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REVIEW

Adipose-derived stromal cell in regenerative medicine: A review

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Abstract

The application of appropriate cell origin for utilizing in regenerative medicine is the major issue. Various kinds of stem cells have been used for the tissue engineering and regenerative medicine. Such as, several stromal cells have been employed as treat option for regenerative medicine. For example, human bone marrow-derived stromal cells and adipose-derived stromal cells (ADSCs) are used in cell-based therapy. Data relating to the stem cell therapy and processes associated with ADSC has developed remarkably in the past 10 years. As medical options, both the stromal vascular and ADSC suggests good opportunity as marvelous cell-based therapeutics. The some biological features are the main factors that impact the regenerative activity of ADSCs, including the modulation of the cellular immune system properties and secretion of bioactive proteins such as cytokines, chemokines and growth factors, as well as their intrinsic anti-ulcer and anti-inflammatory potential. A variety of diseases have been treated by ADSCs, and it is not surprising that there has been great interest in the possibility that ADSCs might be used as therapeutic strategy to improve a wider range of diseases. This is especially important when it is remembered that routine therapeutic methods are not completely effective in treat of diseases. Here, it was discuss about applications of ADSC to colitis, liver failure, diabetes mellitus, multiple sclerosis, orthopaedic disorders, hair loss, fertility problems, and salivary gland damage.

Key words: Adipose-derived stromal cell; Colitis disease; Liver failure; Diabetes mellitus; Multiple sclerosis; Orthopedic disorders; Hair loss; Fertility problems; Salivary gland damage

Core tip: Nowadays, adipose-derived stromal cells (ADSCs) are one of the most important and promising cell sources in the field of regenerative medicine. Unique capabilities of ADSCs caused them to be used in both research and treatment as a valuable resource in basic science and medical researches. In over 15 years

since their discovery, ADSCs have transformed our toolkit for treating human disorder and disease. As the field enters its next decade, a new wave of therapeutic applications, such as hepatic regeneration, diabetes mellitus treatment, multiple sclerosis treatment, and orthopaedic disorders regeneration, has converged with ADSCs to yield new insights for their use in stem cell engineering and regenerative medicine.

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INTRODUCTION

Mesenchymal stromal cells (MSCs) are undifferentiated cells that are able to renew their population and become differentiated to produce all specialized cell types of the tissue from which they are originated[1] (Figure 1). While MSCs are traditionally isolated from bone marrow, over the last few years, they have also been found in many other adult tissues such as liver, cord blood, placenta, dental pulp and adipose tissue[1]. The different stromal cells have some features in common, including morphological and immunophenotypic properties[1]. Although, bone marrow-derived stromal cells (BMSCs) and adipose-derived stromal cells (ADSCs) are better known than others[2-4]. ADSCs share biological properties with stromal cells obtained from bone marrow; however, these candidate cells also have some different properties compared to BMSCs[2,3].

Furthermore, Both Adipose-derived stromal cells and bone marrow-derived stromal cells have played a prominent role in regenerating the defective tissue of patients[4]. In the recent years, as one of the most successfully developed stem cells, adipose-derived stromal cell is a better choice than many other adult stem cells such as bone marrow-derived stromal cell because of its characters[4].

