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Review

The therapeutic potential of human olfactory-derived stem cells

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Summary. Stem cells from fetal and adult central nervous system have been isolated and characterized, providing populations for potential replacement therapy for traumatic injury repair and neurodegenerative diseases. The regenerative capacity of the olfactory system has attracted scientific interest. Studies focusing on animal and human olfactory bulb ensheathing cells (OECs) have heightened the expectations that OECs can enhance axonal regeneration and repair demyelinating diseases. Harvest of OECs from the olfactory bulb requires highly invasive surgery, which is a major obstacle. In contrast, olfactory epithelium (OE) has a unique regenerative capacity and is readily accessible from its location in the nasal cavity, allowing for harvest without lasting damage to the donor. Adult OE contains progenitors responsible for the normal life-long continuous replacement of neurons and supporting cells. Culture techniques have been established for human OE that generate populations of mitotically active neural progenitors that form neurospheres (Roisen et al., 2001; Winstead et al., 2005). The potential application of this technology includes autologous transplantation where minimal donor material can be isolated, expanded ex vivo, and lineage restricted to a desired phenotype prior to/or after re-implantation. Furthermore, these strategies circumvent the ethical issues that arise with embryonic or fetal tissues. The long term goal is to develop procedures through which a victim of a spinal cord injury or neurodegenerative condition would serve as a source of progenitors for his/her own regenerative grafts, avoiding the need for immunosuppression and ethical controversy. In addition, these cells can provide populations for pharmacological and/or diagnostic evaluation.

Key words: Stem cells, Progenitors, Olfactory, Neurosensory epithelium, Human

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Introduction

As the worldwide population over age 65 doubles in the next 20 years, the prevalence and related healthcare costs of Alzheimer's and other neurodegenerative diseases is projected to increase at a staggering rate. Furthermore, the annual incidence of traumatic injury to the spinal cord as a result of automobile accidents, falls, violence, or sport-related injuries is estimated to be greater than 11,000 in the United States (Jackson et al., 2004). The discovery that neurogenesis, once thought to occur only during embryonic development, continues throughout adult life and the identification of stem cells in the adult CNS has opened exciting new therapeutic options. Cellular replacement therapy to functionally repair degenerative or damaged regions of the adult brain and spinal cord has become an area of intensive exploration (Deacon et al., 1998; Rao, 1999).

Populations of stem cells have been identified within both the fetal (Johe et al., 1996; Chalmers-Redman et al., 1997; Vescovi et al., 1999) and adult central nervous systems (CNS) (Gritti et al., 1996; Johe et al., 1996; McKay, 1997; Rao, 1999). Stem cells have been isolated from all levels of the spinal cord (Shihabuddin et al., 1997), the dentate gyrus (Gage et al., 1995), and the subependymal zone (Reynolds and Weiss, 1992; Gritti, 1999; Rao, 1999). Most stem cells are located in areas requiring highly invasive surgery for their harvest. The lack of a suitable donor site is a major limitation of cellular replacement therapies utilizing neural stem cells.

Recently, the olfactory system has attracted interest due to its unique regenerative capacity and its location, which in part, is extracranial. The olfactory system retains regions of active neurogenesis throughout life including the subventricular zone and the olfactory epithelium (OE). The subventricular zone has long been known to replace cells destine for the olfactory bulb (Corotto et al., 1993; Lois and Alvarez-Buylla, 1994). Olfactory receptor neurons (ORNs) and their sustentacular supporting cells within the OE are continually replaced by its endogenous population of stem cells located in the nasal mucosa (Barber and Lindsay, 1982) (Fig. 1). Axonal regeneration is primarily

restricted to the peripheral nervous system (PNS), with one major exception, the olfactory system (Fairless and Barnett, 2005). The ORN axons are able to enter into and extend within the CNS to the olfactory bulb (Graziadei and Graziadei, 1979; Farbman, 1990). Olfactory ensheathing cells (OECs) develop from precursors in the OE (Chuah and Au, 1993) and serve as guides for regenerating axons (Doucette, 1990; Ramon-Cueto and Avila, 1998).

Olfactory ensheathing cells

It has been well established that newly generated ORNs must cross the cribiform plate where they synapse on mitral cells in the glomeruli of the olfactory bulb (Dodd and Castellucci, 1991). Olfactory ensheathing cells (OECs) provide ensheathment for the ORN axons as they leave the nasal cavity and enter the anterior cranial fossa (Doucette, 1984; Raisman, 1985). The OECs have potential use in cellular replacement therapy, in demyelinating diseases and spinal cord injury due to their ability to both support CNS axonal regeneration and remyelination (Bunge et al., 1994; Franklin et al., 1996; Imaizumi et al., 1998).

