Olfactory Ensheathing Cells for Spinal Cord Injury: Sniffing Out the Issues

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Abstract

Olfactory ensheathing cells (OECs) are glia reported to sustain the continuous axon extension and successful topographic targeting of the olfactory receptor neurons responsible for the sense of smell (olfaction). Due to this distinctive property, OECs have been trialed in human cell transplant therapies to assist in the repair of central nervous system injuries, particularly those of the spinal cord. Though many studies have reported neurological improvement, the therapy remains inconsistent and requires further improvement. Much of this variability stems from differing olfactory cell populations prior to transplantation into the injury site. While some studies have used purified cells, others have used unpurified transplants. Although both preparations have merits and faults, the latter increases the variability between transplants received by recipients. Without a robust purification procedure in OEC transplantation therapies, the full potential of OECs for spinal cord injury may not be realised.

Keywords

OECs, spinal cord injury, therapy, regeneration, cellular therapies, transplantation

The Olfactory System and their Ensheathing Cells

Active lifelong neurogenesis is a remarkable feature of the mammalian olfactory system. Primary olfactory neurons are continually replenished by neural stem cells lining the basal layer of the olfactory epithelium[1–5]. This neural regeneration, particularly the guidance of axons from their origin in the peripheral nervous system to their targets in the central nervous system (CNS), has been accredited, at least in part, to a unique type of glia called olfactory ensheathing cells (OECs)[3,6,7]. These cells are present in the lamina propria (Figure 1) of the olfactory mucosa (OM)[8–11], as well as the outer layers of the olfactory bulbs, the inner and outer nerve fibre layers[3,9,12,13]. OECs ensheathe multiple non-myelinated primary olfactory axons, in bundles known as fascicles, as they exit the peripherally-located olfactory epithelium (Figure 1).

Regenerative Characteristics of OECs

OECs support neural regeneration by promoting cell–cell interaction with, and migrating ahead of, olfactory sensory axons as they extend towards the olfactory bulb[14,15]. They have been found to create an environment that is favourable for axon growth and restoration by phagocytosing cellular debris and/or bacteria[16–19], modulating neuroinflammation[20,21], providing neuroprotection[22–24], promoting angiogenesis[25,26], expressing neurotrophic factors[27–32], as well as secreting extracellular matrix (ECM) molecules, which provide a substrate for newly generated axons[28,33–35].

Spinal Cord Injury

In contrast to the olfactory system, the spinal cord is limited in its regenerative capacity. Spinal cord injuries not only result in a loss of sensation and movement control, but also frequently in loss of bladder, bowel, and sexual function, as well as thermal regulation and blood pressure control. In

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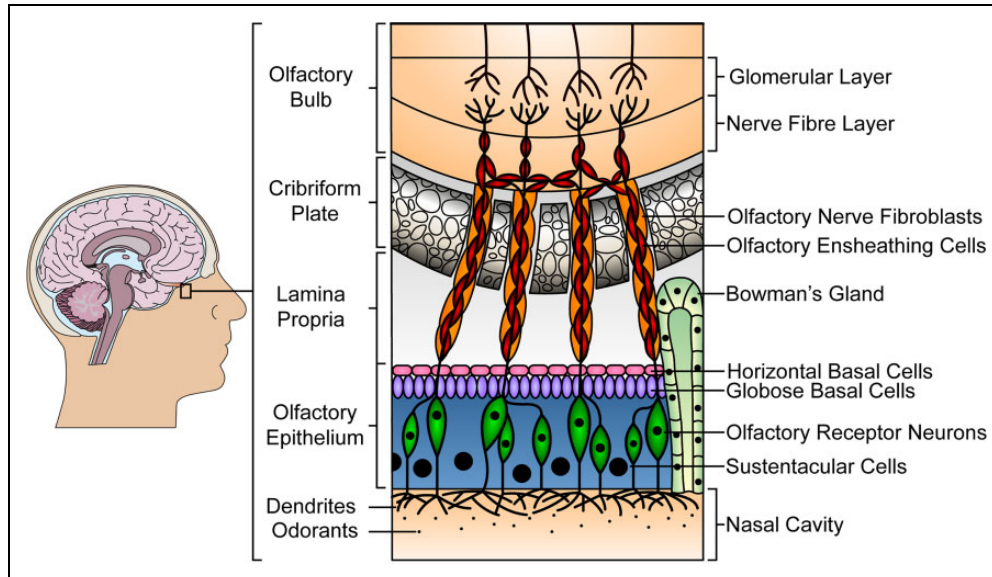Email: j.stjohn@griffith.edu.au

