Review Article

Roles of adipose-derived stem cells in cell-based therapy: current status and future scope—a narrative review

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Background and Objective: Stem cell-based regenerative medicine is a new therapeutic approach for repairing or replacing tissues and organs that have been depleted or damaged by genetic, traumatic, or age-related degenerative disorders by creating functional tissues or supporting wound healing. Adipose-derived stem cells (ADSCs) are a type of mesenchymal stem cell (MSC) isolated from adipose tissue that are an ideal source of cells for treatment of many diseases. In this review, the current challenges for use of ADSCs in regenerative medicine are discussed to understand directions for clinical applications in transplantation, gene therapy, and tissue engineering.

Methods: To explicate recent developments and progress in ADSCs in cell-based therapy, we performed a thorough review of the literature through independent searches using the MEDLINE database within NIH National Library of Medicine PubMed.

Key Content and Findings: Many groups have investigated the roles of ADSCs in treating disease. Administration of ADSCs in animal models has been reported to improve healing benefits through enhanced cell regeneration and engraftment, increased blood supply, immunomodulation, anti-inflammatory effects, and elevation of concentrations of growth factors associated with wound healing. More recently, clinical studies have sought to examine the impact of ADSCs. Exosomes and other extracellular vesicles secreted from ADSCs can be applied directly to recapitulate the beneficial effects of ADSCs.

Conclusions: The emergence of ADSC therapy provides a novel means for tissue regeneration. Numerous clinical and pre-clinical studies have shown the vital roles of ADSCs in reconstructing and repairing target organs, such as bone, cartilage, myocardium, liver, nervous system, and skin. However, there are still many issues that remain to be clarified regarding the mechanisms of therapeutic efficacy and safety. Therefore, further research, including pre-clinical studies, is needed to examine these issues.

Keywords: Cell-based therapy; stem cell; adipose derived stem cells (ADSCs); stromal vascular fraction regenerative medicine; exosomes

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Introduction

Stem cell-based regenerative medicine is a new therapeutic approach for repair or replacement of tissues and organs that have been depleted or damaged by genetic, traumatic, or age-related degenerative disorders by creating functional tissues or improving patients' quality of life (QOL) and appearance (1,2). The therapeutic rationale is based on the idea that stem cells have the potential to replace damaged or dead cells with newly differentiated progeny, making themselves components of tissue reconstruction (cell replacement therapy) (3,4), and on their ability to contribute to tissue repair and regeneration by autocrine and paracrine actions through secretion of growth factors, cytokines, extrecellular matrix (ECM) molecules, and exosomes (cell supportive therapy) (5,6). Biological functions may be improved by stem cells by direct transplantation *in vivo* into host tissue or if combined with a therapeutic gene or biomaterial to generate tissue *ex vivo* (7-10). For clinical application, stem cells should meet several criteria and are generally expected to be abundant, minimally invasive to the patient, and have strong potential to proliferate and differentiate into multiple cell types (11,12). From this perspective, adipose-derived stem cells (ADSCs), a type of mesenchymal stem cell (MSC) isolated from adipose tissue, are an ideal source of cells for treatment of many diseases (11-14). In this review, the current challenges for use of ADSCs in regenerative medicine are discussed, with the goal of understanding directions for clinical applications in transplantation, gene therapy, and tissue engineering. We present the following article in accordance with the Narrative Review reporting checklist (available at https://dmr.amegroups.com/article/view/10.21037/dmr-22-32/rc).

Methods

To explicate recent developments and progress in ADSCs in cell-based therapy, we performed a thorough review of the literature published from March 1968 to May 2022 by independent searches using the MEDLINE database in NIH National Library of Medicine PubMed (*Table 1*). This publicly available and institutionally accessed database was used to search indexed and published articles. Editorials, technical reports and expert opinions were excluded from the literature search. Studies presented at international meetings and conferences, but not published in standard journals, were also excluded.

Properties of multipotency and self-renewal of ADSCs

ADSCs are mesoderm-derived adult stem cells that commonly express markers of a mesenchymal phenotype, such as CD73, CD90, and CD105), but are negative for markers such as CD31, CD45, and HLA-DR; however, a single cell surface marker that uniquely identifies an ADSC has not been found (15,16). ADSCs have strong self-renewal ability based on results from colony forming unit formation (CFU-F) assays (17), and are multipotent, as indicated by their differentiation into various mesenchymal cell lineages, including fat, bone, cartilage, and muscle (11-13,15) (*Figure 1*). It is also of note that ASCs are responsive to inducers of differentiation of non-mesenchymal cell lineages, and can differentiate into desired cells beyond the germline (*Figure 2*) (11-17).

