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Review Article

Matrices, scaffolds & carriers for cell delivery in nerve regeneration

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ABSTRACT

Nerve injuries can be life-long debilitating traumas that severely impact patients' quality of life. While many acellular neural scaffolds have been developed to aid the process of nerve regeneration, complete functional recovery is still very difficult to achieve, especially for long-gap peripheral nerve injury and most cases of spinal cord injury. Cell-based therapies have shown many promising results for improving nerve regeneration. With recent advances in neural tissue engineering, the integration of biomaterial scaffolds and cell transplantation are emerging as a more promising approach to enhance nerve regeneration. This review provides an overview of important considerations for designing cell-carrier biomaterial scaffolds. It also discusses current biomaterials used for scaffolds that provide permissive and instructive microenvironments for improved cell transplantation.

1. Introduction

Peripheral nerve injury (PNI) and spinal cord injury (SCI) are two of the major types of traumatic injury to the nervous system. Every year in the United States, approximately 360,000 people suffer from PNI (Kelsey et al., 1997), and 17,000 people suffer from SCI (UAB, 2017). These injuries often lead to the disruption of neuronal circuitry and denervation of important organs, resulting in functional deficits. Patients can suffer life-long disabilities with minimal recovery. Among various types of PNI, complete nerve transections, especially those that occur more proximally in the nerve or results in a large gap, have a limited chance of recovery leading to decreased motor and sensory function. About one third of SCI patients suffer from complete paraplegia and less than 1% of patients experience complete neurological recovery by the time of hospital discharge (UAB, 2017). The lifetime costs of care for SCI patients can range from $1.5 to $5 million. In order to develop strategies for treating neural injury, scaffold-facilitated cell delivery strategies have been developed. Both PNI and SCI treatment strategies share similar therapeutic cell types and cell delivery platforms, which will be the focus of this review. Cell-based treatment for traumatic brain injury and other neurological disorders have been discussed elsewhere (Gennai et al., 2015; Lindvall and Kokaia, 2006).

The peripheral nervous system (PNS) has an inherent regenerative capacity to regenerate across relatively short injury distances. However, PNI with long gaps (>3 cm) between the two end of the severed nerve usually require surgical intervention, with autologous nerve grafting being the gold standard. Unfortunately, autologous nerve grafts has many limitations, such as limited donor nerves, donor site morbidity, and mismatch between the injury nerve and donor nerve (Mackinnon and Hudson, 1992; Ortiguela et al., 1987). As an alternative to autografts, different types of biologically or artificially-derived tissue-engineered products have been developed. Some of the well-studied clinically approved options include processed allografts, collagen tubes, muscle-vein combination conduits, and vein grafts (Braga Silva et al., 2017). Several FDA approved, commercially available nerve conduits are NeuraGen® (Collagen Type I based, Integra LifeSciences Co),

Abbreviations: PNI, Peripheral nerve injury; SCI, Spinal cord injury; ECM, Extracellular matrix; SC, Schwann cell; OEC, Olfactory ensheathing cell; ESC, Embryonic stem cell; NSC, Neural stem cell; iPSC, induced-Pluripotent stem cell; BBB, Basso Beattie and Bresnahan locomotor scale method; GFAP, Glial fibrillary acidic protein; YAP, yes-associated protein; TAZ, tafazzin; p(HEMA-coAEMA), Poly(2-hydroxylethl methacrylate) and poly(aminoethyl methacrylate); NGF, Nerve growth factor; BDNF, Brain-derived neurotrophic factor; NT-3, neurotrophin-3; GDNF, Glial cell line-derived neurotrophic factor; CNTF, Ciliary neurotrophic factor; FGF, Fibroblast growth factor; VEGF, Vascular endothelial growth factor; BMS, Basso mouse scale; HA, Hyaluronic acid; PEG, Poly(ethylene glycol); ANA, Acellular nerve allograft; HAMC, Hyaluronan and methylcellulose; PDGF, Platelet-derived growth factor; RIP, Receptor-interacting protein; PGA, poly(glycolic acid); PLA, poly(lactic acid); PLGA, poly(lactic-co-glycolic acid); P(AN/VC), poly(acrylonitrile-co-vinyl chloride); PLLA, poly(L-lactic acid); PDLLA, poly(D,L-lactic acid); GGF, Glial growth factor; PCL, poly(ε-caprolactone); Ppy, polypyrrole; PANI, polyaniline; CNT, carbon nanotubes

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Neurotube® (Polyglcolic acid based, Synovis Micro Companies Alliance), and Neurolac™ (Poly(D,L-lactide-co-ε-caprolactone) based, Polyganics BV). Note that most FDA-approved conduits claim functionally substantially equivalent to nerve graft, direct suture and silicone conduit (FDA 510(k) 011168, NeuroGen™ Nerve Guide). Safety evaluations include cytotoxicity, irritation, sensitization, acute and chronic toxicities, genotoxicity, implantation, and hemolysis. Mechanical and physical characteristics are used to examine suture retention, mechanical compression, porosity, and permeability. While these products are approved for use clinically, they still fail to promote full functional recovery in many patients, especially those with long gap injuries that are >3 cm.

In comparison with the PNS, the mammalian spinal cord has very limited capacity for regeneration. The formation of a glial scar surrounding a cystic cavity after SCI prevents the escalation of further damage, but it also hinders the regeneration process by presenting an environment that is both physically and chemically inhibitory (Silver and Miller, 2004). Current interventions offer little functional recovery clinically. Neuroprotective strategies need to be administered within hours after injury, which is often difficult to achieve given the broad distribution of patients at the time of injury. A potential alternative strategy to improve recovery is to transplant exogenous cells to provide a more permissive environment and in some cases reroute neural signals around/through the lesion site.

Many different cell types have shown therapeutic potentials for nerve repair. Schwann cells (SC) are a native glial population in the PNS that support neurons and form the myelin sheath. SCs are also known to support regeneration after injury and transplantation of SCs has been well studied. Although SCs are not normally present in the spinal cord, they have been shown to migrate into injured spinal cords with the potential to promote myelination or trophic effects (Guest et al., 2005). Transplanted SCs have shown the potential to improve recovery in animal models of SCI (Pearse et al., 2007; Takami et al., 2002). The disadvantages of transplanting SCs in SCI may be related to the formation of Schwannoma and neuropathic pain (Campana, 2007; Norenberg et al., 2004). While autologous SCs present minimal risk of host immune rejection, the availability is often limited by the success of cell culture and number of passages before senescence (Guest et al., 2013). On the other hand, allogenic sources can be made readily available but require immune suppression. Clinical trials on the safety of SC transplantation for subacute thoracic SCI showed no adverse effects one year post-transplantation (Anderson et al., 2017).

Olfactory ensheathing cells (OEC) are another glial population studied for transplantation. They reside in a unique environment, the olfactory system, which supports neurogenesis throughout life. Autologous OECs can be easily obtained from olfactory mucosa on the nasal septum of the patients (Féron et al., 2005; Mackay-Sim et al., 2008). This regenerative characteristic of the olfactory system makes OECs particularly appealing for treating both PNI and SCI (Verdu et al., 1999; Watzlawick et al., 2016). In addition, OECs demonstrated good tissue integration and partial functional improvements, providing a possible alternative autologous cell source for transplantation (Kubasak et al., 2008; Moreno-Flores et al., 2006). However, most studies demonstrated the OECs often require adjuvant treatment to increase their efficiency (Cao et al., 2004; Pearse et al., 2007).

Another category of therapeutic cells are stem cells, which can be divided into embryonic stem cells (ESC) and adult stem cells. One of the unique advantages of using ESCs for nerve injury repair is the highly expandable and self-renewal nature of these cells. ESCs are generally differentiated into neuronal or glial cell types for transplantation in the spinal cord (Brown et al., 2014; Keirstead et al., 2005; McCreedy et al., 2014; Mcdonald et al., 1999). For instance, ESC-derived oligodendrocytes demonstrated good host integration as well as remyelination of axons and improved locomotor functions in a rat spinal cord contusion model at the thoracic level with forces from 150 to 250 kilodyne (Keirstead et al., 2005). A clinical trial of phase 1/2a dose escalation study of oligodendrocyte progenitors has recently been conducted with subacute cervical spinal cord injury (Manley et al., 2017; Priest et al., 2015; Wirth III, 2018.). The major challenges of using ESC derived neuronal populations are ethical concerns of cell sources harvested from unused IVF embryos, immunogenicity of allogenic cells, and tumorigenicity due to possible contamination of undifferentiated pluripotent stem cells.

