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Cellulose-Based Materials for Neural Tissue Engineering: From Scaffolds to Interfaces - A Review

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Abstract. Cellulose and its derivatives have emerged as versatile natural polymer platforms for neural tissue engineering due to their intrinsic biocompatibility, low cytotoxicity, and tunable biodegradability. Recent advances demonstrate that cellulose-based materials can be engineered to reproduce key structural and physicochemical features of the neural extracellular matrix, including polysaccharide-rich architectures and fibrillar topographies that support neuronal adhesion, alignment, and network formation. Bacterial cellulose, nanocrystalline cellulose, methylcellulose, ethyl cellulose, and their composite systems exhibit hydrogel-forming capability and abundant chemically active functional groups, enabling chemical modification, injectability, and controlled delivery of bioactive agents. Importantly, the incorporation of conductive fillers or chemical modification strategies has enabled electrically active cellulose-based scaffolds with conductivities spanning approximately 7.8×10^{-7} to 0.49 S cm^{-1}, while largely preserving cytocompatibility, positioning these materials as promising candidates for electrically responsive scaffolds and long-term neuronal interfaces. Despite these advances, challenges remain in achieving precise control over mechanical properties, degradation kinetics, and long-term electrical stability under physiological conditions. This review critically examines the progress in cellulose-

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derived materials for neural tissue engineering and neuronal interface fabrication, with an emphasis on material composition, fabrication methodologies, structure-property-function relationships, and current limitations, and outlines future directions for the rational design of multifunctional cellulose-based neural biomaterials.

Keywords: Cellulose-based Biomaterials, Drug Delivery Conductive Scaffolds, Nerve Conduits, Neural Tissue Engineering, Neuronal Interfaces

INTRODUCTION

Damage to the nervous system, encompassing both the central nervous system (CNS) and peripheral nervous system (PNS), is primarily instigated by traumatic incidents such as accidents, strokes, and neurodegenerative disorders. Traumatic brain injuries resulting from external mechanical forces, such as accidents, falls, and sports-related incidents, adversely impact the brain and neurons, leading to temporary or permanent impairment in neuronal function (Blennow *et al.*, 2016). Strokes, characterized by the disruption of blood supply to the brain, can result from abrupt blockages in brain arteries (Ischemic Stroke) or from blood leakage into the brain due to ruptured or weakened blood vessels (Hemorrhagic Stroke) (Sacco *et al.,* 2013). Such injuries contribute to the demise of neurons and glial cells, disrupting communication between cells and causing a distraction in neuronal circuit activity, ultimately leading to paralysis or brain death. Brain injuries trigger the excessive segregation and accumulation of neurotransmitters, particularly glutamate, which overstimulates neurons, ultimately leading to cell death (Giza and Hovda, 2001). In addition, progressive neurodegenerative diseases like amyotrophic lateral sclerosis (ALS), Alzheimer's disease, Parkinson's disease, Huntington's disease, and brain tumours stem from irregular or deactivated programmed cell death (PCD) of neurons (Gorman, 2008; Moujalled *et al*., 2021). The gradual loss of specific neuronal subsets underlies neurodegenerative diseases. The PNS is particularly susceptible to traumatic injuries resulting from accidents, including penetrating injuries, cuts, compression, thermal injuries, and stretch injuries. Traumatic injuries to motor, sensory, and autonomic nerves within the PNS may result in sensory deficits, loss of motor function, or irregular bodily functions, including impaired blood circulation and urination (Menorca *et al*., 2013). Both CNS and PNS impairments yield severe consequences for individuals, encompassing paralysis, loss of sensation, neuropathic pain, compromised organ function, chronic diseases, and, in extreme cases, death (Adcock *et al*., 2021; Birbeck *et al*., 2015).

Various studies have extensively investigated the repair and regeneration of impaired neurons and neuronal activities (Li, 2022; Nagappan *et al*., 2020; Zamproni *et al*., 2021). Challenges arising from the intrinsic lack of regenerative motivation in neurons and the complex mechanical functions of nerves have hindered the complete recovery of nerves. Despite efforts using techniques such as neuroplasticity and cognitive therapies, achieving comprehensive nerve regeneration remains a formidable task (Nagappan *et al*., 2020; Phillips *et al*., 2011). Surgical management, including interventions for brain bleeding during stroke-related injuries, yields uncertain

outcomes (Thabet *et al*., 2017). Modern tissue engineering and regenerative nanomedicine technologies are emerging as potential alternatives for repairing damaged neurons at the cellular level. Stem cell therapies and therapeutic scaffold technologies significantly enhance nerve tissue restoration and neuron regeneration. Generally, in clinical methods, peripheral nervous system (PNS) nerve injuries are treated by tissue transplantation and nerve grafting. However, persistent challenges with these methods include donor-site limitations, material shortages, susceptibility to infection, and immune responses (Geuna *et al*., 2012; Kornfeld *et al*., 2019; Moore *et al*., 2015; Ydens *et al*., 2012). To address these challenges, the use of tissue-engineered scaffolds and conduits has emerged as a promising solution for nerve repair surgeries and grafting procedures. In nerve implantation, scaffolds, conduits, or conduit-supported allografts successfully repair nerve tissue by mimicking its physicochemical and topographical features, thereby facilitating cell proliferation, migration, and integration (Du *et al*., 2018; Koffler *et al*., 2019; Subramanian *et al*., 2009). These engineering scaffolds also serve as delivery vehicles for cells (such as Schwann and glial cells), drugs, and neurotrophic factors, providing crucial support for cell growth and recovery (Calori *et al*., 2020; Garg *et al*., 2012). In tissue grafting, the transplantation of patient-specific cells is considered a gold standard procedure to prevent immunological responses, highlighting the pivotal role of suitable scaffold materials in enhancing the quality of patient cell cultures for successful nerve grafting (Szynkaruk *et al*., 2013).

Tissue engineering scaffolds play a crucial role in regenerative medical applications, necessitating attributes such as biocompatibility, low toxicity, mechanical strength, mimicking physicochemical conditions, topographical resemblance to the extracellular matrix (ECM), degradability, and ease of sterilization (Chan and Leong, 2008). Numerous natural and synthetic substrates have been proposed for nerve and tissue regeneration, each with its own advantages and disadvantages. Considering nerves' nature as communication devices, electrically conductive substrates are preferred for neuron culture. Synthetic polymers approved by the United States Food and Drug Administration (FDA), like polycaprolactone (PCL), polylysine, Poly Lactic-co-glycolic acid (PLGA), and polyhydroxyalkanoates (PHAs), exhibit lower toxicity and high biocompatibility but face limitations in physicochemical properties, such as wettability and degradability (BaoLin and Ma, 2014). Conductive synthetic polymers like polyaniline (PANI), poly(3,4-ethylenedioxythiophene) (PEDOT), and polypyrrole (PPy) show enhanced performance in nerve tissue restoration. Nevertheless, challenges such as reduced mechanical properties, gradual degradation, and the toxicity of degraded particles adversely affect tissue restoration (Guo and Ma, 2018; Qu *et al*., 2016; Saberi *et al*., 2019; Zhang *et al*., 2019). On the natural side, ECM proteins (collagen, laminin, fibronectin) and natural polymers (silk, chitosan, alginate, elastin, hyaluronic acid) have been explored for nerve tissue engineering (Amini *et al*., 2021; Boni *et al*., 2018; Stratton *et al*., 2016). However, natural materials often lack mechanical strength, pose challenges in clinical use due to rapid metabolism in the human body, and can elicit adverse immunological reactions (Bhattarai *et al*., 2018; Dong and Lv, 2016; Luttikhuizen *et al*., 2006). In this context, cellulose and its

derivatives emerge as promising candidates for tissue engineering, drug delivery, wound healing, controlled-release drug delivery, and biological fluid purification.

Cellulose, a natural and biodegradable biopolymer, finds broad biomedical applications. Its derivatives and composites, including ethyl cellulose, bacterial cellulose, and nanocellulose, are used in wound dressings, tissue engineering, drug delivery, biosensors, cosmetics, and synthetic tissues, contributing to advances in tissue regeneration and recovery as shown in Figure 1 (Fu *et al*., 2019; Liu *et al*., 2020; Pranolo et *al*., 2023; Seddiqi *et al*., 2021). The fibril structures present in most cellulosic materials closely resemble those of collagen, mirroring the fibril structure within the tissue environment. This nanofiber network morphology enhances tissue-mimicking characteristics. Moreover, the surface chemistry of cellulosic components enables the conjugation and incorporation of cell-adhesive proteins, growth factors, and drugs, thereby enhancing cell adhesion and controlling the release of biomolecules (Ciolacu *et al*., 2020; Dutta *et al*., 2019; Mu *et al*., 2018). The synthesis and modification of cellulose materials entail minimal protocols and molecular arrangements (Hidayatulloh *et al*., 2025; Liyanage *et al*., 2021). The crystallinity of cellulose remains resilient in extreme thermal or chemical conditions during manufacturing, surface modification, and sterilization. The remarkable hydrogel properties, along with their higher mechanical strength and flexibility, make cellulose-based materials well-suited for long-term medical implantation in both soft and hard tissue substitutes (Modulevsky *et al*., 2014). Owing to its high biocompatibility, low toxicity, and biodegradability, cellulose, particularly after suitable modification, is an attractive material for tissue engineering scaffolds. For instance, a directly plant-derived cellulose surface has also been proven to be highly biocompatible for nerve tissue applications (Couvrette *et al*., 2023). In this work, cellulose scaffolds were prepared by decellularizing Asparagus officinalis stalks, resulting in structures with aligned vascular bundles and an interconnected pore network that possess mechanical properties suitable for neural tissue. Rat hippocampal NSCs attached as single cells and neurospheres, migrated into scaffold channels, and proliferated over 3–14 days with high viability. At the same time, increased neuronal (ßIII-tubulin) and astrocytic (GFAP) marker expression confirmed the presence of supportive physical and microenvironmental cues for neural stem cell growth and differentiation. In this context, cellulosic materials have emerged as promising candidates for neural tissue scaffold applications, meeting these requirements effectively.

