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Review Article

Application of Nanoscaffolds in Mesenchymal Stem Cell-Based Therapy

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Regenerative medicine is an alternative solution for organ transplantation. Stem cells and nanoscaffolds are two essential components in regenerative medicine. Mesenchymal stem cells (MSCs) are considered as primary adult stem cells with high proliferation capacity, wide differentiation potential, and immunosuppression properties which make them unique for regenerative medicine and cell therapy. Scaffolds are engineered nanofibers that provide suitable microenvironment for cell signalling which has a great influence on cell proliferation, differentiation, and biology. Recently, application of scaffolds and MSCs is being utilized in obtaining more homogenous population of MSCs with higher cell proliferation rate and greater differentiation potential, which are crucial factors in regenerative medicine. In this review, the definition, biology, source, characterization, and isolation of MSCs and current report of application of nanofibers in regenerative medicine in different lesions are discussed.

1. Introduction

Organ rupture has become a pivotal concern for population health. In the US in the year of 2010, 28,664 organs were transplanted while 110,000 more patients were still on the waiting list.

A minimum of 20 patients on the waiting list die every day before transplantation because of suitable donor shortage [1]. Organ transplantation is one of the ways to cure the patients. Because of possibility of posttransplant rejection and crucial donor shortage, scientists are now trying to find alternative ways [2].

Regenerative medicine is an alternative way which is defined as "emerging interdisciplinary field of research and clinical applications focused on the repair, replacement, or regeneration of cells, tissues, or organs to restore impaired function resulting from any cause, including congenital defects, disease, trauma, and aging" [3]. Stem cells and scaffold are the two essential components in regenerative medicine [2]. Clinical application of stem cell is the base of this field [4] that involves stem cell injection (cell therapy), activation of biological administrated molecules or cell infusion (regenerative induction), and *in vitro* cultured tissues or organs transplantation (tissue engineering) [5, 6].

Stem cells are unspecialized cell with self-renewability and potential to generate multiple mature specialized cells [13]. There are two major types of stem cells: embryonic and adult stem cells. Embryonic stem cells are isolated from the early morula stage embryos or the inner cell mass of blastocyst while adult stem cells are derived from different adult organ tissues like liver, heart, skin, teeth, bone, and so forth.

In regenerative medicine and tissue engineering, mesenchymal stem cells (MSCs) are one of the best primary adult stem cell with continual proliferation and multipotent

differentiation potential [14, 15]. Scaffolds are manufactured nanofibers to provide microenvironment which would ease extracellular and intracellular cell contact and signalling which influence cell proliferation, differentiation and biology [16, 17]. Recently, the combination of MSCs and nanofibers is applied in regenerative medicine [13, 18].

2. Biology of MSCs

Mesenchymal stem cells (MSCs) were obtained for the first time by Friedenstein and Petrakova from rat bone marrow (BM). BM contains two types of stem cells: hematopoietic stem cells (HSCs) and MSCs [19]. MSCs are multipotent stem cells that are highly proliferative with the ability of self-renewal and the potential to differentiate into various cell lines such as adipocytes, chondrocytes, osteoblasts, endothelial cells, cardiac myocytes, nerve cells, hepatocytes, and pancreatic cells [20–28]. Differentiation potential of these cells has been observed in *in vivo*, *in vitro,* and *ex vivo* cultures. These characteristics display various mechanisms which can contribute to the therapeutic and beneficial properties of MSCs. These cells are also referred to as BM stromal cells, BM stromal stem cells, colony-forming fibroblastic cells, and mesenchymal progenitor cells [29, 30]. Mesenchymal tissue is an embryonic connective tissue derived from mesoderm that has the potential to differentiate into other types of connective tissue such as blood cell line; however, MSCs lack the ability to differentiate into HSCs. Stromal cells are among the connective tissue cells that form a special supportive structure in which functional cells exist. However, there is not any report to describe the potential of these cells in rehabilitation of tissue damages in regenerative medicine [31, 32].

In terms of morphology, MSCs look like unrestricted somatic stem cells (USSC): small spindle shaped cells, with large round nuclei and explicit nucleolus, some intracellular organelles, and long and short cellular projections. A substantial number of these cells in BM are surrounded by a matrix containing reticular filaments [33, 34]. BM is one of the most important sources to isolate MSCs. However, due to lack of an appropriate method to inhibit growth of other cells in primary culture and passages, isolation and purification of MSCs from BM and obtaining a homogenous population of these cells are difficult [35, 36]. Thus, finding alternative sources for MSCs isolation is necessary.

