JACOBS PUBLISHERS

OPEN ACCESS

Jacobs Journal of Regenerative Medicine

Review article

Potentiality for a Highly Permissive Micro-Environment in Neurogenesis

Lawrence M Agius*

University Of Malta Medical School, Msida, Malta, Europe

**Corresponding author: Dr. Lawrence M Agius, 27 "Ballarat" Guzeppe Caruana Street, TalVirtu, Rabat, RBT09, Malta, Europe, Tel: 35621451752, 356-2545-6444, Fax: 356-2545-6449, Email: lawrence.agius@um.edu.mt*

Received: 08-22-2015

Accepted: 12-29-2015

Published: 12-31-2015

Abstract

Reconstitution is the para-developmental series of system pathways as applicable to modulated neurogenesis in the adult human brain and spinal cord. The significance of modulatory induction implicates astrocytes as not only guiding factors in migration of neuroblasts but also as parameters of induced neuroblast proliferation and differentiation. Permissive operants in cell-induced formulas call into play the circulating macrophages and platelets within foci of breakdown of the blood-brain barrier. Performance indices for such inducing modulation is a potent influence in neurogenesis in further promoting the dimensions of system biologic interference on the one hand and of performance guidance as constitutional migration and differentiation of neuroblasts from regions of subventricular zones and other potential foci in the central nervous system.

Morphogenetic development and progression of both initiated proliferation and subsequent differentiation of neural stem cells (NSCs) have previously been recognized as largely cell-context dependent. This has now been largely replaced by recognized roles for epigenetic modifications to DNA by methylation and to histones by acetylation, methylation and deacetylation. Also, non-coding RNAs have been recognized as sources for modified expression of genes, including during astrogliogenesis.

Introduction

Neurogenesis arising in the subventricular zone and also subgranular zone in the hippocampus is regulated by two sets of genes, affecting either progenitor neural cells that induce proliferation (eg,, Neurogenins) and differentiation neural cells that allow at a subsequent stage the differentiation of the neural stem cells to maturing neurons.

The specificities of regeneration of neurons constitute a dimensional re-orientation of substantial cellular resources that are critically interactive with microenvironmental conditioning of the neuropil. Surface expansion of the dentate gyrus in multiple sclerosis patients possibly involves an inflammatory response of the subgranular zone of the hippocampus[1]. In such terms, the possible important contributions of the extracellular matrix and cell components involve the reconstitution of regions that are initially migratory and later proliferative and differentiating.

The macrophage re-population of neurogenic regions of the adult human brain and spinal cord involves a viable dimensional reconstitution that is allied to neuro-trophic factor delivery and supplement. Indeed, areas that present inhibitory influences to neurogenesis in the adult brain are simply factors of a strictly reparative nature in terms largely implicating astrocytic proliferation and creation of a glial scar. The actively dynamic nature of a focus of injury or of disease in the central nervous system are requisite pre-conditions in the evolution of a multitude of modifying and potentially contributory agents in neuro-injury. Lithium salts are believed to enhance cell proliferation and neurogenesis and to inhibit cell death [2].

Basic HLH Transcription Factors

The collaborative roles of the circulating blood appear to implicate such components as macrophages and platelets oper-

ating in the presence of breakdown of the blood brain barrier and of the blood spinal cord barrier. It is within such context that the emergence of putative regenerative factors operates in essential permissive dynamics of cell reconstitution. Estrogen 17beta-estradiol influences hippocampal morphology and plasticity and enhances neurogenesis, as seen especially in male rodents experimentally [3].

Proneural basic helix-loop-helix transcription factors have important roles in binding to DNA and in dimerization with heterologous partners especially co-activators and E-proteins. In such context, HES-1 and HES-5 proteins negatively regulate bHLH transcription factor functions by competing for E-protein binding. Analogous inhibitory roles affecting bHLH transcription factors are played by ID (Inhibitor of differentiation) proteins.

Consensus sequences of bHLH factors with glycogen synthetase kinase-3 (GSK3) are suggestive for a role of GSK3 phosphorylation in the coupling of extrinsic and intracellular pathways involved in bHLH transcriptional activities.

