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Review

The Potential Therapeutic Applications of Olfactory Ensheathing Cells in Regenerative Medicine

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Olfactory ensheathing cells (OECs) are unique glia cells restricted to the primary olfactory system including the olfactory mucosa, olfactory nerve, and the outer nerve layer of the olfactory bulb. OECs guide growing olfactory axons from the neurons of the nasal cavity olfactory mucosa to the olfactory bulb to connect both the peripheral nervous system (PNS) and central nervous system (CNS). Based on these specialized abilities of OECs, transplantation of OECs to injury sites has been widely investigated for their potential therapeutic applications in neural repair in different injuries. In this article, we reviewed the properties of OECs and their roles in olfactory regeneration and in treatment of different injuries including spinal cord injury, PNS injury, and stroke and neurodegenerative diseases.

Key words: Olfactory ensheathing cells (OECs); Neuronal injury; Regenerative medicine

INTRODUCTION

The life span of olfactory neurons in a normal healthy animal is around 1–3 months in general. Owing to the rapid turnover rate of neurons in the olfactory system (around 1–3% per day), neurogenesis continuously occurs in the basal layer of the olfactory epithelium to generate new sensory neurons to replace the apoptotic neuronal cells (25). The neuronal cells that died after injury induced by acute treatment with trimethyltin could also be replaced by enhanced neurogenesis in the olfactory bulb (58). The notable capacity of neurogenesis is contributed by a particular type of glial cells termed olfactory ensheathing cells (OECs) in the nose (11).

OECs are unique glia cells that are restricted to the primary olfactory system including the olfactory mucosa, olfactory nerve, and the outer nerve layer of the olfactory bulb (38). OECs guide growing olfactory axons from the neurons of the nasal cavity olfactory mucosa to the olfactory bulb to form synapses in the brain. They share properties with astrocytes and Schwann cells (16) and distribute in both the peripheral nervous system (PNS) and central nervous system (CNS), which distinguishes the properties of OECs from typical glia (40). Owing to their strong ability to guide axonal outgrowth, accumulating evidence has shown the potential of OECs in neuronal regenerative medicine. In this article, we review the investigations of OECs on neural regeneration in different kinds of injuries and neurodegenerative diseases.

THE PROPERTIES OF OECs

The morphologies of OECs are diverse, including bipolar, tripolar, and flat, in which the predominant type is of a Schwann cell-like shape that is S-100 protein and 217C (antibody for nerve growth factor receptor; a Schwann-cell marker) positive and A2B5 (antibody for ganglioside GT3) negative; the other type is of an astrocyte-like shape and is negative for the three previously mentioned three markers (S-100, 217C, and A2B5) (33). In general, OECs with an elongated morphology extend to ensheath the olfactory nerves, but those with a rounded shape might impair the processes (51). The heterogeneity of cultured OECs may result from many factors, including the age

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and source of the donor tissue, method of isolation, culture conditions, as well as the extracellular and intracellular molecules such as cyclic adenosine monophosphate (cAMP), dibutyryl cAMP (dBcAMP), endothelin-1, and fibulin-3 (49,52,53). Furthermore, the cultured OECs have been reported to spontaneously transform morphologically from one type to another (35).

The ability of OECs to migrate from the PNS to the CNS is critical for the development of the olfactory system and the enhancement of axonal extension after injury for neural regeneration. In the embryonic development of the olfactory system, L1/neuron–glia cell adhesion molecule (L1/Ng-CAM) and neural cell adhesion molecule (NCAM) in the plasma membranes of OECs enable the olfactory axons to use the glial cell surfaces as a substratum on which to grow, and the secreted laminin and nexin from OECs provide additional adhesive substrates for the olfactory axons as the neurite-promoting agents (9). During neural regeneration, OECs migrate into the injury site and enhance the axon growth due to the permissive OEC environment (5). Stimulation of OEC migration by glial cell line-derived neurotrophic factor (GDNF) leads to faster axonal extension (56).