Such as, ADSCs not only have decreased sampling risk for individual donors compared with BMSCs but also have been needed to an easier method for isolation compared with BMSCs[4]. The adipose tissue, ADSCs' harvested source, could also provide a higher number of stromal cells compared with bone marrow tissue as BMSCs' obtained source[4]. Furthermore, ADSCs are superior to BMSCs in some biological features, including the immune feature regulation[4]. In addition, with an emphasis on adult stem cells rather than on embryonic stem cells, regenerative medicine programs are using ADSCs as more applicable adult stem cells to treat different diseases[4]. Today, Adipose-derived stromal cells are known as a rich source of MSCs which are considered a suitable case for repair and regeneration of various tissues because of their rapid proliferation and multilineage potential[2-5]. Several properties making scientists to pay attention to ADSCs include Immunomodulatory effects and secretion of a variety of growth factors and cytokine as well as anti-apoptosis and anti-inflammation potential[6]. *In vitro* ADSCs are identified by plastic adherence, colony forming capacity, rapid proliferation and lack of major histocompatibility class Ⅱ (MHCⅡ)[7,8]. ADSCs not only are interesting in basic sciences, but also have been used in a broad range of regenerative medicine application, such as orthopaedic damage, fertility problems, hair loss, Colitis disease, liver failure, diabetes mellitus, multiple sclerosis, *etc.* In the treatment of many of different diseases, ADSCs have exhibited a great potential for tissue repair and modulation of host immune response *in vivo*[6]. ADSCs from healthy donors are an attractive cell source for organ regeneration[9]. These cells can be obtained and cultured *in vitro* in sufficient numbers and subsequently used in damaged tissue regeneration[10]. So far it has been well recognized that these cells possess a broad spectrum of differentiated potentials, from cell types of mesodermal origin to ectoderm (such as hepatocyte) and endoderm (such as beta cells), when induced *in vitro*[10-13] (Figure 2). ADSC can be expanded effortlessly in culture for long periods of time without losing their differentiation capacity[12]. They are robust cells, which can easily survive freezing temperatures with limited loss in viability, proliferative capacity and differentiate potency[12]. The most attractive aspect of ADSCs is their immunosuppressive properties that allow transplanting them irrespective of a human leukocyte antigen (HLA) match between the host and the donor[14]. These cells are negative for surface marker proteins, such as CD14, CD34, and CD45, *in vitro*[15]. Although, these candidate cells express CD34 *in vivo*[16].

Moreover, ADSCs express cell surface markers, including CD10, CD13, CD29, CD44, CD71, CD73, CD90, CD105, CD166 and CD271 (Figure 3) and different varieties of trophic factors, such as molecular regulation of cell growth and proliferation, fibrosis, angiogenesis, and immune suppression[7,17-24]. Additionally, the Anti-apoptotic, anti-oxidant, anti-inflammatory activities of the ADSCs are among other important characteristics that can affect theirs regenerative potential[9,25-29].

Furthermore, ADSC treatment is now a widely used therapeutic strategy in the field of medicine because of its intrinsic therapeutic properties, relatively easy approach to harvesting them, and the large number these cells obtained after isolation[29].

In 160 clinical trials, ADSC-based therapy has been also used to treat various diseases such as orthopaedic disorders, hepatic failure, inflammatory diseases, and autoimmune disease[30].

SAFETY ISSUES OF ADSC CELLS

The safety study of ADSCs conducted by the different preclinical and clinical trial has documented that these

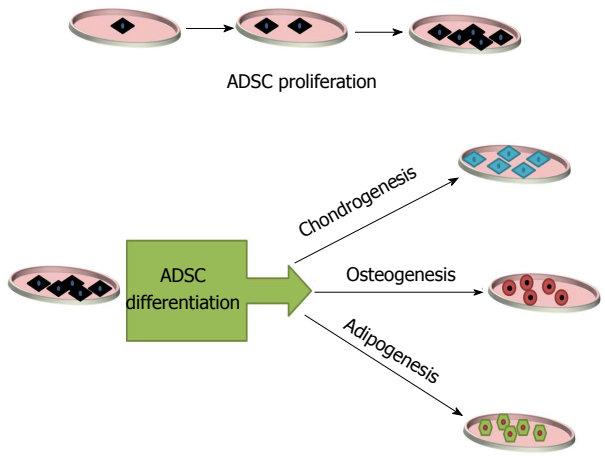

Figure 1 Schematic demonstration of the Biological Properties of human adipose-derived stromal cells. ADSC: Adipose-derived stromal cell.

Figure 2 Schematic demonstration of the multidifferentiation potential of human adipose-derived stromal cells *in vitro*. ADSCs: Adipose-derived stromal cells.

