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REVIEW
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The Immunological Roles of Olfactory Ensheathing Cells in the Treatment of Spinal Cord Injury

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Spinal cord injury (SCI) is a devastating type of neurological disorder of the central nervous system (CNS) with high mortality and disability. The pathological processes of SCI can usually be described as two stages, namely, primary and acute secondary injuries. Secondary injury produces more significant exacerbations of the initial injury. Among all the mechanisms of secondary damage, infection and inflammatory responses, as the principle culprits in initiating the second phase of SCI, can greatly contribute to the severity of SCI and numerous sequelae after SCI. Therefore, effectively antagonizing pro-inflammatory responses may be a promising treatment strategy to facilitate functional recovery after SCI. Olfactory ensheathing cells (OECs), a unique type of glial cells, have increasingly become potential candidates for cell-based therapy in the injured CNS. Strikingly, there is growing evidence that the mechanisms underlying the anti-inflammatory role of OECs are associated with the immune properties and secretory functions of these cells responsible for anti-neuroinflammation and immunoregulatory effects, leading to maintenance of the internal microenvironment. Accordingly, a more profound understanding of the mechanism of OEC immunological functions in the treatment of SCI would be beneficial to improve the therapeutic clinical applications of OECs for SCI. In this review, we mainly summarize recent research on the cellular and molecular immune attributes of OECs. The unique biological functions of these cells in promoting neural regeneration are discussed in relation of the development of novel therapies for CNS injury.

Keywords: olfactory ensheathing cells (OECs), cell therapy, phagocytosis, anti-inflammation, immunomodulation, spinal cord injury (SCI)

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INTRODUCTION

Spinal cord injury (SCI) is a kind of servere neurological disease generally caused by a variety of traumas or diseases that usually result in complete or incomplete neural function deficiency. Among all the directly or indirectly causal external factors resulting in SCI, traumatic factors, such as traffic accidents, falls and sports/recreation, are the most common aetiologies of SCI (1–3). Additionally,

there are a number of nontraumatic causes of SCIs, mainly arising from discopathies and tumors. Due to severe incapacitation of the limbs below the injured segment after SCI, SCI not only causes considerable physical suffering and mental distress to patients themselves, but also incurs substantial economic burdens for families and society (4). According to incomplete statistics, SCI affects more than two million people worldwide (4–6). Therefore, finding ways to repair damage to spinal cord tissue is a common goal in modern medicine. Of course, understanding the molecular and cellular mechanisms contributing to the pathophysiology of SCI is essential for developing more effective therapeutic interventions.

In general, the pathophysiological types of SCI are characterized as acute, secondary and chronic phases (7, 8). Primary damage to the spinal cord occurs as a direct result of the initial trauma, such as compression, shearing, laceration, transection, stretch, or distraction, leading to immediate haemorrhage or vasospasm and rapid cell death (8–10). Concomitantly, Secondary injury closely follows in an ongoing way characterized by further damage to neuronal and glial cells and is accompanied by paralysis, intense pain, and progressive neurological damage (11–13). This phase usually occurs within minutes after injury and can last for weeks even months (14). The concomitant and consecutive pathological events in this phase involve the immune response, inflammation, apoptotic cell death, and formation of cystic cavitations and astroglial scars (15, 16). With the progression of secondary injury, a wide spectrum of subsequent events are triggered, leading to an uncontrolled degenerative cascade with concomitant expansion of the injury site and paralysis to adjacent spinal cord segments (7, 8, 13, 17). During these pathological events following SCI, a striking inflammatory response plays a crucial role in the occurrence and progression of SCI, and the time-course of changes in inflammation also plays a significant role in the recovery of the tissue and motor function (18, 19). Inflammatory stress usually progressively exacerbates secondary cell and tissue damage (18, 20, 21). In comparison, the most susceptible, and first to be affected, cells are the neurons in the injured spinal cord. Furthermore, neurons, unlike other cells, have a limited capacity for spontaneous regeneration and self-repair after SCI (21, 22). This is mainly due to the inhospitable and further deteriorating microenvironment resulting from SCI, which does not support neuronal regeneration (22, 23). Therefore, to achieve an effective neuronal regeneration, it is essential to promptly ameliorate, or even reverse the growth-inhibiting environment created by various unfavorable factors, including inflammation. Although the treatment of SCI has been extensively studied over the past several decades, including surgical, pharmacological, physical, cell-based and biomaterial-based therapies (24, 25), few successful therapeutic strategies are available to provide very effective treatment for patients with SCI. At present, many trials have shown that a wide variety of preclinical therapies are able to only delay the progression of SCI, although some approaches do show limited efficacy.

Owing to the complexity of the CNS and the inhospitable environment in and around the lesion site in SCI, combination strategies to promote tissue regeneration are currently being pursued (24). When considering strategies to improve therapeutic outcomes, cell therapy is envisioned as a promising treatment approach for SCI, particularly in promoting neural repair and/or replenishing lost cell populations in the injured area. Recent research has identified that OEC transplantation as a promising therapeutic approach for SCI in clinical trials due to its unique characteristics such as anti-neuroinflammation, growth-promoting factor secretion, and debris clearance activity (26–29). This review will focus mainly on the immunological role of OECs, including special bio-functions that create an environment conducive to neural regeneration by cell transplantation, to promote recovery following SCI.

