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Advancithe Secretory Role of OECs in Therapy for Spinal Cord Injury

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Abstract: ***Spinal cord injury (SCI) is a devastating type of neurotraumatic state of the central nervous system (CNS) with high mortality and long-term disability. Due to growing prevalence of SCI, combined with the severe incapacitation of the limbs below the level of injury, SCI has imposed considerable physical and psychological stress to victims and huge economic burden on both families and society. Pathophysiologically, SCI is typically categorized into two distinct phases: primary and secondary injury. The primary injury causes immediate disruption of the blood-spinal cord barrier, triggering the release of numerous pro-inflammatory factors. This inflammatory cascade can lead to persistent infection and exacerbated inflammation, which significantly hinder functional recovery. Therefore, effectively mitigating the inflammatory responses is considered a critical therapeutic strategy for improving outcomes after SCI. Among the various therapeutic strategies for treatment of SCI, olfactory ensheathing cells (OECs), a unique type of glial cells, have received considerable interest in the field of cell-based therapy for SCI. Emerging evidence indicates that the anti-inflammatory effects of OECs are closely linked to their intrinsic secretory profile and immunomodulatory properties, which play a crucial role in ameliorating the detrimental microenvironment by injured nerves. Therefore, an in-depth understanding of the mechanisms underlying the secretory roles of OECs in enhancing neural regeneration is of great clinical significance. This review aims to summarize recent advances in molecular characteristics of OECs and the molecular mechanisms of their secretory functions in mitigating neural injury.***

Keywords: Spinal cord injury, Advancithe Secretory Role, OECs, Central nervous system (CNS).

1. Introduction

Spinal cord Injury (SCI) is recognized as one of the most severe neurological disorders globally, and has garnered growing attention in recent years. Patients with SCI often suffer from lifelong neurological deficits and severe disabilities [1]. Epidemiological studies indicate that while SCI has traditionally been more prevalent among younger populations, its incidence among the elderly has been steadily rising in recent years [2]. SCI is frequently associated with risk factors such as violence, risk-taking behaviors, and alcohol use, all of which may directly or indirectly lead to SCI [3]. Globally, SCI affects approximately 236 to 4,000 individuals per million popuplation, and its incidence is rising annually [4]. Typically, Spinal cord injury results from damage to the vertebral bone structures, nerve roots, intervertebral discs, and related ligaments, initiating a cascades of pathophysiological changes. Mechanistically, SCI progresses through two distinct phases: primary and secondary. Most spinal cord injuries are frequently traumatic, with the resulting nerve damage being predominantly primary [5]. This phase is followed by a series of secondary events characterized by widespread neuronal death, disruption of the blood-spinal cord barrier, and activation of complex biochemical cascades [6]. Secondary injury is characterized by the release of pro-inflammatory factors, infiltration of immune cells, hypercalcemia, and lipid peroxidation [7,8]. Inflammation plays a pivotal yet dual role in the pathology of SCI. While a moderate inflammatory response aids in clearing cellular debris and pathogens from damaged tissue areas; excessive inflammation exacerbates tissue damage and hinders recovery efforts Given that neurons within the spinal cord are particularly susceptible to injury during these pathological processes due to their inherent vulnerability [9-11] it is essential to promptly ameliorate, or reverse the pathological microenvironment created by various unfavorable factors, including inflammation. Additionally, a critical issue lies in the intrinsically restricted regenerative potential of adult CNS neurons following injury. Anyway, he poor regenerative potential is largely attributable to an inhibitory microenvironment caused, to a certain extent, by neuroinflammation following SCI [12]. Current treatment strategies for SCI usually encompasses a range of approaches, from surgery and pharmacological agents to physical therapy, and well as cell-based therapies. Unfortunately, these treatment strategies can merely provide palliative benefits, failing to achieve long-term functional recovery or reverse the underlying pathology [13]. Thus, there is a critical need to develop novel interventions capable of mitigating or reversing the devastating consequences of SCI.

