Hamidreza Arzaghi, Bashir Adel, Hossein Jafari, Shaghayegh Askarian-Amiri, Amin Shiralizadeh Dezfuli, Abolfazl Akbarzadeh* and Hamidreza Pazoki-Toroudi*

Nanomaterial integration into the scaffolding materials for nerve tissue engineering: a review

https://doi.org/10.1515/revneuro-2020-0008
Received February 8, 2020; accepted May 21, 2020; published online August 10, 2020

Abstract: The nervous system, which consists of a complex network of millions of neurons, is one of the most highly intricate systems in the body. This complex network is responsible for the physiological and cognitive functions of the human body. Following injuries or degenerative diseases, damage to the nervous system is overwhelming because of its complexity and its limited regeneration capacity. However, neural tissue engineering currently has some capacities for repairing nerve deficits and promoting neural regeneration, with more developments in the future. Nevertheless, controlling the guidance of stem cell proliferation and differentiation is a challenging step towards this goal. Nanomaterials have the potential for the guidance of the stem cells towards the neural lineage which can overcome the pitfalls of the classical methods since they provide a unique microenvironment that facilitates cell–matrix and cell–cell interaction, and they can manipulate the cell signaling mechanisms to control stem cells' fate. In this article, the suitable cell sources and microenvironment cues for neuronal tissue engineering were examined. Afterward, the nanomaterials that impact stem cell proliferation and differentiation towards neuronal lineage were reviewed.

Keywords: differentiation; nanomaterials; neural tissue engineering.

***Corresponding authors: Hamidreza Pazoki-Toroudi**, Physiology Research Center, Faculty of Medicine, Iran University of Medical Sciences, Hemat Highway Next to Milad Tower, Tehran 1449614535, Islamic Republic of Iran; Department of Physiology, Faculty of Medicine, Iran University of Medical Sciences, Hemat Highway Next to Milad Tower, Tehran 1449614535, Islamic Republic of Iran, e-mail: pazoki.h@iums.ac.ir, pazoki49@gmail.com; **Abolfazl Akbarzadeh**, Tuberculosis and Lung Disease Research Center of Tabriz, Tabriz University of Medical Sciences, Tabriz 5165665811, Islamic Republic of Iran; Department of Medical Nanotechnology, Faculty of Advanced Medical Sciences, Tabriz University of Medical Sciences, Tabriz 5165665811, Islamic Republic of Iran; and Iran Universal Scientific and Education Network (USERN), Tabriz 5165665811, Islamic Republic of Iran, e-mail: akbarzadehab@tbzmed.ac.ir
Hamidreza Arzaghi: Department of Medical Biotechnology, Faculty of Allied Medical Sciences, Iran University of Medical Sciences, Hemat Highway Next to Milad Tower, Tehran 1449614535, Islamic Republic of Iran
Bashir Adel: Department of Biology, Faculty of Sciences, The University of Guilan, Rasht 4199613776, Islamic Republic of Iran
Hossein Jafari: Institute for Research in Fundamental Sciences (IPM), Artesh Highway, Tehran 1956836681, Islamic Republic of Iran
Shaghayegh Askarian-Amiri and Amin Shiralizadeh Dezfuli: Physiology Research Center, Faculty of Medicine, Iran University of Medical Sciences, Hemat Highway Next to Milad Tower, Tehran 1449614535, Islamic Republic of Iran

Introduction

The nervous system regulates and controls body functions. The nervous system consists of the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS, including the brain and spinal cord, is the signal producing and processing center and it is connected to other parts of the body by long fibers of the PNS (Engelhardt et al. 2017; Wong et al. 2019; Zarch et al. 2009).

At the cellular level, the nervous system consists of neural and non-neural cells. Neural cells or neurons, which are responsible for the transmission of the signals to other cells via synapses, collect data by their dendrites and soma and transmit signals away by their axons (Arabian et al. 2015, 2017). Two major types of neurons are sensory and motor neurons. The former is responsible for collecting the sensory action potential from the PNS to the CNS, and the latter relays signals from the CNS to their effectors. Glial cells or non-neural cells are the supporting cells that provide nutrition and maintain homeostasis for neurons. These types of cells are subdivided into oligodendrocytes, astrocytes, and microglial cells in the CNS, and Schwann cells and satellite glial cells in the PNS. Schwann cells and oligodendrocytes provide myelin sheaths, which surround the axons in the PNS and the CNS, respectively. These lipid-rich discontinuous structures facilitate axonal signal transmission, and they increase the conduction velocity of the action potentials between two nodes of Ranvier. Nodes of Ranvier are the myelin-sheath gaps between the myelin insulation of Schwann cells where axolemma is exposed to

extracellular space. Impairment of the myelin, which is the symptom of neurodegenerative diseases such as multiple sclerosis, Guillain–Barré syndrome, and Leukodystrophy that result in dysfunction of the neurons and deficiency in cognitive, sensory or movement functions (Amani et al. 2019a, b, c, d; Miyata et al. 2016; Schmidt and Leach 2003).

In addition to demyelination, neurodegenerative diseases such as amyotrophic lateral sclerosis, Alzheimer's disease, and Parkinson's disease can cause progressive neuron loss, including functions or structures of neurons. The brain is protected by the scalp, skull, and meninges layers, and it is suspended in cerebrospinal fluid. Furthermore, it is even isolated from the bloodstream by the blood-brain barrier (BBB), but external damage, trauma, and infection can cause irreversible damage to the CNS. In the U.S., seven million traumatic brain injuries (TBI) or intracranial injuries occur every year. The significant problems with brain injuries are the inadequacy of the treatments and limited options for enhancing clinical outcomes. For instance, the side effect of the tissue plasminogen activator (tPA), which is a gold standard for ischemic strokes is inflammation of the capillaries. In the case of TBI, the only option is reducing the possibility of the second injury with surgical treatments (Amani et al. 2019a, b, c, d; Bradbury and McMahon 2006; Jain 2019).

Like CNS, the spinal cord is susceptible to injuries as well. The mechanical forces can cause spinal cord injuries (SCI), which can occur in primary and secondary damage. Following the cell death in the site of the original injury, the biochemical cascades such as inflammation, apoptosis, and ischemic cascade can produce secondary damage. As mentioned before, the PNS is the bridge between the CNS and the outer body, which unlike the CNS is not protected by the skull or BBB, and not being protected makes the PNS more vulnerable to toxins, mechanical injuries or infections. The general term for the damage to the PNS is peripheral neuropathy, which can cause by elongation, compression, or laceration of the PNS. For example, prolonged mechanical compression can cause endoneurial channels dysfunction and increase the endoneurial fluid pressure by creating the endoneurial edema, alteration of the ionic balance and fascicular microcirculation, and subsequently ischemia. Peripheral neuropathy causes symptoms such as loss of organ functions, muscle loss, and bone degeneration depending on the area of the injuries. For instance, damage to the motor neurons, which is a motor neuropathy, results in muscle weakness and balance impairment; sensory neuropathy can reduce sensitivity, induce numbness, and skin allodynia (Belanger et al. 2016; Bradbury and McMahon 2006; Pollard et al. 2019).

Significantly, nerve repair and regeneration is present in PNS, but it only allows for 1 mm/day regrowth after an injury. Schwann cells control the regeneration by secretion of chemotactic factors. After the injury Schwann cell, macrophages, and phagocytes migrate to the damaged site and clear the debris of damaged tissue and regeneration of the nerve begins (Amani et al. 2019a, b, c, d). Conversely, the neuroregeneration is limited in the CNS compared to the PNS. This low repair of neurons is the consequence of the inhibitory result of the glial scars and the extracellular matrix, which creates a hostile microenvironment in the CNS. For example, the growth factors are not expressed in the CNS, and the extracellular matrix is lacking laminin protein. Moreover, according to Llinás's law, the morphology of the CNS is very complex, and a neuron cannot be functionally replaced by another type even the secretion of the neurotransmitter and the synaptic connectivity is identical. Currently, researchers have introduced several new methods and agents to treat degenerative and other diseases (Firooz et al. 2005; Javedan et al. 2016; Llinás 2014; Pazoki-Toroudi et al. 2010a, b; Rahgozar et al. 2001; Toroudi et al. 1999).

In this review, we will summarize different cell sources that can be utilized in neural tissue engineering along with the intracellular signaling pathways and environmental signaling such as cell–cell interactions, cell–matrix interactions, and soluble factors that control stem cells' maturation towards neural cells. Indeed, we will highlight the effect of nanomaterials on proliferation differentiation, maturation, and cell fate for neural tissue engineering applications.

Cell sources for neural tissue engineering

Nerve tissue engineering relies on combining the biomaterials and external cues such as neurotrophic factors, cell–cell, and cell–matrix interactions (Amani et al. 2019a, b, c, d; Chooi and Chew 2019; Rosso et al. 2004; Solanki et al. 2010). Moreover, such approaches require the application of stem cells that can obtain in various sources with different characteristics. For example, autologous cells can accumulate from a patient; culture and store in the lab and reimplanted into the same individual. These cells distinguished from allogeneic and Xenogeneic stem cells which obtain from different people and different species respectively. Nerve autografting, which utilizes the autologous cells in nerve tissue engineering is the gold standard for peripheral nerve regeneration. Since they have immune rejection risk for the patients, autologous sources are much preferable than other cell sources. However, the limitation

sources for autologous cells should be taken into consideration (Gu et al. 2014; Sensharma et al. 2017; Tajdaran et al. 2016).

Additionally, the stem cells can be classified into several groups regarding their differentiation potential. Pluripotent stem cells can differentiate to all kinds of cell lineage in the body. However, full differentiated somatic cells do not have any differentiation potential, which indicates that the differentiation potential of stem cells decreases through the developmental stages (Jiang et al. 2017).

The more reliable results in nerve tissue engineering depend on the detailed knowledge about the types and characteristics of stem cells. Several stem cells with diverse potential differentiation are available for neural tissue engineerings such as embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs), and neural stem cells (NSCs) (Bhangra et al. 2016). The next section focuses on various types of stem cells that can be utilized in nerve tissue engineering.

Embryonic stem cells

Embryonic Stem cells (ESCs) derived from the inner cell mass of a blastocyte are the cells with pluripotency capability, which enable them to propagate indefinitely as well as differentiate into all derivatives of three embryonic germ layers (Zhang et al. 2001).

Differentiation of the ESCs to the various somatic cell types especially to the neural progenitor cells (NPCs) have been served as an in vitro model for the study of neurogenesis in early human development such as the molecular mechanisms of the proliferation and differentiation (Reubinoff et al. 2001). For instance, Yao et al. utilized mouse ESCs as a model system to demonstrate the crucial role of the PCGF5 protein in the neural differentiation (Yao et al. 2018). The ESCs with plasticity properties and the self-renewal ability paved the way for stem cell transplantation, regenerative medicine, and tissue engineering. Cui et al. utilized ESCs-derived neural progenitor cell transplantation to improve regeneration of the PNS (Cui et al. 2008).

The therapeutic properties of ESCs have been often challenged by stochastic differentiation of the ESCs, which makes unfavorable options for nerve tissue engineering (Dhara and Stice 2008). Likewise, the other concern is the possibility of tumorigenicity including teratoma appearance after transplantation into the patients (Hentze et al. 2009). The principal strategy to overcome this impediment and enhance the potential clinical application of the ESCs is to reduce the tumorigenicity by control differentiation of the ESCs to a particular cell lineage. Consequently, Kumamaru et al. reported the thriving method for differentiation and maintenance of the ESCs derived spinal cord neural Stem cells (NSCs) by activation of the WNT and FGF2/8 and dual inhibition of SMAD signaling pathways for corticospinal regeneration (Kumamaru et al. 2018).

Induced pluripotent stem cells

After the prohibition of utilizing the ESCs cells in regenerative medicine by the Japanese Ministry of Health, Labor and Welfare in 2006, contemporaneously, Yamanaka and his colleagues Takahashi introduced the induced iPSCs from the somatic cells by the transfection of the cells with Yamanaka factors (Oct3/4, Sox2, Klf4, c-Myc) (Nagoshi and Okano 2018; Takahashi and Yamanaka 2006). The iPSCs overcame the ethical concern that rose above ESCs. Moreover, iPSCs properties are analogous to ESCs such as pluripotency, teratoma formation, embroid formation, and differentiation.

The iPSCs technology has been used as autologous cells to reduce immune rejection after the transplantation. Moreover, it can overcome the ethical concern behind the ESCs and created a novel way towards cell therapy and regenerative medicine. For example, Wang et al. cultured neural crest stem cells derived from iPSCs on a tubular nanofibrous scaffold for sciatic nerve regeneration (Wang et al. 2011). In another study, Kimura et al. conducted cell transplantation by neural crest-like cells derived from human induced pluripotent stem cells (hiPSCs) and utilizing a silicon tube as a bridge for sciatic nerve regeneration (Kimura et al. 2018). Okawa et al. utilized the same strategy to improve diabetic neuropathy. They reported the therapeutic activity of the neural crest-like (NCL) cells derived from iPSCs, by the secretion of growth factors such as NT-3 and NGF. Moreover, transplantation of the NCL cells developed the neovascularization induction that mediated by the VEGF and bFGF secretion (Okawa et al. 2013).

Neural stem cells

The formation of the new neurons was long considered to occur in the embryonic state. This concept was challenged by Joseph Altman in 1962 who suggested that an adult brain can generate new neurons (Altman 1962; Obernier and Alvarez-Buylla 2019). Neurogenesis is the process in which new neurons generated by NSCs. Neural stem cells are multipotent cells with self-renewal ability that found in

the subventricular zone (SVZ) and subgranular zone (SGZ) in the CNS (Engler et al. 2018; Kennea and Mehmet 2002).

The therapeutic properties of NSCs has been investigated for decades. Reynolds et al. cultivated NSCs as neurosphere in vitro and demonstrated the proliferation and the potential differentiation of the NSCs into neurons, astrocytes, and oligodendrocytes (Reynolds and Weiss 1992). These properties paved the way for the treatment of neurodegenerative diseases such as Parkinson, Huntington disease, and SCI (Zhao and Moore 2018).

NSCs have great potentials for tissue engineering purposes since they have self-renewal ability as well as the capacity to differentiate to multiple neural lineages such as neurons, astrocytes, and oligodendrocytes. For example, O'Rourke et al. cultured the allogeneic NSCs on the collagen-hydrogel for the reconstruction of the 12 mm sciatic nerve injury model (O'Rourke et al. 2018).

Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are the stromal cells with fibroblast-like morphology that have the potential to differentiate into various cell types (Phinney and Prockop 2007). Moreover, MSCs can be found in the nervous system and wrap around bundles of peripherals axons (Adameyko and Ernfors 2019).

They are great candidates for tissue engineering and regenerative medicine due to availability, immunomodulatory effects, simplicity in isolation, and lack of ethical concerns. Moreover, the potential differentiation of MSC to the neuronal cells generates a substantial and growing attraction to utilizing the MSCs for autologous nerve grafting. Recently, the differentiation ability of the MSCs to the Schwann cells with paracrine activity demonstrated in the peripheral nerve regeneration (Evaristo-Mendonca et al. 2018). Georgiou et al. constructed an engineered neural tissue with Schwann cells aligned in constrained collagen hydrogel utilizing the adipose-derived stem cells (ADSCs) for sciatic nerve regeneration in a rat model (Georgiou et al. 2015). In another study, Zhang et al. showed the tendency of the human gingiva-derived MSCs for the spheroid forming and differentiation into neuronal and Schwann cells. They utilized the spheroids as a component in the 3D bio-printer system for nerve construction, which promoted rat facial nerve regeneration after transplantation (Zhang et al. 2018a, b).

Other stem cells for neural differentiation

Dental pulp stem cells (DPSCs) are another source for neural regeneration that presents in the dental follicle, dental pulp, and periodontal ligament. The self-renewal and multipotency properties in addition to the neural crest origin of DPSCs make them a suitable candidate for neural regeneration (Ghasemi Hamidabadi et al. 2017; Hafner et al. 2017; Mead et al. 2017). Furthermore, other classes of stem cells for nerve tissue engineering are hair-follicle-associated pluripotent (HAP) Stem cells. Obara et al. synthesized the polyvinylidene fluoride membrane encapsulated with HAP and implanted to the thoracic spinal cord of mice, which resulted in improvement and restoration of functional peripheral neurons (Obara et al. 2019).

Other classes of multipotent stem cells such as skeletal muscle-derived stem cells (SMDSCs), skin-derived precursors (SKPs), and perinatal stem cells can be utilized in peripheral nerve regeneration (Bhangra et al. 2016; Jiang et al. 2017; Tamaki et al. 2014).

Key intracellular signaling pathways in neural differentiation

Nerve tissue engineering requires controlling cellular behavior towards cell proliferation and differentiation of neurons. Generation of new neurons from stem cells in the human body depends on the intricate cellular signaling transductions that not only a link between the cell surface and nucleus but also control the cell's fate by regulating the gene expressions (Navarro Quiroz et al. 2018).

The dynamic interactions between microenvironment cues and intracellular pathways regulate the determination of stem cells towards the neural lineage (Faigle and Song 2013). Understanding the essential intracellular pathways such as Wnt, sonic hedgehog, and notch, which control the stem cells fate paved the way for better neuroregeneration strategies.

Wnt signaling

As mentioned before, SGZ of the dentate gyrus in the hippocampus and SVZ of the lateral ventricles, which are the niches for NSCs, are two parts of the CNS. Importantly, SGZ and SVZ utilizing the Wnt ligands for the regulation of the neural differentiation (Armenteros et al. 2018). Numerous studies demonstrate the crucial role of the Wnt signaling

pathway in neurogenesis and neural development (Inestrosa and Varela-Nallar 2015). Expression of the Wnt3 in the astrocytes of the hippocampus, which hindered the B-catenin degradation and activation of TCF/LEF transcription factors and consequently, activation of NeuroD1 and neural differentiation. NeuroD1, which is the member of the basic Helix-loop-Helix (HLH) transcription factors, is sufficient for the differentiation of the NSCs. Interestingly, NeuroD1 activation is depending on the Sox2 repression as a consequence of the overlapping between Sox2 and TCF/LEF (Sox/LEF) in the NeuroD1 promotor. Moreover, LINE1 is another essential regulating factor during neural differentiation that activates and suppresses Wnt/B-catenin and Sox2 respectively. It has been shown that Sox2 Contributes to the maintenance of the self-renewal and undifferentiated state of the NSCs (Dennis et al. 2019; Kuwabara et al. 2009).

Notch signaling

The Notch signaling pathway is another conserved pathway that regulates many aspects of neurogenesis in adult and neural development such as proliferation, differentiation, and apoptosis. The Notch signaling pathway is crucial for cell–cell interactions and communications due to the transmembrane nature of the notch ligand and receptor. The Notch signaling pathway is essential for self-renewal ability and maintenance of NSCs. Direct cell–cell interactions leads to binding the Notch receptor and ligand (DLL or jagged). After the proteolytic release of NICD and formation of a complex with the mastermind and RBPj, the complex translocates to the nucleus and activates the Hes1 and Hes5 transcription factors that inhibit the Neurogenin and DLL1 (Ben-Shushan et al. 2015; Ohtsuka et al. 1999). Furthermore, Hes1 protein suppresses the transcription of Hes1 gene by negative feedback, which is responsible for the Oscillation expression of the Hes1 in progenitor cells. Consequently, Neurogenin and DLL1 present reversed dynamic expressions in correspondence with Hes1 oscillation, which is essential for maintenance and diversity of NPCs (Figure 1–10) (Kageyama et al. 2008; Shimojo et al. 2008); (Table 1).

