

REVIEW

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The therapeutic effect of adipose-derived stem cells on soft tissue injury after radiotherapy and their value for breast reconstruction

Haojing Tang, Yufei He, Zhuokai Liang, Jian Li, Ziqing Dong* and Yunjun Liao* 

Abstract

Background: Postmastectomy radiotherapy is considered to be a necessary treatment in the therapy of breast cancer, while it will cause soft tissue damage and complications, which are closely related to the success rate and effectiveness of breast reconstruction. After radiotherapy, cutaneous tissue becomes thin and brittle, and its compliance decreases. Component fat grafting and adipose-derived stem cell therapy are considered to have great potential in treating radiation damage and improving skin compliance after radiotherapy.

Main body: In this paper, the basic types and pathological mechanisms of skin and soft tissue damage to breast skin caused by radiation therapy are described. The 2015–2021 studies related to stem cell therapy in PubMed were also reviewed. Studies suggest that adipose-derived stem cells exert their biological effects mainly through cargoes carried in extracellular vesicles and soluble secreted factors. Compared to traditional fat graft breast reconstruction, ADSC therapy amplifies the effects of stem cells in it. In order to obtain a more purposeful therapeutic effect, proper stem cell pretreatment may achieve more ideal and safe results.

Conclusion: Recent research works about ADSCs and other MSCs mainly focus on curative effects in the acute phase of radiation injury, and there is little research about treatment of chronic phase complications. The efficacy of stem cell therapy on alleviating skin fibrosis and its underlying mechanism require further research.

Keywords: Breast cancer, Breast reconstruction, Postmastectomy radiotherapy, Adipose-derived stem cells, Stem cell therapy

Introduction

Radiotherapy plays an important role in the treatment of malignant tumors. Postmastectomy radiotherapy (PMRT) is a more commonly performed and safer option. An early comprehensive meta-analysis [1] analyzed the data of 20,000 early breast cancer patients in a breast

cancer clinical trial and showed that PMRT reduced the local regional recurrence rate of lymph node-positive patients from 27% to 9% and had little effect on overall survival during the first decade or so.

However, radiotherapy inevitably causes soft tissue damage and complications, which are closely related to the success rate and effectiveness of and satisfaction with breast reconstruction [2–4]. After radiotherapy, cutaneous tissue becomes thin and brittle, and its compliance decreases. Consequently, it is often impossible to achieve good results when a dilator is simply used for reconstruction. Krueger et al. [5] reported that breast cancer

*Correspondence: doctordongziqing@hotmail.com; yunjun1000@sina.com

The Department of Plastic and Cosmetic Surgery, Nanfang Hospital, Southern Medical University, 1838 Guangzhou North Road, Guangzhou 510515, Guangdong, China



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patients who received radiation therapy had a higher probability of failure and complications during breast reconstruction with dilators or implants than those who did not receive radiation therapy, with failure rates of 37% (7 of 19 cases) and 8% (5 of 62 cases), respectively. Nava et al. [6] showed that the probability of capsular contraction upon breast reconstruction using implants is significantly increased if tissues are undergoing radiotherapy. In addition, PMRT has a considerable impact on the success rate of breast reconstruction after musculocutaneous flap transplantation. The complication rate with the transverse rectus abdominis myocutaneous flap, which has the best cosmetic effect after reconstruction, is as high as 63%, which is much higher than the complication rates with other reconstruction procedures using a myocutaneous flap [7, 8].

The decision of whether to perform radiotherapy as well as the sequence of radiotherapy and breast reconstruction is closely related to the recurrence of breast cancer and the quality of breast reconstruction. The sequelae of radiotherapy hinder reconstruction, and clinicians must therefore make a trade-off between safety and reconstruction quality. Therefore, research of how to prevent skin and soft tissue damage hindering breast reconstruction after radiotherapy is of great value.

In recent years, autologous fat grafting has attracted much attention based on its small residual scar and convenience. There are gradually some studies indicated that autologous fat grafting can partially improve the problem of poor skin compliance after radiation fibrosis [9–11]. ADSCs are believed to be the most important and potent fat component [12]. It is of great value to further explore the therapeutic effect and application prospect of ADSCs in radiation tissue injury for the improvement of breast reconstruction treatment methods.

The basic biological mechanism by which radiotherapy causes cell damage

Direct cellular damage

Radioreistance varies according to the stage of the cell cycle. Cyclin-dependent kinase inhibitors, such as P16, P21, and P53, are common checkpoint proteins expressed during the radiation-resistant phase.

In G1 phase, these inhibitors are expressed to ensure that the cell successfully enters the DNA synthesis phase (S phase). Once the cell enters S phase, these inhibitors and enzymes responsible for DNA repair are over-expressed to ensure the accuracy and integrity of DNA synthesis. Due to residual levels of S phase enzymes and cyclin-dependent kinase inhibitors, cells in G2 phase are also considered to be radiation-resistant.

In early M stage, chromosomes condense, and DNA is very susceptible to radiation damage. In general,

there is a lack of repair mechanisms in M phase, and condensed and concentrated DNA is a perfect target for ionizing radiation. Therefore, M phase cells, i.e., dividing cells, are particularly radiosensitive [13].