ORIGIN AND DISTRIBUTION OF OECS

Olfactory ensheathing cells (OECs) are a specialized type of glial cell population in the olfactory nervous system that accompany and envelop bundles of primary olfactory axons (28, 29). The olfactory system is capable of continually and rapidly turning over its neuronal population throughout the lifespan, mainly owing to the glial environment (29, 30). Among these glial cells, OECs are thought to play pivotal role in neurite outgrowth and the establishment of functional connections along the olfactory neuraxis when new olfactory sensory neurons are generated from the stem cells in the olfactory epithelium (30–32). Unlike other types of glial cells derived from neural crest (peripheral glia) or neural tube (central glia), OECs are speculated to arise from neural progenitors in the neural crest (33–35)and populate as OEC precursors in the olfactory placode during early development (36). Given that mature OECs derived from OEC precursors all originate from the olfactory placode, the olfactory placode is also viewed as the origin of OEC populations (36, 37). During development of the olfactory nervous system, the cluster of epithelial cells in the lamina propria (LP) mainly consists of two different types of neural precursor cells, namely, globose basal cells (GBCs) and horizontal basal cells (HBCs) (31, 32). GBCs are likely to be the prominent progenitor cells in the olfactory epithelium that give rise to both neurons and nonneuronal cells such as OECs. In general, HBCs remain relatively quiescent. When HBCs are specifically induced to divide in response to certain cues and reconstitute the olfactory epithelium by regenerating GBCs, repopulation of both the neuronal and glial lineages of the olfactory epithelium is achieved. Differentiating OEC progenitors leave the invaginating olfactory placode and gradually migrate towards the telencephalic vesicles (31, 32). The differentiated cells keep contact with the developing olfactory nerve, and ultimately penetrate the forebrain to form the olfactory nerve layer (ONL) in the olfactory bulb (OB), indicative of their location (38, 39). The olfactory system mainly consists of the olfactory epithelium in the nasal cavity and olfactory nerves which reside in the peripheral nerve system (PNS), and the OB, which resides in the CNS (**Figure 1**). Currently, it is widely accepted that OECs mainly reside along the olfactory nerve and the outer nerve layer

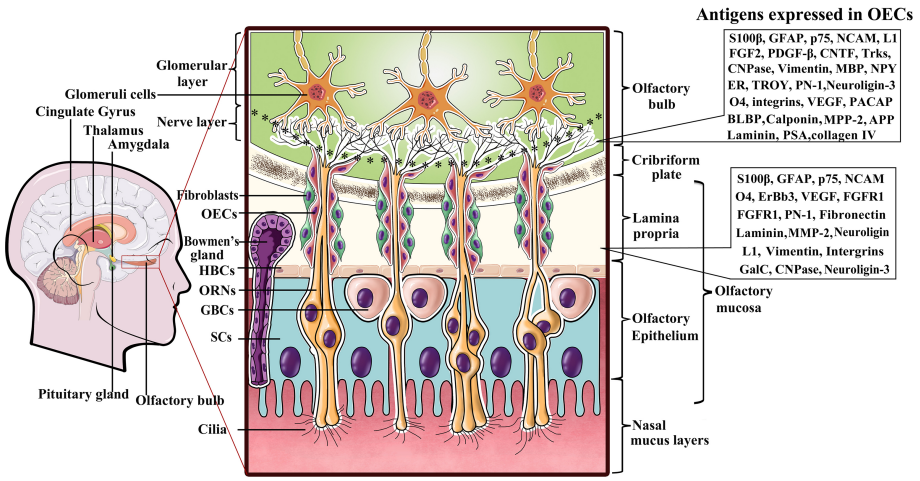

FIGURE 1 | A diagram representing location of olfactory ensheathing cells (OECs) and antigen expression within the primary olfactory system. Listed to the right are several molecules expressed by OECs in the LP and ONL. OECs wrap fascicles of ORN axons along their tortuous route through the LP in the PNS. Olfactory nerves and concomitant OECs pass through the cribriform plate of the skull and enter the OB in the CNS to form the ONL. ORN axon terminals into glomerular layer to form asymmetrical synaptic contacts with glomeruli cells. LP, lamina propria; ORNs, olfactory receptor neurons; GBCs, globose basal cells; HBCs, horizontal basal cells; SCs, sustentacular cells.

of the OB (38, 40, 41). With development and maturation, OECs gradually exit the LP to encase the olfactory nerves, and pass through the cribriform plate and reach the OB at the olfactory nerve layer (**Figure 1**). In the event of lesion formation, OECs guide the olfactory axons of newly generated olfactory neurons through the LP towards the ONL and into the glomeruli layer where they reinnervate their target cells (42). Overall, OECs accompanying the olfactory nerves are connected end-to-end to form a continuous sheath structure enveloping the olfactory axons from their origin in the LP to their termination in the OB.

ANTIGENIC PROPERTIES OF OECS

Although OECs are a specialized type of glial cells that bridge the boundary between the peripheral and central olfactory systems, and exhibit numerous molecular and cellular properties of both Schwann cells and astrocytes, they are obviously distinguishable from both Schwann cells and astrocytes by differential molecular expression characteristics (43, 44). Early evidence that antigenically distinct OEC subpopulations exist in the olfactory system was largely attributed to their different locations and developmental stages. It is now clear that OECs in the peripheral olfactory nerves and the central ONL of the OB express a series of antigens that can be detected with a variety of cellular and molecular techniques (**Figure 1**). Despite the uncertainties regarding the distinct molecular characteristics of OECs from different species, the general consensus is that all OECs in the LP exhibit S100β expression and weak GFAP as well as neural cell adhesion molecule (NCAM) expression, while those in the ONL are positive for the low-affinity neurtrophic receptors p75, NCAM and GFAP (35, 45). Nonetheless, there are distinct molecules expressed in OECs that reside in the LP versus those in the ONL. To date, it has been shown that OECs in the LP are positive for integrins, vascular endothelial growth factor (VEGF) and fibroblast growth factor receptor-1 (FGFR1) in addition to the aforementioned molecules, whereas those in the olfactory nerve layer of the OB are negative for these factors (29, 30, 46). In contrast, those in the ONL are positive for fibroblast growth factor-2 (FGF2), platelet-derived growth factor-beta (PDGF-β), ciliary neurotrophic factor (CNTF), tropomyosin receptor kinases (Trks), Neuropeptide Y (NPY) and estrogen receptor (ER) etc., while those in the LP are not (30, 46, 47). More surprisingly, apparent differences in OEC markers have also been found in the inner and outer layers of the ONL. For instance, NPY was reported to be coexpressed with p75 in OECs in the outer layer but expressed without p75 in the inner layer (48). Although researchers have proposed the possible functions for some OEC markers, such as VEGF, NCAM, p75, and FGF2, the markedly distinct expression patterns remain elusive.