It has been demonstrated that the balance between NPSCs and NSCs population in SVZ regulates by cell–cell interactions through the Epidermal Growth Factor Receptor (EGFR). Epidermal Growth Factor Receptor regulates the Notch signaling pathway by the NUMB protein, which inhibits the internalization of NICD and blocks the Hes1 activity. Moreover, NUMB promotes degradation of the

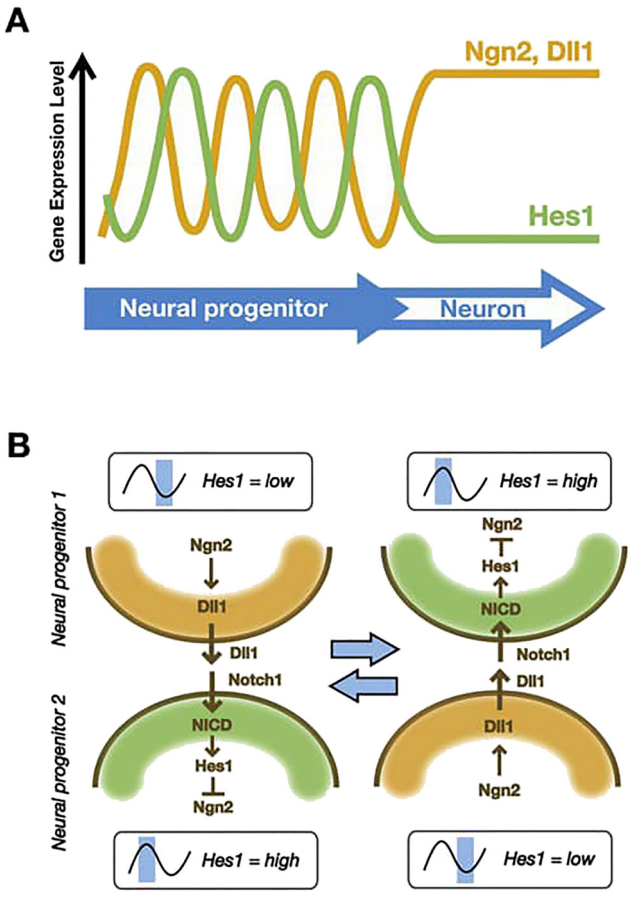

Figure 1: Presence of oscillation in the notch signaling pathway in dividing neural progenitors. (A) In immature postmitotic neurons, the Hes1 downregulated, but Ngn2 and Dll1 are upregulated. (B) the Oscillation of Hes1, DLL1, and Ngn2 expressions is favorable for maintaining and proliferation of neural progenitor cells, which demonstrated the necessity of the sustain upregulation of Ngn2 in neural differentiation (Shimojo et al. 2008).

Notch1 by ubiquitination and downregulation of the notch signaling pathway in SVZ (Aguirre et al. 2010).

Sonic hedgehog signaling

Another ubiquitination and the inhibitory effect of numb protein is suppressing the Gli1, which is a transcription activator of the canonical hedgehog signaling pathway (Di Marcotullio et al. 2006). Sonic hedgehog (Shh) plays a significant role in proliferation, differentiation, neural patterning, and neural development. The Gli transcription factor activates when the soluble extracellular Shh protein binds to Patchy transmembrane receptor protein (Ptc), and it activates Smoothened (Smo) G protein in Canonical Gli-dependent signaling (Antonelli et al. 2019; Carballo et al. 2018). Canonical Gli-dependent signaling pathway

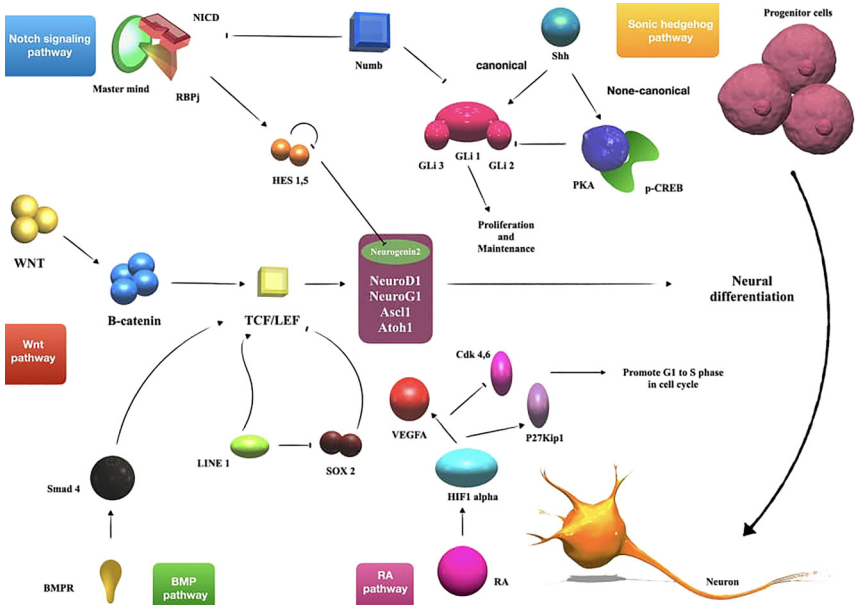

Figure 2: Cross-talk between various signaling pathways in neural differentiation.

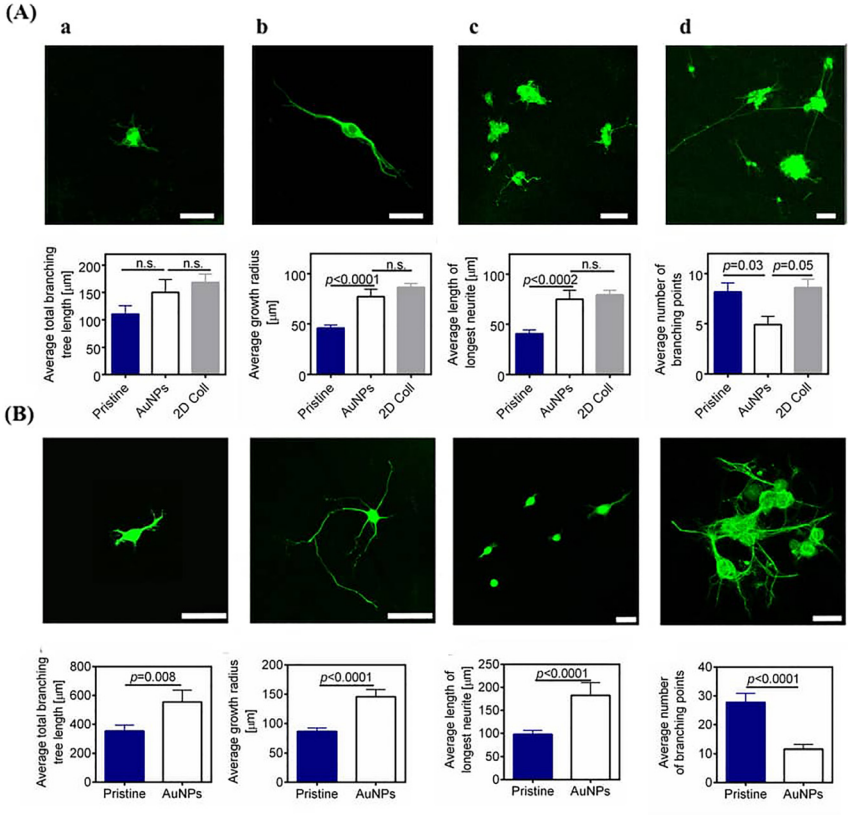

Figure 3: Effect of AuNPs-decorated scaffolds on neural differentiation and maturation. (A) Effect of AuNPs-decorated scaffolds on the growth of PC12 cells and (B) primary neurons by confocal microscopy stained against α-tubulin. (a) Pristine scaffold (electrospinning PCL/gelatin nanofibers) and (b) AuNPs-decorated scaffold. Formation of neural network in (c) Pristine scaffold and (d) Gold nanoparticle decorated scaffold (Baranes et al. 2015).

associated with the proliferation of NSCs and inhibition of apoptosis for maintenance of the SVZ and DG niches. The injection of cyclopamine, which is an Shh inhibitor into the hippocampus resulted in a severe reduction in DG progenitor cells' proliferation. Moreover, activation of Ptc produced none terminal symmetric cell division and conversely, inhibition of Shh resulted in promoting asymmetric cell division and differentiation (Yang et al. 2015).

Shh signaling pathway executes various functions depending on the stage of the development. For example, canonical glial signaling increasing neural progenitor cell specification and proliferation in the neural plate. The

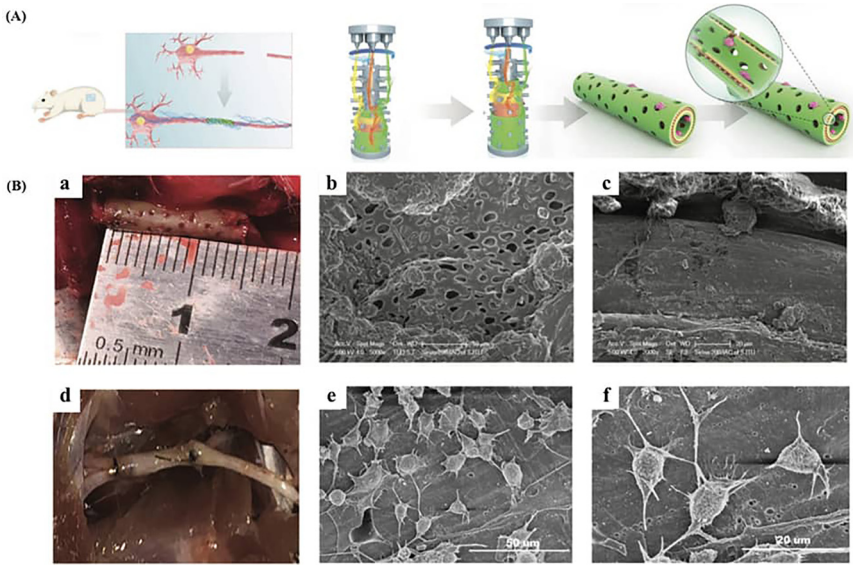

Figure 4: Polydopamine-Gold/PCL nanocomposite nerve conduit facilitates neural differentiation. (A) Schematic representation of synthesizing and implementing of PDA-gold/PCL nanocomposites in a rat model. The gold/PCL membrane (yellow and orange layer) was fabricated by spraying the gold and PCL suspension onto the mold with a 3D printer. Afterward, the PDA (green layer) was sprayed on gold/PCL and the pores made by the microneedles. (B) (a) Implementing PDA-gold/PCL nerve conduit for connecting the sciatic nerve of a rat with a 15 mm in length which was implanted in the hind limb of the Sprague–Dawley rat model. (d) Regeneration of the sciatic nerve after 18 weeks. (b) SEM image of nonporous, (c) multilayered structure of PDA-Gold/PCL nanocomposites and (e, f) SC morphology on PDA-Gold/PCL Scaffold (Qian et al. 2018).

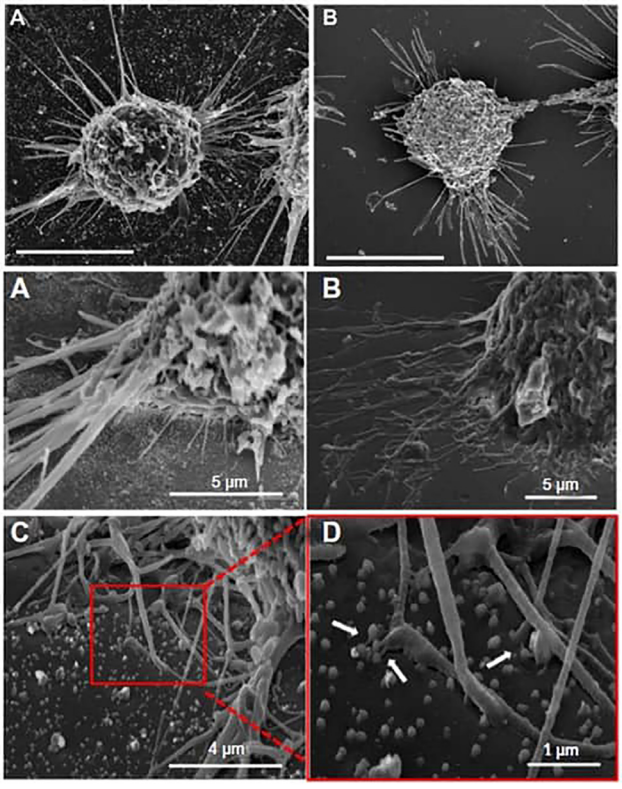

Figure 5: HRSEM image of SH-SY5Y cells on a glass substrate coated with AgNPs show straighten neurites that emerging from the cell body, which attach to the glass substrate coated with AgNPs. White arrows show the AgNPs on the substrate (Alon et al. 2014).

Transition to the spinal cord resulted in the none canonical Shh signaling pathway and Calcium spike, which recruit the PKA and P-CREB to inhibit the Gli activity in the differentiating neuron (Brennan et al. 2012).

Other signaling pathways

The regulation of shifting between proliferation and differentiation is crucial in neurogenesis. The dynamic crosstalk between various signaling pathways provides complex principles for neural development. For example, Armenteros et al. demonstrated that BMP2 and BMP4 have a synergistic effect on the differentiation of NSCs with Wnt signaling via the binding of the Smad4 to LEF/TCF (Armenteros et al. 2018). Moreover, the BMP7 along with Wnt, and FGF/FGF8 improve differentiation by inhibition of the Shh canonical signaling pathways. This antagonist activity between BMP7 and Shh, shifting the differentiation and specification of cells towards rostral phenotypes or floor plate cells during neural development. Similarly, FGF preventing Gli activity by recruiting the ERK and JNK kinase and promoting differentiation (Belgacem et al. 2016).

It should be noted that further studies required to evaluate the role of signaling pathways in the development of the nervous system. For instance, several studies introduced the Retinoic acid (RA) as a differentiation inducer molecule. In contrast Misha et al. demonstrated the proliferation sides of the RA by activation of the HIF1a and VEGFA, which promote the G1 to S phase transition in NPSCs by activation and inhibition of the Cdk4/6 and p27Kip1 respectively (Mishra et al. 2018).

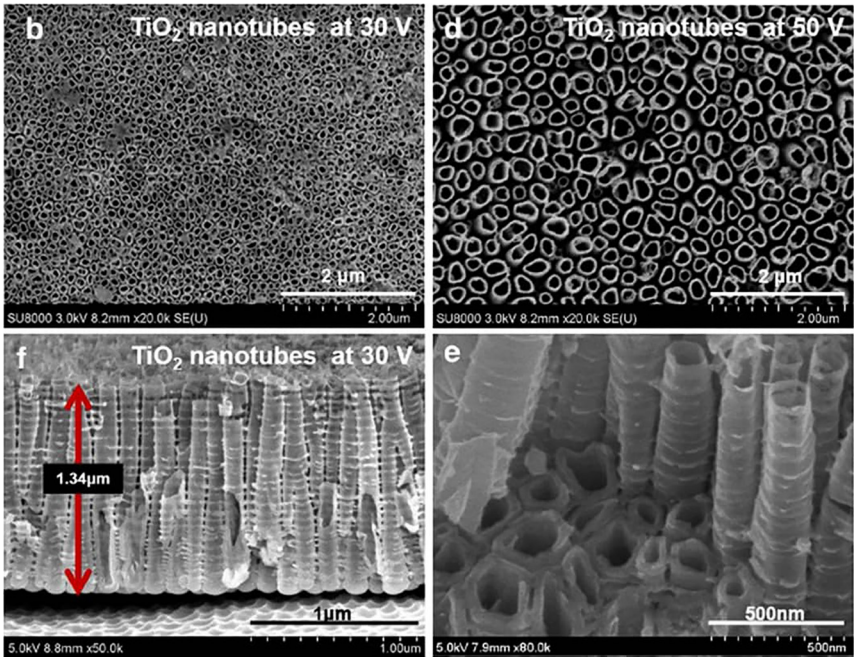

Figure 6: SEM image that shows the surface morphology of TiO_2 nanotubes under different voltage. The average length of the nanotubes were measured approximately 1.34 ± 0.26 μm (Lan et al. 2018).

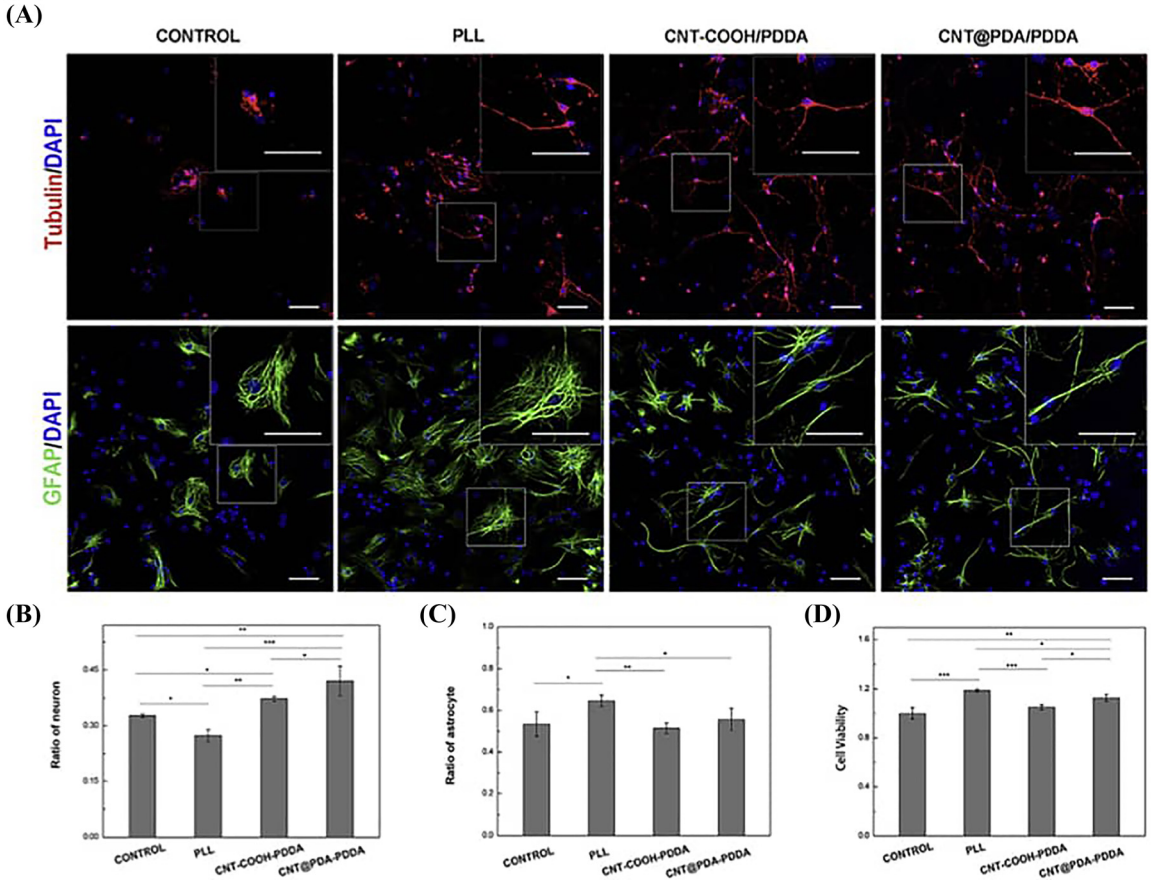

Figure 7: Characterization of NSCs differentiation on Carbon nanotube multilayered nanocomposites. (A) Characterization of NSCs differentiation by immunohistochemical staining. The green (GFAP) and red colors (beta III tubulin) show the neurons and astrocytes respectively, and the nucleus stained by DAPI). (B–D) Statistic analyzing of the differentiation proportion of neurons and astrocytes and cell viability of the NSCs on different substrates (Shao et al. 2018).