Owing to this characteristic, cancer cells are the main target of radiotherapy. However, in addition to cancer cells, some normal cells that divide vigorously, such as stem cells, basal skin cells, and gastrointestinal mucosa cells, are also targeted by ionizing radiation. Unrepaired DNA damage often induces apoptosis and cell cycle arrest [14, 15]. Cell apoptosis owing to radiation can be mediated by either p53 or the sphingomyelin/ceramide pathways [16, 17]. In addition, radiation induces mitochondrial fission by activating the MAPK pathway, which promotes the release of apoptotic factors such as cytochrome c [18]. Endothelial cell damage and apoptosis induced by radiation can lead to vascular leak, edema, and the increase in inflammation [14]. Difficulties in repair and regeneration caused by these changes set obstacles to breast reconstruction.

Indirect cellular damage

Reactive oxygen species (ROS) are an important cause of indirect damage induced by radiation. Ionizing radiation causes the transfer of electrons when it penetrates cells, leading to generation of unstable ROS [19]. In addition to indirectly damaging DNA in the nucleus, ROS also react with key proteins and lipids involved in cell metabolism [20, 21].

Extensive research has found that radiation-induced damage arises at sites outside the irradiated area [22]. This indicates that direct damage of cellular genetic material by penetration of radiation into the nucleus is not a prerequisite for cell damage. Cells damaged by radiation affect bystander cells and cause damage, called the radiation-induced bystander effect, through oxidative metabolism, gap junctions between cells, and paracrine substances [23]. Recent studies have reported that the level of gap junctions is lower between cancer cells than between normal cells, which may mean that it is difficult to specifically kill cancer cells using the bystander effect of radiotherapy [24]. The expansion of radiation damage and poor prognosis caused by the bystander effect are still worthy of attention.

In addition, the radiation-induced inflammatory response is also considered to be important for indirect injury. The acute inflammatory response can cause secondary tissue damage, and the chronic inflammatory response is closely related to radiation-induced soft tissue fibrosis [25].

Types of soft tissue damage caused by radiotherapy and the underlying mechanisms

In the short term, cell damage caused by ionizing radiation induces an acute inflammatory response, and the associated inflammatory cells are mainly neutrophils and macrophages [26]. Adipocytes that perform certain endocrine functions also exhibit transcriptional regulation of hypoxia-inducible factor (HIF)-1 α and secrete a large amount of inflammatory mediators such as vascular endothelial growth factor (VEGF) and interleukin (IL)-6 [27]. The type of acute reaction that appears during the early stage of irradiation depends on the dose and duration of irradiation and is mainly manifested as inflammatory erythema, desquamation, and edema caused by vascular and lymphatic lesions [7].

According to Koenig et al. [28], in addition to acute skin reactions such as transient erythema during the early stage of irradiation, permanent epilation and desquamation can occur approximately 3 weeks after 7 Gy irradiation. Skin atrophy can occur within 12 weeks to 1 year after 10 Gy irradiation, and telangiectasia and pathological fibrosis such as induration may occur after more

than 1 year. In severe cases, skin necrosis may occur in the late stage.

Ultrastructural analysis showed that the basal membrane of capillary vessels duplicates and their lumens are ectatic after radiotherapy. Endothelial cells are rich in cytoplasm, including macropinocytotic vesicles and a large number of Weibel-Palade bodies. Many adipocytes are necrotic. A large amount of accumulated collagen and debris from necrotic adipocytes in connective tissue is visible [29].

Acute inflammation and endothelial injury

The acute phase response is closely related to endothelial cell damage caused by ionizing radiation (Fig. 1). Ionizing radiation-induced apoptosis can release damage-associated molecular patterns (DAMPs), which can act on various pattern recognition receptors (PRPs), not only to activate endothelial cells to switch to a pro-inflammatory phenotype, but also to recruit a series of immune cells to participate in the inflammatory response [30, 31]. Activated endothelial cells secrete cytokines to recruit immune cells and up-regulate the expression