Similar to ESCs, other multipotent stem cells have also attracted a lot of attention for neural tissue engineering. Among them, neural stem cells (NSCs) and induced pluripotent stem cells (iPSCs) have been investigated for treatment options. NSCs naturally reside in the spinal cord and have been shown to integrate well with the host. Studies have shown improvement in behavior outcomes in large animal models of SCI, such as acute primate cervical contusion (Iwanami et al., 2005). These encouraging results make NSCs a potent candidate for cell transplantation therapies. However, similar to ESCs, harvesting NSCs is met with ethical issues of harvesting from human fetal tissue and safety issues of teratoma formation and immunogenicity. iPSCs has the major advantage of patient-specificity if they are derived from autologous sources. They can be derived from adult somatic cells, such as fibroblasts, blood cells, exfoliated renal epithelial cells, and keratinocytes; and can be differentiated into SC-like cells for PNS, neural progenitor cells, neurons, and astrocytes for CNS (Hayashi et al., 2011; Lujan et al., 2012; Maetzel et al., 2014; Sareen et al., 2013; Wang et al., 2011, 2013). Nevertheless, using iPSCs face many challenges including choosing the appropriate reprogramming methods (viral, plasmid, modified RNA, small molecules etc.), low reprogramming and differentiation efficiency (usually $<5\%$), long culture time for human cells ($\sim$8 weeks), and immunogenicity due to genetic and epigenetic abnormalities that can occur during reprogramming and subsequent culture maintenance (Marro et al., 2011; Z P Pang et al., 2011; Pera, 2011). Direct reprogramming of neurons from blood cells, hepatocytes and postnatal fibroblasts can also be achieved without going through a pluripotent state (Marro et al., 2011; Zhiping P. Pang et al., 2011; Tanabe et al., 2018). The advantages of direct reprogramming compared to using iPSCs are the relatively fast conversion and higher potential conversion efficiency. However, transdifferentiated cells usually have limited to no self-renewal capability compared to iPSCs. More details on stem cell therapy for PNI and SCI are reviewed here (Muheremu et al., 2016; Sullivan et al., 2016). In the following sections, we will discuss important bioengineering considerations for designing cell delivery platforms and present the current states of various biomaterials used to fabricate neural scaffolds as cell carriers.

2. Bioengineering considerations

To transplant cells after PNI and SCI, generating a permissible environment for regeneration is critical. This generally entails utilizing biomaterial scaffolds that closely mimic the native environment of the PNS or the spinal cord. The scaffold must satisfy several important design criteria to provide a permissive environment for transplanted cells. For biological applications, it is important to consider the scaffold's biocompatibility, biodegradability, permeability/porosity, biomechanical properties, cell adhesion and migration, and cell encapsulation capabilities (Fig. 1).

2.1. Biocompatibility and biodegradability

Biocompatibility of neural scaffold as cell delivery platform must support cellular functions for both the native cell populations and transplanted cells. This may include promoting the regenerative potential of cells through molecular and mechanical support. Biomaterials must also not elicit undesirable host responses, especially for long-term implantation. When the material comes in contact with host issue, it should not induce hemolysis, destroy blood components, cause coagulation and thrombus formation, have toxic effects on surrounding tissue, or elicit an immune response (Gu et al., 2011).

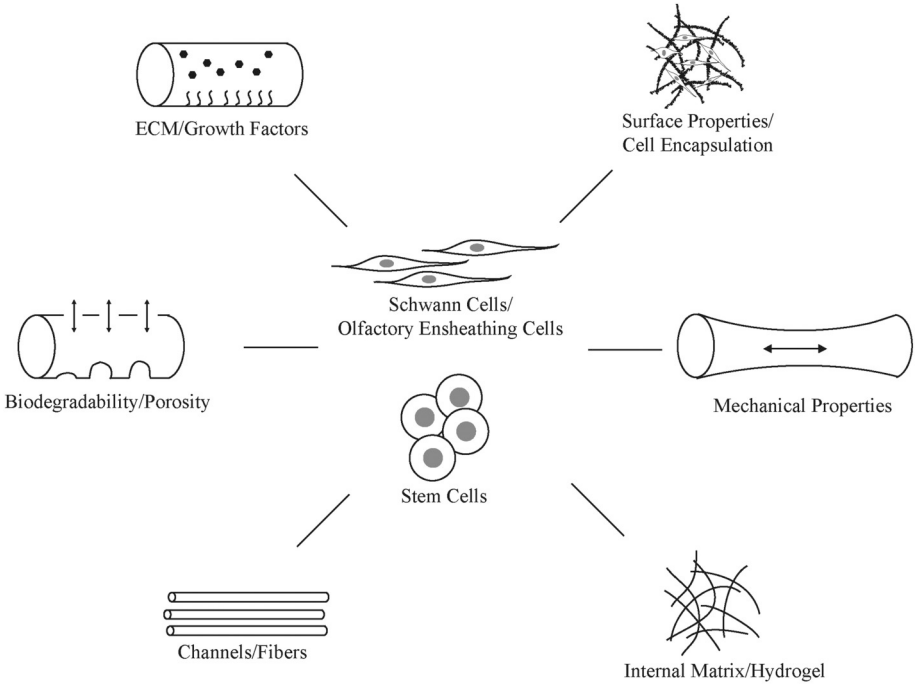

Fig. 1. Schematic diagram showing important bioengineering considerations for neural scaffold as cell delivery platform.

Biodegradability of the biomaterial needs to be considered based on the intended applications. One of the major challenges for cell transplantation-based therapies is the lack of cell sources. For instance, expanding autologous SCs can result in senescence after several passages limiting the number of autologous cells that can be obtained as well as their ability to promote regeneration in the senescent state. Other cell types, such as NSCs are difficult and dangerous to harvest from autologous sources. As a result, allogenic or xenogenic cells are potential alternative cell sources; however, host immune response can limit their use. Non-degradable biomaterials are better suited for situations where immune-isolation of allogenic and xenogenic cells is required (Aebischer et al., 1996; Buchser et al., 1996). Rebuilding neural connections through the biomaterial at the injury site is often desirable to enhance functional recovery. Therefore, non-degradable biomaterials must be biocompatible such that permanent implantation would not cause complications, or require a second surgery to retrieve the scaffold. Long-term implantation of materials can to elicit chronic foreign body response leading to fibrosis and astrocytosis around the scaffold (Chang and Hsu, 2004; Merle et al., 1989; Turner et al., 1999). Biodegradable or bioresorbable materials prevent the need for a second retrieval surgery. This is especially critical if the transplanted cells have established neural connections and integrated with the host tissue. Importantly, both the starting materials and the degradation products must be non-toxic, non-immunogenic and non-carcinogenic (Liu and Cao, 2007; Macaya and Spector, 2012). Controlling the degradation rate is also critical for successful regeneration. Transplanted cells require structural support, because mechanical properties can affect cell survival, differentiation, and hence the regenerative potential (Discher et al., 2005; Saha et al., 2008). Ideally, the degradation rate of the material should closely match that of the regeneration rate, where the scaffold should remain intact for transplanted cells to secrete their own extracellular matrix (ECM) and axons to regenerate across the injury site (Belkas et al., 2005; de Ruiter et al., 2009; Meek et al., 2004).

2.2. Permeability and porosity

Permeability and porosity can significantly affect transplanted cell behavior, both beneficial and harmful host cell infiltrations, and material properties. For PNI, the dominant structure of neural scaffolds is tubular conduits, which usually consist of a semipermeable outer shell that allows for nutrients, wastes, and gas exchange between the regeneration space and host tissue and inner matrices that can support the transplanted cell. The effects of pore sizes on regeneration should be carefully considered to prevent fibrotic tissue infiltration. Early studies of PNI repair with hollow conduits suggest that pore sizes of ~5–10 μm seem to be optimal to facilitate nutrients and waste exchange while minimizing fibrotic tissue infiltration *in vivo* (Chamberlain et al., 1998; Jenq et al., 1987; Vleggeert-Lankamp et al., 2007). It is also important to consider the material properties when considering the effects of pore size. As Meek *et al.* demonstrated, poly(D,L-lactide-*co*-caprolactone) with pore sizes of 10-20 μm showed fractures in the material early and enlarged surface areas for hydrolysis, which made the material swell and block the lumen of the scaffold (Meek and Den Dunnen, 2009). Functional analysis showed there was no improvement in stance for these materials when used as conduits in a 10 mm rat sciatic nerve injury model.

In comparison to PNI, SCI cannot spontaneously regenerate. After initial trauma, secondary injuries can lead to the initiation of central cavitation and eventually forming an inhibitory barrier called the glial scar. Teng *et al.* designed a bi-layer PLGA-based scaffold that simulated the architecture of the spinal cord for studying the repair of thoracic lateral hemisection in rats (Teng et al., 2002). Inner portion of the scaffold aimed to emulate the gray matter, had pore sizes ranging from 250–500 μm and was seeded with NSCs; while the outer portion emulated the white matter with long, axially oriented pores that allow for fluid transport while inhibiting ingrowth of scar tissue. Hindlimb function estimated by Basso, Beattie and Bresnahan (BBB) locomotor score showed significant improvements compared to scaffold alone, cell alone, and lesion control from 2 weeks to 11 weeks post-injury. Importantly, the authors reported that the outer shell of the scaffold inhibited the ingrowth of a variety of cell types, including fibroblasts for at least 2 weeks *in vitro*. *In vivo*, significantly less glial fibrillary acidic protein (GFAP) immunostaining suggested reduced infiltration of reactive astrocytes, which in turn reduced glial scar formation in groups with implanted scaffold. The better functional recovery may be partly attributed to the reduction of scar formation and lesion cavity, which

has been correlated with the degree of functional deficit (Beattie et al., 2000; Noble and Wrathall, 1989).