Recently, amniotic fluid was mentioned in literature as a significant alternative source for MSCs. In some studies, isolation of MSCs was conducted from human amniotic fluid in the second trimester of pregnancy and from C57BL/6 mice amniotic fluid [37, 38]. Other attempts to isolate MSCs from umbilical cord blood (UCB) and peripheral blood (PB) have been carried out with paradoxical results. Some studies reported lack of MSCs in UCB [39, 40], while others have reported their existence in UCB and in umbilical cord vessels' endothelial wall (Table 1) [41, 42]. In one study, mice amniotic fluid MSCs were isolated and compared to MSCs of BM in terms of their differentiation potential. Results showed that both have high potential to differentiate into osteoblasts and chondrocytes; however, MSCs of amniotic fluid lacked the adipogenic potential. This finding showed that adipocytes are present in adult BM while they do not exist during embryonic period and also there is a direct relativity between increasing adipogenesis and aging [38, 43]. Nevertheless, another study demonstrated positive adipogenic potential from c-kit^{+ve} cells isolated from human and mouse amniotic fluid by immunoselection against a stem cell receptor protein, c-kit [38]. These cells were then described as amniotic fluid stem cells rather than amniotic fluid mesenchymal stem cells. It is observed that amniotic fluid MSCs are less differentiated than bone marrow MSCs and have shorter doubling time. These features have drawn more attention in lab research [23].

3. MSCs Immunophenotyping

Identification of MSC specific surface markers is necessary for characterization of these cells, but certain markers have yet to be identified. Some studies introduce markers like Vcam-1, Thyl-2, and Sca-1 as common surface markers of hematopoietic, nonhematopoietic, and epithelial cells and mature T lymphocytes [30, 44]. Another study reports lack of CD45, CD11b, and c-kit expression as isolation markers for mouse bone marrow MSCs [45, 46]. In separate studies, STRO-1^{+ve} cells were introduced as a homogenous population of cells with high junction and proliferation potential [47, 48].

However, differences between STRO-1^{+ve} cells and MSCs are not yet clear. Also, surface markers such as CD29, CD44, CD73, CD90, CD105, CD166, and MHC class I are reported as well-known mesenchymal markers. Desirable as it is, application of one specific antibody profile against surface markers for isolation and purification of MSCs from other cell populations is not yet possible [49]. In two recent studies, neural gangliosides GD-2 and SSEA-4 are reported as surface markers of MSCs [50, 51].

4. Isolation and Purification of MSCs

Isolation of MSCs from BM can be carried out by different protocols such as using cytotoxic materials in culture medium, cell sorting, culture in DMEM medium with high or low density, and positive or negative selection [27, 45, 90]. The basis of these methods relies on the physical tendency of MSCs to attach to plastic surface of cell culture plate. However, these methods produce different lines of hematopoietic cells attached on the stromal layer and together they proliferated with MSCs. As a result, a heterogeneous population of cells formed on the plate. Consequently, in some of these protocols, non-MSC cells are removed from the bottom of the plate, however, leading to reduction in proliferation and differentiation potential of MSCs [91, 92]. In another study a population of unattached MSCs in BM is reported in which a simple and effective method was used to isolate MSCs, after some modifications in culture medium and reducing trypsin treatment time, a purified population of these cells was produced after the first passage [31]. In another study,

an unattached population of MSC is reported in BM which cannot be isolated by methods based on cell attachment [93].

5. Nanofibers and Cell Scaffolds

Most novel protocols of BM-MSC culture are based on isolation of mononuclear cells (MNCs), transferring of cells into cell culture medium, and their attachment to plastic surface of cell culture flask bottom [94–97]. Scaffolds are fabricated nanofibers that provide suitable microenvironment for cell signalling which would influence cell proliferation, differentiation and biology. Recently, designing biocompatible cellular scaffolds is a trend in regenerative medicine and tissue engineering. The aim of designing different scaffolds is to simulate the best structural and environmental pattern for extracellular matrix [22]. Different types of scaffolds like hybrid porous and biodegradable scaffolds based on chitosan-gelatin-triphosphate calcium, porous ceramic, and biphasic scaffold of hydroxyl apatite/tricalcium phosphate (HA/TCP) have been used for attachment, proliferation, and differentiation of MSCs into different tissues for application in tissue engineering and regenerative medicine [97, 98].