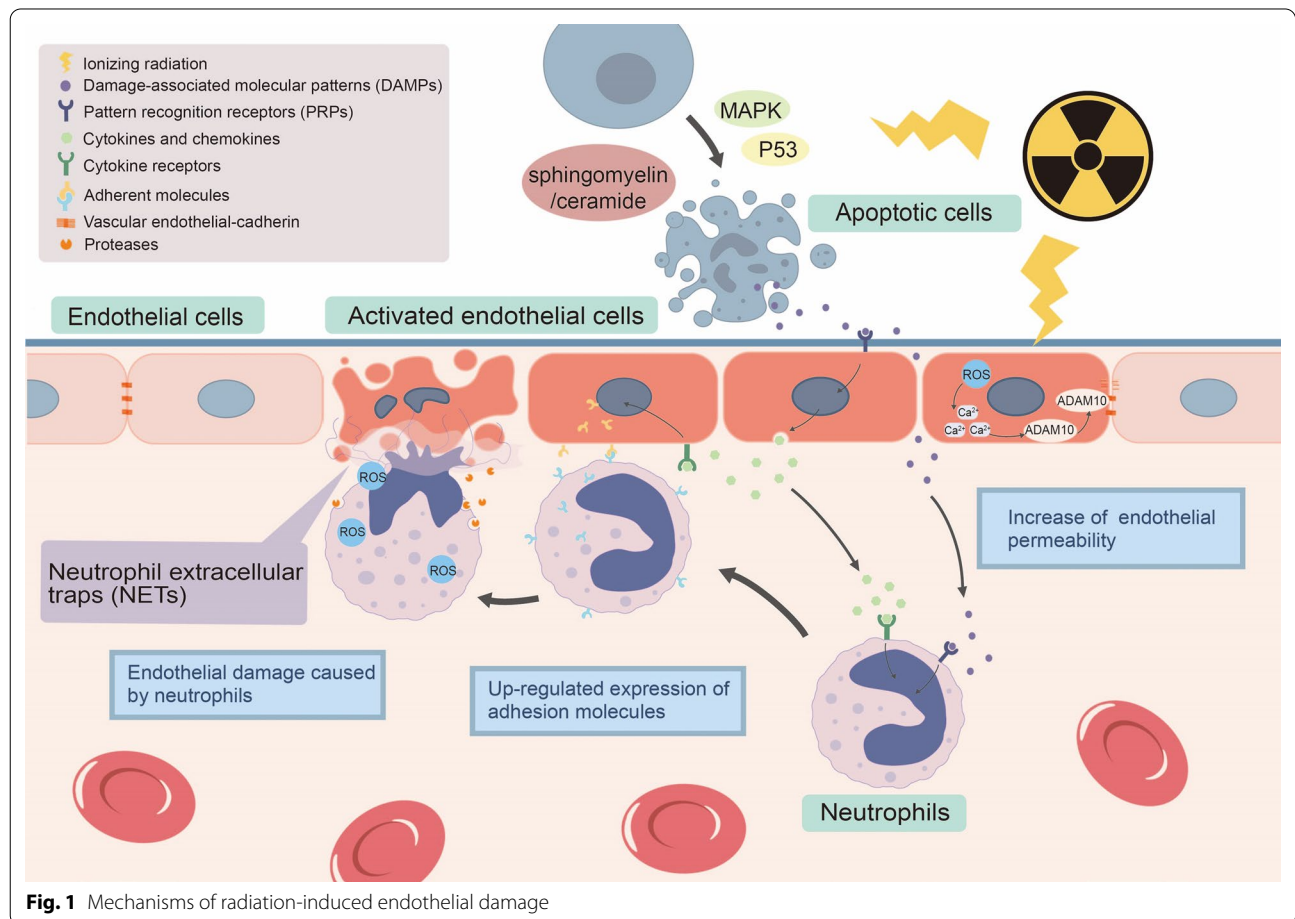


Fig. 1 Mechanisms of radiation-induced endothelial damage

levels of adhesion molecules simultaneously to promote the interaction between endothelial cells and immune cells, which results in inflammatory damage to endothelial cells [32]. Protein kinase C (PKC) family is expressed in various cells and is thought to be an important role of neutrophilic and endothelial pro-inflammatory signaling [33, 34]. In neutrophils, PKC δ can activate the NF- κ B pathway, which is involved in the secretion of cytokines and chemokines and the production of ROS [35, 36]. In endothelial cells, PKC δ can activate the NF- κ B pathway, which is involved in up-regulating the expression of adhesion molecules and promoting the release of inflammatory mediators [34, 37].

Neutrophils play an important role in endothelial injury during acute inflammatory response. The first step in causing damage is to enhance the interaction between neutrophils and endothelial cells. Normal neutrophils have low expression of α 4-integrin. Neutrophils under the action of multiple inflammatory factors up-regulate the expression of α 4-integrin and enhance the interaction with endothelial cells by acting on VCAM-1 on the surface of endothelial cells. In addition, cytokines such as TNF- α and IL-1 also up-regulate the expression of adhesion molecules such as vascular cell adhesion molecular 1 (VCAM-1) and intercellular adhesion molecular 1 (ICAM-1) [37–39]. After completing the adhesion process, neutrophils exert their immune functions and simultaneously damage endothelial cells by secreting proteases, generating reactive oxygen species and forming Neutrophil extracellular traps (NETs) [40–43].

Endothelial cells stimulated by ionizing radiation and inflammatory signals also increase permeability. ROS produced by ionizing radiation raise the concentrations of intracellular Ca²⁺. The increase in intracellular Ca²⁺ activates a disintegrin and metalloprotease 10 (ADAM10), finally causing the degradation of vascular endothelial-cadherin (VE-cadherin) and increasing the endothelial permeability [44–47]. It can be used to explain edema in the acute phase and as one of the pathological basis of fibrosis in the chronic phase.