S100β belongs to the S100 family of Ca^{2+}-binding proteins that participate in regulating numerous intracellular events including protein phosphorylation, cell differentiation and proliferation, and is extensively expressed in Schwann cells (49, 50). GFAP, an intermediate filament cytoskeletal protein, is generally accepted to be an astrocyte marker. Despite S100β and GFAP being OEC-specific antigens, in rodents first appear in the peripheral olfactory nerves of the embryo but also appear in the ONL prior to birth (31, 45, 46). Strikingly, the expression of these markers is initially limited to the outer ONL and then gradually appears later in the inner ONL (31, 51, 52). In addition, there is a remarkable difference in GFAP and S100β expression during the developmental period of major innervation. In adulthood, the expression pattern is generally uniform throughout the ONL, with relatively intense immunoreactivty to S100β and GFAP in both inner and outer layers of the ONL.

The inconsistency in S100β and GFAP expression is likely dependent on animal age (embryo, newborn, or adult), species, OEC neuroplasticity and major innervation of the bulb (31, 36, 46, 48).

p75, NCAM and O4 are mainly markers for OECs throughout the olfactory system during development, and their expression oscillates markedly in adulthood (30, 46, 53). For example, the expression of p75 is entirely absent in innermost ONL. Likewise, O4 was previously demonstrated to be coexpressed with p75. However, subsequent research revealed that OECs do not express O4. This immunopositive signal is likely to arise from the confusion of axonal membrane fragments that adhere to OECs or are engulfed by OECs (53, 54). In addition to NCAM, other adhesion molecules including laminin, L1, fibronectin and collagen IV (55, 56), and extracellular matrix molecules such as metalloproteinase-2 (MMP-2) (57) and amyloid precursor protein (APP) (58), are expressed by OECs at all developmental stages. These molecules potentially regulate axon adhesion migration, guidance and interactions with other cells and act as growth-promoting substrates for ORNs. However, in adults, the levels of these molecules sharply reduced or even negligible (35, 57). These dynamic expression changes are predominantly attributed to the development of the olfactory nerve system and OEC plasticity, leading to the variability in antigenic expression. Nevertheless, the controversy regarding the localization of the described above antigens has not been conclusively resolved.

Due to OEC heterogeneity and anatomic locations, the expression patterns of certain antigens are usually variable. Neuropeptide Y (NPY) is expressed in OECs during the development of the ONL, but its obviously declines, and cannot be detected in OECs in either the inner ONL or the peripheral olfactory system in adulthood (31, 48, 59). Despite the apparent difference in NPY expression between the central and peripheral olfactory systems, different NPY expression patterns also exist in the inner and outer layers of the ONL, with NPY mainly displaying high expression in the inner layer of the ONL and negative or weak expression in the outer layer of the ONL (48, 59, 60). At present, the differential NPY expression pattern remains unknown. However, the variability in antigenic expression is attributed to the heterogeneity of OECs, differential regulation of expression during development and adulthood, and the use of different species.

Apart from the main antigens described, there are some specific antigens that exhibit different expression patterns in the olfactory system, such as integrins, VEGF, and FGFR1 which are expressed in OECs in the LP but not in the ONL of the OB (30, 31, 61, 62). In contrast, the expression of PDGF-β, CNTF, Trks, and ER is prominent in OECs throughout in ONL of OB, rather than in OECs in the LP (30, 31, 63, 64). In addition, a number of differences in antigen expression still exist in OECs both *in vivo* and *in vitro*, as well as in the olfactory mucosa and bulb of neonatal and adult animals. Although no experimental data are available to support the antigenic difference between these two temporally and spatially different sources of OECs, a currently prevalent notion that is widely held is that the antigenic heterogeneity in OECs mainly results from the existence of OEC subpopulations, contamination with astrocyte-like cells, different development phases, various culture conditions, and the number of OEC passages (31, 46, 65). Francesehini et al. (66) reported that distinct culture conditions allowed for OECs to adopt divergent morphologies and vary the expression of certain antigens. For instance, E-NACM expression in OECs was relatively weak in serum-free medium, while progressively increasing high expression in OECs appeared after switching to medium containing-serum (31, 67). Regardless, p75 and GFAP remained relatively constant. These data fully implicate the intrinsic morphological and functional plasticity of OECs.

Given the striking similarities between the characteristics of OECs and Schwan cells, OECs should share multiple antigenic and morphological properties with Schwann cells; for example, spindle-shaped OECs are immunoreactive for myelin basic protein (MBP) in their extending processes (68, 69). In particular, embryonic OECs are myelinating cells when cocultured with dorsal root ganglion (DRG) neurons *in vitro* (68, 70). In a subsequent study, the same medium did not cause upregulation of MBP by OECs in neuron-free cultures (71). These data imply that MBP expression in OECs relies upon the culture system and the different developmental stages of the cells. Nevertheless, the expression of MBP by OECs remains controversial because several studies have found that OECs show only weak expression of the peripheral myelin protein during the early postnatal period (72). The results reveal that OECs require different milieu molecular cues to initiate the intracellular machinery to synthesize MBP to form a myelin sheath within their microenvironment. In addition to MBP, galactocerebroside (GalC), a specific cell-surface antigenic marker for oligodendrocytes and myelin OECs, was found to be expressed by OECs (67, 69, 73, 74). This indicates that OECs also share oligodendrocyte features. Likewise, OECs derived from the neonatal rat OB show weak but unambiguous expression of GalC in explant cultures (53, 67, 74). Despite the disparities in cumulating evidence either supporting or refuting the ability of OECs to myelinate axons with peripheral or central myelin, the GalC expression pattern *in vitro* is generally acknowledged.

