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Review

Transplantation of Olfactory Ensheathing Cells: Properties and Therapeutic Effects after Transplantation into the Lesioned Nervous System

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Abstract: The primary olfactory system (POS) is in permanent renewal, especially the primary olfactory neurons (PON) are renewed with a turnover of around four weeks, even in adulthood. The re-growth of these axons is helped by a specific population of glial cells: the olfactory ensheathing cells (OECs). In the POS, OECs constitute an "open-channel" in which the axons of PON cause regrowth from peripheral nervous system (PNS) to central nervous system (CNS). The remarkable role played by OECs into the POS has led scientists to investigate their properties and potential beneficial effects after transplantation in different lesion models of the CNS and PNS. In this review, we will resume and discuss more than thirty years of research regarding OEC studies. Indeed, after discussing the embryonic origins of OECs, we will describe the in vitro and in vivo properties exert at physiological state by these cells. Thereafter, we will present and talk over the effects of the transplantation of OECs after spinal cord injury, peripheral injury and other CNS injury models such as demyelinating diseases or traumatic brain injury. Finally, the mechanisms exerted by OECs in these different CNS and PNS lesion paradigms will be stated and we will conclude by presenting the innovations and future directions which can be considered to improve OECs properties and allow us to envisage their use in the near future in clinical applications.

Keywords: spinal cord injury; peripheral nerve injury; olfactory ensheathing cells; transplantation

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1. Organization of the Olfactory System

The olfactory system is a tissue in which permanent regeneration occurs even in adulthood [1]. Indeed, the primary olfactory system (POS) is exposed to the external environment and to potential attacks such as pollution or viruses [2]. Moreover, for many animal species including mammals, olfaction is crucial to interact with their environment and their congeners. That is why the olfactory system and particularly the POS possesses intrinsic regeneration abilities. The main role of the POS is assured by the presence of primary olfactory neurons (PON). PON are bipolar neuronal cells that connect the peripheral nervous system (PNS) to the central nervous system (CNS). In effect, in the olfactory epithelium (OE) in the PNS, odorant molecules attach themselves to the PON which project the olfactory information to the olfactory bulbs (OB) into the CNS. Due to their exposition to toxics, PON are periodically renewed throughout life in mammals with a turnover of around four weeks. To do so, there is a persistent population of stem cells into the OE, the basal cells, which can give rise to the PON [3,4]. In the OE, there are also fibroblast-like supporting cells. These cells constitute the conjunctive tissue of the neuroepithelium and also play an active role in detoxification [5]. As mentioned above, PON are renewed every month by the basal cells, this process is very well orchestrated. Indeed, PON are selective of specific odorant molecules. Thus, these neurons constitute several families of cells grouped according to their expression of common olfactory receptors. These neurons are randomly arranged into the OE but project specifically to their

targets into the OB [6,7]. The renewal of PON and their targeted axonal regrowth is facilitated by the presence of a specific population of glial cells. In fact, in the OE and the outer nerve layer (ONL) of the OB, are located the olfactory ensheathing cells (OECs) [8]. These cells in the POS exert the same function as the non-myelinating Schwann cells (SCs) in the PNS, they ensheathe the axons without forming myelin in order to protect and guide them. In contrast to the SCs, OECs allow the regrowth of axons in the PNS (OE) but also in the CNS (OB). The common properties shared by OECs and SCs have sometimes led scientists to describe them as olfactory Schwann cells [9]. In 1990, Doucette called them "ensheathing cells" for the first time [8]. The renewal of OECs at the adult stage in physiological conditions is not well described. It is thought that these cells do not proliferate in adulthood [10]. Their main role would be to constitute an "open-channel" in which the axons of PON could regrowth specifically from PNS to CNS [11].

2. Origin and Cellular Heterogeneity of the OECs

Until 2010/2011, it was thought that the embryonic origin of the OECs was the olfactory placode. However, in 2010 and 2011, two studies, based on fate mapping experiments, demonstrated that OECs such as SCs are derived from the neural crest [12,13]. This common origin shared by SCs and OECs explains the fact that these cells express mainly the same markers and play a similar role in their specific nervous system compartment [14]. Indeed, in vitro, OECs and SCs cultures are characterized by their expression of GFAP and P75NTR [14]. The common origin of these two populations of cells does not mean that OECs and SCs are identical. Indeed, in vivo the POS OECs do not produce myelin, they ensheath PON axons in bundles and not individually as would SCs. Moreover, OECs can migrate from the PNS to the CNS and thereby can intermingle with astrocytes. On the opposite, SCs cannot mix with astrocytes and cannot migrate into the CNS [15]. These different interactions with astrocytes can be explain by the fact that OECs and SCs express differentially extracellular matrix (ECM) genes as demonstrated by transcriptomic studies [16,17].

In the same way, OECs are not constituted by a uniform population of cells. Indeed, as described above, OECs ensheathe PONs and can be found in the PNS, in the OE, or in the CNS, in the ONL of the OB. Several studies have reported that, according to their origin, OM or OB, OECs express distinct properties in vitro [18,19]. Thereafter, based on microarray analyses, we have demonstrated that OECs from OM and OECs from OB, respectively OM-OECs and OB-OECs, display distinct gene expression patterns. In effect, OM-OECs express preferentially genes involved in the regulation of the ECM such as MMP2, TIMP2, ADAMTS-4 or thrombospondin 1 and 2, whereas OB-OECs express preferentially genes involved in "nervous system development" processes such as BDNF, Reelin or MBP [20]. Based on bulk RNA seq experiments, these results have been expanded and confirmed recently [21].

