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Pathophysiology of Spinal Cord Injury and Tissue Engineering Approach for Its Neuronal Regeneration: Current Status and Future Prospects

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Abstract

A spinal cord injury (SCI) is a very debilitating condition causing loss of sensory and motor function as well as multiple organ failures. Current therapeutic options like surgery and pharmacotherapy show positive results but are incapable of providing a complete cure for chronic SCI symptoms. Tissue engineering, including neuroprotective or growth factors, stem cells, and biomaterial scaffolds, grabs attention because of their potential for regeneration and ability to bridge the gap in the injured spinal cord (SC). Preclinical studies with tissue engineering showed functional recovery and neurorestorative effects. Few clinical trials show the safety and efficacy of the tissue engineering approach. However, more studies should be carried out for potential treatment modalities. In this review, we summarize the pathophysiology of SCI and its current treatment modalities, including surgical, pharmacological, and tissue engineering approaches following SCI in preclinical and clinical phases.

Keywords

Neuroprotection · Neuroregeneration · Scaffolds · Spinal cord injury · Stem cells · Tissue engineering

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1 Introduction

The spinal cord (SC), a highly somatotopically organized structure, is a principal component of the central nervous system (CNS) with a long cylindrical structure that initiates from the medulla of the brain above the C1 (through foramen magnum) and terminates at L1–L2 (as conus medullaris). It conducts sensory, motor, and autonomic information (Khan and Lui 2020). An injury may reduce the ability of SC to partially or completely carry out its primary functions.

Thus, a spinal cord injury (SCI) is an injury to the SC that most often results in everlasting changes in the functioning of the body below the site of the injury (Ahuja et al. 2017). The most prevalent cause of SCI is traffic accidents, which is followed by falls among the elderly (Singh et al. 2014). As per age statistics, the highest incidence of SCI is in people who are less than 30 years of age. Even males are more prone to SCI than females. The prevalence rate of SCI indicates that the occurrence of SCI is geographically distinct and different in different regions. The prevalence rate of SCI (per million population) in Canada (~1289) is more than that of the United States of America (~721–1009), followed by Australia (~681) and other notable regions including Finland (~280), Iceland (~316), South and Southeast Asia (~236–464), and India (~236) (Singh et al. 2014; Furlan et al. 2013; Srivastava et al. 2015; DeVivo 2012; Cripps et al. 2011). The clinical outcomes (loss of motor, autonomic, and sensory functions and paralysis) of SCI may be due to four main characteristic injury mechanisms: persistent compression, transient compression, distraction, and laceration/transaction. SCI is considered a major health problem as the physical, emotional, and economic costs are burdensome for the patient, his family, and society, according to World Health Organization (WHO) (Lynch and Cahalan 2017). After an SCI, many patients exhibit loss of respiratory, autonomic, and sensorimotor functions, posttraumatic stress disorder, anxiety, and even depression which has led to a high mortality rate and a lower quality of life (Ahuja et al. 2017; Lynch and Cahalan 2017).

Currently, frontline treatment option available for SCI is a surgical decompression and drugs that aid to improve the condition and reduce the subsequent injury (secondary injury). In surgical decompression, clinicians stabilize vertebral column and remove bone fragments which are inserted in SC during primary injury. This type of surgical intervention only reduces stress over the SC; evidently, CNS has a low regenerative capacity, and therefore this treatment option alone is unable to heal SCI. Another treatment option currently in practice is pharmacotherapy in which various drugs (methylprednisolone [MP], etc.) are used to reduce complex pathophysiology of SCI. Drugs have common side effects such as headache, vomiting, and so on. Aforementioned treatment options are unable to rebuild the damaged neural network. Currently, there is no validated therapy approach that has shown to improve neurological outcomes successfully.

Neuroprotective and neurorestorative approach by using tissue engineering could be a potential alternative treatment for SCI. It involves the use of growth factor (neural growth factor, brain-derived growth factor, FGF, etc.), cells (neural stem cell [NSC], embryonic stem cell [ESC], mesenchymal stem cell [MSC], iPSC, etc.), and scaffolds (hydrogels, 3D printed scaffold, etc.). Preclinical studies by using tissue engineering significantly improved motor function and ultimately resulted in neural regeneration. This review discusses the pathophysiology of SCI and effect of existing approaches such as surgical and pharmacological for SCI. This review puts insights on tissue engineering approaches using growth factors, cell therapies, and scaffolds for treatment of SCI. New findings from clinical trials are also highlighted.

2 Pathophysiology of SCI

SCI can be attributed to both "traumatic and nontraumatic" etiologies. Traumatic SCI (TSCI) is a tormenting condition that alters the integrity of the SC (David et al. 2019). TSCI may be caused by direct mechanical injury like fall (Ahuja et al. 2017; Chen et al. 2016; Kennedy et al. 2013; Medina et al. 2020), vehicle accidents (Medina et al. 2020; Silveira et al. 2020; Kang et al. 2018; Wang et al. 2016), acts of violence (Watane et al. 2021; January et al. 2018), electrical accidents (Zeb et al. 2019; Delgadillo III et al. 2017; Zhirkova et al. 2020), and recreational activities (Babcock et al. 2018; Li et al. 2021; Wu et al. 2020; Hosaka et al. 2020). A nontraumatic SCI may be the result of a tumor or infection. The most common type of nontraumatic SCI is degenerative cervical myelopathy (DCM) (David et al. 2019). The result of

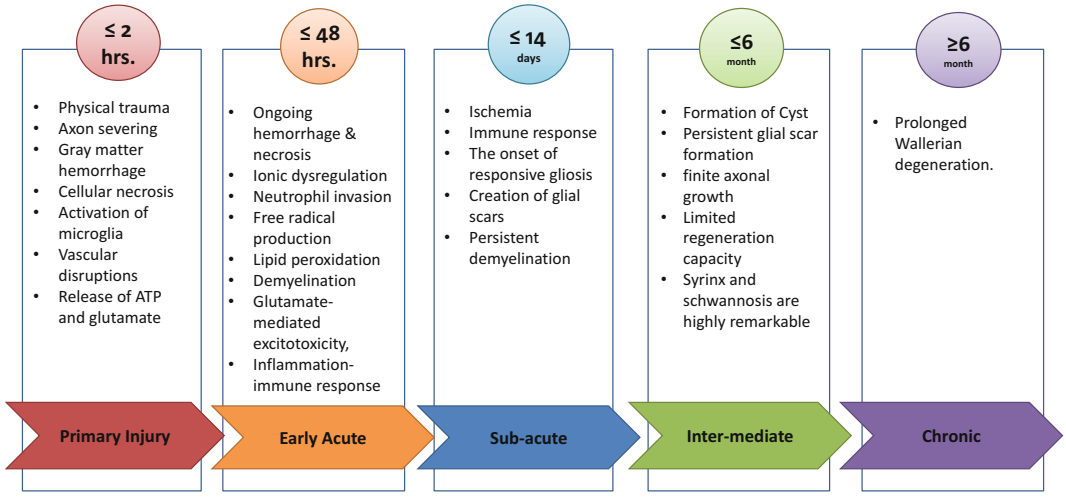

Fig. 1 Timeline of the damage phases and major pathological events following SCI: After any mechanical stress on SC, primary injury occurs with various physiological changes like ischemia, hemorrhage, axon severing, etc. It is followed by early acute and subacute phases which is characterized by evoke immune response, persistent hemorrhage, ischemia, etc. At these phases, most of glial cells aggregate near lesion area to form glial scar which leads to regeneration failure. Injury worsens as it comes to chronic phase ultimately leading to Wallerian degeneration

SCI is the degeneration of motor, sensory, and autonomic functions. After primary injury, secondary injury develops with complex pathological mechanisms and can last for weeks. Timeline of SCI is shown in Fig. 1. There are possible four mechanisms responsible for SCI, viz., hyperflexion, hypertension, axial loading, and penetrating wound. Injury could occur by one of the above mechanisms by one or more biomechanical means, and the characteristics of the tissue damage depend on different aspects of trauma. An in-depth understanding of the pathophysiology and the mechanisms that arise just after SCI are crucial for developing precise therapeutic strategies that can reduce or cure damage. SCI has two phases in its pathophysiology: a main phase, i.e., primary phase (primary injury), and a subsequent secondary phase (secondary injury).

