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REVIEW

Implantable microdevice for peripheral nerve regeneration: materials and fabrications

Devasier Bennet · Sanghyo Kim

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Abstract Rapid innovations in tissue engineering have increased the likelihood that fabricated microdevices for neuro-regeneration can finally be applied to humans. The advent of microdevices has created strong interest in many fields, including diagnostics, drug/gene delivery, and tissue engineering. The integration of microfluidics and tissue engineering is believed to hold promise in applications for neuro-regeneration. Early clinical results suggest that the fabrication of microdevices with appropriate properties indeed yields multi-functional applications with enhanced efficacy and less adverse effects. A prerequisite for advancing this area of research is the development of apt devices for nerve restoration, which can provide molecular, electrical, and micro-environmental cues for efficient neuronal cell regeneration. Based on the increasing clinical application of fabrication methods and continued efforts to advance this technology, it is likely that microdevice fabrication will become an effective method for achieving the above-mentioned criteria. Therefore, the aim of this review is to provide basic information on the fabrication of microdevices by focusing exclusively on several kinds of biomaterials, such as biocompatible, biodegradable, non-conducting, conducing, elastomeric and thermoplastic materials with natural, synthetic polymers, inorganic biomaterials, and physiochemical parameter for neuro-regeneration. We also discuss distinctive nerve growth factors and neural cell types within the context of developing micro-based neuro-degenerative applications. The information provided in this review is important with regards to the safe and widespread use of microdevice fabrication, particularly in the neuro-regenerative field.

D. Bennet · S. Kim (✉)
Department of Bionanotechnology, Kyungwon University, San 65, Bokjeong-Dong, Sujeong-Gu, Seongnam-Si 461-701, Gyeonggi, Republic of Korea
e-mail: samkim@kyungwon.ac.kr

Introduction

Occurrence of nerve injuries has increased in recent decades due to accidents, idiopathic damage, iatrogenic injuries, compression syndromes, and systemic diseases [1, 2]. Restoration of severed nerve pathways using tissue engineering is always desirable to cure such neurodiseases [3–5]. One of the best approaches for restoring severed nerve pathways involves nerve regeneration using a nerve guidance conduit, a type of neuronal network [6]. Gangliosides are the most abundant neuronal cell type in the CNS [7], which suggests that these molecules are of particular importance in the functional development of the CNS [8]. Gilia, squamus, and astrocyte cells of the peripheral nervous system (PNS) potentially have many applications in regenerative therapy, including development of neuronal network, neuronal cues, axonal studies, neuro diagnostics, and nerve growth [9–11]. Manipulating the cells of a local micro-environment has been the focus of much research starting from nerve grafts to engineered constructs such as conduits. Regenerative repair of the PNS is thought to be possible due to the presence of growth promoting cues provided by supportive cells. More serious injuries to the PNS require surgical intervention, most commonly autologous nerve grafts [12, 13]. Regeneration therapy is a useful technique for restoration, but there are many prerequisites such as biocompatibility, combined molecular, electrical, structural, mechanical, and cellular cues, molecular micropatterning, and nerve guidance channel must be satisfied for successful and prompt therapy. Other categories of guidance cues include bound

factors that guide neuron-matrix interactions [14–16], topographical cues that influence nerve growth through contact guidance [17–20], and electrical cues that affect the rate and direction of nerve growth [2, 21, 22]. Nevertheless, neuronal cells exhibit neurotrophic and neuroprotective effects and may reduce the severity of acute neuronal damage [23, 24].

Many scientists have reported the fabrication of emulated nerve guide conduits such as nerve tubes and grafts. The U.S. Food and Drug Administration (FDA) have approved conduits for clinical use, and their properties are listed in Table 1. However, existing fabricated conduits are expensive, time-consuming, and immunogenic and are characterized by oxidative stress-induced cell damage and random signal leaking. The applicability of microchamber platforms to the study of neuronal injury has been explored recently [25]. Microfluidics is a fast emerging field that deals with the flow and phases of circulation in fabricated artificial Microsystems [26]. Such systems require devices with tiny channels of mono or multi-phase structure that have the ability to manipulate small amounts of fluids [27, 28]. This quality miniaturized system was first developed for chemical and biochemical analyses, resulting in better sensitivity, speed, and higher resolution over conventional methods [28, 29]. The first miniaturized gas chromatography system was presented around 1975. Since, silicon-based microelectromechanical systems (MEMS) have eliminated the technical obstacles of simple microfluidic systems [30]. Miniaturization and MEMS gave rise to microfluidics, which now lies at the interface of multiple disciplines, including biotechnology, chemistry, medical industry, and MEMS, and has applicability to molecular biophysical, chemical, and biochemical assays with minimal use of reagents. Recently, regenerative neuromedicine and neuroprotection of the nervous system have gained special attention due to the increased use of bio-nanotechnology for the diagnosis and therapy of patients with neurodiseases [31–33].

The optimization of this modern technique for neuro-applications including in vitro diagnosis and treatment has not been well investigated. Despite the many advantages of this bio-nanotechnology, modifications must be made to eradicate its major drawbacks such as defects in neuronal regeneration and problems relating to chosen materials and fabrication techniques. Figure 1 describes the important properties which are desirable in ideal microchamber device for neuronal regeneration. Furthermore, the synthesis of novel, thin, inert, flexible, porous, biocompatible, biodegradable, compliant, neuroinductive, neuroconductive, non-immunogenic, and non-inflammatory conduits with appropriate surface and mechanical properties from (flexible polyimide and poly (phosphoester)) nanomaterials using microfabrication have been addressed in depth [34–36]. The

Table 1 FDA-approved biomaterials used in the field of medical devices

FDA and/or CE approved nerve guides					
Device name	Company name	Properties/nature	Material used	Size	Web	Ref
Neurotube	Synovis Micro Companies Alliance	Biodegradable synthetic based hollow tubes	Poly-glycolic acid	Up to 4 cm in length	www.synovismicro.com	[170]
Neurolac	Polyganics BV	Biodegradable, synthetic, collapse and acidic by-products	Poly(DL-lactide-€-caprolactone)	Up to 3 cm in length	www.polyganics.com	[171]
NeuroMatrix™	Collagen Matrix Inc	Biodegradable, collapse	Type-I bovine collagen	Up to 2.5 cm in length	www.collagenmatrix.com	[172]
NeuroFlex™	Collagen Matrix Inc	Biodegradable porous, blendable, without collapse	Type-I bovine collagen	Up to 2.5 cm in length	www.collagenmatrix.com	[172]
NeuraGen™	Integra Neuroscience	Biodegradable hollow tubes, collapse, inflammatory responses	Type-I bovine collagen scaffolds	Up to 3 cm in length	www.integra-ls.com	[173]
SaluBridge	SaluMedica	Non-degradable, synthetic materials	Hollow tubes	Several millimeters	www.salumedica.com	[174]