Mechanisms of cell therapy using ADSCs

Behavior and fate of transplanted ADSCs at the site of regeneration

There are several possible mechanisms underlying promotion of tissue regeneration by ADSCs. Some studies have suggested that ADSCs act through differentiation into specific cell types, thereby replacing defective cell populations *in vivo* (cell replacement therapy). However,

Table 1 The search strategy summary

Items	Specification
Date of search	02 June, 2022
Databases and other sources searched	NIH National Library of Medicine PubMed, MEDLINE database
Search terms used	Adipose; Fat; Stem cells; Mesenchymal stem cells; Clinical application
Timeframe	March 1968 to May 2022
Inclusion and exclusion criteria	English only

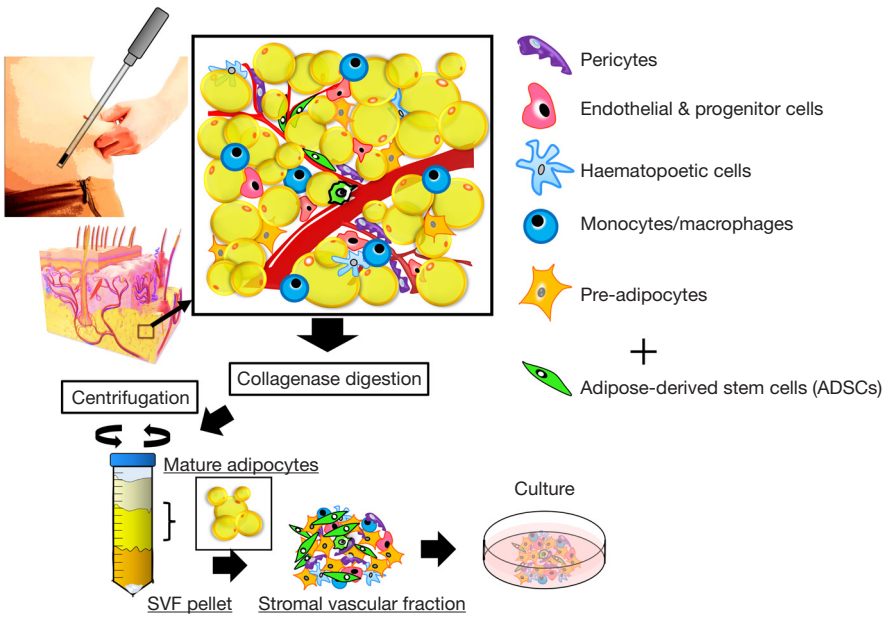

Figure 1 Diversity of stromal cells in adipose tissue and isolated cultures. Collagen fibers and mature adipocytes account for most of the adipose tissue volume, but other stromal cells are also present. These include pericytes, endothelial and progenitor cells, hematopoietic cells, monocytes/macrophages, and pre-adipocytes. Collagenase digestion and centrifugation produces a cell mass referred to as the stromal vascular fraction that contains many of these cells and can be cultured and expanded. SVF, stromal vascular fraction.

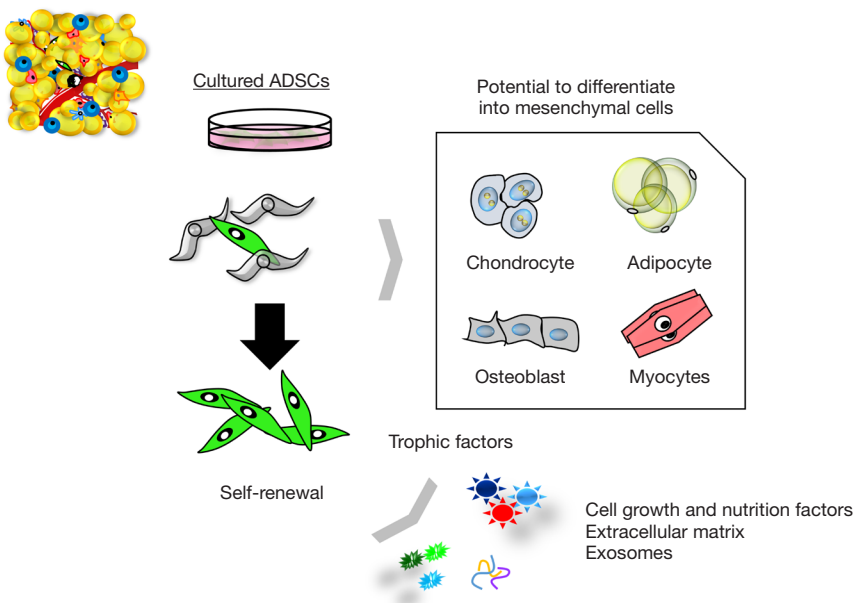

Figure 2 Diversity of ADSCs and their role as a source in cell therapy for wounds. ADSCs are mesenchymal stem cells that are capable of self-renewal and differentiation into adipocytes, osteoblasts, chondrocytes, and myocytes by culturing in specific differentiation induction media. ADSCs can also be converted into target cells beyond the ADSC blastema, which makes them particularly useful for regeneration of various tissues. These cells also produce and release regenerative factors such as cell growth and nutrition factors, extracellular matrix, and exosomes that promote wound healing. ADSCs, adipose-derived stem cells.

