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Transplantation or Transference of Cultured Cells as a Treatment for Spinal Cord Injury

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Abstract

Spinal cord injury (SCI) involves damage to the spinal cord causing both structural and functional changes, which can lead to temporary or permanent alterations. Even though there have been many advances in its treatment, the results of clinical trials suggest that the current therapies are not sufficiently effective. Recently, there has been a lot of interest in regulating this harmful environment by transplanting cultured cells and boosting their antiinflammatory cytokines and growth factors production. Several types of cells have been studied for SCI therapy including, Schwann cells (SC's), olfactory ensheathing cells (OECs), choroid plexus epithelial cells (CPECs), and immune cells (ICs) (lymphocytes, dendritic cells and alternative macrophage and microglia phenotypes). These treatments have shown to be promising and in this chapter, we will review the general aspects of transplanting these cells for SCI therapy as well as the neuroprotective and regenerative responses that different types of cells have reached in different SCI models. The mesenchymal stem cells (MSC) are one of the most well studied cell types; however, they were not included in this section because they will be reviewed in another chapter of this book.

Keywords: spinal cord injury, cultured cells, therapy

1. Introduction

SCI is a catastrophic condition that goes through two successive stages, which involves disturbances on ionic homeostasis, local edema, ischemia, focal hemorrhage, free radicals stress and inflammatory response [1]. SCI also causes partial or complete loss of sensory, motor and autonomic functions below the injury level, due to the interruption of the neural pathways. Nevertheless, cultured cells have successfully proved to achieve neuroprotective effects, by replacing or repairing damaged tissue, by neuronal survival, axonal growth, regulation of cytokine profiles and inflammation and motor recovery in animal models [2]. Cultured cells are promising strategies due to high variety of autologous cells that can be isolated and transplanted to patients; neural cells can up-regulate neurotrophic, growth and vascular factors to enhance the repair process in the spinal cord (SC). Also,

non-neural cells can be polarized in vitro to evoke antiinflammatory responses in order to modulate SCI microenvironment. This still requires intensive investigation because cells from neural tissues such as OECs could only be retrieved by craniotomy with general anesthesia, which needs, optimized surgical practices and excellent preclinical and clinical cares [3]. However, mononuclear cells such as macrophages or lymphocytes isolated from peripheral blood, become a less invasive strategy [4, 5]. Although the current treatments for SCI have proven to have certain improvement effects, there is no actual cure for SCI [6]. That is why in recent years cell transplantation has become one of the most investigated approaches to treat this kind of disorder [7, 8].

2. Cultured cells

In this section, we will review each cell type separately because there are many differences and similarities among them which are worth mentioning.

2.1 Schwann cells

Numerous cell types have been studied and proposed for transplantation, however, SC's have always been considered as one of the best candidates for this treatment [9–11].

SC's are the principal glia of the peripheral nervous system (PNS) [12]. SC's wrap around long segments of peripheral nerves and produce myelin, forming a multilayered membranous sheath that allows axons to propagate action potentials at a high speed [12, 13]. The myelination of the axons by glial cells (oligodendrocytes in the central nervous system (CNS) and SC's in the PNS) is believed to be the last evolutionary step in the vertebrate nervous system and it's key in understanding neurophysiology [12, 14]. There are two types of SC's, the myelinating and non-myelinating both come from the neural crest cells in early development stages [15]. SC's precursors migrate along with growing axons in peripheral nerves where they receive specific signaling such as Neuregulin 1 (NRG 1) in order to survive and later on differentiate into myelinating SC's [15, 16].

SC's are essential for normal motor and cognitive functions, long-time integrity of the axons and they play a crucial role in axonal regeneration in the PNS after injury [6, 14, 17]. SC's regeneration role is more evident when you compare the outcome of a blunt injury in the SC with a similar injury in a peripheral nerve in rodents [18]. In several studies, it was seen that after sciatic nerve crush, the axons were able to rapidly grow back to their targets, also redundant myelin was removed and replaced with new myelin surrounding the regenerated axons, resulting in a generally normal tissue at an impressive speed (3–4 weeks) [14, 19]. On the other hand, crushing the SC results in the formation of a lesion filled with fluid or matrix leading to axonal retraction, permanency of myelin debris and absence of axonal regeneration [20]. In the PNS, the injury triggers a broad set of changes in the differentiation of both injured neurons and SC's, causing neurons to switch their function from cell to cell signaling to axonal growth and SC's change their function from axonal maintenance to support axonal regeneration [18, 21, 22]. This means that the glia in CNS does not suffer the same remarkable transformation as the PNS to repair the nervous tissue after the injury [19].

Those are some characteristic that have led them to become one of the biggest proposed treatments in cell transplants seeking to recover motor functions after SCI [9, 11].