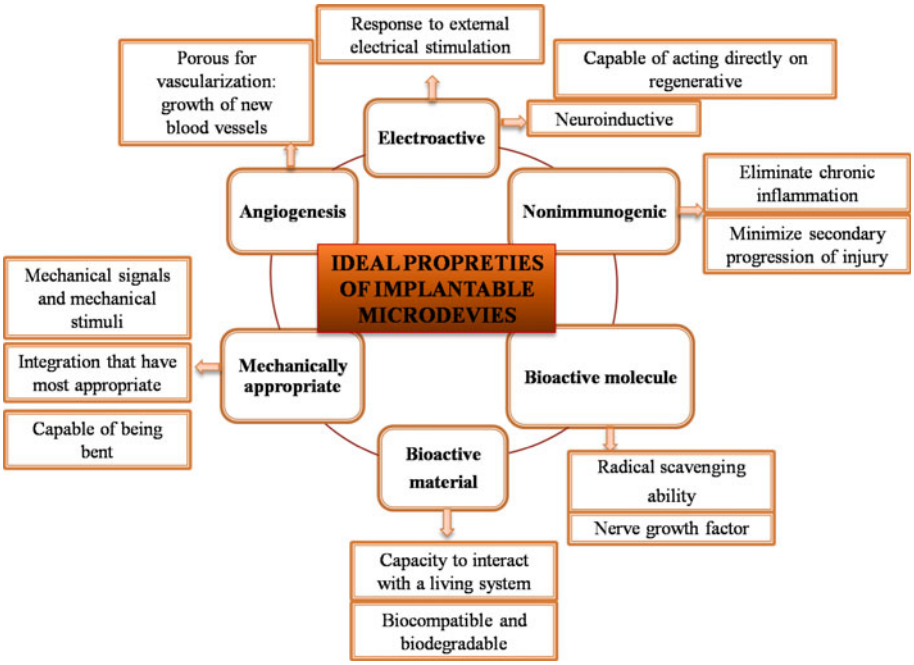

Fig. 1 Ideal schematic representation of the multiple properties which are desirable in microdevices for neural regeneration

construction of microfabricated conduit can be made up of non-conducting and conducting polymer in rolled form having an inner conducting surface and an outer non-conducting surface. The non-conducting material of a microdevice is fabricated using non-electroactive polymers (Fig. 2). Describe the schematic of the important considerations for ideal fabrication of microchamber device for nerve restoration. Indeed, it is very important to understand the signaling interface of a microchamber that directly induces in cell–cell and cell–matrix (glycosphingolipid-enriched microdomains) communication in order to identify the early stages of nerve system development [37, 38]. Table 2 explains the types and importance of the nerve graft materials.

The integration of microfabrication techniques into a neurological system offers additional control of the added reagents with substrate constituents. One clear advantage of using microfabricated devices is the power to control nerve cell growth and regulate reactions with several chemical cues [39]. Microfabrication approaches can be used to create more in vivo platforms for neuronal regeneration, since they allow the generation of precisely controlled microenvironments that mimic specific features of the local in vivo environment [40]. Hence, this review is attempted to address the issues relating to well-established, conventional fabrication methods and also envision the synthesis of ideal conduits using innovative biomaterials, such as biocompatible, biodegradable, non-conducting, conducing, elastomeric and thermoplastic polymeric-based microfabrication platforms. The present article also discusses distinctive vehicles for cell delivery, vascularisation, neurotropic factors and neural cell types within the

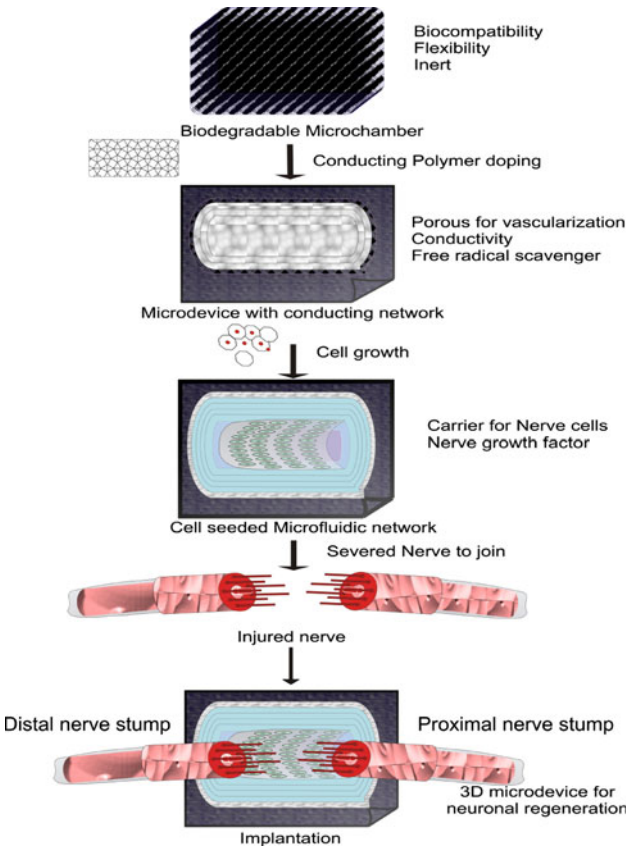

Fig. 2 Ideal schematic of the important considerations for fabricating a microchamber device for nerve regeneration

context of developing micro based neuro-regenerative applications. Additionally, the article discuss the development of novel technologies that directly or indirectly aid

Table 2 Nerve graft materials advantages and disadvantages

Grafts	Advantages	Disadvantages	Ref
Autologous tissue grafts			
Nerve grafts	It's generally from cutaneous nerves, good repair of a peripheral nerve defect	Poorly vascularized, thick, neuroma formation, resurgery to removed and no regeneration in across the lesions	[175, 176]
Vein grafts	Used to bridge the gap	Pain in the post operation	[177, 178]
Vein filled with muscle grafts	Good axonal regeneration, sensory recovery and bridge small nerve gaps	Failure of regeneration with increase gap length and collapse	[179]
Epineurial sheaths	Minimal adhesions at the donor site and matching size of the conduit	Risk of isolation and scale-up	[180]
Tendon grafts	It's still considered the historical gold standard	Increased wound pain, scar formation and Increased level of pain of post operation	[181]
Nonautologous/acellular grafts			
Immunosuppression with allografts	It contains important neurotropic factors, biodegradable, semiflexible	Removal or destruction of the immunogenic cells and a very weak immune response	[169]
Acellular allografts and xenografts	Provides large amount and without any immunosuppressants to enhancing the growth axons, except the autografts	Have some risk of disease transmission and needs to use immunosuppressants	[182]
Natural-based materials			
ECM protein-based materials			
Fibronectin (Fn)	Increase the cell migration and extension	Less toxic, potential difficulties with isolation and controlled scale-up	[183]
Collagen	Peripheral nerve injury, Neural implant, increases in axonal development and repair	Immune response, decellularization of the components is essential and no axon found at the distal end	[184]
Laminin	Short-term recovery and improved regeneration	Rapid degradation and poor mechanical strength	[185]
Hyaluronic acid-based materials	Peripheral nerve injury, neural implant, decreased scarring and neurite extension	Rapid degradation and poor mechanical strength	[186]
Fibrin/fibrinogen	Peripheral nerve injury, neural implant and enhance the speed of cell migration	Decellularization needed otherwise inflammation occur after implanted	[187, 188]
Other materials (alginate and agarose)	Naturally derived molecules, neural implant and neurite extension	Rapid degradation and poor mechanical strength	[189, 190]
Synthetic materials			
Biodegradable synthetic materials			
Poly(lactic acid) (PLA)	Attractive physiochemical properties such as degradation rate, porosity, mechanical strength and neural implant	No cellular differentiation	[191]
Poly(lactic-co-glycolic acid) (PLGA)	Biodegradable, good physiochemical properties, biodegradability, porous structure for vascularization and neural implant	Hydrophobic property and very challenging technique	[144]
Poly(caprolactone)	Easy processing, porous and bridge the longer nerve gaps	Collapse, no successfully restoration	[192]
Poly(urethane)	Easy to handle, mechanical properties, flexible and suture no detectable roughness	Inflammatory response	[193]