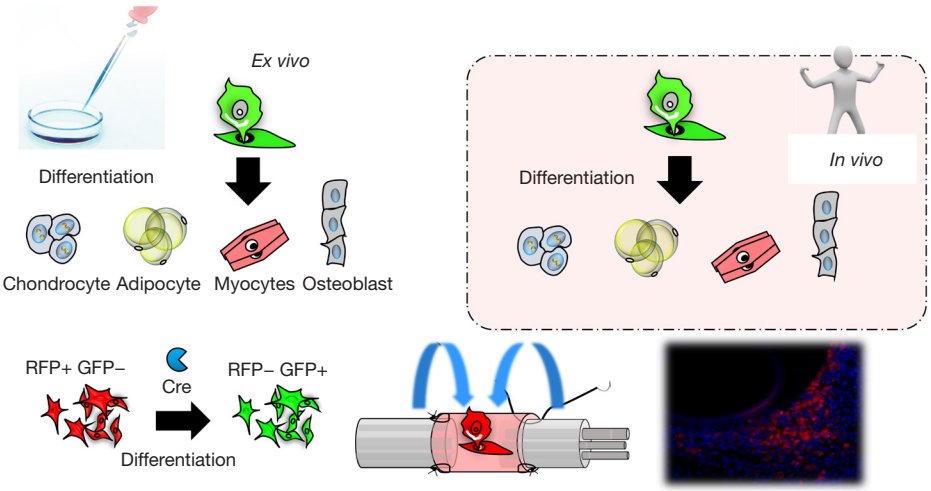

Figure 3 Stem cell therapy utilizing the expansion and differentiation potential of ADSCs and their superior wound healing ability. There are two approaches to therapy with ADSCs: transplant of cells after proliferation and differentiation *ex vivo*, and transplant of undifferentiated ADSCs into the site of tissue damage, with the aim of natural conversion into the required cells. Several studies have examined differentiation into specific lineage cells at the regenerative site. Our regenerative mouse model of the peripheral nerve showed that transplanted ADSCs did not differentiate into Schwann cells, but did promote peripheral nerve regeneration at the injured site. ADSCs may also contribute to tissue regeneration through regulation of the host stem cell niche, such as promoting activation of endogenous stem cells at the site of injury. RFP, red fluorescent protein; GFP, green fluorescent protein; ADSCs, adipose-derived stem cells.

most studies in animal models, in which ADSCs can be tracked *in vivo*, have failed to show this behavior using high-quality cell tracking methods, except for the classic mesenchymal phenotype of differentiation into adipocytes, osteoblasts, and chondrocytes (18). Most studies have shown that differentiation of MSCs may lead to "intermediate two phenotype cells" that co-express certain cellular markers, but without evidence of acquisition of actual functionality (19). Another possibility is that cell fusion is the primary mechanism for forming new functional cells (20), but Aurich *et al.* found no fusion of host hepatocytes with transplanted ADSCs that differentiated into hepatocytes (21). We have used the Cre-loxP-mediated fate tracking system to visualize *in vivo* survival of transplanted ADSCs and to investigate differentiation into Schwann lineage cells at a peripheral nerve injury site. We found that transplanted ADSCs did not differentiate into Schwann cells (SCs), but did promote peripheral nerve regeneration at the injured site (*Figure 3*) (22).

ADSCs may also contribute to tissue regeneration through regulation of effects in the host stem cell niche, such as promotion of activation of endogenous stem cells at the site of injury, as a source of free radical scavengers that isolate and remove toxic substances and allow surviving cells to recover their functions (23). Thus, at present, it is widely believed that ADSCs promote cell regeneration in tissues and organs mainly through release of cytokines, growth factors and free radical scavengers (18).

Paracrine and immunomodulatory properties of ASCs

ADSCs promote tissue regeneration by secreting cytokines and growth and nutrient factors that restore normal tissue function or reduce tissue damage (24,25). Among the cytokines produced by ADSCs, vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), granulocyte/macrophage colony-stimulating factor, hypoxia-inducible factor 1α (HIF1α), hepatocyte growth factor (HGF), insulin-like growth factor (IGF-1), platelet-derived growth factor-BB (PDGF-BB), and fibroblast growth factor (FGF2) have crucial roles in formation of tissue structures due to their angiogenic properties and ability to induce tissue neovascularization (26,27). Anti-apoptotic factors such as IGF-1 also protect cardiomyocytes from apoptosis (28). ADSCs also have neuroprotective effects by promoting regeneration of peripheral and central nervous system cells through secretion of brain-derived neurotrophic factor, glial-derived

neurotrophic factor, nerve growth factor, and IGF (24). We have shown that undifferentiated ADSCs release neurotrophic factors to a similar extent to that of SCs and other glial cells, and have an effect of elongation of nerve axons, which suggests that ADSCs promote peripheral nerve regeneration partly through paracrine secretion of trophic factors and regardless of donor age or anatomic site of origin (29).

Immunomodulatory properties of ASCs

Evidence for the immunomodulatory properties of ADSCs has accumulated from *in vitro* and *in vivo* studies (30,31). ADSCs inhibit the inflammatory process in wound healing by inducing and activating quiescent native MSCs or other support cells at the site of local injury to secrete anti-inflammatory proteins (32). For instance, ADSCs inhibit production of pro-inflammatory cytokines, promote production of anti-inflammatory cytokines, and induce formation of antigen-specific regulatory T cells (33). In addition, control of the polarity of M1/M2 macrophages by ADSCs can promote wound healing (34,35). These cells also protect against organ rejection and prevent graft-versus-host disease after allogeneic stem cell transplantation (36). However, the antiapoptotic and immunomodulatory properties of ADSCs in their use in immune tolerance are still an unexplored area and further studies are needed.