Furthermore, in vitro and in vivo studies have demonstrated that OB-OECs are in fact composed of two different subpopulations of cells [22–24]. Indeed, Windus et al. demonstrated elegantly that OB-OECs constitute a heterogeneous population of cells [25]. Then, a transcriptomic study confirmed that two subpopulations of OECs, characterized by their differential expression of P75NTR, named P75High and P75Low, are present in cultures obtained from OB [26]. Gene expression profiling analysis of these cells allows proposing a specific role during PON renewal. P75High cells are involved in fasciculation and defasciculation of the axons of the PON and P75Low cells in axonal guidance [26].

As described above, P75NTR is used as the main marker of OECs. Although this marker is used to characterize OECs in vitro and in vivo, several studies have tried to find additional markers allowing researchers to differentiate OECs from SCs and to define specifically the sub-populations of OECs. The first studies investigating markers expressed by OECs used markers already known as being expressed by astrocytes or SCs [27,28]. Indeed, OECs, until the beginning of the 1990s, were defined as olfactory nerve SCs or olfactory nerve glia cells. Based on these investigations, it was demonstrated that OECs express GFAP, S100β and P75NTR [27,28]. These markers were found to be expressed both in vitro and in vivo [24,29–33]. Then, additional markers were found to be potentially expressed in vivo by

OECs such as O4, Neuropeptide Y (NPY) or TROY [34–37]. Another marker which is currently used also to define OECs is E-NCAM. The expression of E-NCAM by OECs was reported for the first time in 1996 by Franceschini and Barnett [38]. In this study they demonstrate that E-NCAM is expressed in vitro and in vivo. These studies have mainly investigated the expression of markers of OECs into the OB in vivo or from cultures of OECs obtained from OB in vitro.

In 2003, Au and Roskams characterized the expression of markers of OECs from OM in vivo and in vitro [39]. They showed that OM-OECs express also P75, S100β, GFAP and O4 both in vitro and in vivo. They demonstrated also that OM-OECs express specific markers such as vimentin, nestin, or NG2 in vitro and CD44 or PACAP both in vitro and in vivo [39]. Interestingly, OECs expression markers' characterization has been also investigated in fish. In effect, several studies have demonstrated that OECs in different fish species such as zebrafish express mainly the same markers they do in rodents [40,41].

It is important to summarize and differentiate the markers expressed by OECs in vitro and those expressed in vivo. Indeed, due to differences in experimental paradigms, such as the age of animals used to characterize expression markers; notably, in vivo expression of several markers has been investigated during development in newborn rats. Due to the difficulty of separating the markers expressed, especially by OECs and those by the closely associated cells, to date there is still no consensus regarding the specific and differential expression of OM and OB OECs. However, based on different reviews and meta-analysis, we can summarize that:

In culture, OM and OB OECs express P75NTR, GFAP and E-NCAM [42,43], and in vivo, OM and OB OECs express P75NTR, GFAP, E-NCAM, S100β, vimentin and NPY [42,43] (Figure 1b).

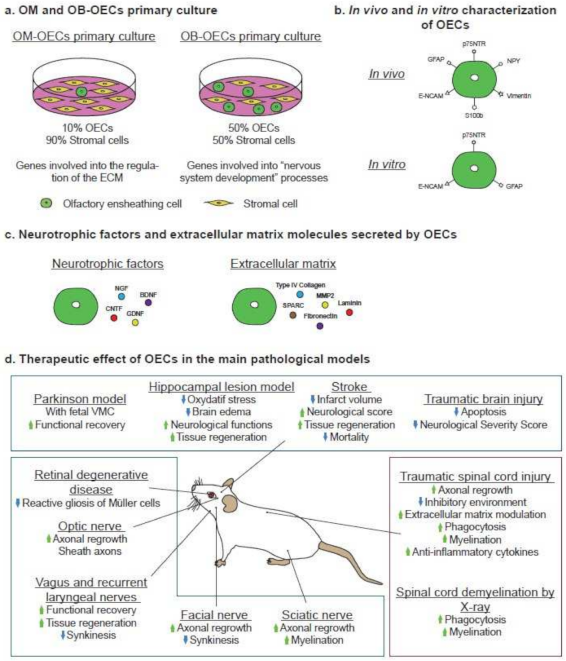

Figure 1. Culture, characterization and main therapeutic application of olfactory ensheathing cells. (**a**) OM primary cultures generate 10% of OECs while OB primary cultures generate 50% of OECs. (**b**) OECs are identified in vivo by the expression of p75NTR, GFAP, E-NCAM, S100b, vimentin and NPY, and in vitro by p75NTR, GFAP and E-NCAM. (**c**) The main therapeutic effects of OECs are linked to secretion of neurotrophic factors (NGF, BDNF, GDNF or CNTF), and by the secretion of molecules modulating the extracellular matrix (laminin, fibronectin, type IV collagen, MMP2 or SPARC). (**d**) The main pathological models showing beneficial effects of the transplantation of OECs. Blue rectangle concerns brain injury models, green rectangle concerns peripheral nerve injury models and red rectangle concerns spinal cord injury models. NGF: Nerve Growth Factor, BDNF: Brain Derived Neurotrophic Factor, GDNF: Glial Derived Neurotrophic Factor, CNTF: Ciliary Neurotrophic Factor.

That is why, due to the absence of consensual specific biomarkers, it is still difficult to differentiate SCs and OECs.

3. OECs Properties

Even if OECs are constituted by several sub-populations, all these cells share common expression of specific markers. Moreover, independently of their origin, we can give an overview of the properties of the OECs. It is important to note that we made a choice to develop deeply the properties of OECs regarding phagocytosis and modulation of inflammation processes. Indeed, the secreting and myelinating properties of OECs have been already the subject of several reviews, whereas the immunomodulatory competencies of OECs have been reported more recently.