The porosity of luminal matrix should provide a favorable environment not only for promoting axon regeneration but also for improving viability and function of transplanted cells. In PNI, Oh *et al.* demonstrated that a pore size in the nanometer scale (~100 nm) resulted in significantly better myelination of regeneration axons, larger muscle diameter, as well as lower collagen fiber area than pores with ~200 μm diameter (Oh et al., 2013). Vleggeert-Lankamp *et al.* also showed that implanted scaffolds with pores sizes from 1–10 μm can increase the number of nerve fibers generated and reduce the refractory period of axons compared to macro-porous scaffolds (Vleggeert-Lankamp et al., 2008; Vleggeert-Lankamp et al., 2007). *In vitro* data also suggest that porosity of the inner matrix can affect cell attachment, proliferation, and differentiation. Decreasing pore size and increasing surface area can increase cell adhesion and proliferation, which in turn may improve nerve regeneration (O'Brien et al., 2005; Vleggeert-Lankamp et al., 2004). This may influence the migration and phenotypes of transplanted cells (Dadsetan et al., 2008).

Overall, these data suggest that the permeability/porosity of the outer shell and inner matrix of neural scaffold for cell transplantation might serve different purposes. Whereas the outer shell needs to prevent tissue infiltration that might cause scarring, the inner matrix should promote axon regeneration and maintain the viability and function of transplanted cells. Although many studies have investigated the effects of pore size on transplanted cells *in vitro,* further studies are required to determine the optimal porosity for improving functional outcomes *in vivo*.

2.3. Biomechanical properties

In selecting materials for neural scaffolds, it is also important to consider whether the biomechanical properties, such as stiffness and flexibility, are suitable for both the injury environment and cell transplantation. For PNI, tubular scaffold needs to bear sufficient *in vivo* physiological stress to support regeneration. Movements in patients or animal model can cause failure of a soft conduit. Materials that are too stiff can result in kinking when bent and inhibit axon growth. A balance between stiffness and flexibility is important when designing an ideal scaffold for PNI. The elastic modulus of the biomaterial can significantly influence cellular behavior. *In vitro* data suggest that substrate stiffness and elasticity can have major effects on SC behavior. The elastic modulus of the peripheral nerves varies from development to maturation. In rat, myelination after birth occurs around 6 kPa in the sciatic nerve, while adult rat sciatic nerves have an elastic modulus of ~50 kPa with single teased fiber at 5.3 kPa (Urbanski et al., 2016). Recent studies have shown that mechanotransducing transcriptional activators yes-associated protein (YAP) and tafazzin (TAZ) have been shown to be involved in proliferation, differentiation and myelination during development (Deng et al., 2017; Grove et al., 2017; Lopez-Anido et al., 2016; Poitelon et al., 2016). These findings showed that TAZ level increased after PNI, while YAP may play a role in modulating intermodal length and regulate myelination and myelin elongation (Fernando et al., 2016; Mindos et al., 2017). While many have investigated the impact of chemical composition as well as incorporating biomolecules for cell transplantation, the mechanical properties of the scaffolds are often not optimized. These mechanotransducing pathways may give rise to therapeutic potentials of fine-tuning the elasticity of SC substrates for scaffolds.

2.4. Cell adhesion and migration

2.4.1. Extracellular matrix proteins

To enhance cell-material interactions as well as improving transplantation outcomes, different biochemical molecules, ECM proteins and growth factors, can be incorporated into biomaterial scaffolds. These biomolecules can improve transplanted cell survival, influence differentiation, and ultimately enhance nerve regeneration. Many biomaterials are not inherently cell adhesive, so many studies have evaluated the effect of ECM proteins or functional peptide sequences crosslinked to the scaffold as adhesion substrate to promote cell adhesion. Cell adhesion to the ECM is primarily mediated by interactions of integrins with ECM sequences through intracellular actin cytoskeleton, which can affect intracellular signaling for survival, proliferation, and migration. Integrin interactions with RGD enable actin assembly and influences cell migration (Hocking et al., 1998).ECM proteins from the native neural environment are often used, since they have been shown to improve neural regeneration *in vitro* and *in vivo*. A variety of ECM proteins have been are used to enhance cell adhesion in biomaterial scaffolds, including laminin, fibronectin, fibrin, and collagen (Barros et al., 2011).

Using ECM proteins presents several limitations. Although precoating ECM proteins onto neural scaffolds is relatively simple, the absorption rate and maintaining native protein function after absorption is hard to control. Another limitation of using naturally derived ECM proteins is the lack of sources for clinical grade materials for some proteins, such as laminin. Using short functional peptide sequences derived from these proteins is a viable alternative in many cases. Well studied peptide sequences derived from ECM proteins, including RGD, YIGSR and IKVAV, have shown the abilities to promote neurite outgrowth *in vitro* and *in vivo* (Itoh et al., 1999; Tashiro et al., 1989, 1991). *In vivo* data suggest fibrin matrices modified with laminin-derived motifs significantly increased axon extension compared to an empty tube and un-modified fibrin in a dorsal root nerve transection model (Schense and Hubbell, 2000).

2.4.2. Growth factors

Another category of biochemical cues incorporated into the scaffold is the growth factors. They can be released to improve regeneration or immobilized in the scaffold to improve functions of the embedded cells and promote host cell infiltration. Specifically, growth factors can enhance transplanted cell survival, promote neuronal differentiation of stem cells, and improve the regenerative capacities of SCs. Growth factors commonly incorporated in neural scaffolds include nerve growth factor (NGF), brain-derived neurotrophic factors (BDNF), neurotrophin-3 (NT-3), glial cell line-derived neurotrophic factor (GDNF), ciliary neurotrophic factor (CNTF), and fibroblast growth factors (FGF) (Barras et al., 2002; Bloch et al., 2001; Edelman et al., 1991; Jain et al., 2006; Maysinger et al., 1996; Taylor and Sakiyama-Elbert, 2006). The role of growth factors in neurogenesis is reviewed elsewhere (Huang and Reichardt, 2001; Oliveira et al., 2013). It is important to ensure that the process of immobilizing proteins does not decrease the efficacy of the growth factors through denaturing the protein or disrupting the receptor binding site (Patel et al., 2007; Wang et al., 2015). Another important parameter to consider when incorporating biomolecules into scaffold is the distribution pattern, being either uniformly distributed or directionally oriented. For instance, NGF distributed in a gradient format has been shown to improve axon myelination, axon density, and gastrocnemius muscle weight compared to uniformly distributed pattern in hydrogels implanted in a rat sciatic nerve injury model (Dodla and Bellamkonda, 2008). Some parameters to consider are the length and concentrations of the gradient needed to achieve effective chemotactic response depending on the injury gap. In addition, nerve regenerations have shown positive dosage dependent effects on growth factors, such as GDNF and BDNF (Santos et al., 2016; Schäfer and Mestres, 1999). More importantly, high concentrations of growth factors may also negatively impact axonal growth. As shown by Blits *et al.* and others, overexpression of GDNF can cause axonal entrapment at the sites of overexpression (Blits et al., 2004; Eggers et al., 2013; Moore et al., 2010; Wang et al., 2018; Wu-Fienberg et al., 2014).

Vascular disruption and ischemia can contribute to secondary injury after SCI. Growth factors, such as angiopoietins and vascular

endothelial growth factors (VEGF), are involved in angiogenesis which can be important for full neurological functional recovery. After mouse spinal cord contusion injury at thoracic level (50 kilodyne), angiopoietin-1 was injected in the jugular veins in the ventral neck region 4 hr post-injury (Han et al., 2010). Decreased inflammation was observed within 24hr post-injury. Treatment also showed improved vascularity at the injury site and reduction in lesion volume as early as day 7. Locomotor deficit estimated by Basso mouse scale (BMS) showed significant improvement starting from day 7 to day 42 compared to vehicle control. These results suggest targeting vascular dysfunction after SCI can improve long-term functional improvement by rescuing vasculature, reducing acute inflammation, and decreasing lesion volumes. Another study combined angiopoietin-1 and VEGF treatment through adeno-associated viral transduction and showed decreased lesion volume and improvement in vascular stability in a rat spinal cord thoracic contusion injury model (Herrera et al., 2010). The combined therapy also improved locomotor function measured by BBB score on day 56 post-injury, although the effects was not dramatically pronounced.

2.4.3. Surface topography

Surface topographic guidance feature is another important parameter to consider. Many *in vitro* studies have shown that longitudinally orientated micro-patterned surface is better for cell alignment and axon directionality (Ahmed et al., 2003; Chew et al., 2008). In addition, topographical features can affect cell differentiation. The major topographic guidance feature types are alternating microgrooves and parallel oriented fibers. They have been shown to affect neurite outgrowth, neural cell morphology, and differentiation (Simitzi et al., 2017).

Alternating microgrooves can affect cell and axon alignments in the scaffolds. Lietz tested microgrooves with width ranging from 2–20 μm (Lietz et al., 2006). Using DRG explant and SCs pre-seeded on the microgroove surface, both neurite and SC aligned longitudinally along the microgroove. Microgrooves can also influence differentiation towards neural lineages. NSCs on micro-grooves have shown an increase in β-tubulin III expression after co-culturing with astrocyte compared to flat substrate controls (Recknor et al., 2006). This may contribute the improving functional recovery. In a 10 mm rat sciatic nerve injury model, Hsu *et al.* showed that microgrooved PLA conduits seeded with NSCs improved functional recovery as assessed by sciatic function index (SFI) compared to silicone conduits as well as autografts 6 weeks after implantation (Hsu et al., 2009). The number of myelinated axons and mean area of axons were also similar to autograft. *In vitro* analysis showed that NSCs were highly aligned along longitudinal features of the conduit. In addition, an increase in NGF and BDNF expression was observed over 72 hrs.

