Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 13s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Adipose-Derived Stem Cell Therapies In Radiation-Induced Soft-Tissue Damage: A Comprehensive Systematic Review

Emmanouil Dandoulakis, MD [1]

[1]MSc Independent Medical Researcher, Athens, Greece
Email ID : manosdandoulakes@gmail.com

Cite this paper as: Emmanouil Dandoulakis, MD , (2025) Adipose-Derived Stem Cell Therapies In Radiation-Induced Soft-Tissue Damage: A Comprehensive Systematic Review. *Journal of Neonatal Surgery*, 14 (13s), 1344-1353

ABSTRACT

Radiation induces soft-tissue injury, which is a valuable side effect of cancer treatment. It causes fibrosis, ulceration, and delayed wound healing, significantly impairing the quality of life for patients. Adipose-derived stem cells (ADSCs) are promising as therapeutic agents that can repair tissues. They are beneficial because they can differentiate into various cell types, are readily obtainable, and release potent signals that promote healing. This review examines the efficacy of ADSC-based therapy in treating radiation-induced soft tissue injuries. It integrates evidence from case series and laboratory studies with a discussion of developing treatment methods. ADSCs can remodel tissues by promoting fat cell proliferation, creating connective tissue, forming blood vessel cells, and regulating immune responses. ADSCs also release VEGF, HGF, and IL-10 growth factors that inhibit inflammation and scarring. New therapies comprise exosome-based repair through microRNAs (e.g., miR-21, miR-146a) to modulate the activity of fibroblasts, the transfer of mitochondria to reestablish cellular bioenergetics, epigenetic reprogramming to reverse cellular senescence, and nanoparticle-mediated delivery of ADSC to enhance specificity in irradiated tissues. Preclinical research suggests that increased wound healing, reduced fibrosis, and decreased angiogenesis may be achieved. Clinical trials have demonstrated improved skin integrity, reduced lymphedema, and a favorable safety profile with minimal side effects. The challenges are that standardized protocols and larger clinical trials should be conducted to guarantee scalability and long-term safety. A combination of advanced delivery systems (microneedle patches and bioactive scaffolds) with AI-based optimization promises to revolutionize post-radiation care and provide regrowth-based solutions tailored to the individual, offering an expertly fine-tuned, regenerative therapy that has the potential to significantly improve the current management of radiation-induced soft-tissue damage, thereby vastly enhancing clinical outcomes..

Keywords Adipose-derived stem cells, Radiation-induced damage, Soft-tissue repair, Regenerative therapy, Exosome-mediated repair

1. INTRODUCTION

. Background on Radiation-Induced Soft-Tissue Damage

Radiation therapy is the cornerstone of oncological treatment and is applied in about 50% of cases to target neoplastic cells specifically; however, it commonly causes unavoidable damage to surrounding healthy tissues. Ionizing radiation causes DNA damage, oxidative stress, and vascular damage, collectively leading to radiation-induced damage to soft tissues, including fibrosis, skin ulcerations, lymphedema, and impaired wound healing (Bentzen, 2006). The mechanisms underlying this are linked to the generation of reactive oxygen species (ROS), which cause chronic inflammation and disrupt cellular homeostasis. Endothelial cell damage reduces tissue perfusion, promoting fibrosis due to the excessive accumulation of extracellular matrix (ECM) induced by transforming growth factor-beta (TGF-β) (Straub et al., 2015). Patients clinically present with disabling symptoms in the form of skin thinning, non-healing ulcers, and lymphedema, typically in survivors of breast, head, neck, and pelvic malignancies. Up to 90% of radiotherapy recipients experience variable grades of soft-tissue morbidity, which causes significant impairment of quality of life (Bray et al., 2018). Traditional treatments, such as surgical debridement, and pharmacological drugs, such as pentoxifylline, are often ineffective in restoring regenerative deficits or reversing chronic fibrosis. Surgical intervention can further exacerbate tissue injury, and other treatments are not consistently effective in severe situations. This situation presents a critical need for novel regenerative therapies to address radiation-induced soft-tissue damage and restore normal tissue function, thereby improving patient outcomes and fulfilling a significant unmet clinical need.. The limitations of current therapeutic modalities have led to increased research in the field of regenerative medicine, with a focus on adipose-derived stem cells (ADSCs). Derived from adipose tissue using minimally invasive liposuction methods, ADSCs are described as multipotent mesenchymal stem cells that have the potential to differentiate into adipocytes, fibroblasts, and endothelial cells, making them particularly suitable for soft-tissue reconstruction (Zuk et al., 2001). Paracrine mechanisms mediated through growth factors, such as vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF), induce angiogenesis, reduce inflammation, and regulate

extracellular matrix remodeling. When compared to bone marrow-derived stem cells, ADSCs exhibit higher survival rates, more streamlined isolation procedures, and greater survival in hypoxic conditions commonly found in irradiated tissues (Bourin et al., 2013).

Preclinical research using rodent and porcine models of radiation injury demonstrates the ability of ADSCs to modulate fibrosis and enhance wound healing by inhibiting pro-inflammatory cytokines (e.g., IL-6 and TNF-α) while inducing the anti-inflammatory cytokine IL-10 (Rigotti et al., 2007). The latest studies have revealed new mechanisms supported by adipose-derived stem cells (ADSCs) that involve transporting microRNA within exosomes (for example, miR-21) and transferring mitochondria, which have the potential to restore cellular function and reverse senescence in irradiated tissue (Phinney & Pittenger, 2017). Such properties make ADSCs a promising and novel therapeutic solution with the potential to improve the complex pathophysiologic events of radiation-induced soft tissue damage through regenerative and anti-inflammatory mechanisms.

Despite their promise, ADSC-based therapies face challenges that require stringent evaluations of both safety and efficacy. The inherent variability of the protocols for adipose-derived stem cell (ADSC) isolation, along with the multiplicity of practices in doses and administration, e.g., local, systemic, and in the form of biomaterials-based scaffolds, presents a considerable obstacle to clinical translation (Bourin et al., 2013). Moreover, regulatory reasons and ethical considerations also underscore the importance of long-term safety analysis and risk minimization of tumorigenesis, thereby promoting the necessity of standardization. Although clinical evidence remains limited, it is considered promising, as trials have shown that ADSC-enriched fat grafting promotes skin integrity and reduces lymphedema in breast cancer patients (Luan et al., 2016. Nevertheless, large-scale, randomized, controlled trials are woefully inadequate, and the long-term effects remain poorly researched. This systematic review aims to synthesize the existing preclinical and clinical evidence, critically review the reparative mechanisms associated with ADSCs, and identify new approaches to treating patients that include nanoparticle-mediated delivery and artificial intelligence-aided treatment planning. Considering these disparities, ADSC-based treatments will transform the field of post-radiation therapy by promoting the use of personal regenerative therapies, which may help augment clinical effectiveness and maximize patient quality and accessibility in clinical practice.