Histone acetylation and histone deacetylation form a self-regulatory series of loops in activating and repressing transcription of genes, as well-exemplified by anti-epileptic valproic acid which exerts inhibitory effects on histone deacetylases (HDACs) with subsequent enhanced differentiation of adult NSCs to form neurons.

ATP-dependent chromatin remodeling such as Brahma-related gene/Brahma-associated factor (SWI/SNF) in terms of specific complex composition can specifically determine neural stem cell fate specification, including the formation of a neural progenitor BAFs (BAF 45a and 53a) to a postmitotic neural BAF (BAF 45 b/c and BAF b).

A novel small double-stranding ncRNA is critically implicated in converting REST/NRSF from a repressor to an activator; the RE1-silencing transcription factor REST otherwise blocks premature neuronal differentiation of neural stem cells.

Neurons have and do present permanent phenotypic attributes in the adult CNS.

Astrocytic Cells

It is perhaps in such milieu that the progressive replacement of new neurons is strongly dependent on astrocytic cells in particular.

Glial Fibrillary Acidic Protein (GFAP) and S100beta genes are models for understanding astrocytic differentiation mechanisms and cytokines in particular (eg IL-6 family of cytokines). The binding of Signal Transducer and Activator of Transcription (in the JAK-STAT pathway) may activate the gfap promoter in astrocytic differentiation.

The NOTCH Intracellular domain and RBP-J/k that binds DNA repress gfap expression in self-renewing progenitors. On the other hand, Nuclear Factor1A/B and stem cell leukemia are important in astroglial versus oligodendroglial differentiation.

In such measure, the permissive micro-environment implicates the reconstitution of a supporting medium within further conformational realization of subsequent delivery of potentially neurogenic elements as well exemplified by dimensions of possible turnover. Microgravity altered miRNA possibly affect apoptosis and neurogenesis, as observed in *Caenorhabditis elegans*[4]. Such cellular turnover is centered within the systems of provision of actively metabolic cell components such as macrophages and platelets from the circulating blood. Insulin-like growth factor-1 is also known to enhance neurogenesis and neuronal survival [5].

Neurotrophic Effects

Increments of supplied neurotrophic factors would appear operative mediators for the regeneration of a normalized micro-environment that permits the emergence of migrating stem cells and of progenitor cells, as exemplified by the dynamics of migration and proliferation of cells from various layers of the subventricular neurogenic layer. In fact, distributional forces create conflicting parameters of regeneration and of repair within highly unstable preconditions of possible cell and stromal components. A significant functional role of Myocyte enhancer factor 2a,-c, and –d in cell and non-cell autonomous control of adult hippocampal neurogenesis appears operative that is distinct from its role during development [6].

NSCs only differentiate to neurons in midgestation, and astrogliogenesis and oligodendroglial differentiation evolve in late gestational stages, since pluripotentiality of NSCs is not present in early embryonic stages.

The central role of methylation in gene expression regulation is illustrated by the lack of response of the methylated sequence binding element TTCGGAGAA in the gfap promotor to binding STAT3, with no increased gliogenesis.

An important aspect of mechanistic control is the positive feedback loops as exemplified by methylated gp130-JAK-STAT pathway controlling gliogenic potential of cortical NSCs; cytokines are inherently inducers of enhanced induction of their cognate pathway mediators.

Vasculogenesis is a critical dimensional set of parameters that introduces elements of permissiveness of cell migration and proliferation to the injured or diseased foci in such conditions as cortical cortex degeneration.

The performance of inclusive dynamics is correlated with the further promotional effects of cells as well-represented by the glial cells in particular.

Permissive Factors

Distributional forces would operatively influence and strictly characterize the dynamics of regeneration well beyond the permissive roles of delivery of neurotrophic factors to the diseased foci. Inclusive reformations of such regions are simply the permissive aspects of a large multitude of operative pathways ranging from cell replacement and of matrix reconstitution. The regulatory processes that coordinate stem cell maintenance can be analyzed mathematically in terms especially of quantifying numbers of cells at different times [7].

The supply of blood is an essential core phenomenon that dominants as a truly multi-turnover series of system pathways that primarily appear to target the reconstitution of the extra-cellular matrix. In some manner, the proliferative activities of neurogenic zones are a derivative functionality of a rich blood-supply of such neurogenic zones.