The studies investigating the properties of the OECs have been mainly conducted in vitro. In 1992, Ramon-Cueto and Nieto-Sampedro described the primary cultures of OECs obtained from OB [44]. They described that these cultures are composed of a mixture of P75 positive cells and fibronectin positive cells. Since then, P75 has been used as a pan-marker to characterize and quantify the OECs in culture. Mostly, the different studies characterizing the OECs report that the ratio between OECs, P75 positive cells, and fibroblasts/stromal cells, fibronectin positive cells, is around 50/50 in primary OB cultures (Figure 1a). Then, several purification techniques have been described allowing to obtain more than 90% of OECs [45–47]. The first descriptions of the cultures of OECs obtained from OM have been reported later [48,49]. It is important to note that in primary cultures the ratio of OECs/fibroblasts is very low. Indeed, the authors mainly report that the proportion of OECs in primary OM cultures is around 10% (Figure 1a). In the same way, several purification technics have been described in order to obtain highly purified cultures of OECs [50]. Based on these different culture models, several studies have reported that OECs secrete a wide range of trophic factors and ECM proteins (Figure 1c). Indeed, it has been demonstrated that OECs express trophic factors such as NGF, BDNF, GDNF or CNTF and ECM molecules or ECM modulating molecules such as: laminin, fibronectin, type 4 collagen, MMP2 or SPARC [51–57] (Figure 1c).

These properties have prompted researchers to investigate the effects of OECs in co-culture with different neural cell lines [58–62]. It appears that OECs enhance axonal and neurite outgrowth, increase survival and differentiation of neural stem cells (NSC) [63]. More interestingly, several studies have described that these positive effects can be induced by conditioned medium obtained from OECs primary cultures [58,60,64].

Myelinating properties of OECs have been also investigated in vitro. Indeed, in vivo in physiological conditions, OECs do not form myelin around the PON. However, it has been hypothesized that this was maybe due to the small size of the PON axons. The myelinating properties of the OECs are still under debate. In effect, some publications described that OECs in vitro ensheathe bundles of axons without forming myelin [65]. Other studies described that OECs form myelin in vitro [63]. Interestingly, in these publications, the authors described that OECs form a "Schwann cell-like" myelin with the expression of the peripheric myelin protein P0.

Another very important aspect which has been widely investigated, is the behavior of OECs with astrocytes and fibroblasts [15,66]. Indeed, in order to mimic the scar present after injury, authors performed co-cultures of OECs with these two cell types. The different studies report that OECs can intermingle with astrocytes and fibroblasts without inducing the hypertrophy of these cells. This behavior constitutes one of the main differences between OECs and SCs. In contrast, SCs do not mix themselves with astrocytes and fibroblasts. Moreover, co-culture of astrocytes and SCs induces astrocyte hypertrophy.

More recently, new properties of OECs have been investigated and reported. Additional to the previous characteristics, OECs possess immunomodulatory competences. Indeed, due to important PON renewal and proximity to the periphery, inflammation in the OB and phagocytosis are substantial in the physiologic state [67].

During early development of the POS, PON apoptosis is induced following inappropriate projections within their target [68,69]. In post-natal mice and in adult lifespan, PON renewal and apoptosis decrease compared to the embryonic stage but are still present [70,71]. Throughout the adult CNS, microglial cells are the main phagocytic and regulatory cells of inflammatory balance. In contrast to the OBs, this role is additionally supported by OECs. Especially, OECs produce macrophage migration inhibitory factor (MIF). MIF is a cytokine which plays important roles in innate immune responses, inflammation, cell proliferation, cell migration and apoptosis. Moreover, MIF limits microglial and macrophage migration to the OB [72–74]. Therefore, several in vitro and in vivo studies have investigated phagocytic properties of OECs [11,75–81]. In these studies, phagocytic activity has been identified as an important mechanism necessary to clear apoptotic and necrotic cells and to initiate neuronal regrowth. Nazareth et al., have shown that OECs phagocytic activity starts from E13.5 in mice, during the development of the olfactory system, and continues throughout life. The phagocytic properties of OECs have been compared to other cells. It appears, that OECs are more efficient than SCs but less efficient than microglial cells. The authors explain that internalization and trafficking of endosomes and lysosomes are slower than those of microglia [79]. Many phagocytic receptors were identified on OECs such as the phosphatidyl serine receptor [75], MFG-E8 receptor [77], toll-like receptors 2 and 4 [75,82] and the mannose receptor [83]. These receptors give the possibility to phagocyte neuronal debris, necrotic cells and bacteria. In adult OB, removal of neuronal debris by phagocytosis is necessary for neuronal survival, their renewal and neurite outgrowth. Indeed, cellular and axonal debris inhibit cellular proliferation and axonal regrowth and increase inflammation processes, which in turn decrease neurogenesis. The inflammation processes allow initiation of tissue regeneration in physiologic and pathologic contexts. In other parts of the CNS, cytokines involved in inflammation processes are secreted by microglial cells, astrocytes and immune cells, as described previously [84]. In the OBs, OECs contribute to inflammatory modulation. In response to olfactory bacteria infiltration, OECs detect lipopolysaccharide and produce tumor necrosis factors alpha (TNF-α), C-X-C Motif Chemokine Ligand 1 and 2 (CXCL1, CXCL2) and IL1-RA [75,85,86]. Lankford et al., showed that TNF-α stimulates proliferation of OECs during chronic exposure and their migration by binding to the TNF receptor 1 [87] as described for microglial cells [88]. In sum, OECs have similar capacity to immune cells, making them the main cells regulating inflammatory and regeneration processes in the OBs.

Altogether, the specific properties of the OECs have led scientists to investigate the effects of OEC transplantation in different lesion models of the CNS and PNS.