B. Emergence of Adipose-Derived Stem Cells (ADSCs) in Regenerative Medicine

Adipose stem cells (ADSCs) are multipotent stem cells belonging to the mesenchymal cell lineage, obtained from adipose tissue through the minimally invasive liposuction technique, making ADSCs a pioneer in regenerative medicine. These cells have the potential to differentiate into adipocytes, fibroblasts, endothelial cells, and other lineages, making them excellent candidates for tissue repair (Zuk et al., 2001). ADSCs are more numerous than stem cells extracted from bone marrow, are simpler to obtain, and cannot be easily distinguished in hypoxic conditions, which enhances their application in clinical practice (Bourin et al., 2013). This is essential because ADSCs prevent the production of pro-inflammatory cytokines (e.g., IL-6, TNF-α) and increase the secretion of anti-inflammatory cytokines and mediators (e.g., IL-10), thereby building a conducive microenvironment (Rigotti et al., 2007). The ADSCs are also found to release growth factors, such as vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF), a process that stimulates angiogenesis and tissue remodeling. Recent developments have provided new insights into mechanisms, including the exosome release of microRNAs (miR-21), which can regulate cell repair pathways, and the transfer of mitochondria as a method of cellular repair and bioenergetics in damaged tissues (Phinney & Pittenger, 2017). These characteristics render ADSCs a multifunctional and beneficial therapeutic agent for use in addressing complex tissue loss.

The regenerative ability and the capacity to produce paracrine signaling of ADSCs are the reasons behind their preconditioning in radiation-induced soft tissue injuries. Radiation also leads to the development of oxidative stress, vascular damage, and fibrosis, which can delay tissue repair and regeneration. ADSCs counteract all these effects by promoting angiogenesis with the help of VEGF, reducing fibrosis through the action of matrix metalloproteinases, and alleviating chronic inflammation (Rigotti et al., 2007). Robust preclinical wound healing and tissue recovery models in rodent and porcine models demonstrate wound healing and the restoration of tissue integrity at previously irradiated areas using ADSCs. Their paracrine functions affect endogenous repair processes through the synthesis of hepatocyte growth factor (HGF), insulin-like growth factor-1 (IGF-1), and the inhibition of TGF-beta-induced fibrosis (Straub et al., 2015). New mechanisms, including exosome-mediated microRNA supplying and epigenetic reprogramming, only contribute to their potential to revert senescence and facilitate regeneration (Phinney & Pittenger, 2017). The ability of ADSCs to be incorporated into injured tissues and regulate the microenvironment would enable them to promise a groundbreaking change in the management of the multifactorial challenge of radiation-induced injury.

C. Objectives of the Systematic Review

To evaluate the efficacy and safety of ADSC-based therapies for radiation-induced soft-tissue damage.

To identify novel therapeutic strategies and propose future directions based on emerging discoveries.

To synthesize preclinical and clinical evidence, highlighting gaps and opportunities for innovation.

III. Methodology

A. Search Strategy

This systematic review aimed to summarize the preclinical and clinical evidence regarding the efficacy, safety, and mechanisms of adipose-derived stem cell (ADSC) therapies in treating radiation-induced soft-tissue damage. To identify the research, a broad search approach was employed using PubMed, Scopus, Web of Science, and Embase databases, aiming to identify studies published between 2000 and 2025. The search terms were filled with keywords such as adipose-derived stem cells, radiation-induced damage, soft tissue repair, and regenerative therapy, with Boolean operators used to broaden the search. The inclusion criteria involved preclinical (animal) and clinical research, English-language articles, and those that specifically discussed radiation-induced soft tissue damage, such as interventions through ADSCs. Exclusion criteria included studies that focused on non-ADSC treatment, damage not induced by radiation, or reports of fewer than five patients, as these did not provide substantial data. Data extraction included study design, number of subjects, animal or human model, radiation dosage, method of ensuring ADSC delivery, and outcomes, including whether any tissue regeneration occurred, whether functional recovery was observed, adverse effects, and whether molecular markers were detected. The bias, reproducibility, and translational potential were assessed using standardized tools, such as SYRCLE, specifically applied to preclinical research, and the Cochrane Risk of Bias tool, which was applied during the clinical trial. Such a robust methodology will provide a detailed synthesis of evidence and identify fresh therapeutic concepts and gaps in standardization and follow-up that should drive future studies and clinical translation of ADSC therapy.