Table 2 continued

Grafts	Advantages	Disadvantages	Ref
Poly(organo)phosphazene	Biodegradable and biocompatible materials with a slow reabsorption rate	Increased scar formation	[194]
Poly(3-hydroxybutyrate)(PHB)	Excellent processibility, mechanical properties, uniform porosity and regeneration of axons	Pore size reduced after implantation	[195]
Poly(ethylene glycol) "glue"	Neural implant and used to "fuse" the severed nerve ends	Only small nerve defects	[196]
Biodegradable glass	Controlled release Nerves regeneration	Inflammatory response and higher risk for infection	[197]
Electrically active materials			
Piezoelectric polymer	Stimulates cell differentiation and recording of neurons	Less formation of neuromas scar	[198]
Conducting polymer	Stimulates cell differentiation, neural implant, Provide mechanical strength and nontoxic	Temperature and pH dependent	[196, 199]
Nonbiodegradable synthetic materials			
Silicone	Flexible and used to bridge short gaps	Immune response, resurgery and nondegradable	[200]
Polytetrafluoroethylene	Thermoplastic polymer, excellent dielectric properties and regeneration across the chambers was seen	Non-degradable, inflammatory response and cannot be cross-linked like an elastomer	[201]

in providing neuroprotection and/or a permissive surroundings and dynamic signaling cues for guided axon growth for neuro-regeneration. To achieve this goal, systematic and detailed studies employing ultra-sensitive, reliable instruments, such as sophisticated microfabricated platforms, characterized by high sensitivity, reproducibility, resolution, and accuracy for the development of facile strategies were investigated in detail.

Bioengineered materials: ideal and recent advances for nerve repair

Fabrication of multichamber implantable microdevice

A microdevice is a splendid tool for controlling the features of individual cells, molecules, and the delivery of therapeutically viable cells [40]. Microdevice-based fabrication processes are fast, efficient, and scalable. Using this technique, polymers can be cured and linked together without the use of any cytotoxic solvents or adhesive materials. Further, multi-layered device fabrication facilitates the incorporation of multiple cells within a three-dimensional (3D) structure. Most importantly, the design and fabrication of the microdevice are very critical for tissue-engineering neuronal guidance to be highly vascularized. These microdevice systems should be biodegradable, which allows them to be integrated with improved nanobiotechnology systems for neuronal-specific applications and increased functionality. Many researchers have reported the microdevice fabrication for nerve growth factor (NGF)/drug-delivery systems [41], cell-patterning [42], and contact guidance cues [43]. The information in the above-mentioned reports can be integrated into microdevices in order to promote growth of embedded cells into composite tissues. Thus, implantable and fully biodegradable systems can be fabricated by integrating highly flexible, existing vasculature with transparent and biocompatible polymer [44, 45].

Existing fabrication methods employ replica-molded gauzy polymers to create tens to hundreds of micrometer-sized multi-compartment cell culture platforms. These tiny chambers are large enough to culture a few hundred cells in well-assured microenvironments [46]. Polydimethylsiloxane (PDMS) plays a major role in the microdevice-based fabrication for neuronal cells culture in vitro [47–49], but the materials used for biodegradable implantation in vivo should allow for effective cellular adhesion as well as the respiration of cells that are enclosed within the compartment, which should be permeable to gases, non-toxic, and sterile [50, 51]. The first step in constructing a PDMS-based microdevice culture platform involves the fabrication of a mask with the desired pattern utilizing computer

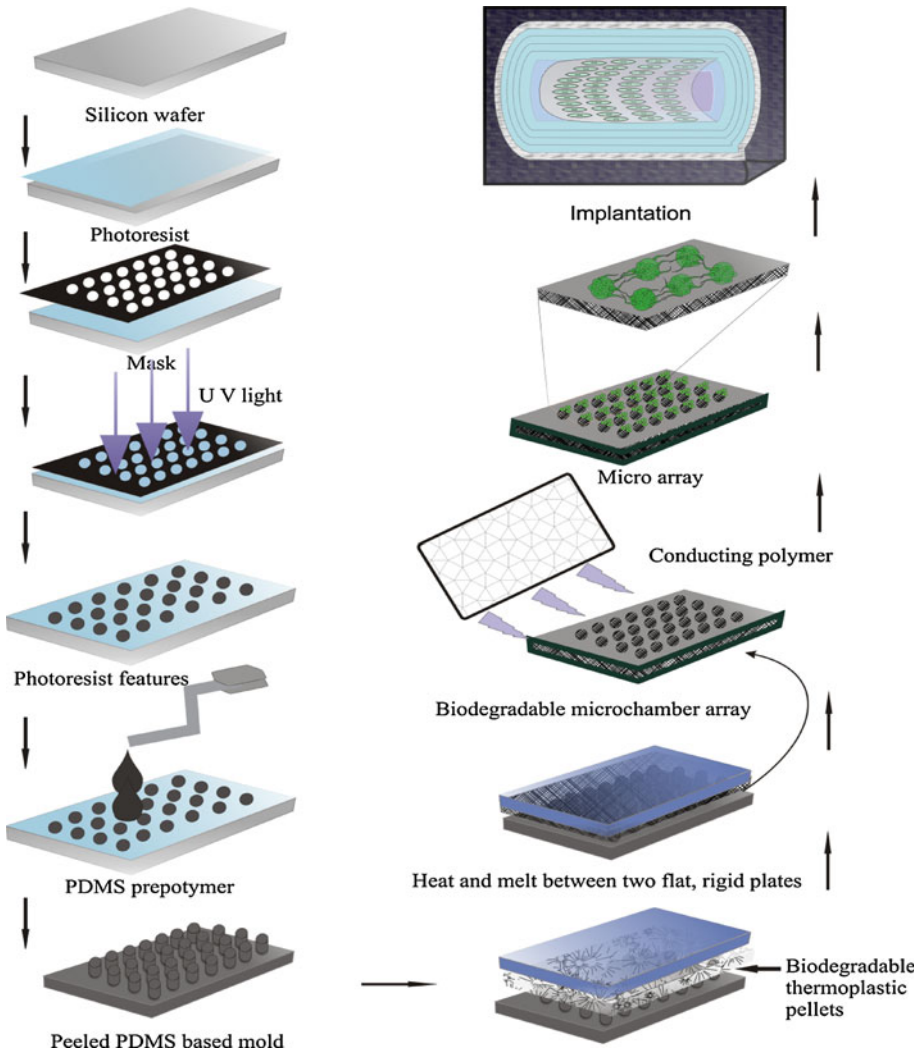

Fig. 3 Schematic representation of the fabrication method using photolithography technique and various suitable polymers (CPs and NCPs)

software. This design is then printed out and used to create a 3D mold using photolithography. Additionally, photomasks and photoresists are used in photolithography for fabrication and patterning of the desired cell culture compartment for neuronal populations [52, 53]. To create the neuronal network, a replica model must be constructed with customized length, width, height, and center-to-center spacing of the hole [54]. The fabricated mold is then used to produce a biodegradable polymeric neuronal cell culture platform. The fabrication model of the microdevice system is well explained graphically in Fig. 3. The microdevice has to be designed so that the concentration of special elements delivered to the cell culture compartment can be determined [55–57]. Further, the quantity of the elements must exactly match the location of each cell or vary over the width of an individual cell [58].

