Mini Review

Neurogenic potential of Müller glia in the adult mammalian retina

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Overturning the long-held dogma that the central nervous system (CNS) of adult mammals never regenerates, recent evidence has revealed that neural stem cells continually generate new neurons in two regions of the adult mammalian CNS: the hippocampus and the olfactory bulb. Although adult neurogenesis is limited outside these two regions, accumulating evidence indicates the existence of neural progenitors even in non-neurogenic regions. In the adult mammalian retina, Müller glia generate new retinal neurons in response to injury. The proliferation and differentiation of Müller glia-derived progenitors can be controlled by intrinsic and extrinsic factors. We propose a retinal regeneration therapy based on the manipulation of these endogenous progenitors. Here, we review adult neurogenesis and retinal regeneration in mammals, with an emphasis on the neurogenic role of glial cells.

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Introduction

Since the discovery of neurogenesis in the adult mammalian brain, much progress has been made in stem cell biology. New neurons are continuously generated in the subventricular zone (SVZ) of the lateral ventricle and the subgranular zone (SGZ) of the hippocampal dentate gyrus[1,2], and are functionally integrated into neural circuits[3-6]. Except for these two regions, neurogenesis appears to be extremely limited in the intact adult mammalian central nervous system (CNS). However, after pathological stimulation, such as brain insults, endogenous progenitors do proliferate in regions otherwise considered non-neurogenic. Thus, stimulating these inactive progenitors could produce new neurons both to replace and to repair damaged compartments of the CNS. Here, we review recent findings regarding neurogenesis and regeneration in the adult mammalian CNS, with special emphasis on the neurogenic potential of glial cells.

Glial Cells Serve as Neural Progenitors

Current evidence indicates that cells once considered glial cells can act as neural progenitors in both the developing and mature mammalian brain. During development, neuronepithelial stem cells in the embryonic neural tube do not show glial characteris-

tics. At the onset of neurogenesis, neuroepithelial cells generate radial glia, which exhibit both neuronepithelial and astroglial properties. Radial glia are more fate restricted progenitors than neuroepithelial cells. Although the primary function of radial glia has been considered the provision of a guidance scaffold for migrating neurons, recent studies have revealed that they also produce new neurons in both the developing brain[7-9] and the mature brain[10]. However, in adult mammals, radial glia are absent from the brain. Instead, astrocytes serve as stem cells in the SGZ and SVZ of adult mammals[11,12]. It should be noted that not all astrocytes are stem cells. Astrocytes with precursor cell characteristics co-express other precursor cell markers, such as Sox2, brain lipid binding protein, and nestin, but are negative for S100β, an astrocytic marker present in most astrocytes.

Astrocytes in the adult SVZ act as slow-dividing neural stem cells, capable of generating progeny neuroblast precursors[11-13]. A subset of GFAP(+)/vimentin(+)/nestin(+) astrocytes gives rise to rapidly proliferating transient amplifying cells (GFAP(-)/Dlx2(+)), which in turn generate migrating neuroblasts (GFAP(-)/Dlx2(+)/PSA-NCAM(+))[2]. These neuroblasts proceed towards the olfactory bulb along an intricate path of migration known as the rostral migratory stream. They migrate tangentially in chains through tubular structures formed by specialized astrocytes. After detaching from these chains and migrating radially from the rostral migratory stream into the olfactory bulb, adult-born cells from the SVZ mature into olfactory inhibitory interneurons of two main types: granule cells and periglomerular cells, in their respective olfactory bulb layers[5,14]. More than 30000 neuroblasts exit the rodent SVZ for the rostral migratory stream each day.