Figure 1. Olfactory Anatomy. With the dendrites of olfactory receptor neurons (green) exposed in the nasal cavity for odorant detection, the somas of neurons are entrenched in the olfactory epithelium of the olfactory mucosa alongside sustentacular cells (blue). As the axons of neurons penetrate through the basal layer where globose (purple) and horizontal basal cells (pink) are found, they are fasciculated by olfactory ensheathing cells (OECs; red) from the lamina propria to the olfactory bulb. Surrounding the OECs are the olfactory nerve fibroblasts (orange), which are thought to assist OECs in their neurosupportive endeavours.
OEC: olfactory ensheathing cell

high-level injuries (e.g. cervical 3–5), breathing may not be possible without an external aid. Injuries of this nature confine its victims to wheelchairs with the need for carers to assist them. However, with advances in research and OEC transplantation emerging strongly as a potential treatment, a cure for spinal cord injury is possible.

OECs in Spinal Cord Repair

Over the years, OEC transplantation has advanced to the forefront of therapeutic innovation for spinal cord repair[36,37]. Although they may be appropriate for the treatment of spinal cord injury, transplantation studies have reported variable findings. While many studies have reported improved neuroanatomical and functional outcomes[22,38,39], their findings have also identified limitations in the cell survivability and functionality of transplanted OECs within damaged nervous tissue[40–42]. While some have likened OECs to meningeal fibroblasts and bone marrow stromal cells in their capacity for neural repair[43], others have observed OECs to exhibit similar myelinating abilities to Schwann cells[44]. Conversely, a few authors have also stated that OECs from adult rats do not form myelin nor exhibit a Schwann cell-like relationship with axons[45]. These variable outcomes may be due to a number of reasons, one of which pertains to cellular purity, the proportion of OECs within a cell culture preparation prior to transplantation.

Cell Types in OM and Bulb Biopsies

When biopsies are derived from the OM or olfactory bulb, other cell types residing in the anatomical niche of OECs appear in subsequent cultures. In order to separate these heterogeneous cells from OECs, an in vitro method for OEC identification is required. However, this can only be accomplished with a clear understanding of the OM and the olfactory bulb, and their respective cellular constituents.

In the OM, various cell types can be found in its two layers; the olfactory epithelium and lamina propria. The olfactory epithelium includes olfactory receptor neurons, globose and horizontal basal cells (neural stem cells), sustentacular cells (non-neuronal supporting cells), and Bowman's gland and duct cells. The lamina propria includes olfactory nerve fibroblasts, mesenchymal stem cells[46–48], OECs, and Schwann cells of the trigeminal nerve[49–52]. Resident macrophages may also be present within both the olfactory epithelium and lamina propria.

In contrast, cultures derived from the olfactory bulb typically contain fewer cell types. Although OECs are most dominant, meningeal fibroblasts and astrocytes are also present[53], along with branches of the trigeminal nerve with its Schwann cells passing adjacent to the nerve fibre layer[54] (Figure 2).