2.1.1 Schwann cell response to injury

Even though axonal degeneration in the distal stump takes about 2–4 days, SC's response to axonal damage can be detected within hours of the injury, suggesting there is some communication between injured axons and SC's which needs further investigation [23]. As said before, right after de injury, SC's and undergo a large series of changes in gene expression to dedifferentiate into a non-myelinating immature type of SC's and proliferate extensively [24]. In this process myelin associated molecules such as the key myelin transcription factor Egr2 (Krox20), cholesterol synthesis enzymes, structural proteins, including P0, myelin basic protein (MBP), and membrane-associated proteins like myelin-associated glycoprotein (MAG) and periaxin are down-regulated, whereas molecules that characterize SC's in their immature stage (before myelination) are up-regulated [25]. These include L1, Neural cell adhesion molecule (NCAM), neurotrophin receptor p75NTR, and glial fibrillary acidic protein (GFAP) [24].

Another process in this response is the presence of phenotypes which are not associated neither with immature SCs nor with the SCs of an undamaged nerve. The appearance of these cells is critical, and since their main function is repairing, we refer to them as repair SC's or Bungner cells (BC's) [24]. The repair process includes, first, the up-regulation of neurotrophic factors such as, Glial cell-derived neurotrophic factor (GDNF), artemin, Brain-derived neurotrophic factor (BDNF), Neurotrophin-3 (NT3), Nerve growth factor (NGF), Vascular endothelial growth factor (VEGF), and pleiotrophin which promotes the survival of injured neurons and axonal regeneration [26]. Second, the BC's up-regulates the expression of inflammatory cytokines including tumor necrosis factor (TNF)- α , interleukin (IL)-1 α , IL-1 β , Leukemia inhibitory factor (LIF), and Monocyte chemoattractant protein-1 (MCP-1), in order to recruit macrophages that will eliminate redundant myelin that inhibit axonal growth [27].

2.1.2 Schwann cell transplantation in spinal cord injury

One of the first clues implicating that SC's transplantation could serve as a treatment for SCI was found in a set of experiments held by David and Aguayo in 1981. The experiments demonstrated that peripheral neurons (PN) lose their ability to regenerate over long distances in the PNS when they are submitted within the environment of a CNS graft and contrariwise the limited ability of CNS neurons to regenerate after an injury was enhanced within the environment of a PNS graft [19, 28]. Thanks to those landmark studies and decades of research, we now know that the introduction of SC's after a SCI can promote axonal regeneration, reduce tissue loss, and facilitate myelination of axons in order to improve sensory motor function [11, 29, 30].

One of the best-known mechanisms by which SC's promotes axonal regeneration is by the formation of bridges across the lesion site. The bridge is a multicellular structure that crosses the lesion rostrally to caudally, providing an environment in which axons can grow and also covering the glial scar which limits axonal regeneration [31]. Furthermore, the transplantation of SCs provides a neuroprotective effect preventing neuronal death from the continuous inflammatory reaction involved in the SCI [10, 11].

The PN-auto graft was one of the first techniques to promote axonal regeneration in the CNS after SCI. The nerve graft, besides providing supportive SCs it also endorses the survival of axotomized SC neurons by upregulating the expression of neuronal nitric oxide synthase (eNOS), furtherly activating the NO- dependent cyclic-GMP pathway, which enhances survival in these neurons [32, 33].

In addition, the PN-grafts promote the expression of growth factors in the host SC such as NGF and BDNF, delaying the formation of the glial scar, which is key for successful regeneration [34]. Another studied strategy is transplanting dissociated SCs alone into the injury. After transplantation, dissociated SCs are able to elicit axonal in-growth and align to secrete substrates, serving as guidance for axonal regeneration [35]. Moreover, when it comes to transplanting, the SCs alone have an advantage over the PN-graft, which is that purified SCs have the potential of being engineered to overexpress growth-promoting factors and/or adhesion molecules to enhance axon growth [36]. Even though several studies indicate that they cannot migrate into the host tissue, therefore regeneration outside the injury/graft site was limited [37].

However, their repair effect is not enough to induce an axonal response that leads to a full recovery of the locomotor function [38]. This could be due to the fact that a high percentage of SCs are lost in apoptotic or necrotic processes in the first 3 weeks after transplant [39]. This low survival rate post transplantation may be attributed to the prejudicial environment of the SCI in which low oxygen levels, inflammatory cytokines, reactive oxygen species (ROS) and cell-mediated immune reactions predominate [10, 39]. Also, after the injury reactive astrocytes, meningeal cells, and microglia form the glial scar which becomes a physical and chemical barrier for axons to grow. The glial scar induces the secretion of axonal growth and myelin-associated inhibitors such as chondroitin sulfate proteoglycans (CSPGs), semaphorins, and myelin-associated proteins which limits the regenerative capacity of SCs when transplanted alone [37]. This suggests that SC transplantation needs to be combined with additional interventions in order to ensure successful axonal regeneration and sufficient functional recovery after SCI [29].

Because of the multiple mechanisms and complex pathophysiology involved in SCI, a significant therapeutic effect on functional recovery may not occur with the transplantation of SCs alone, meaning that a combinational therapy strategy is most likely to be the best option [9]. There are many different strategies that have been studied and have shown to have beneficial results. First, the suspension of SCs in bioactive matrices promotes their survival and enhances their capacity for supporting axonal regeneration. Second, the complementary administration of neuroprotective agents, growth factors and other molecules improves the effects of SCs at the lesion site. Third, the inhibition of the glial scar formation and/or the reduction of its inhibitory cues to obtain axonal growth from grafts into the adjacent SC. Fourth, the co-transplantation of SCs with other cell types such as OECs, neural stem cells (NSCs), MSC and others. The different types of combinations as well as their characteristics and outcomes are described in **Table 1**.