Cellulose can be rendered electrically conductive by chemical surface modification, doping, or crosslinking with conductive materials. Its conductive derivatives and composite nanofibers, membranes, and thin films find widespread applications in various energy devices and electronic components, including solar cells, supercapacitors, fuel cells, conductive soft skin, and electrodes (Hsu and Zhong, 2019; Kim *et al*., 2020; Palanisamy *et al*., 2017; Selyanchyn *et al*., 2020). The distinctive conductive properties of cellulose make it an ideal scaffold and neural interface (NI) for assisting nerve tissue stimulation or recording electrical signals, which are crucial for rehabilitating impaired neurons or restoring functional neuronal activity in target areas (Hatsopoulos and Donoghue, 2009). Similar to neural scaffolds,

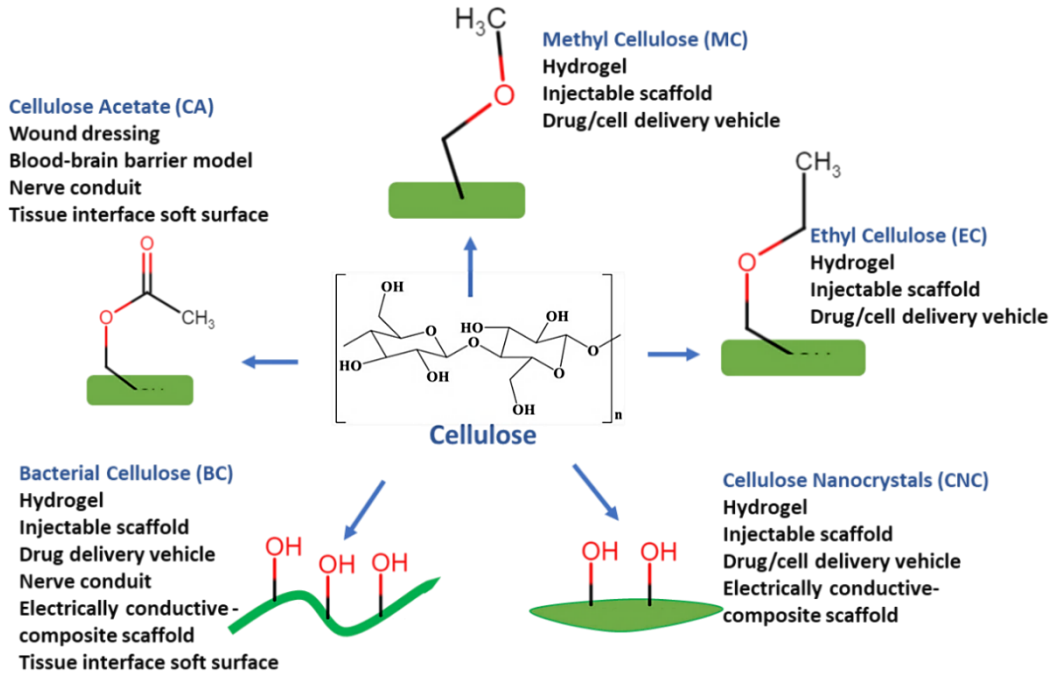

Fig. 1: Cellulose derivatives are used for various neural tissue engineering applications

optimal implantable NI surfaces must exhibit biocompatibility, low toxicity, electrical conductivity, selective performance for high signal-to-noise ratios, durability, and high mechanical strength to gain clinical acceptance (Fattahi *et al.*, 2014). While inorganic materials and conductive polymers, such as gold- and platinum-coated silicon surfaces, are also used for NI fabrication, they often fail to adapt to tissue environments, leading to foreign body reactions, scar formation, and cell death (Redolfi Riva and Micera, 2021). Contrarily, cellulose materials align well with the requirements for ideal NIs, considering their physicochemical and mechanical properties.

In this context, cellulose-based materials are continuously being improved for neural engineering applications due to the advantages of cellulose and its derivatives. Therefore, this review summarizes the recent advances in developing cellulose-based materials in neural tissue engineering scaffolds, neural drug delivery matrices, and prosthetic surface applications. Furthermore, this review provides a comprehensive understanding of the processing methods, biocompatibility, advantages, and challenges associated with cellulose-based materials for nerve tissue engineering applications.

CELLULOSE-BASED SCAFFOLDS

Methylcellulose Scaffolds

Methylcellulose (MC) is a simple alkyl ether widely used as a thickening agent and food additive, recognized for its excellent emulsifying properties, making it a viable choice for drug delivery systems (Vázquez-Rivas *et al.*, 2025). Notably, MC can be dissolved in water and various organic solvents. The water absorption and hydrogel-forming ability of MC are determined by the degree of substitution of methoxy groups. Additionally, MC can be gelled as a hydrogel at room temperature. This characteristic enables the minimally invasive injection of the MC scaffold into voided areas within the

nervous system. Therefore, the MC hydrogel scaffolds can fill irregular voids in injured areas, minimizing the space between host tissues and the scaffold. Furthermore, this hydrogel-based scaffold facilitates the three-dimensional regeneration of nerve tissues. The qualities of MC hydrogels, including high water retention, a porous structure, and adaptable sol-gel conditions, facilitate the influx of cell metabolites and the efficient disposal of cell waste via the hydrogel's pores (Mantha *et al.*, 2019). Additionally, MC-based hydrogels show promising potential for encapsulating drugs, neurotrophic agents, and growth factors, offering features conducive to the construction of controlled-release, intelligent scaffolds (Eskens *et al.*, 2020; Rasoulzadeh and Namazi, 2017; Vázquez-Rivas *et al.*, 2025).

The toxicity of Methylcellulose (MC), used in an injectable hydrogel-based scaffold for nerve tissue regeneration following traumatic brain injury (TBI), has been studied. In vitro assays on primary rat cortical astrocytes and neurons showed that MC gels (2–5 wt%) exhibited no significant cytotoxicity. Viability remained higher than 80% in cultures exposed to 4–5 wt% methylcellulose for 7 days. However, at an 8 wt% concentration, a slight reduction in neuronal viability was observed (Tate, 2001). In vitro primary rat cortical astrocytes and neuron cell viability analyses on 2-5 wt% MC gel showed no significant cytotoxic effects, though a higher concentration (8 wt%) slightly reduced neuron viability. This adverse effect may be ascribed to the higher levels of MC degradation by-products and changes in the pH environment. An in vivo study, in which 2 wt% MC was injected into one-week-old cortical impact injuries in adult rats, decreased scar thickness without exacerbating injury size. Subsequent investigations confirmed MC's non-toxicity for nerve tissue engineering applications, highlighting its efficacy in preventing scar formation during nerve tissue regeneration when used in MC-based gel scaffolds (Tate, 2001). A similar study explored the application of an MC matrix for spinal cord injury recovery in adult rats by injecting 2 wt% MC into poly(2-hydroxyethyl methacrylate-co-methyl methacrylate) (pHEMA-MMA) nerve conduit channels (Tsai *et al.*, 2006). Comparative analyses demonstrated that MC exhibited highly dense and rostral-caudal-oriented nerve fiber regeneration, surpassing the less oriented and denser nerve fibers in collagen and laminin matrices. Notably, MC allowed axon regeneration from reticular, vestibular, and red nucleus neurons, while collagen and laminin facilitated regeneration only from vestibular and reticular neurons (Tsai *et al.*, 2006). Both studies underscore the versatility and biocompatibility of MC, offering valuable insights into its potential for therapeutic applications in nerve regeneration and tissue engineering.

MC demonstrates thermo-responsive and thermos-reversible gelling properties. At low temperatures, MC has low viscosity, whereas at high temperatures it forms a highly viscous solution as MC molecules eliminate water and interact with one to another. Combining MC with low-temperature hydrogel polymers, such as agarose, hyaluronic acid, and gelatin, creates a hydrogel with an optimal gelation temperature that matches physiological conditions (Martin *et al.*, 2008). For example, a mixture of 7 wt% MC and 1.5 wt% agarose yields a gelling temperature of 37 °C (physiological temperature) within approximately 15 minutes. In vitro analyses indicated that all tested MC compositions

had no adverse effect on neuronal cell viability. Additionally, the composition dissolves after 28 days, outlasting the porous holes in the blood-brain barrier, which typically persist for only about 14 days in the injured brain area. The liquid state of the composition at lower temperatures facilitates injection into target areas, allowing for adequate coverage of injured cavities. Additionally, combining MC with hyaluronic acid (HA) yields an efficient delivery system for tissue engineering (Ho *et al.,* 2019). The temperature-responsive gelling property of cellulose, coupled with HA's long polymer chain, makes the HA-MC composite an ideal injectable, high-viscosity matrix at physiological temperatures. Additionally, the performance of the HA-MC (HAMC) injectable gel for spinal cord injury recovery has been extensively studied in previous research (Gupta *et al.*, 2006). 2 wt% HA/7 wt% MC blend (HAMC) and hydrazide-modified HAMC (acet-HAMC) revealed their suitability for injection in the intrathecal space, with HAMC gelling within 2 minutes at 18 °C and acet-HAMC at 31 °C within 20 minutes. Both HAMC and acet-HAMC exhibited notable degradation rates within 14 days. In vitro, acet-HAMC showed lower degradation in CSF, possibly due to the slow hydrolysis of its hydrophobic acetyl groups. Cell adhesion on HAMC gels was negligible in vitro (using 3T3-NIH cells) and in vivo, and studies in clip compression spinal cord-injured rats showed no significant differences between injected and non-injected rats. Generally, in fluid-based matrices, a polymer composition that does not adhere to fibroblasts provides an advantage over non-cell adhesion in vivo. HAMC compositions did not induce adverse effects such as scar formation, arachnoiditis, or syringomyelia, and fully degraded in the intrathecal space after 28 days. The study concluded that HAMC is a suitable material for an injectable scaffold, solidifying at body temperature, effectively covering the cavity, promoting cell attachment, and reducing scar formation (Gupta *et al.,* 2006).