Another topographic guidance feature type is parallel oriented fibers. Electrospinning fibrous material has attracted more attention because the micro and nano features closely mimic the scales of the ECM environment in the nervous system. The high surface area-to-volume ratio makes nanofibers particularly favorable for cell survival and proliferation. Similar to microgrooves, electrospun polymer fibers improve neurite alignment *in vitro* (Leach et al., 2011; Schnell et al., 2007). Fiber diameters also seem to dictate differentiation of NSCs into either neuronal or CNS glial cell types *in vitro* (Christopherson et al., 2009). Rat NSCs demonstrated a 20% increase in neuron-specific marker β-tubulin III expression on larger polyethersulfone nanofibers (~800 nm), compared to polystyrene control. In contrast, oligodendrocyte marker RIP was highest on fibers with diameter of ~300 nm. In addition, as fiber diameter decreased, proliferation and cell migration increased while cell aggregation decreased. In a similar study, Yang *et al.* showed that fiber diameter but not fiber alignment affects NSC differentiation, whereas fiber alignment is critical for cell orientation and neurite alignment (Yang et al., 2005). While strong *in vitro* evidence suggests that alignment of electrospun nanofibers can improve axonal guidance as well as direct cell differentiation and alignment of transplanted cell, very few *in vivo* studies investigated how the alignment of electrospun nanofibers can affect the ability of transplanted cell to promote nerve regeneration to date (Hu et al., 2017).

2.5. Cell encapsulation

Cell encapsulation or the ability of biomaterials to retain cells for transplantation is critical for transplanted cell survival and their therapeutic effects to take place. In addition to cell attachment to the biomaterial surface, cell suspension in 3D hydrogels is also a viable strategy. Biomaterials that are commonly made into hydrogels include collagen, fibrin, hyaluronic acid (HA), chitosan, alginate, and poly (ethylene glycol) (PEG) (Ford et al., 2006; Hatami et al., 2009; McCreedy et al., 2014; Mosahebi et al., 2003; Thompson et al., 2018; Zahir et al., 2008). In recent years, hydrogels have attracted a lot of attention as the internal matrix for nerve guidance conduit. Hydrogels can also be used as stand-alone scaffolds, particularly for SCI as their mechanical properties closely match the native spinal cord ECM (Macaya and Spector, 2012; Madigan et al., 2009). By comparing different macro-architectures used for SCI, it was shown that open path designs performed better than closed designs, such as cylinder, tube, and multichannel, which adversely affected the surrounding tissue, doubling the defect length (Wong et al., 2008). Considering that the spinal cord has both longitudinal connections (i.e. spinocerebellar tract, corticospinal tract etc.), as well as lateral connections among different types of interneurons and motor neurons, neurite extension towards all directions is preferable (Friedman et al., 2002; Kiehn and Butt, 2003). The inherent properties of hydrogels, such as being macroporous and soft, allow molecule exchanges, cell adhesion and migration that could potentially be beneficial to neuronal regeneration (Macaya and Spector, 2012; Madigan et al., 2009; Novikova et al., 2006; Xie et al., 2009; Yuan et al., 2004). Another major advantage of hydrogels is their injectability. Injectable materials can easily conform to the shape of lesion cavity in SCI. This obviates the need to accommodate scaffolds with defined geometry, which may involve removing healthy tissue around the lesion site. Injectable material should solidify under physiological conditions, usually within minutes, to maintain encapsulation of transplanted cells.

Several design parameters need to be considered for hydrogels that are used as cell delivery platforms (Macaya and Spector, 2012; Shoichet et al., 2007). As discussed previously, porosity, mechanical strength, and the rate of degradation are important design parameters for biomaterials. The time for gelation is also critical for cell transplantation. Generally, a relatively rapid gelation or crosslinking process under mild condition is preferred to maintain localization of encapsulated cells and/or therapeutic agents and to avoid additional damage at the lesion site. Since the majority of hydrogels crosslink through either chemical or physical triggers, transplanted cells must be able to survive under these conditions. Chemical crosslinker can be cytotoxic, while physical triggers may involve shifting cells to non-physiological conditions (temperature, pH) that are not favorable to their survival. Chemical initiators and crosslinkers required for the formation of hydrogels should not adversely impact transplanted cell populations. Especially for injectable hydrogels, the chemical crosslinkers usually cannot be washed away *in vivo* or quenched prior to implantation. Common chemical crosslinking methods include photo-initiated polymerization, enzymatic, and molecular crosslinking. Photo-initiated polymerizations often involve using ultraviolet (UV) light with a photo-initiator molecule. While this method allows rapid gelation, UV light and photo-initiator can induce apoptosis (Hynes et al., 2007). For enzymatic crosslinked hydrogels, the effects of enzymes on transplanted cell types need to be considered and investigated (Yang et al., 2016). Molecular crosslinkers presents the advantage fine-tuning shear modulus and degradation rate (Sundararaghavan et al., 2008); however, they also can be cytotoxic depending on the concentration and encapsulated cell types (Barker et al., 1980; Liang et al., 2003). Common physical crosslinking strategies include temperature, ionic crosslinking, and self-

assembling systems. The advantage of physical triggers is that they often can occur in aqueous solutions. Important parameters to consider are drastic temperature and pH changes that can induce cell death (Gillette et al., 2008; Wang et al., 2008). An important class of self-assembly hydrogels is shear-thinning hydrogel. The key requirements for shear thinning hydrogels are the ability to flow under modest pressure, rapidly gel after injection, and maintain sufficient mechanical strength during the implantation process. Slow gelation may result in sedimentation of transplanted cells and drugs. Importantly, physical crosslinking methods often result in weak hydrogels with moduli ranging in tens to hundreds of Pa. This range corresponds to the mechanical strength of the spinal cord, making them suitable for SCI repair. However, such mechanical strength might not be sufficient for PNI repair.

Another potential issue with using hydrogels is whether regenerating axons and supporting cells can efficiently remodel the hydrogels to be a growth permissive environment. Earlier studies using hydrogels showed that long-term peripheral nerve regeneration for sub-critical defect in mice (5 mm) was compromised because of physical impediment posed by the solid hydrogels (Madison et al., 1987; Valentini et al., 1987). This may highlight the importance of matrix remodeling using proteases, such as matrix metalloproteinase (MMP) 9, for efficient regeneration (Nordstrom et al., 1995; Shubayev and Myers, 2004). Additional studies explored the effects of collagen matrix composition on murine ESC differentiation. Specifically, collagen concentration affects the ability of embryoid bodies from ESCs, to differentiate inside of the scaffold (Battista et al., 2005). At high concentrations of collagen, the cells could not migrate and became apoptotic, indicating an optimal concentration of matrix for cell migration and cell–cell contact is required for stem cell survival and differentiation.

3. Biomaterials:

3.1. Natural biomaterials

Commonly used natural polymers include collagen, laminin, fibronectin, fibrin, HA, chitosan, and alginate (Hatami et al., 2009; McCreedy et al., 2014; Mosahebi et al., 2003; Thompson et al., 2018; Zahir et al., 2008). Natural macromolecules may provide beneficial cellular interactions, especially for cell transplantation. The major disadvantages of naturally derived hydrogels are batch variants and limited mechanical strength.

3.1.1. ECM and their derivatives

3.1.1.1. Decellularized ECM. Decellularized ECM have been extensively used as grafting materials to nerve repair. By removing antigenic cellular components, decellularized ECM materials reduce the risk of host immune response (Gulati and Cole, 1994; Hudson et al., 2004a, 2004b). At the same time, intact microstructures of the decellularized ECM along with ECM proteins' growth promoting signaling can significantly improve nerve regeneration. Especially for PNI, acellular nerve allografts (ANAs) have shown superior nerve regeneration in animal models and clinical settings compared with synthetic nerve conduits. The primary drawback of ANAs is the limited migration of endogenous SCs into the scaffold for scaffolds greater than 30 mm in length (Moore et al., 2011; Sun et al., 2009). Saheb-Al-Zamani *et al.* showed that cellular senescence makers were upregulated where axon regeneration ended, suggesting SCs gradually became quiescent during the migration process (Saheb-Al-Zamani et al., 2013). To improve upon ANA's regenerating potential, SCs have been transplanted with ANAs in 14 mm sciatic nerve injury model in rats (Jesuraj et al., 2014). The number of nerve fiber distal to the graft was comparable to isograft and superior to ANA alone. Functional recovery measured by muscle force was also similar to isograft. Decellularized ECM for SCI repair have also been investigated (Crapo et al., 2012; Tukmachev et al., 2016). Tukmachev *et al.* showed decellularized ECM hydrogels can promote neovascularization and axonal ingrowth into the lesion in a rat spinal cord dorsal hemisection injury model at the thoracic level; however, fast degradation of the graft did not prevent scar tissue formation. Only a few preliminary studies have investigated combining cell transplantations with decellularized ECM for SCI repair (Heng et al., 2017; Thompson et al., 2018; Zhu et al., 2015).