The olfactory placode gives rise to the OE as well as the OECs rather than neural crest cells. Schwann cells, the glial cell in the PNS that is responsible for ensheathment arise from neural crest cells (Chuah and Au, 1991; Norgren et al., 1992; Doucette, 1993). Precursor cells within the OE give rise to new OECs (Chuah, 1991). During development, OECs migrate from the OE and extend processes to ensheath axons from the newly formed olfactory receptor neurons. In the olfactory epithelium, OECs surround axon bundles and extend through the transitional zone and accompany olfactory axons into the CNS to the olfactory bulb (Raisman, 1985, 2001; Doucette, 1993; Devon and Doucette, 1995).

The OECs are a type of glia which resides in both the PNS and CNS thus sharing properties with Schwann cells found in the PNS, and astrocytes found in the CNS (Doucette, 1990; Franklin and Barnett, 1997). There are many similarities and some differences between Schwann cells and OECs including surface markers, such as the low affinity neurotrophin receptor ($p75^{NTR}$), laminin and L1 (Miragall et al., 1989; Barnett et al., 1993; Gong et al., 1994; Wewetzer et al., 2002). Furthermore, in common with Schwann cells, OECs wrap around and ensheath bundles of axons without forming myelin sheaths (Franklin and Barnett, 2000). One difference between the two cells is the expression of glial fibrillary acidic protein (GFAP). OECs express a fibrous form of GFAP similar to astrocytes, while Schwann cells express it in either a diffuse or globular form (Franceschini and Barnett, 1996). At the olfactory bulb glia limitans, the PNS-CNS transition zone, OECs function in a manner similar to astrocytes at other cranial and spinal nerve transition zones (Raisman, 1985; Doucette, 1990). At the dorsal root ganglion, the point where incoming sensory axons join glia of the CNS, Schwann cell ensheathment stops and does not accompany the axons to their termination in the CNS. This is in contrast to OECs, which are able to penetrate the CNS from the PNS, demonstrating that they are a unique type of glial cell (Devon and Doucette, 1992, 1995; Ramon-Cueto and Nieto Sampedro, 1994; Navarro et al., 1999).

The OECs are capable of producing many molecules that support and promote axonal growth including E-NCAM and L1 as well as neurotrophins such as NGF (nerve growth factor), brain derived neurotrophic factor (BDNF) and glial cell-line neurotrophic factor (GDNF) (Ronnett et al., 1991; Franceschini and Barnett, 1996; Ramon-Cueto and Avilla, 1998; Wewetzer et al., 2002). Additionally, components of the extracellular matrix are secreted by OECs including laminin, fibronectin and type-IV collagen, which have been shown to promote axonal growth (Doucette, 1990; Mahanthappa et al., 1994).

Both fetal and neonatal mammalian olfactory bulbs and OE have been used as donor sites for OECs that have been transplanted into regions of the nervous systems of different species, including rodents and members of the canine family (Njenga and Rodriguez, 1996; Archer et al., 1997; Li et al., 1997, 1998; Imaizumi et al., 1998, 2000; Rao, 1999). Adult olfactory bulb derived OECs have been used for spinal cord repair in rat and non-human primates (Li et al., 1997; Lu and Ashwell, 2002; Plant et al., 2003; Radtke et al., 2004). These cells when engrafted into damaged spinal cord facilitated regeneration of axons in the region of the graft. Ramon-Cueto and Avila. (1998) and Li et al. (1998) have shown that OECs can help regenerating axons cross a gap in the spinal cord. Recently, Resnick et al. (2003) transplanted adult rat OECs into injured rodent spinal cords at the time of injury. Although the cells survived, no functional recovery was noted after six weeks. However, when Plant et al. (2003) delayed transplantation of OECs for one week following injury, the adult OECs promoted sparing and regeneration of supraspinal axons, resulting in partial functional recovery. Recent work has shown that OECs are not able to support regeneration of DRG neurons (Gomez et al., 2003) but can remyelinate non-human primate spinal cord (Radtke et al., 2004) as well as decrease lesion size and support functional recovery in rats (Ruitenberg et al., 2003; Verdu et al., 2003). However, in the studies of Lu et al. (2001), Lu and Ashwell (2002), Barnett et al. (2000) and others (Gomez et al. 2003; Verdu et al., 2003; Radtke et al., 2004), the repair of injured spinal cords following transplantation of an endogenous mixture of cells derived from either the olfactory bulb or olfactory nerves could not be entirely attributable to OECs.