Among emerging treatments, cell-based therapy is envisioned as a promising treatment approach for SCI, particularly in promoting neural repair and/or replenishing lost neural populations in the injured CNS [14]. Compelling evidence has showed transplantation of various cell types including OECs, mesenchymal stem cells (MSCs), and neural stem cells (NSCs), as a promising therapeutic approach for SCI in pre-clinical trials [15-17]. Although each cell type has demonstrated certain beneficial effects, OECs have emerged as a highly promising candidates due to their unique characteristics such as anti-neuroinflammation, growth-promoting factor secretion, and clearance activity, as well as compatibility with the complex regenerative environment of the CNS [18]. In recent years, OECs have attracted considerable attention for their role in promoting neuroregeneration across a diverse preclinical models of SCI [19,20]. Based on the foundation, this review highlights recent advances in understanding the immuno-modulatory, anti-inflammatory, and secretory roles of OECs in spinal cord repair. It also explores the molecular mechanisms underlying the reparative effects of OECs on SCI. A profound understanding of OEC biological functions is expected to

provide valuable insights to guide future clinical applications in the treatment of SCI.

2. Origin of OECs

OECs are a specialized type of glial cells widely distributed throughout the olfactory nervous system, where they play a crucial role in continually supporting neurogenesis. The olfactory nervous system itself constitutes an interface between the central nervous system (CNS) and the peripheral nervous system (PNS), encompassing the olfactory mucosa (OM), olfactory nerves, and the outer nerve layer of the olfactory bulb (OB). A defining characteristic of this system is the continuous turnover of olfactory receptor neuron (ORN) populations within the olfactory epithelium, which persists under both physiological and injured conditions. Anatomically, the olfactory nervous system consists of two main components: the olfactory bulb (OB) in the brain and the olfactory mucosa (OM) in the nasal cavity [21]. The OM is composed of the olfactory epithelium, the vascularized lamina propria, and peripheral sensory neurons that collectively form the olfactory nerve, whereas the OB belongs to the CNS. Olfactory sensory neurons which are susceptible to damage from environmental exposure, continuously undergo death and are replacement. The axons of these newborn neurons subsequently re-innervate the olfactory bulb, forming new synaptic connections with target cells [22]. This unique regenerative ability is linked to the unique properties of olfactory glia, particularly the specialized architecture of the olfactory system and the characteristics of OECs, which are pivotal for successful functional regeneration in the CNS following injury [23]. OECs, a specialized type of glial cells, can be subdivided into OM-OECs and OB-OECs based on their anatomical origins [24]. Moreover, emerging evidence indicates that these two subtypes also possess distinct gene expression signatures. The distinct gene expression profiles are reflective of their functional specializations: OM-OECs overexpress genes involved in wound healing and extracellular matrix remodeling, whereas OB-OECs express genes that contribute more prominently to neural development [25]. Despite these differences, both subtypes provide a permissive substrate for nascent axon growth [26]. Early studies suggested an olfactory epithelium origin for OECs, proposing that they migrate alongside neurons and wraps their axons [27]. Unlike other types of glial cells derived from the neural crest (peripheral glia) or neural tube (central glia), it is now widely accepted that OECs arise from neural progenitors in the neural crest [28]. Since mature OECs derived from their precursors all originate from the olfactory placode, the olfactory placode is also regarded as a primary origin of OECs. The physiological state of OECs in adults remains incompletely understood; however, olfactory sensory neurons undergo renewal approximately every 28 days. During this process, olfactory neurons extend new axons that fasciculate into bundles, traverse the lamina propria (LP), penetrate the cribriform plate, and ultimately reach the olfactory bulb (OB) in the CNS, where they form synapses with their glomerular targets [29]. OECs play several essential roles in the olfactory system, such as fostering a conducive microenvironment for axon growth and guidances. Within the OM, sensory axon bundles converge to form the first cranial nerve, which enters the CNS and establishes functional synapses in the OB. Along this trajectory, OECs envelop, OECs envelop and accompany the axons from the OM to the OB [26]. By wrapping their cytoplasmic processes around axons, OECs provide insulation and shield them from exposure to inhibitory factors, thereby supporting normal axonal growth and development until they reach the olfactory glomeruli.