2′,3′-Cyclic nucleotide 3′-phosphohydrolase (CNPase), an enzyme ubiquitously localized to noncompact myelin areas, is a critical antigen in OECs (47). CNPase is one of the earliest proteins to be synthesized during development, and it is thought to be mainly involved in myelination (75). Apart from at sites containing myelin, there are smaller amounts of CNPase elsewhere in the body, which are commonly associated with the mitochondria. CNPase immunoreactivity in the thick myelin enclosing larger axons is relatively stable and varies more in the sheaths surrounding thinly myelinated axons (75–77). Once axonal damage occurs, the CNPase distribution becomes more diffuse and returns to normal as the axons are repaired. More interestingly, CNPase was found to exhibit inter-species variation. Namely, CNPase is stably expressed in dog OECs but not in rats. Altogether, in light of the antigen expression patterns of OECs, whether this reflects some special properties of

OECs as a result of their intimate spatial contact with axons and whether OEC biofunction is impacted by the surrounding environments within peripheral and central transitional regions remains to be elucidated.

Although OECs express a high number of detectable antigens and the markers mentioned above, the expression patterns of certain antigens are variable as individual subpopulations of OECs exhibit distinct anatomical localization and behaviour. Recent compelling studies have also revealed that most kinds of antigens or markers of OECs are changeable both *in vivo* and *in vitro*. This mainly depends on the context, such as the developmental stage (embryonic and postnatal stages, early and late development stages, and adult stage), animal species and culture conditions (36). For instance, Franceschini et al. (78) found that GFAP-positive OECs coexpressed polysialic acid (PSA) during developmental stages but that PSA expression rapidly decreased in adults. Similarly, it was stated that Calponin, an actin-binding protein, is specific marker for OECs from the embryonic OB that distinguishes OECs from SCs *in vitro* and *in vivo*. Unfortunately, other studies have shown that calponin is not robustly expressed in adult OECs (79). This discrepancy may be due to the difference in developmental stage. In addition, the expression of several specific markers on OECs fluctuates due to neuropathological and pathophysiological changes in the olfactory system. Previous studies have shown that OECs express brain lipid binding protein (BLBP), a radial glia protein, throughout adulthood, and this potential indicator of the plastic phenotype of OECs displays high expression following olfactory nerve system injury (36, 80). Likewise, due to the continuous neurogenesis in the olfactory system throughout lifespan, the guidance of pioneer neuronal axons and establishment of the olfactory nerve tracts are orchestrated by OECs, thus displaying variability in molecular expression and morphology depending on the context. Indeed, there are still several markers for OECs that are exhibited instable expression pattern. Here, these markers are not described since there is still considerable controversy. Overall, distinct OEC antigen expression profiles are reflective of plasticity in morphology, function and behaviour. Of course, it is not yet clear whether OECs from one species share *in vivo* and *in vitro* antigentic properties with other counterparts, or exhibit an obvious heterogeneity. In light of current data, this is closely associated with the intrinsically different properties of OECs.

IMMUNE PROPERTIES OF OECS

The olfactory system is exposed to the external environment through the nasal cavity and is, therefore, vulnerable to bacteria- or fungus-inflammation. However, most instances of CNS infection do not occur through the olfactory system. Several lines of evidence suggest that OECs exert crucial roles in protecting the dynamic nature of the primary olfactory nervous system against invasion by pathogenic organisms (29, 53, 80–82). This is mainly attributed to the unique biological properties of OECs as follows: innate immune function and immunoregulatory molecule secretion (26, 27, 29, 80). Additionally, OEC phagocytic activity has been shown to maintain microenvironmental homeostasis to support neuronal survival and outgrowth (27, 82, 83). These interesting findings have important implications for improving the efficacy of OEC-based treatments for SCI.

OEC Phagocytic Activity

It is now generally acknowledged that degenerative/dead neurons and apoptotic neuronal debris caused by CNS injury usually create an extrinsic adverse environment, which is envisioned to hamper neural survival and neurite sprouting and regeneration. Therefore, the expeditious removal of apoptotic cells is crucial for preventing neural cell lysis and consequent production of deleterious pro-inflammatory and antigenic autoimmune components. The olfactory system is a specialized physical structure in which olfactory receptor neurons (ORNs) can be continuously renewed throughout the lifespan (29, 84). In the context of olfactory nerve turnover, extensive apoptotic olfactory neural debris is continuously generated during normal development and adulthood (29, 85). Strikingly, no excess neural cell-derived debris is constantly packed in the olfactory system, while microglia/macrophages remain largely absent from the olfactory nerve and are excluded from direct contact with axon fascicles. Conversely, OECs are still the major professional phagocytes that remove dead cells and axonal debris arising from neuronal apoptosis (29, 81). Even after damage to the olfactory nerves, OECs are the primary phagocytic populations responsible for the removal of cellular debris, and thus very few macrophages are recruited to clear neural debris (80, 81). In addition to eliminating neural debris, OECs readily phagocytose bacteria and are of paramount importance in protecting the olfactory nerve from being infected by microbes (82, 83), since some of their normal physiological and immune functions involve combating or controlling more severe infections. *In vitro* studies have reported that OECs possess a number of key phagocytosis-related receptors such as Toll-like receptor 4 (TLR4), phosphatidylserine receptors and mannose receptors (26, 29, 80, 86–88), which bind to and are activated by LPS or various pathogen-associated molecular patterns (PAMPs) or recognize phosphatidylserine on an apoptotic target, leading to the engulfment of various microbes, apoptotic and necrotic cell debris and dead cells by OECs (29, 80, 86). In addition to performing phagocytosis *via* recognition of "eat me" signals, OECs also utilize such bridging molecule (milk fat globule-EGF factor 8, MFGE-8)-mediated phagocytosis for damaged "self" and invading "non-self" clearance (80, 89). Apart from the abovementioned cytokines, some anti-inflammatory cytokines, such as IL-10 and transforming growth factor beta (TGF-β), also promote OEC phagocytic activity *via* the signaling through the other relevant receptors (80, 89, 90). Moreover, OECs were reported to adopt "microglia-like" cells with higher levels of CD11 expression, by which OECs could efficiently internalize and degrade various detrimental targets. Although the molecular mechanisms involved in OEC-mediated phagocytosis remain mostly unknown, an increasing number of studies have demonstrated that OEC phagocytic activity can effectively