Cellulose Acetate Scaffolds

Cellulose acetate (CA) is a versatile acetate ether of cellulose with applications spanning nutraceutical delivery, osmotic drug delivery, rigid tissue scaffolds, biosensing matrices, biofiltration, antimicrobial films, and wound dressing (Farahani *etal.*, 2020; Kamel and A. Khattab, 2020; Rezaei *et al*., 2015; Tsiapla *et al*., 2018). Notably, in wound-dressing applications, CA stands out for its hydrophilic nature and high moisture absorption. Despite its advantages, limited degradability in the human body, the lack of ionic functional groups that facilitate integrin-mediated cell binding, and reduced antibacterial properties limit its use in tissue-engineering scaffold applications. Nonetheless, the linear polysaccharide molecular arrangement of CA mimics the molecular structure of the ECM glycosaminoglycan component, playing a crucial role in the cell signalling process (Farahani *et al*., 2020). Moreover, CA can be electrospun into an ECM-like nanofibril structure, prompting research into chemically modifying CA or crosslinking it with functional polymers and proteins to enhance tissue -engineering scaffold applications. The potential of cellulose acetate (CA) scaffolds for nerve tissue engineering was investigated by comparing the impact of CA electrospun nanofiber substrates on the proliferation and differentiation of PC12 cells and human neural stem cells (NSCs) with polyether sulfone (PES) and chitosan (CS) substrates (Du *et al*., 2014). The substrates exhibited no significant cytotoxicity in PC12 cells, with a

2.5-fold increase in cell population. PC12 cells on CA scaffolds exhibited a bipolar structure with shorter neurite growth than in other groups, attributed to the lack of cell-binding sites and the low degradation rate of CA, which hindered cell penetration. However, both CA and CS polysaccharide scaffolds showed a slightly higher number of neurites per cell, and CA acetate exhibited slightly more neurites than CS. In hNSC culture, CS and CA promoted three times higher cell proliferation than PES, and CA scaffolds demonstrated elevated gene expression of β-tubulin, a marker of early neuronal differentiation. In contrast, CS expressed several genes, including neuronal stem cell markers, early neuronal markers, and mature neuronal markers. While CA outperformed PES in both PC12 and hNSC cultures, it lagged behind CS in cell proliferation and differentiation due to its lower degradability and lack of chemically active components.

Unmodified cellulose CA typically exhibits insolubility in water, challenges in degradation within the human body, and biological inertness, rendering it less favorable for applications involving soft tissue scaffolds. However, these characteristics make CA well-suited for mimicking biological barriers, such as the blood-brain barrier (BBB), blood-brain-tumour barrier (BBTB), and blood vessels. Additionally, the optical transparency of CA enables the construction of transparent structures, making CA-based cell substrates particularly suitable for minimally invasive optical/confocal microscopy applications (Orelma *et al*., 2020; Yang *et al*., 2013). For instance, a study explored the use of cellulose acetate (CA) to construct a biomimetic, highly porous, and transparent blood-brain barrier model that could be analyzed using optical microscopy (Marino *et al.*, 2021). The model aimed to replicate the blood-brain barrier's characteristics, providing a platform for studying its properties and interactions in a controlled, transparent environment. Using vapor-induced phase separation (VIPS) and electrospinning, this study demonstrated that nearly 10 wt% CA solutions yielded a scaffold with high porosity, transparency, and desirable mechanical properties. Electrospinning a 15 wt% CA solution produced a bead-free nanofiber-based scaffold with sufficient transparency. The resulting artificial multicellular BBB model, created by seeding human cerebral microvascular endothelial cells (hCMEC/D3) and astrocytes on the upper and lower surfaces of the membrane, respectively, showed endothelial cell coverage on both the VIPS and the electrospun CA scaffold surfaces. However, VIPS CA surfaces exhibited non-uniform cell density, whereas electrospun CA enabled cell migration within the scaffold, attributed to the nanofiber 3D structure and larger void size (Figure 2). The transendothelial electrical resistance (TEER) values of the VIPS CA membrane were notably higher than those of the electrospun CA membrane before and after cell culture, indicating enhanced cellular barrier tightness in the VIPS CA membrane (Marino *et al*., 2021). The study concluded that CA electrospun nanofibers simulate the blood-brain-tumour barrier by allowing the passage of larger molecules. In contrast, a CA acetate membrane with a smaller pore size can be used for modelling the BBB and for double-cell seeding applications.

Bacterial Cellulose Scaffolds

Bacterial cellulose (BC) is a highly crystalline (approximately 80% degree of crystallinity) and three-dimensional network of cellulose nanofibers produced by bacteria,

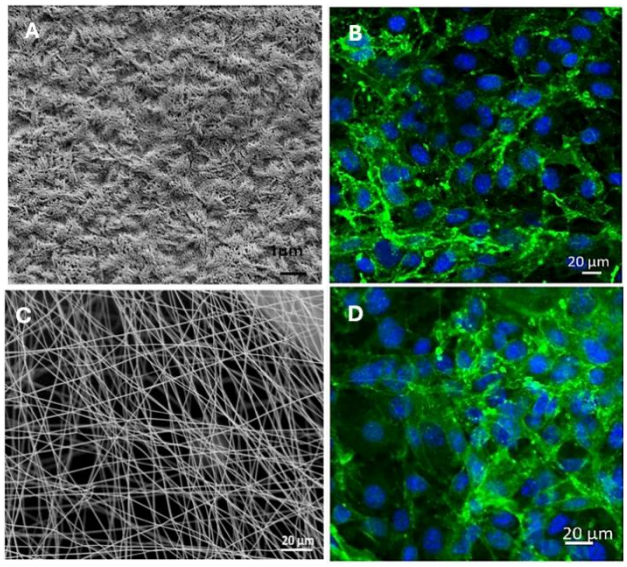

Fig. 2: SEM image of (A). Vapor-induced phase separation CA surface and (B) Confocal laser scanning microscopy imaging of hCMEC/D3 endothelial cells on VIPS surface (C) Electrospun CA scaffold surfaces and, (D) Confocal laser scanning microscopy imaging of hCMEC/D3 endothelial cells on Electrospun CA scaffold surfaces (Marino *et al.*, 2021)

including the genera *Acetobacter, Sarcina, and Agrobacterium* (Raghavendran *et al.*, 2020). Due to its nanofibril structure, featuring a high abundance of reducing ends, along with attributes such as high biocompatibility, low toxicity, and biodegradability, BC is utilized in various applications, particularly in tissue engineering scaffolding, wound healing, drug delivery, and regenerative medicine (Liu *et al.*, 2020; Svensson *et al.*, 2005; Zheng *et al.*, 2020). A study examined patterned BC scaffolds for the culture of neural stem cells. Using cellulose-synthesizing bacteria, *Acetobacter xylinum* was cultured on PDMS micropatterns, enabling cellulose nanofibers to assemble around the microfeatures and generate a multilevel, microstructured BC fleece with well-defined patterns. The resulting patterned BC scaffold effectively guided neural stem cells, neurites, and glial cells along its textured surface, enhancing cell attachment and promoting lineage-specific differentiation (Geisel *et al.*, 2016). Cultures of differentiated neurospheres on BC exhibited higher cell density and neuronal differentiation than on either ECM-coated or noncoated glass coverslips. Neuronal coverage was 0.47% on BC – coated glass, compared to 0.18% on ECM-coated glass and 0.01% on noncoated glass. These results demonstrate that BC, with its nanoscale fibers arranged in a collagen-like pattern, promotes neuronal growth and differentiation more effectively than conventional ECM coatings. Another study examined BC-based conduits and their impact on facial nerve regeneration in Sprague Dawley rats (Binnetoglu *et al.*, 2020). Figure 3 illustrates that the study evaluated nerve regeneration in four experimental models by artificially cutting and transecting the facial nerves in Sprague-Dawley rats using an electrospun BC tube. In this study, BC conduit alone and in combination with primary suturing yielded the highest number of myelinated neurons compared with primary suturing or spontaneous repair models (Figure 3).

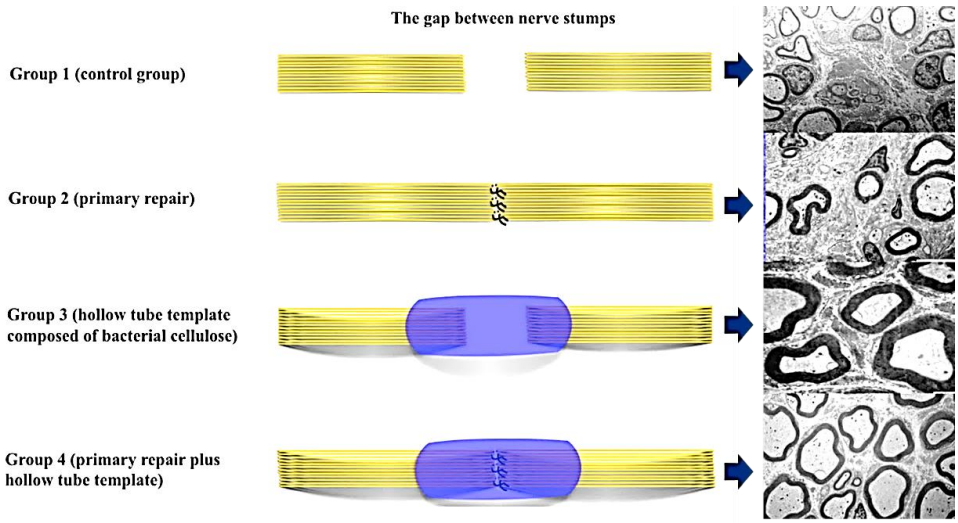

Fig 3. Nerve anastomosis technique using bacterial cellulose conduits (left) and the electron microscope myelination profile of nerves in each group (right) (Binnetoglu *et al.*, 2020)

However, histopathological examination revealed irregular myelinatio n and fibrosis in the BC conduit-only model, while the BC scaffold with a primary sutured nerve exhibited regular myelination without fibrosis. This study unequivocally demonstrated that the BC scaffold, combined with primary suturing, yields superior outcomes in nerve regeneration (Binnetoglu *et al.*, 2020).