3. Molecular Characteristics of OECs

Studies have demonstrated that OECs represent a distinct type of glial cells based on their unique morphological characteristics [30]. In the olfactory system, OECs are slender cells with laminar processes that envelop olfactory nerves. Under experimental culture conditions, they display flat, bipolar, or multipolar morphologies [31,32]. A variety of markers identified through in vivo and *in vitro* immunostaining are expressed in the olfactory nerve layer (ONL) of the OB in the nervous system [33,34]. However, the expression profiles of these proteins vary depending on the differentiation state of the cells and their anatomical location within the CNS and PNS [32]. For instance, *in vivo* studies reveal that OECs within the adult OB express S100β (an intracellular calcium-binding protein) and glial fibrillary acidic protein (GFAP) [35]. Conversely, OECs located outside the ONL exhibit low levels of p75NTR and embryonic form of neural cell adhesion molecule (E-NCAM). In contrast to this pattern, OECs situated inside the ONL do not express p75NTR or E-NCAM; instead, they express neuropeptide Y (NPY) [35]. Furthermore, p75NTR expression is restricted to cells residing the outer ONL while S100β is expressed in cells throughout the ONL. Additionally, GFAP-positive but S100β-negative glial cells have been observed in adult mice.

However, *in vitro* studies have identified two phenotypic subpopulations of OECs. The Schwann-like subpopulation exhibits a spindle-shaped morphology with strong expression of p75NTR, but weak or absent expression of E-NCAM and GFAP. In contrast, the astrocyte-like subpopulation resembles flat astrocytes and expresses both E-NCAM and GFAP [30]. Although these two distinct populations have been described both *in vivo* and *in vitro*, it remains challenging to definitively confirm their existence in the ONL, due to variations in protein expression across different developmental stages. Gene expression profiling further supports the distinction between OEC subpopulations, particularly between those derived from the OM-OECs and OB-OECs [25]. Despite their differences, both phenotypes belong to the same cell lineage and undergo rapid interconversion [36,37]. Additionally, treatment with glial cell line-derived neurotrophic factor (GDNF) has been shown to induce a morphological shift in OECs from a multipolar shape to a form characterized by small cell bodies with longer processes [38]. The migratory ability of OECs is another key feature of interest [39]. Phenotypic variation, such as the transition between flat and spindle-like morphologies, reminiscent of astrocytes and Schwann cells, respectively, is mediated by cytoskeleton reorganization, enabling transformation between subpopulations [40]. Meanwhile, other potential markers such as calmodulin, an actin-binding protein, have been proposed to help distinguish OECs from Schwann cells in both *in vivo* and *in vitro* settings [41,42]. However, research this marker has yielded inconsistent and even contradictory results [43]. In fact, this protein can also be used to define subpopulations

of mucosal connective tissue cells, astrocytes and fibroblasts, and lacks specificity to OECs [44].

Due to their distinct genetic characteristics, OM-OECs and OB-OECs also have significant differences in the cytokine secretion and functional roles. OM-OECs primarily contribute to functional recovery through angiogenesis and modulating inflammatory processes. In contrast, OB-OECs are more involved in axonal extension and growth [45,46], secreting neurotrophins essential for neuronal development and axonal outgrowth. such as, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and various neuregulins [47-51]. OM-OECs, on the other hands, are responsible for cell adhesion and the secretion of matrix molecules like laminin, fibronectin, and NCAM, which provide a supportive substrate for axonal sprouting [52-54]. Among these, laminin has been shown to play a more particularly important role in the axonal extension of olfactory neurons in vitro [55]. More latest study shows that Reelin (Reln) and Connective tissue growth factor (CTGF), also have been identified as critical facilitators of axonal outgrowth into the inhibitory injury core environment. Cytokines and growth factors, including vascular endothelial growth factor (VEGF) and transforming growth factor (TGF-β3), also contribute significantly to neural protection and repair [55,56]. Furthermore, matrix metalloproteinases (MMPs) such as MMP-2 and MMP-9 secreted by OM-OECs also play a important role in axonal regeneration by degrading the extracellular matrix (ECM) and reducing neural scar formation [51]. (summarized in Table 1).