THE ROLES OF OECs IN OLFACTORY REGENERATION

Olfactory regeneration occurs continuously during adulthood, which is quite different from what happens in the CNS. OECs play key roles in the regeneration of the olfactory nervous system. They release diffusible factors to attract neural progenitors into the rostral migratory stream and regulate their proliferation and differentiation (60). For instance, the diffusible factors activate the Notch signaling pathway, leading to increased proliferation and suppression of the differentiation of neural progenitor cells (59). Some of the OEC-released diffusible factors have been identified, including basic fibroblast growth factor (bFGF) (6), nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), GDNF (57), and insulin-like growth factor 1 (IGF-1) (28), suggesting the involvement of these factors in olfactory neurogenesis.

In addition, the cell adhesion molecules involved in glia–axon adhesion, such as NCAM, polysialylated (PSA)-NCAM, and N-cadherin, are expressed on the surface of OECs (12,22,29,30). OECs also express extracellular matrix proteins, such as laminin and fibronectin (10,14,21,55), and neurotrophic factors (4,23,24,27,57), metalloproteinase-2 (32) as well as wingless-type mouse mammary tumor virus (MMTV) integration site family, member 4 (Wnt-4) (42) to enhance axon outgrowth.

THERAPEUTIC APPLICATIONS OF OECs IN NEURAL REPAIR

Based on the abilities of OECs for continuous regeneration and their guidance of olfactory axonal growth between the PNS and CNS, increasing numbers of studies have attempted to transplant OECs into injury sites for the potential therapeutic applications in neural repair from different injuries and neurodegenerative diseases, as detailed below.

Spinal Cord Injury

A variety of cell types have been used in cellular transplantations for the treatment of spinal cord injuries (SCI) over the past two decades, including Schwann cells (SCs), OECs, neural stem/progenitor cells (NSPCs), fate-restricted neural and glial precursors (NRPs and GRPs), and bone marrow stromal cells (BMSCs). Among these cell types, the number of studies in OECs rank them as the second most commonly used cell type after SCs (48). However, OECs from the olfactory mucosa and olfactory bulb are not identical. They vary in antigen expressions (2), growing ability (19), and the outcome of transplantation into the injured spinal cord (41). In previous studies, OECs derived from the olfactory bulbs are most commonly used compared to those from the lamina propria of the olfactory mucosa (48). However, for clinical use, autologous transplantation is a more desirable strategy; thus nasal OECs from the olfactory mucosa are also an important issue. Transplantation of OECs from the olfactory mucosa to dorsal column lesions in rodents triggered migration of host SCs to the injury site, leading to a reduction in size of the scar and lesion cavity and promotion of the regeneration of sensory and motor axons (39). It has been demonstrated that transplantation of whole olfactory mucosa containing olfactory epithelium, lamina propria, and OECs improved functional recovery after spinal cord injury (18). The autologous transplantation of human OECs (hOECs) is desirable for further clinical applications. Gorrie and his colleagues transplanted hOECs into the contused spinal cord of rats to determine their efficiency in SCI recovery. The results showed that hOECs reduced the lesion size and cavity volume and improved locomotor function (15).

Peripheral Nervous System (PNS) Injury

PNS injuries are commonly caused by traumatic events in the workplace or through motor vehicle accidents. They may result in different statuses of peripheral nerve lesions, such as nerve crush and nerve disruption defects. Cell transplantations with different cell types, including SCs and OECs derived from the olfactory mucosa, olfactory bulb, or stromal cells from bone marrow- or adipose tissue-derived cells, have been applied to treat PNS injury (36,37). The migratory potential and capability to penetrate glial scars is higher for OECs than SCs, thus OECs have been used to also promote peripheral nerve regeneration in recent years (34). Transplantation of OECs improves the functional outcomes from PNS injury by promoting axon regeneration, myelination, and nodal formation (8,34).

In addition, several chemokines including neurotrophic factors, such as NGF, BDNF, ciliary neurotrophic factor, platelet-derived growth factor (PDGF) (26,43,54), and neuropeptide Y (50) are synthesized by OECs, suggesting that secretion of trophic factors by OECs may contribute to the promotion of regeneration of damaged axons.