Neuronal cell viability is important to the fabrication of the microdevice compartment. Advantages of this microdevice culture platform include the presence of neurons, compatibility with long-term culture, and non-immunogenic and robust biodegradable devices that allow for leak-free experiments. Neuronal cell attachment and development is higher on hydrophilic surfaces. There are many procedures available for modifying surfaces from hydrophobic to hydrophilic. Surface modification eliminates the need for conventional cell-repellent species, and this is anticipated to greatly contribute to the neuro-regenerative therapy of PNS injuries. A neuronal guidance channel is characterized by high temporal resolution, greatest precision characteristics and minimal mechanical disturbance in device made from prototypical patterns, bio-absorbable thermoplastic materials like poly(lactic-co-glycolic acid) (PLGA) by using melt-processing to form microscale features in bio-absorbable film. It can be achieved from thermal fusion bonding process to control by varying the compression time, temperature, applied

force, and the temperature-dependent polymer between the parallel culture compartments [59]. Most importantly, microdevice-based microchamber arrays are used in the formation of spheroids of various cell types [60–62], this indicates that glial cells are necessary for dendritic and axonal extension and shows that glial cells modulate neurite growth [63–65]. Many reports have shown that the oxygen density of big spheroids is low, resulting in necrosis, and bigger neurospheroids have low cell viability. Therefore, to develop a neuronal spheroid network, functional synaptic connections must be maintained [66–68].

Considerations for fabrication

Biocompatibility for in vivo

The term "biocompatibility", as it relates to nerve guidance, refers to the ability of the nerve guide to perform and allow host response in a particular application without any injury. The biocompatibility of novel polymer-implantable materials can be evaluated by performing in vitro biocompatibility assays or cell viability and growth assays and then comparing with standard polymer as a primary reference material. Silicone is considered to be a reference tool for in vitro and in vivo validation tests by the National Heart, Lung, and Blood Institute of the U.S. For cell encapsulation, the level of biocompatibility of a microdevice must account for not only the interaction between the biomaterials and the host system but also the interaction between the biomaterials and the encapsulated cells [69]. Various kinds of biologically compatible materials have been used to fabricate microdevices, including biodegradable and non-biodegradable polymers. Application of an external electric current to a microdevice can facilitate nerve regeneration. It is also important to note that there should be no failure of regeneration in any of the implantable materials. Although the use of fibronectin mats previously gave good results, there were difficulties relating to rapid reabsorption [70, 71]. For an implantable microdevice to be effective, it should remain in situ without being degraded while it completes the regeneration of cells. Poly-3-hydroxybutyrate (PHB) can be obtained from the bacterial cytoplasm and used as a bioabsorbable sheet. PHB sheets are non-antigenic, easy to handle, have good tensile strength, and undergo hydrolytic degradation over a period of 24–30 months [72, 73]. PHB gives biocompatible and remains in situ long enough to support regeneration. This longer reabsorption time ensures that the regenerating, growing nerve is capable to hold the stress of mobilization [70]. Flexibility of microdevice implantation is also necessary to enable continued protection of the regenerating nerve upon initiation of mobilization of the injured area [74].

Biodegradability and stability

Biodegradability is critical to the biomedical application of microdevices. The degradation behavior of microfabricated materials has critical effects on the long-term performance of the device as well as cellular processes, including cell growth and host response. Biodegradability can be characterized by changes in mass, relative molecular mass and dispersion, surface and inner morphology, and dimensions [69]. The backbones of polymers can be cleaved by water. The more promptly water permeates, the faster bonds are cleaved and the faster the degradation rate. Besides, a faster degradation rate leads to deformation of the microdevice, which could impede the outgrowth of regenerating nerves [75, 76]. This has been proven by degradation tests carried out using Poly(phosphoester) (PPE) conduits [70]. Microdevice swelling is often observed with biodegradable polymers. In devices with porous walls, initial swelling may result from water uptake into the pores, which explains there is a predominant swelling experience in PPE. As the device is degraded, lower relative molecular mass degradation products absorb water and increase swelling. Swelling may then cause problems if sufficient enough to distort the microdevice lumen [70].

It is very important that biodegradable materials be stable in a physiological environment and have sufficient conductivity with the lowest possible concentration of conducting polymers (CPs). The polymer membrane used in microdevice fabrication experienced prolonged electrical stability and large amount micropores caused by hydrolytic degradation [77]. Such degradation will finally destroy the original structure and electrochemical conductivity of the membrane. Nevertheless, the novel composite of CPs can successfully maintain its high level of conductivity after 1000 h without signal degeneration [78, 79]. CPs are also widely used as a means to electrically stimulate cells for neuronal regeneration (Fig. 2). However, the largest limitation to using CPs for regeneration is their natural tendency to degrade [80]. Composites of CPs and degradable polymer, including polylactide, polyglycolide and their different monomers or ester terminals linkage have been created to overcome this issue [81, 82]. This ideal polymer composite design should allow for better control over physicochemical properties such as degradation rate and conductivity. CPs of several dopant characters ranging from small-scale salt to polymers, or bio-specific dopants such as peptides, proteins, and growth factors (GF), are commonly used to prevent signal degeneration. These polymers should be conductive and non-inhibitive to nerve cell development and survival [83]. The presence of coupled covalent bond along the backbone of polymers results in conductivity and the conduction of a utilized electrical stimulus. These bonds between carbon

atoms are alternatively single and double in conjugation. Moreover, chemical techniques are often required for post-fabrication doping in order to increase the conductivity.

Non-conducting polymer for nerve regeneration

The concept of microfabricated conduit, including an insulating material in rolled form having an inner conducting surface and an outer insulating surface (Fig. 2). The insulating material of a microdevice is fabricated using non-electroactive polymers such as polylactide [84], polyglycolide [85], polycaprolactone [86], and their copolymers [87]. Research on natural polymers has focused on the use of pure natural extracellular matrix (ECM) proteins, glycosaminoglycans, and hyaluronic acid, all of which can be modified to serve as appropriate scaffolding [88]. ECM proteins such as laminin, collagen, and fibronectin play a vital role in neuronal development [89]. Further, many other glycosaminoglycans and proteoglycans in the ECM are known to regulate neural activity and neuronal development. Hence, ECM components are potential candidates for use in nerve guidance. Silicone tubes filled with laminin, fibronectin, and collagen show improved regeneration nerve gap compared to empty silicone controls [90]. Although many polymers are obtained from a natural source, they all cannot be used for the fabrication of microdevices due to their inappropriate nature. Further, naturally derived polymers containing appropriate biomolecules to increase neurite extension and nerve repair have been covered. Apart from natural polymers, synthetic materials have been looked into their potential use in nerve repair applications. Synthetic materials are attractive because their unique nature can be optimized for a particular application. To select an appropriate synthetic material for neuronal applications, there are several general properties that must be conceived, including ease of sterilization, handling, suturing ability, resistance to infection, neuroprotection, and maintenance of structural integrity during implantation, permeability, and the inner wall degradation over the course of neuronal regeneration [91].