Astrocytes in the SGZ of the hippocampus also give rise to intermediate progenitors. Quiescent stem cells (GFAP(+)/nestin(+)/vimentin(+) astrocytes) produce amplifying neural progenitors (GFAP(-)), and then migrating neuroblasts (GFAP(-)/ DCX(+)/PSA-NCAM(+))[15,16]. These progenitors mature locally into granule neurons of the dentate gyrus, sending axonal projections to area CA3 and dendritic arbors into the molecular layer[17,18]. These adult-born neurons integrate functionally into the circuitry of the hippocampus[3,5,6]. About 9000 new cells are added to the dentate gyrus in young adult rats each day, and newborn neurons comprise about 6% of the total population in the dentate gyrus[19]. Although the precise function of these new neurons is unknown, adult neurogenesis plays important roles in learning, memory, and depression[20-22].

Neural Progenitor Cells in Non-Neurogeneic Regions

Several lines of evidence indicate the existence of cells with precursor cell properties in the adult CNS other than in the two neurogenic regions of the brain. Following reports of the isolation of neural progenitor cells from the embryonic forebrain[23] and from the adult hippocampus and the SVZ[24,25], cells with similar properties have been isolated from many other regions of the adult mammalian CNS. They have been cultured *in vitro* from caudal portions of the SVZ[25], the striatum, the septum, the corpus callosum[25], the cortex[26], the spinal cord[27,28], the optic nerve[26,29], and the ciliary margin of the eye[30]. These cells exhibit at least limited self-renewal, and produce differentiated cells of the three neural lineages: neurons, astrocytes, and oligodendrocytes. *In vivo*, emerging evidence suggests the presence of adult neurogenesis in the neocortex[31], the amygdala[32], the substantia nigra[33,34], the dorsal vagal complex of the brainstem[35], and the hypothalamus[36], although some of these results remain controversial.

Injury and pathological stimulation also induce neurogenesis in non-neurogenic regions. The selective apoptosis of pyramidal neurons in neocortical layer VI stimulates neurogenesis in the neocortex[37]. Insult also induces neurogenesis in the hippocampal CA1 region[38], the striatum[39], the corticospinal system[40], and the retina[41]. Presumably, insult-induced neurogenesis in non-neurogenic regions is of two types with regard to differences in the precursor cell source: (1) local parenchymal precursor cells are activated to generate new neurons in response to a stimulus associated with a pathological event; and (2) precursor cells from the neurogenic SVZ or SGZ respond to a stimulus and migrate into the parenchyma. These findings indicate that the absence of constitutive neurogenesis does not reflect an intrinsic limitation of neurogenic potential, but more likely results from a lack of appropriate microenvironmental signals for neural regeneration. Elucidation of these signals could facilitate the CNS repair by endogenous neural progenitors.

Glial Cells in the Retina

The neural retina consists of six types of neurons and two types of glia. These cells constitute three cell layers: rod and cone photoreceptors in the outer nuclear layer; horizontal, bipolar, and amacrine cells and Müller glia in the inner nuclear layer; and ganglion and displaced amacrine cells in the ganglion cell layer.

Glial cells in the retina are astrocytes and Müller glia. During development, Müller glia are generated from retinal progenitors,

whereas astrocytes migrate into the retina along the optic stalk from the fourth ventricle of the brain. Astrocytes in the retina are confined to the vitreal surface, where their processes contact the surface blood vessels. Astrocytes are essential for the formation of blood vessels in the developing retina. Understanding the role of glia in the development of blood vessels may provide insights into the mechanisms underlying the abnormal growth of blood vessels in several retinal diseases, including diabetic retinopathy.

Müller glial processes surround neuronal cell bodies in the nuclear layers and contact synapses in the plexiform layers. The distal processes of the Müller glia form the external limiting membrane of the retina, and their endfeet form the inner limiting membrane. Müller glia play an important role in regulating extracellular K+ and pH, and in the synthesis of the neurotransmitter glutamate. Müller glia are also capable of re-entering the cell cycle during reactive gliosis in response to retinal injury.