The use of another cell population like OECs in the combinatory cell therapy had demonstrated to boost the SCs effects.

2.2 Olfactory ensheathing cells

OECs are a population of glia cells that are residents in the PNS and CNS, which are commonly located in the central olfactory bulb (OB) and the nasal olfactory mucosa (OM) [56]. They are accompanied by the envelope of olfactory nerve fibroblasts (ONFs), so they can embrace the bundles of olfactory nerve fibers from the nasal mucosa to allow the synapsis in the OB [57]. Recent studies have demonstrated that OB transplants could be differentiated to create relationships with the periphery and brain [56].

OECs express a lot of neurotrophic factors, including BDNF, GDNF, and NGF which are relevant for the propagations and guidance of axons, sharing properties with astrocytes and SC's [2]. Neurotrophic factors secreted by them is capable

	Outcome	Reference
Suspension matrices		
Matrigel (BD)	Significantly enhances long-term cell survival as well as graft vascularization and the amount of axonal ingrowth	[40]
PuraMatrix (BD)	Promotes their survival in the injured SC and reduces astrogliosis and locomotor impairment.	[41]
Alginate acid hydrogel	Reduces SC apoptosis and enhances recovery of locomotor function.	[42]
Growth factors and other molecules		
GDNF	Reduces astrogliosis and promotes axon regeneration, synapse formation, and locomotor recovery after SCI	[43, 44]
NRG1 + MSC	Reduce the size of cystic cavities, promotes axonal regeneration and locomotor recovery.	[45]
Rolipram + SCs grafts/ analog of cyclic AMP/ D15A	Promote significant supraspinal and proprioceptive axon sparing/regeneration and myelination. Promotes growth of serotonergic fibers into and beyond grafts, and significantly improves locomotion. Increases the size of SC grafts, the number of serotonergic fibers in the grafts, and the number of axons from the reticular formation below the lesion/implant.	[6] [6] [46]
Inhibition of the glial scar formation		
ChABC	Compared grafts treatment, it also improves forelimb and hindlimb movements as well as open-field locomotion. Decreases CSPGs both outside and within the SC transplant.	[47] [5, 48],
Polysialic acid	This leads to improved SC migration, axon regeneration, and locomotion.	[49, 50]
Combination cells		
MSC	Reduction of the size the size of cystic cavities, promotes axonal regeneration and locomotor recovery compared with SCs or MSC transplantation alone.	[45]
NSC	Promotes neuronal differentiation and functional recovery in after SCI in rats. Improves locomotion, increases axonal regeneration/myelination, and reduces neuronal loss.	[51] [52, 53]
OECs	Regeneration of both proprio- and supra-spinal axons beyond the SC bridge. Significantly promotes axonal regeneration and improves locomotion.	[54] [55]

Table 1.
Combination of SCs transplantation with novel molecules/materials.

of protecting neurons, due to its faculty to inhibit scar formation and promote regeneration of axons (see **Table 2**) [58]. They also have an important ability in neural regeneration that consists in their proliferation and migration from PNS and CNS.

This attribute explains that enhancement of axonal extension after injury is possible and it can help neural regeneration, as a result of the expression of molecules implicated in that process (**Table 2**) [2, 59].

OECs phenotypes are different depending on their location in CNS or PNS. It has been shown that they express different types of molecules implicated in neuroregeneration, such as adhesion molecules, neurotrophic factors, proteases, cytokines and inhibitory factors.

Adhesion molecules	L1, E-NCAM, Laminin, Fibronectin, Type-V collagen
Neurotrophic (diffusible) factors/receptors	NGF/p75, BDNF/TrkB, GDNF/GFR α -1, NTN/GFR α -2, NRG-1/ErbB
Proteases (digest CSPG and PNN)	MMP2, MMP9, Serpine-1
Cytokines	IL-6/IL-6R, CX3CL1/Fractalkine, TGF- β 3
Inhibitory factors/receptors	Nogo/NgR, Sema3A, EphrinA

Table 2.
OECs molecules implicated in neuroregeneration.

Otherwise, many studies have proved that OECs are capable of replacing apoptotic or necrotic neural cells, secreting numerous neurotrophins, and contributing to remyelination. Although they do not do the last function in the individual olfactory sensory axons, they enwrap abundant bundles of them, to assemble the nerve fascicles [60]. Recent findings have shown that neuroblasts recently generated in the subventricular zone, migrate into the OB [56].

2.2.1 Olfactory ensheathing cells in response to injury

Studies showed that OECs have a significant therapeutic importance because they [47] interact with astrocytes from the CNS and establish connections with the second neurons. They have the aptitude to guide transected axons of the corticospinal tract throughout the focus of injury that causes the restoration of paw movements, supraspinal control of breathing and improvements in climbing after transplantation into high cervical SC injuries [47, 60].

It is well known that the SC enclose the long motor tracts descending from the brain and the long sensory tracts ascending to the brain. Therefore, it is essential to reconstruct them, and if it is not possible, it is necessary to at least establish a new circuitry with the ability to provide access to the information which was cut off by the injury [61].

