injury. In this article, we discuss how the subventricular zone of the forebrain is the most active neurogenetic area and the richest source of NSCs. This review also focuses on the nature and functional properties of NSCs of the adult mammalian brain, and we propose our views on the strategy from bench to the clinic with particular concerns and considerations.

**Keywords :** Neural stem cell; Transplantation; Neurological disorder

· ; ;

, (CNS)  
가 . CNS

turnover  
dogma가 (1). dogma 1990  
CNS (neu-  
ral precursor cell) 가 ,  
(neurogenesis)  
CNS ,  
. 1990 1992  
(multipoten-  
cy), 가 가 (neural  
stem cell, NSC)가 (2 ~ 4).  
NSCs in vitro  
가 , NSCs

ex vivo  
CNS  
(1, 5~7). , CNS  
(interdigitating  
migration)  
(~3,600  $\mu\text{m}^2$ ) (5).  
germinal zone (hematopoietic stem cell, HSC)  
subventricular zone(SVZ)  
dentate gyrus subgranular layer(SGL) , HSCs (biological niche)  
(8). 가 rodent CNS NSCs niche SVZ  
, SVZ , neurogenesis  
(endogenous neurogenesis) , 'neuropoiesis' , SVZ 'brain marrow'  
(immature neuroblast) (1, 11, 12). SVZ  
rostral migratory stream(RMS) olfacto- BM microenvironment  
ry bulb(OB) GABAergic interneuron . hematopoiesis deep adult  
(9). SVZ bone bony structure bone marrow  
NSCs가 , 가 , neurogenesis  
neurogenesis가 . SVZ . BM  
12~28 neuroblast HSCs (mobilization) bound-  
가 turnover , 30,000 neu- ary HSCs BM 가  
roblast OB (5). , SVZ NSCs  
SVZ - RMS - OB neuroblast mobilization SVZ dorsolateral axis  
(chain migration) , RMS OB  
(homeostasis) (perturbation) ( , , unpublished results). ,  
(10). / (stem/pro-  
가 10 100 genitor cell), Stromal function ,  
가 , neuroblast proliferation, adhesion, migration  
, corpus callosum extracellular matrix(ECM)가 . CNS  
(clustered Stomal cell astrocyte ependymal cell  
migration). , , NSCs

SVZ BM ECM, tenascin proteoglycan, HSCs VEGF, EGF, FGF - 2, SCF, GDNF, BDNF, G - CSF - SDF1 - CXCR4 NGF (18, 19). signaling cascade가 NSCs SVZ - NSCs RMS - OB mobilization ( , , , neurotrophic factor , personal observation). BM NSCs SVZ CSF , endogenous neurogenesis 가 , cell - to - cell contact가 , water co - transport ( aquaporin) (20). Rodent , SVZ neurogenesis / (status epilepticus) niche (1). (epileptogenesis) , 가 seizure

## From Bench to Clinic

1. 가? SVZ endogenous neurogenesis가 (20). endogenous neurogenesis가 rodent (5, 6, 21). stroke endogenous neurogenesis stroke 2~3 7~10 NSCs , neurotrophic factor (13~17). neuro- 1kg blast , ( DARPP - 32 - 가 , rodent SVZ NSCs positive striatal interneuron) 0.2% SVZ NSCs rodent SVZ NSCs (15), SVZ - RMS - OB 가 가 SVZ NSCs NSCs (neurotrophic factor) neuroblast astrocyte fate determination

( ventricular zone NSCs 가 .  
 ) 가 rodent SVZ NSCs ex vivo expansion , NSCs ex vivo  
 (21). (1). mitogen(EGF,  
 FGF - 2) 가 NSCs neurosphere  
 ESC  
 가 . ESCs  
 ESCs (22). HSCs in vitro culture  
 pluripotency (teratoma)  
 ESCs 가 (1).  
 ES cell line( ) ( ,  
 ) NSCs  
 ESCs neuron NSCs pheno-  
 typic drift . , adipocyte  
 NSCs NSCs neural  
 가 가 cell NSCs  
 . NSCs가 origin 가 ( "fat in a brain")  
 neuron, astrocyte oligodendrocyte  
 ,  
 가가 , 가 , allo-  
 genic stem cells , 가 가  
 lineage .  
 HLA matching  
 cue . NSCs  
 가 (plasticity) .  
 MHC class II , NSCs  
 MHC class I (23).  
 NSCs cyclosporine  
 BM ablation technique  
 , team human  
 NSCs  
 (23 ~ 25).  
 2. 가?  
 , ex vivo 가? 가?  
 가?