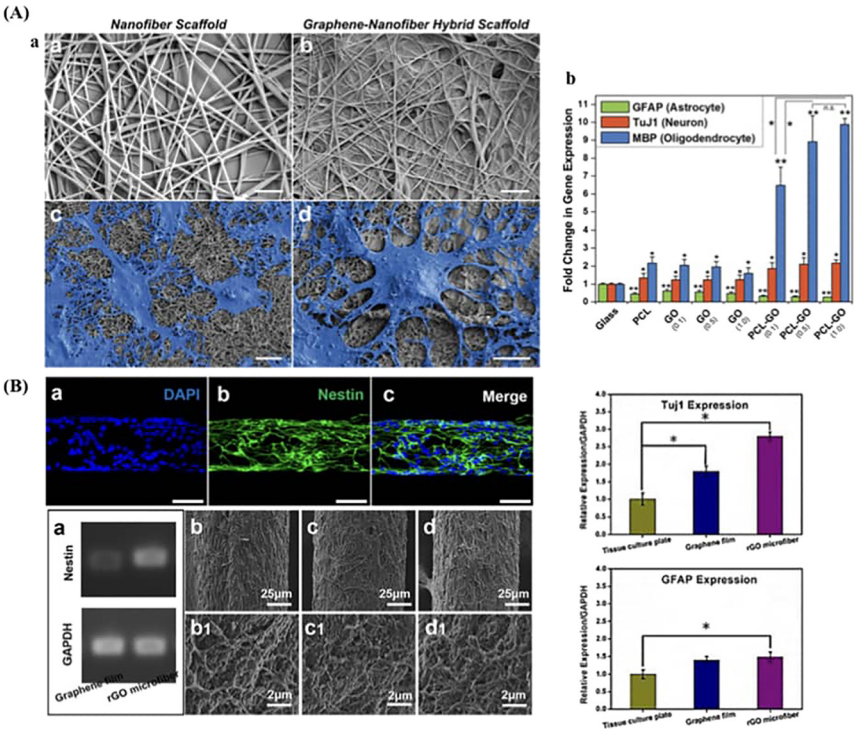

Figure 8: Effect of GO and rGO nanostructures on guiding and differentiation of NSCs. (A) (a) Comparison between PCL nanofibers and PCL nanofibers coated with GO (1.0 mg/mL GO solution) scaffold effects on the morphology of NSCs after 6 days of culture with the FE-SEM microscopy (the cells show by the pseudo-color for a better contrasting). (b) Quantitative PCR analysis of specific fold change gene expression of astrocytes (GFAP), neuron (TuJ1), and oligodendrocytes (MBP) on the various substrates (Shah et al. 2014). (B) (a) Effect of nanostructured rGO microfibers on the differentiation of NSCs, which investigated by the immunostaining. The green color represents the nestin biomarker and the blue color belongs to DAPI (B) (a) electrophoresis analysis of Nestin expressions in NSCs cultured for 3 days on Graphene film and nanostructures rGO microfibers (b) SEM image of NSCs spreading on nanostructures rGO microfibers (c) qPCR analysis of the expression level of GFAP and TuJ1 in tissue culture plate, graphene film, and nanostructured rGO microfibers (Guo et al. 2017).

Environmental cues involved in neural differentiation

The human body consists of numerous cell types derived from a totipotent zygote. During embryonic development, the zygote gives rise to more specialized cells by variation in gene expression, which results in more complex tissues. The process in which immature cells evolve to more specialized cells described as cell differentiation that dramatically changes the size, shape, and metabolic activity of the cells (Amit and Itskovitz-Eldor 2002).

The primary molecular process that regulates the differentiation and determination of cells' fate is cell signaling. Moreover, the regulation of stem cells is established by their microenvironment, which called a niche. The mixture of physical and chemical cues in stem cells' niche influence and instruct them to maintain or determine their fate. The harmony between external environment signals and cellular intrinsic factors is crucial for cells' fate regulation. The ECM-cell interactions, cell–cell interactions, and soluble factors stimulate diverse internal signals that alter the gene expression and cellular behaviors (Mashinchian et al. 2015).

Cell–ECM interactions

The ECM is a three-dimensional biological scaffold that secreted by the resident cells and consists of a complex composition of proteins and glycoproteins. Such heterogeneous structure plays a pivotal role in the unique compositions-dependent response, which is essential for cells' fate determination through cell–matrix interactions (Chen et al. 2007; Wojcik-Stanaszek et al. 2011).

The cell–ECM interactions mediated by the integrin molecules on the cell surface. Integrins are the transmembrane adhesion proteins that directly interact with the ECM Proteins and glycoproteins including collagen, laminin, fibronectin, and vitronectin (Barczyk et al. 2010; Hynes 2002; Wilems et al. 2019). It has been shown that integrins have important functions in neuroregeneration particularly in peripheral nerve regeneration. The heterodimeric structure of the integrins provides diverse functionality in several physiological circumstances (Barros et al. 2011; Kazanis and ffrench-Constant 2011). For instance, in peripheral nerve injury, the interactions between vimentin and B1 integrins in Schwann cells contribute to the peripheral nerve regeneration and axonal

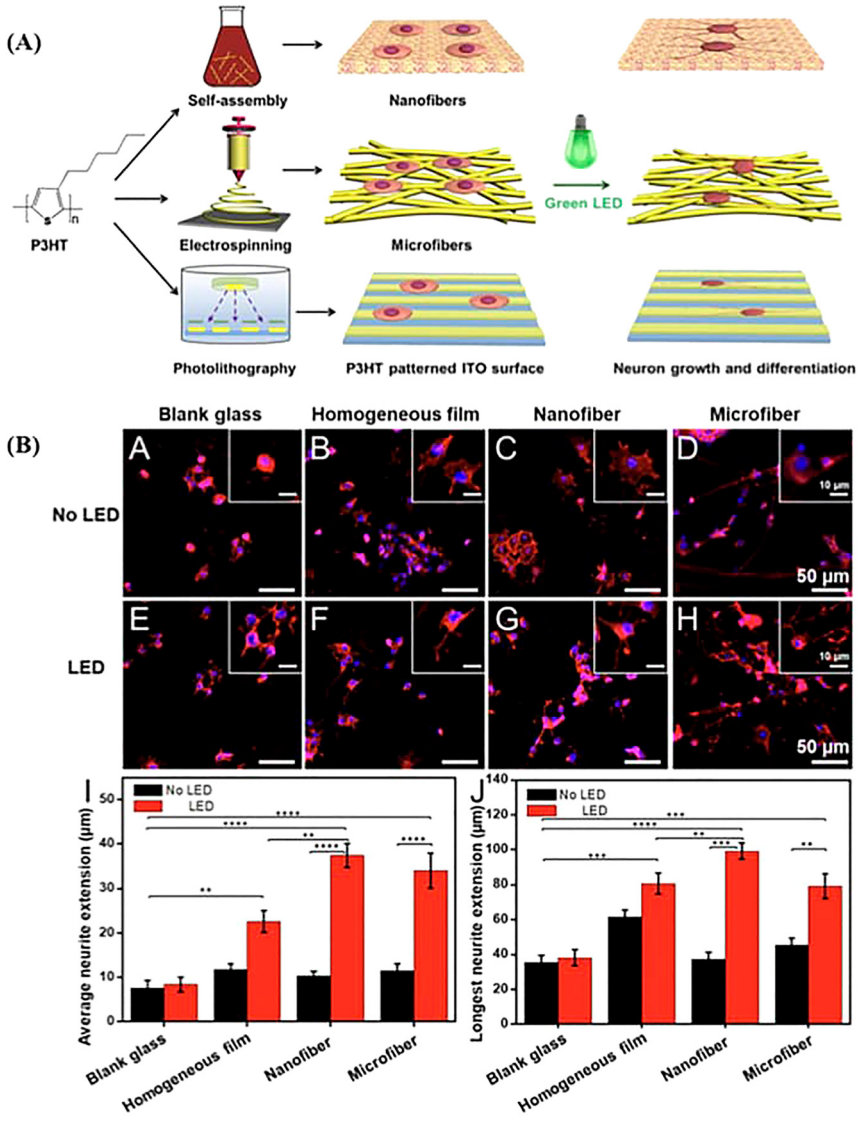

Figure 9: Micro/nanoscale P3HT nanofibers as a substrate for neural differentiation. (A) Schematic representation of PC12 cells differentiation on P3HT nanofibers, microfibers, and patterned surface. (B) The positive effect of P3HT nanofibers on the differentiation of PC12 cells (Wu et al. 2019).

outgrowth (Chang et al. 2012). Moreover, Abe et al. (2018) reported the promotion of the initial and final differentiation stage transition in cerebellar granule cell precursors through the interactions between avB5 integrins and vitronectin. In contrast, adult neurogenesis is limited in the CNS due to the lack of localization of integrins through selective polarized transport. Moreover, axon-repulsive molecules such as Nogo-A, Myelin-associated-glycoprotein (MAG), Aggrecan, and Class III semaphorins inactivate and restrict axonal regeneration in the CNS (Nieuwenhuis et al. 2018).

Study of the cell–matrix interactions and the ECM composition effects on proliferation and differentiation, can contribute to the nerve repair and neural tissue engineering (Ruzicka et al. 2019; Wu et al. 2017; Zhang et al. 2018a, b). Modifying alginate hydrogel with integrin-binding ligands such as LXW64 and LXY30 resulted in inducing differentiation of NPCs to oligodendrocytes (Wen et al. 2019). Moreover, Haggerty et al. demonstrated the acceleration of the axonal growth and functional recovery of motor neurons in the hindlimb through the injection of the soluble laminin polymers (Haggerty et al. 2019).

Cell–cell interactions

Currently, the major approaches in nerve tissue engineering is focused on cell–matrix interactions and neurotrophic factors signaling including design and synthesize various ECM and delivery of cells and neurotrophic factors. Despite the numerous functions of cell–cell interactions in the nervous system such as synapse formation, cell migration, and neural development, utilizing the cell–cell communication in neural development and regeneration

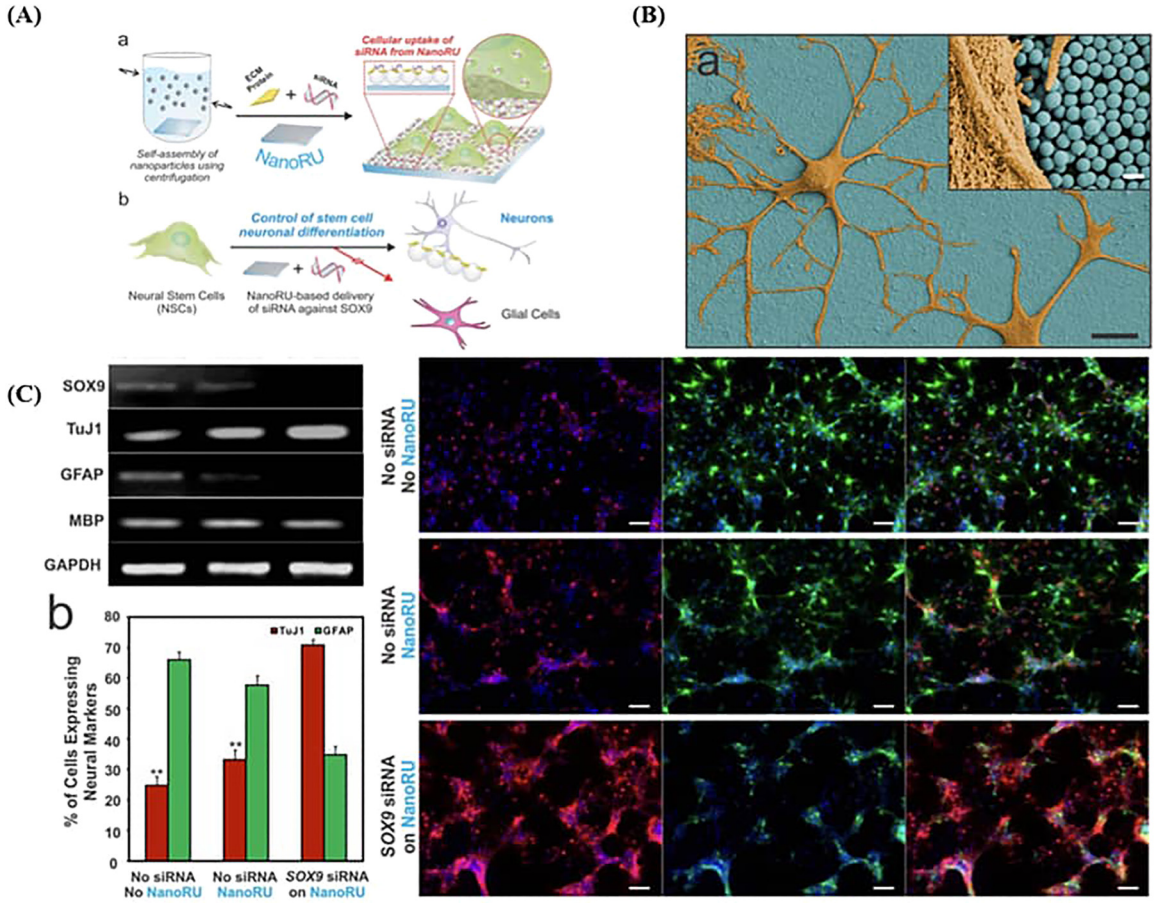

Figure 10: NSC differentiation on NanoRU. (A) Schematic representation of extracellular matrix coated with silica nanoparticles and their applications NSC differentiation on NanoRU coated with SOX9 siRNA. (B) SEM image of NSCs on the scaffold coated with silica nanoparticles. (C) Differentiation of NSCs on NanoRU scaffold (Solanki et al. 2013).

strategies is neglected (Chooi and Chew 2019; Gu et al. 2014; Subramanian et al. 2009).

Cell adhesive molecules (CAMs) located on the cell surface and mediated the direct cell–cell contact. Cadherins and immunoglobulin superfamily (IgSF) is the general category of the CAMs in the nervous system. Dysregulation in the CAMs level contributes to severe neurological disorders and dysfunctionality of the nervous systems. On the other hand, CAMs play a crucial role in cells' fate determination and nerve regeneration (Chooi and Chew 2019; Pollerberg et al. 2013). For example, N-cadherin (NCAD) is the most studied subtype of cadherins in the nervous system that induces neurite outgrowth by stimulation of the FGFR, cytoskeleton linked catenins, and p120 signaling pathways. Besides, NCAD is responsible for neural differentiation of NPCs by recruiting the B-catenin and AKT signaling pathways (Gavard et al. 2004; Miyamoto et al. 2015; Zhang et al. 2013).

The Nerve growth factor is the common soluble factor in nerve tissue engineering, which differentiate the NSCs. It has been suggested that the NCAD and NGF have a synergistic effect on neurite outgrowth, which hallmark the combination effect of cell–cell interactions and neurotrophic factors. Consequently, coating and modifying of biomaterials with NCAD or encapsulation of the NCAD and NGF for co-stimulation of neurite outgrowth and neural differentiation can be utilized neural tissue engineering (Doherty et al. 1991; Ferguson and Scherer 2012; Willerth and Sakiyama-Elbert 2007). In contrast, maintenance and self-renewal ability mediated by ECAD (Dasgupta and Gutmann 2005). Interestingly, the switch between the expressions of ECAD and NCAD modulates the neural differentiation in ESCs (Haque et al. 2012).

Neurotrophic factors

Cell differentiation is a mechanism requiring inclusive biochemical crosstalk between ECM and cellular proteins.

Table 1: A summary of nanomaterials which impact the cellular behavior and their applications in neural tissue engineering.

Nanomaterials	Scaffold	Result	Signaling pathways	Size (nm)	Cell type	Exogenous stimulation	Applications	References
AuNPs	-	ESCs to DA neuron differentiation	mTOR/ p70S6K	5, 25, 30, 60	ESCs	-	Neuronal differentiation	Sershen et al. (2000)
AuNPs	PCL/Gelatin nanofibrous	Differentian, growth and maturation	-	10	PC12	-	Integration into nerve conduits	Chang et al. (2017)
AuNPs	PDA/PCL	Proliferation, differentiation, myelin sheath growth, angiogenesis	-	-	BMSCs, SCs	-	Integration into nerve conduits	Qian et al. (2018)
AuNPs	Silk fibroin nanofiber	Promote adhesion, proliferation of Schwann cells	-	2–22	SCs	-	Integration into Nerve conduit, sciatic nerve regeneration,	Das et al. (2015)
AuNPs	Collagen nanofibers	Neural differentiation and proliferation	-	-	Placental-derived MSCs	Electrostimulation	Myocardial and neuronal differentiation	Orza et al. (2011)
AuNRs	-	Neurite outgrowth, neural differentiation,	-	48.6 × 13.8	NG108-15 Neuroblastoma	Laser irradiation	Peripheral nerve regeneration	Baranes et al. (2015)
AuNRs	2D-plastic substrate	Neural differentiation	-	~36 length × 12 nm diameter,	hMSCs	-	Neural differentiation	Solanki et al. (2013)
AuNPs	Chitosan	Enhance Proliferation and alignment	-	5	NSCs	-	, axonal regeneration, Peripheral nerve regeneration	Cheng et al. (2019)
MnAu NPs	-	Increased neurite length, neuronal differentiation	-	8.6	PC12	-	Peripheral nerve regeneration	Bhang et al. (2015)
AgNWs	PEG hydrogel	Enhance differentiation and guide neurite outgrowth	-	-	NSCs	Electrical stimulation	Peripheral and CNS neural regeneration	Lee et al. (2018)
Fe_3O_4	Functionalized with PEG	Synergistic effect with NGF on neurite outgrowth and differentiation	MAPK signaling pathways	11	PC12	-	Neurologic and therapeutic applications	Vangijzegem et al. (2019)
MWCNT	Fibrin coated Polyurethane	Increase cell attachment, proliferation, growth, and electrical conductivity	-	OD: 20–30 nm	hEnSCs	-	Neural tissue engineering	Hasanzadeh et al. (2019)
MWCNT	Chitosan grafted polyurethane With polypyrole coating	Enhance proliferation, differentiation and migration.	-	10 nm in external diameter prepared by chemical vapor deposition (CVD)	Pc12 and Schwann cells (S42)	-	Nerve condiut applications	Shrestha et al. (2018)
Electrospun carbon nanofibers (ECNFs)	Polyacrylonitrile	Enhance neural proliferation and differentiation with enhance electrical conductivity	-	-	NSCs	Electrical stimulation	Neural tissue engineering	Shi et al. (2007)

Table 1: (continued)

Nanomaterials	Scaffold	Result	Signaling pathways	Size (nm)	Cell type	Exogenous stimulation	Applications	References
GO	PLGA	Enhance cell survival, proliferation, differentiation, and surface properties	-	Air gap distance: 20 cm; inner diameter of spinneret: 0.4 mm	NSCs	-	IGF-1 delivery and neural tissue engineering	Qi et al. (2019)
GO and rGO		Improved the neural differentiation rate But the GO is more effective than rGO	-	Sheet with 1.08 thickness and size distribution of 1 and 1.5 µm	ADSCs	-	Neurogenic differentiation	Feng et al. (2018)
Reduced graphene paper	Silk nanofibrous	Increase neural growth, cell alignment, neural network formation, and neural differentiation	-	5–10 µm in size and 1.2 nm in thickness	SH-SY5Y	-	Neuronal differentiation	Lan et al. (2018)

Neurotrophic factors play an essential role in nerve growth and differentiation in neural development and adult neurogenesis. The most common neurotrophic factors are the brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), neurotrophin-4/5, and NGF, which activate Trk receptors and have a low affinity for the p75 receptor (Willerth and Sakiyama-Elbert 2007).

One of the main neurotrophic factors produced by Schwann cells after peripheral nerve injury is NGF. The direct contact of NGF with TrkA activates the MAPK intracellular pathways, which are responsible for the axonal alignment and outgrowth, differentiation, migration, and cell survival in the site of injury. Furthermore, NGF has a significant role in the development of the cholinergic neurons that makes them efficient in the treatment of neurodegenerative diseases such as Alzheimer's disease (Martorana et al. 2018; Okur et al. 2018; Siegel and Chauhan 2000; Xu et al. 2016). The main problem with the administration of NGF and growth factor therapy are redistribution and rapid enzymatic degradation. These obstacles can be overcome by utilizing a proper delivery vehicle that not only controls the growth factor release in a spatiotemporal manner but also improves the recapitulation of the neural microenvironment (Marcus et al. 2015). For instance, Li et al. acquired the thermo-sensitive heparin-poloxamer hydrogel for the co-delivery of the NGF and basic fibroblast growth factor (bFGF) for the peripheral nerve regeneration (Li et al. 2018).

Turning to BDNF, high expression of the BDNF and its receptor (trkB) in the adult nervous system suggested the neurogenesis activity of the BDNF in the adult brain. Moreover, The BDNF/NSCs transplantation highlighted the improvement in functional recovery after ischemia and brain damage in rats (Ma et al. 2012; Zhu et al. 2011). Furthermore, Li et al. demonstrated the impairment of the neurogenesis in the embryos and adult hippocampus by the ablation of the TrkB receptors (Li et al. 2008).

Another neurotrophic factor in the NGF family is NT-3, which promoting neural differentiation and neurogenesis in peripheral nerve injury and neuronal outgrowth in motor neurons after spinal cord injury with its unique TrkC receptors (Grill et al. 1997; Taylor and Sakiyama-Elbert 2006; Wu et al. 2018).