3.1.1.2. Collagen. Collagen is one of the most extensively used ECM proteins for fabricating neural scaffolds. As a major structural component of connective tissues in mammals, collagen can be used to construct growth permissive environment for transplanted cells with excellent cell adhesion. It can be used as both conduit material as well as luminal filler. One of the earlier successful studies using collagen-based nerve guide conduits showed that it was as effective as nerve autograft for repairing short sub-critical nerve gap (4 mm) in rat (Archibald et al., 1991; Li et al., 1992). More recent endeavors have been focused on treating critical nerve defect by using collagen-based scaffold as cell delivery platform to improve nerve regeneration.

Most studies showed improved regeneration using cell-seeded scaffolds compared to acellular groups. Earlier studies used SCs in collagen nerve guides to repair an 18 mm gap in the rat sciatic nerve (Ansselin et al., 1997). SC populated-graft showed improved myelination as well as nerve conduction velocity approaching un-operated control values 6 months post-injury. Since autologous SCs are difficult to obtain without causing donor site morbidity, the idea of using allogenic SCs was also explored. Udina *et al.* studied the effects of FK506 on allogenic SCs transplanted in a 6 mm mouse sciatic nerve injury model (Udina et al., 2004). SC-seeded collagen conduits with FK506 treatment showed the greatest nerve area and number of myelinated axons in the middle of the conduit and distal of the conduit compared to collagen guide filled with Matrigel with or without SCs. FK506 treated SC scaffold retained ~70% of pain sensitivity of un-operated animal and 50% of sympathetic sudomotor function estimated by sweating. Collagen-based scaffolds have also been used for studying SCI repair. Human ESC-derived neural progenitor cells were seeded in collagen scaffold with intraluminal tubes and transplanted in a rat lateral hemisection injury model (Hatami et al., 2009). Groups with cell-seeded scaffold showed improved hindlimb locomotor function compared to sham (scaffold-only) and lesion control. Sensory function was also significantly better than other groups. These studies show promising uses of cell-seeded collagen scaffold to improve nerve regeneration. Selected examples of neural scaffolds using collagen for cell delivery are listed in Table 1.

It is important to recognize the effects of collagen on different cell types to better design neural scaffolds. In the PNS, collagen trimers are essential for basal lamina ECM assembly, which is critical for SCs maturation and myelination (Carey et al., 1987; Chernousov et al., 1998; Eldridge et al., 1987). *In vitro* studies showed that various types of collagen seem to have different effects on cells. Cook *et al.* studied the effects of different ECM peptides on the differentiation of neural stem cells (Cooke et al., 2010). In particular, NSCs showed significantly higher β-tubulin III expression on a Type I collagen-derived motif (GTPGPQGIAGQRGVV) and fibronectin-derived motif (PHSRN) compared to outer membrane protein A-only control. In contrast, a Type IV collagen motif (MNYYSNS) decreased the expression of β-tubulin III compared to the control. Interestingly, the mixture of Type I and IV collagen-derived peptides negated the positive effects seen with Type I derivative alone and approached control group β-tubulin III expression level. Type IV collagen, however, has also been shown to increase the number and length of neurites from embryonic sympathetic neurons *in vitro* (Lein et al., 1991). In comparison, α4 Type V collagen promoted SC adhesion and migration but inhibited neurite outgrowth (Chernousov et al., 2001; Erdman et al., 2002). Upon further examination, it was shown that the collagen domain of Type V blocked neurite outgrowth, while the non-collagen N-terminal domain

Table 1
Selected examples of neural scaffolds with natural biomaterials for cell delivery

Natural Polymers	Structure	Cell type	Injury model	Outcomes	Pros/Cons
Acellular Nerve Graft (Jesuraj et al., 2014)	Nerve Graft	SC	Rat 14mm sciatic nerve gap	Histology: SC seeded acellular nerve graft (ANGs) showed comparable fiber numbers to isograft and superior to ANGs alone middle and distal to the graft. Behavior: Muscle force evoked in extensor digitorum longus reveal similarly functional recovery between SC seeded ANGs and isograft and superior to ANGs alone.	Pros: Intact endoneurial microstructures can guide regenerating axons. Support equal axonal growth regardless of whether SC source match ANG source. Cons: Nerve fiber width was smaller than isograft, indicating immaturity. May be correlated with the removal of other cues during ANG processing.
Collagen (Ansselin et al., 1997)	Conduit with Kevlar mesh	SC	Rat 18mm sciatic nerve gap	Histology: Number of myelinated fibers was higher in SC seeded collagen guide than un-operated control. Behavior: Nerve conduction velocity in SC seeded collagen guide was approaching un-operated level. SFI showed ~ -70 with cell-seeded guide but compare with autograft or un-operated control. Nerve conduction velocity was 60% of un-operated controls.	Pros: Repaired large injury gaps with myelinated axons in the distal stump Cons: Survival of transplanted SCs at $<5x10^5$ seem to be poor. May be indication of insufficient growth support of collagen and Kevlar fiber mesh. No significant functional recovery was reported.
Collagen (Udina et al., 2004)	Conduit with Matrigel	SC	Mouse 6mm sciatic nerve gap	Histology: SC-seeded collagen conduits with FK506 treatment showed the highest nerve diameter and number of myelinated axons in the middle and distal of the guide. Behavior: FK506 treated SC scaffold retained ~70% of pain sensitivity of un-operated animal and 50% of sympathetic sudomotor function estimated by sweating.	Pros: Effective regeneration with allogenic SCs supplemented with immunosuppressant. Cons: Required immunosuppression throughout study. Matrigel filler is not suitable for clinical use.
Collagen (Hatami et al., 2009)	Gel with 25-30 neural-like tubes	hESC-derived neural progenitor cells (NPCs)	Rat thoracic lateral hemisection SCI	Histology: Transplanted NPCs showed positive stain for nestin, MAP2, and GFAP 5 weeks post-transplantation. Only about 5% of cells were positive for Ki67. No sign of tumor was observed after 1 year. Behavior: Groups with cell-seeded scaffold showed improved hindlimb locomotor function compared to sham and lesion control, though not very pronounced. Sensory function was also significantly better than other groups.	Pros: Maintained survival and differentiation state of NPCs. Migrations of NPCs out of graft area were observed. No tumor indication after 1 year. Cons: No data were reported on glial scar reduction. Scaffold was not present 5 weeks after implantation, which may be insufficient time for nerve regeneration.
Laminin & Fibronectin (Gonzalez-Perez et al., 2017)	Tethered to collagen gel in chitosan conduit	SC	Rat 15mm sciatic nerve gap	Histology: Number of myelinated fibers increased in SC seeded laminin- and fibronectin-tethered scaffolds compared to acellular scaffold at midlevel and distal level. Behavior: Muscle action potentials with laminin- and fibronectin-tethered scaffolds were comparable to autograft. Sensitivity recovery was not obvious. Fibronectin modified scaffold seemed to result in better muscle action potential and higher number of myelinated axons than that of laminin.	Pros: Alignment of ECM directed transplanted cell alignment. Cons: Limited sensory improvement. Locomotor function evaluation was not reported.
Fibrin (Johnson et al., 2010a)	Cell embryoid body (EB) encapsulated in spherical gel	mESC-derived NPCs	Rat thoracic dorsal hemisection SCI	Histology: Neuron maturation marker NeuN was significantly higher in cellular-graft with growth factors and no heparin binding system. This group also showed the highest survival and proliferation 8 weeks post transplantation. Over-proliferations of transplanted cells were observed. Behavior: Grid walk analysis showed graft with cellular-graft with growth factors and no heparin binding system had significantly less missed steps compared to other groups.	Pros: Demonstrated survival and differentiation of NPCs after transplantation. Easily conformed to the lesion shape. Cons: NPCs over-proliferated and formed tumors.

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Table 1 (*continued*)