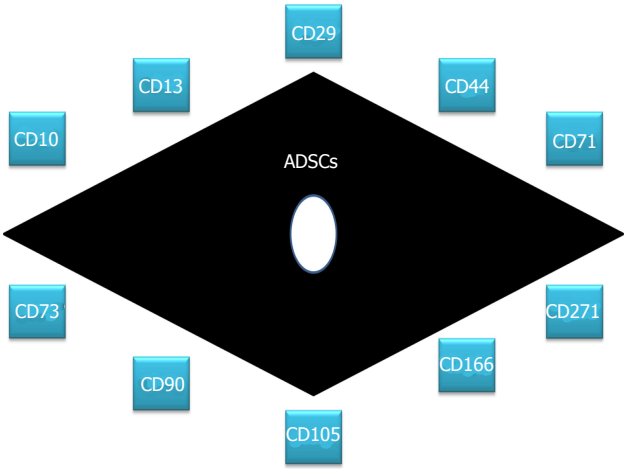

Figure 3 Schematic illustrations of the surface markers of freshly isolated human adipose-derived stromal cells. ADSCs: Adipose-derived stromal cells.

candidate cells are safe enough to be used in various treatment methods and can also play an effective role in the treatment of diseases[31-42]. Such as, the current finding has shown that autologous ADSCs could act as a safety agent in muscle defect regeneration, both smooth and skeletal muscle, due to their profibrotic properties as well as trophic factors[43]. Based on the results obtained from a clinical trial study, it was verified that used adipose-derived stromal cell (ADSC) implantation showed an appropriate safety feature with no serious complication in patients with degenerative disc disease[44]. Furthermore, in phase Ⅱ of the clinical trial study, the ADSC injections into the knee of 18 patients with osteoarthritis (OA) showed that these procedures do not have any severe adverse effects[45].

However, there is little report about severe adverse effects. Such as, some of the adverse effects observed during the study include headache, inflammation, *etc.*[46]. Furthermore, the safe use of ADSCs in cosmetic reconstructive surgery following a tumor is particularly doubtful because of the potential of these candidate cells to promote the development and progression of cancer[47,48].

These cell candidates could be further assessed for understanding their therapeutic potential and safety issues in them.

In review study, we focused on ADSCs application in treat of inflammatory disease, liver failure, complication related to diabetes mellitus, multiple sclerosis diseases, orthopaedic disorders, hair loss, fertility problems, and salivary gland damage, both *in vivo* and clinical study. Also, it was provided the significant number of ADSC-based clinical trials (Table 1)[35-41,45,49-55].

COLITIS DISEASE

Colitis, an inflammation of the colon, was treated with using intraperitoneal injection 10^5-10^6 human ADSCs or murine ADSCs in a study[56,57]. This study was associated with reduced weight loss, improved survival and improved clinical in ADSC groups[57]. In another study, intravenous tail vein administration of 10^6 macrophages cultured with either human ADSCs *vs* mouse ADSC lead to ameliorated disease activity index, alleviated weight loss and mortality in mice treated with ADSCs and ADSC-MF (macrophages cultured with ADSCs)[58]. Also, intraperitoneal infusion 2×10^6 human and mouse ADSCs demonstrated significant attenuate in inflammation scores overall the colon and increase weight[59].

LIVER FAILURE

The liver is a complicated organ that plays a metabolic function in human body. Any damage to this vital organ causes irreparable damage in the body. Due to this fact that adipose-derived stromal cells can differentiate into hepatocyte-like cells, both *in vitro* and *in vivo* condition, as well as capabilities such as homing in

Table 1 List of clinical trials that use stromal vascular fraction or adipose-derived stromal cells for a variety diseases treatment