Table 1: Factors expressed by OM-OEC and OB-OEC

OEC subtype	Factors	References
OM-OEC	E-NCAM Laminin Fibronectin	Chuah et al. [52] Lu et al. [53] Ramón-Cueto et al. [54]
	MMP2 y MMP9	Huang et al. [44]
	Vascular endothelial growth factor(VEGF) transforming growth factorβ 3(TGF)-β3	Au et al. [56] Pastrana et al. [50]
OB-OEC	Brain derived neuro-trophic factor (BDNF)	Pastrana et al. [50]
	Glial cell line-derived neurotrophic factor (GDNF)	Moreno-Flores et al. [60]
	Nerve growth factor (NGF)NGF	Boruch et al. [47]

4. Secretory Activities of OECs

OECs play special roles in the olfactory system, encompassing multiple key functions, Firstly, they providing a conducive environment for the growth and development of sensory axons [57]. Secondly, OECs secrete P0 to form myelin sheaths around demyelinated axons, thereby facilitating the lifelong growth of ORN axons. Furthermore, OECs maintain intercellular communication through calcium signaling pathways triggered by substances such as glutamate [58]. In addition to these roles, OECs can also secrete diffusible neural factors, including neurotrophins (NTs) and other growth factors, which primarily promote axon extension of olfactory neurons in vitro [59]. Neurotrophins exert their effects on axonal growth by binding to specific tyrosine kinase receptors (Trks). These Trks mediate intracellular signaling through the activation of G proteins such as Ras, Rap-1, and Cdc-42 (as shown in Table 2), thereby creating a favorable environment for axonal growth and elongation. Current research indicates that the presence and secretion of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) in OECs are related to neurotrophin signaling pathway [60]. Meanwhile, studies have detected mRNAs encoding S100β, Ciliary neurotrophic factor (CNTF), and artemin in the ONL of the OB. mRNAs encoding RET and TrkC receptors are also present in the ONL. However, as most of these findings derived from studies on cloned OEC lines, it has been hypothesized that these trophic factors may exert autocrine effects on OECs through specific ligand-receptor pairs, such as NGF/p75NTR, GDNF/GFRα-1, and NTN/GFRα-2 [60,61], (as shown in Table 2). Notably, the expression of the co-receptor subunit RET in response to GDNF and NTN appears limited. RET mRNA was undetectable in cultured OECs, suggesting that these cells may lack functional RET-mediated transduction pathways for these neurotrophic factors. Instead, OECs likely operate through an alternative mechanism involving factor sequestration and presentation to neurons [51]. Furthermore, certain trophic factors derived from OECs, such as the NGF-1 isoform, a specific neuregulin, exert their effects through ErbB receptors [62,63].

OECs express multiple neurotrophic factors that play a promoting roles in CNS growth and development, with S100β being particularly significant for brain development [64]. Additionally, these cells produce some cytokines such as interleukin-6 (IL-6), CX3CL1, and transforming growth factor (TGF-β3), which contribute to neuroprotection and repair [56,66], (Table 2). Notably, CX3CL1 is highly expressed in OECs and significantly promotes neurite growth. Furthermore, OECs expressed cytokine receptors including tumor necrosis factor receptor (TNFR) [52], IL-1 receptor [50], and leukemia inhibitory factor receptor (LIFR). (Table 2). Meanwhile, OECs exhibit subtype-specific molecular profiles. Subpopulations with low p75NTR expression exert effects on anti-inflammation and axon guidance through the expression of EphB2 receptors and other molecules [66]. In contrast, the high p75NTR subpopulations express laminin, type V collagen, and type I collagen to regulate the extracellular matrix and neurite growth [67]. LP-OECs express some specific protein combinations, including CD44, vascular endothelial growth factor (VEGF), and NG2. Among these, NG2 appears have a inhibitory effect on axonal growth, but this conclusion is controversial. However, LP-OECs also express secreted acidic proteins and cysteine-containing proteins, which can significantly promote axonal extension and regeneration [68].

Table 2: Expression of pro-regenerative factor

	Factors	Refernces	Receptors	Refernces
Neurotrophic factors/ cytokines	Neuregulins (NRG) Nerve growth factor (NGF) Brain derived neuro-trophic factor (BDNF) Glial cell line-derived neurotrophic factor (GDNF) Neurturin (NTN) Neurotrophin (NT)-4	Boruch et al. [47] Lipson et al. [48] Pastrana et al. [50] Woodhall et al. [51]	ErbB2-4 P75NTR TrkB GFRa-1 GFRa-2	Franceschini et al. [31] Lipson et al. [48] Moreno-Flores et al. [60.64] Woodhall et al. [51]
	S100β	Franceschini et al. [31] Lipson et al. [48]		
	Interleukin-6 (bulbectomy) CX3CL1/fractalkine Other cytokines	Nan et al. [65] Pastrana et al. [50] Ruitenberg et al. [66]	IL-6R and LIFR (bulbectomy IL-6R and LIFR (bulbectomy	Nan et al. [65] Pastrana et al. [50] Roet et al. [59]