Natural Polymers	Structure	Cell type	Injury model	Outcomes	Pros/Cons
Fibrin (McCreedy et al., 2014)	EBs suspended in gel	mESC-derived progenitor Motor neurons (pMN)	Rat thoracic dorsal hemisection SCI	Histology: Fibrin-based scaffold showed good host-tissue integration with minimal scarring, and migration of transplanted cells into host tissue was frequently observed. Behavior: Not reported.	Pros: Minimal scarring tissue was observed. Highly purified pMN population did not show tumor formation. Cons: pMN might be better suited for ventral injury model. No functional testing was reported.
Fibrin (Kalbermatten et al., 2008)	Gel in polyhydroxybutyrate(PHB) conduit	SC	Rat 10mm sciatic nerve gap	Histology: Fibrin-based scaffold showed highest axonal outgrowth and SC penetration compared to acellular group and empty conduit. Highest regeneration distance was ~3.5 mm. Behavior: Not reported.	Pros: Fibrin improved cell adhesion to PHB conduit. Cons: Short regeneration distance even with transplanted SCs. This suggests other growth-promoting cues may be needed.
HA (Zhang et al., 2008)	HA-collagen composite in collagen conduit	NSC	Rabbit facial 5mm nerve gap	Histology: Number and area of myelinated fibers in NSC seeded scaffold was comparable to un-operated control. Myelin sheath thickness was also comparable. Behavior: Progressive decrease in current threshold and increase in voltage amplitude of lip muscles in response to a stimulus in treated groups.	Pros: HA provide high surface area and porosity for cell adhesion. Collagen provide mechanical strength needed for PNI regeneration. The clearance rate of the scaffold was primarily in phase with that of regeneration. Cons: Degeneration and swelling of myelin lamellae was evident and is not desirable for recovery
HA (Mothe et al., 2013)	Hydrogels (HAMC)	NSC with rPDGF	Rat compression SCI at level T2 with a 26 g force for 1 min	Histology: NSC transplanted in HAMC-rPDGF showed significantly reduced lesion cavity and increased neuron sparing. NSCs survival was also increased in HAMC-PDGF scaffold. Behavior: BBB locomotor score was not improved compared to cell only control. Number of footfalls decreased in ladder-walk test 7 weeks post-transplant.	Pros: Easy manipulation as HAMC is injectable. Have antioxidant properties that may reduce the flux of free radicals; hence, reduced lesion cavity and increased host cell sparring. Cons: Incorporation of rPDGF did not maintain differentiation profiles of NSC in vivo compared to in vitro.
HA (Thompson et al., 2018)	Hydrogels incorporated with astrocyte ECM	ESC-derived V2a interneuron	Rat thoracic dorsal hemisection SCI	Histology: Incorporation of protoplasmic astrocyte-derived ECM increased V2a axon extension within lesion, decreased GFAP+, and ED1+ areas of the surrounding lesion. Behavior: Not reported.	Pros: Decrease in CSPG may be related to HA. Incorporated cell derived ECM and showed improved axon outgrowth and reduced lesion reactivity. Cons: Did not seem to reduced GFAP levels within lesion.
Alginate (Mosahebi et al., 2003)	Matrix in poly-3-hydroxybutyrate (PHB) conduit with fibronectin	SC	Rat 10mm sciatic nerve gap	Histology: Alginate conduit with SC and fibronectin increased axon regeneration distance compared to other groups 3 weeks post-transplantation. By 6 weeks, axons were able to cross the entire conduit and reach the distal nerve stump. Behavior: Not reported.	Pros: Fibronectin improved SC survival. Cons: Although axons showed good regeneration and reached distal stump, no functional results were reported. Degradation of the scaffold was also not mentioned.
Silk-fibroin (Tang et al., 2014)	Coating PCLA conduit with Immobilized NT-3	NSC	Rat thoracic complete transection SCI	Histology: Addition of NT-3 increased NSC survival to ~75% compared with no-factor control (~27%). An increase in MAP2 and a decrease in GFAP positive cells were observed. Neurofilament positive axons also increased in Conduit+NT-3+NSCs group. Behavior: BBB locomotor score of Conduit+NT-3+NSCs group was significantly improved compared to cell alone or NT-3 alone conduit group	Pros: Immobilized NT-3 on silk-fibroin had a slow releasing profile. Cons: Implanting PLGA conduit required the complete transection of the spinal cord, which was undesirable as more damage was introduced

improved neurite outgrowth as well as promoting SC migration. These findings highlight the importance of using different collagen types and derivatives for different purposes and cell types. Using a combination of the right collagen and matching cells might significantly impact the regenerative potential of the collagen scaffold. Currently, bovine collagen Type I, is the primary collagen type used in FDA-approved nerve conduits, such as NeuraGen®, NeuroFlex™, and NeuraWrap™.

3.1.1.3. Laminin and fibronectin. Laminin and fibronectin both play important roles in promoting neurite outgrowth and providing guidance cues (Baron-Van Evercooren et al., 1982). Laminin have been shown to support SC proliferation and functionality. Mutation in laminin γ1 caused failure of process extension required for axonal sorting and axon-SC interaction (Yu, 2005). In addition, the mutation led to the activation of the caspase cascade and apoptosis. Similar functional disruption was also observed for mutation of the laminin receptor, β1 integrin in SCs (Feltri et al., 2002). Fibronectin is dispersed in interstitial matrices, and can affect axonal growth and cell migration (Whitworth et al., 1995). Fibronectin mats rolled into nerve conduits showed comparable axon penetration into the graft as autograft and significantly faster rate of regeneration than freeze-thawed muscle graft control (Whitworth et al., 1995). In addition, SC migration into the fibronectin graft was significantly increased. A more recent study combined chitosan tubes with laminin- or fibronectin-tethered collagen gel seeded with SCs transplanted in a rat 15mm sciatic nerve injury model. Incorporation of SCs significantly improved recovery by increasing muscle action potentials compared to acellular scaffold 4 months post-injury, although sensitivity recovery was not observed (Gonzalez-Perez et al., 2017). Comparing to laminin-modified scaffolds, fibronectin-modified scaffolds resulted in a higher number of myelinated axons and higher compound muscle action potentials of the plantar muscle after stimulation.

Besides their effects on SCs, laminin and fibronectin can also influence stem cell differentiation. *In vitro* study showed laminin and fibronectin derived motifs used individually did not show higher β-tubulin III expression in NSCs than Type I collagen (Cooke et al., 2010). However, the combination of laminin and fibronectin derived motifs significantly increased β-tubulin III expression compared to all other combinations with laminin, fibronectin and collagen. Human ESC-derived neural progenitor cells on laminin increased expression of nestin and β-tubulin III compared to fibronectin and collagen, indicating improved differentiation towards neural progenitors and mature neurons (Ma et al., 2008). In addition, neurite outgrowth on human ESCs-derived neurons increased in a dose-dependent manner as laminin coating concentration increased.

3.1.1.4. Fibrin. Fibrin is natural wound healing ECM protein that has inherent cell-binding sites. Longitudinal fibrin cables form spontaneously during peripheral nerve regeneration for short gap injuries (Williams et al., 1987; Williams and Varon, 1985). In addition, these cables also form in empty nerve conduit, which can direct the migration of SCs and promote axonal growth. Using this characteristic, fibrin matrix has been shown to provide growth permissive environment for neurons and promote neurite extensions *in vitro* after being covalently modified to incorporate growth factors (Sakiyama-Elbert et al., 2001). Micromorphology of the fibrin can affect cellular behavior. In particular, an increase in fibrinogen concentration caused a decrease in neurite length but an increase in the number of fiber bundle (Herbert et al., 1998). Others have also investigated the optimal fibrin scaffold condition for the proliferation and differentiation of ESC-derived neural progenitor cells (Willerth et al., 2006). These findings indicate that fibrin scaffold must be adjusted to accommodate different cell types for optimal cell adhesion and functions.

Fibrin-based scaffolds as a cell delivery platform have been investigated to treat both peripheral and central nerve injuries. For SCI repair, our group have demonstrated the survival and differentiation of ESC-derived neural progenitor cells and progenitor motor neurons embedded in 3D fibrin scaffold (Johnson et al., 2010b; Johnson et al., 2010a; McCreedy et al., 2014). The fibrin-based scaffold showed good host-tissue integration with significantly lower glial scarring marked by GFAP positive cells, and migration of transplanted cells into host tissue was frequently observed (McCreedy et al., 2014). Functional recovery estimated by the fraction of missed steps was significantly improved with cells in fibrin and growth factors without heparin-binding system 8 weeks post-implantation (Johnson et al., 2010a). For PNI repair, Kalbermatte *et al.* implanted SC-seeded fibrin gel in poly-3-hydroxybutyrate conduit in a 10mm rat sciatic nerve injury gap (Kalbermatten et al., 2008). Fibrin-based scaffold showed the highest axonal outgrowth and SC penetration compared to acellular group and empty conduit, though functional result was not reported.

3.1.1.5. Hyaluronic acid. Hyaluronic acid (HA) is part of the native ECM in the central nervous system. With the development of acetate-modified HA into co-polymer gel with methylcellulose (HAMC), the scaffold gels at room temperature but becomes liquid under sheer forces when injected through a syringe into lesion area (Gupta et al., 2006). After spinal cord compression injuries at the thoracic level for 1 min with a 35 g clip, rats that received HAMC have significantly smaller lesion cavity and less inflammatory cells compared to cerebrospinal fluid control 1 month post-injury, though functional recovery was only slightly better. The major advantage of injectable scaffold is that it can fill the complex lesion cavity that forms after SCI and deliver embedded cells. These characteristics of HA hydrogels are particularly useful for SCI repair, where the injury lesion can often assume complex shapes. In SCI, the glial scar presents major inhibitory environment that hinders axonal regeneration. High molecular weight HA has been shown to limit chondroitin sulfate proteoglycan deposition, astrocyte reactivity, and reduce scar tissue formation (Estes et al., 1993; Khaing et al., 2011). Together, these findings make HA hydrogels particularly promising for treating SCI.

As a cell delivery scaffold, HA-based hydrogels have demonstrated improved nerve regeneration in both peripheral and central nervous system. Zhang *et al.* embedded NSCs in HA-collagen conduits in a rabbit facial nerve injury model with a 5 mm gap (Zhang et al., 2008). 12 weeks after surgery, NSC embedded in scaffolds supplemented with NT-3 showed similar number of nerve fibers, myelin thickness, axon area, and nerve fiber circumference as un-operated control. Progressive decrease in current threshold and increase in voltage amplitude in treated groups indicate recovery of neuromuscular function. Another study using NSCs in HAMC hydrogels demonstrated improved regeneration in rats with clip compression injury at spinal cord level T2 with a 26 g force for 1 min (Mothe et al., 2013). By incorporating platelet-derived growth factor (PDGF), NSCs in the hydrogels showed increased cell viability and decreased lesion cavity at 9 weeks post-injury. Functional improvement was observed with higher ladder-walk score 7 weeks post-implantation. Immunohistochemistry revealed higher percentage of CC-1 positive oligodendrocytes, as well as host neuronal sparing marked by increased NeuN staining. Our group has recently incorporated ECM harvested from ESC-derived astrocytes into HA hydrogels as a novel scaffold for cell transplantation in the rat spinal cord with thoracic dorsal hemisections (Thompson et al., 2018). The scaffold showed support for ESC-derived V2a interneurons compared to HA alone, reduced size of lesion cavity, and demonstrated an increase in neuronal processes both within the lesion cavity and in the surrounding tissue.