In the olfactory system, OECs do not form myelin; they simply surround bundles of unmyelinated axons (Franklin and Barnett, 2000). Transplantation of tissue from the olfactory bulb containing OECs to replace lost myelin has also been evaluated (Doucette, 1995; Archer

et al., 1997; Barnett et al., 2000). Cell suspensions of neonatal rat olfactory bulb, containing OECs, have been shown to be capable of extensive remyelination and, more importantly, this myelination led to enhanced conduction by the demyelinated axons (Imaizumi et al., 1998). Kato et al. (2000) grafted suspensions of adult human olfactory bulb derived cells and Barnett et al. (2000) grafted purified adult human olfactory bulb-derived ensheathing cells into areas of persistent demyelination in rat spinal cord, which resulted in successful remyelination as demonstrated by the classic "signet ring" appearance characteristic of Schwann cells. Li et al. (1997, 1998) also observed myelination after engrafting of olfactory bulb cells into lesioned corticospinal tract. Collectively these studies suggest a promising therapeutic potential for olfactory derived OECs in demyelinating diseases or traumatic injuries. However, some authors have questioned whether transplantation of non-homogenous cell populations or migration of endogenous Schwann cells into the transplantation site influenced the results (Brook et al., 1998).

Possible sources of OECs are the olfactory lamina propria surrounding olfactory nerves or the nerve fiber layer of the olfactory bulb (Mendoza et al., 1982; Doucette, 1990). Therefore, most studies in the past have focused on OECs obtained from non-human mammals, such as rats. Obtaining sufficient quantities of OECs from olfactory bulbs to produce an effective repair of damaged spinal cords is difficult, and greatly restricts their use in humans. The use of human OECs, obtained from patients undergoing highly invasive surgery for tumor removal, for transplantation into injured spinal cord have been reported (Barnett et al., 2000; Kato et al., 2000; Pagano et al., 2000). However, obtaining olfactory bulb derived tissue from patients requires an anterior craniotomy and is generally felt to be an unfeasible option for routine harvest of tissue for replacement therapy.

Olfactory epithelial progenitors

During embryogenesis, the olfactory neuro-epithelium (OE) develops as a slight invagination of the olfactory placode (Chuah and Farber, 1995), a multipotent group of cells that will eventually give rise to all cell types that comprise the OE. The olfactory neuroepithelium has extraordinary regenerative property undergoing continuous life-long turnover. The adult OE (Fig. 1A) consists of several cell types: proliferative basal cells, non-neuronal sustentacular supportive cells, and both immature and mature olfactory receptor neurons (Uraih and Maronpot, 1990; Morrison and Constanzo, 1992). Apical dendrites of the ORNs terminate as the olfactory vesicle which projects from the mucosal surface and have 6-12 modified non-motile sensory cilia that arise from basal bodies (Fig 1B). The ORNs send axons distally which transmits the signal for odorant detection to the olfactory bulb (Lewis and Dahl, 1995). Depending on the species, ORNs have a normal