contribute to neural cell survival and neurite outgrowth *in vivo* and *in vitro* (26, 27, 89–91). Intriguingly, our recent *in vitro* study of phagocytosis by OECs demonstrated that OEC phagocytic activity could be strengthened by curcumin, a component of turmeric (27), which at low concentrations could augment the OEC-mediated clearance of axonal debris by approximately 10-fold by involving mitogen-activated protein (MAP) kinases (27). In comparison, no impact of curcumin on Schwann cell phagocytic activity was found, highlighting the importance of OEC phagocytic activity in pro-regenerative processes. In summary, phagocytosis by OECs not only plays an active role in creating a favorable environment for neuronal turnover in the olfactory system, but also aids the overall processes of neural regeneration and recovery by transplantation after SCI.

Release of Cytokines

OECs have been shown to share some characteristics with inflammatory cells in addition to sharing features with astrocytes and Schwann cells, allowing OECs to prevent microbes from invading the CNS along the olfactory pathway. By using several advanced techniques including transcriptome and proteome analysis, bioinformatics, high-throughput microscopy, RT-PCR, and image analyses, a much more profound understanding of the specific molecular profiles that form the basis of the synergistic pro-regenerative abilities of OECs can now be promulgated, additional chemokines responsible for the modulation of the immune response and pro-regenerative processes have been progressively uncovered. The expression of cytokines and pro-regenerative molecules in OECs has been reported in a series of studies (**Table 1**). Microarray analyses have shown that OECs express chemokine (CXC motif) ligand 1 (CXCL1), monocyte chemotactic protein 1 (MCP-1), chemokine (CX3C motif) ligand 1 (CX3CL1), and chemokine (CXC motif) ligand 12 (CXCL12) (27, 105–107). Numerous cytokines produced by OECs are likely to interact with immune cells, exerting regulatory functions (106). For example, microglial expression of chemokine (CXC motif) receptor 4 (CXCR4) could have an autocrine impact on OEC-secreted cytokines (106). The primary olfactory nervous system has a great innate capacity to regenerate and repair itself after most injuries, and OECs remove large amounts of degenerative or necrotic cell debris, which requires bridging molecules to aid

TABLE 1 | Main cytokines, chemokines and other factors expressed in olfactory ensheathing cells.

Cytokines/chemokines/other factors	Method of detection	References
CXCL1	Microarray, Immunostaining	Vincent et al. (43, 48)
MCP-1	Microarray, PCR	Su et al. (29)
CX3CL1	Immunostaining	Ruitenberg et al. (92)
CXCL12	Microarray, PCR	Hao et al. (27)
MFGE-8	RT-PCR, Immunostaining	Li YJ, et al. (89)
IL-10	ELISA, RT-PCR	Guo et al. (90)
IL-4	ELISA, RT-PCR	Guo et al. (90)
TGFβ	ELISA, RT-PCR	Guo et al. (90)
IL-1β	Microarray, PCR, Immunostaining	Su et al. (29)
IL-6	Microarray, PCR, Immunostaining	Su et al. (29)
SPARC	*In situ* hybridization, Immunostaining	Au E, et al. (93)
Cebpb	Microarray, PCR	Su et al. (29)
TNFα	Microarray, Immunostaining	Su et al. (29)
MMP2	microarray, Immunostaining	Tisay and Key (94)
SERPIN1	Microarray, Immunostaining	Roet et al. (95)
PAR1	Microarray, proteomics	Au E, et al. (93)
THBD	Microarray, proteomics	Simón et al. (96)
SCARB2	Microarray, RT-PCR, Immunostaining	Roet et al. (95)
RND1	Cellomic assay, Immunostaining	Roet et al. (95)
VAV1	Cellomic assay, Immunostaining	Roet et al. (95)
ESM1	Microarray, RT-PCR	Roudnicky et al. (97)
CYR61	Microarray, RT-PCR, Immunostaining	Brigstock (98)
ANGPT2	RT-PCR, Immunostaining	Roudnicky et al. (97)
S100A9	Microarray, Immunostaining	Roet et al. (95)
BDNF	ELISA, Immunostaining, ELISA	Woodhall et al. (99)
NGF	ELISA, Immunostaining, ELISA	Woodhall et al. (99)
CNTF	RT-PCR, Immunostaining,	Wewetzer et al. (100)
NT-3	RT-PCR, Immunostaining	Lipson et al. (101)
NT-4/5	RT-PCR, Immunostaining, ELISA	Lipson et al. (101)
GDNF	RT-PCR, Immunostaining, ELISA	Woodhall et al. (99)
Neuturin	RT-PCR, Immunostaining	Lipson et al. (101)
CDH2	Immunostaining	Akins et al. (102)
NCAM1	Immunostaining	Tisay and Key (94)
Laminin	Immunostaining	Doucette (56)
Fibronectin	Immunostaining	Doucette (56)
Tenascin	Immunostaining	Deckner et al. (103)
L1	Immunostaining	Witheford M, et al. (104)