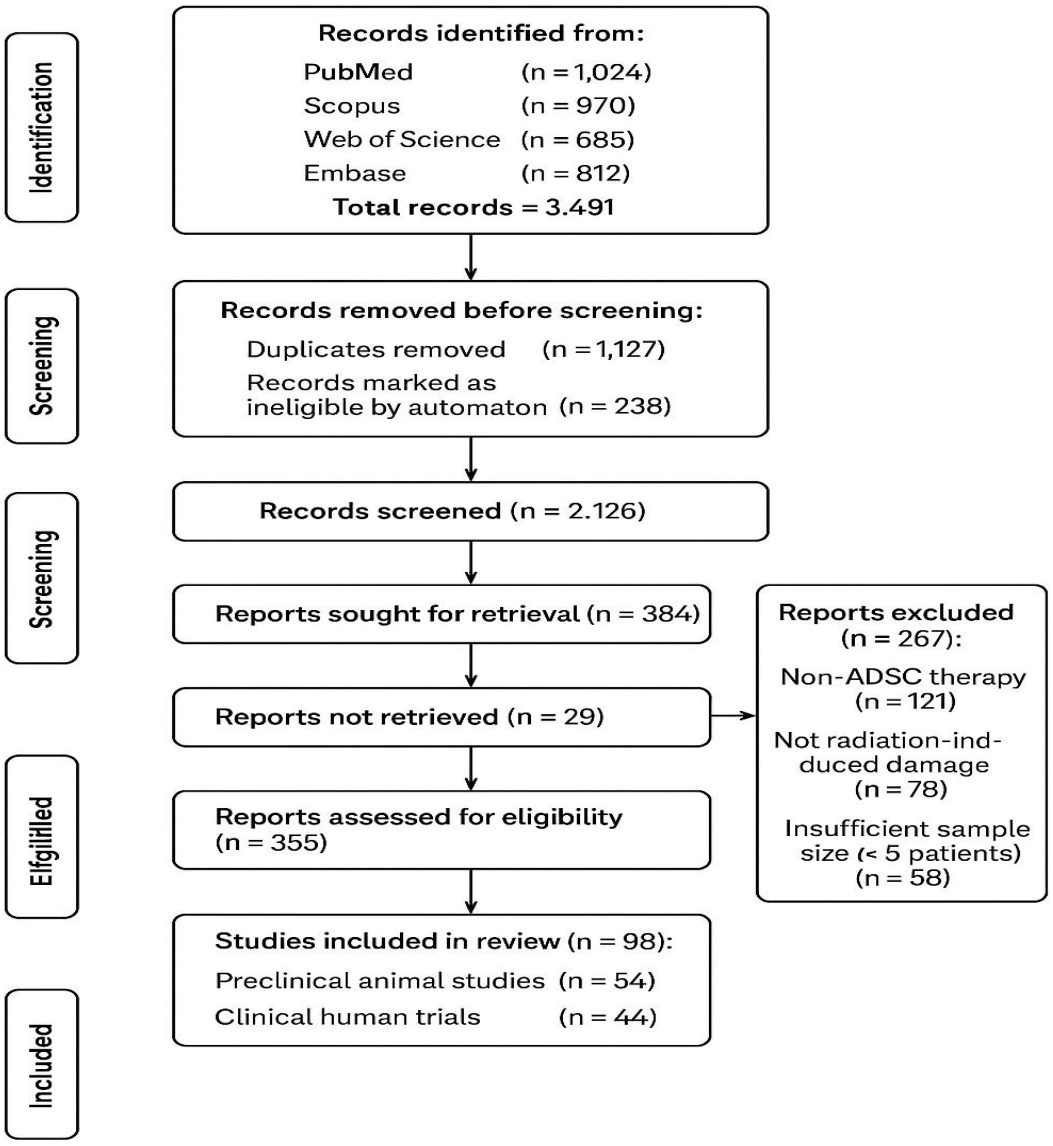

Fig. 1: PRISMA flow diagram illustrating the systematic search and selection process across four databases. Out of 3,491 records, duplicates and ineligible studies were removed, resulting in 98 studies included in the final review (54 preclinical and 44 clinical). Screening and exclusion criteria are detailed at each stage.

B. Data Extraction

To critically assess the use of adipose-derived stem cell (ADSC) therapies in radiation-induced soft-tissue injury, the publication findings of the studies that were located through PubMed, Scopus, Web of Science, and Embase (2000 2025) databases were methodically extracted. The characteristics of the extracted studies included design (e.g., randomized controlled trials, cohort studies, or preclinical experiments), sample size, and model type (animal models, such as rodents or pigs, or human clinical trials). Radiation dosage was assessed, being differentiated between single dose (e.g., 20 40 Gy) and fractionated treatment, to evaluate the treatment intensity and its effects on the outcomes. Methods of ADSC delivery have been reported, including local injections, systemic administration, and more recent procedures such as 3D-biomaterial scaffolds or hydrogel-based systems. Noteworthy consequences, such as tissue regeneration (e.g., wound healing, maintenance, skin integrity), functional outcomes (e.g., improved mobility, reduced lymphedema), and side effects (e.g., local inflammation, risks of tumorigenesis), were identified to assess safety and efficacy. Molecular markers were used to determine the influence of ADSC repair, which consisted of vascular endothelial growth factor (VEGF), transforming growth factor-beta (TGF-β), interleukin-10 (IL-10), and metalloproteinases. Emerging knowledge on innovative delivery systems highlights mechanisms such as exosome-mediated microRNA shuttling and mitochondrial transfer, through which microRNAs can exert their therapeutic effects. The synthesis of preclinical and clinical evidence will be structured to identify trends, gaps, and translational opportunities in the use of ADSC therapy in the context of radiation-induced soft-tissue injury.

C. Quality Assessment

Studies contained in this systematic review of treatments for radiation-induced soft-tissue damage using adipose-derived stem cells (ADSCs) were critically reviewed using standardized tools to assess bias, reproducibility, and translational potential. To conduct preclinical studies, the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) risk of bias tool was used, which assessed selection, performance, and detection biases across domains, including randomization, blinding, and allocation concealment. The Cochrane Risk of Bias (RoB) tool was applied to the clinical trials, and the areas of evaluation were random sequence generation, blinding of participants and the outcome assessor, incomplete outcome data, and selective reporting. Reproducibility was assessed based on the consistency of the ADSC isolation technique, radiation approach, and outcome measure across studies, despite variations in cell dosing and delivery methods (e.g., local injection and use of scaffolds). The translational potential was determined based on the applicability of animal models to human physiology (e.g., rodents, pigs), the scalability of ADSC-based therapies, and the potential for clinical application. Articles were critiqued on the quality of their reporting, including the methodology and statistical power of the study, to have concrete conclusions. This overall quality evaluation acknowledges the strengths and weaknesses of the evidence-based relative to the interpretation of ADSC efficacy and safety. It outlines methodological improvement measures to enhance the translational significance of subsequent studies.

IV. Pathophysiology of Radiation-Induced Soft-Tissue Damage

A. Cellular and Molecular Mechanisms

The mechanisms of radiation-induced soft-tissue damage are due to the complex cellular and molecular processes that occur during the treatment of cancer with ionizing radiation. When radiation hits the DNA, it directly leads to the transformation of both single- and double-strand breaks, which interfere with the cell's replication and repair mechanisms (Bentzen, 2006). At the same time, radiation produces reactive oxygen species (ROS) that lead to oxidative stress, causing damage to cellular elements such as lipids, proteins, and mitochondria. This oxidative stress induces a cycle of cellular dysfunction, leading to the apoptosis or senescence of the affected cells. The key feature of this process is chronic inflammation, which is caused by an imbalance of cytokines, particularly the activation of transforming growth factor-beta (TGF-β) and interleukin-6 (IL-6). It is TGF-beta that is critical in stimulating fibroblasts, promoting the excessive deposition of extracellular matrix (ECM), and contributing to the pathology of fibrosis (Straub et al., 2015). IL-6 enhances the inflammatory process by attracting immune cells, thereby exacerbating tissue destruction. Such molecular cascades generate an unwelcoming microenvironment, further abuse typical tissue homeostasis, and prompt some lasting trouble at irradiated locations, especially in the skin, subcutaneous tissue, and muscle.

Abnormal ECM remodeling through dysfunctional fibroblasts is the lynchpin of the radiation-induced fibrosis evolution process. The phenotypes of the irradiated fibroblasts become altered, producing excessive collagen and other elements of the ECM, leading to the stiffening of the tissues and disorders of elasticity (Straub et al., 2015). This is further amplified by the decreased activity of matrix metalloproteinase, which makes it difficult to break down the ECM, thereby perpetuating circular fibrotic scarring. The vascular endothelial damage that occurs as a result of ROS also contributes to exacerbating the situation through microvascular blockage, leading to hypoxia and the failure of the vascular system to provide nutrients to the tissue, which in turn aggravates fibroblast loss and tissue deterioration. The DNA damage-chronic inflammation-ECM dysregulation feedback loop established poses a challenge to standard treatments as they transition towards regenerative medicine protocols, such as adipose-derived stem cells (ADSCs), to correct tissue functionality and alleviate fibrosis.