4. A Brief History of the Use of the OECs for Repairing the Nervous System

The first studies reporting the effects of the transplantation of OECs in vivo were published in the mid 1990s. Although effects of the transplantations of OECs have been massively studied after spinal cord injury (SCI), the first studies investigated the effects of these cells in other lesion paradigms. Indeed, the first study, in 1994, was based on a rhizotomy lesion model. The thoracic dorsal root ganglion (DRG) was transected, and purified OB-OECs were transplanted [29]. The authors reported that OB-OEC transplantation induced regeneration of the sensory axons. Then, a second model based on a lesion of the brain, a fimbria-fornix transection, showed that transplantation of OB-OECs enhances growth of axons and that, in this model, OECs survive a minimum of 4 weeks after transplantation [89]. In 1996, Franklin et al. studied the role of OB-OEC transplantation in a demyelinating injury model of the ventral spinal cord based on X-ray irradiation and ethidium bromide injection. In this model, they show for the first time that OECs can produce peripheric P0 positive myelin [90]. Finally, in 1997 and 1998, SCI related models were investigated. In 1997, Li et al. demonstrated that transplantation of OB-OECs after corticospinal tract (CST) transection enhances axonal regrowth and functional recovery [91]. In 1998, Ramon-Cueto et al. demonstrated that after a complete transection of the spinal

cord, OB-OEC transplantation induces axonal regrowth. It is very important to note that all these studies were performed in rat models and that OECs were obtained from OBs [92].

In 1999, Verdu et al. investigated for the first time the effects of OECs after a lesion of the PNS, sciatic nerve (SN) transection, and showed that OECs enhance axonal regrowth [93].

In 2000, Kato et al. used for the first time OM-OECs for transplantation after SCI in rats. The cells were obtained from the olfactory nerve [94]. Moreover, in this study the OM-OECs were obtained from human. The same year, the same research team reported that OECs obtained from pigs OB can induce axonal regrowth after transplantation in injured rats [95].

In 2002, Lu et al. showed for the first time that a delayed transplantation of OM-OECs, 4 weeks after SCI, can induce axonal regrowth and functional recovery in rats [96].

The first study regarding the effects of OEC transplantation in a large animal was published in 2004. In fact, the authors transplanted OECs obtained from pigs, into the lesioned spinal cords of non-human primates. They showed also in this study that OEC transplantation enhances remyelination [97].

In 2004, the first study regarding the effects of OEC transplantation in context of degenerative diseases was published. Indeed, Agrawal et al. published a study showing that OEC transplantation can restore deficits induced in an experimental model of Parkinson's disease [98].

Finally, in 2005, Féron et al. reported the first clinical study in human. In this phase one clinical trial, autologous OEC transplantation was performed in patients suffering SCI [99].

5. Transplantation of OECs after Spinal Cord Injury

Between one third and half of the publications related to OECs investigated the effects of their transplantation after SCI. Indeed, as mentioned above, since the second half of the nineties the unique properties of OECs have encouraged researchers to use these cells as therapy after various SCI models such as contusion, transection or demyelination. Therefore, the effects of OEC transplantation after SCI are well documented and the positive and negative effects can be discussed.

It is important to note that, even if DRGs are anatomically included in the PNS, a rhizotomy lesion model will be discussed in this section. The fact that axonal regrowth of the sensory axons into the spinal cord is one of the main outcomes of this lesion model, makes it, in our view, an SCI model.

In this section we will differentiate three lesion paradigms: (1) Lesions of the DRG or rhizotomy, as described above, this model should be considered a CNS lesion model, however, the injury site is in the PNS. (2) Traumatic SCI, lesion models regroup contusion and transection, these models are the most widely used SCI models. (3) Demyelinating SCI, in particular irradiation models, these models are mechanistically very informative however, properties and survival of OECs differ from the other SCI models.

Rhizotomy lesion model: this model is very interesting. As described above, it constitutes the first model in which beneficial effects of the transplantation of OECs was reported. Moreover, it appears that this model is the one in which OEC transplantations are least effective. Indeed, the ratio of studies describing beneficial effects and those describing the absence of effects is around 50%. In fact, the first reported studies describe positive effects after transplantation of OECs in the rhizotomy model [29,100]. In contrast, more recent studies report that OEC transplantation has no effect in this lesion model [101–103]. The main difference between these studies is the injection site. Indeed, in the two first studies the OECs were injected into the dorsal root entry zone (DREZ), at the frontier between the PNS and the CNS, whereas at the opposite in the three other studies OECs have been injected into the DRG, in the PNS. These contradictory results seem to indicate that OECs can promote axonal regrowth of the spinal sensory axons when they are injected into the spinal cord but that these cells cannot migrate from the PNS to the CNS through the

DREZ when they are injected into the PNS. Other research team have reported contradictory results in this model. Ibrahim et al. reported that OB-OECs can induce axonal regrowth after transplantation but that OM-OECs cannot in the same lesion and transplantation model [104,105]. In these publications, primary OECs cultures have been injected. The difference in the ratio of OECs to fibroblasts could explain the different results reported. As described in Section 3, primary OM cultures contain only 5 to 10% OECs.