Lymphedema

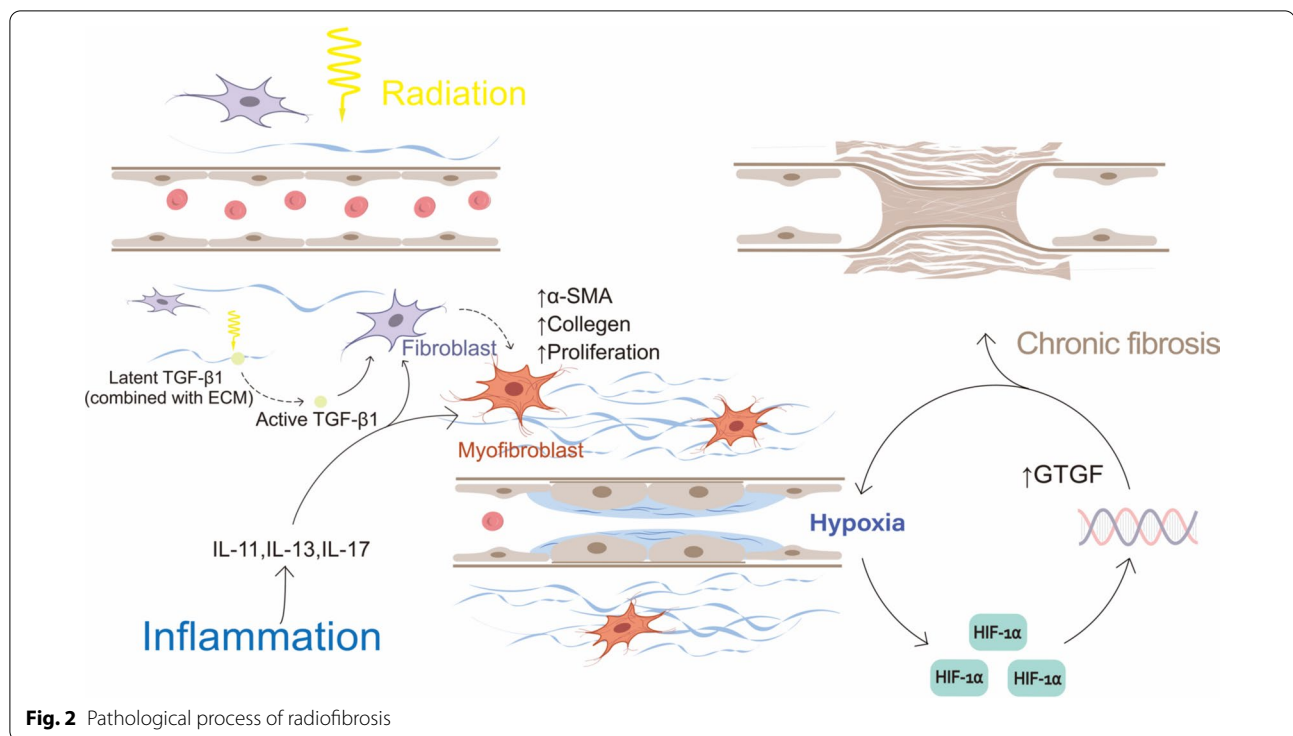
As the most commonly reported complication of breast carcinoma management, the incidence and severity of lymphedema are closely related to axillary radiotherapy and axillary lymph node dissection. However, for most invasive breast cancers, axillary treatment remains indispensable for safety reasons [48]. Three types of lymphedema have been described in breast carcinoma patients, namely arm, truncal, and, in patients who receive breast-conserving therapy, breast lymphedema [49].

There is much speculation and research about the mechanism underlying radiation-induced lymphedema. However, contrary to initial assumptions, early studies performed *in vitro* and *in vivo* in humans and other mammals demonstrated that lymphatic vessels are relatively insensitive to radiation [50]. By contrast, lymph nodes are sensitive to radiation [51]. Therefore, lymphedema during breast cancer treatment is attributable to surgical severing of lymphatic vessels and structural changes around lymphatic vessels caused by radiation fibrosis [52]. Ogino et al. [53] elucidated the pathological process of radiotherapy-induced lymphedema. Radiotherapy transforms type I collagen from a random to parallel arrangement and decreases the levels of extracellular matrix (ECM) and type III collagen. The resulting denser spatial structure prevents lymphatic vessels expanding properly and thus hinders lymphatic return and mediates the occurrence of lymphedema.

Pathological fibrosis and contracture

Radiation-induced fibrosis results in progressive functional and cosmetic impairment, which is a common late complication of PMRT (Fig. 2). Radiation-induced oxidative lysis releases transforming growth factor β 1 (TGF β 1) originally bound to the ECM in a latent form [54]. Owing to the synergistic effect of TGF β 1 and other inflammatory factors such as IL-11, IL-13, and IL-17, fibroblasts that were originally in a static state are transformed into myofibroblasts that exuberantly secrete ECM [26, 55].

