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Review Article

Nanomaterials: Applications in Regeneration of Damaged Tissues

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ABSTRACT

Biomedical engineering has been developed to be applied in repairing/regenerating the damaged tissues or organs to facilitate restoration of the lost biological function. Regenerative medicine has been frequently investigated over years to promote the methodology of the replacement of the injured cells and tissues and improve the life quality of the affected individuals. In this regard, the current study examined the application of various ceramic and metal nanoparticles and polymers in treatment of several tissue/organ damages. It was revealed that application of nanotechnology in tissue regeneration could remarkably improve these approaches and succeed in obtaining low-cost, long-lasting, nanoscale scaffolds to be used in clinical practice where nanomaterial-based tissue regeneration showed greater efficacy than the conventional artificial or animal-derived grafts. In addition, nanomaterials with antibacterial or anti-inflammatory properties may be able to overcome some challenges such as infections, inflammations, and immune responses. With the knowledge of regenerating the damaged tissues using nanomaterials, it is possible to combine the nanomaterials strength or antimicrobial properties with the biological properties, such as tissue-specific growth factors, and create new alternatives that are similar to the original tissues of the human body in terms of their preferred properties and characteristics. Different nanomaterials and their applications in the regeneration of bone, tooth, skin, heart, neurons, and bladder tissues were studied in this review. Despite great promise that these approaches have brought into the replacement of damaged organs, many challenging issues still remain unresolved.

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1. INTRODUCTION

Nanomaterials (NMs) are defined as materials whose size ranges from about 1 to 100 nanometers that are available in different types including nanopatterns, nanofibers, nanotubes, nanoparticles, nanospheres as well as nanopores and nanocomposites with nanometer size [1,2].

With the recent development of nanoparticles, their clinical applications have been extended, and they have been used, for instance, to overcome the restrictions of free therapeutics and crossing biological (microenvironmental, systemic, and cellular) barriers (which differ among the populations of patients and different diseases), thus facilitating the emergence of regenerative medicine (a technique used for tissue

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regeneration based on the replacement or renovation of the damaged tissues or organs to restitute the function of lost, defective, and aged cells in the body). In 2000, National Nanotechnology Initiative (NNI) was established by National Science and Technology Council (NSTC) of the United States to facilitate the appreciation and clinical applications of nanotechnologies. The main challenges in this field were the toxicity of NMs, development of guidelines for safety assessment, industrialization, and affordability, to name a few [3-5].

Nanotechnology aims to design and employ systems and structures in the range of 1-500 nm. NMs are at least one-dimensional particles of about 1-100 nm in length characterized by unique features that, compared to conventional materials, facilitate distinct interactions with the environment. The characteristics of these materials are as follows: (A) they have a higher surface-to-volume ratio than that of bulk materials which in turn provides a higher degree of reactivity; (B) their length is highly suited for effective interaction with cells, particularly in the cases of entrance to cells; and (C) the presence of some dominant physical phenomena such as surface tension in NMs rather than in macroscopic materials while this feature is unexpected or negligible in bulk materials. These features bring about advantageous properties for drug delivery purposes [3,6].

The present study intended to summarize the existing knowledge about the applications of NMs in the reconstruction of damaged tissues of various origins. In addition, efforts were made in this study to discuss the advantages and disadvantages of these approaches compared to the conventional tissue regeneration approaches.

2. APPLICATION OF NANOMATERIALS IN REGENERATIVE MEDICINE

Regenerative medicine, first proposed by Alexis Carrle in 1902, is a method for tissues regeneration that can replace or repair the injured tissues/organs to restitute the function of damaged, lost, or aging cells through replacing them with new healthy cells. Some necessary components for tissue regeneration include cells, growth factors, and scaffolding materials. Application of nanotechnology to each of the essential components of tissue regeneration assists the regenerative medicine in improving the life quality of patients who have not received appropriate medical treatments. Recent advances in the application of nanotechnology in tissue regeneration have focused on applying new functionalized inorganic NMs to tissues and delivering cells, real-time tracking of the process of tissue regeneration, and improving the therapeutic efficiency [5].

The following methods are used mainly in manufacturing NMs that can be used in regenerative medicine. Bottom-up techniques benefit nanotechnology knowledge as an efficient method for the fabrication of new nanoscale materials with different behavior than that of their bulk versions. Polymeric nanoparticles, inorganic nanoparticles, self-assembled NMs, Quantum Dots (QDs), dendrimers, Carbon Nanotubes (CNTs), and Layer-by-Layer (LbL) nanostructures are examples of such materials. It can be anticipated that in the future, nano-based regenerative medicine can develop a new approach to healthcare by designing effective targeting systems for stem cell-based therapies [3].

A multidisciplinary method facilitates the production of unique "smart" materials capable of mimicking the extracellular environment that can result in the triggering of cellular responses. Improving the diagnosis process of diseases at the early stages plays a vital role as the sensitivity and precision of diagnostics tests increased. To date, many nanotechnology applications are at the concept level, thus requiring much more basic studies to achieve commercial exploitation. There are numerous reports on the acceleration of treatments based on tissue regeneration, e.g., for skin, bone, teeth, blood vessels, heart, brain, and bladder tissue (Figure 1). In this regard, biocompatibility and cytocompatibility of various nano-polymers and alloys were evaluated in this research [3,7].