attachment (80). OECs can express milk fat globule-EGF factor 8 (MFGE-8), a bridging molecule, to work with integrin receptors, leading to phagocytosis of apoptotic debris (80, 89, 108). Meanwhile, OECs release anti-inflammatory cytokines such as IL-10 and TGF-β, and promote phagocytosis *via* integrin receptors (29, 89, 90). Consistently, our more recent *in vitro* study showed that OECs were capable of phagocytosing apoptotic and necrotic neural debris under inflammatory insult conditions, which promoted neuronal survival and neurite outgrowth (26, 27, 90). This enhancement is mainly associated with some cytokines released from OECs. These factors include IL-10, IL-4 and TGF-β in addition to neurotrophic factors (brain-derived neurotrophic factor, BDNF; nerve growth factor, NGF; and glia-derived neurotrophic factor, GDNF) (90). Importantly, OECs can be induced to express OX-42, a macrophage marker, indicating that OECs can be attracted to endocytose bacteria (80, 83, 109). Strikingly, a recent study by Su and colleagues revealed that OECs exist in two different states, resting and activated, and that OECs can be activated by LPS and act as phagocytes in the clearance of apoptotic ORNs (29). In their study, they found that exposure of OECs to LPS resulted in increases in the expression of MCP-1, CCAAT/enhancer binding protein (Cebpb), CXCL-1, inducible nitric oxide synthase (iNOS), TNF-α, IL-1β, and IL-6, and enhanced the phagocytic capacity of OECs (29). Although the abovementioned cytokines and chemokines include some pro-inflammatory factors, OEC phagocytosis of necrotic bodies leads to only relatively low levels of IL-6 and TNF-α (80, 110, 111). The increases in the production of pro-inflammatory cytokines do not cause a significant pro-inflammatory response (80). Likewise, it has been documented that OECs actually degrade live *E. coli*, and respond to *Staphylococcus aureus* infection both *in vivo* and *in vitro* with an inflammatory response that involves the secretion of IL-6, TNF-a, NF-κB, and iNOS (87, 112–114). These distinct results are mainly attributed to the heterogeneity of OECs. Generally, the NFκB signaling pathway is a key facilitator of responses to injury and inflammation (115). OECs, or molecules produced by OECs can inhibit NFκB activation, thus exerting a neuroprotective impact after a variety of CNS injuries and stresses. Indeed, OECs secrete several factors such as TNF-α and IL-1β to likely recruit macrophages and modulate inflammation and neurodegeneration (30, 31, 80). However, little clearance of apoptotic neural debris by microglia/macrophages and severe inflammation have been found in the normal or injured olfactory system, implicating a failure to recruit of microglia/macrophages to the olfactory nerve system.

Microarray and proteomic studies have also identified a large number of molecules that are relatively highly expressed in short-term cultured OB-OECs or LP-OECs (30). In light of the microarray data, the roles of matrix metallopeptidase-2 (MMP2), serine protease inhibitor E1 (SERPINE1), protease-activated receptor-1 (PAR1) and thrombomodulin (THBD) are being investigated (30, 96). Several studies have revealed that these factors derived from OB-OECs directly or indirectly participate in the regulation of neurite outgrowth, promoting axonal regeneration (30, 93). Of note, proteomics studies have showed that secreted protein acidic and rich in cysteine (SPARC) expression in LP-OECs plays an important role in axonal extension and regeneration (93). Moreover, using a cellomic approach, scavenger receptor class B member-2 (SCARB2) was identified as protein that promotes regenerating axonal sprouting in injured sensory neurons. This protein is mainly involved in cholesterol transfer and transport of glucocerebrosidase (GBA) to the lysosome which are crucial for rapid axonal membrane biosynthesis during regeneration after nerve injury (95, 116). Apart from SCARB2, Rho-family GTPase-1 (RND1) and VAV1 were also screened out to regulate cytoskeletal remodeling (30, 65, 117, 118) and the formation of cellular protrusions in a cellomic assay. Of particular interest are endothelial cell-specific molecule-1 (ESM1), cysteine-rich protein-61(CYR61) and angiopoietin-2 (ANGPT2), which are secreted by OECs and promote angiogenesis by directly stimulating endothelial cells (97, 98, 118, 119).

Three other immunomodulatory cytokines secreted by OECs, S100A9, CX3CL1 and TGFβ2, can have direct or indirect effects that promote neurite outgrowth and protect neurons (30, 61, 95, 120). S100A9 supports neurite extension by modulating a variety of inflammatory processes in the complex cellular microenvironment after CNS injury (30, 121, 122). It was indicated to protect against microglial and macrophage neurotoxicity. Similar to S100A9, CX3CL1, also known as the cytokines fractalkine, is abundantly expressed in OECs, and has a significant impact on neurite growth (92, 95, 123). In addition to the abovementioned cytokines, a wide variety of neurotrophic factors and extracellular matrix (ECM) molecule involved in neural repair were revealed to be expressed by OECs through classic immunochemistry, ELISA, and qPCR, biochemical and proteomics analyses. These identified molecules include neurotrophic factors such as NGF, BDNF, NT-3 NT4/5, Neurturin, CNTF, and GDNF (35, 99–101, 124–126) and several growth-promoting cell adhesion and extracellular matrix molecules, including cadherin (CDH2), NCAM1, Laminin, Fibronectin, Tenascin and L1 (20, 57, 94, 99, 102, 103, 127). These results suggest that transplantation of OECs is emerging as a favorable and promising strategy for treating PNS and CNS injuries. The regeneration-promoting properties of OECs can be at least partly attributed to these bioactive molecules produced by OECs (61, 101). Nevertheless, it is necessary to further investigate the role of specific molecules in the regeneration-promoting effects of OECs in the complex physiological context of SCI.