Retinal Regeneration by Müller Glia

Endogenous cells in the retina can provide a source of regeneration. The possibility that Müller glia are an intrinsic source of regeneration was first raised by Biaisted et al. in the goldfish[41]. Biaisted et al. demonstrated that laser damage elicited a proliferation of Müller glia and the concomitant replacement of the damaged cone photoreceptors[41]. In addition, the retina of post-hatch chicks has been reported to possess the regenerative capacity from Müller glia[42,43]. Several lines of evidence support a close relationship between the Müller glia and retinal progenitors. Recent gene-expression profiling studies have demonstrated a large degree of overlap in the genes expressed in the Müller glia and late retinal progenitors[45].

We have demonstrated that, in the adult rat retina, Müller glia act as neurogenic progenitors after retinal injury[44]. Intravitreal injection of N-methyl-D-aspartate, an agonist of the glutamate receptor, causes neurotoxicity in amacrine cells and ganglion cells in the adult rat retina. After N-methyl-D-aspartate-induced retinal injury and subsequent labeling with BrdU, BrdU-labeled proliferative cells are mainly distributed in the inner nuclear layer (Fig.1A). Although some proliferative cells positive for the microglial marker OX-42 are observed in the inner plexiform layer, they disappear within one week. Other BrdU-positive and terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling (TUNEL)-positive cells exist in the ganglion cell layer, which can be explained by the uptake of BrdU by apoptotic cells. Besides those cells, all the BrdU-labeled cells in the the inner nuclear layer two days after injury are glutamine synthetase-positive Müller glia. These BrdU-labeled cells express retinal progenitor markers such as Pax6 and Chx10. In addition, injury induces nestin expression in Müller glia. These observations indicate that Müller glia acquire progenitor-like properties after retinal injury. It should be noted that Müller glia are not neural stem cells under normal conditions; de-differentiation and proliferation are required for Müller glia to become progenitors, unlike neural stem cells in the SVZ of the lateral ventricle and the SGZ of the hippocampal dentate gyrus.

After proliferation in response to retinal damage, the BrdU-labeled cells migrate into the retinal neuron-specific layer and differentiate into cells positive for retinal neuron-specific markers, such as rhodopsin (photoreceptors) and PKC (bipolar cells) (Fig. 1B, C). The Müller glia-derived progenitors appear to differentiate into the cell types of the damaged neurons, because Müller glia generate mainly photoreceptors in the photoreceptor-damaged retina. The results of studies using several types of neurotoxic injury in the post-hatch chick retina also suggest that the type of neurons injured in the retina allows or promotes the regeneration of that neuronal type by the Müller glia-derived progenitors[42,43]. Migration of neural progenitors toward damaged sites has also been reported in the brain; SVZ progenitors migrate toward the striatum and the cerebral cortex injured by ischemia[37,39]. Taking together, we conclude that Müller glia proliferate and de-differentiate into retinal progenitors in response to retinal damage, and then migrate and differentiate into various types of retinal neurons.

Factors Regulating Retinal Regeneration

In development, seven types of retinal cells are differentiated from common progenitors in the following order: retinal ganglion cells, cone photoreceptors, amacrine cells, and horizontal cells, followed by rod photoreceptors, bipolar cells, and Müller glia[46]. During retinal development, the retinal progenitors change their competency under the control of intrinsic regulators (such as transcription factors; Table 1) and extrinsic regulators (such as neurotrophic factors; Table 2). Retinal progenitors initially proliferate extensively to increase the cell number. In mice, from embryonic day 10.5, the proliferating progenitors commence differentiation into retinal neurons. Fate-committed cells migrate to fixed positions throughout the laminated retina and establish synaptic connections to other neurons.