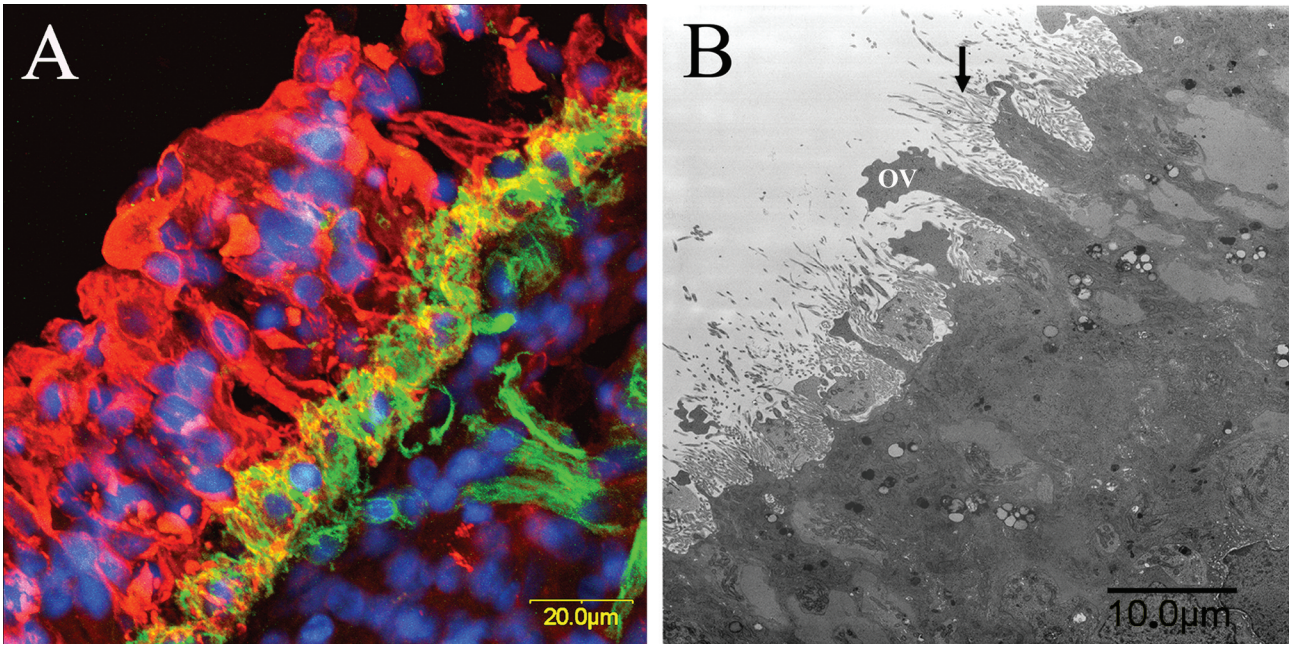

Fig. 1. Olfactory Epithelium. **A.** Cryosection of an olfactory epithelial biopsy immunostained for p75NGFR (green), a neurotrophin receptor associated with olfactory ensheathing cells in situ, and ß-tubulin III, nerve specific tubulin (red). **B.** Ultrastructure study of OE reveals olfactory vesicles (OV) with radiating non-motile kinocilia (arrow).

life span of between four and eight weeks (Moulton, 1974; Mackay-Sim and Kittel, 1991a; Carr and Farbman, 1993; Deckner et al., 1993). The nuclei of the sustentacular cells in the olfactory epithelium form the apical layer of the OE plus secrete detoxifying enzymes (Morrison and Moran, 1995). Newly formed receptor neurons and sustentacular cells are generated by a layer of actively dividing basal stem cells located adjacent to the basement membrane of the OE (Caggiano et al., 1994; Carter et al., 2004). These progenitors are thought to undergo slow, asymmetrical cell divisions, resulting in maintenance of the stem and progenitor populations as