Due to the body's repair mechanism, vascular endothelial cells damaged by radiation exhibit high levels of intracellular trafficking and transport between themselves and their environment and high permeability, and vascular basement membrane replication and lumen expansion are also observed. Therefore, the acute phase of injury is mainly manifested as an inflammatory reaction of blood vessels, such as erythema and edema [26]. This leads to deposition of ECM around blood vessels and stenosis of lumens, resulting in ischemia and hypoxia of local tissues. Simultaneously, the shrinkage of the vessel bed caused by radiation damage exacerbates ischemia and hypoxia, which intensifies tissue damage, leading to a vicious circle [29, 56]. Hypoxia caused by radiation induces accumulation of HIF-1 α , which is degraded by the ubiquitin-proteasome pathway under normoxic conditions. The transcription factor HIF-1 α is the most important regulator of cellular responses to hypoxia and regulates the transcriptional activities of many genes that play important roles in regulating glucose metabolism and promoting angiogenesis, cell migration, ECM deposition, and fibrosis. Fibrosis-related proteins that are transcriptionally regulated by HIF-1 α include lipoxidase and



connective tissue growth factor [57–60]. In the short term, these changes are conducive to tissue repair, but long-term expression of HIF-1 α may cause excessive tissue repair and fibrosis. Relying on the body's natural repair mechanism without treatment can lead to severe fibrosis or tissue necrosis.

In addition, radiotherapy can cause an abnormal morphology of fibroblasts, such as a flattened and enlarged morphology, as well as changes in their biological behavior and synthetic function, leading to modulation of important signaling pathways and adaptive dysfunctions. Fibroblasts injured by radiotherapy exhibit inhibited proliferation but increased migration, invasiveness, adhesion, and contractility. At the same time, activation of the HIF-1 α pathway also initiates a local fibrotic response [22]. A study by Rinkevich et al. [61] indicated that fibrosis, during wound healing or radiation fibrosis, in cutaneous tissue is caused by the unique and local lineage of resident fibroblasts, without the contribution of fibroblasts from circulating or other lineages.

Decreased skin compliance due to radiation fibrosis may hinder breast reconstruction, for example, may reduce the retention of grafted fat and increase the probability of capsular contracture in breast implant reconstruction [4]. Elevated skin tension also exacerbates scarring, which greatly affects reconstruction and breast esthetics [62].

The therapeutic value of adipose-derived stem cells (ADSCs) for breast reconstruction after radiotherapy

In the process of repairing and rebuilding, it is necessary to solve the problem of lack of breast volume and the problem of cell dysfunction and tissue damage caused by radiotherapy. Autologous fat grafting has attracted much attention for these two advantages. It can obviously improve skin tissue suffered from irradiation by improving the compliance and thickness of skin and tissue adhesion [9–11, 54, 63]. A systematic review and meta-analysis published in 2020 confirmed the efficacy and safety of autologous fat transfer for filling defects and improving fibrosis and scar-related conditions [64]. ADSCs are believed to be the most important and potent fat component. Compared with other cell types, such as bone marrow-derived stem cells, ADSCs are favored in the fields of wound healing and tissue regeneration because they are abundant in fat tissue and easily accessible. Additionally, ADSCs appear to be less immunogenic and more genetically stable in long-term culture compared with BMSC [65]. In a clinical study, Rigotti et al. [29] purified Coleman fat to obtain stromal vascular fraction (SVF) and transplanted it into patients who had received radiotherapy. The results indicate that SVF of adipose tissue can induce construction of a new microcirculation.

This phenomenon is probably due to the multi-differentiation potential and paracrine effect of ADSCs [66] (Fig. 3).

Proliferation and differentiation of ADSCs

ADSCs, a type of mesenchymal stem cell (MSC), have the potential of multi-directional differentiation and can differentiate into adipocytes, chondrocytes, osteocytes and endothelial cells. Under specific conditions, ADSCs can replace damaged cells through proliferation and differentiation to repair tissue damage [67, 68].

The mechanisms regulating the proliferation and differentiation of ADSCs are not fully understood. Lin et al. [69] indicated that hypoxia can promote ADSCs differentiation into vascular smooth muscle cells (VMSCs) by mediating Mettl3 gene expression. Isabelle et al. [70] elucidated that Col V can enhance the proliferation and differentiation of rabbit ADSCs. Besides, after receiving the stimulation of TGF-β3 and BMP-6, the ADSCs increase the expression of the cartilage formation gene. The study from Denver et al. [71] manifests that the endogenous Notch signal may have the potential to regulate

the proliferation, differentiation and bone potential of ADSCs.

The paracrine effect of ADSCs

ADSCs can secrete various cytokines, chemokines, growth factors, and paracrine molecules in extracellular vesicles and promote cell survival, modulate the inflammatory reaction, and thus enhance regeneration of injured tissue [19, 72].

Many studies have explored the role of MSCs, represented by ADSCs, in repair of radiation injury and other soft tissue injuries (Table 1).