The MSCs can be also isolated from the adipose tissue or bone of a patient, grow *in vitro,* and be transferred, utilizing an applicable scaffold, onto the defected ocular surface [99]. In the other study, the critical role of mechanotransduction in the regulation of MSC fibrochondrogenesis has been investigated utilizing biomimetic nanofibrous scaffolds [100]. Scientists also investigated the feasibility of osteogenic differentiation of hUC-MSCs via application of nHA/CS/PLGA scaffolds [101].

The application of electrospinning method, which is an easy and cost effective method for designing 3D nanofiber cell scaffolds, has drawn a lot attention in tissue engineering. In this process, degradable biopolymers are used to produce nanofibers. Designed scaffold provides a matrix with pores of less than 10 microns in diameter. This matrix prevents cells from easy transit through empty spaces and provides proper conditions for attachment, proliferation, and growth of MSCs [102, 103]. Biodegradable nanofiber scaffold based on ε-caprolactone (PCL) and poly-L-lactic acid (PLLA) has been used in different studies. In general, cell scaffolds are used in two ways in tissue engineering: (1) MSCs are first placed on the scaffold then the complex of MSCs and scaffold is cultured; (2) MSCs are first cultured and then placed on the scaffold (Table 2) [104, 105]. A number of scaffolds and nanofibers have been applied in culturing MSCs for their usage in regenerative medicine.

6. Application of Tissue Engineered-MSCs in Regenerative Medicine

Application of stem cells in regenerative medicine requires two key elements: (1) the use of stem cells which have high ability in repairing the damaged tissue with the least side effects and (2) designing of biocompatible scaffolds whose clinical use has the least side effects and has no immunologic response. The high ability of proliferation and differentiation to several cell lineages and especially the significant role in immune regulation effects present MSCs as an important source for cell and gene therapy applications in congenital disorders and degenerative diseases [106–108]. Clinical studies reveal that MSCs have high ability in improving allogeneic transplant conditions and reducing side effects caused by chronic reaction of transplant against the host, known as chronic graft versus host disease (cGVHD). In fact, these cells reveal their anti-inflammatory effects by activating inhibitory T lymphocytes and discharging some immunoregulatory agents. On the other hand, these cells also have the ability to recognise damaged region with their paracrine activity, implant themselves in the region and speed up the repair process [109, 110]. There are acceptable reports on application of MSCs in remediation of some human diseases such as osteogenesis imperfecta, spinal cord lesions, Parkinson's disease, and brain stroke [111–114]. Recently, scientists developed PLA/PCEC hybrid fibrous scaffolds to effectively differentiate placenta-derived MSCs into bone-associated cells and verified the capacity of this scaffold in bone tissue engineering [115].

In another study Lü and colleagues in 2013 demonstrated that 3D PHBV/HA scaffolds can induce the differentiation of rat bone marrow derived-MSCs into osteoblast cells. These fibrous scaffolds also displayed remarkable effects on the repair of significant defects of bones, presenting their promising usages in bone tissue engineering [116]. In another attempt, scientist applied hydrogel scaffolds to successfully proceed with the differentiation of hMSCs to chondrocytes [117].

This review will discuss further application of tissue engineering technique in generating MSC-based tissue for treatment of vascular diseases, bone lesions, cartilage diseases, and bladder and lung cancers.

7. Vascular Disease

In vascular tissue engineering, cells derived from BM are utilized. This technique requires plating a mixture of cells recognized as bone marrow stromal cells (BMSCs) in culture dishes to achieve attached cell population. Prior to scaffold seeding, the BMSCs are differentiated to vascular cells. Nevertheless, long phases of cell expansion, high price of different growth factors, reiterated enzymatic digestion, and potential restrictions in cell behaviour which result in supraphysiologic inflexibility of cell culture dishes are the obstacles that should be overcome [118].

Alternatively, bone marrow mononuclear cells (BMNCs), a heterogeneous population containing differently mature B-cells, T-cells, and monocytes, as well as hematopoietic stem cells (HScs), MSCs, endothelial progenitor cells (EPCs), and very small embryonic-like cells (VSELs), could be isolated in order to avoid the long adhesion stage in cell culture dishes. Unlike BMSCs, BMNCs can be directly seeded into the anticipated scaffolds, which could be beneficial in preservation of cell phenotype, viability, and even simplifying the *in vitro* processes. Previous studies showed that culturing

Table 1: Sources for isolation of mesenchymal stem cells.