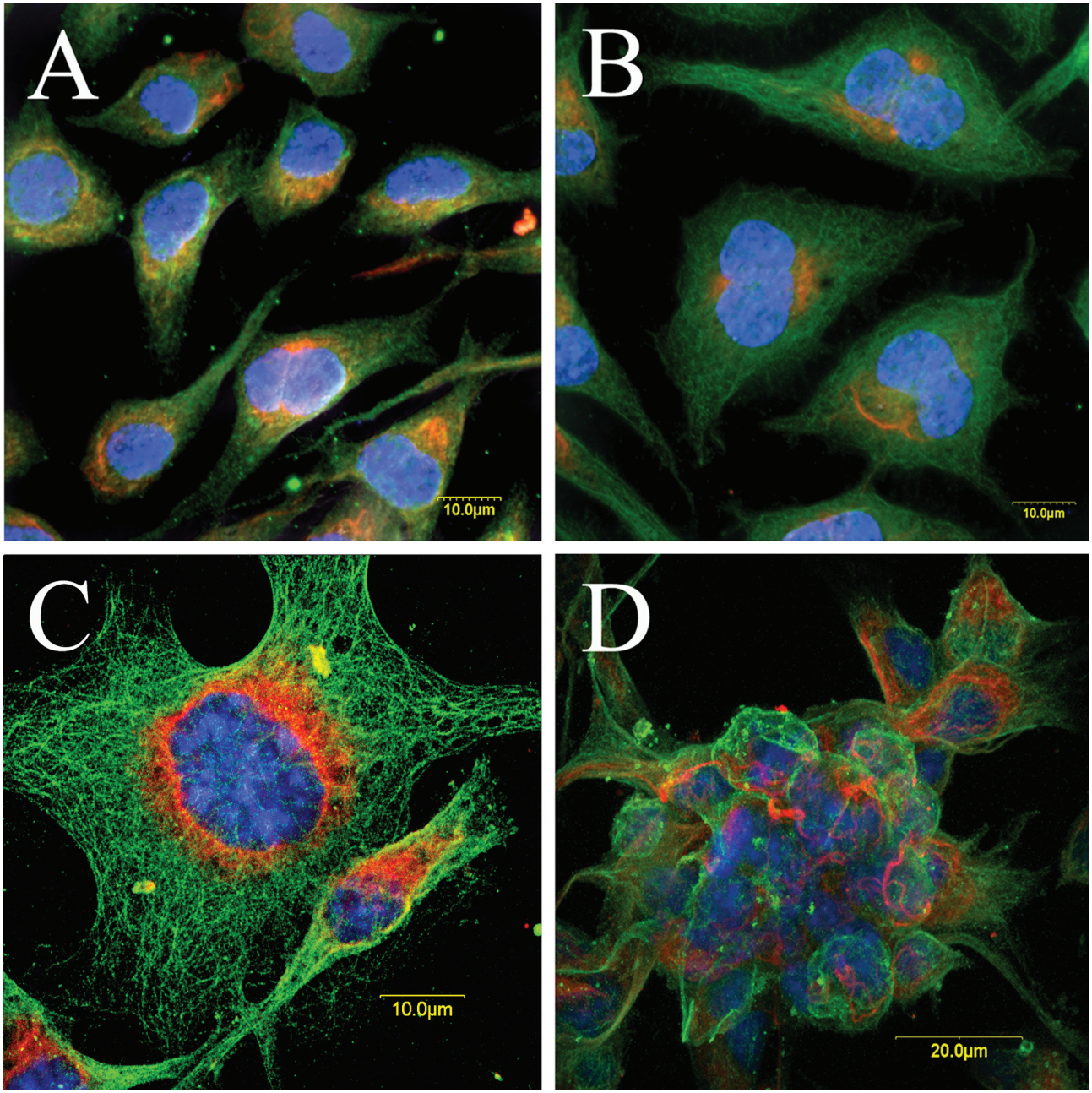

Fig. 2. Subcultured Human OE NSFCs. **A.** NSFCs were immunopositive for nestin (an intermediate filament found in neural progenitors, green) and peripherin (a neural crest intermediate filament, red), which was consistent with their progenitor nature. **B.** The neuronal lineage restriction of NSFCs was probed with ß-tubulin III (nerve specific tubulin, green) and peripherin (red). **C.** ß-tubulin III (green) positive networks were frequently observed throughout individual cells and their processes (red=peripherin). **D.** Subcultures NSFCs form neurospheres within 24 hours of plating at high density, immunopositive for ß-tubulin III (green) and peripherin (red). Nuclear DNA was stained with DAPI (blue).

well as the generation of new receptor neurons and supporting cells (Mackay-Sim and Kittel, 1991b; Beites et al., 2005).

Lu et al. (2002) reported that when pieces of either intact rat olfactory lamina propria or respiratory lamina propria were placed into injured rat spinal cords, only the olfactory tissues promoted axonal outgrowth and functional recovery. The olfactory epithelium in humans is located high in the nasal vault, and is visually indistinguishable from respiratory epithelium. Cultures of OE prepared from fresh postmortem tissue or endoscopic biopsy from patients undergoing sinus surgery have been subcultured to generate neurosphere forming cell lines (NSFC lines), that contain heterogeneous progenitor populations (Roisen et al., 2001; Winstead et al. 2005). These progenitors were immunopositive for nestin, an intermediate filament found in neural progenitors (Fig. 2A). Furthermore these cells frequently contained neuronal specific tubulin networks (ß-tubulin type III) throughout their perikaryal cytoplasm and processes. The neural crest intermediate filament protein, peripherin, was also found in two-thirds of these cells in a perinuclear location (Fig. 2B,C). When plated at high densities, subcultures form neurospheres (Fig. 2D).

Progenitors can be generated from OE biopsy irrespective of age or sex of donor, and remain equivalent despite such variables (Marshall et al., 2005). The neurosphere forming cells (NSFCs) have a remarkable level of resiliency. A comparison of NSFCs over several variables (age and sex of donor, time in culture, donor source) demonstrated that the cells were equivalent in metabolic activity as measured by ornithine decarboxylase activity and cell viability as indicated by the MTT assay (Marshall et al., 2005). Most somatic cells can only undergo a finite number of cell divisions, usually 50 cell cycles, before dying. This is known as the "Hayflick limit" (Hayflick and Moorhead, 1961). Limited cell division is thought to be due to loss of the telomere, the terminal end of the chromosome, during successive divisions (Harley et al., 1990; Thomas-Wynord, 1996). In malignant cells or normal progenitor cells, a ribonucleoprotein, telomerase, essentially replaces the loss chromosome segment, thereby stabilizing the chromosome (Kim et al., 1994) thus telomerase activity can be used as an index of mitotic potential (Yang et al., 2001). Olfactory derived NSFCs have been cultured over 200 passages, representing over 700 population doublings (Marshall et al., 2005). Telomerase levels remained consistent in the NSFCs despite a time in culture range of over two years and a six decade range in patient age. (Fig. 3) These results are consistent with the *in vivo* biology of olfactory stem cells, which are responsible for regeneration of the OE cell population throughout life. The NSFCs remain mitotically in vitro active despite donor age changes or extensive time in culture. Therefore, if ex vivo amplification and/or modification of NSFCs is required to obtain the necessary cell numbers for autologous transplantation, the regenerative potential of the cells should be constant irrespective of donor age or time in culture.