Table 3: Expression of f Inhibitory factors

	Factors	Refernces	Receptors	Refernces
Neurotrophic factors/ cytokines	Nogo Myelin Chondroitin sulphate proteoglycan (CSPG)	Nocentini et al. [69] Reginensi et al. [70] Su et al. [61]	NgR	Nocentini et al. [69] Su et al. [61] Woodhall et al. [51]
	Ephrin A1	Pastrana et al. [50]	Fibulin-3	Vukovic et al. [72]

It is noteworthy that OECs exhibit a dual role in nerve regeneration, exerting both promoting and inhibitory effects. OECs also secrete inhibitory factors such as Nogo and NgR receptors (as shown in Table 3), with the latter particularly affecting OEC migration *in vitro* [67-71]. Strikingly, this inhibitory effect may impair their ability to penetrate glial scars. However, studies have identified some factors that enhance OEC migration, including GDNF [38], chondroitin sulfate proteoglycans (CSPGs) [69], Nogo-A, the axon guidance molecule Slit-2 [45], and fibrin-3 [72]. Additionally, during OEC migration, inhibitory molecules such as EphrinA1 and secreted semaphorins like Sema3A may also be secreted [60]. In conclusion, OECs mediate nerve regulation through the secretion of bioactive molecules, highlighting their pivotal role in the regenerative process.

In addition to secreting molecules beneficial to nerve regeneration, OECs also release some factors that regulate inflammatory responses. The inflammatory response after SCI involves a complex interplay of cytokines and molecular mechanisms. Initially, cellular debris from injury area stimulates inflammation [73]. These stimulants activate resident immune cells, including microglia, macrophages, and astrocytes [74]. Subsequently, the polarization of microglia induce the activation of astrocytes, leading to the massive deposition of chondroitin sulfate proteoglycan (CSPG) and the formation of astrocytic scars, which can inhibit axonal regeneration [75]. Meanwhile, activated glial cells release specific chemokines and cytokines such as IL-1, IL-6, and TNF [76]. Notably, these cytokines recruit peripheral blood cells to the injury site, exacerbating secondary tissue damage as inflammation progresses. The inflammatory response has dual effects: it can cause further damage to secondary nerve tissues [77], but it can also promote axonal and post-injury myelin regeneration [78]. Therefore, leveraging the beneficial aspects of the inflammatory response while minimizing tissue damage is crucial for nerve regeneration and functional recovery after SCI. OECs effectively mediate the inflammatory response, creating favorable conditions for SCI prognosis, underscoring the need to understand the underlying mechanisms.

OECs play a multifaceted role in inflammation regulation. Studies have shown that OECs can upregulate the expression of cytokines such as leukemia inhibitory factor (LIF) and interleukin-4 (IL-4) during mouse neurogenesis [65]. These factors, secreted by macrophages recruited by OECs, exhibit anti-inflammatory effects. OECs also express chemokine (CXC motif) and its cognate ligand (CXCL1), which may function as a neurotrophic chemotactic agents following OEC transplantation to the injury site. Signal factors such as CXCL12, CXCL4, CX3C motif and its ligand CX3CL1 can recruit neutrophils and leukocytes, playing a crucial role in the inflammatory process [79]. Macrophages are recruited to the injury site through the mediation of inflammatory monocyte chemotactic protein-1 (MCP-1) and its receptor (CCR2). TROY, a member of the tumor necrosis factor (TNF) family, activates the nuclear factor κB (NF-κB)-mediated signaling pathway, which is crucial for the activation of macrophages and microglia and the subsequent release of various inflammatory factors. OECs or the cytokines they release can inhibit NF-κB signaling, thereby alleviating the inflammatory response and protecting nerves. Signal molecules such as TNF and IL-1β also recruit macrophages to regulate inflammation and neurodegeneration [80,81]. Moreover, OECs secrete anti-inflammatory factors (IL-10, IL-13, TGF-β) that downregulate pro-inflammatory factors (TNF, IL-1β, IL-6) to a certain extent [82,83]. Studies have confirmed that IL-1α, IL-2β and other factors related to inflammatory responses are significantly downregulated after OEC transplantation. This response is associated with the IL-1 receptor antagonist IL-1Ra secreted by OECs. IL-1Ra reduce the activation of microglia, thereby decreasing the release of related pro-inflammatory factors [84]. The anti-inflammatory factors secreted by OECs also promote cell survival and migration, reducing scarring and promote regeneration [85]. For instance, IL-1 and TGF-β can regulate the expression of harmful molecules such as ROS and the secretion of neurotrophic factors, directly affecting nerve survival [86]. In conclusion, the cytokines secreted by OECs exert a regulatory