Supportive Mechanics

Axonal guidance is a particularly critical phenomenon that appears to precede the process of synaptogenesis. In this regard, parameters of confluence and divergence operate as directional cues in the overall process of neurogenesis. In such context, redistribution of chemical mediators would permit the emergence of a plethora of phenomenal agent-mediated induction and progression of neuronal potentiality in proliferation and differentiation. Included in such emerging systems there is a series of systemic upsets that paradoxically are supportive of a possible neurogenesis. Development of the prefrontal cortex in its earliest phase in gestation and finally during adolescence incorporate two critical periods of cell proliferation and synaptic pruning and may be influenced environmentally in patients who develop schizophrenia [8].

The central core phenomena that impair possible cell and matrix constitution lie within the potentialities of such cells as the circulating macrophages and also the impact of arriving platelets to the diseased region of neuronal cell loss. The performance of further dimensional re-distribution correlates closely with the systems of delivery and supply of trophic growth factors and the specific performance of permissive cell/debris replacement. Regular physical activity may increase angiogenesis and neurogenesis and synaptogenesis, including the synthesis of neurotransmitters with increased liberation of neurotrophic factors and the synthesis of enzymatic anti-oxidants [9].

Performance Attributes

Systems of acquisition are performance-unique in the realization of pathways that generate in their own right the emergence of a truly neurogenic potential. Bone marrow-derived mesenchymal stem cells are potential candidates for ameliorating neurodegenerative states by inducing neurogenesis [10]. Migration tracts represent the actively visible performance of a cellular and matrix dimensionality that is generally severely lacking in disease foci per se.

Increasing the characterization of neurogenesis is often an attribute of targeting that closely follows the ability for creation of migratory tracts and of the appearance of supporting glial cell sub-populations.

The severe diversity of performance dynamics includes the cooperative abilities of a large array of contributing agents as evidenced by the abundance in particular of glial cells on the one hand and of blood-components. Electroconvulsive therapy appears to mediate, on the other hand, Gadd45b induces proliferation of neural stem cells in the hippocampus [11].

Performance dynamics are a series of mediating medium for reconstitution of injured foci within the brain and spinal cord in a manner that predominates the global process of replication and differentiation of stem cells and of progenitor cells in particular.

Constitutive Factors

Constitutional performance is a critical component variable that effectively introduces the emergence of neurogenesis in terms of the provision of multi-faceted spectra of cellular convergence and divergence. Forkhead Box O Transcription factors modulate synaptogenesis and adult hippocampal neurogenesis, and are also considered possible mechanisms in the development of depression [12]. The further dimensions of dynamic turnover are dominated by a proliferative activity that is inherently differentiating and differential.

In such setting the developmental stages of turnover and of replacement in progression of neurogenesis are central mediators in their own right that secondarily characterize a strict stereotype for potential regeneration of injured and diseased CNS tissues. Highly interactive mechanisms of angiogenesis, neurogenesis, oligodendrogenesis, synaptogenesis and axonal sprouting implicate miRNAs and histone deacetylases in post-stroke brain repair, including exosomes' role in intercellular communication [13].

Neuronal Reconstitution

Performance processes are inherently operative in the further reconstitution of regions of replacement in terms of the phenomena of neuronal migration and replication in neurogenesis. Indeed, it would appear that the performance dynamics of neurogenesis are per se the instrumental remodeling of parameters that arise initially and later support in highly characterized manner the replacement by new neurons. Baicalin induces neuronal differentiation of pluripotent stem cells via modulation of basic helix-loop-helix gene expression [14].

In such terms, the actual initiation of performance migration and of performance replication of new neurons is an attribute delivered as profile development foci within the human adult brain.

Indeed, neurogenesis is strictly a self-promoted series of events as further supported by the characterized glial stem cells and by the global developmental process of neuronal re-constitution.

It is further to the profile dynamics of such para-developmental parameters that neuronal regeneration further propagates as systems of operative interference on the one hand and of substantial turnover of cells and of variability micro-environmental conditioning.

System Formulation

Derivation of system formulae is a parameter of central significance in the formative processes of new neuronal populations and networks. The performance of migratory tracts and of glial ensheathing pathways are component constitutional parameters invoking the emergence of system biology that in turn strictly correlates with the immediate preceding events of progressive neurogenesis.