ADSCs can increase proliferation and survival of specific stem or progenitor cells in tissues and organs [73] and promote angiogenesis and lymphangiogenesis in damaged tissue [74–76]. The mechanism underlying ADSC-mediated promotion of cell proliferation is unclear, but studies suggest that activation of the AKT, ERK, and Wnt/β-catenin signaling pathways is closely related to this effect [73, 77–79]. Wnt4 carried in exosomes released by ADSCs induces β-catenin activation and elicits a proangiogenic effect in endothelial cells

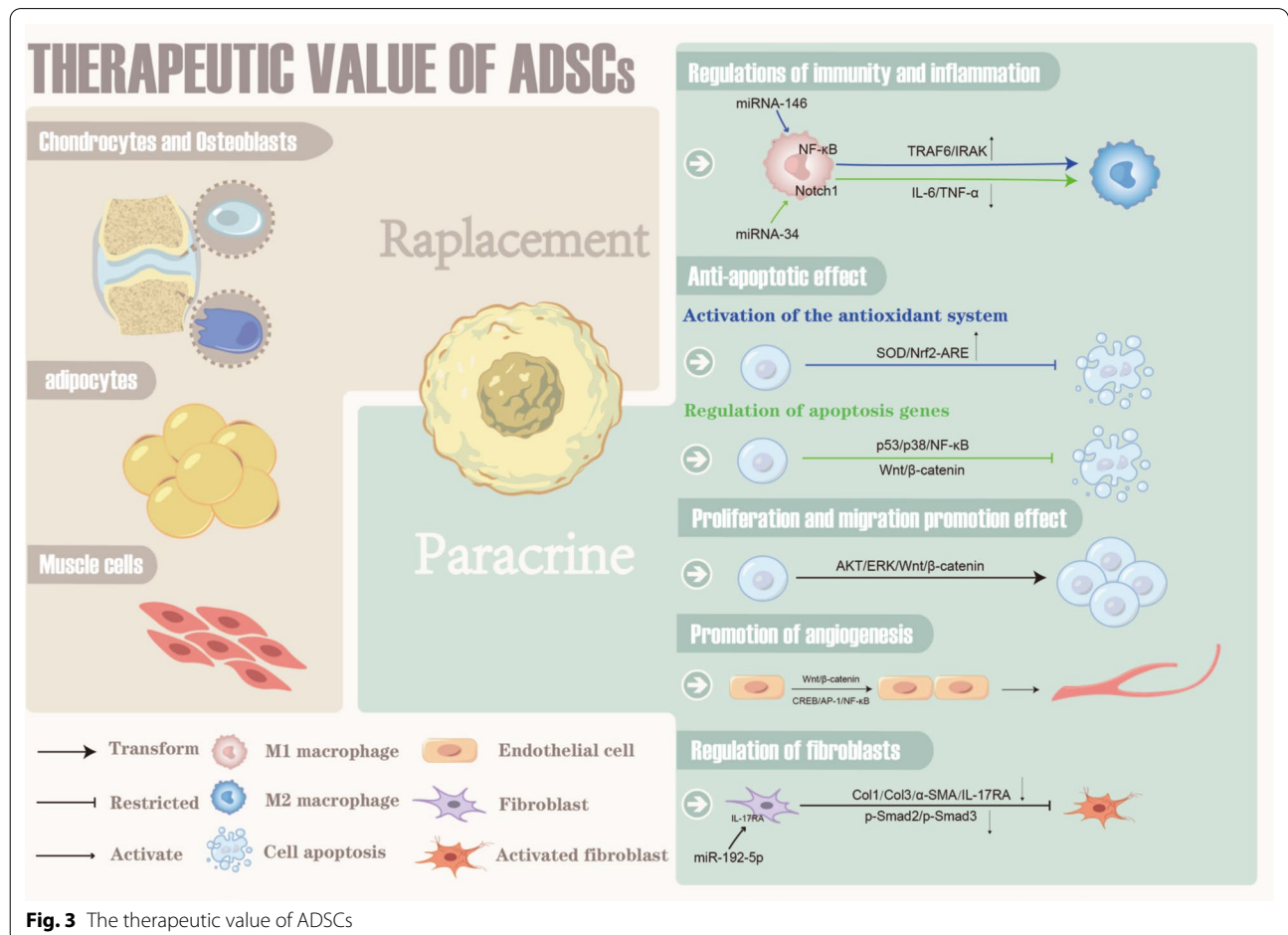


Fig. 3 The therapeutic value of ADSCs

Table 1 HMEC: Human microvascular endothelial cell, HUVEC: Human umbilical vein endothelial cell, HaCaT cell: Human dermal lymphatic endothelial cell, LEC: Lymphatic endothelial cell, hucMSC-Evs: Extracellular vesicles of human umbilical cord mesenchymal stem cells, ADSC-MVs: Microvesicles of ADSCs, PRP: Platelet-rich plasma, HKFs: Human keloid fibroblasts, ADSC-CM: Adipose-derived stem cell concentrated conditioned medium, cGVHD: Chronic graft-versus-host disease, PDGF-ADSC-Evs: Extracellular vesicles of PDGF-treated ADSCs, MSC-Exos: Exosomes of mesenchymal stem cells, BM-MSC: Bone marrow-derived mesenchymal stem cell, hucMSC-Exos: Exosomes of human umbilical cord mesenchymal stem cells, ADSC-Exos: Exosomes of ADSCs, MSC-Evs, Extracellular vesicles of mesenchymal stem cells, α -SMA: α -smooth muscle actin, ESCs: Endometrial epithelial cells