effect on inflammation by slowing the activation of inflammatory cells (microglia and macrophages) and balancing anti-inflammatory and pro-inflammatory factors, thereby forming an important pathway for neuroprotection in injuries.

5. Immunomodulation of OECs

The regenerative capacity of the adult mammalian spinal cord after injury is highly limited, largely owing to a combination of multifaceted inhibitory factors, including the activation of inflammatory cells, which collectively create a non-permissive environment, thereby impeding substantial functional recovery [87,88]. Neuroinflammation, a pivotal response to injury, may be influences by the properties of innate immune cells and immunological molecules present at the lesion site [89]. After SCI, four distinct phases have been identified, characterized by the involvement of cytokines such as IL-1a, IL-6, IL-8, IL-11 as well as TNF-a along with chemokines including granulocyte colony-stimulating factor (GCSF) and granulocyte-macrophage colony-stimulating factor (GMCSF) [90-94]. In addition, resident microglia become activated near the injury site while macrophages, neutrophils, lymphocytes, and natural killer cells are recruited from the systemic circulation. These immune cells contribute to inflammatory damage through the release of destructive species such as free radicals, ROS, nitric oxide (NO), and excitotoxins [92]. Furthermore, numerous astrocytes are activated, leading to the production of chondroitin sulfate proteoglycans (CSPGs) and the formation of glial scar [90-93]. Together, these factors create a microenvironment that is hostile to neural regeneration. When OECs are implanted into the injured the spinal cord, they release a variety of molecules that function as acute positive and negative regulators modulating the expression and activity of cytokines and chemokines [95,96]. For example, OECs produce anti-inflammatory cytokines such as IL-4, IL-10, TGF-b, and IL-13, which help protect against cell degeneration or death by regulating inducing nitric oxide synthase (iNOS) and NO production under of LPS/IFN-g stimulation [97,98]. Concurrently, these anti-inflammatory cytokines suppress the release of the pro-inflammatory cytokines including TNF-a, IL-1β, and IL-6 [93]. Consequently, OECs delay the activation of microglia/macrophages, mitigate the time-dependent multiphasic inflammatory response, and reduce the peak immune response, thereby conferring neuroprotection against further inflammatory injury [99,100]. Notably, our recent study demonstrated that Il-4 released from OECs activated by curcumin can effectively suppress inflammation following SCI by polarizing M1 microglia toward an M2 microglia. This polarization promotes neural survival and axonal regeneration [93]. Moreover, accumulating evidence indicates that both IL-4 and IL-10 can modulate the infiltration of monocytes, neutrophils and macrophages [101]. An recent intriguing study revealed that OECs possess potent innate immunomodulatory properties that facilitate cellular debris clearance through mechanisms involving IL-10 and TGF-β. In addition, the interaction between OECs and reactive astrocytes may reduce glial scar formation via IL-10-mediated upregulation of MMP-13, an enzyme essential for subsequent e CSPG degradation [99]. This suggests that IL-10 can trigger pro-inflammatory monocytes toward a reparative phenotype. Critically, most anti-inflammatory factors secreted by OECs, including IL-4, IL-10, IL-13 and TGF-β, contribute not only to immunomodulation but also to enhancing cell survival, proliferation and migration, thereby fostering regeneration following SCI [96,99]. Among these factors, IL-4 and TGF-β exert more direct effects on neuronal survival or neurite regeneration. These benefits are largely attributed to the ability of these factors to modulate immune cell responses, suppress harmful molecules such as iNOS, NO, ROS, and Caspase, stimulate local neurotrophin secretion, and regulate the synthesis of inflammatory mediators [90,99]. Therefore, OEC-mediated immunomedulation within the injured area, likely via growth factor and cytokine modulation, plays an essential role in cell-based therapies for neural regeneration.