Figure 1. Application of nanomaterials in regenerative medicine for several diseases with no definite treatment

3. BONE REGENERATION

Nanoparticles are commonly used in bone tissue regeneration strategies by conducting the fate of cells into osteogenesis and regenerating remarkable bone deficiencies. Nanoparticles, as multi-purpose compounds, can be used in scaffold-based and scaffold-free approaches of Tissue Engineering (TE) to promote the

osteogenesis and regenerate the bone tissues. These particles can provide an osteogenic niche by regulating the inflammatory reactions and osteo/angio/osteoclastic signaling pathways such as FAK/RhoA/YAP1 pathway which regulates the signaling between stress fibers and osteogenesis, MAPK pathway that connects the cell surface to the nucleus to receive extracellular signals, especially osteoblast signals, BMP/Smad pathway that promotes osteogenesis and upregulates the transcription of osteogenic marker genes such as Runx2, and Wnt/β-catenin pathway that modulates the osteoblast lineage cells and affect various stages of bone formation [8,9]. In addition, the interaction of nanoparticles with biomolecules can improve the bioavailability and half-life of that molecules. Although nanoparticles are relatively ideal candidates for improvement of the osteogenesis processes, the interaction between the nanoparticles and biological environments has its complications, especially the cytotoxicity of the NPs regarding their clinical utilization [8].

Topography is another essential factor in the cellular behavior of NMs that modulates the adhesion, migration, differentiation, and biological function of the cells and tissues. Scaffolds are mostly produced with different topologies including nanoparticles, nanotubes, and nanofibers to better mimic the nano-scale structure of Extracellular Matrix (ECM) for regeneration of bone tissue [10,11].

Earlier research revealed the improved function of osteoblasts on the surface of different NMs, e.g., Black Phosphorous (BP), nano-hydroxyapatite (HA), anodized titanium (Ti), electrospun silk, and nano-structured Ti, compared to the common materials of an orthopedic implant. One of the challenges in this field is identification of the mechanisms that enhance the function of osteoblast cells on these NMs. In this respect, several studies confirmed that high surface energy of NMs would make some alterations in the amount and biological activity of the absorbed proteins (e.g., fibronectin, vitronectin, and collagen), which in turn increased the function of the bone cells [12-14].

Along with the enhanced responses of the bone cells in the presence of NMs, the improved functions of osteoblasts, such as deposition of phosphate and calcium minerals, can last for a more extended period of time on the nanostructural materials. These functions are essential for the osseointegration of implants under orthopedic conditions [12].

BP Quantum Dots (BPQDs) and BP nanosheets, as the emerging layered metal-free two-dimensional materials, were proved beneficial to the bone tissue regeneration. These NMs are characterized by many superior properties such as adjustable direct band gap, distinct pleated structures in layers, great carrier capacity, and several attractive in-layer anisotropies. Moreover, BP NMs show great biodegradability, biocompatibility, PTT and PDT effects, and excellent drug-loading capacity [13].

Ti is another attractive material with good biocompatibility, load-bearing capability, corrosion resistance, and machinability that is commonly used in dental and orthopedic implants [15]. This element is also used in the form of nanostructures. Ti nanostructures provide a large surface area, improved antibacterial properties, bone integrity, and protein interactions, which are advantages for an implant with clinical use [2]. The relevant conducted studies have highlighted that despite the minimal difference between the size of Ti surfaces on a sub-micron and nanometer scale, bone cells behave differently on these surfaces. In other words, one can state that small changes in the characteristics of these materials can have significant effects on the process of bone regeneration. Likewise, the nanophase structures of Ti, CoCrMo, and Ti_6AlV_4 significantly advanced the crystallization of calcium compared to their microphase structures [12].

A novel flax/silk protein-based nanofibrous scaffold has been recently developed for bone regeneration. This scaffold showed biocompatibility in the MG-63 osteoblast cells and long-term antibacterial activity against E. coli and S. aureus. Flax holds bioactive peptides, which can promote the antioxidant activity, antibacterial performance, and anti-inflammation capacity [16].

Webster TJ's reported the first evidence of the improved osteoblast adhesion on nanophase, compared to the conventional metals in 2004 [12,17].

Another parameter that is considered in the design of NMs is the application of aligned nanoscale surface features on the metallic materials that have been indicated to greatly mimic the bone natural anisotropy and consequently improve the function of osteoblasts [18].

The results form different studies indicated that the behavior of the bone cells was strongly affected by the size of the surface features wherever nanoscale and sub-micron surface features could significantly improve the functions of osteoblast cells for a longer time. In fact, it is anticipated that within a short period of time, the commercialization process of the optimized nanostructure implants will be accomplished, and these materials will enter the orthopedic and/or dental implant markets. In this regard, some NMs were already approved by the FDA for implant applications in the human bodies [12].

A variety of studies have been conducted on a large number of different metals and their oxides to produce nanoparticles that can be used in the field of bone regeneration. Nanoparticles of gold, platinum, silver, palladium, tantalum, zinc, copper, iron oxide, Ti dioxide, magnesium oxide, nickel oxide, calcium oxide, cerium dioxide, silicon dioxide, strontium nanoparticles, and zirconia NPs are examples of these nanoscale materials.

Carbon-based NMs such as graphene and CNTs are also used in bone TE [2,19].

Carbon NMs also have exclusive biological and physical characteristics such as antibacterial properties and ability to express different genes that play essential roles in tissue regeneration [16,20]. In addition, NMs with a combination of silver, Ti, and hydroxy apatite, such as Ag:HA/Ti and Ag:HA/TiO_2 nanotubes can be used as antifungal scaffolds for regeneration of the damaged bone [16].

Gold nanoparticles (AuNPs) can drive Periodontal Ligament Stem Cells (PDLSC) sheets toward osteogenic differentiation by upregulating the expression of bone-related proteins and mineralization [21]. In 2019, Liang et al. conducted a study to investigate the modulating effects of a mesopore silica nanoparticle loaded with AuNP (Au-MSNs) on the macrophages and its subsequent impact on the responses of osteoblast cell lines. They reported the potential of Au-MSNs to generate an optimal immune microenvironment by triggering an anti-inflammatory response as well as stimulating the macrophages for secretion of cytokines with osteogenic properties [22]. A list of NMs used in the regeneration of bone tissue is summarized in Figure 2.