Model	In vivo/in vitro	Method	Therapeutic effect	Reference
Irradiation model in rats	In vivo	BM-MSC-derived exosomes	Regulates differentiation and survival of other mesenchymal stem cells Anti-oxidative stress Anti-apoptotic Angiogenesis of endothelial cells	Zuo et al. [73] Tatiana et al. [74]
SCID mice	In vivo	Transplantation of HMECs treated with PDGF-ADSC-Evs		
HUVECs, HaCaT cells, fibroblasts, and wound healing model in BALB/c mice	Both	In vitro: co-culture with ADSC-MVs In vivo: subcutaneous injection of ADSC-MVs	Promotes proliferation: promotes re-epithelialization, collagen deposition, and angiogenesis at the wound site	Ren et al. [77]
Model of skin lesions under oxidative stress using HaCaT cells	In vitro	Co-culture of HaCaT cells with ADSC-Exos	Promotes proliferation and migration Anti-apoptotic	Ma et al. [78]
Skin lesion model exposing to hydrogen peroxide (H_2O_2)	In vitro	Co-culture of HaCaT cells with ADSC-Exos	Promotes proliferation and migration Anti-apoptotic	He et al. [79]
Skin burn model in rats	In vitro	Co-culture of HUVECs with hucMSC-Exos	Angiogenesis of endothelial cells	Zhang et al. [80]
cGVHD mouse model	In vivo	Intraperitoneal injection of hucMSC-Evs	Regulates immunity: suppresses activation of the immune response in macrophages and B cells	Guo et al. [82]
HKFs and hypertrophic scar model in rabbit ear	Both	Transplantation of lyophilized ADSC-CM combined with a polysaccharide hydrogel	Regulates associated cellular behavior: down-regulates α -SMA expression in HKFs in a dose-dependent manner to prevent hypertrophic scarring	Zhang et al. [83]
Ultraviolet irradiation model in mice	Both	In vitro: co-culture with MSC-Exos In vivo: injection of MSC-Exos	Anti-oxidative stress	Wang et al. [93]
SJL mice	Both	In vitro: co-culture with MSC-Ex In vivo: intravenous injection of MSC-Evs	Anti-apoptotic. Stimulates bone marrow hematopoietic cells to restore hematopoiesis and reverse radiation-induced apoptosis	Wen et al. [94]
HDLECs	In vitro	Co-culture with ADSCs	Promote proliferation and migration of LECs	Sajo et al. [100]
Secondary lymphedema model in C57BL/6J mice	In vivo	Transplantation of ADSCs	Promotes proliferation of LECs and improves fibrosis and the expansion capacity of lymphatic vessels	Ogino et al. [53]
Radiation-induced vaginal injury in rats	In vivo	Implantation of a protein scaffold loaded with ADSCs into injury sites	Promotes proliferation: promotes regeneration of vaginal epithelial cells and repairs and improves vaginal stenosis and contractures of vaginal tissue	Ye et al. [101]
Wound healing model in C57BL/6 mice	In vivo	Transplantation of PRP combined with ADSCs	PRP can promote migration of ADSCs through the Rho GTP-LIMK1-Cofilin signaling pathway	Zhang et al. [102]

[80]. In addition, vesicles released by ADSCs can directly carry nuclear factor kappa-B (NF- κ B) and thereby activate the NF- κ B signaling pathway in endothelial cells and promote angiogenesis [81]. ADSCs can also regulate the biological behavior of immune cells and fibroblasts and thereby prevent radiation fibrosis to a certain extent [82–84]. In the TGF- β 1-induced endometrial fibrosis damage model, ADSC-Exosomes can regulate the miRNA-150-5p by raising the expression level of lncRNA-MIAT, which is related to fibrosis [85]. Several studies have shown that some microRNAs (miRNAs) and cytokines carried by ADSC-derived extracellular vesicles can alter the secretion profile of macrophages and transform their phenotype [86–90]. For example, miRNA-146 and miRNA-34 can induce macrophages to switch from a M1- to M2-like phenotype. MiRNA146 [91] upregulates M2-related genes such as *TRAF6* and *IRAK* through the NF- κ B pathway, while miRNA-34 [92] inhibits expression of the M1-related genes *IL-6* and *TNF- α* by targeting the Notch1 pathway. The anti-oxidative stress [93] and anti-apoptotic [94] effects of substances secreted by ADSCs are critical for repairing radiation-induced DNA damage in the acute phase and preventing the exacerbation of damage caused by the bystander effect. ADSC can effectively activate the antioxidant system, such as superoxide dismutase (SOD) [95, 96], Nrf2-antioxidant response element (ARE) pathway [97–99] and so on.

