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REVIEW

Adipose-Derived Stem Cells (ASCs) for Regeneration of Intervertebral Disc Degeneration: Review Article

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Abstract: The intervertebral disc (IVD) is an important structure in the human body because it functions as a weight-bearing. This structure undergoes a process of degeneration like the rest of the body and this process is known as intervertebral disc degeneration (IDD) which is the most common cause of low back pain (LBP). The current common management, either conservative or surgical, is pain-relieving and has not been able to restore degenerated disc optimally. Changes in the IVD microenvironment in IDD conditions make it difficult for the regeneration process to occur. Research to reverse the degeneration process continues to develop, one of them is the use of adipose-derived stem cells (ASCs). ASCs is superior due to the ability to differentiate into several other cells such as adipocytes, chondrocytes, and osteoblasts, it also has ability to act as immunomodulators by stimulating the migration of immune cells to damaged tissues. ASCs becomes a good choice because it is easy to obtain, low donor site morbidity, high proliferation rate, and excellent differentiation abilities. Research on the optimal preparation process for ASCs and their application to various disorders continues to advanced. This study aims to review the potential use of ASCs for regeneration of intervertebral disc degeneration.

Keywords: adipose-derived stem cells, stem cell, intervertebral disc, intervertebral disc degeneration, low back pain

Introduction

One of the health problems that affect a person's quality of life and impact the world's socio-economics is low back pain (LBP).[1,2] Intervertebral disc degeneration (IDD) is the most common cause of LBP.[3] As a degenerative disease, this disorder is part of the aging process and it is estimated that more than 90% of people have this condition, but they mostly are asymptomatic.[4] This disorder begins to appear in the second decade of life.[5,6] This abnormality interferes with the function of the IVD as a weight-bearing structure.[7,8]

Intervertebral disc (IVD) has limitations to recover from damage, including degenerative processes.[9] The current IDD treatment used has not been able to regenerate damaged IVD.[10] Conservative or surgery management has not been able to optimally restore IDD and only for symptomatic relief and muscular stabilization.[10,11]

Recent progress in understanding IVD physiopathology and management led to IVD regenerative medicine. However, owing to the restrictive regulatory framework and the difficult clinical translatability of cell-based therapies, the use of biological factors targeting IVD degenerative processes was also contemplated.[12] In this case, the main

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purpose of regenerative medicine is to overcome the limit of the low regenerative power of tissues, creating strategies to restore their functionality and architecture. One of the potential approaches in animal studies is the use of mesenchymal stem cells (MSCs).[13–16] MSCs can be obtained from various sources.[17,18] Although MSCs can hypothetically be obtained from almost any tissue within the human body, there are practical limitations concerning the difficulty and invasiveness of the procurement process and various donor characteristics. Currently, the main sources of MSCs are bone marrow and adipose tissue. Another sources include; dental pulp, umbilical cord tissue (Wharton's Jelly) or amniotic fluid.[19]

Adipose-derived stem cells (ASCs) is one of MSCs derived from body fat tissue and is often referred to adipose-derived mesenchymal stem cells (ADMSCs).[17,18,20,21] ADMSCs have almost the same characteristics as bone marrow derived mesenchymal stem cells (BMSCs), which can be transformed into tissues in the mesodermal pathway such as bone, cartilage, muscle, and adipose. BMSCs are MSCs often used, but bone marrow has the disadvantage of being limited in number in the body and the retrieval procedure is complicated.[20,21] Research of ASCs in regenerative medicine continues to grow, including for IVD regeneration.[17] The abundant source in the human body and the low risk of harvesting are the advantages of ASCs as an alternative source of MSCs.[21–23] The uniqueness and potential of ASCs in IDD regeneration is an important power to explore further. This study aims to review the potential use of ASCs to regenerate the intervertebral disc degeneration.