Conducting polymer materials for nerve regeneration

CPs are excellent bionic materials that provide utility from the biomolecular to biomechanical level. CPs can be integrated into implants for nerve regeneration applications at the biomolecular level. Typical properties of polymeric materials for nerve growth include flexibility, elasticity, stability, molding ability, ease of handling, and electrical conductivity. Ideally, CPs provide a suitable scaffold for enhancing neuronal cell attachment and proliferation and provide electrical stimulation followed by degradation and elimination. Moreover, some CPs has some limitations which are hydrophobicity, non-degradable, poor thermal stability, hydrolysis in the presence of moisture and inflammatory reaction. In order to overcome these limitations needs to manipulate these materials with biomaterials. Biomaterials for nerve guidance must be engineered to provide electrical conductivity and electrical contacts for external manipulation of nerve growth. Recently, long-term novel bio-absorbable composite CPs was synthesized for its suitability as a substrate for electrically stimulated cell cultures and as a scaffold to explore the potential of electrically stimulated tissue regeneration [79, 92, 93].

CPs have potential in nerve stimulation, and their important characteristics are listed in the Table 3. In vivo biocompatibilities have been reported for polypyrrole (PPy)/poly(D,L-lactide) complex and PPy-coated poly(D,L-lactide-co-glycolide) membranes implanted subcutaneously in rats for 3–130 days [94, 95]. These polymer composites induce no immunogenic responses with extended implantation time [79, 96, 97]. In addition to existing electroactive biomaterials, researches have also established new synthetic strategies [96]. That involves conjugation of conductive polymer (pyrrole-thiophene oligomers) and degradable ester terminal group in presence of aliphatic linker. After degradation of polymer, the remaining oligomers can be readily uptake by macrophages during the regeneration [96, 98]. In another report, a biodegradable conducting polymer implant have been prepared by using polymer with organic semiconductors (such as poly-vinyl alcohol (PVA), cross-linked PVA, 5,5′-bis-(7-dodecyl-9*H*-fluoren-2-yl)-2,2′-bithiophene (DDFTTF) and poly(L-lactide-co-glycolide) (PLGA) with Beta-carotene as natural anti-oxidant [99, 100]. Researchers have also demonstrated the in vitro behavior of hyaluronic acid (HA)-functionalized PPy with pheochromocytoma (PC12) cells. Significant enhancement of PC12 cell attachment in the presence of nerve growth factor promotes this substrate as a good candidate for nerve regeneration and repair applications [101]. PPy-HA films retained for several days and promoted vascularization in vivo. Previous reports have shown that PPy-based complex biomaterials are anticipating candidates for tissue engineering and nerve regeneration and may benefit from both electrical stimulation and increased vascularization [101].

The role of CPs in microdevice fabrication is related to electrical cues for the restoration of neuronal cells [102]. Microdevices have two important layers, an outer insulating layer and an inner conducting layer in a semi-conducting range under ambient conditions. The double-layered microdevice can eliminate unnecessary twitching of muscles and contractions of other tissues adjoining the nerve implant during external application of an electric current. Hence, direct coupling of neurons can be achieved using a

Table 3 Conducting materials and there applicability

Conducting based polymer	Conductivity (S/cm)	Process	Properties	Limitations	Applications	Ref
Polypyrrole (PPy)	40–200	Chemical and electrochemical synthesis	High conductivity biocompatibility possible to modification, good stability and suitable for long-term implants	Not highly porous hydrophobicity rapid release	Neural prosthetics, antioxidants and biosensors	[202–205]
Polyaniline (PANI)	100	Chemical and electrochemical synthesis	Semiflexible and high conductivity cell compatibility with modified polyaniline,	Poor cell adhesion and growth on unmodified polyaniline, less inflammation	Antioxidants, bioactuators and biosensors	[206]
Polythiophenes (PT)	10–100	Chemical and electrochemical synthesis	High conductivity, biocompatibility and optical property	Molecular materials are not covalently bound	Inkjet printer, chemical sensor, label free deduction of DNA and antioxidants	[199, 207]
Polyacetylene (PA) and there compounds	200–1,000	Self-organization processes	Inhibit tumor cell proliferation, promote neurite outgrowth	Difficulty with processing, high instability in air and hypersensitivity	Micropatterning neuronal studies	[208, 209]
Polyphenylene sulfide (PPS)	3–300	Electrochemical synthesis	Chemical resistance, processability, thermoplastic friction and tensile modulus	Inflammatory response microhardness	Photosensor, artificial neural network, electronics applications	[210]
Polyparavinylene (PPv)	1–1,000	Electrochemical polymerization	Good stability and fluorescent property	Highly water-soluble	Detection of antigen–antibody, electrochemical sensor and neural catheters	[211]
Polyparaphenylene(PPP)	100	Cationic polymerization	High-stability, having reversible hydrophobic to hydrophilic properties and printing on PDMS	Forms complexes	Optoelectronics and sensors	[212, 213]
Poly (ester-urethane)	1,500	Using a cross linking agent	Hemocompatibility, flexibility and elasticity toughness	Hydrophobic characteristics	Good antithrombogenicity	[214]
Conductive nylon	10–12	Chemical synthesis	Transparent thermoplastic polymers	Prevented optical scattering	Artificial tactile skin sensor	[215, 216]
Polyethylene composites(polymeric doping)	Varies	Chemical Synthesis (ionomeric doping)	Hydrophobic to hydrophilic by using copolymer	Hydrophilic polymers	Artificial neural network and dynamic neural networks	[217, 218]
Poly (ortho-ethoxyaniline) POEA	10–20	Electrochemical Synthesis, oxidative polymerisation	Good properties as corrosion inhibitor and chemical flexible	Higher solubility	Sensor artificial neural networks	[219]
Poly vinylieddene flouride (PVDF)	8.85	Pyroelectric response	Excellent mechanical and physico-chemical properties	Poor thermal stability and limited applications due to hydrophobic surface	Artificial neural network and microporous hollow fibre ion-exchange performance	[220, 221]
Polyisothionaphthene (PITN)	1–50	Electrochemical polymerization	Process for producing conductive fiber	Precipitation occur in the process and hydrophobicity	Neural probe and biosensors	[129]
Poly(3,4-dimethylthiophene)	10–50	Electrochemical synthesis	Good stabilities and conductivity	Limited ionic conductivity	Neural probe	[129]

Table 3 continued

Conducting based polymer	Conductivity (S/cm)	Process	Properties	Limitations	Applications	Ref
Poly(3-methylthiophene)	100	Electrochemical polymerization	Good stability and high conductivity	Difficulties in conjugation multilayer deposition not sufficiently enough	Connections for molecular devices and neuronal degenerative diseases	[222, 223]
Polyfuran (PF)	20–50	Chemical synthesis	Elastic and viscous properties	High thermal ageing	Artificial neural network antioxidants	[224]
Polyazulene	10–80	Chemical synthesis and polymerization	Provides a suitable environment for their immobilization of biomolecules	Restriction of the photolithography process because of large spacer	Amperometric biosensors	[129, 224]
Polyurethane	2	Chemical synthesis	Biocompatibility, elastomeric, flexibility	Hydrolysis in the presence of moisture and temperature and inflazmmatory reaction	Nerve guidance channel, surgical implantation, vascular graft, bone tissue engineering and artificial neural network	[214, 225, 226]

microdevice that directs the electrical stimulus generated at the nerve stumps in a single direction without substantial leaking. Researchers have demonstrated a method for fabricating micropatterns of molecular guidance cues in combination with conductive polymers [103]. Micropatterned cues permit extremely controlled directional guidance of neuronal attachment and axonal development. Recent advances in microfabrication techniques have enhanced the ability to present directional information on a biologically relevant scale. Optimal dimensions range from tens to hundreds of microns and can be used in combination with other types of guidance cues for synergy in a more complex microenvironment [53, 104].