Potential use of ADSCs in gene therapy

Gene therapy is an innovative method that has the potential for introducing genes into genetically defective host cells, which may produce unprecedented clinical benefits in incurable diseases. Using replication-defective retroviruses, adeno-associated vectors and lentiviruses, genes can be introduced into the DNA of recipient cells to change their traits and produce new functions (37,38). Gene transfer can produce cells that can generate therapeutic proteins *in vivo* and this can be regulated to an extent. Combination of stem cells, which are highly proliferative and viable, with a gene transfer system has increased the therapeutic potential of gene therapy (39-42), and ADSCs are also gaining prominence as a stem cell source for this purpose (43).

ADSC exosomes

Exosomes are extracellular vesicles, microvesicles, and apoptotic bodies of diameter 40–150 nm that are produced by eukaryotic cells and can be isolated from a cell culture medium by ultracentrifugation or precipitation with polyethylene glycol. Exosomes contain proteins, lipids, cytokines, and nucleic acids, including DNA, microRNAs, lncRNA, circRNA, and other non-coding RNAs, and are associated with immunomodulation, mediation of cell survival, proliferation, migration, division, apoptosis, and physiological homeostasis (44,45).

Exosome research has expanded rapidly, with an increased number of publications on the function and application of MSC-derived exosomes (MSC-EXOs) as potential cell-free therapeutics. ADSC exosomes (ADSC-EXOs) contain important paracrine components that are released from ADSCs and have various biological activities. A "vital network", in which growth factors, proteases, progenitor cells, and immune cells producing proinflammatory cytokines work together, is thought to be required for tissue regeneration (46). ADSC-EXOs play important roles in these networks as intercellular messengers. Furthermore, by encapsulation of bioactive substances, ADSC-EXOs can be used for multiple tissue regeneration processes, including mechanical repair for cell survival, migration, proliferation, and promotion of neovascularization. ADSC-EXOs have a good biosafety profile with low immunogenicity, and differ from other MSC-EXOs in promoting proliferation, differentiation and immunosuppressive pathways in target cells (47,48).

ADSC-EXOs have similar functions to those of ADSCs, including promotion of repair of heart muscle, kidney, urethral, liver, skeletal muscle, and other tissues and organs (49-52). Practically, it has been shown that ADSC-EXOs induce proliferation and migration of vascular endothelial cells and angiogenesis (53,54). ADSC-EXOs can also promote various types of wound healing and are being developed as agents for treating diabetic skin ulcers and improving the fat grafting rate for soft tissue defects. These cells also have influential roles as a carrier and combined scaffold for treatment, leading to scarless cutaneous repair (55). Several studies have examined the detailed mechanism of promotion of wound healing. Thus, Choi *et al.* showed that ADSCs-EXOs seem to induce enrichment of fibroblast microRNAs within the fibroblasts that contribute to healing (56). In a murine wound model, Wang *et al.* suggested that intravenous injection of ADSCs-EXOs resulted in reduced scar size and changes in metalloproteinases that may improve healing (57). Ren *et al.* found that ADSC-derived microvesicles stimulate

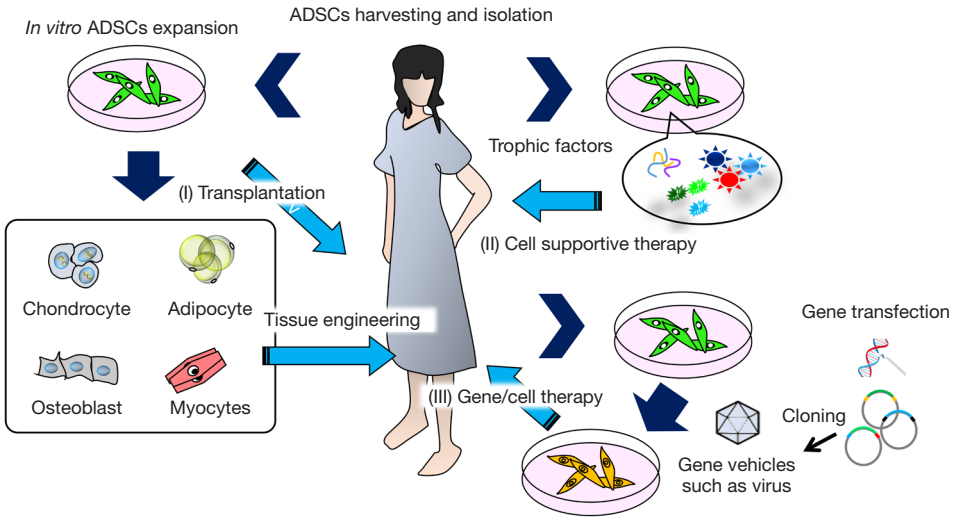

Figure 4 The three current strategies of regenerative medicine. (I) Transplantation, in which autologous ADSCs are expanded *in vitro* and transplanted directly into the host tissue. (II) Cell supportive therapy, using culture supernatants or molecular factories such as exosomes. (III) Gene/cell therapy, in which autologous ADSCs are cultured *in vitro*, transduced with viral vectors carrying therapeutic genes, and implanted into the host tissue. ADSCs, adipose-derived stem cells.

proliferation and migration of fibroblasts, keratinocytes, and endothelial cells *in vitro* and *in vivo*, mainly via the AKT and ERK signaling pathways (58), and ADSC-EXOs have also been shown to promote proliferation and migration and inhibit neuronal cell apoptosis by activating the PI3K/AKT pathway (59).