Compartmentalization of distinctive influences in turnover appears to signify the global characterization of injury to the brain and spinal cord, as well-evidenced by the breakdown of the blood-brain barrier. Bone-marrow stromal cells appear to enhance neurogenesis via vascular endothelial growth factor-induced or Ki-67-mediated angiogenesis [15].

In such formulation, delivery forces of directly and indirectly mediating influences would permit the turnover of components in terms of directional directing of the neurogenic foci as seen in the fetal developing brain. Migratory pathways are semblance pathways that operative developmentally to strictly categorize such development of the brain and spinal cord.

System Targeting

System targeting is itself the permissive element in reconstitution of injured or diseased foci within the central nervous system. The development of neurogenesis is operative in its own right in terms of the constitutive performance of its characterization. Biologic potential is hence an emergence phenomenon that recruits stem cells and progenitor cells that developmentally may be potentially neurogenic as further evidenced in the fetal brain. Sox genes play important roles in neurogenesis as well as sex determination, embryogenesis, oogenesis and larval development [16].

It is the ensuring guidance of migratory neuroblasts that determines the characterization of an essentially permissive series of system attributes as delivered in particular by astrocytes such as radial glial cells.

The roles played by astrocytes in neurogenesis appear to arise as inducing agents, as further formulated by the micro-environmental pre-conditioning. The toxic micro-environment of the diseased foci of brain and spinal cord injury contributes to the further specialization of the pathology of subsequent neuroblast generation or suppression. Valproic acid induces changes in neural development, neural crest migration, apoptosis and modulated transcription [17].

The specificities of the developmental process of neurogenesis would best be characterized as the permissive milieu for neuronal migration and proliferation of the neurons on the one hand and of the performance modulation of subsequent synaptogenesis and of strict neuronal network formulation. Phosphodiesterases mediate fundamental roles in learning, memory and higher cognitive functions, and phosphodiesterase-4B is important in the hippocampus and constitutes a major Disrupted in Schizophrenia 1 binding partners [18]. In such terms, the inclusive re-characterization of the global process of neurogenesis predominantly dictates operative vascularization of the foci of neurogenesis in a manner that implicates essential permissive performance of neurogenesis per se.

Micro-Environmental Preconditioning

Hence, the dynamics of possible replacement by new neurons is primarily constitutive in strictly formulating a highly permissive micro-environment for neogenesis. The paradoxical re-definition of new neuronal replacement is primarily as an emergent reversion to pathway of developmental moment.

The significance of further collaborative influence is a neurotrophic component system in dimensional re-formulation of the possible consequences of injury or disease in neuronal cell loss.

Patterns of apparent autonomy are targeted profiles of reconstitution within highly permissive re-conditioning of events of a para-developmental nature and progression. Neurogenesis occurs throughout life mainly in the subgranular zone of the hippocampus and the subventricular zone of the lateral ventricle; in particular, silencing Sonic hedgehog gene with short hairpin interfering RNA specifically in the mitotic neurons reduces neurogenesis [19]. The distributional parameters for further characterization appear a much repeated reformulation of events as central pathways of migration and replication, as indeed contributed to by radial astrocytes in particular.

Interactive phenomena involve the neuronal network processing of existing pathways that further conform to globality of the putative injurious events. Neuropeptide Y, important in regulation of adult hippocampal neurogenesis, ats via intracellular nitric oxide in induce increased neural progenitor cell proliferation [20]. Consequential modulations of the neuronal loss area significant performance guided in terms the injury in spectral form within the adjacent brain tissue territories around the foci of injury or disease.

Modulators

Characters of biologic import are supplemented modulators in further promoting the essential highly permissive pre-conditions for further constitutional reformulation of the neurogenesis. 14-3-3 proteins regulate neural proliferation and differentiation of progenitors in the cortex [21].

A tightly integrated series of sequential events emerge as proposed mechanisms that determine fate specification of NSCs, including the suppressed accessibility of binding sites to transcription factors, as exemplified by extracellular cues (such as cytokine action) acting on gene promoters secondary to local histone modulation.