OECs from the OM Versus Olfactory Bulb

The differences in cellular populations have given proponents of olfactory bulb biopsies reason to support their
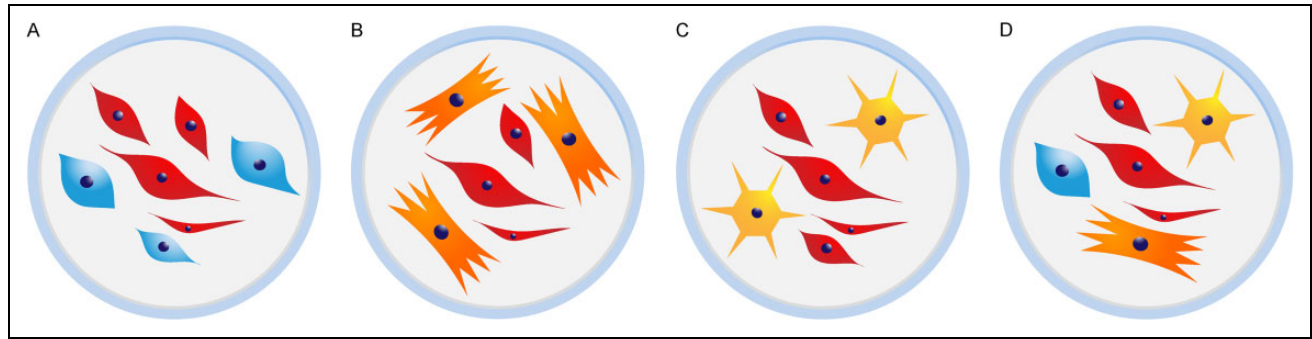
Figure 2. Olfactory Ensheathing Cell Culture Variability. Possible variations in OEC culture compositions. (A) OEC (red) cultures from the olfactory mucosa or olfactory bulb with Schwann cell (blue) contamination of various proportions. (B) OEC cultures from the olfactory mucosa or olfactory bulb with fibroblast (olfactory nerve fibroblast or meningeal fibroblast; orange) contamination of various proportions. (C) OEC cultures from the olfactory bulb with astrocyte (yellow) contamination of various proportions. (D) OEC cultures from the olfactory bulb with a mix of fibroblasts (orange), Schwann cells (blue), and astrocytes (yellow) of various respective proportions. OEC: olfactory ensheathing cell

preference, since the alternative can strain the OEC purification process. However, harvesting biopsies from the bulb requires major intracranial surgery and presents a risk of partial to total anosmia post-operation. Even a small reduction in odorant sensitivity results in a substantial loss of function[55]. As such, most researchers find this approach unacceptable[33,56], and prefer the less invasive procedure of intranasal endoscopy, which is used routinely to obtain mucosal biopsies[57–62].

Not only is the use of OM-OECs advantageous from a surgical and patient olfactory health perspective, there is evidence that these cells may be more beneficial for cellular therapeutic application than their olfactory bulb counterpart. OM-OECs have demonstrated longer proliferation duration in vitro[63,64], higher secretion levels of neurotrophic factors (e.g. brain-derived neurotrophic factor, nerve growth factor (NGF), and neurotrophin-3 (NT-3)) in vivo[65], as well as increased capacity for migration, cavity prevention, and axonal growth in spinal cord injury rat models[25]. Moreover, cadaveric OM was shown to be a more reliable source of human OECs than the olfactory bulb, with the efficacy of culturing OM-OECs being similar to that of living patients, even when procured 180 minutes following cardiac arrest[66]. Unfortunately, despite these positive characteristics, OECs remain difficult to identify in mixed culture populations due to the potential presence of other cell types, particularly when derived from the mucosa[67].

Purity of OEC Preparations

To date, a number of methods have been developed to identify and purify heterogeneous cultures to obtain highly purified OEC cultures. Such methods include, but are not limited to: immunopanning, fluorescence-activated cell sorting (FACS), differential adhesion, differential trypsinization, and selective media[68]. However, these processes often rely on immunocytochemistry to identify OECs after

purification of any given olfactory cell culture or transplant preparation, a technique where specific cell populations are identified by unique markers expressed at distinct levels and/or patterns. Thus, for this method to be successful, at least one, if not more, markers unique to OECs are necessary to assess their degree of purity in any olfactory cell culture.

