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Application of Nanoscaffolds and Mesenchymal Stem Cells in Tissue Engineering

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Abstract

Stem cell research has obtained much prominence in recent years for its therapeutic potential in dealing with serious diseases, many of which are essentially incurable by routine therapies. Mesenchymal stem cells with pluripotency and immunomodulatory properties are suitable candidates for tissue engineering and regenerative medicine. Today, nanofibrous scaffolds are widely used in tissue engineering to improve implantation, function, proliferation and infiltration of the cells. In this regard, porous and biodegradable scaffolds with microstructure and suitable physical-mechanical properties are prepared. We review the application of mesenchymal stem cells nanoscaffolds and in tissue engineering.

Keywords: Mesenchymal stem cells, tissue engineering, tissue scaffolds

Introduction

Stem cell research has obtained much prominence in recent years for its therapeutic potential in dealing with serious diseases, many of which are essentially incurable by routine therapies. Stem cells can be classified into four broad types based on their origin from the embryo, the fetus, the umbilical cord, and the adult. Each of these can be divided into subtypes (Fig. 1). Mesenchymal stem cells (MSCs) are able to differentiate to various mesodermal and non-mesodermal cell lineages [1-3]. These cells have gained much interest in the field of regenerative medicine not only for their great differentiation potential, but also for high capacity of self-renewal and immunomodulatory effects [4, 5].

The ability of engraftment to different tissues makes MSCs promising candidates for gene delivery. Moreover, compared to direct transfer of gene vectors, engineered MSCs are associated with less immunologic interference [6]. One of the hypothetical mechanisms of contribution of these cells to tissue regeneration is the paracrine effect. Indeed, MSCs can recognize the location of injury, reach the site and excrete several soluble factors to accelerate the healing process [7].

The formation and designation of biocompatible scaffolds is critical in MSCs differentiation and tissue engineering. An ideal scaffold must mimic the role, structure and environment pattern of extracellular matrix [8, 9]. Researchers have found that nanofibrous scaffolds could play a vital role in tissue engineering by providing a proper matrix for proliferation, differentiation and attachment of stem cells [10-14]. Recently electrospinning method, a high electric field generated between a needle and a collector, has gained popularity within the tissue engineering community as a potential mean for producing scaffolds [15, 16]. A variety of polymers have been used as scaffolds in tissue engineering. Among them, polyethersulfone (PES) nanofiber can be used in biomedical applications such as hemodialysis, filtration and ultrafiltration due to its positive attributes as a biomaterial. Consequently,

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this polymer has been considered for use in tissue engineering [17-20]. Also, minor efforts have been made to increase the infiltration of the cells into electrospun nanofibrous scaffolds.

Nowadays, tissue engineering has a significant role in science and technology so that many studies have focused on this subject. With regard to the therapeutic potential of this technology, many diseases are expected to be treated by tissue engineering as one of the best therapeutic options, while many defects still do not have a definitive treatment. Currently tissue engineering techniques are used to repair and rebuild damaged tissues such as skin, bone, cartilage, liver, bladder, ligament, heart valve, etc, and remarkable success has been achieved in these areas [21-23].

Regenerative medicine and tissue engineering require two key and complementary components: 1) biologically compatible scaffolds without any immune response; and 2) proper cells such as stem cells, which potentially repair damaged tissue[24]. Three-dimensional scaffolds made of biodegradable and biocompatible polymers, such as poly L-lactic acid (PLLA), provide proper space for storing the mesenchymal stem cells. Utilizing the scaffolds containing stem cells usually includes two different methods. In one of these methods, cells are initially placed within the scaffold and then the complex containing scaffolds and mesenchymal stem cells is cultured; in the second method, cultured cells are placed within the scaffold during operation. The linker materials can be placed before or during the surgery in the space of fiber-forming scaffold [25]. The scaffolds made via electrospinning have a pore size less than 10 µm, so the cellular infiltrations into the nanofibers are reduced and this makes a 3D shape as exists in extracellular matrix [26, 27]. Few efforts have been made to increase infiltration of the cells into electrospun nanofibrous scaffolds [28, 29]. Some of the latest researches on the use of mesenchymal stem cells and nanoscaffolds in tissue engineering are introduced in Table 1.