6. Molecular Mechanism of OEC-Mediated Multifaceted Repair in SCI

Although the precise molecular mechanisms underlying the proregenerative properties of OECs remain incompletely understood, a growing body of evidence suggests that OEC-mediated multifaceted repair in the CNS is attributed to their multifaceted activities. These include promoting axonal sprouting, modulating astrocyte responses to inhibit scar formation, and phagocytosing bacteria and excessive neuronal debris, collectively contributing to functional recovery after nervous system injury [22]. Comparative studies between OM-OECs and OB-OECs transplanted in SCI models reveal that despite distinct characteristics, both cell types can reduce the lesion cavity size and promote axon bundle sprouting and growth [102]. OECs demonstrate remarkable neurotrophic capabilities when interacting with neurons both *in vivo* and *in vitro*, serving as permissive substrate for neurite and axon extension. Notably, OECs appear capable of forming channel-like structures that penetrate astrocytic barriers, which may facilitate regenerating axon growth, a feature that seems critical to their regenerative potential. Furthermore, OEC grafts promote regeneration of specific spinal cord tracts, likely through their secretory profile. The secretion of neurotrophic factors by OECs is conducive to their neural regeneration [50]. In the intact CNS, perineuronal nets (PNNs) surrounding neurons create a growth-inhibitory environment [103]. Fortunately, OECs counteract this by secreting MMP2 which degrades CSPGs within PNNs to enable axon regeneration [49]. This MMP2 production represents a fundamental mechanism of their regenerative properties. *In vivo* studies demonstrate that MMP2 production is particularly associated with corticospinal tract regeneration. Strikingly, OECs also express scavenger receptor class B member 2 (SCARB2), a type III glycoprotein that plays a crucial role in axonal regeneration. SCARB2 gene transfer has been shown to mediate dorsal column sensory axon regeneration, potentially through lipid metabolism and protein synthesis pathways. The lipoprotein secretory function of OECs appears crucial for regeneration. As special type of glial cells, OECs produce lipoproteins, particularly those containing cholesterol, which promote neurite growth and synapse formation in specific regions [104]. The transfer of these lipids to growing axons constitutes a essential aspect of the post-injury regeneration process.

In the complex post-injury environment of SCI, glial scar formation significantly impedes nerve regeneration.

Therefore, effectively preventing and mitigating glial scar formation is crucial for promoting functional recovery. The growth of new axons is particularly influenced by microenvironments rich in inhibitory factors, where the balance between these inhibitory signals and the promoting factors produced by OECs ultimately determines axonal regeneration outcome. Unlike Schwann cells (SCs), OECs can unique interactions with astrocytes and meningeal cells, allowing them to integrate with astrocytes under specific environments [105]. Although both OECs and SCs originate from the neural crest, they differ in their ability to form boundaries with astrocytes. SCs primarily establish these boundaries through the secretion of high level of HSPGs, which they produce greater quantities than OECs [106]. Antibodies against FGF1 and FGF9 disrupt these boundaries by interfering with their receptor signaling, a process regulated by HSPGs but also influenced by the weak expression of extracellular 6-O-sulfatases (Sulf1 and Sulf2) in OECs [106]. This reduced sulfatase expression enables OECs to integrate with astrocytes without forming distinct boundaries. OECs can induce changes in glial scars through their interactions with astrocytes. Their outer membrane continuities can bridge gaps in injured tissue, a feature closely related to axonal regeneration [50]. The absence of effective bridging mechanisms strategies in post-SCI cell transplantation presents a critical challenge: grafted cells frequently fail to traverse the lesion site, necessitating multiple transplantation loci to achieve sufficient coverage. Furthermore, OECs are recognized for their ability to penetrate glial tissue. Their characteristic of attenuating astrocyte reactivity has also been well-established [96]. These combined attributes penetrative capacity and astrocyte modulation, enables OECs to support to axonal regeneration even within glial scar environments. Through their membrane-associated signals and secreted factors, OECs can effectively counteract inhibitory influences.

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