BC is a favorable material for chemical and physical modifications to enhance bioactivities such as bioconjugations, drug encapsulation, cell adhesion, and biodegradability (Gorgieva and Trček, 2019). The nanofibrillated form of BC, characterized by a greater number of reducing ends, provides an excellent substrate for extensive chemical modification. Unlike typical cellulosic materials, which are challenging for human body-produced enzymes to break down due to stable β-(1,4) glucose linkages, BC's high biodegradability makes it an ideal candidate for tissue engineering scaffolds (Echeverria Molina *et al.*, 2021). Notably, the biodegradability of BC has been further improved through chemical modification methods, including oxidation of glucose monomers using metaperiodate, hypochlorite, and nitrogen oxide (Homma *et al.*, 2013; Peng *et al.*, 2012; Singh *et al.*, 1982). For instance, a study demonstrated that oxidation significantly enhanced the biodegradability of BC nerve conduits, thereby improving their effectiveness in peripheral nerve repair (Hou *et al.*, 2018). The study involved the oxidation of BC using sodium periodate ($NaIO_4$), transforming the hydroxyl groups of the glucose monomer glucopyranoside rings into dialdehyde groups. This process disrupted the order packing of glucopyranose rings, making them more susceptible to enzymatic degradation. In vitro hydrolytic degradability (in phosphate-buffered saline) analysis revealed that oxidized BC exhibited a 15- to 40-fold higher degradation rate than unmodified BC, with the rate increasing proportionally to the oxidation percentage. However, the oxidized BC exhibited higher cytotoxicity with increasing oxidation rates, resulting in greater lethality of Schwann cells (SCs) in vitro. In

contrast, untreated BC and BC with a low degree of oxidation promoted SC proliferation (1.7-fold in 5 days), while higher degrees of oxidation in BC correlated with increased apoptotic SCs and dead cells. Furthermore, untreated BC and BC with a low degree of oxidation showed minimal or acceptable hemolysis, whereas highly oxidized BC induced pronounced hemolysis. In summary, the biocompatibility, cytotoxicity, and hemolytic behaviour of BC were found to be oxidation-dependent, with the toxicity level of the aldehyde group and cell response to degraded particles of oxidized cellulose playing pivotal roles in these outcomes (Hou *et al*., 2018).

Cellulose, inherently containing carboxylic and hydroxyl groups, which readily bind with positively charged cell adhesive proteins, facilitating integrin-mediated cell attachment to the scaffold (Hickey and Pelling, 2019; Levy and Shoseyov, 2002). However, these surface charges alone may be insufficient to retain cell-adhesive proteins via electrostatic interactions, necessitating surface modifications or ligand coatings to enhance cell attachment. The study compared two BC surface modifications, CDAP-mediated collagen coating and TMAHP treatment followed by collagen I coating, using SH-SY5Y neuroblastoma cells to evaluate their effects on neural cell behaviour (Innala *et al*., 2014). CDAP treatment covalently attaches collagen to the BC surface, providing firm adhesion sites while still allowing cells to migrate and form clusters. Differentiated neuron cells on CDAP-collagen BC exhibited a more outstretched morphology, indicative of enhanced integrin-mediated spreading. In contrast, TMAHP treatment introduces positive surface charges that facilitate protein adsorption, including collagen, mainly through electrostatic interactions, although some collagen may penetrate the scaffold rather than remain surface-bound. While TMAHP initially supported higher cell attachment, both surfaces ultimately maintained similar cell viability over time, suggesting that the intrinsic BC scaffold itself provides a supportive environment for prolonged attachment and proliferation. Overall, CDAP-collagen provides stronger surface-bound cues for neuron cell morphology and migration, whereas TMAHP-collagen primarily enhances initial protein adsorption and early cell adhesion. In another study, BC nanofibrils were modified with TMAHP, then coated with collagen I, laminin, or fibronectin, and seeded with PC12 cells (Jonsson *et al.*, 2015). The TMAHP collagen combination produced a strong initial response, resulting in approximately 3-fold higher cell attachment than collagen-coated BC without TMAHP, even though overall proliferation remained similar across all scaffold groups. Despite the improved adhesion, all protein-coated scaffolds, including those treated with TMAHP, showed limited neuronal integration, likely because the protein layer, particularly collagen, undergoes minimal proteolytic degradation and restricts deeper neurite penetration into the dense non-remodelable fibrillar network. Nevertheless, neurites were able to extend across the collagen TMAHP BC surface, connect with neighbouring cell ensembles, and form interconnected networks, indicating that although surface bioactivity is enhanced, scaffold architecture and degradability remain key limitations for achieving full three-dimensional neuronal incorporation (Jonsson *et al*., 2015).

Similar to MC composite hydrogels, BC composite hydrogels emerge as a preferred material for generating drug or cell carrier matrices and injectable scaffolds. Compared

to MC, BC composite hydrogels exhibit higher biocompatibility, and the nanofibril structure of BC facilitates effective crosslinking with other polymer gels, resulting in robust hydrogels. Collagen, hyaluronic acid (HA), gelatin (Gel), and polyvinyl alcohol (PVA), when incorporated or cross-linked with bacterial cellulose (BC), have been widely employed to generate hydrogels tailored for tissue engineering applications. For example, in situ–modified BC/HA and BC/HA/Gel hydrogels were successfully fabricated to form stable three-dimensional nanofibrous scaffolds, where HA contributed to the formation of surface micro-aggregates, and Gel became entrapped within the BC network, creating a matrix conducive to nerve tissue regeneration (Unal *et al*., 2021). By introducing HA and Gel directly during BC fermentation, these composites provide topographical cues reminiscent of the tumour microenvironment. Human glioblastoma U251 cells cultured on these scaffolds exhibited enhanced proliferation relative to pure BC, with increases of approximately 10–18% on BC/HA 0.5/Gel 0.5, 15–38% on BC/HA 0.5/Gel 1.0, and more variable responses on BC/HA 0.5/Gel 2.0 over 1–7 days. Higher concentrations of HA and Gel also induced pronounced morphological changes, including the extension of pseudopodia and a higher proportion of cells adopting spindle-like mesenchymal shapes. The enhanced hydrophilicity of Gel–BC scaffolds is thought to facilitate actin-driven protrusions such as invadopodia. Notably, reducing the Gel content (e.g., from 2% to 0.5–1% w/v) can mitigate cytoskeletal irregularities, promoting more controlled cell spreading (Unal *et al.*, 2021).

Table 1 outlines the progress in cellulose materials for nerve tissue scaffold applications. Methylcellulose and its composites are identified as suitable for injectable scaffolds due to their thermoresponsive gelation temperatures. Cellulose derivatives, such as cellulose acetate and regenerative cellulose, exhibit long-term degradability and high biocompatibility, making them ideal for blood-brain barrier (BBB) and blood-brain tumour barrier (BBTB) models. Bacterial cellulose (BC) and its composites are highlighted for their excellent performance in forming 3D neuronal networks, attributed to their remarkable biocompatibility, biodegradability, and hydrogel properties. BC scaffolds can be easily processed using methods such as electrospinning or lyophilization to create intricate 3D scaffolds.

CELLULOSE MATRIX-BASED DELIVERY VEHICLE

Effective delivery of neurotrophic factors and drugs to injured nerves is pivotal for successful tissue recovery. Consequently, the selection of suitable substrates or vehicles for delivering chemical cues to target areas significantly influences the dynamics of drug delivery and nerve tissue recovery (Jonsson *et al*., 2015; Madhusudanan *et al.*, 2020; Pooshidani *et al*., 2021). Mechanisms employed by drug delivery vehicles, such as hydrogels, nanofibers, and highly porous

nanostructures, play a crucial role in controlling drug and biomolecule diffusion and sustaining their release at the target site. Specifically, drug-carrying vehicles within nerve conduits have demonstrated enhanced peripheral nerve recovery and efficient promotion of nerve regeneration (Langert and Brey, 2018; Manoukian et al., 2021). ECM proteins, including collagen (Collagen Matrix, Inc.) and laminin, along with hydrogel polymers such as hyaluronic acid, gelatin, and

Table 1. Advances in cellulose-based scaffolds for nerve tissue engineering

Type of cellulose	Composite polymer	Biocompatibility in vivo	Biocompatibility in vitro	Advantage	Disadvantage	Application	Reference
Methyl cellulose	-	TBI rat cortical	E18 rat embryo primary neurons and postnatal day-1 rat pups (P1) astrocyte	The scar thickness of the damage decreased	A higher concentration of MC may induce toxicity	Injectable hydrogel-based scaffold for traumatic brain injury	(Tate, 2001)
Methyl cellulose	Poly (2-hydroxyethyl methacrylate-co-methyl methacrylate) (pHEMA-MMA)	Female Sprague Dawley rats	-	MC could guide the axonal regeneration within the spinal cord and be compatible with different neurons.	-	Supraspinal and local axonal regeneration	(Tsai *et al.*, 2006)
Methyl cellulose	Agarose (1.5 wt%)	-	Dorsal root ganglion (DRG) neurons	Gelation occurs at a body temperature of 37°C	-	Injected hydrogel scaffold	(Martin *et al.*, 2008)
Methyl cellulose	Hyaluronic acid (HA) (2 wt%)	Sprague Dawley rat intrathecal space	3T3-NIH cells	High degradability rate, high cell attachment, thick dura released and high biocompatibility	-	An injected hydrogel scaffold for spinal cord injury	(Gupta *et al.*, 2006)
Cellulose acetate	-	-	PC12 cells and human neural stem cells (hNSC)	High proliferation rate, a high number of neurite formations per cell	Lack of cell binding, low degradability	Nanofiber scaffold	(Du *et al.*, 2014)
Cellulose acetate	-	-	Human cerebral microvascular endothelial hCMEC/D3 cells and astrocytes	Low degradability rate, high biocompatibility, optically transparent and easily processed by electrospinning and Vapour-induced phase separation (VIPS) methods.	-	Blood-brain barrier (BBB), model and blood-brain-tumour barrier (BBTB).	(Marino *et al.*, 2021)
Bacterial cellulose	-	-	Neural stem cells and neurospheres derived from the postnatal subventricular zone	Increasing cell attachment, improving cell differentiation, high density of differentiated neurospheres and neurons, and high biocompatibility	-	Patterned Scaffold	(Geisel *et al.*, 2016)
Bacterial cellulose	-	Artificially cut transacted facial nerve of Sprague Dawley rats	-	The highest number of myelinated neurons is formed	Without the primary suturing model, irregular myelination and fibrosis occurred	Nerve conduit for facial nerve regeneration	(Binnetoglu *et al.*, 2020)
Oxidized Bacterial cellulose	-	-	Schwann cells (SCs)	High in vitro degradability and high cell attachment	High oxidized BC caused a higher number of apoptotic SCs, dead cells and a strong hemolysis effect	Biodegradable scaffold	(Hou *et al.*, 2018)
Bacterial cellulose	1. Trimethyl ammonium beta-hydroxypropyl	-	SH-SY5Y blastoma cells	Negative surface charge-coated BC results in high cell adhesion and	Positive surface charge-coated BC aggregates the cells	Scaffold for 3D cell culture	(Innala *et al.*, 2014)