Repairing radiation damage with ADSCs: perspective and challenges

Studies suggest that ADSCs exert their biological effects mainly through cargoes carried in extracellular vesicles (exosomes or microparticles) and soluble secreted factors [19]. There are many types of cargoes, and it is insufficient to simply clarify the mechanism underlying the effects of stem cell therapy on radiation damage and the intertwined signaling network [103]. Generation of extracellular vesicles with a single phenotype using specific environmental stimuli or interventional methods and performing in vivo treatment with these vesicles can improve the efficacy and safety of stem cell therapy. Stem cells exposed to radiation highly express the CD29/CD81 complex, making it easier to isolate extracellular vesicles [104]. Treatment of ischemia-related injury can be improved using microvesicles derived from stem cells exposed to hypoxia [74]. Although ADSCs is easy to obtain from adipose tissues and is easy to cultivate in vitro, there are still some studies indicate that ADSCs transplanting and surviving in vivo need more complicated conditions. The survival of ADSCs after injection is not satisfying [105–107]. The co-transplantation between ADSCs and adaptive biomaterial scaffolds can provide an ideal environment for cell survival and promote the

adhesion, proliferation and differentiation of ADSCs. Use of a combination of ADSCs and PRP promotes wound healing, granulation, collagen deposition, and re-epithelialization [102]. Mixed implantation of cell scaffolds with good biocompatibility and ADSCs can prolong the duration of cytokine secretion by these cells [101]. A sheet of ADSCs can achieve better effects than injection of a suspension of ADSCs for treatment of chronic ulcer wounds. Prevention of pericyte escape to a certain extent by a sheet of ADSCs stabilizes angiogenesis, promotes granulation tissue reabsorption, and inhibits scarring. In addition, a sheet of ADSCs more obviously promotes regeneration of skin accessory structures such as hair follicles [108]. In addition, the recruitment of endogenous ADSCs is also a valuable research direction. Li et al. [109] applied the external force to regulate the tissue stiffness, which can affect the migration and differentiation of ADSCs.

Finally, most current research about ADSCs and other MSCs mainly focuses on curative effects in the acute phase of radiation injury, and there is little research about treatment of chronic phase complications. For breast reconstruction, most patients are in the chronic phase of radiation damage, and fibrosis is relatively severe. The efficacy of stem cell therapy to improve skin fibrosis and skin compliance and the underlying mechanism require further research.

Conclusion

ADSCs can promote wound healing and tissue repair. However, the mechanism by which ADSCs improve radiation injury and their ideal application method in this context must be studied. Further research is also needed to determine whether ADSC therapy is efficacious and safe for breast reconstruction after radiotherapy and, if so, to examine the underlying mechanism.

Abbreviations

PMRT: Postmastectomy radiotherapy; ROS: Reactive oxygen species; HIF-1 α : Hypoxia-inducible factor-1 α ; VEGF: Vascular endothelial growth factor; IL-6: Interleukin-6; DAMPs: Damage-associated molecular patterns; PRPs: Pattern recognition receptors; PKC: Protein kinase C; VCAM-1: Vascular cell adhesion molecular 1; ICAM-1: Intercellular adhesion molecular 1; NETs: Neutrophil extracellular traps; ADAM10: A disintegrin and metalloprotease 10; VE-cadherin: Vascular endothelial-cadherin; miRNA: Micro RNA; lncRNA: Long noncoding RNA; SOD: Superoxide dismutase; Nrf2: Nuclear factor erythroid 2-related factor-2; ARE: Antioxidant response element; ECM: Extracellular matrix; TGF β 1: Transforming growth factor β 1; SVF: Stromal vascular fraction; ADSCs: Adipose-derived stem cells; VMSCs: Vascular smooth muscle cells; MSC: Mesenchymal stem cell; NF- κ B: Nuclear factor kappa-B; HMEC: Human microvascular endothelial cell; HUVEC: Human umbilical vein endothelial cell; HaCaT cell: Human keratinocyte; HDLEC: Human dermal lymphatic endothelial cell; LEC: Lymphangial endothelial cell; hucMSC-Evs: Extracellular vesicles of human umbilical cord mesenchymal stem cells; ADSC-MVs: Microvesicles of ADSC; PRP: Platelet-rich plasma; HKFs: Human keloid fibroblasts; ADSC-CM: Adipose-derived stem cell concentrated conditioned medium; cGVHD: Chronic graft-versus-host disease; PDGF-ADSC-EVs: Extracellular vesicles of

PDGF-treated ADSCs; MSC-Ex: Exosomes of mesenchymal stem cells; BM-MSC: Bone marrow-derived mesenchymal stem cell; HucMSC-Ex: Exosomes of human umbilical cord mesenchymal stem cells; ADSC-ex: Exosomes of ADSCs; MSC-EVs: Extracellular vesicles of mesenchymal stem cells; α -SMA: α -Smooth muscle actin.

Acknowledgements

Not applicable.

Author contributions

All authors contributed to the conception and the main idea of the work. HT, YH, ZL and JL drafted the main text, figures, and tables. YL and ZD supervised the work and provided the comments and additional scientific information. HT also reviewed and revised the text. All authors read and approved the final manuscript.

Funding

This work was supported by the National Nature Science Foundation of China (81971852), and the Administrator Foundation of Nanfang Hospital (2018Z010).

Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Received: 24 April 2022 Accepted: 8 June 2022

Published online: 04 October 2022

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