2.2.2 Olfactory ensheathing cells transplantation in spinal cord injury

Studies showed that OECs have a significant therapeutic importance because they interact with astrocytes from the CNS and establish connections with the second neurons. The implantation of these cells into the injured SC can intensify neurite growths into the distal part, promoting functional recovery. They have the aptitude to guide transected axons of the corticospinal tract throughout the focus of injury which causes the restoration of paw movements, supraspinal control of breathing, bladder and improvements in climbing after transplantation into high cervical SC injuries [55, 60, 62, 63]. Likewise, OECs transplanted from rats, dogs, pigs and humans into the lesion site in the SC of the rat, promote remyelination of injured axons and restore impulse conduction [48].

In normal conditions, OECs do not form myelin, but when are transplanted into the demyelinated SC, they have the capacity to form a peripheral pattern of myelin reminiscent of SC's myelin [40]. There is also evidence that they reduce proteoglycans expression in reactive astrocytes after the injury [63]. Otherwise, microenvironment and culture conditions have an important influence on OECs behaviors in vitro and in vivo [41].

It has been demonstrated that OECs transplants can reduce posttraumatic cavity size, increase the sprouting of neurofilaments and serotonin axons, improve

functionality and have neuroprotective effects [42, 64]. Due to these facts, several studies have ranked these cells as the second most commonly used cell type after SCI.

Recent studies have investigated the effect of co-transplantation of OECs and SCs at the injured site 7 days after contusion, demonstrating they significantly reduce the number of astrocytes, microglia/macrophage infiltration, and expression of chemokines (CCL2 and CCL3) at the injured site. These results suggest that OECs and SC's co-transplantation can promote the change of the macrophage phenotype from M1 secreting IFN- γ , to M2 secreting IL-4. The induction to M2 reduces ICs infiltration in the damaged site, regulates inflammatory factors and chemokine expression, which provide ICs environment for SCI repair [65].

2.3 Choroid plexus epithelial cells

The Choroid Plexus (CP) has a relatively simple structure. They consist of single layer of cuboidal to low cylindrical epithelial cells that reside on a basement membrane [43]. The main function is to form the cerebrospinal fluid (CSF). Approximately two thirds of this CSF is produced and secreted by the CP, the remainder produced by other areas such as the ependymal cells (ECs) of the ventricular surface and those cells lining the subarachnoid space. This fluid circulates in the ventricular system, subarachnoid spaces and spinal canal [44]. The CP, is not only implicate in CSF production also is a physical barrier to impede entrance of toxic metabolites to the brain [45]. Besides maintaining CNS homeostasis, CP and CSF have proven to be present in repairing processes after disease or damage [44].

The CP is located in the ventricular system of the brain. The ventricles consists of epithelial tissue which is highly vascularized by fenestrated blood vessels [46, 66]. Within the lateral ventricles, it propels from the choroidal fissure and extends from the interventricular foramen to the end of the temporal horn. It projects into the third and fourth ventricles from the ventricular roof. Grossly, the CP is lobulated with a single continuous layer of cells derived from the ependymal lining of the ventricles. Despite it, these cells possess epithelial cell characteristics and are often referred to as CP epithelial cells (CPECs) [66].

CPECs are the prolongation of ECs of the ventricular wall, and the underlying connective tissue corresponds to the pia mater covering the brain surface. CPECs and ECs are of ectodermal origin and develop from the neuroepithelium in the roof plate [49]. However, unlike ECs, CPECs are directly attached via basal laminae to the connective tissue, a feature characteristic of general epithelial cells pertain to a small group of polarized cells, where the Na-K-ATPase is expressed in the luminal membrane [50]. Ultrastructurally, the CPECs contain numerous mitochondria needed to maintain their metabolic work capability for both secretory activities and maintaining ionic gradients across blood-CSF barriers [54]. Underlying the epithelial cells and basal lamina is a dense vascular bed that provides a blood flow four to seven times greater than the rest of the brain [54]. Elsewhere, the cells have tight junctions closest to the luminal membrane to separate the ventricle lumen from the lateral intercellular and basal spaces. Adherence junctions are situated below the tight junctions, and desmosomes appear further below the adherence junctions [67]. The luminal surface is characterized by microvilli, both primary cilia and motile cilia [43]. The capillaries are large with thin fenestrated endothelial walls and bridging diaphragms overlying the fenestrations. An extensive array of adrenergic, cholinergic, peptidergic and serotonergic nerve fibers innervate the blood vessels and the epithelium [67]. In addition, CP secrete many trophic factors such as Hepatocyte Growth Factor (HGF), Basic fibroblast growth factor (bFGF), insulin-like growth factor-II (IGF-II), NGF, and Transforming growth factor (TGF) [68].

CP recently have been recognized as an important immunological compartment in maintaining and restoring brain homeostasis. It has been reported that the CP is the primary gate for trafficking ICs from the vascular system to the CSF in CNS impairment [69]. In the healthy brain, T lymphocytes are mainly found at the CSF or at the “borders” of the CNS: the CP at the brain’s ventricles, and the meningeal membranes that cover the brain [69].

