Review paper

Stem cells in plastic surgery and aesthetic medicine

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Abstract

Stem cells (SCs) have multiple applications in today's medicine including aesthetic dermatology and plastic surgery. The purpose of this paper is to review some clinical use of mesenchymal SCs. The main focus was put on adipose tissue-derived stem cells (ADSCs) as these cells are easy to harvest and because of their properties showed great potential in many studies, where they proved to accelerate wound healing, reduce scars, cause hair regrowth, or rejuvenate skin. Furthermore, when added to lipofilling procedures, such as breast augmentation they enhance fat graft survival and provide satisfying results. Currently, many different strategies for using SCs in treatments are developed with great efficacy, however, there are still many limitations and concerns regarding their clinical use.

Key words: stem cells, adipose-derived stem cells, aesthetic medicine, wound healing, rejuvenation, fat grafts, lipofilling

Introduction

Although stem cells were discovered in the early 1960s we still have not determined their full potential. Stem cells are divided into totipotent, pluripotent, multipotent and unipotent cells. They are characterized by different mechanisms of self-renewal. Pluripotent stem cells have the ability to produce stem cells from all three germ layers, while multipotent stem cells transform into one of them. Unipotent stem cells produce only one type of cells. There is also another classification of stem cells based on their origin: embryonic stem cells, foetal stem cells, adult stem cells, and induced pluripotent stem cells. Due to ethical concerns, the use of embryonic and foetal stem cells is prohibited in most countries. Thus, adult stem cells have gained a lot of attention. Not a long time ago they were considered multipotent stem cells only, however, after some experiments, it was proven that these cells can regain their pluripotency when moved to another type of cells. Currently, mesenchymal stem cells have a great number of applications in medicine. The most common ones are adipose tissue-derived stem cells (ADSCs) as they are easily obtained and show good efficacy in procedures. ADSCs are harvested from adipose tissue through separation from lipoaspirate. In contrast to ADSCs bone marrow, stem cells are difficult to collect and the procedure is often ineffective. Other sites in human body of resources for mesenchymal stem cells (MSCs) include umbilical cord, tendons, skin, or muscles [1].

Resources, extraction, and molecular mechanism

There are a few types of stem cells used for clinical application and the most controversial are embryonic stem cells. They show great potential due to their pluripotency however ethical barriers and safety issues like tumorigenicity have significantly restricted their clinical use.

The most promising are human MSCs. Recently ADSCs have gained a huge popularity because of their easy extraction and they received the most attention from researchers in aesthetic medicine [2]. Adipose tissue is composed of adipose stem cells and a stromal vascular fraction (SVF) built of fibroblasts, macrophages, smooth muscle cells, and endothelial cells. ADSCs are isolated from the SVF by enzymatic digestion. The next steps of extraction include mixing with foetal bovine serum, filtering, and centrifuging process [3]. ADSCs are able to differentiate into ectodermal or endodermal cells when under certain circumstances. ADSCs compared to BM-SCs have a greater survival rate and are more resistant to apoptosis. Their mechanism of action is based on paracrine and immunomodulatory effects as well as multipotent activity [4].

Using ADSCs as a clinical treatment began with lipoaspirate. The easiest method of application is based

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on the administration of SVF. However, the application is not efficient due to the aggregation of cells and necrosis. For better efficacy researchers now focus on developing culture systems with ADSCs. There is no standard method of harvesting and preparation of the fat grafts and there are still many different protocols of extraction [4, 5].

Limitations and side effects

There are several factors concerning the safety of stem cell-based therapies. The number of these procedures has been increasing although there are not enough clinical trials, which is why the FDA gave specific regulations to researchers. One of the issues includes potential damage and contamination of cells during the manipulation process. For example cell culture mostly has foetal-calf serum which can be contaminated with prions. Another major concern is the similarity of induced pluripotent stem cells (iPSC) to cancer cells. The study demonstrated the spontaneous transformation of stem cells to malignant cells [6].

Currently, to prevent teratoma formation there has been an attempt at the differentiation of cells before transplantation, however, the strategy was not perfect as there was still a risk of teratoma formation coming from residual undifferentiated cells. Fortunately, some successful approaches on eliminating the oncogenic properties of stem cells are undergoing multiple studies. One of them focuses on the manipulation of cells without the pro-oncogenic factor c-myc and the other involves targeting anti-apoptotic signals like survivin. On the market, there is a pluripotent cell-specific inhibitor (PluriSIns) to prevent teratoma formation after therapy with stem cells [7].