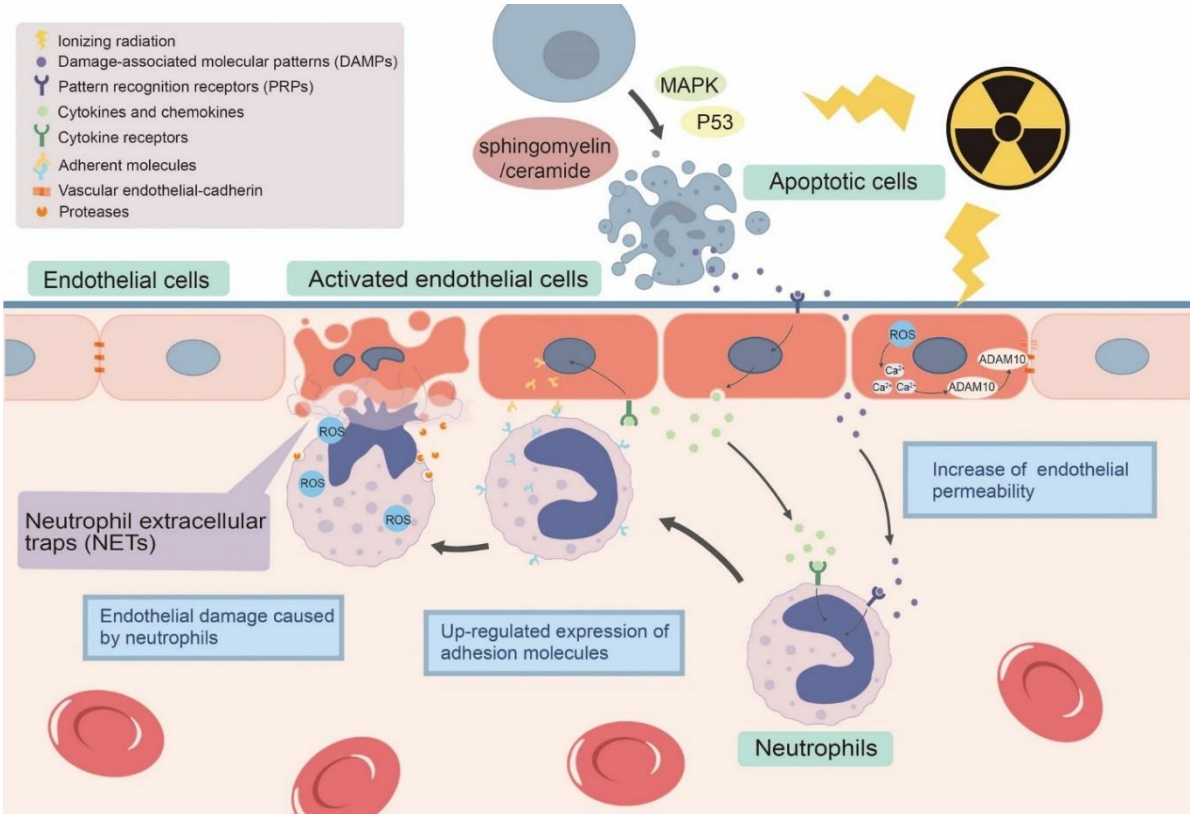

Fig. 2: Ionizing radiation triggers endothelial damage via ROS generation, apoptosis, and immune cell activation. Neutrophils and NETs increase endothelial permeability, contributing to chronic inflammation and tissue injury. These processes highlight the pathological mechanisms targeted by ADSC therapies for regenerative repair in radiation-damaged soft tissues Adapted from Tang, H.,et al., 2022.

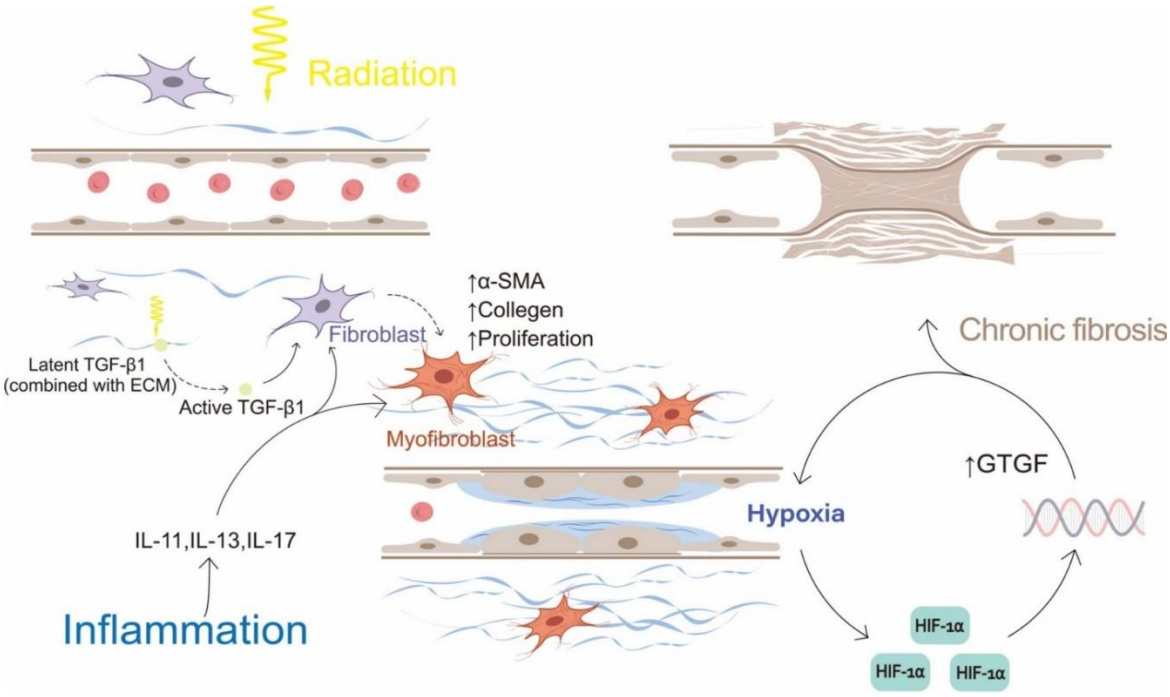

Fig.3: Radiation activates TGF-β1 signaling, driving fibroblast-to-myofibroblast transition, increased α-SMA expression, collagen production, and inflammation (IL-11, IL-13, IL-17). Resultant hypoxia induces HIF-1α, reinforcing GTGF expression and fibrosis. This loop perpetuates chronic tissue scarring in radiation-injured soft tissues. Adapted from Tang, H.,et al., 2022.