At present, three markers are considered to be the benchmark for OEC identification in vitro: glial fibrillary acidic protein (GFAP), S100β, and p75 neurotrophin receptor (p75NTR)[69–71]. Among them, p75NTR is the most widely used, whether it be for mouse[26,64], rat[72,73], canine[74,75], porcine[76], primates[77], or human OECs[78,79]. Unfortunately, several problems exist with such a reliance on this neurotrophin receptor, the most concerning of which is that olfactory fibroblasts[58,69], astrocytes[80–82], lamina propria mesenchymal stem cells[46,48], and Schwann cells have all been reported to express p75NTR in situ and/or in vitro under certain conditions[60,83–86]. Aside from the fact that p75NTR is not expressed by OECs of the inner nerve fibre layer of the mouse or rat olfactory bulb in situ[8,85], a number of research groups have found that the majority of freshly dissociated OECs do not appear to express p75NTR, whether it be from the olfactory bulb or OM[87,88]. Wewetzer et al. (2005) estimated that only 10% of neonatal rat OECs express this neurotrophin receptor, and that p75NTR-negative cells do not appear to upregulate it until after several days in culture. García et al. corroborated this finding in 2012, reporting that a very low number of p75NTR-positive cells were present in cultures derived from both the human olfactory bulb and OM[69]. However, OEC-reminiscent axon regenerative properties still remained, leading them to conclude that the degree of p75NTR expression does not necessarily correlate with OEC performance. Several other research groups have also reported similar observations where the extent of recovery did not appear to depend on the total proportion of p75NTR-positive cells in the transplant population[56,74].

Although the expression of p75NTR in OECs appears rather inconsistent, other cell types, particularly Schwann cells, seem to have little to no problem. In fact, some purification protocols have gone so far as to implement p75NTR specifically for Schwann cell selection[89]. Therefore, markers that are commonly used to identify OECs may not be as specific as once thought, since the two remaining OEC phenotypic markers, GFAP and S100β, also appear to immunolabel Schwann cells[90–92]. Therefore, there appears to be a paucity of defined markers that can unequivocally and consistently distinguish OECs from other cells in vitro.

Of course, there are always two sides to an argument. In the case of Lakatos et al. (2000)[93], purified olfactory cells maintained the ability to intermingle with astrocytes using purification protocols involving either the O4 antibody, p75NTR antisera by FACS, or magnetic nanoparticles conjugated to anti-p75NTR. This result may seem to support the argument that current OEC identification and purification techniques are indeed sufficient. However, from a clinical perspective, a sufficient method may not necessarily be an effective method. If a more effective and reliable identification and purification method of OECs could be developed, cells of high purity can be consistently produced to increase patient safety and perhaps reproducibility of clinical outcomes.

Will OECs alone suffice?

There are many questions that cannot be answered until an effective OEC identification and purification method is developed. One question of paramount importance is whether or not OECs are the optimal cellular composition for transplantation. If not, then can the addition of other cell types be used to enhance their biological performance? With a number of different cell types existing alongside OECs in situ, it is possible that the repair capacity of OECs may be influenced by the presence of other cells. Geoffrey Raisman and colleagues[94], as well as others[95] have argued that olfactory nerve fibroblasts should not be perceived as contaminants targeted for removal. Instead, they claim that the cells are actually of great importance due to their critical roles in assisting the growth-promoting abilities of OEC transplants in rats[63,96,97]. The fibroblasts are thought to provide structural support by producing a semi-solid gel-like matrix in which the transplant cells become embedded[94], and associate with the OECs in a manner similar to a perineural-like outer sheath[98].

Interestingly, the findings of an OEC transplantation study in dogs suggested that the extent of recovery did not appear to depend on the proportion of p75NTR-positive cells (OECs)[74]. From this, they postulated that the effects of OM cell transplants may not solely be elicited by the OEC component of the transplant, or that only a threshold number of OECs, which may be quite low, is required in the transplantation suspension for a therapeutic effect to be observed. However, whether or not olfactory nerve fibroblasts, or other olfactory cells, assist human OECs in their reparative endeavours remains uncertain. Nevertheless, due to the perceived necessity of olfactory nerve fibroblasts, purification procedures were waived in a recent human clinical trial, resulting in the co-transplantation of other cell types, mainly fibroblasts, alongside the OECs[78]. Thus, the degree of recovery that can be attributed solely to OECs cannot be ascertained.