Finally, it is worth mentioning the side effects of fat grafting where the potential of ADSCs is more commonly used nowadays. These complications include scarring, necrosis, swelling, bruising, or cyst formation. There were also more dangerous cases where the patients after getting an injection into the nasolabial fold presented with visual loss. In the case report of a 27-year-old female, a similar serious accident happened after receiving an injection of autologous fat. The tissue entered the nasal artery forming an embolus which later migrated to the ophthalmic artery causing an occlusion, leading to the patient's sudden blindness [8].

Furthermore, there is proof that MSCs have metastatic properties and promote tumour growth which is the reason why using them in cancer patients for breast reconstruction is highly debatable. MSCs not only migrate towards malignancies due to their immunomodulatory properties, but also produce a number of pro-angiogenic factors and enhance the creation of blood vessels [9].

Although fat grafting is a method with easy to obtain sources and is commonly used worldwide, there are still not enough studies demonstrating efficacy. Therefore for further evaluation, high-level evidence is needed.

Wounds and scars

Severe chronic wounds often coexist with tumours, diabetes mellitus, or infections and have a big impact on quality of life. Wound healing is a complicated physiological process that includes angiogenesis, inflammation, creation of new tissue, and scarring. It is regulated by many mediators such as cytokines and growth factors. Nowadays there are some surgical and non-surgical procedures for covering wounds and scars with skin grafts, hyperbaric oxygen therapy, antimicrobial therapy, and negative pressure therapy playing an important role. Tissue engineering gained the attention of many researchers and its main goal is to restore organ function by creating an optimal environment for homeostatic mechanisms. Stem cells also received an interest as it was proven that they impact the wound healing process by producing cytokines and growth factors. These cytokines, comprised of TGF-B, VEGF, GM-CSF, IL-6, IL-10, IL-1, induce cell differentiation and accelerate wound healing, angiogenesis, and re-epithelialization [4, 10]. Progenitor cells can be transplanted directly through injections and spraying or in the matrix material. In the study on 3 people, bone marrow (BM)-derived stem cells were applied into chronic wounds. In all patients reduced scarring along with a restored dermis was observed [11]. There have been successful clinical trials on animals and humans with stem cells derived from bone marrow and adipose tissue, as well as stem cells from the placenta and peripheral blood. An important and perfect source of stem cells was discovered by a Canadian institute. They isolated viable cells from debrided burned skin and proven that they have characteristics of stem cells and can be easily used for skin renewal [12]. The great properties of stem cells were discovered in another case of a 7-year-old child suffering from Junctional Epidermolysis Bullosa which is a severe lethal disease that can lead to skin cancer. The patient received an autologous transgenic epidermis with a limited number of stem cells. The study showed that the regenerated epidermis is maintained thanks to the stem cells and 2 years after the procedure, the boy's skin did not show any signs of ulceration or blisters [13]. ADSCs play a major role in the wound healing process. Their mechanism of action is based on the paracrine effect through secreting growth factors (IGF, TGF-β1, VEGF, HGF, and FGF2) which stimulate fibroblasts and keratinocytes. An important characteristic is that they produce antioxidants. and have ability to transform into keratinocytes and fibroblasts directly.

The best results so far were presented in the studies using platelet-rich plasma with ADSC as it was proven to enhance the survival of grafts [14].

Table 1. Methods of wound treatment with the use of stem cells

Type of stem cells	Method	*In vivo/in vitro*	Outcome	Wound/scar	Year (reference)
ADSCs	Fat grafting/fat grafting + PRP	*In vitro*	Increased angiogenesis, increased graft survival with PRP	Diabetic foot	2021 [17]
BM-SCs-mobilization with plerixafor	Double-blind randomized trial placebo controlled, subcutaneous injections	*In vivo*	No improvement or wound healing	Diabetic foot	2020 [31]
ADSCs-derived exosomes	Prospective double-blind controlled trial, split face	*In vivo*	Milder erythema, scar reduction	Acne scars	2021 [15]
Umbilical-cord mesenchymal stem cells	Randomized controlled trial, transdermal hydrogel UC-MSCs on the surface of the scar	*In vivo*	No significant improvement	Caesarean section scar	2020 [32]
ADSCs + PRP	Randomized controlled trial, injections with e-PRP	*In vivo*	Wound closure rate was significantly higher compared to the control group	Chronic skin ulcers	2016
BM-SCs	Animal model – healthy beagles received injections intradermally	*In vivo*	Rapid wound closure and increased collagen synthesis, cellular proliferation, angiogenesis	Incision wound	2013 [33]

Some clinical trials on treating wounds and scars and their outcomes were presented in Table 1.