Various growth factors such as TGFb, GDNF, CNTF, etc. have been demonstrated to be able to promote neurogenesis, which can be utilized in nerve tissue engineering (Willerth and Sakiyama-Elbert 2007). For example, the FGF family promotes neurogenesis indirectly by angiogenesis and enhances nerve proliferation and axonal outgrowth after an injury (Grothe et al. 2006).

Effect of nanomaterials on neural differentiation

One of the intricate biological phenomena is nerve regeneration. Regeneration in the PNS occurs only in small injuries, and the CNS has limited regeneration potential. Furthermore, the complexity in the properties of the nerve cells such as morphology and electrical activity has raised the challenges for nerve regeneration strategies (Abdal Dayem et al. 2018a, b; Polak and Shefi 2015). Currently, most strategies for neural regeneration including direct cell injection into the injured site and utilizing growth factors for promoting cell regeneration have limited success, considering the inadequate differentiation efficiency in cell therapy (Wei et al. 2017a, b). Consequently, more effective strategies needed for controlling cellular behaviors such as proliferation, migration, and directed cell differentiation for neural regenerations. Moreover, in the case of peripheral nerve injuries, nanomaterials can be utilized for the design and development of engineered nerve guidance channels (NGCs) that contribute to the regeneration of PNS. NGCs have the ability to reduce the scar tissues, and they can contribute to the sprouting of axons from the proximal nerve (Amani et al. 2019a, b, c, d). Nanomaterials provide alternative strategies to affect neuronal behaviors such as differentiation, proliferation, and electrical properties. It has been shown that the nanomaterials can activate the signaling pathways and transcription factors that are responsible for neural proliferation and differentiation (Khan et al. 2018; Polak and Shefi 2015). Nano-constructs could be utilized in various ways. They could be used as suspensions or they could be immobilized on various 2D or 3D substrate that can change the properties of nanomaterials. For example, there are concerns about the toxicity of metallic nanoparticles when they injected directly into the body. However, immobilizing these nanoparticles on different substrates can significantly reduce their toxicity. Moreover, the immobilizing of metallic nanomaterials on the different substrates can improve the electroconductivity of various substrates that could be beneficial for neural regeneration. Another approach is to change the chemical surface properties of nanomaterials. For instance, Alghazali et al. modified gold nanorods with thiolated PEG, which contained -NH_2 groups for enhanced cell adhesion (Alghazali et al. 2017). Nanomaterials can be functionalized with various proteins such as monoclonal antibodies, RGD, and various ECM proteins for different purposes such as targeted delivery and increase in biocompatibility and cell adhesion properties of nanomaterials (Chen et al. 2018; Esmaeely Neisiany et al. 2020; Jodat and Shin 2020). Furthermore, nanomaterials can be utilized with various shapes such as nanorods and nanospheres as well as nano-scaffolds (Abdal Dayem et al. 2018a, b; Paviolo et al. 2013). Besides, nanoparticles can be acquired in nanocomposite; providing a suitable microenvironment capable of modulating the stem cells' fate (Baranes et al. 2015). Such strategies can be combined with cell therapy and growth factor delivery for a desirable outcome in the neural repair, which can pave the way towards neural disease treatment (Dvir et al. 2011).

Metal-based nanomaterials

Metal-based nanomaterials such as Gold nanoparticles (AuNPs), Silver nanoparticles (AgNPs), Iron oxide nanoparticles (IONPs), zinc oxide (ZnO), titanium oxide (TiO_2) with different shapes and sizes, can be synthesized with chemical or biological methods. Such materials with high surface energy, surface plasmon resonance (SPR), high surface area to volume ratio, and conductivity are well known for their biomedical applications such as drug delivery, diagnostic, and anti-microbial activity (Abdal Dayem et al. 2018a, b; Ramos et al. 2018). Moreover, they can influence behaviors of stem cells such as attachment, migration, proliferation, and differentiation by releasing the metal ions, which modulating the gene expressions involved in activation of cell adhesion, cellular rearrangement, and neural differentiation (Paviolo and Stoddart 2015; Polak and Stoddart 2015; Yoo et al. 2004; Yuan et al. 2018). As conductive nanomaterials, they can be utilized in nanocomposites for electrical stimulation based nerve regeneration. Park et al. synthesized 20 nm gold nanoparticles and coated onto a positively charged glass substrate pretreated with PEI for electrical stimulation of PC12 cells, which leads to differentiation and neurite outgrowth after each round of electrical stimulation (Park et al. 2008). Another application is employing the Magnetic nanoparticles (MNPs) for axonal growth and guidance of new neurites towards the distal stump. For instance, Riggio et al. functionalized the MNPs with beta-NGF and aligned the neurite outgrowth with a magnetic field in PC12 cells (Riggio et al. 2014).

One of the main concerns is the safety of the Metal based NPs, which depends on various characteristics such as size, shape, concentration and synthesis methods, etc. Therefore, more toxicological assessment is required to evaluate the safety of Metal based NPs (Amani et al. 2019a, b, c, d; Mordorski and Friedman 2017).

Gold nanoparticles

Gold nanoparticles (AuNPs) have been utilized widely in nanotechnology, drug delivery, photothermal therapy, tumor detection, imaging, and biomedicine (Giljohann et al. 2010; Hernández-Sánchez et al. 2018; Kyriazi et al. 2018). In the past few decades, several approaches for controlling the size, shape, and surface functionality of the AuNPs were developed. In 1951, Turkevich et al. developed the AuNPs synthesis method by utilizing the citric acid as a stabilizer. Afterward, various synthesizing methods developed for producing AuNPs with different sizes and shapes (Freitas de Freitas et al. 2018; Jazayeri et al. 2016; Yeh et al. 2012).

Recently, numerous studies demonstrated the effect of AuNPs on cells' fate and cellular behavior since it can encourage the differentiation of the various stem cells such as ESCs and MSCs to cardiomyocytes and osteoblast cells (Ko et al. 2015; Li et al. 2016; Ravichandran et al. 2014). The effect of AuNPs on ESCs investigated by Wei et al. revealed the promotion of dopaminergic neuronal differentiation in ESCs. Respectively, they showed the significant role of the mTOR/P70S6K signaling pathway by blocking the mTOR with Rapamycin, which reduces the differentiation of the ESCs (Wei et al. 2017a, b). These findings suggested that the interaction between the AuNPs and cellular signaling pathways involved in cells' fate determination. For nerve tissue engineering, integration of the AuNPs into the scaffolding materials have been used by researchers around the world. For example, Baranes and co-workers synthesized PCL/gelatin nanofibers 3D scaffold decorated by AuNPs through electrospinning for differentiation and maturation of neuronal cells. The PC12 cells cultured on the pristine scaffold displayed the limited neuronal outgrowth. Conversely, the cells on AuNPs scaffold exhibited a long neurite extension and able to form basic neuronal networks that envision the possibility of utilizing such approaches for neural repair such as spinal cord injury (Baranes et al. 2015).

Likewise, it has been reported that AuNPs can be integrated into the structure of hydrogels (injectable and stimulus responsiveness structures in tissue engineering) to create advanced controllable substrates with superior electrical and mechanical features. For instance, switchable AuNPs-hydrogel composites can be used as smart materials for the release of growth factors or drugs within the desired tissue via irradiation of light at the AuNPs SPR peak (Sershen et al. 2000; Skirtach et al. 2005; Yoo et al. 2017).

In another example, Qian et al. designed a polydopamine coated gold/PCL for differentiation of the MSCs to neurons for sciatic nerve injury, which improved the proliferation, differentiation, myelin sheath growth, angiogenesis, and functional recovery in vivo after 18 weeks postoperatively (Qian et al. 2018). Similarly, Das et al. fabricated silk-based gold nanocomposite for adhesion of Schwann-like cells for the peripheral nerve regeneration (Das et al. 2015).

AuNPs are prominently unique due to their physical and chemical properties such as easy modification, various optical properties, size, shapes and Localized Surface Plasmon Resonance (LSPR), which can be coupled with the beforementioned roles of AuNPs in cells' fate determination. For instance, collagen nanofibers can be coated by the gold nanospheres, which can be prepared by layer by layer deposition method as an electroconductive substrate for differentiation of the human placental-derived MSCs to neural lineages (Orza et al. 2011).

The repair of large lesions in the nervous system is the main challenge in nerve tissue engineering. An emerging alternative for the rehabilitation of large nerve gaps is NGCs. Since nerves are electrogenic cells, using conductive materials can contribute to the acceleration of neurite growth. For instance, Qian et al. used a multilayer molding method to provides conductive NGC consist of a polydopamine-coated gold/polycaprolactone (Qian et al. 2018). The authors mentioned that conductive NGCs were able to contribute to the differentiation of bone marrow MSCs into Schwann-like cells. Moreover, they found that implantation of conductive NGCs in the site of nerve sciatic injury resulted in angiogenesis and recovery in the animals (Qian et al. 2018).

The different sizes and shapes of AuNPs can influence the potential neural differentiation. It has been reported that the 30 nm AuNPs is the most effective size in promoting differentiation of the ESCs to the dopaminergic neurons with excellent biocompatibility (Wei et al. 2017a, b). Furthermore, the rode shape of AuNPs is acquired for neural differentiation. Utilizing the optically active surface of gold nanorods (AuNRs), which caused by LSPR is reported to enhance axonal extension, cellular activity, and activated membrane ion channels in neuronal cells (Paviolo et al. 2014; Paviolo et al. 2013). Alghazali et al. modulated the differentiation of MSCs through functionalized AuNRs with thiolated polyethylene glycol (PEG). They demonstrated the link between surface properties of AuNRs and the acceleration in the neurogenesis by activation of the LSPR through IR laser source and regulation of the Ca^{2+} channels (Alghazali et al. 2017). Moreover, it is well documented that the introduction of AuNPs into various scaffolds and decellularized natural matrices can changes their stiffness and elastic moduli, which are

fundamental factors for controlling cellular behaviors such as migration, proliferation, and differentiation (Baei et al. 2016; Shevach et al. 2014).

However, there is a controversy in toxicity associated with the sizes and shapes of the AuNPs. For example, utilizing the CTAB in preparation of the AuNRs correlated with the toxicity of the rode shape of gold nanoparticles. Moreover, AuNPs greater than 15 nm is associated with lower toxicity compared to smaller particles (Hornos Carneiro and Barbosa 2016). For example, Senut and co-workers demonstrated the cell death and toxicity of the 1.5 nm AuNPs on hESCs and their neural precursor derivatives (Senut et al. 2016). Therefore, further research and investigation should be addressed considering the none-biodegradability, toxicity, and adverse effects of AuNPs before clinical applications.

Silver nanoparticles

Nowadays, silver nanoparticles (AgNPs) applications are prevalent due to their excellent antibacterial and antifungal activities (Anandalakshmi et al. 2016; Franci et al. 2015; Xu et al. 2011). Generally, AgNPs synthesized by the reduction of silver salt in the presence of sodium borohydride as a reducing agent and a colloidal stabilizer such as PVA, PVP, BSA, citrate, and cellulose. Moreover, ß-D-glucose as reducing sugar and starch as the stabilizer can be utilized to synthesizing AgNPs (Stepanov et al. 2002).

There is a controversy regarding the ability of AgNPs to enhance neurogenesis as well as their toxicity and safety. However, it has been reported that toxicity of Ag-integrated scaffolding materials can be linked to the total release of AgNPs, reactive oxygen species (ROS) production by nanoparticles or ions (Ag^+) is an important factor for cell proliferation and differentiation (Stojkovska et al. 2014). For example, Dayem and co-workers demonstrated the differentiation of SH-SY5Y cells when they expose to AgNPs, which biologically synthesized with E.coli. They suggested that the enhancement of intracellular ROS leads to the activation of AKT and ERK and inhibition of dual-specificity phosphatase (DUSP) (Abdal Dayem et al. 2018a, b; Dayem et al. 2014). Conversely, numerous studies suggested the opposite aspect of AgNPs. For instance, it has been reported that exposure of the embryonic stem cell-derived neurons and astrocyte networks to AgNPs reduces neurite outgrowth and induces neurotoxicology by activation of AKT/GSK-3/caspase-3 signaling pathways (Repar et al. 2018). Similarly, Yamada et al. reported the unfavorable effect of AgNPs on the differentiation of human IPSCs. They showed the down-regulation of the OTX-2 as well as the inhibition of the mfn1 and intracellular level of ATP in human IPSCs (Yamada et al. 2018). Other studies described the effect of sublethal level of AgNPs on adult stem cells, which highlighted the reduction of B-catenin level and disruption of the actin dynamics in NSCs of SVZ (Cooper et al. 2019; Cooper and Spitzer 2015). Recently, Zhang et al. showed the compromise female hESCs differentiation through the interruption of x chromosome inactivation and the impairment of the Xist and Tsix expressions (Zhang et al. 2019a, b). Silver nanoparticles can be integrated into the scaffolding materials to improve their performance for nerve tissue engineering. For instance, Alon et al. (2014) designed a glass substrate coated with AgNPs using the sonochemical method. In this work, the authors tested if the positive promoting effect of nanotopography on the neuronal growth can be reinforced using active materials as the topographic platform. They examined the cell growth on AgNPs coated substrates and substrates sputtered with a homogenous layer of Ag, without topographical patterns (Alon et al. 2014). They found that both substrates significantly increased the number of neurites relative to glass substrates, indicating a material-driven promoting effect on the initiation of neurite outgrowth. With further analysis, the authors mentioned that coating the substrate with AgNPs act as anchoring sites to which the neurites adhere. Induction of tensile forces along the neurites following attachment to the AgNPs results in the promotion of their stabilization and formation of highly straightened neurites. In order to test the biocompatibility of AgNPs coated substrates, the issue of the NPs leaching from the glass substrate was studied by the authors, showing no release of nanoparticles or ions (Ag^+) to the medium (Alon et al. 2014). In another study by the same group, the effects of substrates with various particle densities on the behavior of the SH-SY5Y human neuroblastoma cells were studied (Nissan et al. 2016). Different particle densities onto the substrates were obtained by changing the concentration of the Ag ions and the sonication time. They found that increases in the density of AgNPs deposition increased neurites formation. An optimum concentration of AgNPs that exerted highest in neurite formation relative to other densities of the same diameter or smooth substrates was 45 NPs/μm^2 (diameter of 65–85 nm). The authors also suggested that the positive promoting effect of AgNPs in neurite formation can be linked to ROS generation because they mentioned that the highest generation of ROS was found at 45 NPs/μm^2 (Nissan et al. 2016). Indeed, the release of ROS plays an important role in controlling cell proliferation and differentiation because it can act as a specific second messenger in cell signaling cascades that are relevant to cellular behaviors such as differentiation and proliferation (Nissan et al.

2016). The risk of infection owing to direct contamination of scaffolding materials and implants during surgery and hospitalization remains the main challenge to conquer the realization of such eclectic techniques for routine clinical use. To overcome this problem, Koudehi et al. designed a bio-composite conduit containing nano bioglass/gelatin/AgNPs for peripheral nerve regeneration (Foroutan Koudehi et al. 2019). They have soaked the conduits in 2×10^{-4} to 9×10^{-4} µL of the colloidal nanosilver solution and then tested antibacterial activity using gram-negative (*E. coli*) and gram-positive (*S. aureus*) bacterial strains. They found that 7×10^{-4} µL AgNPs exhibited the most antibacterial activity and the lowest cytotoxicity effect (Foroutan Koudehi et al. 2019). It has been reported that changes in physicochemical properties of AgNPs affect their toxicity and neuroregeneration capacity. In an interesting example, Leynen et al. examined non-coated AgNPs and polyvinylpyrrolidone (PVP)-coated AgNPs (30 nm in diameter) on neurodevelopment in the freshwater flatworm Schmidtea Mediterranea (Leynen et al. 2019). They found that the lowest non-coated AgNPs exposure led to a markedly larger relative brain ganglia size, relative to the nonexposed worms. Additionally, when worms were exposed to the highest exposure concentration, 29% of PVP-AgNP and 10% of non-coated AgNPs-exposed worms failed to regenerate their cephalic brain ganglia. Likewise, the authors mentioned that 59% of the PVP-AgNP-exposed worms showed partial eye regeneration (33%) while disruption of eye regeneration occurred in 24% of non-coated AgNPs-exposed worms. Finally, they concluded that physicochemical properties and concentration of AgNPs significantly influence their regenerative capacity and toxicity (Leynen et al. 2019).

Titanium dioxide

Titanium dioxide (TiO_2) nanomaterials are one of the widely used metal-based nanomaterials in food and cosmetics manufacturing due to anti-microbial activity and high UV radiation (Chen et al. 2014; Kinsinger et al. 2011). TiO_2 nanomaterials have been utilized in the biomedical field and clinical applications in prosthetic implants (Hou et al. 2013). However, they have raised concerns about safety and undesirable outcomes in regenerative medicine and biomedical applications. Generally, physiochemical properties of TiO_2 nanomaterials such as the tube diameter play pivotal roles in affecting cellular behaviors such as attachment, spreading, proliferation, differentiation of stem cells (Park et al. 2007).

Proteomics study of the TiO_2 NPs effects on the human ESCs revealed the disruption of pluripotency, DNA damage, and apoptotic response (Pan et al. 2018). Furthermore, TiO_2 NPs may involved in neurotoxicology by downregulation and upregulation of the Rac1/cdc42 and RhoA proteins respectively, which associate with neural development, axonal outgrowth, neurite formation, and neural differentiation (Hong et al. 2018). Accordingly, differentiation of primary neurons isolated from *Caenorhabditis elegans* (*C. elegans*) in the presence of TiO_2 NPs revealed the direct uptake of TiO_2 NPs by neurons and axonal growth impairment in 200–300 µg/mL, but no significant decrease in axonal length reported in less than 200 µg/mL. Interestingly, surface coating of biomaterials by TiO_2 NPs increases nerve proliferation and differentiation, which suggested the beneficial aspect of TiO_2 NPs attached to the substrate (Hu et al. 2018). There is a close association between neuronal toxicity of TiO_2 nanomaterials, the duration of exposure and their concentration. For instance, Wang et al. found a direct association between brain toxicity of TiO_2 NPs and sample concentrations (Jia et al. 2017). Jia et al. demonstrated that lowest test dose of nano-TiO_2 (50 mg/kg) showed no histopathological changes in the brain of mice after 14 days while intraperitoneal injection of 200 mg/kg nano-TiO_2 once a day for 14 days resulted in infiltration of inflammatory cells in the brain and cracking the neuronal cells (Jia et al. 2017). In another study, Hsiao et al. reported that TiO_2 NPs were mainly taken up by microglial cells and astrocytes (not by neuronal cells) and they can cause TiO_2NP-mediated ROS and secretion of pro-inflammatory cytokines such as TNF-α from microglia, not from astrocytes (Hsiao et al. 2016). An overview of neuronal toxicity of TiO_2 NPs has been recently reported by Baranowska-Wójcik and coworkers (Baranowska-Wójcik et al. 2020). Another study by Liu and co-workers demonstrated the dosage-dependent reduction in proliferation of NSCs by TiO_2 NPs in 24 h. They reported a significant depletion in neural proliferation for the concentrations higher than 100 µg/mL. Furthermore, they investigated the differentiation ability of NSCs when treated with 150 µg/mL of TiO_2 NPs (Liu et al. 2010). In an interesting work, Lan et al. designed TiO_2 nanotubes loaded with minocycline as antioxidant scaffolding materials on the surface of pure titanium through anodization at the voltage of 20, 30, 40 and 50 V and then soaking in minocycline solution (Lan et al. 2018; Leynen et al. 2019). They found that nanotubes at a voltage of 30 V had the diameter nearly 100 nm that makes them good candidates for neurogenesis. Additionally, the authors mentioned that the TiO_2 nanotubes fabricated at the voltage of 30–50 V demonstrated a lower contact angle and stronger hydrophilic surface than others

that can be attributed to the increase in surface area of nanostructures. Generally, they concluded that the optimal concentration of 5–20 μg/mL minocycline loaded in the TiO_2 nanotubes fabricated at the voltage of 30 V exerted the highest effect on the proliferation of Schwann cells and secretion of neurotrophic factors (Lan et al. 2018; Leynen et al. 2019). The physicochemical properties of TiO_2 nanomaterials can be modulated by surface coating to obtain the best outcomes for nerve tissue engineering. Yuan et al. developed nano-TiO_2/HA composite bioceramic on the surface of commercially pure titanium (cpTi, grade 2) discs using sol–gel techniques. Moreover, they demonstrated that the Schwann cells that cultured on nano-TiO_2/HA composite bioceramic were able to secrete much more BDNF at third day compared to smooth Ti discs (Yuan et al. 2007).