The BAF (mammalian SWI/SNF) complexes induce ATP hydrolysis to change chromatin structure and are found in embryonic stem cells, neural progenitors and post-mitotic neurons [22].

A proneural factor, neurogenin 1 appears to simultaneously activate the neurogenic program and inhibits the alternative astrogliogenic program when specifying neuronal fate, especially via modulation of non-coding RNA epigenetic regulation [23].

Performance dynamics of permissive operant influences would therefore be a direct biologic re-characterization of putative neurogenesis, within further fields of subsequent network creation and functionality. The proautophagic proteins Ambra1 and Beclin 1 are highly expressed in the adult subventricular zone and their downregulation induces decreased cell proliferation, increased basal apoptosis and augmented sensitivity to DNA damage [24]. Interleukin-10 suppresses neuroinflammation and is implicated in neurogeneis and hippocampal synaptic plasticity and also in the modulation of the stress response [25]. Simple juxta-positioning of the trophic and vascular components belie a severely interactive process of neogenesis as supported principally by astrocytes and other cell-types such as macrophages. Microglia is implicated in modulating neuronal cell death, neurogenesis and synaptic activity [26].

Sonic hedgehog (Shh) induces expression of OLIG1 and OLIG2 that regulate oligodendrocyte fate-specification.

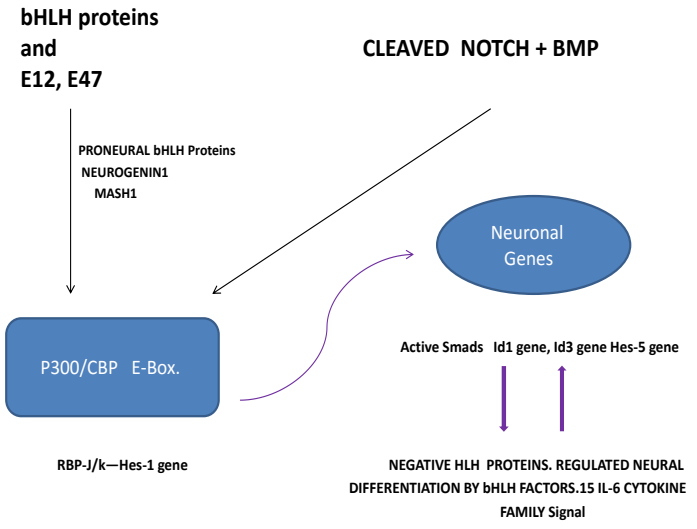
Inhibition of astrogliogenesis by OLIG2 can also be modulated by sequestration of the coactivator p300 from the action of STAT3 as induced by cytokines.

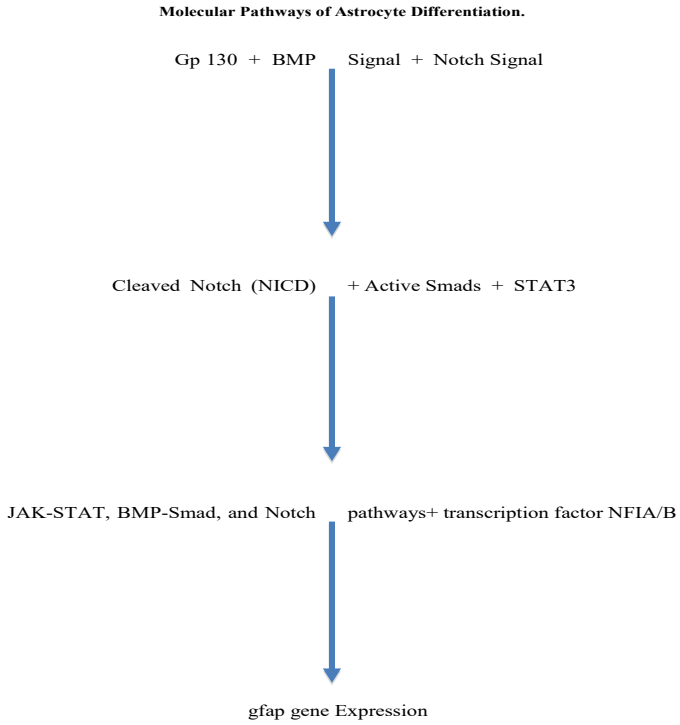
Induction of ID proteins inhibits OLIG proteins by dimerization, as also nuclear export of OLIG proteins by Akt. Downregulation of OLIG2 is required for astrogliogenesis.