Intrinsic factors regulating the specification of retinal cell types are encoded by homeobox genes and are basic helix-loop-helix proteins[46] (Table 1). For example, the generation of photoreceptors is regulated by Crx, Otx2 (homeobox gene products)

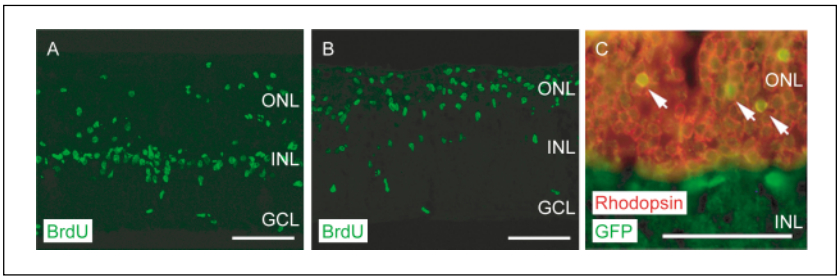

Fig.1 Generation of photoreceptor cells from Müller glia

(A) Cells in the inner nuclear layer proliferate in response to retinal injury. Green: BrdU. INL: inner nuclear layer inner, ONL: outer nuclear layer inner, GCL: ganglion cell layer.

(B) BrdU-labeled cells migrate from the INL to the ONL.

(C)Retroviral gene transfer of Crx/NeuroD promotes the differentiation into rhodopsin-positive cells. Green: Green fluorescent protein (GFP). Red: rhodopsin. Bar, 100 μm.

Table 1 Intrinsic factors regulating retinal cell differentiation

Cell type	homeobox	bHLH
Photoreceptor cells	Crx / Otx2	NeuroD / Mash1
Horizontal cells	Pax6 / Six3	Math3
Bipolar cells	Chx10	Mash1 / Math3
Amacrine cells	Pax6 / Six3	NeuroD / Math3
Ganglion cells	Pax6	Math5
Müller glia	Rx	Hes1 / Hes5

Table 2 Extrinsic factors regulating retinal cell differentiation

Cell type	Soluble factor
Photoreceptor cells	(+) Retinoic acid, (+) Taurine, (+) Thyroid hormone
Horizontal cells	
Bipolar cells	(+) Ciliary neurotrophic factor
Amacrine cells	
Ganglion cells	(-) Sonic hedgehog
Müller glia	(-) Retinoic acid

(+): promoting effect on differentiation

(-): inhibitory effect on differentiation

and NeuroD (basic helix-loop-helix proteins). Mice lacking Crx exhibit deficits in outer segment formation in their photoreceptors[47,48]. Overexpression of Crx in P0 progenitors promotes the genesis of photoreceptors and inhibits amacrine fate *in vivo*. Conditional Otx2 knockout mice lack photoreceptor differentiation[49]. NeuroD expression occurs in photoreceptors, as well as amacrine cells[50]. NeuroD-null mutations moderately decrease photoreceptor numbers, indicating that NeuroD plays a role in photoreceptor development[50].

As an extrinsic determination factor (Table 2), sonic hedgehog inhibits the genesis of ganglion cells and promotes the differentiation of other retinal cells, including photoreceptors[51]. Retinoic acid promotes photoreceptor differentiation, and the inhibition of endogenous retinoic acid synthesis results in a reduction in rod differentiation[52]. Taurine, an amino acid, promotes rod differentiation via the α2 glycine receptor and the $GABA_A$ receptor[53,54]. Blockade of fibroblast growth factor signaling results in a decrease in photoreceptors and an increase in Müller glia[55].

In retinal regeneration, Müller glia-derived progenitors are also regulated by these intrinsic and extrinsic factors. Misexpression of Crx and NeuroD in Müller glia-derived progenitors induces their differentiation into photoreceptors (Fig.1C). Misexpression of NeuroD/Pax6 induces the differentiation of the progenitors into amacrine cells, and Math3 and Pax6 induce amacrine and horizontal cells after retinal injury. As an exogenous factor, retinoic acid induces photoreceptor differentiation. NeuroD expression is also regulated by histone deacetylases[56], and the histone deacetylase inhibitor valproic acid induces NeuroD expression in neural stem cells[57]. The application of valproic acid to the damaged retina promotes the differentiation of Müller glia-derived progenitors into photoreceptor cells.