Since HA is an essential part of the native bone tissue, nanoparticles of HA are widely applied in the manufacture of nanocomposite hydrogels in order to improve the function of HA scaffolds in the regeneration of injured bone [23]. In addition, Nanoclays can be used in bone regeneration approaches. They are layered mineral materials formed naturally with at least one dimension in the range of 1-100 nm. They are engaging in terms of low cost and being environmentally friendly [23,24].

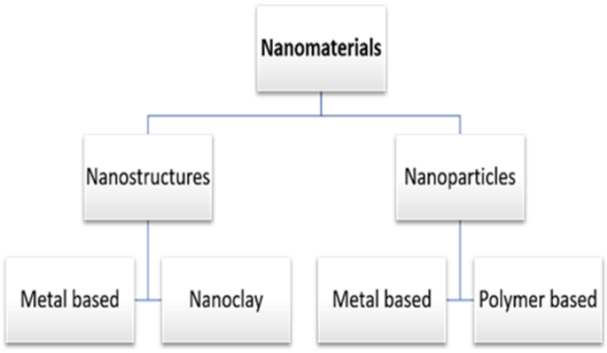

Figure 2. Candidate nanomaterials for repairing and regeneration of bone tissue

Computed tomography and in vivo histology analyses demonstrated that application of the Au-MSNs could enhance the constitution of new bone at the site of a cranial defect of critical size in rats. Outright, the new Au-MSNs can remarkably improve the osteogenic properties through the immune microenvironment modulation, thus approving the therapeutic potential of these NMs for repairing and regenerating bone tissue [22]. Other studies conducted later in this field showed that in a preclinical model, AuNPs (especially 45 nm) have the ability to promote the osteogenic differentiation process of PDLSC sheets both in vitro and in vivo [25].

Despite the great deal of researchs conducted on various NMs with the objective of functionalizing the polymer matrix to enhance the desirable properties, these scaffolds are still under in vivo/in vitro investigation; hence, further experiments should be done before clinical applications [2]. Regardless of the type of materials used in the bone tissue reconstruction, a comprehensive understanding of the dispersal of these materials in a solid phase and interfacial relationships of two phases is required to improve the force transmission and fabricate tissues with the high similarity to the bone tissue in terms of natural toughness and strength [26].

Although developing new construction methods can improve scaffold designing, control the properties of the scaffolds, and enhance their mechanical properties, but nanotechnology alone cannot ensure a promising method for regeneration of bone tissue. Studies have demonstrated the significance of growth factors such as BMP2 and VEGF, osteoinductive factors such as adenosine and ions, and development of antibacterial materials and scaffolds in improvement of osteoinduction and vascularisation to support regeneration of serious bone injuries [27].

4. SKIN RECONSTRUCTION

The objective skin TE pursues is to reduce the scar formation, improve the wound healing, and restore the functional and structural components of the skin. NMs such as nanocomposites, nanoparticles, brackets, and hydrogels are currently used for skin wounds healing purposes; for instance, engineered nanoscale materials are efficiently used for managing infections and therapy purposes, and nanofibrous matrices based on the biomimetic elastomeric peptide and nanotechnology for regeneration and repair of the skin wounds [28]. Nanoparticles composed of a single species of chemicals such as metals and metal oxides are not only excellent antibacterial agents but also can be effective in the healing of skin wounds and lesions. For example, nanoclusters of silver and gold with the size range of 1.1-1.6 nm proved to contribute to repairing the skin lesions of rat models in vivo [6]. On the contrary, according to the in vitro studies, Au nanoclusters are the best effective materials to be used in the wound healing processes due to thier specific anti-inflammatory effects, better uptake by cells, and promoting proliferation and migration of cells. Generally, Au nanoparticles are biologically compatible that can decrease inflammation and improve the constitution of granulation tissue. Instead, AgNPs can

promote the proliferation of keratocytes and fibroblasts. In addition, they can repress the innate immune system which, in turn, accelerate the wound healing rate and decrease the scarring rate. The first commercially available AgNP-containing wound dressing is ACTICOAT. Other instances are copper nanoparticles and nanoceria [6].

Hollow colloidal nanoparticles have gained significance in recent years owing to their unique features including low density, significant loading capacity, great surface permeability, and excellent morphology. The inimitable characteristics of these NPs facilitate their widespread applications in biomedicine, chemical catalysis, electronics, optics, environment protection, storage, and conversion of energy, anti-oxidation, anti-tumor treatment, TE, and drug delivery. A favorite hollow colloid known as HPDAlR was synthesized in 2021 by loading Hollow Polydopamine (HPDA) nanoparticles with RL-QN15 (a peptide with amphibian origin) that enjoy distinct prohealing properties [28].

Skin replacement is one of the first prosperous applications of tissue regeneration that has made the regrowth of damaged tissue possible. Multiple products of TE succeeded in getting FDA approval for applications as the graft materials in the treatment of individuals with severe skin damages caused by burns or diabetic ulcers. Apligraf is a popular product available in the market that is constructed by culturing a layer of human keratinocytes on top of a matrix of human skin fibroblasts and bovine type I collagen. It is successfully used in the treatment of ulcers of the venous leg and diabetic foot. Unfortunately, all the skin products of TE incur high costs due to the expenses of the longtime cell culture that is required for full maturation of the graft in vitro before its clinical applications. However, applying the nanoscale scaffolds may help shorten the culture time and benefit the production of artificial grafts for the treatment of skin damage [29].

In this regard, Chang et al. investigated the application of nano-structured Chitosan Scaffold (CS) for the growth of human skin fibroblasts. Primarily, they cast a flat surface of Poly(ε-Caprolactone) (PCL) and produced a nanoscale PCL model. Then, they cast a crosslinked form of chitosan over this model, followed by introduction of an extra layer of PCL to the smooth side of the chitosan film. These CS/PCL nanostructures demonstrated remarkably improved proliferation rate and viability of fibroblasts, compared to the smooth CS/PCL surfaces or nano-rough PCL surfaces. Therefore, it can be concluded that nano-polymer-based techniques can provide a cost-effective approach to the production of nanoscale scaffolds as advanced synthetic skin grafts [30].