Thermoplastic materials and its mechanical strength for nerve regeneration

The term "thermoplastic" material that turns to a liquid when heated and hard when cooled, mainly thermoplastic are high molecular weight polymer these are sharp melting point of a pure crystalline, elastic, and flexible substance. It can be tested by tensile tests, flexural tests, and pendulum impact tests. However, this class of polymeric materials have different physiochemical properties such as biodegradable thermoplastic and non-degradable thermoplastic polymer. These materials have the advantage of being simple and relatively cheap. It can be used to fabricate a device, which is biodegradable thermoplastic polymer (such as polyester, PLGA, and poly (4-hydroxybutyrate) (PHB)) [99, 105]. This can also allow the elevated temperature for processing through their smooth and roughness nature.

The "mechanical strength" of a microdevice refers to the ability of the device to withstand suturing, remain intact after surgery, and provide proper guidance and support for regeneration. The tensile strength of a synthetic nerve conduit can be evaluated by measuring the suture pullout strength in grams using a tensile tester, wherein the suture is placed through the edge of the microdevice, followed by tying the suture to a hook adapter of a tensile tester. Then, the device is pulled at a speed of 1.0 in/min until the suture is pulled out. Mechanical properties, such as elasticity and resistance to tearing when applying traction to the suture, can be evaluated by making sutures on the microdevice with a polyamide wire (Ethilon 11/0). A qualitative score from 1 to 4 (bad-moderate-good-very good) is then assigned, and the one that exhibits an average of 3 or higher is considered to be an acceptable microdevice. The membrane strength of the device is directly proportional to the membrane thickness. Endured swelling corresponds to lower mechanical strength. This can be improved by checking the relative molecular mass of the polycation and the formation time, which is only suitable for

characterization of the swelling ratio [69]. There are various disputes that need to be covered before implantation, including electrical stability, mechanical strength, and long-term bio-environmental performance.

Annealing can increase the moduli and tensile strengths of CPs which enhance the physiochemical properties [106, 107]. The mechanical properties of a CPs have also been demonstrated to depend upon the protocol methods [106]. The gain of dopant molecules involves the mechanical properties of the CPs, which makes significant reduction in the modulus and strength of the material. Doping sometimes reduces the tensile modulus and properties to about 1% when the effect of doping is higher [107]. Implantation can withstand mechanical strength over an extended period. This can be achieved through modifications or by changing alkyl chain length [108]. Further, solubility can be attained by adding appropriate side chain groups [109]. Hence, the mechanical strength of the CP can be changed based on surface modification. Recent studies have shown that procedures such as melt processability/stretching under increased temperatures allow for the introduction of chain alignment and extension, thereby improving the mechanical strength of CP films [79]. Such modifications of mechanical properties are useful for biological applications.

Biodegradable elastomers and its flexibility for nerve regeneration

Viscoelasticity, amorphous nature, and existence at above their glass transition temperature are the distinguished features of elastomers. Biodegradable elastomer can be categorized such as hydrogels, elastin-like peptides vulcanized rubber, and polyhydroxyalkanoates. Biocompatible elastomers have played a vital role in fabrication of biodegradable implants. Hydroxy group containing monomers were selected for cross linking of elastomers. This forms a covalent crosslinking network which enhances the hydrophilic properties. Biodegradable elastomers match those of the ECM features that provide mechanical stability and structural integrity to the tissues. Hence the elastomer that readily recovers and maintaining the implants proper function without any mechanical disturbance to the host. For instance, polycondensation of glycerol and sebacic acid gives a gauzy and most colorless elastomer. This polymer is referred to as poly(glycerol-sebacate) and noticed by low modulus and prominent elongation ratio, suggesting elastomeric, tough and good mechanical properties received through covalent joining and hydrogen-bonding interactions [110]. On the other hand, polycondensation of polyol and diacid to form poly(1,3-diamino-2-hydroxypropane-co-polyol sebacate)s as a synthetic, biodegradable elastomeric poly(ester amide)s. It exhibits biocompatibility and sustained biodegradation up to 20 months in vivo [98]. Xylitol-based polymers have shown very good biocompatibility compared to the well-known PLGA. Polycondensation of xylitol with sebacic acid produced poly(xylitol-co-sebacate) (PXS) elastomeric materials having tunable mechanical and degradation properties, so these materials are approved by FDA. Enhancing the crosslink density by repeating the flow proportion of the sebacic acid gives a high stiffer elastomer. Water-soluble poly(xylitol-co-citrate)methacrylate) prepolymer synthesized by photopolymerization of hydroxyl groups of poly(xylitol-co-citrate) with vinyl groups using methacrylic anhydride in an aqueous environment have been studied. This is referred to as the poly(xylitol-co-citrate) methacrylate hydrogel. Notably these hydrogels are reported to have no cell attachment; however, at elastomeric stage it exhibits considerable cell adhesion [111]. Further a novel poly(1,8-octanediol-co-citric acid) (POC) have been reported by utilizing nontoxic monomer with crosslinking agents under controlled condensation reaction between 1,8-octanediol and citric acid. Mechanical properties can be modulated by manipulating synthesis conditions such as time, temperature, vacuum, and density. POC is a good elastomeric cell friendly polymer [105].

The term "flexibility" refers to kink resistance (i.e., the maximum angle of bending without kinking). This property is one of the necessary properties of a fabricated microdevice for nerve repair since the nerve ends might not be in the same plane/line and the gap to be bridged might cross a joint. Kink resistance can be measured by bending the tube to 180°, and upon release, flexibility should have the capability to maintain its original shape without forming a crease or kink. High kink resistance results in bending of the device for thoroughly joining such as nerve repair in the hands and wrists. If kink resistance is low, then nerve compression, axonal disturbance, and neuroma formation can result. The flexibility of this chamber has to be maintained in order to deposit cells and expose them to the chambers of a microdevice. Synthetic materials are attractive in this regard due to their desirable flexibility. Matrices and scaffolds closely resemble the ECM; hence, biodegradable synthetic polymers are preferable due to the coinciding properties of the ECM, soft, tough, and elastomeric network that provides flexibility to implants [112]. Flexibility can be altered by employing different kinds of processing techniques, such as complexation with charged biomolecules, temperature, solvent, pH, macromolecules can change the properties of the polymers. This process has allowed polymer-based systems to achieve several applications in the bio-nano arena, ranging from tissue engineering to drug delivery and therapy. Hence, control of polymer characteristics depending on molecular structure is possible over the developed final product.