Progenitors placed in different parts of the CNS respond to site directed factors as well as exogenous growth factors and cytokines (Calof et al., 1998; Ensoli et al., 1998; Mackay-Sim and Chuah, 2000; Simpson et al., 2002) that enhance proliferation and lineage restriction. However, NSFCs isolated from the OE are highly mitotic and do not require exogenous mitogenic support or feeder layers as required by many stem cells from most other sources especially embryonic stem cells (Zhang et al., 2004).

To determine if factors responsible for oligodendrocyte development in lower vertebrates will regulate adult human derived progenitors, two key transcription factors known to regulate vertebrate oligodendrocyte development were cotransfected into the NSFCs. *Olig2* and *Nkx2.2* were selected because their expression is required and sufficient for oligodendrocyte differentiation in avian and murine CNS (Takebayashi et al., 2002; Zhou and Anderson, 2002). Single gene or control vector transfection did not produce any morphologic changes as noted for *Olig2* or *Nkx2.2* alone (Zhang et al., 2005a). In contrast, NSFCs

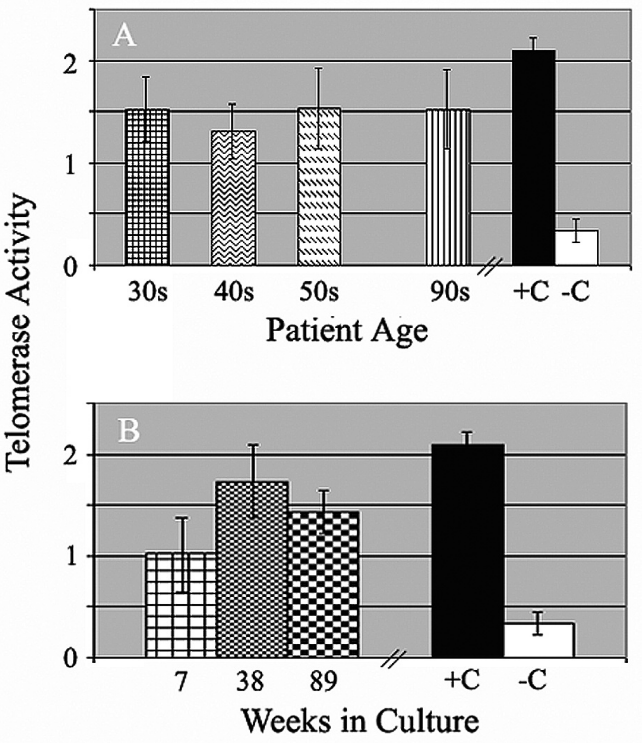

Fig. 3. Telomerase activity in human adult olfactory progenitor cells. **A.** Telomerase activity remained high across a six decade patient age range. **B.** High telomerase levels were exhibited by the OE progenitors despite a time in culture range of greater than 80 weeks in vitro. Cells were passaged over than 200 times.

cotransfected with both Olig2 and Nkx2.2 exhibited characteristic oligodendrocyte morphology plus the cells expressed both *Olig2* and *Nkx2.2* proteins when evaluated by immunohistochemistry (Fig. 4A). Thus, by introducing *Olig2* and *Nkx2.2* transcription factors together into the NSFCs, they were capable of further differentiation into an oligodendrocyte phenotype.