Skin wound healing currently utilizes a novel approach called Autologous Layered Dermal Reconstitution (ALDR). This procedure is based on new TE scaffolds composed of electrospun PCL and gelatin fiber scaffolds of 300-600 nm in diameter and 28 mm in thickness. Human dermal fibroblasts are seeded onto the scaffolds that remain viabile in the scaffold during all times tested (for up to two weeks), and the doubling time of the cells was about every 3 days [31].

Despite the insufficiency of the in vivo results, upon using electrospun TE scaffolds, ALDR proved to be superior to the conventional strategies. Briefly, ALDR ensures rapid reconstruction of the damaged tissue layer-by-layer, in deep wounds, with the overall distribution of skin fibroblasts. Followed by 48-72 hours of implantation, the wound dressing may be replaced with a new scaffold/construct, and this process will be repeated until the wound completely heals. Prior to the implantation, each scaffold was lonely seeded with skin fibroblasts that decreased the prolonged times of in vitro culture, compared to previously described single-layer scaffolds. Through this LbL method, a continuous layer of skin tissue with porous nano-scaffold is fromed, allowing rapid cells proliferation and layers integration. Overall, numerous studies on the TE of skin wounds have been conducted, the results of which were in agreement with those obtained from using nanoscale scaffolds to achieve efficient wound healing properties [31]. In this regard, combination of the biomaterials with innovative scaffold fabrication techniques can improve the resultant scaffolds in an ECM-mimicking bioenvironment and even the scaffolds capable of enhancing the ECM of the injured skin to favor tissue regeneration. Development of some novel strategies such as responsive scaffolds can pave the way for the generation of 4D scaffolds capable of modulating tissue microenvironment by sensing biological and physicochemical parameters. Scaffolds should be constructed from materials that allow many signals and interactions to be activated. Similarly, stem cell-based therapies can be appropriate candidates for treating chronic wounds given their capability of both renewing lost tissue and promoting wound healing via paracrine pathways. It is still necessary to address several questions about the best source of stem cells, ideal approaches of cell delivery, and long-term harmful effects of these cells [32].

Along with all the advances that have been made in skin TE, application of materials with the utmost negligible toxicity can help enhance the efficacy of this treatment [6].

5. DENTAL REGENERATION

Nanodentistry, i.e., application of nanoparticles in dentistry, is affected by specific nanostructure topography of the tooth and promising advantages of NMs. This field benefits the application of NPs for anti-inflammatory and antibacterial activities, remineralization, local anesthesia, differentiation of stem cells, and bone conduction. In addition to the application of NPs in dental tissue regeneration, NMs can improve

the mechanical features of dental composites, enhance their anchorage and bonding, and decrease the possibility of friction [33].

The nanoscale size of NPs facilitates their increased penetration into the areas with more serious damages and enhances the mechanical strength of the dental composites through porosity reduction. Biological activity is also improved by the high surface-to-volume ratio, including bonding and integration, and antimicrobial activity will be enhanced as well. In addition, the controlled release of functional molecules (drugs, growth factors, etc.) from the NPs leads to site-specific precise delivery of these molecules to achieve localized therapy. These characteristics bring advances to multiple fields of dentistry, including endodontics and periodontology as well as the reengineering of dental braces and prosthetics. Nanoparticles of metals or metal oxides intrinsically show bactericidal activity. In addition, encapsulation of drugs within nano-polymers improves the solubility of drugs in the aqueous phase and transfer into bacteria besides the controlled release of the drugs. The higher surface-volume ratio also facilitates the simultaneous loading of multiple drugs resulting in a synergistic antibacterial effect, thus eliminating microbial resistance [33].

Nanoparticles such as CNTs are progressively applied in the resin matrices of orthodontic and prosthetic composites, improving the filler load by filling the gaps up, advancing the mechanical features, and decreasing polymerization shrinkage. There was also an improvement in the bond strength, pressure, flexibility, hardness, and toughness of fractures [33].

Studies have confirmed the improving effect of using biomimetic implants on the prosperity of dental implants for diabetic individuals. The antimicrobial features of these implants may contribute to the prohibition of peri-implantitis. Of note, application of nanostructures of carbon can effectively advance drug delivery and enable mimicking protein channels, thus improving wound healing and reducing the rate of dental implant failure. The adaptation of NPs to alter the biomimetic implants may enable them to solve problems such as infections, slow wound healing, and osseointegration, thus leading to the creation of long-lasting implants and advancement of personalized therapy for dental tissue of individuals with slow wound healing [34].

Periodontal reconstruction consists of a complicated set of tissues and constructions in and around the tooth. Therefore, a good biomaterial-based approach requires a functionalized scaffold where the chemical formula and three-dimensional architecture of each compartment are following the biochemical mixture, fine organization, and mechanical features of the target tissues. The application of multilayered nanoscale scaffolds in tissue regeneration is in its infancy, not limited to dental implants but also for all tissue types, hence the high possibility of promising results for the future of regenerative medicine. The investigated LbL scaffolds for regenerating various tissues are usually manufactured by using NMs that can precisely mimic the fine properties of the tissue to reconstruct [35].

In spite of great advances in the field of nano-biomaterials, nano dentistry is still lagged, and a majority of research studies on dental NMs are in vitro. Given that the effect of the dental NMs was not examined or shown in vivo, more research in real clinical trials/on patients is required to promote the development of efficacious and affordable nanotheranostics [36,37].