Intervertebral Disc Structures

IVD is a fibrocartilage structure that connects the vertebral bodies.[24–26] The total IVDs in the human body are 25 discs.[24,25] This structure plays a role in spine mobility and has a function as a shock absorber.[6,24,25] The nucleus pulposus (NP), the annulus fibrosus (AF), and the cartilaginous endplates (CEPs) are the structures that make up a healthy IVD.[6,26–28]

NP is the core of the IVD structure. The cell composition of NP is NP stem/progenitor cells (NPPCs), notochordal cells, chondrocyte-like cells, water, and extracellular matrix (ECM).[29,30] The ECM composition of NP contains proteoglycan and collagen (COL) type II. Proteoglycan attracts water into the ECM so that the NP is very hydrated. NP plays a role in resisting pressure from the body on the spine structure.[6,30]

The NP is wrapped by AF with CEPs bordering the vertebral bodies on the outer side[6,24,28](AMSU 10,11; Kepler 2013). The most composition of AF is COL type I concentrically arranged.[6,30] There are two parts of AF, inner and outer. The inner AF is the part adjacent to the NP which contains dominant COL type II and proteoglycans, while the outer parts of the COL type I are more dominant[24,31]. Compared to NP, AF has less COL type II. The CEPs is an avascular organ with a capillaries network in the middle that is associated with the vascularization of the vertebral bodies.[29] CEPs become a gateway for nutritional supply by a diffusion mechanism.[31]

Change in Intervertebral Disc Degeneration

Over time, IVD will degenerate and there will be structural and biochemical changes.[32] CEPs will calcify and notochordal cells will disappear, triggering the degeneration process to occur in IVD.[33,34] Calcification in IVD will disrupt the diffusion mechanism causing the supply of oxygen and nutrients for IVD to be disturbed.[6,35] The consequence is an increase in lactic acid causes the IVD environment to become acidic and IVD cells undergo apoptosis.[6,24,34] The loss of notochordal cells and IVD cell apoptosis caused a decrease in ECM production, whereas the production of matrix metalloproteinases (MMPs) as a degradation enzyme did not decrease and even increased. This process accelerated the degeneration process of IVD.[7,34]

Inflammatory mediators, such as interleukin (IL) and tumor necrosis factor (TNF)-α, influence the IDD process. Inflammatory mediators involve cell permeability thereby blocking the synthesis of proteoglycans and collagen. In contrast to proteoglycans and COL, inflammatory mediators increase MMPs activity.[34,36] TNF-α also triggers the secretion of IL-6, IL-8, and various related cytokines stimulating cell movement and inducing inflammatory reactions.[37]

The interaction between TNF-α and IL with nerve fibers triggers pain in IDD.[36,38] In normal IVD, innervation is limited to the outer AF.[30] In the IVD degeneration process, there is an increase in sensory innervation, including in CEPs becomes deeper (Wuertz and Haglund, f 2013; Lyu et al, 2021). This neuronal ingrowth is caused by a brain-derived neurotrophic factor secreted by degenerating IVD cells, and nerve growth factor secreted by vascular tissue.[6]

Mesenchymal Stem Cell

Stem cells can be classified into an embryonic, fetal, adult, and induced pluripotent stem cells.[39,40] Among all groups of stem cells, MSCs are the most widely developed stem cells in the world of research. MSCs are part of adult stem cells.[39,41] The use of MSCs is considered to have no ethical problems and has no genomic stability problems.[42] In addition, MSCs have the ability to differentiate into various connective tissue cells.[39,41]

MSCs can differentiate into the various lineage of mesoderm, ectoderm, and endoderm under specific in vitro conditions.[39] Mesoderm differentiation is the easiest because it comes from the same embryonic origin. Adipogenesis, osteogenic, and chondrogenesis differentiation are included in mesoderm differentiation.[43] The differentiation ability MSCs into ectoderm tissue is utilized for wound healing, cutaneous repair, hair regeneration, sweat gland restoration, corneal restoration, and neuron differentiation.[43,44] With a multistep-protocol, MSCs can differentiate into endoderm tissues such as hepatic and pancreatic tissues.[43,45]