Tissue	Isolation protocol	Properties of isolated cells	Marker of interest in isolated cells	Resource
Warton's jelly of UCB	Sections of Warton's jelly in medium, taking out the sections from the medium after 5 days, and culture of isolated cells for 5 more days.	Isolated MSCs probably lack pluripotency according to lack of NANOG gene expression after 9th culture.	Histochemical study in terms of alkaline phosphatase activity, RT-PCR to study the existence of NANOG mRNA, examining growth graph of isolated cells.	[7]
Knee synovium	Collagenase treatment of human knee synovium tissue, cell culture, and attachment of MSCs to flask.	Isolation from synovium tissue sectioned during knee surgery, high proliferation power compared to similar types, high differentiation potential into adipose and cartilage tissue.	Immunohistochemistry and flow cytometry for CD105 and CD73, gene study with RT-PCR, and specific dying for cells induced towards osteocyte and adipocytes.	[8]
Amnion	EDTA and trypsin treatment, cell culture in DMEM medium with 10% FBS.	MSCs remained undifferentiated after 18–20 steps of passages, these cells beside high differentiation potential into mesodermal cell line, can differentiate into nerve-like cells.	Flow cytometry for CD34, CD45, CD73, CD90, and CD105 and then differentiation into osteoblasts, adipocytes, and nerve cell line.	[9]
Eye conjunctiva	After biopsy, stromal section of eye conjunctiva tissue was cultured in flask.	These cells, other than osteoblasts, chondroblasts and adipogenic cells, have the potential to differentiate into nerve cells.	Expression of markers like CD29, CD44, CD166, CD13, and SH2 and SH3 and genes such as Oct-4, Rex-1, and NANOG.	[10]
Endometrium	Collagenase III and ribonuclease I treatment of endometrium to produce single cell suspension, removal of leukocytes by anti-PTPRC (anti-CD45), and culture of MSCs and epithelial cells in DMEM/F-12 with 10% FBS, isolating epithelial cells using anti-EpCAM.	MSCs produced have high potential of self-renewal and differentiation into osteoblasts, chondrocytes, adipocytes and smooth muscles.	Flow cytometry and immunohistochemistry for expression of ITGB1 (CD29), CD44, NT5E (CD73), THY1 (CD90), ENG (CD105), PDGFRB (CD140B), and MCAM (CD146) and lack of expression of PECAM1 (CD31), CD34, PTPRC (CD45), and EpCAM.	[11]
Adipose tissue	Collagenase III treatment of adipose tissue to produce single cell suspension, culture in ultraculture medium with 2% UltroserG.	MSCs have ability of fast proliferation and differentiation potential into osteoblasts and adipocytes.	Flow cytometry for expression of CD73, CD90, CD105, CD44, and CD166 and lack of expression of CD45, CD34, and CD14.	[12]

vascular smooth muscle cells (VSMCs) on PGS scaffolds demonstrated the expression of elastin and amenability with higher similarity to native vessels than the cells cultured on firmer but more chemically analogous PLGA scaffolds [119]. Another study revealed that the PGS scaffolds could be precoated with natural matrix which improves the functional proteins expression and extracellular matrix (ECM) in endothelial progenitor cells (EPC) [120]. The obtained data

Table 2: Sources of MSCs and scaffolds used in regenerative medicine.