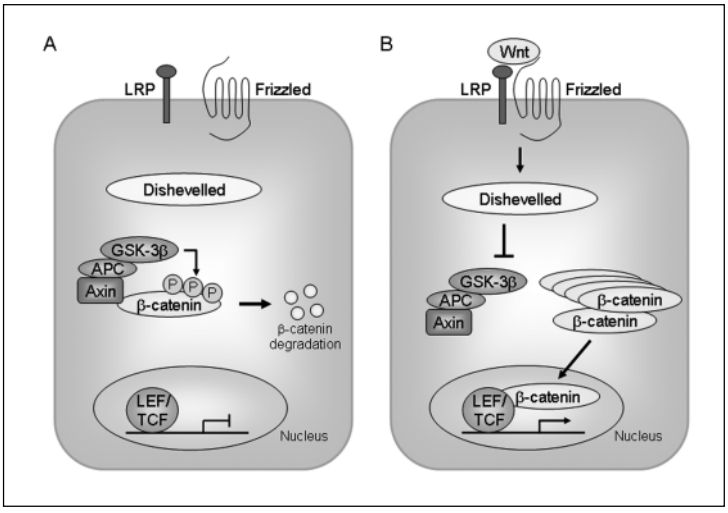

Fig.2 Wnt canonical signaling pathway
(A) In the absence of Wnts, β-catenin forms a complex with Axin, APC and GSK-3β, and is degraded by the ubiquitin-proteasome system.
(B) When Wnts bind thier receptors, such as Frizzled and LRP, GSK-3β is inactivated via Disheveled. Cytoplasmic β-catenin is stabilized and the accumulated β-catenin is translocated into the nucleus, resulting in the activation of the transcription factor, LEF/TCF.
LRP, low density lipoprotein receptor-related protein; APC, adenomatous polyposis coli; GSK-3β, glycogen synthase kinase-3β; LEF/TCF, lymphoid enhancer-binding factor/T-cell factor.

In addition to cell fate determination, the proliferation of Müller glia-derived progenitors can be regulated by the application of extrinsic factors. The activation of Wnt/β-catenin signaling promotes the proliferation of Müller glia-derived progenitors, and the inhibition of this signaling has the opposite effect [58]. Although the number of newly generated neurons is limited in the damaged retina, the strategy targeted to Wnt canonical signaling may be sufficient to compensate for retinal damage. We propose that low-molecular compounds that activate Wnt/β-catenin signaling, such as Wnt receptor agonists and GSK-3β inhibitors, have therapeutic potential for promoting the regeneration of retinal neurons (Fig. 2). Collectively, the proliferation and differentiation of Müller glia-derived progenitors can be controlled by intrinsic and extrinsic factors. These findings indicate that the Müller glia are a potential source of neural regeneration in the adult mammalian retina.

Perspectives

We have shown that (1) Müller glia produce new neurons after retinal injury; (2) the number of Müller glia-derived progenitors can be enhanced by the activation of Wnt signaling; and (3) the cell fate of these progenitors can be controlled by intrinsic and extrinsic factors. Despite these neurogenic properties of Müller glia, there is no direct evidence that Müller glia-derived neurons contribute to the functional regeneration of the retina *in vivo*. There is neither evidence for the integration of newly generated neurons into the pre-existing neural circuitry, nor evidence of functional recovery via synaptic transmission between the new and pre-existing neurons. We propose a potential retinal regeneration therapy based on the manipulation of endogenous progenitors. Considering the risks associated with invasive surgery and rejection of grafted cells, therapies that promote the activation of endogenous retinal progenitors would have significant advantages over cell transplantation. Our next study will investigate the mechanisms underlying the integration of newly generated cells into existing neural networks and functional recovery in animal models closely resembling human diseases.