The roles of ADSC-EXOs have been examined in tissue regeneration in plastic and cosmetic surgery, such as improvement of dermatitis, scar removal, bone tissue repair and regeneration, obesity, fat grafting, breast reconstruction, and anti-aging treatment of skin (46). Elucidation of the biological properties of ADSC-EXOs is likely to lead to new strategies for tissue regeneration in these fields. Compared with cell-based therapy, ADSC-EXOs have high stability and are easily stored. In addition, they are controllable and less prone to rejection and unexpected homing to organs, which may permit development of clinical applications of non-autologous ADSC-EXOs. Thus, future use of various forms of ADSC-EXOs is likely to become more common for wounds, reconstructive surgery, and aesthetic treatment.

Three current strategies for regenerative medicine

The characteristics and utilization of ADSCs described above suggest three therapeutic strategies for regenerative medicine: (I) transplantation, in which autologous ADSCs are grown *in vitro* and transplanted directly into the host tissue, or first combined with biomaterials and then transplanted into the host; (II) cell supportive therapy, using culture supernatants or molecular factories such as exosomes; and (III) gene/cell therapy, in which autologous ADSCs are grown *in vitro*, transduced with viral vectors carrying therapeutic genes, and then implanted into the host tissue (*Figure 4*).

Application of regenerative therapy for wound healing using ADSCs

Skin ulcer

In wounds of the skin and soft tissues, there is damage to the structure and homeostasis of the tissues due to trauma or physical or chemical effects such as heat or radiation (60,61). Wound healing requires a series of molecular events that manifest as inflammation, neovascularization, formation of scar tissue, and tissue remodeling, and these events are strongly regulated by growth factors such as transforming growth factor-beta, FGF, VEGF, and PDGF (62,63). In many cases, wound repair is preceded by scar formation, which promotes collagenous ECM deposition and sometimes recruitment of collagen-secreting fibroblasts,

with angiogenesis required for these activities (64). ADSCs have well-known angiogenic effects, including in promotion of wound healing in intractable ulcers caused by ischemia in diseases such as diabetes (65-67), and can also control inflammation at the wound site by altering macrophage polarization (68,69).

Several preclinical studies of wound healing have reported beneficial effects of cell-based therapy using ADSCs (70-73). Hamada *et al.* demonstrated that transplantation of human ADSC (hADSC) sheets combined with artificial skin in rat increased blood vessel density and dermal thickness, and found that this accelerated wound healing compared with that in controls due to secretion of angiogenic growth factors by the hADSC sheets (70). In immunohistochemical analysis, there was more frequent neovascularization in xenografted rats in the transplantation group, and the transplanted hADSCs were localized to the periphery of new blood vessels. This xenograft model may be useful for identification of factors produced by human cell tissue-based products in use of these products to accelerate wound healing. The same research group also demonstrated that an artificial dermis can maintain autogenetic ADSCs, which can promote vascularization capacity and enhance wound healing in a wound with exposed bone (71). In an excisional wound healing model in rat, Nie *et al.* showed that ADSCs secrete pro-angiogenic mediators (e.g., VEGF-A, HGF, and FGF) that promote neovascularization and re-epithelial regeneration of wounds, which accelerates wound repair (72). A recent study showed that combination therapy of photobiomodulation and ADSCs is an effective and promising treatment by stimulating skin injury repair and modulating the inflammatory response in an MRSA-infected wound model in rats with diabetes mellitus type 1 (73). Taken together, these findings suggest that ADSCs have considerable potential as therapy to promote wound healing.

Cell therapy for radiation-induced skin damage

Radiation therapy has been replaced by tumor resection as the current mainstay for prevention of cancer growth, recurrence, and metastasis. Recurrence is reduced in a radiation dose-dependent manner, but there is a serious problem of deterministic effects in surrounding healthy tissue. In particular, the skin, subcutaneous tissues, and muscles are affected by radiation exposure under certain circumstances (74,75). Specific adverse events include fibrosis, atrophy, minor damage to small blood vessels (ischemia), and dermal thickening (75-77). These radiation-induced injuries cause many clinical manifestations in the skin and subcutis, including radiation dermatitis, scar contracture, lymphedema, and refractory wound healing. In addition, the elasticity and extensibility of the skin are impaired, skin appendages and hair follicles are lost, and joint movement is restricted (77). Impaired tissue regeneration/reconstruction and wound healing after radiation therapy can cause tissue dysfunction and decompensation, and may lead to more serious conditions such as intractable skin ulcers and osteomyelitis many years after radiation exposure (77,78).

Progression of skin disorders has been related to adipose tissue under the skin or ADSCs in this tissue. In vitro studies have shown that ADSCs exposed to radiation are damaged, senescent, and lose their proliferative and differentiation potential (79). Adipose tissue beneath the skin has a function of reducing skin damage from radiation, but this tissue itself remodels and atrophies due to exposure (80). Thus, adipose tissue and its component ADSCs are damaged by exposure and cannot adequately support skin regeneration, further worsening the condition. This suggests that promotion of tissue normalization may be achieved by replenishing the deficient ADSCs.