MSC source	Illness	Scaffold and nanofiber	Resource
Human BM	Liver lesions	PCL/collagen/PES nanofiber scaffold	[52]
Mouse BM	Vascular lesions	1-PLGA, PGS, P-PGS, Pl-P-PGS	[53]
Murine BM	Skin lesions	Integra (R), an artificial dermal matrix	[54]
Human adipose tissue	Bone lesions	Chitosan-based scaffolds	[55]
BM	Vascular lesion	Polyelectrolyte multilayer film	[56]
BM	Bone lesions	Thin film of PEGylated multiwalled carbon nanotubes spray dried onto preheated coverslip	[57]
Induced pluripotent cells	Bone and cartilage lesions	Calcified Structures in Scaffold	[58]
BM	Skin lesions	Pullulan-collagen composite hydrogel matrices	[59]
Sheep BM	Cardiac valves lesions	PGA : PLLA scaffolds	[60]
Human BM	Vascular lesions	PLLA/PCL	[61]
Human BM	Cartilage lesions	Fresh fibrin (FG) and platelet-rich fibrin (PR-FG) glues produced by the CryoSeal (R) FS System	[62]
Human BM	Bone lesions &	Coral scaffold	[63]
Human BM	Bone and cartilage lesions	LIFT three-dimensional scaffold	[64]
Human BM	Vascular lesions	Heparin-releasing PLLA	[65]
Adipose tissue	Muscular and skeletal lesions	Biomaterial scaffolds consisting of native tissue matrices derived from cartilage	[66]
BM	Bone lesions	3D silk scaffolds	[67]
Adipose tissue	Bone lesions	Trabecular titanium scaffolds	[68]
BM	Bone lesions	Scaffold-free cell sheet	[69]
BM	Bladder lesions	Nanofibrous poly-L-lactic acid scaffolds	[70]
Sheep lung	Lung lesions	Fibrinogen-\fibronectin-vitronectin hydrogel (FFVH) scaffolds	[71]
Rat, pig, and rabbit adipose tissue	Bone lesions	Hydroxyapatite scaffolds	[72]
BM	Bladder lesions	3D nanofibrous scaffold, highly porous PLLA scaffold	[73]
BM	Bone lesions	cell-scaffold construct composed of gelatin-based hydrogel and ceramic (CaCO3/beta-TCP) particles	[74]
BM	Bone lesions	Pura matrix (PM)	[75]
BM	Cartilage lesions	3D chitosan scaffold	[76]
BM	Bone lesions	Biodegradable chitosan/polyester scaffold	[77]
BM		Poly (L-lactic acid) microfiber	[78]
Rat BM	Bone lesions	Nonporous, smart, and stimulus responsive chitosan-based scaffolds	[79]
BM	Vascular lesions	3D calcium phosphate (CP) scaffolds	[80]
BM	Bone lesions	Porous hydroxyapatite ceramics	[81]
BM	Bone lesions	Hydroxyapatite scaffolds	[82]
BM	Teeth lesions	Collagen scaffold carrier	[83]
BM	Bone lesions	Porous collagen I/III scaffold	[84]

Table 2: Continued.

MSC source	Illness	Scaffold and nanofiber	Resource
BM	Nerve lesions	PLGA polymer scaffold	[85]
BM	Bone lesions	Ceramic scaffolds	[86]
BM	Bone lesions	PLA	[87]
Amniotic Fluid	Sinus augmentation	MgHA/collagen based scaffold	[88]
BM	liver lesions	Collagen nanofibrous scaffold	[89]

BM: bone marrow.

recommended that creating an environment with features similar to blood vessels *in vitro* could enhance the establishment of vascular tissues derived from progenitor cells. A recent study demonstrated the use of BMNCs with platelets plasma proteins and PGS for vascular tissue development. In the study, they exhibited that biochemical mechanisms and tissue signals from platelets and plasma can together direct BMNCs to change into cells similar to smooth muscle which have the expression of phenotypic markers and individual ECM production [52].

8. Bone Lesions

Another application of MSCs in tissue engineering is the use of these cells to differentiate into bone cells in order to remedy large bone lesions due to trauma or degenerative pathologic damages. As autologous bone transplant has some limitations, application of tissue engineering to regenerate bone lesions using three-dimensional (3D) scaffold MSCs has been proposed [121]. In fact, designing a scaffold that is able to act like a proper support for attachment and proliferation of cells and inducing differentiation into bone cell lines and provide a porous space for appropriate connection between cells in order to reach bone regeneration is a heatedly debated topic. In a preclinical application, the complex of scaffold and MSCs was placed under mouse's skull to study the ability of MSCs to form bone cells. Results showed significant acceleration in regeneration of bone tissue in maxillary sinus using MSCs. In fact histomorphological studies reveal the formation of osteoblasts with the potential of forming an osteoid matrix with the assistance of biphasic HA/TCP scaffolds [122].

Chemical vapor deposition- (CVD-) developed graphene- (G-) sheets display brilliant features in stimulating osteogenic differentiation of MSCs [123]. Lee et al. [124] demonstrated that CVD-developed G-sheets can significantly promote osteogenic differentiation of hMSCs alongside with chemical growth factors. They also found that the presence of chemical inducers highly increased the amount of osteogenic differentiation on G-sheets. Unfortunately, they [125] further discovered that G-sheets were not capable of absorbing enough ascorbic acid which required chemical inducers in the generation of mature osteoblasts [126].