6. REGENERATIVE MEDICINE FOR HEART DISEASES

Recently, great deal of efforts have been made to construct heart functional tissues; however, there are still some challenges such as the need for cardiac myocyte culture. In a a preliminary study, submicron size scaffolds of electrospun Poly(Lactic-co-Glycolic) Acid (PLGA), and Poly(L-Lactide) (PLLA) fibers were produced. They yielded positive results in terms of cardiac tissue regeneration, indicating that cardiomyocytes could attach and grow on the scaffolds and crawling inside and align with the orientation of constructed fibers [12].

In addition to the regeneration of functional myocardium, a considerable number of research studies have been conducted on the development of tissue-engineered heart valves in vitro due to the increasing prevalence of heart valve replacement using artificial/animal-derived valves. There is an expectation that TE will resolve issues related to artificial valves (the need for chronic anticoagulant treatment) as well as animal-derived valves (calcification and hardening). Of note, it can grow to be further adapted with an enlarged heart by maturing pediatric patients [12].

Characterization of the porcine decellularized membrane of aortic valves through Scanning Electron Microscopy and Atomic Force Microscopy revealed a nanoscale fiber matrix of 30 nm with the pore diameter and depth of about 30 nm and 22 nm, respectively. Such nanoscale membranes are remarkably smaller than the endothelial membranes of the mammalian cornea and bladder tissues. Given the nanoscale size of this membrane, a proper TE scaffold for the regeneration of heart valves is required to have a similar surface scale to ensure successful interaction with endothelial cells [12].

Different kinds of NMs are examined as the contrast agents of ultrasound for diagnosis of cardiac diseases, including Nanobubbles (NBs), Microbubbles (MBs), Nanocapsules (NCs), and Nanodroplets (NDs) [38,39].

In order to achieve successful cardiac regeneration, numerous biological properties such as adhesion, proliferation, differentiation, mechanical and electrical properties, and vascularisation are required, all obtained

by combining various NMs (organic/inorganic) with different properties and features. The hybrid scaffolds can provide improved and tunable rheological and mechanical properties that result in their enhanced performance for soft tissue regeneration. In addition, from a biological viewpoint, understanding of the pathways involved in the interaction of the cells with the structural, mechanical, and electrical properties of NMs can be helpful in achieving prosperous myocardial regeneration [40].

7. VASCULAR TISSUE ENGINEERING

Development of surfaces that can enhance the attachment, proliferation, and qualified function of the smooth muscle cells of endothelium. Here the vessels are considered the quickly developing parts of TE. Recent studies have focused on two primary purposes namely the development of vascular grafts with small diameters and fabrication of the next generation materials as a vascular stent. In order to achieve appropriate vascular cell interactions, several investigations have focused on fine-tuning the surface structures at the submicron and nanoscale dimensions. Samaroo et al. reported nano surfaces based on PLGA as well as nitinol and Ti while developing vascular cell function [41]. They also reported the improved attachment and proliferation of the smooth muscle cells of endothelium and vessels on the nanoscale PLGA, compared to the smooth surfaces. Further, they synthesized a series of PLGA nanosurfaces with the same chemical composition and variable submicron scales. They revealed that surfaces with the lateral diameter of 200 nm and spherical surface properties could remarkably enhance the adhesion of the smooth muscle cells, compared to the smooth surfaces or spherical surfaces of 100 or 500 nm [42,43].

In another study, Carpenter et al. found that addition of collagen type IV and fibronectin could improve the adhesion of the endothelial cells to the PLGA surfaces, regardless of their exact size. In addition, they remarked that adsorption of collagen type IV and fibronectin, as well as the attachment of endothelial cells, was highly dependent on the vertical dimension of surfaces rather than the lateral dimension, and approximately 20 nanometers were reported as the ideal vertical dimension for surfaces [44]. Furthermore, a study on the Ti stent surfaces showed that the nanoscale surfaces of Ti showed improved levels of attachment and proliferation of the endothelial cells, compared to the surface features with a micron scale. Altogether, use of nanotechnology in the regenerative medicine of cardiovascular diseases provides promising results in adhesion enhancement and proliferation of endothelial cells [45]. It can be anticipated that nanotechnologists in cooperation with physicians, cellular/molecular biologists, and pharmaceutical companies can design and develop novel nanomedical devices for cardiac regeneration with potential clinical applicability [46].

8. REGENERATIVE MEDICINE FOR NEUROLOGICAL DISORDERS

Nanotechnology has the potential to extend the application of regenerative medicine to the treatment of neurological disorders in the brain as well as eyes and peripheral nervous system (Figure 3). Today, with the emergence of topics such as the applicability of NMs as a tool for understanding the pathology of Central Nervous System (CNS) diseases, stroke treatment through targeting neuroplasticity of the brain using biomaterials, possibility of designing nanotheranostics to treat neurological disorders through personalized medicine, use of NMs as the gene carriers to reprogram the cells, and consideration of the potential of NMs while modulating the immune system for creating an environment suitable for regeneration of nerve cells. Hopefully, it is expected that NMs can be used in the treatment of neurological diseases or regeneration of nerve cells. In this regard, some studies have been conducted to identify nanotechnology-based methods that can promote endogenous regeneration processes in the brain as well as the production of various NMs and their therapeutic effects, especially in the spinal cord [47].

In this respect, several pre-clinical studies were conducted using advanced regenerative therapies, and promising results were obtained. However, the clinical application of these therapeutic approaches is still challenging. To be specific, despite the common characteristics of the CNS disorders, they also have differences, and one should consider these characteristics while designing regenerative nanoparticles. However, nanomaterial-based approaches are considered qualified alternatives for the repair and regeneration of the damaged nervous systems [47].

8.1 Nanomaterial-Mediated Neural Stem Cell Therapy for Neurological Diseases and Their Current Clinical Status

Neural Stem Cell (NSC) therapy with NMs mediation has been developed to treat neurological diseases.