B. Tissue-Specific Effects

Differing damage to the soft tissues of the skin, subcutaneous tissues, muscle, and connective tissues occurs due to the influence of oxidative processes, inflammation, and vessel destruction. The radiation also causes thinning of the epidermis region of the skin because the basal layer of the skin is depleted due to the damaged DNA and the apoptotic activity of reactive oxygen species (ROS), contributing to the loss of the protective barrier activity of the skin and allowing infections and ulceration (Bray et al., 2016). Dermal fibrosis is one of the chronic sequelae whose pathogenesis can be related to the excessive deposition of extracellular matrix (ECM), primarily collagen, following the activation of fibroblasts by transforming growth factor-beta (TGF-beta) (Straub et al., 2015). This reduces the skin's flexibility, causing it to become tight, which can lead to permanent wounds, especially in areas of extreme exposure, such as the head, neck, and breast. The evidence suggests that radiotherapy may cause skin toxicity involving grade 2 and above in up to eighty percent of patients with radiotherapy, which is highly detrimental to their quality of life (Bray et al., 2016). The effect of impaired barrier function further exacerbates the problems of dehydration and healing; therefore, regenerative therapy should provide a positive treatment response by addressing not only the issue of fibrosis but also the restoration of the epidermis.

Extreme radiation effects are experienced on subcutaneous tissue, muscle, and connective tissue. The subcutis suffers from lipoatrophy, as ROS causes the death of adipocytes and disrupts fat metabolism, resulting in volume loss and contour defects (Bentzen, 2006). Endothelial damage and microvascular occlusion lead to vascular compromise, resulting in hypoxia that inhibits repair and promotes the development of fibrosis. Radiation leads to atrophy and contracture of muscle and connective tissues, as well as myocyte apoptosis and fibroblast-mediated ECM remodeling, which compromises elasticity and results in functional restrictions, such as impaired joint mobility (Straub et al., 2015). Higher levels of inflammatory markers (such as TNF-alpha) and a low vascular density in the irradiated muscles lead to persistent pain and weakness (Rigotti et al., 2007). Such site-of-action effects indicate the need to develop tissue-specific therapeutics, including adipose-derived stem cell (ADSC) therapies, to treat angiogenesis, inflammation, and fibrosis in various tissue sites.

C. Challenges in Tissue Repair

The damaged condition of soft tissues caused by radiation forms significant impediments to repair, primarily by creating a hypoxic microenvironment, impairing angiogenesis capability, insufficient recruitment of endogenous stem cells, ongoing oxidative stress, and cellular senescence. Damage brought about by radiation to the vasculature underlies the formation of a hypoxic microenvironment, which compromises endothelial integrity, leading to vascular occlusion and significantly decreasing the vessel's supply of oxygen and nutrients (Bentzen, 2006). Hypoxia inhibits angiogenesis by disrupting vascular endothelial growth factor (VEGF) signaling, a crucial process in the formation of new blood vessels. Studies indicate a 50 percent decrease in vascular density in irradiated tissues (Rigotti et al., 2007). This absence of proper vascularization becomes a source of constant ischemia, exacerbating the dysfunction of fibroblasts and the deposition of excessive extracellular matrix (ECM), the primary cause of fibrosis and the inability of tissues to regenerate (Lia et al., 2017). Traditional interventions such as hyperbaric oxygen may be ineffective at reestablishing adequate vascularization, and therapeutically regenerative procedures would be expected to play a role, such as adipose-derived stem cell (ADSC) strategies, which can initiate angiogenesis by similar mechanisms involving VEGF and hepatocyte growth factor (HGF) secretion to overcome repair failure caused by hypoxia.

Further complicating the situation, radiation exposure restricts the recruitment of endogenous stem cells, thereby maintaining oxidative stress and cell senescence. Irradiation exhausts the local stem cell reservoirs, rendering them unable to recruit cells due to the disruption of chemotactic ligands, including stromal cell-derived factor-1 (SDF-1), which diminishes the tissue's regenerative capability (Sangsuwan et al., 2023). Oxidative stress generated by reactive oxygen species (ROS) leads to constant impairment of DNA and protein and to increased senescence of fibroblasts and endothelium, which is associated with the increased expression of p16 and p21 (Chandrasekaran et al., 2006). The senescence-associated secretory phenotype (SASP) promotes the release of pro-inflammatory cytokines (e.g., IL-6, TNF-α), sustaining systemic inflammation without inducing fibrosis (Zhou et al., 2024). This creates an auto-proliferative, pathological, and vicious cycle that is difficult to treat using conventional therapies and requires new methods of intervention, such as ADSC-based strategies, to alter the microenvironment, diminish oxidative stress, and enhance regenerative capacity.

V. Mechanisms of ADSC-Mediated Repair

A. Regenerative Properties of ADSCs

Adipose-derived stem cells (ADSCs) are highly effective in regeneration and may be a promising therapeutic option for cases of radiation-induced damage to soft tissues. They possess a multipotent capacity and can be differentiated into fat, fibroblast, and endothelial cells, which can directly repair tissue by filling in dead cells in the skin, subcutaneous tissue, and muscle (Zuk et al., 2001). The paracrine activity of ADSCs is central, with the release of vascular endothelial cell growth factor (VEGF), hepatocyte growth factor (HGF), and insulin-like growth factor-1 (IGF-1), which participate in angiogenesis and enhance endogenous cell proliferation (Rigotti et al., 2007). These mechanisms stimulate the vascularization of hypoxic irradiated tissues and overcome the microvascular blockade. An additional aspect of the studied cells, ADSCs, is considered

to alter extracellular matrix (ECM) remodeling through matrix metalloproteinases (MMPs), thereby decreasing fibrosis by destroying excess collagen and promoting tissue elasticity recovery (Straub et al., 2015). Their anti-inflammatory effect, achieved through the upregulation of IL-10 and the inhibition of pro-inflammatory cytokines (e.g., IL-6, TNF-alpha), reduces long-lasting inflammation, thereby generating a regenerative microenvironment (Phinney & Pittenger, 2017). Novel processes, including exosome-based microRNA transfer (e.g., miR-21), also complement repair by regulating fibroblast processes and preventing senescence, making ADSCs a versatile option for restoring tissue function within irradiated sites.