Other nanomaterials containing carbon nanotubes (CNTs) [127] and gold nanoparticles [123] could also promote osteogenic differentiation of MSCs by means of stress mechanism. This method utilizes physical stressor to promote the differentiation of stem cells into various cell lineages [128, 129]. As an example, Dalby et al. [130] showed that proliferation of MSCs on poly-(methylmethacrylate) (PMMA) nanopatterns and in a standard culture medium resulted in the formation of osteoblastic morphologies without utilization of chemical inducers. In addition to such synthetic nanomaterials, it was also demonstrated that usage of some bionanomaterials such as tobacco mosaic virus can also improve the differentiation of stem cells [131].

A recent experience reported the formation of two novel nanostructures, graphene oxide nanoribbon (GONR) and reduced GONR, as two-dimensional (2D) templates to investigate the application of graphene nanostructures in osteogenic differentiation of MSCs with or without the utilization of various chemical inducers. They studied the effects of physical stresses induced by surface topography of the nanogrids on the differentiation of MSCs. The results showed that the utilization of chemical inducers stimulates the reduced graphene oxide nanoribbon (rGONR) grids to display osteogenic differentiation in a short period. These achievements can promote further research on selective differentiation of stem cells on different graphene constructs as biocompatible and implantable scaffolds even with 3D configurations [18]. However, the use of tissue engineering in regeneration of bone lesions has some limitations due to low number of stem cells isolated from BM aspiration [49]. In the end, finding novel sources for MSCs derivation like amniotic fluid and Warton's jelly along with more research about application of different scaffolds for proliferation and differentiation of MSCs and clinical monitoring of implanted MSCs are required [132, 133].

9. Cartilage Disease

The application of various adult-derived stem cells (ASCs) in tissue engineering approaches is considered as a novel method to console the trouble of cell, organ, and tissue scarcity. Cartilage flaws that caused by joint injury, developmental disorders, and aging resulted result in the pain of joints and loss of movement. Tissue engineering methods suggest particular cell-based treatment to overhaul articular cartilage flaws and provide a capable method for reestablishment of joint function [134, 135]. In cartilage tissue engineering methods, chondrocytes and MSCs are normally

utilized for redevelopment of cartilage, but the type of cells will determine the tissue engineering approaches of cartilage *in vitro*. Although expansion of MSCs for regeneration of cartilage is at an initial step, the noticeable MSCs plasticity could supply tissue engineering with ample possibility of utilizing MSCs for manifold cellular differentiation for obtaining strictly multiphasic tissues [136, 137].

To stimulate chondrogenic differentiation, MSCs are proliferated in a 3D situation to improve the need of interaction between cells [138]. Earlier studies have shown that MSCs displayed chondrogenic characteristics when are propagated in a culture [139, 140], a technique which was generally utilized in MSC chondrogenesis analysis [141, 142]. Nevertheless, the technique of cell pellet propagation has manifold innate weaknesses. Small in magnitude and regularly poor mechanical characteristics have made the technique impracticable to repair cartilage flaws. Predesigned biomaterial scaffolds have much more attractive potential in providing the role as a support structure for MSCs, such as preparing a 3D situation with comprehensive mechanical features. Some studies developed several natural and synthetic substances [143, 144], produced gel-, sponge-, or fiber-centered constructions constructs to proliferate MSCs of various species [145–147]. The electrospinning procedure is an easy, economical method to generate ultrafine fiber-derived scaffolds developed from a range of different biodegradable polymers [36, 148]. Nanofiber scaffolds generated through electrospinning method have structures similar to extracellular matrix and can display favourable features for tissue engineering purposes. It has been demonstrated that 3D NFSs are distinguished through high sponginess and similar morphology to natural collagen fibrils, a high ratio of surface area to volume, and wide-ranging pore diameter [149].

These physical structures elevate promising biological responses in cultured cells containing improved proliferation and cell attachment in addition to preservation of the chondrocytic phenotype [150, 151]. In a study, the chondrogenic functions of seeded BM-MSC maintained on polycaprolactone were compared to the cells cultured using cell pellet technique, in a defined medium supplemented with TGF-b1 [152]. The cultured MSCs showed a chondrocytic phenotype differentiation and cartilage-associated ECM proteins synthesis. These findings reported that PCL NFS is a suitable support structure to transplant the MSCs, which suggests practical scaffolds for cell-based cartilage repair using tissue engineering methods [52].