To resolve the question of which cells are required for therapeutic efficacy, purified cultures of OECs and fibroblasts must first be attained before the question of cellular composition can be addressed. This will allow the contribution of each cell type to be systematically tested. Only then can the potential of the various olfactory cells to induce functional recovery be realised.

Inconsistencies Within and Between OEC Studies

To complicate matters further, variations in cell preparations make results of comparative analyses difficult to interpret. Some studies have attempted to directly compare the genetic expression profiles of OECs and Schwann cells when each were cultured under different conditions[99], while others have attempted to compare their efficacy in lesion paradigms using cell preparations containing differing purities[100,101]. Others still, endeavoured to find differences by comparing OECs and Schwann cells isolated at different developmental stages[102]. Although each respective approach may address questions important to their relevant study, without a uniform set of parameters, any observed differences may, in fact, be attributed to differing conditions, rather than to cell type-specific characteristics. Perhaps these inconsistencies may have also contributed to the findings of other studies that report contrariety, or lack thereof, between OECs and other cell types in vitro[93,103,104].

Despite the variable findings of OEC studies to date, a recent systematic meta-analysis of 62 transplantation studies in rodent spinal cord injury models demonstrated that OEC transplants elicit a mean locomotor recovery of 19.2%[105]. Thus, by adjusting for publication bias and missing data, this study has provided evidence to further support the clinical development of OEC transplantation for spinal cord injury.

The Need for Reproducibility in Human OEC Transplantation Studies

OEC research has already advanced into human investigations worldwide, including pilot surgical studies and clinical trials (Table 1)[78,79,106–113]. Such efforts have gleaned vital data points on the safety and efficacy of the surgeries and cellular components involved. Although some participants have experienced modest functional recovery, the therapy still necessitates improvement.

As mentioned previously, researchers have developed and tested various OEC purification methods in non-

Table 1. Source, quality, and functional outcomes of human OEC transplantation studies.

First author (year)	Number of patients	Type of cell source	Cells transplanted	Purification	Cellular composition	No. of cells transplanted	OEC purity (%)	Functional outcomes
Wang (2016)	12 (transplant recipients = 8, control = 4)	Autologous (adult)	OM-OECs (whole tissue pieces)	N/A	Unknown	Unknown	Unknown	Limited recovery, but transplant recipients recovered more motor, sensory, and bladder function compared with sham-operated subjects. At 3 years post-transplantation, one patient improved from ASIA A to C and another from ASIA A to B, two recovered more than three segmental sensory levels, two had less spasticity, two had depressed Hoffman's reflex (H-reflexes) and Somatosensory Evoked Potential (SSEP), two regained bladder and anorectal sensation and had improved bladder compliance on urodynamic studies.
Tabakow (2014)	1	Autologous (adult)	OB-OECs	None	Mainly ONFs and OECs (together comprised >95% of total cellular population)	500,000	16% p75NTR-positive cells	The patient improved from ASIA A to ASIA C. There was improved trunk stability, partial recovery of the voluntary movements of the lower extremities, and an increase of the muscle mass in the left thigh, as well as partial recovery of superficial and deep sensation. Some indication of improved visceral sensation and improved vascular autoregulation in the left lower limb. Pattern of recovery suggests functional regeneration of both efferent and afferent long-distance fibres.
Tabakow (2013)	3	Autologous (adult)	OM-OECs	None	Mainly OECs and ONFs	$1.8–21.2 \times 10^6$	20–50% S100-positive cells	Neurological improvement was observed only in transplant recipients. The first two operated patients improved from ASIA A to ASIA C and ASIA B, respectively. The third operated patient, although remaining ASIA A, showed improved motor and sensory function of the first spinal cord segments below the level of injury. Neurophysiological examinations showed improvement in spinal cord transmission and activity of lower extremity muscles in surgically treated patients but not in patients receiving only neurorehabilitation.
Lima (2010)	20	Autologous (adult)	OM-OECs (Whole tissue pieces)	N/A	Unknown	3×10^6 ($\sim$100,000 stem cells/mm^2) The number of pieces required to fill a cavity (generally more than 30) was dependent on the size of the cavity in the spinal cord after removing some of the scar tissue.	Unknown	ASIA grades improved in 11 of 20 patients, 6 (A→C), 3 (B→C), and 2 (A→B), and declined in 1 (B→A). Improvements included new voluntary electromyography (EMG) responses (15 patients) and somatosensory evoked potentials (4 patients). Scores improved in the Functional Independence Measure and Walking Index for Spinal Cord Injury (WISCI) (13/13 tested), and urodynamic responses improved in five patients.
Chhabra (2009)	5	Autologous (adult)	OM-OECs (whole tissue pieces)	N/A	Unknown	$\sim$9.3–17.28 $\times 10^6$	Unknown	There was no significant improvement in any of the neurological, electrophysiological or urodynatic efficacy variables.