Traumatic SCI: Most of the investigations regarding the effects of OECs transplantation have been conducted after traumatic SCI. Therefore, many reviews and meta-analysis articles have summarized the results induced by OEC transplantations [43,106,107]. Based on the different articles and meta-analyses published, we can build an objective picture of the effects of OEC transplantation in this context. Indeed, since the first studies from the second half of the 1990s, it appears that in the vast majority of the cases, OEC transplantation after SCI modulates the lesion scar, enhances axonal regrowth and induces functional recovery [85,92,96,108–112]. Some studies reported that OEC transplantation after SCI does not improve functional recovery even though they modulate the lesion scar [113]. In contrast, some studies have described the absence of effects after OEC transplantation [102,103,114,115]. These contradictory results can be explained by the different experimental conditions. Indeed, OECs can be obtained from OB or from OM and can be transplanted as primary cultures or after purification step(s) [116]. SCI can be induced by contusion or by transection [114,117]. The cells can be transplanted immediately or several days or weeks after SCI [118,119]. The number of transplanted cells is also different between studies. Due to the fact that more than 200 studies have investigated the effects of OEC transplantation after SCI, a transplantation "gold standard" could be established. Indeed, Watzlawick et al. in 2016 published a meta-analysis summarizing the most effective way to transplant OECs after SCI [120]. It appears that the most effective way to transplant OECs in order to enhance functional recovery after SCI is to transplant 100,000 to 200,000 cells obtained from primary OB-OEC cultures immediately in a transection SCI model [120].

Even if the vast majority of the published studies describe positive effects after transplantation of OECs in SCI, side-effects have also been reported. Nakhjavan-Shahraki et al. have analyzed the effects of OECs transplantation on allodynia [121]. In this meta-analysis, they describe that OEC transplantation did not have an effect on this parameter and can even lead to aggravate hyperalgesia [121].

Altogether, OEC transplantation is one of the most effective therapies after SCI, with limited side effects. That is why many studies have tried to understand the main mechanisms to explain the positive results observed (Figure 1d).

The first thing that has been investigated is the survival of OECs after their transplantation in traumatic SCI. To do so, fluorescent positive OECs have been injected into the lesioned spinal cord and immunohistological studies performed at several time points after transplantation. In most of the studies, it appears that the vast majority of the transplanted OECs do not survive after 2 to 4 weeks after transplantation [122]. This does not mean that OECs cannot be found in the lesioned spinal cord parenchyma, but that the percentage of surviving cells is very low, between 1 to 10% one month post transplantation [106]. A recent study investigated the survival of OECs after transplantation in SCI and compared their survival with those of olfactory fibroblasts [117]. They demonstrated that OECs survive longer than fibroblasts [117]. Collectively these results are of primary importance, indeed they indicate that OECs after SCI mainly exert their effect during the first 2 or 4 weeks after transplantation due to the fact that they die over time and cannot be found anymore 2 or 3 months post SCI, even when at these time points functional recovery and tissue repair can be observed in transplanted animals. Therefore, it has been hypothesized that OECs exert their effect in three ways: (1) secretion of trophic factors and modulation of the endogenous cells, (2) protection and stabilization of axons and (3) immunomodulation and phagocytosis (Figure 1d).

1. In effect, due to the fact that OECs survival is low, the first hypothesis regarding the role played by OEC transplantation after SCI was that they enhance tissue repair and functional recovery by indirect effects such as neurotrophic factors secretion, modulation of the ECM or by recruiting SC into the lesioned spinal cord parenchyma [123,124]. We can summarize this process by the fact that OEC transplantation changes the inhibitory microenvironment which is put in place after SCI for a more favorable one for axonal regrowth and tissue repair. Indeed, as described above many studies have reported that OEC transplantation enhances axonal regrowth after SCI (Figure 1c). However, due to the fact that OECs exert these effects indirectly, the precise mechanisms are not well described. In fact, it has been demonstrated that OECs modulate the expression of chondroitin sulfate proteoglycan (CSPG), which are well known and described as major inhibitory molecules of lesion scarring [112,125]. It is also described that OECs transplantation after SCI enhances myelination [126,127] (Figure 1d). However, the precise role that OECs play after transplantation on astrocytes or oligodendrocytes is not well known. It has been hypothesized that OECs transplantation after SCI enhances SCs infiltration into the injured parenchyma [128]. Nevertheless, this hypothesis seems unlikely, in effect, recently Assinck et al. have demonstrated that P0 positive cells, which can be found in the injured spinal cord after SCI, have their origin in oligodendrocyte progenitor cells [129]. That is why further studies are necessary to understand the precise role played by OECs on endogenous cells such as astrocytes, oligodendrocytes or ependymal cells after SCI.

2. Protection and stabilization of axons has been hypothesized based on the physiological functions of OECs in the POS. Indeed, Li and Raisman have called it the "pathway hypothesis" [130]. This hypothesis describes that OECs in close association with fibroblasts create an open channel in which axons can regenerate. This hypothesis could also explain why transplantation of primary a OB-OEC culture containing a mixture of OECs and olfactory fibroblasts is more efficient than purified OB-OEC transplantation after SCI. This hypothesis was confirmed later by Khankahn et al., who showed that transplanted OECs are associated with axons in the lesion core, enhancing axon survival and axonal regrowth [117] (Figure 1d).

3. Immunomodulation and phagocytosis roles of OECs have been reported more recently. In fact, OECs seem to regulate inflammation by indirect and direct effects. Indeed, OECs can phagocyte PON into the POS, which is why it has been hypothesized that OECs can clear myelin and axon debris at the injury site after SCI [78]. This hypothesis has been confirmed by several studies in vitro and in vivo [76,79,131]. These studies assessed the phagocytic capacities of the OECs and demonstrate that these cells exhibit high capacities for phagocytosis [79]. Based on these particular competences, some authors have defined OECs as "immunocytes" [80]. These direct effects of OECs by phagocytosis on axonal and myelin debris are associated with indirect effects by secretion of immunomodulatory cytokines (Figure 1d). Several studies have demonstrated that OECs can secret anti-inflammatory molecules in vitro and that OECs after transplantation can regulate inflammation in the lesioned spinal cord [79,117]. Indeed, Khankan et al., have demonstrated that OECs after transplantation reduce the infiltration of Iba1 positive cells into the lesion core [117].