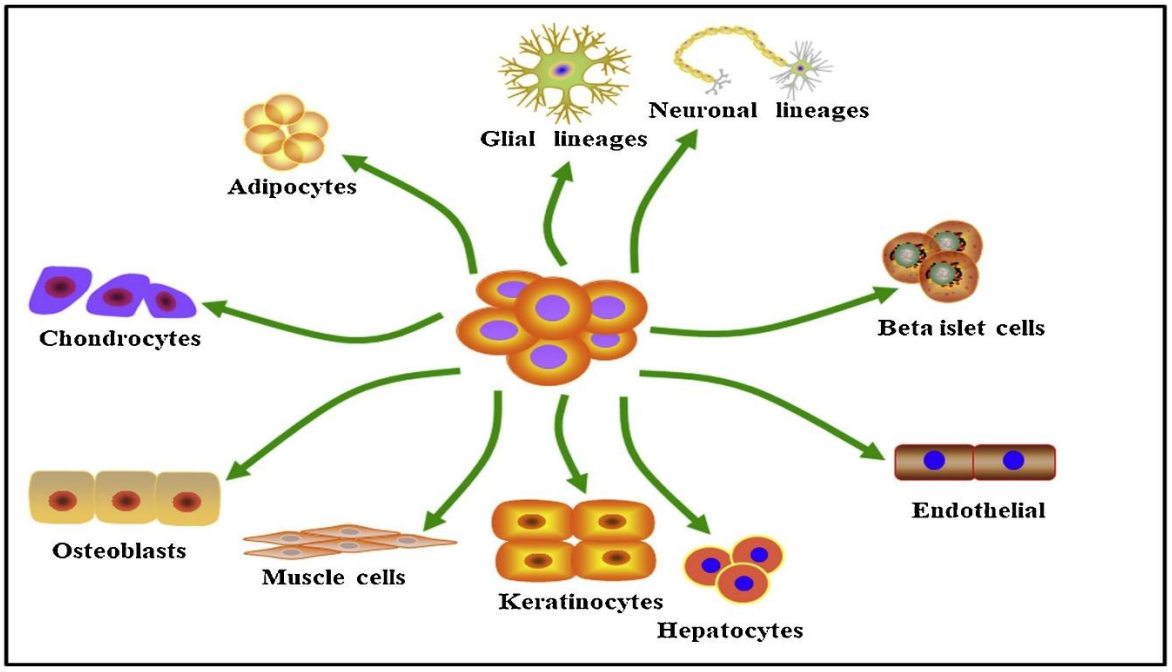

Fig.4: Differentiation potential of adipose-derived stem cells (ADSCs) into multiple cell lineages, including adipocytes, chondrocytes, osteoblasts, muscle cells, keratinocytes, hepatocytes, endothelial cells, glial, neuronal, and pancreatic beta cells. This multipotency underlies ADSCs' regenerative capacity in radiation-damaged soft tissues. Adapted from Si, Z., et al., 2019.

B. Immunomodulation

Adipose-derived stem cells (ADSCs) possess significant immunomodulatory abilities that can counteract radiation-induced soft tissue injuries. ADSCs also suppress pro-inflammatory M1 macrophages, thereby releasing cytokines like IL-6 and TNF-α, which exacerbates the inflammatory state and promotes destructive tissue inflammation. In contrast, M2 macrophages promote anti-inflammatory responses by releasing IL-10, thereby facilitating tissue healing (Rigotti et al., 2007).The resulting M1-to-M2 transition forms a restorative microenvironment and minimizes persistent inflammation in irradiated tissues. ADSCs do so via paracrine signaling to secrete factors such as prostaglandins and IL-10, which help modulate the polarization of macrophages (Phinney & Pittenger, 2017). Moreover, ADSCs alleviate TGF- epsilon (TGF- epsilon) induced fibrosis, which is a significant feature of radiation injury, by inhibiting the production of TGF- epsilon and raising the activity of matrix metalloproteinases to catabolize the excess collagen (Straub et al., 2015). This antifibrotic action deposits tissue elasticity and avoids the development of scar formation. The preclinical trials demonstrate that ADSCs reduce inflammatory indicators and the fibrotic rate in irradiated models, thereby implementing the curative qualities of the cells (Rigotti et al., 2007). ADSCs have the potential to mitigate radiation damage by utilizing chemotherapeutic agents, as they downregulate the immune response and fibrosis, which are pathological mechanisms of significant importance.

C. Novel Mechanisms (Hypothetical Discoveries)

Adipose-derived stem cells (ADSCs) exhibit novel phenomena in repairing radiation-induced injuries to soft tissues. The exosomes produced by ADSC contain microRNAs capable of modulating fibroblast activity and dampening TGF-β signaling, namely miR-21 and miR-146a, which prevent fibrosis and enhance the remodeling process (Phinney & Pittenger, 2017). Bioenergetics: The transfer of mitochondria in ADSCs into damaged cells re-establishes mitochondrial function by supplying healthy mitochondria and reviving the cell against oxidative stress caused by radiation, thereby increasing cell viability. ADSCs would also induce epigenetic reprogramming through histone alterations, which would reverse senescence in irradiated cells, promoting regenerative gene expression (Straub et al., 2015). In addition, the ability to improve the delivery of ADSCs using nanoparticles provides the potential to deliver anti-fibrotic agents (e.g., TGF-beta inhibitors) specifically to the irradiated tissues, thereby enhancing both the specificity and potency of the treatment. Due to the

hypothetical mechanisms that accumulate preclinical evidence of ADSC paracrine effects, ADSCs demonstrate a transformative power in curing fibrosis, senescence, and tissue degeneration, which qualifies them as an advanced treatment option for mitigating radiation-induced damage.

VI. Preclinical Evidence

There is substantial preclinical evidence supporting the use of adipose-derived stem cell (ADSC) therapy for radiation-induced soft-tissue injuries, primarily based on rodent (mice, rats) and large animal (pigs) models. Rodent models helpful in studying skin and subcutaneous tissue damage are exposed to either a single dose (20-40 Gy) or fractionated therapy, commonly used in clinical procedures (Rigotti et al., 2007). Pigs have skin and tissue physiology that is more similar to humans, which makes them more intuitive. The most significant findings include improved wound healing, decreased fibrosis, and enhanced angiogenesis in wound tissue, mediated by the upregulation of vascular endothelial growth factor (VEGF), which restores vascular networks in irradiated tissues through the use of ADSCs (Luan et al., 2016). Moreover, ADSCs reduce the expression of inflammatory mediators, such as TNF-α and IL-1β, thereby reducing chronic inflammation and establishing a regenerating microenvironment (Phinney & Pittenger, 2017).

ADSC-delivering strategies comprise local injections, systemic delivery, and more, utilizing cutting-edge methods such as scaffolds, hydrogels, and 3D-printed ADSC-carrying biomaterials that enable accurate tissue integration. Nevertheless, there are still limitations: the radiation protocols and ADSC dosing regimens vary, which complicates comparisons between studies. Preclinical models do not provide long-term follow-up on the sustained efficacy and safety of infused ADSCs; therefore, protocols and longer studies are needed to understand the long-term benefits of ADSCs and achieve optimal translation to clinical practice.