3 Primary Injury

SCI is caused by an early damage to the spine, for example, by mechanical stress. This is referred to as the primary injury. A direct impact seems to be the most prevalent cause of primary damage, and chronic compression is usually caused by bone fragments during fracture–dislocation injuries. Hyperextension injuries, unlike fracture–dislocation injuries, generally arise in quite frequent manner and impact only temporary compression. The other mechanism is distraction damage, which is characterized by a strain and rupture of the SC through its long axis caused by the separation of two neighboring vertebrae. Lastly, laceration/transection injuries are caused by pointed bone remains, severe dislocations, and missile injuries (Alizadeh et al. 2019). Primary injury can range in severity from full to partial, i.e., complete to incomplete. The primary phase is characterized by disruption in blood vessels, axons, and cell membranes, resulting in cellular necrosis within 2 h following injury (Jeong et al. 2021). The breach of the blood–spinal cord barrier (BSCB) causes necrotic cells to discharge DNA, ATP, and K+ in the proximal injured area, resulting in inflammatory responses by cells such as macrophages, microglia, and T-cells. "Inflammatory cytokines" such as interleukin (IL-6), IL-1, and tumor necrosis factor

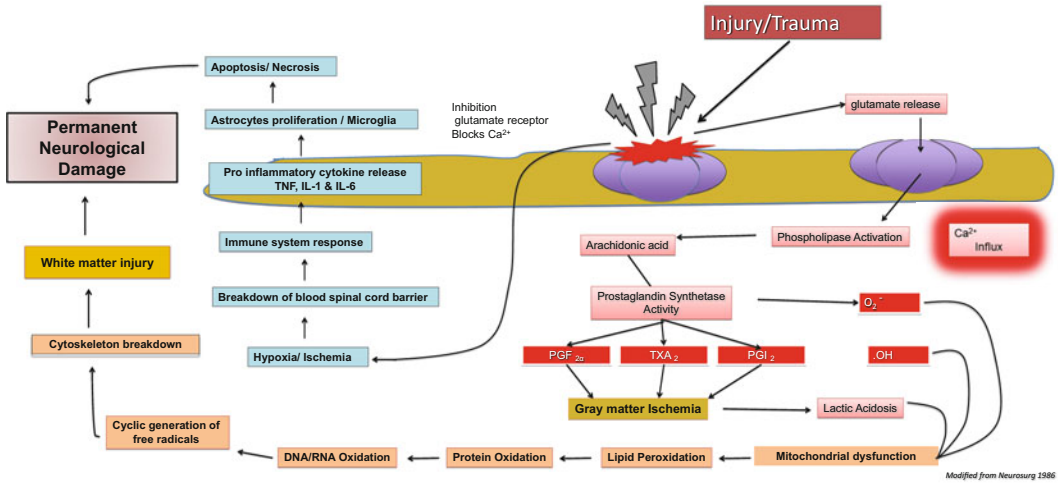

Fig. 2 SCI cascade
Possible pathophysiological changes following SCI. Pathophysiology can be divided into primary and secondary injury. Injury begins with hypoperfusion which results in hypoxia/ischemia to tissue along with excess glutamate release. This leads to initiation of injury cascade consisting of calcium influx, oxidative state, and white and gray matter damage that results in permanent neurological damage to the SC

(TNF) are secreted with optimum levels reaching between 6 and 12 h (Jeong et al. 2021; Ulndreaj et al. 2016). Pathophysiological changes during SCI are shown in Fig. 2.

Primary injury (Fig. 3b) impacts upper as well as lower motor neural connections, leading to a variety of negative consequences on vascular tensions, cardiac output signals, and sensory functions and inhalation, whereas secondary injury worsens the primary injury (Shende and Subedi 2017). Gray matter ischemia causes nerve cell bodies to be destroyed or even connections to be disturbed. Paralysis of muscle can be occurred at injury location due to disruption in motor nerve cell in the ventral horns, but damage to higher nerve cells that cross the injured area causes a loss of efferent impulses to muscles underneath the injury site (Forgione and Fehlings 2013). During trauma, synaptic connections are destroyed and the ability to execute commands by the neural cells is lost due to demyelination and destruction; as a result, neurons die mechanically (Fig. 3c) (Orr and Gensel 2018). The severity of lesion at injury area produces an inhibitory microenvironment that hinders native repair, remyelination attempts, and regeneration (Moriwaki et al. 2016; Liu et al. 2018).

4 Secondary Injury

A variety of pathological processes (more than 20) combine to aggravate the initial damage acquired as a result of primary injury (Jiang et al. 2020; Nakamura et al. 2003). After original trauma, SCIs induce prolonged damage and also the demise of surviving cells. After days or weeks of an injury, a secondary phase begins. Secondary SCI is classified into four stages based on post-injury timeframe and disease pathogenesis, namely, early acute, subacute, intermediate, and chronic (Fig. 1). The early acute phase is defined as the first 48 h after a mechanical trauma on the SC. In this phase, ongoing hemorrhage and ischemia are caused by vascular disruptions. It results in vascular circulation irregularities, swelling, and inflammatory reaction. It is followed by immune reactions, glutamate-mediated excitotoxicity, neutrophil invasion, oxidative stress and free radical production, lipid peroxidation, neurotoxicity

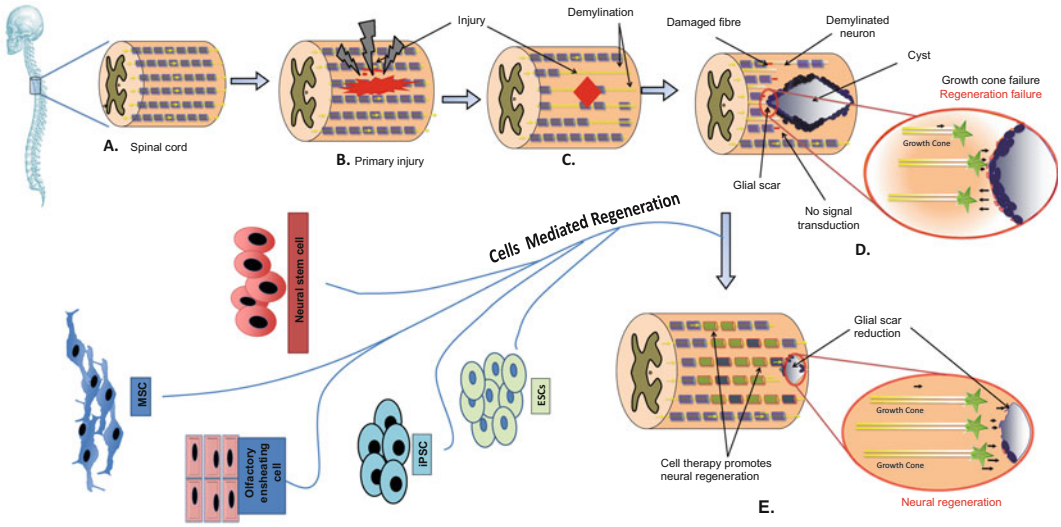

Fig. 3 SCI and cell therapy-mediated SC regeneration and repair
(**a**) Normal SC; (**b**) SCI by mechanical force; (**c**) due to injury, neural tissue is damaged which leads to demyelination of neuron around the injury site; (**d**) immune cell gets activated due to injury; therefore, glial cells migrated toward injury site and aggregate to form glial scar. Due to this, regenerative cell unable to reach injury site leads to no regeneration in that area; (**e**) cell-based therapy will reduce glial scar which ultimately resulted in neuronal regeneration

with changes in regional ionic gradients and Ca^{2++} influx, and apoptosis, which are among the events that contribute to subsequent damage following SCI (Rowland et al. 2008; Ko 2019). Alarmins are released during necrosis, causing resident glia to become reactive and downstream immune cells from the periphery to infiltrate the tissue (Tran et al. 2018). After 48 h to 14 days, subacute phase starts with onset of responsive gliosis in which astrocytes and glial cells are reacted in nonspecific manner in response to injury which results in accumulation of these cells around the injury site and creates glial scar with persistent demyelination (Fig. 3d). Though glial scarring is a restorative action, it is detrimental to axon growth throughout the duration (Silver and Miller 2004). SCI stimulates local astrocytes and peripheral cells, as well as recruiting fibroblasts and invading Schwann cells from periphery, resulting in the formation of lengthy glial scars (cellular) and fibroids (acellular) in the damaged spinal column. The transforming growth factor beta (TGF-β) enhances the activation of astrocytes and the eventual borders of glial scar. ECM molecules can stiffen the surroundings, create a physical obstacle, and provide imprecise topographic cues, all of which can obstruct cell movement (Orr and Gensel 2018). The acute contusions effectively separate gray matter which necrotizes and becomes fluid-like (syrinx) along with the formation of cyst that is highly remarkable in intermediate injury phase ($\leq$ 6 months) (Guest et al. 2018). It is followed by the formation of persistent glial scar which hinders the axonal growth resulting in limited regeneration. If all these pathophysiological cascades continue for more than 6 months, it leads to chronic injury phase. It could cause Wallerian degeneration which is a worsened state of secondary injury. It leads to complete neurological defect, since no regeneration will occur in this region. Therefore, to reduce glial scar is one of the hurdles in neuronal regeneration.

5 Treatment Modalities for SCI

A current SCI therapy focuses on cord stability to avoid additional injury, rehabilitation, non-motor symptom management, and complication prevention.