Many people struggle with visible scars and are determined to get rid of them long after the healing process is finished. The scar formation process remains unclear, however, it is indicated that exaggerated inflammation is responsible for excessive scarring. Most of the researchers focus on applying MSCs during the wound healing process however there has been an increasing interest in the impact of stem cells in the treatment of excessive scars. MSCs travel to the site of a wound through chemotaxis toward wound healing cytokines and secrete paracrine factors that modulate immune cells' response. Some results of their action are downregulation of the proliferation of NK cells, inhibition of neutrophils' chemotaxis, and promotion of differentiation of anti-inflammatory macrophages type 2 (M2). MSCs downregulate fibrosis through the action of PGE-2, IL-10, HGF, and NO. Apart from the immunomodulatory effect they also take part in the scavenging of ROS and modulating fibroblasts' action [2, 15, 16].

The number of people with diabetes mellitus is rising and so is the number of complications associated with this disease. Patients with diabetic foot often undergo many different treatments that in most cases are ineffective. The combination of PRP and ADSCs stimulates the proliferation and migration of fibroblasts and keratinocytes [14]. In a particular study, 18 patients were divided into three groups. One of them was a control group and two others received fat grafts and fat grafts with platelet-rich plasma (PRP). The measure of clinical outcome in this study was a change in the size of the wound. Unfortunately, the low number of people in the trial did not allow to draw a concrete conclusion regarding the efficacy of the treatment. This study demonstrated that five of the patients achieved 100% wound healing (two from the fat only group, two from the fat/PRP group). This concluded the safety of fat grafts in diabetic foot patients however further studies on a greater group of patients need to be done to find out about the effectiveness of this therapy [17].

Stem cells induce hair growth

Hair loss is a problem a great number of people face including the majority of middle-aged men. This condition is associated with several factors: hereditary (androgenic alopecia), nutritional, environmental, and many others. Currently, there has been an interest in using hair follicle stem cells (HFSCs) and derma papilla cells for treatment. It is indicated that SCs can stimulate the activity of hair follicles resulting in the regrowth of hair, and promote neogenesis of hair follicles (HF) and regeneration [18, 19]. The clinical trial on Japanese women with hair loss was highly effective. The applied technique was based on adipose-derived stem cell protein extract (AAPE). The application process was not complicated as patients were given intradermal injections of a serum combined with vitamins. The treatment was administered to more than 1000 patients and no side effects or allergic reactions were observed. Therefore, it was proven to be a useful and safe method of treating of alopecia [20]. Adult SCs, especially ADSCs, were also in the center of attention in a clinical study on 38 patients with androgenetic alopecia. The treatment was based on a topical solution of ADSCs extract, and over the course of weeks, significant hair regrowth was observed [21]. ADSCs act as an activators of epidermal stem cells by secreting growth factors: PDGF-2, VEGF, IGF-1 and HGF.

Additionally, they directly stimulate hair follicle growth and the proliferation of progenitor cells. Adipose tissue around hair follicles is necessary for normal hair growth and this fact was used as an important factor in the research. In another study, umbilical cord-derived stem cells were used without any additional components or manipulation of cells. The patients who underwent treatment suffered from alopecia areata and showed areas of baldness and each of the three of them was given an injection with MSCs in affected spots. The duration of treatment varied depending on the severity of hair loss and each one was successful [22]. Despite the great potential of these treatment methods, all of the described studies need a greater number of clinical trials with more people participating.

Breast reconstruction

A common procedure performed by plastic surgeons is breast reconstruction. Lipofilling is a technique that provides an ideal breast shape and is also used for many other procedures like facial rejuvenation. It has become very popular worldwide due to various reasons such as a natural outcome or an easily-obtained source to fat. There are some downsides to fat transplantation and one of them is the long-term retention and necrosis of injected tissue. To prevent this unwanted effect there have been studies on a novel method which is cell-based therapy with ADSCs called Cell-assisted lipotransfer (CAL) [23, 24]. The studies suggested that ADSCs can prolong the survival of transplanted fat and restore vascularization. Fat injections enriched with ADSCs proved to be an efficient way to maintain the volume of breasts with the survival rate of injected fat of more than 80% for injected fat. The results are promising as also no side effects were observed. A different study on 70 patients who got CAL injections was successful and without any major complications. Compared to implants this method ensures a more natural shape of breasts which generally was satisfying to the patients [25].