Demyelinating SCI: This model is of a particular interest because it has revealed unexpected specific properties of OECs after their transplantation into the CNS [90,132–135]. This model was reported for the first time in 1996, after which it has been investigated by other groups [133,136]. This model is a "demyelination-like" model induced by X-ray irradiation which can be associated with focal ethidium bromide injections. This model allows to induce loss of sensorimotor functions comparable to those occurring after SCI without transection of the descending and ascending tracts. In this model, it has been described that OECs can survive, migrate and form P0 positive myelin around the axons (Figure 1d). These specific and unexpected properties are not commonly described after traumatic SCI. In this model, the properties of OECs have been compared to those of the SCs. It appears that OECs can migrate extensively after transplantation which was not the case with SCs [134]. Moreover, this study is one of the first to report that OECs can

express phagocytic properties [134] (Figure 1d). More recently, the same research group has conducted a study regarding the properties of OECs and SCs in an irradiation-related context, in a brain injury model [136]. In this study, the brains of three-week-old rats were irradiated, and one week later, OECs and SCs were transplanted into their hippocampus. It appears, that in this model, OECs can survive and migrate, but can also proliferate. Indeed, Ki67 staining reveals that some transplanted OECs are still dividing 3 weeks after transplantation [136]. As previously reported in demyelinated spinal cord, in irradiated brains, OECs express phagocytic abilities according to their expression of OX-42 [136].

6. Transplantation of OECs after Peripheral Nerve Injury

Even though OEC transplantations have mainly been applied after SCI, numerous studies have investigated the effects of OECs after peripheral nerve injury (PNI). Indeed, as described above, the first reported study regarding OECs transplantation after PNI was published in 1999 [93]. The effects of OECs after PNI have been assessed in different lesion models. The vast majority of these studies have been performed using SN [137–142]. Different lesion paradigms have been used, such as complete transection or crush injury. It has been demonstrated that OEC transplantation induces axonal regrowth and functional recovery (Figure 1d). More interestingly, in a crush injury model, Dombrowski et al. demonstrated that OECs can survive until 6 months after transplantation and form functional myelin with nodes of Ranvier in which sodium channels can be found [143].

Several studies have been performed using cranial nerve injury models such as facial nerve or optic nerve [142]. In 2001 and 2002, Guntinas-Lichius et al., demonstrated that in facial nerve injury models, transplantation of OECs enhances axonal regrowth and functional recovery of the vibrissae [144,145]. Moreover, in these studies the authors performed retrograde labeling, allowing to highlight muscular co-contraction phenomenon, called synkinesis. To do so, they injected several retrograde tracers into three different facial muscles in order to demonstrate the specificity of the nerve–target muscle connections. They demonstrated that OEC transplantation increases the selectivity of the axonal regrowth and decreases the synkinesis [144,145] (Figure 1d).

Several studies have investigated the effects of OECs transplantation after optic nerve injury. The first study was performed by Li et al. in 2003. They showed that OEC transplantation after a transection of the optic nerve allows axonal regrowth of the retinal ganglion cells [146]. Interestingly, they also showed, in another study, that OECs in this model do not form myelin but ensheathe bundles of axons, whereas in contrast, in the same lesion model transplanted SCs myelinate optic nerve axons [147] (Figure 1d).

A few studies have been also performed after vagus or recurrent laryngeal nerve injuries. In these models, OEC transplantation also induced tissue repair and functional recovery. Based on vocal cord movement analysis the authors demonstrated that OEC transplantation reduces aberrant movements [148,149] (Figure 1d).

In contrast to the SCI, there is no study showing an absence of positive effects after transplantation of OECs in PNI context. Indeed, all the published studies demonstrate that OEC transplantation after PNI enhances tissue repair, axonal regrowth or myelination, and in the vast majority, induces functional recovery.

Some comparative studies demonstrate that according to their origin, OECs can exert different effects. Indeed, it has been demonstrated that transplantation of primary cultures of OECs obtained from OM do not significantly enhance axonal regrowth and functional recovery in a vagus nerve injury model in comparison to the transplantation of primary cultures of OECs obtained from OB [148]. Beyond the different expression profiles of the OECs according to their respective origin, these differences can be also explained by the low amount of OECs in primary OM cultures which is around 5 to 10% in comparison to the ratio of OECs in primary OB cultures which is around 50%.

We described above that after traumatic SCI, OECs mainly exert their beneficial effects within the two first weeks after transplantation. In contrast, it seems that after transplantation in PNI context, OECs can be integrated in the regenerative tissues. Indeed,

OECs can survive several months after crush injury of the SN and can form peripheral-like P0 myelin [143]. Additionally to these direct effects on axonal survival, regrowth and myelination, OECs also have positive effects in an indirect manner by secretion of trophic factors, as described after their transplantation in an SCI context [150].

7. OECs Transplantation in Other CNS Injury Models

The properties of OECs have been studied in other pathological models and human diseases. In this section, studies conducted in animal models and humans studies will be presented.

OECs properties have been investigated in a Parkinson's model (Figure 1d). To do so, authors induced the disease by injection of 6-hydroxydopamine into the substancia nigra of rats [151]. Thereafter, OECs were grafted into the striatum. In this model, the authors did not observe an improvement in the transplanted group [151]. In contrast, using the same lesion model, Agrawal et al. demonstrated that the co-transplantation of OECs with fetal ventral mesencephalic cells (VMC) increases survival of these cells and exhibits better motor recovery compared to the rats receiving VMC transplantation alone [98]. Authors highlight that OECs probably promote the elongation of dopaminergic and serotonergic axons in addition to improving survival [98,152].