Cell therapy has been proposed by the International Atomic Energy Agency (IAEA 2009) as treatment for radiation-induced skin damage (81). The efficacy of products derived from adipose tissue containing ADSCs for radiation skin disorder has been shown in preclinical studies (82-85). In a rat model of chronic radiation wounds, Huang *et al.* showed that ADSCs produced neovascularization at the ulcer surface after transplantation (83). In regenerative medicine, selective use of cell populations from ADSCs is particularly effective, with Borrelli *et al.* reporting that $CD74^+$ cells, which are known to have antifibrotic effects, ameliorate radiation skin impairment *in vitro* and *in vivo* (84). Among adipose-derived stromal cells, it has also been proven that the $CD34^+CD146^+$ population promotes angiogenesis and wound healing (85).

Radiation-induced qualitative and pathological damage of tissues can be partially recovered by fat grafting, with this effect thought to be derived from MSCs and vascular endothelial cells contained in the grafted tissue. In an acute radiation dermatitis model in the back skin of mice irradiated at 45 Gy, Sultan *et al.* showed that fat grafting suppressed inflammation and slowed progression of fibrosis (86). Radiation causes significant skin thinning, depleted blood vessels, and increased scar formation, and fat grafting increased the skin thickness, collagen content,

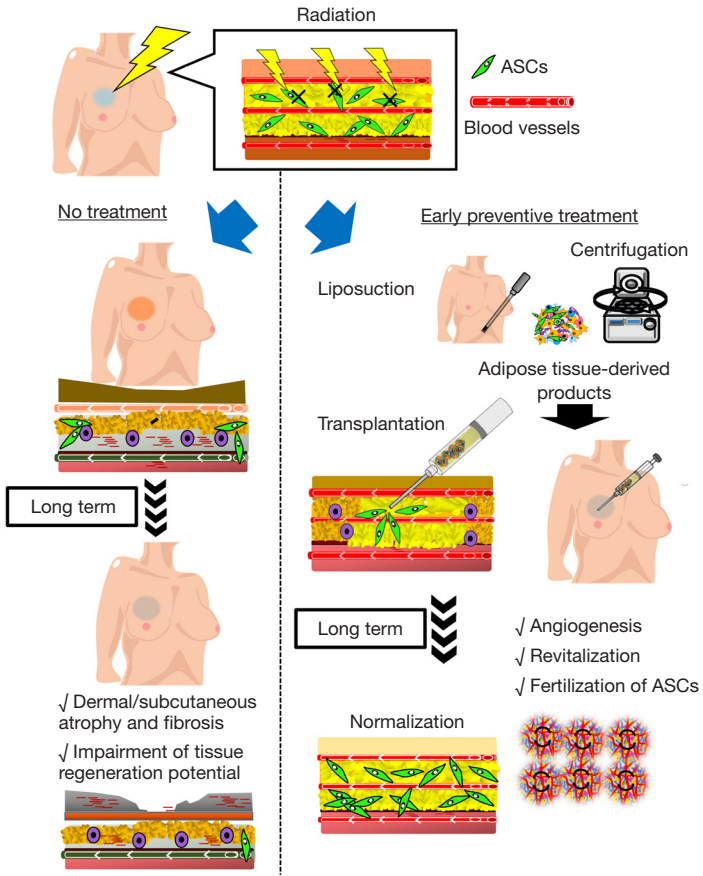

Figure 5 Clinical use of human adipose tissue-derived products to prevent radiation skin disorders. Injection of aspirated adipose tissue-derived or processed ADSC-enriched products at an early stage after radiotherapy may minimize the deterministic effects of radiation. Prophylactic treatment immediately after radiotherapy may avoid fibrosis, ischemia, and impairment caused by radiotherapy. ASCs, adipose stem cells; ADSC, adipose-derived stem cell.

and vascular density in irradiated skin (87,88). Qualitative changes in tissues, including blood circulation, and partial improvement of extensibility and healing ability also occur. Similar effects are obtained with micronized fat adipose transfer, using fractured stromal tissue with mature adipocytes removed (89). These findings suggest that adipose tissue utilizes its various cells and components for different purposes.

Fractionated radiotherapy was developed to maximize therapeutic efficacy and reduce deterministic effects on healthy tissues that result in long-term tissue damage (78). Yoshimura and colleagues applied the commonly practiced fractionated irradiation protocol to nude mice and found that radiation damage was dose-dependent, with mice exposed to a total dose of ≥15 Gy developing spontaneous skin ulcers. Injection of suctioned fat tissue or micronized tissue made the ulcer heal faster than in untreated controls, and these therapeutic effects were comparable to those of cultured ADSCs. More recently, our group showed that prophylactic administration of products containing ADSCs immediately after radiotherapy prevents development of long-term functional disorders in irradiated tissues. These findings could have a substantial impact on anticancer radiotherapy; thus, next-generation radiotherapy may need to be combined with stem cell therapy. Such prophylactic treatment has the potential to improve wound healing of irradiated tissue and the clinical outcomes of reconstructive surgery after radiotherapy (*Figure 5*) (90).