2.3.1 Choroid plexus epithelial cells in response to injury

The evidence that the CP can instantly respond to signals coming from either the CNS itself or circulating immunity, suggests the possibility of controlling brain plasticity by affecting CP function [69], and identifies the cultured cells like CPECs as a novel target for neuroinflammatory conditions may involve a common underlying mechanism of CP immunomodulation.

CSF recirculation within the CNS happens through numerous various pathways. Recent revelations about a previously unappreciated meningeal lymphatic system of the CNS [51, 52]. Although ICs (excluding microglia) have no access to the brain parenchyma under homeostatic conditions, the meninges around the brain are populated by a lot of immune-cell types, which not only provide immune surveillance but also affect brain function [53].

T lymphocytes and their cytokines not only do harm but may also display homeostasis-restoring functions in the CNS [70]. ICs are also found within the CP epithelium, and during inflammatory events their numbers increase [71, 72], giving rise to the hypothesis that the CP is one of the points of immune-cell entry into the CSF [73].

2.3.2 Choroid plexus epithelial cells transplantation in spinal cord injury

When was examined the role of the CPCEs on inflammation after acute SCI: IL-1 β , TNF- α , and hsp70 proved that the CPCEs may serve as an important source of these inflammatory mediators after SCI. There was also an inverse correlation between IL-1 β and hsp70 staining and duration of clinical signs in acute SCI, suggesting that the expression increasing of these proteins by the CPECs could be of particular importance in the immediate-early inflammatory response after acute SCI [52].

Certain studies with CPECs showed that they are capable of promoting neurite extension as well as neuronal survival in vitro: in coculture with CPECs, neurons derived from the dorsal root ganglia or hippocampus presented extensions of long numerous neurites with elaborated branches on the surface of CPECs [74, 75].

Researcher indicating that CPCEs can promote nerve regeneration when grafted into SC lesions, the outcomes indicate by electron microscopy and immunofluorescence that CPECs labelling with green fluorescent protein (GFP) before transplantation closely interacted with growing axons, serving to support the massive growth of regenerating axons. Also, in this study Horseradish peroxidase (HRP) injection at the sciatic nerve showed that many HRP-labeled regenerating fibers from the fasciculus gracilis (FG) elongated into the graft 7 days after grafting. Furthermore, these regenerating axons from the FC were preserved for at least 10 months, with some axons elongating rostrally into the dorsal funiculus [76]. Recently, a study on CPECs transplantation, in which cultured CPECs were directly injected into the SC lesion, engrafted CPECs were located in the astrocyte devoid areas of the SCI; these data suggest that in rat, during the process of cavitation, reactive astrocytes may be reduced. In addition, GAP-43-positive axons were found at the border of the lesion 2 days after transplantation [50]. Other study demonstrated that transplantation of

CPECs and MSC promotes axonal regeneration and enhances locomotor improvements. Overall this evidence suggests that they do not survive long term after transplantation into the SC. These data propose that some neurotrophic factors are released from those transplants to accelerate axonal regeneration through the astrocyte-devoid area formed in the epicenter of the lesion [77].

2.4 Lymphocytes and dendritic cells

Lymphocytes and dendritic cells (DCs) are ICs that are found in many different tissues within the body and work together achieved immunosurveillance and host defense against infection and injury. DCs are professional antigen presenting cells (APC) that capture, process antigens to initiate immune responses and express lymphocyte co-stimulatory molecules not only for activating lymphocytes, but, tolerizing T lymphocytes to antigens [78]. Indeed, lymphocytes are the mediators of the adaptative response by focus release growth factors and cytokine to the target cell, but only an efficient host defense is achieved through coordination of complex signals between innate and adaptative ICs: interaction between APC such as DCs with antigen and T lymphocytes [79].

Lymphocytes and DCs are derived from a hematopoietic stem cell in the bone marrow (BM); however, after certain cytokine secretion and transcription factors (TFs) expression, a common myeloid progenitor and common lymphoid progenitor are developed [80]. The first one differentiates into monocytes and DCs phenotype ($CD8\alpha^+$) [81, 82], while the second one give rise to different lymphocytes subsets, and a small population of $CD8\alpha^-$ DCs. DCs can be classified into myeloid or conventional DCs and plasmacytoid DCs. On the on hand, conventional can be divided into nonlymphoid tissue resident and lymphoid tissue residents and are well known for having a superior antigen processing, presentation machinery and ability to prime naive T lymphocytes responses; while plasmacytoid DCs express low levels of major histocompatibility complex class II (MHC-II) and costimulatory molecules [83]. In the case of lymphocytes, the bone marrow is where B lymphocytes maturation take place, while T lymphocytes development is generated in the thymus, by positive and negative selection to prevent potentially autoimmune reactions; only lymphocytes whose receptors interact weakly with self-antigens, and express a large repertoire of receptors capable of responding to a unlimited variety of non-self structures receive survival signals and are capable of migrating into peripheral lymphoid tissues as $\alpha\beta$ naive T helper (Th), thymic regulatory T (Treg), ($CD4^+$), cytotoxic ($CD8^+$) T lymphocytes [84]. Also, a distinct lineage of T lymphocytes: natural killer and $\gamma\delta$ T lymphocytes, which play role in initial host response and exhibit limited plasticity [79, 85].