Additional recent studies examined the potential of NSFCs to respond to stimuli known to direct differentiation of motor neurons (Zhang et al., 2005b). Retinoic acid (RA) plays a role in synaptic plasticity (Chiang et al., 1998; Misner et al., 2001), neurogenesis (Sockanathan and Jessell, 1998; Maden, 2002) and neurite elongation (Corcoran and Maden, 1999). Forskolin (FN) stimulates axonal elongation by increasing intracellular cAMP (Roisen et al., 1972a,b), and sonic hedgehog (Shh) regulates specification of motor neurons and dopaminergic neurons in the embryonic CNS (Roelink et al., 1994; Perrier et al., 2004). Together, RA and Shh have been shown to influence expression of transcription factors, such as *Olig2* and *Ngn2*, which are partially responsible for neuronal fates, particularly in mouse embryonic stem cells and in the ventral spinal cord (Wichterle et al., 2002; Diez et al., 2003; Novitch et al., 2001, 2003; Sockanathan et al., 2003). After treatment with RA, FN, and Shh (RFS), NSFCs expressed mature neuronal markers, such as NeuN (Fig. 4B), synapsin I, and also expressed motor neuron markers such as HB9 and Isl1/2 (Zhang et al. 2005b). Furthermore, NSFCs treated with RFS then transfected with either Ngn2-HB9 or Olig2-Hb9, gained properties of mature neurons and lost their progenitor characteristics, as indicated by nestin expression (Zhang et al., 2005b). When cocultured with chicken skeletal muscle, transfected NSFCs formed presumptive synapses with the myofibers (Zhang et al., 2005b). These findings suggest that NSFCs can be stimulated to differentiate into mature neurons and may have therapeutic potential in neurodegenerative processes such as Parkinson's disease.

Exogenous brain derived neurotrophic factor (BDNF) (Kwon et al., 2002), the infusion of BDNF (Houle and Ye, 1999; Namiki et al., 2000), or the engraftment of BDNF engineered fibroblasts/OECs (Liu et al., 2002; Ruitenberg et al., 2003) prevents atrophy of Red Nucleus (RN) neurons or enhances regenerative axonal growth by rubrospinal axons in the rubrospinal tract (RST). The NSFCs have the ability to produce BDNF and also may respond to it in an autocrine or paracrine manner (Xiao et al., 2005). Therefore, the RN and the RST in the adult rat provide an ideal model for evaluating the viability and metabolic activity of NSFCs following their engraftment. The NSFCs were engrafted into the lesion site of a partial hemisection of the spinal cord at C3. The NSFCs survived, migrated and integrated into the injured adult rat spinal cord and were able to rescue axotomized rubrospinal tract neurons from retrograde atrophy (Xiao et al., 2005). Furthermore,

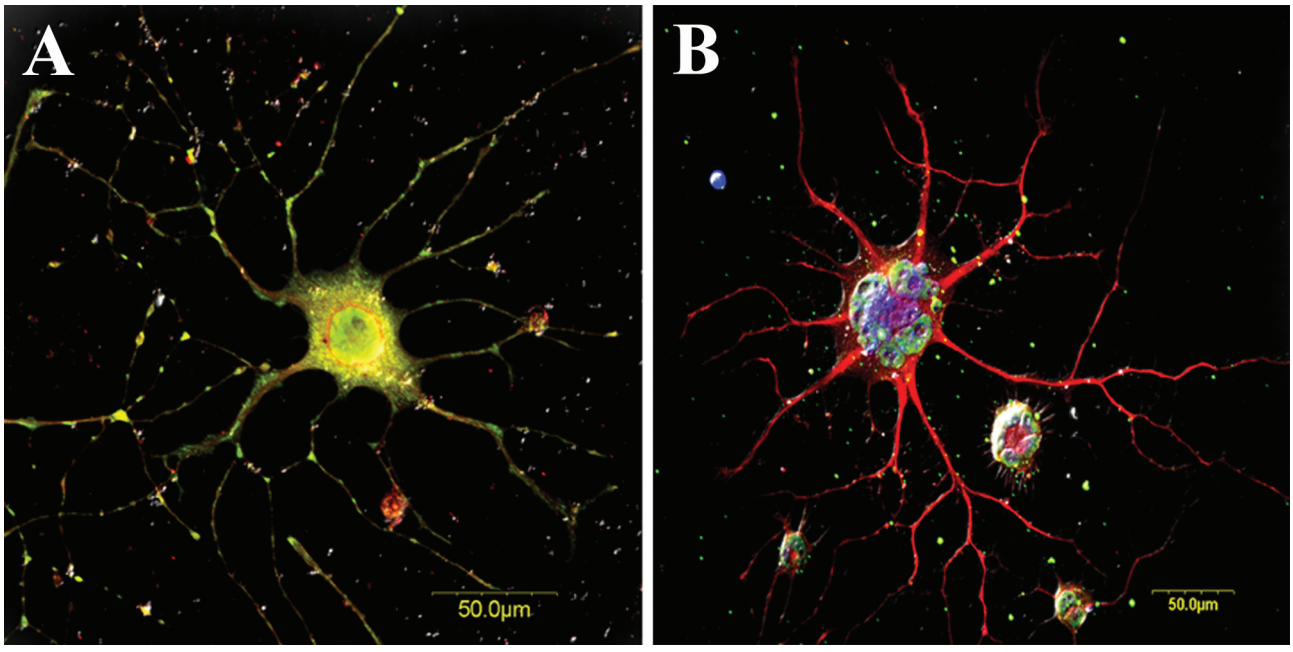

Fig. 4. A. Following transfection with the transcription factors *Olig2* and *Nkx2.2*, cells exhibited an oligodendrocyte phenotype. Cells were immunopositive for two independent oligodendrocyte-specific antigens, CNP (green) and GalC (red). **B.** Following treatment with factors known to contribute to the differentiation of progenitor cells to a neuronal lineage, NSFCs express mature nuclear neuronal markers, such as NeuN (green), and cytoplasmic filament peripherin (red). Confocal images enhanced with DIC.