6 Surgical Decompression

Early surgical intervention is recommended to maximize the healing through neurocompression of remnant partly injured neuronal tissues and to provide early vertebral column stabilization to allow early mobilization for rehabilitation. Posterior and anterior techniques are used in spinal surgery. Excision of the body, open dura technique, open cord technique, anterior fusion, internal fixation, and disc excision are the six types of anterior techniques. Laminectomy, open cord technique, open dura technique, internal fixation, posterior fusion, and disc excision are the techniques categorized for posterior procedures (Duh et al. 1994). The potential for restoring flow of blood and enhancing perfusion while potentially preventing further injury is one of the reasons for immediate surgical decompression (Shank et al. 2019). Within 8 h of a severe SCI, early surgical decompression seems to promote neurological recovery. In addition, partial SCI was found to be more closely linked toward positive neurological recovery as compared to complete SCI (Lee et al. 2018). In individuals with severe traumatic cervical SCI, surgical decompression before 24 h has been more usually linked with neurological recovery of at least two American Spinal Injury Association (ASIA) grades (Eckert and Martin 2017; Ramakonar and Fehlings 2021). Cord edema, epidural hematoma, or bleeding or impinging foreign bodies and bone fragments has already been thoroughly investigated in compressive SCI and their duration during surgical decompression. The degree and duration of cord compression have been shown in preclinical studies to be related to the eventual neurologic deficit (Eckert and Martin 2017). It is hypothesized that parameters such as intramedullary lesion severity may be even more significant than timing of treatments in terms of clinical consequences in SCI (Rouanet et al. 2017). Despite growing acknowledgment that early decompressive surgery is a safe and reasonable therapeutic option, earlier clinical trials have only been suggestive because of low quality of data resulting from small sample sizes, retrospective analysis, and inconsistent methodologies. In incomplete cervical SCI patients, surgery timing had no effect on its neurological outcome (Ter Wengel et al. 2019). Due to operational and logistical reasons, rapid decompression of injured SC is not always possible. Additionally, managing individuals who are clinically fragile as a result of numerous injuries or associated complications may limit immediate spinal decompression. All set of time taking diagnostic procedure may delay the hospitalization of SCI patients. Also, unexpected events, such as global pandemic safety measures, may also pose considerable hurdle in operating early decompressive surgery (Ramakonar and Fehlings 2021).

7 Hemodynamic Management

Following SCI, hemodynamic treatment can be conducted promptly, assisting in the maintenance of adequate SC perfusion and preventing subsequent injury like ischemia. Therefore, practicing to keep constant blood pressure after SCI is a must. Perfusion of the SC is similar to cerebral perfusion (Lee et al. 2021). Hypotension can develop after an SCI even if there is no hemorrhagic shock as sympathetic innervation is interrupted. This is known as "neurogenic shock," and it can lead to SC hypoperfusion and exacerbated injury (Karsy and Hawryluk 2019). It is critical to avoid hypotension and maintain perfusion of the damaged SC by increasing the mean arterial pressure (MAP). Existing medical practice recommendations include keeping MAP in between 85 and 90 mmHg during early 5–7 days after an acute cervical SCI and avoiding systemic hypotension (systolic blood pressure of less than 90 mmHg) (Lee et al. 2021). However, determining a significant link between MAP targets and neurological recovery is difficult due to methodological constraints (Evaniew et al. 2020). Hemodynamic management reduces subsequent ischemia as well as spinal pressure, but, alone, it is unable to heal injured SC. Still there is unclear information about optimizing

hemodynamic management. Further studies on the hemodynamic care of acute SCI are required for enhancing neurological recovery to reduce secondary injury.

8 Pharmacotherapy

On a biological level, current pharmaceutical intervention seeks to decrease the secondary cell death phase. Some common drugs in clinical and preclinical studies are used to reduce additional injury. The use of corticosteroids as a neuroprotective therapy for acute SCI is debatable. MP has emerged as the preferred corticosteroid and a primary treatment option for SCI. MP has been claimed to lessen initial damage along with subsequent harm (Shank et al. 2019; Rouanet et al. 2017). MP has proven to be more effective compared to other corticosteroid substances such as dexamethasone and hydrocortisone. It demonstrates superior antioxidant properties, passes quickly via the cell membranes, and also appears to be more effective in suppressing the neutropenic response and further stimulating the complement components. Naloxone, a nonspecific opioid receptor antagonist, is shown to have anti-inflammatory properties (Tang et al. 2021; Lin et al. 2017). The release of inflammatory factors and microglial activation can be inhibited by naloxone (Tang et al. 2021). Nimodipine (NMD), a calcium antagonist, can improve functional recovery when treated for long period of time following SCI (Leisz et al. 2019; Guo et al. 2021). Tirilazad mesylate has been examined extensively for the protection of neural damage caused by SCI, subarachnoid hemorrhage, head injuries, and stroke (Carratù 2017). Minocycline hydrochloride can have therapeutic benefits resulting in reducing inflammatory microglial, antioxidant, and antiapoptotic activity while improving locomotor activity (Shultz and Zhong 2017; Afshary et al. 2020). Riluzole is a well-known antiglutamatergic agent and appears to be effective in reducing neuropathic pain, improving motor recovery, and reducing abnormal reflexes in initial clinical studies (Srinivas et al. 2019; Meshkini et al. 2018). A potassium channel blocker, 4-AP (4-aminopyridine), has improved motor function recovery, encouraged remyelination, and showed improved axonal region post-injury at a rate too fast to be made clear by axonal regeneration (Noble et al. 2019; Jensen and Shi 2003). Serine protease inhibitors (gabexate mesilate) inhibit NF-B, proinflammatory cytokines, and nitric oxide (Shih et al. 2015; Oh et al. 2020), and rapamycin increases autophagy and provides neuroprotection in a variety of CNS diseases (Li et al. 2018a). N-benzyloxy-carbonyl-Val-Ala-Asp-fluoromethylketone, a caspase inhibitor, improves motor function and prevents lesion severity significantly after SCI. Caspase 1 and caspase 3 have been recognized as major mediators of apoptosis (Li et al. 2000).

Many drugs are in clinical practice because of their safety and efficiency to minimize pathological outcomes, but they may result in common clinical complains such as hypertension, anxiety, osteoarthritis, osteoporosis, adverse drug reactions, depression, headache, and so on due to low/high dose.

9 SC Tissue Engineering

Tissue engineering (TE) is an interdisciplinary area that combines engineering and life science concepts to create tissue-like structures using live cells, suitable materials, and appropriate biochemical clues (e.g., neuroprotective factors/growth factors) (Figs. 3 and 4). The main goal is the tissue reconstruction by developing grafts for implantation into the body to treat an injury or restore the functionality of a dying organ (Langer 1993; Berthiaume et al. 2011).

Thus, TE can be a viable therapeutic option for people with SCI. (Jones et al. 2001)

10 Neuroprotective Factors

Neuroprotective factors are crucial not only for the survivability and development of differentiating neurons but also for the preservation and

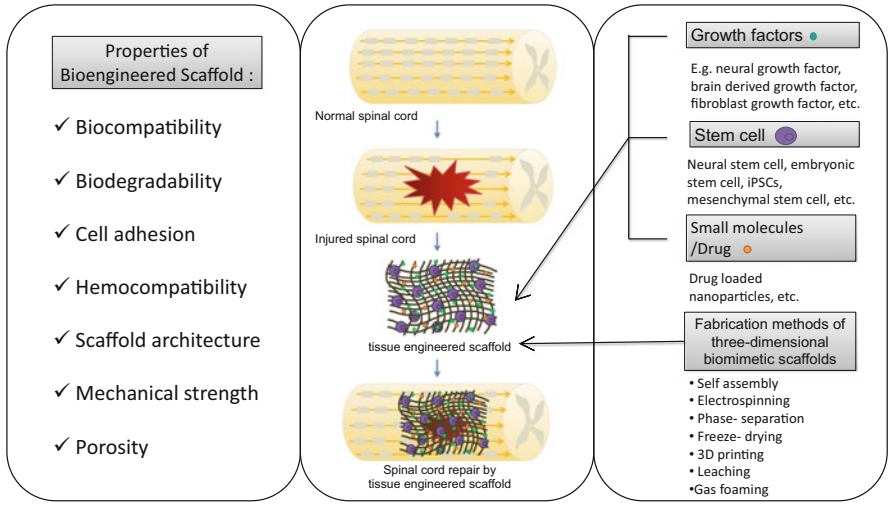

Fig. 4 Tissue engineering approach for repair of SCI: (**a**) Properties of bioengineered scaffold; (**b**) SC regeneration and repair; (**c**) growth factors, drugs or biomolecule stem cells, and scaffold used for tissue engineering of SC

restoration of adult nerve cells during pathological consequences (Solaroglu et al. 2007).