Breast reconstruction recently became popular among breast cancer patients, however, there was some concern regarding the oncogenic properties of cell-assisted lipotransfer. Although CAL is a very effective technique, it still needs further research and understanding of the safety of treatment to make sure that there is no cancer relapse.

Skin rejuvenation

MSCs in procedures like autologous fat grafting have found their clinical application in skin rejuvenation as well. As we age we lose facial fat following a loss of volume, especially to the perioral area. Facial atrophy can be prevented thanks to lipofilling and the role of stem cells. To avoid complications like fat accumulation or transplant migration, scientists recently paid more attention to micro- and ultra-micro-fat grafts. These novel techniques are applied to the restoration of fat in periocular or perioral areas where the skin is thin [26]. Some of the most popular procedures for lipofilling for facial rejuvenation include the correction of dark circles under the eyes [27].

The following study was conducted on a group of 13 patients who were eligible for a facelift. This research aimed to replace stem cells with PRP as it would be more efficient. PRP is rich in growth factors and cytokines so it was indicated that it would be a great replacement for ADSCs due to the ability of PRP to stimulate angiogenesis – an important factor in skin rejuvenation. However, this study suggested that PRP alone did not have an additional impact on skin regeneration. The patients were divided into three groups with different treatments and only one common component of injections which was ADSCs. All of them including the one with PRP had very similar outcomes. Due to the results, it was confirmed that adipose-derived stem cells or SVF-enriched fat were the main cause of an improvement in skin quality, appearance, and hydration [28].

Another study was performed aiming for the proof of cell-assisted lipotransfer efficiency. Half of the group of patients received fat grafts only and the other half got injections with SVF. Although the skin quality was improved in both, the results and survival rate of grafts were much better in the SVF- enriched group. On a 6 months' follow-up appointment the majority of patients were content with the outcome [29].

Vitiligo treatment, rhinoplasty, and other procedures

Vitiligo is a skin disorder characterized by areas of depigmentation and it is caused by the loss of melanocytes. The disease appears as white patches on the skin of the whole body. For the repigmentation to occur, melanocyte precursors are extracted from hair follicle bulges, unaffected areas, or from the border of skin lesions. In order to properly transform into melanocytes they need growth factors and the presence of keratinocytes, fibroblasts, and adipocytes. Cytokines can be provided by ADSCs for melanocytes to undergo mitosis. Numerous studies have proven that melanocytes transplantation efficacy is improved when co-cultured with ADSCs. ADSCs produce hair growth factor after exposure to β-FGF and the migration of melanocytes is enhanced when co-cultured with ADSCs. In fact, when melanocytes monoculture was compared to co-culture, the results were significant and showed increased positive expression of TRP-2 (the expression is associated with immature melanocytes) in the co-culture. The more TRP-2 is expressed, better the outcome of treatment. In conclusion, the addition

of ADSCs improves melanocytes' ability to migrate and proliferate.

Fat grafting found its potential also in the cosmetic surgery field. In rhinoplasty, fat or synthetic implants can improve the nasal side profile; however it is worth pointing out that synthetic ones often result in complications. Lipofilling also plays a role in gluteal augmentation and can replace commonly used implants [10, 30–33].

Conclusions

Over the last decade stem cells have gained enormous popularity in clinical procedures in branches of medicine such as aesthetic medicine and plastic surgery. Adipose tissue-derived stem cells and epidermal stem cells used in treating chronic wounds and scars have proven to be eligible methods due to their ability to produce cytokines that accelerate wound healing. The great potential of stem cells was also shown in patients with alopecia where they stimulated hair follicles and promoted the proliferation of progenitor cells. Studies using fat injections enriched with ADSCs in breast reconstruction surgery or facial rejuvenation suggest that this technique prolongs the survival of fat grafts and overall is more satisfying than regular breast implants. Unfortunately, most of these studies need a greater number of clinical trials as there are still many unexplained aspects such as long-term adverse effects and all of the interactions with cells. To develop a successful strategy for SCs application in aesthetic medicine, further investigations are necessary.

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Conflict of interest

The authors declare no conflict of interest.

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