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References

1) Gage FH: Mammalian neural stem cells. Science, 287: 1433-1438, 2000.
2) Alvarez-Buylla A, Garcia-Verdugo JM: Neurogenesis in adult subventricular zone. J Neurosci, 22: 629-634, 2002.
3) van Praag H, Schinder AF, Christie BR, Toni N, Palmer TD, Gage FH: Functional neurogenesis in the adult hippocampus. Nature, 415: 1030-1034, 2002.
4) Jessberger S, Kempermann G: Adult-born hippocampal neurons mature into activity-dependent responsiveness. Eur J Neurosci, 18: 2707-2712, 2003.
5) Carleton A, Petreanu LT, Lansford R, Alvarez-Buylla A, Lledo PM: Becoming a new neuron in the adult olfactory bulb. Nat Neurosci, 6: 507-518, 2003.
6) Schmidt-Hieber C, Jonas P, Bischofberger J: Enhanced synaptic plasticity in newly generated granule cells of the adult

hippocampus. Nature, 429: 184-187, 2004.
7) Malatesta P, Hartfuss E, Gotz M: Isolation of radial glial cells by fluorescent-activated cell sorting reveals a neuronal lineage. Development, 127: 5253-5263, 2000.
8) Noctor SC, Flint AC, Weissman TA, Dammerman RS, Kriegstein AR: Neurons derived from radial glial cells establish radial units in neocortex. Nature, 409: 714-720, 2001,
9) Miyata T, Kawaguchi A, Okano H, Ogawa M: Asymmetric inheritance of radial glial fibers by cortical neurons. Neuron, 31: 727-741, 2001.
10) Alvarez-Buylla A: Mechanism of neurogenesis in adult avian brain. Experientia, 46: 948-955, 1990.
11) Doetsch F, Caillé I, Lim DA, Garcia-Verdugo JM, Alvarez-Buylla A: Subventricular zone astrocytes are neural stem cells in the adult mammalian brain. Cell, 97: 703-716, 1999.
12) Laywell ED, Rakic P, Kukekov VG, Holland EC, Steindler DA: Identification of a multipotent astrocytic stem cell in the immature and adult mouse brain. Proc Natl Acad Sci USA, 97: 13883-13888, 2000.
13) Garcia AD, Doan NB, Imura T, Bush TG, Sofroniew MV: GFAP-expressing progenitors are the principal source of constitutive neurogenesis in adult mouse forebrain. Nature Neurosci, 7: 1233-1241, 2004.
14) Lois C, Alvarez-Buylla A: Long-distance neuronal migration in the adult mammalian brain. Science, 264: 1145-1148, 1994.
15) Kempermann G, Jessberger S, Steiner B, Kronenberg G: Milestones of neuronal development in the adult hippocampus. Trends Neurosci, 27: 447-452, 2004.
16) Encinas JM, Vaahtokari A, Enikolopov G: Fluoxetine targets early progenitor cells in the adult brain. Proc Natl Acad Sci USA, 103: 8233-8238, 2006.
17) Stanfield BB, Trice JE: Evidence that granule cells generated in the DG of adult rats extend axonal projections. Exp Brain Res, 72: 399-406, 1988.
18) Markakis EA, Gage FH: Adult-generated neurons in the DG send axonal projections to field CA3 and are surrounded by synaptic vesicles. J Comp Neurol, 406: 449-460, 1999.
19) Cameron HA, McKay RD: Adult neurogenesis produces a large pool of new granule cells in the DG. J Comp Neurol, 435: 406-417, 2001.
20) Shors TJ, Miesegaes G, Beylin A, Zhao M, Rydel T, Gould E: Neurogenesis in the adult is involved in the formation of trace memories. Nature, 410: 372-376, 2001.
21) Malberg JE, Eisch AJ, Nestler EJ, Duman RS: Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. J Neurosci, 20: 9104-9110, 2000.
22) Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S, Weisstaub N, Lee J, Duman R, Arancio O, Belzung C, Hen R: Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science, 301: 805-809, 2003.
23) Reynolds BA, Tetzlaff W, Weiss S: A multipotent EGF-responsive striatal embryonic progenitor cell produces neurons and astrocytes. J Neurosci, 12: 4565-4574, 1992.
24) Reynolds BA, Weiss S: Generation of neurons and astrocytes from isolated cells of the adult mammalian central nervous system. Science, 255: 1707-1710, 1992.
25) Palmer TD, Ray J, Gage FH: FGF-2-responsive neuronal progenitors reside in proliferative and quiescent regions of the adult rodent brain. Mol Cell Neurosci, 6: 474-486, 1995.
26) Weiss S, Dunne C, Hewson J, Wohl C, Wheatley M, Peterson AC, Reynolds BA: Multipotent CNS stem cells are present in the adult mammalian spinal cord and ventricular neuroaxis. J Neurosci, 16: 7599-7609, 1996.
27) Shihabuddin LS, Ray J, Gage FH: FGF-2 is sufficient to isolate progenitors found in the adult mammalian spinal cord. Exp Neurol, 148: 577-586, 1997.
28) Palmer TD, Markakis EA, Willhoite AR, Safar F, Gage FH: Fibroblast growth factor-2 activates a latent neurogenic program in neural stem cells from diverse regions of the adult CNS. J Neurosci, 19: 8487-8497, 1999.
29) Kondo T, Raff M: Oligodendrocyte precursor cells reprogrammed to become multipotential CNS stem cells. Science, 289: 1754-1757, 2000.
30) Tropepe V, Coles BL, Chiasson BJ, Horsford DJ, Elia AJ, McInnes RR, van der Kooy D: Retinal stem cells in the adult mammalian eye. Science, 287: 2032-2036, 2000.
31) Gould E, Reeves AJ, Graziano MS, Gross CG: Neurogenesis in the neocortex of adult primates. Science, 286: 548-552, 1999.
32) Bernier PJ, Bedard A, Vinet J, Levesque M, Parent A: Newly generated neurons in the amygdala and adjoining cortex of adult primates. Proc Natl Acad Sci USA, 99: 11464-11469, 2002.
33) Lie DC, Dziewczapolski G, Willhoite AR, Kaspar BK, Shults CW, Gage FH: The adult substantia nigra contains progenitor cells with neurogenic potential. J Neurosci, 22: 6639-6649, 2002.
34) Zhao M, Momma S, Delfani K, Carlen M, Cassidy RM, Johansson CB, Brismar H, Shupliakov O, Frisen J, Janson AM: Evidence for neurogenesis in the adult mammalian