10. Bladder Cancer

Bladder cancer is the ninth most frequent cancer in the world and the incidence is four times higher in males [153] where smoking has been known as a main reason of bladder cancer in western countries [154]. Nowadays, stem cell therapy has become one of the most appropriate therapeutic approaches for bladder cancer. In fact, many studies have shown that bladder smooth muscle cells can be produced from transplanted stem cells [155, 156]. These studies also showed that smooth muscle cells generated from transplanted stem cells can be really valuable in bladder tissue engineering [73].

MSC is known as an appropriate stem cell source to approach this goal. MSC is able to self-renew and also differentiate into different cell types under certain conducive environments [157, 158]. In fact, using MSC for their therapeutic potentials has been very useful to control and treat different types of cancers including bladder cancer. For instance, stimulation of tissue regeneration and prevention of tissue injury after transplantation of stem cell are also very important [159] and paracrine mechanism of MSCs can play a very important role in this area [160].

Indeed, based on recent literatures, the most important issues that researchers are focusing on are the improvement of the isolation procedure and expansion of these cells. Among various methods small intestinal submucosa (SIS) could successfully be applied for bladder tissue engineering [161].

Tissue engineering scaffolds are one of the appropriate regeneration environments that have been used by researchers to isolate and expand MSCs [162]. Using synthetic scaffolds like poly-lactic-glycolic, for instance, instead of SIS, to generate MSCs [163] has proved to be more practical. Tian et al. exhibited bladder engineering potential when such synthetic scaffold was applied [73]. Similarly, it is shown that using poly-lactic-glycolic acid to expand MSC's lead's to maintenance of bladder capacity and compliance [164]. Current studies introduced novel generation of synthetic polymer scaffolds. These nanofibrous scaffolds have improved biomechanical/physical features and have been used in tissue engineering of various organs. This new product can provide a natural environment which improves cell metabolism by improving the exchange of nutrition and gas [165]. Various attempts have been done to establish this new technology but it still needs more examination.

11. Lung Cancer

Lung cancer is the most frequent cancer worldwide with higher incidence in males compared to females [150]. Various methods are available for cancer treatment including the application of engineered tissue; such techniques involve growing lung tissue using artificial scaffold and stem cells *ex vivo* which has been frequently used in regeneration of lung tissue. Particularly, MSCs isolated from different sources are seeded on various biosynthetic scaffolds to generate tracheal cartilage for repairing congenital tracheal defects [166, 167].

Several researchers are focusing on this issue. In one study, fetal rat lung cells were cultured in a biosynthetic gelatin matrix and then injected into normal rat lung which have resulted in induction of lung structure [168]. Another study showed the creation of alveolar-like constructs after culturing fetal rat lung suspensions in a 3D glycosaminoglycan scaffold. Concurrently, seeding the mouse cells in synthetic polymer scaffolds showed the same result [169]. Researchers also showed the ability of 3D scaffold culture systems to assess lung improvement and repair [170]. In fact,

other studies also showed that stem cells isolated from various sources can form airway or alveolar-like structures when cultivated in scaffolding material and after culturing in such an environment, can be used for functional lung regeneration [171, 172]. Scaffolds are used to engineer lung airways by several researchers [173, 174]. Gray et al. showed the importance of MSC-engineered scaffolds for engineered perinatal airway repair. They also demonstrated improvement in remodelling and epithelialization *in vivo* by using engineered human amniotic fluid MSC [175]. Previous studies on engineered airway also showed the same results by using different cells and scaffolds [176, 177]. Revision is still necessary although researchers have found quite a number of appropriate details about synthetic scaffold.

12. Conclusion

In this review, the applications of nanoscaffolds and MSCs in regenerative medicine were discussed. Selection of a proper source for isolation of MSCs like amniotic fluids and umbilical cord and designing biocompatible and biodegradable scaffolds proper for proliferation and differentiation into multiple lineages have great significance in regenerative medicine. Further researches in this field can provide a way for advancement of application of tissue engineered-MSCs in regenerative medicine.

Conflict of Interests

The authors declare that they have no conflict of interests.

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