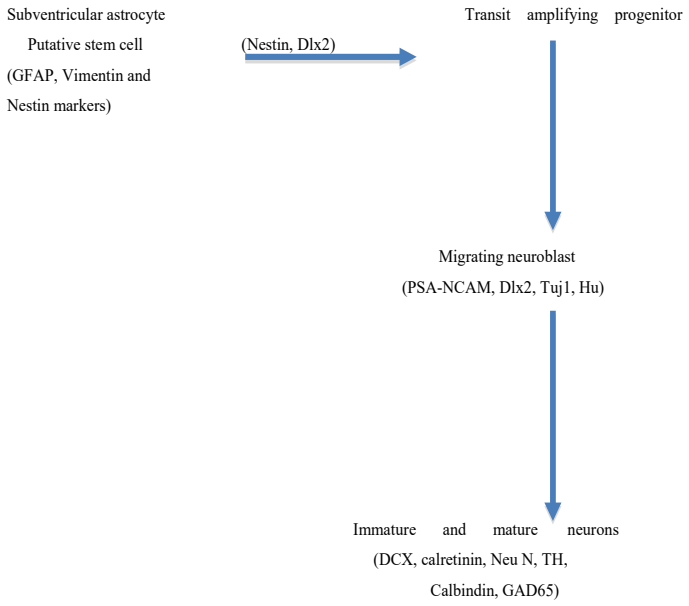
Concluding Remarks

Performance dynamics are themselves constitutive components for stereotyped formulas in neogenesis in further significant dimensions of permissive reconditioning of migrating and proliferating neuroblasts. The astrocytes provide also essential guidance for axonal sprouting and for myelination by differentiating into various cell subtypes and oligodendrocytes.

Reformulation is a constitutional attribute in regenerative measures such as possible neurogenesis. The developmental paradigm of neogenesis is a potentially highly-informative modulator system in induction and maintenance of such cell-types as stem cells and progenitor cells. The profile setting pathways appear to potentially offer directional parameters that include the targeting of disease foci and of pre-determined systems of modulation in a permissive micro-environment.







Overall Scheme of Neurogenesis

TUJ1---Neuron-specific class III beta-tubulin

DCX---Doublecortin (microtubule-associated protein)

PCNA--- proliferating nuclear antigen.

PSA-NCAM—polysialylated-neuronal cell adhesion molecule.

NeuN—neuronal specific nuclear protein.

References

1. Rocca MA, Longoni G, Pagani E, Boffa G, Colombo B et al. In vivo evidence of hippocampal dentate gyrus expansion in multiple sclerosis. Hum Brain Mapp. 2015, 36(11): 4702-4713.

2. Gawlik-Koteinicka O, Mielicki W, Rabe-Jablonska J, Lazarek J, Strzelecki D . Impact of lithium alone or in combination with haloperidol on oxidative stress parameters and cell viability in SH-SY5Y cell culture. Acta Neuropsychiatr. 2016, 28(1): 38-44.

3. Frick KM, Kim J, Tuscher JJ, Fortress AM. Sex steroid hormones matter for learning and memory: estrogenic regulation of hippocampal function in male and female rodents. Learn Mem. 2015, 22(9): 472-493.

4. Gao Y, Li S, Xu D, Wang J, Sun Y. Changes in apoptotic microRNA and mRNA expression profiling in Caenorhabditis elegans during the Shenzhou-8 mission. J Radiat Res. 2015, 56(6): 872-882.

5. Jiang G, Wang W, Chao Q, Gu J, Mi X et al. IGF-1 enhances hippocampal excitatory and seizure activity through IGF-1 receptor-mediated mechanisms in epileptic brain. Clin Sci (Lond). 2015, 129(12): 1047-1060.

6. Latchney SE, Jiang Y, Petrik DP, Eisch AJ, Hsieh J. Inducible knockout of Mef2a, -c, and –d from nestin-expressing stem/progenitor cells and their progeny unexpectedly uncouples neurogenesis and dendritogenesis in vivo. FASEB J. 2015, 29(12): 5059-5071.