Gangliosides, a plasma membrane component that is thought to have a number of physiological effects on the CNS, such as synaptic plasticity and neuroprotection (Geisler et al. 1993; Chinnock and Roberts 2005), showed increased neuronal mitochondrial activity and promoted the production of neuroprotection genes (Finsterwald et al. 2021). Similarly, CNS-specific neurotrophic factors like nerve growth factor (NGF), neurotrophin-4/5 (NT-4/5) brain-derived neurotrophic factor (BDNF), and neurotrophin-3 (NT-3) are supposed to control neuronal survival, axonal development, synaptic plasticity, and neurotransmission in the nervous system (Jones et al. 2001; Bregman, and mcatee M, Dai HN, Kuhn PL. 1997). Likewise, fibroblast growth factor (FGF) has been widely studied for nerve regeneration. It might promote axonal development and reduce glial scarring (Ko et al. 2019). aFGF and bFGF are implicated in the regulation of synaptic plasticity and activities in the CNS; therefore, their possible therapeutic impact has been studied extensively (Ko et al. 2019; Reuss and Halbach 2003; Harvey et al. 2015). In acute, subacute, and chronic CNS disorders, the cytokine granulocyte colony-stimulating factor (G-CSF) appears to have powerful antiapoptotic, anti-inflammatory, myelin-protective, antioxidative, and axon-regenerative capabilities (Aschauer-Wallner et al. 2021). Progesterone (PROG) on the other hand showed neuroprotective and promyelinating properties by reducing expression of inflammatory cytokines such as TNF- and iNOS, NOS2, MCP-1, and IL-1, as well as caspase 3 and GFAP (Jure et al. 2019; Ludwig et al. 2017). Thyrotropin-releasing hormone (TRH) therapy has improved motor and sensory function significantly. Thus, TRH or its analogue has neurological effects (Diaz-Galindo et al. 2020). Magnesium has an antinociceptive effect because it inhibits N-methyl-d-aspartate (NMDA) receptors, preventing calcium ions from entering the cells and causing analgesia which results in stimulation of neuronal regeneration (Shin et al. 2020; Wu et al. 2019). Similarly, activated protein C (APC), a physiologic anticoagulant and anti-inflammatory protein, may help to minimize motor impairments caused by SCI (Hirose et al. 2000; Taoka et al. 2000).

Despite the positive outcomes of this neuroprotective approach, it has some challenges in preclinical studies such as selection of suitable animal model and their sex, age, doses of neuroprotection, etc.

11 Stem Cells for SCI

Stem cells are a unique population of cells that are capable of differentiating into different lineages. These cells have an inherent capacity for self-renewal, differentiation, migration, and tissue repair. Preclinical studies for treating SCI with stem cells as a treatment modality have shown tremendous hope. Stem cell therapy is gaining popularity and recognition, as it promises to (a) alleviate nerve tissue degradation, (b) promote tissue regeneration and neovascularization, and (c) assist endogenous cells in regeneration (Fig. 3e) (Coutts and Keirstead 2008). The type of stem cells that are to be used will largely depend on the cell's potency, self-renewal ability, and ease of processing.

12 ESCs

ESCs can be successfully differentiated into neural cells, neural precursor cells, glial cells, low-purity motor neurons, and high-purity oligodendrocyte progenitors (Coutts and Keirstead 2008). Transplantation of ESCs into the acute SCI model showed transplant integration, axonal elongation, tract regeneration, oligodendrocyte-induced remyelination, and restoration of neuromuscular junctions (Jin et al. 2019). ESC cells that overexpress FGF2 showed neuroprotective behavior (Araújo et al. 2017). Definitive neural stem cells (dNSC) were produced from ESCs by clonal expansion method used for the treatment of SCI. There was differentiation of dNSC into oligodendrocytes which leads to axon remyelination and is indicative of motor function recovery in mice SCI model. There were no reports of teratoma formation (Salewski et al. 2015). A comparative study of rat ESCs and autologous bone marrow-derived neurocytes (ABMDN) showed recovery of SC functionally and neurologically. However, ABMDN showed more clinical potential as compared to rat ESCs (Sadat-Ali et al. 2020). It is also very important to address the legal and ethical aspects related to the use of ESCs in cell-based therapies. Additionally, one of the major obstacles that limits their use in clinical settings is teratoma formation, suggesting the disastrous impact of direct usage of undifferentiated cells. Further studies should majorly focus on eliminating the undifferentiated cells that are formed following ESC transplantation and also at designing protocols with guided differentiation (Nussbaum et al. 2007; Thinyane et al. 2005).

13 Induced Pluripotent Stem Cells

Induced pluripotent stem cells (iPSCs) can be differentiated into neural cells (Cooper et al. 2012; Morizane et al. 2013; D'Aiuto et al. 2014), neural progenitor cells (NPC) (D'Aiuto et al. 2014; Sareen et al. 2014; Nutt et al. 2013), various specific types of neurons like dopaminergic neurons (Nguyen et al. 2011; Chang et al. 2021; Mahajani et al. 2019; Tolosa et al. 2018), and GABAergic interneurons (Iwasawa et al. 2019; Inglis et al. 2020). When undifferentiated iPSCs are directly transplanted at the lesion site, they promoted functional recovery, and there was SC regeneration (Bellák et al. 2020). However, there is a risk of teratoma formation after direct in vivo transplantation of iPSCs, and so they are first differentiated into "subtypes of interest" before any in vivo application. Human-iPSC-derived NS/PCS (hiPSC-NS/PCS) were differentiated into mature oligodendrocytes. After 12 weeks of transplantation of these oligodendrocytes, there was remyelination of the demyelinated axons and functional recovery with no tumor formation (Kawabata et al. 2016). Transplanted iPSC-derived NSCs were survived and differentiated into neurons and glia cells in athymic nude rats with SC lesions. The axons were penetrated into white matter and gray matter of the injured SC, with formation of synapses and improved nerve conduction (Lu et al. 2014). Neural stem/progenitor cells (NS/PCs) with gliogenic potential (GNS/PCs) were differentiated from iPSCs. In vivo results of the transplanted GNS/PCs showed improved motor function and remyelination with no tumorigenic effects (Kamata et al. 2021). iPSC-derived NPCs showed survival of a month and no tumor development or

other side effects in aged SCI rat model (Martín-López et al. 2021). Although iPSCs have immense therapeutic potential for SC repair, still they pose obstacles like designing an appropriate reprogramming protocol, which includes selection of a reprogramming factor and delivery method (Singh et al. 2015). Likewise, genetic instability and the risk of teratoma formation have raised safety concerns for iPSCs for cell-based therapies (Fu and Xu 2012).

14 MSCs

MSCs are an ideal source for tissue engineering and cell-based therapies because of their immunosuppressive, immunomodulatory, and anti-inflammatory and regenerative properties. MSCs can be obtained from various sources like the bone marrow (Pourrajab et al. 2013), arteries and veins (Corselli et al. 2012), amniotic membrane (Alviano et al. 2007), amniotic fluid (Anker et al. 2003), breast milk (Patki et al. 2010), adipose tissue (Wu et al. 2017), synovium (Fan et al. 2009), umbilical cord (El Omar et al. 2014), endometrium (Mutlu et al. 2015), Wharton's jelly (Fong et al. 2011), fetal liver (Joshi et al. 2012), etc. MSCs have been shown to improve bladder function, reduce inflammation, and increase the secretion of trophic factors, all of which contribute to their therapeutic potential after MSC transplantation into SCI animal models (Mukhamedshina et al. 2019).

MSCs can control the extent of secondary injury after SCI by regulating the "macrophage polarization" by secreting factors like IL-4 and IL-13 and chemokines like CCL2 and aid functional recovery (An et al. 2021). BMMSC-derived neuron-like cells showed development of synapse-like structure and evoked action potential in vitro and survived up to 6.5 months at injury site in vivo. These cells were efficient in integrating with host tissue and restored motor function of a paralyzed dog (Wu et al. 2018). Rat cranial bone-derived MSCs (rcMSCs) significantly reduced lesion area and promoted locomotor function as well as electrophysiology recovery (Maeda et al. 2021). When MSCs were transplanted in the vicinity of a spinal cord injury in a rat model, they ameliorated the neuroinflammation and improved the clinical outcomes. There was upregulation of matrix metalloproteinase (MMP) 2 and STAT-3, while there was downregulation of NF-κb p65 and other inflammatory cytokines like IL-1α, TNF-α, and TGF-β (Kim et al. 2019). 3D spheroids of human placenta-derived MSCs (3D-hpMSCs) increased the secretion of anti-inflammatory cytokine and trophic factor such as FGF, VEGF, and PDGF. It minimized lesion area, promoted angiogenic effect, and improved motor function in mice (Deng et al. 2021).

15 NSCs/Neural Progenitor Cell

NSCs are multipotent, self-renewing, highly proliferative, and a heterogeneous population of cells. NSCs have been isolated from the brain (Leong et al. 2013), SC (Curtis et al. 2018), and dorsal root ganglion (Gu et al. 2010). The in vitro stability and viability of NSCs is of particular importance as they retain viability, self-renewability, and differentiation potential even after many freeze–thaw cycles. NSCs are a good choice for repairing injured SC tissue as they are already committed to neurogenic and gliogenic fates (Coutts and Keirstead 2008). When NSCs were grafted at SCI lesion site, they integrated, relayed neuronal signals, and established a neuronal network and synaptic communication between host and the graft (Ceto et al. 2020). Similarly, when human NSCs were grafted into C5 hemisection sites in immunodeficient mice model, the NSCs differentiated into astrocytes and showed long-distance migration. NSC-derived astrocytes formed gap junctions with host cells (Lien et al. 2019). NSCs were isolated from human SC and grafted them in cervical SCI rhesus monkey model. The grafted NSCs survived for almost 9 months and demonstrated functional effects. They integrated themselves in the host tissue (50 mm) and restored neuronal network. Transplantation of NSCs into SCI model reduced the expression of P2X7, P2X4 (expressed in neuropathic pain), and

glial fibrillary acidic protein while increasing the expression of neurofilament proteins. Also, there was axon regeneration and recovery of sensorimotor function (Rosenzweig et al. 2018; Du et al. 2019).