Type of cells	Clinical trial phase	Disease	No. of patient	Highlight finding	Ref.
Autologous ADSCs	Phase Ⅰ	Amyotrophic lateral sclerosis	27 patients	Low back and radicular leg pain were observed, no tumor formation were observed	[35]
Stromal vascular fraction	Phase 0 (CSN111)	Peyronie's disease	11 patients	No serious adverse events were observed	[36]
Autologous adipose-derived stromal vascular fraction	Phase Ⅰ	Impaired hand function in patients with systemic sclerosis	12 patients	Four minor adverse events were observed, hand disability and pain were decreased	[54]
Autologous adipose-derived stromal vascular fraction	Phase Ⅰ (NTC01813279)	Impaired hand function in patients with systemic sclerosis	12 patients	Mobility, strength and fibrosis of the hand was improved	[55]
Autologous adipose-derived stromal vascular fraction	Phase 0	Systemic sclerosis	12 patients	Finger oedema, skin sclerosis, motion and strength of the hands were ameliorated, hand pain was decreased	[49]
Stromal vascular fraction combined with PRP	Phase 0 (NCT02097862)	Degenerative disc disease	15 patients	No serious adverse events were observed	[37]
Autologous ADSCs	Phase Ⅰ/Ⅱ	Osteoarthritis	18 patients	Adverse events were observed in several patients, including urinary stone, arthralgia, pain and tenderness in the pes anserinus of the ipsilateral knee; ADSCs injection into the osteoarthritic knee ameliorated function and pain of the knee joint	[45]
ADSC	Phase 0 (NCT02357485)	Osteoarthritis	6 patients	No serious adverse events were observed, pain for osteoarthritis of the knee was decreased	[38]
Stromal vascular fraction containing ADSCs	Phase 0	Osteochondral lesions of the talus	49 patients	SVF Containing ADSCs administration was a therapeutically beneficial strategy for osteochondral lesions of the talus	[50]
Expanded ADSCs	Phase 0	Patients with a desire to become pregnant (with Crohn's Perianal Fistula)	6 patients	Local administration of ADSCs did not impact on course of pregnancy or newborn development;	[39]
Adipose-derived mesenchymal stem cell	Phase Ⅰ/Ⅱ (NCT02513238)	Salivary gland hypofunction and radiation-induced xerostomia	30 patients	No serious adverse events were observed Change in unstimulated whole salivary flow rate was observed; no serious adverse events were observed	[40]
ADSC	Phase 0	Alopecia	20 patients	Hair diameter and density were improved,the efficacy and the safety of the treatment with ADSCs was confirmed	[51]
Conditioned media of adipose tissue-derived stem cells	Phase 0	Female pattern hair loss	27 patients	Hair density was enhanced, hair thickness was improved	[52]
ADSC conditioned medium	Phase 0	Alopecia	22 patients	Hair numbers were considerably enhanced	[53]
Expanded autologous ADSC	Phase 0	Type 2 diabetes mellitus	3 patients	Blood glucose levels were decreased in all patients, no serious adverse events were observed	[41]

ADSCs: Adipose-derived stromal cells; PRP: Platelet-rich plasma.

the defect location, and immunomodulatory and anti-apoptotic mechanism, they are used for liver failure treatment[29,60,61]. Furthermore, these cells are including anti-inflammatory factors and secrete various factors involved in tissue regeneration and are considered as a new therapeutic strategy to rebuild of liver damage[60,62].

Previous studies have display that ADSC transplantation demonstrates appropriate therapeutic outcomes for multiple diseases, including liver failure[63-65]. It is cleared that human ADSC transplantation could efficiently improve the liver function of acute liver failure (ALF) rats[66]. Furthermore, ADSCs administration increased the survival rates as well as decreased the ALF conditions in an immunocompetent ALF rat model[67].

DIABETES MELLITUS

Diabetes mellitus, a multifactor disease, is one of the main factors of death around the world. Because of the regenerative capacity and growth factors, cytokines, and chemokines secretion, in addition to angiogenesis and vascularization features, stromal vascular fraction has suitable potential for the therapeutical application in major complication of diabetes mellitus including

foot ulcer related to diabetic, nephropathy and retinopathy[68]. An experiment on diabetes athymic rat illustrate that ADSCs injection to vascular network of retina dysfunction site can significantly decrease apoptosis and vascular leakage and increase vascular synthesis and attenuate neurodegeneration[69].