Biodegradable Porous Hybrid Scaffolds for Tissue Engineering

Generally, polymers can be divided into two main groups including biodegradable and non-degradable polymers. Biodegradable polymers of natural origin, including polysaccharides, proteins, lipids and polyesters are produced by micro-organisms or plants. However, a number of biodegradable polymers are synthesized using petrochemical raw materials including: poly (aliphatic esters), polyaromatic esters, polyvinyl alcohol, and polyolefiniccomponents. Most polymeric nanoparticles are made of biocompatible and biodegradable materials and show a good potential for surface modification. Therefore they are the best option for nanomaterial drug delivery. These polymer-based coatings can be applied for

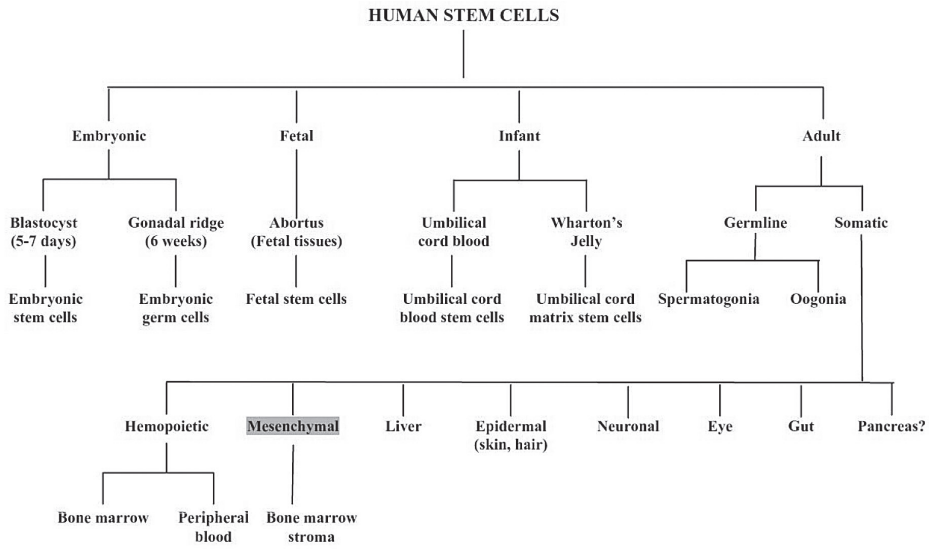

Figure 1: Classification of the human stem cells

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surface modification of other nanoparticles to improve their distribution properties. In addition to using polymeric nanoparticles in controlled drug delivery, these nanoparticles can also be used against breast cancer cells in gene therapy due to their anti-proliferation effect [30].

Chen et al. cultured human MSCs in vitro in a cobweb-like biodegradable polymer scaffold: a poly (dl-lactic-co-glycolic acid)-collagen hybrid mesh. They showed that PLGA-collagen hybrid mesh aggregates the MSCs and provides a stimulus microenvironment for the chondrogenic differentiation of the MSCs. Also, they showed that during chondrogenic differentiation of MSCs in the scaffold the expression of type II collagen and aggrecan increased, whereas the expression of type I collagen decreased [31].