OECS and Anti-Inflammatory Activity

The olfactory epithelium (OE) and the underlying LP are continuously exposed to a variety of potentially infectious environmental agents. However, most microbial invasion does not occur from the olfactory mucosal surfaces *via* the olfactory route to the CNS. It is possible that the key innate immune roles of resident OECs and their unique biological characteristics are envisioned to be efficient in preventing microbial pathogens from invading the CNS *via* the olfactory nerve. Nevertheless, epithelial injury may increase susceptibility to invasion. Inflammation is a primary part of the initial response to CNS injury and is characterized by blood brain/spinal barrier (BBB/BSB)

impairment in the acute phase, which is accompanied by the infiltration of immune cells and accumulation of cytokines near the injury site (128). Infiltrating immune cells are recruited to the injured area through glial chemokines and cytokines released by damaged neural tissue and subsequent upregulation of chemotactic cellular adhesion molecules and selectins on endothelial cells (129–131). During the acute insult phase, which typically lasts for a few hours, the levels of pro-inflammatory cytokines rapidly increase and peak (132–134), seemingly leading to an augmentation in damage (135, 136). However, recent advances in the understanding of CNS injury show that microglia during the first week post-SCI, microglia may exert a rather neuroprotective effect by directly modulating the formation of the astroglial scar and thus sequester blood-derived inflammatory cells in the lesion core to avoid inflammation-mediated tissue damage (137, 138). This finding is consistent with Bellver-Landete's (139) observation that the depletion of microglia using PLX3397, a CSF1R/c-Kit inhibitor, resulted in disrupted glial scar formation, enhanced immune cell infiltrates, delayed astrocyte repopulation and reduced neuronal survival and thus disrupted neurological recovery. The study revealed that microglia-derived cytokines, such as IGF-1, play a pivotal role in modulating astroglial function in pathological conditions. Notwithstanding the beneficial effect of microglia on neural regeneration after SCI, this study suggested that treatment of targeting these cells should be initiated during the first week post-SCI, as this time frame was considered to be the best therapeutic window (139). In the hyper-acute/acute phase ranging from 2 to 7 days following injury, there appear to be large stepwise decreases in the levels of typical pro-inflammatory cytokines (129, 133, 139). In light of these findings, delayed microglial depletion after spinal cord injury reduces chronic inflammation and neurodegeneration. Likewise, a larger number of microglia/macrophages and T cells are also recruited to the damaged area, and the levels of anti-inflammatory factors increase (136, 140, 141). It has been suggested that inflammation is likely to support the later stages of neural regeneration (142, 143), suggestive of the sub-acute phase of transformation from exacerbation to repair in SCI (30, 31). Hence, for regulation of the inflammatory microenvironment, transplantation of OECs should be focused on the sub-acute stage of SCI. As mentioned previously, Schwann cells have the potential to produce some cytokines and their receptors, which are likely to interact with infiltrating immune cells to modulate inflammatory responses (144, 145). Usually, the inflammatory responses following SCI are predominantly modulated by the dynamic balance of the macrophage/microglia quiescence and activation (146, 147). Following nerve injury, neural degeneration initiates the activation of microglia/macrophages, leading to the secretion of several MMPs and the proinflammatory cytokines IL-1β, IL-2, IL-6, TNFα, and IFNγ (148–151). Some cytokines not only further activate resident microglia and recruit much more inflammatory cells (neutrophils, macrophages, lymphocytes, and natural killer cells) from the systemic circulation, amplifying the inflammatory responses, but also destroy the internal microenvironment, resulting in neuronal cell death and reduced axonal regeneration (148, 152, 153). For instance, the proinflammatory cytokines IL-1β, IL-6, and TNF can elicit extensive inflammatory responses, while the chemotactic factors MCP-1 and MIP-1α can promote astroglia and microglia activation and accumulation in the injured area (7, 154–156). Astroglia and microglial, are the major resident innate immune in the CNS and release diverse inflammatory factors involving in the inflammatory signaling cascade, aggravating secondary pathological damage to the CNS; however, miroglia also play a beneficial role in CNS injury in the early stage (138, 139). Nevertheless, implanted OECs in the lesioned spinal cord tissue are likely to interact with these cells to regulate inflammation. Secreted anti-inflammatory cytokines, such as IL-4, IL-10, and TGF-β, are capable of modulating the inflammatory response, resulting in a decrease in the production of several pro-inflammatory factors such as IL-1β, TNF-α and IL-6, by microglia/macrophages (143, 157, 158). Moreover, these cytokines also reduce infiltration of immunocytes, such as macrophages, neutrophils, and monocytes, into inflammatory lesions in the spinal cord by downregulating chemokines *in vivo*, thereby effectively attenuating subsequent inflammation (159, 160). Although a growing number of researchers have achieved a substantial progress in the understanding of the cellular mechanisms underlying these findings, much still remains elusive due to the extremely complex relationship between the nervous and immune systems with the involvement of OECs. Therefore, it is also of pivotal importance to elucidate the effects of cytokines released from OECs in the immunological milieu after SCI.

Immunomodulation

The regenerative capacity of the adult mammalian spinal cord after injury is extremely limited, mainly due to multifaceted adverse factors in addition to inflammatory cell activation that together contribute to a non-permissive environment and minimal functional recovery (1, 16, 160, 161). Neuroinflammation is part of the primary responses to injury and might be linked to the characteristics of innate immune cells and immunological molecules involved in the injury area (19, 162, 163). Four different stages after SCI can involve the cytokines IL-1α, IL-6, IL-8, IL-11 and TNF-α as well as the chemokines granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) (7, 21, 150, 151, 164, 165). Additionally, resident microglia are activated in the vicinity of the injury site, and neutrophils, macrophages, lymphocytes, and natural killer cells are recruited from the systemic circulation, causing inflammatory damage through several destructive species, including free radicals, ROS, nitric oxide (NO), and excitotoxins (7). Furthermore, numerous astrocytes are activated to produce chondroitin sulfate proteoglycans (CSPGs) and form an astroglial scar (7, 21, 150, 151, 164, 166). Overall, these factors constitute an intricate microenvironment that is detrimental for neural regeneration. Once OECs are implanted into the injured spinal cord zone, numerous molecules released from OECs, as acute positive and