7. Miguez DG . A branching process to characterize the dynamics of stem cell differentiation. Sci Rep. 2015, 5:13265.

8. Selemon LD, Zecevic N. Schizophrenia: a tale of two critical periods for prefrontal cortical development. Transl Psychiatry. 2015, 5: e623.

9. Paillard T. Preventive effects of regular physical exercise against cognitive decline and the risk of dementia with age advancement. Sports Med Open. 2015, 1(1): 4.

10. Lee H, Bae JS, Jin HK. Defective Self-Renewal and Differentiation of GBA-deficient neural Stem cells can be restored by macrophage colony-stimulating factor. Mol Cells. 2015, 38(9): 806-813.

11. Jun H, Hussaini SM, Cho CH, Welby J, Jang MH. Gadd45b mediates electroconsulsive shock induced proliferation of hippocampal neural stem cells. Brain Stimul. 2015, 8(6): 1021-1024.

12. Wang H, Quirion R, Little PJ, Cheng Y, Feng ZP et al. Forkhead Box O transcription factors as possible mediators in the development of major depression. Neuropharmacology. 2015, 99: 527-537.

13. Zhang ZG, Chopp M . Promoting brain remodeling to aid in stroke recovery. Trends Mol Med. 2015, 21(9): 543-548.

14. Morita A, Soga K, Nakayama H, Ishida T, Kawanishi S et al. Neuronal differentiation of human iPS cells induced by baicalin via regulation of bHLH gene expression. Biochem Biophys Res Commun. 2015, 465(3): 458-463.

15. Yang Z, Cai X, Xu A, Xu F, Liang Q. Bone marrow stromal cell transplantation through tail vein injection promotes angiogenesis and vascular endothelial growth factor expression in cerebral infarct area in rats. Cytotherapy. 2015, 17(9): 1200-1212.

16. Jiang Y, Han K, Chen S, Hong W, Wang Y et al. Molecular cloning, characterization and expression of Lc-Sox11a in large yellow croaker Larimichthys crocea. Gene. 2015, 574(2): 287-301.

17. Colleoni S, Galli C, Gaspar JA, Meganathan K, Jagtap S et al. A comparative transcriptomic study on the effects of valproic acid on two different hESCs lines in a neural teratogenicity test system. Toxicol Lett. 2014, 231(1): 38-44.

18. McGirr A, Lipina TV, Mun HS, Georgiou J, Al-Amri AH et al. Specific inhibition of phosphodiesterase-4B results in anxiolysis and facilitates memory acquisition. Neuropsychopharmacology. 2015, 14.

19. Hung HC, Hsiao YH, Gean PW. Sonic hedgehog signaling regulates amygdalar neurogenesis and extinction of fear memory. Eur Neuropsychopharmacol. 2015, 25(10): 1723-1732.

20. Toyo-oka K, Wachi T, Hunt RF, Baraban SC, Taya S et al. 14-3-3epsilon and omega regulate neurogenesis and differentiation of neuronal progenitor cells in the developing brain. J Neurosci. 2014, 34(36): 12168-12181.

21. Gray WP, Cheung A. Nitric oxide regulation of adult neurogenesis. Vitam Horm. 2014, 96: 59-77.

22. Son EY, Crabtree GR . The role of BAF (mSWI/SNF) complexes in mammalian neural development. Am J Med Genet C Semin Med Genet. 2014, 166C(3): 333-349.

23. Zhao J, Lin Q, Kim KJ, Dardashti FD, Kim J et al. Ngn1 inhibits astrogliogenesis through induction of miR-9 during neuronal fate specification. Elife. 2015, 4: e06885.

24. Yazdankhah M, Farioli-Vecchioli S, Tonchev AB, Stoykova A, Cecconi F. The autophagy regulators Ambra1 and Beclin 1 are required for adult neurogenesis in the brain subventricular zone. Cell Death Dis. 2014, 5: e1403.

25. Kurowska E, Majkutewicz l. The interleukin-10 in the central nervous system. Postepy Hig Med Dosw. 2015, 69: 886-891.

26. Katsumoto A, Lu H, Miranda AS, Ransohoff RM. Ontogeny and functions of central nervous system macrophages. J Immunol. 2014, 193(6): 2615-2621.