Generally, the classic in vitro model proposed for tissue engineering includes isolation and differentiation of stem cells from the donor tissue and culturing them in three-dimensional scaffolds [32]. Preparation of biocompatible porous scaffolds is a difficult part of tissue engineering because, in addition to having good physical and mechanical properties, these scaffolds must have appropriate micro structure [33, 34]. For example in a study a wide variety of porous and biodegradable scaffolds with fine structure and physical-mechanical properties were prepared. These scaffolds were made through the integration of natural polymers and ceramics by gel freezing technique. Using various methods, chemophysical and biological properties of scaffolds with relevant features were evaluated. The results showed that there was a good control on the amount and porosity of hybrid scaffold microstructure. Furthermore, biocompatible cell growth of chondrocyte on the scaffold was evaluated through light and electron microscopy techniques. The results confirmed the high potential of these scaffolds for supporting cell growth [35].

Improved Nanofibrous Scaffolds in Tissue Engineering

Nanofibrous scaffolds (NFS) have been recently used in the field of tissue engineering because of their nano-size structure which promotes cell attachment, function, proliferation and infiltration. Li et al. have reported the use of MSCs in cartilage repair utilizing a three-dimensional culture in nanofibrous scaffold and treatment by TGF-beta. They showed that due to improved mechanical characteristics of NFS, these scaffolds are a useful carrier for MSC transplantation in cell-based tissue engineering approaches to cartilage repair [36].

There are few studies on the biocompatibility and tissue engineering applications of PES scaffolds. Lin et al. produced PES nanofibers by gas/jet electrospinning [37] and Zhu et al. studied the biocompatibility of PES and surface-aminated PES with hematopoietic stem cells. They showed that surface-modified PES had the highest expansion efficiency of the cells and its biocompatibility was promoted after surface modification. Many polymers have less desired surface properties to be used as biomaterials in tissue engineering. In this regard, surface treatment and modification is used to improve surface characteristics [38-42]. Plasma treatment is one of the best ways to improve surface hydrophilicity [43, 44]. Many studies have shown that protein grafting also improves surface properties of biomaterials. Collagen is a natural polymer which has been used for grafting in some researches. It has a distinctive amino acid sequence which is very important in cell-scaffold interactions [45-48]. In another study, a PES nanofibrous web with modified surface properties was prepared by plasma treatment and collagen grafting. The results indicated that plasma treatment and collagen grafting increased hydrophilicity of nanofibers surface. The cell interaction studies have been done using stem cells due to their ability to differentiate into several kinds of cell lines. The cells had normal morphology on collagen grafted PES nanofibers and showed very high infiltration. This infiltration capability is very useful and needed to make 3D scaffolds in tissue engineering [49].

Production of Hepatocytes-Like Cells

Liver is a target for development of stem cell-based therapy which is greatly promising. Several cases including toxic injuries, viral infections, and autoimmune or genetic disorders may cause hepatic dysfunction resulting in chronic liver disease and/or acute liver failure. Liver transplantation which is still the only therapeutic option for end-stage liver disease is limited by the availability of donor organs [50]. Therefore, it would be greatly beneficial if an unlimited supply of functional hepatocytes from other sources such as stem cells could be

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Table 1 a: Summary of the latest studies on mesenchymal stem cells and nanoscaffolds in tissue engineering