Type of cellulose	Composite polymer	Biocompatibility in vivo	Biocompatibility in vitro	Advantage	Disadvantage	Application	Reference
	(TMAHP)/ Collagen coating (positive surface charge) and 2. Cyano-4-dimethylamino pyridinium (CDAP)/collagen (negative surface charge) coating			better morphology			
Bacterial cellulose	1. Hyaluronic acid and gelatine	-	Human glioblastoma cell line (U251)	Mimicking the topographic features of the tumour microenvironment, high cell adhesion results in a spread shape with a pseudopodia-like extended structure	Irregularity in the cytoskeletal	Three-dimensional network hydrogel matrix scaffold	(Unal *et al.*, 2021)

polyvinyl alcohol (PVA), have been extensively investigated as vehicles, yielding better outcomes compared to empty conduit tubes or tubes with physiological saline (Chang *et al.*, 2020; Huang *et al.*, 2021; Ko *et al.*, 2017; Li *et al.*, 1992; Porzionato *et al.*, 2019). However, these ECM-derived proteins have drawbacks, including the risk of triggering immune responses, low mechanical strength, and complex formulation and sterilization processes (Ye *et al.*, 2010). Conversely, cellulose materials exhibit substantial potential as drug delivery vehicles, given their resistance to ready metabolism in humans and minimal propensity to cause pathological adverse reactions. Additionally, cellulose can be easily processed, sterilized, and modified with biological molecules and drugs in various physiological buffers.

In an early study, the performance of methylcellulose (MC) as a biomolecule delivery vehicle to the nervous system was evaluated in comparison with collagen protein and a laminin-containing extracellular matrix (laminin-ECM), demonstrating its potential as an alternative scaffold material (Wells *et al.*, 1997). The experiment used a silicon conduit tube filled with laminin-ECM (Biomatrix), collagen, a 2% methylcellulose matrix vehicle alone, or a combination of each vehicle with platelet-derived growth factor-BB (PDGF-BB) and insulin-like growth factor-I (IGF-I) to assess sciatic nerve recovery in adult rats (intubation model). The findings indicated that growth factor-treated MC and collagen groups showed nearly equal numbers of regenerated axons in the fourth week, with the growth factor-treated MC group exhibiting a higher neuron survival rate than the other untreated groups. These results suggest that methylcellulose efficiently serves as a vehicle for delivering growth factors and performs comparably to natural ECM proteins, such as collagen. Despite the untreated group yielding fewer myelinated axons, the axonal formation rate in MC was faster than in the other groups, and nearly equal numbers of axons were retrieved in both collagen and MC vehicles alone. The functional recovery of regenerated

neurons, as assessed by electrophysiological measures, transcranial magnetic motor evoked potentials, and somatosensory evoked potentials, was higher in neurons obtained from the GF-treated MC matrix than in all other groups (Wells *et al.*, 1997).

Combining cellulose with natural polymers, such as collagen, hyaluronic acid, and gelatin, has improved biocompatibility and facilitated the controlled and efficient delivery of drugs and cells, including supporting cells and stem cells (Anghel *et al*., 2021; Sood *et al.*, 2021). The abundant hydroxyl and amino groups in cellulose–protein composites enable the conjugation of growth factors and drugs, thereby enabling controlled matrix degradation and sustained therapeutic delivery. For instance, a study presents a transparent cellulose/soy protein isolate (SPI) composite, mould-cast hollow nerve guide conduit functioning as a cellulose-matrix-based delivery vehicle that enables *in situ* visualization of nerve regeneration and localized delivery of biological and biochemical cues (Luo *et al*., 2015). In a 6–8 mm rat sciatic nerve defect model, mould-cast cellulose/SPI conduits containing 30 wt% SPI served as effective structural matrices, while co-loading with Schwann cells (SCs) and pyrroloquinoline quinone (PQQ) (CSSPC) significantly enhanced regenerative outcomes compared with conduit-only (CSC) and SC-loaded (CSSC) groups. Quantitatively, functional recovery at 12 weeks, assessed by the sciatic function index (SFI), improved to −71.60 ± 3.85 in the CSSPC group, compared with −80.59 ± 2.04 (CSSC) and −86.13 ± 4.07 (CSC). However, the study does not clarify why the functional improvement in CSSPC does not scale proportionally with structural outcomes relative to CSC. As shown in Figure 4(A-D), histological and ultrastructural analyses revealed higher axonal density, increased neovascularization, larger axon diameters, greater myelin sheath thickness, and reduced vacuolization in the CSSPC group. However, total axon numbers remained lower than those of the control group. In addition, the cellulose/SPI scaffolds exhibited occasional abnormal myelin sheath morphology with vacuolar structures, possibly related to the degradable nature of the soy protein component and associated local immunological responses, warranting further investigation. Overall, this work highlights the capacity of cellulose-based matrices to serve not only as physical nerve guidance conduits but also as delivery platforms for cells and small bioactive molecules, underscoring the importance of synergistic, multifunctional design strategies beyond passive cellulose scaffolds in peripheral nerve tissue engineering (Luo *et al*., 2015).

Cellulose-based scaffolds, particularly when combined with nanoparticles such as graphene oxide (GO), can support the delivery of stem cells and other supporting cells to enhance nerve tissue regeneration by providing a high surface area for cell incorporation, promoting neuronal network formation, and reducing the immune response (Simsek *et al*., 2025). In this study, a bacterial cellulose/graphene oxide (BC/GO) scaffold was fabricated by impregnating GO into BC membranes, resulting in a porous, hydrophilic structure with well-dispersed GO. Adipose-derived mesenchymal stem cells (AdMSCs) were isolated and engrafted onto the scaffold, which in vitro supported adhesion, proliferation, cytoskeletal organization, and limited infiltration (~20 μm) without cytotoxic effects. In a 10 mm rat sciatic nerve defect model, compound muscle action potential (CMAP) ratios at 4

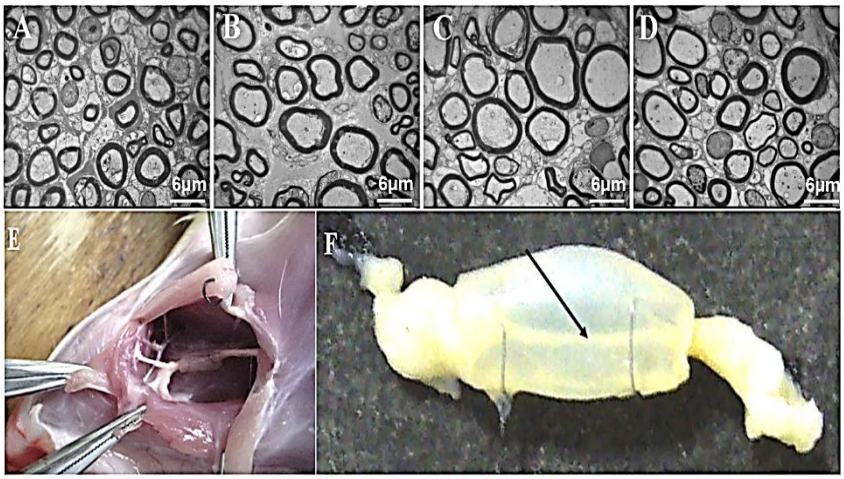

Fig. 4: (A-D) TEM images of sciatic nerve fibers 12 weeks post-surgery. (A) control group, (B) cellulose/SPI hollow tube (CSC), (C) cellulose/SPI conduit combined with Schwann cells (CSSC), (D) cellulose/SPI conduit with SCs and PQQ (CSSPC), (E) harvested regenerative nerve fibers 12 weeks after surgery, and (F) arrows indicating the regenerative nerve connecting the distal and proximal ends of the injured nerve (Luo *et al.,* 2015).

weeks were significantly higher in BC/GO (~0.78) and BC/GO+MSCs (~0.71) groups compared to autografts (~0.43), indicating enhanced early axonal conduction. However, sciatic functional index (SFI) values remained similarly negative (~−85 to −90), reflecting limited functional recovery. By 8 weeks, CMAP ratios declined in BC/GO alone (~0.46) but were maintained in BC/GO+MSCs (~0.58), suggesting that MSCs partially mitigated inflammation-induced degeneration. Histological analysis revealed significant inflammation and axonal degeneration in BC/GO scaffolds, likely due to alloantigen-related immune responses triggered by bacterial cellulose. In contrast, MSC incorporation improved axonal organization and reduced inflammatory effects through immunomodulation. Overall, BC/GO scaffolds facilitate early nerve regeneration; however, long-term functional recovery remains limited by scaffold-associated inflammation, underscoring the need to optimize in-cell-delivery designs.