Stroke

Stroke most commonly results from a disturbance in the blood supply and typically leads to the death of cells within the affected tissue, due to ischemia caused by blockage or hemorrhage (46). A variety of human-derived cell types have been tested in experimental stroke models, including neural stem cells, bone marrow stem cells, umbilical cord blood cells, peripheral blood stem cells, and adipose tissue stem cells (3). However, the effects of OECs in neuronal regeneration in stroke models are not understood. We have demonstrated that intracerebral transplantation of OECs/olfactory nerve fibroblasts (ONFs), which secrete trophic factors including stromal cell-derived factor-1α (SDF-1α), effectively leads to the recovery of the damaged cerebral tissue in murine models of stroke, thereby promoting the reversal of neurological deficit (45). Recently, transplantation of OECs has been shown to protect the white matter from ischemic injury, leading to improving neurological function in rats (44). These results reveal that transplantation of OECs is a potential strategy to recover from ischemic insults.

OECs IN NEURODEGENERATIVE DISEASES

Parkinson's Disease (PD)

PD is a common neurodegenerative disease caused by degeneration of dopaminergic cells in the substantia nigra, a region of the midbrain. Implantation of pure cultured OECs alone was not sufficient to promote tissue repair and functional recovery in a PD rodent model (7). Cotransplantation of OECs with fetal ventral mesencephalic cells in a 6-hydroxydopamine (6-OHDA)-lesioned rat model of PD enhanced the survival of dopamine (DA) neurons, and promoted striatal reinnervation and functional recovery (1,20). Furthermore, intracerebral transplantation of OECs/ONFs eliminated the inhibitory fibrotic scar, thereby facilitating the regeneration of the severed nigrostriatal dopaminergic axons (47).

Amyotrophic Lateral Sclerosis (ALS)

ALS is a lethal neurodegenerative disease caused by the death of motor neurons in the spinal cord. Transplantation of OECs into the frontal lobes of ALS patients appeared to be able to slow the rate of clinical progression in the first 4 months posttransplantation (17). However, the results from another clinical trial from two ALS patients did not support a beneficial effect of fetal OEC implantation into the frontal lobes of ALS patients (13).

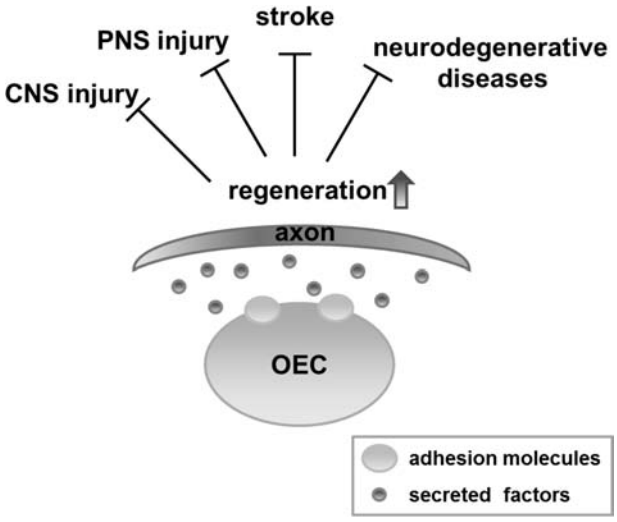

Figure 1. The roles of olfactory ensheathing cells (OECs) in neuronal regeneration and their potential therapeutic applications in regenerative medicine. OECs express adhesion molecules on their plasma membranes to help neural cells attach, and they also secrete a variety of trophic factors to facilitate neural regeneration and axon outgrowth. In this way, OECs have therapeutic potential in aiding recovery from neuron injury and degenerative diseases. CNS, central nervous system; PNS, peripheral nervous system.

In addition, OEC transplantation revealed no significant functional improvement in an ALS mice model (31). Taken together, the efficacy of transplantation of OECs into ALS patients is still controversial, and further experiments will be required to resolve it.