Reference	Scaffold & Nanofiber	Disorder	Markers of differentiation	MSC isolation source	Time of differentiation	In vivo/ In vitro
Kazemnejad S, et al. (2008)	PCL/collagen/PES nanofiber scaffold	Liver tissue engineering	Albumin, AFP & CK-19	hBMSCs	3 Weeks	In vitro
Wu W, et al. (2011)	1- PLGA 2- elastomeric PGS 3-platelet-poor P-PGS 4- PGS coated by Pl-P-PGS	Vascular differentiation	Calponin, α-SMA, Col & Elastin	BMNCs	3 Weeks	In vitro
Formigli L, et al. (2011)	Integra(®), an artificial dermal matrix	Skin regeneration	SDF-1	hMSCs	------	Mouse calvaria model
Costa-Pinto AR, et al. (2011)	Chitosan-based scaffolds	Bone repair(osteogenic differentiation)	ALP	hBMSCs	3 Weeks (in vitro) & 8 Weeks (in vivo)	In vitro & In vivo (mice)
Rada T, et al. (2011)	SPCL	Osteogenic differentiation	RunX-2, Osterix, OP & OCN	hBMSCs hASCs	6 weeks	In vitro & In vivo (mice)
Moby V, et al. (2011)	PMF	Vascular Differentiation (endothelial-like cells)	PECAM & vWF	hMSCs	2 weeks	In vitro
Nayak TR, et al. (2010)	Thin film of pegylated multiwalled carbon nanotubes spray dried onto preheated coverslips	Bone formation (osteoblasts)	OCN	hMSCs	1 week	In vitro
Bilousova G, et al. (2010)	Gelfoam matrix	Mesenchymal lineages of bone, cartilage and fat	OCN & BSP	iPSCs	12 Weeks	In vitro (bone, cartilage and fat) & In vivo (bone)
Suşman S, et al. (2010)	Type IV collagen, chytosan, Matrigel & laminin	Langerhans-like glucagon-secreting cells	Expression of the glucagon gene	Placental mesenchymal stem cell	3 weeks	In vitro
Yamada Y, et al. (2010)	Hydroxyapatite-coated osseointegrated dental implants	Bone formation	Histological analysis	cBMMSCs	8 weeks	In vivo (Canine animal models)
Baba S, et al. (2010)	The PLLA fibers were woven to form a 3-D-structured scaffold	Cranial bone regeneration	Histological analysis	MSCs	8 weeks	In vivo
Wong VW, et al. (2011)	Pullulan-collagen composite hydrogel matrices	Cutaneous wound	VEGF	Murine MSCs	3-14 days	In vitro (Humanized excisional wound model)
Eckert CE, et al. (2011)	PGA:PLLA scaffolds	Heart valve tissue	Col	Ovine BMSCs	4 weeks (in vitro) & 12 weeks (in vivo)	In vitro & In vivo
Centola M, et al. (2010)	PLLA/ PCL scaffold	Vascular endothelium	CD31	hMSCs	2 days	In vitro
Ahmed TA, et al. (2011)	Fresh fibrin (FG) and platelet-rich fibrin (PR-FG) glues produced by the CryoSeal(®) FS System	Cartilage substitute	Collagen II & Aggrecan	hBMSCs	2.5 weeks	In vitro
Tran CT, et al. (2010)	Coral scaffold	Osteogenic differentiation	OCN	hBMSCs	3 weeks	In vitro
Gruene M, et al. (2010)	LIFT three-dimensional scaffold	Differentiated toward bone and cartilage	OCN & ALP (osteogenic differentiation)/ type II collagen & Aggrecan (Chondrogenic differentiation)	MSCs	3-21 days (bone) & 3 weeks (cartilage)	In vitro
Spadaccio C, et al. (2010)	Heparin-releasing PLLA scaffold	Endothelial phenotype	CD31	hMSCs	up to 1 week	In vitro
Guilak F, et al. (2010)	Biomaterial scaffolds consisting of native tissue matrices derived from cartilage	Musculoskeletal phenotypes	Type II collagen & Aggrecan	ASCs	1 week	In vitro
Park SH, et al. (2010)	3D silk scaffolds	Osteogenesis	Collα1, ALP, OP & BSP	hBMSCs	8 weeks	In vitro

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Table 1 a: Summary of the latest studies on mesenchymal stem cells and nanoscaffolds in tissue engineering (Continued)