substantia nigra. Proc Natl Acad Sci USA, 100: 7925-7930, 2003.

35) Bauer S, Hay M, Amilhon B, Jean A, Moyse E: In vivo neurogenesis in the dorsal vagal complex of the adult rat brainstem. Neuroscience, 130: 75-90, 2005.

36) Kokoeva M, Yin H, Flier JS: Neurogenesis in the hypothalamus of adult mice: potential role in energy balance. Science, 310: 679-683, 2005.

37) Magavi SS, Leavitt BR, Macklis JD: Induction of neurogenesis in the neocortex of adult mice. Nature, 405: 951-955, 2000.

38) Nakatomi H, Kuriu T, Okabe S, Yamamoto S, Hatano O, Kawahara N, Tamura A, Kirino T, Nakafuku M: Regeneration of hippocampal pyramidal neurons after ischemic brain injury by recruitment of endogenous neural progenitors. Cell, 110: 429-441, 2002.

39) Arvidsson A, Collin T, Kirik D, Kokaia Z, Lindvall O: Neuronal replacement from endogenous precursors in the adult brain after stroke. Nat Med, 8: 963-970, 2002.

40) Chen J, Magavi SS, Macklis JD: Neurogenesis of corticospinal motor neurons extending spinal projections in adult mice. Proc Natl Acad Sci USA, 101: 16357-16362, 2004.