Particular characteristics of NMs including unique nano-bio interface, minimal size, and high delivery/loading capacity can be considered in regulating the biochemical and mechanical microenvironment of transplanted cells that help advance our knowledge of cell behavior management. Altogether, the unique characteristics of these materials can result in the optimization of tissue regeneration approaches to neurological diseases [21]. For instance, some nanofibers/nanocomposites of Lignin, including Poly (vinyl alcohol)-poly (glycerol sebacate-lignin fibers), can

be beneficial to the regeneration engineering mainly because the lignin promotes the proliferation and differentiation of neural cells in a positive way [48].

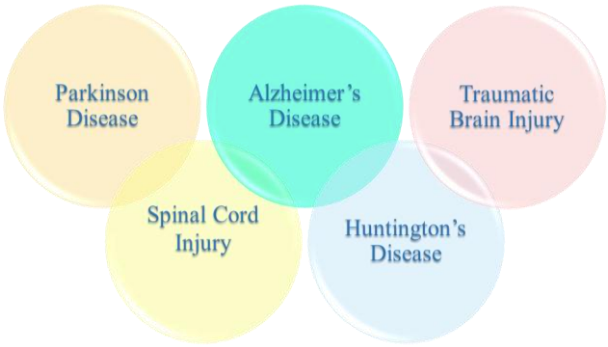

Figure 3. Neurological diseases that nanomaterials play a role in their treatment

8.2. Spinal Cord Injury

Spinal Cord Injury (SCI) is one of the most dangerous disorders of the nervous system, and no efficient treatment for this disease has been reported yet. Nanoparticles can be advantageous in stem cell-based therapy of SCI. For instance, they can be used for the targeted delivery of therapeutics to the site of injury and lessen the adverse effects [49-51]. In addition, NPs can improve the regeneration of axons in order to restart the transmission of neural messages in the damaged spinal cord by accelerating the regrowth of axons. Of note, NMs play a key role in the targeted delivery of neurotrophic factors to the site of damaged tissue, and better the microenvironment for nerve regeneration, stem cell adhesion, and migration [52,53]. Multiple attempts were made in order to find the appropriate NPs for neural regeneration. A study demonstrated that nanocomposites of chitosan-NT3 or PLGA nanoparticles loaded with flavopiridol (CDK inhibitor) could assist in the differentiation of endogenous neural stem cells and regrowth of axons in order to regenerate the damaged spinal cord. These nanocomposites are particularly noteworthy for treatment of spinal cord injuries because they are degradable, characterized by less cytotoxicity to the CNS and significant regeneration functions. Overall, the combination of nanotechnology with NSCs has opened a new chapter in treating neural system injuries [21,53,54].

8.3. Alzheimer's Disease

Alzheimer's Disease (AD) is a chronic disorder of neuro-degeneration that is primarily defined as the deposition of β-amyloid and hyperphosphorylation of tau with an unknown onset and slow development [55]. The cognitive defect as the main symptom of AD can be recovered through the regeneration of the neural network by NSCs transplantation. However, the efficiency of this method is relatively low, and only a few portions of the transplanted stem cells can differentiate into neurons while a majority of them do not end up with the desired fate. Nanoparticles can be applied to improve the transfer of the genes/drugs/stem cells, stimulate the neural differentiation of cells, and ensure real-time monitoring of the nervous system. In one study, charge reversible NPs of Poly(Carboxy Betaine) (PCB) and traceable superparamagnetic iron oxide nanoparticles of ABC/SPIONs/siSOX9 were applied to the AD mice, and the obtained results indicated that the applied nanoparticles were capable of fine-tuning the NSCs to differentiate into neural cells and rescue their memory [21,56]. Fan et al. developed a new nanoparticle, i.e., poly(lactide-co-glycolide)-block-poly(ethylene glycol) (PLGA-PEG) conjugated with B6 peptide and loaded with Curcumin. They studied the effect of this nanoparticle in vitro by administrating it into HT22 cells and APP/PS1 Al transgenic mice and found that this nanoparticle could be effective in reducing the diameter of the cur, enhancing cellular uptake, improving the spatial learning and memory, and decreasing the β-amyloid formation and deposition in hippocamp and hyperphosphorylation [55].

However, it should be noted that use of NMs and NSCs in treating AD is a new and promising field with great deal of uncertainty [21].

8.4. Huntington's Disease

Huntington's Disease (HD) is a neurodegenerative condition with no efficient therapeutic for its recovery or even for its delayed progression [57]. There are some reports about the usefulness of SCs transplantation and tissue regeneration in the rescue of HD in some rodents as well as in humans. Nowadays, Pluripotent Stem Cells (PSCs) are considered novel therapeutic choices for HD treatment. Nevertheless, this approach faces some problems, including ethical limitations, low reprogramming efficiency, and genetic instability. Application of nanotechnology provides a good solution to these problems that in turn encourages conducting further studies on the NPs in the SC-based therapy of HD including lipid NCs, liposomes, dendrimers, poly(ethylene imine) NPs, and chitosan. In addition, there are several reports of the benefits of exosomes in HD treatment. In one study, exosomes from adipose stem cells remarkably reduced the aggregation of mHtt in neuronal cells of R6/2 mice. They raised the abnormal level of apoptotic protein within an HD model in vitro [58,59].

Even though there is limited data about the benefits of applying stem cells with nanocarriers in Huntington's disease treatment, it is still a promising method under investigation [21].

In addition, integration of knowledge about the biological processes that were found to be effective in the development of Huntington's disease with

nanotechnology led to the development of new methods to restore nerve function in this disease. For example, the decreased levels of cholesterol and its biosynthesis in mouse models of HD are indicative of the role of local synthesis of cholesterol in synapse integrity and regeneration. Then, Valenza et al. developed an NP that was modified with glycopeptide (g7) and loaded with cholesterol (g7-NPs-Chol). They found that intraperitoneal injection of this biocompatible and biodegradable NP to the HD mice resulted in the localization of this NP in glial and nerve cells in different parts of the brain [60].