16 Olfactory Ensheathing Cells

In contrast to the SC, which has limited regenerative capacity, the mammalian olfactory system can actively regenerate throughout the organism's life (Coutts and Keirstead 2008). Olfactory ensheathing cells (OECs) are glial cells that wrap around nonmyelinated olfactory axons. OECs aid neural regeneration since they can induce a neuron to cross a glial scar. It has been reported that OECs promote cellular interaction, control neuroinflammation, provide neuro-protection, induce angiogenesis, clear cellular debris, kill bacteria, and release neurotropic and ECM building factors. OECs have been reported to upregulate interleukin-1 receptor antagonist (IL-1Ra) and downregulate (IL-1) and lessen the glial scar. OECs promote regeneration post-intravenous transplantation (Zhang et al. 2021). Meta-analysis data on OEC transplantation shows that OECs are highly capable of neuroregeneration and subsequent functional recovery. Intraspinal transplantation of OECs in rat SCI model showed limb motor recovery and increased motor evoke potential by week 8 (Muniswami and Tharion 2018). Quantum dot-labeled OECs intravenously transplanted into SCI rat showed reduced inflammation and remyelination and improvement in motor function. Intravenous cell transplantation is believed to be more effective than intrathecal or intraspinal cell transplantation (Zhang et al. 2019a). However, the repair of the damaged SC by OECs will require proper isolation, expansion, transplantation, and finally the integration of OECs into the neural circuit (Wright et al. 2018). Further studies are needed to understand the role of OECs in neuropathic pain, their dosages, and their sites of administration (Nakhjavan-Shahraki et al. 2018).

Advancements in stem cell-based therapies are showing tremendous hope for treating conditions with complex pathophysiology like SCI. These therapies are aimed at controlling the extent of secondary injury and restoring lost or damaged tissues. But the possible outcomes of such therapies can be further enhanced by coupling them with various biomaterial scaffolds. Additional knowledge is required to completely validate and ensure the safety of cell-based therapies for treating SCI.

17 Biomaterials for SCI

TE scaffolds made up of biomaterials should possess several properties such as biocompatibility, biodegradability, porosity, mechanical strength, hemocompatibility, noncytotoxic, and so on for being an ideal graft/transplant substrate. A variety of techniques including self-assembly, electrospinning, phase separation, freeze-drying, 3D printing, leaching, and gas foaming has been employed for the synthesis of scaffolds (Fig. 4a, c). Recently used biomaterials and their combinations with cells or other means for neural tissue engineering are discussed in Table 1.

18 Biological Scaffolds/Decellularized Scaffolds

A decellularized (cell-free) neural scaffold can be used as a viable solution for treating SCI. A decellularized matrix as a scaffold has the benefit of being substantially compatible to the tissue being replaced. It is naturally biodegradable and shows fast remodeling in vivo because of its extracellular matrix content (García-Gareta et al. 2020). "The extracellular matrix (ECM) is a non-cellular matrix present in all tissues and organs, which not only provides an appropriate physical framework for intracellular components, but also induces critical physiochemical and physiological cues necessary for tissue morphogenesis, differentiation, and equilibrium" (Frantz et al. 2010). Each tissue and organ's resident cells design and build the ECM, which can be customized in a balanced relationship with its

Table 1 Tissue-engineered materials attempted to promote nerve regeneration

Sr. No	Material	Method of fabrication/modification	Animal experiment	Type of SCI model	Functional recovery	Outcome	References
1	Collagen and stretch-grown tissue-engineered nerve grafts	Encapsulation	Yes	SC complete transections (T10–T11)	Yes	Greater tissue infiltration and less compression No immune reaction Axonal growth	Sadik et al. (2020)
2	Superporous poly (2-hydroxyethyl methacrylate) hydrogel	-Radical polymerization -Plain and MSC-seeded hydrogel	Yes	Underwent transaction (T8)	-	Axon infiltration in gradual manner	Hejčl et al. (2018)
3	Multichannel poly(lactide-co-glycolide) (PLG)	EGFP-progenitor-seeded bridge	Yes	Lateral hemisection (T9–10)	Yes	Reduce inflammation Promote axon regrowth Support spinal progenitors Remyelination	Dumont et al. (2018)
4	Polyethylene glycol (PEG) microspheres/tubes	Free radical polymerization/modified by fibrinogen, thrombin, and cacl2 (Sigma) in tris-buffered saline	Yes	Lateral hemisection (T9–10)	Yes	Supports uniaxial tissue growth Increased regeneration Reduces glial scar	Dumont et al. (2019)
5	Fluorenylmethyloxycarbonyl (Fmoc)- DIKVAV self-assembling peptide hydrogel	Plane and seeded rat mesenchymal precursor cells (rMPC)	Yes	Mild thoracic contusion SCI (T10)	Yes	Anti-inflammatory Axon regrowth Infiltration of astrocyte	Wiseman et al. (2021)
6	Poly(ε-caprolactone) (PCL)	Electrospun, green fluorescent dye, poly (9, 9-dioctylfluorene-alt-benzothiadiazole) (F8BT)	Yes	SC contusion (T9)	-	Provided mechanical support Promotes angiogenesis, neurogenesis, and axon presence	Li et al. (2020)
7	Fibrinogen, thrombin, poly (ethylene oxide), and alginate	Electrospinning	Yes	Dorsal hemisection (T9–T10)	Yes	Scaffold induced the alignment, migration, and proliferation of host cells Remyelination	Yao et al. (2018b)
8	Poly(ethylene glycol) diacrylate (PEGDA)–GelMA	3D printing, NPC-seeded scaffold	Yes	Complete SC transection (T3)	Yes	Axonal regeneration Provide patient specific scaffold	Koffler et al. (2019)
9	Collagen	NSC-seeded, paclitaxel (PTX)-liposome encapsulated collagen scaffold	Yes	Complete transaction (T8)	Yes	Provide instructive microenvironment Axon extension Neural differentiation	Li et al. (2018b)

10	RADA16-RGD peptide and PCL-PEG-PCL-diacrylate (PCECDA)	Photo-cross-linking	Yes	Hemisection SCI model	Yes	Reduced glial scar Neural regeneration	Zhai et al. (2020)
11	Poly(lactide-co-glycolide)/ polyethylene glycol (PLGA-PEG)	Electrospinning	Yes	Complete transection (T10–T11)	Yes	Reduce cavity formation Promote neuronal differentiation	Liu et al. (2015)
12	Chitosan–sodium alginate	Freeze–thaw	Yes	SC hemisection model (T9–T10)	Yes	Reduced scar Motor function recovery Promote regeneration	Yao et al. (2018a)
13	Starch poly-e-caprolactone (SPCL) blend and gellan gum	3D plotting rapid prototyping	Yes	SC hemisection model (T8–T9)	Yes	Noncytotoxic Biocompatible Mechanical property	Silva et al. (2010)
14	Tannic acid (TA) and polypyrrole	–	Yes	Hemisection model (T9–10)	Yes	Mechanical property Good electronic conductivity Promote neurogenesis	Zhou et al. (2018a)

own microenvironment. The native ECM makeup, particularly its tiny components, must nevertheless be preserved, evaluated, and expanded for big tissues and organs (García-Gareta et al. 2020).

Decellularization of the peripheral nerve and SC can be accomplished using a variety of chemicals and enzymes, including triton X-200 (Cerqueira et al. 2018), triton X-100 (Wang et al. 2017; Guo et al. 2010; Jiang et al. 2013), sodium deoxycholate (Wang et al. 2017; Guo et al. 2010; Jiang et al. 2013), and phosphate-buffered saline (PBS) (Jiang et al. 2013). Decellularized scaffold was created by decellularizing sciatic nerves as the SC and had physicochemical qualities similar to autologous neurons and showed low immunological rejection (Gu et al. 2011; Tian et al. 2017). Allogenic rat acellular SC was generated by PBS, triton X-100, and sodium deoxycholate. This acellular SC contained laminin, fibronectin, and collagen contents which induces neural regeneration. 1-Ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride (EDC) cross-linking in combination with chemical extraction techniques enhanced the effectiveness of acellular SC scaffolds and conferred superior biological properties, including improved immunogenicity. These scaffolds promoted the adhesion and differentiation of rat BMMSCs into cells similar to neurons (Xing et al. 2019). Another cross-linker genipin (GP) significantly improves structural stability of acellular rat spinal and promotes cellular adhesion and proliferation in vitro (Jiang et al. 2013). Acellular rat SC seeded with BMMSC reduced inflammation and apoptosis of neural cells. Additionally, it also promotes sensorimotor function recovery in BMMSC-seeded scaffold (Wang et al. 2017). Rat acellular SC scaffolds showed improved bone marrow stem cell survival as well as minimized apoptosis of damaged native neural tissue, conserved the host tissue, and boosted transplant recovery (Chen et al. 2014). Modified acellular peripheral nerve graft was developed by using triton X-100 and sodium deoxycholate followed by freeze–thaw cycle for treating SCI. There was functional recovery after transplantation of acellular nerve graft along with GFP-labeled placental MSCs. It also showed that PMSCs distributed in host SC and differentiated into neuron-like cells and also promoted remyelination (Tian et al. 2017). Acellular rat SC scaffold seeded with rat adipose-derived stem cells (rADSCs) promoted functional recovery in rat SC hemisection model. There was reduction in active gliosis and glial scar formation and increased axon regeneration (Yin et al. 2018). Injectable decellularized peripheral nerve matrix improved efficiency of Schwan cells after transplantation in rat SCI model. It supported Schwan cell survival and axon growth and also promoted locomotor recovery without any immunogenic reaction (Cerqueira et al. 2018). A molded (3D) decellularized SC scaffold is developed by homogenizing bovine SC in 0.1 N NaOH. This method can effectively remove all cells and maintains ECM content. It also showed good cell viability and proliferation (Arslan et al. 2019). Most of decellularized SC scaffold was prepared by using rat SC and few by using bovine SC. Therefore, more research should be carried out to check the efficiency of bovine scaffold in vivo and in vitro for SC repair. The enhanced preparation approach might pave the way for modular acellular biological scaffolds to treat SCIs (Xing et al. 2019).