In addition, CPs modified with charged molecules can have undesirable effects such as being brittle, which would be an obstacle to long-term performance with electrical stimulation through the scaffolds. On the other hand, modification gives flexibility to the overall complex structure. Similar observations have proven that CPs upon modification with non-conducting polymers (NCPs) have improved overall handling and mechanical properties. Microfabrication of polymer-based devices has the advantage of existing simple and comparatively cheap, since a single master can be repeatedly used to develop many devices. Moreover, the inherent mechanical strength of a polymer structure can be used to fabricate a substance that can be controlled by inducing deformations in itself [113].

Implantable microdevice as vehicles for cell delivery

Cell delivery vehicles are promoters that deliver cells to facilitate regeneration. Neural transplantation therapy using neuronal cells has received attention for the effective replacement of nerve cells at sites of injury [114]. Such implantation is influenced by the unique physicochemical properties of biopolymers as well as the biological features of the entrapped cells. Cell microencapsulation and implantation are cell therapy tools for the treatment of a huge range of diseases. A cell-based delivery system can protect cells from the host immune without the demand for immunosuppressive factors or host cells with a polymeric permeable membrane, which allows nutrients and therapeutic agents to pass freely through the membrane. Researchers have developed microencapsulated cell delivery systems for the continuous yield and secretion of bioactive agents from microencapsulated cells [115]. Moreover, biocompatible CPs can be used to envelope neurons and glial cells communicate to the target [116].

Among cell delivery methods, construction of pre-made neural networks on microfabricated devices using tissue engineering technique is an important approach [54, 117]. Pioneering work in the application of these polymeric biomaterials can resolve difficulties associated with cells and fulfill important criteria relating to the control of cellular behavior, cell adhesion, recognition, penetration, and extension. Recently researchers investigated in situ cell delivery and the adhering interactions between cell receptors and the ECM. Cells embedded in the ECM experience enrichment of signaling biomolecules, which basically drive cell adhesion, proliferation, distinction, migration, and aging [118]. The use of such delivery vehicles can be applied to the region of the scaffold that is ready for implantation [119]. It also offers organization to the cells that extends to regeneration [120], and the polymeric component offers micro-environmental cues to the affected cells, with the ultimate goal of achieving optimal neuronal regeneration. Many methods have been developed by researchers for fabrication of biomaterials in order to generate and deliver micro-environmental signals. Advantages of biomaterials include enhanced molecular performance at the cellular level and control of ligand density [121]. These functionalized biomaterials with peptides have significant effects on cellular signaling and function and support cell adhesion and neurite outgrowth during neural regeneration.

Implantable microdevice for vascularisation

There are many requirements when constructing a microdevice, including a level of permeability that can prevent fibrous scar tissue invasion but allow influx of nutrients and oxygen, revascularization to improve the nutrient supply, mechanical strength to maintain a stable support structure (and thus provide a space) for nerve regeneration, immunological inertness with the surrounding tissues, biodegradability to minimize chronic inflammatory reaction or pain by nerve compression and easily regulation of diameter and wall heaviness. Vascularization refers to the organic formation of vascular capillaries from tissues. The matrix should have compatibility with embedded nerve cells forming vessel-like structures, which increases the potential for vascularization of the tissue. CPs and NCPs for nerve repair applications should have neo-vascularization (i.e., establishment of functional micro-vascular networks with red blood cell perfusion) and angiogenesis (i.e., formation of new blood vessels) ability. These two characters encourage by release of angiogenic factors to promote angiogenesis and enhanced tissue survival. Angiogenic factors such as vascular endothelial growth factor (VEGF), acidic fibroblast growth factor (aFGF) and basic fibroblast growth factor (bFGF) was integrated into PLGA and PDLLA-PELA copolymers were proven to stimulate fibroblast proliferation and capillary formation in vivo [122]. Besides Laminin, another ECM protein and collagen-glycosaminoglycan (GAG) matrix proved to help tissue growth and vascularization [123]. Vascularization allows biochemical cues to enhance viability and direct cellular constitution. Moreover, angiogenic factors significantly induce migration, proliferation, and formation of new or large vessels in neuronal cells. Neurotrophin, NGF is an active candidate for targeted therapy as well as a powerful inducer of neovascularization. The fabrication of a microchip-based polymer device is useful for 3D neuronal cell culture engineering applications, and the polymers should be composed of a dense outer surface and a highly porous interior to promote vascularization and angiogenesis [124]. Porous polymer-molded membranes can easily be picked up using soft lithographic methods.

The only criterion that must be followed is the requirement for very low viscosity solution to fill the mold evenly. Microporous patterning can be obtained by micromolding. Alternative methods of fabricating scaffolds with microscale and nanoscale resolution include 3D printing, microsyringe deposition, tissue spin casting, and electro spinning of nanofibers. In 3D printing, polymer particles and salt are printed using a bonding agent, leading to porous formation upon dissolving the salt. Most recently researchers developed, rapid prototyping methods such as soft lithography and microsyringe deposition have been used in originate simple, microfabrication techniques for the building of pattern two dimensional (2D) and 3D biomaterial scaffolds. This can be carried out using two methods; membranous compartments pressure-assisted microsyringe deposition and PDMS-based molding [124]. Further, many biodegradable polymers are used to construct vascularized microfabrication. The porous micropatterned polycaprolactone (PCL) and PLGA scaffolds as an active small-scale diameter blood vessel analog using a novel technique integrating soft lithography, melt molding, and particulate leaching of PLGA micro/nanoparticles [124, 125]. Biocompatible PCL scaffolds increase ease of processing as well as the ability to manipulate physicochemical properties based on the formation of PCL copolymers. Amnion and smooth muscle cells can be aligned on these porous micropatterned scaffolds in order to build artificial capillary networks [126]. Numerous reports of vascularization are present in the literature. The smooth PPy-HA films promote both electrical stimulation and enhance vascularization in vivo due to the presence of HA [127], which prove that larger pores are important to cell growth and for improving signal transfer and vascularization of the microdevice [128]. Further, other micro- or nano-patterned CP surfaces created including 3D honeycomb, porous CP films, microsized circles by the help of electrochemical coating [129, 130]. Neuroprosthetic porous implants made from collagen complex matrix have also been reported from collagen tubes. It is conceived that supplying a suitable matrix to increases the cell movement for nerve repair [88, 131]. Hence, the morphology of the microdevice affects the nutrient supply, which is essential for nerve growth. Many researchers have tried to construct nerve guidance to develop good porous (micro to nano diameter size) to enhance permeability [132–134].

Implantable microdevice material with free radical scavenger

Nanotechnology plays a major role in neuroscience. Particularly, nanomaterials have been used as free radical scavengers for the treatment of ischemic and neurodegenerative diseases [135, 136]. The major concern in neuronal regeneration is cell death due to oxidative stress caused by free radicals at the site of injury. The formed free radicals continue to induce cell damage in nearby cells and affect the regeneration process. These cells cannot be kept in good condition in vitro without antioxidants. Hence, effective antioxidants should be used to overcome this problem when treating stroke symptoms and patients with other neurological disorders. Many free radical-scavenging antioxidants are present in various beverages, fruits, and vegetables as vitamins and polyphenolic compounds and offer protection against several diseases [137, 138].