(continued)

Table 1. (continued)

First author (year)	Number of patients	Type of cell source	Cells transplanted	Purification	Cellular composition	No. of cells transplanted	OEC purity (%)	Functional outcomes
Guest (2006)	1	Allogenic (foetal)	OB-OECs (dissociated)	DMEM-F12 with 10% FBS for 4 days, then serum-free for 10 days	Unclear. Possible stem cells and astrocytes, or neurospheres	1×10^6 (2 injections, 25 µl per injection, 20,000/µl)	Unclear. Anti-p75NTR was not tested since their antibody did not bind to fixed cultures. S100-negative and anti-mitochondrial antibody-negative. Strongly nestin-positive and GFAP-positive	Rapid partial recovery of function in the C5 and C6 spinal segments within a few days of surgery. Mechanism unknown, but clearly linked to the procedure and possibly to the injected cells.
Lima (2006)	7	Autologous (adult)	OM-OECs (whole tissue pieces)	N/A	Basal stem-like progenitor cells and OECs	Unknown	Unknown	Two patients reported return of bladder sensation, and one regained voluntary contraction of anal sphincter. Two of the seven ASIA A patients became ASIA C. Every patient had improvement in ASIA motor scores. Six patients had improvements in ASIA sensory scores. Most of the recovered sensation below the initial level of injury was impaired.
Mackay-Sim (2008) Feron (2005)	3	Autologous (adult)	OM-OECs (dissociated)	DMEM-F12 with 10% FBS for 2 days, then NT-3 Medium	Predominantly OECs, identified by their immunostaining for GFAP, S100, and p75NTR.	$12–28 \times 10^6$	76–88% p75NTR-positive 95% S100- and GFAP-positive cells	No significant neurological recovery was detected.
Huang (2012) Huang (2003)	171 (108 followed-up)	Allogenic (foetal)	OB-OECs (glomerular layers, dissociated)	DMEM-F12 with 10% FBS for 3–4 days, then serum-free medium for 2–3 weeks	Unknown	500,000	Unknown	After surgery, motor scores, light touch scores, and pin prick scores increased in all age groups.

ASIA: American Spinal Injury Association; DMEM-12: Dulbecco's modified Eagle medium F-12; FBS: foetal bovine serum; GFAP: glial fibrillary acidic protein; N/A: not applicable; None: no purification method was implemented; OB-OECs: olfactory bulb olfactory ensheathing cells; OECs: olfactory ensheathing cells; OM-OECs: olfactory mucosal olfactory ensheathing cells; ONFs: olfactory nerve fibroblasts; p75NTR: p75 neurotrophin receptor.

human species. However, only the selective media approach, which uses media supplemented with NT-3, has been used in the field of human OEC transplantation. This approach was developed[60] and used in the first human OEC transplantation clinical trial[79], where OEC purities of >95% and 76–88% were achieved 7 to 14 days prior to transplantation. Each respective purity was defined by GFAP and p75NTR-immunoreactivity, the resulting purified cultures of which were then injected into their participants.