Reference	Scaffold & Nanofiber	Disorder	Markers of differentiation	MSC isolation source	Time of differentiation	In vivo/ In vitro
Gastaldi G, et al. (2010)	Trabecular titanium scaffolds	Bone tissue (osteoblastic-like phenotype)	Type I collagen, OP, OCN & ALP	hASCs	3-4 weeks	In vitro
Akahane M, et al. (2010)	Scaffold-free cell sheet	Bone formation	ALP & OCN	MSCs	4 weeks	In vitro & In vivo
Tian H, et al. (2010)	Nanofibrous PLLA scaffolds	Bladder cells (smooth muscle- and urothelium-like cells)	Urothelium-specific markers: Up-Ia, CK7 & CK13	hBMSCs	7, 14 days (in vitro) & 4 weeks (in vivo)	In vitro & In vivo (athymic mice)
			Smooth muscle cells specific markers: α-SMA, calponin, desmin & myosin			
Ingenito EP, et al. (2010)	FFVH scaffolds	Pulmonary diseases	------	Ovine lung mesenchymal cells derived from lung biopsies	4 weeks	In vitro & In vivo
Arrigoni E, et al. (2009)	Clinical-grade porous (60%) HA granules	Osteochondral defects	ALP, Extracellular calcium deposition, OCN & osteonectin	MSCs isolated from rat, rabbit and pig adipose tissue	1 week	In vitro & In vivo (rabbit model)
Tian H, et al. (2010)	Highly porous PLLA scaffold	Bladder tissues (Myogenic differentiation)	α-SMA, Calponin, Desmin & Myosin	hBMSCs	1 week (in vitro) & 4 weeks (in vivo)	In vitro & In vivo (nude mice)
Ben-David D, et al. (2010)	Gelatin-based hydrogel and ceramic (CaCO(3)/beta-TCP) particles	Bone formation	-------	hBMSCs	8 weeks	In vivo
Yoshimi R, et al. (2009)	Pura Matrix (PM)	Bone regeneration	Histological analysis	Dog MSCs	8 weeks	In vivo (adult hybrid dog's mandible)
Breyner NM, (2010)	3D chitosan scaffold	Cartilage tissue (chondrocytes)	Collagen type II	MSCs	3 weeks	In vitro
Costa-Pinto AR, et al. (2009)	Biodegradable chitosan/polyester scaffolds	Osteogenic differentiation	Runx2, Type 1 collagen, BSP & OCN	hBMSCs	3 weeks	In vitro
Martins AM, et al. (2009)	Nonporous, smart, and stimulus responsive chitosan-based scaffolds	Osteogenic differentiation	ALP	Rat marrow stromal cells (MSCs)	8-21 days	In vitro
Keskar V, et al. (2009)	Macroporous PEGDA hydrogels	Osteogenic differentiation	ALP	hMSCs	3 weeks	In vitro
Moioli EK, et al. (2008)	3D calcium phosphate (CP) scaffolds	Angiogenesis (endothelial differentiation)	Acetylated LDLs & vWF	Hematopoietic & mesenchymal stem/ progenitor	4 weeks	In vivo
Myoui A, et al. (2008)	Porous hydroxyapatite ceramics as a scaffold (IP-CHA)	Osteoblastic differentiation	Bone formation inside the pore areas as evidenced by decalcified histological sections and microcomputed tomography images	MSCs derived from autologous bone marrow	2 weeks	In vivo
Li H, et al. (2009)	Collagen scaffold carrier	Periodontal regeneration	Specimens were evaluated by histomorphometry	Autologous cryopreserved bone marrow mesenchymal stem cells	8 weeks	In vivo (in dogs)
Kwan MD, et al. (2008)	Apatite-coated poly(DL-lactic-co-glycolic acid) (PLGA)	Skeletal regeneration (osteogenic differentiation)	Radiographical analysis	Adipose-derived stromal cells	2-12 weeks	In vivo (adult mice)
Jäger M, et al. (2008)	Porous collagen I/III scaffold	Osteoblastic differentiation	ALP, OP, Runx2, Twist 1 and 2, Notch-1/2, osteonectin, OCN, BSP, & Collagen-a1	hBMSCs	4 weeks	In vitro
Olivo C, et al. (2008)	Ceramic scaffolds	Bone formation	Histological analysis	Goat MSCs	7 weeks	In vivo (immune-deficient mice)
Kanczler JM, et al. (2008)	PLA scaffolds	Bone formation	Type I collagen & vWF	Human bone marrow stromal cells	4 weeks	In vivo (segmental femur defect model)
Zhang L, et al. (2008)	Porous polylacticglycolic- acid in both inner and outer layers, a compact polyurethanes layer in midst	Endothelial cell	α-SMA & vWF	Bone marrow stromal cells	12 weeks	In vivo (canine)
Heckmann L, et al. (2008)	3D (three-dimensional) systems consisting of either a collagen type I gel or a synthetic PLA scaffold	Ligament replacement	MMP-1, MMP-13, Tenascin-C, Integrin Subunits alpha1, Alpha3 and beta1 & Collagen type X	Human mesenchymal stromal cells	2 weeks	In vitro