CELLULOSE-BASED ELECTRICALLY CONDUCTIVE SCAFFOLDS

Neurons operate fundamentally as electrical devices, utilizing electrical signals for signal transduction. While the cell-maintained electrical potential regulates cellular functions, external electrical signals can stimulate signaling pathways and trigger the influx of transduction ions across the cell membrane, such as Ca^{2+} and K^{+} (Nair *et al*., 2019). Numerous studies have demonstrated that external electrical stimulation activates transmembrane ion channels and receptors, accelerating the diffusion of signal transmitters to regulate cell behaviour, enhance migration, and promote growth (Chen *et al*., 2019). Additionally, external electrical stimulation has been demonstrated to release neurotrophic factors (Luo *et al*., 2014). Electroactive scaffolds facilitate tissue regeneration by enabling efficient electrical transfer within the tissue. The conductivity range of nerve tissue is typically 0.03-0.6 S/m, with scaffolds with conductivity above 10^{-4} S

cm^{-1} deemed optimal for enhancing neural differentiation (Ostrakhovitch *et al*., 2012; Saberi *et al*., 2019). Conductive polymers (e.g., PPy, PEDOT, PANI) and inorganic nanomaterials (e.g., graphene, carbon nanotubes) are explored for nerve tissue applications yet face challenges in biocompatibility, biodegradability, and cytotoxicity (Arzaghi *et al*., 2020; Nazarpak *et al*., 2019; Qian *et al*., 2018; Redondo-Gómez *et al*., 2020; Vijayavenkataraman et al., 2019; Wang *et al*., 2017). For instance, PPy-based scaffolds enhance cell proliferation but induce inflammation (Redondo-Gómez et al., 2020; Wang *et al*., 2004). Carbon/graphene materials exhibit cytotoxic effects (Zhang *et al*., 2020). Furthermore, the water-resistant and hydrophobic nature of the conductive polymers may limit the diffusion of drugs and growth factors across the scaffold. Cellulose-based materials offer a potential solution to overcome the drawbacks of conventional conductive polymers or composite scaffolds.

Cellulose materials and their nanoforms, such as nano-fibrillated cellulose (NFC), nanocrystalline cellulose (NCC), and bacterial cellulose (BC), lack inherent conductivity. However, cellulose-based composites and modified cellulose offer conductive substrates with excellent biocompatibility and biophysical properties (Hsu and Zhong, 2019; Pandey *et al*., 2012). A study demonstrated that regenerated cellulose acetate (rCA) nanofibers, rendered conductive through carbonization or the incorporation of multiwall carbon nanotubes (MWCNTs), enhanced neuron regeneration (Kuzmenko *et al*., 2016). MWCNT-incorporated cellulose and carbonized nanofibers, when compared to a pure cellulose scaffold, significantly influenced SH-SY5Y cell differentiation. MWCNT - rCA scaffold-regenerated neurons exhibited long microtubular extensions, while the pure cellulose scaffold yielded neurons forming large clusters with poor microtubular development. These distinctions are attributed to the higher conductivity and surface roughness of the MWCNT- rCA scaffold. While carbonized nanofibers were slightly more conductive than MWCNT-rCA scaffolds, MWCNT offered higher wettability and surface roughness, which favored intracellular-extracellular connectivity. However, concerning cytotoxicity, carbonized nanofiber and pure cellulose demonstrated significantly lower cytotoxicity, with around 90% cell viability, whereas the MWCNT-rCA scaffold exhibited three times higher cytotoxicity. The increased cytotoxicity of the MWCNT-doped cellulose scaffold is hypothesized to be caused by residues of toxic catalysts and dispersants from the synthesis of MWCNT particles (Kuzmenko *et al*., 2016).

A common approach to preparing conductive cellulose scaffolds involves incorporating carbon nanoparticles into the cellulose polymer. Alternatively, a fully three-dimensional graphene scaffold integrated with bacterial cellulose (BC) has been developed as a conductive substrate for neuronal culture (Guo *et al*., 2021). As shown in (Figures 5A and B). In this method, cellulose-producing bacteria *Acetobacter xylinum* are cultured directly on the 3D graphene skeleton, yielding a conductive BC/graphene composite scaffold. This BC/graphene scaffold significantly enhances the viability and proliferation of neural stem cells (NSCs) in vitro, with greater than 99% cell viability and markedly higher expression of proliferation markers (Ki-67, MCM2, PCNA) compared to graphene-only scaffolds. The scaffold promotes extracellular matrix protein self-assembly, supporting NSC growth and

Table 2. Advances in conductive cellulose composite-based scaffold for nerve tissue

Type of cellulose	Conductive material	In vitro biocompatibility	In vivo biocompatibility	Conductivity S cm^{-1}	Advantage	Disadvantage	Application	Reference
De acetylated cellulose acetate	Multiwall carbon nanotube (MWCNT) infusion and carbonized electrospun cellulose nanofiber	Bone marrow-derived SH-SY5Y	-	Cellulose; 7.8×10^{-7} Cellulose + MWCNT; 1.8×10^{-1} CNF; 11.2	CNT offers higher wettability and surface roughness, which increases cell protein adhesion CNF has high conductivity and high biocompatibility	The CNT scaffold exhibited higher cytotoxicity	nanofibrous scaffolds	(Kuzmenko *et al.*, 2016)
Bacterial cellulose	3D graphene skeleton	neural stem cells (NSCs) and primary cortical neurons	-	-	The high number of NSC differentiation and proliferation, regulating gene expression, and a highly dense neuronal network formation	The purification step of scaffold fabrication is complicated	Biomimetic 3D scaffold	(Guo *et al.*, 2021)
Bacterial cellulose	Graphene flakes	Rat hippocampal neurons	-	-	Promote the growth and migration of neurons in 3D directions.	-	Hydrogel Scaffold for 3D culture	(Kim *et al.*, 2017)
Regenerative cellulose (RC)	Polyaniline (PANI)	RSC96 (Schwann cell)	Sciatic nerve regeneration in Sprague-Dawley rats	0.49	well-developed nerve regeneration and myelinated fiber formation on the conductive side	-	Hydrogel Scaffold	(Xu *et al.*, 2016)
hydroxyethyl cellulose	soy protein, PANI brain-derived neurotrophic factor (BDNF), Schwan cell	-	Sprague–Dawley (SD) rat's sciatic nerve	$1.7\ Sm^{-1}$ 20.6 kΩ	With electrical stimulation, BDNF was secreted, Electrical stimulation results in higher nerve function	degraded PANI particles remained	Nerve conduit for peripheral nerve regeneration	(Wu *et al.*, 2020)

the formation of highly developed 3D neural networks, whereas neurons on graphene alone exhibit shorter neurite outgrowth. The BC/graphene scaffold yields a ~3-fold higher cell density and approximately 50% more frequent calcium transients, reflecting enhanced neuronal network formation and increased functional activity. NSCs on this scaffold also maintain stemness and express higher levels of cell cycle and signalling pathway regulatory genes, demonstrating superior biocompatibility and neuroregenerative potential compared to graphene-only constructs. However, challenges remain, including potential toxicity from residual chemicals or bacterial components during scaffold purification, as well as variability in the morphology and distribution of cellulose nanofibrils(Guo *et al.*, 2021). In a similar study, graphene oxide (GO) nanoflakes were dispersed directly into *A. Xylinum* bacterial culture media, producing a highly oriented nanofiber hydrogel scaffold (Kim *et al.*, 2017). Incorporating graphene oxide (GO) into bacterial cellulose (BC) cultures effectively modulates the structural and mechanical properties of the resulting nanofibrillar hydrogel. GO inclusion reduced bacterial cell size and disrupted polysaccharide chain ordering, weakening bacterium-to-bacterium interactions and leading to lower crystallinity and altered Young's modulus of cellulose bundles. Synthesized pristine BC had organized, helical nanofibrils, while GO-BC formed a disordered 3D network with higher porosity and denser