Definition and Function of ASCs

The definition of ASCs should look at the difference between the definition of a progenitor cell and a stem cell. Progenitors are cells that have the ability to differentiate into one or several specific cell types but have limited proliferative capabilities. While stem cells have the ability to self-renew and proliferate into other cells that are wider, so it's called multipotent cell.[46] Multipotent MSCs are able to differentiate into bone, fat, and cartilage.[20] MSCs can be obtained from various tissues.[18,39]

One of the common source tissues for human MSCs is adipose tissue. ASCs are stem cells derived from fat tissue.[18,20] As a stem cell, ASCs have multipotent ability to proliferate and differentiate into several other cells such as adipocytes, chondrocytes, and osteoblasts. ASCs have experienced an exponential increase in their use to treat various types of disorder, especially the muscle and bone system.[47]

Plenty of sources and minimum risk of taking is an advantage of ASCs over MSCs from other sources.[21–23] The source of ASCs can come from different areas all through the body that contains fat. Subcutaneous fat tissue gotten from surgery has restorative potential after reimplantation into the body at the location of the damage.[48,49] Fat tissues are a rich source of multipotent stem cells.[50] In the human body, there are two common types of adipose tissue, brown adipose tissue and white adipose tissue.[51,52]

White and Brown Adipose Tissue

Adipose tissues are spread throughout the body and in normal people makeup approximately 20–30% of body composition. This number can differ depending on the body mass index, gender, and muscle mass in each person. In obese people, the amount of adipose tissue can be more and cause some adverse side effects.[49] However, it turns out that fat tissue can be used as an alternative to stem cell-based treatment that is better and less invasive than bone marrow-derived mesenchymal stem cells (BMSCs), known as adipose-derived stem cells (ASCs).[20,22] Based on their components and functions, there are two types of adipose tissue, brown and white adipose tissues.[51–53] White adipocytes, or white fat cells, have some differences from brown adipocytes, or brown fat cells.[52,53]

Brown fat cells are multilocular with small lipid vacuoles. Vascularization of brown fat tissue is obvious because it requires large amounts of oxygen.[54] The distribution of brown fat is widely in the neck, mediastinum, and interscapular area, while white fat is more in the waist and thighs. Physiologically, brown fat is commonly found in newborns and decreases with age.[49,53] Brown fat has a higher number of mitochondria and contains a lot of iron, which makes brown fat dark red to brown in color. Mitochondria are more stout making brown fat oxygen demand more so that the capillaries are also more than white fat. Brown fat also has many unmyelinated nerves, providing sympathetic stimulation to fat cells.[52,53]

Brown adipocytes tissue plays a role in the thermogenesis process that can burn calories and prevent a person from obesity. This roles make brown fat better than white fat.[49,52,53] The thermogenesis ability of brown adipose tissue because of its rich content of mitochondria.[54] Thermogenesis in brown adipose tissue causes glucose and fat to be burned to generate heat through the action of uncoupling protein (UCP) 1, and mitochondrial membrane protein which interferes with the adenosine triphosphate synthesis process during oxidative phosphorylation by lowering the mitochondrial

membrane potential.[49,53] UCP1 is a brown adipose tissue-specific marker regulated by adrenergic signaling through sympathetic innervations, and this signaling is responsible for thermogenesis.[54]

White fat cells are spread in the subcutaneous and visceral areas. White fat is unilocular shaped, contains large lipid vacuoles, and is colored ivory or yellowish.[54] White fats are considered a bad fat because they can affect the body's metabolism and are a calorie accumulation (triglycerides) from excessive calorie consumption.[49] Different from brown adipose tissue which expresses UCP1, white adipose tissue expresses isoform UCP2.[54] White adipose can supply energy by lipolysis of triglycerides into fatty acids, so if there is too much white fat and lipolysis occurs on a large scale, it can cause insulin resistance.[49]

White adipose tissue, especially inguinal white adipose tissue, has recently been discovered to include beige adipocytes.[54] Beige fat (precursors or mature cells) arises from white fat. Despite its common origin, beige fat has a different metabolic role than white fat, as well as a different transcriptional program.[55] The beige adipocyte is a fat cell with features similar to the white fat cell, which stores energy, and the brown fat cell, which creates heat for thermogenesis.[56]