19 3D Printed Scaffold

The 3D scaffolds provide better cell proliferation and tissue maturation as compared to 2D scaffolds (Kadoya et al. 2016). The main advantage of using 3D printing is that it provides better control over scaffold design and shows improved mechanical properties. 3D scaffolds are highly capable of neuronal regeneration as it guides nerve cells, promotes differentiation, and shows tremendous therapeutic potential. Because of the intricacy of CNS architecture, 3D biomimetic scaffolds provide a way to enhance CNS regeneration via personalized medicine (Koffler et al. 2019).

A novel set of three-dimensional (3D) tubular structures were prepared by using gellan gum and biodegradable blend of starch. In vivo experiments in a rat hemisection SCI model revealed that the structures were effectively

absorbed into the lesion and did not cause persistent inflammation (Silva et al. 2010). Microscale continuous projection printing method (μCPP) can be used to mimic the complex 3D architecture of the CNS organs and even for regeneration of the severed SC. This technique is relatively faster as it can print 2-mm scaffolds in 1.6 s. The polyethylene glycol–gelatin methacrylate (PEG–GelMA) scaffolds prepared by μCPP seeded with neural progenitor cells were transplanted into transection SC rat model. All the 11 rats that received the scaffold retained original scaffold structure even after 4 weeks of implantation. There was no inflammatory response. It supported neuronal growth and modified the astrocyte reactivity to SCI (Koffler et al. 2019). A 3D printed collagen/silk fibroin scaffold seeded with MSCs remyelinated the axon and relayed neural signals (Chen et al. 2022a).

20 Conductive Scaffold

Conductive scaffolds are electrically sensitive scaffolds that regulate signals to electroactive cells for their cellular migration and proliferation. Because neurons respond to electrical signals, conductive scaffolds have a high potential for developing a neural connection within the damaged part. External and internal electrical impulses that convey ECM signals have been demonstrated to be transduced by conductive scaffolds in vitro and in vivo in cardiac and neural scar tissue to enhance organ function and behavior on a macroscopic level (Burnstine-Townley et al. 2020). A conducting polymer hydrogel (CPH) blend with plant-derived polyphenol and tannic acid boosted the differentiation of NSCs and significantly improved locomotor function (Zhou et al. 2018a). Formulating such a conductive scaffold could stimulate the native tissue and provide a bridge to improve the communication between the scaffold and the native tissue. A clinically relevant conductor called "advanced nerve guidance channels (ANGCs)" was developed by using chitosan–gelatin by cryogelation and unidirectional solvent freezing. It showed cellular migration and growth (Singh et al. 2018). This type of study shows it can be an effective tool to guide nerve cells in the scaffold to connect with native cells. An electroconductive and biocompatible nanofiber scaffold was prepared by using polyaniline along with PCL. It provided topographical cues and electrical signals to guide cells in vitro (Garrudo et al. 2019). Polypyrrole–alginate composite incorporated with nanochitosan showed cytocompatibility and promoted neural cell adhesion and proliferation (Manzari-Tavakoli et al. 2020). A novel nanofiber-based fibrin/polyurethane/multiwall carbon nanotube (fibrin/PU/MWCNT) hydrogel was developed. This hydrogel provides a suitable microenvironment that can promote cell adhesion, viability, and their proliferation in vitro. The addition of MWCNT to PU enhanced the conductivity as well as the hydrophobicity of nanofiber hydrogel (Hasanzadeh et al. 2019). 3D printed conductive poly (3,4-ethylenedioxythiophene) (PEDOT):polystyrene sulfonate (PSS) hydrogel with high electrical conductivity retention showed that electrical stimulation of the scaffold can improve neuronal differentiation (Heo et al. 2019). Similarly, polypyrrole/silk fibroin (PPy/SF) electroconductive scaffolds were developed using 3D bioprinting and electrospinning methods. In vitro and in vivo results showed enhancement in axonal regeneration and remyelination when they were electrically stimulated (Zhao et al. 2018). 3D-printed conductive nanocellulose/carbon nanotube scaffolds guided nerve cell attachment, proliferation, and the development of neural networks in vitro (Kuzmenko et al. 2016). Therefore, the development of such scaffold will have more scope in future neural tissue engineering applications.

21 Other Biomaterial Scaffolds

Biocompatible GelMA/ECM hydrogel scaffold developed by decellularization and electrospinning technique promoted NSC differentiation and reduced inflammation and SC regeneration (Chen et al. 2022b). Methacrylated hyaluronic acid (HA)-based hydrogel was modified by the incorporation of ECM components (collagen I and laminin) with suitable mechanical properties. This hydrogel

provided suitable microenvironment for the growth of axon (Spearman et al. 2020). The RADA16-RGD peptide-based hydrogel is prepared by photo-cross-linking of PCL-PEG-PCL-diacrylate (PCECDA). This hydrogel promoted NSC adhesion and proliferation in vitro, while reduction in glial scar enhanced neural regeneration and motor function in vivo (Zhai et al. 2020). An electroconductive, injectable, biocompatible, self-recovering, elastic, and biodegradable hydrogel promoted cell adhesion, proliferation, and differentiation of NSC. The hydrogel showed a unique real-time motion sensing property and a significant gain in motor neuron function and neural regeneration in a zebrafish brain injury model (Xu et al. 2020). The dendritic polypeptides were self-polymerized to form nanofiber scaffolds. It enhanced differentiation of NSCs into functional neurons and eventually increased the motor function (Liu and Li 2018). PLGA-PEG 3D nanofiber scaffold was prepared by electrospinning and showed mouse embryonic fibroblast (MEF) cell adhesion and proliferation. When transplanted into rat SCI model, it regenerated a totally transacted SC (Liu et al. 2015). Chitosan has been extensively used as a scaffolding material as it is biocompatible and shows antimicrobial properties. Similarly, sodium alginate also shows good biocompatibility and stability in vivo. Porous chitosan–sodium alginate scaffolds are prepared by freeze–thaw and transplanted in rat SC hemisection model to examine the locomotor recovery following SCI. After surgery, most of the rats in the control group died, but rats receiving scaffolds showed low death rate. The chitosan scaffold was retained for almost 2 months without any structural change or degradation, which supported to bridge the gap of injury. Additionally, glial fibrillary acid protein (GFAP) expression was very low and the growth of glial scar tissue was inhibited (Yao et al. 2018a).

22 Combinational Tissue Engineering Approach

"Combinational therapy" is the use of two or more therapies in combination. This approach can overcome the disadvantages associated with the use of single therapy. The majority of earlier research has applied drugs or neurotrophic factors along with scaffolds to reduce neuroinflammation and improve axonal regeneration. An endometrial stem cell (EnSC)-seeded biomimetic hydrogel scaffold combined with atorvastatin injection improved locomotion and stopped the progression of secondary injury. Neurotrophic factor combined with collagen-binding domain (CBD) increased the endogenous repair in SCI (Astaneh et al. 2020). A multichannel PLGA scaffold seeded with activated Schwann cells (ASCs) and rat BMMSCs enhanced the survival and differentiation of MSCs into neural-like cells (Yang et al. 2017). A core–shell microfiber scaffold was prepared by using PLGA and FGF 2. This microfiber promoted cellular adhesion and proliferation of PC12 cells and enhanced locomotor recovery after 28 days (Reis et al. 2018). These aforementioned studies (Yang et al. 2017; Reis et al. 2018) were successful in improving neural regeneration and significant gain of sensorimotor function. PLGA surface modified with DOPA-IGF-1, a new recombinant protein, enhanced human umbilical cord MSC (hucMSC) paracrine activity by releasing neurotrophic factors. It showed higher cell adhesion and proliferation (Zhang et al. 2019b). When ASCs and iPSC-derived NSCs were seeded into PCL scaffolds, it promoted functional recovery in rat model (Zhou et al. 2018b). Immunization with neural-derived peptide (INDP), fibrin glue (FG), and dipyridyl (DYP) along with BMMSCs were used for the treatment of acute SCI. It showed significant sensational and functional recovery because of increase in axonal density in tissue (García et al. 2019). Although these results suggest combinational therapy would be beneficial, it is important to note that this is preliminary study, and further investigations are required.