2.4.1 T lymphocytes in response to injury

When traumatic insult is carried out, an immune response is triggered in order to contain the damaged tissue but avoiding a negative impact in the host. That is why a cellular response must be properly balance by regulatory T lymphocytes [86]. $CD8^+$ T lymphocytes can differentiate principally in to regulatory and cytotoxic subsets, like the one that takes out Tc1 through the IL-12 influence, Tc2 differentiation from IL-4 and IL-6 plus TGFB can develop Tc17 with low cytotoxic activity [87]. $CD4^+$ T lymphocytes can differentiate into many classified subsets according to their cytokine pattern TFs, except for Th1 and Th2 subsets discovered by Mosmann and Coffman in the 1980s; who found that clonal population from Th1 principally secret IFN γ and IL-4 in the Th2 subset [88]. Since that, $CD4^+$ T lymphocytes have diversified into a great number: Th9, Th17, T follicular helper (Thf)

lymphocytes, induced regulatory T (iTreg) lymphocytes and Th22. Each CD4⁺ T lymphocytes subset can be defined by their capacity to sense specific cytokines and function to control pathogens, prevent immune pathologies and contain damage in trauma such as SCI [89].

2.4.1.1 Lymphocytes as double-edged sword in spinal cord injury

T lymphocytes the arrival of T lymphocytes is crucial for the development of an autoreactive response and parenchyma destruction, due to unique anatomy-physiology of CNS through the release of proinflammatory cytokine entailing to more axon and cell bodies demyelination [90–92]. During acute phase, SC expresses high amounts of Th1 phenotype which is mainly regulated by IL-2, IL-12 and IFN γ . Moreover, in subacute phases IL-4, IL-13, IL-10, IL-17 and IL-23 cytokines are found in plasma and spleen, indicating the presence of Th2, Treg and Th17 profiles as an inefficient compensatory mechanism [93, 94]. Accordingly to this, for the last 10 years experimental findings have shown that T lymphocytes are not just pathogenic but beneficial. Schwartz and coworkers suggested that T lymphocytes play an important role in plasticity and in injured CNS by a still debated mechanism termed “protective autoimmunity” which it established that under certain physiological circumstances, autoimmune T lymphocytes specific to myelin basic protein (MBP), mostly CD4⁺ can exert positive effect by protecting injured neurons [95].

2.4.1.2 Lymphocyte transferring after SCI

Lymphocytes that play complex role in SCI after antigen priming; the epitopes from neural proteins, can be considered beneficial, and Tregs can secrete growth factors, shown neurotrophic factor receptors and promote progenitor differentiation and remyelination in damaged CNS [36, 96], authors have proposed T lymphocytes against MBP transfer as a therapeutic approach after SCI [97]. However, the only limiting factors are that in order to have a positive response, a genetic background and permissive microenvironment must be needed; susceptible individuals or strains don't possess control mechanism such as appropriate antigen presentation, ability to evoke regulatory T lymphocytes and neuroendocrine effect on ICs regulation [4, 98, 99]. Yoles and cols proved that T lymphocytes evoke a neuroprotective response after injury when animals that received T lymphocytes against MBP from injured animals improves hindlimbs locomotor activity, recovery from optic nerve injury, and mostly evoke an anti-inflammatory cytokine profile in the SC, suggesting that a physiological and beneficial response is developed after trauma [100]. In addition, it has been corroborated in different studies; IL-4-deficient animals enhance neuronal survival and increase functional after trauma when CD4⁺ T lymphocytes from wild-type mice are transferred, but not from IL-4-deficient mice.

Inclusive, adoptive transfer of producing- IL-4, IL-10 and IL-3 CNS activated lymphocytes balance local inflammatory microenvironment by increasing protective cell populations like CD4⁺/Foxp3⁺ and CD68⁺/Arg1⁺ cells and in situ, proving that an increment of Th2 subset is beneficial to CNS repair [97, 101, 102]. But, increasing Treg population must be taking in consideration, due to injection of Treg can increase suppressive functions and limit effector T lymphocytes, which is negative to injured tissue in an optic nerve injury model [103]. Also, other studies proposed that Th1 profile is necessary for neuroprotection in SCI model [104], but not Th2 neither Th17. Only mice with Th1-conditioned cell transfer show motor recovery and present axon arbors extending from the main corticoespinal tract into the gray matter rostral to the lesion site; however, T lymphocytes were never primed with an specific antigen, or isolated from immunized animals [105].

In addition, to boost the restorative response, and reduce the risk of developing an autoimmune disease neural modified peptide (NMP) has been tested by active and passive immunization. A91 is a peptide derived from an encephalitogenic epitope, amino acids 87–99 of MBP, by replacing the lysine residue 91 with alanine, which has evidence neural tissue preservation and paralysis reduction in rat model [106–109]. Also, passive p472 (Nogo-A derived peptide) immunization, promotes a T lymphocytes neuroprotective response, and no significant IgM antibody response, revealing that the design of this therapeutic cell strategies does not depend on humoral response and reduce the possibility of promoting clinical changes in CNS, like myelin oligodendrocyte glycoprotein in resistant and non-resistant strains [107, 110, 111].