ASCs Harvesting

The harvesting procedure of adipose tissue to be used as ASCs is important for regenerative medicine.[46,57] ASCs isolated from white adipose tissue differ from those extracted from brown adipose tissue, and also ASCs isolated from various anatomical sites possess differ.[54] The total number of viable cells that can be retrieved from subcutaneous fatty tissue is unaffected by the anatomical location of the adipose tissue.[58] The latter approach was chosen because is a safe, well-tolerated, and slightly invasive procedure but provides a high amount of stromal/stem cells.[57] The largest source adipose tissue is abdominal fat.[21,23]

Adipose tissue can be harvested in the form of solid adipose tissue or lipoaspirate.[59] Harvesting adipose tissue approaches which can be used are surgical resection, power-assisted liposuction (PAL), and laser-assisted liposuction (LAL).[57,59] Surgical resection was used to obtain solid adipose tissue, while PAL and LAL harvested adipose tissue in the form of lipoaspirate.[46,59] Lipoaspiration facilitates extracting subcutaneous tissues easier. The liposuction technique has no consequence on ASCs function.[54] Due to better multiplication potential and slow degradation of isolated cells, PAL is an excellent method of ASCs collection for clinical purposes.[57,59]

Despite the lack of a standard approach, sliced adipose tissue is often digested by one or more of the following options, such as collagenase, dispase, trypsin, and other enzymes.[46,58] Temperature (37°C), digesting time (ranging, from 30 minutes – >1 hour), and tissue mass to volume ratios are all suggested; however, protease concentrations are considerably more varied.[46,57] Single-layer cultures on standard tissue dishes with a basal medium containing 10% fetal bovine serum are commonly used to grow isolated ASCs.[58] Aspirated adipose tissue provides approximately 3.5×10^5 to 1×10^6 ASCs each gram.[54]

The Process of ASCs Formation

MSCs can differentiate into several cell lines such as osteogenesis, chondrogenesis, myogenesis, marrow stroma, tendogenesis, lipogenesis, and several other pathways such as the dermal pathway. This pathway changes according to the environment and physiological processes that the body needs. If MSCs are in an adipose environment, they can differentiate into endothelium, smooth muscle, white fat cells, and brown fat.[48] Initially. MSCs will develop into adipoblast, then become pre-adipocytes and when the pre-adipocytes go to fat tissue then they will turn into adiposity. However, during ASCs change process did not occur in the presence of stem cell precursors, namely myogenic factor (Myf) 5-positive and Myf5-negative. Myf5-positive precursors converted MSCs to brown adipose tissue whereas Myf5-negative converted MSCs to white adipose tissue. This MSCs pathway in adipose tissue shows that ASCs can assist in the process of tissue wound regeneration through endothelial differentiation and the effect of ASCs on increasing Vascular endothelial growth factor (VEGF).[49,58,60]

ASCs Identification

Clinical interest and scientific approach in the transplant of ASC-derived secretome or purified exosomes is increasing nowadays due to its promising result for regenerative medicine. The secretome itself is a complex of microvesicles and

exosomes secreted by living cell, it can be isolated from almost all body fluids and carrying lots of biologically active proteins, lipid, and nucleic acids. The standardized handling method to ensure a quantity of ASCs secretome product for therapeutic approach is still not established until now. Exosomes is more stable and easily storable compared with the cells, have lower maintenance cost, and having a lower possibility for immune rejection during in vivo transplantation, the molecules is also more protected from degradation. The characterization of ASCs secretomic profile is mostly done by proteomic approach, but the mechanism of ASC isolation and expansion could affect the composition of secretome is not fully understood.[57]