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generated. Many types of stem cells from different sources are being investigated for their hepatic differentiation ability, mostly from mouse, but also monkey and human embryonic stem (ES) cells [51]. Adult human stem cells are favorable candidates for liver regeneration. Currently, many researchers have focused on MSCs found in bone marrow (BM), adipose tissue, scalp tissue, placenta, umbilical cord blood and various fetal tissues. These stem cells can be differentiated in vitro toward multiple cell types such as chondrogenic, osteogenic, adipogenic, myogenic and neurogenic lineages [50]. It has been reported that MSCs isolated from BM, adipose tissue and umbilical cord blood can differentiate into hepatocytes in vitro and/or in vivo [52-54]. In another study, the ability of human Bone Marrow derived Mesenchymal Stem Cells (hBMSCs) used for differentiation into hepatocytes was evaluated on 3D nanofibers. These scaffolds were made from PCL, collagen and PES. Scanning electron analysis of micrographs and MTT showed that the cells were properly attached and proliferated on a hybrid nano-fibrous scaffold. Immunocytochemical analysis of albumin and alpha-fetoprotein (AFP) also indicated the accumulation of these markers on the surface of differentiated cells on the scaffolds. Later, differentiation of MSCs into hepatocytes was confirmed by mRNA expression of albumin, AFP and cytokeratin-19. Finally, the engineered scaffolds are promising for supporting hepatocytes-like cells in transplantation [24].

Bone Tissue Engineering

Differentiation of MSCs in osteoblastogenesis is regulated by different kinds of morphogens, hormones, growth factors, cytokines and extracellular matrix (ECM) proteins. These external signals initiate several signaling cascades and transcription factors that mediate and control osteoblastogenesis. Several transcription factors are known to control bone development and osteoblast differentiation [55].

Bone loss is a great health care problem worldwide so current treatments have been largely focused on replacing the lost bone with tissues of allogeneic or xenogeneic sources as well as synthetic bone substitutes. These methods lead to limited degree of structural and functional recovery. Besides, the use of allogeneic or xenogeneic tissue for bone repair involves risks of immune rejection and disease transmission. Although autogenic bone grafts are commonly used as the most successful ones, they also have limitations such as additional surgery, donor site morbidity, and limited amount available. As a result, tissue engineering has emerged to regenerate the structure and therefore recover the function of the bone tissue rather than replacement alone. One decisive factor in the success of tissue engineering strategies for bone regeneration is the appropriate design of the scaffold [56]. Autogenous bone is the most preferred bone grafting material. However, limitations and complications from using autografts include limited quantity and chronic donor site pain [57, 58]. This has led to the need for an ideal bone graft substitute. Such an ideal substitute must have enhanced capabilities to reduce or eliminate the need for an autograft altogether and would be necessary to provide support, fill voids, and enhance biologic repair of the defects [59].

There are many approaches to bone tissue engineering, but all involve one or more of the following key ingredients: harvested cells, recombinant signaling molecules, and three-dimensional (3D) matrices [60]. One popular approach involves seeding highly porous biodegradable scaffolds, in the shape of the desired bone, with cells and signaling molecules (e.g., protein growth factors), then culturing and implanting the scaffolds into the defect to induce and direct the growth of new bone. The goal is attachment of the cells to the scaffold, multiplying, differentiation and organizing into normal, healthy bone as the scaffold degrades [61].