Unlike the initial trial, subsequent human studies have omitted the purification steps entirely. Instead, mixed suspensions of olfactory cells containing OECs and olfactory nerve fibroblasts[78,114], or in some cases, whole, undissociated pieces of mucosal tissues[106,107,112], have been grafted into spinally injured patients without any descriptions on purification or cellular composition analysis (Table 1). Some authors argue that OECs may be more likely to survive in the transplant site when they are supported by other cells like olfactory nerve fibroblasts or substances like the ECM, which would normally exist alongside them in their natural milieu. Although these conditions may be ideal, where minimal in vitro intervention is involved, results from such studies become difficult to replicate due to unknown cellular compositions and their respective proportions in the transplanted graft. Without this knowledge, study outcomes may be irreproducible, and may also lead to unexpected consequences. Such was the case of a transplant recipient, who developed a tumor-like growth 8 years after receiving an OM autograft in an attempt to treat her paralysis[115]. The mass was found to contain large amounts of thick mucous-like material. Upon histological examination, multiple cysts lined with respiratory epithelium and submucosal glands with goblet cells, interspersed with nerve twigs, were detected. This case highlights the importance of cell identification and purification, without which the identity and purity of transplanted cells remains ambiguous. This may not only expose individuals to unknown risks, but also makes the standardization of transplants across multiple subjects difficult. For example, in the 2013 phase I clinical trial conducted by Raisman and colleagues[78], the percentage of S100β-positive cells, deemed to be OECs, varied from 10%, to 12%, to 25.7% between the three treated patients. The authors even stated that the total cell numbers between patients, as well as OEC to olfactory nerve fibroblast (ONF) ratios in each case, was very difficult to control owing to the absence of a purification step. Without a purification step, the cellular composition of transplantation cultures will likely differ each time, leading to large variability within and between different studies. Consequently, results from such studies become difficult to reproduce, let alone be improved upon by others in the field. A robust OEC identification and purification method is therefore the key to advance the development of the therapy.

Perspective

A clinically viable OEC transplantation therapy needs an identification and purification method for two main reasons: safety and consistency. Although OEC transplants in human studies has witnessed relative procedural safety in the past[79,106], reports like Dlouhy et al., 2014 demonstrate the consequences that may arise when undesirable cell types are involved in the transplantation process[115]. Yet, despite the perceivable benefits to patient safety, most human studies to date have not exercised enough control over their cell purities[78,112,114]. This makes the development of a cell purification step imperative for clinical application, where treatments must be standardized to account for the inherent variability between patients. By establishing such a protocol, treatments will not only have higher safety metrics, but also see an improvement in outcome interpretation with the transplantation purity of each cell type clearly defined. Together, these improvements will help prepare OEC transplantation for clinical application as a more reliable therapy for spinal cord injury.

Conclusion

The translation of human OEC grafts into human subjects requires a judgement on whether or not OECs alone possess sufficient neuroregenerative capacity. Without a reliable OEC-specific marker, or a robust method of identifying OECs from a heterogeneous population, OEC proportions within cell cultures remain difficult to accurately estimate. As it stands, there appears to be no effective means of differentiating between OECs and other cell types in human olfactory cultures. This is one of the major obstacles that ought to be addressed before the full potential of OECs can be understood. It is therefore imperative that a reliable method of purification and identification be developed to yield highly enriched populations of human OECs in culture. However, what if this idealistic OEC purification and identification method cannot be ascertained? Then a method that can, at the very least, achieve OEC cultures with consistent purity and viability should be attained; one with a rapid execution speed so that cells do not deviate substantially from their original phenotype due to culture conditions. Without one or the other, the clinical future of OEC transplantation remains uncertain and may advance no further in becoming a potential therapy for spinal cord injury.

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