Flow cytometric examination of cell surface markers is routinely used to check the presence of ADSC features. The International Society for Cellular Therapy (ISCT) and the International Federation for Adipose Therapeutics and Science (IFATS) describe ASCs following three minimal criteria: (1) cells must be plastic-adherent; (2) they must express CD73, CD90, and CD105 but not CD14, CD11b, CD45, CD19, CD79, nor human leukocyte antigen-DR (HLA-DR); and (3) they have to be able to differentiate into preadipocytes, chondrocytes, or osteoblasts.[46,57,58] Based on another recommendations, ASCs should not express the hematopoietic markers (90%), such as CD13, CD73 CD90. To distinguish from bone marrow MSCs, it is recommended to use at least two additional marker such as CD36 (GPIIIb) and CD106 (VCAM-1). The other reports suggested that in contrast to MSCs, ASCs do not express CD106 but CD36 positive.[59] The ISCT also recommended that MSCs should lack or even be negative for CD117 and CD34 expression; nevertheless, definite markers for efficiently identifying ASCs are still argued.[46,61] ASCs can express CD34, according to existing studies.[46,62] Early passage ASCs express higher amounts of CD117, HLA-DR, and CD34 than late passage ASCs.[46,63] Despite the fact that isolation and culture processes differ, the immunophenotype is constant among facilities.[57]

It is recommended the basic characteristic phenotype of ASCs should include at least two positive and two negative markers in one analysis. A study about a cell surface marker screening analysis conclusing that sample collection method did not significantly influence the expression of surface markers profile. A study analyzing phenotype stability of ASCs in long-term culture in several markers such as CD90, CD44, CD34, CD45 that conducted at the 1st, 3rd and 5th passage. All tested groups, were characterized by high (~90%) expression of CD90 and CD44.[64] Furthermore, surface markers expression was similar among all ASCs groups and was stable during various stages of culture. These results confirmed our previous findings.[59]

ASCs for Regeneration of Intervertebral Disc Regeneration

The number of disc cells decreases as the IVD degeneration process progresses. Based on this, cell transplantation is one of the potential biology approaches for IDD.[65] However, the biochemical microenvironment of IVD is rough, with low oxygen concentrations, inadequate nutrition, excessive osmolarity, and high acidity.[35,66] Although autologous disc cells are a promising cell source, they have a number of weaknesses in the therapeutic setting: (1) Autologous disc cell extraction, whether by image-guided aspiration or open surgical collection, is an intrusive procedure; (2) collecting disc cells from a healthy IVD may hasten IVD degeneration; (3) disc cells from a degenerated disc may not be functionally perfect for re-implantation.[66]

Because of their ease of access, low donor site morbidity, and high proliferation rate, ASCs appear to be a superior choice for tissue engineering in IVD regeneration.[66] ASCs offer excellent differentiation abilities and are well applicable to the treatment of IDD.[61] The transformation of ASCs into ectodermal, endodermal, and mesodermal cells has been reported in the previous study.[39] As ASCs were from the mesodermal origin, development into adipogenic, chondrogenic, and osteogenic cells becomes less contentious.[47,54] This stem cell outperforms BMSCs.[54]

ASCs have the ability to restore degenerated IVDs. ASCs have been shown to enhance disc regeneration by forming a chondrogenic lineage and enhancing aggrecan and COL type II synthesis.[9] By interacting with local chondrocytes or cartilage explants in cartilage defects, transplanted ASCs play a vital role in the success of cell-based therapies for cartilage regeneration.[58] Upregulation of collagen type IIA, type IIB, and aggrecan gene expression is associated with ASCs development along the cartilaginous lineage and is linked to cocultures with NP cells and type II hydrogel. COL type II provides a suitable medium for ASCs attachment and a favorable microenvironment when combined with soluble substances released by NP cells to induce cartilage/NP lineage development. COL type II, the dominant collagen in the nucleus pulposus ECM, has been demonstrated to sustain and even induce the chondrogenic phenotype in MSCs.[25]

Increased quantities of IVD cells and ECM components were reported when ASCs were cultured with TGF-3 in vitro. At the same time, ASCs possessed a stronger ability to develop into NP cells than BMSCs when induced by TGF-1, growth differentiation factor (GDF)-5, or GDF-6, and the expression levels of ECM components such as sulfated glycosaminoglycans and COL II were much higher.[67] ECM forms up a large portion of IVD, injected stem cells are expected to interact with ECM components after being injected into the disc. ECM has been found to be important in the regulation of stem cell differentiation into several lineages, cell proliferation, and cell migration.[25] We try to summarize the mechanism of IVD degeneration and role of ASCs (Figure 1).