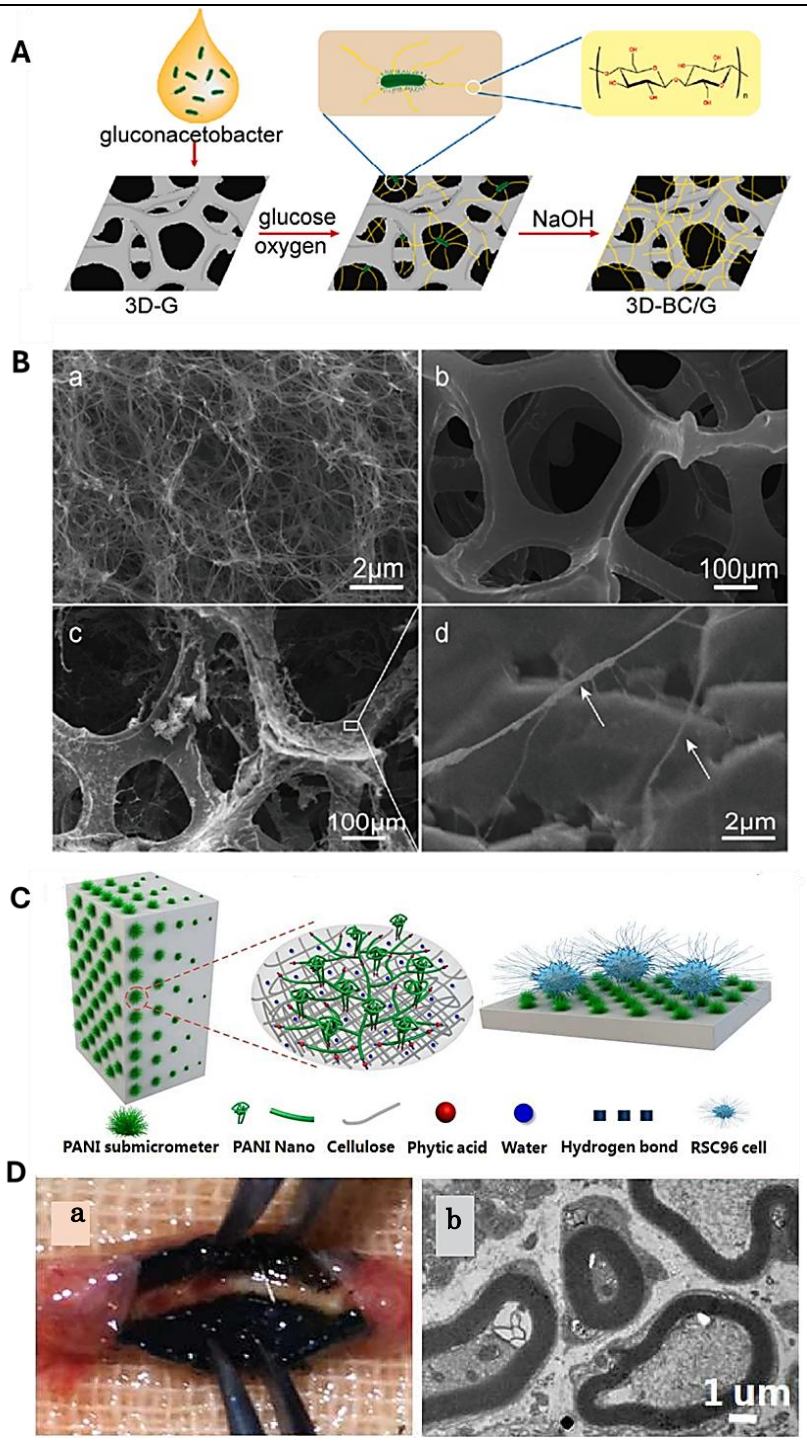

Fig. 5: (A) The schematic diagram for the preparation of 3D-BC/GO. The SEM images of pure 3D-BC nanofiber (B(a)), 3D-GO skeleton (B(b)), and 3D-BC nanofiber-covered GO skeleton scaffold (B(c and d)) (Guo et al., 2021). (C) Schematic illustrations of of the hierarchical micro-nano-structured PANI embedded in cellulose matrix as well as the adhesion for RSC96 cell. (D(a)) Intraoperative photographs of the PANI/RC/2 composite hydrogels after 3 months. (D(b)) TEM images of ultrathin cross sections of PANI/RC charged with regenerated sciatic nerves in rats after 3 months, showing the average thickness of regenerated myelinated fibers (Xu et al., 2016).

differentiation into normal Schwann cell morphology and extended pseudopodia toward PANI particles, resulting in high cell viability (on day 5, PANI/RC proliferation was ~2.1 times higher than the control and ~1.3 times higher than RC). The electrical conductivity of the hydrogels increased with the PANI-to-cellulose ratio, rising from 0.025 $S{\cdot}cm^{-1}$ (for PANI/RC:1) to 0.68 $S{\cdot}cm^{-1}$ (for PANI/RC: 4) as the PANI content increased from 0.5 to 4 relative to cellulose, indicating a direct correlation between the PANI/cellulose ratio and conductivity. As shown in Figure 5D, in an in vivo study on sciatic nerve regeneration in Sprague-Dawley rats, the conductive side exhibited well-developed nerve regeneration over three months, while no tissue formation occurred on the non-conductive side. After three months, the resulting nerves displayed similar morphology, growth, and myelinated fiber formation, indicating successful nerve reconstruction without needing electrical or mechanical stimulation (Figure 5D(b)) (Xu *et al.,* 2016). Notably, the study did not investigate the toxic effects of the PANI-incorporated cellulose scaffold or determine the optimal PANI dose for nerve regeneration.

In a recent study, a conductive nerve conduit was engineered by incorporating polyaniline (PANI) into a hydroxyethyl cellulose (HEC)/soy protein isolate (SPI) scaffold to promote peripheral nerve regeneration, with electrical stimulation (ES) responsiveness systematically evaluated (Wu *et al.*, 2020). The scaffold was fabricated by solvent-casting HEC and SPI, followed by in situ polymerization of aniline to form conductive HEC/SPI/PANI (hsps) conduits. Schwann cells isolated from neonatal rat sciatic nerves were seeded onto the scaffolds, and three experimental groups were applied in vivo to repair 10 mm sciatic nerve defects: HSPS conduits alone, HSPS with brain-derived neurotrophic factor (BDNF), and HSPS with ES. In vitro, BDNF (50 ng/mL) enhanced Schwann cell proliferation and myelination, as indicated by increased PCNA and MBP expression, whereas excessive BDNF inhibited growth. In vivo, ES promoted endogenous BDNF expression, thereby improving Schwann cell activity, axon diameter, myelin thickness, and myelinated fiber density, outperforming both the HSPS alone and the HSPS+BDNF groups. Functional assessments, including the sciatic nerve function index (SFI) and electrophysiological measurements, demonstrated that HSPS+ES restored nerve function to levels comparable to those of autografts. Histological and TEM analyses confirmed enhanced remyelination in the electrically stimulated group, while degraded PANI particles were detected in regenerated nerves but not in other organs, indicating overall biocompatibility. Collectively, this work demonstrates that conductive HEC/SPI/PANI conduits combined with ES effectively facilitate nerve regeneration and remyelination via BDNF-mediated modulation of Schwann cells, offering a promising, safe, and environmentally friendly approach for peripheral nerve repair. (Wu *et al.*, 2020).

Similar to electrically conductive materials, piezoelectric materials are also proposed as suitable candidates for neural tissue engineering, as they provide both electrical and topological cues that facilitate neural cell differentiation, alignment, and network formation. In a recent study, $[K_{0.5}Na_{0.5}]NbO_3$ (KNN), a piezoceramic, was incorporated into cellulose to produce 2D films and 3D scaffolds for neural stem cell (NSC) transplantation (Jarkov *et al.*, 2025). The

3D scaffolds were fabricated using directional freeze casting (DFC) combined with cold regeneration, resulting in highly aligned lamellar pores ranging from 48 to 116 µm that closely mimic the anisotropic hierarchical architecture of central nervous system tissue. Corona poling of the composites imparted significant piezoelectric properties, with 50 vol% KNN-cellulose films achieving a piezoelectric charge coefficient (d_{33}) of 7.7 pC/N and a piezoelectric voltage coefficient (g_{33}) on the order of 10^{-2}–10^{-1} V·m/N, which is sufficient to generate physiologically relevant electrical cues. NSC culture on these scaffolds showed improved cell viability (up to~ 89.4% on poled 50 vol% % composites at 5 days of culture) and supported differentiation into neurons (>17%), astrocytes (>55%), and oligodendrocytes (>4%), with alignment strongly guided by the scaffold's pore orientation. The composites were enzymatically degradable, leaving recoverable KNN particles after 24 h, suggesting potential for safe in vivo bioresorption. Overall, the study demonstrates that KNN-cellulose composites combine electrical functionality, tunable porosity, and biodegradability, providing a multifunctional platform for NSC transplantation and neural tissue regeneration. However, the long-term in vivo biocompatibility and the potential leaching effects of KNN particles remain to be fully evaluated.

NEURAL INTERFACES

Neural interfaces (NIs) or neural prostheses are brain-computer interfaces or bioelectronic devices that could stimulate a region of neurons and nerve fascicles, record or amplify the electrical potential in that region, and read out neuron activity (Redolfi Riva and Micera, 2021). These electrical signals are utilized to interpret cognitive intentions, motor plans, and organ actions, aiming to restore physiological neural activity or reconstruct sensory-motor feedback using prosthetic devices (Andersen et al., 2010; Wellman *et al.*, 2018). Fundamentally, an NI is an electrode comprising an insulating foundation connected to the target tissue interface and a conductive layer that stimulates, records, and amplifies nerve electrical potentials (Andersen et al., 2010; Wellman *et al.*, 2018). The ideal NI material should possess sufficient electrical properties for selective signal capture and transmission with a high signal-to-noise ratio while complying with the tissue environment's physicochemical and mechanical properties for successful implantation (Szostak *et al.,* 2017). Various materials, including conductive and natural polymers, have been explored for NI substrates. Still, challenges such as biocompatibility issues, lack of physicochemical properties, and durability limitations hinder their efficiency in NI applications (Bettinger *et al.*, 2020; Redolfi Riva and Micera, 2021). These materials often trigger foreign body reactions and inflammatory responses, which can affect the sustainability of NI (de la Oliva *et al.*, 2018; Gunasekera *et al.*, 2015). Furthermore, a prolonged implantation period of the proposed materials was observed to induce fibrotic tissue formation at the interface, affecting both tissue and electrode performance (Lotti *et al.*, 2017). In contrast, cellulose is a promising material for NI due to its high biocompatibility and compatibility with the physicochemical properties of the nerve tissue environment. Cellulose and its derivatives, already proven to be effective as tissue engineering scaffolds and drug delivery vehicles, offer lower toxicity, minimal

scar formation, and superior biocompatibility. The high hydrophilicity and hydrogel properties of cellulose make it well suited to the tissue environment, enhancing cell–electrode interactions and ensuring prolonged performance. Cellulose derivatives serve as excellent reinforcing materials in composites, providing optimal mechanical properties, such as rigidity and flexibility, to NI electrodes. Furthermore, cellulose materials are resistant to ready metabolism in the human body, allowing for prolonged subcutaneous implantation of the electrode.

A significant advancement in the development of highly flexible multichannel bacterial cellulose (BC)–gold (Au) electrodes has been reported, with mechanical properties closely resembling those of the extracellular matrix (ECM) and designed for neural interfaces (Yang *et al.*, 2018). The Au-BC soft electrodes were fabricated by directly depositing a gold microarray circuit pattern onto a hot-pressed BC thin film using a shadow mask (Figure 6(A-E)). The resulting electrode exhibited a Young's modulus of approximately 120 kPa, strategically positioned between the Young's modulus of brain tissue (2.7~3.1 kPa) and the peripheral neural tissues (580~840 kPa). Remarkably, the bending stiffness of the Au-BC electrode proved to be 1/5200 of a similar Au-polyimide (PI) layout, retaining 95% conductivity (5.2 mΩ·cm electrical resistivity) even after 100 cycles of 180 ° bending. In a cerebrospinal fluid electrolytic setting, the Au-BC electrode exhibited superior performance with lower impedance than a comparable Au-PI electrode. This enhanced behaviour could be linked to the improved surface roughness of the BC thin film. Moreover, as shown in Figures 6(F-H), PC12 cell culture experiments demonstrate successful attachment and spreading of model neuron cell lines on both cellulose and Au surfaces, with high cell viability of ~97% after 3 days. The hemolysis assay demonstrated that the Au–BC scaffold caused negligible erythrocyte damage, with hemolysis ratios comparable to the saline negative control and far below the accepted safety threshold, confirming its excellent hemocompatibility. In vivo, Au–BC scaffolds were successfully used to record artificially induced epileptic neural activity from the temporal cortex of Sprague–Dawley rats, exhibiting clear electrocorticography (ECoG) signals characteristic of epileptiform activity. The Au–BC electrodes exhibited a low interfacial impedance of 55.6 ± 5.0 kω at 1 kHz, facilitating efficient and stable signal readout. Although a mild inflammatory response was observed at 2 weeks post-implantation, astrocytic activation around Au–BC electrodes was significantly reduced at 4 weeks, with GFAP fluorescence intensity decreasing to 0.31 ± 0.01 compared to 1.10 ± 0.03 for Au–PI electrodes ($P < 0.001$), indicating superior long-term biocompatibility of the cellulose-based neural interface. The in vivo biocompatibility analysis revealed successful integration with curvilinear tissue surfaces, minimal immunological responses, and the generation of neo-blood vessels adjacent to the electrode, underscoring the superior biocompatibility of the Au-BC electrodes. Significantly, the electrode's optimal flexibility and roughness facilitated enhanced conformity with curvilinear brain surfaces (Yang *et al.*, 2018).