2.4.2 Pulsed dendritic cells in spinal cord injury

Other studies support the idea that T lymphocytes response can be controlled from APCs transplantation into the traumatized mice and in non-human primates. Perhaps, APC must be primed first with NMP or SC homogenate (SHC), because, even mature DCs can evoke antigen-specific T lymphocyte response, it is not efficient enough to promote motor recovery [112]. Studies support the idea that only pulsed DCs can influence the secretion of neurotrophic factors like BDNF and neurotrophin-3 (NT3) in culture supernatants and at the SC lesion site via CD4⁺T lymphocyte, motoneuron survival, NSCs proliferation and functional recovery [113–115]. Also, A91 has been used to pulse DCs, proving that motor recovery increase since the eleven days in comparison with control rats and an autoimmune response is not developed when Lewis strain is used but apparently a T lymphocyte response is involved, because when neonatally thymectomized rats are injected DCs treatment has no effect on recovery [116]. Furthermore, to promote regeneration, genetically modified fibroblasts to express BDNF have been tested too. Cell therapy avoids secondary damage such as bleeding or infection that can be caused by growth factors or cytokine delivery in the site of injury [117].

2.4.2.1 Macrophage vs. microglia

In the early 1990s, macrophages and microglia were thought to arise from the same myeloid progenitor cell [118], however multiple sophisticated methods have discarded the bone marrow origin hypothesis, and it is proposed that microglia derives from primitive myeloid precursors that arise in the yolk sac early during embryonic development, maintaining it apart from the rest myeloid lineage [119]. Moreover, it was proved that Tgfb is needed for its differentiation in comparison with other myeloid cells [120], implicating, ontogenically, that microglia are not resident macrophages but, the authentic sentinels of CNS. In healthy CNS and during early post-natal period, microglia possess a resting phenotype with round and amoeboid characteristics [121] however, lately, microglia develops into a ramified phenotype, which is equipped to keep CNS homeostasis in the developing and adulthood brain by phagocytic properties, trophic factors release for developing neurons and guidance of new vasculature [122]. Also, to keep a steady state, microglia maintains interaction between neurons by fractalkine (CXCL1) and CD200 receptors to control inflammatory response and cell death [123, 124].

In respect of macrophage participation in CNS, it seems to be from monocytes which migrate from different sites during embryogenesis and in the adulthood [125]. Nevertheless, mostly are present in normal CSF [118], which contains about 5×10^5 ICs in blood ratio of 1:2000 for monocytes (23%) [119]. Then, macrophages reside in the perivascular space, meninges and within the stromal matrix of CP, but

not in neural parenchyma [126]. So, their principal function is the CNS immunosurveillance, that means, macrophages are one of the first APCs in interacting with antigens and T lymphocytes located in CFS, meninges and subarachnoid space, and thus, quickly phagocytose it or also optimize T lymphocytes reactivation and evoke a deleterious response such as autoimmune disease [127].

2.5 Alternative macrophage and microglia

Macrophages and microglia are both APCs that can be found in CNS under different functional phenotypes depending on the microenvironmental signals they received. In inflammation, microglia and macrophages express morphological changes, upregulate different cell markers and transcription factors. Microglia acquires a shape with shorter and thicker processes, increases CD45 expression and molecules for antigen presentation like MHCII, CD80 and CD86; also some miRNAs are related [128]. However, it is well known that activated macrophages and microglia can encompass two different functions. The first one is the classically activated M1 phenotype that is induced by IFN γ or TNF α and secretes IL-12 and reactive oxygen intermediates. And the second one is an alternative subtype triggered by IL-4 and IL-13 cytokines and secretes TGF β and express arginase 1 [129]. To date, it is not well established the appropriate cell markers to differentiate activated microglia from macrophages in CNS, but some populations have been proposed to differentiate the alternative phenotypes in monocytes: C3XCR1 $^{\text{lo}}$ CCR2 $^{\text{hi}}$ LY6C $^{\text{hi}}$ correspond to an inflammatory phenotype, while CX3CR1 $^{\text{hi}}$ CCR2 $^{\text{lo}}$ LY6C $^{\text{lo}}$ is found in the tissue remodeling phenotype [130, 131] and it has been corroborated in SCI studies; Shechter and cols. Proved that alternative M2 macrophages (Ly6c $^{\text{lo}}$ CX3CR1 $^{\text{hi}}$) derived from monocytes traffic through CSF to provide an inflammatory response in SC [132].

Due to the important role that macrophages can play, several immunomodulatory therapies have been developed to control CNS response to pathological insults [123].

2.5.1 Macrophage and microglia in response to injury

Typically, damage stimulus triggers the activation of the microglia provoking the secretion of several cytokines like interferon gamma-induced protein 10, C-C motif chemokine ligand 1 (CCL1), C-C motif chemokine ligand 2 (CCL2) and C-C motif chemokine ligand 5 (CCL5) which recruit peripheral cells like macrophages. Microglia also participates in the adaptive immune response through the precise chemoattraction of T lymphocytes demonstrated in studies where the inhibition or stimulation of the resident microglia population resulted in abnormal recruitment [133].