Peripheral nerve regeneration

Successful nerve regeneration requires a high level of

coordinated interactions between the cells involved in regeneration, extracellular matrix components, and nerve growth factors. The essential point of peripheral nerve regeneration therapy is to restore peripheral sensory and motor functions as soon as possible after injury (91-93). With the development of stem cell biology, the dream of cell therapy through relocation of effective cells to the site of nerve damage at the right time and place and in the required amounts is gradually turning into reality. Many cell types are involved in maintenance and regeneration of the peripheral nervous system, but Schwann cells (SCs) play the most pivotal roles (93-95), and there is also no alternative to SCs for the unique function of myelinization. Thus, treatment of peripheral nerve injuries has focused on using SCs as cell-based therapy. However, isolating SCs has significant drawbacks in clinical application, including the main disadvantage of sacrificing a functional nerve. Therefore, there is a need for technological advances in methods to acquire SCs, including lineage-specific differentiation and reprogramming to generate SCs from various cell types (96,97). Among many options, ADSCs are promising as alternatives due to easily accessible harvesting in adequate amounts through a minimally invasive procedure. For instance, rat ADSCs can be induced into SC-like cells (SCLCs) (22,98,99), and this method can be applied to human ADSCs. However, strong evidence that SCLCs have the same functional effects as genuine SCs, such as myelin protein formation, has yet to be obtained (100).

More recently, the idea that ADSCs do not necessarily need to be differentiated into SCLCs has been proposed for clinical application (22,101,102). In fact, the neuroregenerative effects of undifferentiated ADSCs (uADSCs) have been confirmed in many studies, including by our group (13,101-103). It is gradually becoming understood that uADSCs secrete trophic factors and cytokines, and application of these functions to nerve disorder therapy is regarded as cell supportive therapy (13,103,104). We found that uADSCs produce and release abundant factors that promote peripheral nerve regeneration (BDNF, NGF, VEGF, GGF, IGF, HGF), and that these ADSC-derived factors promote SC survival and proliferation, as well as dorsal root ganglion cell survival and protrusion. These effects were comparable to those of astrocytes and SCs (103). Moreover, the ability of uADSCs to produce and release factors related to peripheral nerve regeneration was maintained regardless of the site of collection or age of the ADSCs. These results suggest that uADSCs release peripheral nerve regeneration-related factors *in vitro* to a similar extent to that of dADSCs. Furthermore, in 2015, we used Cre/Floxed-reporter mice to track and mark neural crest-derived ADSCs, and found that a portion of ADSCs comprised neural crest cell-derived cells, after which we examined the biological properties of each cell population (29). These results suggest that uADSCs may already contain a population of cells with specific neuroregenerative properties.

In 2017, our research group transplanted ADSCs and SCs with gelatin hydrogel tubes at an artificially blunted sciatic nerve lesion in mice. We used Cre-loxP-mediated fate tracking to visualize survival *in vivo* of transplanted ADSCs and to investigate whether they differentiated into a SC lineage at the peripheral nerve injury site. The ADSCs were found to promote regeneration of axons, formation of myelin, and restoration of denervation muscle atrophy to levels comparable to those achieved by SC transplantation. The ADSCs survived for at least four weeks after transplantation, without differentiating into SCs (105). In this way, it was proven that cell supportive therapy contributes to peripheral nerve regeneration by functioning as a molecular factory that produces and releases nerve regeneration-related factors. The scope of application of ADSCs for nerve regeneration medicine may extend beyond peripheral nerve damage, diabetes-induced neuropathy, and neurodegenerative diseases to spinal cord and brain damage (105-109). There are still many problems to be solved, such as oncological risk and the time and cost required for cell preparation, but future development of cell-based regenerative therapy using ADSCs is very likely to lead to novel clinical applications in peripheral nerve repair therapies.

Ischemic diseases

ADSCs are a type of MSC that may differentiate into fat, cartilage, bone, and smooth muscle after transplantation, but the evidence for this process is less than satisfactory. Differentiation into other cell types is a matter of further debate. Accordingly, the primary mechanism of the function of ADSCs in therapy for internal organs, blood vessels, skin, and nerves seem to be a paracrine effect (110,111). However, the therapeutic value of the ADSC secretome is limited without long-term cell retention and engraftment after transplantation. Therefore, various strategies have been proposed, including genetic, pharmacological, physiological, physical, and cytokine preconditioning,

and tissue engineering, to modulate and stimulate ADSCs to release specific trophic factors (112-116). There are several methods that promote therapeutic paracrine and immunomodulatory properties, but optimal preconditioning and the exact triggering and regulatory mechanisms remain elusive, and the functional proteins and RNAs in the secretome are yet to be completely identified (111,113,117). Also, it is still an open question whether paracrine and immunomodulatory therapy alone is sufficient for cardiac repair. Therefore, further studies are needed to determine these pivotal mechanisms and to establish better therapeutic approaches.

Periodontal tissue regeneration

Bacterial biofilms formed on dental root surfaces occasionally cause periodontitis, which irreversibly destroys periodontal tissues such as alveolar bone, root cementum, periodontal ligament, and gingiva. As a result, oral functions such as mastication and occlusion are impaired, ultimately forcing the tooth to be removed (118). Normal periodontitis treatment primarily consists of coping therapies such as biofilm removal and debridement of necrotic root tissue. However, these treatments are often insufficient for patients with severe periodontitis. Curative treatment of periodontal disease requires regeneration of destroyed periodontal tissues such as alveolar bone, cementum, and periodontal ligament. Therefore, as a clinical approach for patients with severe periodontitis, development of therapies to induce periodontal tissue regeneration using MSCs is currently under investigation (119). MSC transplants isolated from the pulp or periodontal ligament have been investigated in preclinical and clinical trials, and their therapeutic efficacy has been confirmed (120,121). However, these treatments require wisdom teeth that can be extracted, and these teeth must be unaffected by decay or periodontitis, which greatly limits the number of patients. As a replacement, ADSCs have been shown to have therapeutic efficacy comparable to that of pulp stem cells (122-125). This new treatment method is expected to promote periodontal tissue regeneration with various growth factors secreted from ADSCs, and also to regenerate new blood vessels in damaged tissues.