Iron oxide nanoparticles

Iron oxide nanoparticles (IONPs) attracted so much attention due to their superparamagnetic properties, which have numerous applications such as drug delivery and magnetic resonance imaging (MRI) (Du et al. 2019; Vangijzegem et al. 2019). Synthesizing IONPs with the sizes between 10 and 200 nm is a complex process and can be developed with various methods such as microemulsion, electrospray synthesis, hydrothermal reactions, hydrolysis and thermolysis, sol-gel synthesis, and more commonly, chemical co-precipitation technique of iron salts (Mody et al. 2010).

IONPs can be utilized for tracking the transplanted stem cells' fate. Lu et al. acquired an IONPs for visualization of the MSCs differentiation. Iron oxide nanoparticles were utilized for MRI protocol based cell tracking, which reported no significant difference in differentiation and cellular behavior (Lu et al. 2017). Besides, the characterization of the IOPNs and the biological effects is essential. Uptake of IONPs by PC12 cells leads to the upregulation of cell adhesion proteins, which regulate the cell–matrix interactions. Furthermore, IONPs increase the expressions of neural markers and promote the activation of the MAPK signaling pathways, which leads to promoting neurite outgrowth. Interestingly, IONPs and NGF affect neurite outgrowth synergistically, and the neurites start to elongate following one day exposure. Moreover, increasing the IONPs concentration promote the elongation of neurites, which showed the dose-dependent behavior of the IONPs in combination with NGF. It should be noted that the IONPs can not activate the MAPK signaling pathways without NGF. Kim et al. hypothesized that after internalization, the IONPs localized in the lysosomes, and the low pH contributes to the release of Fe ions from IONPs, which can be considered as the neurite outgrowth ability of the Fe ions in the presence of NGF. This ability can improve the cell–matrix interactions by elevating the beta-1 integrin expressions (Katebi et al. 2019; Kim et al. 2011).

Another application of the IONPs is utilizing the dual-modality characteristic of the IONPs. The IONPs can be functionalized with numerous agents such as Growth factors for selective delivery to the central or PNS (Giannaccini et al. 2017). Marcus and co-workers, covalently conjugate NGF on the IONPs for selective differentiation of the PC12 cells in the culture plate through a magnetic field. They confirmed that the functionalization of the NGF extends the NGF half-life and significantly improves neural differentiation and neurite outgrowth compared with free NGF. Furthermore, they showed the localization of the particles utilizing a magnetic field at the sciatic nerve and retina with direct and intravenously injection respectively (Marcus et al. 2015, 2018).

The main concern about utilizing the IONPs is their toxicity. Certainly, IONPs toxicity depends on many factors such as size, shape, surface chemistry, and chemical compositions, which can be modified. For example, coating the IONPs with different substances such as PEG and dextran can efficiently reduce the toxic effect of IONPs (Khalid et al. 2018; Pisanic Ii et al. 2007).

Carbon-based nanomaterials

Carbon nanotubes

The characteristics of CTNs such as thermal and mechanical properties combined with their size, shape, and electroconductivity properties make them unique for neural growth and neural tissue engineering. The CNTs can be utilized as a drug delivery system for neural cells. Moreover, they can be modified with various molecules for improving neural proliferation and differentiation. The bioinformatics studies proposed integrin-based interactions between NSCs and CNTs multilayers, which activate the Fak protein. Subsequently, the Wnt, MAPK, and PI3K/AKT signaling pathways activated, which regulate the proliferation and differentiation in NSCs. Furthermore, RhoGTPase recruits the actin cytoskeleton for neurite extension and synapse formation (Shao et al. 2018).

Carbon nanotubes can be synthesized in various types and sizes, which can be developed with different methods such as chemical vapor deposition (CVD), laser ablation, high-pressure carbon monoxide disproportionation, and

arc discharge method (Takeuchi et al. 2014). Generally, single-wall carbon nanotubes (SWCNTs) with 0.2–3 nm and multi-wall carbon nanotubes (MWCNTs) with 1.4–100 nm in diameter are two types of CNTs. The exposure of PC12 cells to 0.5–2 μm long MWCNTs reveals the activation and augmented stimulation of the neurotrophins through the upregulation of the TrkA/p75 receptors, which leads to neural differentiation. Since shorter MWCNTs can be easily internalized, the effect of shorter and longer MWCNTs can be different.

The shorter MWCNTs able to stimulate the expression of Gap43, Pincher, TH, and other associated protein, which involved in neurotrophins signaling pathways. Conversely, longer MWCNTs accumulated in the cytoplasm, which inhibits the TH protein expressions and has a toxic effect on cytoskeletal structures.

Carbon nanotubes can be utilized in both PNS and CNS tissue engineering. For example, Sang and Liu et al. fabricated the SWCNT- based thermosensitive hydrogel utilizing the PNIPAAM polymer for the SCI regeneration. They utilized an amphiphilic cross-linker for stabilizing the carbon nanotube, which can improve the electroconductivity of the hydrogel. Moreover, they investigated the potential roles of SWCNT-PNIPAAM hydrogel on SH-SY5Y growth as well as the effect of this hydrogel on SCI regeneration. Indeed, they found that SWCNT-PNIPAAM hydrogel enhances neurite outgrowth by inducing the electrical stimulation in vitro. Turning to the SCI model, the SWCNT-PNIPAAM hydrogel not only promotes the neural regeneration but also it reduces scars formation in vivo (Sang et al. 2016). In another study, Jahromi and coworkers fabricated the PLLA/MWCNT conduits filled with fibrin hydrogel containing SCs and curcumin encapsulated chitosan nanoparticles for sciatic nerve regeneration. They concluded that the presence of 0.25 wt% MWCNTs inside the wall of the PLLA conduit is an optimized concentration, which showed an excellent biocompatibility, mechanical properties, and hydrophilicity (Jahromi et al. 2020).

The biocompatibility and neuronal toxicity of the CNTs are debatable and under investigation since some studies addressed the potential toxicity through the agglomeration of CNTs in CNS (Belyanskaya et al. 2009). The study by Zhang et al. demonstrated the concentration and shape dependency cytotoxicity effect of the SWCNTs by measuring the ROS generation and caspase-3 activation (Zhang et al. 2010). Another significant factor in neurotoxicity of SWCNTs is the surface chemistry of, which can be overcome by surface modification methods. The non-covalent p–p stacking between DNA and CNTs and the covalent modification has been established, which the latter significantly influences the neural toxicity of SWCNTs. For example, the functionalization of the SWCNTs by PEG significantly reduces the toxic effect of SWCNTs (Zhang et al. 2011). Furthermore, the toxicity effect of MWCNTs is studied by Meng et al. They investigated the influence of 5–60 μg/mL MWCNTs concentration on PC12 cells, which exhibited no significant toxicity (Meng et al. 2013). Conversely, the potentially detrimental effect of MWCNTs was reported by Wu and co-workers. They confirmed that 0.1 μg/mL does not inhibit neural outgrowth whereas 1, 5, and 10 μg/mL significantly reduce the axonal length, branching, and axonal regeneration (Wu et al. 2012). The comparison between the toxicity of the SWCNTs and MWCNTs revealed that the SWCNTs are more toxic than MWCNTs to PC12 cells. The toxicity mechanisms of SWCNTs compared to MWCNTs are different. The SWCNTs activate the apoptotic cell death by mitochondria disruption through high surface tension, whereas the MWCNTs induce necrotic cell death considering the lower tension of the MWCNTs, which is responsible for cell membrane damage. Moreover, they are responsible for conformational changes and denaturation of the Tau protein, which can influence the toxicity profile of CNTs.

As mentioned before, CNTs can be utilized as scaffold reinforcements since they can improve structural integrity and electrical properties, which make them promising for neural regeneration. Association of the functionalized MWCNTs with polyurethane/silk fibroin utilizing the electrospinning technique improves neural extension and differentiation along the direction of the fibers (Shrestha et al. 2019).

Graphene-based nanomaterials

Graphene (GR) is one of the carbon-based materials with a 2D honeycomb lattice structure. The sigma bond with three other carbon in the aromatic structure responsible for the planar nature of GR, unique physical and mechanical properties, large surface area, thermal conductivity, and chemical stability. Moreover, GR can be chemically and physically manipulated to forms other nanomaterials such as graphene oxide (GO) and reduced graphene oxide (rGO). Simple modifications of GR paved the way for drug and gene delivery since they can be easily functionalized with growth factors, DNA, drugs, and proteins.

Graphene and their derivatives can be utilized in the biomedical fields and regenerative medicine. Their excellent biocompatibility, flexibility, and unique physicochemical properties make them an ideal material for supporting stem cells' proliferation and differentiation. For example, GR can enhance the attachment and osteogenic and adipogenic differentiation of the MSCs. Moreover, GR

can improve the cardiomyogenic differentiation of the hESCs (Lee et al. 2014).

The surface properties of GR and its derivatives can promote distinctive cellular behaviors. Culturing the iPSCs on GR and GO can support proliferation and differentiation although the cell adhesion and proliferation are higher in GO. That is probably due to the chemical groups on the surface, which make the GO more hydrophilic. On the other hand, GO promotes spontaneous differentiation of iPSCs towards endodermal lineage whereas GR increases maintenance of iPSCs (Chen et al. 2012). Conversely Jing and coworkers examined the effects of various concentration of GO (4, 8, 16, 32, and 64 mg/mL) on the maintenance of the pluripotency of mESCs. They concluded that 16 and 32 mg/mL concentrations of GO exhibited the highest effects on inhibition of differentiation potential of mESCs. Likewise, they found that GO exerted this effect by downregulation of vinculin protein, which leads to inhibition of the expression of MEK1. Suppression of MEK1 can induce inhibition of ERK1/2 results in sustaining self-renewal ability (Jing et al. 2018). Such results highlighted the importance of the graphene's physicochemical properties and its derivatives effects on biocomponent interactions and cellular behaviors. Controlling the oxygen contents on the GO by a low-temperature thermal reduction method on few-layer reduced graphene oxide (FRGO) can influence cell adhesion and proliferation. There is a close association between the capability of cells for adhesion and the amount of protein adsorption on the surface of the scaffold. Moreover, the amount of protein adsorption on the surface relies on hydrogen, electrostatic, and hydrophobic interactions. for instance, Shi et al. reported that the reduction state of GO can affects cellular behavior such as cell attachment and proliferation by regulating protein adsorption on the surface. They found that moderately rGO had a higher ability for protein adsorption through hydrophobic interactions compared to highly rGO and GO (Shi et al. 2012).

It has been proven that the GR-based materials are beneficial in nerve tissue engineering since they have unique electrical conductivity owing to their hexagonal aromatic structure. These outstanding properties of graphene increase the neurons to glial cells ratio by promoting the proliferation and differentiation of the hNSCs. A comparison between the graphene film and glass substrate revealed the increasing attachment and differentiation of hNSCs with neurite outgrowth and neural network development on the graphene film. In contrast, the hNSCs on the glass substrate form unstable attachment, which leads to detachment of neuronal cells during long differentiation. It should be noted that the differentiated neurons on graphene film demonstrated the upregulation of genes related to GPCR and calcium signaling pathways, which highlighted the enhancement of differentiation when graphene utilized as a substrate for neural tissue engineering (Park et al. 2011).

In another study, GO supported dopaminergic neural differentiation of mESCs in a dose-dependent manner compared to CNT and GR, which suggested the promising application of GO for cell transplantation therapy (Yang et al. 2014). For dopaminergic neuron differentiation, they utilized the co-culturing methods with PA6 feeder cells, which have stromal cell-derived inducing activity (SDIA).

Recently, Zhang and his coworkers utilized a highly conductive graphene trapped silk fibroin scaffold for neurite growth and differentiation of the PC12 cells by electrical stimulation (Zhang et al. 2019a, b).

Another application of the graphene is utilizing other materials such as natural and synthetic polymers for reinforcement of chemical, mechanical, and electrical properties. Coating of nanofibrous polycaprolactone (PCL) with GO by plasma treatment can promotes differentiation of the NSCs to oligodendrocytes. Evaluation of oligodendrocytes markers showed significant expression of Olig2 and MBP in Hybrid scaffolds compare to PCL and GO alone. Additionally, the PCL–GO promotes differentiation of NSCs towards oligodendrocytes by promoting the FAK, Akt, ILK, and Fyn signaling pathways, which modulate actin dynamics and control the cytoskeletal reorganization (Shah et al. 2014). In another example, the combination of the PLLA nanofibrous scaffold with GO showed that GO not only doesn't disrupt the alignment of nanofibrous but also enhance the surface roughness and hydrophilicity of the substrate, which supports cell adhesion, differentiation and neurite outgrowth of PC12 cells as well as regulation and orientation of the Schwann cells (Zhang et al. 2016). Wang et al. utilized *Antheraea pernyi* silk fibroin (ApF)/(Poly(L-lactic acid-co-caprolactone)) (PLCL) electrospun nanofibers as a substrate for PC12 cell differentiation. They utilized rGO coating for proliferation and myelination of Schwann cells as well as differentiation of PC12 cells by electrical stimulation without any chemical inducer. The nanostructured scaffold combined with 1.14% graphene showed a similar peripheral nerve regeneration in vivo as the autograft, which is a gold standard for repairing the peripheral nerve damage (Wang et al. 2019). Turning to CNS regeneration by utilizing the graphene derivatives, Domínguez-Bajo et al. investigated the regenerative potential of rGO microfibers in cervical spinal cord injury for the first time. They investigated the physicochemical properties of rGO microfibers as well as the neural regeneration capacity in a rat model after 4 months of implantation by behavioral test and immune labeling of neuronal

cytoskeleton protein. They demonstrated that not also the rGO microfibers improve axonal growth but also no sign of inflammatory response was observed after implantation (Domínguez-Bajo et al. 2020).

Polymeric nanomaterials

As mentioned before, growth factor therapy has the potential for nerve regeneration as it could accelerate neurogenesis, angiogenesis, remyelination, synaptogenesis, and axonal outgrowth. However, delivery of neurotrophic factors is an inadequate therapeutic method due to erratic distribution, minimal tissue penetration, short half-life, and enzymatic degradation, which can be overcome by stabilizing or incorporating with natural or synthetic polymers. Polymeric nanomaterials with biodegradable and biocompatible composition play a pivotal role in nerve tissue engineering considering the crossing BBB and utilizing as a drug delivery system for delivery of neurotrophic factors that can impact the cellular behavior and stem cells' fate (Amani et al. 2019a, b, c, d; Mili et al. 2018).

The various methods of delivery can determine the effectiveness of the delivered neurotrophic factors. Adsorption of the cargo on the surface of the vehicles leads to lower cargo-efficiency and the initial burst-release whereas encapsulation or entrapment of the drug by polymers results in sustain-release profile and longer half-life. For example, Lin et al. utilized the polybutylcyanoacrylate (PBCA) nanoparticles for the delivery of the BDNF for neural differentiation of the iPSCs. Interestingly, the comparison between the encapsulation and adsorption of the BDNF on the surface of NPs demonstrate the noticeable efficiency of surface adsorbed BDNF in neural outgrowth and intercellular connectivity compared to encapsulation forms. Moreover, they combined the tween 80 for CNS targeting and SPION for image tracking of PBCA NPs (Lin et al. 2019).

Another application of polymeric nanomaterials in nerve tissue engineering is controlling the differentiation of stem cells by intracellular delivery of neurogenic factors. Polyethyleneimine (PEI) employed as a drug vehicle for the internalization of RA to SVZ stem cells. The polymer can be internalized through endocytosis and subsequently cytoplasmic release of RA after the disruption of the lysosome by proton sponge effect in a few hours. The internalization of the PEI-RA induced differentiation of SVZ stem cells with a minimal impact on proliferation and cell viability in vitro (Maia et al. 2010). Importantly, the internalized release of RA upregulates the Ngn1 and Mash1 by activation of the SAPK/JNK signaling pathways, which result in differentiation and commitment of resident NSCs in SVZ in vivo (Santos et al. 2012).

Another versatile usage of the polymeric nanoparticles is to take advantage of smart nanomaterials such as poly(N-isopropyl acrylamide) (Pnipaam), which is a thermoresponsive polymer as it undergoes a hydrophilic to hydrophobic phase transition above its lower critical solution temperature (LCST). RA-loaded PNIPAM-co-Acrylamide nanoparticles (PCANs) utilized for differentiation of the hiPSCs. RA loaded PCANs with the concentration of 1–2 μg/mL enhanced the neural differentiation potential of hiPSCs (Seo et al. 2015). Utilizing such systems can be proper for future in vivo applications since they can release RA or other differentiating factors in a temperature-dependent manner.

Several studies demonstrated the importance of electrical stimulation in neurite outgrowth and nerve regeneration. Conductive polymers such as polypyrrole, polyaniline, and poly(3,4-ethylene dioxythiophene) can be utilized in neural tissue engineering as they can enhance neural adhesion and differentiation. Wu et al. acquired poly(3--hexylthiophene) (P3HT), which is a semiconductive and photoconductive polymer for synthesizing self-assembled nanofibers with an average diameter of 100 nm. They utilized a green LED for wireless photostimulation of neural outgrowth and neuronal differentiation of the PC12 cells (Wu et al. 2019).

Semiconductor nanomaterials

It has been shown that silica nanoparticles not only cannot promote differentiation but also it has a detrimental effect on stem cell differentiation. A.D. Ducray et al. investigated the uptake of silica nanoparticle by SH-SY5Y cells, which showed a reduction in neural differentiation (Ducray et al. 2017). Moreover, some authors showed a different side of silica nanoparticles. For example, Kouki Fujioka and coworkers synthesized silica nanoparticles with different sizes and showed that all particles increased Nestin and N-FH expression. Furthermore, nanoparticles with 30 and 44 nm at 0.1 mg/mL increased GFAP expressions, which suggest promotion of self-renewal and neural differentiation of hNSCs. Interestingly, they found a slight reduction in HMGA1 after exposure to 30 nm silica nanoparticles which indicates the reduction of neurogenesis of hNSCs (Fujioka et al. 2014).

Despite the controversy over the ability of silica nanoparticles in promoting neural differentiation, These NPs are one of the important semiconductors, which can be recognized as nanocarriers for stem cell neural

differentiation due to their biocompatibility and high loading capacity. For instance, utilizing the silica nanoparticles as non-viral carrier for neural differentiation is popular. Chang et al. used silica nanoparticles for the co-delivery of Nurr1 plasmid (pNurr1) and Rex1 siRNA (siRex1) into iPSCs to achieve dopaminergic neuron differentiation (Chang et al. 2017). In another study, Solanki et al. developed a nanotopography-mediated reverse uptake (NanoRU) coated with laminin for the efficient delivery of the siRNA for the blockage of the SOX9 transcription factor. This transcription factor is responsible for the neuronal differentiation and reduction in glial differentiation. They coated silica nanoparticles with laminin and siRNA with electrostatic force since laminin and siRNA have negative forces and Silica nanoparticles have positive forces (Amani et al. 2019a, b, c, d; Solanki, Shah et al. 2013). Another example of codelivery with mesoporous silica nanoparticle is Cheng et al. work in which they utilized curcumin as a ROS-induced cell damage protective agent and plasmid RhoG-DsRed as an inducer of lamellipodia and filopodia for promoting neurite outgrowth. Moreover, they introduce TAT peptide to this nano-complex through the electrostatic interactions for enhancing the gene expression (Cheng et al. 2019).