23 Clinical Trials

ESCs have been emerged in clinical settings to treat SCI. Safety and efficacy of hESCs was evaluated in phase 1 trial. It showed functional

recovery in both limbs and bowel and bladder function in five patients with either paraplegia or quadriplegia. No contrary event occurred; therefore, hESCs could be considered effective as well as safe therapy for SCI (Shroff and Gupta 2015). In another phase 1 study, four chronic spinal trauma subjects received intraspinal injection of human SC-derived NSCs (NSI-566) at 12–24 months after spinal trauma. Three subjects out of four showed gains in sensorimotor function without any adverse effect. This study has provided only primary safety data and lacks statistical significance because of small sample size (Curtis et al. 2018). Using autologous mesenchymal stromal cells (MSCs), phase 2 trial was conducted in SCI patients. In this study, three intrathecal 100×10^6 doses of MSCs were given to chronic SCI patients, followed by a follow-up period of 10 months. This study showed variable clinical outcomes including not only gain of sensorimotor function, sphincter dysfunction, sexual function, recovery in neuropathic pain, and sensitivity but also improvement in ASIA grade scale for SCI. All the improvements are regardless of age, time, and severity of SCI. This study does not show any adverse effect in patients. It is important to consider dose of cells and their administration, as there is no standard parameter for MSC administration in SCI patients for better outcomes (Vaquero et al. 2018). Combinational therapy of collagen scaffold (NeuroRegen) along with human umbilical cord MSC (hUBMSCs) was able to treat effectively one thoracic and one cervical SCI patient, respectively. A 1-year follow-up study showed significant improvement in sensorimotor function, bladder–bowel function, and muscle function in both patients; as a result, ASIA impairment scale of both SCI patients improved from grade A to C (Xiao et al. 2018). Therefore, this data provides such combinational therapy would able to integrate with host tissue and have potential to develop neural network which leads to significant functional recovery.

Clinical trials for SCI mainly focus on neuroregeneration by means of cell-based therapy that is mentioned in Table 2, while clinical trials on tissue-engineered scaffold are mentioned in Table 3. All neuro-regenerative experiments or preclinical studies now have been reached to clinical trial phases 1 and 2. To date, various cell-based therapies such as neural precursor cells, NSC, olfactory mucosa ensheathing cells, BMMSCs, WJMSCs, UCMSCs, and adipose-derived MSCs were given to SCI patients for their safety and effectiveness at various dosages. Cells are mainly administrated by intrathecal, intraspinal, epicenter of injury, intramedullary, and percutaneous injection. The completed and ongoing clinical trials for SCI show promising results such as recovery of sensorimotor functions, gain of bowel/bladder function, decreased neuropathic pain, reduced lesion area and inflammation that leads to neurogenesis. However, small sample size may limit statistically significant results of such studies. Further clinical trials on a large number of SCI population must be needed to evaluate results significantly.

24 Future Prospective

SCI causes a slew of issues that must be addressed in order to find a solution for the disease. Apart from many in vivo studies, few fail to be duplicated and transfer therapeutically, which is unsatisfactory to people with SCI who are waiting for treatment alternatives. Various injury models used for SCI in preclinical studies might differ because of targeted damage; thus, the actual situations in clinical setting of human patients with SCI are typically distinctive. We cannot completely rely on the preclinical study results for validating the success of SCI therapies. Considering the difference between regeneration capability and behavioral activities of rats and humans, the clinical trials based on preclinical data may yield unsatisfactory or minimal results (Cofano et al. 2019). Therefore, more emphasis should be given on clinical trials to maximize authenticity of the desired therapeutics. There are many obstacles in the field of neural tissue engineering. Increasing graft survival and tissue regeneration, establishing and maintaining viable connections between neurons, identifying the optimal neurons for enhancing communication,

Table 2 Clinical trial on various cell-based therapies for the treatment of SCI listed on www.clinicaltrials.gov

Sr. No.	Clinicaltrials.gov. Id	Phase of study	Scaffold/cell	Level of injury/ type of injury	Study status	Study period	Study summary	Location
1	NCT04812431	Phases 1 and 2	Neural precursor cells derived from human embryonic cell line	Intrathecal injection	Not yet recruiting	Sept. 2021 to Sept. 2023	The goal of this exercise is to assess the preliminary safety and efficacy of neural precursor cells (PSA-NCAM (+) NPC) obtained from the hESC line for the therapy of paralysis as well as other subacute SCI complaints	Yonsei University Health System, Severance Hospital, Seoul, Republic of Korea
2	NCT02326662	Phases 1 and 2	Autologous NSC	Intraspinal and intrathecal injection	Unknown	Jul. 2014 to Dec. 2018	The use of autologous NSCs in individuals with full traumatic SC damage is being investigated in this study	Federal Research Clinical Center FMBA of Russia, Moscow, Russian Federation.
3	NCT01772810	Phase 1	Human SC-derived NSC	–	Recruiting	Aug. 2014 to Dec. 2022	Study focuses on safety of NSCs derived from human SC for treating chronic SCI	UCSD Medical Center, Division of Neurosurgery San Diego, California, United States.
4	NCT01321333	Phases 1 and 2	Human CNS allogenic stem cell	Intramedullary administration	Completed	Mar. 2011 to Apr. 2015	Study exploring the preliminary efficacy of human CNS allogenic stem cell with thoracic spinal SCI	Foothills Medical Center, Calgary, Alberta, Canada Toronto Western Hospital, Toronto, Ontario, Canada. University Hospital Balgrist- Uniklinik Balgrist, Forchstrasse 340 Zurich, Switzerland.
5	NCT01231893	Phase 1	The olfactory mucosa ensheathing cells	Transplanted into focus of SCI	Unknown	May 2008	The goal of this investigational therapy is to see if transplanting autologous olfactory ensheathing glia and olfactory fibroblasts derived from the olfactory mucosa to patients with full SC damage is safe and feasible	Department of Neurosurgery of Wroclaw Medical University, Wroclaw, Poland.

6	NCT03933072	Phases 1 and 2	Autologous bulbar OEC	Transplant cell by using peripheral nerve graft	Recruiting	Mar. 2016 to Mar. 2023	This trial aims to investigate the safeness and efficiency of transplanted cells in chronic complete SCI	Wroclaw Medical University Wroclaw, Poland
7	NCT02482194	Phase 1	Autologous BMMSCs	Intrathecal delivery	Completed	Jun. 2013 to Mar. 2016	This study focuses on intrathecal transplantation of BMMSC to evaluate safety and their efficacy for treatment of SCI and determination of functional recovery	Armed Forces Bone Marrow Transplant Centre, Rawalpindi, Pakistan
8	NCT03505034	Phase 2	Allogeneic Umbilical Cord MSCs	Intrathecal Transplantation	Recruiting	Sept. 2019 to Dec. 2021	This study tries to find out the best time for cell treatment and their safeness with efficacy to treatment chronic SCI patients	The Third Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, China.
9	NCT01694927	Phase 2	Autologous MSCs	Intralesional transplantation	Unknown	Jan. 2012 to Jun. 2014	The purpose of the study is to see if intralesional transplantation of autologous mesenchymal stem cells is a safe and efficient therapy for individuals with SCIs	Clínica Las Condes, Santiago, RM, Chile.
10	NCT03521336	Phase 2	Allogeneic umbilical cord MSCs	Intralesional transplantation	Recruiting	Sept. 2019 to Dec. 2021	This study tries to find out the best time for cell treatment and their safeness with efficacy compared to placebo to treatment in chronic SCI patients	The Third Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, China.
11	NCT02574585	Phase 2	Autologous MSCs transplantation	Percutaneous injections	Not yet recruiting	Dec. 2019 to Jan. 2022	Study tries to find out assurance and effectiveness of autologous mesenchymal cell transplantation to treat patient with chronic thoracic and complete SCI	Ricardo Ribeiro dos Santos, Hospital São Rafael, Salvador, Bahia, Brazil
12	NCT01446640	Phases 1 and 2	BMMSCs	Intravenous combined with intrathecal administration	Unknown	Oct. 2011 to Jun. 2014	This clinical trial aims for safety and effectiveness of BMMSC for the treatment of SCI	Guangzhou General Hospital of Guangzhou Military Command, Guangzhou, Guangdong, China.