behavioral deficits due to the lesion were restored. The enhanced RST axonal regeneration led to a functional recovery either directly or by modification of the microenvironment within and surrounding the lesion site (Xiao et al., 2005).

Importantly, unlike OECs, OE can provide a source of progenitors for autologous transplantation, eliminating the need for immunosuppression thus reducing the problems of graft host rejection. While olfactory bulb derived OECs have been shown to have a remarkable regenerative potential, the olfactory bulb is not a practical site for tissue harvest in therapeutic autologous transplantation strategies. In contrast, the NSFCs derived from primary cultures of olfactory epithelium may provide a good alternative source of autologous progenitors for replacement strategies in neurodegenerative processes and spinal cord injury. Endoscopic biopsy of the OE does not adversely impact olfactory function (Lanza et al., 1994; Winstead et al., 2005), in distinction to the obligatory total loss of olfaction associated with harvest of OECs from the olfactory bulb.

Potential diagnostic uses for OE-derived NSFCs

Deficiencies in the olfactory system have been linked with numerous CNS disorders. Patients suffering from Alzheimer's disease (AD) have demonstrated pathology of the olfactory bulb (Tsuboi et al., 2003; Jellinger and Attems, 2005), and neuronal populations that receive olfactory connections are some of the earliest brain regions to develop pathological legions associated with Alzheimer's (Pearson et al., 1985; Reyes et al., 1987). Neural precursor cells from the olfactory bulb are reduced in patients with Parkinson's disease (Hoglinger et al., 2004). Hyposomnia has been demonstrated as an early diagnostic marker for Parkinson's disease, occurring before Parkinsonian symptoms (Katzenschlager and Lees, 2004). Patients suffering from schizophrenia exhibit deficits in identification, threshold sensitivity, detection, memory and discrimination of odors (Moberg et al., 1999; Good et al., 2002; Kovacs, 2004). Patients diagnosed with bipolar disorder display altered intracellular calcium levels in olfactory receptor neurons (Bauer et al., 2003; Hahn et al., 2005). Therefore, the OE-derived NSFCs may also be able to serve as resource for the diagnosis for certain neurological disorders. Odor identification, discrimination, and threshold are all impaired in patients with Alzheimer's disease (Serby et al., 1991). A decrease in odor identification mirrors changes in the Mini Mental State score in patients with AD, and the loss of olfactory function may precede memory loss (Serby et al., 1991). Graves et al. (1999) confirmed this by following elderly people free from dementia for 2 years. They found that those with hyposmia at the initial screening have an odds ratio of 1.25 for the development of dementia, while those with asomnia had 1.92. These studies suggest that populations of OE-derived NSFCs may have additional potential as an early screening tool for patients suspected of developing a number of disorders.

Conclusions

Although the use of olfactory bulb-derived OECs and NSFCs obtained from the olfactory epithelium for the treatment of neurodegenerative processes and spinal cord injury are still in their infancy, they offer an exciting and viable prospect. OECs have demonstrated much promise; however their utilization is limited by their inaccessible location. In contrast, the olfactory epithelial derived progenitors (NSFCs) arise from the same embryological structures as the olfactory bulb OECs and appear to share many of the beneficial characteristics of OECs. NSFCs have the extreme advantage of being readily accessible without highly invasive techniques, thereby providing a source of autologous tissue. Due to the progenitor nature of these OE NSFCs, they can be modulated towards either oligodendrocytes or neurons. NSFCs have also been shown to survive, incorporate, and promote regeneration following engraftment into a spinal cord injury model. Their use in other models of neurotrauma and neurodegenerative disease awaits further study. Furthermore, the culture of neuronally restricted NSFCs could lead to an early screening tool for many neurological diseases. Therefore, in addition to the obvious benefits of providing an autologous progenitor population for transplantation, there is the added potential of establishing viable neuronal and ensheathment cell populations for pharmaceutical, toxicological, and genetic diagnostic evaluation.

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