Conclusion

The rapid development of nanotechnology provides various nanomaterials with different properties that can impact stem cell microenvironments and behaviors. The combination of nanomaterials and stem cells researches offers new ideas for the treatment of numerous neurodegenerative diseases. However, several challenges should be overcome to utilized nanomaterials to solve critical clinical problems. For example, there is a controversy around the toxicity of nanomaterials due to the small size and chemical composition of nanomaterials. It has been shown that different metallic nanoparticles caused neuronal damage in specific concentrations. Therefore, further studies should be conducted towards various nanomaterials' safety for neural tissue engineering. Among metallic nanoparticles, AuNPs show better compatibility and electroconductivity, which resulted in vast applications of these nanomaterials in different forms in tissue engineering. Other nanomaterials such as carbon-based nanomaterials and polymeric nanomaterials showed great biocompatibility and low toxicity, which can be combined with various metallic nanoparticles to improve their electroconductivity properties. Nanomaterials with various properties especially controlling the cellular behavior and stem cells' fate have broad prospects in neural tissue engineering. Therefore, Understanding the pathophysiological alterations in various neurological disorders and the design of suitable nanomaterials for effective changes in stem cell behaviors can impact neural tissue engineering methods in the future.

Author contribution: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.
Research funding: The authors thank Physiology Research Center and Department of Physiology, Iran University of Medical Sciences, and Tuberculosis and Lung Disease Research Center of Tabriz, Tabriz University of Medical Sciences, Tabriz, for all supports provided (G: 58764).
Conflict of interest statement: The authors declare no conflicts of interest regarding this article.

References

Abdal Dayem, A., Lee, S., and Cho, S.-G. (2018a). The impact of metallic nanoparticles on stem cell proliferation and differentiation. Nanomaterials 8: 761.

Abdal Dayem, A., Lee, S., Choi, H., and Cho, S.-G. (2018b). Silver nanoparticles: two-faced neuronal differentiation-inducing material in neuroblastoma (SH-SY5Y) cells. Int. J. Mol. Sci. 19: 1470.

Abe, A., Hashimoto, K., Akiyama, A., Iida, M., Ikeda, N., Hamano, A., and Miyamoto, Y. (2018). αvβ5 integrin mediates the effect of vitronectin on the initial stage of differentiation in mouse cerebellar granule cell precursors. Brain Res. 1691: 94–104.

Adameyko, I. and Ernfors, P. (2019). Nerves do it again: donation of mesenchymal cells for tissue regeneration. Cell Stem Cell 24: 195–197.

Aguirre, A., Rubio, M.E., and Gallo, V. (2010). Notch and EGFR pathway interaction regulates neural stem cell number and self-renewal. Nature 467: 323.

Alghazali, K.M., Newby, S.D., Nima, Z.A., Hamzah, R.N., Watanabe, F., Bourdo, S.E., and Biris, A.S. (2017). Functionalized gold nanorod nanocomposite system to modulate differentiation of human mesenchymal stem cells into neural-like progenitors. Sci. Rep. 7: 16654.

Alon, N., Miroshnikov, Y., Perkas, N., Nissan, I., Gedanken, A., and Shefi, O. (2014). Substrates coated with silver nanoparticles as a neuronal regenerative material. Int. J. Nanomed. 9: 23.

Altman, J. (1962). Are new neurons formed in the brains of adult mammals? Science 135: 1127–1128.

Amani, H., Arzaghi, H., Bayandori, M., Dezfuli, A.S., Pazoki-Toroudi, H., Shafiee, A., and Moradi, L. (2019a). Controlling cell behavior through the design of biomaterial surfaces: a focus on surface modification techniques. Adv. Mater. Interfaces 6: 1900572.

Amani, H., Habibey, R., Shokri, F., Hajmiresmail, S.J., Akhavan, O., Mashaghi, A., and Pazoki-Toroudi, H. (2019b). Selenium nanoparticles for targeted stroke therapy through modulation of inflammatory and metabolic signaling. Sci. Rep. 9: 6044.

Amani, H., Kazerooni, H., Hassanpoor, H., Akbarzadeh, A., and Pazoki-Toroudi, H. (2019c). Tailoring synthetic polymeric biomaterials towards nerve tissue engineering: a review. Art. Cells Nanomed. Biotechnol. 47: 3524–3539.

Amani, H., Mostafavi, E., Alebouyeh, M.R., Arzaghi, H., Akbarzadeh, A., Pazoki-Toroudi, H., and Webster, T.J. (2019d). Would colloidal gold nanocarriers present an effective diagnosis or treatment for ischemic stroke? Int. J. Nanomed. 14: 8013.

Amit, M. and Itskovitz-Eldor, J. (2002). Derivation and spontaneous differentiation of human embryonic stem cells. J. Anat. 200: 225–232.

Anandalakshmi, K., Venugobal, J., and Ramasamy, V. (2016). Characterization of silver nanoparticles by green synthesis method using *Pedalium murex* leaf extract and their antibacterial activity. Appl. Nanosci. 6: 399–408.

Antonelli, F., Casciati, A., and Pazzaglia, S. (2019). Sonic hedgehog signaling controls dentate gyrus patterning and adult neurogenesis in the hippocampus. Neural Reg. Res. 14: 59.

Arabian, M., Aboutaleb, N., Soleimani, M., Ajami, M., Habibey, R., Rezaei, Y., and Pazoki-Toroudi, H. (2017). Preconditioning with morphine protects hippocampal CA1 neurons from ischemia–reperfusion injury via activation of the mTOR pathway. Can. J. Physiol. Pharmacol. 96: 80–87.

Arabian, M., Aboutaleb, N., Soleimani, M., Mehrjerdi, F.Z., Ajami, M., and Pazoki-Toroudi, H. (2015). Role of morphine preconditioning and nitric oxide following brain ischemia reperfusion injury in mice. Iran. J. Basic Med. Sci. 18: 14–21.

Armenteros, T., Andreu, Z., Hortigüela, R., Lie, D.C., and Mira, H. (2018). BMP and WNT signalling cooperate through LEF1 in the neuronal specification of adult hippocampal neural stem and progenitor cells. Sci. Rep. 8: 9241.

Baei, P., Jalili-Firoozinezhad, S., Rajabi-Zeleti, S., Tafazzoli-Shadpour, M., Baharvand, H., and Aghdami, N. (2016). Electrically conductive gold nanoparticle-chitosan thermosensitive hydrogels for cardiac tissue engineering. Mater. Sci. Eng. C 63: 131–141.

Baranes, K., Shevach, M., Shefi, O., and Dvir, T. (2015). Gold nanoparticle-decorated scaffolds promote neuronal differentiation and maturation. Nano Lett. 16: 2916–2920.

Baranowska-Wójcik, E., Szwajgier, D., Oleszczuk, P., and Winiarska-Mieczan, A. (2020). Effects of titanium dioxide nanoparticles exposure on human health—a review. Biol. Trace Elem. Res. 193: 118–129.

Barczyk, M., Carracedo, S., and Gullberg, D. (2010). Integrins. Cell Tissue Res. 339: 269.

Barros, C.S., Franco, S.J., and Müller, U. (2011). Extracellular matrix: functions in the nervous system. Cold Spring Harbor Perspect. Bio. 3: a005108.

Belanger, K., Dinis, T.M., Taourirt, S., Vidal, G., Kaplan, D.L., and Egles, C. (2016). Recent strategies in tissue engineering for guided peripheral nerve regeneration. Macromol. Biosci. 16: 472–481.

Belgacem, Y., Hamilton, A., Shim, S., Spencer, K., and Borodinsky, L. (2016). The many hats of sonic hedgehog signaling in nervous system development and disease. J. Dev. Biol. 4: 35.

Belyanskaya, L., Weigel, S., Hirsch, C., Tobler, U., Krug, H.F., and Wick, P. (2009). Effects of carbon nanotubes on primary neurons and glial cells. Neurotoxicology 30: 702–711.

Ben-Shushan, E., Feldman, E., and Reubinoff, B.E. (2015). Notch signaling regulates motor neuron differentiation of human embryonic stem cells. Stem Cells 33: 403–415.

Bhang, S.H., Han, J., Jang, H.-K., Noh, M.-K., La, W.-G., Yi, M., and Kim, B.-S. (2015). pH-triggered release of manganese from MnAu nanoparticles that enables cellular neuronal differentiation without cellular toxicity. Biomaterials 55: 33–43.

Bhangra, K.S., Busuttil, F., Phillips, J.B., and Rahim, A.A. (2016). Using stem cells to grow artificial tissue for peripheral nerve repair. Stem Cell. Int. 2016: 7502178.

Bradbury, E.J., and McMahon, S.B. (2006). Spinal cord repair strategies: why do they work? Nat. Rev. Neurosci. 7: 644–653.

Brennan, D., Chen, X., Cheng, L., Mahoney, M., and Riobo, N.A. (2012). Noncanonical hedgehog signaling. In: *Vitamins and Hormones*, Vol. 88, Elsevier, pp. 55–72.

Carballo, G.B., Honorato, J.R., and de Lopes, G.P.F. (2018). A highlight on Sonic hedgehog pathway. Cell Commun. Signal. 16: 11.

Chang, I.A., Oh, M.-J., Kim, M.H., Park, S.-K., Kim, B.G., and Namgung, U. (2012). Vimentin phosphorylation by Cdc2 in Schwann cell controls axon growth via β1-integrin activation. FASEB J. 26: 2401–2413.

Chang, J.-H., Tsai, P.-H., Chen, W., Chiou, S.-H., and Mou, C.-Y. (2017). Dual delivery of siRNA and plasmid DNA using mesoporous silica nanoparticles to differentiate induced pluripotent stem cells into dopaminergic neurons. J. Mater. Chem. B 5: 3012–3023.

Chen, G.Y., Pang, D.-P., Hwang, S.M., Tuan, H.Y., and Hu, Y.C. (2012). A graphene-based platform for induced pluripotent stem cells culture and differentiation. Biomaterials 33: 418–427.

Chen, S.S., Fitzgerald, W., Zimmerberg, J., Kleinman, H.K., and Margolis, L. (2007). Cell-cell and cell-extracellular matrix interactions regulate embryonic stem cell differentiation. Stem Cells 25: 553–561.

Chen, T., Yan, J., and Li, Y. (2014). Genotoxicity of titanium dioxide nanoparticles. J. Food Drug Anal. 22: 95–104.

Chen, W.S., Guo, L.Y., Tang, C.C., Tsai, C.K., Huang, H.H., Chin, T.Y., and Chen-Yang, Y.W. (2018). The effect of laminin surface modification of electrospun silica nanofiber substrate on neuronal tissue engineering. Nanomaterials 8: 165.

Cheng, C.-S., Liu, T.-P., Chien, F.-C., Mou, C.-Y., Wu, S.-H., and Chen, Y.-P. (2019). Codelivery of plasmid and curcumin with mesoporous silica nanoparticles for promoting neurite outgrowth. ACS Appl. Mater. Interfaces 11: 15322–15331.

Chooi, W.H. and Chew, S.Y. (2019). Modulation of cell–cell interactions for neural tissue engineering: potential therapeutic applications of cell adhesion molecules in nerve regeneration. Biomaterials, https://doi.org/10.1016/j.biomaterials.2019.01.030.

Cooper, R.J., Menking-Colby, M.N., Humphrey, K.A., Victory, J.H., Kipps, D.W., and Spitzer, N. (2019). Involvement of β-catenin in cytoskeleton disruption following adult neural stem cell exposure to low-level silver nanoparticles. Neurotoxicology 71: 102–112.

Cooper, R.J. and Spitzer, N. (2015). Silver nanoparticles at sublethal concentrations disrupt cytoskeleton and neurite dynamics in cultured adult neural stem cells. Neurotoxicology 48: 231–238.

Cui, L., Jiang, J., Wei, L., Zhou, X., Fraser, J.L., Snider, B.J., and Yu, S.P. (2008). Transplantation of embryonic stem cells improves nerve repair and functional recovery after severe sciatic nerve axotomy in rats. Stem Cell 26: 1356–1365.

Das, S., Sharma, M., Saharia, D., Sarma, K.K., Sarma, M.G., Borthakur, B.B., and Bora, U. (2015). In vivo studies of silk based gold nano-composite conduits for functional peripheral nerve regeneration. Biomaterials 62: 66–75.

Dasgupta, B., and Gutmann, D.H. (2005). Neurofibromin regulates neural stem cell proliferation, survival, and astroglial differentiation in vitro and in vivo. J. Neurosci. 25: 5584–5594.

Dayem, A.A., Kim, B., Gurunathan, S., Choi, H.Y., Yang, G., Saha, S.K., and Kim, J.H. (2014). Biologically synthesized silver nanoparticles induce neuronal differentiation of SH-SY5Y cells via modulation of reactive oxygen species, phosphatases, and kinase signaling pathways. Biotechnol. J 9: 934–943.

Dennis, D.J., Han, S., and Schuurmans, C. (2019). bHLH transcription factors in neural development, disease, and reprogramming. Brain Res. 1705: 48–65.

Dhara, S.K. and Stice, S.L. (2008). Neural differentiation of human embryonic stem cells. J. Cell. Biochem. 105: 633–640.

Di Marcotullio, L., Ferretti, E., Greco, A., De Smaele, E., Po, A., Sico, M.A., and Screpanti, I. (2006). Numb is a suppressor of Hedgehog signalling and targets Gli1 for Itch-dependent ubiquitination. Nat. Cell Biol. 8: 1415.

Doherty, P., Ashton, S.V., Moore, S.E., and Walsh, F.S. (1991). Morphoregulatory activities of NCAM and N-cadherin can be accounted for by G protein-dependent activation of L-and N-type neuronal Ca^{2+} channels. Cell 67: 21–33.

Domínguez-Bajo, A., González-Mayorga, A., López-Dolado, E., Munuera, C., García-Hernández, M., and Serrano, M.C. (2020). Graphene oxide microfibers promote regenerative responses after chronic implantation in the cervical injured spinal cord. ACS Biomater. Sci. Eng. 6: 2401–2414.

Du, Y., Liu, X., Liang, Q., Liang, X.-J., and Tian, J. (2019). Optimization and design of magnetic ferrite nanoparticles with uniform tumor distribution for highly sensitive MRI/MPI performance and improved magnetic hyperthermia therapy. Nano Lett. 19: 3618–3626.

Ducray, A.D., Stojiljkovic, A., Möller, A., Stoffel, M.H., Widmer, H.-R., Frenz, M., and Mevissen, M. (2017). Uptake of silica nanoparticles in the brain and effects on neuronal differentiation using different in vitro models. Nanomed. Nanotechnol. Biol. Med. 13: 1195–1204.

Dvir, T., Timko, B.P., Kohane, D.S., and Langer, R. (2011). Nanotechnological strategies for engineering complex tissues. Nat. Nanotechnol. 6: 13.

Engelhardt, B., Vajkoczy, P., and Weller, R.O. (2017). The movers and shapers in immune privilege of the CNS. Nat. Immunol. 18: 123–131.

Engler, A., Rolando, C., Giachino, C., Saotome, I., Erni, A., Brien, C., and Taylor, V. (2018). Notch 2 signaling maintains NSC quiescence in the murine ventricular-subventricular zone. Cell Rep. 22: 992–1002.

Esmaeely Neisiany, R., Enayati, M.S., Sajkiewicz, P., Pahlevanneshan, Z., and Ramakrishna, S. (2020). Insight into the current directions in functionalized nanocomposite hydrogels. Frontiers Mater. 7: 25.

Evaristo-Mendonca, F., Carrier-Ruiz, A., de Siqueira-Santos, R., Campos, R.M.P., Rangel, B., Kasai-Brunswick, T.H., and Ribeiro-Resende, V.T. (2018). Dual contribution of mesenchymal stem cells employed for tissue engineering of peripheral nerves: trophic activity and differentiation into connective-tissue cells. Stem Cell Rev. Rep. 14: 1–13.

Faigle, R., and Song, H. (2013). Signaling mechanisms regulating adult neural stem cells and neurogenesis. Biochim. Biophys. Acta 1830: 2435–2448.

Feng, Z.-Q., Yan, K., Shi, C., Xu, X., Wang, T., Li, R., and Zheng, J. (2018). Neurogenic differentiation of adipose derived stem cells on graphene-based mat. Mater. Sci. Eng. C 90: 685–692.

Ferguson, T.A. and Scherer, S.S. (2012). Neuronal cadherin (NCAD) increases sensory neurite formation and outgrowth on astrocytes. Neurosci. Lett. 522: 108–112.

Firooz, A., Bouzari, N., Mojtahed, F., Pazoki-Toroudi, H., Nassiri-Kashani, M., Davoudi, M., and Dowlati, Y. (2005). Topical immunotherapy with diphencyprone in the treatment of extensive and/or long-lasting alopecia areata 11. J. Eur. Acad. Dermatol. Venereol. 19: 393–394.

Foroutan Koudehi, M.F., Imani Fooladi, A.A., Aghozbeni, E.A.H., and Nourani, M.R. (2019). Nano bioglass/gelatin scaffold enhanced by nanosilver as an antibacterial conduit for peripheral nerve regeneration. Mater. Technol. 34: 1–9.

Franci, G., Falanga, A., Galdiero, S., Palomba, L., Rai, M., Morelli, G., and Galdiero, M. (2015). Silver nanoparticles as potential antibacterial agents. Molecules 20: 8856–8874.

Freitas de Freitas, L., Varca, G.H.C., Dos Santos Batista, J.G., and Benévolo Lugão, A. (2018). An overview of the synthesis of gold nanoparticles using radiation technologies. Nanomaterials (Basel, Switzerland) 8: 939.

Fujioka, K., Hanada, S., Inoue, Y., Sato, K., Hirakuri, K., Shiraishi, K., and Yamamoto, K. (2014). Effects of silica and titanium oxide particles on a human neural stem cell line: morphology, mitochondrial activity, and gene expression of differentiation markers. Int. J. Mol. Sci. 15: 11742–11759.

Gavard, J., Marthiens, V., Monnet, C., Lambert, M., and Mège, R.M. (2004). N-cadherin activation substitutes for the cell contact control in cell cycle arrest and myogenic differentiation: involvement of p120 and β-catenin. J. Biol. Chem. 279: 36795–36802.

Georgiou, M., Golding, J.P., Loughlin, A.J., Kingham, P.J., and Phillips, J.B. (2015). Engineered neural tissue with aligned, differentiated adipose-derived stem cells promotes peripheral nerve regeneration across a critical sized defect in rat sciatic nerve. Biomaterials 37: 242–251.

Ghasemi Hamidabadi, H., Rezvani, Z., Nazm Bojnordi, M., Shirinzadeh, H., Seifalian, A.M., Joghataei, M.T., and Salimi, M. (2017). Chitosan-intercalated montmorillonite/poly (vinyl alcohol) nanofibers as a platform to guide neuronlike differentiation of human dental pulp stem cells. ACS Appl. Mater. Interfaces 9: 11392–11404.

Giannaccini, M., Calatayud, M.P., Poggetti, A., Corbianco, S., Novelli, M., Paoli, M., and Parchi, P. (2017). Magnetic nanoparticles for efficient delivery of growth factors: stimulation of peripheral nerve regeneration. Adv. Healthcare Mat. 6: 1601429.

Giljohann, D.A., Seferos, D.S., Daniel, W.L., Massich, M.D., Patel, P.C., and Mirkin, C.A. (2010). Gold nanoparticles for biology and medicine. Angew. Chem. Int. Ed. 49: 3280–3294.

Grill, R., Murai, K., Blesch, A., Gage, F.H., and Tuszynski, M.H. (1997). Cellular delivery of neurotrophin-3 promotes corticospinal axonal growth and partial functional recovery after spinal cord injury. J. Neurosci. 17: 5560–5572.

Grothe, C., Haastert, K., and Jungnickel, J. (2006). Physiological function and putative therapeutic impact of the FGF-2 system in peripheral nerve regeneration—lessons from in vivo studies in mice and rats. Brain Res. Rev. 51: 293–299.

Gu, X., Ding, F., and Williams, D.F. (2014). Neural tissue engineering options for peripheral nerve regeneration. Biomaterials 35: 6143–6156.

Guo, W., Qiu, J., Liu, J., and Liu, H. (2017). Graphene microfiber as a scaffold for regulation of neural stem cells differentiation. Sci. Rep. 7: 5678.

Hafner, K., Montag, D., Maeser, H., Peng, C., Marcotte, W.R., , Jr., Dean, D., and Kennedy, M.S. (2017). Evaluating adhesion and alignment of dental pulp stem cells to a spider silk substrate for tissue engineering applications. Mater. Sci. Eng. C 81: 104–112.