NSCs 가 oxidative stress (5). type (dopaminergic neuron)가 3. 가? , 가 transformation) (pathologic , 가 NSCs (5, 6). 가 parenchyma , (intraventricular) , lym- phatic system systemic infusion (2000 , ) NT - 3 cell , 가 2 가 (28). (26). NSCs host 가 가 NSCs neuronal re- placement( ) (replenishment) , ( ) NSCs limitation 가 , (29). neuron neurotrophic factor NSCs anti - apoptotic protein , Neurogenesis 가 NSCs migration host NSCs angiogenesis가 , transdifferentia- (hostile microenvironment) NSCs tion (23, 27). , host dynamic 가 가 (30, interaction cross - talk 가 31). NSCs systemic circulation brain connectivity , neural process , (29), (23), (24), , scarring , (32), (25), (33) (5).

가 .

NSCs

migration ,

( chemokine, cytokine)

trans-

migration

angiogenesis ,

BM - derived stem cells

가

가

host ,

가

가

가

## Acknowledgement

21

(M102KL010001 - 02K1201 - 01310)



1. Galli R, Gritti A, Bonfanti L, Vescovi AL. Neural stem cells : an overview. *Circ Res* 2003 ; 92 : 598 - 608
2. Ryder EF, Snyder EY. Establishment and characterization of multipotent neural cell lines using retrovirus vector - mediated oncogene transfer. *J Neurobiol* 1990 ; 21 : 356 - 75
3. Snyder EY, Deitcher DL, Walsh C, Arnold - Aldea S, Hartweig EA, Cepko CL. Multipotent neural cell lines can engraft and participate in development of mouse cerebellum. *Cell* 1992 ; 68 : 33 - 51
4. Reynolds BA, Weiss S. Generation of neurons and astrocytes from isolated cells of the adult mammalian central nervous system. *Science* 1992 ; 255 : 1707 - 10
5. Imitola J, Park KI, Teng YD, Nisim S, Iachyankar M, Snyder EY, et al. Stem cells : cross - talk and developmental programs. *Philos Trans R Soc Lond B Biol Sci* 2004 ; 359 : 823 - 37
6. Snyder EY, Daley GQ, Goodell M. Taking stock and planning for the next decade : realistic prospects for stem cell therapies for the nervous system. *J Neurosci Res* 2004 ; 76 : 157 - 68
7. Lindvall O, Kokaia Z, Martinez - Serrano A. Stem cell therapy for human neurodegenerative disorders - how to make it work. *Nat Med* 2004 ; 10 (Supp 1) : S42 - 50
8. Bjorklund A, Lindvall O. Cell replacement therapies for central nervous system disorders. *Nat Neurosci* 2000 ; 3 : 537 - 44
19. McKay R. Stem cells in the central nervous system. *Science* 1997 ; 276 : 66 - 71
10. Alvarez - Buylla A, Garcia - Verdugo JM, Tramontin AD. A unified hypothesis on the lineage of neural stem cells. *Nat Rev Neurosci* 2001 ; 2 : 287 - 93
11. Steindler DA, Kadrie T, Fillmore H, Thomas LB. The subependymal zone : brain marrow. *Prog Brain Res* 1996 ; 108 : 349 - 63
12. Scheffler B, Horn M, Blumcke I, Laywell ED, Coomes D, Steindler DA, et al. Marrow - mindedness : a perspective on