3.1.1.6. Chitosan. Chitosan is obtained from N-deacetylation of chitin, which is the second most abundant polysaccharide found in nature next to cellulose. Pure chitosan showed poor support for neuronal cell types; however, chitosan-based scaffold functionalized with other materials have been used to study different cell types, including SCs and NSCs. Some studies also studied the use of chitosan conduits transplanted with

NSCs in spinal cord injury (Bozkurt et al., 2010; Zahir et al., 2008). Although functional recovery was not improved compared to controls, chitosan-based scaffolds significantly enhanced NSC survival and differentiation markers for oligodendrocytes (RIP), astrocytes (GFAP) and neural progenitors cells (nestin) in the rat spinal cord with clip compression injury at thoracic level (1 min at 35 g force) 9 weeks after injury (Bozkurt et al., 2010).

3.1.1.7. Alginate. Alginate is another biomaterial that can be used for cell delivery for nerve injury repair. In a completely transected rat spinal cord injury model at the thoracic level, Kataoka *et al.* showed alginate allowed axonal growth into the scaffold with smaller lesion cavity size, compared to no implant and collagen controls (Kataoka et al., 2004). In addition, the porous nature of alginate allows the exchange of therapeutic agents, nutrients, waste between encapsulated cells and the host environment (Wong et al., 2014). Note that the composition of alginate need to be considered. High D-mannuronic acid content makes the scaffold mechanically unstable, while high L-guluronic acid can inhibit cell metabolic activity without coating (Novikova et al., 2006; Strand et al., 2000). The addition of fibronectin to alginate, however, increased neurite outgrowth. OECs also showed increased metabolic activity in alginate with the addition of fibronectin (Novikova et al., 2006). Fibronectin in alginate matrices improved cell survival of the transplanted SCs in a 10 mm rat sciatic nerve injury model (Mosahebi et al., 2003). Compared to an empty conduit, conduits with alginate alone, alginate with SCs, and alginate with fibronectin did not improve axonal regeneration at 3 weeks. In contrast, alginate with fibronectin and SCs significantly improved axonal regeneration at 3 weeks. By 6 weeks, axons were able to cross the entire conduit and reach the distal nerve stump. Important to note is that the injury gap is right at the critical defect size which might be less challenging to overcome.

3.1.2. Other naturally-derived polymer

Other commonly used natural polymers are silk-fibroin and Matrigel®. Many of these biomaterials are usually combined with other polymers to form neural scaffold. A particular trait of silk fibroin is that it can spontaneously absorb onto various substrate while forming in aqueous solution (Uebersax et al., 2007). This makes silk fibroin an attractive scaffold material for incorporating growth factors, which are released as silk fibroin degrades. Tang *et al.* showed that silk fibroin matrix containing NT-3 in poly(ε-caprolactone) conduit improved NSCs survival when transplanted in rats with thoracic spinal cord transection (Tang et al., 2014). Locomotor recovery for hindlimb was also improved compared to conduit with NT-3 or NSC alone from week 4 to week 8 post-injury. Currently, Matrigel® is usually used as a comparison group to other materials. Although it offers great potential to enhance cell survival and regenerative capacity of transplanted cells, the sarcoma origin of Matrigel® limits its use in a clinically relevant setting (Haastert et al., 2006; Shoffstall et al., 2012).

3.2. Synthetic biomaterials

Synthetic polymers, such as poly(glycolic acid) (PGA), poly(lactic acid) (PLA), and poly(lactic-*co*-glycolic acid) (PLGA), are usually used for porous scaffold fabrication due to the superior control over porosity and pore diameters (Bryan et al., 2000; Evans et al., 2002; Komiyama et al., 2004). Synthetic polymers are also tunable and offer a great range of mechanical and physical properties, such as tensile strength, elastic modulus, and degradation rate. With defined purity and properties, these characteristics are highly reproducible. The major disadvantages of synthetic polymers, however, might be limited biocompatibility, lack of natural cell adhesion sites, cytotoxicity of solvents for fabrication, and release of toxic degradation products.

3.2.1. Non-degradable materials

Early studies on neural scaffold fabrication used non-degradable materials. Silicone was one of the most prevalent materials used. However, silicone is known to elicit immune response in the host tissue. Currently, silicone is primarily used as an experimental model for studying PNI. Some other non-degradable materials include polyvinyl alcohol, poly(acrylonitrile-*co*-vinyl chloride) (P(AN/VC)), polysulphone, and polypropylene. These polymers all showed the ability to sustain cell transplantation (Hoffman et al., 1993; Kuramoto et al., 2011; Murakami et al., 2003; Sajadi et al., 2006). Even though many positive results have been reported using non-degradable neural scaffolds, the challenges remain as non-degradable scaffold require a second surgery to remove or must be planned for permanent implantation. For PNI, non-degradable material can cause swelling and nerve compression in long-term implantation. As for SCI, non-degradable scaffolds are considered less suitable for the complex regeneration environment of the spinal cord, especially when the goal is to rebuild or replace damage tissue in the cystic cavity. Therefore, non-degradable neural scaffolds are not the focus of current research endeavors.

3.2.2. Biodegradable

3.2.2.1. Poly(glycolic acid) (PGA) and Poly(lactic acid) (PLA). PLA and PGA are two of the most extensively studied polyester links of lactic and glycolic acid. It has been shown SCs embedded in PGA-based tissue-engineered nerve combined with pluronic F127 gel resulted in comparable numbers of regenerated axons to autograft control in 10mm gap sciatic nerve injury in rat (Komiyama et al., 2004). SFI of PGA with SCs was not significantly different from autograft, while silicone conduit showed a much lower score. It is important to note that the degradation products of PLA and PGA usually result in lower pH of the surrounding environment. Common variants of PLA are poly(L-lactic acid) (PLLA) and poly(D,L-lactic acid) (PDLLA). Evans *et al.* explored the potential of using PLLA conduits seeded with SCs for repairing 10mm sciatic nerve gap (Evans et al., 2002). Although SC-seeded PLLA showed fewer axons, the gastrocnemius muscle weight was not significantly different from that of autograft 4 month after implantation. However, the slow degradation rate of PLLA makes it an undesirable scaffold material for long term implantation (Evans et al., 2002). Multiple studies have demonstrated that cell seeded PDLLA-based scaffolds can enhance neuronal regeneration as well as improve functional recovery (Hsu et al., 2009; Rutkowski et al., 2004). In particular, Hsu *et al.* showed that micropatterned PDLLA conduits increased NSCs alignment and significantly up-regulated NGF and BDNF gene expressions in a 10mm rat sciatic nerve injury model (Hsu et al., 2009). In addition, functional recovery estimated by SFI indicates the fabricated scaffold with NSCs performed better than the autograft group. Selected examples of polyester-based scaffolds are list in Table 2.

3.2.2.2. Poly(lactic-co-glycolic acid). Another well-studied polyester is PLGA, which is a co-polymer of PLA and PGA. A variety of cells are transplanted in PLGA-based neural scaffold to improve peripheral and central nerve regeneration. Teng *et al.* used PLGA-based scaffold embedded with NSCs to repair hemisection model of SCI in adult rat (Teng et al., 2002). Inner portion of the scaffold aimed to emulate the gray matter, has pore sizes ranging from 250-500μm and seeded with NSCs; while the outer portion emulated the white matter with long, axially oriented pores. Functional improvement was observed 70 days after injury and persistent for up to 1 year. Significant reduction in tissue loss and glial scar was also observed in the cell-seeded scaffold. In addition, corticospinal tract fiber growing through the scaffold was observed as well. Interestingly, NSCs in the scaffold were mostly nestin positive, suggesting the maintenance of progenitor identity rather than differentiation. The authors suggest the improvement in regeneration was mainly a result of NSCs trophic support rather than cellular replacement or differentiation. In addition to SCI repair, PLGA-based

Table 2
Selected examples of neural scaffolds with synthetic polymers for cell delivery