Sawada and colleagues showed that autologous transplantation of ADSCs is effective for periodontal tissue regeneration in an experimental periodontitis model in beagles, and found that factors released from ADSCs promote periodontal ligament cell differentiation (123). Requicha *et al.* demonstrated that the proposed double-layer scaffold supports proliferation and selectively promotes osteogenic differentiation of ADSCs seeded onto functionalized mesh, which means the 3D structure and asymmetric composition of the scaffold in combination with ADSCs may provide an alternative therapy to treat periodontal defects more efficiently (124). Takedachi *et al.* conducted a single-arm, exploratory Phase I clinical trial of the therapeutic effect of ADSCs in 12 patients with periodontal disease and found that the depth of periodontal pockets was reduced and alveolar bone regeneration was induced. The next challenge is that, unlike other diseases, in which a single administration of MSCs is sufficient, several surgeries are needed for periodontal tissue regeneration, and countermeasures against adverse effects are required. Therefore, it will be desirable to study the use of allogeneic ADSCs in the future (125).

Treatment of internal organ failure and infection

ADSCs have been proven in many studies to have immunomodulatory, proangiogenic, neurotrophic, and epithelization activities, and can potentially be used for neurodegenerative, cardiovascular, respiratory, inflammatory and autoimmune diseases, as well as wound healing. More recently, the indication has been further expanded into new areas, such as treatment of internal organ failure, including the liver and lungs, and related pneumonia. Hepatocyte dysfunction often leads to intractable liver diseases, and orthotopic liver transplantation is currently the only treatment available for patients with end-stage liver disease. However, this method is limited due to the invasiveness associated with the need for donor organs. Hepatocyte transplantation may be an alternative to full liver transplantation for liver failure, and recent studies have suggested that stem cell-derived hepatocytes could be used as therapeutic liver cells (126-128). Some studies have examined the possibility of therapeutic application of liver fibrosis using the antifibrotic effect of undifferentiated ADSCs before they are induced to differentiate (129-131).

COVID-19 is a viral pneumonia that is currently having a huge impact worldwide. This disease has the potential to cause multiple organ damage and there is currently no specific treatment or drug available. However, several positive findings for the application of stem cells as treatment for COVID-19 have now been reported (132-134) and clinical trials have been started to investigate the safety and efficacy of stem cell or stem cell-derived exosome

transplantation therapy for patients with COVID-19. Indications under investigation are COVID-19-related diseases such as severe pneumonia, respiratory failure, ARDS, and pulmonary fibrosis (135). Adipose tissue has yielded the most promising results among use of stromal vascular fraction (SVF), placental cells, natural killer cells and platelet lysates (134,136,137), and aerosol inhalation and intravenous routes are being investigated as methods of administration (138). Thus, ADSCs, SVF, and other adipose tissue-derived products, including micronized fat tissue, are likely to become more recognized as a relatively safe way to suppress immune responses in severe COVID-19-related diseases associated with cytokine storm and other conditions (135-137). First, however, it is important to have a standardized and universal protocol for administration and a detailed mechanistic understanding of the effects of these therapies. In this regard, there is a particular need for studies with a high level of evidence, especially prospective randomized controlled trials that include ethical considerations.

Future challenges in clinical application of ADSCs

The emergence of ADSC therapy provides a novel means for tissue regeneration. Numerous clinical and preclinical studies have shown the vital role of ADSCs in reconstructing and repairing target organs, such as bone, cartilage, myocardium, liver, nervous system, and skin. ADSCs are MSCs that may differentiate into fat, cartilage, bone, and smooth muscle after transplantation, but there is limited evidence for this behavior. Differentiation into other cell types is also in question. A paracrine mechanism seems to underlie the function of ADSCs in therapy for internal organs, blood vessels, skin, and nerves. However, the therapeutic value of trophic factors derived from ADSCs is limited without long-term cell retention and engraftment after transplantation. Strategies including genetic, pharmacological, cellular and tissue engineering, use of biomaterials, and cytokine preconditioning have been proposed to modulate and stimulate ADSCs to release the secretome for a certain period. These methods enhance the therapeutic value of the secretome, but optimal preconditioning and the triggering and regulatory mechanisms are uncertain, and the functional proteins and RNAs in the secretome are not fully understood. It is also unclear if secretome therapy using ADSCs alone is sufficient. Therefore, further studies are needed to evaluate these mechanisms and develop better therapeutic approaches. Additionally, many safety issues need to be addressed, from the preparation of ADSCs to their application, and additional studies are required to identify appropriate scaffolds and potent bioactive factors to induce an optimal microenvironment for ADSC proliferation and differentiation. Long-term studies are needed to confirm implant-tissue interactions, resorption and hierarchical structure, and finally to produce a clinically viable method. Due to differences between preclinical studies and clinical trials, the oncogenicity of ADSC differentiation also warrants further research. Despite the current challenges, the remarkable pace of progress in this field suggests that ADSC-based approaches will play increasingly important roles in regenerative medicine.

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