CONCLUSION

In summary, OECs express adhesion molecules, such as L1/Ng-CAM and N-CAM, on their plasma membranes, which help neural cells to attach. They also secrete extracellular matrix proteins, such as laminin and fibronectin, and neurotrophic factors, such as NGF, BDNF, and PDGF, to facilitate neural regeneration and axon outgrowth. Based on the properties of OECs, transplantation of OECs has therapeutic potential to recover from neuron injury including CNS injury, PNS injury, stroke, and neurodegenerative diseases, such as PD (Fig. 1).

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REFERENCES

1. Agrawal, A. K.; Shukla, S.; Chaturvedi, R. K.; Seth, K.; Srivastava, N.; Ahmad, A.; Seth, P. K. Olfactory ensheathing cell transplantation restores functional deficits in rat model of Parkinson's disease: A cotransplantation approach with fetal ventral mesencephalic cells. Neurobiol. Dis. 16(3):516–526; 2004.
2. Au, E.; Roskams, A. J. Olfactory ensheathing cells of the lamina propria in vivo and in vitro. Glia 41(3):224–236; 2003.
3. Bliss, T.; Guzman, R.; Daadi, M.; Steinberg, G. K. Cell transplantation therapy for stroke. Stroke 38(2 Suppl):817–826; 2007.
4. Carter, L. A.; Roskams, A. J. Neurotrophins and their receptors in the primary olfactory neuraxis. Microsc. Res. Tech. 58(3):189–196; 2002.
5. Chehrehasa, F.; Windus, L. C.; Ekberg, J. A.; Scott, S. E.; Amaya, D.; Mackay-Sim, A.; St John, J. A. Olfactory glia enhance neonatal axon regeneration. Mol. Cell. Neurosci. 45(3):277–288; 2010.
6. Chuah, M. I.; Teague, R. Basic fibroblast growth factor in the primary olfactory pathway: Mitogenic effect on ensheathing cells. Neuroscience 88(4):1043–1050; 1999.
7. Dewar, D.; Bentley, D.; Barnett, S. C. Implantation of pure cultured olfactory ensheathing cells in an animal model of parkinsonism. Acta Neurochir. 149(4):407–414; 2007.
8. Dombrowski, M. A.; Sasaki, M.; Lankford, K. L.; Kocsis, J. D.; Radtke, C. Myelination and nodal formation of regenerated peripheral nerve fibers following transplantation of acutely prepared olfactory ensheathing cells. Brain Res. 1125(1):1–8; 2006.
9. Doucette, R. Glial influences on axonal growth in the primary olfactory system. Glia 3(6):433–449; 1990.
10. Doucette, R. Immunohistochemical localization of laminin, fibronectin and collagen type IV in the nerve fiber layer of the olfactory bulb. Int. J. Dev. Neurosci. 14(7–8):945–959; 1996.
11. Ekberg, J. A.; Amaya, D.; Mackay-Sim, A.; St John, J. A. The migration of olfactory ensheathing cells during development and regeneration. Neurosignals 20(3):147–158; 2012.
12. Franceschini, I. A.; Barnett, S. C. Low-affinity NGF-receptor and E-N-CAM expression define two types of olfactory nerve ensheathing cells that share a common lineage. Dev. Biol. 173(1):327–343; 1996.
13. Giordana, M. T.; Grifoni, S.; Votta, B.; Magistrello, M.; Vercellino, M.; Pellerino, A.; Navone, R.; Valentini, C.; Calvo, A.; Chio, A. Neuropathology of olfactory ensheathing cell transplantation into the brain of two amyotrophic lateral sclerosis (ALS) patients. Brain Pathol. 20(4):730–737; 2010.
14. Gong, Q.; Shipley, M. T. Expression of extracellular matrix molecules and cell surface molecules in the olfactory nerve pathway during early development. J. Comp. Neurol. 366(1): 1–14; 1996.