negative regulators participate in modulating the expression and activity of cytokines and chemokines (167). For instance, the anti-inflammatory cytokines IL-4, IL-10, TGF-β, and IL-13 produced by OECs protect against cell degeneration or death by modulating iNOS and NO production in the context of LPS/IFN-γ stimulation (90, 158, 159, 161). Meanwhile, these anti-inflammatory cytokines are indicative of inhibition of the release of the pro-inflammatory cytokines TNF-α, IL-1β, IL-2, and IL-6 (161, 165). As a consequence, OECs delay the activation of microglia/macrophages, the time-dependent multiphasic inflammatory response, and the peak of the immune response, leading to neuroprotection against further inflammatory damage (26, 29, 35, 63, 112, 167). More significantly, our latest study also found that exosomes released from OECs could efficiently inhibit inflammation following SCI *via* polarization of M1 microglia to M2 microglia, leading to neural survival and axonal regeneration (165). In addition, a growing number of studies have revealed that IL-4 and IL-10 can effectively modulate the infiltration of monocytes, neutrophils and macrophages (149, 160, 168–170). Recently, an interesting study revealed that OECs possess strong innate immune modulatory properties, displaying clearance of cellular debris mediated by IL-10 and TGF-β (29). Moreover, the interaction between OECs and reactive astrocytes may diminish the formation of a CSPG scar due to IL-10-mediated upregulation of MMP-13, an enzyme necessary to later degrade CSPG (35, 167). This indicates that IL-10 can skew pro-inflammatory monocytes into a producive phenotype. Most importantly, most of the anti-inflammatory factors (IL-4, IL-10, IL-13 and TGF-β) derived from OECs aside from innate immune cells, participate in modulating cell survival, proliferation and migration, and thus promote regeneration after SCI (29, 35, 170). Others (IL-4, and TGF-β) have a more direct impact on neuronal survival or neurite regeneration. This is mainly attributed to the modulatory effects of these factors on acute and chronic immune cell responses, the expression of detrimental molecules [iNOS, NO, reactive oxygen species (ROS) and Caspase], the local secretion of neurotrophin, and the synthesis of inflammatory factors (7, 35, 143, 167). Thus, the OEC-mediated regulation in the injured area, possibly through growth factor and cytokine modulation, plays a crucial role in cell-based therapy for neural regeneration.

POSSIBLE MECHANISM OF BY WHICH OEC TRANSPLANTATION PROTECTS AGAINST INFLAMMATION IN THE TREATMENT OF SCI

Although the molecular mechanism underlying the pro-regenerative properties of OECs is currently unknown, compelling studies have revealed that implantation of OECs promotes neural repair and functional recovery of the injured spinal cord (30, 35, 45, 63, 69, 90, 167), and that the therapeutic potential of OECs is mainly due to their unique immune cell properties and consequent modulatory abilities. First, OECs secrete several growth factors, axon-guiding molecules and basement adhesion components, which create a supportive environment conducive to neural survival, migration and neurite extension (7, 104, 126, 167). The relevant molecules are described in the above sections. Second, the critical aspects of nerve tissue repair include structural remodeling and support, immunomodulation, neurotrophic factor production and antigenic stimuli. OECs reduce the levels of inhibitory molecules in the lesion core, preventing neuronal death and axonal dieback. Furthermore, OECs limit immune cell activation and infiltration and mitigate secondary tissue damage (25, 62, 105, 126, 167). Third, the other aspects of OECs conducive to achieving improvements in the microenvironment include moderating the detrimental effects of the glial scar, stimulating angiogenesis and metabolizing toxic macromolecules (30, 31, 167). Regardless of the pro-regenerative potential of OECs in the treatment of SCI, the hostile and inhibitory environment arising from acute SCI may result in the progressive death of transplanted OECs, ultimately resulting in abortive or unsatisfactory outcomes for neuroregeneration. Accordingly, identifying an effective strategy to boost the ability of OECs to proliferate is of pivotal importance. Our latest study found that curcumin, a natural polyphenol derived from turmeric, could effectively activate OECs, achieving improved proliferation and migration. Therefore, use of curcumin-activated OECs can overcome low cell survival (27, 90). Similarly, Khankan et al. (167) showed that cyclosporin-A, a potent immunosuppressant, could enhance graft survival and augment the beneficial effects of OECs, thus ensuring the efficiency of implanted OECs. Overall, utilizing OECs as a cell-based therapeutic agent for nerve repair in the injured spinal cord has focused on the ability of these cells to support the regeneration of injured neurons. This is mainly based on the potential of OECs to display innate immune properties, produce cytokines, and create an specific environment, identifying these cells as a useful therapeutic agent for SCI.

PERSPECTIVE ON OEC RESEARCH

OECs are cells that harness a promising neural repair-promoting potential that can be useful for promoting neural regeneration in the injured spinal cord. The specific molecular mechanisms underlying the synergistic pro-regenerative properties of OECs have been revealed. A growing number of studies have showed that OECs possess unique abilities to secrete growth factors, modulate the immune response, stimulate angiogenesis, and phagocytose cell debris, which actively contribute to spinal cord regeneration. The unique features of OECs appears to orchestrate the molecular signaling for many of these processes related to neural regeneration in a coordinated fashion in other inner cell types. A profound understanding of the different molecular and cellular biological characteristics of OECs is very important for utilizing at the appropriate stage for specific clinical applications. In addition, the different molecular pathways in these diverse cells that are present in OECs will provide specific insights into the factors that could prove crucial

in determining a favorable outcome for cell transplantation. Hence, important new molecular insights into the mechanisms that govern successful neural regeneration will probably be yield useful results in the near future.

AUTHOR CONTRIBUTIONS

HY conceived of the review and supervised the project. YJ wrote the manuscript. JG and XT contributed to literature review and editing. XW contributed to literature review and compiled figures. DH contributed to content and editing. All authors contributed to the article and approved the submitted version.

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Figure 1 included in the present manuscript was created using biorender.com.

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