Haggerty, A.E., Bening, M.R., Pherribo, G., Dauer, E.A., and Oudega, M. (2019). Laminin polymer treatment accelerates repair of the crushed peripheral nerve in adult rats. Acta Biomater. 86: 185–193.

Haque, A., Yue, X.-S., Motazedian, A., Tagawa, Y.-I., and Akaike, T. (2012). Characterization and neural differentiation of mouse embryonic and induced pluripotent stem cells on cadherin-based substrata. Biomaterials 33: 5094–5106.

Hasanzadeh, E., Ebrahimi-Barough, S., Mirzaei, E., Azami, M., Tavangar, S.M., Mahmoodi, N., and Ai, J. (2019). Preparation of fibrin gel scaffolds containing MWCNT/PU nanofibers for neural tissue engineering. J. Biomed. Mater. Res. 107: 802–814.

Hentze, H., Soong, P.L., Wang, S.T., Phillips, B.W., Putti, T.C., and Dunn, N.R. (2009). Teratoma formation by human embryonic stem cells: evaluation of essential parameters for future safety studies. Stem Cell Res. 2: 198–210.

Hernández-Sánchez, D., Villabona-Leal, G., Saucedo-Orozco, I., Bracamonte, V., Pérez, E., Bittencourt, C., and Quintana, M. (2018). Stable graphene oxide–gold nanoparticle platforms for biosensing applications. Phys. Chem. Chem. Phys. 20: 1685–1692.

Hong, F., Zhou, Y., Ji, J., Zhuang, J., Sheng, L., and Wang, L. (2018). Nano-TiO2 inhibits development of the central nervous system and its mechanism in offspring mice. J. Agric. Food Chem. 66: 11767–11774.

Hornos Carneiro, M.F. and Barbosa, F. Jr. (2016). Gold nanoparticles: a critical review of therapeutic applications and toxicological aspects. J. Toxicol. Environ. Health, Part B 19: 129–148.

Hou, Y., Cai, K., Li, J., Chen, X., Lai, M., Hu, Y., and Xu, D. (2013). Effects of titanium nanoparticles on adhesion, migration, proliferation, and differentiation of mesenchymal stem cells. Int. J. Nanomed. 8: 3619.

Hsiao, I.-L., Chang, C.-C., Wu, C.-Y., Hsieh, Y.-K., Chuang, C.-Y., Wang, C.-F., and Huang, Y.-J. (2016). Indirect effects of TiO2 nanoparticle on neuron-glial cell interactions. Chem. Biol. Interact. 254: 34–44.

Hu, C.-C., Wu, G.-H., Hua, T.-E., Wagner, O.I., and Yen, T.-J. (2018). Uptake of TiO_2 nanoparticles into *C. elegans* neurons negatively affects axonal growth and worm locomotion behavior. ACS Appl. Mater. Interfaces 10: 8485–8495.

Hynes, R.O. (2002). Integrins: bidirectional, allosteric signaling machines. Cell 110: 673–687.

Inestrosa, N.C. and Varela-Nallar, L. (2015). Wnt signalling in neuronal differentiation and development. Cell Tissue Res. 359: 215–223.

Jahromi, H.K., Farzin, A., Hasanzadeh, E., Barough, S.E., Mahmoodi, N., Najafabadi, M.R.H., and Ai, J. (2020). Enhanced sciatic nerve regeneration by poly-L-lactic acid/multi-wall carbon nanotube neural guidance conduit containing Schwann cells and curcumin encapsulated chitosan nanoparticles in rat. Mater. Sci. Eng. C 109: 110564.

Jain, K.K. (2019). Neuroprotection in traumatic brain injury. In: Jain, K.K. (Ed.). *The handbook of neuroprotection*. Springer, New York, NY, pp. 281–336.

Javedan, G., Shidfar, F., Davoodi, S.H., Ajami, M., Gorjipour, F., Sureda, A., and Pazoki-Toroudi, H. (2016). Conjugated linoleic acid rat pretreatment reduces renal damage in ischemia/reperfusion injury: unraveling antiapoptotic mechanisms and regulation of phosphorylated mammalian target of rapamycin. Mol. Nutr. Food Res. 60: 2665–2677.

Jazayeri, M.H., Amani, H., Pourfatollah, A.A., Pazoki-Toroudi, H., and Sedighimoghaddam, B. (2016). Various methods of gold nanoparticles (GNPs) conjugation to antibodies. Sen. Bio-Sen. Res. 9: 17–22.

Jia, X., Wang, S., Zhou, L., and Sun, L. (2017). The potential liver, brain, and embryo toxicity of titanium dioxide nanoparticles on mice. Nanoscale Res. Lett. 12: 478.

Jiang, L., Jones, S., and Jia, X. (2017). Stem cell transplantation for peripheral nerve regeneration: current options and opportunities. Int. J. Mol. Sci. 18: 94.

Jing, G., Wang, Z., Zhuang, X., He, X., Wu, H., Wang, Q., and Zhu, R. (2018). Suspended graphene oxide nanosheets maintain the self-renewal of mouse embryonic stem cells via down-regulating the expression of Vinculin. Biomaterials 171: 1–11.

Jodat, Y.A. and Shin, S.R. (2020). Functional carbon-based nanomaterials for engineered tissues toward organ regeneration. In: *Biomaterials for organ and tissue regeneration*. Elsevier, pp. 529–550.

Kageyama, R., Ohtsuka, T., Shimojo, H., and Imayoshi, I. (2008). Dynamic Notch signaling in neural progenitor cells and a revised view of lateral inhibition. Nat. Neurosci. 11: 1247.

Katebi, S., Esmaeili, A., Ghaedi, K., and Zarrabi, A. (2019). Superparamagnetic iron oxide nanoparticles combined with NGF and quercetin promote neuronal branching morphogenesis of PC12 cells. Int. J. Nanomed. 14: 2157.

Kazanis, I., and ffrench-Constant, C. (2011). Extracellular matrix and the neural stem cell niche. Develop. Neurobio. 71: 1006–1017.

Kennea, N.L. and Mehmet, H. (2002). Neural stem cells. J. Pathol. 197: 536–550.

Khalid, M., Asad, M., Henrich-Noack, P., Sokolov, M., Hintz, W., Grigartzik, L., and Sabel, B. (2018). Evaluation of toxicity and neural uptake in vitro and in vivo of superparamagnetic iron oxide nanoparticles. Int. J. Mol. Sci. 19: 2613.

Khan, F.A., Almohazey, D., Alomari, M., and Almofty, S.A. (2018). Impact of nanoparticles on neuron biology: current research trends. Int. J. Nanomed. 13: 2767.

Kim, J.A., Lee, N., Kim, B.H., Rhee, W.J., Yoon, S., Hyeon, T., and Park, T.H. (2011). Enhancement of neurite outgrowth in PC12 cells by iron oxide nanoparticles. Biomaterials 32: 2871–2877.

Kimura, H., Ouchi, T., Shibata, S., Amemiya, T., Nagoshi, N., Nakagawa, T., and Sato, K. (2018). Stem cells purified from human induced pluripotent stem cell-derived neural crest-like cells promote peripheral nerve regeneration. Sci. Rep. 8: 10071.

Kinsinger, N., Tantuccio, A., Sun, M., Yan, Y., and Kisailus, D. (2011). Photocatalytic titanium dioxide composite. J. Nanosci. Nanotechnol. 11: 7015–7021.

Ko, W.-K., Heo, D.N., Moon, H.-J., Lee, S.J., Bae, M.S., Lee, J.B., and Kwon, I.K. (2015). The effect of gold nanoparticle size on

osteogenic differentiation of adipose-derived stem cells. J. Colloid Interface Sci. 438: 68–76.

Kumamaru, H., Kadoya, K., Adler, A.F., Takashima, Y., Graham, L., Coppola, G., and Tuszynski, M.H. (2018). Generation and post-injury integration of human spinal cord neural stem cells. Nat. Methods 15: 723.

Kuwabara, T., Hsieh, J., Muotri, A., Yeo, G., Warashina, M., Lie, D.C., and Gage, F.H. (2009). Wnt-mediated activation of neuroD1 and retro-elements during adult neurogenesis. Nat. Neurosci. 12: 1097.

Kyriazi, M.-E., Giust, D., El-Sagheer, A.H., Lackie, P.M., Muskens, O.L., Brown, T., and Kanaras, A.G. (2018). Multiplexed mRNA sensing and combinatorial-targeted drug delivery using DNA-gold nanoparticle dimers. ACS Nano 12: 3333–3340.

Lan, A., Xu, W., Zhao, J., Li, C., Qi, M., Li, X., and Zhou, Y. (2018). Surface functionalization of TiO_2 nanotubes with minocycline and its in vitro biological effects on Schwann cells. Biomed. Eng. Online 17: 88.

Lee, J.M., Moon, J.Y., Kim, T.H., Lee, S.W., Ahrberg, C.D., and Chung, B.G. (2018). Conductive hydrogel/nanowire micropattern-based sensor for neural stem cell differentiation. Sensor. Actuator. B Chem. 258: 1042–1050.

Lee, T.-J., Park, S., Bhang, S.H., Yoon, J.-K., Jo, I., Jeong, G.-J., and Kim, B.-S. (2014). Graphene enhances the cardiomyogenic differentiation of human embryonic stem cells. Biochem. Biophys. Res. Commun. 452: 174–180.

Leynen, N., Van Belleghem, F.G., Wouters, A., Bove, H., Ploem, J.-P., Thijssen, E., and Artois, T. (2019). In vivo toxicity assessment of silver nanoparticles in homeostatic versus regenerating planarians. Nanotoxicology 13: 476–491.

Li, J., Zhang, J., Wang, X., Kawazoe, N., and Chen, G. (2016). Gold nanoparticle size and shape influence on osteogenesis of mesenchymal stem cells. Nanoscale 8: 7992–8007.

Li, R., Li, Y., Wu, Y., Zhao, Y., Chen, H., Yuan, Y., and Wang, J. (2018). Heparin-Poloxamer thermosensitive hydrogel loaded with bFGF and NGF enhances peripheral nerve regeneration in diabetic rats. Biomaterials 168: 24–37.

Li, Y., Luikart, B.W., Birnbaum, S., Chen, J., Kwon, C.-H., Kernie, S.G., and Parada, L.F. (2008). TrkB regulates hippocampal neurogenesis and governs sensitivity to antidepressive treatment. Neuron 59: 399–412.

Lin, M., Chung, C.-Y., Chen, K.-T., Yeh, J.-C., Lee, T.-H., Lee, M.-H., and Yang, J.-T. (2019). Comparison between polybutylcyanoacrylate nanoparticles with either surface-adsorbed or encapsulated brain-derived neurotrophic factor on the neural differentiation of iPSCs. Int. J. Mol. Sci. 20: 182.

Liu, X., Ren, X., Deng, X., Huo, Y., Xie, J., Huang, H., and Wen, T. (2010). A protein interaction network for the analysis of the neuronal differentiation of neural stem cells in response to titanium dioxide nanoparticles. Biomaterials 31: 3063–3070.

Llinás, R.R. (2014). Intrinsic electrical properties of mammalian neurons and CNS function: a historical perspective. Front. Cell. Neurosci. 8: 320.

Lu, C.-W., Hsiao, J.-K., Liu, H.-M., and Wu, C.-H. (2017). Characterization of an iron oxide nanoparticle labelling and MRI-based protocol for inducing human mesenchymal stem cells into neural-like cells. Sci. Rep. 7: 3587.

Ma, H., Yu, B., Kong, L., Zhang, Y., and Shi, Y. (2012). Neural stem cells over-expressing brain-derived neurotrophic factor (BDNF) stimulate synaptic protein expression and promote functional recovery following transplantation in rat model of traumatic brain injury. Neurochem. Res. 37: 69–83.

Maia, J., Santos, T., Aday, S., Agasse, F., Cortes, L., Malva, J.O., and Ferreira, L. (2010). Controlling the neuronal differentiation of stem cells by the intracellular delivery of retinoic acid-loaded nanoparticles. ACS Nano 5: 97–106.

Marcus, M., Skaat, H., Alon, N., Margel, S., and Shefi, O. (2015). NGF-conjugated iron oxide nanoparticles promote differentiation and outgrowth of PC12 cells. Nanoscale 7: 1058–1066.

Marcus, M., Smith, A., Maswadeh, A., Shemesh, Z., Zak, I., Motiei, M., and Shefi, O. (2018). Magnetic targeting of growth factors using iron oxide nanoparticles. Nanomaterials 8: 707.

Martorana, F., Gaglio, D., Bianco, M.R., Aprea, F., Virtuoso, A., Bonanomi, M., and Colangelo, A.M. (2018). Differentiation by nerve growth factor (NGF) involves mechanisms of crosstalk between energy homeostasis and mitochondrial remodeling. Cell Death Dis. 9: 391.

Mashinchian, O., Turner, L.-A., Dalby, M.J., Laurent, S., Shokrgozar, M.A., Bonakdar, S., and Mahmoudi, M. (2015). Regulation of stem cell fate by nanomaterial substrates. Nanomedicine 10: 829–847.

Mead, B., Logan, A., Berry, M., Leadbeater, W., and Scheven, B.A. (2017). Concise review: dental pulp stem cells: a novel cell therapy for retinal and central nervous system repair. Stem Cell 35: 61–67.

Meng, L., Chen, R., Jiang, A., Wang, L., Wang, P., Li, C.Z., and Chen, C. (2013). Short multiwall carbon nanotubes promote neuronal differentiation of PC12 cells via up-regulation of the neurotrophin signaling pathway. Small 9: 1786–1798.

Mili, B., Das, K., Kumar, A., Saxena, A.C., Singh, P., Ghosh, S., and Bag, S. (2018). Preparation of NGF encapsulated chitosan nanoparticles and its evaluation on neuronal differentiation potentiality of canine mesenchymal stem cells. J. Mater. Sci. Mater. Med. 29: 4.

Mishra, S., Kelly, K.K., Rumian, N.L., and Siegenthaler, J.A. (2018). Retinoic acid is required for neural stem and progenitor cell proliferation in the adult hippocampus. Stem Cell Rep. 10: 1705–1720.

Miyamoto, Y., Sakane, F., and Hashimoto, K. (2015). N-cadherin-based adherens junction regulates the maintenance, proliferation, and differentiation of neural progenitor cells during development. Cell Adhes. Migrat., https://doi.org/10.1080/19336918.2015.1005466.

Miyata, S., Taniguchi, M., Koyama, Y., Shimizu, S., Tanaka, T., Yasuno, F., and Tohyama, M. (2016). Association between chronic stress-induced structural abnormalities in Ranvier nodes and reduced oligodendrocyte activity in major depression. Sci. Rep. 6: 23084.

Mody, V.V., Siwale, R., Singh, A., and Mody, H.R. (2010). Introduction to metallic nanoparticles. J. Pharm. BioAllied Sci. 2: 282–289.

Mordorski, B. and Friedman, A. (2017). Chapter 4–metal nanoparticles for microbial infection. In: Boukherroub, R., Szunerits, S., and Drider, D. (Eds.). *Functionalized nanomaterials for the management of microbial infection*. Elsevier, Boston, pp. 77–109.

Nagoshi, N. and Okano, H. (2018). iPSC-derived neural precursor cells: potential for cell transplantation therapy in spinal cord injury. Cell. Mol. Life Sci. 75: 989–1000.

Navarro Quiroz, E., Navarro Quiroz, R., Ahmad, M., Gomez Escorcia, L., Villarreal, J., Fernandez Ponce, C., and Aroca Martinez, G. (2018). Cell signaling in neuronal stem cells. Cells 7: 75.

Nieuwenhuis, B., Haenzi, B., Andrews, M.R., Verhaagen, J., and Fawcett, J.W. (2018). Integrins promote axonal regeneration after injury of the nervous system. Biol. Rev. 93: 1339–1362.

Nissan, I., Schori, H., Lipovsky, A., Alon, N., Gedanken, A., and Shefi, O. (2016). Effect of different densities of silver nanoparticles on neuronal growth. J. Nanoparticle Res. 18: 221.

O'Rourke, C., Day, A.G.E., Murray-Dunning, C., Thanabalasundaram, L., Cowan, J., Stevanato, L., and Sinden, J. (2018). An allogeneic 'off the shelf'therapeutic strategy for peripheral nerve tissue engineering using clinical grade human neural stem cells. Sci. Rep. 8: 2951.

Obara, K., Tohgi, N., Shirai, K., Mii, S., Hamada, Y., Arakawa, N., and Amoh, Y. (2019). Hair-follicle-associated pluripotent (HAP) stem cells encapsulated on polyvinylidene fluoride membranes (PFM) promote functional recovery from spinal cord injury. Stem Cell Rev. Rep. 15: 59–66.

Obernier, K. and Alvarez-Buylla, A. (2019). Neural stem cells: origin, heterogeneity and regulation in the adult mammalian brain. Development 146: pii: dev156059.

Ohtsuka, T., Ishibashi, M., Gradwohl, G., Nakanishi, S., Guillemot, F., and Kageyama, R. (1999). Hes1 and Hes5 as notch effectors in mammalian neuronal differentiation. EMBO J 18: 2196–2207.

Okawa, T., Kamiya, H., Himeno, T., Kato, J., Seino, Y., Fujiya, A., and Hamada, Y. (2013). Transplantation of neural crest-like cells derived from induced pluripotent stem cells improves diabetic polyneuropathy in mice. Cell Transplant. 22: 1767–1783.

Okur, Z., Senturk, O.I., Yilmaz, C., Gulseren, G., Mammadov, B., Guler, M.O., and Tekinay, A.B. (2018). Promotion of neurite outgrowth by rationally designed NGF-β binding peptide nanofibers. Biomat. Sci. 6: 1777–1790.

Orza, A., Soritau, O., Olenic, L., Diudea, M., Florea, A., Rus Ciuca, D., and Biris, A.S. (2011). Electrically conductive gold-coated collagen nanofibers for placental-derived mesenchymal stem cells enhanced differentiation and proliferation. ACS Nano 5: 4490–4503.

Pan, L., Lee, Y.M., Lim, T.K., Lin, Q., and Xu, X. (2018). Quantitative proteomics study reveals changes in the molecular landscape of human embryonic stem cells with impaired stem cell differentiation upon exposure to titanium dioxide nanoparticles. Small 14: 1800190.

Park, J., Bauer, S., von der Mark, K., and Schmuki, P. (2007). Nanosize and vitality: TiO_2 nanotube diameter directs cell fate. Nano Lett. 7: 1686–1691.

Park, J.S., Park, K., Moon, H.T., Woo, D.G., Yang, H.N., and Park, K.-H. (2008). Electrical pulsed stimulation of surfaces homogeneously coated with gold nanoparticles to induce neurite outgrowth of PC12 cells. Langmuir 25: 451–457.

Park, S.Y., Park, J., Sim, S.H., Sung, M.G., Kim, K.S., Hong, B.H., and Hong, S. (2011). Enhanced differentiation of human neural stem cells into neurons on graphene. Adv. Mater. 23: H263–H267.

Paviolo, C., Haycock, J.W., Cadusch, P.J., McArthur, S.L., and Stoddart, P.R. (2014). Laser exposure of gold nanorods can induce intracellular calcium transients. J. Biophot. 7: 761–765.

Paviolo, C., Haycock, J.W., Yong, J., Yu, A., Stoddart, P.R., and McArthur, S.L. (2013). Laser exposure of gold nanorods can increase neuronal cell outgrowth. Biotechnol. Bioeng. 110: 2277–2291.

Paviolo, C., and Stoddart, P.R. (2015). Metallic nanoparticles for peripheral nerve regeneration: is it a feasible approach? Neural Regen. Res. 10: 1065.

Pazoki-Toroudi, H., Nassiri-Kashani, M., Tabatabaie, H., Ajami, M., Habibey, R., Shizarpour, M., and Firooz, A. (2010a). Combination of azelaic acid 5% and erythromycin 2% in the treatment of acne vulgaris. J. Dermatol. Treat. 21: 212–216.

Pazoki-Toroudi, H.R., Ajami, M., and Habibey, R. (2010b). Pre-medication and renal pre-conditioning: a role for alprazolam, atropine, morphine and promethazine. Fund. Clin. Pharmacol. 24: 189–198.

Phinney, D.G., and Prockop, D.J. (2007). Concise review: mesenchymal stem/multipotent stromal cells: the state of transdifferentiation and modes of tissue repair—current views. Stem Cell. 25: 2896–2902.