ASCs are considered to play a part in the regeneration process by releasing cytokines and growth factors (GFs) that promote healing via paracrine signals.[48,49,68] Several factors influence angiogenesis, including paracrine factors, stromal cell-derived factor-1 (SDF-1) chemokines, and vascular endothelial growth factors (VEGF), that causes more ASCs to migrate to damaged cells.[48,49] The effect of angiogenesis/neovascularization on brown adipose tissue has been explored in various studies on rats that reported an enhanced VEGF. Endothelial cell proliferation and angiogenesis activation are induced by VEGF, which aids homeostasis.[69]

Animal Studies and Clinical Trials

An animal study with an IDD model injected with ASCs showed reduced disc height loss and restoration of disc signal intensity on magnetic resonance imaging.[70] These stem cells can develop into NP-like cells and release an ECM composed of anionic proteoglycans, COL type II, and aggrecan.[25,61,66] A set of traits distinguish nucleus pulposus cells from chondrocytes in articular cartilage.[25]

A study evaluated the effects of matrilin-3-primed adipose-derived MSCs (Ad-MSCs) on the repair of the degenerated disc in vitro and in vivo in rabbits model disc degeneration is searching for an optimal priming concentration and duration and developed an optimal protocol for Ad-MSC spheroid generation. Priming with 10 ng/mL matrilin-3 for 5 days resulted in the highest mRNA expression of type 2 collagen and aggrecan in vitro, it also showed the increased secretion of favorable growth factors such as transforming growth factor beta (TGF-β1), TGF-β2, interleukin-10 (IL10), granulocyte colony-stimulating factor (G-CSF), and matrix metalloproteinase 1 (MMP1) and decreased secretion of hypertrophic ECM components. Matrilin-3-primed Ad-MSC spheroid implantation was associated with optimal repair in a rabbit model. This result suggested that priming MSCs with matrilin-3 and spheroid formation could be an effective strategy to overcome the challenges associated with the use of MSCs for the treatment of IVD degeneration.[71]

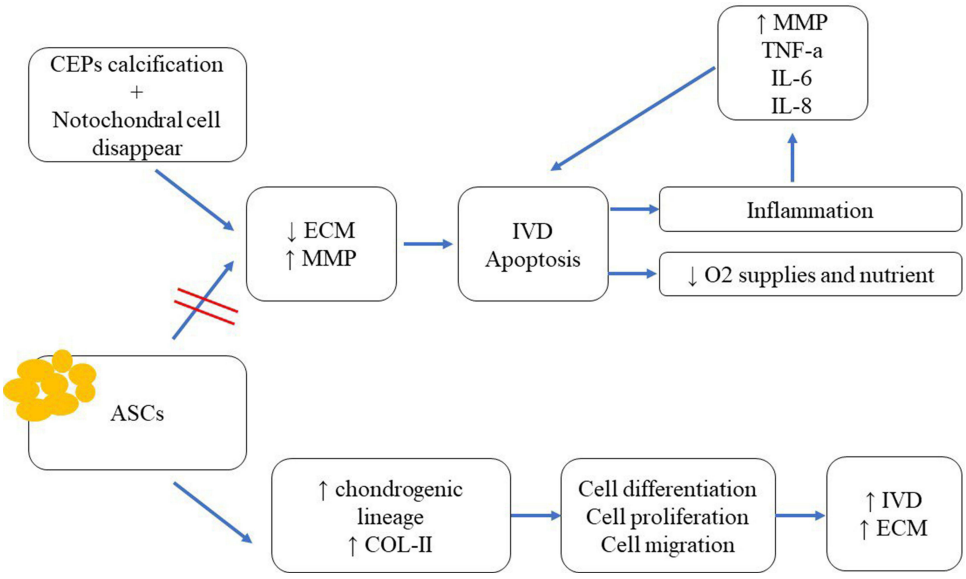

Figure 1 Mechanism of intravertebral disc (IVD) degeneration and role of ASCs increasing regeneration of IVD and extracellular matrix.