15. Gorrie, C. A.; Hayward, I.; Cameron, N.; Kailainathan, G.; Nandapalan, N.; Sutharsan, R.; Wang, J.; Mackay-Sim, A.; Waite, P. M. Effects of human OEC-derived cell transplants in rodent spinal cord contusion injury. Brain Res. 1337:8–20; 2010.
16. Gudino-Cabrera, G.; Nieto-Sampedro, M. Schwann-like macroglia in adult rat brain. Glia 30(1):49–63; 2000.
17. Huang, H.; Chen, L.; Xi, H.; Wang, H.; Zhang, J.; Zhang, F.; Liu, Y. Fetal olfactory ensheathing cells transplantation in amyotrophic lateral sclerosis patients: A controlled pilot study. Clin. Transplant. 22(6):710–718; 2008.
18. Iwatsuki, K.; Yoshimine, T.; Kishima, H.; Aoki, M.; Yoshimura, K.; Ishihara, M.; Ohnishi, Y.; Lima, C. Transplantation of olfactory mucosa following spinal cord injury promotes recovery in rats. Neuroreport 19(13):1249–1252; 2008.
19. Jani, H. R.; Raisman, G. Ensheathing cell cultures from the olfactory bulb and mucosa. Glia 47(2):130–137; 2004.
20. Johansson, S.; Lee, I. H.; Olson, L.; Spenger, C. Olfactory ensheathing glial co-grafts improve functional recovery in rats with 6-OHDA lesions. Brain 128(Pt 12):2961–2976; 2005.
21. Kafitz, K. W.; Greer, C. A. Role of laminin in axonal extension from olfactory receptor cells. J. Neurobiol. 32(3):298–310; 1997.
22. Key, B.; Akeson, R. A. Olfactory neurons express a unique glycosylated form of the neural cell adhesion molecule (N-CAM). J. Cell Biol. 110(5):1729–1743; 1990.
23. Lipson, A. C.; Widenfalk, J.; Lindqvist, E.; Ebendal, T.; Olson, L. Neurotrophic properties of olfactory ensheathing glia. Exp. Neurol. 180(2):167–171; 2003.
24. Mackay-Sim, A.; Chuah, M. I. Neurotrophic factors in the primary olfactory pathway. Prog. Neurobiol. 62(5):527–559; 2000.
25. Mackay-Sim, A.; Kittel, P. Cell dynamics in the adult mouse olfactory epithelium: A quantitative autoradiographic study. J Neurosci. 11(4):979–984; 1991.
26. Marshall, C. T.; Lu, C.; Winstead, W.; Zhang, X.; Xiao, M.; Harding, G.; Klueber, K. M.; Roisen, F. J. The therapeutic potential of human olfactory-derived stem cells. Histol. Histopathol. 21(6):633–643; 2006.
27. Martin, L. V.; Weston, S.; West, A. K.; Chuah, M. I. Nerve growth factor promotes olfactory axonal elongation. Neuroreport 13(5):621–625; 2002.
28. McCurdy, R. D.; Feron, F.; McGrath, J. J.; Mackay-Sim, A. Regulation of adult olfactory neurogenesis by insulin-like growth factor-I. Eur. J Neurosci. Eur. J. Neurosci. 22(7):1581–1588; 2005.
29. Miragall, F.; Kadmon, G.; Husmann, M.; Schachner, M. Expression of cell adhesion molecules in the olfactory system of the adult mouse: Presence of the embryonic form of N-CAM. Dev. Biol. 129(2):516–531; 1988.
30. Miragall, F.; Kadmon, G.; Schachner, M. Expression of L1 and N-CAM cell adhesion molecules during development of the mouse olfactory system. Dev. Biol. 135(2):272–286; 1989.
31. Morita, E.; Watanabe, Y.; Ishimoto, M.; Nakano, T.; Kitayama, M.; Yasui, K.; Fukada, Y.; Doi, K.; Karunaratne, A.; Murrell, W. G.; Sutharsan, R.; Mackay-Sim, A.; Hata, Y.; Nakashima, K. A novel cell transplantation protocol and its application to an ALS mouse model. Exp. Neurol. 213(2):431–438; 2008.
32. Pastrana, E.; Moreno-Flores, M. T.; Gurzov, E. N.; Avila, J.; Wandosell, F.; Diaz-Nido, J. Genes associated with adult axon regeneration promoted by olfactory ensheathing cells: A new role for matrix metalloproteinase 2. J. Neurosci. 26(20):5347–5359; 2006.