OECs were tested in hippocampal lesion models induced by carbon monoxide [153] or kainic acid [154] (Figure 1d). In the first model, it was demonstrated that OEC transplantation decreases oxidative stress and apoptosis in the hippocampus, reduces cerebral edema in rats and improves neurological function [153]. In the second model the authors decided to transplant OECs in addition to neural progenitor cells (NPC). Interestingly, transplantation of OECs or NPCs alone shows efficacy in improving learning and memory; however, co-transplantation of these two cell types significantly enhances tissue repair over transplantation of OECs or NPCs alone [154]. These two studies underline the major role played by neurotrophic factor release of OECs on NPCs survival [154].

Traumatic brain injury (TBI) is a frequent pathology that can be very disabling. For the last decade, researchers have been trying to find effective therapies. That is why some studies have investigated the effects of OEC transplantation after TBI (Figure 1d). In 2014, Wang et al. demonstrated that OEC transplantation in a contusive TBI model improves neurological severity score (NSS), based on motor ability, balancing and alertness. This improvement is correlated with an increase in GAP-43 fibers and synaptophysin vesicles, generally considered to be markers of neuronal plasticity [155]. Moreover, in the same study the authors demonstrate that OEC transplantation downregulates BAD expression, which is a transcription factor implicated in apoptosis [155]. Other teams have evaluated the effects of OEC transplantation in association with other cell types in a TBI model. In effect, OEC transplantation has been combined with bone mesenchymal stem cells (BMSC) after contusive TBI [156]. The results obtained by Fu et al. confirm those described in the Wang et al. study. In fact, NSS was improved in the OEC and BMSC groups but the maximum efficiency was obtained in the co-transplanted group (OECs + BMSC group). The authors highlight the Janus kinase/signal transducer and activator of transcription pathway, as a signaling pathway involved in these therapeutic effects [156]. Liu et al. have combined OECs with NSC. Their results show a reduction in BAD signaling, as described previously by Wang et al. [155], but also a decrease in IL-6 expression at the lesion site [157]. These effects are observed in each transplanted cell group but co-transplantation leads to better effects in comparison to the other groups [157]. Interestingly, the same co-transplantation has been tested in retinal degenerative disease [158]. This study results show that co-transplantation induces beneficial effects by decreasing reactive gliosis of Müller cells after retina damage [158].

Two studies based on the stroke model have investigated the effects of OEC transplantation (Figure 1d). The first one studied the effects on OEC transplantation in a middle cerebral artery occlusion (MCAO) model [159]. Researchers show that OEC transplantation reduces infarct volume and increases neurological score and tissue repair 56 days

after MCAO. These results are also associated with a reduction in mortality in the OEC-transplanted group [159]. The second study is based on an intracerebral hemorrhage model. Here, OECs were transplanted with NSC and serve as trophic support for NSC survival and differentiation. The authors highlight that co-transplantation decreases neurological deficit score from 14 days, whereas the transplantation of each of these cell types alone brings the effect from 30 days. They explain this difference by a better survival, migration, and differentiation of NSCs into neurons, astrocytes and oligodendrocytes in the presence of OECs [160].

Finally, another interesting application of OECs in an animal model was reported by Carvalho et al. In this study OECs were used to transport and to deliver transgenes to glioblastoma cells. Authors have injected OECs into the nasal cavity and OECs have migrated to glioblastoma inducing slower tumor growth and increased mice survival [161].

All the studies described above showed beneficial effect after transplantation or co-transplantation of OECs. However, several studies have investigated the effects of OEC transplantation in amyotrophic lateral sclerosis (ALS). These studies reported mitigating effects of OECs in animal studies as well as in clinical studies.

In effect, several studies conducted on human showed opposite results in terms of beneficial effects of OEC transplantation. The first study, based on 327 patients, demonstrated that OEC transplantation in the spinal cord and/or bilateral corona radiata of the frontal lobes provided improvement or stabilization of the pathology. To demonstrate the results, patients were assessed on the ALS-Functional Rating Scale (ALS-FRS) [162]. However, other studies wanted to reproduce these beneficial effects. Based on the same protocol but using fetal OECs, a second study on 14 patients was conducted and showed that seven patients had neurological improvement, two were stabilized and five presented a decrease in their ALS-FRS score [163]. In an animal study, Morita et al., demonstrated in an ALS mouse model that OEC transplantation has no positive effect [164]. This was confirmed in human by an Italian team who studied the post-mortem brains of two ALS patients who had received OECs. They did not find any evidence of axonal regeneration, neuronal differentiation and myelination in connection with the OEC transplantation [165]. Finally, another study of OECs transplantation in ALS patients prospectively followed seven patients before and after treatment. Despite subjective positive effects directly after treatment in three patients, no individual objective improvement was measured, and outcome measurements gradually declined in all patients [166].

Chen et al. were the only ones to test OECs in human cerebral palsy. They performed bilateral transplants into the corona radiata in the frontal lobes with human fetal OECs in patients ranging from 1 to 12 years old. They showed that there is no side effect related to the transplant and that patients of OECs group got better Gross Motor Function Measure scores than control [167].

8. Future Directions

As we tried to demonstrate in this review, OEC transplantation enhances tissue repair and functional recovery in the majority of the lesion models studied. Although these abilities make OECs a unique cell type, several studies have tried to potentiate OECs properties or to associate OECs with other therapies or even to skirt some limitations which are intrinsically related to cellular transplantation.

Indeed, in 2002, Ruitenberg et al. reported for the first time that OECs' gene expression can be modified by adeno or lenti viruses [168]. Thereafter several studies investigated the effects of genetically-modified OEC transplantation after SCI [122,169–171]. To our knowledge, the first one was published in 2004; in this study Cao et al., report that transplantation of OECs genetically modified to secrete GDNF improves functional recovery after SCI [169]. These studies tried to enhance one specific ability of the OECs: secretion of trophic factors and ECM molecules. Collectively, they report that genetically enhanced OECs improve functional recovery and tissue repair.