Other Tissue Engineered Organs

Cartilage is a flexible connective tissue derived from the mesoderm embryonic layers and is found in many areas of the body such as joints, chest, ears, nose, and breathing tubes. Cartilage consists of specific cells called chondroblasts that produce a large amount of extracellular matrix, type 2 collagen fibers, an abundant and rich matrix containing proteoglycan and elastin fibers. Chondroblasts trapped in the matrix are called chondrocytes. Cartilages are classified into three main groups including elastic cartilage, hyaline cartilage and fibrocartilage. There are many diseases influencing the cartilage, including chondrodystrophy, osteoarthritis, achondroplasia,

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costochondritis, etc. Today with the help of tissue engineering techniques to create suitable three-dimensional space, cartilage production has taken important steps [62-66]. In one study, mesenchymal cells were isolated from cord blood and their potency was investigated for conversion to cartilage with promising results [67]. Successful development of a tissue engineered replacement heart valve may hold the key to better treatment of end-stage valve disease [68].

Development of Gene Delivery Methods by MSCs and Regenerative Medicine

MSCs transplantation has been proven to be an efficient method in treating a large spectrum of diseases. It is noteworthy that both autologous and allogeneic MSCs do not induce host immunoreactivity upon local transplantation or systemic administrations. Therefore, MSCs are an ideal carrier to deliver genes into the tissues of interest for gene therapy applications [69]. Genetically manipulated MSCs can be used in different therapeutic strategies, either as immunosuppressive agents or as engineered cells to secrete a variety of different proteins in vitro and in vivo. The latter could potentially treat a variety of serum protein deficiencies and other genetic or acquired diseases, such as bone, cartilage, and BM disorders. Moreover, the ability to genetically modify these MSCs would further contribute to tissue engineering settings, enabling the selective enhancement of specific differentiation pathways [70]. As MSCs are not immunologically rejected and possibly home in damaged tissues, they represent an opportunity for delivering therapeutic proteins. The advantages of MSCs-based gene therapy over pharmaceutical agents are the potential of long-term effects after a single intervention and the local expression of the desired gene. Genetic engineering can enhance survival of engrafted stem cells when transgenes are inserted into the cell to prevent or reduce apoptosis and inflammatory injury [71].

Despite the promise of stem cell-based gene therapy to have an impact on human health, technical challenges remain to be solved in order to harness the full potential of stem cells. Presently, the widely used method to transfer genes to MSC is through viruses, such as adenovirus, lentivirus and retrovirus [72]. In a few reports, some lipofection reagents were described to successfully introduce transgenes and small interfering RNAs (siRNAs) into MSCs. These cells maintained their proliferation capacity and ability to differentiate into different mesodermal lineages (bone, cartilage and fat) without loss of transgene expression [73]. Non-viral methods are commonly less effective for gene transfer to MSCs. Although transducing these cells by viral methods has some advantages such as the ease of handling and the larger capacity of vectors, non-viral methods are favored. In contrast to retroviral/lentiviral systems used for stable genetic modifications, non-viral gene transfer methods are applicable to both stable and transient expression of genes. Transient gene expression could be a desirable feature for some gene therapy strategies where only a short-term expression of the gene product is required [74]. For instance, some studies have tried to optimize non-viral methods to transfect rat MSCs. They isolated and differentiated MSCs to osteoblasts, adipocytes and chondroblasts. The cells were positive for CD90 and CD73 and negative for CD31, CD45, CD11b and VEGFR2 markers [75]. The success of these experiments depends on selecting an appropriate method for gene delivery to the cells. Therefore, future research should emphasize on improving non-viral techniques, with high efficiency of transfection, into tissue engineering as a novel method for regenerative medicine.

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