- neurogenesis. *Trends Neurosci* 1999 ; 22 : 348 - 57
13. Magavi SS, Leavitt BR, Macklis JD. Induction of neurogenesis in the neocortex of adult mice. *Nature* 2000 ; 405 : 951 - 5
14. Temple S, Alvarez - Buylla A. Stem cells in the adult mammalian central nervous system. *Curr Opin Neurobiol* 1999 ; 9 : 135 - 41
15. Arvidsson A, Collin T, Kirik D, Kokaia Z, Linnvall O. Neuronal replacement from endogenous precursors in the adult brain after stroke. *Nat Med* 2002 ; 8 : 963 - 70
16. Jin K, Minami M, Lan JQ, Mao XO, Batten S, Greenberg DA, et al. Neurogenesis in dentate subgranular zone and rostral subventricular zone after focal cerebral ischemia in the rat. *Proc Natl Acad USA* 2001 ; 98 : 4710 - 5
17. Kokaia Z, Lindvall O. Neurogenesis after ischaemic brain insults. *Curr Opin Neurobiol* 2003 ; 13 : 127 - 32
18. Parent JM, Vexler ZS, Gong C, Derugin N, Ferriero DM. Rat forebrain neurogenesis and striatal neuron replacement after focal stroke. *Ann Neurol* 2002 ; 52 : 802 - 13
19. Nakatomi H, Kuriu T, Okabe S, Yamamoto S, Hatano O, Nakafuku M, et al. Regeneration of hippocampal pyramidal neurons after ischemic brain injury by recruitment of endogenous neural progenitors. *Cell* 2002 ; 110 : 429 - 41
20. Jung KH, Chu K, Kim M, Jeong SW, Song YM, Roh JK, et al. Continuous cytosine - b - D - arabinofuranoside infusion reduces ectopic granule cells in adult rat hippocampus with attenuation of spontaneous recurrent seizures following pilocarpine - induced status epilepticus. *Eur J Neurosci* 2004 ; 19 : 3219 - 26
21. Sanai N, Tramontin AD, Quinones - Hinojosa A, Barbaro NM, Gupta N, Alvarez - Buylla A, et al. Unique astrocyte ribbon in adult human brain contains neural stem cells but lacks chain migration. *Nature* 2004 ; 427 : 740 - 4
22. Rothstein JD, Snyder EY. Reality and immortality - neural stem cells for therapies. *Nat Biotech* 2004 ; 22 : 283 - 5
23. Chu K, Kim M, Jung KH, Park KI, Lee ST, Roh JK, et al. Human neural stem cells improve sensorimotor deficits in the adult rat brain with experimental focal ischemia. *Brain Res* 2004 ; 1016 : 145 - 53
24. Jeong SW, Chu K, Jung KH, Kim SU, Kim M, Roh JK. Intravenous human neural stem cell transplantation promotes functional recovery with experimental intracranial hemorrhage in the adult rats. *Stroke* 2003 ; 34 : 2258 - 63
25. Chu K, Kim M, Jung KH, Jeon D, Lee ST, Roh JK, et al. Human neural stem cell transplantation reduces spontaneous recurrent seizures following pilocarpine - induced status epilepticus in adult rats. *Brain Res* 2004 ; 1023 : 213 - 21
26. Kondziolka D, Wechsler L, Goldstein S, Meltzer C, Thulborn KR, Bynum L, et al. Transplantation of cultured human neuronal cells for patients with stroke. *Neurology* 2000 ; 55 : 565 - 9
27. Wurmser AE, Nakashima K, Summers RG, Toni N, D'Amour KA, Gage FH, et al. Cell fusion - independent differentiation of neural stem cells to the endothelial lineage. *Nature* 2004 ; 430 : 350 - 6
28. Lang AE, Obeso JE. Challenges in Parkinson's disease : restoration of the nigrostriatal dopamine system is not enough. *Lancet Neurol* 2004 ; 3 : 309 - 16
29. Chu K, Kim M, Jeong SW, Kim SU, Yoon BW. Human neural stem cells can migrate, differentiate and proliferate after intravenous transplantation in the adult rats with transient forebrain ischemia. *Neurosci Lett* 2003 ; 343 : 129 - 33
30. Chu K, Jeong SW, Jung KH, Han SY, Lee ST, Roh JK, et al. Celecoxib Induces Functional Recovery after Intracerebral Hemorrhage with Reduction of Brain Edema and Perihematomal Cell Death. *J Cereb Blood Flow Metab* 2004 ; 24 : 926 - 33
31. Jung KH, Chu K, Jeong SW, Han SY, Lee ST, Roh JK, et al. HMG - CoA reductase inhibitor, atorvastatin, ameliorates sensorimotor dysfunctions in experimental intracerebral hemorrhage. *Stroke* 2004 ; 35 : 1744 - 9
32. Pluchino S, Quattrini A, Brambilla E, Gritti A, Salani G, Martino G, et al. Injection of adult neurospheres induces recovery in a

---

chronic model of multiple sclerosis. Nature 2003 ; 422 : 688 - 94

33. Aboudy KS, Brown A, Rainov NG, Bower KA, Liu S, Snyder EY, et al. Neural stem cells display extensive tropism for pathology in adult brain : evidence from intracranial gliomas. Proc Natl Acad Sci USA 2000 ; 97 : 12846 - 51

- |    |     |
|----|-----|
| 1. | 6.  |
| 2. | 7.  |
| 3. | 8.  |
| 4. | 9.  |
| 5. | 10. |