Another study revealed that insufficient amounts of selenium (Se) in the brain of HD patients contribute to the neurological loss and dysfunction. Accordingly, Cong et al. used nanoparticles of Se (Nano-Se NPs) to treat the disease in transgenic HD models of Caenorhabditis elegans (C. elegans). They found that low doses of Nano-Se NPs could reduce the neuronal deaths, relieve the behavioral disorders, and protect the C. elegans against stress-related damages. According to their observations, Nano-Se can be a great potential treatment for Huntington's disease [61].

8.5. Traumatic Brain Injury

Traumatic Brain Injury (TBI) is a severe head injury caused by events such as car accidents. It is found that degradable NMs, particularly nanocomposites, can positively affect the self-renewal and differentiation of stem cells to neurons in TBI amelioration [21]. For example, Zinger et al. developed a novel leukocyte-based biomimetic nanoparticle system to directly access the inflamed areas in a mouse model of TBI through the peripheral organs 24 hours after injury [62].

Development of nanomaterial-based NSC therapy for neurological disorders benefits from the particular properties of NMs, including inimitable nano–bio interface, small size, and high delivery capacity that can regulate the mechanical and biochemical microenvironment of the transplanted stem cells in order to control the behavior of cells and optimize tissue regeneration process. Despite the advent of promising results obtained from nanotechnology-based NSC therapy, there are yet many challenges to overcome before this approach can go under clinical evaluations. These challenges include the safety of the applied NMs, metabolism of these scaffolds in the body, their toxicity to the target organ, genotoxicity, and neurotoxicity. In addition, NMs and neural stem cells of different origins should be optimized for TE purposes. Eventually, a problem may arise regarding the underlying mechanisms in the complicated systems of the nanomaterial-based NSC therapy. In this respect, alterations of the hub-gene and their related signaling pathways followed by addition of NMs was recommended, a fascinating field to explore [21].

Briefly, nanomaterial-based approaches can ensure a promising way to recreate an intimate environment for nerve regeneration. However, application of these materials requires consideration of their toxicity, biosafety, and metabolic effects on the living organism as well as investigation of the impacts of NMs in large animals or non-human mammals [63]. An additional demand still exists for further studies on the synthesis and design of the optimized multifunctional nano scaffolds with characteristics that can improve neuroregeneration in clinical models [64].

9. BLADDER TISSUE

Congenital abnormality or acquired disorders of the urinary system may damage the organs of this system, hence the damand for tissue regeneration. A standard approach to the reconstruction of the bladder is to use the parts of the gastrointestinal system. However, there are essential physiological differences between these tissues so that bladder cells inhibit the absorbance of some solutions while digestive tissue usually absorbs these solutes. These differences can result in complications such as metabolic disorders. In this regard, it is recommended that regenerative studies be carried out to achieve a proper alternative graft for the reconstruction of bladder tissue [65]. A favorite method for this purpose is the application of synthetic biomaterials since their material composition is defined, and they can be provided off-the-shelf with constant features for all the batches. Poly-dl-Lactide-co-Glycolide (PLGA) is a biodegradable material with FDA approval that can successfully promote the growth of smooth muscles of the bladder and urothelial cells in vitro [12,65,66]. However, not all biodegradable conventional synthetic polymers and natural polymer scaffolds succeeded in the reconstruction of bladder tissue mainly due to the weak strength and negative immune and tissue responses [67].

Therefore, development of new strategies for the reconstruction of the bladder using advanced newly designed biodegradable polymers rather than conventional polymers is required. Application of these advanced polymers results in the rapid and efficient replacement of the synthetic biodegradable material by healthy bladder tissues of the host. The response of bladder cells to some features such as nanosize, microsize, and flat surface is different probably because the surface of these nanoscale synthesized materials mimics the natural environment of these cells. In line with this observation, recent studies have found that the nanoscale polymers of PLGA and polyurethane (PU), compared to the conventional PU and PLGA, enhanced the growth of smooth muscle cells in the bladder [68]. Surprisingly, the reconstructed bladders also face a challenge related to the recurrent formation of calcium oxalate stones [69].

Chun et al. remarked that application of rough nanometer PU with submicron pores, compared to conventional materials, would lead to the adhesion and proliferation improvement of the urothelial cells as well as a decrease in the formation of calcium oxalate stones. It seems that the surface pores of the advanced nanoscale polymers can absorb calcium and oxalate separately, hence prevention of the required interactions for forming calcium oxalate [69].

Another study investigated the new 3D porous scaffolds of PLGA in comparison with the conventional microscale scaffolds, and the results highlighted the advancing effect of new polymers in promoting the adhesion, growth rate, and protein production of the smooth muscle cells of the bladder [70]. These synthesized nanoscale scaffolds can guarantee advancement of favorite in vivo alternatives for the bladder wall in the future [12].

In one study, a three-layer PLGA mesh was seeded by cells and fibrin that confirmed some useful pressure-withholding features. In addition, PLGA scaffolds seeded with human adipose stem cells produced smooth muscle cells as an engineered bladder. These cells are capable of regenerating the muscular layer of the bladder and supporting urothelial ingrowth that results in an entirely functional bladder. Further, inspection of the bladder structures regenerated after two weeks of implantation indicated that the PLGA scaffolds remained intact and visible with no collapse or shrinkage, and there were no apparent signs of inflammation, infection, or necrosis. These observations confirm that the PLGA scaffolds that are biocompatible with the host have the sufficient mechanical strength to provide pressure-withholding properties [65].