Another way to improve OECs' effects after transplantation is to associate them with other cell types. Interestingly, as described in part 7, many studies have reported the co-transplantation of OECs and additional cells in numerous lesion models such as PNI, SCI, Parkinson lesion model, hippocampus lesion model, intracerebral hemorrhage model or TBI [142,149,154,156,157,160,172–174]. Mainly, OECs have been transplanted in addition to three different cell types: stem cells, SCs and differentiated neurons. Indeed, the vast majority of the "co-transplantation" studies have investigated the effects of co-grafts of OECs with stem cells such as adipose stem cells, neural stem cells or bone marrow stem cells [175–178]. Co-transplantation of OECs and SCs has also been widely investigated [142,173,179]. Finally, few studies have assessed the effects of co-grafts of OECs with neurons or neuron-derived stem cells [172,180]. Only one study reports the absence of beneficial effects after co-transplantation of OECs and mesenchymal stromal cells (MSC) [181]. In this publication, the authors found that all transplanted groups (OECs, MSC and OECs + MSC) showed enhancement of their functional recovery but without differences between groups. With the exception of this study, all the other published works show additional effects of the co-transplantations, independently of the nature of the co-grafted cells. The expected benefits of such co-transplantations are specific to the co-transplanted cells. Indeed, when OECs are co-transplanted with SCs, the purpose is to combine the properties of the two cellular types. Whereas, the main aim in co-grafting OECs with stem cells or neurons is to use the release of secreting factors by OECs to enhance the survival and integration of the co-transplanted cells; stem cells or neurons.

Another approach which has been widely explored, is to combine OEC transplantation with additional exogenous molecules or with biomaterials. The first reported studies investigated the behaviors of OECs with chondroitinase of cAMP in vivo after SCI [182,183]. These studies report additional functional benefits in the co-grafted groups. One study assessed the effects of complex co-transplantation of SCs and OECs with the addition of chondroitinase pumps and demonstrated that this strategy induces functional recovery after SCI in rats [184].

The co-transplantation of OECs with different biomaterials such as: chitosan polymers, electrospun nanofibers or collagen scaffolds has been also investigated first in vitro [80,175,185–188]. Secondly, these combined therapies have been used to enhance axonal regrowth and functional recovery mainly after PNI or SCI in vivo [189–192]. In all these studies, it appears that the co-administration of OECs with biomaterials induces beneficial effects. More recently, these co-transplantation of OECs and biomaterials studies have al investigated the effects of the injection of microencapsulated OECs after SN injury in rats [193,194]. In these studies, OECs were encapsulated in alginate biogel and then transplanted in the SN after injury. The studies demonstrate that encapsulated OEC administration decreases nociception in this lesion model.

Recently, a new paradigm related to cellular therapy has been proposed and tested after injury. One of the main limitations of cellular therapy is that ideally cells should be transplanted as an autograft in order to limit the transplant rejection. To skirt this limitation, extracellular vesicle transplantation has emerged as a new and promising therapy. As such, OEC extracellular vesicles (OEC-EVs) properties have been assessed in vitro and in vivo. To date, two studies have demonstrated in vitro that OEC-EVs in co-culture with NPC display neuroprotective effects [195,196]. In the same way, one study has investigated the effects of OEC-EVs after PNI and demonstrated that OEC-EVs, when transplanted in an artificial nerve conduit, enhance nerve regeneration and functional recovery after transection of the SN [197]. Another limitation of cellular transplantation is this invasiveness. In fact, transplanted cells are mainly injected into the spinal cord parenchyma. Therefore, the effects of intravenous transplantation of OECs have been investigated. Two studies have demonstrated that intravenous administration of OECs can induce functional recovery and tissue repair by reducing neuroinflammation after SCI [85,198].

Lastly, in order to enhance the survival rate of OECs, which is very low after SCI, OEC transplantation has been combined with repetitive magnetic stimulation (RMS) [199]. This

study demonstrates that RMS treatment does not enhance OEC survival after transplantation in the injured spinal cord and that the combination of the two therapies does not induce any additional benefit.

Finally, as discussed above, one study assessed the potential that OECs could have to deliver therapeutic transgenes through the nasal pathway. In this study, researchers demonstrated that OECs can migrate from the PNS to the CNS and be used as a vector to deliver antitumor drugs to the brain [161].

To conclude: very few cell types possess the same properties as OECs and the same ability to improve tissue repair and functional recovery in such wide range of injury models. That is why we can hope that the few limitations regarding their use in clinical, notably the invasiveness of the biopsy needed to obtain OB-OECs, could be overcome in the near future, allowing their transplantation after CNS or PNS injury.

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Abbreviations

ALS	amyotrophic lateral sclerosis
BMSC	bone mesenchymal stem cells
CNS	central nervous system
CSPG	chondroitin sulfate proteoglycan
CST	corticospinal tract
CXCCL	C-X-C motif chemokine ligand
DREZ	dorsal root entry zone
DRG	dorsal root ganglion
ECM	extracellular matrix
FRS	functional rating scale
MCAO	middle cerebral artery occlusion
MIF	migration inhibitory factor
MSC	mesenchymal stromal cells
NPC	neural progenitor cells
NPY	neuropeptide Y
NSS	neurological severity score
OB	olfactory bulb
OE	olfactory epithelium
OECs	olfactory ensheathing cells
ONL	outer nerve layer
PNI	peripheral nerve injury
PNS	peripheral nervous system
PON	primary olfactory neuron
POS	primary olfactory system
RMS	repetitive magnetic stimulation
SCs	Schwann cells
SCI	spinal cord injury
SN	sciatic nerve
VMC	ventral mesencephalic cells
TBI	traumatic brain injury
TNF-α	tumor necrosis factors alpha

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