MULTIPLE SCLEROSIS

Multiple sclerosis, one of the most devastating autoimmune diseases of the nervous system, can be found throughout the entire world[70]. Several animal studies have been performed on this disease using ADSC and stromal vascular fraction (SVF)[68,71-75]. In other studies the beneficial effects of ADSC and SVF have been evaluated on experimental autoimmune encephalitis (EAE), another disease of the nervous system[76,77]. One such animal study indicated that SVF may also have a therapeutic effect on multiple sclerosis[76]. In another study, the use of both ADSC and SVF resulted in a reduction in the demyelination and pathological features of EAE[78]. Both of these studies demonstrate that SVF, when employed in combination with ADSC, can lead to an amelioration of EAE in a murine model[78]. In one study, the expression level of interleukin-10 as an immunomodulator factor was high[78]. Additionally, an *in vivo* study identified that an ADSC-conditioned medium, along with ADSC, has both neuroprotective and immunomodulatory effects, suggesting the use of this conditioned medium as a valuable agent for treatment of EAE[79]. Meanwhile, neither pre-clinical results nor clinical evidence have demonstrated any serious adverse effects of ADSC administration[75-78]. In one clinical study, four patients with multiple sclerosis were treated using ADSC injection[75]. The clinical outcome demonstrated that ADSC administration is an effective treatment strategy for patients with multiple sclerosis[75]. Moreover, the murine EAE model has demonstrated that ADSC may be used to ameliorate motor function and decrease inflammation[76].

Moreover, in a phase Ⅰ dose-escalation safety trial noted that intrathecal treatment of autologous adipose-derived stromal cells appears safe at the tested doses in amyotrophic lateral sclerosis[35]. Compared to use of fat transplantation, use of ADSCs in systemic sclerosis (SS) patients improved mouth functional disability, demonstrating the importance of ADSCs administration in patients suffering from SS[80].

ORTHOPAEDIC DISORDERS

Orthopaedic disorders have been considered as leading problems in the human community.

Since ADSCs contain therapeutic properties (*i.e.,* differentiation capability into a variety of cell lineage *in vitro* as well as having immunosuppressive, osteoinductive and anti-inflammatory features), they might be used for treatment of orthopedic major diseases such as degenerative OA[81,82].

It was reported that ADSCs increased the expression of osteogenic genes [*i.e.,* runt related transcription factor 2 (*RUNX2*), Alkaline phosphatase, Type Ⅰ collagen] and chondrogenic genes [*i.e.,* Type Ⅱ collagen, SRY-box 9 (*SOX9*) and aggrecan] on biomaterials in a chondrogenic inducing medium[83].

Previous studies showed that administration of both ADSCs and SVF in early OA is a safe and therapeutically efficient approach[82-86].

A study on rabbit model indicated that an eight week ADSCs/hydroxyapatite implantation to critical size tibial defects could remarkably enhance mineral content and bone regeneration[87]. Additionally, two clinical trials on bone healing illustrated that ADSCs in combination with synthetic bone graft and biomaterials may affect the regeneration, augmentation and vascularization of bone fracture[88].

Injection of ADSCs *via* second-look arthroscopy improved cartilage regeneration and decreased pain in patients with OA[89]. In addition, Jo *et al*[45] (2014) reported that the injection of 1×10^8 cell/mL ADSCs improved degenerative OA of 18 patients histologically and clinically after 6 mo of injection.

HAIR LOSS

Hair loss is one of the most crucial cosmetic challenges in both women and men these days. It's a problem for the young and old alike.

ADSCs have great potential in hair repair and regeneration, so they are an important option for hair loss treatment[51,53,90-93]. The paracrine characteristics of ADSCs may include the specific factors released by them, including VEGF, HGF, IGF, and PDGF, which exert the specified effects on hair loss regeneration[51-53,93-95]. These factors are too therapeutically appropriated to be used for clinical application in patients with hair loss[51-53,93-95]. According to recent studies, it has been found that using ADSCs can stimulate hair growth in animal models[93]. Studies have shown that the conditioned medium (CM) derived from ADSCs also had proliferative effects on hair cells *in vitro*[91]. It was declared that a conditioned medium of ADSCs could lead to hair regeneration by promoting hypoxia[96]. Furthermore, a clinical trial involving 22 participants with alopecia documented that intradermal administration of a conditioned medium of ADSCs may lead to an ameliorating effect in hair regeneration process[53].