33. Pixley, S. K. The olfactory nerve contains two populations of glia, identified both in vivo and in vitro. Glia 5(4):269–284; 1992.
34. Radtke, C.; Aizer, A. A.; Agulian, S. K.; Lankford, K. L.; Vogt, P. M.; Kocsis, J. D. Transplantation of olfactory ensheathing cells enhances peripheral nerve regeneration after microsurgical nerve repair. Brain Res. 1254:10–17; 2009.
35. Radtke, C.; Lankford, K. L.; Wewetzer, K.; Imaizumi, T.; Fodor, W. L.; Kocsis, J. D. Impaired spinal cord remyelination by long-term cultured adult porcine olfactory ensheathing cells correlates with altered in vitro phenotypic properties. Xenotransplantation 17(1):71–80; 2010.
36. Radtke, C.; Schmitz, B.; Spies, M.; Kocsis, J. D.; Vogt, P. M. Peripheral glial cell differentiation from neurospheres derived from adipose mesenchymal stem cells. Int. J. Dev. Neurosci. 27(8):817–823; 2009.
37. Radtke, C.; Vogt, P. M. Peripheral nerve regeneration: A current perspective. Eplasty 9:e47; 2009.
38. Raisman, G. Specialized neuroglial arrangement may explain the capacity of vomeronasal axons to reinnervate central neurons. Neuroscience 14(1):237–254; 1985.
39. Ramer, L. M.; Au, E.; Richter, M. W.; Liu, J.; Tetzlaff, W.; Roskams, A. J. Peripheral olfactory ensheathing cells reduce scar and cavity formation and promote regeneration after spinal cord injury. J. Comp. Neurol. 473(1):1–15; 2004.
40. Ramon-Cueto, A.; Avila, J. Olfactory ensheathing glia: Properties and function. Brain Res. Bull. 46(3):175–187; 1998.
41. Richter, M. W.; Fletcher, P. A.; Liu, J.; Tetzlaff, W.; Roskams, A. J. Lamina propria and olfactory bulb ensheathing cells exhibit differential integration and migration and promote differential axon sprouting in the lesioned spinal cord. J. Neurosci. 25(46):10700–10711; 2005.
42. Rodriguez-Gil, D. J.; Greer, C. A. Wnt/Frizzled family members mediate olfactory sensory neuron axon extension. J. Comp. Neurol. 511(3):301–317; 2008.
43. Sasaki, M.; Black, J. A.; Lankford, K. L.; Tokuno, H. A.; Waxman, S. G.; Kocsis, J. D. Molecular reconstruction of nodes of Ranvier after remyelination by transplanted olfactory ensheathing cells in the demyelinated spinal cord. J. Neurosci. 26(6):1803–1812; 2006.
44. Shi, X.; Kang, Y.; Hu, Q.; Chen, C.; Yang, L.; Wang, K.; Chen, L.; Huang, H.; Zhou, C. A long-term observation of olfactory ensheathing cells transplantation to repair white matter and functional recovery in a focal ischemia model in rat. Brain Res. 1317:257–267; 2010.
45. Shyu, W. C.; Liu, D. D.; Lin, S. Z.; Li, W. W.; Su, C. Y.; Chang, Y. C.; Wang, H. J.; Wang, H. W.; Tsai, C. H.; Li, H. Implantation of olfactory ensheathing cells promotes neuroplasticity in murine models of stroke. J. Clin. Invest. 118(7):2482–2495; 2008.
46. Sims, N. R.; Muyderman, H. Mitochondria, oxidative metabolism and cell death in stroke. Biochim. Biophys. Acta 1802(1):80–91; 2010.