(continued)

Table 2 (continued)

Sr. No.	Clinicaltrials.gov. Id	Phase of study	Scaffold/cell	Level of injury/ type of injury	Study status	Study period	Study summary	Location
13	NCT02481440	Phases 1 and 2	Allogeneic human umbilical cord MSCs	Intrathecal administrations	Completed	Mar. 2018 to Mar. 2020	This clinical trial aims for safety and effectiveness of repeated subarachnoid administration of hUCMSCs for the treatment of SCI	The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China.
14	NCT02152657	Phase 1	Autologous MSCs	Percutaneous injection	Completed	Jan. 2015 to Dec. 2016	This is pilot study to evaluate autologous MSC transplantation through percutaneous injection for their safety and effectiveness in patient with chronic SCI	Hospital São Rafael, Salvador, Bahia, Brazil.
15	NCT02981576	Phases 1 and 2	Autologous BMMSC and AT-MSC	Intrathecal administrations	Completed	Nov. 2016	This is comparative study which evaluates safeness and efficacy of BMMSC and ATMSC for the treatment of SCI patients	Cell Therapy Center, University of Jordan, Amman, Jordan.
16	NCT04520373	Phase 2	Autologous adipose-derived MSCs	Intrathecal injection	Recruiting	Jun. 2020 to Jun. 2024	This study focuses on safety and effectiveness of therapy based on autologous AT-MSCs with patients having paralysis	Mayo Clinic in Rochester, Rochester, Minnesota, United States.
17	NCT01769872	Phases 1 and 2	Autologous adipose tissue-derived MSCs	Intrathecal injection	Completed	Jan. 2013 to Jan. 2016	Study investigates the effect of treatment of AT-MSCs for efficacy and their safety to treat SCI patients	Korea University Anam Hospital, Seoul, Republic of Korea
18	NCT05152290	Phase 1	Allogeneic adult umbilical cord-derived MSCs	Intrathecal injection and intravenous infusion	Recruiting	Jan. 2022 to Jan. 2026	This study aims to investigate effects of intravenous infusion and intrathecal injection of allogeneic UCMSC in patient with SCI	Medical Surgical Associates Center, St. John's, Antigua and Barbuda.
19	NCT01624779	Phase 1	Autologous adipose tissue-derived MSC (AT-MSCs)	Intrathecal injection	Completed	Apr. 2012 to May 2014	This study checks the effect of intrathecal AT- MSC administration in patients with SCI	Korea University Anam Hospital, Seoul, Seongbukgu, Republic of Korea

20	NCT03003364	Phases 1 and 2	Wharton's jelly MSCs	Intrathecal administration	Completed	Dec. 2016 to Feb. 2020	To study the safety data and efficiency of intrathecal administration of expanded WJ-MSCs in patient affected with chronic TSCI	Hospital de Neurorehabilitació Institute GuttmannBadalona, Barcelona, Spain.
21	NCT04288934	Phase 1	Autologous bone marrow-derived MSCs (auto BMMSCs) and Wharton's jelly-derived MSCs (WJ-MSCs)	Spinal medulla	Completed	Aug. 2017 to Sept. 2020	This was comparative study which aims to access safety and effectiveness of auto BMMSCs and WJ-MSCs cell treatment in SCI patients	Cell Therapy Center, University of Jordan, Amman, Jordan.
22	NCT01873547	Phase 3	Umbilical cord MSCs	Subarachnoid infusion by lumbar puncture	Completed	Jun. 2012 to Dec. 2015	This study aims to find out the effective therapy for SCI which includes cell therapy, rehabilitation therapy, and control group	General Hospital of Chinese People's Armed Police Forces Beijing, Beijing, China.
23	NCT01325103	Phase 1	Autologous MSC	Direct transplantation injured area	Completed	Jul. 2010 to Dec. 2012	To evaluate the safety and effect of auto BMMSCs for the treatment of SCI	Hospital São Rafael Salvador, Bahia, Brazil.
24	NCT01909154	Phase 1	MSCs	Subarachnoid and intramedullary	Completed	Mar. 2013 to Mar. 2015	This was a pilot study to check the safety of local delivery of autologous MSCs derived from BM stroma in SC traumatic injuries	Hospital Puerta de Hierro Majadahonda, Madrid, Spain.
25	NCT00816803	Phases 1 and 2	Autologous bone marrow-derived cells	Sites of injury	Completed	May 2005 to Dec. 2008	The goal of this study is to see if autologous BM-derived cell transplantation is safe in chronic SC damage patients	Cairo University School of Medicine Cairo, Egypt.
26	NCT02165904	Phase 1	Adults' autologous MSCs	Subarachnoid administration	Complete	May 2014 to May 2016	Examine the potential therapeutic effectiveness of administering major adult mesenchymal autologous cells that have been grown "in vitro" in individuals with incomplete and chronic SCI	Hospital Puerta de Hierro Majadahonda, Madrid, Spain.

Table 3 Clinical trial on SCI using various types of graft/scaffolds listed on www.clinicaltrials.gov

Sr. No.	Clinicaltrials.gov. Id	Phase of study	Scaffold/cell	Level of injury/ type of injury	Study status	Study period	Study summary	Location
1	NCT02138110	–	Poly(lactic-co-glycolic acid)-b-poly(L-lysine) scaffold	T2–T12 (thoracic acute SCI)	Active, not recruiting	Oct. 2014 to Aug. 2024	In participants with thoracic AIS, multicenter research was conducted to assess the safety and potential utility of the poly(lactic-co-glycolic acid)-b-poly(L-lysine) scaffold	United States, Arizona United States, California United States, New Jersey United States, North Carolina United States, Oregon United States, Pennsylvania
2	NCT02510365	Phase 1	Collagen scaffold	Acute SCI	Unknown	Apr. 2015 to Dec. 2021	The goal of the trial is to determine the safety and effectiveness of a functional neural regeneration collagen scaffold implanted into patients with acute SCIs	Beijing, China Chongqing, China Suzhou, China Tianjin, China Yinchuan, China
3	NCT02688049	Phases 1 and 2	MSCs or NSCs combined with NeuroRegen scaffold	Chronic SCI	Unknown	Jan. 2016 to Dec. 2021	The objective of this study is to see if MSC- or NSC-seeded NeuroRegen scaffold transplantation in patients with SCIs are effective and safe	Tianjin, China
4	NCT02352077	Phase 1	NeuroRegen scaffold TM with BMMSCs or BMMNCs	Chronic SCI	Unknown	Jan. 2015 to Dec. 2021	The objective of this study is to see if bone marrow mononuclear cells or mesenchymal stem cells paired with NeuroRegen scaffold transplantation in patients with SCI are effective and safe	Tianjin, China Suzhou, China Beijing, China
5	NCT03966794	Phases 1 and 2	Collagen scaffold	SCI	Unknown	Aug. 2019 to Dec. 2021	The goal of the study will be how functional neural regeneration collagen scaffold transplantation paired with epidural electrical stimulation affects individuals with SCIs	Tianjin, China

6	NCT02688062	Phases 1 and 2	NeuroRegen scaffold with BMMSC transplantation	Chronic SCI and complete SCI	Unknown	Jan. 2016 to Dec. 2021	The target of this investigation is to check the effectiveness and efficiency of NeuroRegen scaffold with BMMNCs to surgical intradural decompression and adhesiolysis alone for neurological recovery following chronic and total SC damage	Beijing, China
7	NCT03105882	–	Neuro-Spinal Scaffold^{tm}	C5–T1 traumatic cervical acute SCI	Withdrawn (the study did not enroll any subjects)	Mar. 2017 to Mar. 2018	Pilot Study of the Neuro-Spinal Scaffoldtm Clinical Safety and Feasibility in the treatment of complete (AIS A) acute TSCI at the C5–T1 levels.	Toronto, Ontario, Canada
8	NCT03762655	–	Neuro-Spinal Scaffold™ – poly (lactic-co-glycolic acid)-b-poly (L-lysine) (PLGA-PLL)	Complete T2–T12 SCI	Recruiting	May 2019 to Jul. 2028	This study aims to see if the scaffold is safe and effective for the treatment of complete T2–T12 SCI when compared to standard of care open spine surgery	United States, California United States, Colorado United States, Florida United States, Iowa United States, Maryland United States, New Jersey United States, New York United States, North Carolina United States, Oregon United States, Pennsylvania United States, Rhode Island United States, Texas United States, Wisconsin
9	NCT03933072	Phases 1 and 2	Olfactory ensheathing cells (OECs) and olfactory nerve fibroblasts (ONFs)/collagen scaffold and autologous dural nerve grafts	C5 and Th10 complete SC transection	Recruiting	Mar. 2016 to Mar. 2023	The goal of this study is to find if transplanting autologous OECs and ONFs from the olfactory bulb with synchronous reconstruction of the posttraumatic SC gap with peripheral nerve grafts are safe and effective in patients with chronic complete SCIs	Wroclaw, Poland

guiding grafted cells to suitable destinations, and avoiding inappropriate connectivity are all things that must be addressed. There are some crucial considerations in cell treatment such as method standardization, cell potency evaluation, quality management, good manufacturing practice (GMP) and their scale-up, and finally logistics. Clinical translation of the TE products will require testing the biomaterial for its biodegradability as well as biocompatibility. An accurate understanding of its composition, 3D structure, and safety in vivo must also be taken into consideration while using 3D biomaterials to distribute cells. Chronic SCIs to date remain one of the least explored SCIs because more and more focus is given to acute and subacute SCI; it is therefore necessary to increase transplantation studies on the more severe chronic SCI (Duh et al. 1994).

25 Conclusion

In this review, we have discussed the pathophysiology of the SCI and current treatment modalities with their advantages and limitations. It is important to understand that the pathophysiology of SCI is complicated and that a single solution is unlikely to overcome the diverse array of obstacles. Therefore, a combinational tissue engineering therapy might be the future treatment option. More preclinical and clinical studies should be carried out for the most effective treatment modality in order to address the SCI in the near future.

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