These medium candidates, in combination with LL-37, could also induce hair regeneration *in vivo*[90]. Furthermore, a study demonstrated that ADSCs-conditioned medium not only has a stimulated alkaline phosphatase activity, but is also related to dermal papillae cells and dermal papillae markers[97].

In addition, a retrospective observational study noted that hair density and thickness could be improved following 12 wk of CM-ADSC administration[52].

Previous evidence has demonstrated that ADSCs and adipocytes could act as a niche for hair follicles,

due to providing an increase in the skin's thickness and progress in the intradermal adipocyte layer during the anagen phase, as well as creating a decrease in the intradermal adipocyte layer during the catagen and telogen phases[98,99]. In addition, ADSCs and adipocytes regulate the hair cycle *via* the release of signaling molecules, *i.e.,* WNTs, PDGF, BMPs, and FGFs[98,99]. These signals could lead to activation of the stem cell differentiation in the hair follicle and bulge stem cell activation during the telogen phase[98,99]. Canine ADSCs administration could also be caused by the increase in the vascularization process in the dermal papillae and has a beneficial effect on hair growth and repair in the nude mice model[100].

In addition, an animal study showed that ADSCs in combination with core-shell sphere could help in the formation of hair[97].

ADSCs can also support auditory hair cells, and these cells are capable of regenerating damaged hair[101].

Furthermore, protein secreted by ADSCs may be considered an appropriate tool for hair repair[93]. Such as, an observational pilot experiment performed on twenty seven patients with female pattern hair loss demonstrated that administration of protein extract derived from ADSCs could be caused to enhance in hair density and thickness since 12-wk follow up treatment. Furthermore, no serious complication was observed in patients[93].

Similarly, another pilot experiment verified the beneficial effect of ADSCs protein extract in patients with male pattern hair loss[93].

FERTILITY PROBLEMS

Infertility is one of the most common problems impacting both men and women. This health issue could lead to decreased populations, and treatment strategies are necessary to address it. However, many current therapeutic strategies are not very effective. As a result, more efficient treatments should be developed. One such solution is ADSCs-based therapy, which has been demonstrated to lead to improvements in fertility rates.

An animal study illustrated that the administration of ADSC could be considered as a therapeutic strategy in chemotherapy-induced ovarian dysfunction in rat models[102].

For example, the use of ADSCs caused a significant increase in the number of maturing follicles and corpora lutea with definite oocytes inside[103].

In another preclinical experiment, the use of collagen scaffold in combination with ADSCs enhances the short-term maintenance of ADSCs in ovaries[104].

It aims for long-term recovery of ovarian function, in addition to improving the fertility of rats with premature ovarian failure[104].

Similarly, Sun *et al*[105] (2013) demonstrated that intraperitoneal injection of ADSCs could ameliorate ovarian function in mice with chemotherapy-induced ovary damage.

Furthermore, on considering an *in vitro* study, it was identified that conditioned medium obtained from ADSCs could lead to human oocyte maturation and embryo formation following intracytoplasmic sperm injection through secretion of paracrine factors[106].

It is elucidated that the administration of ADSCs could promote fertility restoration in azoospermia rats, as well as the generation of sperm in them[107].

In addition, a human *in vitro* study reported that supernatant product of ADSCs (SPAS) could be ameliorate sperm motility in male infertile patients that can be due to existence of bioactive molecules and growth factors, which have a positive effect on sperm motility parameter[108].

In several animal studies, it was identified that ADSCs injection or transplantation have a positive impact on the viability of ovarian follicles and could increase the retention of short-term cryopreserved ovarian grafts, as well as improve the graft quality in the rat model[102-105,109].

Several preclinical and *in vivo* experiments have verified that the administration of ADSCs may have a beneficial effect on Peyronie's disease, which is a problem that could lead to infertility[110-113].