Apart from natural sources, soluble CPs such as polyaniline (PANI) embedded to lignin, poly(aniline sulphonic acid), poly(3,4-ethylenedioxythiophene) (PEDOT), and polypyrrole (PPy) are known to be good scavengers of free radicals. This property has benefits in tissues affected by oxidative stress and results in lower levels of reactive radical species in biological media [137]. Recently, the term "self-healing" has received special attention in the tissue engineering field. Self-healing just needs the above-mentioned polymers to be coated on the microfabricated device [139]. This simple procedure can increase antioxidant activity with long-term stability. Since microdevice fabrication requires polymers with self-healing properties, a synergy effect can be produced at the same time. The major role of antioxidant CPs is in the development of microdevices for stimulation of nerve regeneration with low cytotoxicity, a low degree of inflammation, and high biocompatibility with free radical scavenging applications [137].

Implantable microdevice with neurotropic factors for promotion of regeneration

The term "growth factor" refers to a naturally obtained substance capable of stimulating cellular development, maturation, and cellular distinction. Growth factors are required for neural tissue regeneration. Neurotrophins are the most commonly used growth factors for neuronal restoration. Neurotrophins are known for making various neuron responses, including neurite growth, and are controlled by NGF immobilized on polymer surfaces. This has shown to be efficient in inducing neurite outgrowth, turning, and sprouting [99]. Available neurotrophins with their application and responses are listed in Table 4. Typically, growth factors act as signaling molecules between cells, and several growth factors play roles in neural growth. Hence, loading these factors into the microdevice would enrich nerve repair. The major drawback of using NGF is the occurrence of severe events due to a high concentration of growth factors at the site of nerve injury. GF can be fixed through controlled delivery of growth factors for

Table 4 Neurotrophins that promote neuronal regeneration

Neurotrophic factors (neurotrophins) for peripheral nerve regeneration				
Name	Source	Neural response	Applications	Ref
Nerve growth factor (NGF)	Guinea pig prostate is a rich source	Increases the number of myelinated axons, thickness of myelin sheaths, improvement and to enhance peripheral nerve regeneration	Development of sympathetic nerve cells. Binding specific cell surface receptors: p75 and tyrosine kinase receptor	[227]
Neurotrophin-3 (NT-3)	Synthesized by r-DNA technology using NTF3 gene code from humans	Supports survival, growth and differentiation	Peripheral nerve repair	[228, 229]
Glial cell line-derived growth factor (GDNF)	Rat B49 glioblastoma cell-line supernatant	Enhanced regeneration of both sensory and motor axons	Peripheral nerve regeneration	[230]
Neurotrophin-4/5(NT-4/5)	Encoded by the NTF4 gene by recombinant human (rh) NT4/5	Promotes survival of motor and sensory neurons, regenerated axons with increased axonal diameter and myelin thickness	Effects on subpopulations of neurons	[231]
Ciliary neurotrophic factor (CNTF)	Neuropoietic cytokines	Elongation axon tips into the distal nerve stump	Peripheral nerve regeneration	[232]
Basic fibroblast growth factor (bFGF)	Human form of the molecule, synthesized in *E. coli* by recombinant DNA technology	Promoters of angiogenesis	Survival and regeneration of neurons	[233]
Acidic fibroblast growth factor (aFGF)	Recombinant DNA technology	Increase the formation of primary sensory and motor neurons and myelinated axons	Peripheral nerve regeneration	[234]
Transforming growth factor (TGF)	Bovine	Anti-TGF-β2 antibody was associated with decreased scarring following injury in the CNS	Blocking Inhibitory biomolecules in the nervous system	[235]
Brain-derived neurotrophic factor (BDNF)	Using N-terminal methionine residue with *E coli* by r-DNA technology	Supports motor neuron survival and promotes axonal growth	Peripheral nerve regeneration	[236]

enhanced neuron regeneration. There are many techniques for estimating the appropriate amount of growth factors to be loaded into the conduits, such as high performance liquid chromatography and in vitro growth factor release assays [140]. There are detailed reviews available on cell cultures used for nerve regeneration using NGF [141, 142].

Further, NGFs play crucial roles in sympathetic and sensory neuron survival, development and maintenance [143]. They have been investigated as an effective therapeutic agent for the treatment of neuro-degenerative diseases and PNS injuries [144]. Other GF also have the ability to promote nerve regeneration, including ciliary neurotrophic factor (CNTF), acidic fibroblast growth factor (aFGF), basic fibroblast growth factor bFGF, and glial cell line-derived growth factor (GDNF). Among all neurotrophins, neurotrophin-3 (NT-3) and brain-derived neurotrophic factor (BDNF) behave significant roles in neurogenesis by encouraging the differentiation of new neurons throughout development, whereas CNTF plays a fundamental function in motor neuron survival and outgrowth [145, 146]. The cells can be seeded into a microchannel for fabrication before securing the conduit to the proximal and distal nerve stumps with sutures. NT-3 is the favored GF for neuronal growth [147]. Microfluidic channels should be ordered to generate dynamic gradients of special factors in order to influence their growth on neural cells. Microfluidics was precoated with biopolymers such as poly(L-Lysine) and laminin in order to study the effect of various concentrations of combined growth factors on neural stem cell growth and distinction [148, 149]. Biological mediators are used to inhibit intracellular signal transduction pathways that result from the binding of GFs and the extracellular domain of a target GF receptor [150–154]. The GF delivery system using polymers provides sustained release of its target over a period of course. Most synthetic polymers used in the delivery of bioactive factors for regeneration are polyglycolic acid (PGA), polylactic acid (PLA), and their derivatives [155, 156]. However, for

neuronal regeneration, biocompatible electrically CPs should be used for neural diseases, in vitro and in vivo examines for nerve regeneration, and other tissue engineering applications [157–168]. Since it is difficult to effectively produce a combination of electrical stimulation from polymer containing biochemical ligands on the surface, appropriate functionalization has to be utilized for surface modifications [169]. Modifications that combine biomolecules and CPs can synergistically accelerate cellular responses. Consequently, this approach represents an alternative to chemical and electrical interfacing with cells. Hence, surface-changed biomaterials are a key factor in nerve repair therapies.

Future perspectives

Research on nerve regeneration dates back to many years. Specifically, the role of polymer components in microfluidic-based nerve regeneration has been investigated, particularly novel, artificial nerve guide conduits and tissue-engineered nerve grafts. The major drawbacks of nerve regenerative devices include surgery to remove the implants, generation of free radicals, immunogenicity, high concentration of NGF, secondary cell damage, and an inflexible structure. This review discussed the applicability of micro chambers to nerve regeneration, ideal fabrication techniques, and the effects of biomaterials and their properties, including biocompatible, degradability, flexibility, conductivity, mechanical strength, vascularization, cell vehicle, non-immunogenic, free radical scavenging activity, and biomolecule delivery. The challenges facing the application of nerve regeneration implants include maintaining a microenvironment that facilitates neurite outgrowth of damaged neurons and achieving appropriate reinnervation by guiding axons to their targets. The surgical implantation of such conduits involves inserting both the proximal and distal nerve stumps into the open ends of the microdevice and then performing fixation with epineural sutures to direct the electrical stimulus generated at the nerve stumps in a single direction without substantial leaking. Hence, bridges between the proximal and distal stumps of the severed nerve end will become indispensable to the discovery and development of innovative nerve regenerative microdevices. Most of the research relevant to this field has provided a better understanding of fabrication and has advanced the synthesis of innovative multifunctional microdevices. Fabrication of biodegradable multifunctional implants can be achieved by producing microdevices using the appropriate multi-characteristic biomaterials.

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