10. RISKS AND CHALLENGES OF APPLICATION OF NANOMATERIALS FOR TISSUE REGENERATION

Although NMs have unique characteristics owing to their nanoscale size that facilitates regeneration of damaged tissues, they may cause some potential risks to tissues and cells. According to an in vitro study, NMs exhibit higher toxicity than micromaterials even at limited concentrations and short term exposure [71]. A study by Napierska et al. highlighted an obvious relationship between the cytotoxicity and concentration of silica NMs. According to the findings of that study, localized concentration and nanotopography are main causes of nanotoxicity [72]. In another study, Yang et al. investigated the toxicity of various NMs including CNT, carbon black, ZnO, and SiO_2 nanoparticles at different concentrations. They found that NMs with the concentrations of > 50 μg/ml show higher cytotoxicity in vitro while under this threshold, no significant difference was observed [73].

Recent observations indicated that even lower concentrations of NMs (5 μg/cm^2) may result in cellular malfunction by irreversibly binding to biomolecules and cellular organelles, interfering with the replication of DNA, inducing cell death by disrupting membrane integrity, and causing systemic inflammation through blocking microcirculation [74,75].

In addition, the morphology of a nanomaterial can also affect its cytotoxicity [76]. Biological molecules, lipids,enzymes, nucleic acids, and polysaccharides are structurally and dimensionally analogous to NMs and for this reason, they can easily interact with different kinds of biological receptors, easily cross the biological membranes, travel all over the body and then being accumulated in organs that results in potentially harmful reactions [77,78]. In many studies, nanotubes are more likely to damage DNA than other NMs with spherical shapes or crystal structures. It was concluded that the shape of NMs may contribute to the genotoxicity of NMs at lower exposure doses [73]. In addition, NMs smaller than 10 nm were proved to be toxic and reactive due to the increased density of their surfaces and increased number of electrons present on them [79]. According to Wang et al. and Lee et al., several types of NMs, such as nHA and TiO_2 nanoparticles, can accumulate in heart, kidney, liver, lungs, and spleens of animals via blood circulation [80,81] and could be toxic to humans when tested in vivo [82,83]. A toxic effect has also been demonstrated by overproducing Reactive Oxygen Species (ROS) and cytokines such as IL-4 and IL-13 in vitro [84]. Accordingly, the results of these studies suggest that the localized concentrations and topography of the NMs may contribute to their toxicity. The threshold concentration of NMs can induce inflammation, cause the formation of free radicals, accumulate the peroxide products, and reduce antioxidants, and trigger cellular apoptosis [74,85]. To investigate the potential risks of NMs in cells with specific organs and tissues, Wu et al. conducted RNA sequencing on the body-wide organ transcriptome data. His lab research developed Nano Genome Atlas (NGA) that analysed NMs. According to their findings, some of them not only triggered inflammation but also significantly affected ion transport activities, metabolism, and cell behavior [86]. It is inevitable for NMs to cause nanotoxic effects due to their nanoscale size and high surface activity. Thus, prior to their in vitro and in vivo applications, biocompatibility, biodistribution, bioelimination, and environmental impact, as well as their nanotoxicity should be assessed [87].

11. CONCLUSION

Biomedical engineering has been developed to facilitate restoration of normal biological function of the

damaged tissues or organs. Regenerative medicine as a branch of biomedical engineering has attracted considerable attention concerning replacement or reconstruction of the injured cells and tissues in order to improve the life quality of the affected individuals. Introduction of nanotechnology to the regenerative studies remarkably improved the relevant investigations and advanced the tissue regeneration approaches towards obtaining low-cost long-lasting nanoscale scaffolds to be further applied in clinical practices. In many cases, the nanomaterial-based tissue regeneration process exhibited higher efficacy than the conventional artificial or animal-derived grafts facing some issues related to high costs, infection probability, inflammatory responses, immune responses, and need for replacement after a time period. Overall, nanomaterial-based tissue regeneration have brought promising results in tissue regeneration and repair of the damaged tissues of the bone, skin, tooth, cardiovascular disorders, neurological diseases, and abnormality of bladder tissue. Of note, one should be cautious that the nanotechnology in regenerative medicine is still in its early stages, and further research studies are required to broaden its applications from laboratories to clinics and the market.

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NOMENCLATURE

AD	Alzheimer's disease
ADV	Acoustic Droplet Vaporization
ALDR	Autologous Lamellar Dermal Regeneration
AMI	Acute Myocardial Infarction
AuNPs	Gold Nanoparticles
BP	Black Phosphorous
BPQDs	Black Phosphorous Quantum Dots
C. elegans	Caenorhabditis elegans
CDK	Cycline Dependent Kinase
CNS	Central Nervous System
CNTs	Carbon Nanotubes
CS	Chitosan Scaffold
ECM	Extracellular Matrix
FDA	Food And Drug Administration
HA	Hydroxyapatite
HD	Huntington's Disease
HNSS	Hollow Nanometer Silica Structures
HPDA	Hollow Polydopamine
IL	Interleukin
LbL	Layer-by-Layer
MBs	Microbubbles
NBs	Nanobubbles
NCs	Nanocapsules
NDs	Nanodroplets
NGA	Nano Genome Atlas
NMs	Nanomaterials
NNI	National Nanotechnology Initiative
NPs	Nanoparticles
NSC	Neural Stem Cell
NSTC	National Science And Technology Council
PCB	Poly(carboxybetaine)
PCL	Poly(ε-caprolactone)
PDLSC	Periodontal Ligament Stem Cells
PDT	Photodynamic Therapy
PLGA	Poly (lactic-co-glycolic) acid
PLGA	Poly-dl-Lactide-co-Glycolide
PLGA-PEG	Poly(lactide-co-glycolide)-block-poly(ethylene glycol)
PLLA	Poly(L-lactide)
PSCs	Pluripotent Stem Cells
PTT	Photothermal Therapy
PU	Polyurethane
QDs	Quantum Dots
ROS	Reactive Oxygen Species
SCI	Spinal Cord Injury
TBI	Traumatic Brain Injury
TE	Tissue Engineering
Ti	Titanium
TiO_2	Titanium Dioxide
TIDE	Titanium Inductively Coupled Plasma Etching
UTMD	Ultrasound-Centered Microbubble Destruction

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