41) Braisted JE, Essman TF, Raymond PA: Selective regeneration of photoreceptors in goldfish retina. Development, 120: 2409-2419. 1994.

42) Fischer AJ, Reh TA: Müller glia are a potential source of neural regeneration in the postnatal chicken retina. Nat Neurosci, 4: 247-252, 2001.

43) Fischer AJ, Reh TA: Exogenous growth factors stimulate the regeneration of ganglion cells in the chicken retina. Dev Biol, 251: 367-379, 2002.

44) Ooto S, Akagi T, Kageyama R, Akita J, Mandai M, Honda Y, Takahashi M: Potential for neural regeneration after neurotoxic injury in the adult mammalian retina. Proc Natl Acad Sci USA, 101: 13654-13659, 2004.

45) Blackshaw S, Harpavat S, Trimarchi J, Cai L, Huang H, Kuo WP, Weber G, Lee K, Fraioli RE, Cho SH, Yung R, Asch E, Ohno-Machado L, Wong WH, Cepko CL: Genomic analysis of mouse retinal development. PLoS Biol, 2: E247, 2004.

46) Marquardt T, Gruss P: Generating neuronal diversity in the retina: one for nearly all. Trends Neurosci, 25: 32-38, 2002.

47) Chen S, Wang QL, Nie Z, Sun H, Lennon G, Copeland NG, Gilbert DJ, Jenkins NA, Zack DJ: Crx, a novel Otx-like paired-homeodomain protein, binds to and transactivates photoreceptor cell-specific genes. Neuron, 19: 1017-1030, 1997.

48) Furukawa T, Morrow EM, Cepko CL: Crx, a novel otx-like homeobox gene, shows photoreceptor-specific expression and regulates photoreceptor differentiation. Cell, 9: 531-541, 1997.

49) Nishida A, Furukawa A, Koike C, Tano Y, Aizawa S, Matsuo I, Furukawa T: Otx2 homeobox gene controls retinal photoreceptor cell fate and pineal gland development. Nat Neurosci, 6: 1255-1263, 2003.

50) Morrow EM, Furukawa T, Lee JE, Cepko CL: NeuroD regulates multiple functions in the developing neural retina in rodent. Development, 126: 23-36, 1999.

51) Shkumatava A, Fischer S, Muller F, Strahle U, Neumann CJ: Sonic hedgehog, secreted by amacrine cells, acts as a short-range signal to direct differentiation and lamination in the zebrafish retina. Development, 131: 3849-3858, 2004.

52) Hyatt GA, Schmitt EA, Fadool JM, Dowling JE.: Retinoic acid alters photoreceptor development in vivo. Proc Natl Acad Sci USA, 93: 13298-13303, 1996.

53) Altshuler D, Cepko C: A temporally regulated, diffusible activity is required for rod photoreceptor development in vitro. Development, 114: 947-957, 1992.

54) Young TL, Cepko CL: A role for ligand-gated ion channels in rod photoreceptor development. Neuron, 41: 867-879, 2004.

55) McFarlane S, Zuber ME, Holt CE: A role for the fibroblast growth factor receptor in cell fate decisions in the developing vertebrate retina. Development, 125: 3967-3975, 1998.

56) Lunyak VV, Burgess R, Prefontaine GG, Nelson C, Sze SH, Chenoweth J, Schwartz P, Pevzner PA, Glass C, Mandel G, Rosenfeld MG: Corepressor-dependent silencing of chromosomal regions encoding neuronal genes. Science, 298: 1747-1752, 2002.

57) Hsieh J, Nakashima K, Kuwabara T, Mejia E, Gage FH: Histone deacetylase inhibition-mediated neuronal differentiation of multipotent adult neural progenitor cells. Proc Natl Acad Sci USA, 101: 16659-16664, 2004.

58) Osakada F, Ooto S, Akagi T, Mandai M, Akaike A, Takahashi M: Wnt signaling promotes regeneration in the retina of adult mammals. J Neurosci, 27: 2007.