Synthetic polymers	Structure	Cell type	Injury model	Outcomes	Advantages and disadvantages
Silicone (Murakami et al., 2003)	Conduit with collagen gel	NSC	Rat 15 mm sciatic nerve gap	Histology: NSC embedded conduit resulted in significantly higher number of myelinated fibers and larger fiber diameter. Inflammatory response was not reported. Behavior: Nerve action potentials from NSC-conduit showed similar delay time and lower amplitude compared to un-operated control.	Pros: One of the earlier uses of NSCs in peripheral nerve injury and showed myelination occurs. Cons: Silicone tube likely requires removal in clinical settings.
PGA (Komiyama et al., 2004)	Nerve-like 3D scaffold with pluronic F127 gel	SC	Rat 10mm sciatic nerve gap	Histology: SC-scaffold showed higher number of axons than silicone tube and was not statistically different from autograft. Axonal diameter was similar to silicone tube and lower than autograph. Behavior: SC-scaffold showed similar SFI as autograft group, whereas silicone conduit did not improve functional recovery.	Pros: Bioresorbable, consistent physical and mechanical properties. Enable high SC seeding density. SCs are allowed to deposit ECM and change the scaffold prior to implantation. Cons: Degraded product can be acidic to the host tissue. Degraded shortly after implantation and may not provide sufficient time for regeneration.
PLLA (Evans et al., 2002)	Conduit with collagen matrix	SC	Rat 12mm sciatic nerve gap	Histology: SC-conduit with lower density of SCs showed the highest nerve fiber density in the distal stump of injured nerve; however, it was still significantly lower than isograft. Behavior: SFI demonstrated no difference among all groups, including silicone conduit, over 4 months.	Pros: Bioresorbable, consistent physical and mechanical properties. Cons: Long degradation time of PLLA makes it an undesirable scaffold material for long term implantation.
PDLLA (Hsu et al., 2009)	Conduit with aligned micro-pattern	NSC	Rat 10mm sciatic nerve gap	Histology: NSC-conduit showed similar mean area of axons, number of myelinated axons, and number of blood vessels as autograft. NSC on micro-patterned scaffold have higher NGF and BDNF gene expression. Behavior: SFI of NSC-conduit was significantly higher than all other groups including autograft.	Pros: Bioresorbable, consistent physical and mechanical properties. Micropatterned inner lumen promotes NSC alignment. Cons: Low permeability of the conduit wall makes host tissue integration difficult.
PLGA (Liu et al., 2017)	Conduit with salidroside (SDS)	SC	Rat 12mm sciatic nerve gap	Histology: SC with aligned orientation was observed. Neurofilament was positive in both PLGA and PLGA + SDS group. No quantitative information was reported. No inflammation was observed. Behavior: SFI values suggest PLGA-SDS have the best functional recovery compared to SDS alone, PLGA alone, and direct suture control. Nerve conduction velocity was also the highest with PLGA-SDS group.	Pros: Remained structurally intact throughout the study. Cons: Lack of cell adhesion molecules may affect SC viability
PLGA (Teng et al., 2002)	Bi-layer scaffold with different pore size and structure	NSC	Rat thoracic lateral hemisection SCI	Histology: Reduction in tissue loss from secondary injury and glial scar. Corticospinal tract ingrowth was observed. Behavior: NSC + scaffold had significantly higher BBB score for both ipsilateral and contralateral hindlimb functions, than cell alone or lesion control. Upward inclined plane test showed no difference between groups but downward incline indicated NSC + scaffold group showed improvement in function.	Pros: Bi-layer scaffold that emulate both the gray and white matter. The outer portion effectively reduced scar tissue infiltration while the inner portion maintained NSC survival. Cons: The structure of the scaffold is fixed such that host tissue may need to be further removed to accommodate the scaffold.

scaffolds have also been used to repairing PNI. SC transplantation in PLGA foam guides combined with glial growth factor (GGF) showed improvement on axonal regeneration and conduction velocity in 10mm-gap sciatic nerve injury model in rats (Bryan et al., 2000). In addition, OECs embedded in PLGA conduit demonstrated increase in conduction velocity of nerve fibers 16 weeks after injury, when used to repair a 15mm-gap sciatic nerve injury in rat (Tan et al., 2013). Transplanted OECs showed positive expression of S100β and signs of ECM deposition.

3.2.3. Other synthetic polymers

Some other synthetic polymers used for neural scaffold fabrication include poly(ε-caprolactone) (PCL), polypyrrole (Ppy), polyaniline (PANI), carbon nanotubes (CNT), and polythiophene. PCL is also a poly (α-hydroxyester), obtained by ring opening polymerization of ε-caprolactone. Uemura *et al.* used iPSC-derived neurospheres-seeded PLA/PCL conduits to bridge a 5mm sciatic nerve gap in mouse (Uemura et al., 2012). Walking track analysis relative to un-operated side and foot withdrawal from hot water showed improvements in motor and sensory function, respectively, with cell-seeded conduits compared to acellular conduits from 4 weeks to 12 weeks post-injury. The number of regenerated axons and S-100 positive cells were also significantly higher in cell-seeded group than the acellular control group. It is important to note PCL has slow degradation rate (~1-2 years), which may be unfavorable for nerve injury repair (Jansen et al., 2004). It is usually combined with PLA to increase degradation rate; however, the degradation products may be acidic to the host tissue. Another class of polymers is categorized functionally as electrically conducting polymers. These include Ppy, PANI, CNT, and polythiophene. Evidence suggests electrical stimulation without biochemical cues can influence stem cell differentiation to assume a neuronal fate (Yamada et al., 2006). Electrical stimulation using these polymers have been shown to improve nerve regeneration and induced differentiation of stem cells towards neuronal lineages *in vivo* (Schmidt et al., 1997). Ppy films have increased β-tubulin III and GFAP expression in NSCs, along with increased neurite length and number (Stewart et al., 2015). Similarly, PANI on PCL/Gelatin increased NSCs proliferation and neurite outgrowth (Ghasemi-Mobarakeh et al., 2009). For PNI, Ppy/chitosan have been shown to increase SC proliferation as well as induce NGF and BDNF secretion 24hrs after direct current stimulation (Huang et al., 2010). *In vitro* study showed that electrical stimulation also plays a role in the directionality of SC migration on Ppy substrates (Forciniti et al., 2014). Most studies using electrically conducting materials as neural scaffold are done *in vitro*. Further *in vivo* investigations for host tissue compatibilities and method of electric stimulations are required.

3.3. Summary and observations from the reviewed studies

To repair nerve injuries, biomaterials are designed into 3D scaffolds with the primary objective of regenerating and repairing tissues with similar anatomical structures to the original tissue. The requirements for PNI and SCI scaffolds can be very different. Scaffold for PNI repair is often tubular in shape with an internal matrix/filler to support cell transplantation. As previously discussed, PNI neural scaffolds need to maintain a balance between stiffness to bear physiological stress and flexibility to avoid kinking. Collagen nerve guides crosslinked by chemical or physical methods presents the major advantage of mechanical stability over many other naturally-derived biomaterials. Several studies have demonstrated the effectiveness of collagen conduits with SCs in axon regeneration and functional improvements for large sciatic nerve injury gaps in rodents (Ansselin et al., 1997; Udina et al., 2004). In addition, the availability and biocompatibility of collagen makes it a favorable material for neural scaffold. To enhance the functional outcomes of collagen conduit, other ECM proteins, such as laminin and fibronectin should be added as part of the internal matrix. In terms of synthetic polymer, PLGA seems to be the most versatile materials with minimal side-effects for conduit construction. Effective functional improvements have also been shown with PLGA conduits (Liu et al., 2017).

In comparison, hydrogels made from natural polymers, such as HA, seem to be a better scaffold for SCI repair. They can closely simulate the morphology and mechanical properties of the native spinal cord ECM and are conducive to neuronal and axonal growth. Moreover, injectable hydrogels can easily conform to the shape of lesion cavity in SCI. This obviates the need to remove additional spared tissue to implant scaffolds with a fixed geometry. Studies using fibrin and HA seem to show the best, albeit limited functional recovery for natural materials (Johnson et al., 2010a; Mothe et al., 2013). Both fibrin and HA have been shown to effectively reduce lesion cavity, which may partially contribute to the better recovery (Johnson et al., 2010a; Mothe et al., 2013; Thompson et al., 2018).

4. Conclusions and future perspectives

Currently, complete functional recovery for traumatic nerve injury remains challenging for PNI with critical gap and SCI. With more understanding of cellular function and behavior, we can engineer more effective neural scaffold that incorporate therapeutic cells to improve the regeneration process. In this review, we have discussed important criteria of designing neural scaffold for cell delivery. Different aspects of a suitable scaffold including biocompatibility, biodegradability, permeability, biomechanical properties, cell adhesion and migration, and cell encapsulation capabilities are discussed in detail. A combination of these aspects may prove helpful for developing better scaffold-facilitated cell therapies. A better understanding of cellular behaviors of transplanted cells can be important towards this endeavor. An ideal scaffold for cell delivery should have control over the survival, migration, differentiation, and regeneration of the transplanted cells. For instance, prolonging the repair phenotype of SCs or differentiate SCs into such a phenotype may enhance the PNI regeneration process (Benito et al., 2017). Using stem cells as transplanted cell types also faces many challenges. While current neural scaffold can influence stem cell differentiation towards neuronal lineages, differentiation specificity of each neuronal and glial subtypes, especially those in the spinal cord, are still being elucidated.

In this review, we also discussed the commonly used biomaterials for neural scaffolds. Natural biomaterials have inherent bioactivity that can promote the regenerative capacity of transplanted cells. However, it is often difficult to control their degradation rates as well as mechanical properties. In comparison, synthetic polymers have highly tunable degradation and mechanical properties, but inferior abilities to support cellular functions. To capture the merits of both types of materials, the combination of natural and synthetic biomaterials functionalized with biochemical molecules are emerging as the better approach. To conclude, as our understanding of the injury progression and cellular behavior improves, we can incorporate more components into neural scaffold embedded with therapeutic cells to enhance nerve regeneration.

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