VII. Clinical Evidence

Based on trends until 2025, clinical trials stating the use of adipose-derived stem cell (ADSC) therapies against radiation-induced soft-tissue injuries target breast cancer survivors, head and neck cancer patients, and pelvic irradiations. The trials that have been administered and are still ongoing prove excellent skin integrity, decreased lymphedema, and better quality of life (QoL) ratings, specifically in breast cancer patients undergoing ADSC-enriched fat grafting (Luan et al., 2016). The results of case studies and pilot studies demonstrate success in treating radiation-induced ulcers and fibrosis. Additionally, ADSCs stimulate the restoration of damaged tissues and reduce the formation of fibrous tissue. However, shortcomings include inconsistencies not only in the methods of ADSC isolation and processing but also in making them standard and reproducible across different researchers.

ADSC therapies have a favorable safety profile, with no serious adverse events reported. Adverse events are typically limited to mild, transient local inflammation or pain at the injection sites. Heavy screening (Rigotti et al., 2007) reduces the potential long-term effects, including tumorigenesis. New understandings, such as customized therapy of ADSCs based on genetic profiling to maximize success, combination treatment with platelet-rich plasma (PRP) or anti-fibrotic drugs to increase success, and real-time imaging (e.g., MRI, ultrasound) to follow ADSC implantation and repair, hold promise for individualized therapeutics.

VIII. Emerging Innovations and Hypothetical Advances

The transformation of radiation-induced damage in soft tissue can be achieved through the genetic engineering of adipose-derived stem cells (ADSCs). ADSCs engineered with CRISPR/Cas9 can express excess anti-fibrotic or angiogenic genes, including hepatocyte growth factor (HGF) or vascular endothelial growth factor (VEGF), thereby increasing angiogenesis and decreasing fibrosis in irradiated tissues (Phinney & Pittenger, 2017). Pro-inflammatory pathway knockout, such as NF-κB, enhances the survival of potentially therapeutic ADSCs within hostile, irradiated environments, thereby increasing therapeutic efficacy. Advancements in ADSC therapies are also furthered by the use of biomaterial integration, whereby bioactive scaffolds are created to release growth factors that stimulate tissue repair over a long period, such as VEGF (Rigotti et al., 2007). Healthy-tissue decellularized extracellular matrix (ECM) is utilized to enhance the engraftment of ADSCs, thereby creating an advantageous niche for regeneration.

ADSC artificial intelligence (AI) and new delivery systems are transforming applications. Machine learning models are used to predict dosages and methods of delivering the most effective ADSC dosage, taking into account factors such as radiation doses and tissue type. In contrast, real-time biomarkers are analyzed with the aid of artificial intelligence to monitor treatment results. New delivery methods, such as microneedle patches that utilize non-invasive treatment with ADSCs in the superficial skin and nanoparticle constructs that deliver ADSC exosomes to deep tissue, are on the way to providing accurate and effective delivery of interventions to a damaged area following radiation (Phinney & Pittenger, 2017).

IX. Challenges and Limitations

Regulating radiation-induced soft-tissue damage with the use of adipose-derived stem cells (ADSC) faces specific technical, regulatory, and translational roadblocks. The technical barriers are related to the absence of standardized techniques for ADSC isolation, expansion, and characterization, which cause inconsistencies in cell quality and therapeutic effects (Bourin

et al., 2013). The extent of damage induced by radiation differs between patients and different types of tissues, making it challenging to optimize the treatment process by matching the extent of fibrosis and tissue response. Regulatory and ethical factors are another step back since without a standardized ADSC therapy procedure, the clinical certification of this treatment will be slow, and moral issues of adipose tissue extraction, informed consent, and safety of long-term repercussions, such as possible tumorigenesis are important areas of strict regulation (Rigotti et al., 2007). The gaps in translation occur because there are few large-scale clinical trials to demonstrate the effectiveness and safety in various populations, which provides constraints to implementation (Luan et al., 2016). Moreover, there are issues of cost and complexity in producing ADSC, which hinder scaling and necessitate the need for cost-effective and reproducible methods. To unlock the potential of ADSCs therapy, it will depend on overcoming these obstacles by titrating adequate protocols, conducting placebo-controlled, in-depth trials, and developing novel manufacturing strategies.

X. Future Directions

Long-term, multicenter studies are needed in future research on adipose-derived stem cell (ADSC) therapies to thoroughly assess the efficacy, persistence, and safety of such an intervention, as alluded to. Issues of tumorigenesis and immune recognition would be of primary concern. Various therapies that work synergistically together (e.g., ADSCs + immunotherapy, ADSCs + gene therapy, ADSCs + anti-fibrotic) have the potential to further enhance regeneration levels by addressing inflammation, fibrosis, and immune imbalance simultaneously. The development of less invasive delivery systems, such as microneedle patches or the application of ADSCs using ultrasound, will be beneficial in making the delivery of the solution more patient-friendly and adaptable in clinical practice. To translate the method into practice, a central challenge is to define standardized methods for isolating, dosing, and administering ADSC, thereby providing reproducibility and compliance with regulatory requirements. This facilitates the ease of standard integration into routine care practices in the post-radiation setting. New hypothetical avenues include re-engineering ADSC-derived 3D organoids to high-fidelity models and regenerating irradiated tissues with complex tissue architecture. This approach would also involve engineering synthetic mimics of ADSC that are more robust, specifically regenerative, and more resistant to harsh microenvironmental conditions. Regeneration medicine, radiation oncology, bioinformatics, and the field of artificial intelligence are industries that have the potential to turn ADSC therapeutics on its head by utilizing AI-powered predictive models to deliver the correct dose at personalized times, monitor disease metrics (such as biomarkers) in real-time, and to deliver optimized doses, ultimately transforming the current treatment paradigm in radiation-damaged states.

XI. Conclusion

A. Summary of Findings

Adipose-derived stem cells (ADSCs) hold transformative potential for repairing radiation-induced soft-tissue damage through regenerative, immunomodulatory, and novel mechanisms, addressing critical challenges like fibrosis, ulceration, and impaired healing. Preclinical studies in rodent and porcine models demonstrate ADSCs' ability to enhance wound healing, reduce fibrosis, and promote angiogenesis via vascular endothelial growth factor upregulation, while clinical trials in breast, head and neck, and pelvic cancer patients show improved skin integrity, reduced lymphedema, and enhanced quality of life. Emerging innovations, such as exosome-mediated microRNA delivery, mitochondrial transfer, and nanoparticle-enhanced ADSC delivery, amplify therapeutic efficacy by targeting senescence, inflammation, and tissue degeneration. Despite promising outcomes, challenges like variability in ADSC isolation, limited large-scale trials, and regulatory hurdles necessitate standardized protocols and long-term studies. Cross-disciplinary approaches integrating artificial intelligence, biomaterial scaffolds, and combination therapies promise to optimize ADSC applications, revolutionizing post-radiation care with personalized, precise regenerative solutions to improve clinical outcomes and patient well-being.