47. Teng, X.; Nagata, I.; Li, H. P.; Kimura-Kuroda, J.; Sango, K.; Kawamura, K.; Raisman, G.; Kawano, H. Regeneration of nigrostriatal dopaminergic axons after transplantation of olfactory ensheathing cells and fibroblasts prevents fibrotic scar formation at the lesion site. J. Neurosci. Res. 86(14):3140–3150; 2008.
48. Tetzlaff, W.; Okon, E. B.; Karimi-Abdolrezaee, S.; Hill, C. E.; Sparling, J. S.; Plemel, J. R.; Plunet, W. T.; Tsai, E. C.; Baptiste, D.; Smithson, L. J.; Kawaja, M. D.; Fehlings, M. G.; Kwon, B. K. A systematic review of cellular transplantation therapies for spinal cord injury. J. Neurotrauma 28(8):1611–1682; 2011.
49. Tisay, K. T.; Key, B. The extracellular matrix modulates olfactory neurite outgrowth on ensheathing cells. J. Neurosci. 19(22):9890–9899; 1999.
50. Ubink, R.; Halasz, N.; Zhang, X.; Dagerlind, A.; Hokfelt, T. Neuropeptide tyrosine is expressed in ensheathing cells around the olfactory nerves in the rat olfactory bulb. Neuroscience 60(3):709–726; 1994.
51. Valverde, F.; Santacana, M.; Heredia, M. Formation of an olfactory glomerulus: Morphological aspects of development and organization. Neuroscience 49(2):255–275; 1992.
52. Vincent, A. J.; West, A. K.; Chuah, M. I. Morphological plasticity of olfactory ensheathing cells is regulated by cAMP and endothelin-1. Glia 41(4):393–403; 2003.
53. Vukovic, J.; Ruitenberg, M. J.; Roet, K.; Franssen, E.; Arulpragasam, A.; Sasaki, T.; Verhaagen, J.; Harvey, A. R.; Busfield, S. J.; Plant, G. W. The glycoprotein fibulin-3 regulates morphology and motility of olfactory ensheathing cells in vitro. Glia 57(4):424–443; 2009.
54. Wewetzer, K.; Grothe, C.; Claus, P. In vitro expression and regulation of ciliary neurotrophic factor and its alpha receptor subunit in neonatal rat olfactory ensheathing cells. Neurosci. Lett. 306(3):165–168; 2001.
55. Whitesides, 3rd., J. G.; LaMantia, A. S. Differential adhesion and the initial assembly of the mammalian olfactory nerve. J. Comp. Neurol. 373(2):240–254; 1996.
56. Windus, L. C.; Chehrehasa, F.; Lineburg, K. E.; Claxton, C.; Mackay-Sim, A.; Key, B.; St John, J. A. Stimulation of olfactory ensheathing cell motility enhances olfactory axon growth. Cell. Mol. Life. Sci. 68(19):3233–3247; 2011.
57. Woodhall, E.; West, A. K.; Chuah, M. I. Cultured olfactory ensheathing cells express nerve growth factor, brain-derived neurotrophic factor, glia cell line-derived neurotrophic factor and their receptors. Brain Res. Mol. Brain Res. 88(1–2):203–213; 2001.
58. Yoneyama, M.; Kawada, K.; Ogita, K. Enhanced neurogenesis in the olfactory bulb in adult mice after injury induced by acute treatment with trimethyltin. J. Neurosci. Res. 88(6):1242–1251; 2010.
59. Zhang, J.; Wang, B.; Xiao, Z.; Zhao, Y.; Chen, B.; Han, J.; Gao, Y.; Ding, W.; Zhang, H.; Dai, J. Olfactory ensheathing cells promote proliferation and inhibit neuronal differentiation of neural progenitor cells through activation of Notch signaling. Neuroscience 153(2):406–413; 2008.
60. Zhu, Y.; Cao, L.; Su, Z.; Mu, L.; Yuan, Y.; Gao, L.; Qiu, Y.; He, C. Olfactory ensheathing cells: Attractant of neural progenitor migration to olfactory bulb. Glia 58(6):716–729; 2010.