These cells are considered essential screening damage monitoring constantly the microenvironment. Another important cell subgroup is the perivascular microglia which is replaced during 3 month period from bone marrow; its function is safeguarding the blood-brain barrier (BBB) through the recruitment of activated cell to BBB and parenchyma [134, 135].

2.5.2 Macrophage and microglia trafficking in response to injury

After a SCI take place an uncontrolled immune response that depends on the severity, level and mechanism of injury [136]. This cascade processes are characterized by pro-inflammatory and anti-inflammatory alternatively activated cells [135]. The activation of phenotype M1 provokes neurotoxicity while type M2 promotes

Therapy	Treatment outcome	Reference
Adoptive transfer of M2 in rats	M2 phenotype reduces inflammation by increasing the number of CD4 ⁺ GATA3 ⁺ Th2 cells in the injured SC.	[144]
Incubated autologous macrophages in complete SCI: Phase I study	The study provides a preliminary evidence of safety and electrophysiological results. Also some patients present beneficial effects showing the efficacy of cell therapy.	[145]
Autologous macrophages delivery in patients with SCI	The clinical trial can be implemented in patients, however many factors contribute to a funnel effect in the study.	[5]
Azithromycin (AZM)	Increase M2 activation. Decrease M1 macrophage gene expression and potentiate M2 macrophage gene expression. Also, potentiate microglia vs. monocyte derived M2 macrophage activation. AZM improved locomotor function and coordination of mice recovering.	[146]
Anti- IL6-receptor (MR16-1 Ab)	Increased the area of spared myelin. Promoted functional recovery by promoting the formation of alternatively activated M2 macrophages.	[143]
Activated cultured microglia	Reduce the size of liquefaction necrosis area. Activated antiinflammatory mechanisms. Promote the hind limb motor function recovery.	[147]
Microglia/Macrophages activated with IL-1	Decrease of IL-1 participates in both the classical and alternative activation of microglia.	[148]
Recruitment of M2 macrophages	CP provide a route of macrophages derived monocyte (Ly6cloCX3CR1hi) to entry into the CNS to evoke an inflammatory response.	[132]

Table 3.
Immunomodulatory strategies for the microglia/macrophages response.

axon growth and remyelination [137]. This lead the efforts to develop immunomodulatory therapies to modify phenotypic and functional properties.

The activation of the glia occurs the first 24 hours after trauma [138]; while the peripheral monocytes migrate into the injury within the following 2 or 3 days post-injury, then they differentiate into macrophages that become phenotypically and morphologically indistinguishable [139].

The proinflammatory M1 macrophages vary along early stages releasing high levels of ROS to increase phagocytosis and cell recruitment removing foreign microbes and wound debris [140]; meanwhile M2 macrophages have some tissue repair properties through the release of immunosuppressive cytokines like IL-10 and C-C motif chemokines ligand 17, 18 and 22 to attract antiinflammatory leucocytes that increase the phagocytic receptors and upregulate growth factors [141].

There are three important chronological stages in the inflammatory response: the inflammatory, proliferative and remodeling phase and each one is characterized by certain cytokines and events. In the first one are present both M1 and M2a phenotypes, M1 secrete IL-1 β , IL-12, TNF- α and IL-6 and M2a express high levels of IL-4, arginase-1 and Ym1 [142]. Comparative analysis of lesion development and intraspinal inflammation in four strains of mice following spinal contusion injury); during the second stage, keep going secreting proinflammatory cytokines but transition toward the expression of IL-10 and other antiinflammatory markers distinguished by the M2b macrophages followed by the M2c; in the third stage, the

M2c release high concentrations of IL-10, IGF1 [138]. Macrophage activation and its role in repair and pathology after SCI. TGF- β and a mannose receptor (CD206) with the decrease of arginase-1 and IL-12. At the end, the macrophages are deactivated and the inflammation resolves, this process can last several months. In brief, this sequence will provoke the axon dieback (classical macrophages) and remyelination, axon regeneration and the reduction of the dieback [143].

2.5.3 Macrophage and microglia in spinal cord injury

The manipulating macrophages facilitate maturation events typical of normal healing, for this reason it has been studied several methods to activate alternative macrophages and another strategy is better to improve the normal healing response by blocking certain pro-inflammatory mechanisms (**Table 3**).

3. Conclusions

The beneficial effects of cultured cells transplantation or transference in SCI have been demonstrated by numerous investigators and they are one of the main hopes for developing an effective treatment for SCI. This may be due to their great potential to amplify and genetically manipulate them *in vitro*, as well as all the complicated functions in axonal regeneration they possess. Furthermore, the development of cell transplantation derived from precursors show a higher ability to survive, integrate well with host tissue and support brainstem axon growth into and beyond the graft. However, the optimal source needs further investigation.

Recently, several clinical studies suggest their safety and feasibility, meaning that the transplantation of cultured cells have a significant therapeutic potential in persons with SCI. Nowadays, they are currently at an early stage of clinical testing following preclinical development.

Acknowledgements

We gratefully acknowledge to Universidad Anáhuac México Norte for your support to this project.

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