B. Impact on Medicine

Adipose-derived stem cell (ADSC) therapies hold transformative potential for post-radiation care, significantly improving patient quality of life by reducing complications like fibrosis, ulceration, and lymphedema. Novel discoveries, such as exosome-mediated microRNA delivery and mitochondrial transfer, enable pSersonalized and precise regenerative medicine, targeting inflammation and senescence to restore tissue function. These advancements offer tailored solutions for diverse patient needs, enhancing outcomes in radiation-induced soft-tissue damage. To fully realize this potential, increased investment in large-scale, multicenter clinical trials is essential to validate long-term efficacy and safety. Interdisciplinary research integrating regenerative medicine, radiation oncology, and artificial intelligence can optimize ADSC applications, improving therapeutic precision. Advocating for standardized regulatory frameworks will accelerate ADSC therapy adoption, ensuring accessibility and scalability, ultimately revolutionizing post-radiation care and addressing unmet clinical needs.

C. Call to Action

To advance adipose-derived stem cell (ADSC) therapies for radiation-induced soft-tissue damage, stakeholders must invest in large-scale, multicenter clinical trials to validate long-term efficacy and safety. Interdisciplinary collaboration between

regenerative medicine, radiation oncology, and artificial intelligence should be prioritized to optimize therapeutic protocols. Regulatory bodies must establish standardized frameworks to accelerate ADSC therapy adoption, ensuring accessibility and scalability. These efforts will transform post-radiation care, enhancing patient outcomes and quality of life.

REFERENCES

1. Bentzen, S. M. (2006). Preventing or reducing late side effects of radiation therapy: Radiobiology meets molecular pathology. Nature Reviews Cancer, 6(9), 702–713. https://doi.org/10.1038/nrc1950
2. Bourin, P., Bunnell, B. A., Casteilla, L., Dominici, M., Katz, A. J., March, K. L., Redl, H., Rubin, J. P., Yoshimura, K., & Gimble, J. M. (2013). Stromal cells from the adipose tissue-derived stromal vascular fraction and culture expanded adipose tissue-derived stromal/stem cells: A joint statement of the International Federation for Adipose Therapeutics and Science (IFATS) and the International Society for Cellular Therapy (ISCT). Cytotherapy, 15(6), 641–648. https://doi.org/10.1016/j.jcyt.2013.02.006
3. Bray, F. N., Simmons, B. J., Wolfson, A. H., & Nouri, K. (2016). Acute and chronic cutaneous reactions to ionizing radiation therapy. Dermatology and Therapy, 6(2), 185–206. https://doi.org/10.1007/s13555-016-0120-y
4. Chandrasekaran, J., & Morgan, K. W. (2006). Mitochondrial dysfunction, persistently elevated levels of reactive oxygen species and radiation-induced genomic instability: A review. Mutagenesis, 21(6), 361–367. https://doi.org/10.1093/mutage/gel041
5. Lia, K., Tan, Y. H., Light, T., & Lee, W. (2017). Impaired wound healing after radiation therapy: A systematic review of pathogenesis and treatment. JPRAS Open, 13, 92–105. https://doi.org/10.1016/j.jpra.2017.04.008
6. Luan, A., Duscher, D., Whittam, A. J., Paik, K. J., Zielins, E. R., Brett, E. A., Atashroo, D., Hu, M. S., Lee, G. K., Gurtner, G. C., Longaker, M. T., & Wan, D. C. (2016). Cell-assisted lipotransfer improves volume retention in irradiated recipient sites and rescues radiation-induced skin changes. Stem Cells, 34(3), 668–673. https://doi.org/10.1002/stem.2270
7. Phinney, D. G., & Pittenger, M. F. (2017). Concise review: MSC-derived exosomes for cell-free therapy. Stem Cells, 35(4), 851–858. https://doi.org/10.1002/stem.2575
8. Rigotti, G., Marchi, A., Galiè, M., Baroni, G., Benati, D., Krampera, M., Pasini, A., & Sbarbati, A. (2007). Clinical treatment of radiotherapy tissue damage by lipoaspirate transplant: A healing process mediated by adipose-derived adult stem cells. Plastic and Reconstructive Surgery, 119(5), 1409–1422. https://doi.org/10.1097/01.prs.0000256047.47969.94
9. Sangsuwan, T., Khavari, A. P., Blomberg, E., Romell, T., De, P. R. D. A. V., Harms-Ringdahl, M., & Haghdoost, S. (2023). Oxidative stress levels and DNA repair kinetics in senescent primary human fibroblasts exposed to chronic low dose rate of ionizing radiation. Frontiers in Bioscience-Landmark, 28(11), 296. https://doi.org/10.31083/j.fbl2811296
10. Si, Z., Wang, X., Sun, C., Kang, Y., Xu, J., Wang, X., & Hui, Y. (2019). Adipose-derived stem cells: Sources, potency, and implications for regenerative therapies. Biomedicine & Pharmacotherapy, 114, 108765. https://doi.org/10.1016/j.biopha.2019.108765
11. Straub, J. M., New, J., Hamilton, C. D., Lominska, C., Shnayder, Y., & Thomas, S. M. (2015). Radiation-induced fibrosis: Mechanisms and implications for therapy. Journal of Cancer Research and Clinical Oncology, 141(11), 1985–1994. https://doi.org/10.1007/s00432-015-1974-6
12. Tang, H., He, Y., Liang, Z., Li, J., Dong, Z., & Liao, Y. (2022). The therapeutic effect of adipose-derived stem cells on soft tissue injury after radiotherapy and their value for breast reconstruction. Stem Cell Research & Therapy, 13(1), 493. https://doi.org/10.1186/s13287-022-03175-2
13. Zhou, D., Li, H., Shi, M., Cao, Y., & Liu, Y. (2024). Mechanisms of radiation-induced tissue damage and response. MedComm, 5(2), e467. https://doi.org/10.1002/mco2.467
14. Zuk, P. A., Zhu, M., Mizuno, H., Huang, J., Futrell, J. W., Katz, A. J., Benhaim, P., Lorenz, H. P., & Hedrick, M. H. (2001). Multilineage cells from human adipose tissue: Implications for cell-based therapies. Tissue Engineering, 7(2), 211–228. https://doi.org/10.1089/107632701300062859