The experiment used hematopoietic stem cells (HSCs) on IDD in animal models and clinical trials in patients. The animals experiments showed that the IVD could be regenerated by injection of HSCs, but in clinical trials none of the ten patients had significantly improved symptoms of discogenic low back pain at the 6-month and 1-year follow-up visits.[72] Another research analyzed small case studies found that stem cell therapy for patients with IDD may be useful in alleviating pain or improving IVD function, but the overall data on efficacy and safety did not reveal any major findings, and it was not clear whether the changes in symptoms were clinically important.[53] In general, there are no multicenter clinical studies and studies have only been on small numbers of patients. Also, the study protocols widely differ in the choice of inclusion criteria, the chosen cell sources for MSCs, the methods of transplantation and in the follow-up conditions.[35]

Although many reports have demonstrated the advantages of stem cells in the treatment of IDD, there are some reports that described deficiencies the application of stem cells. A clinical trials found that cell injection therapy exceeding the normal range of cell dose was ineffective in delaying IDD or led to worse outcomes.[73] Local injection of excessive numbers of cells may cause cell accumulation and death, thus triggering an inflammatory response. When injecting stem cells, the amount of injection is of great concern. MSCs may undergo unnecessary cell migration or cell leakage after IVD injection, resulting in ineffective treatment and osteophyte formation. An improper puncture operation can lead to disk infection or diskitis.[61]

Conclusion

ASCs appear to be a superior choice for tissue engineering in IVD regeneration. ASCs are one of the MSCs that are continuously being developed and have various advantages over autologous disc cells, BMSCs, and other MSCs. These advantages like ease of obtaining, low donor site morbidity, high proliferation rate, and excellent differentiation abilities. ASCs also have the ability to act as immunomodulators by stimulating the migration of immune cells to damaged tissues. With the harvesting process to the right and appropriate application, ASCs can be used for IVD regeneration in extreme IDD microenvironments.

The clinical trials of ASCs application is still lacking and some of the result is not linier with the animal experiments result. Therefore, further research is needed to use ASCs in regular clinical applications. Research on specific markers for ASCs, ex vivo genetic modification of cells, and regulators of differentiation, migration, and cell survival after transplantation must be clearly explained. Along with the development of scientific awareness regarding the regenerative ability and potential use of these cells, along with the development of scientific awareness regarding the regenerative ability and potential use of these cells, potentially dangerous consequences must be clarified, and the regulatory system that regulates their clinical usage must mature. The microenvironment during treatment may also play role as prognostic indicators, further research is needed to create a best result.

Abbreviations

ADMSCs, adipose-derived mesenchymal stem cells; AF, annulus fibrosus; ASCs, adipose-derived stem cells; BMSCs, bone marrow-derived mesenchymal stem cells; CEPs, cartilaginous endplates; COL, collagen; ECM, extracellular matrix; GDF, growth differentiation factor; HLA-DR, human leukocyte antigen-DR; IDD, intervertebral disc degeneration; IFATS, International Federation for Adipose Therapeutics and Science; IL, interleukin; ISCT, International Society for Cellular Therapy; IVD, intervertebral disc; LAL, laser-assisted liposuction; LBP, low back pain; MMPs, matrix metalloproteinases; MSCs, mesenchymal stem cells; Myf, myogenic factor; NP, nucleus pulposus; NPPCs, nucleus pulposus progenitor cells; PAL, power-assisted liposuction; SDF-1, stromal cell-derived factor-1; TNF, tumor necrosis factor; UCP, uncoupling protein; VEGF, vascular endothelial growth factors.

Disclosure

The authors report no conflicts of interest in this work.

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