In a study, a conductive composite structure was developed by coating poly(3,4-ethylenedioxythiophene) (PEDOT) onto bacterial cellulose (BC) nanofibers, aiming to enhance the electrode–cell interface for various applications (Chen *et al.*, 2015). The

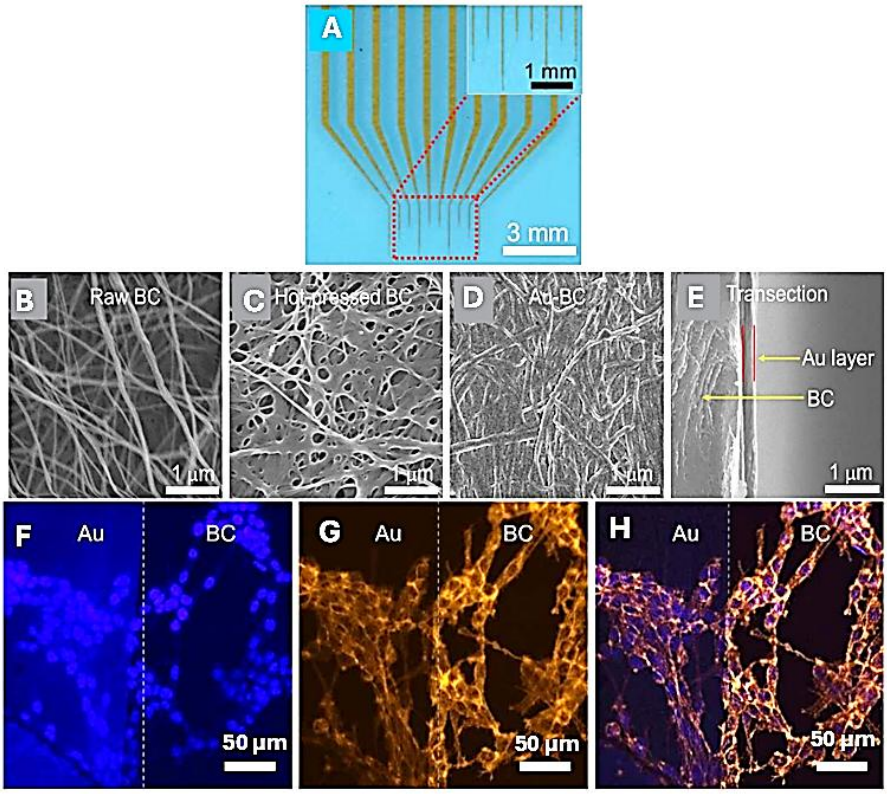

Fig. 6: (A) Photograph of a 10-channel Au-BC electrode. Morphological characterization of the Au-BC electrode: (B) Raw BC, (C) Hot-pressed BC, and (D) Au-coated BC, characterized by SEM. (E) Cross-sectional image of a 200 nm-thick Au layer deposited on BC observed by SEM. Double immunofluorescence staining of PC-12 cells on the Au-BC electrode: (F) Cells stained with Hoechst 33342 (blue), (G) Alexa Fluor 568 Phalloidin (orange), and (H) Merged image of both stains (Yang *et al.*, 2018).

PEDOT-coated BC nanofibers were prepared through $FeCl_3$-mediated in situ polymerization of PEDOT monomers on the BC nanofiber surface, resulting in a solid conductive layer on the BC nanofiber. This BC-PEDOT composite demonstrated robust mechanical properties, including tensile strength and Young's modulus of approximately 4 and 0.83 MPa, respectively, with a twofold increase in elongation compared to uncoated BC film, making it suitable for curvilinear brain tissue surfaces. The conductivity of BC nanofibers increased significantly with the addition of PEDOT coating, and optimization was achieved by adjusting the monomer concentration and polymerization time. Electrochemical analysis by cyclic voltammetry (CV) revealed clear anodic and cathodic peaks, characteristic of traditional electrochemical electrodes. Notably, the BC-PEDOT composite interface demonstrated high durability, maintaining its CV plots after 1000 cycles of redox reactions and bending at angles of 60–180°. In vitro studies with PC12 cells cultured on BC-PEDOT electrodes showed excellent cell growth, with higher cell viability (95% at 24 hours) observed on both BC and BC-PEDOT surfaces. Notably, BC-PEDOT exhibited superior cell attachment, attributed to its higher conductivity and surface roughness. Electrical stimuli applied to PC12 cells on BC-PEDOT scaffolds and indium tin oxide (ITO) electrodes revealed increased fluorescent

intensity, indicating higher Ca^{2+} ion transport in response to electrical charge injection. This observation was consistent with the CV redox curves, indicating that the BC-PEDOT electrode exhibited higher electrical capacitance than the ITO electrode, potentially enabling enhanced cell stimulation at higher current densities. The 3D BC/PEDOT nanofiber electrode-cell interfaces hold promise for various applications, including biosensing devices, intelligent drug delivery systems, and implantable electrodes for tissue engineering (Chen *et al*., 2015).

CONCLUSIONS

The process of nerve regeneration is inherently complex, presenting challenges such as limited regenerative capacity, scar formation, inflammation, immunological responses, and the effective delivery of biomolecules, including neurotrophic factors and drugs. Ideal nerve tissue recovery scaffolds must possess crucial characteristics, including the ability to mimic the native brain extracellular matrix (ECM), minimal toxicity, high biocompatibility, and the capacity to induce a minimal immunological response, thereby enhancing nerve tissue recovery while minimizing scar formation. Cellulose, a linear polymer saccharide, is a promising candidate for constructing brain ECM-mimicking scaffolds in nerve tissue engineering applications. Its resemblance to the proteoglycan skeleton, such as heparan sulfate and chondroitin sulfate, presents an excellent opportunity. Additionally, nanofibrillated structures in cellulose derivatives, such as bacterial cellulose (BC) and nanocellulose, replicate the topographical features of the ECM, providing a biomimetic scaffold with high biocompatibility. Cellulose derivatives, such as methylcellulose, with enhanced water-retention properties, can be used to fabricate hydrogel-based scaffolds and drug-delivery matrices for peripheral nerve conduits, thereby facilitating the delivery of nerve growth factors and anti-inflammatory drugs. While pure cellulose is electrically inert, the addition of conductive polymers and carbon nanotubes enhances conductivity, enabling both internal and external electrical stimulation for nerve growth. The review concludes that cellulose and modified cellulose-based composite materials hold promise for constructing versatile nerve tissue engineering scaffolds and neuronal interfaces, offering properties such as high biocompatibility, conductivity, flexibility, and low degradation, thereby enabling the development of long-term implantable neuronal interfaces without triggering adverse immunological responses or scar formation.

FUTURE OUTLOOK

Cellulose and its derivatives emerged as promising materials for nerve regeneration and conductive neural interfaces, attributed to their outstanding biocompatibility, low toxicity, robust mechanical strength, processability, and widespread availability. Notably, regenerative cellulose (RC) and cellulose acetate (CA) closely replicate the molecular and topographical characteristics of the nerve tissue extracellular matrix (ECM), presenting significant potential for nerve guidance and extended implantable neural interfaces. Methylcellulose (MC), known for its thermal inverse gelling property, forms injectable scaffolds or biomolecule/cell delivery vehicles, such as MC-agarose, MC-hyaluronic acid, and MC-collagen

composites. These injectable MC matrices solidify at physiological temperature, covering the injured cavity to minimize scar formation and enhance nerve recovery. Bacterial cellulose (BC), with its high biocompatibility and nanofibril structure resembling native collagen fibers, is an excellent material for nerve regeneration. BC exhibits low toxicity in nerve tissues and high blood compatibility on nerve tissue scaffolds and prosthetic surfaces. Its nanofibrillated structure allows for easy conjugation with other polymers, drugs, and growth factors, enabling the use of drug-delivery vehicles.

However, a significant challenge arises from the limited metabolic breakdown of cellulose in the human body, necessitating chemical modifications, such as oxidising β-(1,4) glucose linkages, to enhance degradability. However, the resulting aldehyde groups from oxidation can induce cytotoxicity in neurons. Injecting cellulase enzymes for enzymatic degradation has been explored, but their impact on nerve tissue cells remains incompletely understood. Therefore, elucidating the optimal degree of surface modification or the appropriate amount of degrading enzyme that avoids toxicity in nerve tissue is imperative. Achieving suitable surface modification or combining it with conductive polymers is essential in preparing conductive cellulose-based scaffolds or neural interfaces. Although crosslinking, grafting, or physical mixing of conductive polymers, such as PPy and PANI, enhances conductivity, these methods often trigger cytotoxic responses in nerve cells. Thus, comprehensive investigations into selecting the suitable conductive polymer and determining the optimum crosslinking level are crucial. In summary, cellulose-based materials offer versatility in drug delivery, scaffolding, and nerve guidance for nerve tissue engineering applications. In contrast, while cellulose-based conductive composites hold promise for the fabrication of highly biocompatible, flexible, and durable soft prosthetic electrodes or surfaces.

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