Considering obtaining data from a pilot study, the application of autologous SVF in combination with shock wave may have a therapeutic effect on Peyronie's disease[36].

In addition, this study on 11 patients documented that the administration of these adult stem cells is a safe process for the treatment of Peyronie's disease[36].

SALIVARY GLAND DAMAGE

The salivary gland is considered as one of the most exocrine glands that generate saliva, which helps the chewing and swallowing process.

Radiotherapy is one of the most well-known agents that may cause damage to the salivary gland.

Due to their capacity to differentiate into salivary gland cells and their potential to secrete bioactive molecules, as well as their capability to induce regeneration following salivary gland failure, ADSCs have been considered promising tools for salivary gland damage regeneration[114-124].

There are a number of researches and clinical studies which have looked into salivary gland damage regeneration through ADSC application, by means of local and systemic use[114-124].

It was demonstrated that systemic use of ADSCs could provide a support against salivary gland damage induced by irradiation[114]. In addition, it was identified that ADSCs may migrate engrafting to an injured location *via* the blood stream[114,120,121].

Similarly, Maria *et al*[119] (2011) documented that ADSCs non-permanently supply a salivary gland cell of the endothelial or salivary acinar cell phenotypic trait by transdifferentiation into salivary gland cells.

It was identified that ADSC administration may be decreased in the apoptosis process through secreted growth factor with anti-apoptotic action[114,116,117,120,122]. Furthermore, the fibrosis reaction was diminished after ADSC administration[114,120]. It has been proposed that a paracrine mechanism could be responsible for the improvement of induced damage by radiation through providing growth factors related to neovascularization[120].

Both animal and human experiments have verified that ADSCs could represent a safe treatment strategy for salivary gland damage[40,114,115,117,120,123].

In addition, secreted bioactive factors from ADSCs could promote epithelial proliferation and a stimulated angiogenesis process[114,120,124].

One study explored the local administration of ADSCs for improved tissue remodeling effectiveness in impaired salivary glands induced by radiation[117]. This study showed that ADSCs could lead to beneficial results by ameliorating the tissue remodeling of impaired salivary glands induced by radiation[117].

Furthermore, it was elucidated that ADSC secretome from a hypoxic-conditioned medium may provide a positive outcome on radiation damaged salivary glands, as well as supplying ameliorating and remodeling effects on damaged tissue by paracrine mechanisms[118].

It was noted that ADSC application could also amend xerostomia induced by radiation, a problem related to salivary dysfunction that it is created following radiotherapy for head and neck cancer, through high expression of a variety of growth factors, including hepatocyte growth factor, and vascular endothelial growth factor[40,120,121].

CONCLUSION

Cell-based therapy has been used during the recent years to treat a variety of body damages and lesions. A variety of stromal stem cells harvested from several different tissue types have therapeutic characteristics, but BMSCs and ADSCs are widely considered more usable candidates for regenerative medicine among them. The application of ADSCs is greater than that of BMSCs in regenerative medicine because ADSCs have need to more easily technique for isolation compared to BMSCs, as well as they have a much greater rate in number than to BMSCs. because the technique for isolating ADSCs is easier and, consequently, they can be used in greater number than BMSCs.

As a result of their inherent therapeutic properties, ADSCs could also provide a hopeful strategy in the field of regenerative medicine for treatment a wide range of diseases and lesions. This will ensure the availability of ADSCs for research, trial and clinical applications in the future. Due to the promising results obtained from preclinical and clinical trials as well as their unique features in term of regenerative potential, these cells can be useful in the treatment of different diseases. Furthermore, it has been shown that the administration of ADSCs can provide a safe treatment strategy in regenerative medicine approaches. There have been few reported serious side effects resulting from the clinical use of ADSCs, although there have been some reports concerned with adverse effects. Such limited adverse effects observed in some trial studies include headache, inflammation and *etc.* additionally, considering to previous data, ADSC promote carcinoma progression and for that reason appear to increase the risk of cancer relapse in breast augmentation procedures. Therefore, there are needs for further research on understanding the potential application of ADSC as a safe and effective therapeutic option on diseases treatment in future.

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