Pisanic Ii, T.R., Blackwell, J.D., Shubayev, V.I., Finones, R.R., and Jin, S. (2007). Nanotoxicity of iron oxide nanoparticle internalization in growing neurons. Biomaterials 28: 2572–2581.

Polak, P., and Shefi, O. (2015). Nanometric agents in the service of neuroscience: manipulation of neuronal growth and activity using nanoparticles. Nanomed. Nanotechnol. Biol. Med. 11: 1467–1479.

Pollard, K.J., Sharma, A.D., and Moore, M.J. (2019). Neural microphysiological systems for in vitro modeling of peripheral nervous system disorders. Bioelectron. Med. 2: 101–117.

Pollerberg, G.E., Thelen, K., Theiss, M.O., and Hochlehnert, B.C. (2013). The role of cell adhesion molecules for navigating axons: density matters. Mech. Dev. 130: 359–372.

Qi, Z., Guo, W., Zheng, S., Fu, C., Ma, Y., Pan, S., and Yang, X. (2019). Enhancement of neural stem cell survival, proliferation and differentiation by IGF-1 delivery in graphene oxide-incorporated PLGA electrospun nanofibrous mats. RSC Adv. 9: 8315–8325.

Qian, Y., Song, J., Zheng, W., Zhao, X., Ouyang, Y., Yuan, W., and Fan, C. (2018). 3D manufacture of gold nanocomposite channels facilitates neural differentiation and regeneration. Adv. Funct. Mater. 28: 1707077.

Rahgozar, M., Pazokitoroudi, H., Bakhtiarian, A., and Djahanguiri, B. (2001). Diazoxide, a KATP opener, accelerates restitution of ethanol or indomethacin-induced gastric ulceration in rats independent of polyamines. J. Gastroenterol. Hepatol. 16: 290–296.

Ramos,M.A.D.S.,DaSilva,P.B.,Sposito,L.,DeToledo,L.G.,Bonifacio,B.V., Rodero,C.F.,andBauab,T.M.(2018).Nanotechnology-baseddrug deliverysystemsforcontrolofmicrobialbiofilms:areview.Int.J. Nanomed.13:1179.

Ravichandran, R., Sridhar, R., Venugopal, J.R., Sundarrajan, S., Mukherjee, S., and Ramakrishna, S. (2014). Gold nanoparticle loaded hybrid nanofibers for cardiogenic differentiation of stem cells for infarcted myocardium regeneration. Macromol. Biosci. 14: 515–525.

Repar, N., Li, H., Aguilar, J.S., Li, Q.Q., Drobne, D., and Hong, Y. (2018). Silver nanoparticles induce neurotoxicity in a human embryonic stem cell-derived neuron and astrocyte network. Nanotoxicology 12: 104–116.

Reubinoff, B.E., Itsykson, P., Turetsky, T., Pera, M.F., Reinhartz, E., Itzik, A., and Ben-Hur, T. (2001). Neural progenitors from human embryonic stem cells. Nat. Biotechnol. 19: 1134.

Reynolds, B.A. and Weiss, S. (1992). Generation of neurons and astrocytes from isolated cells of the adult mammalian central nervous system. Science 255: 1707–1710.

Riggio, C., Calatayud, M.P., Giannaccini, M., Sanz, B., Torres, T.E., Fernández-Pacheco, R., and Cuschieri, A. (2014). The orientation of the neuronal growth process can be directed via magnetic nanoparticles under an applied magnetic field. Nanomed. Nanotechnol. Biol. Med. 10: 1549–1558.

Rosso, F., Giordano, A., Barbarisi, M., and Barbarisi, A. (2004). From cell–ECM interactions to tissue engineering. J. Cell. Physiol. 199: 174–180.

Ruzicka, J., Romanyuk, N., Jirakova, K., Hejcl, A., Janouskova, O., Machova, L.U., and Jendelova, P. (2019). The effect of iPS-derived neural progenitors seeded on laminin-coated pHEMA-MOETACl hydrogel with dual porosity in a rat model of chronic spinal cord injury. Cell Transpl. 28: 400–412.

Sang, L., Liu, Y., Hua, W., Xu, K., Wang, G., Zhong, W., and Qiu, X. (2016). Thermally sensitive conductive hydrogel using amphiphilic crosslinker self-assembled carbon nanotube to enhance neurite outgrowth and promote spinal cord regeneration. RSC Adv. 6: 26341–26351.

Santos, T., Ferreira, R., Maia, J., Agasse, F., Xapelli, S., Cortes, L.S., and Bernardino, L. (2012). Polymeric nanoparticles to control the differentiation of neural stem cells in the subventricular zone of the brain. ACS Nano 6: 10463–10474.

Schmidt, C.E. and Leach, J.B. (2003). Neural tissue engineering: strategies for repair and regeneration. Annu. Rev. Biomed. Eng. 5: 293–347.

Sensharma, P., Madhumathi, G., Jayant, R.D., and Jaiswal, A.K. (2017). Biomaterials and cells for neural tissue engineering: current choices. Mater. Sci. Eng. C 77: 1302–1315.

Senut, M.C., Zhang, Y., Liu, F., Sen, A., Ruden, D.M., and Mao, G. (2016). Size-dependent toxicity of gold nanoparticles on human embryonic stem cells and their neural derivatives. Small 12: 631–646.

Seo, H.I., Cho, A.-N., Jang, J., Kim, D.-W., Cho, S.-W., and Chung, B.G. (2015). Thermo-responsive polymeric nanoparticles for enhancing neuronal differentiation of human induced pluripotent stem cells. Nanomed. Nanotechnol. Biol. Med. 11: 1861–1869.

Sershen, S., Westcott, S., Halas, N., and West, J. (2000). Temperature-sensitive polymer–nanoshell composites for photothermally modulated drug delivery. J. Biomed. Mater. Res. 51: 293–298.

Shah, S., Yin, P.T., Uehara, T.M., Chueng, S.T.D., Yang, L., and Lee, K.B. (2014). Guiding stem cell differentiation into oligodendrocytes using graphene-nanofiber hybrid scaffolds. Adv. Mater. 26: 3673–3680.

Shao, H., Li, T., Zhu, R., Xu, X., Yu, J., Chen, S., and Ruan, Y. (2018). Carbon nanotube multilayered nanocomposites as multifunctional substrates for actuating neuronal differentiation and functions of neural stem cells. Biomaterials 175: 93–109.

Shevach, M., Fleischer, S., Shapira, A., and Dvir, T. (2014). Gold nanoparticle-decellularized matrix hybrids for cardiac tissue engineering. Nano Lett. 14: 5792–5796.

Shi, H., He, X., Wang, K., Yuan, Y., Deng, K., Chen, J., and Tan, W. (2007). Nanomed. Nanotechnol. Biol. Med. 3: 266–272.

Shi, X., Chang, H., Chen, S., Lai, C., Khademhosseini, A., and Wu, H. (2012). Regulating cellular behavior on few-layer reduced graphene oxide films with well-controlled reduction states. Adv. Funct. Mater. 22: 751–759.

Shimojo, H., Ohtsuka, T., and Kageyama, R. (2008). Oscillations in notch signaling regulate maintenance of neural progenitors. Neuron 58: 52–64.

Shrestha, S., Shrestha, B.K., Kim, J.I., Ko, S.W., Park, C.H., and Kim, C.S. (2018). Electrodeless coating polypyrrole on chitosan grafted polyurethane with functionalized multiwall carbon nanotubes electrospun scaffold for nerve tissue engineering. Carbon 136: 430–443.

Shrestha, S., Shrestha, B.K., Lee, J., Joong, O.K., Kim, B.-S., Park, C.H., and Kim, C. S. (2019). A conducting neural interface of polyurethane/silk-functionalized multiwall carbon nanotubes with enhanced mechanical strength for neuroregeneration. Mater. Sci. Eng. C 102: 511–523.

Siegel, G.J. and Chauhan, N.B. (2000). Neurotrophic factors in Alzheimer's and Parkinson's disease brain. Brain Res. Rev. 33: 199–227.

Skirtach, A.G., Dejugnat, C., Braun, D., Susha, A.S., Rogach, A.L., Parak, W.J., and Sukhorukov, G.B. (2005). The role of metal nanoparticles in remote release of encapsulated materials. Nano Lett. 5: 1371–1377.

Solanki, A., Shah, S., Memoli, K.A., Park, S.Y., Hong, S., and Lee, K.B. (2010). Controlling differentiation of neural stem cells using extracellular matrix protein patterns. Small 6: 2509–2513.

Solanki, A., Shah, S., Yin, P.T., and Lee, K.-B. (2013). Nanotopography-mediated reverse uptake for siRNA delivery into neural stem cells to enhance neuronal differentiation. Sci. Rep. 3: 1553.

Stepanov, A.L., Popok, V.N., and Hole, D.E. (2002). Formation of metallic nanoparticles in silicate glass through ion implantation. Glass Phys. Chem. 28: 90–95.

Stojkovska, J., Kostić, D., Jovanović, Žinović- Sekulić, M., Mišković- Stanković, V., and Obradović, B. (2014). A comprehensive approach to in vitro functional evaluation of Ag/alginate nanocomposite hydrogels. Carbohydr. Polym. 111: 305–314.

Subramanian, A., Krishnan, U.M., and Sethuraman, S. (2009). Development of biomaterial scaffold for nerve tissue engineering: biomaterial mediated neural regeneration. J. Biomed. Sci. 16: 108.

Tajdaran, K., Gordon, T., Wood, M.D., Shoichet, M.S., and Borschel, G.H. (2016). A glial cell line-derived neurotrophic factor delivery system enhances nerve regeneration across acellular nerve allografts. Acta Biomater. 29: 62–70.

Takahashi, K. and Yamanaka, S. (2006). Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 126: 663–676.

Takeuchi, K., Hayashi, T., Kim, Y.A., Fujisawa, K., and Endo, M. (2014). The state-of-the-art science and applications of carbon nanotubes. Наносистемы: физика, химия, математика 5.

Tamaki, T., Hirata, M., Soeda, S., Nakajima, N., Saito, K., Nakazato, K., and Mochida, J. (2014). Preferential and comprehensive reconstitution of severely damaged sciatic nerve using murine skeletal muscle-derived multipotent stem cells. PloS One 9: e91257.

Taylor, S.J. and Sakiyama-Elbert, S.E. (2006). Effect of controlled delivery of neurotrophin-3 from fibrin on spinal cord injury in a long term model. J. Contr. Release 116: 204–210.

Toroudi, H.P., Rahgozar, M., Bakhtiarian, A., and Djahanguiri, B. (1999). Potassium channel modulators and indomethacin-induced gastric ulceration in rats. Scand. J. Gastroenterol. 34: 962–966.

Vangijzegem, T., Stanicki, D., and Laurent, S. (2019). Magnetic iron oxide nanoparticles for drug delivery: applications and characteristics. Expet Opin. Drug Deliv. 16: 69–78.

Wang, A., Tang, Z., Park, I.-H., Zhu, Y., Patel, S., Daley, G.Q., and Li, S. (2011). Induced pluripotent stem cells for neural tissue engineering. Biomaterials 32: 5023–5032.

Wang, J., Cheng, Y., Chen, L., Zhu, T., Ye, K., Jia, C., and Mo, X. (2019). In vitro and in vivo studies of electroactive reduced graphene oxide-modified nanofiber scaffolds for peripheral nerve regeneration. Acta Biomater. 84: 98–113.

Wei, M., Li, S., and Le, W. (2017a). Nanomaterials modulate stem cell differentiation: biological interaction and underlying mechanisms. J. Nanobiotechnol. 15: 75.

Wei, M., Li, S., Yang, Z., Zheng, W., and Le, W. (2017b). Gold nanoparticles enhance the differentiation of embryonic stem cells into dopaminergic neurons via mtor/p70s6k pathway. Nanomedicine 12: 1305–1317.

Wen, H., Xiao, W., Biswas, S., Cong, Z.-Q., Liu, X.-M., Lam, K.S., and Deng, W. (2019). Alginate hydrogel modified with a ligand interacting with α3β1 integrin receptor promotes the differentiation of 3D neural spheroids toward oligodendrocytes in vitro. ACS Appl. Mater. Interfaces 11: 5821–5833.

Wilems, T., Vardhan, S., Wu, S., and Sakiyama-Elbert, S. (2019). The influence of microenvironment and extracellular matrix molecules in driving neural stem cell fate within biomaterials. Brain Res. Bull. 148: 25–33.

Willerth, S.M. and Sakiyama-Elbert, S.E. (2007). Approaches to neural tissue engineering using scaffolds for drug delivery. Adv. Drug Deliv. Rev. 59: 325–338.

Wojcik-Stanaszek, L., Gregor, A., and Zalewska, T. (2011). Regulation of neurogenesis by extracellular matrix and integrins. Acta Neurobiol. Exp. 71: 103–112.

Wong, F.S., Tsang, K.K., and Lo, A.C. (2019). Nanoengineered biomaterial for brain tissue reconstruction and functional repairment. In: *Nanoengineered biomaterials for regenerative medicine*. Elsevier, Amsterdam, pp. 145–166.

Wu, D., Pak, E.S., Wingard, C.J., and Murashov, A.K. (2012). Multi-walled carbon nanotubes inhibit regenerative axon growth of dorsal root ganglia neurons of mice. Neurosci. Lett. 507: 72–77.

Wu, D., Zhang, Y., Xu, X., Guo, T., Xie, D., Zhu, R., and He, L. (2018). RGD/TAT-functionalized chitosan-graft-PEI-PEG gene nanovector for sustained delivery of NT-3 for potential application in neural regeneration. Acta Biomater. 72: 266–277.

Wu, T., Li, D., Wang, Y., Sun, B., Li, D., Morsi, Y., and Mo, X. (2017). Laminin-coated nerve guidance conduits based on poly (l-lactide-co-glycolide) fibers and yarns for promoting Schwann cells' proliferation and migration. J. Mater. Chem. B 5: 3186–3194.

Wu, Y., Peng, Y., Bohra, H., Zou, J., Ranjan, V.D., Zhang, Y., and Wang, M. (2019). Photoconductive micro/nanoscale interfaces of a semiconducting polymer for wireless stimulation of neuron-like cells. ACS Appl. Mater. Inter. 11: 4833–4841.

Xu, C.-J., Wang, J.-L., and Jin, W.-L. (2016). The emerging therapeutic role of NGF in Alzheimer's disease. Neurochem. Res. 41: 1211–1218.

Xu, H., Shi, X., Ma, H., Lv, Y., Zhang, L., and Mao, Z. (2011). The preparation and antibacterial effects of dopa-cotton/AgNPs. Appl. Surf. Sci. 257: 6799–6803.

Yamada, S., Yamazaki, D., and Kanda, Y. (2018). Silver nanoparticles inhibit neural induction in human induced pluripotent stem cells. Nanotoxicology 12: 836–846.

Yang, D., Li, T., Xu, M., Gao, F., Yang, J., Yang, Z., and Le, W. (2014). Graphene oxide promotes the differentiation of mouse embryonic stem cells to dopamine neurons. Nanomedicine 9: 2445–2455.

Yang, R., Wang, M., Wang, J., Huang, X., Yang, R., and Gao, W.-Q. (2015). Cell division mode change mediates the regulation of cerebellar granule neurogenesis controlled by the sonic hedgehog signaling. Stem Cell Rep. 5: 816–828.

Yao, M., Zhou, X., Zhou, J., Gong, S., Hu, G., Li, J., and Hutchins, A.P. (2018). PCGF5 is required for neural differentiation of embryonic stem cells. Nat. Commun. 9: 1463.

Yeh, Y.-C., Creran, B., and Rotello, V.M.(2012). Gold nanoparticles: preparation, properties, and applications in bionanotechnology. Nanoscale 4: 1871–1880.

Yoo, J., Lee, E., Kim, H.Y., Youn, D.-H., Jung, J., Kim, H., and Baek, S. (2017). Electromagnetized gold nanoparticles mediate direct lineage reprogramming into induced dopamine neurons in vivo for Parkinson's disease therapy. Nat. Nanotechnol. 12: 1006.

Yoo, Y.-E., Hong, J.-H., Hur, K.C., Oh, E.-S., and Chung, J.-M. (2004). Iron enhances NGF-induced neurite outgrowth in PC12 cells. Molecules and cells. Spring. Sci. Business Media BV 17, https://doi.org/10.1021/acschemneuro.7b00488.s001.

Yuan, M., Wang, Y., and Qin, Y.-X. (2018). Promoting neuroregeneration by applying dynamic magnetic fields to a novel nanomedicine: superparamagnetic iron oxide (SPIO)-gold nanoparticles bounded with nerve growth factor (NGF). Nanomed. Nanotechnol. Biol. Med. 14: 1337–1347.

Yuan, Q., He, G., Tan, Z., Gong, P., Li, X.Y., Chen, Z.Q., and Man, Y. (2007). Biocompatibility of nano-TiO2/HA bioceramic coating for nerve regeneration around dental implants. Paper Pres. Key Eng. Mat. 330: 1393–1396.

Zarch, A.V., Toroudi, H.P., Soleimani, M., Bakhtiarian, A., Katebi, M., and Djahanguiri, B. (2009). Neuroprotective effects of diazoxide and its antagonism by glibenclamide in pyramidal neurons of rat hippocampus subjected to ischemia-reperfusion-induced injury. Int. J. Neurosci. 119: 1346–1361.

Zhang, C., Fan, S., Shao, H., Hu, X., Zhu, B., and Zhang, Y. (2019a). Graphene trapped silk scaffolds integrate high conductivity and stability. Carbon 148: 16–27.

Zhang, J., Chen, Y., Gao, M., Wang, Z., Liu, R., Xia, T., and Liu, S. (2019b). Silver nanoparticles compromise female embryonic stem cell differentiation through disturbing X chromosome inactivation. ACS Nano 13: 2050–2061.

Zhang, J., Shemezis, J.R., McQuinn, E.R., Wang, J., Sverdlov, M., and Chenn, A. (2013). AKT activation by N-cadherin regulates beta-catenin signaling and neuronal differentiation during cortical development. Neural Dev. 8: 7.

Zhang, K., Zheng, H., Liang, S., and Gao, C. (2016). Aligned PLLA nanofibrous scaffolds coated with graphene oxide for promoting neural cell growth. Acta Biomater. 37: 131–142.

Zhang, Q., Nguyen, P.D., Shi, S., Burrell, J.C., Cullen, D.K., and Le, A.D. (2018a). 3D bio-printed scaffold-free nerve constructs with human gingiva-derived mesenchymal stem cells promote rat facial nerve regeneration. Sci. Rep. 8: 1–11.

Zhang, X.F., Liu, H.X., Ortiz, L.S., Xiao, Z.D., and Huang, N.P. (2018b). Laminin-modified and aligned poly (3-hydroxybutyrate-co-3-hydroxyvalerate)/polyethylene oxide nanofibrous nerve conduits promote peripheral nerve regeneration. J Tis Eng Regen Med. 12: e627–e636.

Zhang, S.-C., Wernig, M., Duncan, I.D., Brüstle, O., and Thomson, J.A. (2001). In vitro differentiation of transplantable neural precursors from human embryonic stem cells. Nat. Biotechnol. 19: 1129.

Zhang, Y., Ali, S.F., Dervishi, E., Xu, Y., Li, Z., Casciano, D., and Biris, A.S. (2010). Cytotoxicity effects of graphene and single-wall carbon nanotubes in neural phaeochromocytoma-derived PC12 cells. ACS Nano 4: 3181–3186.

Zhang, Y., Xu, Y., Li, Z., Chen, T., Lantz, S.M., Howard, P.C., and Mustafa, T. (2011). Mechanistic toxicity evaluation of uncoated and PEGylated single-walled carbon nanotubes in neuronal PC12 cells. ACS Nano 5: 7020–7033.

Zhao, X. and Moore, D.L. (2018). *Neural stem cells: developmental mechanisms and disease modeling*. Springer, New York City.

Zhu, J.M., Zhao, Y.Y., Chen, S.D., Zhang, W.H., Lou, L., and Jin, X. (2011). Functional recovery after transplantation of neural stem cells modified by brain-derived neurotrophic factor in rats with cerebral ischaemia. J. Int. Med. Res. 39: 488–498.